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VESSEL OCCLUSION AND FUNCTIONAL OUTCOME AFTER ACUTE STROKE— PREDICTION AND EVALUATION

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Vessel Occlusion and Functional Outcome after Acute Stroke—Prediction and Evaluation

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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My beautiful wife, precious daughter and darling son—you are my sun, my moon and my star.

Ammi and Thathi—for giving me everything.

In remembrance of my late grandfather, Leo Gervasius Fernando. Stroke prevented you from ever being part of my life.

ABSTRACT

In the acute setting of ischaemic stroke, two proven treatments are available: intravenous thrombolysis (iv-tPA) with alteplase and endovascular thrombectomy. The main aim of this thesis was to investigate the associations between symptom severity in the acute setting of ischaemic stroke and

1) the presence of arterial occlusions and
2) long-term functional outcome assessed at 3 months.

The first 3 studies were based on patients registered in the large Safe Implementation of Treatments in Stroke - International Stroke Thrombolysis Register (SITS-ISTR). In the final project, conceptually separated from the first 3 studies, we aimed to investigate a novel method for assessing 3-month functional outcome after acute stroke.

Study 1. We aimed at finding thresholds for baseline stroke severity as measured by National Institutes of Health Stroke Scale (NIHSS) scores that predicted long-term functional outcome and baseline arterial occlusion. We analysed 44 331 iv-tPA treated ischaemic stroke patients with available functional outcome assessed by the modified Rankin Scale (mRS) at three-months and 11 632 patients with available computed tomography/magnetic resonance angiography data at baseline. For functional independency (mRS 0-2), NIHSS scores of 12 [area under the curve (AUC) 0.775] and for baseline arterial occlusion, NIHSS scores of 11 (AUC 0.678) were optimal threshold values. NIHSS thresholds decreased with time from stroke onset to imaging, with 2–3 points, respectively, if time to imaging exceeded three-hours. We concluded that an NIHSS threshold of 9 or 10 points could be considered in the pre-hospital selection of patients for immediate transfer to centres with arterial imaging and availability of endovascular thrombectomy.

Study 2. ASTRAL and DRAGON are two recently developed scores for predicting long-term functional outcome after acute stroke in unselected acute ischaemic stroke patients and in patients treated with iv-tPA, respectively. We aimed to perform external validation of these scores. We calculated the ASTRAL and DRAGON scores in 36131 and 33716 iv-tPA treated patients, respectively, registered in the SITS-ISTR between 2003 and 2013. The proportion of patients with death or dependency at 3 months (mRS 3-6) was observed for each score point and compared with the predicted proportion according to the risk scores. Predictive performance was assessed using the AUC of the receiver operating characteristic. The ASTRAL showed an AUC of 0.790 (95% CI, 0.786–0.795) and the DRAGON an AUC of 0.774 (95% CI, 0.769–0.779). We concluded that the ASTRAL and DRAGON scores show an acceptable predictive performance and may have a role for prognostication of outcome after acute ischaemic stroke.

Study 3. We aimed to assess the predictive value of various models based on baseline NIHSS sub-items, ranging from simple to more complex models, for predicting large arterial occlusions (LAO) in anterior circulation stroke. Patients registered in the SITS-ISTR with clinically defined anterior circulation stroke, and available NIHSS and radiological arterial occlusion data were analysed. We compared 1975 patients harbouring an LAO with 2036 patients having no/distal occlusions. Using binary logistic regression, we developed models ranging from a simple 1 NIHSS-sub-item to full NIHSS-sub-items models. Sensitivities and specificities of the models for predicting LAO were examined. The model with highest predictive value included all NIHSS sub-items as well as other relevant parameters for predicting LAO (AUC 0.78), yielding a sensitivity and specificity of 74% and 72% respectively. The simplest model included only deficits in arm motor-function (AUC 0.72) for predicting LAO, yielding a sensitivity and specificity of 69% and 70% respectively. Differences between the models were not large. We concluded that assessing grade of arm-dysfunction along with an established stroke-diagnosis model may serve a surrogate measure of LAO status, thereby assisting in triage decisions.

Study 4. Assessment of long-term functional outcome is lacking in many settings. We aimed to investigate whether automatic assessment of the mRS based on a mobile phone questionnaire may serve as an alternative to mRS assessments at clinical visits after stroke. We enrolled 62 acute stroke patients admitted to our stroke unit during March to May 2014. Forty- eight patients completed the study. During the hospital stay, patients and/or caregivers were equipped with a mobile phone application in their personal mobile phones. Three months after inclusion, the mobile phone application automatically prompted the study participants to answer an mRS questionnaire in the mobile phones. A few days later, a study personnel performed a clinical visit mRS assessment. The 2 assessments were compared using quadratic weighing κ-statistics. We found a 62.5% agreement between clinical visit and mobile mRS assessment, weighted kappa 0.89 (95% CI 0.82–0.96), and unweighted kappa 0.53 (95% CI 0.36– 0.70). Mobile phone–based automatic assessments of mRS performed well in comparison with clinical visit mRS and may serve a supplementary role to traditional assessments, especially in settings where clinical follow-up visits are scarce because of economic and time-restraining factors.

LIST OF SCIENTIFIC PAPERS

I. Cooray C, Fekete K, Mikulik R, Lees KR, Wahlgren N, Ahmed N.

Threshold for NIH stroke scale in predicting vessel occlusion and functional outcome after stroke thrombolysis.

International Journal of Stroke. 2015 Aug;10(6):822-9

II. Cooray C, Mazya M, Bottai M, Dorado L, Skoda O, Toni D, Ford GA, Wahlgren N, Ahmed N.

External Validation of the ASTRAL and DRAGON Scores for Prediction of Functional Outcome in Stroke.

Stroke. 2016 Jun;47(6):1493-9

Poster presentation at the European Stroke Organisation Conference in Barcelona, 2016.

III. Cooray C, Mazya MV, Bottai M, Scheitz JF, Abdul-Rahim AH, Prazeres Moreira T, Mikulik R, Krajina A, Nevsimalova M, Toni D, Wahlgren N, Ahmed N.

Are you suffering from a large arterial occlusion? - Please raise your arm!

Submitted, currently in manuscript form.

Poster presentation at the European Stroke Organisation Conference in Prague, 2017.

IV. Cooray C, Matusevicius M, Wahlgren N, Ahmed N

Mobile Phone-Based Questionnaire for Assessing 3 Months Modified Rankin Score After Acute Stroke: A Pilot Study.

Circulation: Cardiovascular Quality and Outcomes. 2015 Oct;8(6):S125-30

CONTENTS

LIST OF ABBREVIATIONS

ACA -	Anterior Cerebral Artery
aOR -	adjusted odds ratio
ATLANTIS -	Alteplase Thrombolysis for Acute Non-Interventional Therapy in Ischaemic Stroke trials
ATP -	Adenosine Triphosphate
AUC -	Area under the curve
BBB -	Blood Brain Barrier
BI -	Barthel Index
CBF -	Cerebral Blood Flow
CT -	Computer Tomography
CTA -	Computed Tomography Angiography
DALY -	Disability Adjusted Life Years
DM -	Diabetes Mellitus
ECASS -	European Cooperative Acute Stroke Study
ECASS-II -	2nd European Cooperative Acute Stroke Study
ECASS-III -	3rd European Cooperative Acute Stroke Study
EEG -	Electroencephalography
EMEA -	The European Medicines Evaluation Agency
EMS-	Emergency Management of Stroke Trial
ESCAPE -	The Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times
EU -	European Union
EXTEND-IA -	Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial
GOS -	Glasgow Outcome Scale
GWTG -	Get With the Guidelines Stroke Registry
Ia -	Intra-arterial
ICA -	Internal Carotid Artery
IMS -	Interventional Management of Stroke Study
IPD -	Individual Patient-Data Meta-Analysis

IQR -	Interquartile Range
IST -	International Stroke Trial
IST-3 -	3rd International Stroke Trial
ITT -	Intention to Treat Analysis
Iv -	Intravenous
Iv-tPA -	Intravenous tissue Plasminogen Activator
LAO -	Large Arterial Occlusion
MCA -	Middle Cerebral Artery
M1 -	First segment of middle cerebral artery
M2 -	Second segment of middle cerebral artery
MMP -	Matrix Metalloproteinases
mNIHSS -	modified National Institute of Health Stroke Scale
MRA -	Magnetic Resonance Angiography
MR CLEAN -	The Multicentre Randomized Clinical Trial of Endovascular Treatment for Acute Ischaemic Stroke in the Netherlands
MR RESCUE -	The Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy
MRI -	Magnetic Resonance Imaging
MR-DWI -	Magnetic Resonance Diffusion Weighted Imaging
mRS -	modified Rankin Scale
MTT -	Mean Transit Time
NC -	National Coordinator
NIHSS -	National Institute of Health Stroke Scale
NINDS -	The National Institute of Neurological Disorders and Stroke
NNT -	Number Needed to Treat
NPV -	Negative Predictive Value
OR -	Odds Ratio
PCA -	Posterior Cerebral Artery
PDGF-CC -	Platelet Derived Growth Factor CC
PP -	Per Protocol Analysis
PPV -	Positive Predictive Value
PROACT -	The Prolyse in Acute Cerebral Thromboembolism trial
RCT -	Randomised Controlled Trial

REVASCAT -	Randomized Trial of Revascularization with Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke due to Anterior Circulation Large Vessel Occlusion Presenting Within 8 h of Symptom Onset
RFA -	Rankin Focused Assessment
ROC -	Receiver Operating Characteristic
rtPA -	Recombinant tissue Plasminogen Activator
SICH -	Symptomatic Intracerebral Haemorrhage
SITS -	Safe Implementation of Treatments in Stroke
SITS-MOST -	Safe Implementation of Thrombolysis in Stroke-Monitoring Study
SITS SC -	SITS Scientific Committee
smRSq –	simplified mRS questionnaire
SYNTHESIS-	Local versus Systemic Thrombolysis for Acute Ischemic Stroke
SWIFT PRIME -	Solitaire with The Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischaemic Stroke
TACI -	Total Anterior Circulation Syndrome
TCD -	Trans Cranial Doppler
TIA -	Transient Ischaemic Attack
THERAPY -	Randomized Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke
THRACE -	Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke
US-FDA -	United States- Food and Drug Administration
WHO -	World Health Organization
WHO-ICF -	World Health Organization International Classification of Functioning, Disability and Health

1 INTRODUCTION

The World Health Organization (WHO) definition of stroke from the 1970s is the following: "Rapidly developing clinical signs of focal or global disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin" (1). Patients with symptoms resolving within 24h are denoted as suffering from a transient ischaemic attack (TIA).

This definition of stroke does not reveal the underlying pathophysiology. The proportion of stroke caused by cerebral infarction is 70-85%, while 15-30% is caused by intracerebral and subarachnoid haemorrhage (bleeding). Infarction is defined as irreversible cell death caused by ischaemia. Cerebral ischaemia denotes a state of insufficient blood flow to uphold the energetic requirements of the brain. This disruption of the blood flow is caused by obstruction of the blood vessels supplying the cerebral tissue.

The focus of this thesis is patients suffering from cerebral ischaemia/infarction. We will now continue with a brief overview on the epidemiology of stroke.

1.1 EPIDEMIOLOGY

Stroke is one of the major causes of death and disability, being the 2nd leading cause of death worldwide, accounting for 6.5 million deaths (51% ischaemic strokes) in 2013. In 2013, the worldwide incidence in absolute numbers of first-time stroke was 10.3 million (67% ischaemic strokes) and the global prevalence 26 million (71% ischaemic strokes), having increased by 66% and 84% respectively compared to 1990 (2). Despite these increased absolute numbers, mortality rates have reduced in both low-, middle- and high-income countries, probably due to improved stroke-care (3). This increased survival has important implications however, as a large proportion of patients survive with long-term disabilities. According to 2015 data from the WHO, stroke was estimated to cause a total loss of 140 million Disability Adjusted Life Years (DALY´s), accounting for 5 % of the total number of DALY´s lost worldwide (4). The societal economic costs are enormous, both directly through costs for in-patient-care, rehabilitation etc. and indirectly through loss of income. In 2010, the estimated cost of stroke in the EU area was estimated at a staggering 64.1 billion Euros (5).

With an increasing life-expectancy, the incidence of stroke is expecting to increase further. One estimation is an increase in incident stroke cases from 1.1 million to 1.5 million between 2000 and 2025 in the EU area (6).

The situation in Sweden is similar to the trends seen in other high-income countries. In 2015 close to 23000 incident cases of stroke were registered in RiksStroke, the Swedish national quality register for stroke care (7). During the same period the WHO registered a total of 7900 deaths attributable to stroke in Sweden (8). Stroke incidence in Sweden has declined over the last decades, for ischaemic stroke reducing from 152 to 123 (per 100 000 person-years) between 1995-2010. Mortality has declined during the same time period from 38 to 24 (per 100 000 person-years) (9).
This decline, seen in absolute numbers as well, has occurred in spite of an increasingly aging population. Notably, however, there is an increase in the stroke incidence among young and middle aged in Sweden (10). It is still an open question whether Sweden will be facing the same problems as the rest of the Western world, with increased costs on society due to both direct and indirect causes. The estimated cost of stroke, both directly and indirectly, has been estimated at roughly 640 000 SEK/case, with an estimated yearly cost of 18.3 billion SEK on society (11).

Figure 1A shows the overall global trend in incidence rate and mortality over the last two decades. Although the incidence rate overall is not increasing, and mortality overall has decreased, as seen in Figure 1B in absolute numbers the global incidence is steadily increasing. Alarmingly, an increased incidence rate of ischaemic stroke is seen in the younger population. The above-mentioned figures highlight the need for improving both primary and secondary prevention of stroke, as well as improving both the treatments in the acute setting and post-stroke rehabilitation, in order to reduce the incidence of stroke and improve long-term outcome after incident stroke.

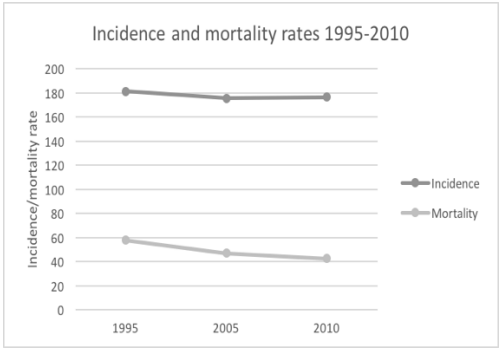

***Figure 1A**. Global incidence and mortality rates (per 100 000 person-years) between 1995 and 2010.*

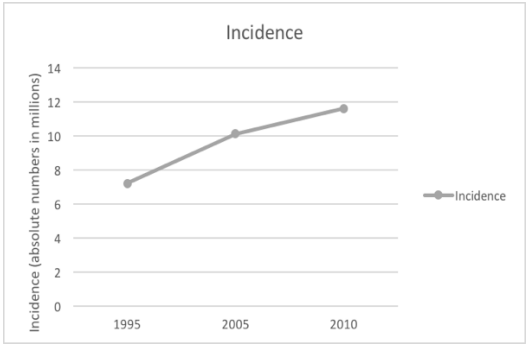

***Figure 1B**. Global incidence in absolute numbers (millions) between 1995 and 2010.*

1.2 CEREBRAL VASCULAR ANATOMY

The brain is supplied by blood from four main arteries: the paired carotid and vertebral arteries. The gross anatomy of these originating vessels can vary, with several anatomical variations, however in most humans, the general anatomy is the following, see Figure 2 (12).

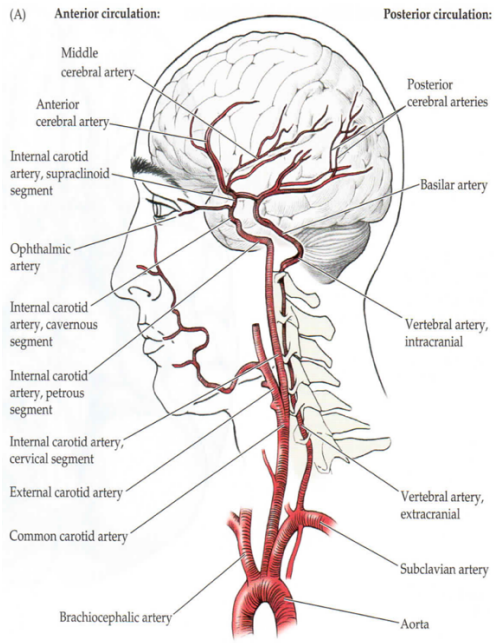

***Figure 2**. Anatomy of the cerebral vasculature. From Blumenfeld, 2010 (12). Permission for use obtained from Sinauer.*

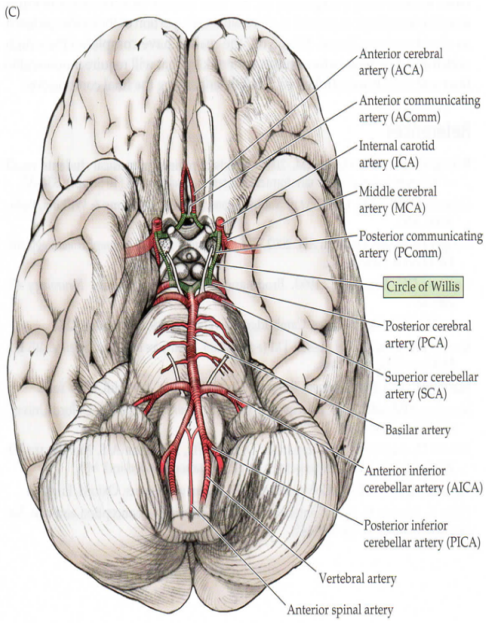

***Figure 3**. Circle of Willis. From Blumenfeld, 2010 (12). Permission for use obtained from Sinauer.*

The right common carotid artery usually arises as a branch from the brachiocephalic trunk, which in turn arises as a branch from the aortic arch. The brachiocephalic trunk also branches into the right subclavian artery. The left common carotid artery arises directly from the aortic arch. Both the left and right common carotid arteries branch into the internal and external carotid arteries, approximately at the level of the thyroid cartilage (C3-C5). The internal carotid artery (ICA) continues unbranched to the carotid canal at the base of the skull. This segment is called the cervical or extracranial segment. Subsequently it passes through the petrous segments of the temporal bone, and after giving off several branches terminates at the base of the brain in an anastomosis called the circle of Willis, see Figure 3 (13).

The ICA branches into the middle and anterior cerebral arteries (ACA), as well as the posterior communicating arteries.

The paired anterior cerebral arteries are connected through a short arterial segment called the anterior communicating artery. The anterior and middle cerebral arteries form the so called anterior cerebral circulation. The ICA supplies approximately 80% of the total cerebral blood flow (14).

The right and left vertebral arteries arise from each subclavian artery, and enter the cranial cavity at the C1 level. They anastomose and form the basilar artery at the pontomedullary junction. The basilar artery subsequently extends cranially to the terminal bifurcation and gives rise to the paired posterior cerebral arteries at the level of the midbrain. The posterior cerebral arteries are connected to the anterior circulation through the posterior communicating arteries, completing the full circle of Willis. Variants of the circle of Willis are common, and in one MR angiography study only approximately 42% of all subjects had a complete circle of Willis (15).

The cerebral vascular architecture is intricate, made of several collateral backup systems, stepping in if acute or chronic vascular obstruction ensues. These consist of one principal collateral system including extracranial sources of blood flow and two principal intracranial collateral systems divided into a primary and secondary system (16), see Figure 4:

1) Extracranial collaterals: this collateral system consists of anastomoses between the extracranial and intracranial arterial systems, for example several anastomoses exist between the external and internal carotid arteries.
2) Intracranial collaterals, primary pathways: This primary collateral system consists of the circle of Willis, and provides immediate redirection of blood to ischaemic regions in case of obstruction to parent vessels.
3) Intracranial collaterals, secondary pathways: Also known as leptomeningeal or pial collaterals (17), this system consist of a vast network of arterial anastomoses between distal segments of major cerebral arteries along the surface of the brain. This system forms a rescue network in case of arterial obstructions distal to the circle of Willis. The majority of anastomoses in the pial network connect the anterior cerebral circulation with the middle cerebral circulation, less between the middle and posterior cerebral circulations, and even more scarce between the anterior and posterior circulations. Anastomoses also exist between the vertebral and basilar arteries in the posterior circulation.

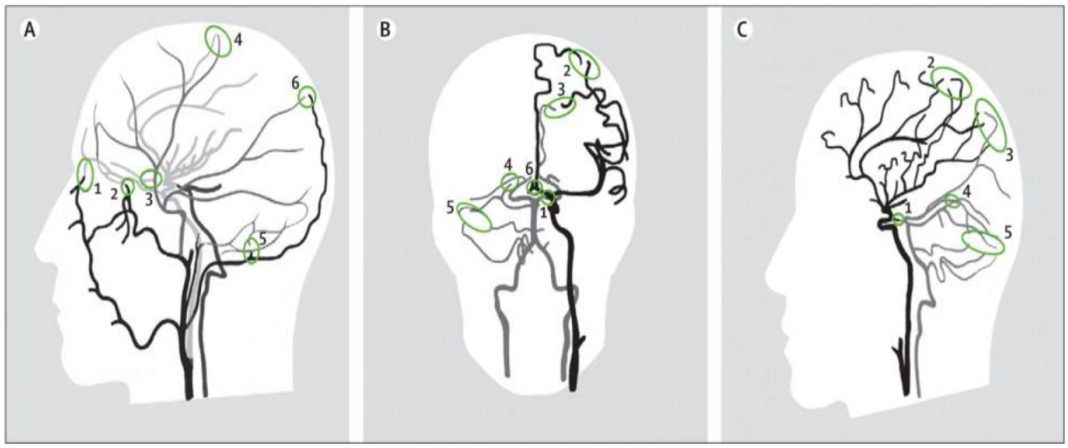

***Figure 4**. A) Extracranial arterial collateral circulation. Anastomoses from the 1) facial, 2) maxillary and 3) middle meningeal arteries to the ophthalmic artery and 4) dural arteriolar anastomoses from the middle meningeal artery and 5) occipital artery through the mastoid foramen and 6) parietal foramen. B, C). Intracranial arterial collateral circulation in frontal (B) and lateral(C) views. 1) Posterior communicating artery; 2) leptomeningeal anastomoses between anterior and middle cerebral arteries and 3) between posterior and middle cerebral arteries; 4) tectal plexus between posterior cerebral and superior cerebellar arteries; 5) anastomoses of distal cerebellar arteries and 6) anterior communicating artery. Reproduced from Liebeskind, 2003 (16). Permission for use obtained from Wolters Kluwer Health Inc.*

A description of the cerebrovascular anatomy would not be complete without mentioning some important aspects of the microscopic anatomy. The vessel-wall architecture of systemic arterial vessels is as follows: The innermost layer, the tunica intima, consists of a single layer of endothelial cells, surrounded by a small amount of connective tissue. The intima is separated from the tunica media through a membrane called the internal elastic membrane. The tunica media is the thickest layer, consisting of mainly smooth muscle cells, elastic fibres and connective tissue. The media is separated from the tunica adventitia through a membrane called the external elastic membrane. The outermost layer of the systemic artery is the tunica adventitia, composed of connective tissue, small vessels (vasa vasorum) supplying nutrients to the vessel wall, as well as autonomic nerves. A picture describing the structure of the systemic artery can be seen in Figure 5.

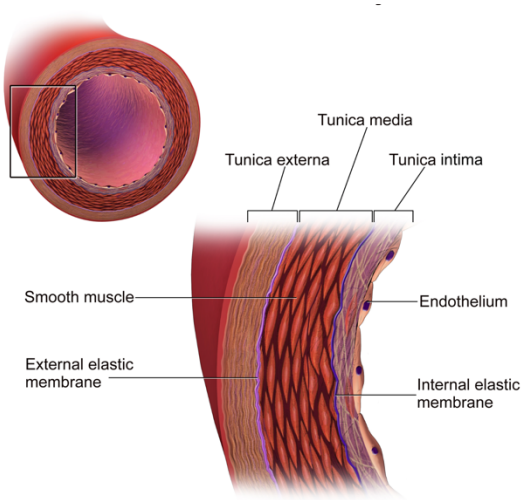

Figure 5. *Macroscopic structure of the systemic arterial vessel wall. Blausen.com staff; "Blausen gallery 2014". Wikiversity Journal of Medicine. In the public domain.*

The vessel walls of intracranial arteries however, after passing intradurally, adopt a unique structure. The walls of the larger intracranial vessels have a substantially thinner vessel wall compared to systemic arteries with the same lumen width, mainly due to a substantial reduction in thickness of the adventitia, which is reduced by approximately five times. The tunica media is about half as thick as corresponding systemic arteries with the same lumen dimensions (13). Intracranial vessels also lack the external elastic lamina, and receive nutrients through gaps in the internal elastic lamina, as the vasa vasorum are lacking. The weaker vessel wall is compensated by both the arterial localization being within the protective cranial vault as well as being encompassed by the cerebrospinal fluid space. As the internal carotid artery passes through the skull-base, the diameter of intracerebral arteries gradually decreases in diameter. As an example, the internal diameter of the proximal part of the middle cerebral artery (MCA) is approximately 2.5 mm, 75% of the calibre of the ICA (18). The intracranial arteries gradually branch to smaller arteries and form the intricate network of pial vessels enclosing the brain surface as outlined above (16).

Intracerebral arteries gradually decrease in size, partly due to fewer layers of smooth muscle cells in the tunica media. The pial arteries finally form penetrating arteries, which after entering the brain parenchyma form parenchymal arterioles. The parenchymal arterioles are nearly completely surrounded by astrocytic end-feet (19, 20), and deliver blood to the cerebral microcirculation, the neurovascular unit.

1.3 THE NEUROVASCULAR UNIT

Parenchymal arterioles finally form a dense capillary network in the brain parenchyma. This network is the main site for oxygen and nutritional exchange. Cerebral capillaries are perfused with blood at all times (21), and it has been estimated that each neuron is supplied by its own capillary (22).The final destination of cerebral blood flow is the so-called neurovascular unit, see Figure 6 (23). The neurovascular unit is a conceptualized cooperation between several cell-types, including endothelial cells of capillaries, basal lamina continuous with astrocytic end-feet, astrocytes, pericytes, neurons and other supporting cells.

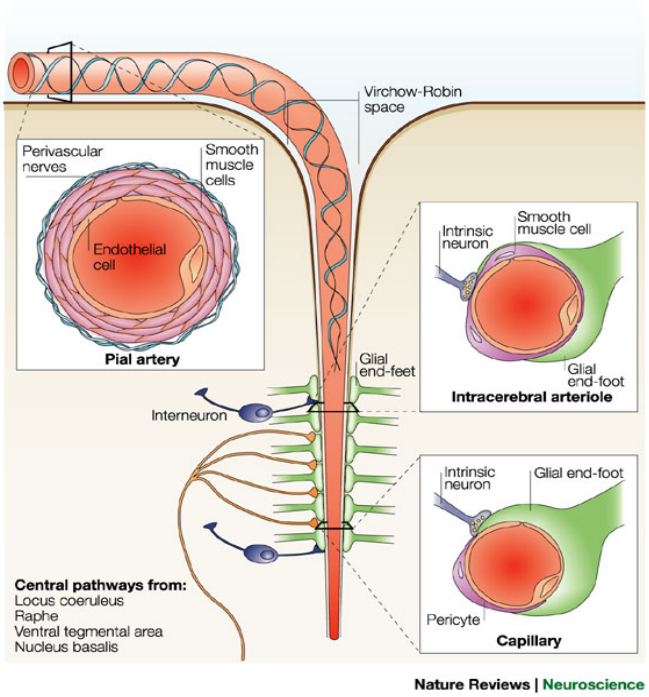

***Figure 6**. The neurovascular unit. From Cipollo et al, 2009 (23). Permission for use obtained from Nature Publishing Group.*

A complex and intricate dialogue takes place between the included structures, each cell type or structure having its specific roles, and we will here briefly discuss some of these unique functions. The vascular part of the unit consists of cerebral capillaries, the vascular wall containing a single layer of endothelial cells. Unlike systemic capillaries, adjacent endothelial cells are fused together through so called tight junctions, forming the blood-brain-barrier (BBB) and limiting molecular traffic to a transcellular route through the endothelial cells, hindering paracellular transport between the adjacent endothelial cells as is the case in systemic capillaries (24). The BBB facilitates the entry of selected and desired molecules, such as amino-acids and glucose, while excluding potentially harmful molecules as well as other cellular components of the blood-plasma such as erythrocytes and leukocytes.

The separating function of the BBB can be disrupted in cases of ischaemia, haemorrhage, inflammation, trauma and neoplasm, leading to the emancipation of neurotoxic products disturbing the function of the neurovascular unit (24).
As seen in Figure 6, both pericytes and astrocytes serve important roles in the neurovascular unit. Pericytes share a common basement membrane with the endothelium, and serve a role in stabilizing the vessel, as well as releasing growth factors/matrix important for angiogenesis and vessel wall permeability (25).
The role of astrocytes in the neurovascular unit include regulation of regional cerebral blood-flow (CBF), an involvement in ion and water homeostasis through the expression of water channel aquaporin 4 in astrocytic end-feet, and upregulation of tight-junction proteins (26).
Finally, there is an important interplay between neurons and cerebral capillaries, neurons modulating CBF through neurovascular coupling, a bi-directional communication between neurons and the microvasculature (27).

1.4 ISCHAEMIC STROKE - PATHOPHYSIOLOGY

In this section, the basics of normal cerebral neuronal physiology will be outlined, followed by a description of the pathophysiology of acute ischaemic stroke.

The adult human brain constitutes approximately 2% of the complete body weight (28, 29), however its high metabolic demands are clear when considering that it demands approximately 20% of the cardiac output in a resting state (30). In contrast to other organs, the brain uses glucose as its sole energy substrate, the glucose metabolism generating adenosine triphosphate (ATP). Among other uses, ATP is used for maintaining ion homeostasis across the cell-membranes as well as for cellular maintenance. The main role of ion homeostasis involves keeping Na^+ and Ca^{2+} outside the cells and K^+ inside. Average glucose consumption is estimated at 5.6 mg/100g/min, and average oxygen consumption is estimated at 3.5 ml/100g/min (31, 32).Despite alterations in systemic blood pressure, the cerebral blood flow needed to provide a constant flow of glucose and oxygen is kept relatively stable, remaining constant between mean arterial blood pressures of 50-150 mmHg (30). This ability is termed cerebral autoregulation. The cerebral blood flow is on average at a level of 50 ml/100g/min, higher in grey matter (80 ml/100g/min) and lower in white matter (20 ml/100g/min) areas of the brain (33).

