Endovascular treatment of Acute Ischemic Stroke

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Cover illustration: *Distal basilar artery occlusion – Embolectomy with Amplatz GooseNeck snare*

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ABSTRACT

Background: Intravenous thrombolysis is effective in patients with minor stroke but not in patients with moderate or major stroke due to large vessel occlusion. Endovascular stroke treatment offers a high recanalization rate, which is associated with favorable neurological outcome. The aim of our studies was to evaluate the efficacy and safety of the endovascular stroke treatment in the anterior and posterior circulation, respectively, as performed in the neurointerventional unit of Sahlgrenska University Hospital. Two major anesthesia forms are used in endovascular stroke treatment, general anesthesia and conscious sedation. The aim was also to evaluate the impact of intra-procedural hypotension and to compare general anesthesia and conscious sedation with respect to radiological and neurological outcome.

Methods: Paper I and Paper II are retrospective studies on efficacy and safety of endovascular stroke treatment in the anterior and posterior circulation, respectively. Paper III is a retrospective study on the impact of intraprocedural hypotension on neurological outcome in patients treated under general anesthesia. Paper IV is a prospective randomized study, where patients eligible for endovascular stroke treatment were randomized to general anesthesia or conscious sedation.

Results: Paper I showed that the successful recanalization rate in endovascular stroke treatment in the anterior circulation was 74%, the complication rate was 5% and favorable neurological outcome at 3 months was found in 42%. Paper II showed successful recanalization in 73% of patients treated for stroke in the posterior circulation with serious procedural complications in 5 % and favorable outcome in 35% at 3 months. Paper III showed that a fall in mean arterial pressure of >40% is an independent predictor of poor neurological outcome. Paper IV showed no difference in neurological outcome at 3 months between patients randomized to general anesthesia or conscious sedation when a strict protocol for avoidance of intra-procedural hypotension was followed.

Conclusion: Endovascular treatment in patients with acute ischemic stroke in the anterior and posterior circulation can achieve high recanalization rates with low complication rates. Intra-procedural hypotension is associated with poor neurological outcome but the choice of anesthesia method does not influence the neurological outcome if severe hypotension is avoided.

Keywords: stroke, endovascular treatment, embolectomy, thrombectomy, general anesthesia, conscious sedation

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SAMMANFATTNING PÅ SVENSKA

Bakgrund: Intravenös trombolys är effektiv hos patienter med mindre stroke men inte hos patienter med måttlig eller större stroke på grund av storkärlsocklusion. Endovaskulär strokebehandling kan erbjuda hög rekanaliseringsgrad vilket är förenat med gynnsamt neurologiskt resultat. Målsättningen med studierna var att utvärdera effekten och säkerheten av den endovaskulära strokebehandlingen i hjärnans främre och bakre cirkulation, med den metodik som används på neurointerventionsenheten på Sahlgrenska Universitetssjukhuset. Två anestesiformer används vid endovaskulär strokebehandling - generell anestesi och sedering. Ytterligare målsättningar var att utvärdera effekten av blodtrycksfall under proceduren med avseende på neurologiskt utfall och att jämföra radiologiskt och neurologiskt utfall vid generell anestesi jämfört med sedering under proceduren.

Metoder: Arbete I och Arbete II är retrospektiva studier avseende effektivitet och säkerhet av endovaskulär strokebehandling i främre respektive bakre cirkulationen. Arbete III är en retrospektiv studie om betydelsen av blodtrycksfall under proceduren med avseende på neurologiskt utfall hos patienter som behandlas under generell anestesi. Arbete IV är en prospektiv randomiserad studie där patienter som genomgår endovaskulär strokebehandling randomiserades till generell anestesi eller sedering, och undersöktes med avseende på radiologiskt och neurologiskt utfall.

Resultat: Arbete I visade att framgångsrik rekanalisering vid endovaskulär strokebehandling i främre cirkulationen uppnåddes i 74 %, komplikationsfrekvensen var 5 % och gynnsamt neurologiskt resultat uppnåddes hos 42 % vid 3 månader. Arbete II visade framgångsrik rekanalisering hos 73 % av patienterna som behandlades för stroke i den bakre cirkulationen, med allvarliga procedurkomplikationer i 5 % och ett gynnsamt neurologiskt resultat i 35 % av fallen vid 3 månader. Arbete III visade att ett genomsnittligt arteriellt blodtrycksfall på > 40 % är en oberoende prediktor för dåligt neurologiskt utfall. Arbete IV visade ingen skillnad i neurologiskt resultat vid 3 månader mellan patienter som randomiserades till generell anestesi respektive sedering, när ett strikt protokoll för att undvika blodtrycksfall under proceduren följdes.

Slutsats: Endovaskulär behandling hos patienter med akut ischemisk stroke i den främre och bakre cirkulationen medför rekanalisering i en stor andel av patienterna, med låg komplikationsfrekvens. Blodtrycksfall under proceduren

är förknippat med dåligt neurologiskt resultat men anestesimetoden påverkar inte det neurologiska resultatet om svårt blodtrycksfall undviks.

LIST OF PAPERS

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

I. Rentzos A, Lundqvist C, Karlsson JE, Vilmarsson V, Schnabel K, Wikholm G. **Mechanical embolectomy for acute ischemic stroke in the anterior cerebral circulation: The Gothenburg experience during 2000-2011**. *AJNR Am J Neuroradiol. 2014;35(10):1936-41*

II. Rentzos A, Karlsson JE, Lundqvist C, Rosengren L, Hellström M, Wikholm G. **Endovascular treatment of Acute Ischemic Stroke in the Posterior Circulation.** *Manuscript submitted 2017.*

III. Löwhagen Hendén P, Rentzos A, Karlsson JE, Rosengren L, Sundeman H, Reinsfelt B, Ricksten SE. **Hypotension during endovascular treatment of ischemic stroke is a risk factor for poor neurological outcome.** *Stroke. 2015;46(9):2678-2680*

IV. Löwhagen Hendén P*, Rentzos A*, Karlsson JE, Rosengren L, Leiram B, Sundeman H, Dunker D, Schnabel K, Wikholm G, Hellström M, Ricksten SE. **General anesthesia vs. conscious sedation for endovascular treatment of acute ischemic stroke - The AnStroke trial**. *Stroke. 2017;48(6):1601-1607.*

**Contributed equally*

CONTENT

ABBREVIATIONS

ACA	Anterior Cerebral Artery
ACoA	Anterior Communicating Artery
AICA	Anterior Inferior Cerebellar Artery
ASPECTS	Aspects Stroke Program Early CT Score
ASTER	Interest of Direct Aspiration First Pass Technique (ADAPT) for Thrombectomy Revascularization of Large Vessel Occlusion in Acute Ischemic Stroke
ATP	Adenosine Triphosphate
BATMAN	Basilar Artery on Computed Tomography Angiography score
Carotid-T	Carotid Terminus
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
CI	Confidence Interval
CS	Conscious Sedation
CT	Computed Tomography
CTA	Computed Tomography Angiography
CTA-SI	Computed Tomography Angiography-Source Image
CTP	Computed Tomography Perfusion
DAWN	Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo
DSA	Digital Subtraction Angiography
DWI	Diffusion Weighted Imaging
ECASS	European Cooperative Acute Stroke Study
ESCAPE	Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times
EXTEND-IA	Extending The Time for Thrombolysis in Emergency Neurological Deficits –Intra-Arterial
FAST-ED	Field Assessment Stroke Triage to Emergency Destination
FDA	Food and Drug Administration

GA	General Anesthesia
HERMES	Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials
ICA	Internal Carotid Artery
IST	International Stroke Trial
LAMS	Los Angeles Motor Scale
MAP	Mean Arterial Pressure
MCA	Middle Cerebral Artery
MERCI	Mechanical Embolus Removal in Cerebral Ischemia
MR CLEAN	Multicenter Randomized Clinical Trial on Endovascular Treatment for Acute Ischemic Stroke in the Netherlands
MRI	Magnetic Resonance Imaging
MR-RESCUE	Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy
mRS	Modified Rankin Scale
mTICI	Modified Treatment In Cerebral Ischemia
MTT	Mean Transit Time
NCCT	Non-Contrast Computed Tomography
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
PCA	Posterior Cerebral Artery
pc-ASPECTS	Posterior circulation ASPECTS
PCoA	Posterior Communicating Artery
PICA	Posterior Inferior Cerebellar Artery
PMI	Pons Midbrain Index
PreHAST	Prehospital Ambulance Stroke Test
PROACT	Prolyse in Acute Cerebral Thromboembolism
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 Eight Hours of Symptom Onset
RLS	Reactive Level Scale
rt-PA	Recombinant tissue Plasminogen Activator
SAMMPRIS	Stenting vs. Medical Management for Preventing

	Recurrent Stroke in Intracranial stenosis
SCA	Superior Cerebellar Artery
sICH	symptomatic Intracranial Hemorrhage
SIESTA	Sedation vs. Intubation for Endovascular Stroke Treatment
SITS	Safe Implementation of Thrombolysis in Stroke
SITS-ISTR	SITS-International Stroke Treatment Registry
SITS-MOST	SITS-Monitoring Study
SITS-Open	SITS-Open Artery by Thrombectomy in Acute Occlusive Stroke study
SYNTHESIS	Local versus Systemic Thrombolysis for Acute Ischemic Stroke
SWIFT-PRIME	The Solitaire With The Intention For Thrombectomy as Primary Endovascular Treatment
THRACE	Thrombectomie Des Arteres Cerebrales
TREVO	Thrombectomy Revascularization of Large Vessel Occlusion
USA	United States of America
VISST	Vitesse Intracranial stent Study for Ischemic Therapy

1 INTRODUCTION

Endovascular stroke treatment is the treatment of large intracranial vessel occlusion causing a major ischemic stroke, by the introduction of intravascular catheters and devices in order to dissolve, disintegrate or remove the obstructing clot. In Sahlgrenska University Hospital, endovascular stroke treatment is performed since 1991 when the only endovascular method available was intraarterial thrombolysis. A milestone in the endovascular stroke treatment was the introduction of the mechanical embolectomy with the Amplatz GooseNeck snare in 1994, making the treatment faster and at the same time avoiding the contraindications of the pharmacological treatments. The development of the endovascular stroke treatment brought new devices such as stent-retrievers and aspiration catheters which led to the worldwide adaptation of the embolectomy technique. The mechanical embolectomy reached a new, evidence based clinical acceptance level with the publication of several consecutive positive randomized trials in 2015.

This project started in 2012 when endovascular stroke treatment was still considered an experimental treatment and an alternative treatment to unsuccessful treatment with intravenous thrombolysis. The aim of the work was to assess the effectiveness and safety of the endovascular stroke treatment and of the methods used in the Sahlgrenska University Hospital in both the anterior and posterior cerebral circulation. At the same time, new evidence emerged about the role of anesthesia in the stroke treatment, causing a long tradition in our institute of using general anesthesia to be aborted as the main method. The reason for this was the result of a series of studies showing association of general anesthesia with poor neurological outcome. This led to the initiation of two studies investigating the role of anesthesia in the endovascular stroke treatment and its outcome.

2 STROKE

It is estimated that each year around 17,000,000 people worldwide suffer a stroke. Stroke is the most frequent cause of physical disability and the second leading cause of death worldwide with around 6,500,000 deaths[1, 2]. In the 27 EU countries, the total annual cost of stroke is estimated at 27 billion euros. Stroke is associated with greater use of informal care involving family and friends of stroke patients. This informal care adds a sum of 11.1 billion euros to the annual cost of stroke. The stroke incidence and mortality are declining mainly due to the reduction of risk factors and access to better healthcare, particularly in high-income nations. It is predicted, however, that the prevalence of stroke events will rise significantly worldwide secondary to the increase of the population older than 65 years of age. The number of new stroke events is expected to rise from 1.1 million stroke events/year to 1.5 million by 2025 in Europe due to the aging population[3].

In Sweden, 25,000 people are estimated to suffer a stroke every year[4]. Based on data from the Swedish Stroke Register (Riksstroke), the annual cost of stroke is estimated at 18.3 billion Swedish kronor (1.9 billion euros) excluding the cost of the informal care.

2.1 Types

Stroke is divided into two main types; the **hemorrhagic** stroke accounting for 13% of all strokes, caused by a ruptured vessel leading to an intracranial bleeding, and **ischemic** stroke accounting for 87% of all strokes, caused by a clot occluding an intracranial vessel[5]. **Transient Ischemic Attacks (TIA)** are caused by small clots that cause temporary short-lasting symptoms with no permanent brain injury and are considered a separate entity of stroke because the blood flow is obstructed only briefly. TIAs are regarded as a warning sign for a future more severe stroke.

Ischemic stroke can be caused by an occlusion of moderate or small size arteries distally in the cerebral circulation, causing mild stroke symptoms, or by an occlusion of a larger artery, causing a major stroke. In the anterior cerebral circulation, large intracranial vessel occlusion is defined as occlusion of the internal carotid artery (ICA), carotid Terminus (carotid T), M1 and usually M2 segment of the middle cerebral artery (MCA), and in the posterior cerebral circulation symptomatic occlusion of one of the vertebral arteries, occlusion of any segment of the basilar artery and P1/P2 segments of the posterior cerebral artery (PCA) (figure 1). A high-grade stenosis in the carotid

carotid bifurcation or less frequently a vertebral stenosis can be found in combination with an intracranial vessel occlusion.

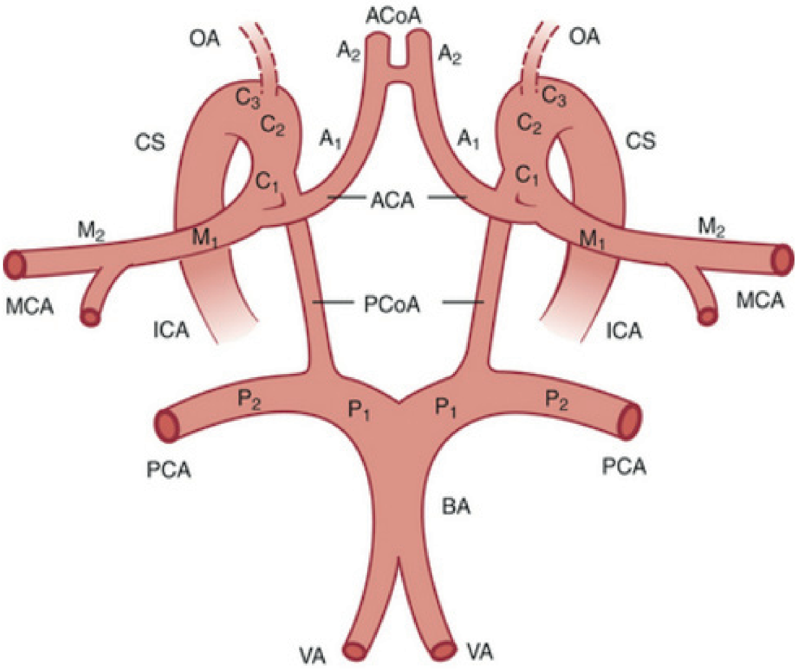

Figure 1: Circle of Willis and locations of large vessel occlusion. ICA: Internal carotid artery, CS: Carotid siphon with segments C1-C3, OA: ophthalmic artery, MCA: Middle cerebral artery, M1/M2: First and second segments of MCA, ACA: Anterior cerebral artery, A1/A2: First and second segment of ACA, ACoA: Anterior communicating artery, PCoA: Posterior communicating artery, PCA: Posterior cerebral artery, P1/P2: First and second segments of PCA, BA: Basilar artery, VA: Vertebral artery (image reprinted with permission from Radiologykey.com).

2.2 Causes of ischemic stroke and risk factors

Ischemic stroke can be caused by a **thrombus**, a clot that forms in the occluded vessel itself, or by an **embolus**, a clot which forms usually at the heart or large vessels of the neck and travels to the cerebral circulation. In 30% of the cases the cause of ischemic stroke is cardioembolic, in 20% large vessel disease, most frequently atherosclerotic disease of the neck arteries, and in 20% small vessel disease causing lacunar infarcts. In the remaining 30% of the cases, other causes such as dissection of the carotid arteries or cryptogenic causes are included. The leading cause of stroke is high blood pressure followed by smoking, high blood cholesterol, obesity, diabetes and lack of physical activity. Atherosclerotic diseases of the arteries and diseases of the heart, such as atrial fibrillation or coronary heart disease are known major factors that significantly increase the risk of stroke. Low socioeconomic status, even when all other factors can be controlled, increase the stroke occurrence[5].

2.3 Clinical presentation

The clinical symptoms and signs depend on the anatomical regions involved in the ischemic process. With occlusion of a major vessel in the **anterior circulation** symptoms on the contralateral side of the body arise and correspond to the area supplied by this vessel. Occlusion of the ophthalmic artery may cause monocular loss of vision. Occlusion of the middle cerebral artery (MCA) may give rise to functional loss of the contralateral face and arm, sensory loss in the contralateral face and arm, aphasia, dyslexia, dysgraphia or dyscalculia. Anterior cerebral artery (ACA) occlusion may present with motor and sensory loss in the contralateral leg. Symptoms correlated to occlusion of the posterior cerebral artery may arise in an anterior circulation stroke due to an occlusion of a fetal posterior communicating artery (PCoA) or embolism directly to the posterior cerebral artery through the posterior communicating artery. Contralateral homonymous hemianopia suggests involvement of the posterior cerebral artery. In case of an internal carotid artery occlusion a combination of all the above symptoms, with involvement of the face, arm, and leg with or without homonymous hemianopia, may arise.

The early clinical course in **vertebrobasilar occlusion** can be abrupt as in the anterior circulation. It can also be abrupt with prodromal symptoms, and it may be progressive and fluctuating with or without prodromal symptoms. In cases of large vessel occlusion, prodromal symptoms due to transient ischemic attacks or minor strokes are frequently caused by unstable atherosclerotic occlusion in the posterior circulation. In cases of embolism in the posterior circulation, transient ischemic attacks and minor strokes are warning signs for a future major stroke, as in the anterior circulation. A large proportion of patients with posterior circulation stroke present with reduced consciousness or coma due to disturbances in the reticular activating system caused most often by middle and distal basilar artery occlusions (perforating basilar branches and thalamic perforating branches). Locked-in syndrome is a condition that often is mistaken for coma, caused by a large stroke in the pons. The patient with locked-in syndrome is awake and alert but suffers from quadriplegia, bilateral facial plegia, aphagia, anarthria and horizontal gaze paresis. The only form of communication is through some preserved eye movements such as blinking. When cranial nerves are affected the patient presents with one or combinations of double vision (cranial nerves II, IV and VI), facial numbness (cranial nerve V) facial weakness (cranial nerve VII), vertigo (cranial nerve VIII) or dysphagia (cranial nerves IX and X). Lesions to the cerebellum can cause dysarthria, ataxia, and loss of coordination and balance. Hemiparesis /hemiplegia or quadriparesis/quadriplegia and unilateral or bilateral hypoesthesia are caused when the corticospinal and spinothalamic tracts are affected. Depending on the amount of collateral flow from the anterior circulation through the posterior communicating artery, symptoms from the posterior cerebral artery territory such as hemianopia and cortical blindness can be present or totally absent.

2.4 Pathophysiology

The brain is responsible for 20% of the body´s total oxygen consumption and this is almost entirely for the metabolism of glucose, which is the exclusive substrate for the brain´s energy metabolism in normal physiological conditions. When a vessel obstruction occurs the delivery of oxygen to the cells decreases due to decreased blood flow and the cells lose their ability to form energy in the form of Adenosine Triphosphate (ATP) through aerobic metabolism. The cell then depends on anaerobic metabolism for energy production but this energy is 15 times lesser than the energy produced by aerobic metabolism. With ATP depletion cell depolarization ensues. The Na^+/K^+ pump stops working and leads to increased concentration of Na^+ in the cell, causing cytotoxic edema. At the same time also the Na^+/Ca^{2+} pump stops working, which causes an increase in Ca^{2+} concentration. This increase in Ca^{2+} concentration causes glutamate release and consequently an excitatory effect transmitted to other cells, but also activation of degrading enzymes which break down the cell membrane (excitotoxicity). Lastly, free radicals, produced in the cell, and apoptotic factors released from the breakdown of mitochondria, lead to further cell damage. With the breakdown of cells, the released chemicals and the inflammatory process cause damage to the blood-brain barrier and eventually vasogenic edema occurs[6].

2.4.1 Infarct core and ischemic penumbra

When the blood flow decreases the functional threshold is crossed first. The functional threshold represents the level where functional failure of the cell occurs but it is still reversible. If the perfusion decreases further a lower threshold is reached, below which irreversible damage is caused in the membrane leading to cellular death. All cells with perfusion below this lower threshold belong to the **infarct core** while all cells with perfusion in the range between the functional and the lower thresholds correspond to the **ischemic penumbra**[6]. The thresholds show large variability, with different thresholds for example in gray and white matter areas, in different brain regions and even in neurons belonging to the same cortical regions. The functional failure occurs immediately after the blood flow drops below the first threshold but the occurrence of irreversible damage is time dependent. In absence of a minimal collateral blood flow to the ischemic region, the irreversible damage can occur within minutes. A good collateral circulation might preserve sufficient blood flow in the affected region, sustaining perfusion above the critical second threshold. Consequently, the cells in this region are not functioning properly but if the blood flow provided by collateral circulation can be maintained until the occlusion is treated and the blood flow is restored, then functional recovery can be expected. If treatment is not provided or is unsuccessful the irreversible damage will sooner or later expand from the infarct core to the surrounding ischemic penumbra despite the good collateral circulation (figure 2).

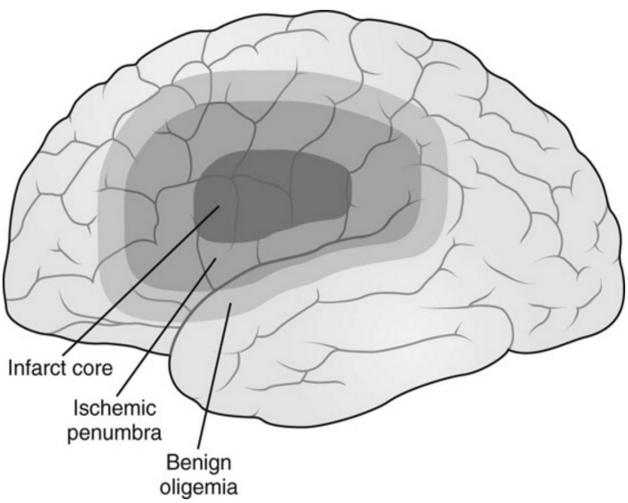

Figure 2: Illustration of infarct core-ischemic penumbra concept: The central area corresponds to regions with irreversible damage termed infarct core. The area surrounding the infarct core includes regions with reversible damage and is termed ischemic penumbra. The infarct core will gradually expand into the ischemic penumbra area if no treatment is offered. An area surrounding the ischemic penumbra exists that has only a mild reduction in perfusion but will never undergo infarction and is termed benign oligemia (image reprinted with permission from Radiologykey.com)

2.4.2 Cerebral autoregulation

Cerebral autoregulation is the inherent ability of the brain circulation to maintain a constant blood flow as the cerebral perfusion pressure can change over a wide range of mean arterial pressure (MAP) in healthy subjects (60 mm Hg to 150 mm Hg). This constant blood flow is maintained by complex myogenic, neurogenic and metabolic mechanisms and matches the metabolic demands of the brain. In acute ischemic stroke the cerebral autoregulation is impaired or lost and the brain tolerates poorly changes in the MAP. The blood flow then becomes directly proportional to the MAP (figure 3). When occlusion of a vessel occurs, the intracranial vessels dilate to maintain blood flow which results in an increase in cerebral blood volume. At the same time, the oxygen extraction from the blood increases and reaches 100% (oxygen extraction fraction) thus maintaining the metabolic cellular activity in the penumbra regions. If the vessel remains occluded, maximum vasodilatation is reached and further falls in cerebral perfusion pressure results in fall in blood flow. Then the cellular metabolism is impaired and the cerebral metabolic rate of oxygen begins to fall despite the maximal oxygen extraction from the blood because the blood flow is inadequate to meet the metabolic demands. Progression of the penumbral regions to infarction occurs then, with expansion of the infarct core[7, 8].

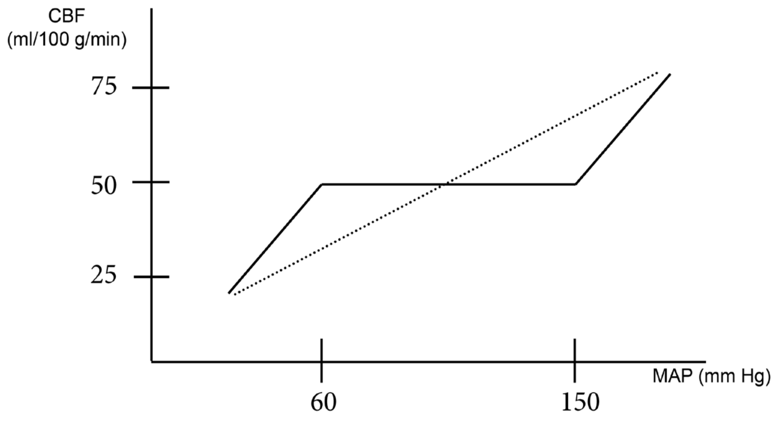

Figure 3: Cerebral autoregulation. In a normal brain, the cerebral blood flow is maintained constant over a wide range of mean arterial pressures (between 60 mm Hg and 150 mm Hg). In acute ischemic stroke, the autoregulation is impaired or totally lost and the brain cannot tolerate pressure changes. As a result, the blood flow becomes directly dependent on the mean arterial pressure (dotted line).

Patients with acute stroke commonly present with acute elevations in blood pressures. This is believed to be a protective mechanism to maintain blood flow through the collateral circulation to the affected region. Disturbances in the maintenance of adequate perfusion pressure will affect the collateral blood flow to the affected tissue and lead to a more rapid progress of penumbra to infarct core[9].

2.4.3 Collateral circulation

The intracranial circulation has an anterior and a posterior part (figure 1). The anterior part is composed of the two internal carotid arteries which give rise to the middle and anterior cerebral artery on each side. The anterior cerebral arteries can be interconnected through the anterior communicating arteries. These arteries are responsible for blood supply of the cerebral hemispheres. The posterior part is composed of the two vertebral arteries which unite to form the basilar artery. From the basilar artery, the two posterior cerebral arteries arise. The posterior part provides blood supply to the brainstem, cerebellum and occipital lobes. The anterior and posterior parts can also be interconnected through the posterior communicating arteries. The above principal arteries with their main branches and the communicating arteries form the **Circle of Willis**, which can be presented with numerous anatomical variations, being complete in only 40% of the population[10]. It serves as s circuit which can provide alternative routes of supply in case of a large vessel occlusion.

