Tampere University

JUHA-PEKKA PIENIMÄKI

Factors Affecting the Outcome of Mechanical Thrombectomy in Stroke

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ACADEMIC DISSERTATION
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To Nemo, Luke and Peppi

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ABSTRACT

Acute brain ischaemia due to an obstructed blood vessel in cerebral circulation is a serious condition that, without efficient treatment, can lead to a cerebral infarction, severe disability or even death. In Finland and elsewhere in the Western world, ischaemic stroke is one of the major causes of death and the main reason for losing quality-adjusted life years.

Most often, ischaemic stroke is caused by a thrombus that obstructs brain circulation. The only treatment for a cerebral infarction is to restore blood flow quickly enough. Previously, the only approved treatment was intravenous thrombolysis. Over the past decade, intra-arterial mechanical thrombus removal methods have evolved significantly. Particularly, mechanical intra-arterial methods for removing occlusions caused by thrombi of the larger arteries have proven to be superior to thrombolysis therapy alone.

This thesis focuses on factors affecting the outcome of mechanical thrombectomy (MT) in patients suffering an acute anterior circulation ischaemic stroke caused by a large vessel occlusion. We analysed over 400 thrombectomy patients admitted to Tampere University Hospital between 2013 and 2019. Their status at admission was evaluated with standard clinical and laboratory parameters, as well as computed tomography (CT) and CT angiography (CTA) of the brain and neck vessels. These data were collected from patient records. The technical success of the thrombectomy intervention was evaluated from the final DSA runs of the intervention. A control head CT was acquired a day after the MT to evaluate possible infarct and haemorrhagic complications. The clinical outcome was determined with the modified Rankin Score (mRS) three months after the MT and used as the clinical endpoint.

In our study, MT patients aged 60 years and older with pre-stroke chronic ischaemic lesions (CILs) experienced significantly increased dependency and elevated mortality after the procedure. Patients without CILs were 3.7 times more likely to achieve a good three-month clinical outcome, when compared with patients with CILs.

Patients with severe carotid stenosis were four times more likely to have very good intracranial collateral circulation in an admission CTA than patients with no or

slight carotid stenosis. On the other hand, the MT intervention lasted significantly longer in patients with severe carotid stenosis (41 min, compared to 29 min in patients without severe stenosis). At three months, 54% of the patients achieved a good clinical outcome, with the severity of carotid stenosis having no significant effect.

The prognosis of anaemic MT patients was significantly weaker than that of non-anaemic patients. After the MT, non-anaemic patients had over 2.5 times better odds of achieving a good three-month clinical outcome. A 0.1 g/dl increase in haemoglobin improved the odds of a good clinical outcome by 2%. The effect of anaemia was seen only in patients with intracranial collaterals. If the collateral status was poor, the odds of a good clinical outcome were lower irrespective of the blood haemoglobin level.

The patients who could be transferred to MT immediately after diagnosis had significantly better odds of an excellent clinical outcome (mRS 0 or 1) if intravenous thrombolysis was not administered. In this setting of a minimal in-hospital delay, the patients who were administered thrombolysis had 2.6-fold higher odds of a poorer clinical outcome at three months. An excellent clinical outcome was three times more frequent in patients who did not receive thrombolysis. A trend of more deaths was found among the thrombolysis-treated patients.

TIIVISTELMÄ

Äkillinen aivoverenkierron häiriöstä johtuva aivokudoksen hapenpuute on vakava tila, joka hoitamattomana johtaa aivokudoksen kuolemaan eli aivoinfarktiin. Aivoinfarkti voi aiheuttaa hankalia neurologisia puutosoireita tai jopa kuoleman. Aivoinfarkti on Suomessa ja muissa länsimaissa merkittävin yksittäinen laadukkaiden elinvuosien vähentäjä sekä yksi yleisimmistä kuolinsyistä.

Tavallisimmin aivoverenkierron häiriö aiheutuu veritulpasta eli trombista, joka estää normaalin verenkierron aivokudokseen. Merkittävin hoitokeino aivoinfarktin kehittymisen välttämiseksi on verenkierron riittävän nopea palauttaminen avaamalla tukkeutunut suoni. Aikaisemmin tukoksen aukaisuun käytettiin ainoastaan laskimonsisäisesti annettua trombin liuotushoitoa, trombolyysiä. Viimeisen vuosikymmenen aikana valtimonsisäiset trombin poistomenetelmät, eli mekaaninen trombektomia, ovat kuitenkin kehittyneet merkittävästi. Erityisesti suurten kaula- ja aivovaltimotrombien poistossa mekaaniset menetelmät ovat osoittautuneet ylivertaisiksi pelkkään liuotushoitoon verrattuna.

Tämän väitöskirjatutkimuksen tavoitteena oli selvittää mekaanisella trombektomialla hoidettujen potilaiden toipumiseen vaikuttavia tekijöitä. Tutkimusaineisto koostuu yli 400:sta vuosina 2013–2019 Tampereen yliopistollisessa sairaalassa trombektomialla hoidetusta aivohalvauspotilaasta. Sairaalaan tulovaiheen tilanne arvioitiin aivojen ja kaulasuonten tietokonekuvausten sekä potilastietojärjestelmästä kerättyjen tietojen pohjalta. Toimenpiteen onnistuminen määritettiin trombektomian yhteydessä tapahtuvan suonensisäisen kuvauksen perusteella. Vuorokauden kuluttua toimenpiteen jälkeen aivojen tilanne selvitettiin tietokonekuvauksella, josta arvioitiin mahdollisen infarktin kehittyminen sekä toimenpiteeseen mahdollisesti liittyvät verenvuotokomplikaatiot. Kolmen kuukauden kohdalla neurologi arvioi potilaiden toipumisen ja omatoimisuusasteen, joihin liittyvät tiedot kerättiin potilastietojärjestelmästä. Kolmen kuukauden omatoimisuusastetta käytettiin toipumistuloksen ensisijaisena mittarina.

Yli 60-vuotiailla potilailla krooniset aivoverenkiertoperäiset vauriot heikensivät selvästi potilaiden omatoimisuusastetta ja lisäsivät kuolleisuutta. Potilailla, joilla näitä kroonisia vaurioita ei ollut, oli tutkimuksessamme 3,7-kertainen todennäköisyys

saavuttaa hyvä omatoimisuusaste kolmen kuukauden kohdalla verrattuna potilaisiin, joilla näitä vaurioita oli havaittavissa.

Potilailla, joilla todettiin merkittävä kaulasuonen ahtauma, todettiin sairaalaan tulovaiheen tietokonekuvauksessa neljä kertaa todennäköisemmin erittäin hyvät kallonsisäiset valtimokollateraalisuonet verrattuna potilaisiin, joilla ei ollut merkittävää kaulasuonen ahtaumaa. Ahtautuneen tai tukkeutuneen kaulasuonen läpi suoritetut toimenpiteet kestivät selvästi pidempään (41 min vs. 29 min potilailla, joilla ei ollut merkittävää ahtaumaa). Keskimäärin hyvän omatoimisuusasteen kolmen kuukauden kohdalla saavutti trombektomian jälkeen 54 % potilaista, eikä kaulasuonen merkittävällä ahtaumalla todettu olevan tähän tilastollisesti merkittävää vaikutusta.

Anemiasta kärsivien potilaiden kuntoutuminen oli selvästi heikompaa verrattuna potilaisiin, joilla anemiaa ei todettu. Sairastetun, trombektomialla hoidetun aivoinfarktin jälkeen hyvä omatoimisuus kolmen kuukauden kohdalla oli yli 2,5 kertaa todennäköisempää, jos potilaalla ei ollut anemiaa. Hemoglobiiniarvon nousu yhdellä grammalla litraa kohden paransi hyvän lopputuloksen todennäköisyyttä kahdella prosentilla. Parempi ennuste havaittiin potilailla, joilla oli todettavia kallonsisäisiä valtimokollateraaleja. Kollateraalisuonten puuttuessa hyvän kuntoutumisen todennäköisyys oli pienempi veren hemoglobiinitasosta riippumatta.

Mikäli suuren suonen tukoksesta johtuvaa äkillistä aivoverenkiertohäiriötä sairastava potilas pääsi välittömästi sairaalaan saapumisen jälkeen trombektomiaan, erinomaisen kuntoutumisen todennäköisyys oli kolminkertainen, jos hänelle ei annettu edeltävästi trombolyysiä. Minimaalisen sairaalansisäisen viiveen toimintamallilla hoidetulla potilasryhmällä trombolyysihoito 2,6-kertaisti huonomman omatoimisuusasteen todennäköisyyden kolmen kuukauden kohdalla. Lisäksi tässä potilasryhmässä havaittiin myös viitettä trombolyysin aiheuttamasta kuolleisuuden lisääntymisestä.

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ABBREVIATIONS

A1	First segment of the ACA
A2	Second segment of the ACA
A3	Third segment of the ACA
A4	Fourth segment of the ACA
ACA	Anterior cerebral artery
ACoA	Anterior communicating artery
AICA	Anterior inferior cerebellar artery
ASPECT	Alberta stroke program early CT score
BA	Basilar artery
CBV	Cerebral blood volume
CBF	Cerebral blood flow
CCA	Common carotid artery
CS	Collateral circulation
CT	Computed tomography
CTA	Computed tomography angiography
CTP	Computed tomography perfusion
EEG	Electroencephalography
FPSS	Finnish Prehospital Stroke Scale
ia	Intra-arterial
ICA	Internal carotid artery
ICH	Intracranial haemorrhage
iv	Intravenous
IVT	Intravenous thrombolysis
LVO	Large vessel occlusion
M1	First segment of the MCA
M2	Second segment of the MCA
M3	Third segment of the MCA
M4	Fourth segment of the MCA
MCA	Medial cerebral artery
MT	Mechanical thrombectomy

MTT	Mean transit time
MRI	Magnetic resonance imaging
mRS	Modified Ranking Scale
NIHSS	National Institutes of Health Stroke Score
OCT	Time from symptom onset to the beginning of CT imaging (Onset-to-CT)
OMT	Time from symptom onset to groin puncture in MT (Onset-to-MT)
OR	Odds ratio
P1	First segment of the PCA
P2	Second segment of the PCA
P3	Third segment of the PCA
P4	Fourth segment of the PCA
PCA	Posterior cerebral artery
PCoA	Posterior communicating artery
rt-PA	Recombinant tissue plasminogen activator
sICH	Symptomatic intracranial haemorrhage
TIA	Transient ischaemic attack
TICI	Thrombolysis in cerebral infarction score
Tmax	Time to maximum of the residue function
TTP	Time to peak
VA	Vertebral artery

ORIGINAL PUBLICATIONS

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Publication I	Sillanpää N, **Pienimäki JP**, Protto S, Seppänen J, Numminen H, Rusanen H. Chronic Infarcts Predict Poor Clinical Outcome in Mechanical Thrombectomy of Sexagenarian and Older Patients. J Stroke Cerebrovasc Dis. 2018 Jul;27(7):1789-1795
Publication II	**Pienimäki JP**, Sillanpää N, Jolma P, Protto, S. Carotid Artery Stenosis Is Associated with Better Intracranial Collateral Circulation in Stroke Patients. Cerebrovasc Dis. 2020;49(2):200-205.
Publication III	**Pienimäki JP**, Protto S, Hakomäki E, Jolma P, Sillanpää N. Anemia Predicts Poor Clinical Outcome in Mechanical Thrombectomy Patients with Fair or Good Collateral Circulation. Cerebrovasc Dis Extra. 2020 Oct 22;10(3):139-147
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AUTHOR'S CONTRIBUTION

The author performed a significant proportion of the thrombectomies analysed herein. The author was responsible for planning the data collection and assembling all of the data on the thrombectomy procedures analysed in this dissertation.

Additionally, in Publication I, the author provided revisions to the scientific content of the manuscript.

In Publications II–IV, the author conceived the ideas for the studies and was the primary author of the manuscripts. The author collected the data from the medical records with the co-authors. The author performed all statistical analyses of the data and interpreted the results together with the co-authors.

1 INTRODUCTION

There are two main types of strokes. An ischaemic stroke is caused by insufficient cerebral blood flow. The rupture of a weakened cerebral vessel into the brain is known as a haemorrhagic stroke. Ischaemia is a cause of stroke in approximately 80 percent of cases. If the symptoms of stroke last for less than 24 hours, the condition is considered a transient ischaemic attack (TIA) (Albers et al., 2002). If the symptoms are permanent or if a parenchymal infarction is detected in brain imaging, the diagnosis is cerebral infarction.

In the Western world, a cerebral infarction is one of the leading causes of death and the main reason for the loss of quality-oriented years of life. A cerebral infarction also has a significant economic impact. In Finland, the cost of treating stroke patients is over one billion euros per year. Therefore, an effective treatment for cerebral infarctions has an important role in increasing quality-oriented life years but also in terms of the national economy. (Feigin, Norrving, & Mensah, 2017; Finnish Institute for Health and Welfare, 2014b; GBD 2013 Mortality and Causes of Death Collaborators, 2015; Meretoja, 2012; Norrving et al., 2015; O'Donnell et al., 2016; World Health Organization, 2016.)

Typically, the more proximally an artery is occluded, the larger the volume that becomes hypoxic and, without effective treatment, the larger the infarct that develops. Most often, the occlusion is due to a blood clot, i.e. thrombus. The larger the occluded artery, the larger the thrombus volume as per the rules of basic geometry. An attempt can be made to dissolve the thrombus by intravenous thrombolysis. In the case of larger thrombi, the effect of IV thrombolysis is very limited (Riedel et al., 2011; Tsivgoulis et al., 2018). Mechanical thrombectomy (MT) takes a different approach by removing the occluding clot through the arteries using catheter-based technology. With MT, over 90 percent of large cerebral artery occlusions can typically be removed. This study investigates the factors affecting the outcome of MT.

2 REVIEW OF THE LITERATURE

2.1 Arterial supply of the brain

The brain constitutes only about 2% of the total body weight, but it accounts for 20% of the total oxygen consumption and up to 25% of the total cardiac output (Amin & Schindler, 2017). Normally, four major arteries enter the skull base to supply brain circulation: the internal cerebral arteries and vertebral arteries on both sides.

2.1.1 Anterior circulation

From the aortic arc arise the brachiocephalic artery, the left common carotid artery (CCA) and the left subclavian artery. The brachiocephalic artery bifurcates into the right subclavian artery and the right CCA. The CCAs bifurcate into the internal and external carotid arteries (ICAs and ECAs, respectively). The ICAs pass through the skull base via the carotid canal into the intracranial space. The intracranial circulation via the ICAs is the anterior circulation. Intracranially, the terminal ICA divides into two major branches, the middle cerebral artery (MCA) and the anterior cerebral artery (ACA). The vascular territories of these arteries are depicted in Figure 1.

The small but functionally critical anterior choroidal artery (AChA) is the last to branch off from the ICA before the ICA terminus. The AChA provides arterial supply to the posterior limb of the internal capsule containing the neurofibres of the corticospinal tract and thus relaying motor commands. The AChA also supplies the optic tract and the lateral geniculate nucleus, relaying visual information. The obstruction of the AchA typically leads to motor and visual dysfunction. (Javed & Das, 2021.)

The MCA supplies a large volume of the brain parenchyma. From the proximal part of the first segment of the MCA (M1) arise the lateral lenticulostriate arteries that supply the lateral portion of the putamen and the external capsule, as well as the upper internal capsule. Most M1 segments bifurcate into two M2 trunks, the superior and the inferior. In rest of the cases, M1 segments have a trifurcation and, seldomly,

≥ 4 distal branches. (Cilliers & Page, 2017; Fox, Gallacher, Shevde, Loftus, & Swayne, 1993.) The MCA branches supply the temporal lobe and the major parts of the frontal and parietal lobes. These areas are responsible for initiating voluntary muscle activity, the sensation of muscles and the skin, as well as hearing, speech and language comprehension.

The ACA supplies the most midline portions of frontal lobes and the superior medial parts of parietal lobes. These areas contain the cortex responsible for motor and sensory functions of the lower limb. From the most proximal ACA segment (A1) originate the medial lenticulostriate arteries, which supply blood to the globus pallidus and the medial portion of the putamen.

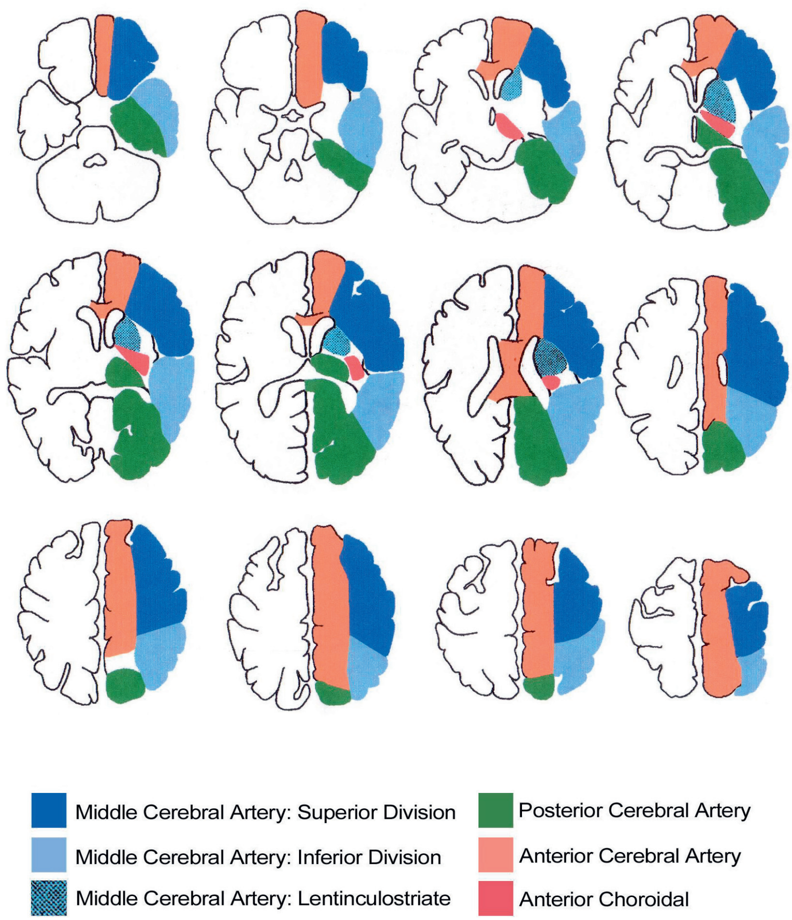

Figure 1. The brain vascular territories of the anterior circulation (Adapted from emedicine.madscape.com).

2.1.2 Posterior circulation

From both subclavian arteries arise the vertebral arteries (VA). The VAs enter the intracranial space through the skull base via the foramen magnum and fuse into the basilar artery (BA). There are three major cerebellar artery pairs. The posterior inferior cerebellar artery (PICA) originates from the distal VAs, while the anterior inferior cerebellar artery (AICA) and the superior cerebellar artery (SCA) originate from the BA. The circulation via the VAs is the posterior circulation.

The distal parts of the intracranial VAs and the BA with its branches supply the brainstem (the pons, midbrain and medulla) and the movement coordinating the cerebrum. The medial part of the brainstem is supplied by the penetrating paramedian branches of the BA. The dorsolateral parts of the brainstem are supplied by direct circumferential branches of the VA or BA, or by branches of the major cerebellar arteries (PICA, AICA, SCA) as they curve around the brainstem on their way to the part of the cerebellum they supply.

The brainstem is crucial to maintaining life, even though it makes up only roughly 2.6% of the total brain weight. The brainstem is responsible for vital functions such as the heart rate, breathing, sleeping and eating. Additionally, all information relayed from the cerebrum and the cerebellum to the body must traverse the brainstem.

The BA divides into the left and right posterior cerebellar arteries (PCA), which supply the posterior part of the brain, the occipital lobe, that is responsible for sight and visual recognition. The P1 and P2 are considered to be the deep PCA segments. The P1 segment lies between the termination of the BA and the posterior communicating artery (PCoA). Arterial branches arising from the deep segments supply parts of the midbrain, the thalamus, the lateral geniculate body, the pulvinar, the hippocampus and the parahippocampal gyrus. Arterial branches arising from the superficial segments (P3 and P4) supply the temporal and occipital lobes.

2.1.3 Collateral circulation

Intracranial arteries have their own primary areas that they supply. If the circulation is interrupted, neurological symptoms arise due to a misfunction of the ischaemic brain parenchyma. If the disruption is prolonged, death of the neurons ensues, leading to an infarct. Even if the blood supply through the principal routes is interrupted, however, properly functioning collateral arteries can secure the viability of the ischaemic brain area.

The primary arterial collateral system is located at the skull base and is known as the Circle of Willis (Figure 2). It forms connections between anterior (ICA) and posterior (PCA) circulation via the PCoAs, as well as an interhemispheric connection via the anterior communicating artery (ACoA) between the ACAs.

There is a lot of normal variation in the Circle of Willis. An absence of the ACoA is found in 5% of individuals, an absence or hypoplasia of the proximal ACA (A1) in 10%, and an absence or hypoplasia of either the PCoA or the first segment of the PCA (P1) in 30% (Dimmick & Faulder, 2009; Kovac, Stankovic, Stankovic, Kovac, & Saranovic, 2014).

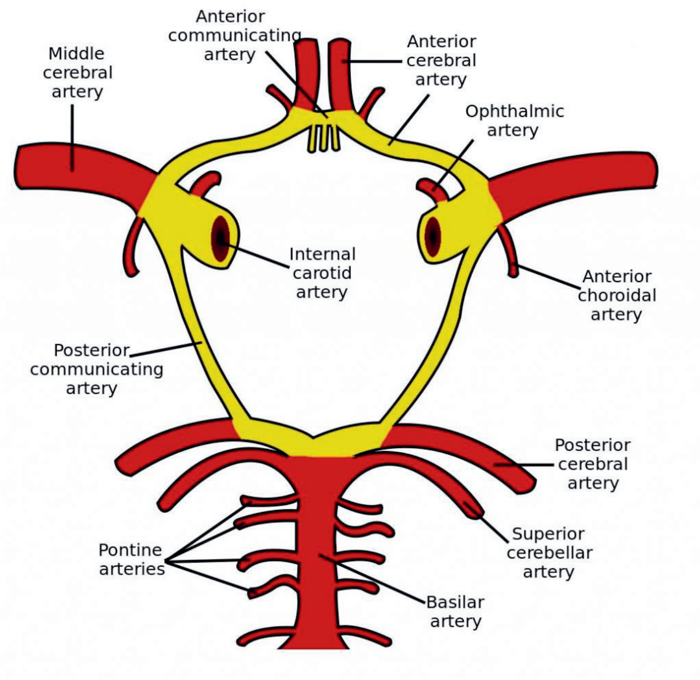

Figure 2. Circle of Willis (Case courtesy of OpenStax College, Radiopaedia.org, rID: 42608)

There are secondary collaterals between extra- and intracranial arteries: anastomoses from extracranial facial, maxillary and middle meningeal arteries to the intracranial ophthalmic artery (ICA branch), as well as dural arteriolar anastomoses from the middle meningeal artery and occipital artery. Another type of secondary collaterals is leptomeningeal, pial-arteriolar-like anastomoses between the anterior and middle cerebral arteries and between the posterior and middle cerebral arteries. (Liebeskind, 2003.)

The integrity of secondary anastomoses is affected by numerous factors. Higher age and hypertension are among the more prevalent reasons for weak collaterals. Smoking and a high blood glucose level at admission are also common findings among patients with poor collateral circulation (Arsava et al., 2014; Faber et al., 2011).

2.2 Ischaemic stroke

Stroke, a cerebrovascular accident, is defined as an abrupt onset of a focal neurological deficit lasting more than 24 hours. A stroke occurs when the blood supply to the brain is interrupted or reduced, preventing brain tissue from receiving oxygen and nutrients. Brain cells begin to die within minutes after the cessation of blood flow.

Stroke is divided into two subtypes. A haemorrhagic stroke is caused by bleeding in the brain. An ischaemic stroke is caused by the interruption of blood flow to the brain. Of all strokes, 75% to 80% are ischaemic. Without proper treatment, a stroke may lead to devastating conditions of disability or to death. Worldwide, stroke is the second most common cause of death, with 5.5 million deaths attributed to it in 2016, and it is a major cause of loss of disability-adjusted life-years (DALYs), with 116 million lost DALYs worldwide. Twelve percent of all deaths occurred because of stroke in 2013, half of which were due to ischaemic stroke. (Feigin et al., 2017; GBD 2013 Mortality and Causes of Death Collaborators, 2015; Norrving et al., 2015; O'Donnell et al., 2016; World Health Organization, 2016.)

In Finland, 5,040 patients died due to stroke in 2014, which amounted to 8% of all deaths in the country. Approximately half of these strokes (2,618 patients) were due to a brain infarction. In 1991, the numbers were 6,648 and 3,716, respectively. (Finnish Institute for Health and Welfare, 2014a.)

In Finland, the annual incidence of stroke was 259/100,000 in 2000. Since, there has been a slow decline in incidence and in 2000 the incidence was 199/100,000 (Finnish Institute for Health and Welfare, 2014). There is also a global trend of decreasing stroke incidence, prevalence and mortality. However, the absolute number of stroke patients still continues to increase (Feigin et al., 2017). In the early 21st century, one million people in Europe suffer a stroke annually, and, due to the ageing population, the number is estimated to reach 1.5 million in 2025 (Bejot, Bailly, Durier, & Giroud, 2016). In 2009, the prevalence of stroke in Finland was 82,000, which corresponds to 1.5% of the Finnish population (Meretoja et al., 2010).

Stroke also has an economic impact. The annual cost attributable to the care of stroke patients was already over 1 billion euros in Finland in 2008, which represented 0.6% of the gross domestic product. Based on the 2003 data, the average lifetime health care costs after a stroke are 86,300 euros per patient, two thirds of which arise directly due to stroke. (Meretoja et al., 2011.)

2.2.1 Pathophysiology

The cerebral circulation is highly autoregulated in normal situations (Figure 3). The goal of all regulatory functions is to maintain the cerebral blood flow (CBF) and thus the cerebral perfusion at a constant level. Normal cerebral perfusion pressure (CPP) is 50–150 mmHg. CPP is determined as the mean arterial pressure (MAP) minus intracranial pressure (ICP). A normal CBF is 50–55 ml/100 g/min.

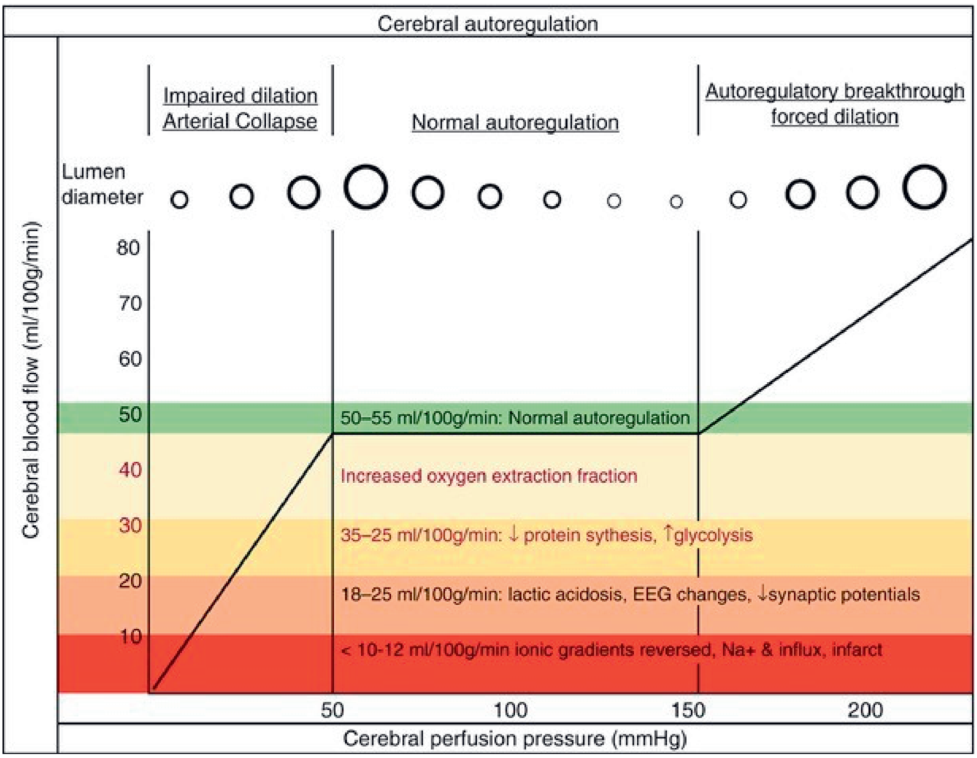

Figure 3. Cerebral autoregulation (Amin & Schindler, 2017)

Neurons have very limited energy reserves. After a drop in CBF, energy reserves can be depleted in a few minutes. Without energy, the cell membrane functions stop, and due to a $Na+/K+$ pump dysfunction, pathological amounts of $Na+$ and $Ca++$ enter the cell. This leads to a water influx into the cell and to the development of cytotoxic oedema. The elevated intracellular $CA++$ level also activates phospholipases and proteases, leading to BBB breakdown, and eventually triggers an excitotoxic cell death. (Amin & Schindler, 2017; Broughton, Reutens, & Sobey, 2009.)

The occlusion of a cerebral artery leads to a reduction of CBF in the tissue that the artery is responsible for. This causes, for example, a general dilatation of cerebral arteries and increased systemic blood pressure, leading to the opening of potential pial collateral vessels. If the collateral circulation is insufficient, the brain tissue becomes ischaemic. In the case of oligaemia, the CBF decreases to 25–35 ml/100 g/min, protein synthesis decreases and glycolysis increases. In cerebral ischaemia, CBF is reduced to 18–25 ml/100 g/min. In ischaemia, synaptic potentials are reduced, which is seen in electroencephalography (EEG). Anaerobic glycolysis and lactic acidosis are also initiated. If the CBF drops down to < 10–12 ml/100 g/min, neuronal cell death begins within a few minutes to form an infarct.

Typically, CBF decreases the most in the central part of the ischaemic area, leading to the formation of the infarct core. More peripherally, better collateral circulation compensates for the occluded normal circulation longer, keeping the ischaemic tissue salvageable, if the CBF is restored to a normal level fast enough. This possible salvageable area is called the penumbra.

2.2.2 Aetiology

The majority of ischaemic strokes are caused by an embolus that has travelled with the blood flow into the cerebral artery and caused an occlusion (Figure 4). Most often, an embolus is thrombosis-mediated and cardiogenic. These emboli are thought to be the reason behind roughly half of all ischaemic strokes. (Bogiatzi, Hackam, McLeod, & Spence, 2014.) Most cardiac emboli are formed in chambers, and they are fibrin-rich and associated with atrial fibrillation (AF). The cardiac emboli are usually larger than the platelet-rich emboli from a plaque rupture in arterial thrombi. Less often, cardiac emboli originate in pathologic cardiac valves. These emboli more often contain calcified or infective material. In rare cases, the embolus can also consist of other non-thrombotic material, such as air, fat or a tumour. (Hart et al., 2014; Ntaios & Hart, 2017.)

The origin of an arterial thrombus is most frequently a ruptured atherosclerotic plaque. Carotid stenosis (> 50%) is the reason for symptoms in 15%–20% of ischaemic stroke and TIA patients (Ay et al., 2005a; Cheng, Brown, Simister, & Richards, 2019; Lovett, Coull, & Rothwell, 2004). In the general population, the prevalence of a moderate (50%–70%) asymptomatic carotid stenosis in men under 50 years of age is 0.2%, increasing to 7.5% among men aged over 80 years. Women have a lower prevalence, 0% and 5.0% among women aged under 50 and over 80 years, respectively. The prevalence of severe (> 70%) asymptomatic stenosis increases in men from 0.1% to 3.1% and in women from 0% to 0.9% from the age of < 50 to > 80 years. (de Weerd et al., 2010.) The annual stroke risk with asymptomatic ipsilateral carotid stenosis is quite low, 0.4%–0.5% (den Hartog et al., 2013). For patients who have previously suffered a stroke due a carotid stenosis, the risk of a recurrent stoke within three months is elevated by up to 20% (Johansson et al., 2016). In the carotid stenosis stroke group, the odds ratio (OR) for a new stroke within 30 days is 3. The OR in for the other stroke subtypes is notably lower (OR of 1 in for cardioembolic and OR 0.2 for small-vessel strokes). (Lovett et al., 2004.)