Ischaemic stroke affects the delicate physiologic balance outlined above, and through a plethora of different mechanisms leads to infarcted and thereby irreversibly damaged brain tissue. The common denominator in all cases of acute ischaemic stroke is a vascular lesion causing a seized or diminished blood flow to downstream tissue. The mechanism of this obstruction is commonly divided into stroke caused by thrombosis, embolism and hypoperfusion. In this thesis, and especially in the third paper, we will focus on large arterial occlusion (LAO) which both can have thrombotic, and embolic aetiologies (and other more unusual aetiologies such as dissection or external compression).

As outlined above, normal CBF is approximately 50 ml/100g/min. Through increased O_2 uptake, oxygen consumption can be maintained at a level of 3.5ml/100g/min until cerebral blood flow reaches a level of 20-25 ml/100g/min. Animal models have shown an association between reduction of CBF below these levels and reduced electroencephalographic (EEG) activity (30). In monkey models, the emergence of neurologic dysfunction has been seen at levels <20 ml/100g/min (34, 35).

At levels below 10 ml/100g/min, cell membrane functions are affected severely and the time window for neuronal viability is extremely limited (36). Even though neurological impairment ensues directly as blood flow falls beyond approximately 20 ml/100g/min, irreversible tissue damage at CBF levels between 10 and 20 ml/100g/min takes time to occur, illustrating the importance that duration of ischaemia has on the final fate of the brain tissue (37, 34).
The effects of ischaemia on neurons and microvasculature will now be discussed separately.

Already 2 minutes after seized CBF, the intracellular reserves of ATP are depleted. ATP drives the Na^+/K^+-ATPase necessary for upholding a high intracellular K^+ concentration and a low Na^+ concentration. Failure to uphold the membrane potential leads to depolarization, release of the excitatory neurotransmitter glutamate, and further depolarization (38). In the ischaemic, hypoxic and hypoglycemic environment, increased availability of glutamate has toxic effects on neurons, as well as causing cytotoxic oedema through the opening of cell membranes and influx of Na^+ and Ca^{2+} together with water. Increased intracellular Ca^{2+} causes mitochondrial dysfunction (31), and through activation of proteolytic enzymes leads to degradation of the cytoskeleton, among other detrimental effects. The hypoxic environment leads to both a low-pH environment through anaerobic metabolism and lactic acid production, as well as production of free oxygen-radicals which cause organelle and membrane lipid peroxidation (39). All these mentioned changes lead to neuronal dysfunction and ultimately neuronal cell death.

Not only neurons are affected by ischaemia, but so too the microvasculature. Changes are seen here shortly after the onset of ischaemia, depending on the degree of cerebral blood flow reduction (40). Among the first processes that start involve loss of the endothelial barrier due to disruption of tight junctions. This leads to the exposure of tissue factor to plasma coagulation factors, leading to the deposition of fibrin in the vascular lumen, entangling leukocytes and platelets and causing a vascular obstruction. Concomitantly, leukocyte adhesion molecules are expressed on the endothelial surface, leading to the interaction of white blood cells with the endothelium, further increasing the permeability and disruption of the BBB (41). This early disruption of the BBB enables interactions between cell-types such as astrocytes and microglia with various factors in the plasma, leading to the release of enzymes which degrade the microvascular basal lamina (42). This process is seen within 1-2h of onset of ischaemia.
All of these processes lead to an inflow of inflammatory cells into brain tissue, which further injures the ischaemic brain tissue (43). In addition to the cell necrosis caused by these processes, programmed cell death, apoptosis, is seen in

cells surrounding the necrotic cells. This process of apoptosis occurs even though the severity of reduced CBF in these areas is not sufficient to cause irreversible cell necrosis.

In vascular occlusion and reduced downstream perfusion, CBF rates are not homogenous. The central parts of the vascular supply suffer the lowest blood flow and the worst ischaemic damage, while more peripheral parts usually have a better perfusion. The central areas, with blood flows 0-10 ml/100g/min sufficient to cause necrosis, are surrounded by areas with reduced perfusion between 10-20 ml/100g/min, which causes disruption of neuronal electrical activity, however not permanent damage to the cells. This area of still viable but electrically silent tissue is termed penumbra, salvageable areas of ischaemia, and is the target of all reperfusion treatments in acute ischaemic stroke. Figure 7 illustrates the time-dependence of the final fate of brain tissue during a reduction in cerebral blood flow.

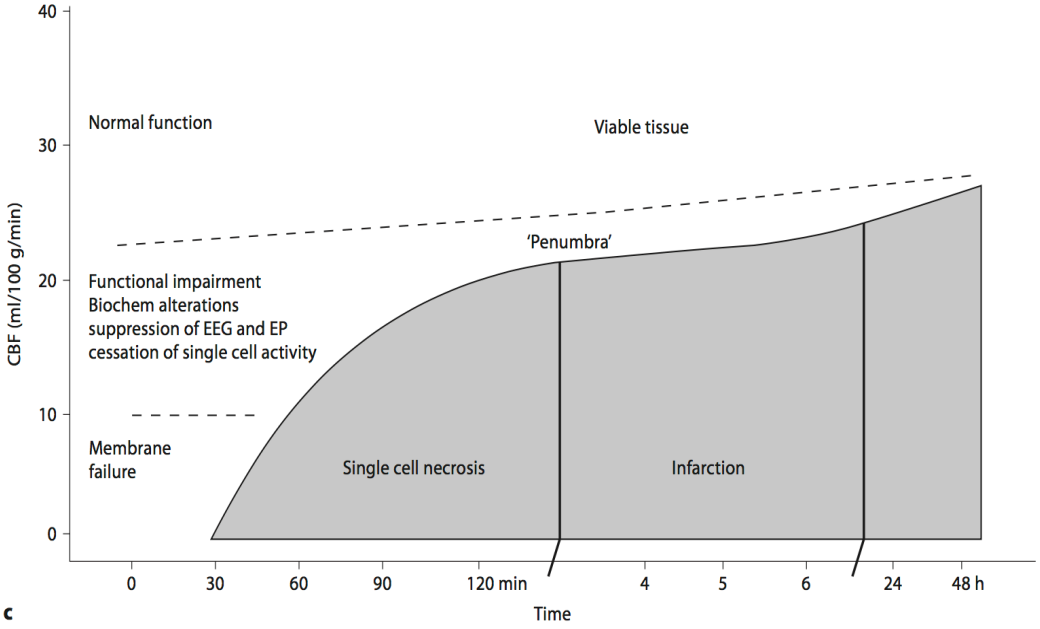

***Figure 7**. Time dependence of the final fate of under-perfused cerebral tissue. Modified from Heiss, 2011(37). Permission for use obtained from Karger Publishers.*

The factors which determine the life span of the penumbra before its transformation into irreversibly infarcted and necrotic tissue depend on several factors (36):

1) Collateral circulation, including both extracranial collateral circulation, intracranial primary and secondary collateral circulation
2) The systemic circulation
3) Various systemic metabolic factors
4) Resistance of the microvasculature
5) Dynamic changes in the vascular obstruction lesion

1.5 LARGE ARTERY OCCLUSION

Obstruction of cerebral arteries (or tributary extracranial arteries) causing stroke can occur at any level, affecting both larger vessels such as the ICA as well as small penetrating arteries/arterioles such as the lenticulostriatal penetrating branches of the MCA. The most widely used classification of ischaemic stroke, the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification (44), separates between the main etiological subtypes of large-artery atherosclerosis, cardio-embolism and small-artery occlusion. In the first subtype, large-artery atherosclerosis, the definition of a large artery is not clearly specified, defined as *"…stenosis or occlusion of a major brain artery or branch cortical artery, presumably due to atherosclerosis"*. The specific arteries that are included, or not included, in this definition are unclear, the main point being the presumable atherosclerotic origin. Cardioembolism, through embolization to these major brain arteries or their branches, can also cause large artery occlusion. The two major and potential contributors of LAO are thus, using the TOAST classification; large-artery atherosclerosis and cardioembolism, together accounting for roughly 50% of all ischaemic strokes (45). Important to note though, the proportion of LAO forms a subset of this group. Figure 8 illustrates an LAO removed at necroscopy.

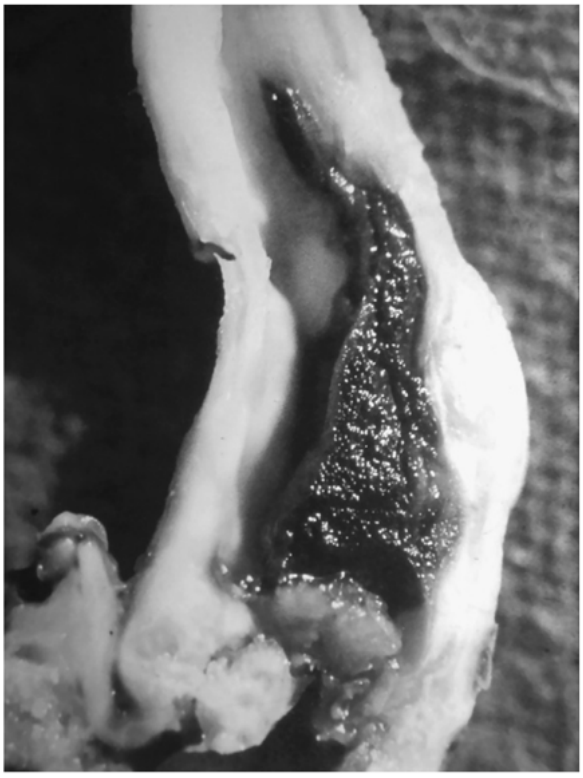

***Figure 8**. Internal carotid artery with atherosclerotic plaque causing almost complete occlusion. Removed at necropsy. From Caplans Stroke: A clinical approach, 2009 (36). Permission for use obtained from Elsevier.*

The last three years, results from several randomised controlled trials have been published, showing the benefit of endovascular thrombectomy of LAO in acute

anterior ischaemic stroke (46-50). In all of these trials, the benefit of acute endovascular treatment was shown for intracranial occlusions of the ICA (including T- and L-occlusions) as well as the first segment of the MCA, M1. In two of these studies, endovascular intervention was permitted in M2 occlusions as well (49, 50). Posterior circulation LAOs were not included.
The definition of an LAO varies between studies. The classification does not merely serve a role for academic categorization but also bears with it implications on the arsenal of therapeutic possibilities. These variations in the definition of an LAO as well as a marked heterogeneity of study populations are witnessed in the large variation in the prevalence of LAO documented in the literature. Across studies, prevalence ranges from 22·5–88·5% (51-58). In a large prospective single-centre Danish study on an unselected ischaemic stroke cohort admitted within 4.5h (N=637 patients), the prevalence of LAO was reported at 28.7% (59). In this study, 74% of single occlusions were located in the anterior circulation, the majority of which were situated in the middle cerebral artery (85%). One large US study on an unselected ischaemic stroke cohort (N= 578 patients) assessed within 24h found a 46% prevalence of LAO (53). Another study found a 54% prevalence of proximal occlusions in an unselected cohort of 699 acute ischaemic stroke patients (54).In the third article of this thesis, based on patients undergoing thrombolysis and/or thrombectomy, a 49% proportion of LAO was seen.

In the following section, we will discuss the common arterial localisations and clinical presentation of large arterial occlusions in the anterior circulation, separately discussing occlusions/stenosis of the ICA, MCA and ACA.

1.5.1 Internal carotid artery

Intrinsic lesions of the ICA can affect the entire course of the artery, the origin of the artery at the bifurcation of the common carotid artery is however most commonly affected (especially in Caucasian populations). Less commonly, the carotid siphon is affected, with an increased prevalence in certain ethnic groups, such as African-Americans (36). In disease at the bifurcation of the common carotid artery, the most common aetiology is atherosclerotic narrowing. Progressively decreasing luminal width as plaques gradually increase in volume increase the risk of clot formation in crevices of the plaques as well as increased acute thrombus formation due to plaque rupture. Therefore, lesions of this area can lead to symptoms of brain ischaemia either due distal embolization of thrombi from the vascular lesion, or due to hypo-perfusion caused by impeded

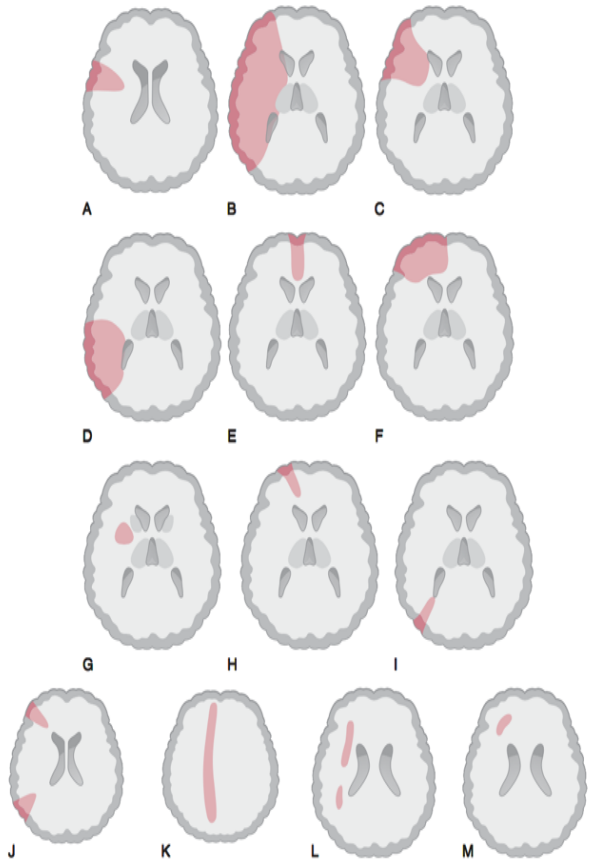

***Figure 9**. Common CT-locations of anterior circulation infarcts. (**A**) wedge-shaped MCA infarct, (**B**) entire MCA territory, (**C**) superior-division MCA, (**D**) inferior division MCA, (**E**) ACA, (**F**) ACA and MCA, (**G**) striatocapsular infarct, (**H**) wedge-shaped anterior watershed infarct, (**I**) wedge- shaped posterior watershed infarct, (**J**) anterior and posterior watershed infarcts, (**K**) linear watershed infarct, (**L**) ovular deep watershed infarct, and (**M**) small white-matter watershed infarct. Reproduced from Caplans´ Stroke: A Clinical Approach, 2009 (36). Permission for use obtained from Elsevier.*

blood flow through the stenosis, or in some cases due to both. Figure 9 shows common cerebral ischaemic patterns of patients with anterior circulation strokes. Ischaemic lesions following disease of the origin of the ICA usually affect the MCA territory, and are clinically difficult to differ from intrinsic pathology of the MCA (60). Motor and sensory (most often cortical sensation) deficits usually affect the contralateral face and arm (more than the leg), other cortical symptoms such as aphasia, neglect and anosognosia varying according to the side of the affected hemisphere. Transient Ischaemic Attacks (TIA) such as

amaurosis fugax and transient limb paresis can precede the ischaemic stroke caused by ICA origin disease, by weeks or months, and are an important warning sign of impeding stroke. Recent data show that the 1-year risk of stroke after a TIA or minor stroke is approximately 5 %, lower than previously reported (61).
Carotid siphon disease has been shown to be associated with a worse prognosis than origin disease, as well as with an association with coronary artery disease (62, 63). It commonly occurs concomitantly with extracranial ICA disease, one series showing tandem extracranial ICA and intracranial siphon stenosis in 62% of patients (62). TIAs are thought to be less common in siphon disease compared to extracranial ICA disease (36).

1.5.2 Middle cerebral artery

The main cause of occlusion in this arterial segment is considered to be distal embolism from more proximal sources: heart, aorta and extracranial carotid artery. However, although considered rare, intrinsic disease of the MCA may be

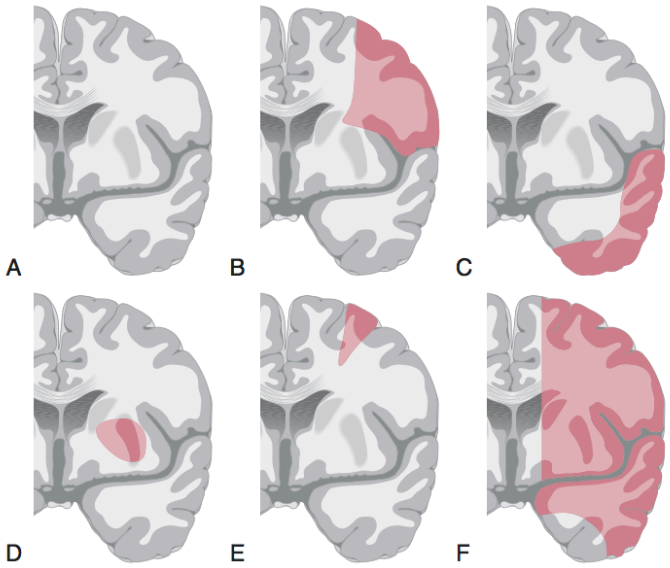

Figure 10.
*Common distributions of ischaemia following MCA occlusion. (**A**) normal cerebral hemisphere in coronal section, (**B**) occlusion of the upper trunk of the MCA, (**C**) occlusion of the lower trunk of the MCA, (**D**) infarct of the deep basal ganglia, (**E**) wedge infarct in the pial territory, and (**F**) whole MCA occlusion. Reproduced from Caplans Stroke: A Clinical Approach, 2009 (36). Permission for use obtained from Elsevier.*

more common than we thought. The first reports on prevalence were generated from mainly Caucasian populations, studies of Asian and African-American patients have showed a higher prevalence of intrinsic disease of the MCA (64, 65). Common distributions of cerebral ischaemia in the MCA territory are shown in Figure 10.
The symptoms of cerebral ischaemia in MCA disease can vary widely depending on which segments of the artery that are affected. The three main divisions of the MCA consist of the lenticulostriatal perforators and the superior and inferior divisions. An occlusion of the entire distribution of the MCA may give a total anterior circulation syndrome (TACI) consisting of contralateral severe hemiparesis, hemisensory loss, conjugate eye deviation, hemianopia and depending on the side of the lesion global aphasia (left hemisphere) or severe

neglect (right hemisphere). Affliction of only certain segments, either lenticulostriatal, upper or lower divisions, usually give a more restricted spectrum of symptoms.

1.5.3 Anterior cerebral artery

Pure anterior cerebral artery (ACA) infarcts are uncommon, and intrinsic pathology of the ACA is even rarer. The majority of ACA disease is embolic, originating from more proximal lesions. Different studies and registries report different percentages of ACA infarcts, varying from 0.5-3% (66).
Presence of intrinsic pathology of the ACA is often associated with concomitant pathology of the MCA/ICA. In a report from the Lausanne Stroke Registry, only 27 out of 1470 (1.8%) patients had isolated ACA infarcts, 17 patients with more proximal sources (ICA or cardiac emboli), and in only one patient was intrinsic ACA pathology considered the cause of infarction. The remaining ACA infarcts had an unknown source of emboli (67). Even though unusual, interventional treatment of the ACA is sometimes performed. In the MR CLEAN trial, the first randomised controlled trial showing a benefit of endovascular therapy in acute ischaemic anterior circulation stroke, A1 and A2 occlusions were included per-protocol, and one thrombectomy was performed on an ACA occlusion (50). Figure 11 shows common distributions of cerebral ischaemia following ACA occlusion.

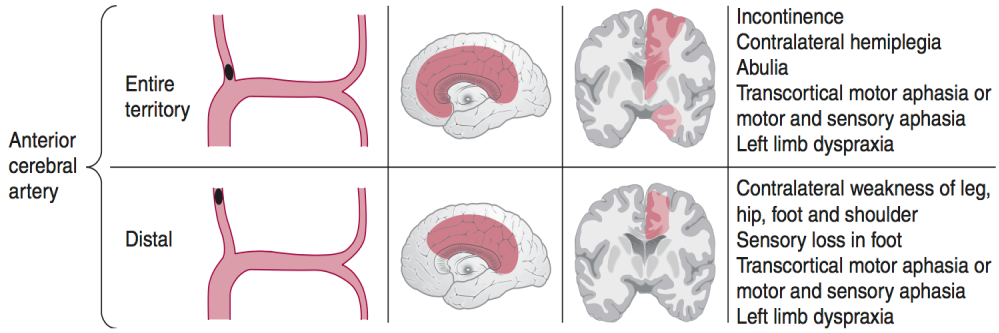

Figure 11. *ACA occlusion and affected cerebral territories. Reproduced from Caplans´ Stroke: A Clinical Approach, 2009 (36). Permission for use obtained from Elsevier.*

The most clinically striking symptoms are usually a paralysis greatest in the lower extremity, especially the foot and proximal thigh, the face and hand are usually spared. Sometimes, in cases of extensive and large infarcts, complete hemiplegia is seen, the upper limb dysfunction however being secondary to infarction of the premotor cortex rather than the motor cortex itself. Another common tell-tale sign is the presence of left arm apraxia, caused by infarction of the corpus callosum and adjacent white matter tracts, referred to as an anterior disconnection syndrome. Apathy and aboulia are often seen, as well as incontinence.

1.6 TREATMENT

1.6.1 Intravenous thrombolysis

Thrombolytic drugs have been explored for a number of different thromboembolic conditions since the 1950´s, using both streptokinase and different human and bovine thrombolysins. Small randomised trials in the 1960´s, treating worsening ischaemic stroke patients with streptokinase within 3 days of ictus, showed some positive effects on lysis of occlusions (68, 69). However, a high mortality rate and cases of intracerebral haemorrhage lead to serious questioning of the safety of the drug, and finally to contraindication of the drug also for other indications if past or present intracerebral lesions were present. In the 1980s studies on thrombolytic therapy in acute ischaemic stroke saw yet another revival, the main agents tested in these mainly observational studies being streptokinase, urokinase and recombinant tissue plasminogen activator (rtPA) (36, 70-72). In some of these studies, intra-arterial therapy was used, in others intravenous therapy. A common denominator in all of these studies was the use of angiography for identifying arterial occlusions prior to therapy. The intra-arterial studies combined showed a 64% recanalization, 18.5% haemorrhagic complication rate and 42% good outcome, whilst the intravenous studies showed a lower recanalization (approximately 1/3 of patients) and an overall higher frequency of both haemorrhagic infarct transformation and haematomas (70-72, 36). Three RCTs in the 1990s, testing intravenous streptokinase in the setting of acute ischaemic stroke, were halted due to a high rate of intracerebral haemorrhages in treated patients (73-75).

Sparked by beneficial effects in the treatment of acute myocardial infarction with intravenous tissue plasminogen activator (iv-tPA), the NINDS trial investigators performed dose-finding studies in the early 1990s aiming at finding suitable dose-regimens of iv-tPA for acute ischaemic stroke (76, 77). These studies together with evidence from other studies on iv-tPA, both observational and small RCTs (78, 79), strongly suggested the need for larger RCTs evaluating the efficacy of iv-tPA in acute ischaemic stroke.

1.6.1.1 Rationale

Endogenous plasminogen activator is a fibrin specific serine protease produced by the vascular endothelium. It is part of the endogenous fibrinolytic system in conjunction with plasminogen, the main physiological role being limitation of thrombus formation and growth, as well as the maintenance of an intact vasculature in the setting of thrombus formation. The mode of action is the

cleavage of inactive precursor plasminogen to active plasmin, which in turn effectuates local fibrinolysis through the degradation of fibrin.

Recombinant tissue plasminogen activator, rtPA (alteplase), is almost identical to endogenous plasminogen activator. It has a high fibrin specificity, higher than that of streptokinase and urokinase, which results in a lower depletion of circulating coagulation factors (80). The half-life of unbound alteplase is 4-6 minutes (81), however, fibrin-bound alteplase is more resilient to degradation by plasminogen activator inhibitor type 1, the thrombolytic effects at thrombus loci persisting several hours after administration (82).
The mode of action is on the surface of the thrombus, where alteplase binds to fibrin strands, while other cell-receptors anchor plasminogen and plasminogen activator. The rate of fibrinolysis naturally also depends on the local blood flow and clot burden. Increasing fibrinolysis leads to gradually improved perfusion, and the increasingly higher throughput of alteplase by microstreaming through the thrombus as fibrinolysis proceeds finally leads to complete breakdown of the clot owing to arterial blood pulsations.

Apart from pure fibrinolysis, rtPA has other effects, some physiologically beneficial, others potentially harmful. One of the potentially deleterious effects involves the activation of matrix metalloproteinases (MMPs), and more specifically MMP 2 and 9. In a setting where rtPA does not lead to the intended disruption of the clot, the simultaneous activation of these proteolytic enzymes can cause further ischaemic tissue damage, damaging both the neurovascular unit and the brain in large (83). MMPs confer these effects by degrading the basilar lamina surrounding the vascular endothelium (84). This leads to a disruption of the BBB and increases the risk of haemorrhagic transformation of already infarcted brain tissue, as well as brain oedema (85). Another specific deleterious effect accountable to tPA is its activation of platelet derived growth factor CC (PDGF-CC). Activated PDGF-CC stimulates PDGF receptors situated on astrocytic end-feet. The activation of these receptors leads to further opening of the BBB, increasing further neuronal and tissue damage. A randomised controlled pilot study at Karolinska University Hospital, studying the effects of a specific tyrosine kinase inhibitor, Imatinib, selectively targeting and blocking the PDGF-receptor in the setting of iv-tPA treated acute ischaemic stroke has recently been completed and showed promising results (86). This safety- and feasibility study confirmed the safety of this novel drug treatment in acute ischaemic stroke, and suggested a benefit regarding neurological outcome for patients treated with Imatinib. A larger confirmatory efficacy trial is in preparation, expected to recruit its first patient in late autumn 2017.

1.6.1.2 Clinical evidence

The first large RCT was the European Cooperative Acute Stroke Study (ECASS), which enrolled 620 patients with acute ischaemic stroke between 1992 and 1994 and was published in October 1995. Three hundred and thirty-three patients were randomised to iv-tPA administered at a dose of 1.1 mg/kg. The primary endpoint was the modified Rankin Scale (mRS) and Barthel index (BI) at 90 days, and there was no difference between the two arms in the intention to treat (ITT) analysis. However, the per protocol analysis (PP) showed a statistically significant difference in median mRS at 90 days favouring iv-tPA (87).
Shortly thereafter, in December 1995, results from the pivotal NINDS (The National Institute of Neurological Disorders and Stroke) study were published (87). This trial consisted of two parts. The second part assessed functional outcome at 3 months, randomising 333 patients to either placebo or 0.9 mg/kg iv-tPA, a lower dose than in ECASS. Outcome at 3 months was assessed with a global statistic, combining 3 months BI, mRS, Glasgow outcome scale and NIHSS. Results were in favour of the iv-tPA group, the odds of a favourable outcome amounting to 1.7 (95% CI 1.2-2.6). In 1996, the US FDA approved the use of intravenous thrombolysis for treatment of acute ischaemic stroke within 3h from symptom onset, followed by the publication of guidelines recommending the treatment (88, 89).

Nearly 3 years later results from the ECASS-II, enrolling 800 patients, were published. The treatment arm received rtPA at the same dose as is in NINDS. The study, although negative, showed a trend toward better outcome for the rtPA treated arm (90). 1 year later, results from the Alteplase Thrombolysis for Acute Non-Interventional Therapy in Ischaemic Stroke trials (ATLANTIS A and B) (91, 92) were published, mainly enrolling patients after the 3h time point. These two studies failed to show benefit of iv-tPA after the 3h time-point.

Although several of these large RCTs were negative on the primary endpoint, an individual patient-data meta-analysis (IPD), pooling the data from the 6 mentioned trials, showed a clear benefit of iv-tPA on favourable 3 months outcome (mRS<2, Barthel >94, NIHSS<2) in the 3h time-window (93). Odds for a favourable outcome stratified by onset to treatment time was in favour of iv-tPA treatment: 2·8 (95%CI 1·8–4·5) for 0–90 min, 1·6 (1·1–2·2) for 91–180 min, 1·4 (1·1–1·9) for 181–270 min, and 1·2 (0·9–1·5) for271–360 min. Figure 12 shows the adjusted odds ratio for a favourable outcome after iv-tPA as a function of time.

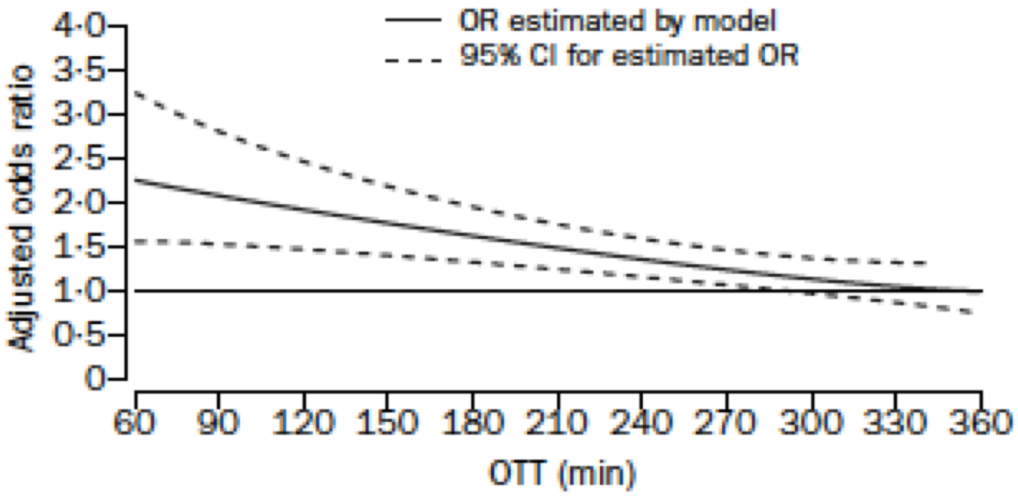

Figure 12. *Adjusted odds ratio for a favourable 3-months favourable outcome by onset-to-treatment time (OTT). Reproduced from Hacke et al, Lancet 2004 (93). Permission for use obtained from Elsevier.*

Symptomatic intracerebral haemorrhage (SICH) was seen in approximately 6% of patients, as compared to approximately 1 % in the placebo groups. In the 4.5h time-window, the hazard-ratio for death was not significantly different between the two arms.

In September 2002, The European Medicines Evaluation Agency (EMEA) conditionally approved the use of iv-tPA in Europe for treatment of acute ischaemic stroke within 3h of symptom onset. The conditions were:

1) Entering of all iv-tPA treated patients in an observational study for 3 years, aiming at monitoring treatment safety. Physicians treating patients with iv-tPA were urged to enter patients into the observational Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) (94).
2) Initiation of a new RCT, ECASS-III (95), studying the effects of iv-tPA at 3- 4.5h after symptom onset.

The SITS-MOST enrolled a total of 6483 patients from 285 centres in 14 countries. Results from this study were compared with the pooled results from the previous RCTs. A comparison of SITS-MOST and RCT data, comparing mortality, the proportion of patients with SICH and functional outcome at 3 months is seen in Figure 13.