The **leptomeningeal (or pial) collateral system** is another way to provide supply in case of an occlusion. They are connections along the surface of the brain between arteries of the anterior cerebral, middle cerebral and posterior cerebral arteries. During an occlusion of one of the above arteries, the leptomeningeal anastomoses can take over the supply of the region at risk. Similar anastomoses are also seen in cases of posterior ischemic stroke where connections between the superior cerebellar and posterior anterior inferior cerebellar arteries can be seen over the surface of the cerebellum (figure 4). In cases where the supply through the leptomeningeal anastomoses is sufficient, the patient might present with only minor symptoms or even be asymptomatic. An established leptomeningeal collateral system which promptly provides sufficient blood supply is seen usually in cases of a chronic extra- or intracranial stenosis. In cases of an acute occlusion of a large intracranial vessel, the leptomeningeal collateral system can only in part compensate the lack of blood flow through the main route and its role is mainly to sustain the penumbra until the vessel is recanalized. In case of unsuccessful recanalization, it is only a matter of time before the ischemic penumbra will subsequently become part of the infarct core despite the collateral system. In some individuals with poor collateral system, a manifest infarct can develop in the first half hour after the occlusion, while in individuals with good collaterals the penumbra can be sustained for several hours or even up to a day.

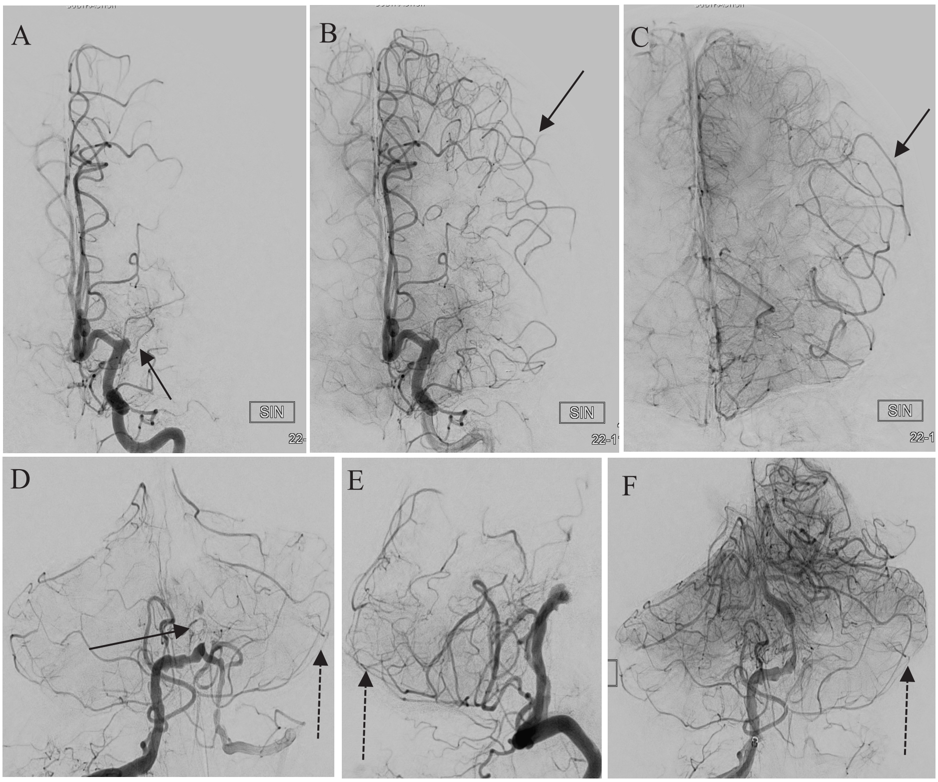

Figure 4: ***<u>A-C:</u>*** *Carotid artery angiography (frontal projection) in a patient with occlusion in MCA.* ***A****: Early arterial phase. No filling of MCA branches distally to the M1 segment occlusion (arrow). Normal filling of the anterior cerebral artery and the pericallosal arteries.* ***B****: Image taken one second later. Retrograde filling of the distal MCA branches (arrow) over the leptomeningeal anastomoses.* ***C****: Image taken 3 seconds after the first image (A), early venous phase. Retrograde filling of more proximal MCA branches.*

<u>D-F:</u> *Vertebral artery angiography in a patient with acute occlusion in a significant proximal basilar stenosis.* ***D:*** *Frontal projection. The solid arrow shows the stenosis in the proximal basilar artery. A collateral system is already established through anastomosis between the PICA and SCA (dotted arrow).* ***E:*** *The same anastomosis between PICA and SCA (dotted arrow) in lateral projection.* ***F:*** *Frontal projection after angioplasty and embolectomy in basilar artery. The anastomosis between PICA and SCA is still visible (dotted arrow) but now the SCA is filling anterograde.*

The **pio-dural system** is another complex collateral system which can help in sustaining flow in the hypoperfused brain until recanalization of the main artery takes place. This system is constructed mainly by connections between meningeal arteries from the external carotid arteries with pial arteries arising from the internal carotid but also the vertebrobasilar arteries. The most characteristic anastomosis of the pio-dural system, observed during acute ischemic stroke, is blood supply of the distal internal carotid artery through the ophthalmic artery in cases of an occlusion of the proximal internal carotid artery[11]. Other pio-dural anastomoses can exist between meningeal arteries of the internal carotid, vertebral or external carotid artery and pial arteries from the anterior cerebral, posterior cerebral and main branches of the basilar artery, but these are observed most often when a preexisting condition is present, such as for example dural arteriovenous malformations.

2.4.4 Time is brain

There is a variability in the progression of penumbral regions to infarct core between individuals. The establishment of an infarct can take only some minutes but also become apparent hours later. Even patients with good collateral circulation and consequently a good chance of recovery are destined to suffer from a large infarction if the underlying vessel occlusion is not treated promptly.

Physiological studies have shown that for every minute delay in reperfusion an average of 2 million neurons are lost[12]. Patients treated with intravenous thrombolysis alone gain 1.8 days of healthy life for every minute saved from stroke onset to treatment initiation[13]. Lately, studies based on cohorts that include patients treated with endovascular methods have shown that the gain of patients with large vessel occlusion is 4.2 days of healthy life for every minute of earlier treatment[14]. Younger patients and females will gain even more days reaching more than a week gain for every minute saved (figure 5).

Avoiding delays in the stroke workflow will increase the number of patients who could receive intravenous thrombolysis if they arrive at the hospital within 4.5 hours from stroke onset, but also the number of patients with large vessel occlusion that could receive endovascular treatment within 6 hours. Studies have shown that using imaging-based selection criteria, patients who could benefit from endovascular treatment even beyond the 6 hours may be identified. We should keep in mind though, that time is always important even if an imaging-based selection is performed as the majority of patients gain the most from any treatment in the first hours after stroke onset with the benefit decreasing as time passes. The role of image-based selection is to identify patients outside the current time windows (wake-up stroke, unknown stroke onset and admission >6 hours from onset) who could benefit from treatment and avoid futile recanalization in patients who might appear in the acceptable time window for treatment but have no salvageable brain tissue.

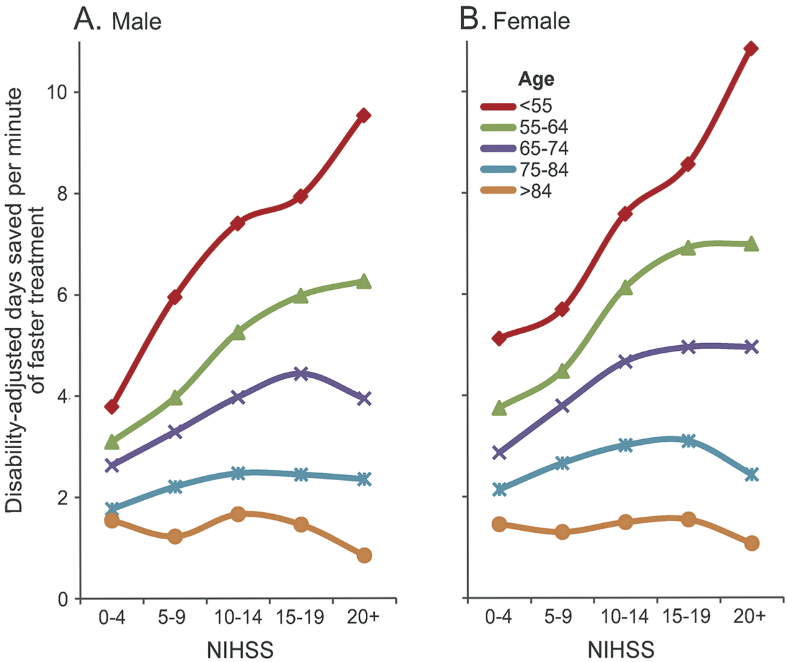

Figure 5: Relationship between disability-adjusted days gained per minute of faster treatment by sex ([A] male, [B] female), age, and stroke severity (NIHSS). Younger patients and women with longer life expectancy gain more over their lifetime from a faster treatment (Image reprinted from Meretoja et al. Neurology 2017, with permission from the publisher).

3 TREATMENT OF ISCHEMIC STROKE

The first to describe a case of stroke with arm paralysis and loss of speech was Hippocrates (460 to 370 BC), who named this phenomenon apoplexy (struck with violence). The invention of cerebral arteriography by Egas Moniz in 1927, made possible the visualization of occlusive lesions of the extra- and intracranial arteries with the first description of a carotid occlusion by Sjöqvist in 1936. While the disease was known and many of its aspects were described, no treatment was available except in cases of extracranial occlusive disease of the carotid. The first end-to-end anastomosis between external carotid and distal internal carotid arteries was performed by Mollins and Murphy in 1951. Later, carotid endarterectomy was added in the treatment arsenal with the first procedure performed by DeBakey in 1953. Unfortunately, these treatments are not helpful when also an intracranial occlusion exists as Strully, Hurwitt and Blankenberg showed in 1953 when they performed a surgical thrombectomy in a patient with a totally occluded internal carotid artery without succeeding restoring patency in the intracranial portion of the artery[15].

3.1 History of ischemic stroke treatment and intravenous thrombolysis

For patients presenting with stroke due to intracranial vessel occlusion, no treatment was available until the late 1950s when Thrombolysin (streptokinase-plasmin mixture) was used both intravenously but also intraarterially after direct puncture of carotid arteries[16, 17]. Streptokinase was discovered in 1933 and tested in coronary thrombosis with promising results that led some centers to start testing streptokinase in ischemic stroke[18]. Until the early 1990s, case reports and randomized studies with inclusion criteria that we now know to be suboptimal were the only available evidence with mixed results[19]. Urokinase type plasminogen activator or its precursor form pro-urokinase was later used because of its increased efficacy but also because of decreased bleeding and other complications compared to streptokinase[20].

The breakthrough in intravenous thrombolysis treatment came with the NINDS trial in 1995 which showed that patients receiving recombinant tissue Plasminogen Activator (rt-PA) had a 30% higher chance to be independent at 3 months compared to patients receiving placebo[21]. This led to the approval of Alteplase by the FDA (USA) in 1996 for patients presenting with acute ischemic stroke within 3 hours from stroke onset. In Europe, rt-PA was approved in 2002 under the conditions that the results would be followed up by an observational study (SITS-MOST) and that a randomized study would be initiated studying the effect of rt-PA after the 3 hours window (ECASS III) [22].

The time window for intravenous thrombolysis was extended to 4.5 hours from stroke onset when results from ECASS III and SITS-ISTR studies showed that it was safe[23] (figure 6).

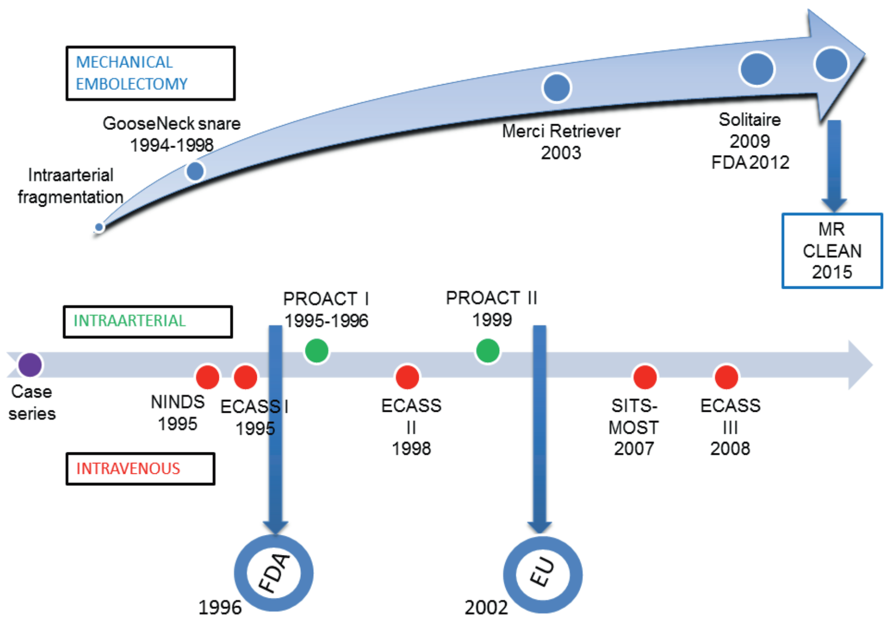

Figure 6: Illustration of the most important studies and dates in intravenous thrombolysis treatment (NINDS 1995, ECASS I 1995, ECASS II 1998, SITS.MOST 2007, ECASS III 2008, FDA 1996 and EU 2002 approval), intraarterial thrombolysis (PROACT I 1995, PROACT II 1999), and mechanical embolectomy (GooseNeck snare 1994, Merci Retriever 2003, Solitaire Stent 2009 and MR CLEAN 2015).

3.2 Intraarterial thrombolysis

It was quite clear from the beginning of intravenous thrombolysis treatment that patients presenting with a large vessel occlusion had worse outcome compared to patients with a stroke due to a more distal occlusion. Case series were published showing positive results of intraarterial thrombolysis in patients with large vessel occlusion but no concrete evidence existed until the first randomized trials PROACT I and II conducted in 1995 and 1998, respectively[24, 25]. PROACT I trial showed that local intraarterial pro-urokinase infusion was associated with superior recanalization compared to placebo and PROACT II trial showed that patients receiving intraarterial pro-urokinase within 6 hours from stroke onset had a significantly more favorable outcome at 3 months compared to patients receiving only intravenous heparin infusion.

While these trials showed an effect of intraarterial thrombolysis, a direct comparison to intravenous thrombolysis, which was approved as standard of care in the treatment of ischemic stroke in 1996, was never done. Many centers started using intraarterial thrombolysis in patients with large vessel occlusion in the 6-hour window but intravenous thrombolysis remained the only approved treatment for acute ischemic stroke. In the Sahlgrenska University hospital, pro-urokinase was used since 1991 in patients with basilar occlusion while the use of intraarterial rt-PA started only when rt-PA was approved in Europe, in 2002.

Intraarterial thrombolysis was the only alternative to intravenous rt-PA but it had major disadvantages such as similar contraindications as for intravenous thrombolysis and long infusion times which could extend from one to two hours.

3.3 Embolectomy

Embolectomy techniques today are divided into techniques using the **proximal approach**, where the microcatheter and the embolectomy device are placed proximal to the clot and the extraction is performed without crossing the occlusion, and techniques using the **distal approach**, where a microcatheter used to deliver the embolectomy device is placed with its tip distal to the clot.

3.3.1 Proximal approach

Dr. Gunnar Wikholm, at the Sahlgrenska University Hospital, introduced the use of **Amplatz GooseNeck snare** as an embolectomy tool in 1994. Amplatz GooseNeck was and still is a quite common endovascular tool used in angiography suites all around the world for extraction of misplaced material or foreign bodies. During the endovascular treatment of an anterior communicating aneurysm, a thromboembolic complication occurred occluding the middle cerebral artery (figure 7). The occluding material was extracted with the Amplatz GooseNeck snare and was sent to the pathology lab. The lab report showed that the extracted material was a simple clot. An embolus differs from a thrombus in the way that it is a coherent body which can usually be extracted in one piece. A thrombus which forms acutely, for example in a stenosis, is usually more erythrocyte rich and any manipulation of the stenosis and thrombus can cause the thrombus to dislocate and even fragment into small pieces causing embolic events in more distal branches. Different approaches of the technique were tested, but the most reliable was the proximal approach to the embolus as shown in figure 8 and it is the way it is used until today. The technique was presented in neurointerventional congresses and finally published in 1998, becoming the main embolectomy method in the Sahlgrenska University Hospital[26, 27]. It offers the advantage of quick embolus extraction without any incubation time, no crossing of the occlusion site blindly and numerous atraumatic passes. The most frequent size used for embolectomy is the 4 mm Amplatz GooseNeck snare but in more distal branches a 2 mm snare can also be used. A disadvantage of this technique is that the proximal vessel with the occluded vessel should lie at an acceptable angle for the snare to be able to fully deploy in 90^{o} degrees angle and ensnare the whole clot. The extraction is performed slowly in order not to lose the embolus and under aspiration through a guide catheter placed in the extracranial internal carotid or vertebral artery (figure 9).

In 2006, extraction of a basilar embolus was performed with the proximal approach, but this time by aspiration through the largest available microcatheter at that time (VASCO+35, BALT, figure 10). The relatively accessible anatomy of the vertebral artery and absence of atherosclerotic changes made the placement of such a large microcatheter easy, making the aspiration of the clot in the basilar artery possible. Usually, the intracranial anatomy, especially in the skull base, is hostile to the navigation of relatively large and lesser flexible catheters. More flexible catheters on the other hand which could easily navigate in the intracranial circulation were not available at that time and it is doubtful if optimal suction could be achieved in the tip of such a catheter without collapsing the catheter. The first catheter dedicated to aspiration in intracranial circulation came many years later in 2012 with the **Penumbra 5MAX** catheter (figure 11). This was the end result of earlier aspiration system from Penumbra Inc. which used aspiration together with a separator placed in the embolus to facilitate the extraction. Now a handful new aspiration catheters exist, such as Penumbra 5MAX ACE 68 and SOFIA Plus with their usage becoming very popular worldwide. These catheters offer great navigational properties in the level of the skull base reaching even out to relatively large M2 and M3 segments of the middle cerebral artery. At the same time, these catheters are reinforced in their tip delivering the suction needed for extraction of the embolus without the catheter collapsing.

Embolectomy with the Amplatz GooseNeck snare and late generation aspiration catheters are the main components in the proximal approach technique. This technique offers a quick extraction regardless of the vessel anatomy distal to the clot. The interaction with the vessel wall is minimal and atraumatic. Because of these reasons, the proximal approach is the first line method in the Sahlgrenska University Hospital reserving the distal approach as an alternative in case of unsuccessful recanalization.

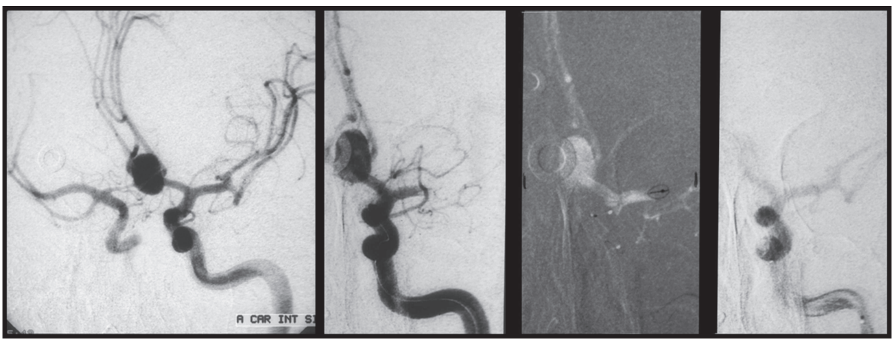

Figure 7: The first case where the Amplatz GooseNeck snare was used as an embolectomy device in 1994 during treatment of a ruptured anterior communicating aneurysm. The first angiography on the left shows a large aneurysm in the ACoA and normal filling of MCA and ACA branches. During the procedure, an acute occlusion of the MCA is detected (second image). The Amplatz GooseNeck snare is deployed along the occlusion (third image). Angiography during retrieval of the Amplatz GooseNeck snare. The Amplatz GooseNeck snare with the embolus are located in the carotid siphon and the MCA is now open.

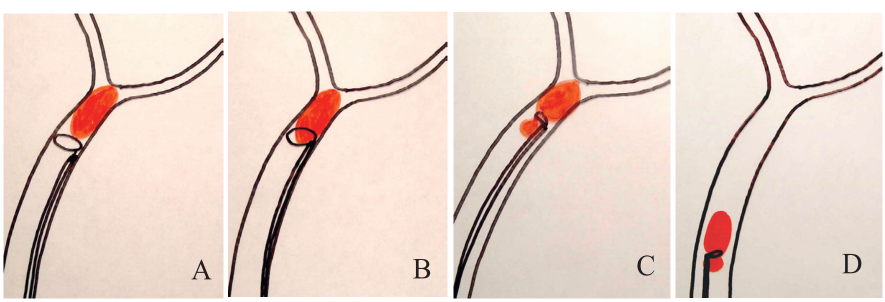

Figure 8: Illustration of the proximal approach embolectomy with the Amplatz GooseNeck snare. ***A:*** *First the Amplatz GooseNeck snare is deployed proximal to the embolus in its natural configuration at 90 degrees.* *(Continues on next page).*

(Continued from the previous page) ***B:*** *Then the Amplatz GooseNeck snare is pushed forward to ensnare the embolus.* ***C:*** *Next the snare is partially retrieved to secure the embolus. A fibrin rich or calcified embolus can be felt as a resistance to further retrieval of the snare inside the microcatheter but a softer erythrocyte-rich embolus causes minimal resistance. In this case, caution should be exercised to avoid full retrieval of the snare and cause fragmentation of the embolus.* ***D:*** *Retrieval of the Amplatz GooseNeck snare with the ensnared embolus.*

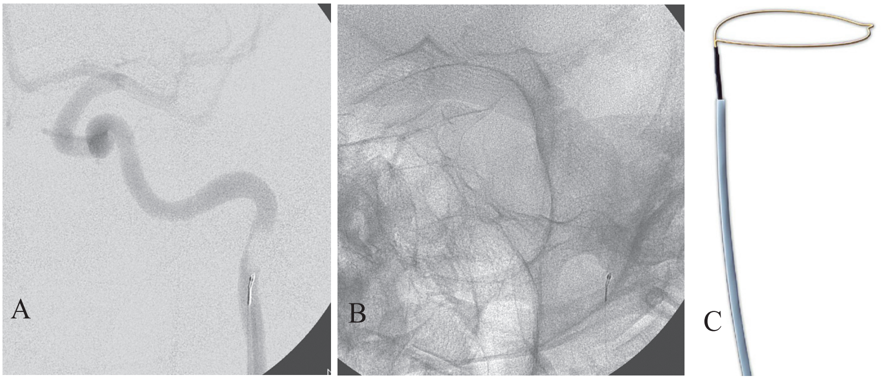

Figure 9: ***A:*** *The Amplatz GooseNeck snare with the ensnared embolus can be retrieved directly under continuous aspiration through an intermediate or large guide catheter (not shown in image).* ***B:*** *Unsubtracted image showing the partially retrieved Amplatz GooseNeck snare in the microcatheter.* ***C:*** *Illustration of the Amplatz GooseNeck snare (image reprinted with permission from Medtronic).*

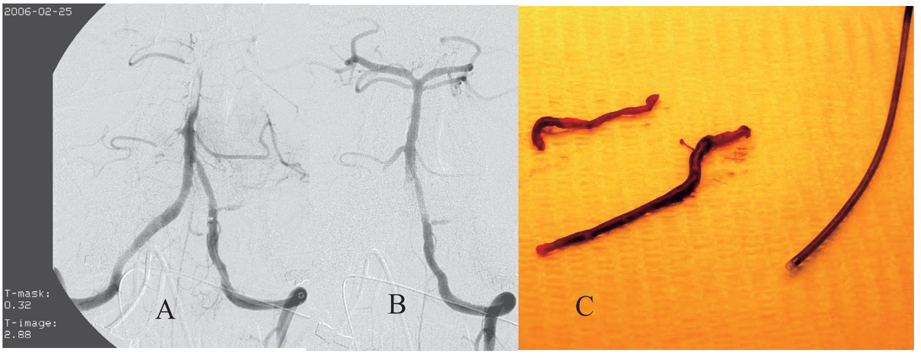

Figure 10: Extraction of a basilar embolus with aspiration through a VASCO 35+ catheter after unsuccessful embolectomy with Amplatz GooseNeck snare. ***A:*** *Before aspiration.* ***B:*** *After aspiration.* ***C:*** *The extracted embolus.*

3.3.2 Distal approach

Throughout the years, neurointerventionists tried to treat embolic occlusions with available methods such as angioplasty of the occlusion and simultaneous intraarterial thrombolysis or stenting of the occlusion. The first embolectomy device, specially designed for intracranial embolectomies was the **Merci Retrieval System**[28] (figure 11). A microcatheter is placed distally to the clot and when the Merci Retriever is in place the microcatheter is retrieved. Then the Merci Retriever will take its helical shape mostly distally to the clot but in some extend also along the occlusion site. The goal is to retrieve the system together with the clot into a guide catheter placed in the parent neck vessel under continuous aspiration. A balloon guide catheter is recommended which is inflated during extraction to minimize distal embolization due to small fragments that can break away. The first results were promising showing good recanalization results and favorable outcome in patients with successful recanalization[29-31].

The breakthrough in the endovascular stroke treatment came with the advent of the so called "**stent-retrievers**". The first stent to be used for ischemic stroke, the **Solitaire stent**, was intended for intracranial use but only for the treatment of aneurysms[32, 33] (figure 11). The advantage, in contrast to the other intracranial stents, is that these stents can be temporally placed in the vessel, fully deployed, but still could be retrieved back into the microcatheter and repositioned. The Solitaire stent was first used in single cases in 2008 and 2009. With time many case series were published showing that embolectomy with the Solitaire stent is not only feasible but also safe[34, 35]. A number of stent-retrievers developed such as for example the Catch and the Trevo devices but the technique of deployment and clot extraction is essentially the same[36, 37]. The encouraging results of mechanical embolectomy with stent-retrievers caused a spreading of the technique in neurointerventional centers worldwide.