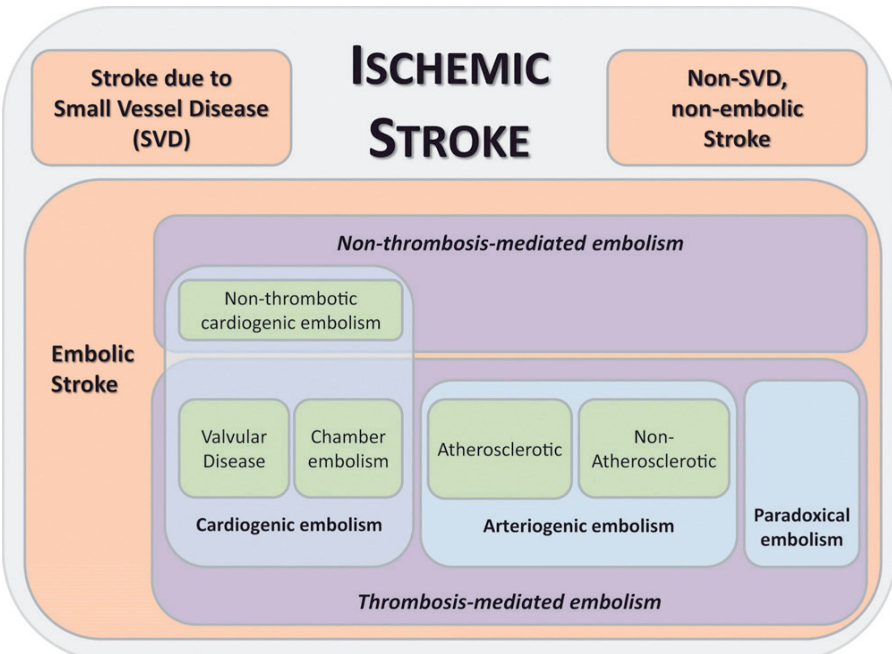

Figure 4. Aetiology of stroke (Ntaios & Hart, 2017)

Paradoxical embolism is a term for a thrombus that originates in a vein and traverses through an intracardiac or pulmonary arteriovenous shunt into the arterial circulation. Commonly, a paradoxical embolus passes the pulmonary circulation through a patent foramen ovale (PFO) between the right and left atrium. The prevalence of a PFO is 25%, but most of the individuals with a PFO are asymptomatic. (Mazzucco, Li, Binney, Rothwell, & Oxford Vascular Study Phenotyped Cohort, 2018; Windecker, Stortecky, & Meier, 2014.)

Cerebral small vessel disease (cSVD) is a syndrome affecting the small vessels of the brain. cSVD causes approximately 20% of all strokes. It typically also causes dementia, depression, as well as cognitive and gait problems. Typical clinical findings include lacunar infarcts or a spontaneous parenchymal haemorrhage. The two main types of cSVD are the amyloidal form due to chronic degenerative disease of amyloid angiopathy, and the non-amyloidal or "hypertensive arteriopathy" form often related to common vascular risk factors like hypertension and diabetes mellitus. (Cuadrado-Godia et al., 2018; Li, Q. et al., 2018; Pantoni, 2010.)

Other aetiologies of ischaemic stroke include a category of a heterogenous group of rare causes. The homeostasis between blood clotting and clot dissolution (anticoagulant and fibrinolytic) forces is unbalanced towards clotting in varied haematological syndromes, such as non-atherosclerotic vasculopathies, hypercoagulable states (often associated with oral contraceptives, systemic inflammatory disorders, malignancies, or trauma), or haematologic disorders like sickle cell disease. In rare cases (0.5%–1% of all strokes), an ischaemic stroke is caused by cerebral vein thrombosis associated with increased blood clotting. (Stam, 2005.)

Previously, different causative classification systems were used to establish the most probable cause of ischaemic stroke. The most widely used classification system is the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) (Adams et al., 1993). Several other classification systems have also been developed to improve the reliability of the classification. Newer classification systems include, among others, the Stop-Stroke Study TOAST (SSS-TOAST) (Ay et al., 2005b), the Causative Classification System (CCS) (Ay et al., 2007) and the A-S-C-O (Amarenco, Bogousslavsky, Caplan, Donnan, & Hennerici, 2009). There is still no gold standard of aetiological classification for ischaemic stroke. The advances in diagnostics, such as refined imaging data of CT, MRI and echocardiography, a have reduced the need for aetiological classification systems in clinical work (Radu, Terecoasa, Bajenaru, & Tiu, 2017).

2.2.3 Potentially modifiable risk factors

The risk factors for stroke are the same as for other cardiovascular diseases. The global INTERSTROKE study carried out in 32 countries estimated the modifiable stroke risk factors. The ten most common modifiable risk factors collectively accounted for over 90% of the population attributable risk (PAR) of all ischaemic strokes worldwide (O'Donnell et al., 2016).

Hypertension is the most important risk factor for stroke, and hypertension has been reported in over 60% of stroke patients. The PAR of hypertension is as high as 50%. Blood pressure (BP) of 140/90 mmHg or higher yields a roughly 3-fold risk of stroke (Feigin et al., 2017; O'Donnell et al., 2016). Lowering high BP also lowers the risk of stroke. In a large meta-analysis, treatment to lower BP reduced the relative risk of stroke to 0.69 in patients with systolic BP ≥160 mmHg. The relative stroke risk was also reduced to 0.85 in normotensive patients (systolic BP <140 mmHg) with treatment. (Amarenco et al., 2009; Brunstrom & Carlberg, 2018.) The beneficial effect of lowering BP is found down to level of 115/75 mmHg (Lewington et al., 2002).

Heart disease (such as atrial fibrillation and flutter, as well as a previous myocardial infarction) had a PAR of 9.1% of stroke and an OR of 3.17. Atrial fibrillation is the main cardiac risk factor, with an OR 4.59. (O'Donnell et al., 2016.)

The stroke risk caused by smoking is dose-dependent. The average stroke risk for smokers is double compared to non-smokers, but it can be as high as 9-fold for heavy smoker women. The PAR of smoking for stroke is 12% (Bhat et al., 2008; O'Donnell et al., 2016).

It has been thought that there is a J-shaped relationship between the amount of alcohol intake and stroke risk, where low alcohol intake reduces the stroke risk. (Zhang, C. et al., 2014). Other data suggest that a reduction in alcohol consumption is beneficial for cardiovascular health, including stroke, even for light drinkers (Holmes et al., 2014). High consumption and frequent use of alcohol also have a clear association with higher stroke risk in the Finnish population, with frequent alcohol use having the capacity to double the stroke risk (Rantakomi, Kurl, Sivenius, Kauhanen, & Laukkanen, 2014; Sundell, Salomaa, Vartiainen, Poikolainen, & Laatikainen, 2008).

A healthy diet can protect against chronic diseases, whereas an unhealthy diet increases the risk of stroke by 28%. The healthiness of the diet can be measured with the Alternative Healthy Eating Index (AHEI) (Chiuve et al., 2012; McCullough et al., 2002; O'Donnell et al., 2016).

Obesity increases the risk of cardiovascular diseases. Three quarters of the increased stroke risk associated with a high body mass index (BMI) is due to elevated BP, high cholesterol and high blood glucose (Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration [BMI Mediated Effects] 2014; Strazzullo et al., 2010). An increased waist-to-hip ratio and diet are also significant stroke-risk-increasing factors, with an OR of 1.44 (O'Donnell et al., 2016).

Dyslipidemia is associated with a higher stroke risk, but the association was weakened after adjusting for BP and blood glucose level (Pikula et al., 2015; Prospective Studies Collaboration et al., 2007; Zhang, Y. et al., 2012).

Diabetes yields a 60% increase in the ischaemic stroke risk (O'Donnell et al., 2016). The risk is elevated due to the comorbidities of diabetes, not so much the elevated blood glucose level itself. Therefore, it is critical to maintain a good blood glucose balance and treat any comorbidities well. The stroke risk is increased across all age groups, but especially within the younger population (Khoury, J. C. et al., 2013).

Physical activity is shown to reduce the stroke risk. Regular moderate or strenuous activity for four hours or more per week decreases the OR of stroke to 0.6.

2.2.4 Non-modifiable risk factors

Like in other vascular diseases, age is a factor of poorer prognosis and elevates the risk of stroke. In adulthood, each year of age increases the risk by 9% in men and by 10% in women (Asplund et al., 2009). Men develop cardiovascular disease approximately 10 years earlier than women due to, for instance, environmental, hormonal and genetic factors. Men have a higher stroke risk at all ages (Hyvarinen et al., 2010; Pilote et al., 2007).

While the prevalence of risk factors among stroke patients is lower in developing countries, the in-hospital mortality is higher than in developed countries. This is likely due to delays in access to treatment and treatment of acute stroke. (Feigin et al., 2015; Khatib, Arevalo, Berendsen, Prabhakaran, & Huffman, 2018.)

Low socioeconomic status, depression and psychosocial stress increase the stroke risk (Andersen, Steding-Jessen, Dalton, & Olsen, 2014; Cesaroni, Agabiti, Forastiere, & Perucci, 2009; Fransson et al., 2015; O'Donnell et al., 2016).

2.3 Diagnosis of ischaemic stroke

The diagnosis of ischaemic stroke is based on the combination of clinical symptoms and radiological imaging findings. The diagnostics often entail a multidisciplinary effort by an acute neurologist and radiologist. The symptoms of stroke depend on the brain region with impaired cerebral perfusion. Over 80% of ischaemic strokes are in the anterior circulation.

2.3.1 MCA stroke

Fifty percent of all ischaemic strokes occur in the MCA vascular territory (Ng, Stein, Ning, & Black-Schaffer, 2007). The MCA supplies the largest cerebral volume. Consequently, the occlusion of the MCA has the most potential to lead to a devastating stroke outcome (Walcott et al., 2014). A decrease in blood perfusion in the precentral gyrus (primary motor cortex) or in the postcentral gyrus (primary sensory cortex) causes a loss of motor or sensory function, respectively, of the head, limbs (upper emphasized) and trunk, on the opposite side of the body.

The precentral sulcal (pre-rolandic) branch of the MCA supplies the Broca's area of expressive speech, and the occlusion of this branch impairs speech production. An occlusion of the posterior branches of the lower M2 trunk of the MCA causes a stroke in the posterior temporal lobe involving Wernicke's area. An infarct of Wernicke's area disturbs the comprehension of written and spoken language. In 95% of right-handed individuals, language function is lateralized to the left cerebral hemisphere and in ca. 70% of left-handed individuals to the right cerebral hemisphere. (Corballis, 2014.) Thus, the side of the MCA infarct is associated with the severity of the language dysfunction disorder.

2.3.2 ACA stroke

Ischaemic stroke solely involving the supply territory of the anterior cerebral artery is relatively rare, accounting for only 0.5%–3% of all ischaemic strokes. The most common symptoms of an ACA stroke are motor and sensory deficits of the lower limb. Symptoms of the arm and face are associated with an involvement of Heubner's artery and other medial lenticulostriate arteries. Altered psychiatric conditions, such apathy and difficulties in decision making, urinary incontinence, memory impairment and emotional lability, may also occur. An infarct of the corpus callosum can cause involuntary limp movements due to a disruption of the interhemispheric connection. (Arboix et al., 2009; Bogousslavsky & Regli, 1990; Kang & Kim, 2008; Toyoda, 2012.)

2.3.3 ICA occlusion stroke

The symptoms of an ICA occlusion are very dependent on collateral circulation. If the occlusion is located below the PCoA and the circle of Willis is open, the symptoms can be minimal or even absent. In the case of a poor or absent ACoA and PCoA, ICA occlusion presents with the symptoms of MCA and ACA strokes.

2.3.3.1 ICA terminus (ICA-T) occlusion stroke

The ICA-T occlusion is a special type of ICA occlusion where the occluding material is present in the terminal ICA, and in the ipsilateral M1 and A1 segments. Because the occlusion is located above the PCoA, the open PCoA is not able to play its collateral circulation role. An open ACoA is also unable to supply MCA circulation from the contralateral side due to the occlusion of the ACA–MCA connection at the terminal ICA.

2.3.4 PCA and BA stroke

Posterior circulation strokes constitute 10%–20% of all ischaemic strokes and solitary BA occlusion 20% of all posterior ischaemic strokes. The most typical symptoms of BA stroke are somnolence and decreased consciousness. In a distal BA occlusion, the mesenchephalon and thalamus are rendered ischaemic, causing visual and oculomotor deficits, as well as quadriparesis. If the proximal and middle parts of the BA are occluded, the pons is affected and symptoms typically include hemi- or quadriplegia, dysartria and dysphagia as well as horizontal gaze paresis. Large pontine strokes can lead to locked-in syndrome, in which the patient has a complete loss of movement due to quadriplegia and lower cranial nerve dysfunction. Locked-in patients are awake, and blinking and vertical eye movements remain preserved. While a hemispheric infarct often has a sudden onset and focal symptoms, a BA occlusion may mimic other neurological conditions and may present a diagnostic challenge. Without recanalization, total BA occlusions have a mortality rate of up to

90%. (Demel & Broderick, 2015; Mattle, Arnold, Lindsberg, Schonewille, & Schroth, 2011; Voetsch, DeWitt, Pessin, & Caplan, 2004.)

The incidence of PCA stroke is 5%–10% of all ischaemic strokes. The stroke of proximal PCA segments causes hypersomnolence, cognitive deficits and vertical oculomotor paresis due the occlusion of perforating arteries to the midbrain (P1 segment), in addition to contralateral hypesthesia, ataxia and sectoranopia due to the occlusion of infarction in the territory of the thalamogeniculate and lateral geniculate body arteries (P2 segment). An occlusion of distal PCA segments (P3 and P4) causes visual field defects and somatosensory deficits. Reading disorders, disorientation of place and visual neglect are also seen occasionally. Bilateral PCA infarcts can cause amnesia and cortical blindness. (Cereda, C. & Carrera, 2012.)

2.3.5 Neurological symptom scales

In 1989, Brott et al. described a 15-item neurological symptom scale to standardize the examination of an acute ischaemic stroke patient (Brott, T. et al., 1989). Since then, the NIHSS scoring system has been the gold standard of standardized neurological examination scales. The NIHSS is comprehensive, but more or less designed for neurologists, which makes it quite complex if used infrequently. Easier to use and simpler symptom, scales such as the Cincinnati Prehospital Stroke Scale (Kothari, Pancioli, Liu, Brott, & Broderick, 1999) and the FAST (Face, Arm, Speech, Time to call help) (Nor et al., 2004), have been developed for use in first aid and emergency call centres to detect stroke patients.

In particular, to distinguish an anterior large vessel (internal carotid artery and proximal segments of middle cerebral artery) occlusion (LVO) from smaller vessel occlusions is critical, because, as per current guidelines, LVO patients are preferably treated with mechanical thrombectomy (MT) in tertiary stroke centres.

The Finnish Prehospital Stroke Scale (FPSS) (Table 1; Ollikainen et al., 2018) was designed to identify stroke and especially the LVO of anterior circulation. It is a simple and fast gaze-weighted stroke scoring scale for paramedics to use in the field. The FPSS provides support for deciding whether a patient should be transferred directly to an MT-capable centre, even if it is not the nearest hospital. In the Pirkanmaa Hospital District, potential MT patients are identified based on the FPSS and transferred directly to the tertiary stroke centre of Tampere University Hospital.

Table 1. FPSS

Symptoms	score
Facial paresis	1
Limb weakness	1
Difficulty to speak	1
Loss of visual field	1
Gaze or head deviation away from the paretic side	4
Total score ≥5 predicts LVO	0-8

There is a slew of other scoring systems designed to detect LVO and thus identify MT candidates in out-of-hospital settings: The Rapid Arterial oCclusion Evaluation Scale (RACE) (Perez de la Ossa, N et al., 2014), the FAST modifications: FAST-ED (Lima et al., 2016) and G-FAST (Scheitz et al., 2017), C-STAT (Katz, McMullan, Sucharew, Adeoye, & Broderick, 2015), the Prehospital Acute Stroke Severity Scale (PASS) (Hastrup, Damgaard, Johnsen, & Andersen, 2016) and the NIHSS-8 (Demeestere et al., 2017).

2.3.6 Stroke mimics

Up to 30% of acute stroke-like symptoms are due to stroke mimics. The numerous causes for stroke-mimicking symptoms include migraine, seizures, tumours, infection, intoxication, peripheral nerve injuries, hypoglycaemia, and other metabolic disorders, among others (Liu, X., Almast, & Ekholm, 2013; Merino et al., 2013; Ollikainen et al., 2018).

2.3.7 Imaging

In order to distinguish between haemorrhagic and ischaemic stroke, and stroke mimicking conditions, medical imaging of the brain and cerebral vessels is needed. Making the correct diagnosis and selection of treatment are based on a combination of clinical and imaging findings. The degree of brain injury and the clinical outcome are dependent on the duration of brain ischaemia. This makes fast decision making and initiation of treatment vital.

CT imaging is available in most hospitals in the developed world. It is fast and easy to use for emergency patients. Non-contrast CT (NCCT), combined with CT angiography (CTA) and possibly CT perfusion (CTP), constitutes the basic stroke imaging workup. If the stroke centre has a routine of using emergency MRI (Magnetic Resonance Imaging), it can also be used instead of CT in acute stroke imaging, if there are no contraindications.

2.3.7.1 NCCT

NCCT can reveal haemorrhages and an already infarcted brain, as well as some stroke-mimicking causes, such as tumours. The hypoattenuation of the brain, the loss of the interface between grey and white matter, and the narrowing of cortical sulci and/or ventricles due to tissue swelling are the first signs of an ischaemic brain. Sometimes, a red-blood-cell-rich thrombus can be seen as a hyperdense vessel sign. The interobserver agreement on these acute ischaemic chances is suboptimal, especially in the hyperacute phase. The most commonly used scoring scale to make these findings comparable and more reproducible is the Alberta Stroke Programme Early CT Score (ASPECTS) (Barber, Demchuk, Zhang, & Buchan, 2000).

The ASPECTS is a 10-point semiquantitative score of the MCA vascular territory that is assigned based on findings in NCCT. In the ASPECTS scale, the brain parenchyma supplied by the MCA is divided into ten areas, each of which represents 1 point. These areas include six cortical MCA parts, the nucleus caudatus, the insular ribbon, the nucleus lentiformis and the internal capsule (Figure 5). If no ischaemic changes are found, the score is ten. Every ischaemic area (scored based on hypoattenuation) decreases the score by one. ASPECTS at admission correlates with the clinical outcome and can be used to evaluate which patients potentially benefit from revascularization. (Hill et al., 2014.)

ASPECTS evaluation can be challenging and requires training (Coutts et al., 2003). Therefore, automated programmes have been developed to calculate ASPECTS automatically from NCCT images. Automated software, such as RAPID ASPECTS, Brainomix e-ASPECTS and Syngo.via Frontier ASPECT Score, offer improved sensitivity, specificity, reliability and consistency in scoring (Albers et al., 2019; Herweh et al., 2016; Hoelter et al., 2020; Maegerlein et al., 2019; Nagel et al., 2017).

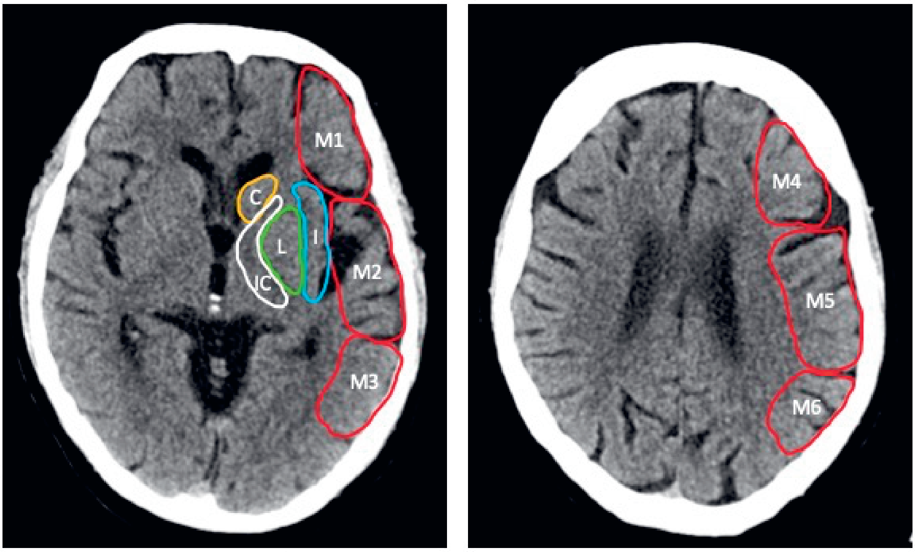

Figure 5. The ten ASPECTS areas in the estimation of an MCA circulation infarct: C (yellow) = nucleus caudatus; IC (white) = capsula interna; L (green) = nucleus lentiformis; I (blue) = insular ribbon; M1-6 (red) = cortical MCA areas.

Pc-ASPECTS (the posterior circulation Acute Stroke Prognosis Early CT score) (Figure 6) has been devised to detect the posterior circulation ischaemic stroke patients who may have a poor prognosis even with revascularization therapy (Puetz et al., 2008). Pc-ASPECTS is also a 10-point scoring system, where ischaemic changes subtract from the score: 2 points each for the midbrain and pons, 1 point each for the left and right thalamus, the cerebellum and the PCA territory. Because the sensitivity of CT imaging to detect early ischaemic changes is poor, particularly in a posterior circulation stroke, NCCT is used only to effectively rule out contraindications for recanalization therapy (ICH, large infarction). (Merwick & Werring, 2014.)

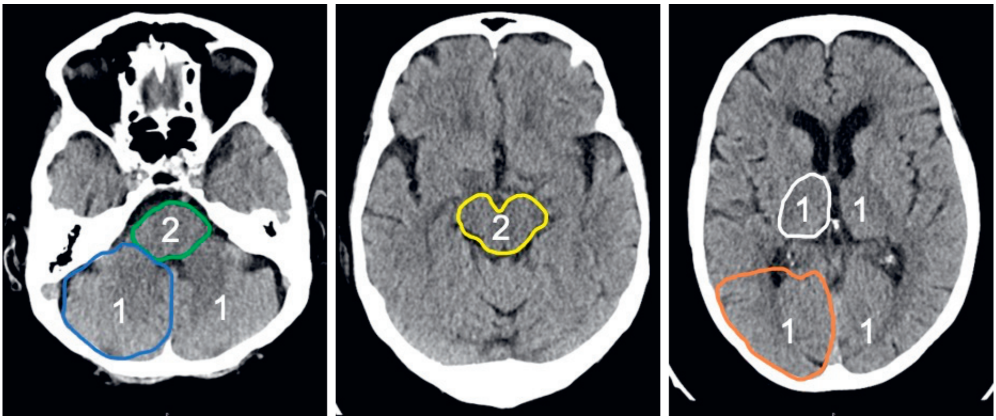

Figure 6. pcASPECTS areas of posterior circulation: 1 point for the left or right thalamus (white), cerebellum (blue) or PCA territory (orange); 2 points for any part of the midbrain (yellow) or pons (green).

2.3.7.2 CTA

Angiography performed with modern CT devices provides highly accurate data on the anatomy of cerebral and carotid vessels and sites of stenosis or occlusion with short imaging and preparation times. The quality of vascular data provided by CTA is essentially comparable with the data obtained using the gold standard of DSA (digital subtraction angiography). (Lee, S. J. et al., 2021; Qazi, Al-Ajlan, Najm, & Menon, 2016; Randoux et al., 2001.)

Typically, the CTA imaging volume of stroke patients covers the area from the aortic arch to the top of the skull. In addition to the main goal of finding the occlusion causing the ischaemic stroke, CTA provides important data for the planning of endovascular treatments and for device selection. The anatomy of the aortic ach and carotid vessels, with possible stenoses, can be evaluated with CTA. Proper planning enables a shorter duration of endovascular treatment (Schwaiger, Gersing, Zimmer, & Prothmann, 2015).

2.3.7.3 Collateral circulation in imaging

The cerebral collateral circulation is an arterial system that secures the energy and oxygen supply of the brain parenchyma (in more detail in section 2.1.3). The quality of the cerebral collateral circulation correlates with the long-term outcome of acute ischaemic stroke patients. (Arsava et al., 2014; Berkhemer et al., 2016; Boers et al., 2018; Fransen et al., 2016; Liebeskind, 2009; Renu et al., 2019.)

The reference method to evaluate the cerebral collateral circulation is DSA, but collateral circulation can also be estimated with reasonable accuracy with CTA. CTA is widely available for this purpose, in addition to being fast and non-invasive. The major limitation of CTA is that, unlike DSA, it shows the contrast media in vessels only at a certain time point and thus provides no blood flow information. There are many CTA-based collateral scoring (CS) scales. One of the more widely adopted systems is that described by Souza et al. (Souza et al., 2012) (Figure 7).

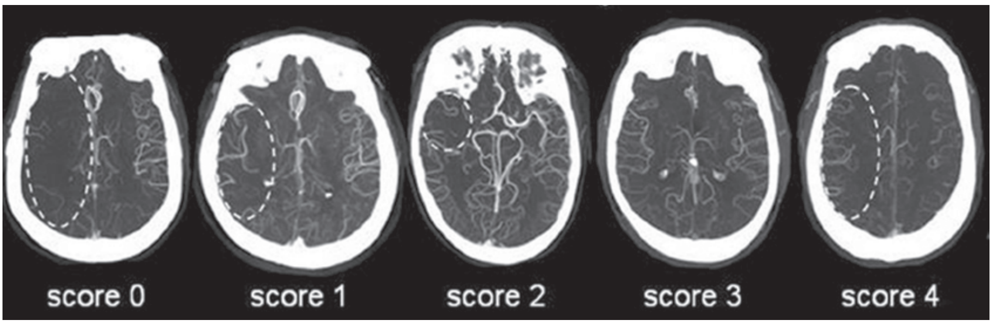

Figure 7. Collateral score system: 0 = no collaterals in M2 territory; 1 = diminished collaterals in > 50% of the M2 territory; 2 = diminished collaterals in < 50% of the M2 territory; 3 = collaterals equal to the contralateral side; 4 = increased collaterals. Adapted from Souza et al. (Souza et al., 2012).

2.3.7.4 CTP

To select the right patients for MT, it is crucial to know the possible risk-to-benefit ratio and the amount of salvageable penumbra. NCCT is insensitive to early ischaemic changes. (Chalela et al., 2007; Hwang, Silva, Furie, & Greer, 2012; Powers et al., 2018.) CTP is rapid to acquire and provides both qualitative and semiquantitative evaluation of the cerebral blood perfusion. In CTP, a bolus of contrast media is injected intravenously, and the attenuation of contrast media within the voxel is measured as a function of time through repetitive scanning. To calculate the brain perfusion maps, CT attenuation is measured in the arteries (arterial input function, AIF) and in the parenchyma. The attenuation in the veins is used to standardize the AIF curves.

The basic idea of CTP is to detect the hypo-perfused but potentially viable and the irreversibly ischaemic brain parenchyma. When you subtract the latter from the former, you get an estimation of possibly salvageable penumbra. An often-used term to describe the result is the mismatch ratio, the ratio of the total hypoperfused volume to the infarct core. The mismatch volume is the difference between the whole perfusion defect and the infarct core, which estimates the volume of the penumbra. (Figure 11.) A high mismatch ratio and large mismatch volume indicates a large penumbra and thus an optimal target for intervention.

Five perfusion parametric maps (Table 2) are used in the evaluation of an ischaemic stroke patient: time to peak (TTP), cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) and time to maximum residue function (Tmax). A large variety of mathematic algorithms have been devised to be used post-procedurally to calculate these parametric maps out of the CTP source images.

The TTP is the simplest parameter to acquire, as it requires no complex calculations. After starting the CTP acquisition, the TTP is the time measured from start to the peak concentration in each voxel. A prolonged TTP is not a direct correlate of decreased cerebral blood flow but means only that the injected contrast medium is arriving later than in some other brain vascular regions. The blood flow through collateral circulation can be adequate for brain perfusion even if the TTP is prolonged due to the longer pathway that the contrast medium must take. At present, TTP is considered a secondary parameter when evaluating brain perfusion. (Figure 8.)

Table 2. The typical CTP parameters

TTP	The time to maximum contrast medium concentration in tissue: the simplest parameter to calculate, requiring no complex mathematics. The TTP is prolonged in ischaemic brain parenchyma.
CBV	The total volume of blood in the brain mass (ml/100 g): the CBV is decreased in an infarct, and thresholded CBV is thought to represent the infarct core.
CBF	The volume of blood moving through the brain tissue (ml/100 g/min): a CBF value of < 30% in nonischaemic (contralateral) parenchyma is considered to be a good indicator of the true infarct core.
MTT	The average time that blood spends transitioning through brain tissue: MTT = CBV/CBF. It represents the microvascular/capillary circulation of the tissue and identifies the tissue at risk of an infarct, or ischaemic penumbra, and other hypoperfusion.
Tmax	Reflects the time that the contrast medium bolus takes to travel from the artery to the parenchyma: increased Tmax (sec) correlates to the final infarct volume if blood perfusion is not restored. A Tmax higher than 4 to 6 seconds is supposed to define the penumbra.

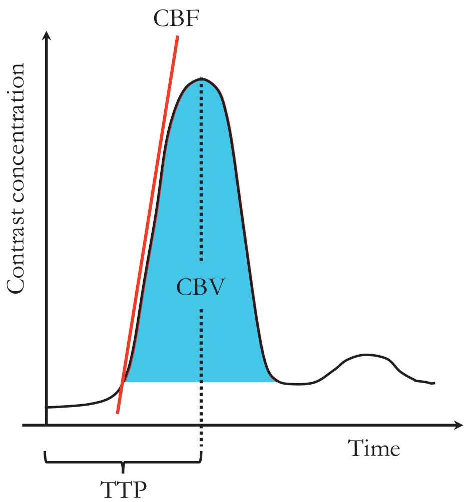

Figure 8. CTP concentration curve over time: TTP = time to highest contrast medium concentration in brain tissue; CBF = maximum slope of increase in contrast medium concentration; CBV = area under the first-pass concentration curve (blue area).

The CBF is a measure of the maximum flow rate of blood through the brain tissue (ml/100 g/min). CBF is decreased in ischaemic tissue. CBF of less than 30% compared to an unaffected contralateral of similar tissue volume is considered to represent, and often used to estimate, the infarct core in clinical practice (Mokin et al., 2017; Rao et al., 2019). In perfusion imaging, the CBF is characterized by the maximum rate of increase in contrast medium concentration, or the maximum slope of the first-pass concentration curve (Figure 8). Many factors, including the contrast type, the injection volume and rate, the vascular anatomy (stenosis and collaterals) and the intravenous mixing of contrast media cause random errors in the CBF value. Theoretically, the ideal way to measure the CBF and mitigate most of the error sources would be to have all contrast media distributed evenly throughout the brain tissue at the same time and measure the washout speed of the contrast medium.

The CBV is a measure of the blood volume per brain tissue mass (ml/100 g). In infarcted brain tissue, the blood volume is decreased. The area under the first-pass concentration-time curve represents the CBV (Figure 8). To get a correct estimate of CBV, the whole area under the first-pass curve should be taken into account. A major cause of error is the recirculation of contrast agent that produces a second peak (and further peaks) in the concentration-time curve. This leads to artificially low CBV in the tissue with slow flow, which can lead to an underestimation of the CBV values and the overestimation of the infarct core.

MTT is the time that it takes for blood to go through the brain tissue. It can be derived from a CTP concentration-time curve using the simple formula MTT = CBV/CBF. An increased MTT represents sluggish blood flow through the tissue, and thus the tissue at risk of an infarct. Like CBF and CBV, MTT is influenced by injection kinetics artefacts of the concentration curve.

