Acta Universitatis Tamperensis 2303

SARA PROTTO

Mechanical Thrombectomy in Acute Anterior Circulation Stroke

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ACADEMIC DISSERTATION
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UNIVERSITY OF TAMPERE

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A mio papá,

Mi hai dato tutto senza chiedere mai nulla in cambio.

Mi manchi ogni ora, ogni minuto, ogni secondo.

Contents

Abstract

Stroke continues to be one of the leading causes of morbidity and mortality worldwide. Acute ischemic stroke is caused by insufficient blood flow to the brain tissue and it most often due to occlusion of an intracranial artery by a thrombus. There have been great advances in the treatment of this condition recently with the development of the stentretriever-based techniques that allow rapid restoration of perfusion to the ischemic area. The superiority of these mechanical thrombectomy (MT) techniques over the previous pharmacological therapies (intravenous thrombolysis, IVT) has been demonstrated in recent randomized trials. However, the introduction of interventional techniques has amplified the need to improve our ability to more precisely stratify risk and refine the treatment decision-making process to select the correct treatment for patients among these diverse therapeutic modalities.

This thesis examines in a prospectively collected, observational cohort the principal parameters that influence the technical and clinical outcomes in patients presenting acute anterior circulation stroke and treated via MT between January 2013 and December 2014 in Tampere University Hospital. The 3-month modified Rankin Scale (mRS) was used as the primary functional outcome measure and the Thrombolysis in Cerebral Infarction scale (TICI) was used to describe the technical outcome. The parameters studied included the location of the clot in computed tomography angiography (CTA) and the device used to perform the intervention. We also investigated the prognostic value of data derived from perfusion CT studies (CTP), especially the utility of cerebral blood volume maps (CBV). Moreover, we compared the results of patients at our institution treated with only IVT to those treated with MT to assess the differences in clinical outcomes and to clarify the patient subgroups for which MT outperforms IVT.

Mechanical thrombectomy was clearly superior to IVT in the treatment of proximal large vessel occlusions whereas neither therapy outperformed the other in distal large vessel occlusions. In our cohorts, surviving an internal carotid artery (ICA) or a proximal M1 segment of the middle cerebral artery (MCA) occlusion without any disability-causing neurological deficits required MT. The site of the occlusion does not seem to have a significant effect on the technical success rates of MT. Further, the selection of the newer generation stent retriever does not appear to result in differences in technical or clinical outcomes. This supports the notion that the decision of which device to use should be left to the operator based on his/her own experience.

Cerebral blood volume mapping assessed semiquantitatively with the Alberta Stroke Program Early CT score (ASPECTS) is an established predictor of outcome in a variety of clinical settings. In our study, a low CBV-ASPECTS score at admission was associated with a large infarct core in follow-up imaging and was a significant predictor of poor clinical outcome, especially in the setting of poor collateral circulation and/or moderate or severe stroke. The collateral score was also a significant predictive factor. Having no visible collateral circulation in the admission CTA was specifically related to poor clinical outcome.

Keywords: ASPECTS, mechanical thrombectomy, intravenous thrombolysis, stroke, computed tomography perfusion, collateral score, modified Rankin scale, Thrombolysis in Cerebral Infarction scale.

Tiivistelmä

Aivoinfarkti on yksi johtavista sairastavuuden ja kuolleisuuden aiheuttajista maailmanlaajuisesti. Äkillinen iskeminen aivoinfarkti aiheutuu riittämättömästä verenkierrosta aivoihin, joka yleensä johtuu verihyytymän aiheuttamasta kallonsisäisen valtimon tukkeutumisesta. Viime vuosina äkillisen iskemisen aivoinfarktin valtimonsisäiset hoidot ovat kehittyneet huomattavasti. Nämä hoidot mahdollistavat veren virtauksen nopean palauttamisen iskemiselle alueelle. Viimeaikaisissa satunnaistetuissa tutkimuksissa erityisesti mekaaninen verihyytymän poisto takaisin vedettävällä stentillä on osoitettu ylivertaiseksi hoidoksi verrattuna lääkkeelliseen hoitoon eli laskimonsisäiseen verihyytymän liuotukseen. Näiden tekniikoiden käyttöönotto kuitenkin vaati välineitä tarkempien ennusteiden ja siten oikeiden hoitopäätösten tekemiseksi.

Tässä väitöstutkimuksessa tutkiin havainnoivassa asetelmassa prospektiivisesti Tampereen yliopistollisessa sairaalassa tammikuun 2013 ja joulukuun 2014 välillä kerättyä kohorttia potilaita, jotka olivat sairastuneet äkilliseen etukierron valtion tukkeutumisesta aiheutuneeseen aivoinfarktiin, jota hoidettiin mekaanisella verihyytymän poistolla. Tutkimuksen tavoite oli tunnistaa muuttujia, jotka vaikuttavat hoidon teknisiin ja kliinisiin lopputuloksiin. Kliinisen lopputuloksen ensisijaisena mittarina käytettiin muokatun Rankinin asteikon (mRS, modified Rankin Scale) tulosta kolmen kuukauden kohdalla sairastumisesta. Teknisen lopputuloksen mittarina käytettiin Thrombolysis in Cerebral Ischemia (TICI) -asteikkoa. Näiden ennustemuuttujina tutkittiin verihyytymän sijaintia tietokonetomografiatutkimuksessa, hyytymän poistamiseen käytetyn välineen valinnan vaikutusta, tietokonetomografia perfuusiotutkimuksen parametreja (erityisesti aivojen veritilavuus, Cerebral Bloob Volume, CBV) sekä kollateraalikierron tilaa. Lisäksi vertasimme laskimonsisäisellä liuotushoidolla ja mekaaniselle verihyytymän poistolla hoidettujen potilaiden tuloksia selventääksemme minkä potilasryhmisen hoitoon mekaaninen verihyytymän poisto sopii paremmin kuin liuotushoito.

Mekaaninen verihyytymän poisto osoittautui selvästi paremmaksi kuin laskimonsisäinen liuotushoito erityisesti proksimaalisen suuren suonen tukosten

(sisempi kaulavaltimo tai keskimmäisen aivovaltimon M1-segmentin proksimaaliosa) hoidossa siinä missä kumpikaan näistä hoidoista ei ollut selvästi toista parempi distaalisen suuren suonen tukosten (keskimmäisen aivovaltimon M1-segmentin distaaliosa tai M2-segmentti) hoidossa. Lisäksi havaitsimme, että proksimaalisesta suuren suonen tukoksesta selviytyminen ilman merkittävää pysyvää haittaavaa oiretta edellytti mekaanista verihyytymän poistoa. Tukoksen sijainnilla ei ollut merkittävää vaikutusta toimenpiteen tekniseen onnistumiseen. Myöskään takaisinvedettävän stentin valinta ei näytä vaikuttavan tekniseen onnistumiseen tai kliiniseen lopputulokseen. Aivojen veritilavuutta arvioitiin ASPECTS-pisteytyksellä (Alberta Stroke Program Early CT Score). Matalat ASPECTS-pisteet tulovaiheessa ennustivat kookasta infarktia seurantakuvantamisissa ja huonoa kliinistä lopputulosta erityisesti, jos kollateraaliverenkierto oli heikko ja/tai infarktioireisto oli vaikeusasteeltaan kohtalainen tai vakava. Kollateraalikierron tila osoittautui myös tärkeäksi ennustavaksi tekijäksi: Jos potilaan kollateraalikierto oli lähtötilanteessa heikko, kliininen lopputulos oli yleensä huono.

Avainsanat: ASPECTS, mekaaninen verihyytymän poisto, laskimonsisäinen liuotushoito, aivoinfarkti, tietokonetomografiaperfuusio, kollateraalikierto, muokattu Rankinin asteikko, Thrombolysis in Cerebral Infarction -asteikko.

ABBREVIATIONS

2D two-dimensional

3D three-dimensional

A1 A1 segment of the anterior cerebral artery

ACA anterior cerebral artery

ACommA anterior communicating artery

AF Atrial Fibrillation

AHA American Heart Association

AIS acute ischemic stroke

aPTT activated partial thromboplastin time

ASPECTS Alberta Stroke Program Early CT Score

BA basilar artery

BMI body mass index

CBF Cerebral Blood Flow

CBS clot burden score

CBV Cerebral Blood Volume

CCS Causative Classification System for Ischemic Stroke

CI confidence interval

CNS central nervous system

CT Computed Tomography

CTA computed tomography angiography

CTA-SI computed tomography angiography source images

CTP Computed Tomography Perfusion

CW circle of Willis

DALY Disability-Adjusted Life Year

DEFUSE Diffusion-weighted imaging Evaluation For Understanding Stroke Evolution

DSA digital subtraction angiography

DWI diffusion-weighted imaging

EIC early ischemic change

FDA Food and Drug Administration

HIS hyperacute ischemic stroke

HMCAS the hyperdense MCA sign

H-L Hosmer-Lemeshow

IAT intra-arterial thrombolysis

ICA internal carotid artery

ICH intracranial hemorrhage

IQR interquartile range

IMS Interventional Management of Stroke

INR International Normalized Ratio

IS ischemic stroke

IVT intravenous thrombolysis

LVO large vessel occlusion

M1 M1 segment of the middle cerebral artery

M1D distal M1 segment of the middle cerebral artery

M1P proximal M1 segment of the middle cerebral artery

M2 M2 segment of the middle cerebral artery

M3 M3 segment of the middle cerebral artery

M4 M4 segment of the middle cerebral artery

MCA middle cerebral artery

MIP maximum intensity projection

MRI magnetic resonance imaging

mRS modified Rankin Scale

MT Mechanical Thrombectomy

MTT mean transit time

NECT nonenhanced computed tomography

NIHSS National Institutes of Health Stroke Scale

NNT number needed to treat

OR odds ratio

PAR Population Attributable Risk

PCA posterior cerebral artery

PCommA posterior communicating artery

PS Penumbra System

ROC receiver-operating characteristic curve

r-proUK recombinant prourokinase

RR risk ratio

rtPA recombinant tissue plasminogen activator

SPSS Statistical Package for the Social Sciences

TIA Transient Ischemic Attack

TICI Thrombolysis in Cerebral Infarction Scale

tPA tissue plasminogen activator

TTP time to peak

VA vertebral artery

LIST OF ORIGINAL COMMUNICATIONS

This thesis is based on the following publications, referred to in the text by their Roman numeral:

I. **Stent Retriever Thrombectomy in Different Thrombus Locations of Anterior Cerebral Circulation**. **Protto** S, Sillanpää N, Pienimäki JP, Matkaselkä I, Seppänen J, Numminen H. Cardiovasc Intervent Radiol. 2016 Jul;39(7):988-93. doi: 10.1007/s00270-016-1315-4.