Until then, the only approved embolectomy device by the FDA in the USA was the Merci Retrieval system. Two randomized trials, comparing the Solitaire and Trevo devices respectively to the Merci Retriever, clearly showed that recanalization was achieved more often with the stent-retrievers than the Merci Retriever, without significant difference in the procedure related complications[38, 39]. Soon thereafter, the Stent-retrievers were established as the main embolectomy device in most of the neurointerventional centers and endovascular stroke treatment become a daily practice among operators trained in catheterization of intracranial circulation and treatment of cerebrovascular diseases.

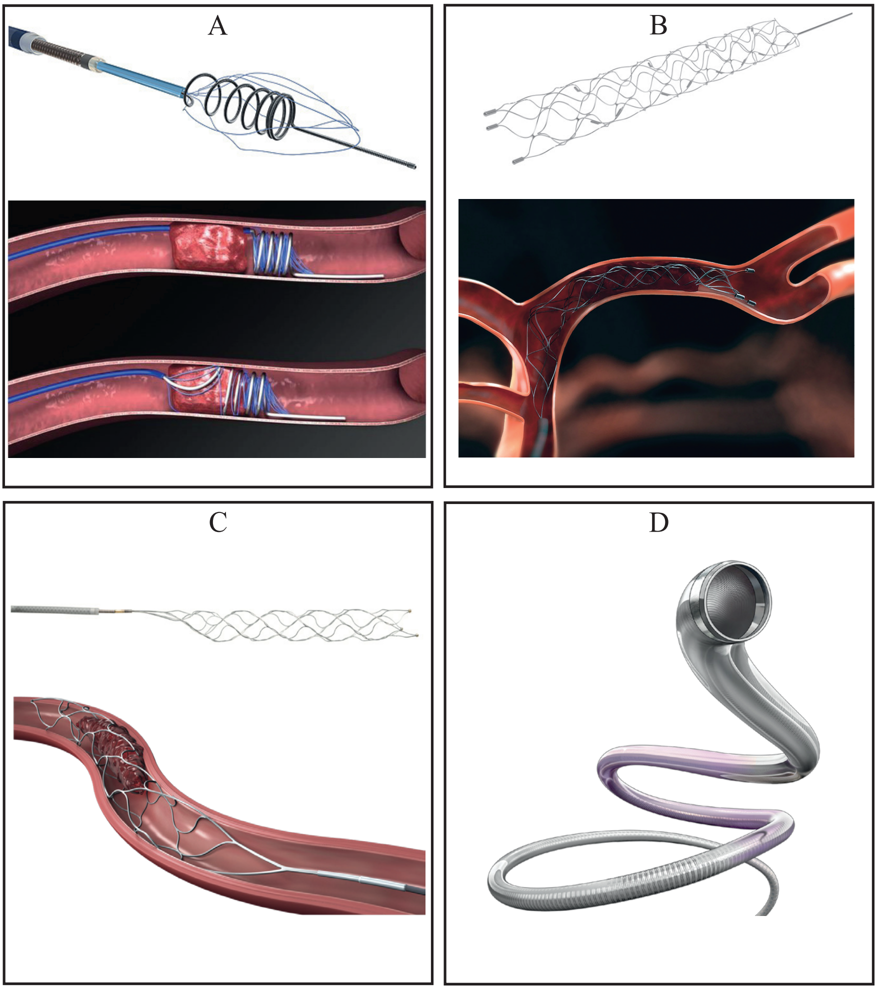

Figure 11: ***A:*** *The Merci Retriever (image reprinted with permission from Stryker).* ***B:*** *The Solitaire Platinum device (image reprinted with permission from Medtronic).* ***C:*** *Trevo XP ProVue device (image reprinted with permission from Stryker).* ***D:*** *Penumbra 5MAX ACE 68 (image reprinted with permission from Penumbra Inc.).*

3.3.3 Tandem occlusions

In approximately 20% of cases, the acute intracranial occlusion is accompanied by an extracranial occlusion, most frequently in the carotid bifurcation but occlusions can also be seen in the vertebral arteries[40, 41]. Patients with tandem occlusions respond poorly to intravenous thrombolysis[42, 43] and are associated with poor neurological outcome[44, 45]. The neurointerventionists usually have to treat the extracranial occlusion in order to gain access distally and treat the intracranial occlusion. Another reason for treating the extracranial occlusion is that clots attached to the atherosclerotic plaque might cause new embolization during catheterization or even after the treatment. In cases of dissections, a high risk of new embolization also exists, even after the treatment of the intracranial occlusion, and stenting is almost always necessary even in the presence of good flow across the dissected segment. Lastly, a significant stenosis could have been tolerated by the patient until the acute stroke onset secondary to the intracranial occlusion occurred. When the intracranial occlusion is treated the stenosis can be unstable and might acutely occlude. The patient might be functionally impaired due to the stroke and testing the patient for tolerance of the occluded stenosis is not always reliable or possible. Moreover, the patients might be treated under general anesthesia and neurological evaluation of patient's tolerance, in that case, cannot be performed. In such cases, treating of the stenosis is recommended.

There is an ongoing debate on whether the extracranial stenosis should be treated in all or only in some cases, and if so whether the extracranial stenosis should be treated first or after the intracranial occlusion[46]. In our institute, we prefer if possible, to treat the intracranial occlusion first. The extracranial stenosis on the basis of atherosclerosis is always a chronic disease and the brain circulation has already adapted to the decreased flow with development of the collateral circulation. Treating the intracranial occlusion first restores the circulation which could be sufficient for adequate reperfusion due to the already developed collaterals. Then, the operator has the opportunity to focus on the extracranial stenosis taking the extra time needed for careful assessment of the situation and for choice of the right strategy. If the stenosis shows no signs of residual clots and no signs of re-occlusion in the repeated angiograms then the stenosis is left untreated. The rationale behind this is that we do not know at that time if an infarct has already been manifested and neither do we know the size of it. Stenting of the stenosis means that a double anticoagulation regime should be prescribed as soon as possible. In the presence of a large infarct, the bleeding risk is high due to the anticoagulation. On the other side, discontinuation of anticoagulation in case of large infarct or hemorrhage increases the risk of thrombosis in the stent and subsequently the risk for new stroke. In many cases however, the stenosis re-occludes and the only choice then, if evaluation of patient´s neurological status is not possible, is to treat the stenosis. A single anticoagulation regime is preferred in these cases and a double anticoagulation is started when a large infarction is excluded on postprocedural imaging the day after.

Sometimes, the stenosis is of high grade or totally occluded and the intracranial occlusion cannot be reached. Then the extracranial stenosis will be treated first. Balloon dilatation of the stenosis is preferred in our institute for rapid access distally and treatment of the intracranial occlusion. When the intracranial occlusion is treated the stenosis will always be treated with stenting as in most of the cases the initial balloon dilatation is not sufficient for such unstable lesions. Sometimes the stenosis cannot be crossed even after dilatation and then stenting is performed before the embolectomy.

3.4 Anesthesia

	General Anesthesia	Conscious Sedation
Advantages	- No patient movement - Easier navigation in intracranial circulation - Shorter procedural time - Airway protection - Control of ventilation and oxygenation	- Shorter time to procedure start - No/minimal hypotension due to sedation - Neurological assessment - Avoid or minimize time in ICU
Disadvantages	- Delay of procedure start - Induction-related hypotension -Neurotoxic effect of anesthesia drugs - Risk for aspiration during induction and risk for pneumonia - Risk for delayed extubation and prolonged stay in ICU - Autoregulation impairment by anesthetic drugs	- Risk for longer procedural time - Increase complication rate - Risk of aspiration during the procedure - Respiration depression

Table 1: Advantages and disadvantages of GA and CS.

There are two main types of anesthesia used in the endovascular stroke treatment; general anesthesia (GA) and conscious sedation (CS) with spontaneous breathing, both having advantages and disadvantages (table 1). The role of anesthesia in endovascular stroke treatment was never debated until retrospective studies on the subject showed that general anesthesia is associated with less favorable outcome[47-64] and the debate continued with strong and valid arguments from both sides[65-71]. Before 2010, the choice of anesthesia method depended on local preferences of the neurointerventionists and the degree of engagement of anesthesiologists in the management of acute ischemic stroke. In the Sahlgrenska University hospital, the first patients who were candidates for endovascular stroke treatment in the first half of the 1990s were patients with posterior circulation stroke and general anesthesia was always used to maintain airway patency. As the endovascular stroke treatment in our institute was expanding into the anterior circulation, the method of anesthesia remained the same, mostly because the method was already established and could provide optimal work conditions for the neurointerventionist.

The increasing number of retrospective studies showing worse outcome in stroke patients treated under general anesthesia led to the change of the local routine in 2012, making CS the main method in anterior circulation stroke as it is recommended nowadays in international guidelines[72-73]. GA remained the main method in posterior circulation stroke and the alternative method in anterior circulation when contraindications to CS existed or the patient remained agitated despite adequate sedation.

Blood pressure is a crucial factor in the management of ischemic stroke. More than 85% of the patients presenting with stroke have a systolic blood pressure >150 mm Hg. Maintaining a sufficient cerebral perfusion pressure is key for keeping adequate blood flow through the collateral circulation in the ischemic penumbra and prohibiting the expansion of the infarct core until recanalization occurs.

The current recommendation during intravenous thrombolysis is to keep the blood pressure under 185/105 mm Hg due to high risk of intracerebral hemorrhage with higher blood pressure[74]. On the other hand, low blood pressure has also been associated with worse outcome probably due to impaired blood flow in the ischemic penumbra secondary to low cerebral perfusion pressure. This U shaped relationship between blood pressure during ischemic stroke and the neurological outcome (very low and very high blood pressure values associated with worse outcome) have been shown in several studies and are the basis for the current recommendations, i.e. to keep a systolic blood pressure between 140 to 180 mm Hg[75].

3.5 Randomized controlled trials

The advent of stent-retrievers led to the mobilization of all primary stroke centers to add embolectomy in the treatment options for large vessel occlusion together with intravenous thrombolysis, but also as a sole treatment in case, the patient was not eligible for intravenous treatment. Even referral centers with experienced physicians specialized in stroke would start the intravenous treatment but arrange for immediate transport of the patients with large vessel occlusion to the nearest neurointerventional center, the so called “drip and ship” method[76].

Despite the increasing use of embolectomy worldwide, the method was not validated against the standard of care treatment which was intravenous thrombolysis and many centers would first try intravenous thrombolysis and refer the patient to a neurointerventional center only when no effect was seen from the intravenous treatment. The only evidence on the effectiveness of mechanical embolectomy was single or multicenter case series and individual experiences communicated in neurointerventional and neurological congresses[77].

In 2013, three randomized trials, **the IST-III, the SYNTHESIS and the MR RESCUE** were published, failing to show superiority of endovascular stroke treatment in combination with intravenous thrombolysis compared to intravenous thrombolysis alone[78-80]. These trials had a great impact on the daily practice of stroke management. Some primary centers halted endovascular treatment and many countries withdrew reimbursement for endovascular stroke treatment.

The three trials were questioned by neurointerventionists and experts in stroke management. First, all three trials had a long recruiting period with slow enrollment of patients per center which can be attributed to the unwillingness of many physicians to randomize patients with large vessel occlusion that in their judgment would clearly benefit from endovascular treatment. This caused a selection bias during enrollment in the trials. Moreover, older endovascular methods were used with the most frequent methods being the intraarterial thrombolysis and Merci Retriever, while the stent-retrievers were only infrequently represented. This led to as low as 27% of successful recanalization reported in some cases (MR RESCUE, supplementary material). The above studies lacked also advanced radiological examinations in the vast majority of patients. Consequently, the patients were randomized to the different treatment arms without evidence of a large vessel occlusion and salvageable tissue. In MR RESCUE, patients were not only randomized to endovascular treatment and intravenous thrombolysis but also to patients with or without salvageable tissue according to imaging with perfusion techniques. The low number of patients in each of the groups, together with the slow enrollment and the use of older generation endovascular devices led to the low acceptance of this study among centers that treat stroke patients daily with newer or more effective devices.

Nonetheless, these trials were a wakeup call for the stroke community to design better trials. In 2015, the first in a series of positive trials was presented. **MR CLEAN** showed a clear superiority of the endovascular stroke treatment over intravenous thrombolysis alone without difference in mortality or occurrence of intracerebral hemorrhage between the study arms[81]. MR CLEAN succeeded to enroll most of the patients presenting with large vessel occlusion as the Dutch authorities did not allow reimbursement of endovascular stroke treatment if the treatment was not part of a clinical trial. Moreover, the patients had a proven large vessel occlusion and in the majority of cases devices with proven efficacy were used.

Because of the positive results from the MR CLEAN the enrollment in four other similar trials **(SWIFT PRIME, ESCAPE, EXTEND-IA, REVASCAT)** was halted and the interim control showed that endovascular stroke treatment was superior to intravenous thrombolysis in all four trials despite different design characteristics between them[82-85]. In 2016, the **THRACE** randomized trial was published, in which stent-retrievers but also aspiration catheters were used. Better neurological outcome was also seen in the endovascular group adding this study to the evidence for the superiority of the endovascular stroke treatment[86].

Meta-analyses of the randomized studies, as the HERMES collaboration, confirmed the results and also showed that the benefit of the treatment can be up to 7.3 hours from stroke onset[87, 88].

3.6 Posterior circulation stroke

Large vessel occlusion of the posterior cerebral circulation was not included in the randomized trials described above. Ischemic stroke in the posterior circulation is a devastating disease with a mortality of 85% if left untreated or if treatment is unsuccessful[89]. Moreover, posterior circulation stroke has a varying clinical severity ranging from mild symptoms to unconsciousness. The clinical presentation can be abrupt, abrupt with prodromal symptoms or progressive and fluctuating. This variation makes the clinical diagnosis difficult for the inexperienced physician. Moreover, the etiology of the posterior circulation stroke can be due to an embolus but in a large number of patients can be due to atherosclerotic disease of the vertebrobasilar arteries. A combination of embolus and atherosclerosis is not uncommon either. This necessitates the use of Computed Tomography Angiography (CTA) even in cases of slight suspicion of posterior circulation stroke. The time window for intravenous treatment is the same as in the anterior circulation, 4.5 hours, but for endovascular stroke treatment, it is extended to 12 hours and in some cases even further[90, 91]. This extended window is largely justified on a solidarity and humanitarian basis due to the high mortality and morbidity rates in untreated posterior circulation strokes but also to reports of favorable outcome in patients treated after 6 hours and even up to 48 hours. The larger proportion of white matter in the brainstem and sufficient collateral circulation in the cases with favorable outcome are thought to sustain the penumbral tissue longer and lead to favorable outcome even after 6 hours[92-95]. Lastly, a large portion of these patients can be unconscious before the endovascular stroke treatment can be started prompting for acute intubation and making the evaluation of the patients impossible. Patients with basilar stenosis may be in need of acute stenting and angioplasty to restore flow. The decision to treat with stent a basilar occlusion is not easy in the acute setting especially in the intubated patient. Procedural complications as occlusion of basilar perforators after stent and angioplasty or postprocedural stent thrombosis and in-stent stenosis can complicate the recovery of the patient (figure 12). Experience from stenting in symptomatic intracranial stenosis was not in favor of endovascular treatment compared to standard medical treatment and intracranial stenting is reserved for patients with new symptoms despite adequate medical treatment, and in the acute setting as a last resort treatment[96-99].

For all the above reasons, patients with posterior circulation stroke were not included in the randomized trials and until now the only evidence in endovascular treatment of posterior circulation stroke comes from case series or reports from registries[100-103]. Randomized trials are ongoing or will start in the near future[104, 105].

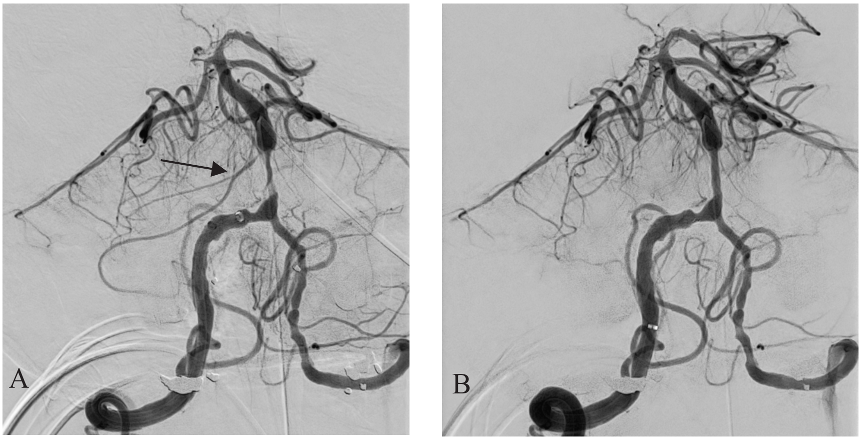

Figure 12: Patient with stenosis in proximal basilar artery (same patient as in figure 4, D-F). ***A:*** *after angioplasty and before stenting. The right AICA (arrow) originates near to the atherosclerotic plaque but is open.* ***B:*** *After stenting and repeated angioplasty. The right AICA is now occluded.*

4 STROKE WORKFLOW

4.1 Awareness

The first step in identifying eligible patients and bring them to the hospital in time is to increase the knowledge about the disease among the population. Lower educational level and income are associated with stroke recurrence even after adjusting for cardiovascular risk factors[106]. Studies have also shown that when the public is not informed, stroke symptom awareness and intention to call emergency services are very low especially among males and people with low education[107]. Many campaigns have been done and are ongoing around the world to promote stroke awareness. In Sweden, the National Stroke Campaign was initiated in October 2011 and finished in December 2013 aiming to increase awareness of stroke symptoms. The results showed a significant improvement in public knowledge of the stroke symptoms and in intention to call the emergency services during and directly after the campaign. A moderate decline was noticed afterward but the campaign was still effective 21 months later[108]. To sustain the gains of the first stroke campaign, follow-up campaigns are needed.

4.2 Prehospital workflow

Recognizing the stroke symptoms by the patient or a witness is not enough if a well-functioning prehospital workflow is not in place. The ambulance personnel should be trained not only to recognize the stroke symptoms but also to evaluate the severity of stroke and gather all the necessary information such as time of stroke onset, past medical history, and co-morbidities. This is not an easy task especially when the patient is non-communicable or unconscious.

Evaluation of stroke severity using complicated scales such as National Institutes of Health Stroke Scale (NIHSS) can be difficult for the ambulance personnel. Different scales have been created and are used such as a **modified NIHSS** created by Dr. J-E. Karlsson, Neurology Department, Sahlgrenska University Hospital and used in Västra Götaland Region, Sweden, the **Prehospital Ambulance Stroke Test (**PreHAST, created by Andsberg G, Esbjörnsson M, Olofsson A, Norrving B, von Euler M, Lund and Karolinska University, Sweden), the **A2B2** (created by Dr. N. Wahlgren and colleagues, Neurology Department, Karolinska University Hospital, Sweden), the **Los Angeles Motor Scale** (LAMS) or the **Field Assessment**

Stroke Triage to Emergency Destination (FAST-ED). Studies to validate these scales are currently under way[109]. These scales can give a quick estimation of the severity of the stroke which can help enormously in identification and transport of patients with major stroke and possible large vessel occlusion, in centers that can offer endovascular stroke treatment. Moreover, a technology that can enable direct communication between the ambulance personnel and a physician expert in stroke is currently the focus of many projects in Prehospital care[110]. A direct video feed in these cases makes possible the direct evaluation of the patient by a neurologist and mobilization of the stroke team at an earlier stage.

Over the last few years, diagnosis of an ischemic stroke in the ambulance was the focus in many projects aiming to decrease the time to treatment initiation[111]. In large metropolitan areas, ambulances and even helicopters with the capability to carry a CT scanner have been added in the prehospital workflow[112, 113]. A patient with an ischemic stroke would receive a CT scan in the ambulance and intravenous thrombolysis could then be initiated directly if no contraindications are found. In the case of large vessel occlusion, the ambulance can be directed to the nearest neurointerventional center without the need to land first in the nearest radiology department for a CT scan. The disadvantages, on the other hand, are the need of expert personnel for handling the CT scanner and the quality of the images in cases where more advanced imaging is necessary. Lastly, the proximity of such ambulances to the stroke patient can be crucial as a large number of ambulances equipped with CT scanners and with expert personnel are necessary to cover a large metropolitan area on a daily basis.

4.3 Intrahospital workflow

The transportation of stroke patients to the emergency room causes unnecessary delay in the workflow because the stroke team meets the patient in a crowded place with a lot of other acute cases. All stroke patients must undergo a CT scan to exclude intracerebral bleeding irrespectively of the neurological evaluation. Thus, a second transportation to the radiology department cannot be avoided before any decision is taken. Since 2010, all stroke cases in the Sahlgrenska University hospital are transported by the ambulance personnel directly to the radiology department bypassing the emergency room. The stroke team (stroke nurse and vascular neurologist or neurologist on call), neuroradiologist or radiologist on call and anesthesiology personnel assemble in the CT room and wait for the patient. Communication between neurologist and radiologist is essential for a quick decision. The neurologist will report the case and inform if it is anterior or posterior stroke suspicion, about the side of symptoms, the symptom onset time and the points according to the modified NIHSS or the original NIHSS if the evaluation is already performed. When the patient arrives, the neurologist will start the NIHSS evaluation but will interrupt the assessment if the radiology personnel is ready for the CT scan and continue the evaluation while the radiologist assesses the first scan. In case of no radiological and medical contraindications, the stroke nurse will give the bolus dose of intravenous rtPA. Ideally, everybody is already informed that a suspicion of large vessel occlusion exists and the radiology personnel is prepared for the CTA and Computed Tomography Perfusion (CTP) scans. When the radiologist confirms the existence of a large vessel occlusion the patient is transported to the neurointerventional angiography suite where the personnel is already warned and hopefully already prepared for the treatment. The post processing of the CTP maps is done while the patient is transported to the neurointerventional unit and the results are reported per telephone.

In case a stroke patient is referred to the Sahlgrenska University hospital from another regional hospital, the patient is usually transported directly to the neurointerventional unit. The ambulance personnel should contact the on call neurologist 20 to 30 minutes prior to arrival and if needed the patient will be re-directed to the CT laboratory for a new CT scan.

Many hospitals are adopting another approach, namely the installation of a CT scanner in the emergency room that primarily is used for stroke cases. A more advanced version of this approach is the installation of an angiography suite next to the CT scanner. This approach can guarantee the shortest transportation distance and time of the patient after arrival to the hospital. The disadvantage of this approach is that part of the neurointerventional and anesthesiology teams will be acutely re-located to the angiography suite at the emergency department. This will remove valuable resources from the neurointerventional unit, something that most of the centers cannot afford on a daily basis.

4.4 The neurointerventional unit

In the neurointerventional unit, there is always a standby stroke kit and a neurointerventionist with at least one neurointerventional nurse are always available. The stroke kit contains all the appropriate basic material to perform an angiography. Depending on the findings of the CTA (for example straightforward M1 occlusion or tandem occlusion etc.) the neurointerventionist will instruct the assisting personnel which material will be unpacked and handed over to the neurointerventional nurse. The decision to use general anesthesia or conscious sedation should already have been taken either in the CT room where the team assembled earlier or under transportation of the patient to the neurointerventional unit. In case general anesthesia is used, the process should be finished in maximum 15 minutes. During intubation and induction of GA, the neurointerventionist will try to establish a femoral access.

With a 45 cm long femoral sheath in place, a diagnostic Digital Subtraction Angiography (DSA) is performed on the side of the occlusion and at the same time the neurointerventional nurse assembles the “embolectomy catheter package”. This package consists currently of an 8F guide catheter, aspiration catheter SOFIA Plus and aspiration microcatheter Penumbra 3MAX. A quick exchange of the diagnostic catheter with the “embolectomy catheter package” takes place over a long 0.35” wire. Then, for navigation in the intracranial circulation, a 0.014” microwire is used. This is the standard method for a straightforward case, for example, an M1 occlusion but different variations of the package exist depending on the anatomy as assessed on CTA or special conditions as tandem occlusions.

The baseline blood pressure is measured non-invasively until a radial arterial catheter is in place. After two failed attempts to obtain an invasive blood pressure measurement, the blood pressure is measured non-invasively in order not to delay the procedure with more attempts. Measures are taken to avoid hypotension during intubation but also under the procedure with a systolic blood pressure between 140 and 180 mm Hg and a minimum mean arterial pressure of 100 mm Hg.

A urinary bladder catheter should be inserted before the arrival of the patient in the neurointerventional unit if no delay in the workflow is caused. Otherwise, catheter insertion is delayed as long as the patient is calm until the first available moment according to the neurointerventionist.

The key factors for a successful workflow in the angiography suite are good communication between the teams, straightforward and worked out guidelines but also knowledge of the fundamental moments and steps of the treatment. The anesthesiological team is usually working on the right side of the patient and the neurointerventional team on the left. Nevertheless, the anesthesiology nurse must quite often change sides in order to insert new intravenous access, to change infusion bags and so on without compromising the sterility on patient table and without causing delays in other aspects of the patient preparation. Both teams should clearly communicate every important moment during the procedure. For example, attempt to gain femoral access during intubation, treatment moments such as stent-retriever retrieval, balloon dilatation in carotid arteries, complications, respiratory changes and so on that can affect the patient's status should be reported.

Staff members that never or seldom take part in endovascular stroke treatment should not participate in the treatment without adequate education, guidance, and training.

4.5 Postoperative ward and stroke unit

Uncomplicated cases, treated under conscious sedation, are transported directly to the stroke unit. The stroke unit is an advanced unit dedicated to the care of stroke patients where a multidisciplinary approach in the care of the stroke patient takes place. Apart from neurologists and nurses specialized in stroke, a stroke unit includes internal medicine physicians and physiotherapists. Care in the stroke unit has been shown to decrease morbidity and mortality rates[114, 115]. Patients treated under general anesthesia are first transferred to a postoperative ward and when the patients are deemed stable will be transferred to the stroke unit. In some cases, certain postprocedural measures may be ordered as for example lowering of the blood pressure in case of carotid stenting or even sustained high blood pressure in case of an unsuccessful recanalization attempt until the effect of the anesthetic drugs wears off.