Various (de)convolution algorithms have been devised to correct for the random errors and alleviate the restrictions imposed by the theoretical assumptions of the models. These algorithms use complex equations to convert concentration-time curves into clinically useful CTP parameters. (Fieselmann, Kowarschik, Ganguly, Hornegger, & Fahrig, 2011; Nael et al., 2019; Pennig et al., 2020.)

Based on the theoretical model, the residue function can be convolved with the arterial input function (AIF) to obtain a tissue concentration output function curve (C_t) (Figure 9). The AIF and C_t are measurable from the CTP source images and can thus be used to calculate the residue function by deconvolution. The time to maximum of the residue function is directly the Tmax parameter, and CBF can also be easily calculated from this function. Tmax is not a physiologic value, but it reflects the arrival time of the contrast medium bolus from the artery to the brain parenchyma. It is expressed in seconds. An increased Tmax is a signal of weaker collateral circulation. The tissue volume with an increased Tmax correlates with the final infarct volume. Like with CBF, Tmax is not dependent on whether the volume contains grey or white matter. A Tmax higher than 4 to 6 seconds has often been defined as a boundary of the penumbral region. The Tmax and CBF are widely used parameters in estimating the mismatch ratio and penumbra, as well as in patient selection. An example of automated CTP maps including the Tmax and CBF maps is shown in Figure 10. (Albers et al., 2018b; Campbell, B. C. V. et al., 2017; Davis et al., 2008; Kidwell et al., 2013; Ogata et al., 2013; Olivot et al., 2009.)

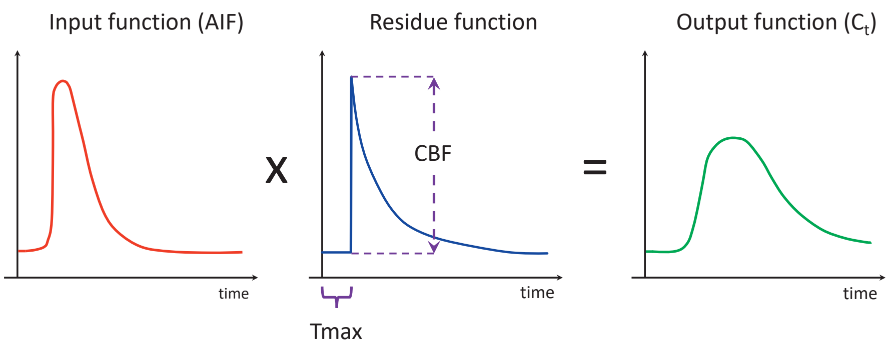

Figure 9. Tissue concentration-time curve (Output function, C_t) as a convolution of the AIF (input function) with the residue function. CBF and Tmax are calculated from the residue function.

The sensitivity and specificity of MRI (magnetic resonance imaging) are superior to those of CT in brain imaging. This also pertains to imaging ischaemic changes, especially within the first hours after stroke onset. Diffusion-weighted MRI (DWI) detects the infarct core more accurately than CT, although CBF < 30% corresponds closely to DWI-based infarct core estimation and the final infarct volumes, if the occlusion is not recanalized. The quality of MRI angiography is also comparable with CTA. Early ischaemic changes in the brainstem are particularly challenging to detect with NCCT. Thus, MRI is especially suited to studying acute ischaemia in the posterior circulation. (Albers et al., 2016; Cereda, C. W. et al., 2016; Chalela et al., 2007; Hwang et al., 2012.)

The preparation of a patient for MRI is more complicated due to the magnetic field. The imaging itself takes more time than a CT study, even with modern, fast imaging sequences. Current-generation CT machines are able to scan the whole brain volume and automatically generate the penumbra and the infarct core estimations with an accuracy comparable to MRI. However, MRI can essentially replace CT imaging in patient selection for endovascular treatments, if the availability of MRI for emergency department patients is as good as that of CT. The diagnostic imaging modality appears to have no effect on the clinical outcome of an acute ischaemic stroke patient. (Chalela et al., 2007; Dehkharghani et al., 2015; Hwang et al., 2012; Nael et al., 2014; Provost et al., 2019; Simonsen, Yoo, Rasmussen et al., 2018.)

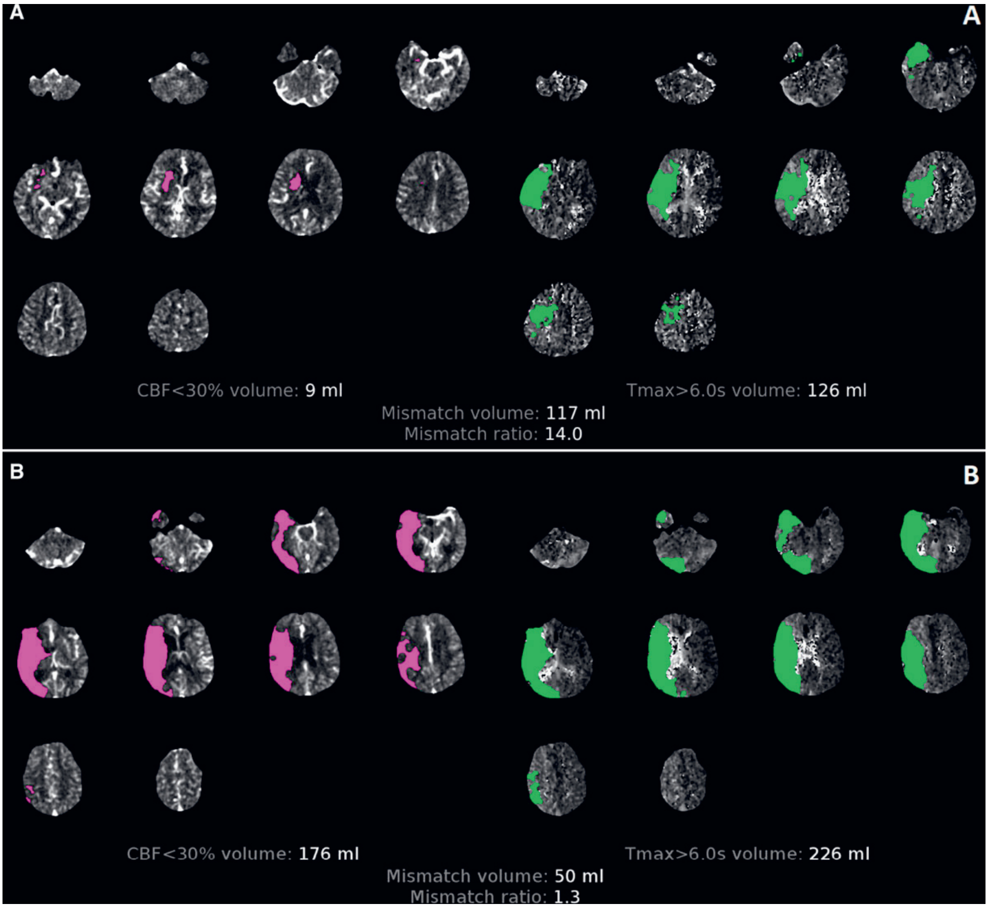

Figure 10. CT perfusion maps of two patients made by RAPID software, showing two different mismatch ratios. Ischaemic cores (pink) and whole perfusion deficit (green). Above (A), a patient with a high mismatch ratio (14.0), a small infarct core (9 ml) and a large mismatch volume, penumbra (117 ml). Below (B), a patient with a small mismatch ratio (1.3) and a large ischaemic core (176 ml) which largely overlaps the perfusion deficit, and with a low mismatch volume, penumbra (50 ml). Patient A is optimal for interventions. Adapted from Demeestere et al. (Demeestere, Wouters, Christensen, Lemmens, & Lansberg, 2020).

2.4 Acute management

Restoration of the cerebral blood flow has the most substantial impact on the clinical outcome of acute ischaemic stroke (Rha & Saver, 2007). If the restoration of tissue-level perfusion happens fast enough, the ischaemic brain tissue can be rescued. The probability of a good clinical outcome decreases as the time from symptom onset increases, which is encapsulated in the 'Time is Brain' paradigm.

A cerebral artery occlusion can potentially be dissolved with intravenous thrombolysis (IVT) that is administered systemically. The occlusion can also be directly engaged mechanically and/or locally with intra-arterial treatments.

In addition to different recanalization therapies, treatments supporting the recovery from the ischaemic stroke and targeting aetiological factors are valuable. Hyperglycaemia weakens the outcome of stroke patients due to an increased risk for brain oedema and, hence, a larger infarct volume, as well as an elevated risk for infarct bleeding. A blood glucose level of ≥ 8 mmol/l is an independent factor associated with a poorer outcome. This association is found especially in patients without diabetes mellitus and after recanalization. Even if there is no significant evidence of strict blood glucose control with insulin, it is important to maintain an appropriate blood glucose level, particularly in the acute stroke phase, as with other hospitalized patients. (Fuentes et al., 2018; Goyal, N. et al., 2018; Li, X. et al., 2021; Putaala et al., 2011; Zang, Zhang, Yao, & Wang, 2021.)

There is strong evidence that ischaemic stroke patients, regardless of stroke severity, benefit from treatment in dedicated stroke units. Stroke unit treatment reduces the duration of hospitalization, as well as overall dependency and deaths when compared to treatment on other wards. The functional outcome is better. The benefit of stroke unit treatment is particularly large among the elderly. (Chan et al., 2013; Jorgensen et al., 2000; Langhorne, Ramachandra, & Stroke Unit Trialists' Collaboration, 2020; Stroke Unit Trialists' Collaboration, 2013.)

In large, malignant cerebral infarcts, decompressive hemicraniectomy significantly reduces mortality and improves the odds of a better clinical outcome. However, the proportion of patients requiring assistance with most daily activities is also increased. (Gul, Fuller, Wright, & Sen, 2018; Juttler et al., 2014; Wei, Jia, Yin, & Guo, 2020.)

2.4.1 Intravenous thrombolysis (IVT)

The idea of dissolving the thrombus that causes an occlusion of an intracranial artery in ischaemic stroke was first tested in a clinical trial published in 1992 (Brott, T. G. et al., 1992; Haley et al., 1992).

IVT with recombinant human tissue-type plasminogen activator (rt-PA, alteplase) has been a standard ischaemic stroke treatment since the pivotal trials of ECASS and NINDS were published in 1995 (see below). Plasminogen activator selectively binds to fibrin and converts plasminogen into plasmin. This leads to the degradation of the fibrin matrix and lysis of the thrombus. (Hoylaerts, Rijken, Lijnen, & Collen, 1982.)

In 1995, the National Institute of Neurological Disorders and Stroke (NINDS) study group reported that patients who were given rt-PA within three hours of stroke onset were 30% more likely to reach a better three-month clinical outcome. (National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995). The following year, the American Food and Drug Administration (FDA) approved IVT in the treatment of acute ischaemic stroke. The efficacy of rt-PA has been proven in multiple other randomized and registry studies: ECASS III, ATLANTIS, NINDS rt-PA, STARS, SITS-MOST (Albers et al., 2000; Albers, Clark, Madden, & Hamilton, 2002; Hacke et al., 2008; Marler et al., 2000; Wahlgren et al., 2007).

In Finland, IVT has been a standard of ischaemic stroke care since 2003, after the recommendation by the European Stroke Initiative (EUSI) (European Stroke Initiative Executive Committee et al., 2003). The standard dose of rt-PA is 0.9 mg/kg (maximum of 90 mg), 10% of which is administered as a bolus and the remainder slowly infused over one hour.

The safety and efficacy of IVT is highly dependent on the time from the onset of symptoms. In a pooled analysis of the ATLANTIS, ECASS and NINDS rt-PA trials, the odds ratio (OR) for a favourable outcome was 2.8 for patients treated within 1.5 hours from symptom onset, decreasing to 1.6 in patients treated within the 1.5–3 hours window (OR 1.4 for 3–4.5 h, and OR 1.2 for 4.5 to 6 h). (Hacke et al., 2004.)

The most relevant complication of IVT is a symptomatic intracerebral haemorrhage (sICH). The prevalence of sICH in the IVT group is 2.4%–11%, depending on the definition of sICH, as opposed to the 0%–1.1% in the control group. As a rule of thumb, IV rt-PA increases the risk of sICH 10-fold. However, there is no significant difference in overall mortality. (Chapman et al., 2014; Wahlgren et al., 2007.)

The rt-PA is effective, especially in distal small vessel occlusions, where the thrombus is small. In larger vessel occlusions, the efficacy of rt-PA is severely limited and often insufficient. Two large meta-analyses reported complete recanalization with rt-PA in only 11%–20% of anterior circulation LVO patients. Proximal occlusions had a lower recanalization rate compared to the more distal occlusions. (Seners et al., 2016; Tsivgoulis et al., 2018.) Thrombus size has a critical effect on the probability of recanalization of the M1 segment (Figure 11) (Riedel et al., 2011).

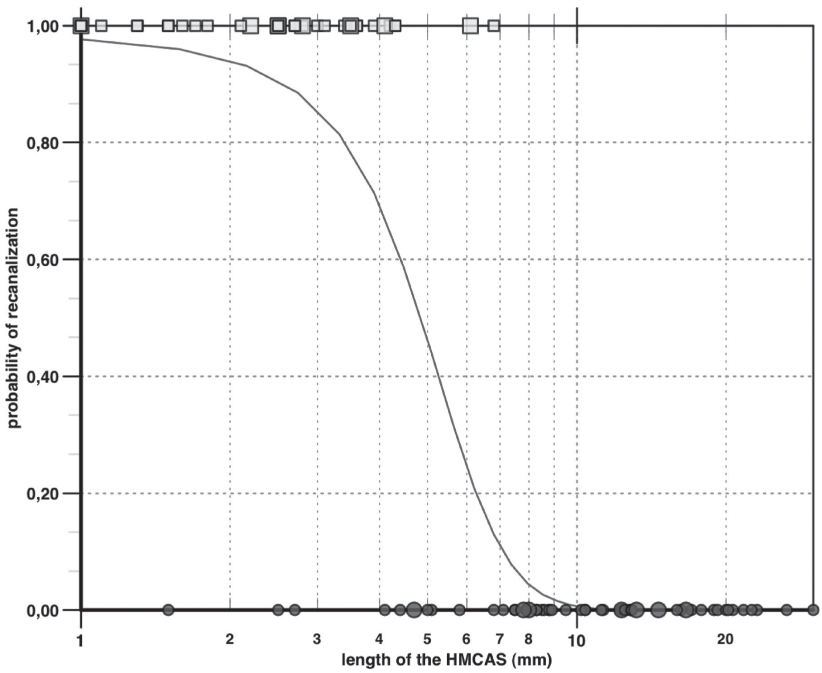

Figure 11. Effect of thrombus size on M1 recanalization with IV thrombolysis (Riedel et al., 2011).

When ischaemic stroke patients are treated with IV rt-PA, several conditions must be fulfilled. The time window of rt-PA treatment is generally limited to up to 4.5 hours (up to 9 h in selected cases) from the onset of symptoms. The age of the patient is recommended to be over 18 years. IVT has several absolute and relative contraindications mostly related to the increased risk of bleeding complications (Table 3) (Berge et al., 2021; Hasan et al., 2018; Powers et al., 2018).

Table 3. The most relevant contraindications for IV rt-PA in acute ischaemic stroke. Adapted from Hasan et al. (Hasan et al., 2018).

Absolute contraindications

- ICH
  acute or previuous
- Developed acute infarction > 1/3 cerebral hemispere
- Elevated blood pressure that cannot be lowered safely
  (systolic > 185 mmHg or diastolic > 110 mmHg)
- Acute bleeding diathesis, including but not limited to
  - anticoagulant with INR > 1.7
  - current use of heparin
  - current use of
  - platelet count < 100 E^9/l
- Suspicion of subarachnoid hemorrhage
- Severe head trauma in previous 3 months
  (including intracranial and spinal surgery)
- Intracranial neoplasm
- Aortic arch dissection
- Acute internal bleeding
- Infective endocarditis

Relative contraindications

- Mild and nondisabling or rapidly improving stroke symptoms
- Very severe deficits (NIHSS >25) within the 3-4.5 hour from the onset
- Seizure at onset
  (IV rt-PA if neurologic deficits are thought to be caused by a stroke)
- Pregnancy
- Major surgery or trauma within previous 14 days
- Intestinal bleeding within previous 21 days
- Ischemic stroke or myocardial infarction within previous 3 months
- Untreated intracranial arteriovenous malformation or giant aneurysm
- Low blood glucose
  (IV rt-PA if deficits still present after glucose normalization)

2.4.2 Intra-arterial (IA) treatment

The limitations of IVT spurred the development of different intra-arterial treatments. Direct intra-arterial thrombolysis (IAT) was a logical first step, as it appears to have a significantly higher probability to open an occluded intra-cranial artery than IVT. However, IAT also increases the risk of symptomatic intracerebral haemorrhage. Overall, IAT seems to have a favourable effect on the clinical outcome over IVT. (del Zoppo et al., 1998; Ma, Chu, & Song, 2015; Ogawa et al., 2007.) After the emergence of strong evidence for the beneficial effect of MT, the role of IAT has become minor in the treatment of acute ischaemic stroke patients.

2.4.2.1 Thrombolysis in Cerebral Infarction (TICI) score

In 2003, Higashida et al. described TICI, the standard scoring to evaluate the effect of IVT on reperfusion (Higashida et al., 2003). A decade later, the modified TICI (mTICI) scoring was introduced to include features of intra-arterial recanalization (Zaidat et al., 2013). Technical success of endovascular treatments is most commonly reported based on mTICI. In 2014, mTICI was improved by adding the 2c score. This latest version is called the extended TICI (eTICI, Table 4) (Goyal, M. et al., 2014). All versions of the TICI are scored from the post-intervention DSA runs.

Table 4. Extended TICI (eTICI) (Goyal et al., 2014)

Score	Angiologic correlation	
0	No perfusion or anterograde flow beyond site of occlusion	
1	Penetration but not perfusion. Contrast penetration exists past the initial obstruction but with minimal filling of the normal territory	
2	Incomplete perfusion wherein the contrast passes the occlusion and opacifies the distal arterial bed but rate of entry or clearance from the bed is slower or incomplete when compared with non-involved territories	
	2A	Some perfusion with distal branch filling of <50% of territory visualized
	2B	Substantial perfusion with distal branch filling of ≥50% of territory visualized
	2C	Near-complete perfusion except for slow flow in a few distal cortical vessels or presence of small distal cortical emboli
3	Complete perfusion with normal filling of all distal branches	

2.4.2.2 The evolution of intra-arterial recanalization therapies

In the beginning of the 21st century, angioplasty (with or without IA thrombolytics) was used to break a thrombus that was resistant to IVT. The underlying problem of this therapy was thrombus breakup and distal scattering. Self-expanding stents were also experimentally used to achieve a flow channel through the occlusion as a rescue therapy. Even though the stent compressed the thrombus to the vessel wall, thus mostly preventing distal embolization compared to angioplasty, the stent also pushed the thrombus into the perforating branches, blocking these permanently. A problem of this therapy is also the need for dual antiplatelet medication, leading to an increase in the rate of haemorrhagic transformations. (Fitzsimmons, Becske, & Nelson, 2006; Gralla, Brekenfeld, & Schroth, 2012; Ringer, Qureshi, Fessler, Guterman, & Hopkins, 2001; Ueda et al., 1998.)

In the early era of MT, various devices were added to increase the effect of IVT and IAT therapies. The two most widely used devices were the different versions of the Merci retriever and the Penumbra System aspiration catheter (Figure 12).

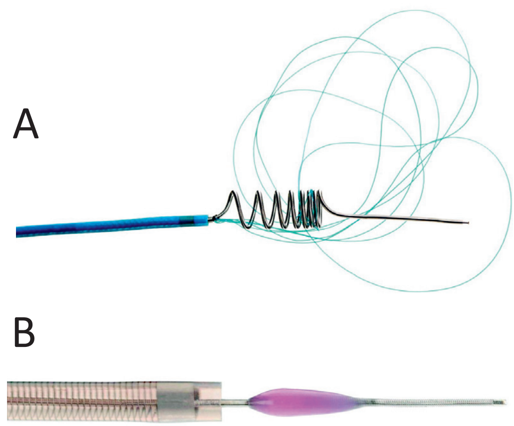

Figure 12. Later-generation Merci device (A) and Penumbra system device; distal aspiration catheter with a matched separator wire (B).

The Merci device is a coil-like tool with additional microfilaments, in later iterations meant to be opened distally to the thrombus and then retrieved with the thrombus. There were two pivotal prospective, nonrandomized, multicentre trials, the Mechanical Embolus Removal in Cerebral Ischaemia (MERCI) trials. In the first trial, all the included patients were ineligible for IVT. Recanalization (TIMI 2–3) was achieved in 48% (68/141) of patients in whom the device was deployed. In the later trial, successful recanalization was achieved in 57.3% and 69.5% of the cases, the latter with adjunctive IAT therapy. According to a review by Alshekhlee et al., the trials and observational studies in the MERCI registry amounted to a total of 1,226 patients. A good clinical outcome (90-d mRS ≤2) was achieved in 32% of the patients, with an overall mortality rate of 35.2%. The Penumbra Pivotal Stroke Trial reported successful recanalization (TIMI 2–3) in 81.6% of the treated vessels and a 32.8% mortality rate and good clinical outcome in 25% of the cases (90-d mRS ≤2).

The results of the MERCI and Penumbra trials were comparable to the largest IAT trial (PROACT II, Prolyse in Acute Cerebral Thromboembolism). (Alshekhlee et al., 2012; del Zoppo et al., 1998; Penumbra Pivotal Stroke Trial Investigators, 2009; Smith et al., 2005; Smith et al., 2008.)

The Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trial with 118 patients compared the MERCI and Penumbra thrombectomy methods with IVT and found no significant difference between these therapies. Recanalization (TICI 2a to 3) was achieved in 67% of the thrombectomy patients. Ninety-day mRS, mortality (21%) or the rate of sICH (4%) did not differ significantly between the groups. (Kidwell et al., 2013.)

The Interventional Management of Stroke trials (IMS I–III) tried to clarify the additional effect of IA therapies on IVT-treated patients. IMS I and II revealed a similar safety profile compared to the IVT group of the NINDS trial and a significantly higher likelihood of achieving an excellent clinical outcome (90-d mRS of ≤ 1) compared to the placebo arm of the NINDS trial. This led to the randomized IMS III trial involving 656 patients, which failed to reveal any significant benefit in terms of clinical outcome attributable to IA therapy after IVT when compared to IVT alone. The SYNHESIS Expansion trial with 362 randomized patients also failed to show any advantage of IA therapy over standard IVT. (Tissue plasminogen activator for acute ischaemic stroke. the national institute of neurological disorders and stroke rt-PA stroke study group.1995; Broderick et al., 2013; Ciccone, Valvassori, & SYNTHESIS Expansion Investigators, 2013; IMS II Trial Investigators, 2007; IMS Study Investigators, 2004.)

After three major trials – IMS III, MR RESCUE and SYNTHESIS Expansion – failed to show a benefit of MT over IVT, many critical issues, such as patient selection, were raised for discussion. These trials used old-generation MT devices like the Merci retriever and the Penumbra system, while thrombectomy devices were rapidly developing towards the modern stent-like designs. Furthermore, treatment delays were shortening substantially, and there was a far better availability of modern brain imaging methods. (Broderick et al., 2013; Ciccone et al., 2013; Kidwell et al., 2013; Nogueira, Gupta, & Davalos, 2013.)

In a report from 2008, Kelly et al. held a partially opened non-retrievable nitinol stent at the occlusion site for 20 minutes then removed the stent. The occluded M1 segment was successfully recanalized after failed local thrombolysis. (Kelly, Furlan, & Fiorella, 2008.) The first MTs with a stent retriever were subsequently performed with the Solitaire AB stent (ev3). Solitaire AB was initially designed for stent-assisted coiling. The stent can be fully opened and retrieved until electrical detachment. In 2010, Castaño et al. reported a case series of 20 patients treated with Solitaire AB. They used a guiding catheter with a tip balloon, into which an opened but undetached stent was retrieved. They achieved a good recanalization (TICI 2b–3) in 90% of the cases (18 patients) with no significant procedural complications. A good clinical outcome was achieved for 45% (9) of the patients (90-d mRS ≤2). (Castano et al., 2010.) Later, a non-detachable FR version of the Solitaire stent became the first real stent retriever (or "stentriever") designed for this purpose that was approved by the regulatory authorities. Soon after this, numerous devices were released to the market. Trevo® (Stryker; Figure 13) was one of these early stentrievers. In Tampere University Hospital, the first MT with the Trevo stentriever was performed in January 2011.

Figure 13. Trevo was the first stentriever used in the Tampere University Hospital in January 2011

In 2012, trials comparing the Merci retriever to the Solitaire and Trevo stentrievers showed a significant advantage for the stent retrievers (Nogueira et al., 2012; Saver et al., 2012).

The real game changer in the management of acute stroke patients came with the five pivotal RCTs published in 2015, comparing modern thrombectomy devices and IVT. The first to appear was the Endovascular Treatment for Acute Ischaemic Stroke in the Netherlands (MR CLEAN) multicentre trial, which randomly assigned

500 patients eligible to receive IVT to either MT with IVT or IVT alone. The patients had an LVO in the anterior cerebral circulation and were treated within six hours of symptom onset. All patients had IVT before randomization. Among patients who received IA therapy, a stent retriever was used in 96.9% of the cases. Additional IAT was administered to 12.6% of these patients. Good reperfusion (mTICI 2b or 3) was achieved in 58.7% of the IA-treated patients. The clinical outcome (90-d mRS ≤ 2) was significantly in favour of MT, as opposed to IVT only (32.6% vs 19.1%), with no significant differences in mortality or the occurrence of symptomatic intracerebral haemorrhage (sICH). (Berkhemer et al., 2015.)

The multicentre Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial studied acute anterior LVO patients treated up to 12 hours after symptom onset, with the exclusion of patients with a large infarct core or poor collateral circulation. The trial was stopped early because of efficacy. Successful reperfusion (TICI 2b or 3) was achieved in 72.4% of the patients in the MT group. The odds of a good clinical outcome (90-d mRS ≤ 2) were 2.6 times higher in the MT-treated group (53.0%, vs 29.3% in the IVT only group). Mortality was reduced to 10.4% in the MT group from the 19.0% in the IVT only group. (Goyal, M. et al., 2015.)

In the Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial (EXTEND-IA) trial, patients were treated with IVT in less than 4.5 hours after stroke onset. In the MT group, patients additionally had thrombectomy with the Solitaire FR stent retriever. All patients had anterior circulation LVO and imaging evidence of salvageable brain tissue with an infarct core of less than 70 ml. Like the ESCAPE trial, the EXTEND-IA was also stopped early because of efficacy after the randomization of only 70 patients. The reperfused ischaemic territory at 24 hours was significantly greater in the MT group than in the IVT only group (100% vs 37%). MT resulted in a good clinical outcome (90-d mRS ≤2) in 71% of the patients in the MT and in 40% in IVT only groups, with no significant differences the in rates of death or sICH. (Campbell, B. C. et al., 2015.)

The SWIFT PRIME trial was also stopped early because of efficacy; 196 patients with anterior circulation LVO were randomized into the MT with IVT or IVT only groups. MT was performed within 6 hours after stroke onset. The rate of functional independence (90-d mRS ≤ 2) was higher in the MT group (60%) than in the IVT only group (35%), with no significant difference in mortality or sICH. (Saver et al., 2015.)

The 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 (REVASCAT) randomized 206 anterior circulation LVO patients to receive MT or IVT only within 8 hours after the stroke onset, if they did not have a large infarct core. MT reduced the severity of disability and improved the clinical outcome (90-d mRS ≤ 2) in the MT group versus the IVT only group (43.7% vs 28.2%). REVASCAT was stopped early after positive results in favour of MT were reported from other similar trials. (Jovin et al., 2015.)

The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke (THERAPY) compared the efficacy of a direct distal aspiration thrombectomy after IVT with IVT alone in patients with an anterior circulation LVO. The enrolment was again stopped early due to positive results from other trials. The THERAPY trial itself failed to reveal a statistically significant difference between the groups in the primary endpoint of functional independence. Still, a favourable trend for additional aspiration thrombectomy compared to IVT-only patients was seen (38% vs. 30%, p-value 0.44). (Mocco et al., 2016.)

In the THRACE (THRombectomie des Artères CErebrales) trial, a total of 414 patients were randomised at multiple centres in France. Functional independence (mRS ≤ 2) was achieved by 42% of the IVT only group and 53% of the MT group (83% stent retriever and 16% aspiration interventions) at 3 months. The two groups had no significant differences in mortality or the incidence ofsICH. (Bracard et al., 2016.)

A few other trials (EASI and PISTE) were also interrupted prematurely but still showed the benefit of MT over IVT-only therapy (Khoury, N. N. et al., 2017; Muir et al., 2017).

2.4.2.3 Posterior circulation thrombectomy

The techniques used in endovascular treatments of posterior vertebral to basilar artery occlusions are analogous to those used in anterior circulation strokes. Randomized trials on the efficacy of endovascular interventions versus medical therapy were absent until recently. Previously, only retrospective investigational studies had been published. These retrospective studies demonstrated a potential benefit of endovascular therapy in achieving a better clinical outcome, if combined with medical therapy. Kaneko et al. reported a recanalization rate of 95.9% and good clinical outcome in 34.2% of acute basilar artery occlusion patients. Of these patients, 23.3% died within 3 months after the stroke. (Kaneko et al., 2021.)

In a Swedish study, 251 patients with a basilar artery occlusion (2016–2019) were treated with modern endovascular techniques. The total 3-month mortality rate was still as high as 38.6%, and even 50.7% if the proximal part of the basilar artery was occluded. (Ramgren, Frid, Norrving, Wasselius, & Ullberg, 2021.)

The BEST study on patients with a vertebrobasilar occlusion was terminated after only 131 randomly assigned patients. The study was not able to show a difference in favourable clinical outcomes between an endovascular intervention and standard medical treatment. The study suffered from a high crossover rate between the treatment groups, as well as poor recruitment. Furthermore, only 22% of the patients in the standard medical group received IVT (32% in the endovascular treatment group). (Liu, X. et al., 2020.)

Langezaal et al. published the BASICS study of 300 patients randomly assigned to the endovascular and medical care groups. The enrolment was done between 2011 and 2019. A favourable functional outcome was achieved in 44.2% of the patients in the endovascularly treated group and in 37.7% of those in the medical therapy group. The difference between the groups was not statistically significant. (Langezaal et al., 2021.)

A recently published prospective analysis of the Chinese ATTENTION registry study included 462 patients treated with best medical management alone (BMM) and 1,672 patients who received MT. A favourable outcome (90-d mRS ≤ 3) was significantly more common among the MT patients than the BMM patients (40.4% vs 28.5%). The mortality was significantly lower in the MT group (36.9% vs 47.5%). (Tao, Qureshi et al., 2022.)

It has been very difficult to carry out large, good-quality RCTs aiming to show additional benefit of MT in the treatment of posterior circulation strokes due to the severity and, on the other hand, the symptom fluctuation characteristic of basilar thrombosis. The results of randomized patients in the ATTENTION trial (Tao, Li et al., 2022) were first presented in the European Stroke Organisation Conference in Lyon, France, in May 2022 (ESOC 2022). In the ATTENTION RCT trial, the patients who received MT (226 patients) had a significantly better clinical outcome (90-d mRS ≤ 3) compared to BMM alone (114 patients) (46% vs 22.8%). Treatments were started within 12 hours of symptom onset. Only approximately 25% of the patients received IVT in both groups. The 90-day mortality was significantly lower among the MT-treated patients than in the BMM group (36.7% vs 55.3%).

The results of the BAOCHE trial were also presented at ESOC 2022. In this trial, the time from symptom onset to randomization was 6 to 24 hours. The clinical outcome (90-d mRS < 3) was significantly better in the MT-treated than in the BMM alone group (46.4% vs 24.3%, p=0.001) despite the higher rate of SICH (ECASS II criteria) among the MT-treated patients (8.8% vs 2.3%, p=0.054). In the BAOCHE trial, IVT was administered very infrequently – 13.6% in the MT group and 21.5% in the BMM group. (Li, C. et al., 2022.) ATTENTION and BAOCHE were the first RCTs able to show significant additional benefit of MT in posterior circulation strokes.