II. **TREVO and Capture LP have equal technical success rates in mechanical thrombectomy of proximal and distal anterior circulation occlusions. Protto** S, Pienimäki JP, Seppänen J, Matkaselkä I, Ollikainen J, Numminen H, Sillanpää N. J Neurointerv Surg. 2016 Jun 17. pii: neurintsurg-2016-012354. doi: 10.1136/neurintsurg-2016-012354. [Epub ahead of print]

III. **Low Cerebral Blood Volume Identifies Poor Outcome in Stent Retriever Thrombectomy.** Protto, S., Pienimäki, JP., Seppänen, J. et al. Cardiovasc Intervent Radiol (2017) 40: 502. doi:10.1007/s00270-016-1532-x

IV. **Internal Carotid Artery and the Proximal M1 Segment are Optimal Targets for Mechanical Thrombectomy.** Sillanpää N, Protto S, Saarinen J, T, Pienimäki J, -P, Seppänen J, Numminen H, Rusanen H. Intervent Neurol 2017;6:207-218

1 INTRODUCTION

Stroke is one of the largest contributors to death and disability worldwide and furthermore has a major impact to the economy. Stroke is the third-leading cause of disease burden as measured in disability-adjusted life years (DALYs) in developed countries and the second leading cause of DALYs in developing countries [1]. According to the Global Burden of Disease: 2004 Update, stroke continues to be the second leading cause of death among people aged 15 years and over.

The Global Burden of Stroke study estimated 6.5 million deaths from stroke and 10.3 million new strokes in 2013. Although the number of people who have suffered a stroke has increased every year, the global incidence, mortality and the number of DALYs lost are decreasing. However, this trend is more evident in developed countries, while the people in developing countries carry a higher burden of stroke. [1]

In Finland, the number of first-ever stroke episodes in 2007 was 10338. The yearly medical expenses attributable to the treatment of stroke patients were close to 1.6 billion €, which corresponds to 7 % of all healthcare expenditure. [2]

Most strokes (87%) have an ischemic etiology meaning that they are caused by insufficient blood flow to the brain tissue. The remainder of strokes is hemorrhagic in origin, with 10% caused by intracerebral bleedings and 3% by subarachnoidal hemorrhages [3, 4]. Ischemic stroke (IS) is generally due to a thrombotic or embolic event in an intracerebral artery, which significantly decreases blood flow to the tissue distal to the occlusion inducing cell death. Typically, patients present a sudden onset of symptoms, the most common symptoms being motor disruption, hemiparesis with or without hemisensory deficits, facial droop, ataxia, aphasia, dysarthria, visual impairment, and variable decrease of consciousness.

Ischemic stroke is operationally defined as a neurological deficit lasting more than 24 h or an imaging finding in a patient with transient symptoms. Correspondingly, a transient ischemic attack (TIA) is defined as a self-limiting episode of

neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction, lasting less than 24 h. [5] Thus, imaging has a central role in the evaluation of patients with acute stroke. Generally, multimodal computed tomography (CT) is performed because it is widely available in most centers and a fast imaging technique, but stroke magnetic resonance imaging (MRI) has also been used extensively [6]. Both imaging techniques enable the differential diagnosis between intracranial or subarachnoidal hemorrhage and ischemic stroke and allow evaluation of the anatomy of the cerebral and cervical vasculature, the location of the occlusive lesion and the extent of irreversible and/or reversible changes [7-9].

Prompt and effective revascularization of the affected area is crucial for improving the patient´s prognosis. The time window between symptom onset and treatment is a pivotal factor in determining the final outcome [10]. Therefore, in recent decades, several therapies have been developed, namely, intravenous thrombolysis (IVT) and intra-arterial interventions that aim to rapidly restore perfusion to the affected areas. While IVT has been endorsed by different stroke treatment guidelines for almost two decades, the efficacy of intra-arterial therapy was demonstrated only recently [11-17]. Based on diverse technical approaches, stent retriever-based mechanical thrombectomy (MT) provided a breakthrough in the efficacy and safety of intra-arterial treatment of IS [18].

To better understand the role of the innovative stent retriever technique, this thesis reports a prospectively collected, observational cohort of patients with acute anterior circulation stroke who were treated via mechanical thrombectomy (MT) with a focus on the clinical and imaging parameters that influence the technical and clinical outcomes. These factors included the location of the clot on admission computed tomography angiography (CTA) and type of the stent retriever device used during the intervention. We also investigated the prognostic performance of data derived from perfusion CT studies (CTP), especially cerebral blood volume maps (CBV). Moreover, we compared the results in patients treated in our institution with only IVT to those treated with MT to assess the differences in clinical outcomes and to clarify the patient subgroups for which MT outperforms IVT. The 3-month modified Rankin Scale (mRS) was used as the functional outcome measure and the Thrombolysis in Cerebral Infarction scale (TICI) was used to define the technical outcome.

2 REVIEW OF THE LITERATURE

2.1 ACUTE ISCHEMIC STROKE

2.1.1 Pathophysiology and etiology

Acute ischemic stroke results from a sudden reduction of cerebral blood flow (CBF) to the brain parenchyma. Typically, this decrease in blood flow follows thrombosis or embolism in the artery supplying a part of the brain, inducing insufficient delivery of oxygen and glucose which leads to cell death in the absence of sufficient collateral circulation or revascularization (Figure 1). The decrease in perfusion triggers a cascade of events in cells, which eventually results in irreversible changes: inhibition of protein synthesis, anaerobic glycolysis, inflammation, release of excitatory neurotransmitters, disturbance of energy metabolism and oxidative/nitrative stress, and finally anoxic depolarization and loss of membrane integrity [19]. In the core of the ischemic area, where the CBF is drastically impaired (<15 ml/100 g/min), neuronal cell death occurs within a few minutes, whereas in the periphery, the events leading to irreversible changes take more time. The so-called ischemic penumbra is an area of the brain parenchyma where blood flow is moderately reduced (15-20 ml/100 g/min) but the tissue remains viable if restoration of normal flow is achieved in sufficiently short time. Benign oligemia (20-55 ml/100 g/min) defines the volume of mild hypoperfusion, which normally does not lead to infarction even without revascularization. [20, 21] Hypoperfusion and irreversible ischemic damages can also be caused or aggravated by systemic hypotension. Hence it is important to control the blood pressure in patients suffering from IS in order to maintain or improve both antegrade and collateral circulation. [22]

Ischemic stroke etiology is classified based on the mechanism of the injury. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification defines five stroke subtypes: large-artery atherosclerotic infarction (19%), embolism from a cardiac source (9%), small-vessel disease (44%), stroke of other determined

etiology (5%), and infarcts of undetermined cause (23%) [23]. However, because of the evolution and the precision of the diagnostic tools, more than one cause of stroke can often be recognized in a single patient. For instance, a potential source of cardiac embolism can be detected using echocardiography in 50 to 70% of ischemic stroke patients. Further, 12% of patients with a cardiac source of embolism and 22% of patients with a lacunar infarction harbor ipsilateral large artery atherosclerosis causing a narrowing of greater than 50% of the vessel diameter [24]. Application of the TOAST classification criteria often results in most strokes being classified to the undetermined category, which led to the development of new, more refined classification systems. The Stop Stroke Study TOAST (SSS-TOAST) system uses the same five etiological categories, but based on the weight of evidence, further classifies each category into "evident", "probable" or "possible" [24]. The Causative Classification of Ischemic Stroke (CCS) is an automated version of SSS-TOAST that maximizes inter-examiner reliability and limits inter-examiner variability in the classification. [25] The distribution of ischemic stroke subtypes varies largely between different populations and reports and is dependent on the availability of modern diagnostic tools and the age distribution of the population. Recently, an increase in the prevalence of some stroke subtype over others has been observed, with the cardioembolic category now being the dominant etiology in western countries (e.g. 48% in Sweden). [3]

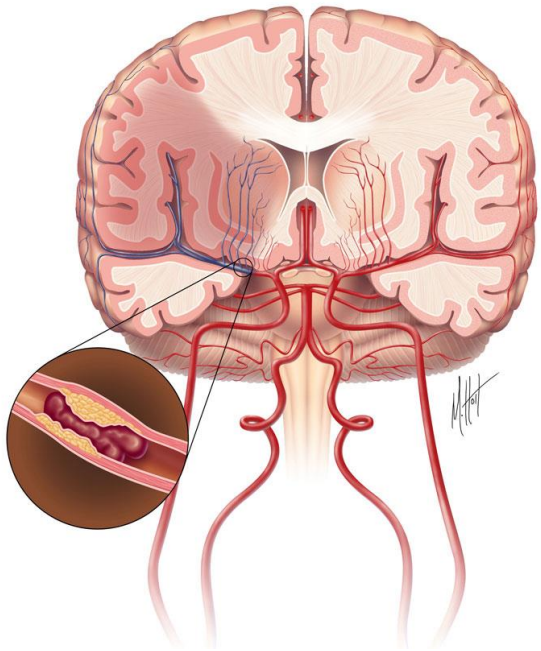


Figure 1. Occlusion of the right M1 segment of the MCA. Adapted from http://www.strokecenter.org/patients/about-stroke/ischemic-stroke/

2.1.2 Risk factors

Numerous risk factors are associated with ischemic stroke. Modifiable risk factors play an important role in the prevention of stroke. The INTERSTROKE study recently conducted in 32 countries demonstrated that ten preventable risk factors (hypertension, current smoking, abdominal obesity, unhealthy diet, lack of regular physical activity, high alcohol intake, psychosocial stress and depression, cardiac disease, diabetes mellitus and unfavorable lipid profile) contribute to 91.5% of the total risk of ischemic stroke. [26] These findings corroborated the results of the Global Burden of Disease 2013 (GBD) study, in which 90.5% of the stroke burden (measured in DALYs) was attributable to modifiable risk factors. Both studies identified hypertension as the most significant factor influencing the Population Attributable Risk (PAR) with estimates for the parameter ranging from 47.9 to 64.1%.