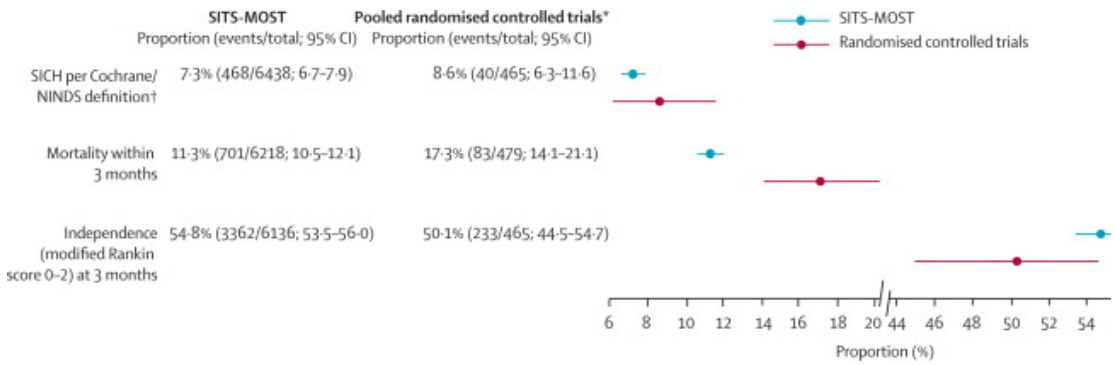

Figure 13. *Results from the SITS-MOST study. Reproduced from Wahlgren et al, Lancet 2007 (94). Permission for use obtained from Elsevier.*

The SITS-MOST study clearly showed the safety and benefit of iv-tPA administered within 3 h from symptom onset in routine clinical practice, as well as illustrating the benefit of therapy even in non-experienced centres, a concern which had not been addressed previously. In summary, gathering the evidence from pooled randomised data and a large prospective observational registry, the beneficial effects of intravenous thrombolysis within 3h of symptom onset were very clear.

In September 2008, the results of the ECASS-III trial and the SITS observational study in ischaemic stroke patients treated with IV thrombolysis in the 3-4.5h were published (95). The ECASS-III study enrolled patients with acute ischaemic stroke between 2003 and 2007 and 418 patients were randomised to the treatment arm. The study was positive, showing an odds ratio of 1.34 (95% CI 1.02-1.76) in favour of the treatment group. No significant differences in mortality were seen between treatment and placebo arms, however in line with previous results, rates of SICH per ECASS-III definition differed between the groups, 2.4% in the treatment arm vs. 0.2% in the placebo group; P = 0.008.

Similar results were seen in a SITS publication from the same year, comparing the 0-3h treatment window with the 3-4.5h window. No significant differences in mortality, SICH or functional outcome were seen between the two treatment time windows.

The results of ECASS-III and the SITS publication led to a widening of the European and US guidelines, now including the 3-4.5 h time-window as a possible treatment frame (96, 97). These guidelines were further strengthened by a pooled meta-analysis published in 2010, including ECASS-III, and confirming the beneficial effects of iv tPA up-to 270 minutes (98).

Based on this study, Table 1 shows the Number Needed to Treat (NNT) by increasing onset-to-treatment time.

Treatment delay	Number needed to treat (NNT)
0-90 min	4.5
91-180 min	9
181-270 min	14.1

Table 1. *The Number Needed to Treat (NNT) with iv-tPA for gaining one additional patient with an excellent functional outcome (mRS 0-1) (98).*

Despite changes in guidelines regarding the extended time-window for iv-tPA treatment, questions still remained to be answered. Doubts had been lingering for a long time regarding the efficacy and safety of treatment in elderly patients, as well as in patients suffering from both very mild as well as very severe strokes. Observational data from SITS published in 2010 had already indicated the safety and beneficial effects of iv-tPA irrespective of age, however no RCT had yet proven the efficacy and safety of iv-tPA in the elderly (99, 100).
The 3rd International Stroke Trial (IST-3) sought to shed light on these and other issues (101). The results of this study were published in June 2012. The trial enrolled a total of 3035 patients from 12 different countries, 1515 patients randomised to iv-tPA (dose 0.9mg/kg) and the rest to placebo. 53% of patients were older than 80. The trial was negative at the primary endpoint of functional status (measured as a dichotomy on the Oxford Handicap Score). On a pre-specified secondary analysis examining a shift on the same scale however, a common odds ratio of 1.27 (95% CI 1.10-1.47) in favour of treatment was seen. In another pre-defined subset analysis, a trend toward better efficacy was seen in elderly patients, and trends were also seen toward increased benefit in more severe strokes.

Following IST-3, two large meta-analyses, one pooled data and one Individual Patient Data (IPD) meta-analysis, have been published (102, 103).
The first pooled meta-analysis was published just one month after the publication of IST-3, and included a total of 12 trials and 7012 patients (103). A clear benefit of iv-tPA administered within 3h regarding functional independency (mRS 0-2) at final follow-up was seen (OR 1·53, 95% CI 1·26–1·86, p<0·0001). An increased mortality within 7 days was seen in the treated arm. This was however offset by a subsequent lower mortality, resulting in no significant differences at final follow-up. No statistically significant differences in functional outcome at final follow-up in the patients randomised to treatment in the 3-6h time-window were seen.

The largest IPD meta-analysis, based on data from thrombolysis RCTs, was published in 2014, including a total of 6756 patients from 9 different trials (102). It finally answered several questions previously lacking clear answers, such as the effect of thrombolysis in the elderly and in patients with very mild or severe strokes. Overall an OR of 1.75 (95% CI 1.35–2.27) favouring iv-tPA for a good 3-6 month functional outcome (mRS 0-1) in the 0-3h time-window was seen. In the 3-4.5 h time-window the odds ratio was 1.26 (95% CI 1.05–1.51) and in the time-window >4.5h the odds ratio was 1.15 (95% CI 0.95-1.40). Alteplase, as shown in all previous trials, significantly increased the risk of intracranial haemorrhage, however the relative increase in risk was similar irrespective of age, stroke severity or treatment delay. Important to note though, the absolute increase in risk in iv-tPA-treated patients was higher for patients who had more severe strokes. The results are summarized in Figure 14.

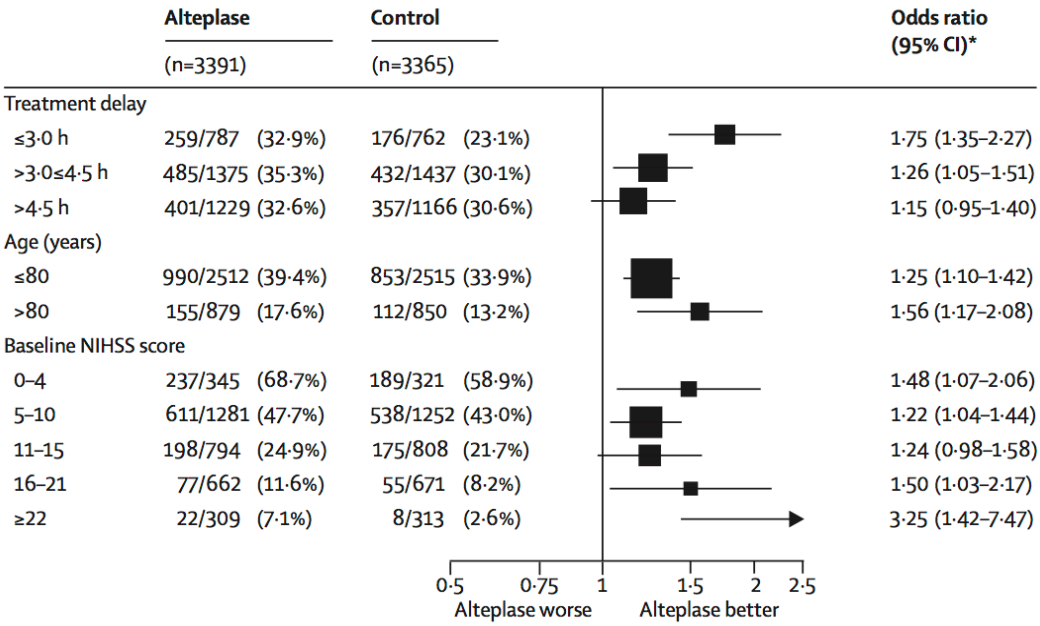

***Figure 14**. Main results from the largest IPD (Individual Patient Data) meta-analysis for iv-tPA in acute ischaemic stroke, presenting the proportion of patients with a good functional outcome (mRS 0-1). * Each subgroup after adjustment for the other two baseline characteristics. Reproduced from Emberson et al, Lancet 2014 (102). Permission for use obtained from Elsevier.*

Emberson et al´s meta-analysis is the most extensive and clarifying summary of the available evidence on intravenous thrombolysis in acute ischaemic stroke.
Finally, before concluding this section on the clinical evidence of iv-tPA in acute ischaemic stroke, one recent study needs to be mentioned. The ENCHANTED trial, published in June 2016, sought to investigate the efficacy and non-inferiority of a lower dose alteplase, 0.6 mg/kg, compared to the standard dose of 0.9 mg/kg (104). The main rationale was investigating whether a low dose was as effective at improving recovery, but possibly with a lower incidence of intracerebral haemorrhage. A total of 3310 patients were enrolled and

randomised to either low-dose or standard-dose alteplase. The study was negative and non-inferiority not proven (OR for poor functional outcome 1.09, 95% CI 0.95-1.25, P=0.51 for non-inferiority). However, in a secondary outcome analysis assessing a shift on the Rankin scale, non-inferiority was shown. Significantly less intracerebral haemorrhage was seen in the low-dose group compared to standard-dose. For the time being, standard-dose alteplase has remained the mainstay treatment. Nonetheless, future RCTs might shed light on the clinical situation in which, due to a concern over SICH, selected patients may be chosen for a low-dose approach.

1.6.2 Endovascular thrombectomy

Iv-tPA for acute ischaemic stroke has been an approved treatment for close to 15 years in Europe, and even longer so in North America. However, the efficacy of iv-tPA in patients with increasingly larger thrombotic burden varies. Previous studies have shown decreasing rates of recanalization following iv-tPA treatment the more proximal the occlusion site. One retrospective study of 335 iv-tPA treated patients monitored using bed-side transcranial Doppler showed a decreasing rate of 2h post thrombolysis recanalization the more proximal the site of occlusion (105). Recanalization was seen in: 44% of distal MCA occlusions, 30% of proximal MCA occlusions, 27% of tandem ICA/MCA occlusions and in only 6% of terminal ICA occlusions. Similar results were seen in earlier pre-NINDS iv-tPA dose-escalation studies (106). In an observational study of 138 iv-tPA- treated patients, thrombus length, measured as length of hyper-intensity on non-contrast enhanced CT scans (hyper-dense middle cerebral artery sign), was correlated with recanalization status post-thrombolysis. No patients with clot lengths 8 mm or above recanalized after iv-tPA(107). These and other findings suggested the need for other revascularization therapies in acute ischaemic stroke.

1.6.2.1 Clinical evidence

Early attempts at endovascular treatment of acute ischaemic stroke caused by identifiable vessel occlusions can be found from the early 1980s. These first studies examined recanalization rates and efficacy of intra-arterial thrombolysis. Two cases series(108, 4) and one retrospective cohort study(109) reported positive results of this approach as compared to best medical treatment at the time of the studies. This led to the first randomised attempts at investigating the efficacy of intra-arterial (ia) thrombolysis in acute ischaemic stroke with confirmed vessel occlusion: PROACT I and PROACT II (both published in the late 90s) (110, 111). Both studies showed higher recanalization in the patients treated with ia thrombolysis compared to placebo (PROACT I: 57 vs. 14 %) or

heparin alone (PROACT II: 66% vs 18%). PROACT II showed a significantly higher rate of 90-day functional independence as measured by mRS 0-2 (40% vs 25%). Despite these positive results, the therapy was not approved by the US FDA. Following PROACT I and II, in late 1999 the results from the Emergency Management of Stroke Trial (EMS) were published (112). This small pilot trial showed a better recanalization rate in patients treated with combined ia and iv thrombolysis compared to ia thrombolysis alone. EMS was followed by the larger Interventional Management of Stroke Study (IMS-I), a study comparing patients treated with a combined ia and iv thrombolysis approach with historical controls from the NINDS study (both placebo and iv-tPA treated). This study showed a non-significant lower mortality in the iv and ia thrombolysis as compared to iv-tPA alone and encouraged a future RCT comparing the two approaches. IMS-I was followed by IMS-II, an extension cohort study with a similar design, showing a significantly better functional outcome comparing combined ia and iv-tPA with both sole iv-tPA-treatment as well as placebo controls from the NINDS study (113).

During this time period, in which the ia thrombolysis approach was subject to investigation, several innovations and developments were seen in the technical field of interventional neuroradiology. New techniques and methods were being developed and tested. The first device for neurovascular thrombectomy to gain approval was the MERCI coil retriever in 2005, see Figure 15.

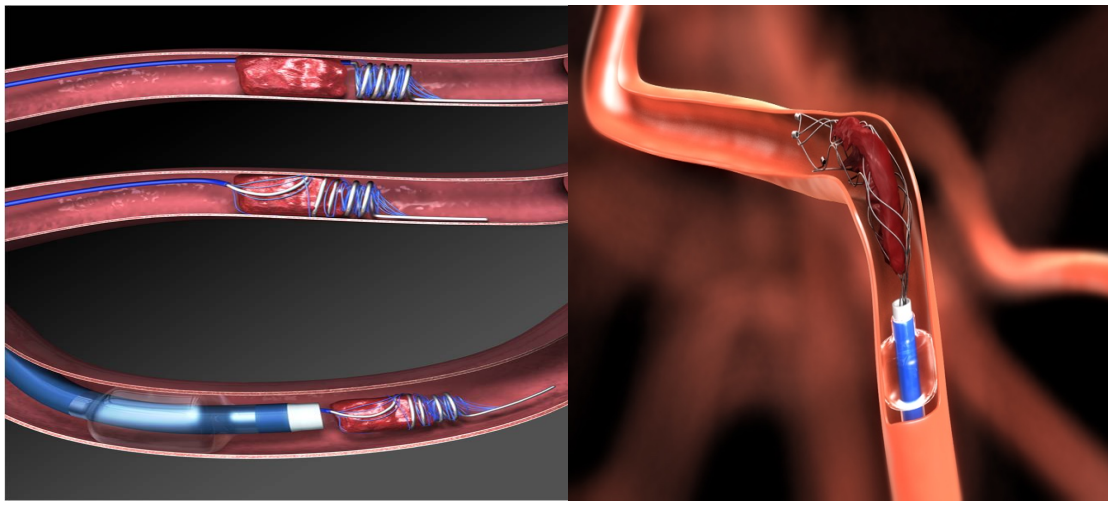

***Figure 15**. Merci retriever system to the left and stent-retriever to the right. Picture to the left from Wikipedia.org, in the public domain. Picture to the right with permission from Medtronic.*

The principle was clot retrieval through a corkscrew shaped coil for engagement and retrieval of a thrombotic occlusion. The device showed a favourable recanalization rate of 64% in patients treated with concomitant ia-tPA infusion (114).

The second device gaining approval was the Penumbra system, thrombectomy performed either through direct aspiration or by clot fragmentation followed by aspiration (115). In a prospective, multicentre single-arm study, a total of 125 patients were treated with the Penumbra system within 8h from symptom onset. 82% of patients recanalized post-treatment. The latest devices entering the market were the so-called stent retrievers, of which Solitaire and Trevo were among the first. These stent retrievers had advantages over older devices, including better engagement with the occlusion as well as immediate restoration of blood-flow even before the thrombus was removed. The superiority of both devices over the older MERCI were shown in two randomised clinical trials, Solitaire with Intention For Thrombectomy (SWIFT) and Trevo versus MERCI retrievers for thrombectomy revascularization of large-vessel occlusions in acute ischaemic stroke (TREVO-2) (116, 117). Higher rates of revascularization (89 vs. 67 % in SWIFT and 86% vs. 60% in TREVO-2) and improved functional outcome (36% vs. 29 % functional independence in SWIFT comparing Solitaire with MERCI and 40% vs. 22 % in TREVO-2 comparing TREVO with MERCI) were seen.
These results were published in 2012.

Thus, major developments were seen in the field of interventional neuroradiology in the first decade of the 21st century. However, enrolment of patients is a time-consuming process, and the first three randomised trials comparing endovascular therapy with best medical management/iv tPA were published jointly in 2013, IMS-III, SYNTHESIS and MR RESCUE (118-120). These three trials took between 5-7 years to complete. To the dismay of the stroke physician community, all three trials were negative, and did not show any benefit of endovascular therapy over standard medical treatment. Seemingly, the therapeutic options available in the acute management of stroke were back to square one. However, important and serious drawbacks in the design of these studies soon became evident. In IMS-III, approximately 20% of patients randomised to the interventional arm were subsequently not treated due to lacking a large vessel occlusion. Time from symptom onset to endovascular treatment was also long, probably reducing the experienced benefit in the endovascular arm, and finally less than 5% of the patients were treated with the newer stent-retrievers, previously shown to be clearly superior to the older devices. In SYNTHESIS, documentation of a large vessel occlusion prior to randomisation was not mandatory, and 60 % of the patients randomised to the endovascular arm were treated with IA thrombolysis, only 13% with modern stent-retrievers. In MR RESCUE, no patients were treated with modern stent retrievers. A sub-analysis of IMS-III, only including patients with documented large vessel occlusion, showed a statistically significant benefit of endovascular

treatment over standard therapy. Importantly, all these three trials proved the safety of interventional treatment, as intracerebral haemorrhages and other serious adverse events did not differ between the treatment arms. The need for new trials comparing endovascular treatment using modern stent-retrievers with standard care including iv-tPA in patients with verified arterial occlusions were much needed.

Finally, in late 2014 and early 2015, the long-awaited break-through finally came. In December 2014, results from the first RCT comparing modern stent-retrievers with standard care including intravenous thrombolysis, the Multicentre Randomized Clinical Trial of Endovascular Treatment for Acute Ischaemic Stroke in the Netherlands, MR CLEAN, were published (50). The trial enrolled a total of 500 acute ischaemic stroke patients with occlusions in the anterior circulation, 233 patients randomised to intra-arterial treatment (or both iv-tPA and intra-arterial intervention) within 6h of symptom onset, the control group receiving standard care including iv-tPA. Of the patients randomised to the endovascular arm, retrievable stents were used in 82% of patients. The trial showed a clear benefit of endovascular treatment, a common adjusted odds ratio of 1.67 (95% CI 1.21-2.30) for a favourable shift in the 90 days modified Rankin Scale, in favour of the endovascular arm. No significant differences in mortality or SICH were seen.

This breakthrough was followed by four other randomised clinical trials, all published in The New England Journal of Medicine early 2015. These were: The Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) (48), Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND-IA) (49), Randomized Trial of Revascularization with Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke due to Anterior Circulation Large Vessel Occlusion Presenting Within 8 h of Symptom Onset (REVASCAT) (47) and Solitaire With The Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME) (46). These 4 subsequent trials were stopped after interim analysis crossed pre-specified boundaries of efficacy. In 2016, final results from two additional trials, Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial (121) and the Randomized Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke, THERAPY (122), were published.

In summary, all of these studies but one, THERAPY, showed clear statistically significant beneficial effects on long-term functional outcome in patients with documented large vessel occlusion treated with mechanical thrombectomy. THERAPY was halted prematurely after the publication of the previous positive studies and was thus underpowered to show the intended treatment effect, although the direction of effect was similar as in the other trials. In addition, THERAPY was the only trial using the Penumbra system instead of modern stent-retrievers.

Safety regarding mortality and intracerebral haemorrhage was consistent. The effect size, measured by the number needed to treat (NNT) varied in an impressive range of 3.2-7.1 (123). The trials did vary in inclusion criteria, in the intervention used as well as in the therapeutic time window, a summary of the main study details and results can be seen in Figure 16 (123). All trials except THERAPY used mainly modern stent retrievers. Age-limitations were applied in REVASCAT, THERAPY, SWIFT-PRIME and THRACE, whereas EXTEND-IA, MR CLEAN and ESCAPE had no age-limits. In all trials, CT/MR angiography was performed pre-randomisation to determine the mandatory presence of a large vessel occlusion for trial enrolment. Only patients with occlusions in the anterior circulation were included, and in most studies the site of vessel occlusion was limited to the terminal internal carotid and M1 segment of the middle cerebral artery. MR CLEAN (50) and EXTEND-IA (49) were the only studies also including more distal M2 occlusions.

	Number	Onset-to-groin puncture time window	Age limits (years)	Mean age (years)	NIHSS score limits	Median NIHSS score	Proportion treated with alteplase	Device	Vessel occlusion	Imaging selection	Proportion given general anaesthesia	Median onset-to-groin puncture time (min)	Proportion with successful revascularisation (mTICI 2b or 3)	Independent functional outcome at 90 days (mRS 0–2; endovascular vs control)	Mortality at 90 days (endovascular vs control)
IMS III[7]	656	6 h	18–82	69*	≥10 (or 8–9 if occlusion)	17	100% (656)	Any approved	Not assessed	Non-contrast CT	35% (98 of 284)	208†	41% (116 of 283)	41% *vs* 39% (RR 1·0, 0·8–1·2)	19% *vs* 22% (RR 0·9, 0·6–1·2)
MR CLEAN[1]	500	6 h	≥18	65·8*	≥2	18	89% (445 of 500)	Any approved (82% stent retriever)	ICA, M1, M2, A1, A2	CT, CTA	38% (88 of 233)	260	59% (115 of 196)	33% *vs* 19% (RR 1·7, 1·2–2·3)	21% *vs* 22% (RR 1·0, 0·7–1·3)
EXTEND-IA[2]	70	6 h	≥18	69·4	No limits	15	100% (70)	Solitaire	ICA, M1, M2	CT, CTA, CTP	36% (12 of 33)	210	86% (25 of 29)	71% *vs* 40% (RR 1·8, 1·1–2·8)	9% *vs* 20% (RR 0·4, 0·1–1·5)
ESCAPE[3]	316	12 h (84% in <6 h)	≥18	69·5	≥6	17	76% (238 of 315)	Any approved (79% stent retriever, 61% Solitaire)	ICA, M1, M1 equivalent (all M2s)	CT, CTA, mCTA collateral scoring, +/- CTP	9% (15 of 165)	200‡	72%§ (113 of 156)	53% *vs* 29% (RR 1·8, 1·4–2·4)	10% *vs* 19% (RR 0·5, 0·3–0·8)
SWIFT PRIME[4]	196	6 h	18–80 (initially 18–85)	65·7	≥8	17	100% (196)	Solitaire	ICA and M1	CT, CTA, +/- CTP or MRI	37% (36 of 98)	224	88% (73 of 83)	60% *vs* 35% (RR 1·7, 1·2–2·3)	9% *vs* 12% (RR 0·7, 0·3–1·7)
REVASCAT[5]	206	8 h (90% in <6 h)	18–80¶	66·5	≥6	17	73% (150 of 206)	Solitaire	ICA and M1	CT, CTA, +/- CTP	7% (7 of 103)	269	66% (67 of 102)	44% *vs* 28% (RR 1·6, 1·1–2·3)	18% *vs* 16% (RR 1·2, 0·6–2·2)
THRACE‖[6]	414	Alteplase <4 h; endovascular treatment <5 h	18–80	62·5	10–25	18	100% (414)	Any approved	ICA, M1, basilar**	CTA, MRA	..	..	..	..	..
THERAPY‖[33]	108	5 h	18–85	69	≥8	17·5	100% (108)	Penumbra aspiration	ICA, M1, M2	CT: clot length ≥8 mm, CTA	..	..	..	..	..

NIHSS=National Institutes of Health Stroke Scale. mTICI=modified Treatment in Cerebral Ischaemia grading of angiographic reperfusion (2b=>50% reperfusion of the affected territory; 3=complete restoration of flow to the affected territory). mRS=modified Rankin Scale. RR=unadjusted relative risk (95% CI). ICA=internal carotid artery. M1=first segment of middle cerebral artery. M2=second segment of middle cerebral artery. A1=first segment of anterior cerebral artery. A2=second segment of anterior cerebral artery. CTA=CT angiography. CTP=CT perfusion. mCTA=multiphase CT angiography, for collateral scoring. MRA=magnetic resonance angiography. *Median values. †Mean value. ‡ESCAPE had the shortest onset-to-groin puncture delay despite the longest inclusion window of up to 12 h. §ESCAPE used the original Thrombolysis in Cerebral Infarction scale, in which 2b is more than 66% reperfusion of the affected territory. ¶REVASCAT amended the protocol to include patients aged 80–85 years if the Alberta Stroke Program Early CT score was >8. ‖THRACE and THERAPY have not yet been published. **Two patients with basilar artery occlusion.

Figure 16. *Summary of study characteristics and results from the major randomised controlled trials on endovascular intervention in acute ischaemic stroke. Reproduced from Campbell et al, Lancet 2015 (123). Permissions obtained from Elsevier.*

The majority of studies recruited patients within the 0-6h time-limit, and the beneficial effects of endovascular therapy after this time-limit are therefore lacking. The ESCAPE trial did include 49 patients treated within the 6-12 h time-period and showed trends toward benefit even in this late time-period (OR 1.7 in favour of the endovascular arm), however the results did not reach the 0.05 significance level. In SWIFT-PRIME (46) and EXTEND-IA (49), more rigorous selection criteria were employed, advanced techniques assessing collateral status and perfusion imaging in selection of patients probably resulting in the observed higher recanalization rates and higher proportion of beneficial functional outcome in these studies. These two trials and ESCAPE (48) also emphasized the importance of minimizing time from symptom onset to endovascular treatment, and are the three trials showing the highest probability of functional independence (OR 2.73-3.75) and revascularization (72 to 89 %).

Most of the studies were stopped prematurely after the release of the MR CLEAN results, and therefore were underpowered to answer specific questions regarding the beneficial effects in certain subgroups. After the publication of these five main studies, several meta-analyses publications have appeared in the literature (124-128). However, the most powerful and efficient way of addressing questions that have not been previously resolved in individual trials is pooled data analyses in IPD meta-analysis, thereby adjusting for various prognostic factors at the individual patient level. The most recent pooled patient-level meta-analysis of the recent thrombectomy trials was published in The Lancet in April 2016 (129). This meta-analysis managed to answer several questions still remaining after the individual trials were published. The main results can be seen in Figure 17.

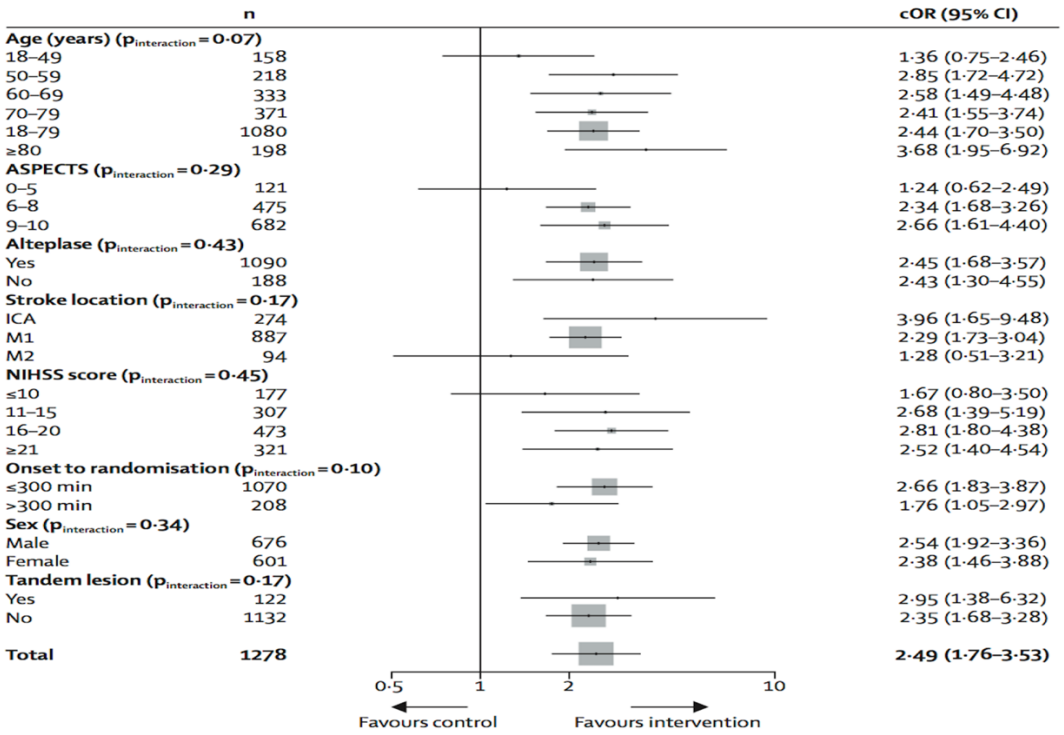

Figure 17. *Adjusted treatment effects for mRS at 90 days. cOR=common odds ratio. Subgroup outcomes from individual patient-data meta-analysis of the major randomised controlled trials on mechanical thrombectomy in acute ischaemic stroke (129). Reproduced from Goyal et al, Lancet 2016. Permission for use obtained from Elsevier.*

The main message from this analysis is the following:

1) The number needed to treat (NNT) with thrombectomy to reduce the functional disability by one level on the mRS scale is an impressive 2.6
2) Effect sizes favouring thrombectomy were seen across several subgroups, including: Patients >80 years of age, patients not receiving alteplase, patients treated after 300 minutes.
3) In patients with low NIHSS scores, trends toward a good functional outcome favouring the endovascular group were seen, however not reaching statistical significance.

Some questions still remain open. The trials so far included only patients with occlusions in the anterior circulation. Studies are underway investigating the beneficial effects of thrombectomy in the posterior circulation (130). Other studies investigating treatment in a later time-window, 6-24h, are ongoing (DAWN- Trevo and Medical Management Versus Medical Management Alone in Wake Up and Late Presenting Strokes; ClinicalTrials.gov NCT02142283 and POSITIVE- Perfusion Imaging Selection of Ischaemic Stroke Patients for Endovascular Therapy; ClinicalTrials.gov NCT01852201).

1.7 FUNCTIONAL OUTCOME

1.7.1 Assessing outcome after stroke

Stroke is an acute condition, causing immediate symptoms of neurological dysfunction at the time of disease onset. The aftermath however, in case the patient survives, is often a life-long debilitating condition with multilevel effects. Due to these multilevel effects, outcome after stroke can be difficult to describe without overlooking important aspects significant to the patient´s overall recovery.

The only way of assessing treatment effects is by measuring changes in outcome parameters. Investigating treatment effects on parameters such as hypertension or hyperlipidemia are straightforward, while the multilevel effects of stroke complicate outcome assessment. In order to conceptualize the multidimensional effects of a chronic disease, the World Health Organization (WHO) has stipulated the WHO International Classification of Functioning, Disability and Health (WHO-ICF), a framework aiding and structuring the description of a chronic disease such as stroke (131). In this framework, the effects of a chronic disease are separated into pathology (e.g. the stroke lesion), impairment (e.g. hemianopia), limitations in activity (e.g. cessation of driving due to a visual disturbance) and societal participation (e.g. social isolation due to difficulties leaving the home). Figure 18 depicts this concept, illustrating the feed-back loops that often ensue.