2.4.2.4 Widening of the treatment time window

After the pivotal RCTs, MT was widely recommended in treatment guidelines for eligible stroke patients presenting within 6 hours of the onset of symptoms.

The DAWN trial focused on longer delays before the MT treatment in LVO stroke and utilized rigorous imaging-based selection (Albers et al., 2018a). A total of 203 randomized patients with an acute LVO stroke were included in the study. The patients were last known to have been well 6 to 24 hours earlier. The patients either had a contraindication for IVT due to a late presentation or had persistent LVO after IVT. MTs were performed with the Trevo® stent retriever. The functional independence (90-d mRS ≤ 2) was found in 49% of the patients in the MT group compared to 13% in the control group. The recanalization rate at 24 hours was 77% among the MT patients and 36% in the control group. (Nogueira et al., 2018.)

At the same time with DAWN, the DEFUSE 3 trial enrolled 182 patients. They were treated within a 6-to-16-hour window after last having been known to be well. An initial infarct size had to be less than 70 ml, and a mismatch ratio 1.8 or more in CT perfusion imaging. MT with medical therapy had an odds ratio of 2.77 for a shift towards better functional outcome. A 90-d mRS ≤ 2 was found in 45% of the patients in the MT group versus 17% in the control group. The 90-day mortality rate was 14% in the MT group and 26% in the medical therapy group, and there was no significant difference between the groups in the frequency of sICH. The trial was terminated early due to the clear beneficial effect of MT also shown in the DAWN trial. (Albers et al., 2018a.)

All these trials studied the effect of modern IA therapies and found MT to be significantly beneficial in comparison to medical therapy in various settings. The delay from the onset of the symptoms to treatment was found to be less critical than previously thought, if the infarct core was limited in size and there was a mismatch between the severity of the clinical findings and the infarct volume assessed with DWI or CTP, indicating that there was substantial salvageable penumbra.

2.4.2.5 The evolution of thrombectomy techniques

Two major techniques are used in cerebral artery thrombectomy, stent retrieval and distal aspiration. Another important component is temporary disruption of antegrade flow while retrieving the clot. This was present already in the setup of the Merci retriever system where a large-inner-diameter balloon-tip guiding catheter (BGC) was inflated to temporarily occlude the vessel to arrest the antegrade flow. The Merci device was then retrieved into the guiding catheter while simultaneously aspirating the guiding catheter. This was considered to counteract fragmentation (and thus distal embolization) and facilitate total removal of the clot. Originally, the Penumbra system took a different approach of a distal aspiration catheter with a separator tip guidewire (Figure 12 B) to break down the thrombus and aspirate it into the catheter.

Current thrombectomy methods combine the ideas of the original Merci and Penumbra systems. The Merci retriever is no longer in use, but has been replaced by different types of stent retrievers, like the ones used in the pivotal MT trials. The aspiration catheters have also evolved, and the separator tip wire has been removed.

The two main MT techniques, stentriever thrombectomy and direct aspiration, are not competitors but rather complement each other. In a typical setup, a distal aspiration catheter is used with BGC or with a stentriever and BGC. In ADAPT (A Direct Aspiration first Pass Technique), the primary recanalization method is aspiration: a proximal large-bore catheter (often without a tip balloon) is used together with a direct distal thrombus aspiration catheter. If the aspiration is ineffective, a stentriever is used. In some centres, ADAPT is found to be faster and more cost-effective when compared to the other techniques. However, in 30% of cases, a stentriever is eventually needed to achieve an acceptable recanalization result. (Turk, Frei et al., 2014; Turk, Spiotta et al., 2014; Turk et al., 2015.)

After the ADAPT results were first released, there was a hypothesis of a better outcome from direct aspiration versus the stentriever technique. However, the ASTER and COMPASS trials showed no significant difference in the recanalization results between the two techniques. (Gariel et al., 2018; Lapergue et al., 2017; Turk et al., 2014; Turk et al., 2019.)

In 2013, Lee et al. published a case series of 10 patients with an ICA-T occlusion recanalized with a combination of the Solitaire stentriever and a Penumbra distal aspiration catheter ("Solumbra", Figure 14) (Lee, J. S. et al., 2013). Subsequently, numerous Solumbra modifications, such as ARTS, ASAP, TCET, ADVANCE, CAPTIVE and PROTECT, were introduced. These evolutional modifications of the Solumbra technique have raised the recanalization rates (TICI 2b-3) to up to 90%–95%. (Goto et al., 2018; Gurkas, Akpinar, & Aytac, 2017; Humphries et al., 2015; Liu, Z. S. et al., 2018; Maegerlein et al., 2018; Massari et al., 2016; McTaggart et al., 2017.)

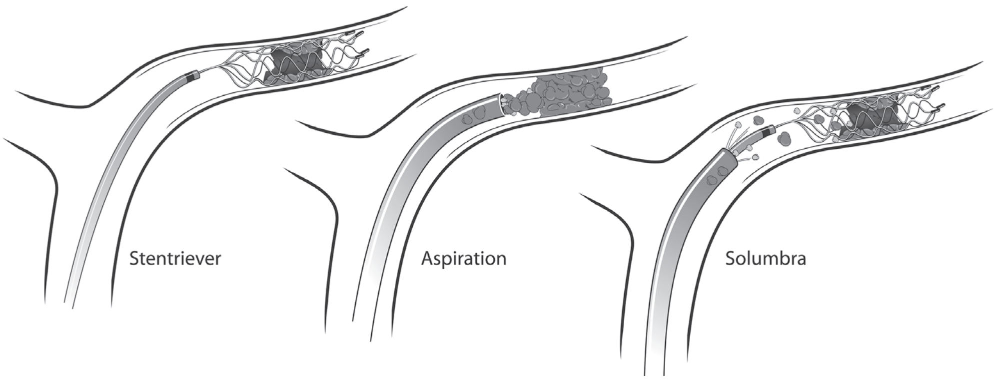

Figure 14. Different mechanical thrombectomy techniques: original stentriever, distal aspiration and the Solumbra technique as a combination of stenriever and distal aspiration. Adapted from Munich et al. (Munich, Vakharia, & Levy, 2019).

A recent meta-analysis of more than 5,500 patients investigated the effect of BGC and confirmed a benefit for using BGC in MT. A first-pass recanalization was almost two times more likely in the BGC group than the non-BGC group (42.3% vs 28.1%, OR 1.92). The rate of successful reperfusion (TICI 2b-3) was 84.8% in the BGC group versus 76.7% in the non-BGC group. The mean procedural time was also significantly shorter in the BGC group (73.7 min versus 98.7 min, p=0.009). The use of a BGC improved the odds of good clinical outcome (90-d mRS $\leq$ 2) in both the stentriever (OR 1.6, $p < 0.001$) and the contact aspiration (OR 1.26, $p < 0.001$) group. This effect was not seen in the combined approach (Solumbra) group. There was a mortality signal in the stentriever group (OR 0.72, $p < 0.01$) favouring the use of BGC. This was not seen in the contact aspiration group. (Podlasek et al., 2021.)

Previous meta-analyses including fewer studies have showed a similar benefit of using BGC (Ahn, Cho, Kim, Kim, & Jeon, 2019; Brinjikji et al., 2018).

2.4.2.6 Distal thrombectomy in small- and medium-sized vessels

The pivotal MT studies included patients with a large vessel occlusion (LVO) in the anterior cerebral circulation, typically up to the M1 segment. There were too few patients with M2 occlusions in these studies to draw solid conclusions. Technically, the large vessel category in this context includes arteries with an over 2.0 mm lumen diameter. These include the ICA and the M1 and M2 segments of the MCA. In the posterior circulation, the vertebral artery, the basilar artery and the P1 segment of the PCA are classified into the large vessel group. Distally to the large vessels are intermediate-size cerebral arteries with lumen diameters of 0.75–2.0 mm (medium vessels). In the medium vessel category are the M3 and M4 segments of the MCA, the A2 to A5 segments of the ACA, and the P2 to P5 segments of the PCA. The cerebral arteries with a lumen diameter under the threshold of 0.75 mm are categorized as small vessels. This category includes the deep penetrator arteries, long pial penetrator arteries and cortical pial arteries. IVT usually treats the small vessel occlusion (SVO) thrombi effectively due to the low thrombus size. At present, SVOs remain out of the reach of endovascular therapies. (Saver et al., 2020.)

The development of new versions of aspiration catheters and stentrievers enables a safe access for MT to treat distal and medium vessel occlusions (DMVO). Both stentriever and direct aspiration techniques are feasible in this domain. In a registry study, DMVO patients appear to have higher odds of a good clinical outcome compared to LVO patients after MT (45% vs 36%, $p = 0.03$) even with a lower rate of successful reperfusion (78% vs 84%, $p = 0.04$). There was no difference in sICH or mortality rates. (Anadani et al., 2021.) MT in a posterior circulation DMVO (P2 and P3 segments of PCA) also appears to be feasible and relatively safe (Altenbernd, Kuhnt, Hennigs, Hilker, & Loehr, 2018; Barchetti et al., 2020; Meyer et al., 2021; Nogueira et al., 2020; Rikhtegar et al., 2021).

2.4.2.7 Factors predicting the clinical outcome after endovascular intervention

The most important aspect of treating an ischaemic stroke is to recanalize the occlusion (Rha & Saver, 2007). Thus, recanalization status and antegrade reperfusion grades after the intervention have a large impact on the clinical outcome. A TICI score of 2b or higher is usually referred to as the angiological target result. TICI 2b–3 was also the target in the pivotal stroke trials, such as MR CLEAN (Berkhemer et al., 2015). More recently, attention has been directed towards a goal of eTICI 2c or 3 after MT rather than ≥ 2b. Recent studies and meta-analyses imply that a significantly higher proportion of MT patients achieve an excellent clinical outcome (3-month mRS 0–1) if the recanalization grade is 2c–3 rather than 2b. Also, the 90-day mortality was significantly lower in the eTICI 2c–3 group (Figure 15). (Dargazanli et al., 2018; LeCouffe, N. E. et al., 2020.)

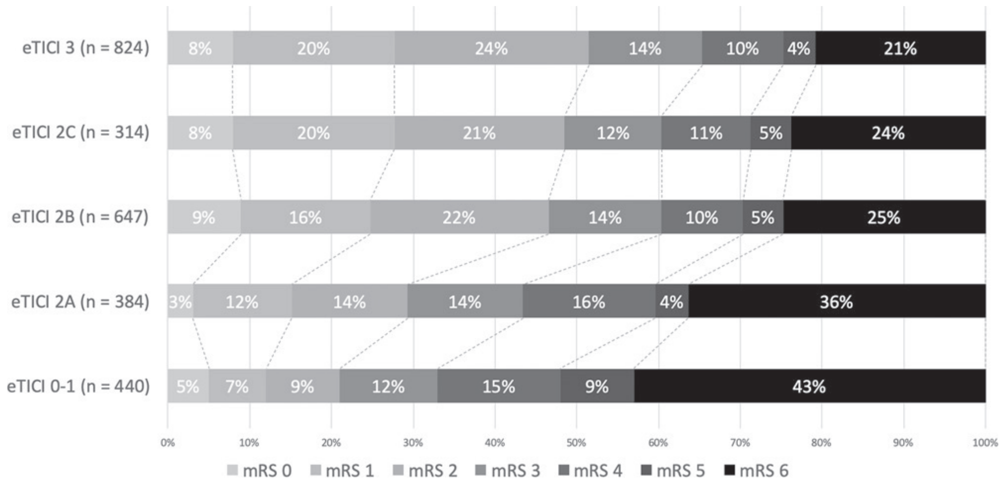

Figure 15. Clinical outcome (3-month mRS) per eTICI recanalization grade. Adapted from LeCouffe et al. (LeCouffe et al., 2020).

The selection of thrombectomy devices and catheters varies between centres and individual interventionists. Both first-line techniques, aspiration and stentriever thrombectomy, have been shown to have similar efficacy in the anterior circulation. (Lapergue et al., 2018; Turk et al., 2019). There also appears there to be no significant difference in efficacy between the different newer-generation stentriever designs or aspiration catheters currently in use. The only statistically significant differences that have been found are between the types of guiding catheters used. A guiding catheter with a balloon tip enabling temporary occlusion of the antegrade blood flow during thrombus retrieval has a beneficial effect on the recanalization result in both aspiration and stentriever techniques (described in section 2.4.2.5).

IVT appears to be beneficial prior to MT, if there is no possibility of proceeding immediately to MT (Katsanos et al., 2019). If thrombolysis is administered just before MT, the beneficial effect is not as clear-cut. Recently published RCTs (i.e. DIRECT-MT, SKIP and DEVT) were unable to show a significant advantage of IVT as regards clinical outcome, when anterior circulation LVO patients were treated directly with MT. The mortality and symptomatic intracerebral haemorrhage rates were similar. In these trials, the IVT to MT delays were quite short. (Suzuki et al., 2021; Wu et al., 2021; Yang et al., 2020; Zi et al., 2021.) The MR CLEAN–NO IV and DIRECT-SAFE trials were also unable to show either the superiority or inferiority of MT without IVT (LeCouffe, Natalie E. et al., 2021; Mitchell et al., 2022). The multicentre SWIFT DIRECT trial reported a benefit of prior IVT in MT patients. A good clinical outcome (3-month mRS) was achieved in 57% of MT-only patients, as opposed to the 65% of prior IVT patients.

The impact of pre-existing lacunar and cortical chronic ischaemic lesions (CILs) on the clinical outcome of MT has been little studied. The recent milestone RCTs on MT did not report the prevalence of CILs in either treatment group, nor was the presence of CILs included in the predictive models (Berkhemer et al., 2015; Campbell et al., 2015; Goyal et al., 2015; Jovin et al., 2015; Saver et al., 2015). In the general acute stroke population, CILs, especially lacunar infarcts, predict a decline in multiple facets of cognitive performance and poorer clinical outcome (Makin, Turpin, Dennis, & Wardlaw, 2013; Mandzia et al., 2016; Shi et al., 2012). There are more reports on the effect of chronic microvascular white matter lesions (WMLs, leukoaraiosis) on MT patients. Moderate or severe WMLs are associated with haemorrhagic complications, futile recanalization and a poor clinical outcome. (Gilberti et al., 2017; Giurgiutiu et al., 2015; Henninger, Khan, Zhang, Moonis, & Goddeau, 2014; Kongbunkiat et al., 2017; Shi et al., 2012).

Anaemia has been shown to be related to a poorer clinical outcome in the general ischaemic stroke population (Barlas et al., 2016; Hao et al., 2013; Kellert et al., 2011; Milionis et al., 2015; Tanne et al., 2010). However, very high haemoglobin levels may also have a deteriorating effect on the clinical outcome (Furlan, Fang, & Silver, 2016; Tanne et al., 2010). One report found that anaemia has no effect on the 3-month outcome of patients suffering from ischaemic stroke (Sharma, Johnson, Johnson, Frank, & Stevens, 2018). A recent study by Nizar et al. showed an association between anaemia and a poorer clinical outcome in MT patients, particularly within the male population (Nisar et al., 2021).

It has been speculated that the type of anaesthesia has an impact on the clinical outcome. The relatively small RCTs GOLIATH and SIESTA reported that patients under general anaesthesia during thrombectomy have an advantage in terms of clinical outcome over conscious sedation patients (Schonenberger et al., 2016; Simonsen, Yoo, Sorensen et al., 2018). A recent meta-analysis of 4,802 patients by Shen et al. and the GASS RCT trial found no difference in functional independence after MT between the two anaesthesia modalities. The achieved recanalization grade, the rate of interventional complications and mortality were also similar (Shen et al., 2021).

Optimal blood pressure (BP) is important during the intervention but also after the treatment. A prolonged drop in mean arterial pressure (MAP) during MT is an independent predictor of poor clinical outcome and larger infarct volumes. Xu et al. suggested that every additional 1 minute of a 10 mmHg MAP drop during MT compared to the admission-MAP-level increased odds of a poorer outcome by 1.3%. (Petersen et al., 2019; Valent et al., 2020; Xu et al., 2021.)

Twenty-four hours after the recanalization, elevated systolic BP is associated with lower three-month mRS scores. Higher systolic BP increases the odds of sICH and death. Matusevic et al. set the systolic BP level of poorer outcome at ≥ 160 mmHg, based on SITS International Thrombectomy Registry data. Poorer outcomes were seen independently of the achieved TICI score. (Anadani et al., 2020; Katsanos et al., 2021; Matusevicius et al., 2020.)

2.4.3 Intracerebral haemorrhage (ICH) as a complication

Post-stroke intracerebral haemorrhage (ICH), and especially symptomatic ICH (sICH), is a serious complication of stroke and stroke therapies. Definitions of sICH vary, but it is widely accepted that neurological deterioration of ≥ 4 NIHSS points and an ICH in the post-stroke brain scan is to be considered a sICH. Patients with sICH are at a high risk of a poor clinical outcome. In the ISET-III study, only 8% of stroke patients with sICH were independent in their daily activities six months after an ischaemic stroke. (Whiteley et al., 2014.)

In the most widely used classifications, like ECASS II and III (European Cooperative Acute Stroke Study) (Hacke et al., 1998; Hacke et al., 2008) as well as the SITS-MOST (Safe Implementation of Thrombolysis in Stroke-Monitoring Study), the basic categories are haemorrhagic infarction (HI), parenchymal haemorrhage (PH), and remote primary intracerebral haemorrhage (PHr). The grades of HI, PH and PHr are further divided into two categories. ICH is detected in post-treatment imaging – in the SITS-MOST database, for example, at 22 to 36 hours after the treatment. (Wahlgren et al., 2007.) SITS-MOST established the definition of sICH to include neurological deterioration of ≥ 4 NIHSS points.

In the SWIFT trial (Solitaire With the Intention for Thrombectomy), seven types of ICH were recognized: four types of haemorrhage within the infarct area (HT1, HT2, PH1 and PH2), in addition to subarachnoid haemorrhage (SAH), intraventricular haemorrhage (IVH) and an intraparenchymal haemorrhage remote to the infarction. The haemorrhagic complication was considered to be a sICH, if PH1, PH2, SAH, IVH or a remote intracerebral haemorrhage was associated with a neurological deterioration of ≥ 4 NIHSS points within 24 hours of the end of the treatment. (Saver et al., 2014.)

Because of variation in the classifications of haemorrhagic complications, the Heidelberg Bleeding Classification (HBC) (Table 5) was presented in 2015 (von Kummer et al., 2015). The HBC describes all types of ICH and potentially has higher inter-rater reliability.

When comparing the results of different studies, careful attention must be paid to the relevant differences in the classifications (Neuberger et al., 2017).

Table 5. The Heidelberg Bleeding Classification of Intracerebral Hemorrhages (von Kummer et al., 2015)

Class	Description	
1	Haemorrhagic transformation of infarcted brain tissue	
a	HI 1	Scattered small petechiae, no mass effect
b	HI 2	Confluent petechiae, no mass effect
c	PH 1	Hematoma within infarcted tissue, occupying <30%, no substantive mass effect
2	Intracerebral haemorrhage within and beyond infarcted brain tissue	
	PH2	Hematoma occupying 30% or more of the infarcted tissue, with obvious mass effect
3	Intracerebral haemorrhage outside the infarcted brain tissue or intracranial-extracerebral haemorrhage	
a	Parenchymal hematoma remote from infarcted brain tissue	
b	Intraventricular haemorrhage	
c	Subarachnoid hemorrhage	
d	Subdural haemorrhage	

2.5 Modified Rankin Scale (mRS) measures the functional outcome of an ischaemic stroke patient

Standardization of the measures of treatment outcome is critical when comparing the effects of different treatment modalities and studies. The most widely used scale of clinical outcome is independence in daily activities, defined with dichotomizing the modified Rankin scale (mRS) (van Swieten, Koudstaal, Visser, Schouten, & van Gijn, 1988). The evaluation of functional outcome is usually performed one, three and six months after the acute phase. Most often, the patients are evaluated at three months. mRS is a seven-step scale, where 0 means “no symptoms” and 6 is death. Scores of 0 to 2 (independence) are considered to represent a good clinical outcome. Correspondingly, scores of 0 to 1 represent excellent outcomes. The mRS scores are described more detail in Table 6.

Table 6. The Modified Ranking Scale (mRS)

Score	Description
0	No symptoms
1	No significant disability; able to carry out all usual activities, despite some symptoms
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 unassisted
4	Moderately severe disability; unable to attend to own bodily needs without assistance, and unable to walk unassisted
5	Severe disability; requires constant nursing care and attention, bedridden, incontinent
6	Dead

3 AIMS OF THE STUDY

The aims of this study were as follows:

I To clarify the impact of chronic ischaemic lesions on the clinical outcome of patients aged 60 years and older, suffering an acute ischaemic stroke and treated with mechanical thrombectomy.

II To analyse the effect of carotid artery stenosis on intracranial collateral circulation in acute stroke patients.

III To clarify whether anaemia influences the clinical outcome of MT with acute anterior circulation LVO patients at different integrities of the collateral circulation.

IV To compare the clinical outcomes of anterior circulation stroke patients treated by means of mechanical thrombectomy patients with a minimal in-hospital delay with or without intravenous thrombolysis.

4 PATIENTS, MATERIALS AND METHODS

4.1 Participants and variables

In this thesis, all the analysed patients had an acute ischaemic stroke due an anterior LVO and were treated with MT. The patients were admitted between 2013 and 2019 to Tampere University Hospital. All data were recorded prospectively and collected retrospectively from the patient records and imaging archives. The baseline clinical characteristics included age, sex and clinical stoke risk factors, including hypertension, diabetes, coronary heart disease and atrial fibrillation.

An acute neurologist examined all patients at admission and evaluated the level of previous independence. In order to receive MT, the patients were required to have been functionally independent before the stroke. The neurointerventional radiologist made the initial imaging evaluation, which consisted of NCCT and CTA, as well as CTP if considered necessary. The selection of patients for MT was based on the absence of extensive irreversible ischaemic changes and haemorrhage in NCCT, in addition to a proximal vessel occlusion. The decision to proceed to MT was multidisciplinary and made by an acute neurologist and a neurointerventional radiologist. The NIHSS score at admission, the process time points and the mTICI grading evaluated from the post-intervention DSA runs were collected. In wake-up strokes, the onset of symptoms was recorded based on when the patient had last been seen to be symptomless. The CT imaging time point was recorded as the timestamp of the first scout image.

NCCT and CTA images were reviewed by experienced radiologists for data analysis. The ASPECT Score was evaluated from admission and next-day follow-up NCCT images. The admission NCCT was also evaluated for the presence of chronic ischaemic findings (Study I). The collateral score was assessed from the admission CTA and the location of the thrombus from DSA, where the most proximal position of the occlusion was considered to be the site of the thrombus. In case the scoring or the assignment differed, a consensus opinion was agreed upon.

Haemorrhagic complications and post-infarct oedema were classified according to the SITS-MOST criteria (Wahlgren et al., 2007) from the follow-up NCCT. The mRS was evaluated three months after the stroke as a clinical outcome based on a follow-up visit to a neurologist or a telephone interview by a neurologist.

The studies included in this thesis were approved by the Tampere University review board and adhered to the Declaration of Helsinki.

4.1.1 Study I

Between January 2013 and December 2014, 130 consecutive patients were admitted to Tampere University Hospital, and the effect of chronic ischaemic lesions (CILs) detected in admission imaging on the 3-month outcome was studied in stent retriever thrombectomy patients. The patients included were 60 years of age or older and had an occlusion of the ICA or MCA up to the M2 segment. The final infarct volume was measured from the 24-hour follow-up CT. Patients with infarct volumes greater than 100 ml are very likely to have a poor clinical outcome (Albers et al., 2006), and these patients were excluded because the acute lesions would mask the effect of the CILs on the clinical outcome.

Sixty-eight patients were included in the final population. Sixty-two were excluded: 37 patients were under 60 years of age or had final infarct volume of over 100 ml. Eight patients had a vertebro-basilar stroke. Two patients had a more distal thrombus. In 15 cases, only diagnostic DSA was performed because the clot had dissolved or there was no access to the thrombus, or thrombus aspiration was the only intervention.

4.1.2 Study II

The effect of ipsilateral carotid stenosis on intracranial collateral circulation and the clinical outcome was studied in MT patients. The data of 385 consecutive patients who underwent MT between December 2013 and December 2017 were collected. The inclusion criteria were an occlusion of the M1 segment to minimize the effect of variation in the circle of Willis, and a sufficient-quality admission CTA to enable the assignment of the collateral circulation. In all, 247 patients met these criteria. Twenty-two of the excluded patients had a vertebro-basilar occlusion, 109 had an anterior circulation occlusion without occlusion in the M1 segment and 7 patients had poor-quality CTAs.

4.1.3 Study III

This was an observational study on 347 consecutive MT patients between December 2013 and December 2017 to clarify the effect of haemoglobin level on clinical outcome. The inclusion criteria were an occlusion of the ICA and/or the M1 segment. A total of 285 patients met these criteria, and the remaining 62 patients were excluded for a more distal occlusion. The flowchart of patient selection is shown in Figure 16. Haemoglobin (Hb) values at admission were recovered from the laboratory database. According to the calibration of the local haematological laboratory, a patient was considered anaemic when the haemoglobin level was < 11.7 g/dl in females and < 13.4 g/dl in males. Nineteen patients could not be reached for the three-month mRS control. An admission NIHSS was not available for nine patients because of sedation. In three cases, the NCCT was of such quality that an ASPECTS could not be reliably calculated. The admission Hb could not be found for 12 patients. The exact onset of symptoms was unknown or unreliable in 12 cases.

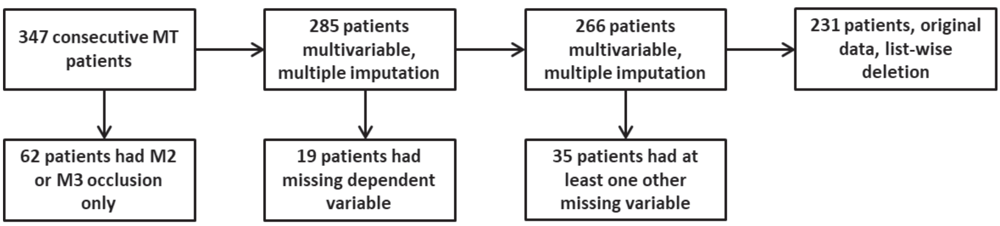

Figure 16. Flowchart of patient selection and analysis in Study III

4.1.4 Study IV

We studied the effect of IVT on the clinical outcome of short-delay MT patients. The data of 479 consecutive patients with an acute LVO between October 2016 and October 2019 were collected. The inclusion criteria were short-delay MT and no contraindications for IVT. Patients referred from consulting hospitals were excluded because of the longer delay. The patients were admitted as MT candidates principally based on the Finnish Prehospital Stroke Scale (FPSS) scoring (Ollikainen et al., 2018) by the emergency services, or after a clinical neurological examination in the emergency room or, in the case of an in-hospital emergency, on a ward. After the decision to treat, the patients were immediately transferred to an angiography suite for MT. Because of minimal in-hospital delays, the neurologist had the option to withhold from administering IVT and to proceed directly to MT. In ten cases, the effect of the thrombolytic agent was waited for before proceeding with MT. These patients were excluded because of the delay induced. Ten patients received IVT after the MT to dissolve the remaining thrombus and were excluded. (Flowchart shown in Figure 17.)

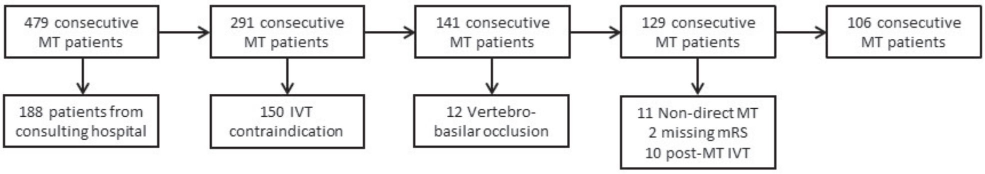

Figure 17. Flowchart of patient selection in Study IV

4.2 Statistics

The data were analysed with SPSS versions 25 and 26 (SPSS Inc., Chicago, IL). The analyses were performed using the maximum number of patients available with regard to missing data. Group comparisons were performed by using Student's t-test, the Chi-squared test, Fisher's exact test and the Mann-Whitney U test according to the type and distribution properties of the variable studied. In ordinal regression analyses, odds ratios (OR) with 95% confidence interval (CI) were calculated for each covariate. A p-value of < 0.05 was considered statistically significant. Patients who had a three-month mRS of ≤ 2 were considered to have reached a good clinical outcome. An mRS of 0–1 was considered an excellent outcome. An mTICI score of 2b–3 was considered a good recanalization result.

In Publications I, III and IV, clinical outcome scores (mRS) were used as a dependent variable. The variables with a p-value of < 0.20 in group comparisons were considered potential confounding factors and included as covariates along with the admission NIHSS in Publication I.

In Publication II, patients with collateral scores (CSs) of 3 and 4 were combined due to the small number of patients (6) in the CS 4 group. Different CS values were used as a dependent variable in ordinal regression analyses.

In Publication III, a patient was considered anaemic when the Hb level was < 11.7 g/dl in females and < 13.4 g/dl in males, according to the calibration of the local haematological laboratory. Patients with a CS from 2 to 4 were regarded as having good collateral vessel filling and those with a score of 1 as having fair collateral filling. Hb values were normalized by subtracting the lower bound of the normal range from the value measured at admission for each sex.

4.3 Imaging parameters

CT scans were obtained using a 64-row multidetector scanner. Brain NCCT was performed using the following parameters: 120 kV with AUTO mA and SMART mA technique, noise index 3.3, collimation 4 x 5 mm, 40% adaptive statistical iterative reconstruction (ASIR), and rotation 0.5 s. Images were obtained axially (0.625 mm thick slices), and contiguous axial slices were then reconstructed to the thickness of 5 mm and coronal slices to the thickness of 2 mm.

CTA was performed with a helical technique using a scanning range from the aortic arch to the vertex of the skull. The contrast agent was administered via an antecubital vein with an 18-gauge cannula using a double-piston power injector with a flow rate of 5 ml/s, administering 70 ml of contrast agent, followed by a 50 ml saline flush. Automatic bolus triggering from the aortic arch was used.

CTP was performed using the parameters 80 kV, 250 mA, 50% ASIR, collimation 8x5 mm, and rotation 0.4 s. A total of 272 slices covering a range of 80 mm were generated in 46 s using the alternating toggle table protocol to increase the z-axis coverage. Contiguous slices were reconstructed to a thickness of 5 mm at even intervals. The contrast agent was administered via an 18-gauge cannula using a double-piston power injector with a flow rate of 5 ml/s, administering 40 ml of contrast agent, followed by a 40 ml saline flush. Digital subtraction angiographic images were obtained using the Artis Z angiographer (Siemens, Munich, Germany) with the parameters 102 kV, AUTOmA and SMARTmA.

4.4 Revascularization Therapies

Patients referred from an outside hospital received IVT according to a drip-and-ship protocol, if there were no contraindications. If a patient received IVT in our institution, the IVT bolus was given on the CT table and the IVT infusion was continued until reperfusion in MT or the full dose. MT was performed through a groin puncture. A biaxial system consisting of a guiding catheter with a tip balloon and co-axially a microcatheter was used. If more distal support or aspiration was considered, a triaxial approach was applied by adding an intermediate catheter to the system. The microcatheter was navigated through the occluded segment of the artery, and a suitable stentriever was positioned through the microcatheter to the site of the thrombus, deployed and pulled back under aspiration. Only very few MTs were performed using only distal aspiration without a stentriever. The selection of the catheters and stentrievers was based on the judgment of the operator.

5 SUMMARY OF RESULTS

5.1 Study I

The median age of the 68 included patients was 70.6 years. The median infarct volume was 3.1 ml (interquartile range = 45.0 ml) in the 24-hour follow-up CT, and four patients (6%) developed a sICH. The occluded vessel was ICA in 23 patients (34%), the M1 segment in 28 patients (41%), and the M2 segment in 17 patients (25%). Forty-four patients (65%) received IVT before MT, and 55 patients (85%) achieved a TICI of 2b–3. In five cases (7%), the time of the onset of the symptoms was unknown. A good clinical outcome (mRS ≤2) was seen in 37 patients (55%) at three months.