There is strong evidence that cigarette smoke is intimately related to stroke with a greater risk for women or younger smokers. Ex-smokers have double the risk of

experiencing a stroke before the age of 75 compared to lifetime non-smokers. [27-29] The INTERSTROKE study estimated the PAR of cigarette smoking at 12.4%. [26]

Obesity is also correlated with stroke risk. In the upper body mass index (BMI) bracket (25 to 50 kg/m^2), each 5 kg/m^2 increment is associated with 40% higher stroke mortality. Similar to cigarette smoking, the association of BMI with stroke is stronger among the younger population. [30-32] Physical activity and healthy lifestyle have been shown to reduce the risk of stroke. Compared with sedentary lifestyle, the risk reduction for active individuals has been estimated at 26%. [33, 34] Using the American Heart Association (AHA) recommendation (2.5 hours or more of exercise per week), increased physical activity was associated with a reduction in all stroke risk (OR 0.41 [0.35–0.48], PAR 53.0% [47.0–59.0]). [26]

High alcohol consumption increases the risk of all stroke subtypes. However, the association of alcohol intake and stroke risk appears to be J-shaped. [35] In a recent study on monozygotic twins, heavy alcohol consumption shortened the time to first stroke by 5 years. [36]

Psychosocial stress and depression, defined in the INTERHEART study as a combination of stress (life and work), life events and depression [37], is also associated with higher risk of stroke. [26] A recent study found that in diabetic patients there was an association between elevated stress or depressive symptoms and increased incidence of stroke (Hazard Ratio 1.57 [95% CI 1.05, 2.33]). [38]

Atrial fibrillation (AF), coronary artery disease, and cardiac failure are all well-known risk factors for stroke [39]. In the INSTROKE study AF was significantly associated with ischemic stroke (PAR ranging from 3.1% in southern Asia to 17.1% in western Europe, North America and Australia). According to recent studies, coronary artery calcification (CAC) is a predictor of IS in both genders, especially among younger patients, independently of AF. CAC was a good discriminator of stroke risk particularly in subjects presenting a low or intermediate (< 20%) Framingham risk score. [40, 41]

The relation between diabetes mellitus (DM) and stroke has been widely demonstrated [42, 43] Many risk factors for stroke such as hypertension, hypercholesterolemia, ischemic heart disease, and vascular claudication are more prevalent among diabetic individuals. Subcortical and lacunar infarctions are more frequent in diabetic patients than in their non-diabetic counterparts. [44]

Several studies have shown that there is also a correlation between atherogenic lipid profiles and stroke risk. In particular, low levels of high-density lipoprotein (HDL), high levels of total cholesterol (TC) and a high TC-HDL ratio increase the risk of IS in both men and women. [45, 46]

Interestingly, at younger age, all the risk factors seem to exert a stronger negative effect. [26, 47] Pregnancy has been demonstrated to increase risk especially during the third trimester and the post-partum period, probably because of hormonal changes and hypercoagulability due to activated protein C resistance, lower levels of protein S, increased fibrinogen, pregnancy-related hypertension and venous stasis. [48]

An important non-modifiable risk marker is age, with increased risks each year after the age of 19 of 9% for men and 10% for women. [47] Previous history of stroke or TIA, family history of stroke and male gender are associated with increased risk of IS. [49-51].

2.1.3 Vascular anatomy and the brain vascular territories

Blood supply to the brain is generally divided into anterior and posterior circulation. The anterior circulation consists of the middle cerebral artery (MCA) and the anterior cerebral artery (ACA). The posterior circulation comprises infratentorially the basilar artery (BA), which branches in the supratentorial space into the posterior cerebral arteries (PCA). The anterior circulation is supplied by the common carotid arteries (CCA), which typically originates on the right side from the brachiocephalic trunk and on the left side directly from the aortic arch. The common carotid artery is divided into the external carotid artery (ECA) and the internal carotid artery (ICA), which eventually supplies the intracranial anterior circulation. The posterior circulation is supplied by the vertebral arteries in both sides (VA), which usually originate from the subclavian arteries (SA). Normally, there are many connecting vessels that enable collateral flow and a communication between the carotid and the vertebrobasilar systems. The ACAs are connected by the anterior communicating artery (ACommA) and the ICAs and the posterior cerebral arteries are connected by the posterior communicating arteries (PCommA). Overall the communicating arteries form the circle of Willis (CW)

together with parts of the ACA, ICA and PCA (Figure 2). The ACA supplies the medial part of the frontal and parietal lobes. The MCA is divided in named segments based on distal subdivisions: M1, M2, M3, and M4. The MCA mainly supplies a large part of the lateral cerebral cortex, the temporal lobes and the insular cortex, the lateral parts of the frontal cortex and the anterior parts of the parietal cortex. The lenticulostriate perforating arteries, which perfuse the basal ganglia, originate from the M1, or sphenoidal, segment. This segment can be further divided into proximal M1 (M1P) and distal M1 (M1D) subsegments [52, 53]. The M2 segments are variable: The M1 segment normally bifurcates into superior and inferior divisions but sometimes trifurcates into temporal, parietal and frontal branches. The M3 and M4 segments are more distal and supply the cortex. The posterior cerebral arteries (PCAs) supply the occipital lobes and the posteromedial temporal lobes. The branches of the BA and VAs supply the cerebellum, the medulla oblongata and the pons. Anatomical variations in the cerebral vasculature are commonplace. [54, 55] Each artery supplies, in a near end-artery fashion, a different area of the brain, i.e. their vascular territories [56, 57] (Figure 3). There is a clear correlation between the vascular territory affected by stroke and the symptoms presented by the patient. [58-60]

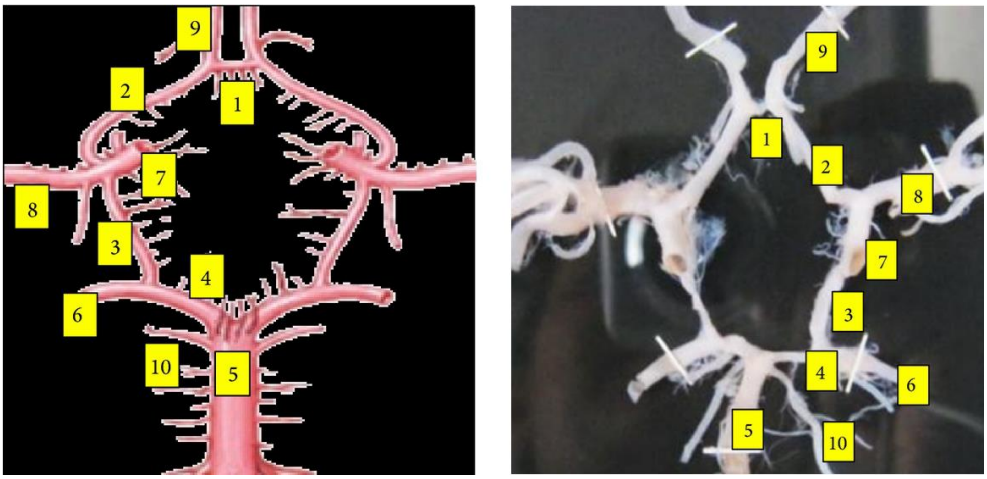


Figure 2. **Classical circle of Willis.** (1) ACommA, anterior communicating artery, (2) A1, precommunicating segment of the anterior cerebral artery (ACA), (3) PCommA, posterior communicating artery, (4) P1, precommunicating segment of the posterior cerebral artery (PCA), (5) BA, basilar artery, (6) P2, postcommunicating segment of the PCA, (7) ICA, internal carotid artery, (8) MCA, middle cerebral artery, (9) A2, postcommunicating segment of the ACA, and (10) SCA, superior cerebellar artery. From Gunnal et al. [55]

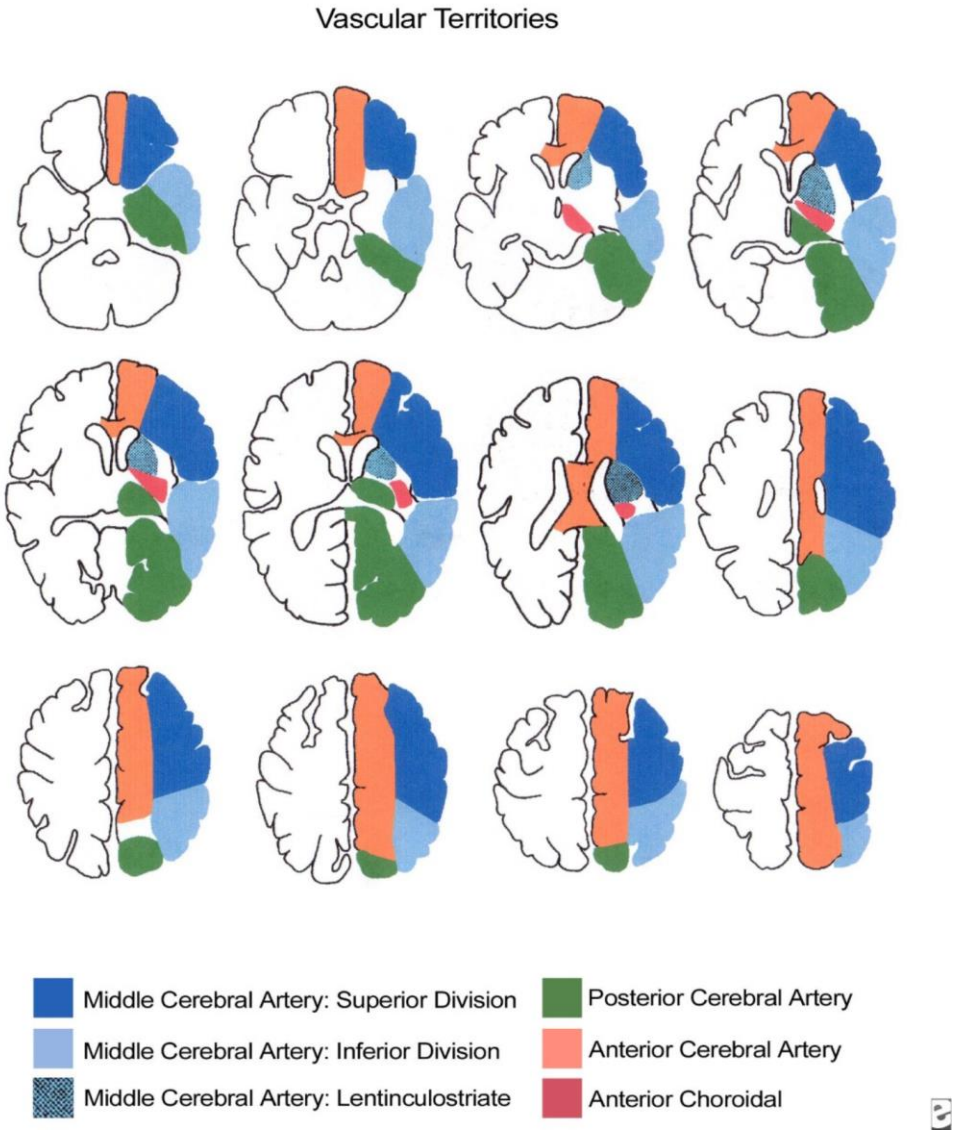


Figure 3. Vascular territories of the supratentorial brain parenchyma. Image adapted from http://emedicine.medscape.com/article/1159900-overview

2.1.4 Functional outcome measures

The modified Rankin Scale (mRs) is the most commonly used measure of global disability when evaluating recovery from stroke. Thus, it is also used as a primary functional outcome measure in the majority of randomized clinical trials (64%) [61,62]. The evaluation is usually performed at different time points (1-, 3-, and 6-months) after the onset of the episode. The scale consists of 6 categories as depicted in Table 1. The score is often dichotomized using mRS=2 as a cut-off value because it differentiates between functional independence and dependence. Thus, mRS≤2 in considered to indicate good clinical outcome. Excellent clinical outcome is indicated by a mRS ≤1. The use of structured templates for interview improves the inter-rater reliability [61]. Another rather common score system (41%) is the Barthel activities of daily living (ADL) index [62]. The dichotomization cut-off is generally ≥ 90 points.