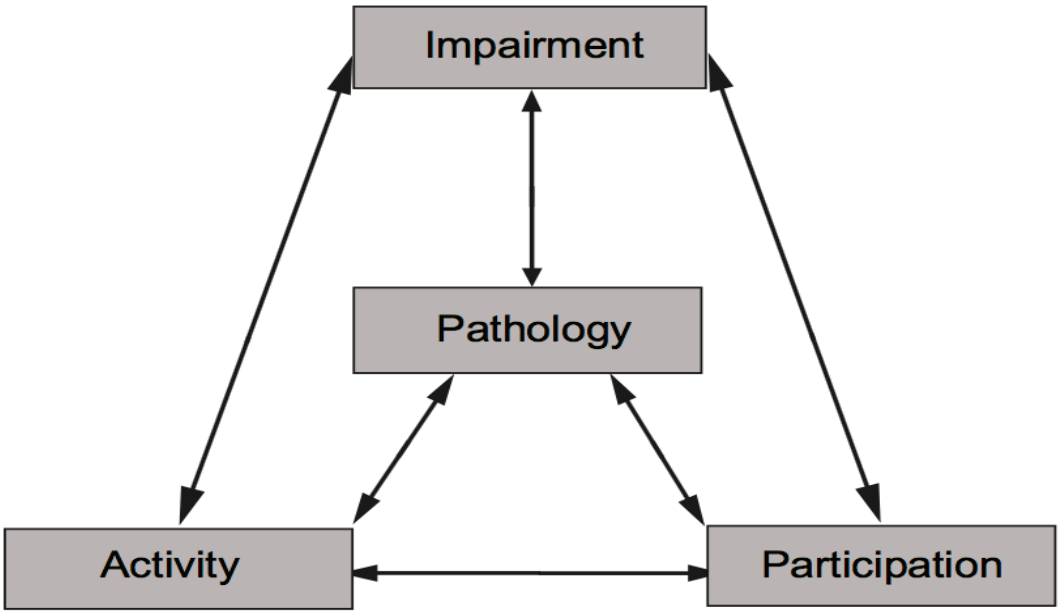

Figure 18. *The World Health Organization International Classification of Functioning, Disability and Health (WHO-ICF) framework. Reproduced from Harrison et al, 2013 (132). Permission not required.*

The individual elements of the WHO-ICF are conceptually separate, however there may be significant overlap, and the underlying relationships between the different elements are not fully understood (133). No single scale or score can assess the outcome at all different levels of the WHO-ICF, a review article from 2009 found 47 different stroke outcome scales currently used in clinical trials (134).

Various scales focus at different levels, and which level to focus on is not obvious. Deficits at the level of impairment, such as neurological deficits after a stroke, are relatively easy to measure, are clearly correlated with site and the mass of damaged cerebral tissue and therefore measurements at this level probably reflect the pathophysiology that the trial drugs/interventions purport to affect. However, patients are probably more interested in their level of activity, which is described in the third level of the WHO-ICF framework. Further, the effects on future societal participation are naturally highly prioritized by the stroke patients. Assessing outcome after stroke in a meaningful way, both in trials but also in routine clinical practice, is clearly not a simple task. Furthermore, apart from the choice of level to focus on, the chosen score needs to be both valid, i.e. truly measure the concept meant to be measured, reliable, i.e. show consistency in scoring between assessors (inter-rater-reliability) and reproducible in repeat scoring by the same assessor (intra-observer-reliability). A common measure of inter-rater variability is the kappa score, ranging 0-1 (135). Following standard convention, a kappa between 0-0.2 is usually considered poor, 0.21-0.4 fair, 0.41-0.6 moderate, 0.61-0.8 good, and 0.81-1.00 excellent (136). In addition, the scale needs to be responsive i.e. in a satisfactory way measure change over time. Finally, it needs to be acceptable to both assessor and patient (132). The demands on an outcome scale are extensive.
In a systematic review of the outcome measures used in all published RCTs on drug intervention in acute stroke, reviewing close to 60000 patients, the distribution of outcome level studied as the primary endpoint were the following: 20 studies used a measure of activity limitation as the primary outcome, 7 studies used some measure of level of impairment, and no study used a measure of participation (137). A more recent review from 2009 examined outcome assessment in recent stroke trials from major high-impact journals (134). The three most common outcome assessments described were the following: the mRS (64.3%); followed by Barthel index (40.5%) and the NIHSS (27.8%) (134). The mRS is a global outcome assessment, incorporating elements from both level of impairment, activity and participation. The Barthel Index is a measure of activity while the NIHSS is an impairment measure. These three major outcome scores will now be reviewed in more detail, with emphasis on the mRS which is the focus of the last project in this thesis (138).

1.7.1.1 The National Institute of Health Stroke Scale

The National Institute of Health Stroke Scale, NIHSS, is a 15-item ordinal non-linear measure of neurological deficits, mainly assessing symptoms associated with acute anterior circulation stroke. The score covers symptoms of consciousness, motor function, sensory function, coordination, neglect, language, visual fields and extraocular movements (139).

The scale ranges from 0-42, increasing scores representing increasingly severe stroke. Table 2 summarizes the included items.

NIHSS sub-item	Results	Scoring
Level of consciousness	Alert	0
	Not alert (arousable to minor stimulation)	1
	Not alert (arousable to painful stimulation)	2
	Unresponsive	3
Level of consciousness Questions	Answers both correctly	0
	Answers one correctly	1
	Answers neither correctly	2
Level of consciousness Commands	Performs both tasks correctly	0
	Performs one task correctly	1
	Performs neither correctly	2
Best gaze	Normal	0
	Partial gaze palsy	1
	Forced deviation	2
Visual	No visual loss	0
	Partial hemianopia	1
	Complete hemianopia	2
	Bilateral hemianopia	3
Facial palsy	Normal	0
	Partial central paralysis	1
	Complete central paralysis	2
	Peripheral or bilateral paralysis	3
Motor function (arm) **a) Left** **b) Right**	No drift within 10 seconds	0
	Drift within 10 seconds, does not reach bed	1
	Drift within 10 seconds, reaches bed.	2
	No effort against gravity	3
	No movement	4
Motor function (leg) **a) Left** **b) Right**	No drift within 5 seconds	0
	Drift within 5 seconds, does not reach bed	1
	Drift within 5 seconds, reaches bed.	2
	No effort against gravity	3
	No movement	4
Limb ataxia	No ataxia	0
	Ataxia in one limb	1
	Ataxia in two limbs	2
Sensory	No sensory loss	0
	Mild sensory loss	1
	Severe sensory loss	2
Language	Normal	0
	Mild aphasia	1
	Severe aphasia	2
	Mute or global aphasia	3
Dysarthria	Normal	0
	Mild to moderate dysarthria	1
	Severe dysarthria	2
Extinction and inattention	Absent	0
	Mild (1 sensory modality)	1
	Severe (2 modalities)	2

Table 2. *National Institute of Health Stroke Scale. Image created by the author of this thesis.*

In patients with a reduced level of consciousness, all elements are not assessable, and rules are available for scoring in these situations. The score was initially developed in the 1980s as a measure of neurological deficits in acute-stroke trials, incorporating elements from several earlier scores, and was further refined in an acute stroke trial of naloxone (140). Since then, the usage has spread from a neurological impairment assessment in stroke trials to use in clinical routine acute-stroke practice as well. Several important trials on treatment in acute stroke have used the NIHSS as either primary or secondary endpoint.
As discussed above, an outcome scale needs to have both a high validity, reliability, responsiveness and ease of use. Regarding validity, the NIHSS has shown both high content, concurrent and predictive validity. Content validity, assessing the internal structure of the NIHSS and correlations with clinical stroke-related neurological deficits has been shown (141). Concurrent validity has been shown in several studies with clear correlations between NIHSS scoring and volume of infarct (142, 143). Predictive validity, assessing associations between NIHSS scoring and long-term outcome has also been demonstrated (144, 145).

Regarding reliability, high both inter-rater and intra-rater reliability has been shown, both in neurologist as well as non-neurologist assessors (146, 147) as well as in remote assessment by telemedicine (148). The score is often used in trials and clinical routine for assessing changes in neurologic deficits over time using serial NIHSS assessments, and a change in 2 points over time has been considered a fair approximation of either clinical deterioration or improvement (145). The score is fairly simple and can be completed within 6 minutes.
Certain drawbacks need to be addressed though. Certain elements of the score (facial motor function, dysarthria, level of consciousness and ataxia in particular) have either shown redundancy or poor reliability (149). Differences in median NIHSS scores of equal sized infarcts of left vs right cerebral localization have been demonstrated, probably due to the NIHSS including 7 points correlated to language function, but only 2 points to neglect (150). Additionally, the score is poor at recognizing and grading deficits from the posterior circulation.
In summary, the NIHSS is a wide-spread scoring model, used in both clinical and trial settings, with an overall good reliability, validity, responsiveness and ease of use. However, certain drawbacks and limitations of use need to be kept in mind.

1.7.1.2 The Barthel Index

The second measure of outcome after stroke that will be reviewed is the Barthel Index (BI). The BI was developed in the mid 60´s and according to a review from 2009 is the second most commonly used assessment tool in clinical stroke trials (134). The score assesses outcome at the level of activity. The BI assesses 10 different functional tasks (activities of daily living), the score ranging from 0 to 100. Lower scores indicate higher levels of dependency, while higher scores are associated with higher levels of independency. Figure 19 summarizes the included elements and scoring.

Domain assessed	Score			
	0	5	10	15
Feeding	Unable	Requires assistance	Independent	
Bathing	Dependent	Independent		
Grooming	Needs help	Independent		
Dressing	Dependent	Needs some help	Independent	
Bowels	Incontinent	Occasional accident	Continent	
Bladder	Incontinent or catheterized	Occasional accident	Continent	
Toilet use	Dependent	Needs some help	Independent	
Transfers (bed to chair and back)	Unable	Major help	Minor help	Independent
Mobility (on level surface)	Immobile	Wheelchair independent > 50 yards	Walks with help of one	Independent
Stairs	Unable	Needs help	Independent	

Figure 19. *The Barthel Index. Reproduced from Harrison et al, 2013(132). Permission not required.*

Earlier systematic reviews suggested that the BI was the most commonly used endpoint in acute stroke studies, however in more recent meta-analysis the score has fallen down to a second place (137, 134). The scale has shown promising inter-rater and intra-rater variability (151, 152). This has also been confirmed in studies assessing reliability of the BI administered over telephone as well as in proxy's vs patients (153). The scale has shown a good validity for forecasting recovery, required care level and duration of rehabilitation post-stroke (154, 155). Moderate correlations between the score and infarct volumes have been shown, i.e. concurrent validity (143).

However, important drawbacks limit its use. These include the lack of the endpoint death complicating analysis in stroke trials, as well as problems with "floor and ceiling" effects (156). The original intended use of the scale was a measure of responsiveness, assessing improvements in recovery over time in order to assist in discharge planning. This parameter is however the most important limitation of the scale. Floor and ceiling effects describe the insensitivity of the score in differentiating between levels of functioning at the two ends of the scale. For instance, patients may score 100 points, suggesting a completely independent level of functioning, however deficits such as language dysfunction which are not included in the assessment would in practice mean

full-time assistance when the patient is outside his/her home. On the lower end of the scale, important recoveries in a severely affected patient in the rehabilitation setting may not be reflected by a change in BI scoring.
Optimally, instead of only assessing the total BI score, assessment of the individual items would give the best overall picture of the patients´ needs. However, in a trial setting, dichotomizations of the total score are often performed, and controversy exists as to the most optimum definition of good outcome vs poor outcome according to the BI. Different cut-points have been employed in different studies, complicating comparisons between studies as well as proper meta-analysis (157).
In summary, the BI demonstrates several advantages, showing both a high validity and reliability. However, important floor-and-ceiling" effects limit its use, and it has increasingly been replaced by the modified Rankin Scale.

1.7.1.3 The modified Rankin Scale

John Rankin published the original Rankin Scale in the Scottish Medical Journal in 1957 (158). The scale was originally intended for assessment of stroke patients in his prototypic stroke-unit in Glasgow, Scotland. The scale was subsequently modified slightly in 1988 in the UK TIA-aspirin trial in order to improve its comprehensiveness (the main modification involving the addition of the previously not included grade 0, as well as minor changes in the wording for minimizing ambiguity : the mRS was born (159).
The mRS is a 6-item ordinal and hierarchical scale, ranging from 0 (no residual symptoms) to 5 (indicating very severe disability). In clinical trials, an additional score of 6 is usually added, denoting death. Figure 20 summarizes the levels of the mRS. The scale is today the most commonly used primary/secondary endpoint in clinical stroke trials (134) and is used in routine clinical follow-up assessments after acute stroke.

Grade 0	No symptoms at all
Grade 1	No significant disability despite symptoms; able to carry out all usual duties and activities
Grade 2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
Grade 3	Moderate disability; requiring some help, but able to walk without assistance
Grade 4	Moderately severe disability; unable to walk without assistance, unable to attend to needs without assistance
Grade 5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
Grade 6	Dead

***Figure 20**. Modified Rankin Scale. Reproduced from Harrison et al, 2013 (132). Permission not required.*

Numerous studies have ascertained the validity of the mRS (160). In summary, the mRS score has shown both clear correlations between increasing stroke severity and higher mRS scores in the long-term. In one study, the specific association between baseline stroke severity, measured with the NIHSS, and favourable outcome (mRS 0-1) was measured, showing that patients with mild strokes (NIHSS 1-5) had a higher chance of achieving a favourable outcome compared to more severe strokes (NIHSS 11-15, 16-20 and >20) (161). Several studies have shown clear associations between increasing stroke lesion volume, measured through Magnetic Resonance Diffusion Weighted Imaging (MR-DWI) among other techniques, and higher mRS grades (162, 163). Comparisons between the mRS and other outcome scales have shown good agreement, especially with the Glasgow Outcome Scale (GOS) (164).

Regarding responsiveness of the score, being able to detect changes over time, limited evidence is available (160). Comparisons with the BI have shown a better ability of the mRS in detecting changes in mild-moderate disability (165). The mRS is poor at detecting short-term changes as each category encompasses a broad range of clinical phenotypes, whereby smaller short-term changes may not be sufficient for a transition of grading.

Due to several reports on a high rate of inter-rater variability for the mRS, the clinometric property of reliability has received most attention. Intra-rater reliability has generally been encouraging (166), however less so for inter-rater reliability. A meta-analysis covering 10 studies and close to 600 patients investigating the reliability of the scale, demonstrated an overall un-weighed kappa of 0.46 (166), defined as only moderate agreement according to existing conventions (136). Another study investigating the agreement across multiple raters displayed an unweighted kappa of 0.25 (167). Various methods for increasing the inter-rater-agreement of the mRS have been proposed, including the use of a structured interview (168, 167), use of digital training resources (169) as well as remote consensus grading by experienced trialists. The benefits of the structured interview have been varying, the initial publications assessing the new method showing improvement (weighted kappa 0.91 vs 0.71), however subsequent validations in independent groups failing to show significant improvement (unweighted kappa 0.5 vs 0.64, no significant difference at the 0.05 p-level) (167, 170).

One specific form of the structured interview that needs mention is the Rankin Focused Assessment (RFA) (171), as it forms the base for the last study in this thesis. The RFA was developed by Jeffrey Saver and colleagues and published in 2010. It is a modified version of the structured interview proposed by Wilson et

al (168). The main differences compared to the previously proposed structured interview is the encouragement of eliciting outcome information from multiple sources, as well as rating current functional status without the need for factoring out pre-stroke disability, a factor complicating the assessment in the previous structured interview. In the original article, an extremely impressive weighted kappa of 0.99 and unweighted kappa of 0.93 was seen. To our knowledge, no external validations of the RFA have subsequently been performed.

Comparisons between studies are difficult to interpret due to a high level of heterogeneity in the specific manner in which the endpoint mRS is analysed: either various dichotomizations spanning the entire range of the scale or overall shifts. To complicate matters even more, there is no clear consensus regarding the statistical method for assessing inter-rater variability. Inter-rater variability is usually assessed using kappa statistics, however various forms of the kappa statistic are described: unweighted and weighted (linear or quadratic).
The weighted kappa values give an overall assessment of variability, penalizing large discrepancies more than smaller. The unweighted kappa values however reflect disagreement irrespective of the magnitude of disagreement, and small discrepancies are penalized to the same extent as larger discrepancies. The weighted kappa therefore usually exhibits more favourable agreement than the unweighted kappa, smaller discrepancies not affecting the overall kappa to the same extent. Assessment of both measures is important, as a mere assessment of weighted kappa may give a false impression of low variability. Consider most trials on thrombolysis, where the outcome studied has been a dichotomization of the mRS, one common threshold being mRS grade 2. Differentiating between grade 2 and 3 can sometimes be difficult, the highest rate of disagreement occurring in the middle region of the score, whereas score assignment at the two ends usually is considered more straightforward (172, 173). Choosing a dichotomy as an endpoint in a clinical trial, especially at a grading threshold where disagreement may be highly significant, can pose serious problems, increasing the risk of type II-errors.

The choice of how to analyse the mRS as an endpoint in clinical trials has received increasing attention, partly due to concerns over the risk of missing true treatment effects in major clinical trials. An example are the results from the ECASS II trial, in which the primary endpoint, a dichotomization at mRS≤1, yielded a negative result, while post-hoc analysis extending the dichotomization to mRS ≤2 yielded a result statistically in favour of iv-tPA (157). Dichotomizations restrict assessment of outcome transition to one specific level, favourable transitions at other levels going undetected. In order to address this problem, several newer statistical methods for outcome analysis have been proposed,

including the global statistic, responder analysis and shift analysis (174). Briefly, shift-analysis assesses changes in outcome distribution over the entire range of the mRS, instead of at specific cut-offs. This improves the possibility of detecting relevant treatment effects. An example of this is the IST-3 trial which as a primary outcome used a dichotomy of the Oxford Handicap Scale (a modification of the original Rankin Scale, basically identical to the mRS despite a somewhat different wording). The study was negative using the dichotomized primary outcome, however a secondary endpoint employing shift analysis showed a statistically significant shift in odds ratios in favour of iv tPA (101). A highly interesting study by Jeffrey Saver, assessing the results from several mock trials employing both shift analysis and dichotomizations, in general supported shift analysis over dichotomy. However, in certain situations in which a therapy is predicted to cause major changes in the distribution of the outcome mRS, such as early and late recanalization trials, dichotomized analysis at mRS ≤ 1 or mRS ≤ 2 might be more appropriate (175).

The evolution of statistical reasoning in the setting of acute stroke trials is evidenced by the increasing frequency of shift analysis in recent trials on mechanical thrombectomy. Outcome analysis needs to be tailored to the specific treatment and population under investigation.

Finally, a few words regarding timing of outcome assessment. In one of the above-mentioned reviews investigating the most commonly used outcome assessments in clinical trials, the most common time-frame for outcome assessment was 3 months (137). For severely affected patients, spontaneous improvement may not level off until five or six months' post-stroke. Therefore, outcome assessment could if possible be performed at a later time-point. This is however a trade-off against the sensitivity of detecting relevant treatment-caused changes, as there may be an increased risk of other factors not connected to the administered stroke therapy affecting outcome with a longer elapsed time.

1.7.2 Modified Rankin Scale - alternative methods of assessment

In a large meta-analysis summarizing data from 126 trials involving interventional studies in stroke patients between 2001 and 2006, the methodologies for assessment of stroke functional outcomes were described. For a majority of trials (73.2%), no description of methodology was given, while telephone interviews were most common among the studies where details of methodology were available. Other methodologies used included face-to-face interviews (likely the most common assessment overall), case-sheet reviews, postal surveys, questionnaires and structured interviews, see Figure 21.

Method for collecting functional outcomes data	Number of trials
Case-sheet review	4 (3·1%)
Face to face interview	13 (10·2%)
Postal survey	2 (1·6%)
Questionnaire	3 (2·4%)
Structured interview	2 (1·6%)
Telephone interview	17 (13·4%)
No description of method	93 (73·2%)

Figure 21. *Methods for collecting functional outcomes data. From a large meta-analysis. Reproduced from Quinn et al, 2009 (134). Permission for use obtained from SAGE Publications.*

Studies validating the performance of these alternative assessment methodologies are limited. A couple of studies have investigated the role of mRS telephone assessment with mixed results (172, 173, 176-178).

A major drawback limiting the possibility of properly assessing these studies are inconsistencies in the statistical methods used, some studies reporting only weighted kappa values, some only un-weighted kappa values and only a few both. Most of the studies were relatively small with low numbers of included patients. One study found a poor inter-rater-variability when comparing telephone interviews with face-to-face interviews with an un-weighted kappa value of 0.30-0.38 (172). Two other studies have found more promising results with higher weighted kappa results, ranging from 0.71-0.89 (176, 178). Yet the same studies showed relatively low un-weighted kappa results close to 0.4. Although telephone mRS assessments may not be able to replace traditional visits completely, they may have a role in certain circumstances.

One study assessed the role of mRS derivation using case-records from standard hospital records compared to face-to-face interviews, showing poor results (179). Another study assessed the performance of a simplified mRS questionnaire (smRSq), reporting a promising weighted kappa of 0.82 between two raters using the smRSq (180). The smRSq was further tested in a study comparing postal questionnaires based on the smRSq with telephone RFA-based assessments. The reported agreement between postal smRSq and telephone interviews was

weighted kappa 0.73 and unweighted kappa 0.55 (181). A major limitation of the smRSq studies is the lack of validation of the new proposed methods, the studies assessing reliability but merely assuming validity and not comparing with traditional face-to-face mRS assessments.

In summary, alternative methods for assessing the mRS are probably wide-spread, the exact extent uncertain because of a poor description in the methods sections of most articles. The studies investigating these alternative assessments are unfortunately generally small-scale studies, and in several cases validity has not been ascertained by comparison with traditional face-to-face interviews.

In the SITS-ISTR stroke register, on which three of the sub-studies in this thesis are based on, there is an approximately 20-25% frequency of missing outcome assessments at 3 months. In order to find ways of bridging this void of missing outcome data, we have evaluated a new mobile phone-based questionnaire for self-assessment of the mRS after acute stroke (138).
The results from this fourth study of the present thesis will be presented and discussed later.

1.8 PREDICTING FUNCTIONAL OUTCOME IN ACUTE STROKE

Stroke is a multifactorial disease, and the most common underlying causes and risk factors such as hypertension, hyperlipidemia, older age, diabetes mellitus, smoking and cardiac disease among others are well-known and have been extensively studied (182). We will here, however, focus the discussion on the parameters and risk factors associated with long-term functional outcome once the ischaemic stroke has become an established fact. The association between various parameters in the acute setting of ischaemic stroke and long-term functional outcome have been extensively investigated, and several prediction rules and models have been proposed. An article from 2015, reviewing the currently available models predicting functional outcome after acute ischaemic stroke, has illustratively summarized the most commonly included parameters, see Figure 22 (183).

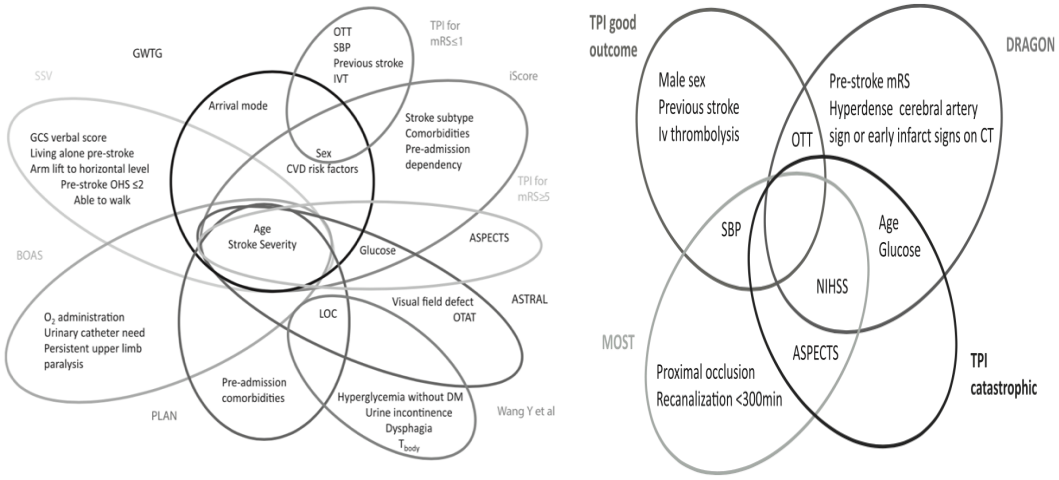

***Figure 22A/B**. Venn diagrams illustrating the included parameters in models predicting functional outcome after acute ischaemic stroke. Each eclipse represents a specific model. A) Models predicting functional outcome in unselected ischaemic stroke cohorts. B) Models predicting functional outcome in iv-tPA treated patients Reproduced from Ntaios et al, Stroke 2015 (183). Permission obtained from Wolters Kluwer Health.*

Figure 22A is a Venn diagram summarizing parameters predicting outcome in unselected ischaemic stroke cohorts, and Figure 22B summarizes parameters predicting outcome in iv-tPA treated patients. In the coming sections the most commonly used parameters will be discussed in detail. At first, parameters common to both the unselected and thrombolysed cohorts will be reviewed, followed by a discussion on parameters specifically relevant for iv-tPA treated stroke cohorts.

We will now discuss these parameters in more detail.

1.8.1 Predictive parameters in ischaemic stroke patients (unselected)

1.8.1.1 Stroke severity

As discussed in a previous section of this thesis, the NIHSS score is the most widely recognized and utilized scale for assessing baseline stroke severity, showing an acceptable inter-rater variability both for expert neurologists and general users (184). Clear associations between baseline NIHSS scoring and long-term outcome were already demonstrated in the original NIHSS article by Brott et al, in which a Spearman correlation coefficient of 0.53 between scoring and 3-months outcome was seen (the statistic ranges -1 to 1) (139). Further studies have confirmed the severity of stroke, measured in the acute setting of the disease, as the most important determinant of long-term functional outcome in acute stroke (145, 139, 185, 186, 161, 187, 188). This trend is also seen in iv-tPA treated patients, as demonstrated in the large IPD by Emberson et al, as well as in patients treated with mechanical thrombectomy, as seen in the IPD by Goyal et al (102, 129). Important to note, the effect of treatment, whether iv-tPA or mechanical thrombectomy, is similar across a wide range of stroke severity.

The predictive value of stroke severity on functional outcome is clearly established, stroke severity in the majority of cases being measured using the NIHSS. Drawbacks of the NIHSS include its complexity, necessitating assessment of 15 different items. Most studies investigating the predictive role of stroke severity on long-term functional outcome, including the first project of this thesis, have examined the NIHSS in its total sum (in some cases categorized, in other cases examined as a numerical variable), however not specifically studying the predictive performance of individual sub-items. We will therefore briefly discuss the outcome validity of individual NIHSS score items. Already in the original NIHSS article, certain sub-items were shown to display a low reliability, including limb ataxia, facial palsy, dysarthria and level of consciousness (139). A most interesting analysis by Lyden et al. from 1999 investigated the underlying structure of the NIHSS (141). This study found 4 main “factors” that represented the NIHSS, interpreted as left and right cortical function, and left and right motor function. Each sub-item of the 15-item NIHSS “loaded” on one of these 4 factors, it was however shown that items ataxia, facial motor function and level of consciousness (LOC 1A) either loaded poorly or were redundant. These observations sparked the development of a modified NIHSS, mNIHSS, where poorly reliable/redundant sub-items including level of consciousness, facial palsy, dysarthria and ataxia were removed (189). This mNIHSS was shown to carry a similar prognostic value regarding long-term functional outcome as the original 15-item NIHSS, both in a retrospective as well

as a prospective study (189, 190). Another interesting study examining the predictive value of individual NIHSS sub-items creating multivariable models for predicting long-term outcome in stroke, found the following items as most predictive: right lower extremity motor function, left lower extremity motor function, gaze, visual fields, aphasia, level of consciousness, facial motor function and dysarthria. This simplified scale was termed sNIHSS-8, and a further refinement termed sNIHSS-5 only kept the five most predictive items. Both the sNIHSS-8 and sNIHSS-5 retained much of the predictive value of the full 15-item NIHSS (191). A Swedish study by Appelros and Terént from 2004 identified level of consciousness items and motor leg functions as most predictive of long-term functional dependency (192). The importance of individual sub-items in prediction was further strengthened in an analysis by Sucharew et al, where a statistical technique called "Latent Class Analysis" was used to group stroke patients into profiles with similar sub-item phenotypes. This study found 6 different profiles, A-F, where profile A had the highest probability of deficits in several NIH sub-items including level of consciousness, whilst profile E and F included patients with milder deficits. Despite having similar median total NIHSS score values, profiles C and D differed significantly in outcome, the main difference being profile C representing more patients with aphasia (193). The importance of considering individual NIH sub-items in addition to the total sum NIHSS score is evident.

One of the main aims of project 1 in this doctoral thesis was the identification of thresholds on the baseline NIHSS for predicting long-term functional outcome. Few studies have specifically examined NIHSS threshold values for predicting functional outcome in acute stroke. Optimum cut-offs for predicting long-term unfavourable functional outcome at NIHSS scores of 13, 16 and 17 have been presented in these studies (145, 194, 195). Importantly, patients in these studies were not treated with iv-tPA. Regarding iv-tPA treated patients, one smaller study (108 iv-tPA treated patients) did not find a good predictive value (AUC 0·634) of the baseline NIHSS in predicting poor functional outcome (196). Patients in that study had a high stroke severity (median NIHSS 17), and excluded patients with NIHSS ≤ 7 as well as absence of occlusion on MR angiography. The results of the findings from the first project of this theses will be discussed in the context of the currently available evidence later on in the Discussion section.

1.8.1.2 Age

Age at stroke-onset is alongside with stroke severity one of the strongest predictors of functional outcome after stroke. Numerous studies have investigated this relationship, confirming the inverse relationship between increased age and good functional outcome after stroke (197, 198, 192, 185). One study found a steady decrease in chance of good functional outcome from age strata 18-35 to 75, with an average decrease of 3.1%-4.2% per decade, with a steep decrease seen after 75 years of age (197).Importantly, increasing age shows a clear inverse association with favourable 3-months functional outcome in thrombolysed patients as well (199, 200, 100). However, age does not affect the relative effect of thrombolysis compared to control (102, 101, 103, 99). There has been considerable debate as to the efficacy of iv-tPA in older patients, the large individual patient data meta-analysis by Emberson et al from 2014 (including the large IST-3 trial) clearly showing that patients >80 years show a proportionally similar benefit from iv-tPA as compared to younger patients, albeit in absolute numbers having a higher proportion of patients with poor functional outcome (102).