5.1.1 Chronic Ischaemic Findings and Their Impact on Clinical Outcome

Twenty-one (31%) patients had a CIL in the admission CT. Fourteen (21%) patients with CILs had more than one lesion, and 13 (19%) had only lacunar-type lesion(s). Nine (43%) patients had lesions on both hemispheres. Two patients (10%) had lesions only in the posterior circulation vascular territory and two had lesions in both anterior and posterior circulation territories. Thirty-one patients (46%) had chronic white matter lesions (WML), 11 of which (16%) were grade 2 or 3 (moderate or severe).

Table 7. Logistic regression analysis for good clinical outcome (mRS ≤ 2)

	Odds ratio	CI 95%	p
No CIL	3.7	1.0 - 10.7	0.05
Male sex	1.5	0.51 - 4.6	0.45
Age	1.04	0.95 - 1.1	0.37
mTICI ≤2	0.36	0.08 - 1.6	0.19
Additional NIHSS point	0.92	0.83 - 1.03	0.16

CI: confidence Interval, CIL: chronic ischaemic lesion, mTICI: modified Thrombolysis in Cerebral Ischaemia, NIHHS: National Institutes of Health Stroke Scale at admission

The presences of CILs and WMLs were highly correlated: 81% of the patients with CILs also had WMLs, whereas only 30% of patients with no CILs had WMLs. Eight of the 21 patients (38%) with a CIL achieved a good clinical outcome, compared with the corresponding 29 of the 47 (62%) patients among those with no chronic infarcts ($p = 0.06$) (Figure 18). The absence of CILs emerged as the only statistically significant covariate that predicted a good clinical outcome, increasing the odds of a good outcome almost four-fold, as demonstrated in Table 7. The major difference is the shift of patients with a good clinical outcome (90-day mRS 0–2) to mRS = 3 in the presence of CILs. (Figure 18.)

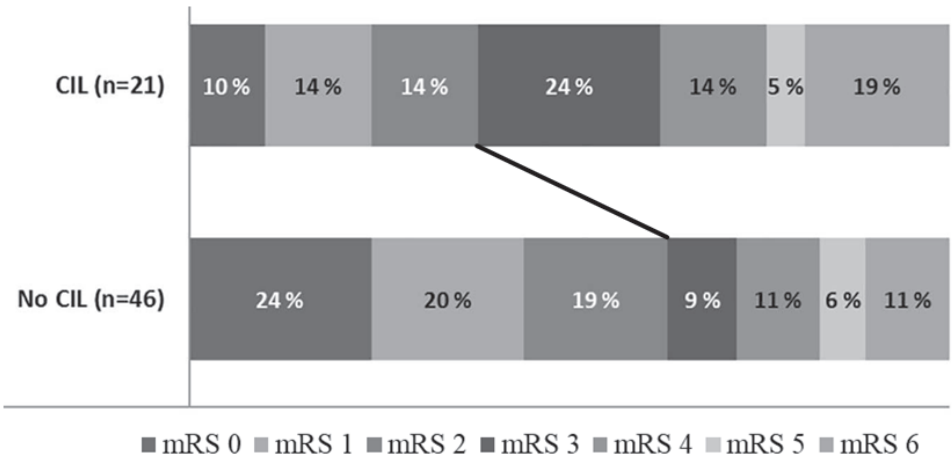

Figure 18. The distribution of 3-month mRS scores between patients with and without chronic ischaemic lesions (CIL). The line indicates the division between functional independence (mRS ≤ 2, left side) and dependence (right-hand side)

5.2 Study II

The inclusion criteria were met by 247 patients. Sixty-five patients (26.3%) had an ICA-T occlusion, and the rest had an isolated M1 segment occlusion, 80 (32.3%) of which were proximal M1 occlusions and 102 (41.3%) distal M1 occlusions. Fifty-one patients (21%) had a severe (≥ 75%) ipsilateral carotid stenosis. The main baseline and admission imaging characteristics between the patients with different collateral statuses are summarized in Table 8.

Table 8. Demographic, baseline and admission imaging characteristics of all patients in Study II by the collateral score.

Characteristic	All patients n=247	Collateral score 0	1	2	3 - 4	p
Age (y), mean (SD)	68 (12)	70 (11)	67 (12)	70 (11)	67 (14)	0.219
Female sex (%)	104 (42)	12 (5)	17 (7)	48 (19)	27 (11)	0.4
NIHSS, median (IQR)	17 (6)	18 (6)	17 (5)	17 (8)	17 (8)	0.052
IVT (%), n=245	149 (61)	15 (6)	32 (13)	65 (27)	37 (15)	0.067
Carotid stenosis ≥75% (%)	51 (21)	4 (2)	5 (2)	18 (7)	24 (10)	0.003
ASPECTS, median (IQR)	8 (3)	7 (4)	8 (3)	9 (2)	9 (3)	<0.001
Onset-MT (min), mean (SD), n=236	192 (111)	140 (76)	189 (97)	193 (108)	220 (134)	0.012
Coronary artery disease n (%)	36 (15)	6 (2)	3 (1)	22 (9)	5 (2)	0.016
Diabetes n (%)	40 (16)	7 (3)	3 (1)	21 (9)	9 (4)	0.101
Atrial fibrillation n (%)	145 (59)	23 (9)	28 (11)	63 (26)	31 (13)	0.058
Hypertension n (%)	124 (50)	15 (6)	18 (7)	51 (21)	40 (16)	0.168

ASPECTS: The Alberta Stroke Program Early CT Score; IVT: intravenous thrombolysis; IQR: interquartile range; NIHSS: National Institutes of Health Stroke Scale; Onset-MT: delay from symptoms onset to groin puncture in MT; *p*: p-value; SD: standard deviation

5.2.1 The timeline and outcome differences between patients with or without severe carotid stenosis

The delay from symptom onset to diagnostic imaging (OCT) was not significantly different between the patients with or without severe carotid stenosis (153 min vs 162 min, respectively, $p = 0.605$). The duration of MT (time from groin puncture to reperfusion) was significantly longer in severely stenotic patients (41 min vs 29 min, respectively, $p = 0.004$). However, the mean delay from onset to reperfusion was not significantly different (229 min vs 222 min, $p = 0.734$). The proportions of good recanalization (mTICI 2b-3) and good clinical outcome were slightly more favourable among patients without severe carotid stenosis, but the differences were not statistically significant. (Table 9.)

Table 9. Characteristics of the MT operation and clinical outcome between groups with or without signifigant carotid stensosis.

Characteristic	All patients n=247	Stenosis <75% (196)	≥75% (51)	p
Onset-MT (min), mean (SD), n=236	192 (112)	194 (118)	184 (81)	0.575
MT duration (min), mean (SD), n=235	32 (26)	29 (24)	41 (30)	0.004
mTICI 2b-3 n (%), n=246	228 (93)	183 (93)	45 (90)	0.414
3-month mRS ≤2 n (%), n=232	133 (57)	109 (58)	24 (53)	0.546

MT duration: time from groin puncture to achieved recanalization; mTICI: modified Thrombolysis in Cerebral Ischaemia; mRS: modified Rankin scale; Onset-MT: delay from symptom onset to groin puncture in MT; *p*: p-value

5.2.2 The factors influencing intracranial collateral circulation

Ordinal logistic regression analysis, using CS at admission as a dependent variable, is detailed in Table 10. Among MT patients, each ten minutes of additional delay from the onset of the symptoms to CT imaging was associated with 6% odds of a better CS ($p < 0.001$). Female sex also significantly increased the odds of a better CS. Chronic hypertension was borderline significantly associated with a higher CS (OR 1.79, $p = 0.051$). Patients with severe ipsilateral carotid stenosis were four times more likely to have better collaterals (OR 4.01, $p = 0.001$).

Table 10. Ordinal logistic regression analysis of collateral score at admission evaluated from CT

	Odds ratio	CI 95%	p
Age	0.98	0.96 - 1.01	0.240
Female	2.27	1.24 - 4.16	0.008
Systolic blood pressure	1.01	1.00 -1.02	0.211
Blood glucose	0.93	0.78 - 1.12	0.392
Onset-CT/10	1.06	1.03 - 1.09	<0.001
ASPECTS	1.55	1.32 - 1.84	<0.001
Hypertension	1.79	1.00 - 1.84	0.051
Coronary artery disease	1.07	0.47 - 2.44	0.864
Atrial fibrillation	0.62	0.33 - 1.16	0.135
Diabetes	0.80	0.33 - 1.92	0.618
Carotid stenosis ≥75%	4.01	1.78 - 9.01	0.001

ASPECTS: The Alberta Stroke Program Early CT Score; CI: Confidence Interval; Onset-CT/10: delay from symptoms onset to imaging in admission (by every 10 minutes); p: p-value

5.2.3 The distribution of collateral scores by carotid stenosis status

Very good collaterals (CS 3–4) were found in 47% of all patients presenting with severe carotid stenosis, while only 22% of the patients with a non-stenotic or slightly stenotic carotid artery had very good collaterals ($p < 0.001$). The proportion of poor collateral circulation (CS 0–1) was significantly higher in the non-stenotic/slightly stenotic group in comparison to the severely stenotic patients (36% versus 18%, $p = 0.012$). Overall, there was a shift towards a better CS in severely stenotic patients. (Figure 19.)

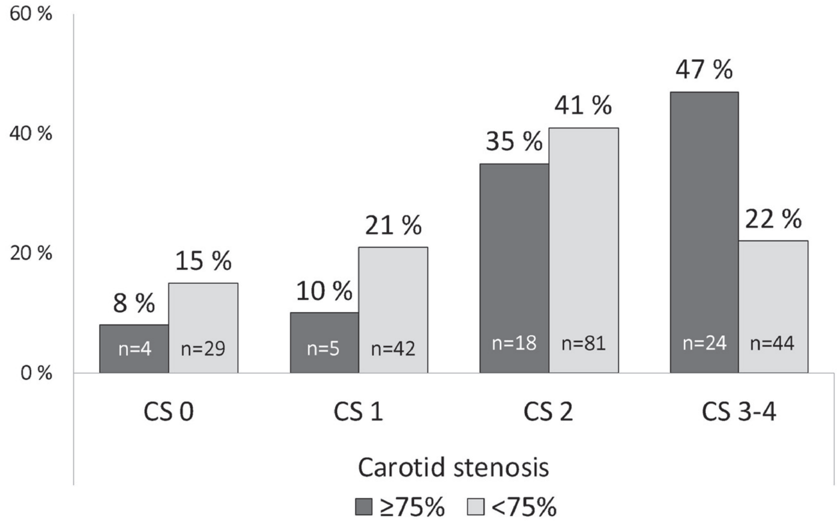

Figure 19. The interplay of severe carotid stenosis with the collateral score (CS)

5.3 Study III

The inclusion criteria were met by 285 patients, with 118 patients (41%) presenting with an occlusion of the ICA and the rest with an M1 segment occlusion. Out of the patients, 243 (85%) had fair or good collateral circulation (CS 1–4). Ninety-four patients (33%) were anaemic. A good three-month clinical outcome (mRS ≤2) was achieved by 54% of the patients. Advanced age, a high NIHSS score, an ICA occlusion, acute ischaemic changes in the admission NCCT, poor collaterals, a suboptimal recanalization result, and a low haemoglobin value at admission, especially in females, were significantly associated with a poor clinical outcome.

5.3.1 Haemoglobin value is an independent predictor of a good three-month clinical outcome in MT patients

Non-anaemic patients had better clinical outcomes (3-month mRS ≤ 2) among patients with a fair or good CS at admission CTA (CS 1–4). Conversely, anaemic patients had borderline significantly better outcomes in the CS = 0 group (no collaterals). However, this result was based on a small number of patients. Figure 20 depicts a shift analysis of the three-month mRS in anaemic and non-anaemic patients with CS in the 1–4 range. The proportion of patients in each of the categories of good clinical outcome (mRS 0–2) is larger in the non-anaemic group. Anaemic patients had significantly higher mortality (mRS 6, $p < 0.001$).

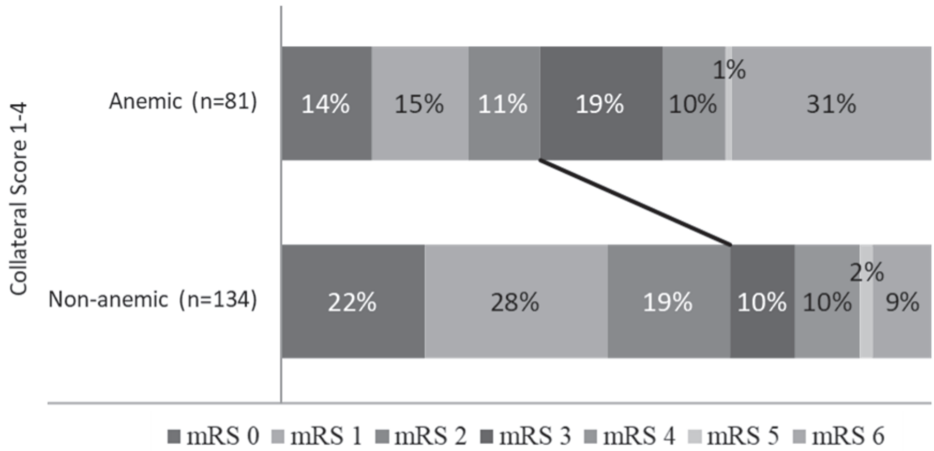

Figure 20. The distributions of the three-month mRS in the anaemic and non-anaemic groups collateral scores 1 to 4. The line indicates the division between functional independence (mRS≤2, left hand side) and dependence (right hand side).

Binary logistic modelling for the dichotomized 3-month clinical outcome was performed using the baseline and imaging variables as covariates. Normalized Hb value was used instead of dichotomization into anemic/non-anemic. The results of a model including all patients having data points for all variables (n=231) are outlined in Table 11. A 0.1 g/dl increase in Hb improved the odds of good clinical outcome by 2% (p=0.03). Younger age, higher ASPECTS in admission NCCT, male gender, higher CS, and more distal site of occlusion also significantly predicted good clinical outcome.

Table 11. Logistic regression analysis of good clinical outcome at 3 months (mRS≤2), all collateral scores included

Covariate	Odds ratio	p	CI 95%
Normalized haemoglobin value	1.02	0.03	1.0 – 1.04
Age	0.97	0.03	0.94 – 0.98
ASPECTS in admission	1.30	0.01	1.06 – 1.59
Hypertension	0.60	0.11	0.32 – 1.13
Diabetes	0.61	0.24	0.27 – 1.39
NIHSS, admission	0.96	0.18	0.90 – 1.02
mTICI ≥ 2b	3.97	0.05	0.99 – 15.9
Female	2.14	0.03	1.10 – 4.17
Collateral Score	1.61	0.01	1.14 – 2.27
ICA occlusion	0.45	0.01	0.24 – 0.85
Onset–MT	1.00	0.56	0.996 – 1.002
Atrial fibrillation	0.98	0.96	0.51 – 1.90
Coronary artery disease	1.79	0.20	0.74 – 4.33
IV thrombolysis	1.27	0.47	0.67 – 2.41

ASPECTS: Alberta Stroke Program Early CT Score; CI: confidence interval; ICA: internal carotid artery; IV: intravenous; mTICI: modified Thrombolysis In Cerebral Infarction score; NIHSS: National Institutes of Health Stroke Scale; Onset–MT: delay from symptom onset to groin puncture in MT; p: p-value

5.4 Study IV

Fifty-eight patients (55%) received IVT and MT, whereas 48 patients had MT only. The distributions of the sites of occlusion were not significantly different between the treatment groups and reflected the distribution in the general MT population. (Table 12.)

Table 12. The occlusion sites in Study IV

Occlusion site	All patients n = 106	IVT + MT n = 58	Only MT n= 48	p
ICA, n (%)	5 (5)	3 (5)	2 (4)	0.808
ICA-T	26 (25)	11 (19)	15 (31)	0.143
M1	58 (57)	33 (57)	25 (52)	0.620
M2	15 (14)	10 (17)	5 (10)	0.316
M3	2 (2)	1 (2)	1 (2)	0.892

ICA: internal carotid artery; ICA-T: ICA terminus; IVT + MT: intravenous thrombolysis with MT; M1-3: 1st, 2nd and 3rd segments of medial cerebral artery; p: p-value

The median NIHSS at admission was 15 (IQR 9), and the mean delay from symptom onset to reperfusion (onset–reperfusion) was 158 minutes (SD 79 min). The mean intrahospital delay from CT imaging to groin puncture (CT–groin time) was 26 minutes (SD 11 min).

The only significant difference in baseline characteristics between the IVT + MT and MT only groups was found in the proportion of atrial fibrillation (64% vs 40%, $p = 0.013$). The onset–reperfusion and CT–groin times were not significantly different (150 min vs 166 min, $p = 0.458$, and 26 min vs 25 min, $p = 0.739$, respectively). Thus, the administration of IVT did not significantly prolong the CT–groin time. Almost the same proportion of patients achieved good recanalization in both the MT + IVT and the MT only group (91% vs 92%, $p = 0.958$). In the MT only group, there was a trend of fewer distal emboli (10% vs 24%, $p = 0.067$), but more device passes were needed for a satisfactory recanalization result (mean 2.3 vs 1.8 passes, $p = 0.093$). The IVT + MT group had a non-significantly lower frequency of haemorrhagic complications (21% vs 29%, $p = 0.313$). The characteristics of the MT procedure and clinical outcomes are summarized in Table 13.

Table 13. Characteristics of MT operation and clinical outcome between IVT+MT and MT only groups

Characteristic	All patients n = 106	IVT + MT n = 58	Only MT n = 48	p
Onset–reperfusion (min), mean (SD)	158 (79)	150 (71)	166 (86)	0.458
CT–groin (min), mean (SD)	26 (11)	26 (12)	25 (9)	0.739
mTICI 2b-3 n (%)	97 (92)	53 (91)	44 (92)	0.958
3-month mRS 0-1 n (%)	51 (48)	22 (38)	29 (60)	0.021
3-month mRS 6 n (%)	12 (11)	9 (16)	3 (6)	0.134
aICH n (%)	26 (25)	12 (21)	14 (29)	0.313
Distal embolus n (%)	19 (18)	14 (24)	5 (10)	0.067
Number of passes, mean (SD)	2.1 (1.7)	1.8 (1.6)	2.3 (1.9)	0.093
ASPECT 24h, median (IQR)	9 (3)	9 (3)	9 (4)	0.780

aICH: any intracranial haemorrhage in CT 24 h after; ASPECTS: The Alberta Stroke Program Early CT Score; CT–groin: delay from imaging to groin puncture in MT; Distal embolus: embolus further in the vessel territory; IVT + MT: intravenous thrombolysis with MT; IQR: interquartile range; mRS: modified Rankin Scale; mTICI: modified Thrombolysis in Cerebral Ischaemia; Onset–reperfusion: delay from onset of symptoms and recanalization in MT; p: p-value; SD: standard deviation

5.4.1 The distribution of three-month mRSs and factors predicting the three-month clinical outcome

Figure 21 depicts the shift analysis of the three-month mRS between the two groups. The proportion of patients with an excellent clinical outcome (mRS 0–1) was significantly larger in the MT only group (60% vs 38%, $p = 0.021$), whereas IVT + MT patients had a trend towards higher mortality (16% vs 6%, $p = 0.134$).

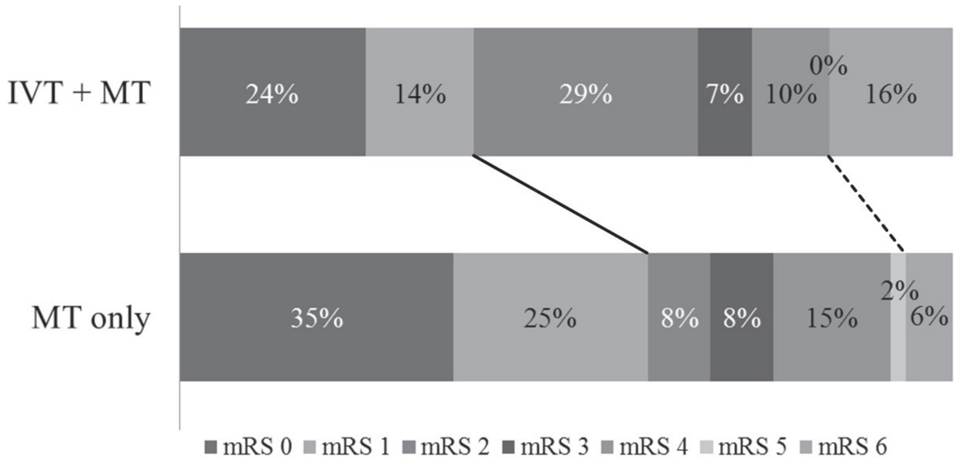

Figure 21. The distributions of 3-month mRSs in the IVT + MT and MT only groups The line indicates the division between an excellent clinical outcome (mRS 0–1, left side) or not having an excellent outcome (right-hand side). The dotted line indicates the division between patients who were alive and dead (mRS 6, right-hand side).

Binary logistic regression analysis, using excellent three-month clinical outcome (mRS 0–1) as the dependent variable, is detailed in Table 14. Among patients selected for MT, each ten minutes of additional delay in onset–reperfusion time reduced the odds of an excellent clinical outcome by 7% ($p = 0.025$). Every additional NIHSS point lowered the odds of an excellent clinical outcome (mRS) by 8% ($p = 0.037$). MT only patients were over three times more likely to have an excellent clinical outcome (OR 3.37, $p = 0.009$). The analysis was repeated after adding the site of occlusion as an additional covariate. The favourable result in MT only patients remained essentially unchanged (OR 3.45, $p = 0.011$).

Table 14. Binary logistic regression analysis of excellent 3-month clinical outcome (mRS 0–1)

	Odds ratio	p	95% CI
Age	0.99	0.637	0.95–1.03
Onset–reper/10	0.93	0.025	0.87–0.99
NIHSS	0.92	0.037	0.85–1.00
Atrial fibrillation	1.26	0.610	0.52–3.03
MT only	3.37	0.009	1.36–8.33
mTICI 2b-3	3.00	0.207	0.54–16.54

CI: confidence interval; MT only: mechanical thrombectomy patients without intravenous thrombolysis; mTICI: modified Thrombolysis In Cerebral Infarction score; mRS: modified Ranking Scale score; NIHSS: National Institutes of Health Stroke Scale; Onset–reper/10: delay from symptoms onset to acheved recanalization in MT (for every 10 minutes); p: p-value

The proportions of patients with a good three-month clinical outcome (mRS 0–2) were practically equivalent in the IVT + MT and MT only groups (67% vs 68%, $p = 0.868$). In univariate analysis, more deaths were found in the IVT + MT group, but the difference was not significant (16% vs 6%, $p = 0.134$). In logistic regression analysis, using mRS = 6 (death) as the dependent variable, IVT increased the odds of death 9-fold (OR 8.98, $p = 0.030$). Every additional year of age increased the odds of death by 17% ($p = 0.005$) and every 10-minute delay in the onset–reperfusion time by 13% ($p = 0.021$).

The odds of an excellent clinical outcome remained essentially the same when the ten patients who received IVT after MT were included in either the IVT + MT or the MT only group (OR 3.45, $p = 0.005$, and OR 2.65, $p = 0.022$, respectively). An additional device pass or the presence of distal emboli did not significantly change the odds of an excellent outcome in the regression analysis (OR 0.95, $p = 0.750$, and OR 1.19, $p = 0.750$, respectively).

6 DISCUSSION

Predictors of a good clinical outcome in the context of MT for an acute anterior circulation stroke have been extensively studied in recent years. Younger age, a lower admission NIHSS, a distal site of occlusion, adequate collateral circulation, small irreversibly ischaemic volume in admission imaging, missing or mild chronic WMLs, successful recanalization, as well as short process times and other delays are associated with good three-month clinical outcomes (Espinosa de Rueda et al., 2015; Gilberti et al., 2017; Goyal, M. et al., 2016; Hausegger, Hauser, & Kau, 2014; Linfante et al., 2016; Protto, Pienimaki, Seppanen, Numminen, & Sillanpaa, 2017; Sarraj et al., 2013; Shi et al., 2014).

Rapid and effective recanalization of the occluded vessel is a crucial determinant of a good clinical outcome in the treatment of acute anterior circulation ischaemic stroke (Fields, Lutsep, Smith, & MERCI Multi MERCI Investigators, 2011; Rha & Saver, 2007). A good clinical outcome (mRS ≤ 2) is achieved only in roughly half of the anterior circulation stroke patients despite high rates (85%–90%) of successful reperfusion with modern MT treatments (Berkhemer et al., 2015; Campbell et al., 2015; Goyal, M. et al., 2011; Jovin et al., 2015). Our results are in alignment with these observations.

6.1 CILs as a prognostic factor in MT patients

Pre-existing infarctions have received little attention in previous MT studies. For example, baseline imaging data of CILs were not reported in the pooled analysis of the ATLANTIS, ECASS and NINDS intravenous thrombolysis treatment stroke trials (Hacke et al., 2004) or in the SITS-MOST thrombolysis registry (Wahlgren et al., 2007). We investigated the impact of CILs on the prognosis of sexagenarian and older patients treated with MT for an acute large-vessel occlusion of the MCA or distal ICA. We found that, after accounting for confounding factors, the absence of CILs emerged as an independent predictor of a good clinical outcome.

Patients with a total infarct volume greater than 100 ml in the 24-hour follow-up CT were excluded from analysis because of the known high likelihood of a poor clinical outcome simply because of the extensive acute lesion (Albers et al., 2006). Considering the epidemiology of CILs and ischaemic stroke, the protocols and results of the previous randomized controlled clinical trials and the general dependence of functional status on age, we restricted our analysis to previously functionally independent sexagenarian and older patients with an anterior circulation stroke.

We found that the most notable difference in the distribution of mRSs between the CIL and the no CIL groups was a shift from a good clinical outcome (mRS $\leq$ 2) to moderate disability (mRS 3) in the presence of CILs, pushing patients just beyond functional independence and into being classified as having experienced a poor clinical outcome. It is debatable whether moderate disability is still an acceptable or even desirable outcome compared with the more severe disability categories of mRS 4–6. There were also similar but milder shifts towards higher mRS categories in the mRS 4–6 range, but these differences did not yield statistical significance in our small cohort.

The mechanisms of action of CILs worsening the outcome of acute stroke that have been proposed include (1) the effect of disease burden that stacks deficits and decreases the compensatory capacity of the brain even if the patient had fully recovered from the previous episodes or the episodes were symptomless, (2) "hits" on multiple systems that potentiate the deleterious effect of a new ischaemic lesion, and (3) CILs as an indicator of poor collateral circulation or general cardiovascular disease burden and thus a higher probability of more severe endpoints (Mandzia et al., 2016). Our findings did not provide support to the third hypothesis, considering that there were no significant differences between the groups in the integrity of collateral circulation or in the clinical risk factors of stroke.

Leukoaraiosis has been shown to predict poor outcome after an acute large-vessel occlusion and is associated with haemorrhagic complications and futile recanalization (Gilberti et al., 2017; Giurgiutiu et al., 2015; Henninger et al., 2012; Kongbunkiat et al., 2017; Shi et al., 2012). Ischaemic stroke outcomes are worse with larger leukoaraiosis volumes and may be affected differentially by leukoaraiosis, depending on stroke subtype (Ryu et al., 2017). The presence of severe small-vessel disease on baseline CT graded based on the extent of leukoaraiosis and chronic lacunar infarcts is associated with a poor clinical outcome in patients treated with IVT (Arba et al., 2016). In our study, almost half of the patients had chronic WMLs, and in one third of these patients, these were graded as moderate or severe. Although having WMLs was not a statistically significant independent predictor of clinical outcome, the presence of WMLs was strongly associated with having CILs and may potentiate their detrimental effect. A grading system capturing both of these aspects of chronic ischaemic injury might have added prognostic value.

6.2 The role of carotid stenosis in MT

Collateral circulation is an established predictor of clinical outcome in the acute ischaemic stroke population (Arsava et al., 2014; Berkhemer et al., 2016; Renu et al., 2019). The factors influencing the integrity of the collateral circulation are not completely known. Old age, hypotension or overt hypertension at presentation, as well as high blood glucose and chronic hypertension have been linked with poor collateral status (Arsava et al., 2014; Faber et al., 2011; Menon et al., 2013). The role that chronic ipsilateral carotid stenosis plays in this setting is controversial (Dankbaar et al., 2018; Guglielmi et al., 2019).

We found that the presence of a severe ipsilateral carotid stenosis increases the odds of a good collateral score four-fold. This finding is in line with the results of a recent study by Guglielmi et al. (Guglielmi et al., 2019). Their study also included patients with more peripheral clot locations. Based on anatomical considerations, we believe that limiting the analysis to M1 occlusions more accurately portrays the development and reflects the impact of the leptomeningeal collateral circulation by decreasing the effect of the variability of the circle of Willis. On the other hand, the setup of the study by Dankbaar et al. is similar to that of our study (Dankbaar et al., 2018). However, they found no correlation between carotid stenosis and the integrity of the collateral circulation.

Few studies have reported an association between advanced age and poor collateral circulation (Arsava et al., 2014; Menon et al., 2013). We did not find age to have a significant effect in our cohort. This can be due to elderly patients with insufficient collateral circulation and haemodynamic perturbations having too extensive irreversible ischaemic changes at presentation to be eligible for MT.

In our study, a history of chronic hypertension had a borderline significant association with having improved collateral circulation (OR 1.79 $p = 0.051$). This is contrary to the findings of two previous publications (Liebeskind et al., 2014; Lima et al., 2010). There is no obvious theoretical explanation for this borderline finding. We also evaluated systolic blood pressure at admission in the model, and a higher pressure had a non-significant positive effect on collateral circulation, as expected. All the chronically hypertensive patients had been prescribed adequate medication, which may play a role here, but data on meeting the target blood pressure levels was not available.

The time from symptom onset to reperfusion is a prognostic factor, with longer delays contributing towards poorer clinical outcome. We found no significant difference in the time from symptom onset to the beginning of the endovascular treatment between patients with or without severe carotid stenosis. However, the severe carotid stenosis population had a significantly longer MT–operation time. Nevertheless, this was not reflected in the clinical outcome. Correspondingly, there was no statistically significant difference between the groups in the overall delay from symptom onset to reperfusion or in the rate of successful recanalization (mTICI 2b–3). It appears that the better collateral circulation associated with severe carotid stenosis compensates for the longer duration of the procedure and other possible negative determinants associated with having more advanced atherosclerotic lesions.

6.3 Anaemia and MT

The integrity of the collateral circulation is an established predictor of clinical outcome, whereas studies on anaemia have yielded conflicting results. We studied the interplay of these two potentially modifiable factors and found both to be significant and independent predictors of the clinical outcome, with anaemia being associated with a poor outcome especially among those who have good or fair collateral circulation.

Anaemia has been generally linked to a poor clinical outcome in ischaemic stroke patients (Barlas et al., 2016; Hao et al., 2013; Kellert et al., 2011; Milionis et al., 2015; Tanne et al., 2010). We also observed this linkage in anterior circulation MT patients. Akpinar et al. reported poor clinical outcome in a small cohort of moderately and severely anaemic LVO patients treated with MT (Akpinar, Gurkas, & Aytac, 2018). Our data confirms and further elucidates this finding to especially concern patients with good or fair collateral circulation. Tanne et al. proposed that anaemia and clinical outcome are non-linearly correlated, with patients having either very low or high Hb concentrations experiencing worse clinical outcomes (Tanne et al., 2010). Our results suggest a more linear mode of action throughout the Hb range: lower Hb values predicted a worse outcome not only in anaemic patients but also within the normal range. This finding is theoretically sensible, considering the increased oxygen transfer capacity per each additional unit of Hb. However, there were only few patients with very low or high Hb concentrations in our cohort, and the follow-up period was shorter. LVO patients have larger ischaemic parenchymal volumes than the average patient in the general ischaemic stroke population and, correspondingly, suffer from a more severe condition. Thus, reduced oxygen delivery because of anaemia potentially has a larger impact in LVO patients. This may, in part, explain the differences between our findings and the previously published studies that address the general stroke population (Barlas et al., 2016; Furlan et al., 2016; Hao et al., 2013; Kellert et al., 2011; Milionis et al., 2015; Sharma et al., 2018; Tanne et al., 2010). In our data, anaemia appeared to have a paradoxical beneficial effect on the outcome in the absence of visible collateral circulation. This finding is based on a small number of patients and is probably artefactual, considering that there is no conceivable mechanism for this effect.