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

Table 1. The modified Rankin scale (mRS). mRS is a 6-point scale, with higher scores indicating a worse functional outcome

2.2 DIAGNOSIS OF ISCHEMIC STROKE

Ischemic stroke is a serious condition that requires fast diagnosis and treatment. Acute ischemic stroke is generally diagnosed based on signs and symptoms revealed during neurological and physical examinations, the anamnesis of the patients and imaging findings. Patients suffering from stroke should be prioritized in the triage in the emergency department in a similar manner to patients with hemodynamically significant bleeding or myocardial infarction.

2.2.1 Symptoms and signs of acute ischemic stroke

Typical signs and symptoms of stroke are motor disruption, such as hemiparesis with or without hemisensory deficits, monocular vision loss, visual field deficits, diplopia, dysarthria and/or aphasia, facial droop, ataxia, a decrease in the level of consciousness and vertigo. These symptoms can be better depicted and evaluated during a fast neurological and physical examination with a standardized, systematic and uniform stroke scale [63, 64]. The National Institutes of Health Stroke Scale (NIHSS) is the most widely used assessment tool for evaluating stroke patients (Table 2). This scale is a 42-point scoring system that quantifies neurological deficits in 11 categories. A higher score indicates worse deficits; severe stroke is defined as NIHSS >16, moderate as NIHSS between 8 and 16 and mild as NIHSS <8. When a patient is suspected of having IS, other possible conditions that can mimic neurovascular syndrome (i.e., "stroke mimics") must be excluded. [65-67] The most common conditions that mimic stroke are postictal states, sepsis, tumors, toxic and metabolic disturbances, syncope, intracranial abscesses, migraine, hypoglycemia, hypertensive encephalopathy, neuroimmunologic disease, polyradiculitis and myasthenia gravis [65-67]

Category	Score/Description
1a. Level of Consciousness (LOC)	0 = Alert 1 = Drowsy 2 = Stuporous 3 = Coma
1b. LOC Questions **(Month, age)**	0 = Answers both correctly 1 = Answers one correctly 2 = Incorrect
1c. LOC Commands **(Open/close eyes, make fist/let go)**	0 = Obeys both correctly 1 = Obeys one correctly 2 = Incorrect
2. Best Gaze **(Eyes open – patient follows examiner's finger or face)**	0 = Normal 1 = Partial gaze palsy 2 = Forced deviation
3. Visual Fields **(Introduce visual stimulus/threat to patient's visual field quadrants**	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia (blind)
4. Facial Paresis **(Show teeth, raise eyebrows and squeeze eyes shut)**	0 = Normal 1 = Minor 2 = Partial 3 = Complete
5a. Motor Arm – Left **5b. Motor Arm – Right** **(Elevate arm to 90 degrees if patient is sitting, 45 degrees if supine)**	0 = No drift 1 = Drift 2 = Cannot resist gravity 3 = No effort against gravity 4 = No movement
6a. Motor Leg – Left **6b. Motor Leg – Right** **(Elevate leg to 30 degrees with patient supine)**	0 = No drift 1 = Drift 2 = Cannot resist gravity 3 = No effort against gravity 4 = No movement
7. Limb Ataxia **(Finger-nose, heel down shin)**	0 = No ataxia 1 = Present in one limb 2 = Present in two limbs
8. Sensory **(Pin prick to face, arm, trunk, and leg – compare side to side)**	0 = Normal 1 = Partial loss 2 = Severe loss
9. Best Language **(Name item, describe a picture and read sentences)**	0 = No aphasia 1 = Mild to moderate aphasia 2 = Severe aphasia 3 = Mute

10. Dysarthria **(Evaluate speech clarity by patient repeating listed words)**	0 = Normal articulation 1 = Mild to moderate slurring of words 2 = Near unintelligible or worse X = Intubated or other physical barrier
11. Extinction and Inattention **(Use information from prior testing to identify neglect or double simultaneous stimuli testing)**	0 = No neglect 1 = Partial neglect 2 = Complete neglect

Table 2. The National Institute of Health Stroke Scale (NIHSS). The NIHSS quantifies neurological deficits into 11 categories. Higher scores indicate greater deficits. Adapted from Richardson et al. [68]

2.2.2 Imaging of acute ischemic stroke

Primarily, imaging of a patient suffering symptoms of stroke is performed to distinguish between hemorrhagic and ischemic stroke, as these categories have completely different general treatment approaches. Other important information that can be obtained with imaging includes the extent of the ischemic brain parenchyma, the site of the occlusion, and an estimate of the volume of the irreversibly damaged parenchyma.

Diagnostic imaging of acute IS is performed with multimodal computed tomography (MCT) or MRI [69]. Due to the widespread availability and shorter scanning durations MCT is used more frequently [70, 71]. MCT is based on a multidetector technology, which allows continuous scanning of thin section-widths in a short time. MCT consists of three modalities: 1) non-enhanced CT (NECT), which permits the exclusion of hemorrhage and highlights early ischemic changes (EICs); 2) CT angiography (CTA), which gives information about the intra- and extracerebral vasculature, the location of the clot and possible stenosis of large vessels; and 3) CT perfusion (CTP), which provides a functional perspective of the brain circulation by providing information on the perfusion of the parenchyma and on the regional hemodynamic status.

2.2.2.1 Non-enhanced CT and Alberta Stroke Program Early CT Score (ASPECTS)

NECT is the first imaging modality obtained using an MCT protocol. The main purpose of the study is to discriminate between hemorrhagic and ischemic stroke. Secondarily, NECT can be used to detect EICs and to exclude pathologies, which could mimic a stroke, such as central nervous system (CNS) tumors. NECT can to some degree predict the possibility of post-treatment hemorrhagic complications following IVT or intra-arterial interventions. [72-74]

EICs observed in an NECT scan within 8 h of symptom onset include 1) loss of visualization of the gray-white matter interface, which operationally constitutes subtle parenchymal hypoattenuation with or without swelling, 2) isolated parenchymal swelling without hypoattenuation, and 3) focal hyperattenuation of an arterial trunk, which is an additional sign that can be considered a surrogate for ongoing parenchymal ischemia. These categories include some well-known imaging signs such as the dense media sign or hyperdense middle cerebral artery sign (HMCAS), which indicates M1 and proximal M2 segment thrombosis, the MCA dot sign, which may indicate thrombosis in the insular branches of the MCA (the distal M2 and M3 segments), and the insular ribbon sign, which indicates loss of definition of the gray-white interface of the insula and the obscuration or partial disappearance of the lentiform nucleus. Unfortunately, the interobserver agreement and reproducibility of EICs is poor and they are insensitive for detecting acute ischemic stroke especially in the hyperacute phase (onset to imaging time < 3h). [73] The presence of EICs depends on the duration of the hypoperfusion. [75] Nevertheless, these findings cannot reliably differentiate between irreversibly damaged brain tissue and penumbra. However, isolated focal swelling is associated with penumbra and frank parenchymal hypoattenuation with the infarct core and thus poor functional outcome [75-80]. The extent EICs is predictive of the risk of hemorrhagic transformation. [72-74, 81, 82] The issues arising from the difficulties to reliably detect EICs have been in part overcome with the use of standardized semiquantitative methods such as the Alberta Stroke Program Early CT Score (ASPECTS). This method is an algorithmic, topographically structured scoring system that allows semiquantitative assessment of the extent of acute ischemic changes in the anterior circulation. [83-85] Only parenchymal hypoattenuation is considered a finding in the scoring system. Each hemisphere is divided into 10 regions (Figure 4) and each of these regions can be scored 1 point. This point is deducted if the region shows EICs. Thus, a full negative finding yields a score of 10, and extensive ischemia covering the entire MCA region yields a score of 0. If

the ASPECTS score is ≤6, based on volumetric correlates more than one-third of the MCA territory is affected. When the ASPECTS score is ≤7 (3 or more regions affected) the patient is unlikely to achieve an independent functional outcome. [86] Overall, ASPECTS applied to NECT images is predictive of the clinical outcome, the effectiveness of IVT and IAT and the rate of hemorrhagic complications but remains a suboptimal technique for intra-arterial treatment decision making because of the inherent insensitivity of NECT. [84, 87-90]