1.8.1.3 Hyperglycaemia

Previous studies have found that approximately 60% of all acute ischaemic stroke patients suffer from hyperglycaemia at some point after stroke-onset (201). A systematic review from 2001 summarized the findings from several previous studies and concluded the increased risk of poor functional recovery in non-diabetic patients with hyperglycaemia at stroke presentation. The same review could not ascertain the detrimental effects of hyperglycaemia on long-term functional outcome in diabetic patients, (202). The detrimental effects of baseline hyperglycaemia and increasing baseline glucose concentration on 3-months functional outcome after iv-tPA treated ischaemic stroke, both diabetic and non-diabetic, are well established (203, 204). However, no randomised clinical trial to date has shown a benefit of intensive insulin therapy in the acute setting of stroke, the largest of these the negative GIST-UK trial which enrolled 933 patients (205).

The underlying mechanisms leading to the detrimental effects of hyperglycaemia include among other glucose-mediated increase in oxidative stress and inflammation (206), upregulation of thrombin-antithrombin complexes (207) and reduced cerebral blood flow due to inhibited vasodilation (208). The effects of hypoglycaemia in humans show conflicting results (209).

1.8.1.4 Gender

Previous studies have shown gender differences in the presentation, severity of stroke and long-term functional outcome. In general females present at a higher age with a higher stroke severity and more cortical symptoms (210). Review studies summarizing the findings from previously conducted studies have consistently shown a higher rate of 3-month dependency among women (210, 211), in part but not completely explained by differences in stroke-severity and age at stroke-onset. The natural history of stroke seems to be in a disadvantage for women considering long-term functional outcome (212, 213).However, interestingly several studies examining the gender effect in iv-tPA treated patients show no difference in 3-months functional outcome between the sexes (214-216). It appears that iv-tPA reverses the natural history of ischaemic stroke, efacing the differences in outcome between the two sexes.

1.8.2 Predictive parameters in ischaemic stroke patients (iv-tPA treated)

1.8.2.1 Imaging

In the hyperacute assessment of stroke patients, radiologic assessment of cerebral tissue and vascularization is a cornerstone of the diagnostic workup. Even though various techniques based on magnetic resonance imaging (MRI) have a higher sensitivity and specificity for detecting acute ischaemic changes compared to computer tomography (CT), as evidenced by a sensitivity of 75% on CT compared to MR-DWI for detecting acute ischaemic changes (217), CT still remains the most common mode of assessment of stroke. A systematic review from 2005 investigating the association between early changes on CT (hypoattenuation of MCA territory, obscuration of lentiform nucleus, cortical sulcal effacement, focal hypoattenuation, hyperattenuation of vessel etc.) and long-term clinical outcome found a combined odds ratio of 3.11 (95% CI 2.77-3.49) for poor functional outcome. The review could not leave any guidance as to which specific sign was most predictive, and did not find any effect of iv-tPA on the association between infarct changes and outcome (218). Data from the largest RCT on iv-tPA in acute ischaemic stroke, IST-3, did not find a detrimental effect of iv-tPA on outcome in patients with any infarct changes (101). Important to mention however, specific infarction of more than 1/3 of the MCA territory was found to be associated with large SICH after iv-tPA in a review from 2008 (219).

A small study on 22 acute ischaemic stroke patients with MCA occlusion treated with intra-arterial thrombolysis found a clear association between perfusion deficits on perfusion weighted CT scans and long-term outcome (220).
The hyper-dense middle cerebral artery-sign (see Figure 23) is one of the early

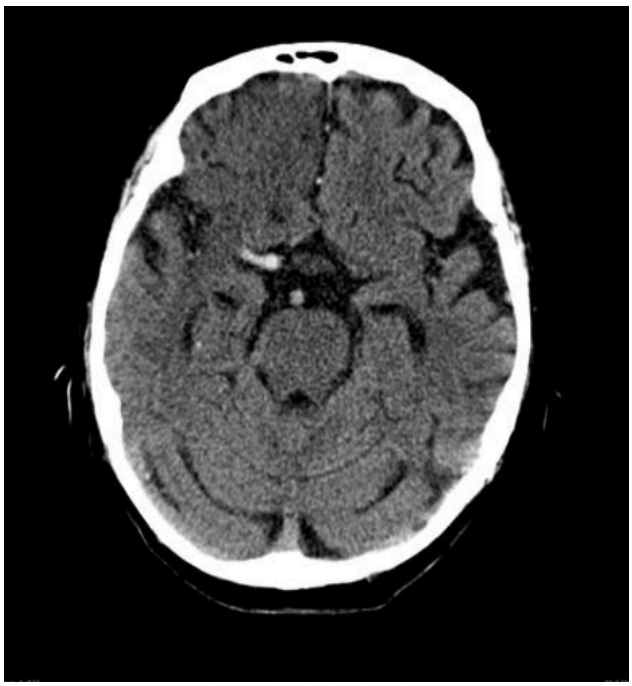

Figure 23. *The hyperdense middle-cerebral artery sign. From Radiopaedia.org. No permission required, in the public domain.*

signs of a large arterial occlusion and is seen on non-enhanced CT-scans in the acute setting, prevalent in about 20% of all patients registered in the SITS-ISTR (221). In this paper presence of the sign was associated with a median NIHSS of 17, twice the mortality and half the frequency of functional independence compared to patients without the sign. In a most recent article published in Neurology 2015, analysis of patients from the IST-3 were performed, comparing subjects with and without the dense-artery sign (222). The presence of the sign independently predicted poor 6-month outcome (OR 0.66), however there was no evidence of a difference in effect of iv-tPA on outcome irrespective of presence or absence of the sign.
New MRI techniques such as MR diffusion weighted imaging (MR-DWI) in the acute setting of stroke have been shown to carry independent prognostic value on long-term functional outcome after stroke (186, 223). A study from 2010 showed that MR-DWI, applied as DWI-ASPECTS scores in the acute setting of stroke, independently predicted functional outcome at 3 months (224). Other studies have found clear associations between long-term outcome in iv-tPA treated patients and both pre-thrombolysis MR-DWI lesion volumes as well as reductions in hypoperfusion volume (pre- and 2h post iv-tPA) measured on mean transit time (MTT) maps (225, 162).

1.8.2.2 OTT (Onset to treatment)

The effect of iv tPA on outcome is time-dependant, the theoretical base being the increasing conversion of ischaemic penumbra to infarct as time proceeds. A pooled analysis of several RCTs on stroke thrombolysis published 2010 in the Lancet (98), showed an increasing Number Needed to Treat (NNT) for achieving mRS 0-1 as OTT increased. During the first 1.5 h, NNT was 4.5, between 1.5-3h NNT 9 and between 3-4.5h NNT 14, see table 1. Figure 12 illustrates the time-dependence of iv-tPA treatment on favourable outcome. The same trend was seen in a previous pooled analysis published in 2004 (93). An increased onset-to-treatment time with iv-tPA in acute ischaemic stroke was clearly associated with reduced 3-months favourable outcome in the meta-analysis by Emberson et al in 2014, comparing iv-tPA with placebo (102).

1.8.2.3 Blood Pressure

High blood pressure in the acute setting of stroke is associated with long-term death and dependency (226). Data from the International Stroke Trial (IST)showed a U-shaped relationship between baseline systolic blood-pressure and long-term death and dependency, the most favourable baseline blood-pressure being around 150 mmHg (227). A subsequent review study including close to 11000 patients confirmed the relationship between both high systolic, diastolic and mean arterial blood pressures and death and dependant functional outcome (228). Regarding post-thrombolysis levels of blood pressure, a study from the SITS group showed an inverse U-shaped relationship between post-thrombolysis (within 24 hours) blood pressure and 3-month functional outcome, patients with systolic blood-pressure between 141-150 mmHg showing the highest proportion of functional independency, in line with the data from IST, see Figure 24 (229).

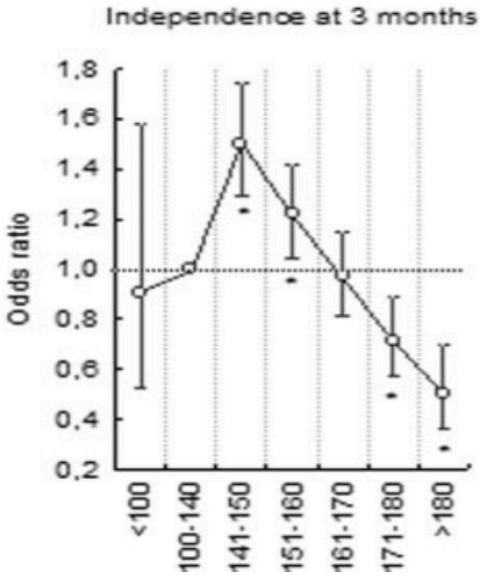

***Figure 24**. Association between post-thrombolytic systolic blood-pressure (x-axis) and odds-ratio for functional independency (y-axis). Reproduced from Ahmed et al, Stroke 2009 (229). Permission for use obtained from Wolters Kluwer Health.*

The relationship between pre-thrombolysis blood-pressure and long-term outcome were not equally clear in this study. The same study suggested a more active approach to blood-pressure lowering than current guidelines, as did an analysis of IST-3 data (230). Despite these observational data, no large RCT to date has shown any benefit of blood pressure lowering therapy in the acute setting of stroke (231, 232).

1.9 EXISTING MODELS FOR PREDICTING FUNCTIONAL OUTCOME

As outlined above, several individual parameters have been associated with functional outcome in acute ischaemic stroke, both in untreated as well as in iv-tPA treated patients.
Prediction of outcome after AIS may serve several purposes (183):

1) Early prognostication may aid patients and caregivers in planning long-term living arrangements
2) May be implicated in treatment decisions, such as de-escalating treatment in patients with a predicted excellent outcome regardless of treatment or in patients with a predicted poor outcome despite treatment.
3) Prediction may be used in research and trial settings for selection of patients with the highest chance of benefitting from the investigated treatment, which could reduce required sample size and eliminate "noise" created by patients with a low likelihood of benefit.

Prediction based on singular parameters may increase the risk of missing important predictive information, a multivariable consideration may give a more balanced and accurate prediction for the individual patient. Prognostic models however need to be simple, including only a few important but readily available parameters applicable in the clinical setting, easily reproducible with a high reliability, validated in various cohorts for increased generalizability and finally shown to improve clinical decision making. The demands on the optimum predictive model/risk score/prognostic model/prediction rule are high, and a guide toward the development of high-quality models has been outlined in a highly informative and appreciable article series by Moons, Altman and Royston et al (233-236). Several studies have been published aiming at developing models for predicting functional outcome after stroke. These studies can be divided into two groups, on the one hand studies predicting outcome in unselected acute ischaemic stroke patients, and on the other hand in patients treated with iv-tPA. As to prediction of functional outcome in acute ischaemic stroke patients undergoing endovascular therapies, predictive models have been proposed, however this discussion is beyond the scope of this thesis (237). Tables 3 and 4 summarize the currently existing predictive models for unselected and iv-tPA treated patients respectively.

Model/Score	Included variables
ASTRAL	Age, Stroke-severity, Onset-to-Admission-time, Visual field defect, Glucose on admission, Level of consciousness
BOAS	Age, Stroke-severity, Persistent upper limb paralysis, Need for O_2 administration, Need for urinary catheter
GWTG	Age, Stroke-severity, Mode-of-arrival, Gender, CVD risk-factors, Co-morbidities.
iScore	Age, Stroke-severity, Stroke-subtype, Gender, CVD risk-factors, AF, CHF, MI, Smoking, Co-morbidities.
PLAN	Age, Neurological deficit, Level of consciousness, Co-morbidities.
SSV	Age, living alone pre-stroke, pre-stroke disability, normal GCS verbal score, Arm-paresis, Walking ability.
Wang et al	Consciousness, Dysphagia, Urinary incontinence, Body-temperature, Hyperglycemia.
Weimar et al.	Age, Stroke-severity.

Table 3. *Prognostic models for unselected acute ischaemic stroke populations.*

Models for prediction of outcome in unselected ischaemic stroke patients include: The ASTRAL score (238), the BOAS score (239), the GWTG risk score (240), the iScore (241), the PLAN score (242), the SSV score (243), the Prognostic Index by Wang et al (244)and finally the prognostic model by Weimar et al (245). Models for prediction of outcome in iv-tPA treated patients include: The stroke thrombolytic predictive instrument, TPI (246), MOST (247) and DRAGON (248).

Model/Score	Included parameters
TPI for good outcome	Gender, Systolic Blood-Pressure, Previous stroke, Onset-to-treatment time, Iv-tPA
TPI for catastrophic outcome	Age, Stroke-severity, Glucose, ASPECTS-score
MOST	Stroke-severity, Proximal occlusion, Systolic Blood-Pressure, Recanalization
DRAGON	Age, Hyperdense cerebral artery sign/Early Infarct Changes, Prestroke mRS, Glucose, Stroke-severity, Onset-to-Treatment time.

Table 4. *Prognostic models for thrombolysed acute ischaemic stroke populations. Created by the author of this thesis.*

I will now very briefly summarize these predictive models, where possible mentioning the development of the model, validation and where applicable possible impact that the scale may have on clinical decision making.

1.9.1 Predictive models in unselected ischaemic stroke patients

ASTRAL-score (238): Included parameters- Age, Stroke-severity, Onset-to-Admission-time, Visual field defect, Glucose on admission, Level of consciousness.
This simple model not requiring an advanced calculation was developed on an unselected cohort of 1645 previously independent ischaemic stroke patients. The score ranged from 5-63 in the original study, median 23, increasing scores representing increasingly poor functional outcome (mRS>2). The area under the curve (discriminative capacity) was 0.850 in the derivation cohort and validation in two separate cohorts in the original article resulted in AUCs of 0.771 and 0.937 respectively. Subsequently, the ASTRAL score was validated in a Chinese cohort with promising findings (AUC 0.82) (249) and in a Greek cohort investigating functional outcome at 5 years (AUC 0.89) (250). The first validation in an iv-tPA treated cohort was study 2 of this thesis, showing an AUC of 0.790 (251). No imaging data are included in the original score, and a subsequent study did not find an improvement of the scores accuracy after addition of multimodal acute imaging data (252).

BOAS score (239): Included parameters- Age, Stroke-severity, Persistent upper limb paralysis, Need for O_2 administration, Need for urinary catheter.
This simple model not requiring an advanced calculation was developed on 221 ischaemic stroke patients and validated on 100 patients. AUCs in derivation and validation cohorts were 0.891 and 0.839 respectively. The major drawback is that the score assesses the parameters at discharge, not in the acute setting, complicating acute assessment of outcome. Included score parameters such as upper limb paralysis may change during the course of the hospital stay. To my knowledge no external validation has been performed.

GWTG (240): Included parameters- Age, Stroke-severity, Mode-of-arrival, Gender, CVD risk-factors, Co-morbidities.
This risk score was developed on a very large unselected ischaemic stroke cohort for predicting in-hospital stroke mortality (total patient cohort nearly 275 000). It requires a mathematical calculation for risk prediction, necessitating a calculator or access to the score internet site. The score was internally validated in the original article with a C-statistic of AUC 0.72, and a sub-analysis including stroke severity measured using the NIHSS resulted in a model with AUC 0.85. Significant individual predictors after adjustment for stroke severity included mode of arrival, age, atrial fibrillation, female sex, dyslipidaemia and previous myocardial infarction. A model only including the NIHSS resulted in an AUC of 0.83. The model has been validated in a large Chinese stroke cohort, AUC 0.87, a model only including the NIHSS showing a AUC of 0.85. This external validation showed excellent calibration (253). Drawbacks could be differences in

in-hospital duration and care in different geographic and clinical settings which would affect the results, as a fixed point of outcome assessment was not defined. Further, the model predicts mortality, not long-term functional outcome, the main measure of outcome investigated in this thesis.

Iscore (254): Included parameters- Age, Stroke-severity, Stroke-subtype, Gender, CVD risk-factors, AF, CHF, MI, Smoking, Co-morbidities.

The Iscore was originally developed on a large ischaemic stroke cohort (12262 patients) for predicting 30-day and 1-year mortality. It showed a good AUC for both outcomes in the derivation cohort (AUC 0.85 and 0.82 respectively) and AUC 0.79 and 0.78 in the external validation cohort of the original study. Score calculation demands the use of a web application, and predicted outcome can be assessed from available risk-stratification bar-charts. The score was subsequently validated for 30-day mRS>2 with different patients from the same registries used in the development of the model. High correlations between observed and predicted outcome were seen (241). The Iscore has been extensively validated for long-term functional outcome, both in unselected and iv-tPA treated cohorts, showing promising results (255-257). Few scores have been assessed for predictive capability compared to informal clinician prediction, and the Iscore is one of few scores that has actually shown a better prediction of long-term outcome compared to clinician prediction (258). Though externally validated and showing promising results, one important drawback limiting its use is the stroke severity measurement used, the Canadian Neurological Scale, which in current practice has been increasingly replaced by the NIHSS. Another important limitation is the complexity of the model.

PLAN (242): Included parameters- Age, Neurological deficit, Level of consciousness, Co-morbidities.

This simple score was developed for the assessment of severe disability or death at discharge, as well as 30-day and 1-year mortality. A post-hoc analysis for prediction of discharge functional outcome resulted in a C-statistic of 0.80. For assessment of prognosis bar-charts from the original article can be used. Instead of using a formalized stroke severity instrument, sole assessment of paresis and language/neglect is performed, which may be attractive for non-neurologist physicians assessing outcome. In the original study, poorer results for iv-tPA treated patients were seen, reducing the generalizability of the score. To our knowledge no external validation has been performed.

SSV (243): Included parameters- Age, living alone pre-stroke, pre-stroke disability, normal GCS verbal score, Arm-paresis, Walking ability.

This model for predicting 30-day survival and 6-months functional independence (Oxford Handicap Scale score<3) showed promising results in internal validation cohorts (AUC 0.84-0.88). Calibration was reasonable, however overoptimistic in patients with the highest predicted probability of functionally independent outcome. No details on how to calculate the score were given (however details were subsequently described in a validation study by the original authors, revealing a fairly complex score calculation) (259). Score assessment was performed within 30 days, hindering its use for prognostication in the hyper-acute phase of stroke where most therapeutic decisions are made. Subsequent external validation however showed promising results in hyper-acute patients as well (260, 261). In my opinion, important limitations of this model include the complex calculation needed for prediction, as well as the inclusion of prestroke disability rated on the Oxford Handicap Scale (essentially the same assessment as the modified Rankin Scale). One study suggested a low validity of pre-stroke mRS assessment, the wording of the categories of the mRS not suiting for pre-stroke assessment (262). In addition, one study investigating the performance of the SSV among other stroke prognostication scales found no significant difference between informal clinician predictions of outcome compared to the prediction model (263).

Prognostic index by Wang et al (244): Included parameters- Consciousness, Dysphagia, Urinary incontinence, Body-temperature, Hyperglycemia.

Prognostic model for 30-day mortality, score ranges from 0-16. The authors proposed a cut-off of ≥11 as the optimum threshold, higher scores associated with 75% risk of death, and lower scores only 3%. To my knowledge, the score has subsequently not been validated, and important drawbacks include lack of a formal and broad assessment of stroke severity, the parameter recognized as bearing the highest predictive value regarding outcome in stroke.

Prognostic model by Weimar et al (245): Included parameters- Age, Stroke-severity.

This is the first prediction model showing the predictive value of stroke severity measured by the NIHSS and age as most important predictors of incomplete functional recovery (measured on the Barthel Index) in the hyper-acute setting of stroke. AUC in the internal validation cohort amounted to 0.86. Details in the original study enable future prediction of outcome in new patients, however a complex calculation is needed for this assessment. In the original study the model predicted outcome better than informal clinician prediction, however subsequent studies found no significant difference between informal clinician

predictions of outcome compared to the prediction models (263) The model has been validated in the large Virtual International Stroke Trials Archive (VISTA) with promising results (AUC 0.81) (188). Major drawbacks are the use of the Barthel Index for outcome assessment, limiting comparison with models using the more common mRS, as well as a complicated calculation needed for outcome prediction.

1.9.2 Predictive models in iv-tPA-treated ischaemic stroke patients

TPI (246): Included parameters in favourable outcome model- Gender, Systolic Blood-Pressure, Previous stroke, Onset-to-treatment time, Iv-tPA. Included parameters in catastrophic outcome model- Age, Stroke-severity, Glucose, ASPECTS-score.

The Stroke Thrombolytic Instrument was developed on patients from 5 large RCTs on iv-tPA within 0-3 h in acute ischaemic stroke, and consisted of two models aiming at predicting a favourable 3-month outcome (mRS≤1) and a catastrophic outcome (mRS≥5) in the presence/absence of iv-tPA, in order to help clinicians in treatment decisions. Prediction assessment is dependent on a handheld or internet access to the instrument internet site. In the original article, AUCs of 0.79 and 0.77 for the two outcomes respectively were described. The first model, as seen in table 4, includes neither age nor stroke severity, the two parameters now widely recognized as the most important predictors of outcome. However, the second model predicting a catastrophic outcome does include these parameters. Subsequent external validation of the instrument revealed a tendency for overestimating good outcome and underestimating poor outcome (264, 265), one of these studies showing improved prediction of a favourable outcome when signs of brain infarction was added as a predictive variable. This was probably due to at least partially resolving the issue of the original model lacking a measure of stroke severity (264).

MOST (247): Included parameters- Stroke-severity, Proximal occlusion, Systolic Blood-Pressure, Recanalization.

This highly interesting predictive model was developed with the aim of finding clinical and radiological predictors apart from early recanalization after thrombolysis that could predict a favourable 3-months outcome (mRS ≤2). The model found increasing stroke severity, early infarct changes on CT, proximal occlusion and systolic blood pressure as most important variables apart from early recanalization for predicting a favourable long-term outcome. Scores ranged from 0-7, and at a cut-off of <4, a sensitivity and specificity of 77% and 82% respectively was seen. AUC for the model was 0.862. Of all predictive models discussed above, this is the only model specifically incorporating

proximal vessel occlusion as a predictor of outcome (this association will be further scrutinized in section 1.10). In this study, Transcranial Doppler ultrasound (TCD) was the modality used for vascular imaging, and an important drawback would be the need for imaging of the cerebral vasculature not available at all centres. To our knowledge, the model has not undergone any external validation.

DRAGON (248): Included parameters- Age, Hyperdense cerebral artery sign/Early Infarct Changes, Prestroke mRS, Glucose, Stroke-severity, Onset-to-Treatment time.

The DRAGON score, a simple integer score used in conjunction with a simple outcome chart, was developed in a single-centre cohort of acute ischaemic stroke patients treated with iv-tPA, using multivariate logistic regression analysis for predicting 3- months favourable outcome (mRS≤2). It consists of 7 parameters, two of which require an admission brain CT scan (early infarct signs and/or presence of the dense vessel sign). The score ranges from 0 to 10, increasing scores associated with a decreasing chance of a favourable outcome. Discrimination assessed by the C-statistic was good, 0.84 in the development cohort (1319 patients) and 0.80 in a smaller external validation cohort (333 patients). The DRAGON score has been validated in 3 separate studies showing promising results (266-268). The largest validation so far was in the second project of this thesis, AUC 0.77 (251). An alteration of DRAGON, replacing CT-imaging with MRI, had a similar performance and was subsequently validated with good performance (269, 270). Although predicting outcome reasonably well, the DRAGON does not serve a purpose in the prehospital setting due to the need of imaging data.

1.10 ARTERIAL OCCLUSION AND FUNCTIONAL OUTCOME

In the preceding section, we have *inter alia* discussed the relationship between stroke severity and outcome, and in the coming sections the relationship between stroke severity and presence of arterial occlusion will be discussed as this may have important implications for pre-hospital decisions on proper triage of patients. However, prior to this discussion, a short review of the association between the presence of arterial occlusions and long-term functional outcome is in place, in order to fully appreciate the interplay between stroke severity, presence of arterial occlusion and long-term outcome.

As already described, stroke severity is probably the most important determinant of long-term functional outcome in acute ischaemic stroke. As we will see in the coming sections, clear correlations exist between increasing stroke severity and presence of LAO in the acute setting as well. The heart of the matter is whether LAO in itself carries predictive value, independent of stroke severity, in predicting long-term functional outcome. The MOST score from 2004, described above, found that the presence of a proximal occlusion on the MCA, identified on TCD, predicted functional outcome at 3 months in patients treated with iv-tPA independently of stroke severity (247). This analysis was based on a small cohort of 177 patients. A similar sized study from 2006 studying ischaemic stroke patients examined with CTA showed how intracranial LAO predicted discharge functional outcome with an OR of 4.5, independently of stroke severity. Presence of a LAO conferred a similar OR for functional outcome as an 8p increase on the NIHSS score (55). The authors of the latter study subsequently published a paper based on over 700 unselected ischaemic stroke patients undergoing CTA. In univariate analysis, presence of a LAO negatively predicted 6-months outcome (OR 0.33). In multivariable analysis, presence/absence of ICA terminus or basilar occlusion was independently associated with the outcome (53). In 2007, Nedelchev et al published the results from an interesting study aiming at finding predictors of poor outcome in patients with mild or rapidly improving symptoms eligible for iv-tPA but not treated due to a perceived likelihood of a favourable course without treatment. The presence of a LAO and NIHSS≥10 were independent predictors of a poor outcome, and the presence of LAO increased the risk of a poor outcome by more than 7-fold (271).

Finally, a meta-analysis from 2015, covering 39 different studies, showed clear correlations between proximal arterial occlusion and a poor functional outcome in patients treated with iv-tPA. The OR for a favourable outcome (mRS≤2) was 0.24 comparing ICA occlusions (exact site not specified) with isolated MCA occlusions (272). Although stroke severity and vessel occlusion are closely

correlated, patients with similar sites of vessel occlusions may present with varying stroke severity. Other vascular factors such as variations in collateral circulation play an important role in the final outcome of patients with occlusive acute ischaemic stroke.

In summary, arterial occlusion carries a predictive value on long-term functional outcome, independent of initial stroke severity. We will now proceed to the final part of this thesis introduction, where the associations between stroke severity and vessel occlusion will be scrutinized.

1.11 PREDICTING ARTERIAL OCCLUSIONS IN ACUTE ISCHAEMIC STROKE

We will now mainly discuss the predictive value of baseline stroke severity on the presence of arterial occlusion, owing to the established beneficial effects of thrombectomy within 6h in anterior circulation stroke and the need for swift and proper patient selection. Prior to this discussion though, a few words need to be mentioned about the aetiology of LAO.

The two most prevalent risk factors associated with the formation of LAO are extra- and intracranial atherosclerosis and atrial fibrillation.

Atherosclerotic disease

The relationship between atherosclerosis and LAO is as of today known to be due to artery-to-artery embolization, usually from the atherosclerotic arterial narrowing at the common carotid artery bifurcation. Another important mechanism is due to a combination of atherosclerotic stenosis and a superimposed propagating thrombosis leading to distal insufficiency of blood flow, hypoperfusion. Among the most well-recognized risk factors for ischaemic stroke are diabetes, hypertension and smoking. These three risk factors do not on their own account directly lead to LAO, however they facilitate the progress of atherosclerotic disease, thereby leading to LAO. We will here briefly describe the association between each of these risk factors and atherosclerosis.

- Diabetes mellitus (DM)- The relative risk of stroke comparing diabetic with non-diabetic patients ranges between 2.3 – 6.8 in women and 1.4 – 4.1 in men (273). Previous studies have shown both the increased prevalence of atherosclerosis in diabetic vs non-diabetic patients (274) as well as DM being an independent risk factor for both small and large vessel occlusive stroke (275)

- Hypertension – The pathophysiological effects of hypertension lead to lipohyalinosis and subsequently to lacunar-type stroke, while the risk of LAO mainly is attributed to the acceleration of atherosclerosis development due to hypertension caused damage to the endothelium of vessels. Endothelial injury leads to plaque progression. In addition, chronic heightened intravascular pressure can cause vascular remodelling and stiffening which can lead to a reduced vascular lumen size.

- Smoking is a potent risk-factor for stroke, and previous studies have shown the aggravation of carotid artery atherosclerosis due to smoking (276, 277). The mechanisms behind increased atherosclerosis are numerous, including direct toxic effect of incomplete combustion products such as 1,3-butadiene on the endothelium, reduced levels of HDL-cholesterol and carboxyhaemoglobinemia (278). Nicotine in tobacco leads to impaired nitric oxide mediated vasodilation (279), while simultaneously promoting vasoconstriction by increasing the concentrations of the powerful vasoconstrictor endothelin (280). The effect is decreased cerebral perfusion.

Atrial Fibrillation

Atrial fibrillation is the most common cardiac arrhythmia (281). The association between atrial fibrillation and increased risk of thromboembolism and ischaemic stroke has been known for a long time, conferring a fivefold increased risk of ischaemic stroke (282). The atrial fibrillation associated strokes are caused by embolization of embolic material from the left atrium and left atrial appendage, and studies have shown the association of this condition with more severe ischaemic strokes than emboli from carotid artery disease, possibly due to embolization of larger particles in the case of atrial fibrillation (283). The underlying mechanisms facilitating thromboembolism in atrial fibrillation are complicated, and involve both abnormal changes in blood flow, vessel/atrial wall and blood constituents, leading to a hypercoagulable state in atrial fibrillation (284).

Whether caused by atherosclerosis or cardiac embolization, occlusion of an intracranial artery finally leads to impaired blood flow and the ischaemic stroke is a fact, evidenced by neurological symptoms. The remainder of the introduction of this thesis will cover prediction and identification of patients with LAO based on baseline findings, of which stroke-severity is the most important.

1.11.1 Severity of stroke and cerebral large arterial occlusion

When the stroke has become a clinical fact, evidenced by acute neurological symptoms, several studies have found an association between symptom severity and the presence of an arterial occlusion. The first study showing this direct relationship was the Emergency Management of Stroke Bridging Trial (EMS), comparing iv-tPA/IA with placebo/IA patients (58). A subsequent study by Derex et al investigated this association specifically, 54 acute ischaemic stroke patients being assessed with MRA in the hyper-acute phase. Each point of increase on the NIHSS conferred an odds ratio of 1.28 (95% CI 1.11-1.46) for the presence of an arterial occlusion. Further studies confirmed these findings (285, 56). The arterial occlusions have been evidenced by either digital subtraction angiography or by CT/MR angiography (CTA/MRA) (286, 56, 285, 57, 58). These studies found varying optimal NIHSS cut-offs for predicting arterial occlusion, one study encompassing all occlusions when setting the NIHSS cut-off at 15 (58), another study detecting 80% of occlusions with NIHSS cut-off at 16 (57). One study found the best compromise of sensitivity and specificity for prediction of arterial occlusion at an NIHSS cut-off of 10 (285), another study showed a PPV of 91% at NIHSS cut-off 12 (56). Major limitations of these studies were relatively small cohort sizes, ranging from 35 (58) to 226 (56), as well as high average stroke severity (median and mean NIHSS around 14). The definition of arterial occlusion varied, some studies only including only proximal occlusions (terminal ICA, M1) while other studies included more distal occlusions (M2).
A later study by Maas et al (54) enrolling 699 patients in a prospective cohort study involving CT angiographic imaging in acute stroke, found that although high NIHSS scores correlated with the presence of proximal arterial occlusions (LAO), no NIHSS score threshold could be applied without missing the majority of occlusive lesions (the authors concluded that a NIHSS cut-off≥2 would be needed to identify 90% of proximal occlusions).