5 STROKE IMAGING

5.1 Preprocedural imaging

	CT	MRI
Advantages	• Available in all hospitals 24/7 • All radiologists can evaluate CT scans • Regular radiology staff can perform CT scan • Anesthesiology staff do not need any special training	• No radiation • Can be performed without contrast agent • Can detect infarcts minutes after stroke onset and has greater sensitivity in lacunar infarcts and posterior circulation stroke
Disadvantages	• Radiation • Contrast agent is needed • Low sensitivity in detecting infarcts the first hours after stroke onset, in lacunar infarcts and in posterior circulation stroke	• Not available 24/7 • Not all radiologists can evaluate MR • Special protocol should be in place to shorten scan time • Trained MR staff is needed • Anesthesiology staff also needs training

Table 2: Advantages and disadvantages of CT and MRI.

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are the two most frequently used modalities today in the imaging of stroke. Most frequently, CT is the method of choice in stroke imaging, mostly because of logistic reasons (table 2) but even because of the familiarity with this modality of the on call radiologists who often are residents in radiology. A clear advantage of the MRI is the higher sensitivity and specificity in detecting fresh infarcts even minutes after the stroke (figure 13). This advantage is most pronounced in lacunar infarcts and in posterior circulation stroke, especially in infarcts of the brainstem.

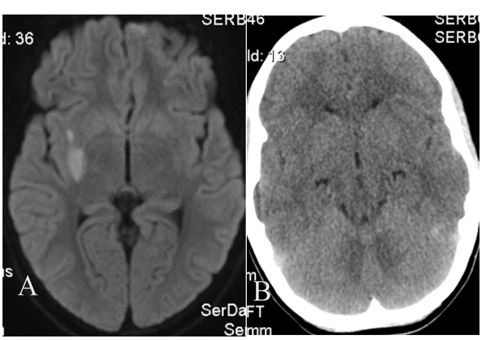

*Figure 13: Young patient presenting with acute ischemic stroke. **A:** An MRI is performed 35 minutes after stroke onset showing infarct in the posterior part of lentiform nucleus and posterior limb of internal capsule. **B:** A CT is performed 30 minutes later because of worsening clinical status. The infarct seen on MRI is not visible on the CT scan.*

5.1.1 Computed Tomography

The main use of CT is to exclude intracerebral hemorrhage and extensive infarct (for example, >1/3 of middle cerebral artery territory) before the administration of intravenous rtPA. CT can detect within an hour from stroke onset early signs of infarction such as loss of grey-white matter differentiation and hypoattenuation but also, mass effect due to edema and subsequent sulcus effacement. A significant sign of a large vessel occlusion is the "dense vessel sign" which represents the actual embolus but part of it can be due to stagnated flow proximal to the embolus. All radiologists are familiar with these early signs but a great variability is noticed in the accuracy of the detection. In cases of large vessel occlusion usually, a CT Perfusion is performed that can more accurately detect the infarct core.

CT Angiography

CTA is performed after intravenous injection of contrast media, timed to acquire images in the arterial phase. The major role of the CTA is the visualization of the occlusion site. Moreover, atherosclerotic changes in the vessels, stenosis of the carotid vessels, dissections and tortuous anatomy can be detected and evaluated directly, playing an important role in the planning of the neurointerventional procedure (figure 14).

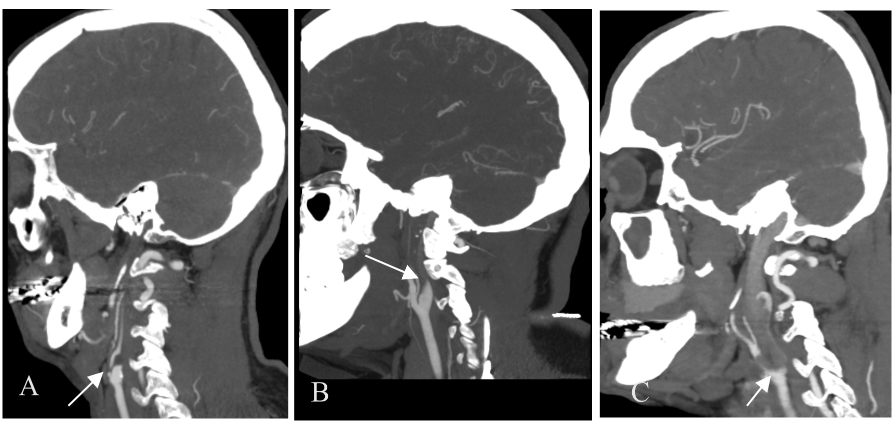

Figure 14: CTA – sagittal projections. ***A:*** *Stenosis in proximal ICA (arrow).* ***B:*** *Dissection in ICA (arrow).* ***C:*** *Large embolus lodged in the carotid bifurcation (arrow).*

A useful component of the CTA is the use of the source images to create the so called "**Poor man´s perfusion CT**". From the source images, a set of images can be created with 5 mm slice thickness and brain parenchyma window setting, which can show areas of hypoperfusion (figure 15). The detection of any hypoperfusion defect should not be interpreted as infarct core or penumbra, but solely as a hypoperfusion defect because this examination is time dependent and can include both reversible and irreversible damaged tissue in variable degrees. In the past, when older and slower generation CT scanners were used in stroke the “Poor man´s perfusion CT” was more volume-weighted and the detected defects were representing mostly infarct core. With the newer CT scanners, the source images are more flow-weighted but still lack credibility as the CTA depends greatly on timing and the operator[116]. Still, the “Poor man´s perfusion CT” can play an important role in helping less experienced radiologists to quickly verify that a hypoperfusion exists and then re-evaluate the CTA for a missed occlusion.

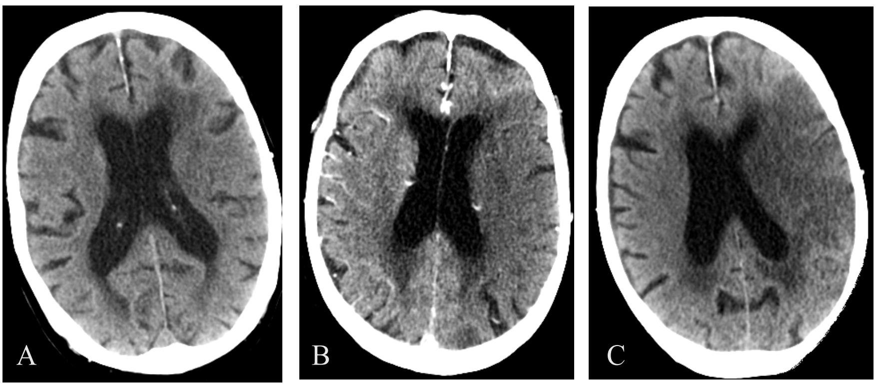

*Figure 15: Patient with acute ischemic stroke – left MCA occlusion. **A**: NCCT. **B**: “Poor man´s perfusion CT” created from the CTA. **C**: Postprocedural CT at 24 hours.*

CT Perfusion

CTP is a bolus tracking computed tomography technique studying microcirculation at the capillary level[117]. A bolus intravenous injection of contrast media is followed dynamically during its passage through the cerebral vasculature. The main parameters generated after postprocessing of the acquired images are Mean Transit Time (MTT), defined as the time needed for the contrast to pass through a given brain region, depending on the distance travelled between arterial inflow and venous outflow, the Cerebral Blood Flow (CBF), defined as the volume of blood passing through a given unit volume of brain per unit time (ml/100gr/min) and Cerebral Blood Volume (CBV) defined as the total amount of blood in a given unit volume of brain (ml/100g). These parameters are the main perfusion parameters used in stroke and are interconnected according to the central volume principle (MTT= CBV / CBF).

The role of CTP is to distinguish between infarct core (irreversible damage) and ischemic penumbra (reversible damage, salvageable tissue). Areas with prolonged MTT and diminished CBF where CBV is preserved or even increased correspond to areas with reversible damage, while areas with prolonged MTT and diminished CBF but with decreased CBV correspond to areas with irreversible damage (figure 16). Consequently, areas of mismatch between MTT/CBF and CBV means that a penumbra exists and this patient can be a candidate for reperfusion treatment. With CTP we can more accurately estimate the infarct core volume compared to NCCT, and at the same time, it can help with undetected occlusions in a similar way as "Poor man´s perfusion CT". The presence of a perfusion defect prompts the re-examination of CTA with focus now on the arteries supplying the hypoperfused region. Moreover, CTP can also help distinguish a major stroke mimic, a seizure episode which can cause the same clinical presentation as stroke. A perfusion imaging with increased CBV, increased CBF and shorter MTT along gray substance regions of the brain is characteristic of a seizure episode (figure 17). This can help physicians avoid intravenous thrombolysis and even a DSA.

CTP is a method used increasingly in centers offering endovascular stroke treatment. It was used as the sole selection method in one of the randomized trials which showed the superiority of endovascular stroke treatment versus intravenous thrombolysis, the EXTEND IA, which also showed the best neurological outcome with 71% of patients in mRS ≤2 at three months[84]. Lately, another randomized trial, the DAWN trial, showed that patients with a large vessel occlusion can benefit from endovascular stroke treatment even outside the current therapeutic window of 6 hours up to 24 hours from symptoms onset[118]. In this trial, CTP was the main imaging method for enrollment of patients in the study. These groundbreaking studies, together with a numerous other studies on CTP´s role in stroke management, show us that stroke patients can benefit from advanced imaging prior to decision making not only by selecting the appropriate patients with signs of salvageable tissue but also by including patients arriving outside the current accepted time window, who would normally be excluded, such as patients with wake-up stroke, unknown stroke onset and people presenting >6 hours from stroke onset. One of the disadvantages of CTP is that it lacks standardization of the mismatch profile. Different local protocols exist with different mismatch ratios between infarct core and ischemic penumbra. The accepted mismatch volume vary among centers from only 20% salvageable tissue to 50%. A heterogeneity exists also in acquisition and postprocessing algorithms of the perfusion parameters. Numerous vendors use different algorithms (deconvolution, maximum slope technique) for postprocessing of the perfusion parameters. This leads to the use of different maps (for example Tmax, Time to Peak etc.) and different thresholds for the definition of infarct core and ischemic penumbra[119, 120]. A more strict selection of patients according to the perfusion profile can increase the percentage of good neurological outcome at 3 months as shown in the EXTEND-IA trial where 25% of patients otherwise eligible for endovascular treatment were excluded based on CTP. This increase in favorable outcome most probably do not reflect advances in the treatment of stroke or genuine exclusion of futile recanalization but may be attributed to exclusion of large patient groups with a relatively unfavorable perfusion profile. These patients, however, could be capable of reaching an acceptable level of independency at 3 months but are excluded from the treatment.

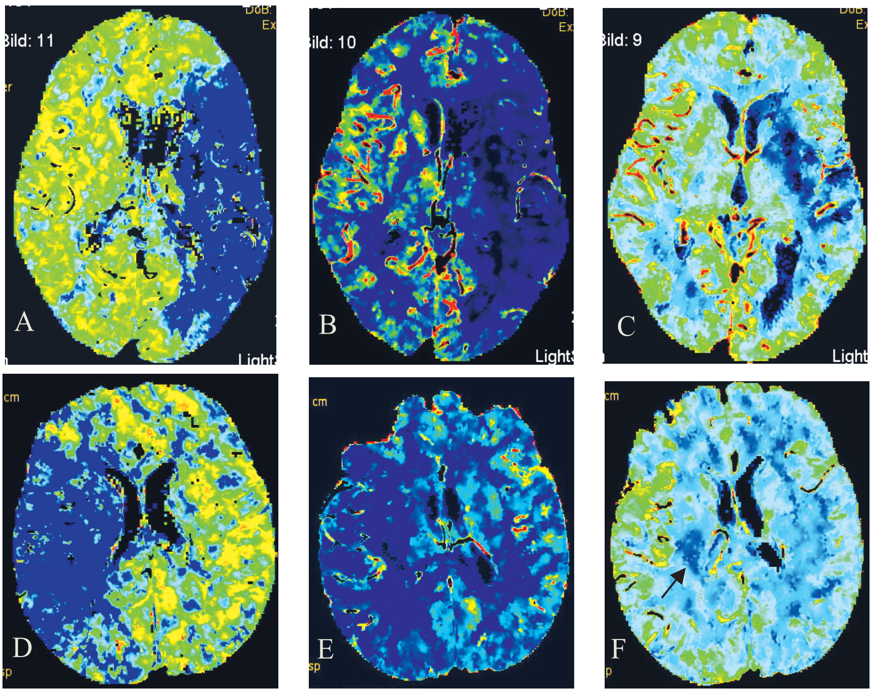

Figure 16: Patient with right-sided symptoms and aphasia ***(A-C). A:*** *Prolonged MTT is seen in the left MCA territory (blue color).* ***B:*** *Low CBF is seen in the left MCA territory.* ***C:*** *Low CBV (blue color) is seen in the lentiform nucleus, external capsule and part of the left temporal cortex corresponding to the infarct core. The rest of the regions with normal CBV but prolonged MTT and low CBF correspond to the ischemic penumbra.*
Patient with left-sided symptoms ***(D-F). D:*** *Prolonged MTT is seen in the right MCA territory (blue color).* ***E:*** *Low CBF is seen in the right MCA territory.* ***F:*** *Increased CBV is seen in the MCA territory (intense green color) except a small area of decreased CBV in the posterior part of the lentiform nucleus (black arrow). The latter corresponds to the infarct core with an estimated ischemic penumbra at > 90% of the hypoperfused area.*

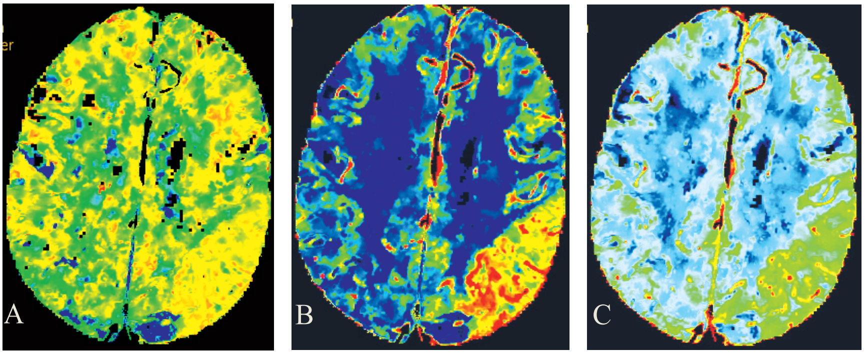

*Figure 17: Patient with right-sided symptoms (**A:** MTT, **B:** CBF, **C:** CBV). Shortened MTT (yellow), increased CBF (red/green) and increased CBV (green) are seen in the cortex of the left parietal lobe. The suggested diagnosis was seizure episode, which was verified with electroencephalography.*

Multiphase CT Angiography

The development of faster CT scanners made possible the acquisition of scans in the arterial, the venous and late venous phase during a single contrast media injection. This multiphase CTA makes possible the evaluation of the collateral circulation in a more accurate way than single CTA[121]. A good collateral circulation is associated with a favorable outcome in case of successful recanalization which has been shown in many studies but is also a self-evident fact based on the physiology of the brain circulation[122]. If the occlusion remains, the quality of the collateral system will only affect the time the infarct core will expand in the entire region at risk.

A number of different grading scales of the collateral system have been proposed through the years, both in CTA and DSA[123]. Good collateral status has shown association with reduced infarct expansion and with favorable outcome, if recanalization was successful and salvageable tissue was present at the time of imaging[124].

The presence of penumbra is directly related to the presence of collateral system and the time passed from the occlusion[6]. Multiphase CTA is an excellent way to grade the collateral system but does not give direct information on infarct core and penumbra. On the other hand, CTP has exactly this role, to detect the infarct core and penumbra. At the same time, the collateral system is indirectly reflected in the presence of a penumbra mostly when the scan is performed soon after stroke onset. If the patient appears late and the penumbra has already been transformed to infarct core, the good collaterals will still be present but the patient would not benefit from a recanalization.

In clinical practice, it is very difficult to deny treatment to a patient who arrives at the CT room and has poor collateral system according to a grading scale but still no or little manifest infarct with a visible penumbra at the same time.

A disadvantage of the CTP compared to multiphase CTA is the need for a time-consuming postprocessing. In an experienced center, the need for postprocessing is not more than 5 minutes and can be even faster with new commercially available fully automated software. But even this delay can easily be diminished if the patient is directly transported to the neurointerventional unit after the acquisition of the CTP raw data and the postprocessing is done while the patient is transported or prepared for the procedure.

5.1.2 Magnetic Resonance Imaging

The great advantage of MRI is its superiority in detecting ischemic changes as soon as seconds after vessel occlusion[125-127]. The best sequence used for early detection of the infarct core is the Diffusion Weighted Imaging (DWI). MR Angiography with and without contrast media but as well as MR Perfusion can also be performed. Performing all the usual sequences including angiography and perfusion sequences can be time-consuming but experienced centers have worked out protocols that can narrow down the examination time to lesser than 10 and even 5 minutes[128, 129]. Another disadvantage is that important contraindications to MRI such as a pacemaker or other implants must be confirmed and in the acute setting, this can be a difficult task. Then, performing the MRI examination and MRI evaluation needs expertise and experience that is not always available, especially during on call hours which interfere with the standardization of the stroke workflow.

Despite the great disadvantages of MRI in acute ischemic stroke imaging, MRI can be particularly useful in the assessment of ischemic changes in the posterior circulation and especially in the brainstem. Taking into account that CT and CTP imaging have a very low sensitivity in detection of brainstem ischemia, MRI should always be considered in suspected posterior circulation stroke, when the local workflow conditions allow it.

5.2 Postprocedural imaging

A follow-up imaging is recommended 22-36 hours after the procedure to exclude an intracerebral hemorrhage and malignant infarct. When worsening in the patient´s status is noticed the follow up can be performed earlier.

Furthermore, an earlier follow up is indicated in cases where acute stenting of carotid stenosis has taken place during the procedure, and exclusion of hemorrhage is of paramount importance before prescription of anticoagulation.

Usually, the follow-up modality is CT. The postprocedural CT should be interpreted with caution as sometimes it can underestimate the final infarct volume due to contrast staining in areas of the otherwise infarcted brain parenchyma that increase the attenuation and can resemble noninfarcted parenchyma. Sometimes the contrast leakage can be so intense that it can resemble hemorrhage. Usually, this intense contrast leakage is homogeneous and respects anatomical boundaries but in practice, it may be very difficult to exclude hemorrhage in these areas.

In general, postprocedural CT in the first 24 hours should be mostly used to exclude intracerebral hemorrhage and an already manifest malignant infarct. Otherwise, for a more precise evaluation of the infarct volume imaging is recommended 3 to 5 days after the procedure. In case of a posterior circulation stroke, where evaluation of the brainstem is needed for prognostic purposes, an MRI is the best choice.

6 BASELINE AND OUTCOME MEASUREMENTS

A number of scales and scores exist that are used to assess stroke severity but also treatment effect. The main scales and scores that were used in this thesis are presented below.

National Institutes of Health Stroke Scale (NIHSS)

The NIHSS is the most common and one of the most reliable scales used for assessment of stroke severity. It is an 11 item scale, evaluating levels of consciousness, language, visual field, extraocular movement, motor function, ataxia, dysarthria and sensory loss (table 3). According to the total points in NIHSS assessment, stroke severity is divided into four groups: Minor stroke (1-4 points), moderate stroke (5-15 points), moderate/severe stroke (16-20 points) and severe stroke (21-42 points). Apart from the stroke severity, the NIHSS is used to monitor the effect of treatment by using the scale in the immediate postoperative period and compare it with the score at admission. It has been also shown that NIHSS is a strong predictor of neurological outcome[130]. Moreover, NIHSS correlates with the affected brain volume and the level of occlusion[131, 132]. The scale has shown excellent correlation with the severity of an anterior circulation stroke but it can underestimate the severity of a posterior circulation stroke[133, 134]. Moreover, the complexity of the scale makes it very difficult to be used by inexperienced personnel, and it may even waste time. That is why a modified version has been created, the *modified* NIHSS which is a simplified version but with the same accuracy[135]. Lastly, the left hemisphere is the language-dominant one in the majority of people and language impairment can contribute with up to 7 points in the NIHSS score. This can result in higher NIHSS score in the left sided occlusions compared to the right sided ones.

In our institute, in the early years of endovascular stroke treatment, an NIHSS score of equal to or higher than 14 was one of the indications for further investigation of the patient with angiography (DSA until 2006 and CTA after 2006). This inclusion criterion was revised later to a score of 14 points in left-sided occlusions and 10 points in right-sided occlusions to avoid missing large vessel occlusions in the right hemisphere when language skills were intact[136]. When the last randomized studies were published the NIHSS cut off point for advanced radiological investigation with angiography was revised once more and decreased to 6 points[82-85].

NIHSS		
1a. Level of Consciousness (LOC)	0 = Alert; keenly responsive 1 = Arouses to minor stimulation 2 = Requires repeated stimulation to arouse 3 = Unresponsive, coma	
1b. LOC Questions (Month, age)	0 = Answers both correctly 1 = Answers one correctly 2 = Incorrect	
1b. LOC Commands (Open/close eyes, squeeze hands)	0 = Obeys both correctly 1 = Obeys one correctly 2 = Incorrect	
2. Best Gaze (Eyes open – patient follows examiner's finger or face)	0 = Normal 1 = Partial Gaze Palsy 2 = Forced deviation	
3. Visual Fields (Introduce visual stimulus/threat to patients visual field quadrants)	0 = No visual loss 1 = Partial Hemianopia 2 = Complete Hemianopia 3 = Bilateral Hemianopia (Blind)	
4. Facial Paresis (Show teeth, raise eyebrows and squeeze eyes shut)	0 = Normal 1 = Minor 2 = Partial 3 = Complete	
5a Motor Arm – Left 5b Motor Arm – Right (Elevate arm to 90° if patient is sitting, 45° if supine)	0 = No drift 1 = Drift 2 = Can't resist gravity 3 = No effort against gravity 4 = No movement x = Untestable (joint fusion or amputation)	Left Right
6a Motor Leg – Left 6b Motor Leg– Right (Elevate leg 30° with patient supine)	0 = No drift 1 = Drift 2 = Can't resist gravity 3 = No effort against gravity 4 = No movement x = Untestable (joint fusion or amputation)	Left Right
7. Limp ataxia (Finger-nose, heel down shin)	0 = No ataxia 1 = Present in one limb 2 = Present in two limbs	
8. Sensory (Pin prick to face, arm, trunk, and leg – compare sides)	0 = Normal 1 = Partial Loss 2 = Severe loss	
9. Best language (Name items, describe a picture and read a sentence)	0 = No aphasia 1 = Mild to moderate aphasia 2 = Severe aphasia 3 = Mute	
10. Dysarthria (Evaluate speech clarity by patient repeating listed words)	0 = Normal articulation 1 = Mild to moderate alluring of words 2 = Near to unintelligible or worse x = Intubated or other physical barrier	
11. Extinction and Inattention (Use information from prior testing to identify neglect or double simultaneous stimuli testing	0 = No neglect 1 = Partial neglect 2 = Complete neglect	

Table 3: National Institutes of Health Stroke Scale (NIHSS)

The Reaction Level Scale (RLS-85)

The Reaction Level Scale (RLS-85) is a scale used to measure the level of consciousness[137, 138]. It was constructed as an alternative to the widely used Glasgow Coma Scale (GCS) in order to overcome weaknesses of the latter[139]. The RLS-85 is an 8-point grading scale which takes into account only the motor response to pain stimulus. The first three grades (RLS 1-3) are different responsiveness grades in conscious patients while RLS 4-8 regard unconscious patients (Table 4). In cases of posterior circulation stroke, where stroke severity assessment according to NIHSS is challenging, the RLS can be useful in identifying possible posterior circulation insults that can be caused by large vessel occlusion.

Reaction Level Scale (RLS-85)	
1	Alert, with no delay in response (responds without stimulus).
2	Drowsy or confused, but responds to light stimulation.
3	Very drowsy or confused, but responds to strong stimulation.
4	Unconscious; localizes (moves a hand towards) a painful stimulus but does not ward it off.
5	Unconscious; makes withdrawing movements following a painful stimulus.
6	Unconscious; stereotypic flexion movements following painful stimuli.
7	Unconscious; stereotypic extension movements following painful stimuli.
8	Unconscious; no response to painful stimuli.

Table 4: Reaction Level Scale (RLS-85)

Estimation of manifest infarct size

The first time an inclusion criterion, based on the size of the manifest infarct on the CT, was introduced in the ECASS trial in 1995[140]. All patients with a manifest infarct exceeding **1/3 of the middle cerebral artery (MCA) territory** were excluded because this sign was associated with hemorrhagic transformation and poor outcome. This became also the main exclusion CT sign in clinical practice for patients eligible to receive intravenous thrombolysis. This raised, over the years, questions about the sensitivity and specificity of this exclusion criterion due to reports that showed poor agreement even between experienced neuroradiologists on detection of early ischemic signs and estimation of infarct size[141]. Moreover, patients with a manifest infarct in more than 1/3 of MCA territory could benefit from treatment, especially in large vessel occlusions, by either avoiding malignant infarct or even by gaining at least some functionality back if not full neurological independence. Later, **the Alberta Stroke Program Early CT Score (ASPECTS)** was introduced in an effort to produce a more standardized way to estimate manifest infarct[142]. In ASPECTS two regions of MCA territory are evaluated, one in the basal ganglia level and one in the supraganglionic level. In these two regions, 10 areas are evaluated for presence of early ischemic signs. The caudate nucleus, the lentiform nucleus, the insular cortex and MCA cortex divided into 3 areas (M1-frontal, M2-middle and M3-posterior) are evaluated at the basal ganglia level. At the supraganglionic level, the MCA cortex is evaluated, divided again into three areas (M4-frontal, M5-middle, and M6-posterior). A normal CT scan is awarded 10 points while 0 points indicate total infarction of the MCA territory. A cut-off point at 7 points has been used for inclusion and exclusion of patients in trials but also in clinical practice, as studies have shown association of ≤7 points with poor outcome. Again the decreased sensitivity and specificity of the CT scan in detecting early ischemic changes affect the efficacy also of the ASPECTS method. Moreover, training and experience is required for the proper implementation of ASPECTS which is very hard to achieve in centers where the evaluation of the CT scan during on call hours relies on less experienced radiologists and residents.