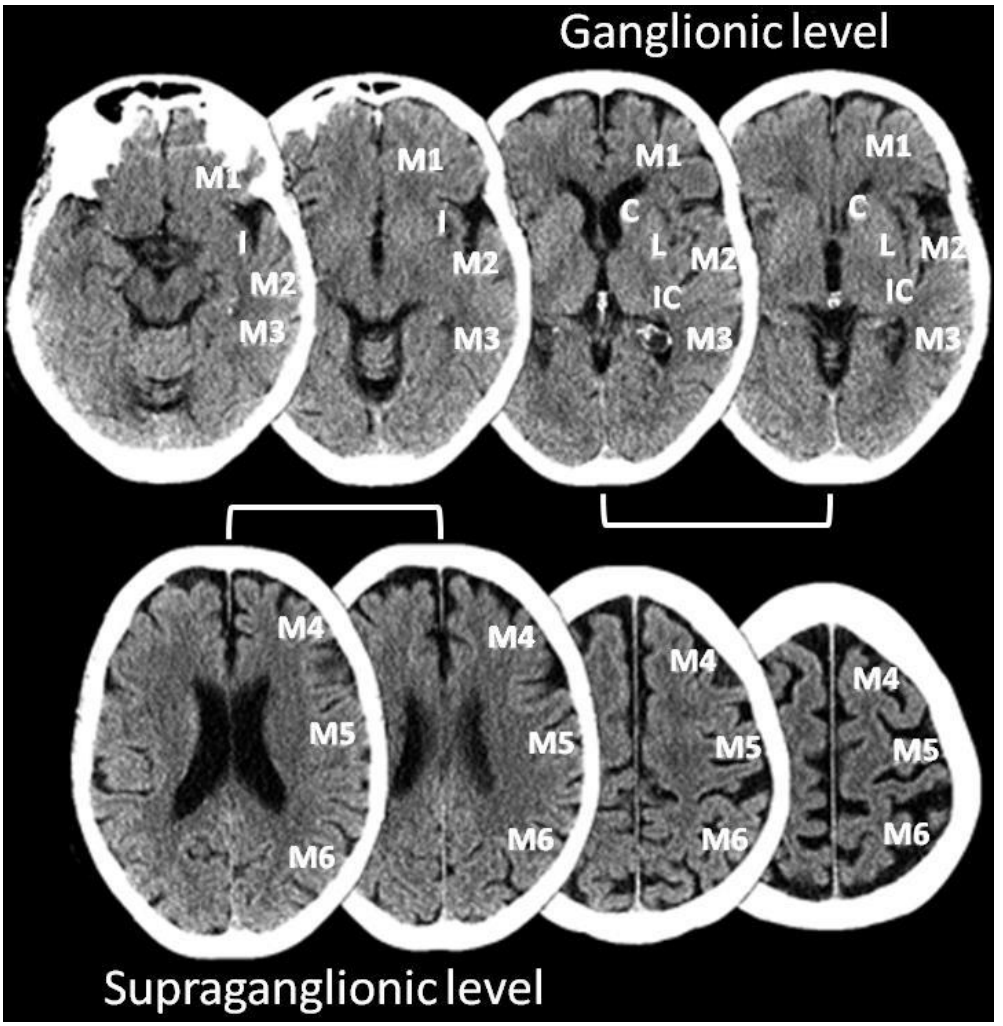


Figure 4. Axial NECT images showing the MCA territory subregions as defined by ASPECTS. White brackets indicate the ganglionic and supraganglionic levels. C - Caudate nucleus, I - Insular ribbon, IC - Internal capsule, L - Lentiform nucleus, M1 - Anterior MCA cortex, M2 - MCA cortex lateral to the insular ribbon, M3 - Posterior MCA cortex, M4, M5, and M6 - the anterior, lateral and posterior MCA territories immediately superior to M1, M2 and M3, respectively, and rostral to the basal ganglia. Subcortical structures are allotted 3 points and the MCA cortex is allotted 7 points. The image is adapted from www.aspectsinstroke.com

2.2.2.2 Computed tomography angiography

CTA is generally the second modality acquired in a multimodal CT protocol. Typically, a volume from the aortic arch up to the vertex of the skull is obtained to cover both the intra- and extracerebral vasculature. Thin-section slices of isotropic spatial resolution are calculated to enable the reconstruction of two-dimensional (2D) reformatted images in arbitrary planes, maximum intensity projection (MIP) images and three-dimensional (3D) images. They provide detailed information on the cerebral vasculature that is comparable with that obtained using digital-subtraction angiography (DSA) [91-96]. Hence, large- and small vessel occlusions and stenosis can be detected by CTA highly accurately (95-99%) both intracranially and extracranially [23, 23, 97, 98].

The importance of this imaging tool in the triage of acute stroke patients to different revascularization therapies was recently demonstrated in five randomized and controlled trials, which assessed the possible superiority of MT over IVT treatment. All these trials used vascular imaging with CTA as a diagnostic tool in their protocol [13-17]. CTA not only allows the detection of a thrombus in the intracerebral vasculature but also enables the evaluation of the length and density of the clot, which plays a role in the treatment decision-making process. [95] These are all independent prognostic factors of acute ischemic stroke for which proximal, high-volume, organized clots predict poor clinical outcomes compared with distal, low-volume, fresh clots. [99-101] This is related to the rate of recanalization with IVT, which is lower in proximal vessel positions, with high clot burden and clots with lower average Hounsfield Unit (HU) values. These intrinsic factors also influence the recanalization rate with IAT and should guide therapeutic decision making and the choice between IVT, intra-arterial interventions or refraining from revascularization therapy [52, 101-111]

To simplify the evaluation of the location and extent of the thrombus a semiquantitative clot burden score (CBS) has been developed. [110, 112] The CBS is a 10-point scoring system. Points are assigned based on the number and location of arterial segments affected in the anterior circulation (Figure 5). Similar to ASPECTS, a higher score indicates a lower clot burden. CBS correlates with technical and clinical outcomes. Patients with higher scores are more likely to experience better functional outcomes, smaller infarct volumes, and lower hemorrhagic complication rates. [109, 110, 112]

Other important roles of CTA are facilitating proper planning of the endovascular procedure for device selection and enabling shorter intervention durations [113, 114] Limitation of CTA include the use of ionized radiation and the use of iodinated contrast medium, which in rare cases, can lead to contrast induced nephropathy (CIN).

Figure 5. Schematic representation of the clot burden score (CBS). One or two points each are subtracted from a total score of 10 when no contrast opacity is detected using CTA in the infraclinoid ICA (1 point), supraclinoid ICA (2 points), proximal M1 segment (2 points), distal M1 segment (2 points), M2 segment branches (1 point each) and A1 segment (1 point), as indicated by the numbers next to the corresponding vessel segments. CBS applies only to the symptomatic hemisphere. From Puetz et al. [110]

2.2.2.3 Computed tomography angiography source images

Unprocessed source images of CTA (CTA-SI) can also be used to estimate EICs and have increased sensitivity compared to NECT. [115] When capturing the steady state of the contrast agent, CTA-SI is a surrogate of CBV and, thus, approximates the extent of irreversible ischemic damage [116, 117]. The

attenuation values for brain tissue are directly proportional to the amount of contrast material that has arrived within the parenchyma at the time of imaging. The reduction and/or delay of blood supply to the ischemic area leads to hypoattenuation in CTA-SI in contrast to later cytotoxic edema on NECT [118](Figure 6). Therefore, CTA-SI is more sensitive to acute ischemia than NECT and subsequently more precise in the prediction of infarct extension, hemorrhagic complications and clinical outcome. [115, 116, 118-121] Rapid CTA image acquisition at an early time point precludes the contrast agent from fully traversing collateral vessels and reaching the distal vascular bed, thereby increasing the volume and severity of hypoattenuation in the ischemic parenchyma and leading to overestimation of the infarct core [122-124]. In contrast, frank hypoattenuation on NECT is highly specific for irreversible tissue damage suggesting that CTA-SI must be interpreted carefully in relation to NECT findings in addition to adjusting CTA protocols to minimize the overestimation problem [75-80].

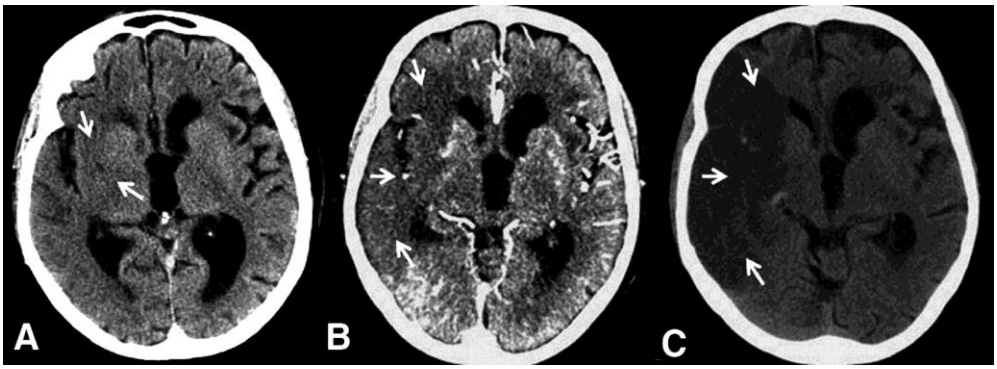


Figure 6. **Baseline NECT (A**) showing early ischemic changes in the right MCA territory (arrows). CTA-SI image (**B**) reveals hypoattenuation in the right MCA territory (arrows), which corresponds to the final infarct (**C**) on follow-up CT scan (arrows). NECT indicates noncontrast CT; MCA, middle cerebral artery; CTA-SI, CT angiography source image. From Bhatia et al. [116]

2.2.2.4 Evaluation of the collateral circulation

The cerebral collateral circulation is a dynamic, interconnected vascular system that preserves the brain parenchyma from ischemic damage. There is large variation in this vascular network among individuals. Collateral vasculature can be divided into primary and secondary pathways. The former pathways make up a system that

allows communication between the two hemispheres and consists of artery-to-artery communications, i.e., the circle of Willis. The latter pathways become evident during the occlusion of large intracranial vessels and include the vascular network between the internal and external carotid arteries and the leptomeningeal pial arteriolar anastomoses. Sufficient flow through the collateral pathways allows the brain tissue to remain viable even if the normal antegrade flow supplying the tissue volume is diminished or interrupted [125-128]. The most important factor influencing the integrity of collaterals is age, each 10-year increment in patient age increases the odds of inadequate collateral circulation by 1.8-fold [129-131]. Smoking, hypertension, elevated uric acid and glucose levels at the time of presentation are other factors that negatively influence the development of collateral circulation [130, 132]. Even though digital subtraction angiography (DSA) is the gold standard for anatomical and functional evaluation of collateral vessels [133], collateral circulation can also be assessed non-invasively. Typically, CTA is used to evaluate the collateral network before stroke therapy. Many collateral scoring (CS) systems have been proposed. One of the more widely adopted systems is that described by Souza et al., which is based on the evaluation of maximum intensity projection (MIP) reconstructions (Figure 7)[134].