These disparate findings lead to further investigation into the association between baseline NIHSS and arterial occlusion in acute ischaemic stroke. In a study published in Neurology 2011 (52), the validity of the NIHSS in predicting arterial occlusions (not only LAO) was found to be time-dependant, with increasing time from stroke onset to imaging resulting in a decreased predictive value and lower NIHSS threshold values. The association between NIHSS and arterial occlusion was investigated separately in patients presenting prior to or later than 6 h after stroke onset. Within 6h, the best cut-off was NIHSS 7 (sensitivity 76% and specificity 70%) while the cut-off after 6h was 4 (sensitivity 65% and specificity 62%). This time-dependence was subsequently confirmed in a later study by Heldner et al (51) investigating the relationship between baseline NIHSS and arterial occlusion, stratifying time from onset to clinical evaluation

as 0-3h, 3-6h and >6h. The optimal NIHSS cut-off for predicting LAO (ICA, M1/M2, intracranial vertebral artery and basilar artery) at 0-3 h was 9 (PPV 80.7%)and at 3-6 h 7 (PPV 77%). In posterior strokes, the association was poor irrespective of time elapsed between stroke and clinical evaluation.
In project 1 of the current thesis, which is the largest study investigating this association, the same tendency was observed, the best NIHSS cut-off in general predicting arterial occlusion (without specification whether proximal or distal) being 11 (PPV 63.6%), but reducing to 10 at imaging time points past 2h after stroke onset (287). The time from symptom onset to evaluation clearly plays an important role regarding the ability of the NIHSS to predict the presence of arterial occlusions.

1.11.2 Existing models for predicting large arterial occlusion

Clear and strong associations between increasing baseline stroke severity measured by the NIHSS and presence of LAO open up for the possibility of predicting the likely presence of LAO already in the prehospital phase before vascular imaging is available. The recently updated Karolinska Stroke Update guidelines on mechanical thrombectomy in acute ischaemic stroke, supported by the European Stroke Organization amongst others, open up for the possibility of prehospital selection of patients with NIHSS≥9 within 3h of symptom onset for transfer to centres with multimodal imaging and availability of thrombectomy (288).
Although baseline stroke severity measured by the NIHSS score predicts the presence of LAO, the full NIHSS is time-consuming and probably too complicated in the prehospital setting. This has sparked the development of several simplified scales, aiming at predicting LAO in the prehospital stage based on assessment of only a few highly predictive parameters, mostly derived from the NIHSS.
We will now discuss the available prediction models published so far, as the third project of this thesis investigates the value of various models based on simplifications of the NIHSS
for predicting LAO. Table 5 summarizes the available scores.

	3-ISS	LAMS	RACE	CPSSS	PASS	FAST-ED	VAN	G-FAST
LoC	0/1/2			0/1	0/1			
Gaze	0/1/2		0/1	0/2	0/1	0/2	0/1	0/1
Facial motor		0/1	0/1/2			0/1		0/1
Arm motor	0/1/2	0/1/2	0/1/2	0/1	0/1	0/2	0/1	0/1
Grip strength		0/1/2						
Leg motor			0/1/2					
Aphasia			0/1/2			0/2	0/1	0/1
Neglect			0/1/2			0/2	0/1	

***Table 5**. Existing simple models based on NIHSS sub-items for predicting vessel occlusion. Numbers indicate available scoring option. LoC= Level of Consciousness, 3-ISS =3-item-Stroke-Scale, LAMS = Los Angeles Motor Scale, RACE = Rapid Arterial Occlusion Evaluation scale, CPSSS = Cincinnati Prehospital Stroke Severity Score, PASS = Prehospital Acute Stroke Severity Scale, FAST-ED = Field Assessment Stroke Triage for Emergency Destination, VAN = Vision, Aphasia, Neglect Assessment, G-FAST = Gaze-Face-Arm-Speech-test.*

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Simple 3-item Stroke Scale (3-ISS) (286) - The 3-ISS is a prehospital LAO prediction algorithm, based on a prospectively collected cohort of 171 patients, 83 of which underwent MRA. The 3-ISS is composed of modified versions of the NIHSS sub-items level of consciousness, gaze and motor function (composite of arm and leg function). These items were chosen from a clinical sense, not from a statistical analysis of best predictors. The score ranges 0-6. A high correlation between 3-ISS and NIHSS was seen. A score of ≥4 predicted proximal vessel occlusion with an overall accuracy of 0.86 (sensitivity 67%, specificity 92%, positive predictive value 74% and negative predictive value 89%), compared to NIHSS≥14 which had an overall accuracy of 0.93 (sensitivity 86%, specificity 95%, positive predictive value 86% and negative predictive value 95%). The scale has been externally validated, generally showing a poorer predictive value mainly due to a reduced sensitivity at the optimum cut-off (289, 290).

Los Angeles Motor Scale (LAMS) (291) - The LAMS is a motor stroke deficit scale derived from the motor examination part of the broader stroke recognition instrument Los Angeles Prehospital Stroke Screen (LAPSS). The score consists of facial motor function, arm motor function and grip strength. The score ranges 0-5. The LAMS has previously shown a high correlation with the NIHSS. In a retrospective analysis using two databases, one with patients enrolled in clinical randomised trials and one with patients entered into a stroke registry (GWTG), the association between LAMS and proximal arterial occlusion was assessed in 119 <12h acute ischaemic stroke patients. Median NIHSS was 14, and 62% of the

patients had arterial occlusions (58% ICA or M1 occlusions). Median LAMS score was 5 vs 2 in patients harbouring arterial occlusions vs no occlusions. LAMS predicted the presence of arterial occlusions well, AUC 0.85, and at the optimal cut-off ≥4, a sensitivity of 81% and a specificity of 89% were seen. The AUC for the full-item NIHSS was 0.933, optimum cut-off NIHSS≥11 with overall accuracy 0.89 (sensitivity 91%, specificity 87%). External validation has shown promising results, however poorer than that presented in the original study (AUC 0.74) (289)

Rapid arterial occlusion evaluation scale (RACE) (292) - The RACE scale was developed on a retrospective cohort of 654 acute ischaemic stroke patients evaluated in the acute setting. Univariate analysis discovered the NIHSS sub-items most closely associated with large arterial occlusions, and subsequent ROC-analysis was then performed to find the combination of items with highest AUC. The following sub-items were included in the score: facial motor function, arm motor function, leg motor function, gaze, agnosia (if left hemiparesis) and finally aphasia (i.e. LOC commands if right hemiparesis). The score ranges 0-9. The scale was subsequently validated by emergency medical technicians in the field, who scored patients upon first contact and then transferred them to a comprehensive stroke centre where NIHSS evaluation and imaging was performed. The validation was based on 357 patients. Strong associations between prehospital RACE scoring and arrival NIHSS were seen (Spearman correlation coefficient 0.76). Median NIHSS was 8. LAO was detected in 21.3% of patients. ROC analysis resulted in an AUC of 0.82 for detection of LAO, and slightly higher in the subgroup with anterior occlusions. The RACE cut-off ≥5 resulted in a sensitivity of 85%, specificity 68%, positive predictive value 42% and negative predictive value 94%. The full-item NIHSS predicted LAO with an AUC of 0.85. Best NIHSS cut-off ≥11was associated with a sensitivity of 88% and a specificity of 72%. The RACE score is the only LAO score so far prospectively evaluated in the prehospital setting. External validation has shown varying results, generally with a poorer sensitivity at the optimum cut-off (289, 293, 290). An RCT is currently recruiting patients in Spain, randomising acute stroke patients with RACE ≥4 for either direct transfer to a tertiary centre with endovascular capabilities or to the nearest centre lacking endovascular capabilities. The main hypothesis is that direct transfer to a tertiary centre with endovascular capabilities will lead to an improved distribution of the 3-months mRS (ClinicalTrials.gov NCT02795962).

Cincinnati Prehospital Stroke Severity Score (CPSSS) (294) - The CPSSS was developed using data from the two NINDS trials, and designed for predicting NIHSS≥15 (624 patients), and subsequently validated on IMS-III data (650

patients), where a secondary outcome was the presence of large arterial occlusions. In the derivation cohort, the individual NIH sub-items most predictive of severe stroke were chosen. The items most predictive of severe stroke were gaze, motor function (right arm, right leg and left leg) and language, for simplicity and ease of use in the prehospital setting the following parameters were chosen to be included in the score: gaze, arm motor function and level of consciousness commands and questions (replacing language function). The score ranges from 0-4, higher scores reflecting higher stroke severity. In the derivation cohort, AUC for detecting NIHSS≥15 was 0.89. The score was then validated in IMS-III patients, 303 patients with known vascular status. For LAO, CPSSS had an AUC of 0.67, scoring ≥2 resulted in an 83% sensitivity and a 40% specificity. External validation has shown varying results, generally with a poorer sensitivity at the optimum cut-off (289, 293, 290).

Prehospital Acute Stroke Severity (PASS) scale (289) - The PASS scale was developed on a retrospective analysis of a Danish multicentre cohort of 3127 iv-tPA and/or thrombectomy treated patients. Individual NIHSS sub-items most predictive of vascular occlusion (site not specified) were selected and the most optimum combination chosen. Pre-analysis, consensus on maximum 4 items was decided upon, excluding certain parameters such as facial palsy, ataxia, neglect etc. which were expected to be difficult to evaluate in the pre-hospital setting. The best model included items level of consciousness questions, gaze and arm motor function. The score ranges 0-3. The model was derived on 2/3 of the cohort, and validated in the remaining 1/3. Median NIHSS was 7 and 35% of the patients had occlusions. The model showed an AUC of 0.75 for detecting vessel occlusion in the derivation cohort (0.74 in the validation cohort) and the optimum cut-off ≥2 yielded a sensitivity and specificity of 64% and 83% respectively in the entire population. The previously published scores discussed above were validated in the same cohort showing similar performance. To our knowledge, the scale has not undergone validation prospectively in the prehospital setting. The scale has undergone external validation in SITS data with decent results (295).

Field Assessment Stroke Triage for Emergency Destination (FAST-ED) (293) - The FAST-ED score was developed choosing items of the NIHSS with a higher predictive probability of LAO, and derived from NIHSS assessments performed by certified research personnel at hospital admission. The score consists of the NIHSS sub-items facial motor function, arm weakness, speech, gaze and neglect, ranging 0-9. The score was tested in 727 patients consecutively entered in a prospective cohort study at two university hospitals, in whom vascular imaging data were obtained. Median baseline NIHSS was 5, and LAO was detected in 33%

of patients. In patients undergoing vascular imaging within 6h, AUC of the score for predicting LAO was 0.83 (not significantly different from the full-item NIHSS but significantly better than RACE and CPSSS which were tested in the same cohort). At the optimum cut-off of ≥4, a sensitivity and specificity of 61% and 89% respectively were seen. To our knowledge, the score has not undergone prospective validation, and the main limitations here would be complexity and inclusion of certain sub-items with poor reliability.

Vision, Aphasia, Neglect (VAN) Assessment (296) - VAN was developed using clinical reasoning, including those parameters most likely to be associated with large arterial occlusion and cortical ischaemia. The model classes patients as either VAN positive or negative, after an initial screening for arm paresis. If no arm paresis is detected, the patients are classed as VAN negative. If paresis is present, further screening for any one of visual field defects/gaze, aphasia or neglect is performed. Presence of any one of these cortical symptoms classes the patient as VAN positive. In this study, stroke-research nurses were trained in the use of the model, and it was subsequently tested on 62 consecutive code stroke activations. No VAN-negative patient had an occlusion amenable to endovascular intervention, and all 14 patients going on to mechanical thrombectomy were VAN-positive. Sensitivity in this small pilot-study was 100%, specificity 90%, PPV 74% and NPV 100%. The results need to be interpreted with caution. The sample size was small, and applicability in a prehospital setting may not be equally favourable considering the rigorous training and preparation that study-members of the pilot-study went through, which may not be possible on a larger scale. The reliability of some of the included items (gaze) may entail problems in a larger-scale implementation, Nonetheless, the results of this small study are definitely interesting.

Vanacker et al (297) - This Swiss group developed a LAO prediction model aiming at investigating whether other baseline parameters in addition to NIHSS would improve prediction. The model was developed on a cohort of consecutively enrolled patients (1645 patients) in the ASTRAL database with vascular imaging performed within 12 h of symptom onset, and subsequently validated in an independent cohort of 848 patients. Five predictors of LAO were found: admission NIHSS (1p per point), female gender(3p), hemineglect(5p), prestroke independence(3p) and atrial fibrillation(2p). The percentage of LAO in the derivation and validation cohorts was 21% and 28% respectively. The AUC in the pooled derivation and validation cohorts was 0.84, with an optimum cut-off of the new score (based on an algorithm simultaneously maximising sensitivity and positive predictive value) at 16. At this cut-off, the sensitivity and specificity in the validation cohort was 84% and 71% respectively. Compared to

the NIHSS score alone (AUC 0.83), the new score performed significantly better, albeit with questionable clinical relevance. The authors therefore concluded that, although other baseline parameters may improve the predictive accuracy of a model based on the NIHSS alone, the gain in clinically meaningful improvement is negligible at the cost of increased complexity. Therefore, models based solely on the NIHSS are to be preferred. This study is interesting, the only one so far incorporating other elements than stroke severity into an LAO prediction model. The main drawback of this model is the complexity, requiring both a full NIHSS assessment in addition to other predictive parameters.

Scheitz et al (295) - This latest publication from the SITS Investigators validated several of the above mentioned scores on SITS data, as well as performed novel investigations into the predictive value of the NIHSS profiles described by Sucharew et al (193) (see section 1.8). This retrospective study was based on 3505 prospectively enrolled patients in the SITS database, with complete NIHSS data and vascular imaging. Median NIHSS of the entire cohort was 9, and large anterior vessel occlusion was detected in 23.6% of the population. One main finding was the graded relationship between all prehospital scores and the NIHSS symptom profiles with LAO, increasing scores in all models associated with higher odds ratios for LAO. In this analysis, the single item most predictive of occlusion was gaze, and addition of gaze to the items of the FAST-score, G-FAST (gaze, facial motor function, arm motor function and speech), significantly improved the model (from AUC 0.645 to 0.722). The previously published prehospital scores, the new G-FAST model and the NIHSS profiles all showed similar predictions as the full NIHSS. The main conclusion of this article was not the superiority of any prehospital scale over another, rather the feasibility of using simplified scales rather than the full NIHSS, as the simplified scales performed similar to the NIHSS. The authors also pointed out how different cut-offs of the scales may serve different purposes in various settings. In some situations, a high specificity cut-off may be desirable, in other cases a high-sensitivity cut-off. These concepts will be discussed in the Discussion section of Study 3.

In conclusion, several models for predicting the likelihood of patients harbouring a large vessel occlusion have been published, however only one to our knowledge has actually been validated in a prehospital setting (292). No globally agreed upon consensus on the optimum method for triage of acute stroke patients to Comprehensive Stroke Centres with endovascular capabilities exists. Part of the stroke community is sceptical towards prehospital triage based on stroke severity, arguing that any threshold, whether on the full NIHSS or a simplified score, will inevitably lead to either futile transfers or missed

opportunities for intervention (298). The last word on LAO prediction has not yet been said, and the final project in this thesis will further investigate possible alternative strategies for identifying this highly important patient group.

2 AIMS

The overall aim of this thesis was to investigate the association between symptom severity in the acute setting of ischaemic stroke and

1) The presence of arterial occlusions and
2) long-term functional outcome assessed with the mRS.

In the final project, conceptually separated from the first 3 studies, we aimed to investigate a novel method for assessing 3-month mRS follow-up after acute stroke.

Prediction of long-term functional outcome in the acute phase may help planning of resource allocation, may serve a role in treatment decisions and may allow for improved patient selection in randomised trials and control of cohort composition in non-randomised trials. To date, several predictive models have been proposed, however no one has yet gained any widespread use. Prediction of large arterial occlusions in acute ischaemic stroke, before vessel imaging has been performed, may have important implications on prehospital triage of patients likely harbouring large arterial occlusions potentially amenable to endovascular intervention.

Routine assessment of long-term functional outcome after stroke is lacking in some settings, and methods for increasing the rate of follow-up are important, especially in circumstances with limited resources and infrastructure.

Based on the above, the following hypotheses were formulated:

Study 1:

1) Threshold values on the baseline NIHSS predict the presence of arterial occlusions in the acute setting of stroke with a sufficient accuracy, and
2) Threshold values on the baseline NIHSS predict long-term functional outcome after acute ischaemic stroke with a sufficient accuracy.

Study 2:

1) THE ASTRAL and DRAGON scores, two already available stroke prognostication models, predict long-term functional outcome with sufficient accuracy in the large SITS-ISTR cohort.

Study 3:

1) NIHSS sub-items together with other clinical parameters predict the presence of large artery occlusions in patients with suspected acute stroke

Study 4:

1) A novel mobile phone-based self-assessment tool of mRS at 3 month after acute stroke is comparable to that in clinical assessments.

3 MATERIALS AND METHODS

Study 1-3 of the present thesis are based on the Safe Implementation of Treatments in Stroke- International Stroke Treatment Register (SITS-ISTR, http://sitsinternational.org).
I will therefore start by giving a short introduction to the background and rationale for this world-wide stroke treatment register.

3.1 THE SITS INTERNATIONAL STROKE TREATMENTS REGISTER

The SITS-ISTR is an international non-profit, internet-based, academic-driven global stroke treatments register, today containing data on close to 140 000 patients from over 70 countries across the world. The SITS registry is coordinated from the Karolinska Stroke Research Unit and represented by the SITS Scientific Committee, SC. The SITS SC provides guidance for the various projects and activities taking place in the organization. Each participating country is represented by one or more National Coordinators, NC, responsible for the SITS-ISTR in the specific country. The NC coordinates and supports participating centres, oversees the regulatory and ethical requirements and has access to complete data from all national centres. Each centre is represented by a local coordinator, LC, an authorized stroke physician responsible for the hospitals stroke unit. Each individual centre owns its own data.
The initiative for the register was sparked in 1996 by the European-Australian randomised stroke thrombolysis trial (ECASS) participants. The register gained a broader international role in 2002, when the EU license for intravenous alteplase in acute ischaemic stroke was approved under the condition that an observational safety study be initiated, SITS-MOST. SITS-MOST recruited 6843 patients between 2002-2006, this pivotal observational study proving the safety of use of iv-tPA within 3h in acute ischaemic stroke (299). SITS-MOST data are embedded within the SITS-ISTR database. Approval for patient-enrolment is obtained in countries that require this; other countries approve the register for conduct as an anonymized audit. Patient data are entered electronically and encrypted in order to preserve patient integrity. Data withdrawals for researchers are provided with individual patients denoted by anonymized case-control numbers according to the structure: [Nation and Centre code] [Date of initial data entry] [Number from 01 and up, in case of several patients being entered by the same centre on the same date].

3.2 STUDY SUBJECTS

3.2.1 Study 1

All patients registered in the SITS-ISTR between December 2002 and March 2013 were considered. In total, 57 213 ischaemic stroke patients with iv-tPA treatment, treated within and outside license criteria, were recorded in SITS-ISTR at 793 centres from 44 countries of whom 94.6% were from Europe. Mean age was 68.2 years, 56.4% men, and median baseline NIHSS score 11. From the entire cohort, data on three-months mRS were available in 44 331 patients (77·5%), and data on baseline vessel occlusions were available in 11 632 patients (20·3%). Exact localization of vessel occlusions was not available, merely the presence/absence of arterial occlusions was stated. Only patients with complete data for all included variables were included in the multivariate models.

3.2.2 Study 2

The same cohort and data-file as in study 1 was used for this study, with the same recruitment period and the same number of patients. Only patients with complete mRS outcome data and with complete data for the ASTRAL and DRAGON scores respectively were entered into the study. A total of 36131 iv-tPA-treated patients with complete data for the ASTRAL score and 33716 iv-tPA-treated patients with complete data for the DRAGON score were included in the respective analyses.

3.2.3 Study 3

The study was based on patients registered in the Safe Implementation of Treatments in Stroke (SITS)- International Stroke Treatment Register (SITS-ISTR) between December 1st 2012 and October 23rd 2015. Only patients with available CT angiography/MR angiography (CTA/MRA) and baseline NIHSS data treated with iv alteplase and/or endovascular thrombectomy were considered. The time period was chosen based on the time of implementation in the database of additional variables for registering detailed information on arterial occlusion site using baseline CTA/MRA. Data for this study were contributed by hospitals which reported specified arterial occlusion sites in at least 20 patients in whom any occlusion was reported as present. This selection of experienced centres was done in order to ensure a high-quality registration of arterial occlusion data. Between 1st December 2012 and 23rd October 2015, 5573 patients with available CTA/MRA data from large-volume centres were registered in the database. After selecting patients with specified anterior circulation occlusion site and clinically defined as anterior circulation strokes in cases of no visible occlusion, 4011 patients remained. Baseline NIHSS (and

complete NIHSS sub-item data) was available in 97% of the study group (3897/4011). Of these, 1896 patients (49%) had a large arterial occlusion, while 2001 patients (51%) had either no occlusion or more distal occlusions.

3.2.4 Study 4

Acute stroke patients (ICD code I61=haemorrhagic and I63=ischaemic) admitted to the Stroke unit at the Karolinska University Hospital– Solna during the period March to May 2014 were consecutively offered participation in the study, regardless of acute interventions or stroke severity. All acute stroke patients were screened during regular working hours (08.00–17.00) and informed about the study and offered participation. The following inclusion criteria were used:

1. Clinical signs and symptoms concurring with a diagnosis of acute stroke.

2. The patient and/or a close relative/caregiver had an available compatible mobile phone.

3. The patient received an ICD diagnosis of either I.61 (haemorrhagic) or I.63 (ischaemic) at discharge.

The following exclusion criteria were used:

1. Clinical signs and symptoms concurring with a diagnosis of transient ischaemic attack.

2. Neither the patient nor a close relative/caregiver had an available compatible mobile phone.

During the study period, 74 patients fulfilled study inclusion criteria. 12 patients declined participation and 11 patients dropped out after inclusion for personal reasons. 3 included patients died. 48 patients completed the entire study, completing both outcome assessments. The mean age of the final 48 patients completing the study was 67 years, 37.5% were female, median baseline NIHSS score was 5 (interquartile range [IQR] 2–10.5, range 0–23), and 12.5% patients had a haemorrhagic stroke.

3.3 STUDY DESIGN

3.3.1 Studies 1-3

The first 3 studies which are based on SITS data are observational. In all iv-tPA/thrombectomy-treated patients in SITS, data was collected at 0 h (baseline), 2 h, 24 h and 7 days post-treatment. Brain imaging (CT and/or MRI) performed at baseline and at 22-36 h was required in all patients. Additional imaging, such as CT/MR-angiography, was optional and could be added if available. Functional evaluation using the mRS was performed at 3 months. Figure 25 gives an overview over the standard time points of data gathering and outcome assessment in SITS-ISTR.

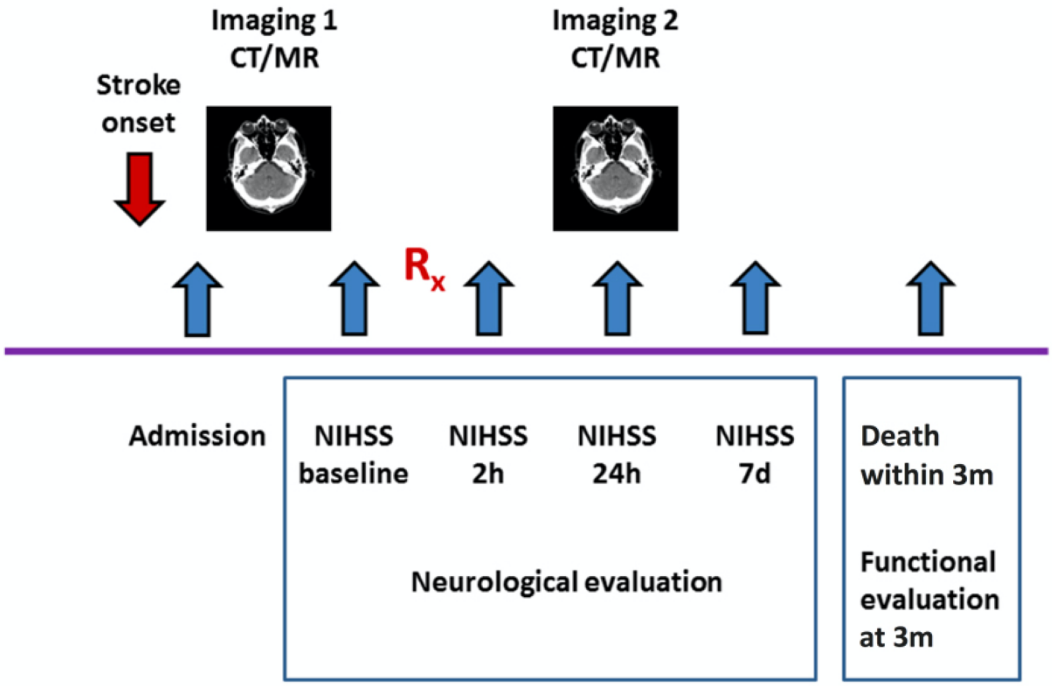

***Figure 25**. Overview of the time-line for data gathering in SITS-ISTR. Rx denotes the acute intervention (iv-tPA and/or thrombectomy).*

3.3.2 Study 4

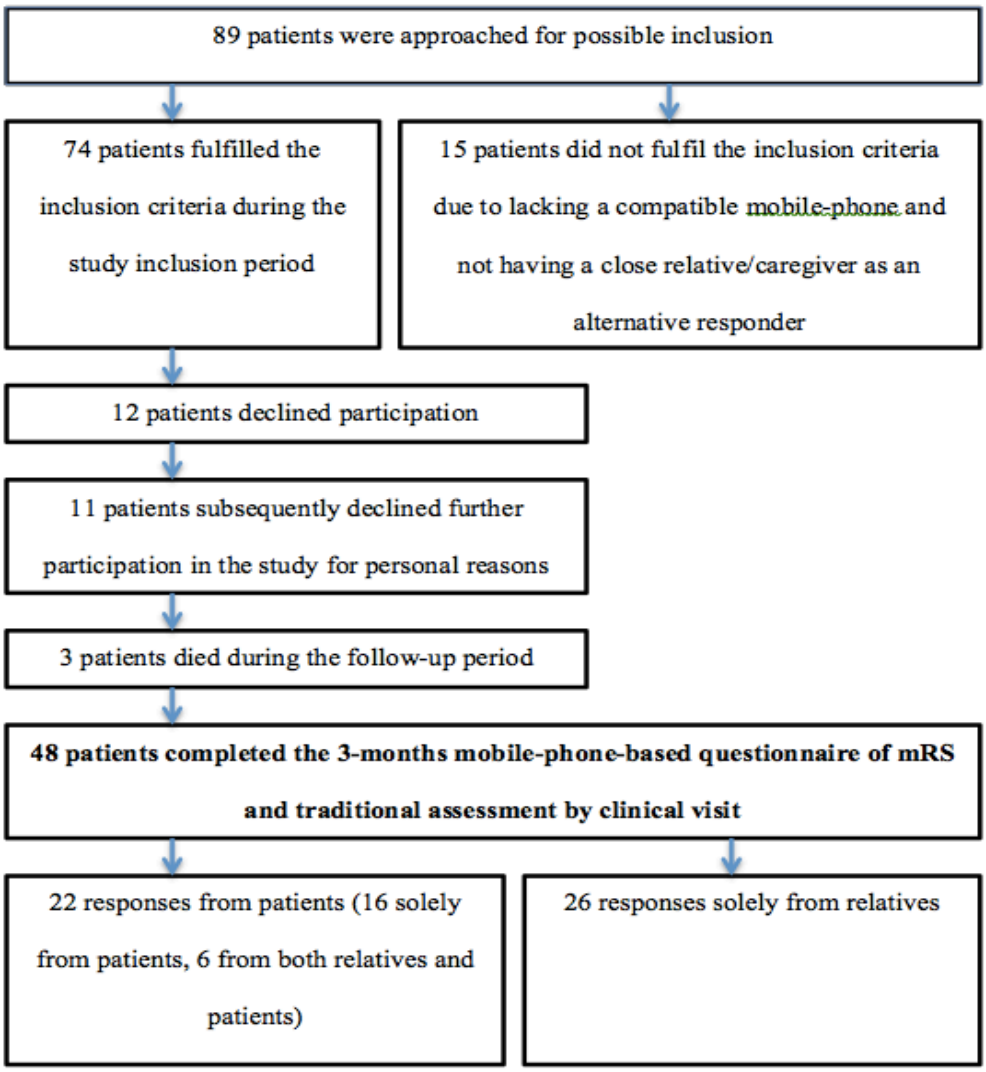

***Figure 26**. Flow chart of patient inclusion in study 4. Reproduced from Cooray et al, Circulation: Cardiovascular quality and outcomes 2015 (138). Permission for use not required.*

A flow chart depicting the process of selecting the final study cohort is shown in Figure 26. Acute stroke patients were consecutively offered participation in the study. If included, the mobile phone application (MA) was installed on the patient's personal mobile phones. In cases where the patients could not participate themselves, we included a close relative/caregiver who would answer in the patient's place. All study participants were equipped with an instruction sheet containing detailed instructions on how to answer the mobile phone based mRS questionnaire. During the follow-up period, the study participants were reminded about participation in the study through automatic monthly messages in MA. No instructions were given regarding the questions to be answered in the

MA, apart from the written instructions sheet. Within a week after answering the questionnaire, a blinded mRS-certified study personnel rated the patients with a clinical visit mRS assessment. This assessment was performed in 2 parts. The first part consisted of a conventional unstructured interview followed by a second part, where the RFA questionnaire was used in a standard structured manner. An overall assessment of the interview taking into account both parts of the interview was done, and the patients assigned an mRS score by the first rater. The entire interview was filmed and subsequently judged by a second blinded study personnel. The second rater, however, also rated the 2 parts of the interview separately, generating scores for the 2 parts of the interview separately in addition to an overall interview score. In cases where the first 2 raters ranked the patient differently on the overall interview, a 3rd rater viewed the footage, and in collaboration with the first 2 raters assigned a final score. Participants' mobile phone–based questionnaire responses were translated to an mRS score using a predefined protocol. In cases where both patient and relative/caregiver sent in MA responses and 2 different mRS scores were obtained for a certain patient, patient scores were used in the subsequent statistical analysis. During the study period, no technical problems were reported, and responses from the study participants were received smoothly after encryption and stored securely. The mobile phone questionnaire responses were first opened after final adjudication of the clinical visit assessment score.