The delay from symptom onset to reperfusion is a well-established prognostic factor, with longer delays contributing towards poorer clinical outcomes. We found no significant difference in delays from symptom onset to the beginning of the MT procedure between the good and poor clinical outcome groups. This may be explained by brain imaging being the primary patient selection method. Still, a prolonged duration of MT was associated with a worse outcome and lower mTICI scores. Successful reperfusion (mTICI 2b–3) was an independent predictor of good clinical outcome. However, the difference in successful reperfusion rates was relatively small between the two outcome groups (95% vs 89%). This small difference highlights variations in the rate of expansion of the infarct core (Desai, Rocha, Jovin, & Jadhav, 2019), which is heavily dependent on the intracranial collateral flow (Nordmeyer et al., 2017; Pereira et al., 2013; Tan et al., 2007).

6.4 Delay from IVT to MT

IVT with rt-PA and a modern MT intervention are well-proven treatments of acute ischaemic stroke (Goyal et al., 2016; Tsivgoulis, Safouris, & Alexandrov, 2015). The efficacy of IVT alone is limited in the treatment of large vessel occlusions (Riedel et al., 2011). The time from symptom onset to reperfusion is a critical determinant of clinical outcome (Prabhakaran, Ruff, & Bernstein, 2015). Thus, the minimization of delays has a key role in the strategies to improve the outcome. Drip-and-ship protocols with IVT have been clearly shown to improve the odds of a good clinical outcome, when direct access to MT is not available (Katsanos et al., 2019). Protocols combining IVT with MT in a within-institution setting have also been studied (Bellwald et al., 2017; Broeg-Morvay et al., 2016; Choi, J. H. et al., 2018; Guimaraes

Rocha et al., 2019; Phan et al., 2017; Wang, H. et al., 2017; Weber et al., 2017). Guidelines state that IVT should always been given prior to MT, if the patient is within the treatment time window and there are no contraindications (Pierot et al., 2018; Powers et al., 2018; Turc et al., 2022).

In our study, the odds of an excellent clinical outcome (mRS 0–1) improved three-fold, if IVT was not administered to patients eligible to receive this therapy in a within-institution, minimal in-hospital delay setting. To our knowledge, there are no previous reports signalling that IVT might have this kind of limited unfavourable effect in conjunction with MT.

Some previous multicentre studies (Casetta et al., 2019; Gariel et al., 2018; Mistry et al., 2017) have found that patients who received combined IVT and MT to treat an LVO had a better clinical outcome. In all these studies, IVT was always administered if not contraindicated. The average in-hospital delays were considerably longer than in our study. Furthermore, the setup of these studies was different from ours, considering that they compared MT with IVT bridging therapy to MT in patients having contraindications for IVT. In our study, neither group had contraindications for IVT, and both groups had direct, minimal-delay access to MT.

On the other hand, in several other studies (Bellwald et al., 2017; Broeg-Morvay et al., 2016; Choi et al., 2018; Guimaraes Rocha et al., 2019; Wang et al., 2017; Weber et al., 2017), no significant benefit in outcome was found when combining IVT and MT. Again, the average in-hospital delays in these studies were long. In three of the studies (Choi et al., 2018; Guimaraes Rocha et al., 2019; Weber et al., 2017), IVT was always given if not contraindicated. In the studies by Weber et al. and Wang et al. (Wang et al., 2017; Weber et al., 2017), the process times in the IVT combined with MT and the MT only groups were markedly different. Both Broeg-Morvay et al. and Bellwald et al. found higher mortality in matched-pair analyses, when IVT was combined with MT, and IVT was not associated with better outcome (Bellwald et al., 2017; Broeg-Morvay et al., 2016).

After Study IV, the results of six RCTs addressing this problem have been published. The DEVT trial concluded that MT only is non-inferior to MT with prior IVT, when comparing functional independence (90-d mRS 0–2). Randomization in the DEVT trial was stopped earlier than planned due to the efficacy signal after 234 patients (970 patients planned). Functional independence was achieved in 54.3% of the MT alone patients versus 46.6% of the IVT + MT patients ($p = 0.003$ for noninferiority of MT alone). The median delay from IVT to reperfusion was 109 minutes and the median door-to-needle time 61 minutes. (Zi et al., 2021.)

The SKIP trial found no significant difference in functional outcome between MT only and IVT + MT patients (90-d mRS 0–2 59.4% and 57.3%, respectively). The median time from IVT to groin puncture was very short, and 21.4% of the patients ended up receiving only IVT after groin puncture. The delay from IVT to reperfusion was not reported. The rt-PA dose was lower than the dose used in Europe (0.6 vs 0.9 mg/kg). (Suzuki et al., 2021.)

The DIRECT-MT trial enrolled 656 Chinese patients to show non-inferiority of MT alone versus IVT + MT, with a 20% margin of confidence. MT alone was associated with a lower rate of successful reperfusion (79.4% vs 84.5%). The rate of reperfusion before thrombectomy was higher in the IVT group, as expected (7.0% vs 2.4%). In this trial, the median delay from IVT to endovascular revascularization was almost 90 minutes. (Yang et al., 2020.)

The MR CLEAR-NO IV trial of 539 patients found neither superiority nor inferiority in the MT alone arm with regard to the 90-day clinical outcome. In this trial, the median IVT-to-reperfusion delay was 80 minutes. (LeCouffe, N. E. et al., 2021.)

The most recent multicentre RCT of European and American patients is the SWIFT DIRECT trial that was not able to show non-inferiority of MT alone in terms of clinical outcome. The median door-to-groin puncture time in the two groups was as long as 75 or 80 minutes (MT alone vs IVT + MT, respectively) and the median delay from puncture to reperfusion 36 or 37 minutes. The delay from door-to-needle was 55 minutes. The delay from needle to reperfusion was 62 minutes (Fischer et al., 2022.)

The ongoing DIRECT SAFE trial is accepting patients with a door-to-groin time of 90 minutes or less (Mitchell et al., 2022).

Overall, in these new RCTs, no significant differences were found in clinical outcome, the rate of sICHs, or mortality between the groups. In our Study IV, the median delays from CT to arterial puncture were 22 minutes in the MT only group and 23.5 minutes in the IVT + MT group, and the median delay from the arterial puncture to reperfusion was 25 minutes in the MT only and 20 minutes in the MT + IVT group. We achieved reperfusion in the IVT + MT group with a median delay of 43.5 minutes after the start of CT imaging. These delays are in sharp contrast with, for example, those of the SWIFT DIRECT trial in which the median delay from door to reperfusion in the IVT + MT group was 123 minutes. In Study IV, the time of arrival was not registered, and, thus, the beginning time of CT imaging was used, but an independent report on Finnish stroke care centres published in 2019 cited our median door-to-CT was 6 minutes and the door-to-groin time was 22 minutes. Patients referred from outside hospitals are included in these figures, leading to a slight underestimation of the delay in this context. However, the difference is substantial when comparing, for example, to the 75–80-minute door-to-groin time in the SWIFT DIRECT study. This delay closely tracks the functioning of the intrahospital protocols. The delay from IVT to reperfusion is of particular interest when studying the effect of IVT prior to MT, as this is the time that IVT has to work on the thrombus before flow restoration with MT. In Study IV, the exact time of the first IVT bolus is not shown, but IVT was administered on the CT table, usually after NCCT but sometimes after CTA or CTP. Therefore, the IVT-to-reperfusion time is shorter than the CT-to-reperfusion time (median 43.5 min). In most of the recent RCTs, the IVT-to-reperfusion times are long enough for IVT to reach its full dose and effect on the thrombus – in the SWIFT DIRECT trial, for instance, the IVT-to-reperfusion time was 62 minutes. In our study, IVT had a much shorter time to act before the reperfusion, and the effect of IVT may therefore not have been as complete as in the RCTs. This might explain the differences between our results and those of the RCTs.

Our finding of a better clinical outcome in the MT only group may partially also be due to differences in other parameters, such as the technical details of MT, shorter time delays in general and the type of anaesthesia. We found no significant differences in the frequency of symptomatic or non-symptomatic post-treatment ICHs in the follow-up CT between the two groups. These findings are in congruence with the new RCTs. There were also no significant differences in process times or stroke severity at admission. We observed that patients treated with the combination of IVT and MT were more likely to have macroscopic distal emboli in comparison to the MT only patients (24% vs 10%, $p = 0.067$), similarly to the findings of Yi et al. (Yi, Sung, & Lee, 2019). Interestingly, fewer stent retriever passes were needed for patients treated with the IVT + MT combination to achieve a satisfactory recanalization result (mean 1.8 vs 2.3 passes, $p = 0.093$), which is in line with a report by Mistry et al. (Mistry et al., 2017). However, neither macroscopic distal embolization nor the number of retriever passes had a direct effect on the overall technical or clinical outcome.

The potential detrimental effect of IVT on the clinical outcome may be explained by microscopic distal embolization. Alteplase can make the thrombus more fragile and prone to fragmentation during the procedure and thus increase the incidence of microinfarctions and post-ischaemic microhaemorrhages in the brain parenchyma. Patients with cerebral microhaemorrhages in a follow-up MRI after intravenous thrombolysis are known to have a poorer clinical outcome (Charidimou et al., 2017;

Choi, K. H. et al., 2018; Wang, S., Lv, Zheng, Qiu, & Chen, 2017; Zand et al., 2018). In the DVT trial, distal clot migration was slightly more frequent with IVT-treated patients (17.7% in MT alone vs. 23.9% in IVT + MT) (Zi et al., 2021). Furthermore, alteplase has been reported to have undesirable effects on the brain parenchyma due to neurotoxicity (Balami, Sutherland, & Buchan, 2013).

Overall, our results suggest that withholding IVT when immediate access to MT can be offered may lead to more patients having an excellent clinical outcome and averting death. If the in-hospital delays are longer and no immediate MT is available, it appears obvious in light of the recent RCTs that IVT should be administered if there are no contraindications.

6.5 Implications for future research

We observed a signal in Study IV that, in the context of a very short in-hospital-delay protocol, IVT can be harmful for acute ischaemic stroke patients. In Study II, we presented results of prolonged MT procedure times among patients with severe carotid stenosis. It is tempting to hypothesize that these patients with longer groin-puncture-to-reperfusion times stand to benefit more from IVT and, vice versa, that IVT may potentially be withheld from patients with non-stenotic and otherwise straightforward vascular access in CTA.

In Study I, we found chronic ischaemic lesions to be a predictor of poorer outcome in MT patients. Chronic ischaemic lesions are associated with a higher sICH rate in ischaemic stroke patients treated with IVT (Kongbunkiat et al., 2017). The potential risks of IVT in direct-MT patients with CILs and leukoaraiosis remain to be studied further, considering the findings of Study IV.

A subgroup analysis of previous RCTs on MT patients with or without previous IVT would further elucidate the potential benefits and harms of proceeding directly to MT and thus find the best candidates for direct MT.

6.6 Limitations

Our studies have limitations. The formation of the observational MT cohorts was clinically driven and, as such, nonrandomized, meaning that there can be selection biases. Because of the relatively small number of patients available for analysis, the subgroup analyses may be underpowered. This issue was present especially in Study I that is not statistically geared up to detect small differences between subgroups.

Missing data and the multiple imputation method in Study III may introduce biases and increase variability, even if the percentage of missing data was small.

The exact pre-stroke degree of disability and dependence were not prospectively recorded (other than mRS being ≤ 2, defined as slight disability but able to look after own affairs without assistance) for most patients in the original studies. Generally, slight disability (mRS 2) is a common finding due to numerous non-stroke related aetiologies. Thus, the effect of the treatments on the clinical outcome can be biased in this way.

The use of CTA at a certain common time point to define the exact collateral circulation score can be problematic due to different flow rates of blood (contrast) between patients. Therefore, the delay to maximal visualization of the collateral vessels also varies between the patients after contrast injection. This can be result in biases in the CS scoring.

A 24h follow-up NCCT, which we used in all the studies, is not the ideal method to estimate final infarct volume because infarcted parenchyma and surrounding oedemic tissue cannot be accurately delineated. Therefore, the volumes reported probably exaggerate the actual final infarct volumes.

All studies were carried out in Tampere University Hospital, which as a single, highly standardized tertiary stroke centre with a high average recanalization rate, and the minimal delay setup limits the generalizability of the findings.

7 CONCLUSIONS

I

Chronic cortical and lacunar infarcts in admission imaging are associated with poor clinical outcome in sexagenarian and older patients treated with MT for acute large-vessel occlusion of the MCA.

II

The presence of severe carotid stenosis correlates with better intracranial collateral circulation in patients presenting with acute ischaemic stroke due to a large vessel occlusion. However, this did not translate into a difference in the three-month clinical outcome.

III

Anaemia has an independent role in predicting poorer clinical outcome in MT-treated patients.

IV

Proceeding directly to MT without prior IVT might improve the rate of excellent three-month clinical outcomes in acute LVO patients, if treated in a minimal in-hospital delay tertiary stroke centre.

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PUBLICATIONS

PUBLICATION
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Chronic Infarcts Predict Poor Clinical Outcome in Mechanical Thrombectomy of Sexagenarian and Older Patients

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Chronic Infarcts Predict Poor Clinical Outcome in Mechanical Thrombectomy of Sexagenarian and Older Patients

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Background: The impact of lacunar and cortical chronic ischemic lesions (CILs) on the clinical outcome of mechanical thrombectomy (MT) has been little studied. Clinical trials suggest that older patients benefit from MT. We investigated the effect of CILs on the clinical outcome of sexagenarian and older patients with acute middle cerebral artery (MCA) or distal internal carotid artery (ICA) stroke who received MT to treat large-vessel occlusion (LVO). *Methods:* We prospectively collected the clinical and imaging data of 130 consecutive MT patients of which 68 met the inclusion criteria. We limited the analysis to sexagenarian and older subjects and occlusions no distal than the M2 segment. Baseline clinical, procedural and imaging variables, technical outcome, 24-hour imaging outcome, and the clinical outcome were recorded. Differences between patients with and without CILs were studied with appropriate statistical tests and binary logistic regression analysis. *Results:* Twenty-one patients (31%) had at least 1 CIL. Thirty-eight percent of patients with CIL(s) compared with 62% without ($P = .06$) experienced good clinical outcome (3-month modified Rankin Scale ≤ 2). A similar nonsignificant trend was seen when lacunar lesions, lesion multiplicity, and chronic white matter lesions were examined separately. Absence of CIL increased the odds of good clinical outcome 3.7-fold (95% confidence interval 1.0-10.7, $P = .05$) in logistic regression modeling. *Conclusions:* Chronic cortical and lacunar infarcts in admission imaging are associated with poor clinical outcome in sexagenarian and older patients treated with MT for LVO of the MCA or distal ICA. **Key Words:** Ischemic stroke—mechanical thrombectomy—lacunar infarct—cortical infarct.

Introduction

The impact of pre-existing lacunar and cortical chronic ischemic lesions (CILs) on the clinical outcome of mechanical thrombectomy (MT) has been little studied. The recent milestone randomized clinical trials on MT reported the prevalence of CILs in neither treatment group nor was the presence of CILs included in the predictive models.[1-5] In the general acute stroke population, CILs, especially lacunar infarcts, predict a decline in multiple facets of cognitive performance and poorer clinical outcome.[6-8] There are more reports on the effect of chronic microvascular white matter lesions (WMLs, leukoaraiosis) on MT patients. Moderate or severe WMLs are associated with hemorrhagic complications, futile recanalization, and poor clinical outcome.[8-12]

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The presence and extent of both CILs and WMLs are closely related to advanced age. A meta-analysis of the MT trials suggests that MT can benefit sexagenarian and older patients.[13] Many of these older patients that are candidates to MT are bound to have CILs.

The objective of this investigation was to clarify if CILs have a detrimental impact on the clinical outcome of sexagenarian and older patients with acute stroke who are treated with MT.

Methods

Participants and Variables

The study was approved by the institutional review board. We prospectively collected the clinical and imaging data of 130 consecutive patients presenting with stroke symptoms admitted between January 2013 and December 2014 to Tampere University Hospital. They underwent clinical and imaging evaluation and proceeded to digital subtraction angiography with an intention to perform MT. The inclusion criteria for this study were 60 years of age or older, occlusion of the internal carotid artery (ICA) and/or middle cerebral artery (MCA) up to the M2 segment, MT with stent retriever, and the final infarct volume measured in the 24-hour follow-up computed tomography (CT) less than 100 cubic centimeter (ccm). Patients with infarct volumes greater than 100 ccm are very likely to have poor clinical outcome.[14] These patients were excluded because the acute lesions would mask the effect of the CILs on the clinical outcome. The baseline clinical characteristics included age, sex, and clinical risk factors (hypertension, diabetes, coronary heart disease, atrial fibrillation). These data were collected from the patient records. National Institutes of Health Stroke Scale (NIHSS) score at the presentation, time from symptom onset to reperfusion or end of the MT intervention, and Thrombolysis in Cerebral Ischemia (TICI) grading evaluated from the final digital subtraction angiography run had been recorded prospectively. A follow-up non–contrast-enhanced computed tomography (NCCT) was performed 24 hours after MT. Hemorrhagic complications and post-infarct edema were classified according to Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) criteria.[15] The clinical outcome measure was the modified Rankin Scale (mRS), evaluated 3 months after the stroke based on a follow-up visit to a neurologist or a phone interview by a neurologist.

Imaging Protocol, Clinical Decision-making, and Image Analysis

The initial imaging evaluation consisted of NCCT, CT angiography (CTA) and, in more than half of the cases, CT perfusion (CTP). The selection of patients as candidates for MT was based on absence of extensive irreversible ischemic changes (frank hypodensity more than one third of MCA territory) and hemorrhage in NCCT, evaluation of the amount of salvageable tissue in CTP imaging (when available), and proximal clot position in CTA. The patient was required to be functionally independent before the stroke (prestroke mRS ≤2). The decision to proceed to MT was multidisciplinary (stroke neurologist and neurointerventional radiologist). Patients transferred to our institution from other hospitals were re-evaluated with at least NCCT and CTA upon arrival before proceeding to the angiographic suite. In the case of wake-up strokes, CTP was performed if no large infarct was seen in NCCT.

CTA images were reviewed by examining both the raw data and the maximum intensity projection reconstructions. The Alberta Stroke Program Early CT Score was assessed from admission and 24-hour follow-up NCCT images. Admission NCCT was also evaluated for presence of chronic ischemic findings: (1) territorial infarcts and (2) lacunar infarcts (including branched atheromatous disease type lesions). The vascular region and side of these lesions were recorded. The extent of chronic WMLs was graded based on a 4-point scale.[16] CTA was used to evaluate the occlusion site, the Clot Burden Score, and the Collateral Score as described in our previous report along with validation of scorings and measurements.[17] The location of the clot was recorded based on the most proximal position of the occlusion. The examinations were reviewed in the order NCCT, CTA, and CTP. Two radiologists assigned Alberta Stroke Program Early CT Score, Clot Burden Score, and Collateral Score. In case the scoring or the assignment differed, a consensus opinion was agreed on. The reviewers were provided with only the side and nature of the acute symptoms. One radiologist measured the final infarct volumes on the 24-hour NCCT. The boundaries of the affected areas were determined visually. Volume was calculated by multiplying the measured area with the slice thickness.

Revascularization Therapies

Intravenous thrombolysis (Actilyse 0.9 mg/kg, Boehringer-Ingelheim, Ingelheim, Germany) was administered as bridging therapy to patients with no contraindications. The Actilyse bolus was given on the CT table. Patients coming from an outside hospital received intravenous thrombolysis (IVT) according to drip-and-ship protocol. Actilyse drip was continued until groin puncture. Mechanical thrombectomy was performed with different stent retrievers and sometimes with multiple devices based on the judgment of the operator. We used a biaxial system consisting of an 8F or 9F guiding catheter with a tip balloon and coaxially a .021″ micro-catheter or a triaxial system consisting of an 8F guiding catheter, a distal access catheter through which a micro-catheter was inserted with the aid of a .014″ micro-guidewire. The micro-catheter was navigated through the occluded segment of the artery, and a suitable stent retriever device was positioned through the micro-catheter to the site of the thrombus and deployed. The stent was left in place for 4 minutes and then retrieved, and at the same time the guiding catheter or the intermediate catheter was aspirated forcefully. The same procedure was repeated until satisfactory circulation was restored. Different stent retrievers were used: The TREVO device (Stryker Neurovascular/Concentric Medical, Mountain View, CA) was used in 41% of cases, CAPTURE LP (eV3/COVIDIEN/Medtronic, Santa Rosa, CA) in 37%, ERIC (MicroVention, Tustin, CA) in 13%, Aperio (Acandis, Pforzheim, Germany) and REVIVE (Codman & Shurtleff, Raynham, MA) in 3%, and in 10% of cases multiple device types were used.

Imaging Parameters

CT scans were obtained using a 64-row multidetector CT scanner (General Electric LightSpeed VCT, GE Healthcare, Milwaukee, WI). Brain NCCT was performed using the parameters 120 kV with AUTO mA and SMART mA technique, noise index 3.3, collimation 4 × 5 mm, 40% adaptive statistical iterative reconstruction (ASIR), and rotation .5 seconds. Images were obtained axially (.625-mm-thick slices) and then contiguous axial slices were reconstructed to the thickness of 5 mm and coronal slices to the thickness of 2 mm. CTA was performed with helical technique using a scanning range from the aortic arch to the vertex of the skull. The imaging parameters were 100 kV, AUTO mA and SMART mA, noise index 9, 40% ASIR, collimation 40 × 0.625 mm, rotation .5 seconds, and pitch factor .984. The contrast agent (iomeprol, 350 mg I/mL, IOMERON, Bracco, Milan, Italy) was administered via an antecubital vein with 18-gauge cannula using a double-piston power injector with a flow rate of 5 mL/s using 70 mL contrast agent followed by a 50 mL saline flush. Automatic bolus triggering from the aortic arch was used. CTP was performed using the parameters 80 kV, 250 mA, 50% ASIR, collimation 8 × 5 mm, and rotation 0.4 seconds. A total of 272 slices covering a range of 80 mm were generated in 46 seconds using alternating toggle table protocol to increase the z-axis coverage. Contiguous slices were reconstructed to a thickness of 5 mm at even intervals. The contrast agent (IOMERON 350 mg I/mL) was administered via an antecubital vein with an 18-G cannula using a double-piston power injector with flow rate of 5 mL/s using 40 mL of contrast agent followed by a 40 mL saline flush. Digital subtraction angiographic images were obtained using the Artis Z angiographer (Siemens, Munich, Germany) using the parameters 102 kV, AUTOmA, and SMARTmA.

Statistics

The data were analyzed with SPSS Statistics version 23 (SPSS Inc., Chicago, IL). Group comparisons were performed by using the chi-square test, the Fisher exact test, and the Mann-Whitney *U* test according to the type and distribution properties of the variable studied. Patients who had 3-month mRS less than or equal to 2 were considered to have experienced good clinical outcome. TICI scores 2b or 3 were considered good recanalization results. Multivariable binary logistic regression analyses using good clinical outcome as dependent variable were performed, and odds ratios with 95% confidence intervals were calculated for each covariate. Variables having *P*-value less than .20 in group comparisons were considered potential confounding factors and included as covariates along with admission NIHSS, which was included for theoretical reasons based on literature. A *P*-value less than .05 was considered statistically significant.

Results

Study Population and Baseline Characteristics

The inclusion criteria were met by 68 patients, and 62 patients were excluded: 8 patients were excluded because of posterior circulation stroke, 1 patient had occlusion of the A3 segment of the anterior cerebral artery and another of the M3 segment, in 15 cases MT was not performed because the clot had dissolved or there was no access to the thrombus, or aspiration thrombectomy was the only intervention, and finally 37 patients were younger than 60 years of age (27 patients) or had final infarct volume more than 100 ccm (13 patients).

The main baseline characteristics along with admission and follow-up imaging findings are summarized in Table 1. The median age was 70.6 years (interquartile range = 8.8 years). The median infarct volume was 3.1 ccm (interquartile range = 45.0 ccm) in the 24-hour follow-up CT and 4 patients (6%) had a hemorrhagic complication that caused symptom worsening. The occluded vessel was ICA in 23 patients (34%), M1 segment in 28 patients (41%), and M2 segment in 17 patients (25%). Forty-four patients (65%) received IVT before MT and 55 patients (85%) achieved TICI 2b or 3. In 5 cases, the time of the onset of the symptoms was unknown (the wake-up strokes). One patient could not be reached for the 3-month clinical control. Good clinical outcome was seen in 37 patients (55%) at 3 months.

Chronic Ischemic Findings and Their Impact on 3-Month Clinical Outcome

Of the 68 patients studied, 21 (31%) had chronic ischemic lesions (i.e., old lacunar or territorial infarcts) in the admission CT. Fourteen patients (21%) had more than 1 lesion, and 13 (19%) had only lacunar-type lesion(s). In one-third of the patients, the chronic ischemic lesions were only on the right side, whereas 24% had them only on the left and 43% had lesions on both sides. Two patients out of 21 (10%) had chronic lesions only in the posterior circulation vascular territory and an additional 2 had infarcts both in the anterior and in the posterior

Table 1. *Baseline and admission imaging characteristics and the clinical and imaging outcomes of all patients and patients with or without chronic ischemic lesion in the admission imaging*

Characteristic	All patients (n = 68)	No CIL (n = 47)	CIL (n = 21)	P_1
Age (y), median (IQR)	70.6 (8.8)	69.3 (8.2)	73.0 (6.9)	.08
Male sex (%)	36 (53)	22 (47)	14 (67)	.13
NIHSS before treatment, median (IQR)	15 (5)	15 (5)	15 (5)	.65
ASPECTS score at admission NCCT, median (IQR)	10 (2)	9 (2)	10 (1)	.20
Onset to reperfusion time (min), median (IQR)	197 (128)	195 (108)	252 (173)	.21
Clot Burden Score, median (IQR)	6 (4)	6 (4)	7 (3)	.25
Collateral Score, median (IQR)	1 (2)	1 (2)	1 (2)	.58
Received IVT (%)	44 (65)	32 (68)	12 (57)	.38
TICI 2b or 3 (%)	58 (85)	42 (89)	16 (76)	.16
Hypertension n (%)	37 (54)	27 (57)	10 (48)	.45
Diabetes n (%)	14 (21)	10 (21)	4 (19)	.99
Atrial fibrillation n (%)	39 (57)	26 (55)	13 (62)	.61
Coronary artery disease n (%)	13 (19)	10 (21)	4 (19)	.83
3-Month modified Rankin Scale 0-2 (%)	37 (54)	29 (62)	8 (38)	.06
Total infarct volume at 24 h (ccm), median (IQR)	3.1 (45.0)	3.6 (32.7)	2.2 (56.1)	.61
Hemorrhagic complication at 24 h (%)	13 (19)	8 (17)	5 (24)	.53
– Major space-occupying effect (PH2 or PHr2, %)	4 (6)	3 (7)	1 (5)	.78
Postinfarct edema COED2 or COED3 (%)	12 (18)	7 (15)	5 (24)	.40

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; CIL, chronic ischemic lesion in admission imaging; COED, cerebral edema; IVT, intravenous thrombolysis; NCCT, non–contrast-enhanced computed tomography; NIHSS, National Institutes of Health Stroke Scale; P_1, *P*-value between groups; PH, parenchymal hemorrhage; PHr, parenchymal hemorrhage remote; TICI, Thrombolysis in Cerebral Ischemia.

circulation territories. Thirty-one patients (46%) had chronic WMLs, 11 of them (16%) had grade 2 or 3 (moderate or severe). The presence of CILs and WMLs were highly correlated: 81% of patients with CILs also had WMLs, whereas only 30% of patients without CILs had WMLs.

Eight of the 21 patients (38%) with chronic ischemic lesions achieved good clinical outcome at 3 months compared with 29 of the 47 (62%) patients among those without chronic infarcts (*P* = .06, Table 2). The same pattern was seen when lacunar lesions, lesion multiplicity, and chronic white matter lesions were examined separately, but with a milder trend toward statistical significance (Table 2). Considering the borderline statistically significant association of not having chronic ischemic lesions in admission imaging with good clinical outcome, a binary logistic multivariable model with good 3-month clinical outcome as the dependent variable and variables with *P* value less than .2 in univariable analysis (Table 1) and admission NIHSS included as covariates was devised. As presented in Table 3, not having chronic ischemic lesions emerged as the only statistically significant covariate that predicted good clinical outcome, increasing the odds of good outcome almost 4-fold (odds ratio = 3.7, 95% confidence interval = 1.0-10.7, *P* = .05). Figure 1 depicts the distribution of mRS among those with and without CIL(s). The major difference is the shift of patients from mRS

Table 2. *Number and proportion of patients with different chronic ischemic and white matter lesions who had good clinical outcome (mRS ≤ 2)*

	Number (proportion) mRS ≤ 2		
	Yes	No	*P* value
Chronic ischemic lesion(s)	8 (38%)	29 (62%)	.06
Chronic lacunar lesion(s)	5 (39%)	32 (59%)	.18
Multiple chronic lesions	5 (36%)	32 (60%)	.10
Chronic WM lesions	15 (48%)	22 (61%)	.30

Abbreviation: WM, white matter.

Table 3. *Logistic regression analysis for good clinical outcome (mRS ≤ 2)*

	MT (H-L = .49, C = .67)		
	Odds ratio	CI 95%	*P* value
No chronic ischemic lesions	3.7	1.0-10.7	.05
Male sex	1.5	.51-4.6	.45
Age	1.04	.95-1.1	.37
TICI 2a or worse	.36	.08-1.6	.19
Admission NIHSS	.92	.83-1.03	.16

Abbreviations: C, C statistic; H-L, Hosmer-Lemeshow significance. Odds ratios are per year for age and per 1 point for NIHSS.

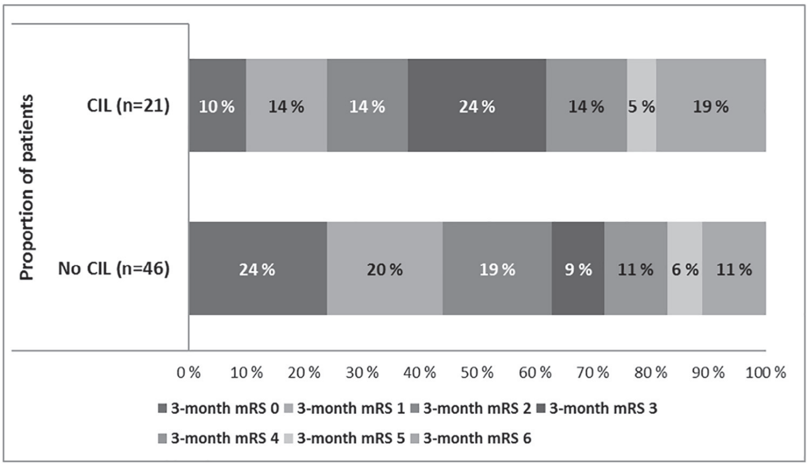

Figure 1. *The distribution of 3-month mRS among patients with and without chronic ischemic lesions. Abbreviations: CIL, chronic ischemic lesion; mRS, modified Rankin Scale.*

less than or equal to 2 categories to mRS = 3 in the presence of CILs.