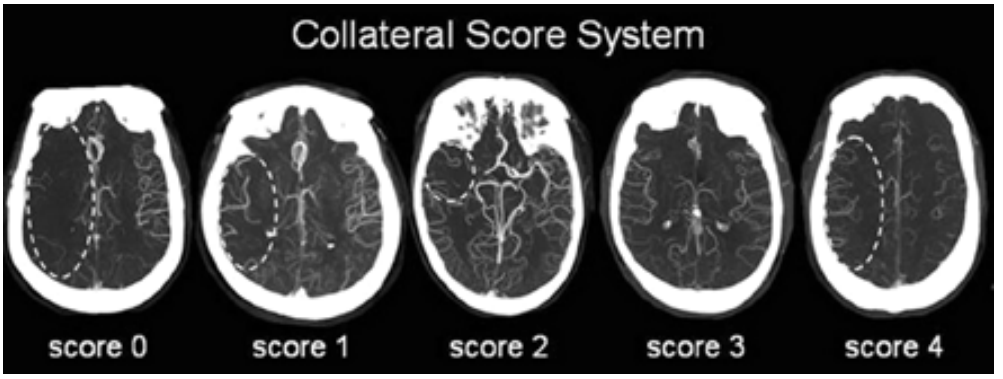


Figure 7. CS system: 0 = absent collaterals >50% of an M2 territory; 1 = diminished collaterals >50% M2 territory; 2 = diminished collaterals <50% M2 territory; 3 = collaterals equal to contralateral side; 4 = increased collaterals. From Souza et al. [134]

Adequate collateral flow reduces the baseline infarct core and the expansion of the core, decreases the risk of hemorrhagic transformation and increases the odds of a

good clinical outcome in-hospital, at discharge and six months after the stroke. [112, 132, 135-140] The richness of the collateral network predicts the final infarct volume in both patients with persistent arterial occlusion and those experiencing recanalization [132, 141, 142]. Two recent randomized trials (ESCAPE and EXTEND-IA)[14, 17] validate the concept of CS as a central feature in the evaluation of stroke patients who were candidates for MT by employing CTP instead of single-phase CTA. Single-phase CTA does not provide temporal resolution. Therefore, collateral status may be mischaracterized in many patients and is usually underestimated. Dynamic CTA is a technique that derives time resolved images of pial arterial filling from CTP images; however, dynamic CTA requires postprocessing and whole-brain CTP. As an alternative, multiphase (arterial, arteriovenous, and venous phases) dynamic CTA rapidly provides easily interpretable information regarding the degree and extent of pial arterial filling in the whole of brain parenchyma in a time-resolved manner. Supporting this concept, the inter-rater reliability for multiphase CTA is excellent. In multiphase collateral scoring (ranging 0 to 5) collateral status on the affected side is considered to be poor compared to same arterial trunks in the asymptomatic contralateral hemisphere when there are no vessels visible in any phase within the occluded vascular territory, only a few vessels visible, or minimal to no collaterals visible in a region greater than 50% of the MCA territory [143-146].

2.2.2.5 Computed tomography perfusion

The third and final modality acquired in a multimodal protocol is CTP, a dynamic imaging modality that provides information on cerebral hemodynamics. CTP consists of serial CT imaging of a volume of brain parenchyma in rapid succession after an injection of an iodinated contrast agent. This procedure enables quantification of capillary level phenomena of cerebral blood flow. The concentration of the iodinated contrast agent in the brain parenchyma and, hence, the CT density changes time-dependently as depicted by time-density curves. These curves are used to derive CTP parametric maps, which reflect different aspects hemodynamics [147-151]:

1) Cerebral Blood Flow (CBF): the volume of blood moving through a brain volume (mass) of interest per unit time ([CBF] = ml/100 g/min).

2) Cerebral Blood Volume (CBV): the total volume of blood in a given brain volume (mass) of interest ([CBV] = ml/100 g). This volume includes the intracellular, intravascular and extravascular interstitial spaces.
3) Mean Transit Time (MTT): the average difference in time between the arterial inflow and the venous outflow of a brain region-of interest ([MTT] = s). This time is dependent on the average distance travelled. MTT can be calculated from the CBF and CBV based on the central volume principle [152]: MTT = CBV/CBF.
4) Time to Peak (TTP): the time from the beginning of the arterial enhancement to the peak of the enhancement curve ([TTP] = s).

There is a large variety of algorithms available to calculate the different perfusion parametric maps from the raw CT data. These algorithms can be classified as 1) non-deconvolution or 2) deconvolution techniques [150]. Non-deconvolution techniques use first-pass contrast agent measurements and apply several simplifying assumptions, which lower the accuracy of the results. Deconvolution techniques discard some of these assumptions and also take into consideration recirculation of the contrast agent, collateral flow, delays in the delivery of the contrast agent and venous output. Thus, the deconvolution algorithms are more complex and sensitive [153-155]. There are also differences in image acquisition protocols. Standardization and validation of the quantitation of perfusion parameters across different vendor platforms or even across different platforms from the same vendor remain ongoing processes [153, 156-158]. Further, different manual, semi-automated and fully automated image reconstruction workflows add to the variation caused by differences in algorithms. In particular, the selection of arterial input and venous output vessels may vary. Generally, the A2 segment of the anterior cerebral artery and the sagittal sinus are chosen as arterial input and venous output because this seems to minimize problems caused by volume averaging [159-161].

The main goal of an acute stroke perfusion study is to assess the viability of the ischemic tissue, i.e., to identify the irreversibly damaged tissue (the infarct core), the tissue that is at risk for progression to infarction if reperfusion is not achieved (the penumbra) and the normally perfused, benignly hypoperfused or hyperemic tissue [151, 156, 162, 163]. Experimental studies have demonstrated that these hemodynamic states are characterized by different functionally defined CBF thresholds, as follows: 1) The threshold below which cortical function ceases without an increase in extracellular potassium or reduction in pH (the penumbra)

and 2) the threshold below which there is disruption of cellular integrity (the core) [20]. These functional definitions have been correlated with advanced neuroimaging findings— perfusion parametric maps—to define a more clinically relevant operational penumbra identified as hypoperfused but potentially salvageable tissue. [162, 164-167] The operational penumbra is the mismatch (subtraction) volume between the CBF or MTT (or TTP) and the CBV, in which the CBV lesion reflects the infarct core and the CBF or MTT (or TTP) lesion reflects the boundaries of the hypoperfused penumbral tissue [153]. This concept was initially validated for MRI, and MRI and CT results were later correlated [121, 168]. The perfusion parameters that best define the core and the penumbra remain a topic of discussion. This task is challenging, as both regions are dynamic in character because of the nature of the disease process. MTT maps potentially overestimate the size of perfusion defects, while CBV maps may overestimate or underestimate the volume of the irreversibly damaged brain parenchyma [157, 169]. Some studies suggest that threshold CBF values may assess the core more accurately than CBV cut-offs [154, 158, 170, 171] and that TTP could be more closely related to penumbra than MTT [172].

Accurate evaluation of the infarct core at presentation seems to be one of the most valuable imaging–based prognostic factors. An infarct core volume of 70-100 ml strongly indicates poor outcome regardless of recanalization and penumbra volume [173-176]. Moreover, even successful large vessel recanalization reperfusion at the capillary level can be insufficient. This could be due to downstream embolization and microvascular obstruction or cytotoxic edema within the penumbral region precluding tissue perfusion. Hence, the predictive role of penumbra volume at presentation remains partly unclear and it only becomes a relevant predictive factor if evaluated in the context of recanalization data [176-180].

In two of the recent pivotal randomized trials comparing MT to IVT (EXTEND-IA and SWIFT PRIME [15, 16]) CTP evaluation of the size of the infarct core and the volume of salvageable tissue was successfully used as inclusion criteria.

The ASPECTS scheme has been validated for CTP parametric maps, which provides another method for quantifying CTP findings in the anterior circulation, including calculating the perfusion mismatch [21, 180-184]. CTP-ASPECTS, especially CBV-ASPECTS, better predicts clinical outcome compared to admission NECT and CTA-SI [17, 86, 86, 180, 185]. Kloska et al. suggested that the optimal threshold value for CBV-ASPECTS that best differentiated between good and

poor clinical outcomes was ≤7. Furthermore, Aviv et al. found that no patients with CBV-ASPECTS ≤7 achieved good clinical outcome [21, 89]. In our previous study patients having CBV-ASPECTS ≥7 performed best in an ROC analysis [184].

2.2.2.6 Evaluation of recanalization

The Thrombolysis in Cerebral Infarction (TICI) score grading system was originally described in 2003 by Higashida et al. [133] to evaluate the grade of reperfusion following IVT in patients suffering from acute stroke. In neurointerventional radiology, TICI scores are commonly applied to grade the DSA control runs of endovascularly-performed recanalization.

The original definition was based on the angiographic post-intervention appearance of the site of the occlusion and the distal branches:

- TICI 0: no perfusion
- TICI 1: penetration of the contrast agent with minimal perfusion
- TICI 2: partial perfusion
    - 2a: only partial filling (less than two-thirds) of the entire vascular territory is visualized
    - 2b: complete filling of all of the expected vascular territory is visualized but the filling is slower than normal
- TICI 3: complete perfusion

Because of marked variability in the application of this score, in 2013 a consensus paper from three collaborative groups [53] proposed a modified scale, the m-TICI score:

- m-TICI 0: no perfusion
- m-TICI 1: antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion
- m-TICI 2:

- 2a: antegrade reperfusion of less than half of the previously occluded target artery ischemic territory
- 2b: antegrade reperfusion of more than half of the previously occluded target artery ischemic territory

- m-TICI 3: complete antegrade reperfusion of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches

2.3 ACUTE ISCHEMIC STROKE MANAGEMENT

Acute stroke therapy aims to 1) restore perfusion of the ischemic brain tissue as rapidly as possible [186-188], 2) limit the amount of damage to the ischemic tissue whether caused by primary (hypoperfusion) or secondary (for example, hyperglycemia or hyperthermia) mechanisms, and 3) decrease the probability of complications (such as hemorrhagic transformation) [189]. Based on data from both experimental models and clinical trials, the duration and severity of ischemia determines the extent of irreversible damage [10, 186, 190]. However, potentially viable ischemic tissue (i.e., the penumbra) has been demonstrated to exist for at least 24 h after symptom onset [191, 192]. Overall, the time elapsed from the onset of the symptoms to treatment is a critical determinant of the outcome, which guides decision–making processes and pre- and in-hospital management. [10, 193-195]

The following interventions have been explicitly proven to improve the prognosis after acute IS: 1) management of the patient in a stroke unit [196, 197], 2) use of aspirin within the first 48 h from onset [198-200], 3) decompressive surgery (hemicraniectomy) for supratentorial malignant hemispheric cerebral infarction [201, 202], 4) administration of IVT within 4.5 h from symptom onset [201-203], and 5) MT with a stent retriever in the case of large vessel occlusion (up to the M1 segment) [204-207]. The goal of the last two therapies is to achieve a prompt revascularization and reperfusion of the ischemic area by pharmacologically or mechanically disrupting the occluding thrombus.

Currently available revascularization therapies include IVT, intra-arterial thrombolysis (IAT) possibly assisted with balloon angioplasty, IVT followed by an intra-arterial intervention, MT using aspiration, stent retrievers, other specific

retrieval devices or a combination of these therapies, and bypass stenting. Recently, the completion of five randomized trials on MT performed with stent retrievers led to a shift in treatment paradigm towards intra-arterial therapies as a first-line approach [13-17].

2.3.1 Intravenous thrombolysis

IVT is a well-established treatment of acute IS that was approved by the Food and Drug Administration (FDA) in 1996. It essentially entails the intravenous administration of a tissue plasminogen activator (TPA), a serine protease that elicits dissolution of the clot by activating plasmin by conversion of plasminogen [208]. Streptokinase and urokinase were originally used for this purpose, but they were subsequently replaced by a new generation of recombinant tissue plasminogen activators (r-tPAs) that selectively activate fibrin-bound plasminogen and thus have better efficacy and specificity [209].