The above methods for estimation of manifest infarct size are not applicable in the posterior circulation. The **pc-ASPECTS** was constructed for estimation of infarct size in the posterior circulation. One point is subtracted for early ischemic changes in the left or right thalamus, cerebellum or posterior cerebral artery (PCA) territory respectively, and 2 points in any part of midbrain or pons, awarding 10 points in a normal CT scan. **The Pons Midbrain Index (PMI)** is also used in the posterior circulation, focused on ischemic changes in the midbrain and pons. Each side of the midbrain and pons is graded as 0 (no ischemic changes), 1 (ischemic changes in ≤50%) and 2 (ischemic changes in >50%). An index of 0 indicates a normal CT scan regarding pons and midbrain while 8 indicates ischemic changes in more than 50% of pons and midbrain bilaterally. Both methods were initially used in non-contrast CT (NCCT) scans and in source images of the CTA (CTA-SI) scans. The low sensitivity and specificity of NCCT in detecting early ischemic changes is even more pronounced in the posterior circulation and both methods showed a better correlation with the neurological outcome if used in CTA-SI[143]. Even in CTA-SI, a reliable estimation of the ischemic changes is not always possible because, as discussed previously, the CTA is time dependent and this can interfere with the estimation. Taking into account that a large vessel occlusion in the posterior circulation can have devastating consequences with an 85% mortality if left untreated, it is very difficult to exclude a patient from endovascular treatment if the estimation of early ischemic signs is uncertain. In this case, an MRI could definitively be more helpful if local logistical factors permit such an approach.

In our institute, the 1/3 of MCA territory method was used mainly for selection of patients who could receive intravenous thrombolysis. In cases of proximal vessel occlusion, this method was not an absolute contraindication.

Nevertheless, no patients with more than ½ of the MCA territory were identified in the retrospective studies while in the prospective AnStroke trial, patients with a manifest infarct in more than 1/3 of MCA territory, detected on initial NCCT, were excluded. ASPECTS was used only in the evaluation of the included cases during retrospective analysis of the data and never in clinical practice. In the posterior circulation, the clinical criteria for selection of patients for endovascular stroke treatment were quite liberal in regard to infarct estimation and only clearly visible signs of infarct in the brainstem were a contraindication. The pc-ASPECTS and PMI were also used in the retrospective evaluation of the included cases and not in clinical practice.

Assessment of collateral circulation

Different scales have been used for retrospective assessment of collateral circulation and many have shown association with outcome. The scale used in the thesis is a 5-point scale according to **Christoforidis**[144] (table 5). This scale was used in the CTA but a similar version exists for DSA[145]. The disadvantage with assessment of collaterals on DSA is that angiography of the contralateral side and the posterior circulation might be needed for correct assessment of the collateral circulation, which can be time-consuming. On the other hand assessment of collaterals on CTA can be over- or underestimated depending on the timing of the scan. That is the reason why multiphase CTA is a more accurate method in depicting collateral circulation than single-phase CTA, but multiphase CTA has its disadvantages especially when CTP method is available.

Collateral system according to Christoforidis	
1	Collaterals reconstituted the distal portion of the occluded vessel segment (i.e., if there was M1 segment occlusion the M1 segment distal to the occlusion reconstituted).
2	Collaterals reconstituted vessels in the proximal portion of the segment adjacent to the occluded vessel (i.e. if there was M1 segment occlusion with reconstitution to the proximal M2 vessel segments).
3	Collaterals reconstituted vessels in the distal portion of the segment adjacent to the occluded vessel (i.e. if there was M1 segment occlusion with reconstitution to the distal portion of the M2 vessel segments).
4	Collaterals reconstituted vessels two segments distal to the occluded vessel (i.e. if there was M1 segment occlusion with reconstitution up to the M3 segment branches).
5	Little or no significant reconstitution of the territory of the occluded vessel.

Table 5: Collateral system according to Christoforidis.

In the posterior circulation, the collateral circulation was retrospectively assessed with the **Basilar Artery on Computed Tomography Angiography (BATMAN)** which is a 10-point grading scale based on CTA. A score of 10 points means that one point is assigned if the following arteries and segments are patent: either intracranial vertebral artery, each segment of the basilar artery, (the proximal segment, extending from the vertebrobasilar junction to the origin of AICAs, the middle segment from the origins of AICAs to the origin of SCAs, and the rostral segment from the origin of SCAs to its rostral end) and for each patent P1 segment of PCA. Two points are allocated for each posterior communicating artery and 1 point for a hypoplastic posterior communicating artery (defined as smaller than 1 mm) if in continuity with the top of the basilar artery via a P1 PCA segment. Three points are allocated for each fetal posterior communicating artery. The BATMAN score has the advantages of earlier scales without their weakness and at the same time incorporates thrombus burden[146].

These scales were used only during the evaluation of the data for the studies in order to compare our results to other international studies. In clinical practice, the assessment of collateral circulation can be time-consuming and as mentioned earlier it is very difficult to deny treatment to a patient presenting with bad collateral circulation but no or little manifest infarct at the time.

For calculation of the infarct volume the **ABC/2** method was used which assumes an ellipsoid shape of the infarct but makes adjustments to slices based on the proportional representation of the largest volume. This method is reproducible, accurate and has been validated for assessment of intracerebral hemorrhage and for infarct volume[147].

Modified Treatment in Cerebral Ischemia (mTICI)

In the early trials in the 1990s the reperfusion was assessed with the Thrombolysis in Myocardial Infarction (TIMI) grading scale, a scale already used in interventional cardiology[148]. Later the Thrombolysis in Cerebral Infarction (TICI) was created based on the TIMI scale[149]. A modified version was developed (mTICI) later with a difference in the size of the target artery territory showing reperfusion[150]. In the modified TICI a 2b grade is defined as reperfusion in more than 50% of target artery territory while in the original TICI the 2b grade was defined as reperfusion in more than 2/3 of the target artery territory. In both the original and modified TICI scales reperfusion of almost the whole MCA territory with only very distal embolus remaining would be classified as a 2b grade. A proposal to add an extra grade in the TICI scores, the 2c grade, was adopted by many institutes in order to distinguish the last entity[151, 152]. The numerous scales led to confusion and difficulty to compare studies. A consensus recommendation for the standardization of grading in endovascular stroke treatment was made with the proposal of the modified Treatment in Cerebral Ischemia[153] (table 6).

modified Treatment In Cerebral Ischemia (mTICI)	
Grade 0:	no perfusion
Grade 1:	antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion
Grade 2:	
Grade 2a:	antegrade reperfusion of less than half of the occluded target artery previously ischemic territory (e.g. in one major division of the middle cerebral artery (MCA) and its territory)
Grade 2b:	antegrade reperfusion of more than half of the previously occluded target artery ischemic territory (e.g. in two major divisions of the MCA and their territories)
Grade 3:	complete antegrade reperfusion of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches

Table 6: modified Treatment in Cerebral Ischemia (mTICI)

Modified Rankin Scale (mRS)

The most commonly used scale for assessment of the degree of disability in daily activities of stroke patients is the modified Rankin Scale (mRS) [154, 155]. It is most often evaluated 3 months after the stroke and it is composed of 7 groups extending from group 0 representing healthy and independent patients without symptoms to group 6 representing death (table 7). In most trials and in the studies in this thesis, patients that achieved mRS ≤2 are considered having a favorable neurological outcome. A moderately favorable outcome was defined as mRS ≤3 and it was proposed by some registries to also be included in the results due to the devastating nature of posterior circulation stroke.

modified Rankin Scale (mRS)	
0	- No symptoms.
1	- No significant disability despite
2	- Slight disability; able to look after own affairs without assistance, but unable to carry out all previous activities.
3	- Moderate disability; requires some help, but able to walk without assistance.
4	- Moderately severe disability; unable to attend to own bodily needs without assistance, and unable to walk without assistance.
5	- Severe disability; requires constant nursing care and attention, bedridden, incontinent.
6	- Dead.

Table 7: modified Rankin Scale (mRS)

Time Intervals

The time intervals used in this thesis are the following:

-Stroke onset to CT: This time interval includes time for the ambulance to arrive at patients' location, initial examination in place and transportation time to nearest CT room until the first image of the CT scan.

-Stroke onset to groin puncture: This time interval includes time for the ambulance to arrive at patients' location, initial examination in place, transportation time to nearest CT room, CT examination and neurological evaluation time in the CT laboratory, transportation to neurointervention suite, time for patient preparation and anesthesia induction until groin puncture.

-Stroke onset to recanalization/end of procedure: This time interval includes time for the ambulance to arrive at patients' location, initial examination in place, transportation time to nearest CT laboratory, CT examination and neurological evaluation time in the CT laboratory, transportation to neurointervention suite, time for patient preparation and anesthesia induction, time of procedure until first image where recanalization is visualized or until time of final angiographic run in case of unsuccessful embolectomy.

-CT to groin puncture: This time interval includes time from first image of the NCCT examination, CT examination and neurological evaluation time in the CT room, transportation to neurointervention suite, time for patient preparation and anesthesia induction until groin puncture.

-CT to recanalization/end of procedure: This time interval includes time from first image of the NCCT examination, CT examination and neurological evaluation time in the CT room, transportation to neurointervention suite, time for patient preparation and anesthesia induction, time of procedure until first image where recanalization is visualized or until time of final angiographic run in case of unsuccessful embolectomy.

-Arrival to neurointervention suite to groin puncture: This time interval includes time for patient preparation and anesthesia induction until groin puncture.

-Groin puncture to recanalization/end of procedure: This time interval includes time of procedure from groin puncture until first image where recanalization is visualized or until time of final angiographic run in case of unsuccessful embolectomy.

7 AIM

This thesis had the following aims:

- To study the efficacy and safety of the endovascular stroke treatment in the anterior and posterior circulation ischemic stroke and its effect on neurological outcome (Papers I and II)
- To evaluate the impact of intra-procedural hypotension on the neurological outcome in patients with ischemic stroke undergoing endovascular treatment under general anesthesia (Paper III)
- To compare the neurological outcome after endovascular stroke treatment in patients randomized to undergo the treatment under general anesthesia or conscious sedation (Paper IV).

8 PATIENTS AND METHODS

8.1 Papers I-III

8.1.1 Patients

The first three papers of the thesis are retrospective studies. Approval by the Regional Ethical Review Board in Gothenburg was obtained (No: 455-12). All patients were identified in the prospective hospital-certified database of the Neurointerventional unit at the Sahlgrenska University Hospital. Patients were either directly admitted to the Sahlgrenska University Hospital or referred from other hospitals in the Västra Götaland region (population of approximately 1.7 million). Occasionally patients from nearby regions were referred to our center due either to geographic proximity or to unavailability of neurointerventional service.

In paper I, 156 cases with acute ischemic stroke in the anterior circulation who have been treated intra-arterially in the period 2000-2011 were included. Although endovascular stroke treatments started 1994 and 179 patients could be identified since then, the overwhelming majority of the radiological data between the years 1994 and 1999 could not be retrieved from the regional archive. For this reason, the inclusion of patients in the study started the year 2000.

In paper II, 110 patients with acute ischemic stroke in the posterior circulation were included. All patients underwent endovascular treatment in the period 1991-2015.

Paper III includes 108 patients with acute ischemic stroke in the anterior circulation treated intra-arterially under general anesthesia in the period 2007-2012. In this paper, no patients treated before 2007 were included due to lack of sufficient anesthesiological data in the hospital's medical archive.

8.1.2 Methods

Radiological data were retrieved from the regional archive. Neurological and anesthesiological data were retrieved from the hospital's medical archive. The re-evaluation of the radiological data was performed by trained neuroradiologists. The neurological data was obtained by vascular neurologists. If the mRS was obtained by a nonvascular neurologist or in case of incomplete data, a vascular neurologist would contact the patient or close relatives to confirm the data. In paper III, the anesthesiological data were collected and interpreted by an experienced anesthesiologist.

Statistical analysis

In papers I-III descriptive statistics were used depending on the distribution of the variables. Univariate analysis was performed using the Mann-Whitney U-test or t-test as appropriate. For dichotomous data, the Fisher´s exact test was used. In papers II and III, the cohorts were divided into favorable and poor neurological outcome groups. All parameters with probability value <0.1 in the univariate analysis were included in the multiple logistic regression for assessment of independent predictors of poor neurological outcome. Statistical significance was set at $P <.05$.

8.2 Paper IV

8.2.1 Patients

The fourth paper is a randomized controlled trial and it was approved by the Regional Ethical Review Board in Gothenburg (No: 013-13). The trial was registered on https://clinicaltrials.gov with a unique identifier: NCT01872884.

A total of 321 patients, admitted to our Institute with acute ischemic stroke in the anterior circulation from November 2013 to June 2016, were assessed for eligibility in the AnStroke trial (figure 18). An oral informed consent from the patient or next of kin was mandatory for inclusion in the study. Written informed consent was obtained as soon as the patient was in a status to understand and sign the consent after the treatment or from next of kin if the patient was unable to consent or deceased. Inclusion criteria were: a) ≥ 18 years of age, b) proven occlusion in the anterior cerebral circulation by CTA and/or NIHSS score ≥ 10 (if right sided occlusion) or ≥ 14 (if left sided occlusion), c) treatment initiated within 8 hours after onset of symptoms. Exclusion criteria were: a) the patient was not eligible for randomization due to anesthesiological concerns (airway, agitation etc.) at the discretion of the attending anesthesiologist b) occlusion of posterior cerebral circulation c) intracranial hemorrhage d) spontaneous neurological recovery and/or recanalization before or during angiography e) premorbidity mRS ≥ 4 or other comorbidity contraindicating embolectomy.

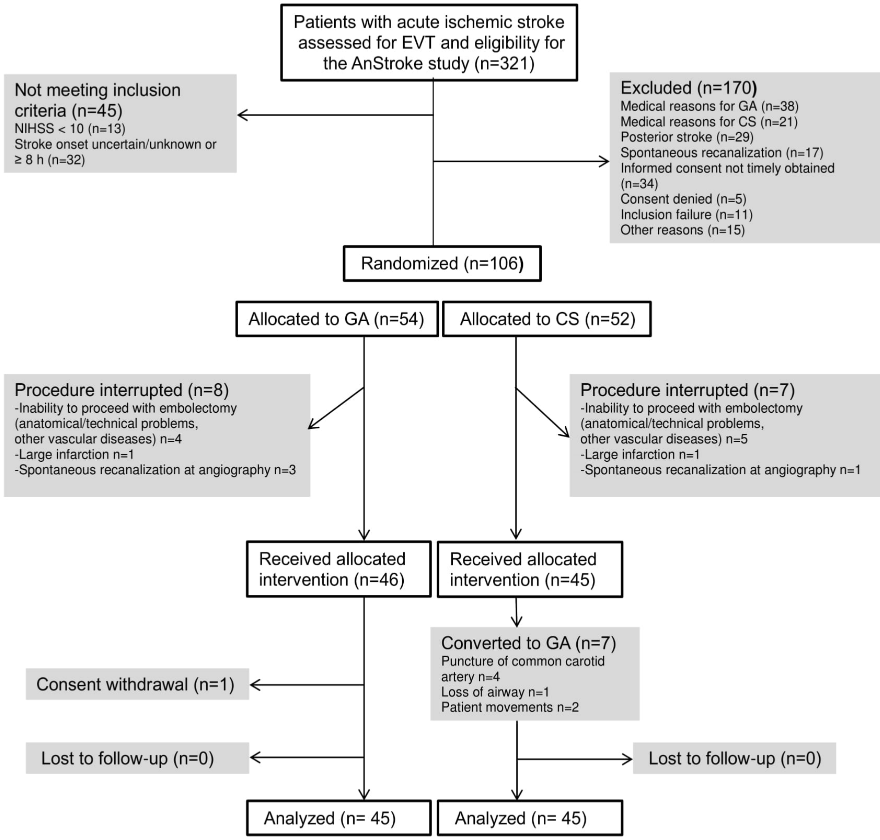

Figure 18: Consort diagram AnStroke Trial (Paper IV). EVT: Endovascular treatment.

8.2.2 Methods

When informed consent was obtained, the patients were randomized to general anesthesia or conscious sedation in a 1:1 ratio using sealed non-transparent envelopes.

All treatments were performed in accordance with pre-specified radiological, neurointerventional and anesthesiological study protocols. All patients received NCCT and CTA before treatment. Patients admitted directly to our institute received in addition CTP. All four neurointerventionists were trained interventional neuroradiologists in the same institute using the same methodology in endovascular stroke treatment. The assisting personnel was two trained neurointerventional nurses during office hours and one trained neurointerventional nurse with a nurse assistant during on call hours. All pre-specified neurointerventional parameters, as time points, devices used, number of passes, patient reaction according to the neurointerventionist and complications were registered during and directly after the procedure.

Assessment of vessel tortuosity, quality of angiography and patient movements according to pre-specified scales were also registered. The choice of endovascular technique was at the discretion of the neurointerventionist in charge but most often the technique that was chosen as the primary one was the proximal approach with aspiration or Amplatz GooseNeck snare. When the proximal approach failed, a combination of techniques was used. In fourteen patients, stent-retrievers were the first choice due to the inclusion of these patients in the SITS-Open trial where the use of stent-retrievers as first choice was mandatory. The angiographic result was defined according to the modified Treatment in Cerebral Ischemia (mTICI) scale.

In all cases, an anesthesiologist was involved in the decision to treat and include the patient in the study. Both methods of anesthesia were performed according to a standardized protocol and blood pressure measurements were obtained by a radial arterial catheter as soon as possible during the procedure. The baseline MAP (last recorded MAP before induction) was always measured non-invasively. A systolic blood pressure of 140-180 mmHg was the target blood pressure in all patients until reperfusion was achieved. GA was induced by propofol and remifentanil, maintained with sevoflurane and remifentanil. Normoventilation was the standard setting in all patients. CS was maintained with remifentanil infusion. Dopamine, ephedrine, phenylephrine or norepinephrine was used for inotropic and/or vasoactive treatment. All anesthesiological data were registered during the procedure and stored in the patient's study file.

A routine NCCT was performed 22-36 hours after the procedure for evaluation of infarct volume, hemorrhagic complication, and mass effect. For more reliable evaluation of the infarct volume, an MRI was performed day 3 after the procedure. An MRI was also performed at 3 months after the procedure at the same time as the return visit to the vascular neurologist for clinical evaluation. The purpose of the extra MRI was to exclude a new infarct or another process during the 3 months that could interfere with the clinical evaluation.

The stroke severity was evaluated with NIHSS at admission by a neurologist. Patients who were referred to our institute were re-evaluated by a neurologist upon arrival to the neurointerventional unit. The neurological status of the patient was evaluated with NIHSS day 1, day 3 and day 4-7 or at discharge. The primary outcome of the study was the mRS at 3 months assessed by a vascular neurologist with a personal interview of the patient.

The review of the radiological data was done by trained neuroradiologists blinded to the neurological outcome. The mRS was assessed by vascular neurologists blinded to treatment allocation and angiographic result.

Statistical analysis

The power analysis was based on a pilot study conducted at the Sahlgrenska University Hospital prior to design of the AnStroke trial as well as on the retrospective studies[47-50]. The pilot study showed a 50% mRS ≤2 at 3 months for patients treated with endovascular treatment under GA and the retrospective studies showed an mRS ≤2 from 20 to 40% units lower in the CS group. The sample size needed to detect a difference of 30% was calculated to be approximately 80 patients. The primary analysis was done according to the intention-to-treat principle. Descriptive statistics were used for the variables according to their distribution. Differences in outcome data between GA and CS were studied using the Mann-Whitney U-test or t-test as appropriate for continuous data and the Fisher´s exact for dichotomous data. The mRS at 3 months were compared using a 2x7 χ^2 test. Statistical significance was set at $P < .05$.

9 RESULTS

9.1 Paper I

The study criteria were met in 156 cases (155 patients) who had undergone endovascular stroke treatment in the anterior circulation from 2000 to 2011. The mean age of the cohort was 64±13.9, 63% were men and in 60% of the cases, the occlusion involved the left hemisphere. In 54% of the cases the M1 segment of the middle cerebral artery was involved and in 29% the occlusion was located in the terminal carotid segment occluding proximal parts of anterior and middle cerebral arteries. The most frequent cause of stroke was cardioembolic in 61%. The median NIHSS score was 20 and the median stroke onset to groin puncture time was 171 minutes.

Successful recanalization (mTICI grades 2b/3) was seen in 74% of the cases. The Amplatz GooseNeck snare was the first device in 129 cases and it was successful in 70% of these cases. The Solitaire FR was used in 33 cases, the MERCI retriever in 18 cases but a combination of different devices was used in 49 cases.

Hypoattenuation in <1/3 of MCA territory in the initial NCCT was not an absolute contraindication to endovascular stroke treatment in our institute and 22% of the patients who underwent treatment had a hypoattenuation between 1/3 and 1/2 of the MCA territory. Analysis of the two groups with less and more than 1/3 hypoattenuation of the MCA territory showed no difference in the favorable outcome at 3 months with 56% and 42% mRS ≤2 respectively in patients with successful recanalization (Table 8).

	mRS ≤2		MRS 6	
	mTICI 0-2a	mTICI 2b/3	mTICI 0-2a	mTICI 2b/3
Hypoattenuation <1/3 MCA 119 (78%)	6 (19%)	49 (56%)	10(32%)	5 (6%)
Hypoattenuation >1/3 MCA 34 (22%)	1 (15%)	8 (42%)	6 (40%)	6 (32%)

Table 8: Results of patients with hypoattenuation in <1/3 of MCA territory and patients with hypoattenuation in >1/3 of MCA territory.

Serious procedural complications were seen in 5% of the cases. All complications occurred during microcatheterization distal to the occlusion site or during retrieval of a stent-retriever. No complications were seen during treatment using only the proximal approach. The lowest recanalization rate was seen in Carotid-T occlusion with only 55.5%.

Symptomatic Intracranial Hemorrhage (sICH) was seen in 4%. At 3 months, 42% of the patients reached an mRS ≤2 and the mortality rate was 17%.

9.2 Paper II

From our database, 110 patients who underwent endovascular stroke treatment in the posterior circulation between 1991 and 2015 met the criteria for inclusion in the study. Mean age in the whole cohort was 62±13 and 67% of the patients were males. The most frequent site of occlusion was the distal basilar artery, comprising 44.5%. The median NIHSS score was 31 (13-31) and 52% of the patients were in an unconscious state (RLS severity levels 4-8). The median time from stroke onset to groin puncture was 300 (175-463) minutes. Successful recanalization was seen in 73% and the most frequent method was embolectomy, performed in 65%, followed by intraarterial thrombolysis in 15%. Stenting and angioplasty were used in 11% of the cases. Serious procedure related complications were seen in 5%. Most of these complications occurred while trying to place the guidewire or the microcatheter distal to the clot or under retrieval of a stent-retriever. The rest of the complications occurred during placement of the guide catheter in the vertebral artery or catheterization of a tortuous and atherosclerotic iliac artery. No complications occurred during the proximal approach of embolectomy. Clot migration into a territory previously not affected was seen in 11%.

A favorable neurological outcome (mRS ≤2) at 3 months was reached in 35% while a moderately favorable neurological outcome (mRS ≤3) at 3 months was reached in 44%. An mRS ≤2 of 44% and mRS ≤3 of 55% was seen when the recanalization was successful compared to only 10% mRS ≤2 and 13% mRS ≤3 with unsuccessful recanalization. A huge difference was also seen in the mortality rate with 70% in case of unsuccessful recanalization which dropped to 30% when the occluded vessel was recanalized. The mortality rate at 3 months in the whole cohort was 41% with the majority being in hospital mortality (38%). A severity level of 4-8 in RLS at admission, occlusion of the whole basilar artery and occurrence of sICH were associated with poor outcome. In the binary logistic regression, the BATMAN score and successful recanalization were independent predictors of poor neurological outcome.

9.3 Paper III

In this study, 108 patients who underwent endovascular stroke treatment under GA in the period 2007-2012 were included and the impact of the intraprocedural hypotension on the neurological outcome was studied. The median age of the whole cohort was 70 (62-77) years and 61% of the patients were male. Median NIHSS was 21 (18-24). Successful recanalization was seen in 77% and the median time from stroke onset to groin puncture was 171 (136-248) minutes. Favorable outcome with mRS ≤2 was seen in 38%. Baseline mean arterial pressure was 107 (93-120) mm Hg.

The cohort was divided into groups with favorable and poor neurological outcome. The NIHSS in the poor neurological outcome group was 22 (19-24) compared to 19 (16.5-22) in the favorable neurological outcome group (p=.024). The frequency of successful recanalization was significantly higher in the favorable outcome group (98% compared to 64%), (p<.0001) and the time from stroke onset to recanalization/end of procedure was significantly shorter (234 vs 301 minutes) (p=.005). A substantial fall in the arterial blood pressure was seen in all patients but more pronounced in patients with poor neurological outcome (figure 19).

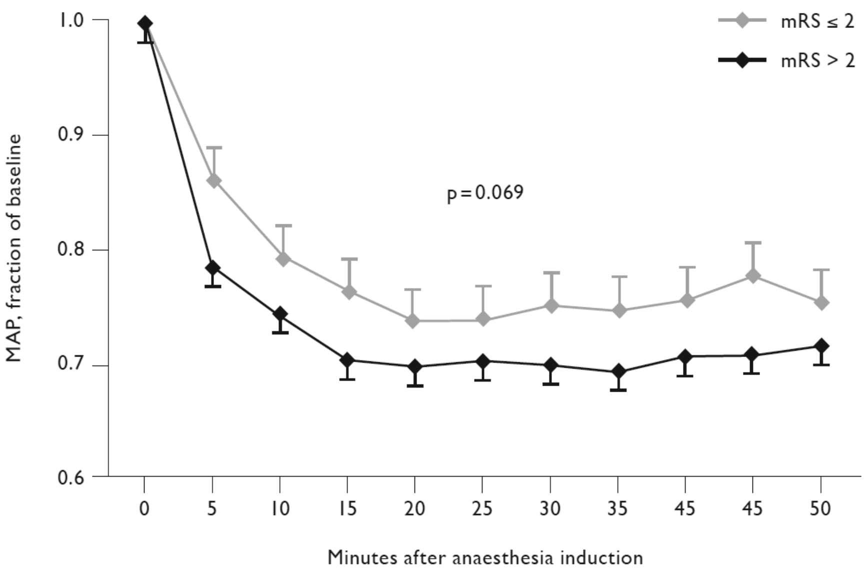

Figure 19: Changes in MAP, expressed as a fraction of baseline MAP. In patients with poor neurological outcome (mRS > 2), a more pronounced fall in MAP was seen after induction of anesthesia (Image created by Pia Löwhagen Hendén).