Discussion

Predictors of good clinical outcome in the context of MT of the acute anterior circulation stroke have been extensively studied in the recent years. Younger age, lower admission NIHSS, distal site of occlusion, adequate collateral circulation, small irreversibly ischemic volume in admission imaging, missing or mild chronic WMLs, successful recanalization, and short process times and other delays are associated with good 3-month clinical outcomes.[9,13,17-22] Pre-existing infarctions have received surprisingly little attention in these studies. Further, baseline imaging data of CILs were not reported in the pooled analysis of Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke, European Cooperative Acute Stroke Study, and National Institute of Neurological Disorders and Stroke intravenous thrombolysis treatment stroke trials[23] or in the SITS-MOST thrombolysis study.[15] We investigated the impact of CILs on the prognosis of sexagenarian and older patients treated with MT for acute large-vessel occlusion of the MCA or distal ICA. We found that after accounting for confounding factors, the absence of CILs emerged as an independent predictor of good clinical outcome.

Patients with total infarct volume greater than 100 ccm in the 24-hour follow-up NCCT were excluded from analysis because of the high likelihood of poor clinical outcome just because of the extensive acute lesion.[14] Considering the epidemiology of CILs and ischemic stroke, the protocols and results of the recent randomized controlled clinical trials and the general dependence of functional status on age, we restricted our analysis to previously functionally independent sexagenarian and older patients with anterior circulation stroke.

In our study, the most notable difference in the distribution of mRS between the CIL and the no CIL groups was the shift from mRS less than or equal to 2 categories to mRS = 3 in the presence of CILs, pushing patients just beyond functional independence and into being classified as having experienced poor clinical outcome. It is debatable whether moderate disability (mRS = 3) is still an acceptable or even desirable outcome compared with mRS 4-6. There were similar but milder shifts to higher mRS categories also in the mRS 4-6 range, but these differences did not yield statistical significance in our small cohort (Fig 1).

The mechanisms of action of CILs worsening the outcome of acute stroke that have been proposed include (1) the effect of disease burden that stacks deficits and decreases the compensatory capacity of the brain even if the patient had fully recovered from the previous episodes or the episodes were symptomless, (2) "hits" in multiple systems that potentiate the deleterious effect of a new ischemic lesion, and (3) indicator of poor collateral circulation or general cardiovascular disease burden and thus higher probability of more severe end points.[7] Our findings did not provide support to the third hypothesis considering that there were no significant differences between the groups in the integrity of collateral circulation or in stroke clinical risk factors.

Leukoaraiosis has been shown to predict poor outcome after acute large-vessel occlusion and is associated with hemorrhagic complications and futile recanalization.[8-12] Ischemic stroke outcomes are worse with larger leukoaraiosis volumes and may be affected differentially by leukoaraiosis depending on stroke subtype.[24] Presence of severe small-vessel disease on baseline CT graded based on the extent of leukoaraiosis and chronic lacunar infarcts is associated with poor clinical outcome in patients treated with IVT.[25] In our study, almost half of the patients had chronic WMLs, and in one-third of these patients these were graded moderate or severe. Although having WMLs was not a statistically significant independent predictor of clinical outcome, the presence of WMLs was strongly associated with having CILs and may potentiate their detrimental effect. A grading system capturing both these aspects of chronic ischemic injury might have added prognostic value.[25]

Our study has limitations. The formation of this observational MT cohort was clinically driven and as such nonrandomized; there can be selection biases. Because of the relatively small number of patients available for analysis, subgroup analyses may be underpowered to detect small differences between the subgroups and parse apart the effect of CILs and WMLs. The exact prestroke mRS had not been prospectively recorded (other than it being ≤2) for most patients in our cohort. Generally, among elderly patients, mRS = 1 or 2 is a common finding of numerous etiologies, many unrelated to stroke. NCCT at 24 hours is not the ideal method to estimate final infarct volume because infarcted parenchyma and surrounding edemic tissue cannot be accurately delineated. Thus, the volumes reported probably exaggerate the actual final infarct volumes.

Conclusions

Chronic cortical and lacunar infarcts in admission imaging are associated with poor clinical outcome in sexagenarian and older patients treated with MT for acute large-vessel occlusion of the MCA. This preliminary finding having potential implications for design of future clinical trials and treatment decision-making should be verified in larger cohorts.

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PUBLICATION
II

Carotid Artery Stenosis Is Associated with Better Intracranial Collateral Circulation in Stroke Patients

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Carotid Artery Stenosis Is Associated with Better Intracranial Collateral Circulation in Stroke Patients

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Keywords

Ischemic stroke · Carotid stenosis · Collateral circulation · Mechanical thrombectomy

Abstract

Background: Adequate collateral circulation improves the clinical outcome of ischemic stroke patients. We evaluated the influence of ipsilateral carotid stenosis on intracranial collateral circulation in acute stroke patients. ***Methods:*** We collected the data of 385 consecutive acute stroke patients who underwent mechanical thrombectomy after multimodal computed tomography (CT) imaging in a single high-volume stroke center. Patients with occlusion of the first segment (M1) segment of the middle cerebral artery were included. We recorded baseline clinical, laboratory, procedural, and imaging variables and technical, imaging, and clinical outcomes. The effect of carotid stenosis on intracranial collateral circulation was studied with appropriate statistical tests and ordinal regression analysis. ***Results:*** Fifty out of the 247 patients eligible for analysis had severe ipsilateral carotid stenosis (≥75%). These patients were 4-times more likely to have very good intracranial collaterals (Collateral Score 3–4, $p = 0.001$) than the nonstenotic and slightly stenotic (<75%) patients. The severely stenotic patients had a longer mean operation time (41 vs. 29 min to reperfusion, respectively, $p = 0.001$). Nevertheless, 54% of severely stenotic patients had good 3-month clinical outcome (modified Rankin Scale ≤2) with no significant difference between the 2 groups. ***Conclusions:*** Carotid artery stenosis of over 75% of vessel diameter was associated with better intracranial collateral circulation of patients with acute ischemic stroke. This did not significantly change the 3-month clinical outcome.

Introduction

Collateral circulation protects the brain parenchyma from ischemic damage in case the normal antegrade flow is obstructed. This system is of crucial importance in patients presenting with acute ischemic stroke due to large vessel occlusion (LVO) [1]. The integrity of collateral circulation correlates with the progression of irreversible ischemic changes. Thus, LVO patients are an optimal population to investigate the effect of leptomeningeal and upstream collateral circulation systems. The currency of good collaterals manifests as having larger salvageable penumbra and permitting longer delays in achieving reperfusion [2, 3]. Factors such as age, chronic hypertension, diabetes, blood glucose levels, and systolic blood pressure at presentation influence the integrity of collat-

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eral circulation [4–6]. The effect of chronic carotid stenosis is controversial. Dankbaar et al. [7] found no correlation between carotid stenosis and collateral circulation in patients having occlusion of the first segment of middle cerebral artery (MCA). Conversely, Guglielmi et al. [8] recently reported an association between carotid stenosis and better cerebral collateral circulation.

The objective of this investigation was to clarify whether ipsilateral carotid artery stenosis influences the collateral status in patients presenting with acute MCA occlusion.

Methods

Participants and Variables

We conducted an observational study on 385 consecutive patients who underwent mechanical thrombectomy (MT) to treat acute LVO in a single high-volume stroke center. The patients were treated between December 2013 and 2017. The inclusion criteria for this study were occlusion of the first segment of the MCA (M1) and access to a sufficient quality admission CT angiography (CTA) study to enable assignment of the Collateral Score (CS). Two hundred and forty-seven patients met these criteria and 138 patients were excluded: 22 patients had vertebro-basilar occlusion, 109 patients had anterior circulation occlusion without occlusion in the M1-segment, and 7 patients had poor quality CTA studies. Baseline clinical characteristics included age, gender, and clinical risk factors for ischemic stroke (hypertension, diabetes, coronary heart disease, atrial fibrillation) that were collected from the patient records. National Institutes of Health Stroke Scale (NIHSS) score at the admission, process time points, modified thrombolysis in cerebral ischemia (mTICI) grading evaluated with DSA at the end of the procedure and procedural complications had been prospectively collected. A follow-up noncontrast-enhanced computed tomography (NCCT) was performed 24 h after MT. The clinical outcome measure was the modified Rankin Scale (mRS), evaluated 3 months after the stroke based on a follow-up visit to neurologist or a phone interview by neurologist. Fifteen patients could not be reached for this control because they resided in another hospital district or abroad, or for other reasons. Admission NIHSS was not available for 7 patients because of sedation during transportation. The exact onset of symptoms was unknown or unreliable in 8 cases. All other data were available for all patients. In wake-up strokes, the onset of symptoms was recorded based on when last seen symptomless. The study was approved by the institutional review board and adhered to the Helsinki Declaration. A written consent was not deemed necessary by the review board.

Imaging Protocol, Clinical Decision Making, and Image Analysis

The initial imaging evaluation consisted of NCCT and CTA. CT perfusion (CTP) was optional and was performed in 182 cases (74%). The selection of patients as candidates for MT was based on absence of extensive irreversible ischemic changes and hemorrhage in NCCT, evaluation of the amount of salvageable tissue in CTP imaging (when available) and LVO in CTA. The decision to proceed to MT was multidisciplinary involving a stroke neurologist and a neurointerventional radiologist. Patients referred to our institution from other hospitals were reevaluated with at least NCCT upon arrival before proceeding to the angiographic suite to rule out bleeding and extensive irreversible ischemic lesion. In the case of wake-up strokes, CTP was performed if no large infarct was seen in NCCT. Imaging examinations were reviewed using dedicated medical imaging workstations. CTA images were reviewed from raw data and MIP images. The Alberta Stroke Program Early CT Score was retrospectively assessed from admission NCCT images. The version of CS used is described in Souza et al. [9]. The location of the clot was recorded based on the proximal end of the occlusion. The examinations were reviewed in the order NCCT, CTA, and finally DSA. In cases the scoring or assignment differed, a consensus opinion was agreed on. Carotid stenosis was determined on CTA using the NASCET criteria. The reviewers were blinded to the clinical data apart from the side and nature of the acute symptoms. Validation of the scorings with intraclass correlation coefficients and Cohen's kappa values can be found in our previous publication [10].

Recanalization Therapies

Please see online supplemental Material (for all online suppl. material, see www.karger.com/doi/10.1159/000506826).

Imaging Parameters

Please see online supplementary Material.

Statistics

The data were analyzed with SPSS version 25 (SPSS Inc., Chicago, IL, USA). The analyses were performed using the maximum number of patients available with regard to missing data. Group comparisons were performed by using the Student *t* test, the chi-square test, the Fisher exact test, and the Mann-Whitney U test according to the type and distribution properties of the variable studied. Patients with CS 3 and 4 were combined together due to small number of patients (6) in the CS 4 group. Patients who had 3-month mRS ≤2 were considered to have good clinical outcome. An mTICI score 2b–3 was considered a good recanalization result. Ordinal regression analyses using different CSs as dependent variable were performed, and OR with 95% CI was calculated for each covariate. A p value <0.05 was considered statistically significant.

Results

Baseline Characteristics

The inclusion criteria were met by 247 patients. Sixty-five patients (26.3%) had an internal carotid artery terminus1 (ICA-T) occlusion and the rest had an isolated M1 segment occlusion of which 80 (32.3%) had a proximal M1 and 102 (41.3%) a distal M1 occlusion. Fifty-one patients (21%) had a severe (≥75%) ipsilateral carotid stenosis (50 in the ICA, and 1 in the common carotid artery). The mean delay from symptoms onset to CT imaging (onset-to-CT time) was 160 min (SD 113 min). The main baseline and admission imaging characteristics between the patients with different CS statuses are summarized in

Table 1. Demographic, baseline, and admission imaging characteristics of all patients by the CS

Characteristic	All patients (n = 247), n (%)	CS, n (%)				P_1
		0	1	2	3–4	
Age, years, mean (SD)	68 (12)	70 (11)	67 (12)	70 (11)	67 (14)	0.219
Gender, female	104 (42)	12 (5)	17 (7)	48 (19)	27 (11)	0.4
NIHSS, median (IQR)	17 (6)	18 (6)	17 (5)	17 (8)	17 (8)	0.052
IVT (n = 245)	149 (61)	15 (6)	32 (13)	65 (27)	37 (15)	0.067
Carotid stenosis ≥75%	51 (21)	4 (2)	5 (2)	18 (7)	24 (10)	**0.003**
ASPECTS, median (IQR)	8 (3)	7 (4)	8 (3)	9 (2)	9 (3)	**<0.001**
Onset-MT (n = 236), min, mean (SD)	192 (112)	140 (76)	189 (97)	193 (108)	220 (134)	**0.012**
CAD	36 (15)	6 (2)	3 (1)	22 (9)	5 (2)	**0.016**
Diabetes	40 (16)	7 (3)	3 (1)	21 (9)	9 (4)	0.101
Atrial fibrillation	145 (59)	23 (9)	28 (11)	63 (26)	31 (13)	0.058
Hypertension	124 (50)	15 (6)	18 (7)	51 (21)	40 (16)	0.168

CS, Collateral Score; NIHSS, National Institutes of Health Stroke Scale; IVT, intravenous thrombolysis; ASPECTS, Alberta Stroke Program Early CT Score; MT, mechanical thrombectomy; Onset-MT, delay from symptoms onset to groin puncture of MT (in minutes); CAD, coronary artery disease; P_1, p value between groups. Bold values represent statistically significant p values.

Table 2. Characteristics of MT operation and clinical outcome between groups with or without significant carotid stensosis

Characteristic	All patients (n = 247)	Stenosis		P_1
		<75% (196)	≥75% (51)	
Onset-MT (n = 236), min, mean (SD)	192 (112)	194 (118)	184 (81)	0.575
MT operation time (n = 235), min, mean (SD)	32 (26)	29 (24)	41 (30)	**0.004**
mTICI 2b–3 (n = 246), n (%)	228 (93)	183 (93)	45 (90)	0.414
3-Month mRS ≤2 (n = 232), n (%)	133 (57)	109 (58)	24 (53)	0.546

MT, mechanical thrombectomy; MT operation time, time between groin punture and achieved recanalization; mTICI, modified thrombolysis in cerebral infarction score; mRS, modified Ranking Scale; Onset-MT, delay from symptoms onset to groin puncture of MT (in minutes); P_1, p value between groups. Bold value represents statistically significant p value.

Table 1. The median NIHSS at admission was 17 (interquartile range 6), and the mean delay from symptoms onset to groin puncture (onset-to-MT time) was 192 min (SD 111 min).

The Timeline and Outcome Differences between Patients with or without Severe Carotid Stenosis

The onset-to-CT time was not significantly different between the patients with or without severe carotid stenosis (153 vs. 162 min, respectively, p = 0.605). The duration of MT (time from groin puncture to reperfusion) was significantly longer in severely stenotic patients (41 vs. 29 min, respectively, p = 0.004). The mean delay from onset to reperfusion was not significantly different (229 vs. 222 min, p = 0.734). The proportions of good recanalization (mTICI 2b–3) and good 3-month clinical outcome (mRS ≤2) were slightly more favorable among patients without severe carotid stenosis, but the differences were not statistically significant: mTICI 2b–3 was achieved in 90% of patients with severe carotid stenosis and in 93% of patients without (p = 0.414). At 3 months, 53% of severely stenotic patients and 58% of patients without severe carotid stenosis had mRS 0–2 (p = 0.546, Table 2).

The Factors Influencing Intracranial Collateral Circulation

Ordinal logistic regression analysis, using CS at admission as dependent variable, is detailed in Table 3. Among patients selected for MT, each 10 min of additional delay from the onset of the symptoms to CT imaging was associated with 6% odds of better CS (OR 1.06, 95% CI 1.031–1.094, p < 0.001). Female gender also sig-

Table 3. Ordinal logistic regression analysis of CS at admission evaluated on CT

	OR	Significant	95% CI
Age, years	0.98	0.240	0.956–1.011
Gender, female	2.27	**0.008**	1.236–4.158
Systolic BP	1.01	0.211	0.996–1.020
Blood glucose	0.93	0.392	0.776–1.105
Onset-CT/10	1.06	**<0.001**	1.031–1.094
ASPECTS	1.55	**<0.001**	1.315–1.837
Hypertension	1.79	0.051	0.998–3.222
CAD	1.07	0.864	0.472–2.440
Atrial fibrillation	0.62	0.135	0.334–1.157
Diabetes	0.80	0.618	0.334–1.919
Carotid stenosis ≥75%	4.01	**0.001**	1.782–9.007

Model Fitting significance <0.001, Goodness-of-Fit significance 0.609, Cox and Snell significance 0.297, test of parallel lines 0.875. Bold values represent statistically significant *p* values.

CS, Collateral Score; BP, blood pressure; Onset-CT/10, delay from symptoms onset to CT in thrombectomy center (for every 10 min); ASPECTS, Alberta Stroke Program Early CT Score; CAD, coronary artery disease.

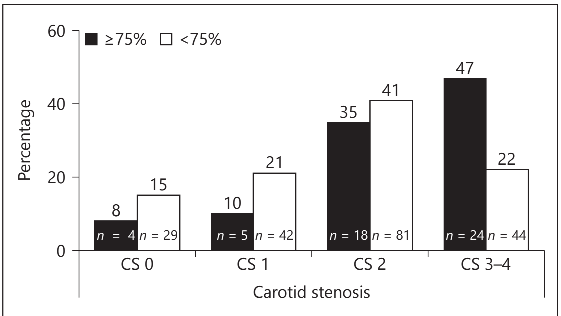

Fig. 1. Proportion of patients with or without significant carotid stenosis by CS. Brackets indicate the statistical significance of the difference between the 2 groups. CS, Collateral Score; *n*, number of patients in group.

nificantly increased the odds of better CS. Chronic hypertension was borderline significantly associated with higher CS (OR 1.79, $p = 0.051$). Those patients having severe ipsilateral carotid stenosis were 4 times more likely to have better collaterals (OR 4.01, 95% CI 1.782–9.007, $p = 0.001$). Three sensitivity analyses were performed by recalculating the model while including patients with acute occlusion in any position from the proximal ICA to distal M1, including ICA only occlusions while excluding M1 only occlusions and including M1 only occlusions. The result for severe carotid stenosis remained essentially the same with OR 3.19 (95% CI 1.589–6.412, $p = 0.001$), OR 2.85 (95% CI 1.114–7.286, $p = 0.029$), and OR 3.31 (95% CI 1.181–9,291, $p = 0.023$), respectively.

The Distribution of CSs by Carotid Stenosis Status

Figure 1 depicts the interplay of severe carotid stenosis with CS. Very good collaterals (CS 3–4) were found in 47% of all patients presenting severe carotid stenosis, while only 22% of patients with a nonstenotic or slightly stenotic carotid artery had very good collaterals ($p < 0.001$). The proportion of poor collateral circulation (CS 0–1) was significantly higher in the nonstenotic/slightly stenotic group in comparison to the severely stenotic patients (36 vs. 18%, $p = 0.012$). Overall, there was a shift toward better CS in severely stenotic patients.

Discussion

Collateral circulation is an established predictor of clinical outcome in the acute ischemic stroke population [4, 11, 12]. The factors influencing the integrity of the collateral circulation are not completely known. Old age, hypotension, or overt hypertension at the presentation, high blood glucose, and chronic hypertension have been linked with poor collateral status [4, 6, 13]. The role chronic ipsilateral carotid stenosis plays in this setting is controversial [7, 8].

We found that the presence of a severe ipsilateral carotid stenosis increases the odds of good CS 4-fold. This finding is in line with the results of a recent study by Guglielmi et al. [8]. Their study included also patients with more peripheral clot locations. Based on anatomical considerations, we believe that limiting the analysis to M1 occlusions more accurately portrays the development and reflects the impact of the leptomeningeal collateral circulation by decreasing the effect of the variability of the circle of Willis. On the other hand, the setup of the study by Dankbaar et al. [7] is similar to that of our study. However, they found no correlation between carotid stenosis and the integrity of the collateral circulation. Nevertheless, the number of patients with ipsilateral stenosis in their study is low, which could affect the results.

Few studies have reported an association between advanced age and poor collateral circulation [4, 6]; we did not find age to have a significant effect in our cohort. This can be due to elderly patients with insufficient collateral circulation and hemodynamic perturbations having too extensive irreversible ischemic changes at presentation to be eligible for MT.

History of chronic hypertension had a borderline significant association with having improved collateral circulation (OR 1.79, $p = 0.051$). This is contrary to the findings of 2 previous publications [14, 15]. There is no obvious theoretical explanation for this borderline finding. We also evaluated systolic blood pressure at admission in the model and a higher pressure had a nonsignificant positive effect in collateral circulation as expected. All the chronically hypertensive patients had been prescribed adequate medication which may play a role, but the data about meeting the target blood pressures were not available.

Onset-to-recanalization time is a prognostic factor with longer delays contributing toward poorer clinical outcome. We found no significant difference in onset-to-groin puncture times between patients with or without severe carotid stenosis. However, the severe carotid stenosis population had a significantly longer groin puncture-to-recanalization time. Nevertheless, this was not reflected in the 3-month clinical outcome. Correspondingly, there was no statistically significant difference between the groups in the overall onset-to-recanalization time or in the rate of successful recanalization (mTICI 2b–3). It appears that the better collateral circulation associated with severe carotid stenosis compensates for the longer duration of the procedure and other possible negative determinants associated with having more advanced atherosclerotic lesions.

The inherent limitations of this study are the relative small sample size that does not permit subgroup analyses of, for example, Ipsilateral tandem stenosis, and the observational and retrospective design which is prone to selection bias. The single, tertiary care center setup and limiting the analysis to the MT patients potentially limits the generalizability of the findings. Missing data may introduce biases but considering the robustness of the results in the sensitivity analyses this risk appears small.

Conclusions

The presence of severe carotid stenosis correlates with better intracranial collateral circulation in patients presenting with acute ischemic stroke due to LVO. However, this did not translate into difference in the 3-month clinical outcome.

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Statement of Ethics

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Disclosure Statement

All authors declare that they have no conflicts of interest relevant to this manuscript.

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Author Contributions

J.-P.P.: conception and design of the work, acquisition analysis and interpretation of data, drafting of the work and final approval. P.J.: acquisition of clinical data, revising of the work and final approval. N.S.: conception of the work, analysis and interpretation of data, revising the work and final approval. S.P.: conception and design of the work, acquisition analysis and interpretation of data, revising and final approval.

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PUBLICATION
III

Anemia Predicts Poor Clinical Outcome in Mechanical Thrombectomy Patients with Fair or Good Collateral Circulation

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Anemia Predicts Poor Clinical Outcome in Mechanical Thrombectomy Patients with Fair or Good Collateral Circulation

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Keywords

Ischemic stroke · Anemia · Collateral circulation · Mechanical thrombectomy

Abstract

Background and Purpose: Anemia predicts poor clinical outcome of ischemic stroke in the general stroke population. We studied whether this applies to those treated with mechanical thrombectomy for proximal anterior circulation occlusion in the setting of differing collateral circulation. ***Methods:*** We collected the data of 347 consecutive anterior circulation stroke patients who underwent mechanical thrombectomy after multimodal CT imaging in a single tertiary stroke care center. Patients with occlusion of the internal carotid artery and/or the first segment of the middle cerebral artery were included. We recorded baseline clinical, laboratory, procedural, and imaging variables, and the technical, imaging, and clinical outcomes. Differences between anemic and nonanemic patients were studied with appropriate statistical tests and binary logistic regression analysis. ***Results:*** Ninety-four out of the 285 patients eligible for analysis had anemia, and 243 had fair or good collateral circulation (collateral score, CS, >0). Fifty-four percent of the patients experienced good 3-month clinical outcome (modified Rankin Scale ≤2). In pooled analyses of the CS 1–4 and 2–4 ranges, nonanemic patients had good clinical outcome significantly more often (p < 0.001 for both). This effect was not seen in patients with poor collateral circulation (CS = 0). Nonanemic patients had significantly better odds of good clinical outcome (OR = 2.6, 95% CI 1.377–5.030, p = 0.004) in a binary regression model. A 0.1 g/dL increase in hemoglobin improved the odds of good clinical outcome by 2% (OR = 1.02, 95% CI 1.002–1.044, p = 0.03). ***Conclusions:*** Low hemoglobin on admission predicts poor clinical outcome in mechanical thrombectomy patients with fair or good collateral circulation.

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Introduction

Anemia and ischemic stroke are common conditions among the elderly [1]. Anemia has been shown to be related to poorer clinical outcome in the general ischemic stroke population [2–6]. However, very high hemoglobin levels may also have a debilitating effect on the clinical outcome [2, 7]. One report found that anemia has no effect on the 3-month outcome of patients suffering from ischemic stroke [8].

Mechanical thrombectomy (MT) has been proven to be a superior treatment of acute large vessel occlusion (LVO) strokes in several randomized trials [9]. Despite successful recanalization of the ischemic territory in post-MT digital subtraction angiography, the patient occasionally experiences poor clinical outcome. Adequate collateral circulation into the ischemic area is crucial to having a salvageable penumbra and also permits longer delays in achieving reperfusion and a favorable clinical outcome [10, 11]. Thus, the integrity of the collateral circulation is an important predictor of clinical outcome in patients undergoing MT [12, 13].

The objective of this investigation was to clarify how low hemoglobin at presentation influences the 3-month clinical outcome of MT of acute anterior circulation LVO at different integrities of the collateral circulation.

Methods

Participants and Variables

We conducted an observational study on 347 consecutive patients who underwent MT to treat acute anterior circulation occlusion (LVO) in a single stroke center. The patients were treated between December 2014 and December 2017. The inclusion criteria were occlusion of the internal carotid artery (ICA) and/or the first segment of middle cerebral artery (M1). In total, 285 patients met these criteria, and 62 patients were excluded because of a more distal occlusion. The baseline clinical characteristics (Table 1) were collected from the patient records. Hemoglobin values on admission were recovered from the laboratory database. According to the calibration of the local hematological laboratory, a patient was considered anemic when hemoglobin was <11.7 g/dL in females and <13.4 g/dL in males. National Institutes of Health Stroke Scale (NIHSS) scores at presentation, process time points, modified Thrombolysis in Cerebral Ischemia (mTICI) grading evaluated with digital subtraction angiography at the end of the procedure, and procedural complications had prospectively been stored to patient records. A follow-up non-contrast-enhanced computed tomography (NCCT) was performed 24 h after MT. The clinical outcome measure was the 3-month modified Rankin Scale (mRS) evaluated 3 months after the stroke based on a follow-up visit to or a phone interview by a neurologist. Nineteen patients could not be reached for this control. Admission NIHSS could not exactly be evaluated for 9 patients because of sedation during transportation. In 3 cases, NCCT was of such quality that ASPECTS could not be reliably calculated. Admission hemoglobin was missing for 12 patients. The exact onset of symptoms was unknown or unreliable in 12 cases. The study was approved by the institutional review board and adhered to the Declaration of Helsinki. A written consent was not deemed necessary by the review board.

Imaging and Clinical Decision Making

The initial imaging evaluation consisted of NCCT and CT angiography. CT perfusion was optional and performed in 203 cases (71%). The decision to proceed to MT was multidisciplinary involving an acute neurologist and a neurointerventional radiologist. Patients that

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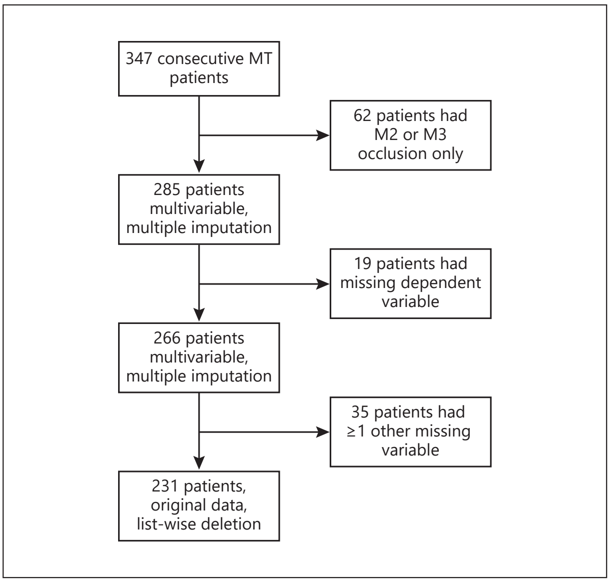

Fig. 1. Flowchart of patient selection and analysis.

were not functionally independent and/or had short life expectancy because of uncontrolled malignant disease were considered noneligible for MT. Patients referred to our institution from other hospitals were reevaluated with at least NCCT upon arrival to rule out bleeding and extensive irreversible ischemic lesions. Image analysis and imaging parameters are described in our previous publication [14].

Recanalization Therapies

Please see the online supplementary Material (for all online suppl. Material, see www.karger.com/doi/10.1159/000510228).

Statistical Analysis

The data were analyzed with SPSS version 25 (SPSS Inc., Chicago, IL, USA). A p value <0.05 was considered statistically significant. Univariable analyses were performed using the maximum number of patients available considering missing data. Group comparisons were performed using the Student t test, the χ^2 test, the Fisher exact test, and the Mann-Whitney U test according to the type and distribution properties of the variable studied. Patients with collateral scores (CS) from 2 to 4 were regarded as having good collateral vessel filling and those with a CS of 1 fair. Patients who had 3-month mRS ≤2 were considered to have experienced good clinical outcome. mTICI scores 2b–3 were considered a good recanalization result. Hemoglobin value was normalized by subtracting the lower bound of the normal range from the value measured on admission for each gender. Multivariable binary logistic regression analyses using good clinical outcome as dependent variable were performed and odds ratios (OR) with 95% confidence intervals (CI) were calculated for each covariate. We discovered no pattern in the distribution of missing data. We used chained equation multiple imputation to generate approximations for the missing data used in the multivariable models, and 1.7% (78/4,482) of the data points were missing in 9/16 variables included in the full model. Both the independent and depended variables were imputed in the full model using 5 iterations.

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Table 1. Demographic, baseline, and admission imaging characteristics of all patients by the clinical outcome at 3 months

Characteristics	All patients (*n* = 285)	RS >2 (*n* = 122)	mRS ≤2 (*n* = 144)	P_1
Mean age (SD), years	68 (11)	71 (10)	67 (13)	**0.01**
Female sex, *n* (%)	115 (40)	55 (45)	52 (36)	0.14
Median NIHSS (IQR) (*n* = 276)	16.5 (7)	17 (6)	15.5 (8)	**0.005**
Intravenous thrombolysis, *n* (%)	175 (61)	71 (59)	92 (65)	0.31
ICA occlusions, *n* (%)	118 (41)	60 (49)	46 (32)	**0.004**
Median ASPECTS (IQR) (*n* = 282)	9 (3)	8 (3)	9 (2)	**0.01**
Mean onset-to-groin puncture (SD), min (*n* = 273)	200 (119)	202 (113)	196 (117)	0.72
Collateral score >0, *n* (%)	243 (85)	94 (81)	133 (93)	**0.004**
mTICI 2b–3, *n* (%)	261 (92)	109 (89)	136 (95)	0.08
Hypertension, *n* (%)	139 (49)	68 (56)	64 (44)	0.07
Anemia on admission, *n* (%)	94 (33)	52 (44)	36 (27)	**0.003**
Mean hemoglobin (SD), g/dL				
Female (*n* = 110)	12.5 (1.4)	12.2 (1.5)	12.9 (1.3)	**0.02**
Male (*n* = 163)	13.7 (1.6)	13.5 (1.6)	13.8 (1.7)	0.34
Diabetes, *n* (%)	46 (16)	25 (21)	20 (14)	0.15
Atrial fibrillation, *n* (%)	164 (58)	72 (59)	83 (58)	0.82
Coronary artery disease, *n* (%)	42 (15)	17 (14)	24 (17)	0.54

P_1, *p* value between groups; ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction score; NIHSS, National Institutes of Health Stroke Scale. Boldface denotes statistical significance.