The most relevant trials on IVT are the Neurological Disorders and Stroke Trial (NINDS), which proved the feasibility and efficacy of IVT in a time window of 3 h from symptom onset [203], The European Cooperative Acute Stroke Study (ECASS), ECASS II, and the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) study, which evaluated the efficacy and safety of IVT within a time window up to 6 h, but did not demonstrate treatment benefit [210-212]. Nonetheless, two later studies, ECASS III and the Safe Implementation of Thrombolysis in Stroke–International Stroke Treatment Registry (SITS-ISTR), succeeded in demonstrating efficacy and safety of IVT within a prolonged time window of 4.5 h [213, 214]. Further studies have examined the feasibility of IVT beyond the 4.5 h window using MRI to evaluate the ischemic penumbra. The Desmoteplase in Acute Ischemic Stroke (DIAS) study used an extended the time window of 9 h and failed to demonstrate efficacy [215-217]. The Diffusion-weighted Imaging Evaluation For Understanding Stroke Evolution (DEFUSE) study demonstrated the utility of different MRI mismatch profiles for evaluating patients who are likely to have good outcome after IVT when treated between 3 h and 6 h from symptom onset [218]. The Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) and the Third International Stroke Trial (IST-3) also evaluated a treatment time window beyond 4.5 h with no positive results. Recently, the introduction of new MT devices has reduced the interest in an IVT-only approach [219-224].

A feared complication of IVT is intracerebral hemorrhage (ICH), which can be fatal [203, 213]. Other potential adverse effects include systemic bleeding, myocardial rupture if IVT is administered within a few days of AMI, and immunological reactions such as anaphylaxis or orolingual angioedema, although these events are rare [65]. Exclusion criteria have been defined to minimize the possibility of complications (Table 3).

The relative exclusion criteria for IVT include minor or spontaneously rapidly improving symptoms, pregnancy, seizure at onset with postictal residual neurological impairments, major surgery or serious trauma within the previous 14 days, recent gastrointestinal or urinary tract hemorrhage (within the previous 21 days) and recent AMI (within the previous 3 months) [65]. Further, relative exclusion criteria within 3 to 4.5 h after symptom onset include >80 years of age, severe stroke (NIHSS>25), taking an oral anticoagulant regardless of INR and histories of both diabetes and prior to IS [65]

Exclusion criteria
Significant head trauma or prior stroke in previous 3 months
Symptoms suggest subarachnoid hemorrhage
Arterial puncture at noncompressible site in previous 7 days
History of previous intracranial hemorrhage
Intracranial neoplasm, arteriovenous malformation, or aneurysm
Recent intracranial or intraspinal surgery
Elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg)
Active internal bleeding, acute bleeding diathesis, including but not limited to Platelet count <100000/mm
Heparin received within 48 h, resulting in abnormally elevated aPTT greater than the upper limit of normal

Current use of anticoagulant with INR >1.7 or PT >15 s
Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests
Blood glucose concentration <50 mg/dL (2.7 mmol/L)
CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)

Table 3. IVT exclusion criteria. Absolute exclusion criteria for patients with ischemic stroke who could be treated with IVT within 4.5 h of symptom onset

2.3.2 Intra-arterial therapy

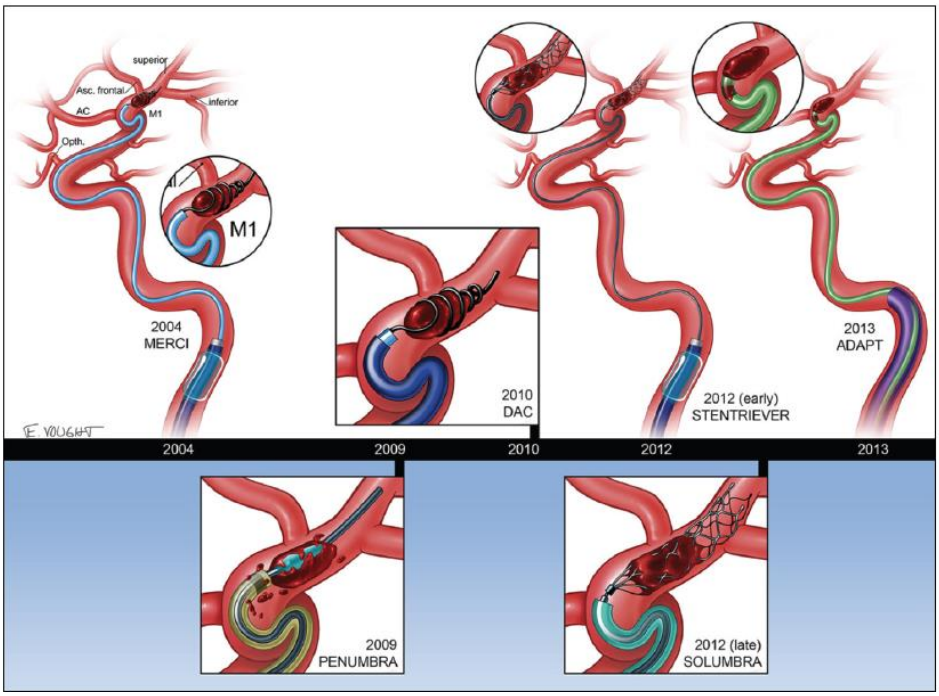
The options for endovascular treatment to elicit recanalization of an intracranial or extracranial artery supplying the brain tissue include balloon angioplasty, (bypass) stenting, intra-arterial thrombolysis (IAT) and mechanical thrombectomy (MT) with either aspiration-based or stent-based devices.

Angioplasty and stenting of extracranial ICA are predominantly performed for secondary or primary prevention rather than to treat acute IS but may be combined with MT in some cases: when the primary cause of stroke is acute attenuation or cessation of flow in the extracranial ICA, such as from total or near-total occlusion caused by an active, severe atherosclerotic lesion or dissection or when catheter access to an intracranial clot is impeded by severe stenosis of the extracranial ICA and angioplasty/stenting of the ICA is required prior to treatment of a more distal intracranial occlusion [189, 225].

Two of the most important studies on IAT were the phase two Prolyse in Acute Cerebral Thromboembolism (PROACT) and PROACT II trials [11, 12]. In both studies, the pharmacological intervention consisted of intra-arterial injection of recombinant prourokinase (r-proUK) with or without intravenous heparin, which were both administered within 6 h of symptom onset. The recanalization rates and clinical outcome were better than with IVT only; however, the probability of intracranial hemorrhagic complication was higher. The Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) also suggested the trend that excellent clinical outcomes were achieved more often with IAT [226]. Further

studies on IAT included the Interventional Management of Stroke (IMS) trials I and II [227, 228]. They combined intra-arterial and intravenous thrombolysis with r-tPA administration within the 3-h time window and compared the results with the NINDS study population. The investigators reported that the 3-month outcome was significantly better compared to the NINDS placebo arm, whereas there was only a trend toward improved outcomes compared with the NINDS r-tPA arm. The Interventional Management of Stroke III (IMS III) trial patients were administered IVT within 3-h of symptom onset and then randomly assigned to receive IVT alone or IVT followed by endovascular therapy. Despite the higher rate of partial or complete recanalization at 24 h in the endovascular group, clinical outcomes of the two groups were similar, and the trial was stopped early due to futility [229]. Vagal et al., using the data from the IMS III, demonstrated in a post hoc model that endovascular therapy after IVT is preferable to IVT alone if the reperfusion time was less than 347 min [230]. These findings highlight the importance of developing new techniques to achieve faster and more efficient recanalization with intra-arterial devices.

The introduction of stent retrievers launched a period of a great progress regarding the intra-arterial treatment of acute IS. Stent retrievers are soft nitinol stents that are deployed within the thrombus to push the thrombus against the vessel wall, immediately reperfusing the distal brain tissue. After a short incubation period, which is suggested to be up to 5 minutes [231], the thrombus usually adheres to the struts of the stent, and the stent is then retrieved along with the clot by withdrawing the stent under aspiration from a more proximal catheter. Removal of the stent also eliminates the need for acute double-antiplatelet therapy, which is needed for permanent stent placement in the cerebral vasculature (Figure 8).



A

Figure 8. A timeline depicting the strategies and techniques employed over the time to achieve recanalization of a large vessel occlusionan ELVO in the setting of acute ischemic stroke. Adapted, From Spiotta A.M. et al. [232, 233]

Stent retriever technology was preceded by the MERCI retriever system introduced in the early 2000s (Figure 8). This device included most of the mechanisms of action of stent retrievers, but the design was not stent-based. The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial was a single-arm study that included patients between 3-8 h from symptom onset or within 3 h if there was a contraindication to IVT or if the treatment had failed [234]. This trial was extended in the Multi MERCI study, an international, multicenter study in which a newer device (the L5 retriever) was used if available [235]. In the late 2000s, a second device was approved, the Penumbra endovascular aspiration device. In the Penumbra Pivotal Stroke Trial 81% of patients achieved recanalization of the occluded vessel but only 25% had mRS≤2 at three months [236]. Penumbra caused fewer hemorrhagic complications than MERCI but corresponded to worse neurological outcome, possibly due to distal embolization [237]. The Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trial compared thrombectomy (performed using MERCI or a Penumbra device) to

IVT, and no statistical significant difference was found between the two groups, but the rate of TICI grade 2b/3 recanalization was low (25%) and the onset to groin puncture time was 381 +/- 74 (mean+/-SD) [238]. Overall, sufficient proof of efficacy of these devices was not obtained in these studies or meta-analyses thereof.

During the past eight years, a number of studies and trials have investigated the feasibility, safety and efficacy of MT with newer generation stent-based thrombectomy devices [239-243]. This effort culminated in six multi-center, prospective, randomized and controlled trials (MPRCTs), which were set up to compare MT in association with IVT to IVT alone. As a result of these trials, endovascular therapy with stent retriever thrombectomy is now the standard of care for patients with acute large-vessel occlusion in the anterior circulation [189].

The first of those trials, the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) enrolled 500 patients. Retrievable stents were used in 190 of the 233 patients (82%) in the intervention group, and simultaneous acute cervical carotid stenting was performed in 30 patients (13%). Good reperfusion rate was achieved in 59% of patients in the intervention group, and there was a significant shift in the distribution of mRS scores of 0-5 at 90 days in favor of the intervention, regardless of age. There was no difference in the complication rate. However, in the presence of extracranial ICA occlusion, admission NECT ASPECTS of <8 or NIHSS <20, the adjusted odds ratios (ORs) were accompanied by wide confidence intervals (CIs) [13].