A fall of >40% from baseline was associated with worse neurological outcome and it was significantly higher in the poor neurological outcome group (p=.04) (figure 20).

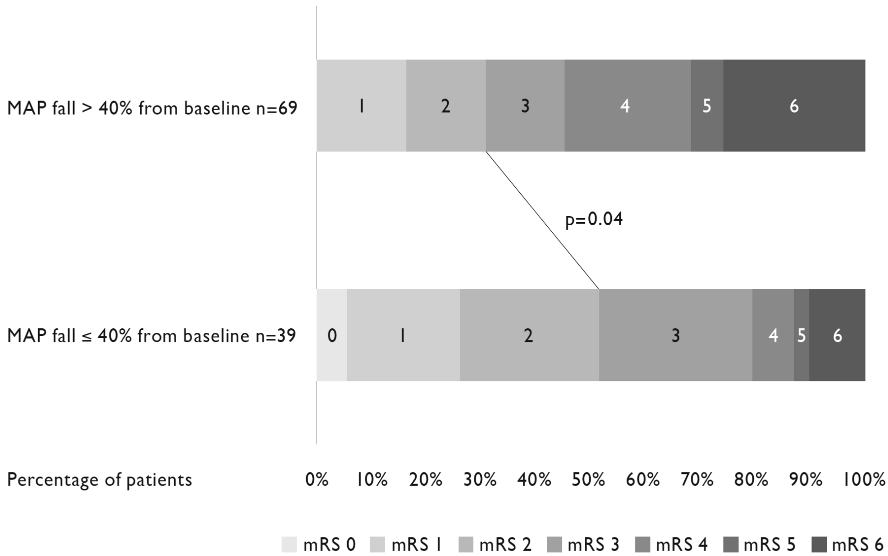

Figure 20: Neurological outcome expressed as mRS at 3 months in patients with and without a fall in MAP > 40% from baseline during general anesthesia. The proportion of patients with poor neurological outcome (mRS > 2) was higher in patients experiencing a fall in MAP > 40% from baseline. (Figure reprinted from Löwhagen Hendén et al, Stroke 2015 with permission from the publisher).

The independent predictors of poor neurological outcome according to the multiple logistic regression were, the NIHSS with odds ratio 1.18 (CI 95%: 1.05-1.34), (p=.008), the lack of successful recanalization with odds ratio 25.6 (CI 95%: 2.96-250), (p=.003) and the occurrence of >40% fall in MAP from baseline with odds ratio 2.8 (CI 95%: 1.09-7.19), (P=.032).

9.4 Paper IV

Totally, 90 patients, eligible for endovascular stroke treatment in the anterior circulation were included in the AnStroke trial and randomized to GA or CS. The median age of the whole cohort was 72 years (65-80) and 54% of the patients were men. The median NIHSS was 18 (15-22) and median ASPECTS was 10 (8-10). Successful recanalization was seen in 90% of the patients and the median time from stroke onset to groin puncture was 91(59-122) minutes. Two time intervals could be influenced by the method of anesthesia, the time from arrival to neurointervention suite to groin puncture and from groin puncture to recanalization/end of procedure. The first was 27 (16-45) minutes for the whole cohort and the second was 62 (39-105) minutes. The baseline MAP for the whole cohort was 107 (93-120) mm Hg. Favorable outcome with mRS ≤2 was seen in 41%.

The groups were well balanced for patient characteristics. The median NIHSS score at admission was higher in the GA group (20 vs 17 in the CS group). Most frequent occlusion site was the M1 segment in both groups (58%). The majority of the occlusions in the GA group was in the left hemisphere (58%) while in the CS group the majority of the occlusions was in the right hemisphere (62%). No differences were found between the groups in any of the time intervals. Median arrival to neurointervention suite – groin puncture time was longer in the GA group (34 compared to 25 minutes) while groin puncture – recanalization/end of procedure media time was longer in the CS group (74 compared to 55 minutes). Nonetheless, none of the differences in these time intervals were statistically significant. Substantial patient movements with lower angiographic quality were more frequent in the CS group as expected. No difference was seen between the groups in baseline mean arterial pressure or mean arterial pressure fraction during the procedure (figure 21). No difference was seen in occurrence of >40% fall in mean arterial pressure. Finally, no differences were seen regarding interventional or anesthesiological complications.

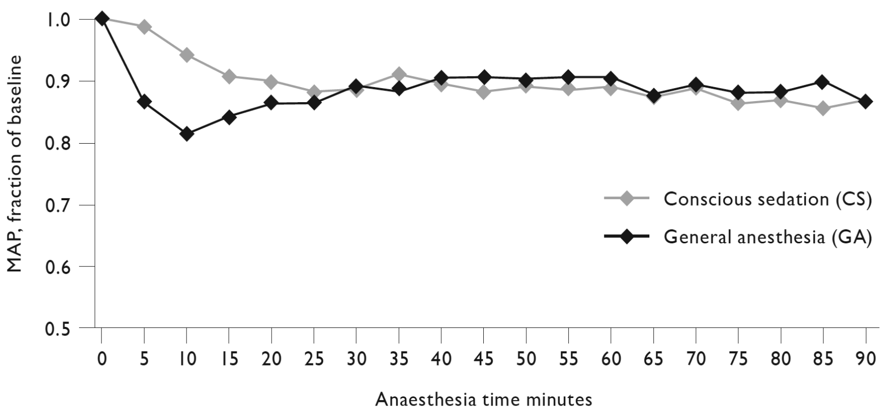

Figure 21: Changes in MAP, expressed as a fraction of baseline MAP in patients under GA versus CS. Mean values. (Image created by Pia Löwhagen Hendén).

The primary outcome of the study, the mRS at 3 months was similar in both groups with 42% mRS ≤2 in the GA group and 40% in the CS group. No differences were found in the median 24 hours NIHSS (8 in the GA group compared to 9 in the CS group) or postprocedural infarct volume (20 ml in both groups).

The AnStroke trial consequently, found no difference between the two methods of anesthesia regarding the primary or the secondary outcomes.

10 DISCUSSION

10.1 Papers I and II: Endovascular stroke treatment in anterior and posterior circulation

General considerations

Intravenous thrombolysis has been shown to significantly reduce mortality and dependency in patients suffering acute ischemic stroke[156]. However, intravenous thrombolysis is less effective in proximal occlusion of large intracranial vessels with recanalization rates ranging from only 5% in internal carotid occlusions to 30% in the middle cerebral artery[157, 158]. Local intraarterial thrombolysis was a promising technique and the only available option in the early years of endovascular stroke therapy. With this method, the occluded vessel is directly accessed and the thrombolysis can be infused into the embolus. The method showed promising results compared with placebo and standard of care at the time but still was limited by the same contraindications as intravenous thrombolysis as well as relative ineffectiveness in cases with large clot burden.

In our institute, mechanical embolectomy with the Amplatz GooseNeck snare was started in 1994 and with the first case series published, its use became standardized[26, 27]. At the same time, endovascular stroke treatment was almost exclusively performed in other centers with intraarterial thrombolysis until the Merci Retriever obtained clearance from the FDA. Later when the Solitaire stent-retriever became available, embolectomy became the main endovascular method in most of the neurointerventional centers in the world[35]. New devices emerged and studies showed the superiority of embolectomy in recanalization of large vessel occlusion[38]. At the same time, the treatment is an invasive one and it carries all the risks of an interventional procedure. That is why calls for randomized studies increased, as popularity and usage of embolectomy were increasing. This caused an ethical dilemma regarding participation in randomized studies because many centers had already seen the beneficial results of the method in their patients. In our institute, mechanical embolectomy with the Amplatz GooseNeck snare was already established as the standard method and remained the main method despite the advent of stent-retrievers. All other devices, from the Merci Retriever to the Solitaire and newer devices were tested but remained the second choice of the method in case the Amplatz

GooseNeck snare did not work. The primary goal of the papers I and II was to study if the primary methods of endovascular stroke therapy in our institute was as effective and safe as other case series have shown for newer devices. When the data for the paper I were collected, the trials IST III, MR-RESCUE and EXTEND-IA were published (in 2013) and all failed to show superiority of endovascular treatment over intravenous thrombolysis[78-80].

Paper I

In this study, we found that mechanical embolectomy and in particular embolectomy with Amplatz GooseNeck snare, which was the first device in the majority of the cases, was effective in 74% (70% in cases when Amplatz GooseNeck snare was the first device). Embolectomy with Solitaire FR and the Merci Retriever, the second and third most common device in our cohort, yielded a recanalization rate of 42% and 30% respectively. These rates are not representative of the efficacy of the devices as they were mainly used as alternative devices when Amplatz GooseNeck failed in the first attempts. As primary devices, they were used only in very few cases, usually during testing periods when they were first introduced as embolectomy devices. These and newer stent-retriever devices have good recanalization rates as shown in cohorts where they were used as primary devices but also in randomized trials[34-39, 81-86]. The worst recanalization rate was seen in carotid-T occlusions, even when a combination of devices was used, with only 55.5% mTICI 2b/3 grades. The Amplatz GooseNeck that most commonly was used was the 4 mm snare but usually, it was difficult to ensnare and retrieve the larger clots in carotid-T occlusions. A solution to this problem came later with the 7 mm microsnare which could ensnare larger clots more efficiently but no case in the studied cohort was done with a larger than 4 mm microsnare. The introduction of large aspiration catheters changed the recanalization rates in carotid-T occlusions as retrieval, or at least reduction of the clot burden, was now possible. Aspiration through the guide catheters was only possible in more proximal occlusions in the internal carotid but not in the terminal parts. In our cohort, stent-retrievers in carotid-T occlusions were used only in combination with Amplatz GooseNeck and a sub-analysis cannot be performed. Theoretically, stent-retrievers can at least come in contact with a larger portion of the clot surface and retrieve a part of it or mobilize it more proximally and in combination with aspiration achieve satisfactory recanalization. Unfortunately, stent-retrievers in the carotid-T occlusion can cause fragmentation of the clot with migration into a territory previously unaffected, as for example in the anterior cerebral region. The consequences of such a complication can be devastating not only because of an eventual infarct in the new territory but also due to worsening of any collateral circulation that existed previously through the pial anastomoses.

Serious procedural complications were seen in 5% of the cases, which is lower or in line with rates seen in other similar cohorts and randomized studies[38, 76, 82-86]. An important finding was that all complications were observed while trying to bypass the occlusion or under retrieval effort after placement of the devices distal to the occlusion. This finding confirmed what we had already observed in clinical practice the previous years, namely that the complications during embolectomy occur more often with catheterization distal to the occlusion. This is the main reason that the proximal approach in embolectomy, nowadays with aspiration embolectomy, remains the first method of choice for endovascular stroke treatment in our institute. Still, in almost a third of the cases (31%), a combination of methods was needed and the availability of different devices in a neurointerventional unit is a prerequisite for achieving high recanalization rates. Moreover, cases, where the Amplatz GooseNeck snare cannot be used due to the anatomy, or aspiration catheters cannot reach the occlusion due to small vessel diameter (for example in M2 or M3 segments), stent-retrievers can be used, but the operator should weigh the gain of a distal embolectomy against the risk of complication.

In the majority of cases in the randomized studies published in 2015, the primary device was stent-retrievers but a proportion of cases were treated with aspiration. Lately, a randomized study, the ASTER trial, compared the direct aspiration method to embolectomy with stent-retrievers (proximal vs distal approach)[159]. Successful recanalization was equal between the methods with 85.4% mTICI 2b/3 with direct aspiration and 83.1% with stent-retrievers. A tendency to change strategy and use adjunctive device or method was less common with stent-retrievers (23.8%) compared to the direct aspiration method (32.8%) ($p=.053$). The combination of methods in the direct aspiration group was similar to our cohort (31%) confirming that different strategies should be available in endovascular stroke treatment. The ASTER study showed shorter time from groin puncture to clot contact (21 vs 18 minutes) as well as shorter time from clot contact to recanalization (23 vs 13 minutes) with the direct aspiration method.

Taking into account all of the above, we advocate the use of the proximal approach as the first method of choice. A very important factor is the experience and training of the operator to judge if the anatomy or other factors prompt for a different approach already from the start of the procedure or at least an early change of strategy after one or two attempts with the proximal approach.

The mRS ≤2 at 3 months was 42%, mortality was 17% and the sICH 4%. As it has been shown from other case series and studies, successful recanalization is the most important parameter for favorable outcome[158, 160]. Patients with unsuccessful recanalization in our cohort reached a favorable outcome only in 15% while patients with successful recanalization reached a favorable outcome in 51%. Moreover, patients that presented with a manifest infarct in >1/3 but no more than 1/2 of the MCA territory, still reached a favorable outcome in 42% of cases. Even if we know that many patients with extensive infarct sizes at admission do not reach a favorable outcome, they might gain some degree of independency. None of the patients in our cohort was examined with CTP, as this method was added in our stroke workflow in 2012. Consequently we have no evidence of the presence and size of penumbra in these cases but taking into account that all these patients had more than 14 points in the NIHSS, indicative of a large vessel occlusion and some showed a moderate or excellent recovery, the <1/3 of MCA territory rule should not be an absolute contraindication to endovascular treatment. This is supported also by other studies where the use of the cutoff values <1/3 of MCA territory and the ≤7 in ASPECTS was questioned[141, 161, 162]. In fact, a number of studies and meta-analyses of recent randomized trials showed that patients with ASPECTS score as low as 5 can actually benefit from treatment without increasing hemorrhagic or other complications[86, 162-164].

Consequently, the selection of patients should be individualized and many factors should be considered. Patient´s age, health and working status, infarct core to penumbra ratio and regions at risk, anatomical characteristics and degree of procedural risk are some of the factors that should play role and be discussed in the stroke team before a decision to offer the treatment is taken.

Overall, the main radiological and neurological outcomes in Paper I are in line with the results in our institute in later periods (Paper III, Paper IV) but also with the randomized studies on anterior circulation stroke published in 2015 (table 9).

	Paper I	Paper III	Paper IV	MR CLEAN		HERMES [a]		THRACE	
	EVT	EVT	EVT	EVT	IVT	EVT	IVT	EVT	IVT
Number	156	108	90	233	267	634	653	204	208
Age [b]	67	70	72	66	66	68	68	66	68
NIHSS [b]	20	21	18	17	18	17	17	18	17
<1/3 MCA ASPECTS [b]	78% -	85% -	- 10	- 9	- 9	- 9	- 9	- (8)	- (8)
"mTICI 2B/3"[c]	74%	77%	90%	59%	-	71%	-	69%	-
mRS ≤2	42%	38%	41%	33%	19%	46%	26,5%	53%	42%
Mortality	17%	21%	19%	9%	8%	15%	19%	12%	13%
GA CS	91% 9%	100% -	50% 50%	38% 62%	NA	(GA in majority)	NA	48% 52%	NA
Stroke-CT (min)[b]	83	83	78	204[d]	196[d]	195[d]	196[d]	112	111
Stroke-groin puncture (min)[b]	171	171	180	260	NA	-	NA	-	NA
Stroke-recanalization (min)[b]	288	278	253			285	NA	303	NA

Table 9: Baseline characteristics and outcomes from Papers I, III and IV (anterior circulation strokes) and from MR CLEAN, THRACE and HERMES collaboration (intervention and control groups are shown). EVT: Endovascular treatment. IVT: Intravenous thrombolysis.

a: In HERMES meta-analysis data from MRCLEAN, ESCAPE, EXTEND IA, REVASCAT and SWIFT PRIME are included.

b: Median values.

c: mTICI or TICI are used in the studies.

d: From stroke to randomization (directly after imaging).

Paper II

Endovascular stroke treatment in the posterior circulation was excluded from all major randomized studies and the efficacy of this method has only been studied in case series and registries[100-103]. Acute ischemic stroke in the posterior circulation is a devastating disease with high mortality (85%) if left untreated and this led to a liberal use of endovascular treatment in the posterior circulation based on the solidarity and humanitarian principles[89]. The clinical picture can differ significantly from anterior circulation stroke with a large proportion of patients being in an unconscious state at admission. Even the radiological signs can be very difficult to interpret but also to be used for the selection of eligible patients for treatment. Finally, the higher frequency of atherosclerotic causes, especially in the basilar artery, makes the management of acute ischemic stroke in the posterior circulation challenging.

Three types of endovascular treatment techniques were used with a total mTICI 2b/3 of 73%. In the majority of cases (65%), embolectomy with either the proximal or distal approach was used with 79% mTICI 2b/3. As in paper I, all serious procedural complications occurred only with the distal approach but still, they were comparable with rates seen in other studies and registries. Intraarterial thrombolysis was used in 15% and mostly in the first part of the study period with 71% mTICI 2b/3. Migration of embolus to a new territory was seen in 12 cases and half of them were seen after intraarterial thrombolysis. More importantly, none of these new emboli could be retrieved because of very distal location or further fragmentation of the embolus. Additional intraarterial thrombolysis could not be given in these cases. On the other hand, migration to new territories after embolectomy could be solved with retrieval of the embolus in three of the six cases. In our cohort, good recanalization rates were seen with embolectomy and intraarterial thrombolysis. Taking into account the higher proportion of unresolved embolus migration to new territory, the long infusion time of rt-PA needed and the same contraindications as intravenous rt-PA, intraarterial thrombolysis should be nevertheless used only in cases where embolectomy is not feasible or as a complement to embolectomy in cases of significant but unreachable distal emboli.

In cases where stenting and angioplasty were needed secondary to significant atherosclerotic changes, the recanalization rate was as expected high (83%) and the neurological outcome was comparable to the rest of the cohort (33%). Nevertheless, stenting and angioplasty should be used as a last resort treatment because of the high risk for occlusion of perforating arteries to the brainstem. Two randomized studies, the SAMMPRIS and the VISSIT studied stenting of intracranial stenosis versus best medical treatment[96, 97]. In both studies patients with stenosis in ICA, MCA, vertebral and basilar arteries were included. Both studies showed increased risk for early stroke or TIA after stenting. We should always keep in mind that stenotic lesions secondary to atherosclerosis occur over time and patients presenting with acute symptoms suffer usually from acute thrombosis in the stenotic lesion. If the thrombosis could be treated with any one of the endovascular methods, those options should be preferred before stenting and angioplasty are considered. Of course, the majority of the patients are intubated and a neurological estimation of any treatment is impossible. The experience and training of the neurointerventionist are of paramount importance in estimating collateral flow, anatomical variants, and clinical information in order to decide if stenting and angioplasty are justified. Moreover, the postprocedural risk of thrombosis in the stent is always a factor that should be considered. An analysis of the SAMMPRIS cohort for nonprocedural symptomatic infarction and in-stent restenosis 3 years after the trial showed that 25% of the patients treated with stenting had suffered a stroke or TIA[98].

A favorable outcome (mRS ≤2) was seen in 35% and a moderately favorable outcome (mRS ≤3) in 44%. This result is as good as results seen in some of the randomized studies in anterior circulation stroke, for example MR CLEAN (33%) and stroke registries as BASICS (32% mRS ≤3) and

ENDOSTROKE (34% mRS ≤2, 42% mRS ≤3) but worse than some of the randomized studies and other case series with more effective stroke workflow and strict selection criteria. This can reflect that our cohort includes patients treated in the early days of endovascular stroke therapy when a reliable stroke workflow and a dedicated stroke protocol did not exist. Another reason for the results can also be the higher proportion of unconscious patients (RLS levels 4-8). Still, these results are better compared to the natural history of this devastating disease, where 85% die and the rest survive with severe morbidity. Even compared to intravenous thrombolysis in posterior circulation stroke, where low frequencies of favorable outcome (19%-26%) have been reported in patients treated within 4.5 hours from stroke onset[89, 165], the results in our cohort are better taking into consideration that 35% had a favorable outcome and that the mortality dropped to 30% in case of successful recanalization compared to a 70% mortality when endovascular treatment was unsuccessful.

In our study, we evaluated also known radiological scales as pc-ASPECTS and PMI but also a new scale, the BATMAN score which recently was validated[146]. The BATMAN score, together with successful recanalization were the only independent predictors of favorable neurological outcome. The reason that we added the BATMAN score in our review is that it is almost similar to a scale we constructed in our institute, but we left it out during data analysis in favor of the BATMAN score as the latter was recently validated. The BATMAN score incorporates advantages seen in other older scales, as for example the presence and the size of posterior communicating arteries, but also takes into consideration the clot burden. One disadvantage of the scale is the allocation of one point if either vertebral artery is patent. An occlusion of one vertebral artery at the level of PICA origin, with a patent vertebral on the other side, will still get one point as any other occlusion of the vertebral artery where PICA territory is not at risk. This can lead to underestimation of the severity of the occlusion. Moreover, the BATMAN score only indirectly evaluates the territories at risk. It gives no information about manifest infarct in any of these territories, thus suffering from the same disadvantage as similar scales evaluating collateral status in the anterior circulation. A patient with a moderate score in BATMAN but appearing early after stroke onset might have no manifest infarct, but the same patient, presenting late after stroke onset might already have a manifest infarct in all territories previously at risk despite the same moderate BATMAN score. Consequently, visualization of the manifest infarct and penumbra is needed also in the posterior circulation but here, CT and CTP have low sensitivity. MR imaging can better depict manifest infarct but as described earlier certain logistical and methodological limitations exist.

Two randomized studied are ongoing, the BASICS and BEST trials[104, 105]. These trials will compare endovascular treatment in combination with intravenous thrombolysis to intravenous thrombolysis alone. Consequently, only patients within the time window 4.5 hours can be randomized and only patients where a previous status and clinical history can be obtained. This excludes many patients presenting in a later time window and patients in the unconscious state who represent a large proportion of the patients we see in our daily practice. Ethical considerations are raised for the need of randomized studies in the posterior circulation stroke due to the now proven efficacy of endovascular stroke treatment in the anterior circulation, but also due to the poor results of intravenous thrombolysis according to registries or published case series.

10.2 Papers III and IV: Endovascular stroke treatment and anesthesiological aspects

Retrospective studies

In most of the retrospective studies that showed association of GA with poor outcome, several known and assumed predictive factors of neurological outcome, such as blood pressure, blood glucose, ventilation parameters and anesthetic drugs were missing[47-64]. The best known predictive factor, the blood pressure, was reported in only four of these studies[51, 54, 56, 60] (table 10). Other GA related factors, such as time-consuming intubation and intubation related aspiration pneumonia were also suggested as possible reasons for the association of GA to poor neurological outcome[49, 63].

Serious **selection bias** was seen in these retrospective studies. In some of the studies, posterior circulation strokes were included in the GA group despite the fact that CS is not an option if airway patency needs to be artificially supported, as is the case in the majority of posterior circulation strokes[50-53, 55, 57, 60]. Then, the GA group in the vast majority of the studies had significantly more severe strokes according to NIHSS at admission, which has been shown to be associated with worse outcome[47-57, 61-62]. At the same time, a higher proportion of ICA, carotid T or tandem occlusions were seen in the GA group, which contributed not only to the higher NIHSS at admission but probably also to lower recanalization grade in some studies[47, 49, 51, 55, 57, 58]. In some studies, emergency intubation was performed prior to transportation of the patient to the angiography suite due to respiratory compromise and was reported in proportions as high as 43% in the GA group[55]. A heterogeneity was noted in the recanalization scale used (TIMI, TICI, mTICI) while in some studies the recanalization rate was not reported at all[47, 51, 52, 60, 63, 64].

Author	n	GA %	Admission NIHSS Median			Posterior circulation %			Successful recanalization %			mRS ≤ 2 at 3 months %			Data on BP
			GA	CS	p-value	GA	CS	p-value	GA	CS	p-value	GA	CS	p-value	
Abou-Chebl 2010	980	43	NA	NA	NA				NA	NA	NA	25	45	<.0001	no
Jumaa 2010	126	42	18	15	.004				70	82	.103	23	46	.009	no
Nichols 2010	75	35	21	19	.03				73	35	.01	23	60	<.01	no
Sugg 2010	66	14	28	17	<.01	1	0	0.1493	77[e]	70[e]	.331	11	51	.033	no
Davis 2012	96	50	19	16	.03	40	21	0.08				15	60	<.0001	yes
Hassan 2012	136	39	NA	NA	.0001							17	45	.0009	no
Abou-Chebl 2014	281	70	19	16	.002	13	3	0.3	74	73	.9	37	53	.01	no
John 2014	190	48	16	15	.364				58	48	.182	15	23	.293	yes
Li 2014	109	32	18	15	.059	20	4	0.018	63[e]	76[e]	.392	11	15	.631	no
McDonald 2014	1014	50												[c]	no
Whalin 2014	216	61	20	17	.009				72	84	.039	30	49	.007	yes
vandenBerg 2015	348	20	16	15	.76				49	43	.37	14	26	.04	no
Abou-Chebl 2015[a]	434	34	18	16	<.0001	4	3	ns	76[e]	73[e]	.48	31	48	.0006	no
Berkhemer 2016[b]	216	37	18	17	ns				52	63	.19	23	38	.024	no
Just 2016	109	39	13	13	.771	NA	NA	NA				33	46	.182	no
Jagani 2016	99	38	16	18	.67	34	2	<.0001				16	39	.02	yes
Bekelis 2017	1174	38				NA	NA	NA						[d]	no

Table 10: The retrospective studies on anesthesia technique in endovascular stroke treatment. For each study, the percentage of patients treated under GA, the median NIHSS at admission, the percentage of posterior circulation stroke, the recanalization rate, the percentage of good neurological outcome at 3 months and inclusion of data on blood pressure (BP) are presented (the table is a modified version of a table created by Pia Löwhagen Hendén).

a: Post-hoc analysis of data from IMS III.

b: Post-hoc analysis of data from MR CLEAN.

c: Hospital mortality 25 % (GA) vs 12 % (CS) p<0.0001

d: Case fatality difference for GA vs CS 7.2% (95% CI: 2.6-12%)

e: TICI score 2-3 defined as successful recanalization

Finally, in most of the studies, estimation of the initial manifest infarction is missing, except in four studies[48, 54, 57, 59], where ASPECTS is equal between the groups, and in two studies, where significantly lower ASPECTS score was seen in the GA group[55, 56].