3.4 DATABASE VARIABLES IN SITS

With a few exceptions, most qualitative data were entered in a binary form, registering presence/absence of the variable in question. Ordinal or continuous variables were entered as their respective numerical value. An option for entering "unknown" distinct from "missing" was possible. Demographic characteristics included gender, age, country of origin and centre-code. Past medical history included hypertension, atrial fibrillation, congestive heart failure, hyperlipidemia, smoking (current or previous), history of previous stroke and pre-stroke functional status as measured by the mRS. Current medication at stroke-onset included antihypertensive treatment, aspirin, dipyridamole, clopidogrel, any other antiplatelet, statins and anticoagulants. Time-points recorded were time of stroke onset, time to admission, time to imaging, time to treatment with related time-intervals. Laboratory values included blood glucose prior to treatment and serum cholesterol. Thrombolysis-specific data included patient's weight and dose of alteplase. Treatments during the hospital stay, including antiplatelet therapy, anticoagulants and antihypertensive medications, were registered at discharge. NIHSS (with complete breakdown into sub-items) were registered at admittance, 2h, 24h and 7 days. Systolic and diastolic blood pressure was recorded at the same time-points.

CT and/or MRI at baseline and 22-36 h post-treatment was mandatory, and recorded imaging variables at baseline included information on the presence/absence of dense-vessel sign and early infarct signs. At 22-36 h, presence/absence of the dense vessel sign, early infarct changes, intracerebral haemorrhage and cerebral oedema were registered. Optional imaging findings such as CT/MR-angiography was possible to register. Up until December 2012, only a simple option ticking in the presence or absence of a vascular occlusion, without information on vascular occlusion site, was available. In December 2012, additional variables for registering detailed information on arterial occlusion site using baseline CTA/MRA were implemented.

3.5 OUTCOME VARIABLES

3.5.1 Study 1

The outcomes were functional independency at three-months measured by mRS scores 0–2 and presence of baseline vessel occlusion diagnosed with CT/MR angiography (registered as presence/absence of arterial occlusion, site not specified). All assessments of imaging studies and neurological status were done according to clinical routine at centres participating in the SITS-ISTR. All imaging scans and vessel occlusions on CT/MR angiography were evaluated locally.

3.5.2 Study 2

Functional dependency and death at 3 months measured by mRS scores of 3 to 6 was the main outcome used in the development of both the ASTRAL and DRAGON scores.

3.5.3 Study 3

Main outcome was presence of an anterior circulation large arterial occlusion. Arterial occlusion was defined as a complete occlusion or less than 50% filling of the affected vascular territory on CTA/MRA. LAO in the anterior circulation was defined as occlusion of any segment of the internal carotid artery, carotid terminus or the M1 branch of the middle cerebral artery. Patients harbouring posterior circulation occlusions were not included in the analysis. In cases where more than one arterial segment was reported as being occluded, the most proximal vessel was registered for the analysis. The control population was defined as patients with no occlusions or with more distal occlusions. In order to ensure that patients registered as having no occlusions were clinically suffering from anterior circulation infarction, only patients specifically registered as suffering from an anterior circulation syndrome were included in the analysis. All assessments of imaging studies were done according to clinical routine at centres participating in the SITS-ISTR, and no central assessment of imaging data was performed.

3.5.4 Study 4

The main outcome measure was the 3 month mRS score, comparing the overall clinical assessment of the mRS with the mRS derived from the mobile phone-questionnaire. In cases where both patient and caregiver answered the mobile phone questionnaire, patient answers were used in the main outcome analysis. Secondary outcomes included comparison of the mRS score derived from the clinical structured-interview with the mRS derived from the mobile phone-questionnaire.

3.6 STATISTICS

3.6.1 Study 1-3

Descriptive statistics for baseline, demographic, and imaging data were performed, comparing groups of patients in accordance with the purposes of each respective study. Proportions were calculated for categorical variables, dividing the number of events with the total number excluding missing/unknown cases. Medians were calculated for continuous variables. For calculation of statistically significant differences between proportions, we used the χ^2 method, for medians, we used the Mann–Whitney *U*-test, and for means we used the Student t-test. To adjust for baseline differences between the various comparator groups in the three first studies, multivariate binary logistic regression was subsequently performed. In all three studies, area under the curve (AUC) using Receiver Operating Characteristics (ROC) analysis were used to assess the discriminative performance of predictive models. Sensitivities, specificities, positive predictive values, negative predictive values and likelihood ratios were given where relevant. In study 2, calibration was assessed by plotting observed outcome against predicted outcome. In study 3, for each model we assessed the sensitivity and specificity for LAO at three different cut points: at an optimal cut-point maximising the Youden index, at a cut-point maximising the specificity (as close to 80% as possible) and at a cut-point maximising the sensitivity (as close to 80% as possible). In study 1, statistical analysis was performed in IBM SPSS Statistics 15.0 ®, and in studies 2 and 3 Stata 14.1® was used.

3.6.2 Study 4

The main outcome measure was the weighted kappa score (quadratic). Unweighted kappa scores were also calculated. In addition, unweighted kappa scores were calculated for various dichotomizations of the mRS. Following standard convention, a kappa of 0 to 0.2 was considered poor, 0.21 to 0.4 fair, 0.41 to 0.6 moderate, 0.61 to 0.8 good, and 0.81 to 1.00 excellent. Percentage agreement was calculated as well. All responses from study participants were compared with the overall clinical visit mRS assessment, as well as with the structured assessments separately. We also performed analysis for discrepancies between the first and second ratings.

Statistical analysis was performed in IBM SPSS Statistics 15.0 ®, and Medcalc® statistical software.

4 RESULTS

4.1 STUDY 1

In this study, 57 213 patients treated with iv-tPA from 793 centres in 44 countries recorded in the database were considered, 94·6% from Europe. Mean age was 68 years, median baseline NIHSS score 11 and 56.4% men. Data on baseline vessel occlusions were available in 20% of the patients (11 632 patients) and 3-months mRS data were available in 78% of patients (44 331 patients).

The calculated area under the curve (AUC) for predicting functional independency (mRS 0-2) from baseline NIHSS score was 0.775. The optimal cut-off value for baseline NIHSS was estimated at 12 (73.4% specificity, 69.4% sensitivity, 75.0% NPV and 67.7 % PPV). ROC analysis on the anterior sub-cohort resulted in an area under the curve of 0.78 (specificity 73.16% and sensitivity 70.96 %). ROC analysis in the posterior subcohort resulted in an AUC of 0.734 (specificity 80.15% and sensitivity 53.80%). In Figure 27, adjusted odds ratios (aOR) for functional independency are shown as a function of baseline NIHSS scores. With increasing baseline NIHSS, aORs for functional independency decreased. The aOR for functional independency was 0.07 (CI 95% 0.05–0.11) at NIHSS score 12 when compared with NIHSS 0.

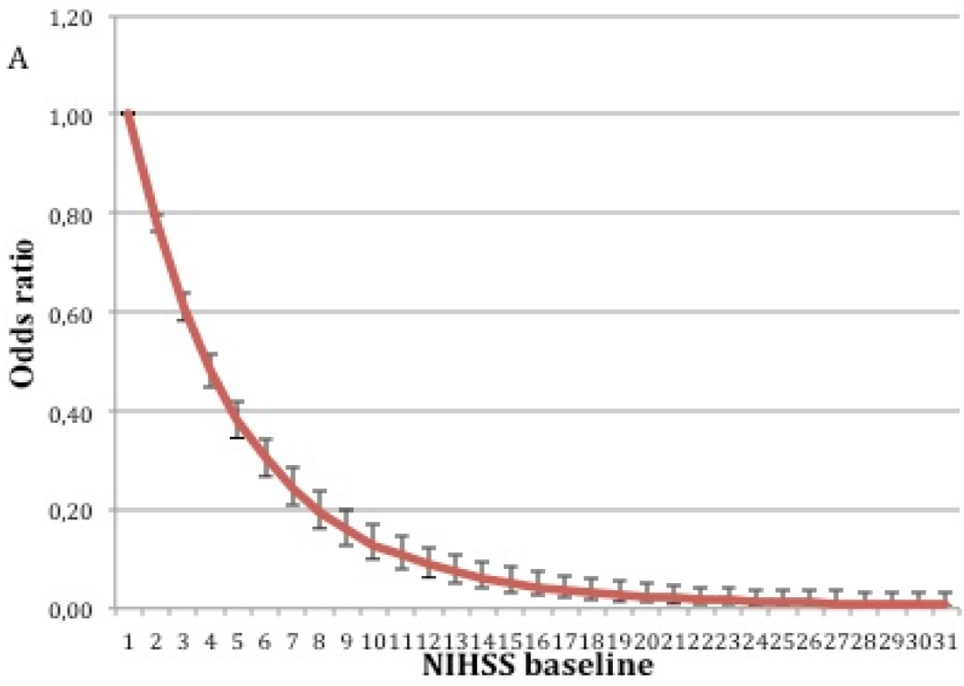

Figure 27. *Odds ratios for functional independency, multivariately adjusted with 95% confidence intervals (vertical bars). Reproduced from Cooray et al, 2015 (287). Permission for use not required.*

The calculated AUC for prediction of baseline vessel occlusion from baseline NIHSS score was 0.678. The optimal cut-off value for baseline NIHSS was 11

(64.4% specificity, 64.5 % sensitivity, NPV 65.3% and PPV 63.6%). Adjusted ORs for baseline vessel occlusion for the spectrum of baseline NIHSS scores are shown Figure 28. With increasing baseline NIHSS scores, aORs for baseline arterial occlusions increased. Comparing patients with NIHSS score 11 with NIHSS score 0, a 3.3 times increased risk of baseline occlusion was seen.

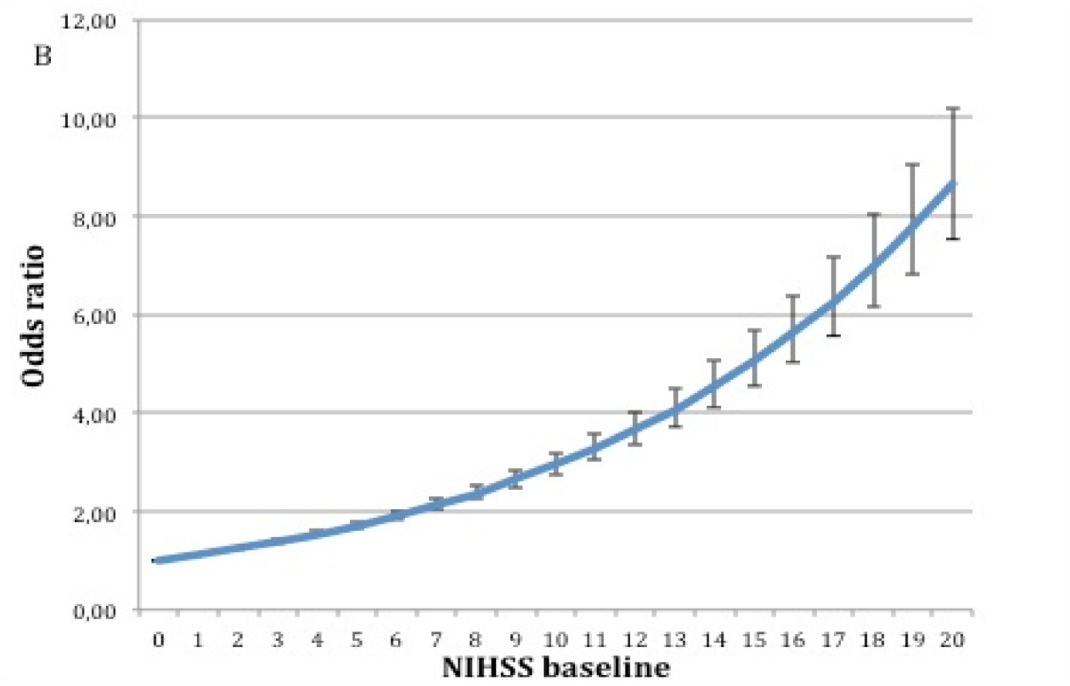

Figure 28. *Odds ratios for baseline vessel occlusion, multivariately adjusted with 95% confidence intervals (vertical bars). Reproduced from Cooray et al, 2015 (287). Permission for use not required.*

The patients with arterial occlusions had significantly lower rates of functional independency as compared to the patients without, independently of the NIHSS score. Considering patients with an NIHSS >12, the presence of a vessel occlusion led to an approximately 40% lesser chance of functional independency at 3-months compared to non-occluded patients. These results held strong after multivariate adjustment. Figure 29 shows the aORs for functional independency at 3-months between patients with and without vessel occlusion as per baseline NIHSS strata.

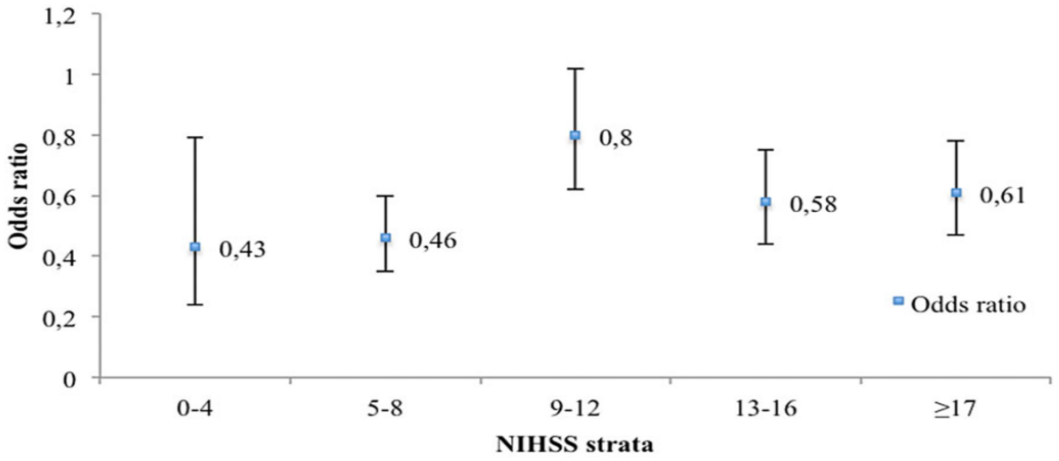

***Figure 29**. Odds ratio for functional independency, comparison between patients with and without baseline occlusion for different NIHSS strata (reference group patients without occlusions). Multivariately adjusted with 95% confidence intervals (vertical bars). NIHSS, National Institutes of Health Stroke Scale. Reproduced from Cooray et al, 2015 (287). Permission for use not required.*

The final important finding in the first study was the time-dependence of NIHSS thresholds for predicting both vessel occlusion and 3-months functional outcome. Comparing the cut-offs in patients undergoing imaging within 2-3 hours after symptom onset with subjects scanned within the 1st hour, thresholds were 1p lower for functional independency and 2p lower for vessel occlusion in the later time-windows, see Table 6 (300).

Onset to Scan time (min)	Baseline NIHSS cut-off for 3-m functional independency (number of patients)	Baseline NIHSS cut-off for baseline occlusion (number of patients)
0-60	12 (6574)	12 (1732)
61-120	12 (23225)	11 (5784)
121-180	11 (10931)	10 (2756)
181-270	9 (2607)	10 (838)

Table 6. Variations in baseline NIHSS thresholds for three-month functional independency and baseline occlusion and median NIHSS for patients withand without vessel occlusions depending on time from stroke onset to imaging. Reproduced from Cooray et al, 2015 (287). Permission for use not required.

4.2 STUDY 2

A total of 36131 iv-tPA-treated patients with complete data for the ASTRAL score and 33716 iv-tPA-treated patients with complete data for the DRAGON score form the base for this study. Only patients with complete data for the respective score, with complete outcome data, and fulfilling the original inclusion criteria for the respective score cohort were included.

ASTRAL

The mean age (68 vs. 68 years), the proportion of female patients (42% vs. 43%) and the mean baseline glucose (7.1 vs. 7.1. mmol/L) were similar between the SITS and the ASTRAL cohorts. The mean stroke severity in the SITS-ISTR cohort was NIHSS 12 compared to 9 in the ASTRAL cohort. The onset-to-arrival time on average was lower (82.2 versus 395.8 minutes) in the SITS-ISTR cohort compared to the ASTRAL cohort. The AUC-receiver operating characteristic value for functionally dependent outcome (mRS 3–6) of the ASTRAL score on the SITS-ISTR cohort was 0.790 (95% CI 0.786–0.795). A calibration plot comparing predicted vs observed percentage functional dependence (mRS 3-6) is seen in Figure 30. The largest discrepancy between the observed and the predicted proportion of functional dependency, over the entire range of score points, was acceptable at 11%, i.e. the maximum vertical distance between the predicted outcome line and the actual outcome line. ASTRAL underestimated the proportion of functional dependency in scores <40, and overestimated the proportion of functional dependency in scores >40. With increasing score cut-offs on the ASTRAL score, an increasing likelihood ratio for functional dependency is seen.

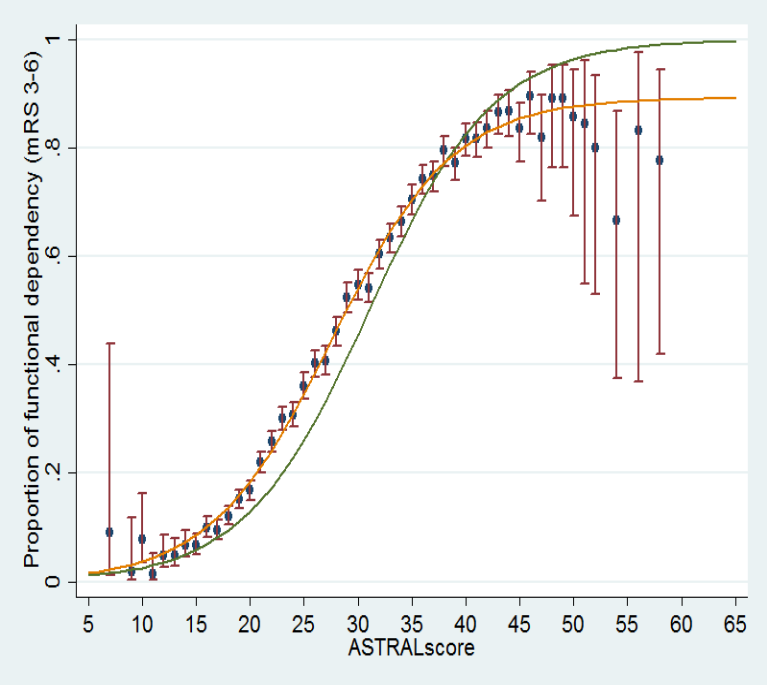

Figure 30. *Calibration plot displaying the observed proportion of functionally dependent patients in SITS (dots) with 95% CI (vertical lines) as a function of the ASTRAL score; the green curve shows the predicted outcome according to the ASTRAL score, the yellow curve shows the best fitting logistic model depicting the actual observed outcome in the SITS cohort. Reproduced from Cooray et al, 2016 (251). Permission for use not required.*

DRAGON

The median age was 70 vs. 69, the proportion of female patients 43% vs. 45%, and the median baseline blood glucose 6.5 vs. 6.6 mmol/L in the SITS-ISTR population compared to the DRAGON derivation cohort. Median stroke severity in the SITS cohort was NIHSS 12 compared to 9 in the DRAGON cohort. The proportion of patients with a dense vessel sign on first non- contrast CT scan was only marginally different between the 2 groups (19.9% vs 17.7% in SITS and DRAGON cohorts respectively). However, proportions of early infarct signs differed more significantly (16.5% in the SITS cohort versus 30.6% in the DRAGON cohort).

The AUC-receiver operating characteristic value for functionally dependent outcome (mRS 3–6) of the DRAGON score on the SITS-ISTR cohort was 0.77 (95% CI 0.769–0.779). A calibration plot comparing predicted vs observed percentage functional dependence (mRS 3-6) is seen in Figure 31. The largest discrepancy between the observed and the predicted proportion of functional dependency, over the entire range of score points was close to 17%. The DRAGON score generally overestimated the proportion of functional dependency.

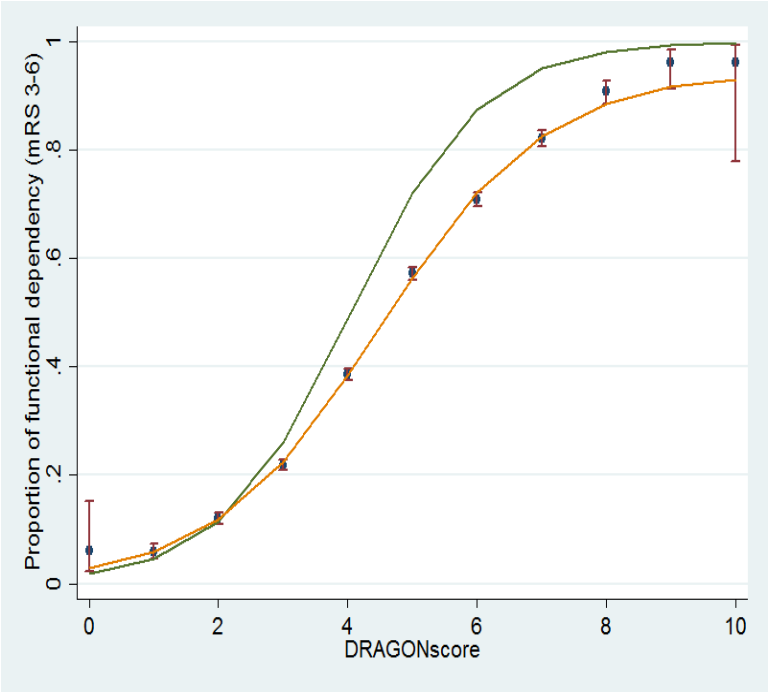

Figure 31. *Calibration plot displaying the observed proportion of functionally dependent patients in SITS (dots) with 95% CI (vertical lines) as a function of the ASTRAL score; the green curve shows the predicted outcome according to the ASTRAL score, and the yellow curve shows the best fitting logistic model depicting the actual observed outcome in the SITS cohort. Reproduced from Cooray et al, 2016 (251). Permission for use not required.*

With increasing DRAGON score cut-offs, decreasing positive likelihood ratios for functional independency are seen (data given in original article).

4.3 STUDY 3

A total of 5573 patients with available CTA/MRA data from large-volume centres were extracted from the database, registered between 1st December 2012 and 23rd October 2015. After selecting patients with specified anterior circulation occlusion site and clinically defined as anterior circulation strokes in cases of no visible occlusion, 4011 patients remained. Baseline NIHSS was available in 97% of the study group (3897/4011). Of these, 1896 patients (49%) had a LAO, 2001 patients (51%) had either no occlusion or more distal occlusions. Patients with and without LAO differed regarding several baseline variables, however not to any larger extent although being statistically significant. The most notable difference between LAO and non-LAO patients was in the total baseline NIHSS score at 16 versus 8 respectively. Higher systolic blood pressures were seen in non-LAO patients as well as a higher prevalence of atrial fibrillation in LAO patients.

Table 7 shows the most predictive models with increasing number of included sub-items.

Model		**Optimum Youden cut-off**		**High specificity cut-off**		**High sensitivity cut-off**	
	AUC (adjusted)	Sens (adjusted)	Spec (adjusted)	Sens (adjusted)	Spec (adjusted)	Sens (adjusted)	Spec (adjusted)
NIH item 5	0.72(0.74)	69(68) *(NIHSS 5 ≥ 3)*	70(72) *(NIHSS 5 ≥ 3)*	55(55) *(NIHSS 5 = 4)*	79(80) *(NIHSS 5 = 4)*	79(81) *(NIHSS 5 ≥ 2)*	55(53) *(NIHSS 5 ≥ 2)*
NIHSS item 5 + NIHSS item 2	0.75 (0.76)	70(72)	71(71)	64(59)	76(80)	78(80)	61(58)
NIHSS item 5 + NIHSS item 2 + NIHSS item 4	0.76(0.76)	68(70)	74(73)	60(61)	80(80)	81(80)	57(59)
NIHSS item 5 + NIHSS item 2 + NIHSS item 4 + NIHSS item 3	0.76(0.77)	65(72)	77(72)	57(61)	82(80)	80(81)	59(59)
Full-item NIHSS	0.78 (0.78)	72(74)	72(72)	62(64)	80(80)	81(80)	59(60)
Total NIHSS score	0.76 (0.77)	67(73)	75(70)	57(61)	81(80)	79(79)	60(59)
NIHSS item 5 + NIHSS item 6	0.73(0.75)	68(67)	72(73)	58(58)	79(80)	80(81)	53(53)

Table 7*. Sensitivity and specificity for predicting LAO for various models at optimum cut-off, high specificity cut-off and high sensitivity cut-off. Numbers in parenthesis are multivariately adjusted values, adjusting for baseline systolic blood pressure, prestroke modified Rankin Score, previous stroke and baseline treatment with Aspirin. For the 1-item model including sub-item 5, arm function, we have in italics given the respective sub-item cut-off for the three sensitivity/specificity scenarios. NIHSS item 2 = gaze; NIHSS item 3 = visual fields; NIHSS item 4 = facial motor function; NIHSS item 5 = arm motor function; NIHSS item 6= leg motor function.*

Four predictors other than NIHSS score remained significantly associated with the outcome in the multivariate models and were thus adjusted for, the numbers

given in parentheses. These additional predictors were: baseline systolic blood pressure, pre-stroke modified Rankin Score, previous stroke and baseline treatment with Aspirin.

The 1-item model associated with the highest AUC (0.720) included solely NIHSS sub-item 5, arm motor function. The optimum Youden cut-off (NIHSS item 5 ≥ 3) resulted in a sensitivity and specificity of 69% and 70% respectively, patients above the cut-point presenting with median NIHSS 17 (IQR 14-21) and below the cut-point presenting with median NIHSS 7 (IQR 5-10). At the high-specificity cut-off (NIHSS item 5= 4) a sensitivity and specificity of 55% and 79% respectively was seen, patients above the cut-point presenting with median NIHSS 18 (IQR 15-21) and below the cut-point presenting with median NIHSS 8 (IQR 5-12). The high sensitivity cut-off (NIHSS item 5 ≥ 2) resulted in a sensitivity and specificity of 79% and 55% respectively, patients above the cut-point presenting with median NIHSS 16 (IQR 12-20) and below the cut-point presenting with median NIHSS 6 (IQR 4-8). The full-item model resulted in an AUC of 0.775. The optimum Youden cut-off yielded a sensitivity and specificity of 72% and 72%, at the high-specificity cut-off a sensitivity and specificity of 62% and 80% was seen, and the high sensitivity cut-off resulted in a sensitivity and specificity of 81% and 59%. Figure 32 shows the area under the curve for LAO comparing the most predictive 1-item, 4-item and full-item models.

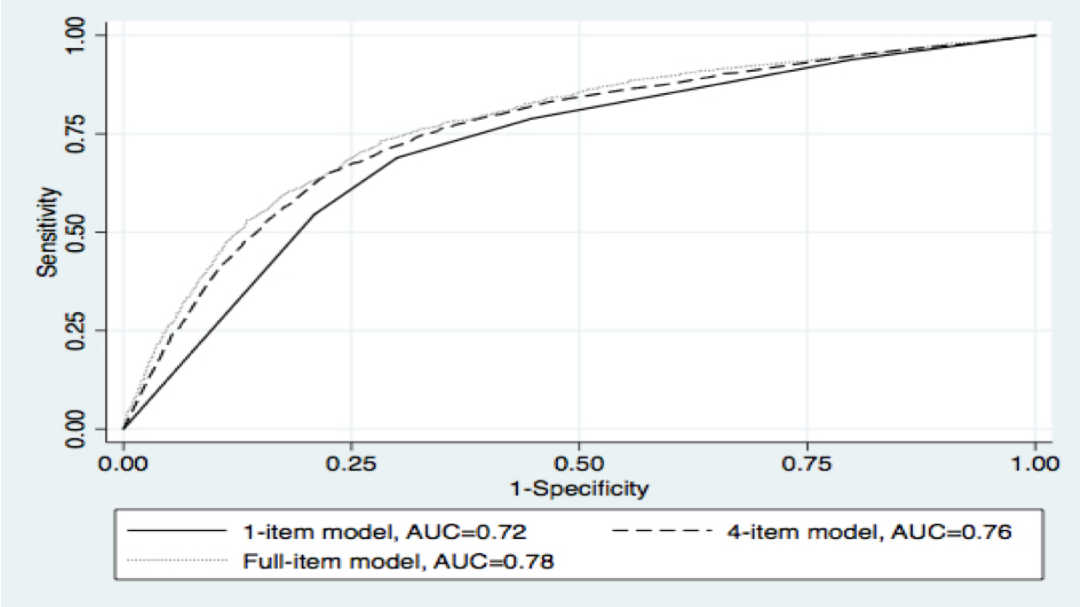

***Figure 32**. Area under the curve (AUC) for predicting LAO, comparing the most predictive NIHSS 1-item, 4-items and full-items models. The 1-item model included NIHSS sub-item 5 (arm function), the 4-item model included sub-items 2, 3, 4 and 5 (gaze, visual fields, facial and arm motor function. The full-item model included all NIHSS sub-items.*

4.4 STUDY 4

The mean age of the 48 patients completing the study was 67 years, 37.5% were female, median baseline NIHSS score 5 (interquartile range [IQR] 2–10.5, range 0–23). A total of 12.5% patients had a haemorrhagic stroke. Among the patients lost to follow-up (dropouts because of personal reasons), the mean age was 69, 63.6% were female, median baseline NIHSS score was 4 (IQR 3–7.5, range 1–14), and 1 patient had a haemorrhagic stroke. The mean follow-up-time was 90.2 days (SD 3.9 days).

Table 8 shows a summary of the agreement between clinical mRS assessment and MA mRS assessment for the overall and structured assessments, respectively.