Table 2. Anemia, etiological breakdown (*n* = 94)

	n (%)
B_{12} deficiency	2 (2.1)
Iron deficiency	2 (2.1)
GI bleeding	3 (3.2)
Urinary tract bleeding	1 (1.1)
Soft tissue bleeding	2 (2.1)
Postoperative anemia	1 (1.1)
Blood thinning medication	2 (2.1)
Immune suppression sequelae	1 (1.1)
Chronic rheumatoid disease	4 (4.3)
Chronic renal failure	2 (2.1)
Mild anemia of unclear etiology after diagnostic workup	74 (78.7)

Results

Baseline Characteristics

The inclusion criteria were met by 285 patients (Fig. 1), and 118 patients (41%) had ICA as the most proximal site of occlusion, the rest in the M1 segment. The baseline characteristics along with differences between the patients with good (mRS ≤2) and poor 3-month clinical outcome are summarized in Table 1. The median NIHSS on admission was 16.5 (IQR 7), the mean onset-to-groin puncture time was 200 min (SD 119 min), and 243 patients (85%) had fair or good collateral circulation (CS 1–4). Ninety-four patients (33%) had anemia (etiological factors are outlined in Table 2). Anemia was usually mild, i.e., hemoglobin levels were

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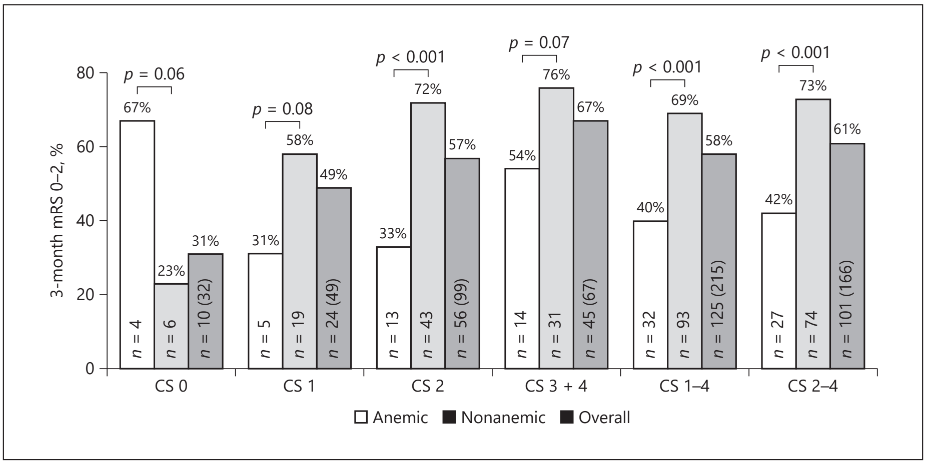

Fig. 2. The proportion of good clinical outcome (3-month modified Rankin Scale, mRS, ≤2) in the anemic and nonanemic groups in proximal occlusions by collateral score (CS). Brackets indicate statistically significant differences between 2 groups. *n*, number of patients in each group.

0.9 g/dL below the lower limit of the median (IQR 1 g/dL). The 3-month mRS was recorded from 266 patients of whom 144 (54%) had good clinical outcome. Advanced age, high NIHSS score, ICA occlusion, acute ischemic changes on the admission NCCT, poor collaterals, suboptimal recanalization result, and low hemoglobin value on admission especially in females were significantly associated with poor clinical outcome. There were no significant differences in baseline variables between these patients and the 19 patients with missing 3-month mRS apart from the proportion of ICA occlusions that was higher in the latter group (63.2 vs. 39.8%, $p = 0.05$).

Effect of Anemia on the 3-Month Clinical Outcome in Different CS Categories

The dichotomized 3-month clinical outcomes of anemic and nonanemic patients with different collateral statuses are described in Figure 2. As expected, the 3-month clinical outcome was consistently better in patients with higher CS. Nonanemic patients had significantly better outcomes in the CS = 2 groups (mRS ≤2, 72 vs. 33%, $p < 0.001$). There was a statistical trend in the same direction in the CS = 1 and CS = 3–4 groups ($p = 0.08$ and $p = 0.07$, respectively). Paradoxically, anemic patients had a trend towards better outcomes in the CS = 0 group. However, this result is based on a small number of patients and is probably coincidental. In pooled analyses of the CS 1–4 and 2–4 ranges (vs. CS = 0 and CS = 0–1, respectively), nonanemic patients experienced good outcome significantly more often ($p < 0.001$ for both). Figure 3 depicts shift analysis of the 3-month mRS in anemic and nonanemic patients with CS 1–4 (fair to good collateral circulation). The proportion of patients in mRS categories 0–2 is larger in the nonanemic group whereas anemic patients had significantly higher mortality (mRS = 6, $p < 0.001$).

Anemia and Hemoglobin Value Are Independent Predictors of Good 3-Month Clinical Outcome

Binary logistic modeling for the dichotomized 3-month clinical outcome was performed using all the baseline and imaging variables described in Table 1 as covariates considering that they are all theoretically meaningful predictors of clinical outcome. Multiple imputation

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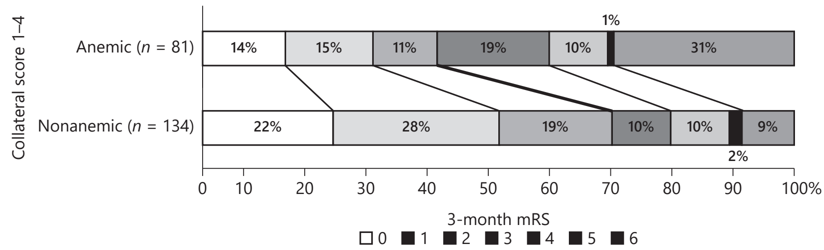

Fig. 3. The distributions of 3-month modified Rankin Scale (mRS) in the anemic and nonanemic groups in proximal occlusions, collateral scores 1–4. The thick line indicates the division between functional independence (mRS ≤2, left-hand side) and dependence (right-hand side).

was used to generate approximations for missing data to avoid 54 patients from being dropped in list-wise deletion. The results for dichotomized hemoglobin (anemic/nonanemic) are outlined in Table 3. Not having anemia improved the odds of good clinical outcome 2.6-fold (95% CI = 1.377–5.030, $p = 0.004$). Younger age, higher ASPECTS (admission NCCT), higher CS, higher mTICI score, and more distal sites of occlusion were also significantly associated with good clinical outcome. The analysis was repeated using hemoglobin values normalized with respect to the lowest normal range value (online suppl. Table 1). A 0.1 g/dL increase in hemoglobin improved the odds of good clinical outcome by 2% (OR = 1.02, 95% CI 1.002–1.040, $p = 0.03$). Models with no imputation (original data, $n = 231$) and the independent variables only being imputed ($n = 266$) were calculated as sensitivity analyses (online suppl. Tables 2–5). The results for the 2 hemoglobin variables remained essentially unchanged in all these models.

Discussion

Rapid and effective recanalization of the occluded vessel is a crucial determinant of a good clinical outcome in the treatment of acute anterior circulation ischemic stroke [15, 16]. Good clinical outcome (mRS ≤2) is achieved only in roughly half of the anterior circulation stroke patients despite high rates (85–90%) of successful reperfusion with modern MT treatments [17–20]. Our results are in agreement with these observations. The integrity of the collateral circulation is an established predictor of clinical outcome whereas studies on anemia have yielded conflicting results. We studied the interplay of these 2 potentially modifiable factors and found both to be significant and independent predictors of clinical outcome, with anemia being associated with poor outcome especially among those who have good or fair collateral circulation.

Anemia has been generally linked to poor clinical outcome in ischemic stroke patients [2–6]. We observed this linkage also in anterior circulation MT patients. Akpinar et al. [21] reported poor clinical outcome in a small cohort of moderately and severely anemic LVO patients treated with MT. Our data confirm and further elucidate this finding to especially concern patients with good or fair collateral circulation. Tanne et al. [2] proposed that anemia and clinical outcome are nonlinearly correlated so that patients having either very low or high hemoglobin concentrations experience worse clinical outcomes. Our results suggest a more linear mode of action throughout the hemoglobin range: Lower hemoglobin values predicted

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Table 3. Logistic regression analysis of good clinical outcome at 3 months (mRS ≤2), dichotomized hemoglobin value, multiple imputation (n = 285)

	OR	Sig.	95% CI
Nonanemia	2.63	**0.004**	1.377–5.030
Age	0.96	**0.02**	0.936–0.993
ASPECTS, admission NCCT	1.20	**0.04**	1.007–1.441
Hypertension	0.58	0.07	0.320–1.053
Diabetes	0.69	0.34	0.321–1.486
NIHSS, admission	0.95	0.07	0.893–1.004
mTICI 2b–3	3.26	**0.05**	1.014–10.461
Male	1.53	0.17	0.832–2.812
Collateral score	1.59	**0.009**	1.125–2.234
Non-ICA occlusion	2.26	**0.009**	1.230–4.135
Onset-to-groin puncture	1.00	0.60	0.996–1.002
Atrial fibrillation	1.07	0.82	0.588–1.952
Ischemic heart disease	1.62	0.25	0.713–3.655
IV thrombolysis	1.00	1.00	0.539–1.859

ASPECTS, Alberta Stroke Program Early CT Score; CI, confidence interval; ICA, internal carotid artery; IV, intravenous; mTICI, modified Thrombolysis in Cerebral Infarction score; NCCT, non-contrast-enhanced computed tomography; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio. Boldface denotes $p < 0.05$.

worse outcome not only in anemic patients but also within the normal range. This finding is theoretically sensible considering the increased oxygen transfer capacity per each additional unit of hemoglobin. However, there were only few patients with very low or high hemoglobin concentrations in our cohort (online suppl. Fig. 1), and the follow-up period was shorter. LVO patients have larger ischemic parenchymal volumes than the average patient in the general ischemic stroke population and correspondingly suffer from a more severe condition. Thus, reduced oxygen delivery because of anemia potentially has a larger impact on LVO patients. This may in part explain the differences between our findings and the previously published studies that address the general stroke population [2–8]. In our data, anemia appeared to have a paradoxical beneficial effect on outcome in the absence of visible collateral circulation (CS = 0). This finding is based on a small number of patients and is probably artifactual considering that there is no conceivable mechanism for this effect.

Onset-to-reperfusion time is a well-established prognostic factor with longer delays contributing towards poorer clinical outcomes. We found no significant difference in onset-to-groin puncture times between the good and poor clinical outcome groups. This may be explained by brain imaging being the primary patient selection method. Still, prolonged duration of MT was associated with worse outcome and lower mTICI scores (data not shown). Successful reperfusion (mTICI 2b-3) was an independent predictor of good clinical outcome. However, the difference in successful reperfusion rates was relatively small between the 2 outcome groups (95 vs. 89%). This small difference highlights variations in the rate of expansion of the infarct core [22] which is heavily dependent on the intracranial collateral flow [23–25].

The inherent limitation of this study is the observational and retrospective design. The single, tertiary high-volume stroke care center setup potentially limits the generalizability of the findings. Missing data and the multiple imputation method may introduce biases and increase variability. However, the percentage of missing data is small, and the results were robust in sensitivity analyses.

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Conclusions

Low hemoglobin on admission predicts poor clinical outcome in mechanical thrombectomy patients with fair or good collateral circulation.

Acknowledgment

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Statement of Ethics

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Pirkanmaa Hospital District Science Center (R14551). For this type of study formal consent is not required.

Conflict of Interest Statement

All authors declare that they have no conflicts of interest relevant to this manuscript.

Funding Sources

There are no funding sources to declare.

Author Contributions

J.-P.P.: conception and design of the work; acquisition analysis and interpretation of data, drafting of the work, and final approval; S.P.: conception and design of the work; acquisition analysis and interpretation of data, revising of the work, and final approval; E.H. and P.J.: acquisition of clinical data, revising of the work and final approval; N.S.: conception of the work, analysis and interpretation of data, revising the work, and final approval.

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PUBLICATION
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In-Hospital Intravenous Thrombolysis Offers No Benefit in Mechanical Thrombectomy in Optimized Tertiary Stroke Center Setting

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In-Hospital Intravenous Thrombolysis Offers No Benefit in Mechanical Thrombectomy in Optimized Tertiary Stroke Center Setting

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Abstract

Purpose Mechanical thrombectomy (MT) is the first-line treatment in acute stroke patients presenting with large vessel occlusion (LVO). The efficacy of intravenous thrombolysis (IVT) prior to MT is being contested. The objective of this study was to evaluate the efficacy of MT without IVT in patients with no contraindications to IVT presenting directly to a tertiary stroke center with acute anterior circulation LVO.

Materials and Methods We collected the data of 106 acute stroke patients who underwent MT in a single high-volume stroke center. Patients with anterior circulation LVO eligible for IVT and directly admitted to our institution who subsequently underwent MT were included. We recorded baseline clinical, laboratory, procedural, and imaging variables and technical, imaging, and clinical outcomes. The effect of intravenous thrombolysis on 3-month clinical outcome (mRS) was analyzed with univariate tests and binary and ordinal logistic regression analysis.

Results Fifty-eight out of the 106 patients received IVT + MT. These patients had 2.6-fold higher odds of poorer clinical outcome in mRS shift analysis ($p = 0.01$) compared to MT-only patients who had excellent 3-month clinical outcome (mRS 0–1) three times more often ($p = 0.009$). There were no significant differences between the groups in process times, mTICI, or number of hemorrhagic complications. A trend of less distal embolization and higher number of device passes was observed among the MT-only patients.

Conclusions MT without prior IVT was associated with an improved overall three-month clinical outcome in acute anterior circulation LVO patients.

Keywords Ischemic stroke · Intravenous thrombolysis · Mechanical thrombectomy

Abbreviations

IVT	Intravenous thrombolysis
LVO	Large vessel occlusion
MT	Mechanical thrombectomy
mRS	Modified ranking scale

Supplementary Information The online version of this article (https://doi.org/10.1007/s00270-020-02727-8) contains supplementary material, which is available to authorized users.

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Introduction

Intravenous thrombolysis (IVT) has been proven to have a positive effect on patient survival and functional outcome in ischemic stroke if administered within a strict time window from symptom onset [1]. However, the effect of IVT is very limited on large vessel occlusions (LVO) thrombi [2]. Mechanical thrombectomy (MT) performed with modern methods is vastly superior in treating this patient group [3]. IVT prior to MT appears to have a favorable effect on clinical outcome [4–7]. However, some studies have reported no significant effect on the outcome [8–13]. Bellwald et al., moreover, found that there were more deaths at 3 months among the IVT-treated patients [14].

The objective of this study was to evaluate the efficacy of MT without IVT in patients with no contraindications to IVT presenting directly to a tertiary stroke center with acute anterior circulation LVO in comparison with patients who received both MT and IVT in the same setting.

Methods

Participants and Variables

We conducted an observational study on patients who underwent MT to treat anterior circulation acute LVO in a single high-volume stroke center. We collected the data of 479 consecutive patients having acute LVO (from ICA up to the M3 segment of the MCA) and no contraindications to IVT, who were treated with MT between October 2016 and October 2019, and had not been first evaluated in a referring hospital. All patients were admitted as MT candidates based principally on Finnish Prehospital Stroke Scale (FPSS) [15] scoring by the emergency services, or after clinical neurological examination in the emergency room or in case of in-hospital emergency in a ward. Patients underwent CT, and after treatment, decision was transferred immediately to an angiography suite for MT. Because of a highly standardized routine protocol with optimized in-hospital delays of less than an hour, neurologists on-call had the option to withhold from giving IVT, provided that the neurointerventional team was promptly available. Skipping IVT potentially further reduces the delay and the incidence of hemorrhagic complications, especially if a stent is implanted requiring initiation of antiplatelet medication. If the patient was given IVT, the bolus was administered on the CT table and the infusion was started on the way to the angiography suite and continued while MT was being performed. The infusion was stopped if satisfactory recanalization result (mTICI 2b-3) was obtained.

We identified ten cases where the effect of the thrombolytic agent was waited for before proceeding with MT. These patients were excluded because of the added delay to maintain comparability. Ten other patients received IVT after the MT to dissolve the remaining thrombi. They were excluded from the main analysis. Two patients could not be reached for the 3-month mRS control and were excluded. Finally after excluding patients who had contraindications to IVT, in total 106 patients met the inclusion criteria of whom 58 patients (55%) had IVT (flowchart in Fig. 1).

Baseline clinical characteristics included age, gender, and clinical risk factors for ischemic stroke (hypertension, diabetes, coronary heart disease, atrial fibrillation) collected from the patient records. National Institutes of Health Stroke Scale (NIHSS) score at the admission, process time points, mTICI (modified Thrombolysis in Cerebral Ischemia) grading evaluated with DSA at the end of the procedure, and procedural complications had been prospectively collected. A follow-up non-contrast-enhanced computed tomography (NCCT) was performed 24 h after MT. The clinical outcome measure was the modified Rankin Scale, evaluated 3 months after the stroke based on a follow-up visit or a phone interview by a neurologist. Shift analysis of mRS was the main outcome measure; the widely used dichotomization cutoffs and mortality were also analyzed. The CT imaging time point was recorded as the timestamp of the first scout image. The study was approved by the institutional review board and adhered to the Helsinki Declaration. A written consent was not deemed necessary by the review board.

Imaging Parameters

Please see online supplementary material.

Recanalization Therapies

All MT procedures were performed under conscious sedation. All procedures except one were performed with a balloon guide catheter. In 96% of cases, a stent retriever was used (Trevo®, Stryker, Salt Lake City, USA or EmbotrapII®, Neuravi, Galway, Ireland). An intermediate catheter was used for distal aspiration in 59% of cases in conjunction with stent retriever thrombectomy. IVT bolus of recombinant tissue plasminogen activator (rt-PA, Actilyse® 0.9 mg/kg, Boehringer-Ingelheim, Ingelheim, Germany) was administered after NCCT followed by infusion according to international guidelines.

Statistics

The data were analyzed with SPSS version 25 (SPSS Inc., Chicago, IL). The analyses were performed using the maximum number of patients available with regard to missing data. Group comparisons were performed by using the Student *t* test, the Chi-squared test, the Fisher exact test, the Kruskal–Wallis test, and the Mann–Whitney *U* test according to the type and distribution properties of the variable studied. An mTICI score 2b-3 was considered a good recanalization result. Logistic regression analyses using dichotomized mRS as dependent variable were performed, and odds ratio (OR) with 95% confidence interval (CI) were calculated for each covariate. We performed

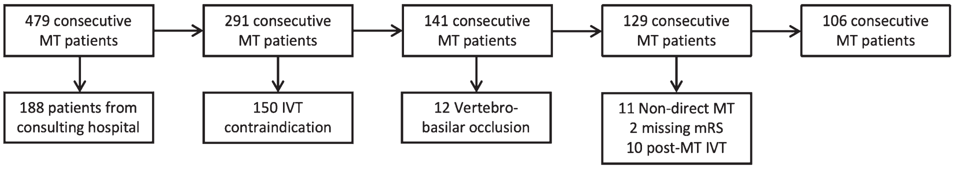

Fig. 1 Flowchart showing the patient exclusion process

Table 1 Demographic, baseline, and admission imaging characteristics of all patients by the recanalization therapy

Characteristic	All patients n = 106	IVT + MT n = 58	MT-only n = 48	P_1
Age (y), mean (SD)	71 (12)	69 (12)	72 (11)	0.168
Female sex (%)	39 (37)	21 (36)	18 (38)	0.891
NIHSS, median (IQR)	15 (9)	16.5 (8)	14 (9)	0.580
ASPECTS, median (IQR)	10 (2)	9.5 (2)	10 (2)	0.995
Onset reperfusion (min), mean (SD)	158 (79)	150 (71)	166 (86)	0.458
CT groin (min), mean (SD)	26 (11)	26 (12)	25 (9)	0.739
Collateral score > 1, n (%)	79 (65)	41 (71)	28 (58)	0.184
Hypertension, n (%)	60 (57)	29 (50)	31 (65)	0.132
Diabetes, n (%)	24 (23)	13 (22)	11 (23)	0.951
Atrial fibrillation, n (%)	56 (53)	37 (64)	19 (40)	**0.013**
Coronary artery disease, n (%)	19 (18)	12 (21)	7 (15)	0.415

ASPECTS: Alberta Stroke Program Early CT Score, CT-groin: delay from first CT image to groin puncture in MT, IVT: intravenous thrombolysis, MT: mechanical thrombectomy, NIHSS: National Institutes of Health Stroke Scale, Onset-reperfusion: delay from onset of symptoms and recanalization in MT, P_1: *p*-value between groups. Boldface denotes statistical significance

shift analysis for mRS using ordinal regression analysis and calculated common odds ratio. A p value < 0.05 was considered statistically significant.

Results

Baseline and Technical Characteristics

Fifty-eight patients (55%) received IVT and MT, and 48 patients had MT only. Twenty-five percent of the patients had occlusion of terminus of internal carotid artery (ICA-T) and 57% in the first segment of median cerebral artery (M1). Isolated ICA occlusion with open anterior communicating artery was found in 5%, and the rest had M2 (14%) or M3 (2%) occlusions (occlusion site distribution in Supplementary Table 1).

The median NIHSS at admission was 15 (IQR 9), and the mean delay from symptom onset to reperfusion (onset-to-reperfusion time) was 158 min (SD 79 min). The mean delay from CT imaging to groin puncture (CT-to-groin time) was 26 min (SD 11 min). The main baseline and admission imaging characteristics are summarized in Table 1.

The only significant difference in baseline characteristics (Table 1) between the IVT + MT and MT-only groups was found in the proportion of atrial fibrillation (64% vs. 40%, respectively, $p = 0.013$), which is very likely a coincidental finding, considering there is no logical explanation for this. Onset-to-reperfusion and CT-to-groin times were not significantly different (150 min vs. 166 min, $p = 0.458$, and 26 min vs. 25 min, $p = 0.739$, respectively). Thus, administration of IVT did not significantly prolong the CT-to-groin time. Almost the same proportion of patients achieved good recanalization (mTICI 2b-3) in both groups (91% vs. 92%, $p = 0.958$). In the MT-only group, there was a trend of fewer distal emboli (10% vs. 24%, $p = 0.067$), but more device passes were needed for a satisfactory recanalization result (mean 2.3 vs. 1.8 passes, $p = 0.093$). The IVT + MT group had a nonsignificantly lower frequency of hemorrhagic complications (21% vs. 29%, $p = 0.313$). Characteristics of the MT procedure and clinical outcome are summarized in Table 2.

The Distribution of 3-Month mRS and Factors Predicting the 3-Month Clinical Outcome

Figure 2 depicts shift analysis of the 3-month mRS between the two groups ($p = 0.06$ for overall difference). Analyzing the commonly used dichotomization cutoffs, the proportion of patients with good 3-month clinical outcome (mRS 0–2) was equivalent in the IVT + MT and MT-only groups (67% vs. 68%, $p = 0.868$), while the proportion of patients with excellent clinical outcome (mRS 0-) was significantly larger in the MT-only group (60% vs. 38%, $p = 0.021$), whereas the IVT + MT patients had a trend toward higher mortality (mRS = 6, 16% vs. 6%, $p = 0.134$).

The main established predictive factors of the 3-month clinical outcome were included as covariates in multivariable analyses along with variables having significant differences between the groups in univariable analyses.

Ordinal logistic regression analysis using 3-month clinical outcome as the dependent variable is detailed in Table 3. The common OR (shift analysis) between the IVT + MT and MT-only groups was 2.6 (95% CI 1.22–5.58, $p = 0.01$) with the IVT + MT patients having poorer clinical outcome. As expected from literature, each additional ten-minute delay in onset-to-reperfusion time increased the odds of poorer clinical outcome by 9% (OR = 1.09, 95% CI = 1.04–1.15, $p < 0.001$) and every additional NIHSS point by 8% (OR = 1.08, 95% CI = 1.02–1.15, $p = 0.02$).

Binary logistic regression analysis, using excellent 3-month clinical outcome (mRS 0–1) as dependent variable, is described in Supplementary Table 2. MT-only patients were over 3 times more likely to have excellent clinical outcome (OR = 3.37, 95% CI = 1.36 to 8.33, $p = 0.009$). The result of the analysis remained essentially unchanged after adding the site of occlusion, number of device passes, or detected distal embolization as an additional covariate. Further, the odds for excellent clinical outcome remained very similar when the ten patients who received IVT after MT were included to either the IVT + MT or the MT-only group (OR = 3.45, 95% CI = 1.44 to 8.23, $p = 0.005$, and OR = 2.65, 95% CI = 1.15 to 6.12, $p = 0.022$, respectively).

Using mRS = 6 (death) as the dependent variable (Supplementary Table 3), IVT increased the odds of death ninefold (OR = 8.98, 95% CI = 1.23 to 65.3, $p = 0.030$).

Discussion

Intravenous thrombolysis with rt-PA and modern mechanical thrombectomy are well-proven treatments of acute ischemic stroke [1, 3]. The efficacy of IVT is limited in the treatment of large vessel occlusions [2]. The time from symptom onset to reperfusion is a critical determinant of clinical outcome [16]. Thus, the minimization of delays has a central role in the strategies to improve the outcome. Drip-and-ship protocols with IVT have been shown to improve the odds of good clinical outcome when direct access to MT is not available [17]. Protocols combining IVT to MT in a within-institution setting are less well studied [8–14]. Current guidelines state that IVT should always been given prior to MT if the patient is within the treatment time window and there are no contraindications [18–20].

Table 2 Characteristics of MT operation and clinical outcome between IVT + MT and MT-only groups

Characteristic	All patients $n = 106$	IVT + MT $n = 58$	MT-only $n = 48$	P_1
mTICI 2b-3, *n* (%)	97 (92)	53 (91)	44 (92)	0.958
Distal embolus, *n* (%)	19 (18)	14 (24)	5 (10)	0.067
Number of passes, mean (SD)	2.1 (1.7)	1.8 (1.6)	2.3 (1.9)	0.093
ICH n (%)	26 (25)	12 (21)	14 (29)	0.313
ASPECT 24 h, median (IQR)	9 (3)	9 (3)	9 (4)	0.780
3-month mRS 0–1, *n* (%)	51 (48)	22 (38)	29 (60)	**0.021**
3-month mRS 0–2, *n* (%)	72 (68)	39 (67)	33 (69)	**0.868**
3-month mRS 6, *n* (%)	12 (11)	9 (16)	3 (6)	0.134

ASPECTS 24 h: Alberta Stroke Program Early CT Score 24 h after MT, Distal embolus: embolus further vessel territory, ICH: any intracranial hemorrhage in CT 24 h after MT, IVT: intravenous thrombolysis, mRS: modified Ranking Scale, MT: mechanical thrombectomy, mTICI: modified Thrombolysis In Cerebral Infarction score, mRS 0–1: excellent clinical outcome, mRS 0–2: good outcome, mRS 6: death, number of passes: number of passes of thrombectomy device, P_1: *p* value between groups. Boldface denotes statistical significance

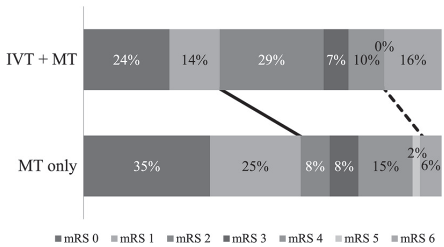

Fig. 2 The distributions of 3-month mRS in the IVT + MT and MT-only groups. The line indicates the division between excellent clinical outcome (mRS 0–1, left-hand side) or not (right-hand side). The dotted line indicates the division between alive and dead (mRS 6, right-hand side). mRS: modified Rankin Scale

In our study, treating the patient with both MT and IVT in comparison with proceeding directly to MT increased the odds of poorer 3-month clinical outcome 2.6-fold among patients eligible to receive IVT in a within-institution, minimal in-hospital delay, tertiary stroke center setting. To our knowledge, there are no previous studies reporting a signal that IVT might have this kind of limited unfavorable effect in conjunction with MT.

Some previous multicenter studies [4–6] have found that patients who received combined IVT and MT to treat LVO had better clinical outcome. In all these studies, IVT was always administered if not contraindicated. The average in-hospital delays were considerably longer than in our study. Further, the setup of these studies was different from ours, considering that they compared MT with IVT bridging therapy to MT in patients having contraindications for IVT. In our study, neither group had contraindications for IVT, and both groups had direct access to MT. On the other hand, in several other studies [8, 9, 11–14], no significant benefit in outcome was found when combining IVT and MT. Again, the average in-hospital delays in these studies were long. In three of the studies [8, 9, 11], IVT was always given if not contraindicated. In the studies by Weber et al. and Wang et al. [8, 12], the process times in the IVT + MT and MT-only groups were markedly different. Both Broeg-Morvay et al. and Bellwald et al. found higher mortality in matched-pair analyses when IVT was combined with MT, and IVT was not associated with better outcome [13, 14]. These two findings are in congruence with our results.

We found no significant differences in the frequency of symptomatic or non-symptomatic post-treatment ICH in the 24-h follow-up CT scans between the two groups, meaning that IVT appears to be safe and did not lead to more bleeding complications. However, both Broeg-Morvay et al. and Bellwald et al. found higher rates of hemorrhagic complications in the bridging therapy groups. We stopped the IVT infusion when satisfactory revascularization result was achieved in MT. Thus, a number of patients did not receive the full IVT dose, which may in part explain the difference. Moreover, we found no significant differences in process times or stroke severity at the admission, signaling that the administration of IVT does not add significant delay in an optimized tertiary hospital setting. We observed that the IVT + MT patients were more likely to have macroscopic distal emboli in comparison with the MT-only patients (24% vs. 10%, $p = 0.067$) similar to the findings of Yi et al., which potentially worsens the outcome [21]. On the other hand, fewer stent retriever passes were needed in the IVT + MT patients to achieve a satisfactory recanalization result (mean 1.8 vs. 2.3 passes, $p = 0.093$), which is in line with a report by Mistry et al. [4]. However, neither macroscopic distal embolization nor the number of retriever passes had a

Table 3 Ordinal logistic regression analysis of 3-month clinical outcome (mRS)

	O.R	Sig	95% C.I	
			Lower bound	Upper bound
Age	1.03	0.118	0.99	1.06
Onset-reper/10	1.09	**< 0.001**	1.04	1.15
NIHSS	1.08	**0.02**	1.02	1.15
AF	0.81	0.585	0.39	1.70
IVT + MT	2.61	**0.013**	1.22	5.58
mTICI 2b-3	0.69	0.540	0.20	2.30

Age: 1-year increase in age, AF: atrial fibrillation, C.I.: confidence interval, MT-only: mechanical thrombectomy patients without intravenous thrombolysis, mTICI: modified Thrombolysis In Cerebral Infarction score, mRS: modified Ranking Scale score, NIHSS: 1-point increase in National Institutes of Health Stroke Scale, Onset-reper/10: Delay from symptoms onset to achieve recanalization in MT (for every 10 min), O.R.: common odds ratio for worse outcome. Boldface denotes statistical significance. *Chi-square model significance < 0.001* statistically significant effect on the overall technical or 3-month clinical outcome in multivariable analyses.

One potential unfavorable effect of IVT on the clinical outcome may be destabilization of the thrombus leading to fragmentation and microscopic distal embolization [21]. Alteplase can make the thrombus more fragile and prone to fragmentation during the procedure and thus increase the incidence of microinfarctions and post-ischemic microhemorrhages in the brain parenchyma. Microembolization and the sequelae are not readily detected in standard CT or DSA imaging. Patients with cerebral microhemorrhages in a follow-up MRI study after intravenous thrombolysis are known to have poorer clinical outcome [22–25]. A possible other mechanism not readily visible in follow-up CT, alteplase has been reported to have undesirable effects on the brain parenchyma due to neurotoxicity [26].

Two recent randomized trials (DIRECT-MT and SKIP trial) demonstrated non-inferiority but no advantage of MT only in comparison with IVT + MT in thrombectomy-capable centers. These trials had longer process times than in our study, which may diminish the efficacy of the MT-only approach [27, 28].

The inherent limitations of this study are the relatively small sample size that does not permit subgroup analyses of, for example, different occlusion sites and the observational and retrospective design that is prone to selection bias. The single, highly standardized tertiary stroke center with high average recanalization rate and minimal delay setup limits the generalizability of the findings. Further, our findings do not apply to drip-and-ship patients.

Conclusions

MT without prior IVT was associated with improved overall three-month clinical outcome or was at least non-inferior in the treatment of acute anterior circulation LVO patients admitted directly to a tertiary stroke center. The ongoing randomized clinical trials, MRCLEAN_NoIV, SWIFT-Direct and DIRECT SAFE will help verifying or refuting this finding.

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Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflicts of interest relevant to this manuscript.

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