A factor that can greatly affect the outcome is the **experience of the neurointerventional and the neuroanesthesiology teams**. In some of the studies, this issue is discussed but no data are presented. Centers that perform few endovascular stroke treatments per year might have lower recanalization rates, higher complication rates and might be accustomed to only one type of anesthesia technique. Moreover, the anesthesiology team should be aware of the pathophysiology of stroke and the need to preserve airway patency but also to sustain sufficient cerebral perfusion pressure, which is not apparent by the results in some of the studies. The importance of experience and familiarity with the team managing patients under endovascular stroke treatment was highlighted in the SIESTA trial[166] which was also a randomized study comparing GA and CS, as the AnStroke trial. The SIESTA trial had a different primary outcome, namely the early neurological recovery assessed by NIHSS at 24 hours and showed no difference between the groups. What was interesting in this trial was the great difference between the groups in mRS at 3 months. The GA group showed a significantly higher proportion of mRS ≤2 with 37% compared to 18% in the CS group. According to the authors, this result could be explained by the fact that their team was less experienced with the CS technique.

In all four studies reporting blood pressure values, **intra-procedural hypotension** was noticed in all patients treated under GA despite treatment with vasopressors. In Davis et al. 2012, the intra-procedural minimum and maximum MAP were reported but not the baseline MAP[51]. The baseline MAP, but mostly the intra-procedural variations in blood pressure as fractions of baseline values are of great importance, as the baseline MAP can vary considerably among patients presenting with acute ischemic stroke. In John et al. 2014 the baseline and intraprocedural, minimum and maximum MAP were reported with no differences between the GA and CS group[54]. It is worth noticing that this study, in which no differences were detected in the blood pressure values, showed only a trend in poor neurological outcome with GA but no significant association. On the other hand, Jagani et al. 2016, showed higher variability in MAP (p=.003) and a greater drop in systolic and diastolic blood pressure of >10 mmHg under GA which was associated with poor neurological outcome[60]. Similar results were reported also in Whalin et al. 2014, where a higher percentage of drop in MAP after induction was seen (p=.003) with 54% of patients treated under GA showing >20% drop in MAP (p=.001)[56].

Paper III and Paper IV

In Paper III, patients with poor neurological outcome suffered more frequently from intra-procedural hypotension. The strength of this study was that only patients treated under GA were included and consequently any confounding of anesthesia type and blood pressure variation was avoided. In 89% of the patients included, a 20% fall from the baseline MAP was seen but this had no effect on the outcome. A fall of >40% in MAP was an independent predictor of poor neurological outcome together with unsuccessful recanalization and a high NIHSS score (p=.04, figure 20). Favorable outcome (mRS ≤2) at 3 months was found in 38% of the patients in our study, despite the fact that 42% of the patients experienced a MAP <60 mm Hg. This outcome was still better than in the majority of the retrospective than in the majority of the retrospective studies, where the favorable outcome frequency was between 11% and 30%[48, 50-54, 56-60].

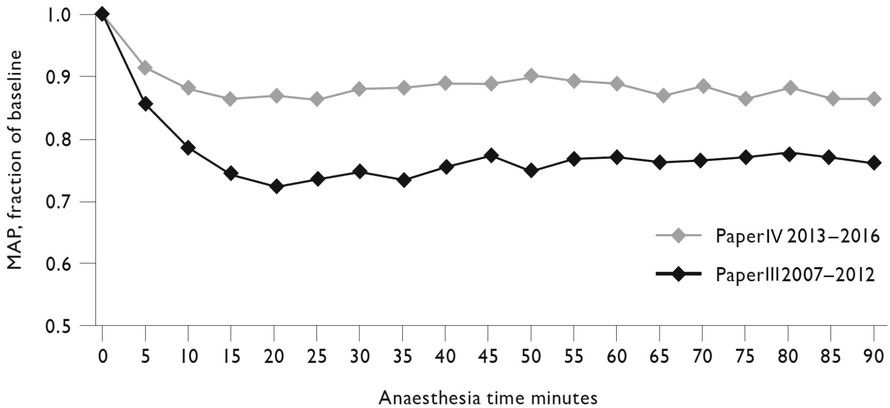

Figure 22: MAP fraction during EVT for patients in Paper III versus patients in Paper IV. Mean values.

When the AnStroke study started recruiting patients, a more aggressive management of intra-procedural hypotension had already been added to the institutional protocol. The result of this change was that the MAP fraction in the AnStroke study cohort was higher than in Paper III (figure 22). Moreover, a lower occurrence of MAP <40% from baseline was now seen, but in those patients with a MAP fall of >40%, a trend for worse outcome was noticed (p=.08, figure 23) as in Paper III.

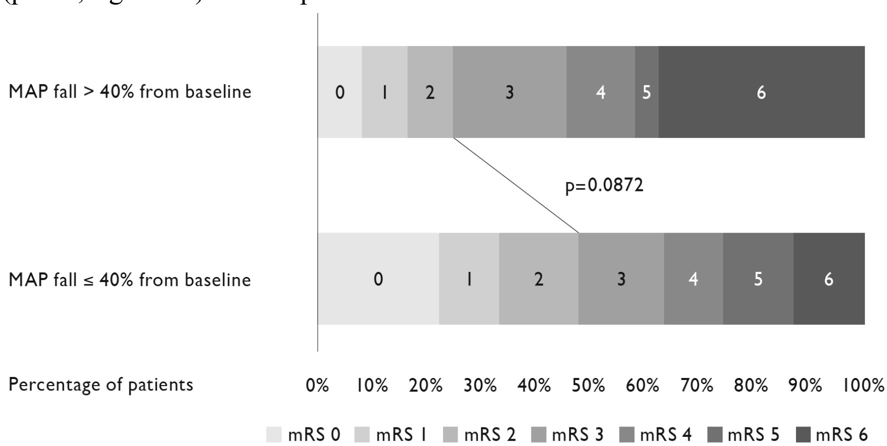

Figure 23: Neurological outcome expressed as mRS for patients in AnStroke trial with MAP fall > 40 % and ≤ 40 % from baseline respectively (image created by Pia Löwhagen Hendén).

Other anesthesiological aspects

The role of anesthetic drugs per se in endovascular stroke treatment has been discussed in several studies and it is suggested that they impair the cerebral autoregulation. Inhalation anesthetics and especially isoflurane have a more pronounced effect on the autoregulation but the significance of this effect is debatable taking into account that the autoregulation is already impaired in acute ischemic stroke[167-169]. Other studies have suggested a neuroprotective effect of anesthetic drugs[170]. The alleged neuroprotective mechanism is supposed to act by reducing the cerebral metabolic rate while retaining cerebral blood flow when using inhalation anesthetics[167]. In our studies, the inhalation anesthetic of choice was sevoflurane which is supposed to reduce the cerebral metabolic rate without affecting the cerebral blood flow but no specific measurements of this effect were performed.

Considering that the GA group in the AnStroke trial had higher NIHSS, more left-sided and proximal occlusions and at the same time showed no difference in recanalization rate, average MAP fraction, infarct volume and neurological outcome compared to CS group, a neuroprotective effect of GA cannot be excluded.

Complications

Neurointerventional and anesthesiological complications are factors that can influence the radiological and neurological outcomes. GA carries a risk for anesthesiological complications other than induction related hypotension, such as pneumonia requiring treatment due to invasive ventilation. In the AnStroke trial, no differences were seen between the GA and CS groups in anesthesiological complications. Also, no differences were seen in neurointerventional complications. Other aspects where the type of anesthesia method can influence the outcome or increase the complication risk are patient movements, angiographic quality, and vessel tortuosity. As expected, significant differences were seen in the quality of angiography and patient movements but this was not associated with more complications or inferior recanalization outcome. No difference in vessel tortuosity was seen between groups.

Influence on time intervals

The last matter of debate is the influence of anesthesia type on time intervals. GA is considered to be associated with delayed start of the endovascular procedure, while CS can prolong procedural time. In the AnStroke trial we registered two time intervals that could possibly be affected by anesthesia type; the time from arrival to the neurointerventional suite to groin puncture and the time from groin puncture to recanalization/end of procedure (table

11). A trend towards shorter time from arrival to the neurointerventional suite to groin puncture was seen in the CS group and a similar trend in procedural time was seen in the GA group. Nevertheless, no significant difference exists between the groups and in total, the time lost before groin puncture in the GA group is compensated by the time that eventually is lost during the procedure under CS.

	GA	CS	P value
Arrival to neurointerventional suite – groin puncture	34 (18-47)	25 (15-36)	0.0555
Groin puncture – recanalization/end of procedure	55 (38-110)	74 (37-104)	0.6572
Arrival to neurointerventional suite – recanalization/end of procedure	90 (68-148)	99 (61-140)	0.9856

Table 11: Time intervals that could be influenced by the anesthesia type; time from arrival to the neurointerventional suite to groin puncture and the time from groin puncture to recanalization/end of procedure.

10.3 Limitations and strengths

Papers I-III

The major limitations of the first three papers are the retrospective design and that a direct comparison of the different devices and techniques was not possible. Moreover, some anesthesiological data, such as more accurate chart-recorded blood pressure values (limited to ± 5 mm Hg) and certain clinical data, such as length of stay in the intensive unit and intensive care-related complications were not available. The data collection time span, especially in Papers I and II, was very long and a number of workflow characteristics, as time delays during transportation, different organization in the emergency room, neurology and radiology departments, different standards of care and different inclusion and exclusion clinical criteria could not always be controlled. The CT and MRI quality became better in the later years of the study periods and this could have influenced the evaluation and the results of the different radiological evaluation scales.

On the other hand, the studies have several strengths. First, a standardized re-evaluation of all radiological data was done by trained neuroradiologists, blinded to the original reports, to the procedural outcome, and to the neurological outcome. It is also a strength that the clinical status before and after the treatment in all patients was performed by neurologists and that the medical charts were re-evaluated by neurologists. In case of missing clinical data, the neurologists contacted the patient or next of kin, otherwise, the patient would be excluded from the studies.

Paper IV

The sample size in Paper IV was based on a pilot study conducted at the Sahlgrenska University Hospital and on retrospective studies published before 2012, which showed a large difference in the outcome between GA and CS (20-40% units). Consequently, the power calculation showed that the size needed was only 80 patients. We included 90 patients to secure the study in case of a 10% loss to follow-up. The final outcomes in the groups were equal, but a smaller difference between the groups would be difficult to interpret. Moreover, the sample size does not allow for a detailed analysis of other parameters of the study, such as the devices used.

The NIHSS limits used in the study were established before the randomized studies published in 2015 and were higher (≥10 in case of a right sided occlusion and ≥14 in left sided occlusions) than the currently accepted limit for endovascular stroke therapy at 6 points. Consequently, patients with less severe stroke severity (<10 points) were not included in the study and the results are not representative of this patient group.

The AnStroke trial is a single center study with all patients treated under the same stroke workflow characteristics, anesthesiological protocols and neurointerventional methods. It is important to mention that all these parameters differ between centers that offer endovascular stroke therapy and the interpretation of the results should take into consideration these differences.

The major strength of the study is the prospective, randomized nature and the inclusion of several important predictive neurological, anesthesiological and neurointerventional factors for neurological outcome. Another strength is that the personnel involved in the treatment of the included patients were physicians and nurses, experienced in the treatment of stroke and that strict procedural protocols were followed in all patients. Lastly, no patients were lost to follow-up.

11 CONCLUSION

The first two papers evaluate endovascular stroke treatment in the anterior and posterior circulation as it has been performed during the last 25 years in the neurointerventional Unit of the Sahlgrenska University hospital and include older and newer generation techniques. Our studies show that endovascular stroke treatment is effective and safe. We advocate the use of the proximal approach as the first method of choice when all relevant factors have been considered from an experienced operator.

Two main anesthesia forms are used in endovascular stroke treatment, general anesthesia and conscious sedation. Intraprocedural hypotension >40% from the baseline blood pressure during endovascular stroke treatment under general anesthesia is an independent predictor of poor neurological outcome at 3 months.

Randomization of patients eligible for endovascular stroke treatment to general anesthesia or conscious sedation did not show any difference in neurological outcome at 3 months when strict anesthesiological protocol is used to avoid intra-procedural hypotension. No difference was seen in early neurological recovery or infarction volume between the groups.

12 FUTURE PERSPECTIVES

The great challenge in today's stroke treatment is to raise awareness among the population, identify all patients that could benefit from a treatment and lastly create the infrastructure needed to offer the opportunity for treatment to all eligible patients. In Sweden, in the year 2013, 232 endovascular stroke treatments were performed according to the Swedish national stroke registry. While an increase in number of treatments is noticed every year, it has been estimated that 1232 treatments would have been performed in 2013 if the new guidelines for endovascular stroke therapy had been implemented in 2013[171]. This means that the authorities should invest in identifying all potential candidates for endovascular stroke treatment and create the necessary **infrastructure for an effective stroke workflow**. A continuous campaign to educate and inform the population of the symptoms and consequences of stroke is the first step but resources should also be invested in the prehospital identification of eligible patients. Taking into consideration the recently presented results of the DAWN trial, which showed that the benefit of endovascular stroke treatment can be extended up to 24 hours with the help of advanced radiological examinations, investment in education and increase of the resources in all referral hospitals should be highly prioritized. Studies are ongoing to study if **direct transportation** of the patient to a neurointerventional center is the best choice even if access to intravenous thrombolysis is delayed. Considering the low recanalization rates of intravenous thrombolysis in large vessel occlusion it is possible that the patient has the best chance for recovery if endovascular stroke treatment is offered as soon as possible. Thus, it is important to confirm the suspicion of a large vessel occlusion as soon as an ambulance has arrived at the patient's location. The technological advances nowadays can enable a **secure communication** of the field team with an experienced vascular neurologist that can lead the team to the nearest neurointerventional center in case of a large vessel occlusion[110]. Moreover, direct examination with a mobile CT scanner is already performed in some metropolitan areas. This can enable not only early diagnosis but also the early start of intravenous thrombolysis before arriving at the hospital. The major disadvantage of an **ambulance or helicopter equipped with a CT** scanner is the availability of such vehicles. A promising new technology, which potentially can overcome such difficulties in the prehospital diagnosis of ischemic stroke is the **Strokefinder MD100.** This device was developed by Medfield Diagnostics AB, Gothenburg, Sweden and has the capacity to differentiate between ischemic and hemorrhagic strokes based on microwave technology[172]. The technology is already being tested in the prehospital triage and if the results are positive can lead to the direct transportation of the patient to a neurointerventional center but also to initiation of intravenous thrombolysis already before the arrival to the hospital and before advanced radiological imaging.

A lot of studies have been done in the field of **neuroprotection** with mixed results on the efficacy of neuroprotection on patients suffering from stroke[173]. Even if no clear evidence exists for the use of neuroprotection, ongoing studies with new substances and neuroprotective techniques might offer the evidence needed in the future. If the transformation of penumbra to infarct core can be halted until treatment can be initiated, the number of patients receiving the treatment and also the patients reaching favorable neurological outcome will increase.

The focus during endovascular stroke treatment nowadays is to avoid intra-procedural hypotension. As many of the guidelines for blood pressure management in ischemic stroke are based on data from old studies with different objectives, further research is needed **in individualizing blood pressure** during stroke treatment depending on patient's characteristics. Aiming for high blood pressure, at least higher than pre-stroke blood pressure, might be beneficial for the patients until recanalization occurs and irrespectively of the anesthesia method used. Furthermore, other aspects of anesthesia management, such as **ventilation and oxygenation** might also contribute to sustained penumbra until recanalization occurs and should be explored in future studies.

The overwhelming evidence for the efficacy of endovascular stroke treatment from the randomized studies in 2015 started vigorous research in new devices for embolectomy. Many centers report nowadays excellent recanalization rates up to 90 and 95% with the use of a combination of techniques and devices. Ongoing research on the **properties of the different clots** in stroke would further increase our ability to choose the best method of embolectomy depending on the composition and other characteristics of the clot[174].

Research in **stem cell transplantation** is ongoing in many fields of the modern medicine. Stem cell transplantation in stroke patients has shown some promising results[175-177]. Regeneration of regions previously affected by stroke could potentially lead to the total or partial recovery of patients that never had the opportunity to receive treatment or when the treatment was unsuccessful.

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REFERENCES

1. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. Lancet. 2014;383(9913):245-54.
2. Feigin VL, Krishnamurthi R, Parmar P, Norrving B, Mensah GA, Bennett DA, et al. Update on the global burden of ischaemic and haemorrhagic stroke in 1990–2013: THE GBD 2013 STUDY. Neuroepidemiology. 2015;45(3):161-76.
3. Kaplan W, Wirtz VJ, Mantel-Teeuwisse A, et al Priority Medicines for Europe and the World 2013 Update World Health Organization 2013 ISBN: 978 92 4 150575 8.
4. Årsrapport. Stroke och TIA 2014. Riksstroke. http://riksstroke.org, 2014
5. Kaplan W, Wirtz VJ, Mantel-Teeuwisse A, et al Priority Medicines for Europe and the World 2013 Update World Health Organization 2013 ISBN: 978 92 4 150575 8. Background Paper 6.6
6. Heiss WD. The ischemic penumbra: correlates in imaging and implications for treatment of ischemic stroke. The Johann Jacob Wepfer award 2011. Cerebrovasc Dis. 2011;32(4):307-20.
7. Jordan JD, Powers WJ. Cerebral autoregulation and acute ischemic stroke. Am J Hypertens. 2012;25(9):946-50.
8. Markus HS. Cerebral perfusion and stroke. Journal of Neurology, Neurosurgery & Psychiatry. 2004;75(3):353-61.
9. Armstead WM. Cerebral Blood Flow Autoregulation and Dysautoregulation. Anesthesiol Clin. 2016;34(3):465-77.
10. Krabbe-Hartkamp MJ, Grond Jvd, Leeuw FEd, Groot JCd, Algra A, Hillen B, et al. Circle of Willis: morphologic variation on three-dimensional time-of-flight MR angiograms. Radiology. 1998;207(1):103-11.
11. Bhogal P, Makalanda HL, Brouwer PA, Gontu V, Rodesch G, Mercier P, et al. Normal pio-dural arterial connections. Interv Neuroradiol. 2015;21(6):750-8.
12. Saver JL. Time is brain--quantified. Stroke. 2006;37(1):263-6.
13. Meretoja A, Keshtkaran M, Saver JL, Tatlisumak T, Parsons MW, Kaste M, et al. Stroke thrombolysis: save a minute, save a day. Stroke. 2014;45(4):1053-8.
14. Meretoja A, Keshtkaran M, Tatlisumak T, Donnan GA, Churilov L. Endovascular therapy for ischemic stroke: Save a minute—save a week. Neurology 2017;88(22): 2123-2127.

15. Thompson JE. The Evolution of Surgery for the Treatment and Prevention of Stroke. The Willis Lecture. 1996;27(8):1427-34.
16. Sussman BJ, Fitch TS. Thrombolysis with fibrinolysin in cerebral arterial occlusion. Journal of the American Medical Association 1958;167:1705-9.
17. Sussman BJ, Fitch TS. Thrombolysis with fibrinolysis in cerebral arterial occlusion; the role of angiography. Angiology 1959;10(4):268-82.
18. Tillett WS, Johnson AJ, McCarty WR: The intravenous infusion of the streptococcal fibrinolytic principle (streptokinase) into patients. J Clin Invest 1955;34:169-185.
19. Wardlaw JM, Warlow CP. Thrombolysis in acute ischemic stroke: does it work? Stroke. 1992;23(12):1826-39.
20. Fletcher AP, Alkjaersig N, Lewis M, Tulevski V, Davies A, Brooks JE, et al: A pilot study of urokinase therapy in cerebral infarction. Stroke 1976;7:135-142.
21. Tissue plasminogen activator for acute ischemic stroke: The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med 1995;333:1581-1587.
22. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al: Thrombolysis with alteplase 3 to 4.5 h after acute ischemic stroke. N Engl J Med 2008;359:1317-1329.
23. Wahlgren N, Ahmed N, Davalos A, Hacke W, Millan M, Muir K, et al: Thrombolysis with alteplase 3-4.5 h after acute ischaemic stroke (SITS-ISTR): an observational study. Lancet 2008;372:1303-1309.
24. del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M. PROACT: A Phase II Randomized Trial of Recombinant Pro-Urokinase by Direct Arterial Delivery in Acute Middle Cerebral Artery. Stroke. 1998;29:4–11.
25. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, et al: Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. J Am Med Assoc 1999;282:2003-2011.
26. Wikholm G. Mechanical intracranial embolectomy: a report of two cases. Interv Neuroradiol 1998;4:159–64.
27. Wikholm G. Transarterial embolectomy in acute stroke.AJNRAmJ Neuroradiol 2003;24:892–94
28. Felten RP, Ogden NR, Peña C, Provost MC, Schlosser MJ, Witten CM. The Food and Drug Administration medical device review process: clear- ance of a clot retriever for use in ischemic stroke. Stroke.2005;36:404–406.
29. Gobin YP, Starkman S, Duckwiler GR, et al. MERCI 1: a phase 1 study of Mechanical Embolus Removal in Cerebral Ischemia. Stroke 2004;35:2848-54.

30. Smith WS, Sung G, Starkman S, Saver JL, Kidwell CS, Gobin YP, et al; MERCI Trial Investigators. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. Stroke. 2005;36:1432–1438.
31. Smith WS. Safety of mechanical thrombectomy and intravenous tissue plasminogen activator in acute ischemic stroke. Results of the multi Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial, part I. AJNR Am J Neuroradiol 2006;27:1177-82.
32. Henkes H, Flesser A, Brew S, et al. A novel microcatheter-delivered, highly-flexible and fully retrievable stent, specifically designed for intracranial use. Technical note. Interv Neuroradiol 2003;9:391-3
33. Perez MA, Miloslavski E, Fischer S, Bazner H, Henkes H. Intracranial thrombectomy using the Solitaire stent: a historical vignette. J Neurointerv Surg 2012;4:e32.
34. Castano C, Serena J, Davalos A. Use of the New Solitaire (TM) AB Device for Mechanical Thrombectomy when Merci Clot Retriever Has Failed to Remove the Clot. A Case Report. Interv Neuroradiol 2009;15:209-14.
35. Costalat V, Machi P, Lobotesis K, et al. Rescue, combined, and stand-alone thrombectomy in the management of large vessel occlusion stroke using the solitaire device: a prospective 50-patient single center study: timing, safety, and efficacy. Stroke 2011;42:1929-35.
36. Mourand I, Brunel H, Costalat V, Riquelme C, Lobotesis K, Milhaud D, et al. Mechanical Thrombectomy in Acute Ischemic Stroke: Catch Device. American Journal of Neuroradiology. 2011;32(8):1381-5.
37. San Roman L, Obach V, Blasco J, et al. Single-center experience of cerebral artery thrombectomy using the TREVO device in 60 patients with acute ischemic stroke. Stroke 2012;43:1657-9.
38. Saver JL, Jahan R, Levy EI, et al. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel group, non-inferiority trial. Lancet 2012;380:1241-9.
39. Nogueira RG, Lutsep HL, Gupta R, et al. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. Lancet 2012;380:1231-40.
40. Behme D, Mpotsaris A, Zeyen P, Psychogios MN, Kowoll A, Maurer CJ, et al. Emergency Stenting of the Extracranial Internal Carotid Artery in Combination with Anterior Circulation Thrombectomy in Acute Ischemic Stroke: A Retrospective Multicenter Study. American Journal of Neuroradiology. 2015;36(12):2340-5.
41. Marnat G, Mourand I, Eker O, Machi P, Arquizan C, Riquelme C, et al. Endovascular Management of Tandem Occlusion Stroke Related to Internal Carotid Artery Dissection Using a Distal to Proximal Approach: Insight

from the RECOST Study. American Journal of Neuroradiology. 2016;37(7):1281-8.
42. Kim YS, Garami Z, Mikulik R, Molina CA, Alexandrov AV; CLOTBUST Collaborators: Early recanalization rates and clinical outcomes in patients with tandem internal carotid artery/middle cerebral artery occlusion and isolated middle cerebral artery occlusion. Stroke 2005; 36: 869–871.
43. Christou I, Felberg RA, Demchuk AM, Burgin WS, Malkoff M, Grotta JC, Alexandrov AV: Intravenous tissue plasminogen activator and flow improvement in acute ischemic stroke patients with internal carotid artery occlusion. J Neuroimaging 2002; 12: 119–123.
44. Rubiera M, Ribo M, Delgado-Mederos R, Santamarina E, Delgado P, Montaner J, Alvarez-Sabin J, Molina CA: Tandem internal carotid artery/middle cerebral artery occlusion: an independent predictor of poor outcome after systemic thrombolysis. Stroke 2006; 37:2301–2305.
45. Linfante I, Llinas RH, Selim M, Chaves C, Kumar S, Parker RA, Caplan LR, Schlaug G: Clinical and vascular outcome in internal carotid artery versus middle cerebral artery occlusions after intravenous tissue plasminogen activator. Stroke 2002; 33: 2066–2071.
46. Behme D, Molina CA, Selim MH, Ribo M. Emergent Carotid Stenting After Thrombectomy in Patients With Tandem Lesions. Stroke. 2017;48(4):1126-8.
47. Abou-Chebl A, Lin R, Hussain MS, Jovin TG, Levy EI, Liebeskind DS, et al. Conscious sedation versus general anesthesia during endovascular therapy for acute anterior circulation stroke: Preliminary results from a retrospective, multicenter study. Stroke; a journal of cerebral circulation. 2010;41:1175-1179
48. Jumaa MA, Zhang F, Ruiz-Ares G, Gelzinis T, Malik AM, Aleu A, et al. Comparison of safety and clinical and radiographic outcomes in endovascular acute stroke therapy for proximal middle cerebral artery occlusion with intubation and general anesthesia versus the nonintubated state. Stroke; a journal of cerebral circulation. 2010;41:1180-1184
49. Nichols C, Carrozzella J, Yeatts S, Tomsick T, Broderick J, Khatri P. Is periprocedural sedation during acute stroke therapy associated with poorer functional outcomes? J Neurointerv Surg. 2010;2:67-70
50. Sugg RM, Jackson AS, Holloway W, Martin CO, Akhtar N, Rymer M. Is mechanical embolectomy performed in nonanesthetized patients effective? AJNR. American journal of neuroradiology. 2010;31:1533-1535
51. Davis MJ, Menon BK, Baghirzada LB, Campos-Herrera CR, Goyal M, Hill MD, et al. Anesthetic management and outcome in patients during endovascular therapy for acute stroke. Anesthesiology. 2012;116:396-405

52. Hassan AE, Chaudhry SA, Zacharatos H, Khatri R, Akbar U, Suri MF, et al. Increased rate of aspiration pneumonia and poor discharge outcome among acute ischemic stroke patients following intubation for endovascular treatment. Neurocritical care. 2012;16:246-250
53. Abou-Chebl A, Zaidat OO, Castonguay AC, Gupta R, Sun CH, Martin CO, et al. North American solitaire stent-retriever acute stroke registry: Choice of anesthesia and outcomes. Stroke; a journal of cerebral circulation. 2014;45:1396-1401
54. John S, Thebo U, Gomes J, Saqqur M, Farag E, Xu J, et al. Intra-arterial therapy for acute ischemic stroke under general anesthesia versus monitored anesthesia care. Cerebrovascular diseases (Basel, Switzerland). 2014;38:262-267
55. Li F, Deshaies EM, Singla A, Villwock MR, Melnyk V, Gorji R, et al. Impact of anesthesia on mortality during endovascular clot removal for acute ischemic stroke. Journal of neurosurgical anesthesiology. 2014;26:286-290
56. Whalin MK, Lopian S, Wyatt K, Sun CH, Nogueira RG, Glenn BA, et al. Dexmedetomidine: A safe alternative to general anesthesia for endovascular stroke treatment. J Neurointerv Surg. 2014;6:270-275
57. Abou-Chebl A, Yeatts SD, Yan B, Cockroft K, Goyal M, Jovin T, et al. Impact of general anesthesia on safety and outcomes in the endovascular arm of interventional management of stroke (ims) iii trial. Stroke; a journal of cerebral circulation. 2015;46:2142-2148
58. van den Berg LA, Koelman DL, Berkhemer OA, Rozeman AD, Fransen PS, Beumer D, et al. Type of anesthesia and differences in clinical outcome after intra-arterial treatment for ischemic stroke. Stroke; a journal of cerebral circulation. 2015;46:1257-1262
59. Berkhemer OA, van den Berg LA, Fransen PS, Beumer D, Yoo AJ, Lingsma HF, et al. The effect of anesthetic management during intra-arterial therapy for acute stroke in mr clean. Neurology. 2016;87:656-664
60. Jagani M, Brinjikji W, Rabinstein AA, Pasternak JJ, Kallmes DF. Hemodynamics during anesthesia for intra-arterial therapy of acute ischemic stroke. J Neurointerv Surg. 2016;8:883-888
61. Just C, Rizek P, Tryphonopoulos P, Pelz D, Arango M. Outcomes of general anesthesia and conscious sedation in endovascular treatment for stroke. The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques. 2016;43:655-658
62. Brinjikji, W., et al., Conscious sedation versus general anesthesia during endovascular acute ischemic stroke treatment: a systematic review and meta-analysis. AJNR Am J Neuroradiol, 2015. 36(3): p. 525-9.