	Overall clinical assessment vs MA			**Structured assessment vs MA**		
	Percentage agreement	Weighted kappa	Unweighted kappa	Percentage agreement	Weighted kappa	Unweighted kappa
Entire range of scores (0-5) excluding dead patients	62.5%	0.89 (0.82-0.96)	0.53 (0.36-0.70)	64.6%	0.89 (0.82-0.96)	0.56 (0.39-0.72)
Entire range of scores (0-6) including dead patients	64.7%	0.92 (0.86-0.97)	0.57 (0.41-0.73)	66.7%	0.92 (0.87-0.97)	0.59 (0.44-0.75)
mRS 0-2 vs 3-5	83.3%	-------	0.66 (0.45-0.87)	87.5%	-------	0.74 (0.56-0.93)
Patient vs MA	72.7%	0.82 (0.70-0.94)	0.59 (0.33-0.85)	72.7%	0.81 (0.67-0.95)	0.58 (0.32-0.85)
Caregiver vs MA	59.4%	0.86 (0.76-0.96)	0.51 (0.30-0.71)	62.5%	0.87 (0.77-0.96)	0.55 (0.35-0.75)

Table 8. *Overall and structured assessment vs Mobile phone application (MA). Reproduced from Cooray et al, 2016 (138). Permission for use not required.*

In 30/48 patients, the mRS scores concurred perfectly (total agreement 62.5%). Of the remaining 18 patients, scores differed by 1 level in 16 patients and by 2 levels in 2 patients. The weighted kappa was 0.89 (95% CI 0.82–0.96), and the unweighted kappa was 0.53 (95% CI 0.36–0.70). Results were similar comparing the structured RFA judgement with the MA mRS assessment. Percentage agreement dichotomizing independent from dependent functional level (mRS 0–2 versus 3–5) was 83.3%, and the unweighted kappa score was 0.66 (0.45 to 0.87). In table 9, a cross-tabulation summarizes the percentage agreement and unweighted kappa for all possible dichotomizations.

		Clinician assessment score (mRS)					
		0	**1**	**2**	**3**	**4**	**5**
Mobile phone based assessment-Score (mRS)	**0**	2	1				
	1	1	9	2			
	2		2	7	2		
	3		2	4	4	1	
	4				1	2	1
	5					1	6

Table 9. *Cross tabulation of paired ratings. Reproduced from Cooray et al, 2016 (138). Permission for use not required.*

The percentage agreement between the 2 raters´ was 79% (38/48; the maximum disagreement was 1 score level), weighted kappa 0.95 (95% CI 0.92–0.99), and unweighted kappa 0.74 (95% CI 0.59–0.88).

5 DISCUSSION

5.1 STUDY 1

There is a well-established association between baseline stroke severity measured on the NIHSS and arterial occlusions in the acute setting of ischaemic stroke (58, 285, 56). Likewise, the predictive value of the NIHSS in predicting long-term functional outcome after acute ischaemic stroke is firmly established (145, 139, 185, 186, 161, 187, 188). Although several studies have reported NIHSS thresholds for predicting baseline vessel occlusion, a large heterogeneity in the presented thresholds is seen. Moreover, studies examining specific NIHSS thresholds for predicting long-term functional outcome in iv-tPA treated patients are scarce. Most importantly, to our knowledge, no study so far has simultaneously studied and presented thresholds for predicting both the presence of arterial occlusions as well as poor long-term functional outcome. The major findings from this study were that NIHSS thresholds predicted the presence of arterial occlusions and long-term functional outcome with a fair and moderate discrimination respectively. NIHSS thresholds of 11 (AUC 0.68) and 12 (AUC 0.78) were optimum for predicting the presence of arterial occlusions and long-term functional dependency in this study material. These optimum thresholds were derived using ROC-analysis, and further strengthened by odds ratio calculations derived after multivariate adjustment. Comparing patients with NIHSS=12 and NIHSS=0, a 10-fold reduction in the chance of a favourable outcome (mRS 0-2) was seen in patients with NIHSS 12. Comparing patients with a NIHSS 11 and NIHSS 0, a 3-fold increase in the risk of an arterial occlusion was seen in patients with NIHSS 11.

NIHSS thresholds for predicting the presence of cerebral arterial occlusions have been presented previously. These studies found varying optimal NIHSS cut-offs for predicting cerebral arterial occlusion, one study encompassing all arterial occlusions when setting the NIHSS cut-off at 15 (58), another study detecting 80% of occlusions with an NIHSS cut-off at 16 (57). One study found the best compromise of sensitivity and specificity for prediction of any arterial occlusion at an NIHSS cut-off of 10 (285), another study showed a PPV of 91% at NIHSS cut-off 12(56). Important limitations of these studies were relatively small sample sizes, ranging from 35 (58) to 226 (56), as well as a high average stroke severity (median and mean NIHSS around 14). Our study is the largest study so far obtaining NIHSS thresholds for predicting arterial occlusions, and our median NIHSS was lower than that of several previous studies which included more selected patient populations. To our knowledge, only one previous study is based on a comparatively large cohort (n = 1603), presenting a favourable predictive

value of the NIHSS (baseline NIHSS>9 predicting arterial occlusion in the anterior circulation within 3-hours after symptom onset with a PPV of 86.4%) (51). Our study found a lower predictive value (baseline NIHSS>11 predicting arterial occlusion within 3-hours after symptom onset with a PPV of 63.9 %), possibly explained by our inability of separating distal from proximal occlusions.

Few studies have specifically examined NIHSS threshold values for predicting functional outcome in patients with acute stroke, presenting optimum cut-offs for predicting long-term unfavourable functional outcome at NIHSS scores of 13, 15 and 17 (145, 194, 195). Importantly, patients in these studies were not treated with iv-tPA. Regarding iv-tPA treated patients, one smaller study (108 patients) did not find a good predictive value (AUC 0·634) of the baseline NIHSS in predicting poor functional outcome (196). Patients in that study had a higher stroke severity (median NIHSS 17), and excluded patients with NIHSS ≤ 7 as well as absence of occlusion on MR angiography. Our results are more representative of the average stroke thrombolysis patient examined in the acute setting.

Regarding ORs for 3-months favourable outcome (mRS 0-2) in specified NIHSS strata, patients with arterial occlusions in general had poorer outcome compared to patients without, irrespective of NIH strata. Comparing the occluded with the non-occluded patients in NIHSS strata 13-16, a more than 40% reduction in functional independency (after multivariate adjustment) was seen in the occluded subgroup compared to the non-occluded subgroup. A smaller study based on 72 patients has previously compared an 8-point increase in the baseline NIHSS with the presence of a large arterial occlusion, both carrying a similar prognostic value for functional dependency (OR 4·68). Our findings from a subgroup analysis confirm the independent predictive value of baseline arterial occlusions for predicting a poor functional outcome.

One interesting finding from this study was the lowering of NIHSS thresholds for both predicting arterial occlusions as well as long-term functional outcome with increasing time from stroke onset to imaging. Regarding arterial occlusions, this may be explained by improved collateral blood-flow following occlusion, as well as some degree of spontaneous yet partial recanalization. The movement of a proximal thrombus to a more distal vessel may also play a role. The time dependence of NIHSS thresholds for predicting 3-months favourable outcome (mRS 0-2) may be explained by an accelerating transformation from penumbra to infarct, each NIHSS level bearing a worse prognosis due to less reversibility of the underlying ischaemia. This time dependency has previously been shown for NIHSS thresholds predicting arterial occlusions (51, 52), however to our knowledge this has not been shown regarding prediction of long-term functional outcome.

To conclude, we propose that patients with NIHSS levels above our cut-offs need to be identified, especially when vessel imaging is not available, as these patients show both a higher rate of arterial occlusions as well as a lower rate of a favourable 3-months outcome despite iv-tPA. Considering the time-dependency of the procured thresholds, a NIHSS score threshold of 9 or 10 may be considered for immediate referral to tertiary centres with endovascular capabilities.

5.1.1 Study limitations

Our results are based on a large cohort of patients from over 40 different countries, and should therefore be generalizable to clinical practice across various demographics and geographies. However, it is based on a retrospective and explorative analysis of observational data, with all the limitations of this type of study design. Important drawbacks of register based studies include difficulties in ascertaining unbiased reporting, lack of confounder information, absence of important data, loss to follow up and variations in coding between persons and institutions.

Multivariate adjustment for differences in demographics and patient characteristics may not account for all imbalances. The amount of missing data for 3 month follow-up of the mRS (22.5%) may carry a bearing on our results. Another important limitation is the absence of specified site of vascular occlusion in our dataset, the pooling of proximal and more distal occlusions may have influenced the results of this study. Further, angiography data were only available in a subgroup of the patient population, probably resulting in inherent bias due to a highly-selected subgroup. Important to note however, the size of our patient cohort as well as the representation of general stroke patients from nearly 800 centres from different geographical locations, increases the generalizability of our results.

5.1.2 Post-publication developments

The ground-breaking randomised trials proving the benefit of endovascular thrombectomy in anterior acute ischaemic stroke with LAO were presented and published after the submission of this article to the International Journal of Stroke. Although endovascular treatment in AIS was performed in selected tertiary centres already prior to these trials, their results settled a controversy, in part due to previous negative studies, regarding the benefits of this new treatment modality. In light of this, the importance of identifying patients likely harbouring vessel occlusions amenable to endovascular intervention is further made more evident, and the results of this study add important knowledge for this identification. A major limitation of the present study was the inability to separate proximal arterial occlusions amenable to endovascular treatment from

more peripheral occlusions. After the publication of this paper, a German group attempted to replicate our results on a single-centre thrombolysis cohort, where site of occlusion was specified. They found a similar threshold as our study, NIHSS≥10, for predicting proximal vessel occlusion (AUC 0.77, sensitivity 76·3%, specificity, 76·5%, NPV 81·5% and PPV 70·5%) (301), confirming our findings. A Danish study published at the same time as this study presented the results from their unselected cohort of acute ischaemic stroke patients evaluated within 4.5h, and found NIHSS≥7 as the best cut-off for prediction of arterial occlusion in the anterior circulation within 4.5h (59). The median NIHSS in this cohort was substantially lower than in our cohort (NIHSS 10 in occluded patients and 3 in patients without visible occlusions), in line with the unselected nature of this cohort. This study included more peripheral cerebral artery occlusions (M2, ACA) in the definition of arterial occlusion, in contrast to the mentioned German study which only included more proximal occlusions. The more selective definition employed in the German study is in line with the inclusion criteria of the majority of the newly published RCTs on endovascular thrombectomy in AIS.

5.2 STUDY 2

This study is to date the largest external validation attempt of ASTRAL and DRAGON, the 2 most recent outcome prediction scores in acute stroke. Extensive validation is a prerequisite for clinical implementation of a prognostic tool. Both scores have been validated previously, however to our knowledge the ASTRAL has not prior to this study been validated in an iv-tPA-treated cohort (268, 302, 266, 267). In this study, both scores showed promising performance with some limitations. The ASTRAL and DRAGON scores showed an acceptable or fair discriminative performance separating functional independency (mRS 0–2) from functional dependency (mRS 3–6) in our cohort, with AUC-receiver operating characteristic values of 0.79 and 0.77 respectively. Despite some differences, discussed below, the overall visual and numeric trend and concurrence between the predicted and the actual outcomes in the calibration plots are promising. The largest discrepancy between predicted and actual outcome, comparing SITS-ISTR with the ASTRAL and DRAGON original cohorts, amounted to 11% and 17% respectively (larger discrepancies for ASTRAL at scores >46, but patient data here were limited). To facilitate the understanding of the current results we will now separate the discussion of the two scores, concluding with an overall discussion.

ASTRAL- With increasing ASTRAL score cut-offs, increasing likelihood ratios for a poor outcome were seen in both the original ASTRAL cohort as well as in the SITS-ISTR. The main difference between the SITS-ISTR and ASTRAL cohorts was a higher proportion of functional dependency at 3 months in SITS-ISTR, most likely explained by a higher stroke severity in SITS-ISTR compared to ASTRAL (NIHSS 12 vs 9). All parameters of the ASTRAL score apart from visual field defects were significantly associated with functionally dependent outcome in our material. The two parameters showing the largest discrepancy between our data and the original ASTRAL cohort were level of consciousness and onset-to-admission time. The difference in the regression coefficients for onset-to-admission between the 2 cohorts is expected, as thrombolysed patients in SITS-ISTR would be expected to arrive much earlier than the original unselected ASTRAL cohort. Regarding the differences in absolute magnitude of the regression coefficients for a low level of consciousness, one possible explanation could be that a larger proportion of patients in the ASTRAL cohort with a low level of consciousness arrive outside the time frame for thrombolysis, missing the opportunity for acute revascularization therapy and subsequent improvement. The difference in outcome between the patients with a low level of consciousness and alert patients could thus potentially become magnified in the ASTRAL compared to SITS cohorts. The differences in stroke severity is probably caused by the higher inclusion of patients with mild strokes in the

original ASTRAL cohort, explaining the higher proportion of favourable outcome in the ASTRAL cohort when compared with the SITS cohort (66% versus 57.4%).

DRAGON- With increasing score cut-offs, lower likelihood ratios for favourable outcome were seen in both the SITS-ISTR and original DRAGON cohort. The main differences between the SITS-ISTR and DRAGON cohorts were: higher baseline stroke severity, lower proportion of early infarct signs and higher onset to treatment time in the SITS material. Despite these differences in baseline characteristics, all parameters of the DRAGON score were significantly associated with the outcome in the SITS-ISTR. The regression coefficients were relatively similar too, the biggest differences seen in age≥80 and onset-to-treatment time. The difference in regression coefficient for onset-to-treatment time could be caused by the baseline difference between the two cohorts with regard to this parameter.

Comparing the ASTRAL and DRAGON scores, the DRAGON parameters have an overall better fit to the SITS-ISTR cohort, suggesting a better prognostic value of the DRAGON score compared to the ASTRAL score. However, both the ASTRAL and the DRAGON show an acceptable prognostic value considering both the calculated AUCs and the visual assessment of the calibration plots. Most interestingly, we were surprised that the discriminative performance of the ASTRAL, developed in an unselected ischaemic stroke cohort, differed so little from the DRAGON score, which was developed using a thrombolysis cohort. Intuitively, we had expected ASTRAL to underestimate good outcome and have a weaker performance in our thrombolysis cohort, but both showed a similar discriminative performance.

Apart from conveying prognostic information to patients and caregivers early on, as well as a use for patient selection in RCTs, both scores may serve a potential use in the acute clinical setting. In settings without 24/7 access to multimodal imaging, both scores could be used to identify which patients who despite iv-tPA have a high probability of an unfavorable outcome (i.e. high scores). Both scores are heavily weighted by stroke severity measured on the NIHSS, and important correlations between increasing stroke severity and the presence of LAO have been described previously, as well as in the 1st and 3rd studies of this thesis. Therefore, high-score patients could be expected to harbour an increased proportion of LAO, suggesting transfer to tertiary centres with endovascular treatment capabilities. Prior to clinical implementation, we would need to prospectively validate the models to confirm the association between increased scoring and the presence of large vessel occlusions, as well as confirm the benefit of endovascular treatment in these selected patients.

In conclusion, our study has validated two of the most recently published stroke outcome prognostication tools and confirms their acceptable predictive value. Before clinical implementation of these scores, prospective evaluation of the impact of their use on patient outcomes after intravenous thrombolysis and mechanical thrombectomy are needed.

5.2.1 Study limitations

For general limitations of the SITS-ISTR cohort, please refer to section 5.1.1. One limitation specific for this study was that patients with basilar artery occlusion were excluded from the original DRAGON study. Site of occlusion was unfortunately not registered in our database. We were therefore not able to identify and exclude these patients, potentially affecting the predictive capability of the DRAGON score presented in this study.

5.2.2 Post-publication developments

After publication of this study, a most interesting paper was published in the European Journal of Neurology (303). This study invited physicians interested in stroke to provide outcome estimates in 720 real-life acute ischaemic stroke clinical scenarios, comparing the estimated outcome with that of the DRAGON and ASTRAL scores. Regarding unfavourable functional outcome (mRS>2), 56.8% of physicians made a correct assessment, as compared to 86.5% of ASTRAL score estimates. Regarding catastrophic outcome (mRS 5-6), 24.8% of physicians made a correct estimation in comparison to 37.3% of DRAGON score estimates.

In conclusion, ASTRAL and DRAGON both predicted with a higher accuracy compared to stroke physicians. In addition, at the ESOC 2016 stroke conference in Barcelona, the results of a new validation of the ASTRAL score was presented, assessing performance across stroke etiological subtype, showing a high accuracy of the score in predicting 3-month favourable outcome across all TOAST subtypes (304).

5.3 STUDY 3

In this study, we show that although increasing numbers of included NIHSS sub-items in LAO prediction models lead to better prediction, the differences do not seem to be clinically relevant. A simple predictive model only including an assessment of degree of arm motor dysfunction, derived from the NIHSS, shows sensitivities, specificities, PPVs and NPVs (69%,70%,68% and 70% respectively) similar to the values for an adjusted model including the full range of NIHSS sub-items (74%,72%, 71% and 73% respectively).

Different settings and situations may need different trade-offs between sensitivity and specificity. In certain cases, a high specificity may be preferred, while another situation warrants a high sensitivity. These decisions are dependent on factors such as time remaining in the thrombolysis time window, as well as transport distances to secondary vs tertiary stroke centres. Using a high sensitivity model with an unadjusted cut-off NIHSS item 5 (arm function) ≥ 2, gave a sensitivity, specificity, PPV and NPV of 79%, 55%, 63% and 73%, similar to the adjusted full-item NIHSS model, which gave a sensitivity, specificity, PPV and NPV of 80 %, 60%, 65% and 76% respectively. This corresponds to a cut-off of the total NIHSS score ≥ 10. Using a high specificity model with an unadjusted cut-off NIHSS item 5 (arm function) = 4 gave a specificity, sensitivity, PPV and NPV of 79%, 55 %, 71% and 65%, not very far from the adjusted full-item NIH model which gave a specificity, sensitivity, PPV and NPV of 80%, 64 %, 75% and 69%. This corresponds to a cut-off of the total NIHSS score ≥ 15.
In summary, our simple arm-dysfunction model performs reasonably well in both clinical scenarios.

Addition of clinical parameters other than the NIHSS sub-items to the models do not substantially change the predictive value. For each sub-item model, addition of other relevant predictors of LAO (the adjusted models) resulted in a model with a similar or slightly worse predictive value as compared to the simple addition of another NIHSS sub-item. The dominance of the NIHSS over other baseline clinical predictors in LAO prediction has been shown previously (297).

Prediction of LAO without vessel imaging will always lead to either missing patients harbouring a treatable arterial occlusion, or unnecessary transfer of patients without treatable occlusions to comprehensive stroke centres. However, simple prediction rules may improve patient selection and potentially lead to improved onset to reperfusion times. Using the high-specificity cut-off (NIH item 5 = 4) as a triage tool to endovascular centres would identify roughly

40% of our study population as possible LAO candidates, the PPV amounting to 71%, i.e. 7/10 successful transfers. Using the high-sensitivity cut-off (NIH item 5 ≥ 2) as a triage tool would identify roughly 60% of our study population, the PPV amounting to 63%, i.e. 6/10 successful transfers. The choice of cut-off depends on the clinical situation and local circumstances as outlined above. We suggest that a screening for severity of arm motor function can be used as an LAO screening step after confirmation of likely stroke diagnosis has been performed using a good stroke recognition score at the primary screening step, such as the FAST score (305).

In conclusion, although increasingly more complex clinical models yield a higher discriminative performance for predicting LAO, the differences compared to very simple models are not large. Balancing predictive performance against ease of use and practicality, simply assessing the grade of arm dysfunction may serve as a surrogate measure of LAO status in anterior circulation stroke, and in conjunction with a validated stroke recognition instrument, may assist in decision making in guiding high-risk patients to comprehensive stroke centres with endovascular treatment capabilities.

5.3.1 Study limitations

For general limitations of the SITS-ISTR cohort, please refer to section 5.1.1. Although we propose to extend our results to a prehospital setting, assessments of the NIHSS registered in the database were performed in a hospital setting. Also, our study is based on patients treated with iv-tPA and/or endovascular thrombectomy and may not be valid for unselected patients with a prehospital suspicion of stroke. Our selection of iv-tPA treated patients is a potential source of bias, as haemorrhagic stroke patients will be a part of the assessed population in the prehospital phase.

5.3.2 Post-publication developments

At the time of submission of the thesis for printing, this manuscript is under review. Therefore, no new data are available for discussion.

5.4 STUDY 4

The modified Rankin Scale is the most common long-term outcome assessment tool in both clinical trials as well as in routine clinical follow-up after stroke. Routine clinical follow-up after stroke is lacking in many countries, partly due to limitations in resources and time-restraints.

In this study, we show the possibility of using a mobile phone-based questionnaire for automatic assessment of functional outcome after stroke, which performed excellent in comparison with clinical visit mRS assessments. An excellent weighted kappa of 0.89 was seen for the main outcome assessing reliability for the whole spectrum of functional outcome, comparing mobile phone based self-assessments with an overall clinical assessment. Results were similar comparing the mobile phone-based method with a structured clinical assessment. A good interrater variability unweighted kappa (0.66) was found for the dichotomized analysis separating independent (mRS score 0–2) from dependent functional outcome (mRS score 3–5).

Our results are in line with previous studies studying inter-rater reliability of mRS between healthcare professionals (306, 168). A systematic review, including 10 studies on mRS reliability, found a combined unweighted kappa of 0.46 and weighted kappa of 0.90 for a traditional mRS assessment (166). Our results show an overall better inter-rater variability than these combined data, considering both the weighted and unweighted kappa.

Common methods used for assessment of mRS include face-to-face interviews, telephone interviews, case sheet reviews, postal surveys, questionnaires and structured interviews (307). The most common methodology is probably face-to-face interviews.

Studies validating the performance of alternative assessment methodologies are limited. A couple of studies have investigated the role of mRS telephone assessment with mixed results (172, 173, 176-178). One study found a poor agreement when comparing telephone interviews with face-to-face interviews, with an un-weighted kappa value of 0.30-0.38 (172). Other studies have found more promising results with higher weighted kappa results, ranging from 0.71-0.89 (176, 178). Yet the same studies show relatively low un-weighted kappa results close to 0.4.

One study assessed the role of mRS derivation using case records from standard hospital records compared to face-to-face interviews, showing poor results (179). Another study assessed the performance of a simplified mRS questionnaire (smRSq) displayed a promising weighted kappa of 0.82 between two raters using the smRSq (180). The smRSq was further tested in a study comparing postal questionnaires based on the smRSq with telephone RFA-based assessments.

Agreement between postal smRSq and telephone interview was weighted kappa =0.73 and unweighted kappa=-0.55 (181). A major limitation of the smRSq studies is the lack of validation of the new proposed methods, the studies assessing reliability but merely assuming validity and not comparing with traditional face-to-face mRS assessments.

Our alternative assessment, a mobile phone–based questionnaire answered by either the patient or a close relative/caregiver, with the response automatically translated into an mRS rating, resulted in an excellent weighted kappa value of 0.89 when compared with clinical visit face-to-face interviews. Only 15 out of totally 89 patients (17%) could not participate in the study because of lacking access to a compatible mobile phone, suggesting a high penetration of compatible mobile phone use in the general Swedish population, in all age groups. This novel form of assessment requires practically no time or resource allocation from the healthcare system because the patient/caregiver responses automatically can be converted into an mRS score without the need for professional score judgment.

In conclusion, our findings suggest that mobile phone–based questionnaires may serve a supplementary role to traditional clinical visit assessments. In settings where clinical visit follow-up assessments are scarce because of limitations in infrastructure and resources, this novel form of assessment may find an especially important role.

5.4.1 Study limitations

One important limitation of the current study is the relatively small size of the study cohort. Although we did not perform a formal power calculation, the study is of a similar size as the median of previously conducted studies on mRS interrater variability. The results need to be replicated in a larger multicentre setting before clinical implementation. A large confirmatory study is currently being planned, study enrolment starting by the end of 2017. In some cases, the analysis is based on answers from patients, and in other cases from relatives. This could affect the interpretation of the results, as patients participating and answering by themselves had milder strokes (median NIHSS 2 versus 7.5) and were younger (55 versus 73) compared to patients in whom a relative/caregiver answered the questionnaire. This however, reflects the real-life clinical situation. Elderly and more disabled patients may, due to various reasons, have difficulties using mobile phones. The proxy option is necessary to maximize follow up data, and encouragingly kappa values for the caregiver and patient responses analyzed separately were similar, suggesting the feasibility of using caregiver responses as a proxy for patient responses. The original RFA encourages eliciting information

from several sources, including patients, caregivers, physiotherapists, medical records etc. A future improvement of the methodology used in this study could be to encourage patients to answer the questionnaire together with a relative or caregiver.

5.4.2 Post-publication developments

The modified Rankin Scale is the most common assessment of functional outcome used in clinical stroke trials, decisions on the effectiveness of new therapeutic agents being based on this final outcome measurement. Measures for improving reliability, as well as increasing follow-up in routine clinical follow-up should be highly prioritized. It is thus somewhat disconcerting that studies investigating methods of improving and increasing follow-up assessments are relatively scarce. Since the publication of this study, few studies have been published investigating outcome assessment after stroke. One interesting study by the REVASCAT investigators examined the feasibility and reliability of central video adjudication of 3 month modified Rankin Scale as well as telephone interviews compared to local evaluation by certified investigators. Using local evaluation as a reference, central video adjudication performed better than telephone interviews (weighted kappa 0.92 vs 0.77). In conclusion, the authors stated that central video adjudication was feasible and probably preferable to local-site assessments in clinical trials, avoiding potential problems related to lacking of blinding (308). Finally, a new version of the Rankin Focused Assessment was recently published with a small alteration in the wording of wheelchair mobility, RFA-A, which could be used in settings in which trialists wish to focus less on handicap (309).

6 CONCLUSIONS AND FUTURE DIRECTIONS

Forecasting the outcomes of patients with various diseases is a cumbersome task since they depend on several factors, many often unknown at the time of prognostication. Nonetheless, a number of prognostic models have found their firm place in modern-day clinical practice, two examples being the "ABCD" and CHADS-VASc scores, both predicting the risk of ischaemic stroke following transient ischaemic attacks and atrial fibrillation respectively.
As to prediction after an established stroke, whether concerning the presence of large-arterial occlusions and hyper-acute management on the one hand, or long-term outcome on the other hand, no model has yet gained any widespread use. Reasons for this could at least partly be due to a seemingly impossible compromise between the complexity and wide variance in phenotype of injured human brains and the need for simplicity in score-prognostication for widespread use. However, based on the large empirical knowledge that randomised clinical trials and vast registry-based data have made available to us, prognostic models and tools have been developed. Despite this availability, which could assist in prognostication, they are infrequently used in clinical practice. Instead, individual physicians often communicate prognosis based on personal experiences and views.

As to prediction of large-arterial occlusion in the setting of acute ischaemic stroke, now amenable to a proven highly effective treatment, several models have been proposed, the absolute majority including some measure of stroke severity as the most important prognostic variable. The accuracy of these mostly simple models or stroke severity thresholds are generally quite promising. Despite a relatively favourable accuracy, in many cases probably better than our clinical assessment, their use has not yet been widely supported by large neurological or neurovascular societies. North American societies are silent in the issue, only recently did the European Stroke Organization support a statement from the ESO Karolinska Stroke Update Consensus meeting, stating that an NIHSS threshold of ≥9 within 3h of stroke onset could indicate the presence of a large arterial occlusion in the absence of non-invasive arterial imaging. Swift prehospital decision making could probably increase the number of patients offered endovascular treatment, with improvements in post-stroke functional level and potentially vast socio-economic effects. Triage based on the likelihood of patients harboring large arterial occlusions has not undergone any prospective large pre-hospital validation yet. The results from a large planned prehospital triage study on identifying large arterial occlusions in acute stroke starting in the Stockholm area in Sweden later this year will shed much needed light on the issue. Similar studies are planned/ongoing in the southern part of

Sweden. In the third project of this thesis, we present a simple arm paresis model for prediction of large-arterial occlusions in the acute setting of stroke. This model has a similar prognostic ability compared to the previously published models. It is the to date simplest model presented, and I believe that simplicity and ease of use are factors that are important in deciding the fate of all proposed models.

As to predicting functional outcome after stroke, numerous models have been proposed as well, many with decent prognostic abilities spanning AUCs´ of 0.7-0.8, a few compared to and shown to be superior to lone individual physician assessment. Their use could span from tools assisting in the communication with patients and care-givers to methods for patient selection in randomised trials and control for cohort composition in non-randomised trials. Despite a potential beneficial role, they have not gained any widespread use, neither in clinical practice nor in research settings. The first three projects of this thesis have sought to shed more light on the field of prognostication in acute ischaemic stroke. The final project has investigated the role of a novel method for increasing follow-up of functional outcome after acute stroke.
Based on the results generated in this thesis, we have drawn the following conclusions:

1) NIHSS thresholds can simultaneously predict both the presence of arterial occlusions as well as long-term functional outcome in acute ischaemic stroke. Considering an observed lowering of thresholds with increasing time delay from stroke onset to imaging, a threshold NIHSS score of 9 or 10 may be considered for immediate patient referral to comprehensive centres with endovascular capabilities, identifying patients with a higher risk of large arterial occlusion and poor outcome despite iv-tPA. The threshold is likely not optimal for use in the prehospital setting, considering the relative complexity of the NIH stroke scale. However, in the communication between centres with a limited availability of vascular imaging, and tertiary centres, it may serve an important role. Prior to clinical implementation, such a threshold would need further validation in independent cohorts. If the prognostic ability is confirmed and deemed sufficient, the threshold would subsequently need to undergo clinical evaluation during a test period, comparing threshold based decisions of transfer with pre-existing policies.

2) Existing stroke prognostication models predict stroke outcome with a sufficient accuracy. Choice of model depends on the specific clinical query under investigation, but in the end, will need to show an improved patient outcome following their use for wide-spread implementation. I believe that

the field of stroke outcome prognostication deserves increased attention. Illuminating the benefits and potential pitfalls of a wider use of these models should be of interest to the stroke community. A suitable setting could be focused discussions at future international consensus meetings or conferences.

3) In the prehospital setting, simple models predicting the presence of large arterial occlusions amenable to endovascular intervention may facilitate triage decisions, potentially reducing time to recanalization in selected patients. Increasingly more complex clinical models yield a slightly higher discriminative performance for predicting LAO, however, the difference compared to extremely simple models is not large. Balancing predictive performance against ease of use and practicality, simply assessing the grade of arm dysfunction may serve as a surrogate measure of LAO status in anterior circulation stroke, and in conjunction with a validated stroke recognition instrument may assist in decision-making in guiding high-risk patients to comprehensive stroke centres with endovascular treatment capabilities. Our proposed model needs extensive validation in independent cohorts prior to clinical testing. A planned prehospital triage study using a similar hemiparesis model will commence within shortly in the Stockholm area in Sweden. Depending on the primary interim results from this study our arm-paresis model could serve as a simpler alternative, with retained prognostic ability.

4) Self-assessment of functional outcome as measured by modified Rankin Scale based on a mobile phone application questionnaire performs well compared to routine in-clinic assessments. Mobile phone–based questionnaires may serve a supplementary role to clinical visit assessments, especially in settings where clinical follow-up visits are scarce because of economic and time-restraining factors. A larger confirmatory study is planned and will start recruitment later this year.

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