63. McDonald JS, Brinjikji W, Rabinstein AA, Cloft HJ, Lanzino G, Kallmes DF. Conscious sedation versus general anaesthesia during mechanical thrombectomy for stroke: A propensity score analysis. J Neurointerv Surg. 2015;7:789-794
64. Bekelis K, Missios S, MacKenzie TA, Tjoumakaris S, Jabbour P. Anesthesia technique and outcomes of mechanical thrombectomy in patients with acute ischemic stroke. Stroke; a journal of cerebral circulation. 2017;48:361-366
65. Molina CA, Selim MH. General or local anesthesia during endovascular procedures: Sailing quiet in the darkness or fast under a daylight storm. Stroke; a journal of cerebral circulation. 2010;41:2720-2721
66. Meyers PM, Heyer EJ. Stroke: Sedation and anesthesia during endovascular stroke therapy. Nature reviews. Neurology. 2010;6:474-475
67. Heyer EJ, Anastasian ZH, Meyers PM. What matters during endovascular therapy for acute stroke: Anesthesia technique or blood pressure management? Anesthesiology. 2012;116:244-245
68. Hemmer LB, Zeeni C, Gupta DK. Generalizations about general anesthesia: The unsubstantiated condemnation of general anesthesia for patients undergoing intra-arterial therapy for anterior circulation stroke. Stroke; a journal of cerebral circulation. 2010;41:e573; author reply e574-575
69. Hassan AE, Adil MM, Zacharatos H, Rahim B, Chaudhry SA, Tekle WG, et al. Should ischemic stroke patients with aphasia or high national institutes of health stroke scale score undergo preprocedural intubation and endovascular treatment? Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2014;23:e299-304
70. Gupta R. Local is better than general anesthesia during endovascular acute stroke interventions. Stroke; a journal of cerebral circulation. 2010;41:2718-2719
71. Brekenfeld C, Mattle HP, Schroth G. General is better than local anesthesia during endovascular procedures. Stroke; a journal of cerebral circulation. 2010;41:2716-2717
72. Jauch EC, Saver JL, Adams HP, Jr., Bruno A, Connors JJ, Demaerschalk BM, et al. Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American heart association/American stroke association. Stroke; a journal of cerebral circulation. 2013;44:870-947
73. Wahlgren N, Moreira T, Michel P, Steiner T, Jansen O, Cognard C, et al. Mechanical thrombectomy in acute ischemic stroke: Consensus statement by eso-Karolinska stroke update 2014/2015, supported by eso, esmint, esnr and ean. International journal of stroke: official journal of the International Stroke Society. 2016;11:134-147

74. Ahmed N, Wahlgren N, Brainin M, Castillo J, Ford GA, Kaste M, et al. Relationship of blood pressure, antihypertensive therapy, and outcome in ischemic stroke treated with intravenous thrombolysis: Retrospective analysis from safe implementation of thrombolysis in stroke–international stroke thrombolysis
75. Talke PO, Sharma D, Heyer EJ, Bergese SD, Blackham KA, Stevens RD. Republished: Society for neuroscience in anesthesiology and critical care expert consensus statement: Anesthetic management of endovascular treatment for acute ischemic stroke. Stroke; a journal of cerebral circulation. 2014;45:e138-150
76. Qureshi AI, Chaudhry SA, Rodriguez GJ, Suri MFK, Lakshminarayan K, Ezzeddine MA. Outcome of the 'Drip-and-Ship' Paradigm among Patients with Acute Ischemic Stroke: Results of a Statewide Study. Cerebrovascular Diseases Extra. 2012;2(1):1-8.
77. Kuntze Söderqvist Å, Kaijser M, Söderman M, Holmin S, Wahlgren N, Andersson T. Mechanical thrombectomy in acute ischemic stroke—experience from 6 years of practice. Neuroradiology. 2014;56(6):477-86.
78. Broderick JP, Palesch YY, Demchuk AM, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med 2013;368:893-903.
79. Ciccone A, Valvassori L, Nichelatti M, et al. Endovascular treatment for acute ischemic stroke. N Engl J Med 2013;368:904-13.
80. Kidwell CS, Jahan R, Gornbein J, et al. A trial of imaging selection and endovascular treatment for ischemic stroke. N Engl J Med 2013;368:914-23.
81. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015;372(1):11-20.
82. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015;372(24):2285-95.
83. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372(11):1019-30.
84. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372(11):1009-18.
85. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015;372(24):2296-306.
86. Bracard S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone

after stroke (THRACE): a randomised controlled trial. The Lancet Neurology. 2016;15(11):1138-47.

87. Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. The Lancet. 2016;387(10029):1723-31.
88. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, et al. Time to Treatment With Endovascular Thrombectomy and Outcomes From Ischemic Stroke: A Meta-analysis. JAMA. 2016;316(12):1279-88.
89. Mattle HP, Arnold M, Lindsberg PJ, Schonewille WJ, Schroth G. Basilar artery occlusion. Lancet Neurol. 2011;10(11):1002-14.
90. Lindsberg PJ, Soinne L, Tatlisumak T, Roine RO, Kallela M, Häppölä O, Kaste M. Long-term outcome after intravenous thrombolysis of basilar artery occlusion. J Am Med Assoc. 2004; 292: 1862–1866
91. Ezaki Y, Tsutsumi K, Onizuka M, Kawakubo J, Yagi N, Shibayama A, et al. Retrospective analysis of neurological outcome after intra-arterial thrombolysis in basilar artery occlusion. Surgical Neurology.60(5):423-9.
92. Sliwka U, Mull M, Syelzer A, Diehl R, Noth J. Long-term follow-up of patients after intraarterial thrombolytic therapy of acute vertebrobasilar artery occlusion. Cerebrovasc Dis. 2001; 12: 214–219
93. Levy EI, Firlik AD, Wisniewski S, Rubin G, Jungreis CA, Wechsler LR, Yonas H. Factors affecting survival rates for acute vertebrobasilar artery occlusions treated with intraarterial thrombolytic therapy: a meta-analytical approach. Neurosurgery. 1999; 45: 539–545.
94. Lindsberg PJ, Mattle HP. Therapy of Basilar Artery Occlusion. A Systematic Analysis Comparing Intra-Arterial and Intravenous Thrombolysis. 2006;37(3):922-8.
95. Strbian D, Sairanen T, Silvennoinen H, Salonen O, Kaste M, Lindsberg PJ. Thrombolysis of basilar artery occlusion: impact of baseline ischemia and time. Ann Neurol 2013;73:688-94.
96. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, et al. SAMMPRIS Trial Investigators. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med. 2011;365:993–1003 doi: 10.1056/NEJMoa1105335.
97. Zaidat OO, Fitzsimmons BF, Woodward BK, Wang Z, Killer-Oberpfalzer M, Wakhloo A, et al. Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: the VISSIT randomized clinical trial. JAMA. 2015;313(12):1240-8.
98. Derdeyn CP, Fiorella D, Lynn MJ, Turan TN, Cotsonis GA, Lane BF, et al. Nonprocedural Symptomatic Infarction and In-Stent Restenosis After

Intracranial Angioplasty and Stenting in the SAMMPRIS Trial (Stenting and Aggressive Medical Management for the Prevention of Recurrent Stroke in Intracranial Stenosis). Stroke. 2017;48(6):1501-6.
99. Derdeyn CP, Chimowitz MI, Lynn MJ, Fiorella D, Turan TN, Janis LS, et al. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. The Lancet. 2014;383(9914):333-41.
100. Andersson T, Kuntze Söderqvist Å, Söderman M, Holmin S, Wahlgren N, Kaijser M. Mechanical thrombectomy as the primary treatment for acute basilar artery occlusion: experience from 5 years of practice. Journal of NeuroInterventional Surgery. 2013;5(3):221-5.
101. Mohlenbruch M, Stampfl S, Behrens L, Herweh C, Rohde S, Bendszus M, et al. Mechanical thrombectomy with stent retrievers in acute basilar artery occlusion. AJNR Am J Neuroradiol. 2014;35(5):959-64.
102. Schonewille WJ, Wijman CAC, Michel P, et al. Treatment and outcomes of acute basilar artery occlusion in the Basilar Artery International Cooperation Study (BASICS): a prospective registry study. The Lancet Neurology. 2009;8(8):724-30.
103. Singer OC, Berkefeld J, Nolte CH, et al. Mechanical recanalization in basilar artery occlusion: the ENDOSTROKE study. Ann Neurol. 2015;77(3):415-24.
104. Liu X, Xu G, Liu Y, et al. Acute basilar artery occlusion: Endovascular Interventions versus Standard Medical Treatment (BEST) Trial-Design and protocol for a randomized, controlled, multicenter study. Int J Stroke. 2017:1747493017701153.
105. van der Hoeven EJ, Schonewille WJ, Vos JA, et al. The Basilar Artery International Cooperation Study (BASICS): study protocol for a randomised controlled trial. Trials. 2013;14(1):200.
106. Pennlert J, Asplund K, Glader E-L, Norrving B, Eriksson M. Socioeconomic Status and the Risk of Stroke Recurrence. Persisting Gaps Observed in a Nationwide Swedish Study 2001 to 2012. 2017;48(6):1518-23.
107. Nordanstig A, Jood K, Rosengren L. Public stroke awareness and intent to call 112 in Sweden. Acta Neurol Scand. 2014;130(6):400-4.
108. Nordanstig A, Asplund K, Norrving B, Wahlgren N, Wester P, Rosengren L. Impact of the Swedish National Stroke Campaign on stroke awareness. Acta Neurol Scand. 2017.
109. Andsberg G, Esbjörnsson M, Olofsson A, Lindgren A, Norrving B, von Euler M. Scand J Trauma Emerg Med. 2017;25(1):37
110. Prehospital ICT Arena: “ViPHS: Video communication from ambulances saves time, lives and costs to society”.

https://picta.lindholmen.se/en/news/video-communication-ambulances-saves-time-lives-and-costs-society
111. Audebert HJ, Saver JL, Starkman S, Lees KR, Endres M. Prehospital stroke care: New prospects for treatment and clinical research. Neurology. 2013;81(5):501-8.
112. Ebinger M, Winter B, Wendt M, et al. Effect of the use of ambulance-based thrombolysis on time to thrombolysis in acute ischemic stroke: A randomized clinical trial. JAMA. 2014;311(16):1622-31.
113. John S, Stock S, Cerejo R, Uchino K, Winners S, Russman A, et al. Brain Imaging Using Mobile CT: Current Status and Future Prospects. Journal of Neuroimaging. 2016;26(1):5-15.
114. Jørgensen HS, Nakayama H, Raaschou HO, Larsen K, Hübbe P, Olsen TS. The Effect of a Stroke Unit: Reductions in Mortality, Discharge Rate to Nursing Home, Length of Hospital Stay, and Cost. A Community-Based Study. 1995;26(7):1178-82.
115. Terént A, Asplund K, Farahmand B, Henriksson KM, Norrving B, Stegmayr B, et al. Stroke unit care revisited: who benefits the most? A cohort study of 105 043 patients in Riks-Stroke, the Swedish Stroke Register. Journal of Neurology, Neurosurgery & Psychiatry. 2009;80(8):881-7.
116. Konstas AA, Goldmakher GV, Lee T-Y, Lev MH. Theoretic Basis and Technical Implementations of CT Perfusion in Acute Ischemic Stroke, Part 1: Theoretic Basis. American Journal of Neuroradiology. 2009;30(4):662-8.
117. Konstas AA, Goldmakher GV, Lee T-Y, Lev MH. Theoretic Basis and Technical Implementations of CT Perfusion in Acute Ischemic Stroke, Part 2: Technical Implementations. American Journal of Neuroradiology. 2009;30(5):885-92.
118. DAWN Trial. Results presented at European Stroke Organisation Conference (ESOC 16-18 May 2017 Prague, Czech Republic).
119. Wintermark M, Flanders AE, Velthuis B, Meuli R, van Leeuwen M, Goldsher D, et al. Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. Stroke. 2006;37(4):979-85.
120. Campbell BC, Christensen S, Levi CR, Desmond PM, Donnan GA, Davis SM, et al. Cerebral blood flow is the optimal CT perfusion parameter for assessing infarct core. Stroke. 2011;42(12):3435-40.
121. Menon BK, d'Esterre CD, Qazi EM, Almekhlafi M, Hahn L, Demchuk AM, et al. Multiphase CT Angiography: A New Tool for the Imaging Triage of Patients with Acute Ischemic Stroke. Radiology. 2015;275(2):510-20.
122. Boers AM, Jansen IG, Berkhemer OA, Yoo AJ, Lingsma HF, Slump CH, et al. Collateral status and tissue outcome after intra-arterial therapy for

patients with acute ischemic stroke. J Cereb Blood Flow Metab. 2016:271678X16678874.

123. McVerry F, Liebeskind DS, Muir KW. Systematic review of methods for assessing leptomeningeal collateral flow. AJNR Am J Neuroradiol. 2012;33(3):576-82.

124. Miteff F, Levi CR, Bateman GA, Spratt N, McElduff P, Parsons MW. The independent predictive utility of computed tomography angiographic collateral status in acute ischaemic stroke. Brain. 2009;132(Pt 8):2231-8.

125. Rother J, de Crespigny AJ, D'Arceuil H, et al. Recovery of apparent diffusion coefficient after ischemia-induced spreading depression relates to cerebral perfusion gradient. Stroke 1996;27:980-986.

126. Gonzalez RG, Schaefer PW, Buonanno FS, et al. DiffusionweightedMRimaging: Diagnostic accuracy in patients imaged within 6 hours of stroke symptom onset. Radiology 1999;210:155-162.

127. Mitomi M, Kimura K, Aoki J, Iguchi Y. Comparison of CT and DWI findings in ischemic stroke patients within 3 hours of onset. J Stroke Cerebrovasc Dis. 2014;23(1):37-42.

128. U-King-Im JM, Trivedi RA, Graves MJ, Harkness K, Eales H, Joubert I, et al. Utility of an ultrafast magnetic resonance imaging protocol in recent and semi-recent strokes. Journal of Neurology, Neurosurgery & Psychiatry. 2005;76(7):1002-5.

129. Paolini S, Burdine J, Verenes M, Webster J, Faber T, Graham CB, et al. Rapid Short MRI Sequence Useful in Eliminating Stroke Mimics Among Acute Stroke Patients Considered for Intravenous Thrombolysis. Journal of neurological disorders. 2013;1:137.

130. Adams, H. P. Jr. MD; Davis, P. H. MD; Leira, E, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) Neurology. 1999 1(53);126-131.

131. Glymour M, Berkman L, Ertel K, Fay M, Glass T, Furie K (2007). "Lesion characteristics, NIH Stroke Scale, and functional recovery after stroke". American Journal of Physical Medicine & Rehabilitation. 86 (9): 725–733.

132. Heldner MR, Zubler C, Mattle HP, Schroth G, Weck A, Mono ML, et al. National Institutes of Health stroke scale score and vessel occlusion in 2152 patients with acute ischemic stroke. Stroke. 2013;44(4):1153-7.

133. Linfante I, Llinas RH, Schlaug G, Chaves C, Warach S, Caplan LR. Diffusion-weighted imaging and national institutes of health stroke scale in the acute phase of posterior-circulation stroke. Archives of Neurology. 2001;58(4):621-8.

134. Inoa V, Aron AW, Staff I, Fortunato G, Sansing LH. Lower NIH Stroke Scale Scores Are Required to Accurately Predict a Good Prognosis in Posterior Circulation Stroke. Cerebrovascular Diseases. 2014;37(4):251-5.
135. Lyden PD, Lu M, Levine SR, Brott TG, Broderick J. A Modified National Institutes of Health Stroke Scale for Use in Stroke Clinical Trials. Preliminary Reliability and Validity. 2001;32(6):1310-7.
136. Woo D, Broderick JP, Kothari RU, Lu M, Brott T, Lyden PD, et al. Does the National Institutes of Health Stroke Scale Favor Left Hemisphere Strokes? Stroke. 1999;30(11):2355-9.
137. Stalhammer D, Starmark JE. Assessment of responsiveness in head injury patients. The Glasgow Coma Scale and some comments on alternative methods. Acta Neurochir. 1986; Supplement 36: 91-94.
138. Starmark J-E, Stalhammer D, Holmgren E. The reaction level scale (RLS85). Manual and guidelines. Acta Neurochir. 1988; 91: 12-20.
139. Starmark J-E, Stalhammer D, et al. A comparison of the Glasgow coma scale and the Reaction Level Scale (RLS85). J Neurosurg. 1988; 69: 699-706.
140. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: The European cooperative acute stroke study (ecass). JAMA. 1995;274(13):1017-25.
141. Grotta JC, Chiu D, Lu M, Patel S, Levine SR, Tilley BC, et al. Agreement and Variability in the Interpretation of Early CT Changes in Stroke Patients Qualifying for Intravenous rtPA Therapy. Stroke. 1999;30(8):1528-33.
142. Pexman JH, Barber PA, Hill MD, et al. Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. AJNR Am J Neuroradiol 2001;22:1534-42.
143. Puetz V, Sylaja PN, Coutts SB, et al. Extent of hypoattenuation on CT angiography source images predicts functional outcome in patients with basilar artery occlusion. Stroke. 2008;39(9):2485-90.
144. Christoforidis GA, Mohammad Y, Kehagias D, Avutu B, Slivka AP. Angiographic assessment of pial collaterals as a prognostic indicator following intra-arterial thrombolysis for acute ischemic stroke. AJNR Am J Neuroradiol. 2005;26(7):1789-97.
145. Seker F, Potreck A, Möhlenbruch M, Bendszus M, Pham M. Comparison of four different collateral scores in acute ischemic stroke by CT angiography. Journal of NeuroInterventional Surgery. 2016;8(11):1116-8.
146. Alemseged F, Shah DG, Diomedi M, Sallustio F, Bivard A, Sharma G, et al. The Basilar Artery on Computed Tomography Angiography Prognostic Score for Basilar Artery Occlusion. Stroke. 2017;48(3):631-7.

147. Sims JR, Gharai LR, Schaefer PW, Vangel M, Rosenthal ES, Lev MH, et al. ABC/2 for rapid clinical estimate of infarct, perfusion, and mismatch volumes. Neurology. 2009;72(24):2104-10.
148. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group. N Engl J Med 1985;312:932-6.
149. Higashida RT, Furlan AJ, Roberts H, et al. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. Stroke 2003;34:e109-37.
150. Investigators IIT. The Interventional Management of Stroke (IMS) II Study. Stroke 2007;38:2127-35.
151. Goyal M, Fargen KM, Turk AS, Mocco J, Liebeskind DS, Frei D, et al. 2C or not 2C: defining an improved revascularization grading scale and the need for standardization of angiography outcomes in stroke trials. J Neurointerv Surg. 2014;6:83–86. doi: 10.1136/neurintsurg-2013-010665
152. Almekhlafi MA, Mishra S, Desai JA, Nambiar V, Volny O, Goel A, et al. Not all "successful" angiographic reperfusion patients are an equal validation of a modified TICI scoring system. Interv Neuroradiol. 2014;20:21–27.
153. Zaidat OO, Yoo AJ, Khatri P, et al. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. Stroke 2013;44:2650-63.
154. Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. J Neurol Neurosurg Psychiatry 1991;54:1044-54.
155. Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: Implications for stroke clinical trials: A literature review and synthesis. Stroke; a journal of cerebral circulation. 2007;38:1091-1096
156. Wardlaw JM et al (2003) Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev 3: CD000213
157. Wolpert SM et al Neuroradiologic evaluation of patients with acute stroke treated with recombinant tissue plasminogen activator. The rt-PA Acute Stroke Study Group. Am J Neuroradiol 1993;14(1):3–13
158. Bhatia R, Hill MD, Shobha N, Menon B, Bal S, Kochar P, et al. Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action. Stroke. 2010;41(10):2254-8.
159. ASTER TRIAL. Results presented at European Stroke Organisation Conference (ESOC 16-18 May 2017 Prague, Czech Republic).
160. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. Stroke. 2007;38(3):967-73.

161. Farzin B, Fahed R, Guilbert F. et Al. Early CT changes in patients admitted for thrombectomy: Intrarater and interrater agreement. Neurology. 2016;87(3):249-56.
162. Schröder J, Thomalla G. A Critical Review of Alberta Stroke Program Early CT Score for Evaluation of Acute Stroke Imaging. Frontiers in neurology. 2016;7:245.
163. Yoo AJ, Berkhemer OA, Fransen PSS, van den Berg LA, Beumer D, Lingsma HF, et al. Effect of baseline Alberta Stroke Program Early CT Score on safety and efficacy of intra-arterial treatment: a subgroup analysis of a randomised phase 3 trial (MR CLEAN). The Lancet Neurology.15(7):685-94.
164. Yoo AJ, Zaidat OO, Chaudhry ZA, Berkhemer OA, González RG, Goyal M, et al. Impact of Pretreatment Noncontrast CT Alberta Stroke Program Early CT Score on Clinical Outcome After Intra-Arterial Stroke Therapy. Stroke. 2014;45(3):746-51.
165. Lindsberg, P.J. and H.P. Mattle, Therapy of basilar artery occlusion: a systematic analysis comparing intra-arterial and intravenous thrombolysis. Stroke, 2006. 37(3): p. 922-8.
166. Schonenberger S, Uhlmann L, Hacke W, Schieber S, Mundiyanapurath S, Purrucker JC, et al. Effect of conscious sedation vs general anesthesia on early neurological improvement among patients with ischemic stroke undergoing endovascular thrombectomy: A randomized clinical trial. Jama. 2016;316:1986-1996
167. Hoffmann U, Sheng H, Ayata C, Warner DS. Anesthesia in experimental stroke research. Translational stroke research. 2016;7:358-367
168. Gupta S, Heath K, Matta BF. Effect of incremental doses of sevoflurane on cerebral pressure autoregulation in humans. British journal of anaesthesia. 1997;79:469-472
169. Matta BF, Heath KJ, Tipping K, Summors AC. Direct cerebral vasodilatory effects of sevoflurane and isoflurane. Anesthesiology. 1999;91:677-680
170. Sivasankar C, Stiefel M, Miano TA, Kositratna G, Yandrawatthana S, Hurst R, et al. Anesthetic variation and potential impact of anesthetics used during endovascular management of acute ischemic stroke. J Neurointerv Surg. 2016;8:1101-1106
171. Kuntze Söderqvist Å, Andersson T, Ahmed N, Wahlgren N, Kaijser M. Thrombectomy in acute ischemic stroke: estimations of increasing demands. Journal of NeuroInterventional Surgery. 2016 [Epub ahead of print]
172. Persson M, Fhager A, Trefna H, Yu Y, McKelvey T, Pegenius G, Karlsson J-E, Elam M. Microwave-based stroke diagnosis making global prehospital thrombolytic treatment possible. IEEE Trans. Biomed. Eng. 2014;61:2806-2817

173. Padmanabhan, A. and S.M. Haldar, Neuroprotection in ischemic stroke: AhR we making progress? Circulation, 2014. 130(23): p. 2002-4.
174. Gunning GM, McArdle K, Mirza M, Duffy S, Gilvarry M, Brouwer PA. Clot friction variation with fibrin content; implications for resistance to thrombectomy. J Neurointerv Surg 2017 [Epub ahead of print]
175. Banerjee, S., et al., Human stem cell therapy in ischaemic stroke: a review. Age Ageing, 2011. 40(1): p. 7-13.
176. Janowski, M., D.C. Wagner, and J. Boltze, Stem Cell-Based Tissue Replacement After Stroke: Factual Necessity or Notorious Fiction? Stroke, 2015. 46(8): p. 2354-63.
177. Steinberg, G.K., et al., Clinical Outcomes of Transplanted Modified Bone Marrow-Derived Mesenchymal Stem Cells in Stroke: A Phase 1/2a Study. Stroke, 2016. 47(7): p. 1817-24.

APPENDIX I-IV