In the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial imaging was used to exclude participants with a large infarct core and/or poor collateral circulation. Stent retrievers were used in 130 of the 151 participants (86%) who underwent an endovascular procedure, and the rate of the good reperfusion was 72%. In contrast, in the control group, successful recanalization was observed in 43 of 110 patients (31%). The proportion of patients with mRS≤2 at 90 days was 53% in the intervention group and 29% in the control group, and mortality at 90 days was 10% in the intervention group and 19% in the control group. However, for the presence of a carotid T- or L- occlusion, admission NECT ASPECTS of <8 or patient age >80 years, the adjusted ORs were accompanied by wide CIs. The study was suspended prematurely because of high efficacy in the intervention group [14].

The Extending the Time for Thrombolysis in Emergency Neurological Deficits — Intra-Arterial (EXTEND-IA) trial was also stopped early because of high efficacy in the intervention group. The trial had recruited just 70 patients, 35 in each group. This study used CT perfusion to identify salvageable brain tissue. The rate of successful revascularization immediately after the procedure was 86% (with a restoration of flow of >50% of the affected vascular territory), and the reperfusion rate at the 24 h follow-up was 100%. In the IVT-only group, the recanalization rate was 15 of 35 (43%). In addition, early neurologic improvement was observed significantly more often in the intervention group (80% vs. 37%). Endovascular therapy improved the functional outcome at 90 days with a significantly larger proportion of patients achieving functional independence (71% vs. 40%). Subgroup analyses could not be performed given the small number of patients [17].

The Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) trial compared IVT followed by MT with the Solitaire FR or Solitaire 2 stent retriever to IVT alone. The study was also stopped early because of efficacy and it enrolled 196 patients from 39 different centers, (98 patients in each group) Similar to EXTEND-IA, viable tissue demonstrated in CTP was an inclusion criterion. Eighty-eight percent of patients treated with MT exhibited substantial or complete reperfusion defined as perfusion of 50% or more of the vascular distribution of the occluded artery. Functional independence at 90 days was significantly more common in the intervention group compared to the control group (60% vs. 35%). There was no evidence of heterogeneity in the treatment effect in the subgroups. In the subgroup corresponding to patients admitted with NECT ASPECTS of 6-7, 10 of 24 patients were independent in the intervention group compared to 5 of 19 in the IVT-only group [16].

The Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to an Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT) trial compared MT with medical therapy alone in eligible patients who received IVT within 4.5 h after the onset of symptoms without revascularization after 30 min of t-PA infusion or who exhibited a contraindication to IVT. Two-hundred-six patients were enrolled, 103 in each group. A NECT ASPECTS less than 7 or an MRI ASPECTS less than 6 were exclusion criteria. Substantial or complete reperfusion in the MT group was achieved in 67 of 102 (66%) patients. The absolute between-group difference in the proportion of patients who were functionally independent was 15.5%, favoring MT (43.7% vs.

28.2%). The benefits appeared to be least consistent in subgroups with advanced age (≥70 years) or a long time window after symptoms unset (>4.5 h from onset to randomization) [15].

The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke (THERAPHY) trial is another notable study and is the only randomized study that utilized an aspiration-based thrombectomy technique. This trial compared MT and IVT to IVT only. The trial was terminated when the results of other studies were published and MT became the standard of care for acute IS. Seventy percent of patients treated with aspiration only achieved successful reperfusion; the results suggest a potential for benefit for aspiration thrombectomy compared to IVT only but had a low statistical power because of early termination. [244]

A recent randomized controlled multicenter trial published in 2016, the THRombectomie des Artères CErebrales (THRACE) trial compared standard treatment to IVT plus MT within 4 h of symptom onset. In total 412 patients were enrolled, 208 in the IVT only group and 204 in the IVT+MT group. This study had a broad patient selection with randomization within 20 min after the administration of IVT. The reperfusion rate was 69%, and good clinical outcome was obtained for 53% of patients in the MT group. This study also demonstrated the superiority of MT combined with IVT over IVT alone and was terminated early, because a second unplanned interim analysis showed significantly better results in the intervention group [245].

In all the trials utilizing stent retrievers mentioned above, there was no sign of increased risk of bleeding compared to IVT alone. There was an overall trend toward a reduction in stroke-related mortality in all of the trials [14-17, 244-246].

While the efficacy and safety of MT has now been robustly demonstrated [204-207], it is still of great interest to study whether there are differences in technical and clinical outcomes with respect to the site of occlusion, the stent retriever type used and the evaluation of the admission imaging along with other subgroup analyses based on different clinical and imaging markers. These data can facilitate patient selection, avoid unnecessary treatment and improve results by making best use of devices in relation to the patient imaging and clinical details. The type of anesthesia (general anesthesia or conscious sedation) used during the thrombectomy procedure may also influence the patient outcome. This is still an

open issue with some reports supporting the use of conscious sedation. The only randomized trial so far did not find any significant difference in clinical outcome between these two types of anesthesia [232, 247-249].

For a comprehensive guideline regarding the selection of patients with acute ischemic stroke, different revascularization therapies, performing endovascular procedures, and setting up systems of care to facilitate endovascular treatment, please refer to the 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment [189].

3 AIMS OF THE STYDY

The aims of this study were as follows:

I. To analyze the impact of the location of the thrombus, visualized by means of CTA and DSA in the anterior circulation, on the technical and clinical outcomes of IS patients treated with MT.

II. To analyze the influence of two commonly used stent retriever devices on technical and clinical outcomes.

III. To clarify which clinical and imaging variables can predict poor clinical outcome (mRS>2) in patients presenting acute anterior circulation stroke and to improve patient selection.

IV. To compare the clinical outcomes of MT with or without IVT to IVT alone for the treatment of hyperacute anterior circulation stroke (<3h from symptom onset) in the subgroups of patients with proximal (ICA and the proximal M1 segment) and distal (the distal M1 and M2 segments) large vessel occlusions.

4 SUBJECTS, MATERIALS AND METHODS

4.1 Overview

All studies (I-IV) had an observational prospective cohort design. We prospectively collected and analyzed the clinical and imaging data of consecutive patients admitted to Tampere University Hospital from January 2013 to December 2014 due to acute ischemic stroke symptoms and who underwent clinical and imaging evaluation and proceeded to digital subtraction angiography (DSA) with an intention to perform MT. In addition, study IV had a retrospective observational IVT-only cohort as a control group. This cohort had been collected between January 2004 and December 2007 at our institution [52].

The general inclusion criteria for the studies were occlusion of the internal carotid artery (ICA) and/or middle cerebral artery (MCA) up to the M2 segment and MT performed with a stent retriever. The initial imaging evaluation consisted of NECT, CTA and CTP in the majority of patients. The selection of patients as candidates for MT was based on absence of extensive irreversible ischemic changes (frank hypodensity more than 1/3 of the MCA territory) and hemorrhage in NECT, evaluation of the amount of salvageable tissue in CTP imaging (when performed) and proximal clot position in CTA (evaluated with raw data and MIP reconstructions). The decision to proceed to MT was multidisciplinary (stroke neurologist and neurointerventional radiologist). Patients referred to our institution from other hospitals were re-evaluated with at least NECT and CTA upon arrival before proceeding to the angiographic suite to rule out bleeding and extensive irreversible ischemic lesions. In the case of wake-up strokes, CTP was performed if no large infarct was seen in NECT. IVT was administered as a bridging therapy to patients with no contraindications. The r-tPA bolus was given on the CT table. In one case the bolus was withdrawn, because the time interval between symptom onset and groin puncture was expected to be minimal (i.e., an inpatient during office hours). Patients coming from an outside hospital received IVT according to drip-and-ship protocol. IVT was continued until groin puncture. Majority of patients were treated under conscious sedation: Dexmedetomidine was chosen in

51 cases (47%) and other combinations of drugs in 33 patients (31%). General anaesthesia was preferred if the patient was restless rendering the procedure difficult to perform (21 patients, 20%).

The technical outcome was measured with TICI (Thrombolysis in Cerebral Ischemia), evaluated with DSA at the end of the procedure. The clinical outcome measure was the modified Rankin Scale (mRS), evaluated three months after the stroke based on a follow-up visit with a neurologist or a phone interview with a neurologist. One patient could not be reached for this control. A follow-up NECT was performed for all patients 24 h after treatment to assess the infarct volume and possible hemorrhagic complications.

IVT was administered according to guidelines of the American Heart Association (AHA) [250]: Actilyse® (Boehringer-Ingelheim, Ingelheim, Germany), total dose 0.9 mg/kg, was administered in a 10% bolus and continued, if necessary, until groin puncture. Mechanical thrombectomy procedures were performed with different stent retrievers and sometimes with multiple devices based on the judgment of the operator. The used devices were TREVO® (Stryker Neurovascular/Concentric Medical, Mountain View, CA, USA), CAPTURE LP™ (eV3/ COVIDIEN/Medtronic, Santa Rosa, CA, USA), ERIC® (MicroVention, Tustin, CA,USA), Aperio® (Acandis, Pforzheim, Germany) and REVIVE® (Codman &Shurtleff, Raynham, MA, USA).

4.2 Subjects, study population and baseline characteristics

	I. IMPACT OF CLOT LOCATION			II. DEVICE INFLUENCE		III. PREDICTORS OF POOR PROGNOSIS		IV. COMPARISON BETWEEN MT AND IVT	
	ICA	M1	M2	TREVO®	Capture LP™	3-mo mRS ≤2	3-mo mRS >2	MT	IVT
Patients	37	46	22	42	43	58	47	67	98
Total	105			85		105		165	
AGE, mean (SD)	64.8 (10)	65.3 (13)	69.8 (9)	68 (13)	64 (10)	65 (12)	67(10)	68(10)	69(14)
Total	66 (11)			66 (12)		66 (11)		67(12)	
Female sex (%)	14 (38)	16 (35)	15 (68)	22 (52)	17 (39)	24(42)	20(43)	37(55)	43(44)
Total	45 (43)			39 (46)		45 (43)		80(48)	
ASPECT-CBV at admission, (IQR)	7 (5)	7(5)	9 (2)	7(4)	9(5)	9(7)	3(5)	7(4)	8(4)
Total	7 (4)			8(4)		7 (4)		8(3)	
CBS, median (IQR)	3(4)	6(1)	8(1)	5 (3)	6 (2)	6(3)	6(5)	6(4)	6(4)
Total	6 (3)			6 (4)		6(3)		6(4)	
CS >1 n (%)	11 (32)	14 (29)	18 (82)	1(2)	1(2)	23(22)	6(27)	1(2)	2(3)
Total	43 (41)			1 (1)		43(41)		1(3)	
NIHSS at admission, median (IQR)	15 (7)	14 (6)	14 (6)	16(6)	14(8)	14(9)	16(5)	14(5)	14(9)

Total	15(5)	14 (6)	15(5)	14(9)	
Stroke risk factors					
Atrial fibrillation	No statistical differences	No statistical difference	No statistical difference	37(55)	37(38)
Coronary disease				11(16)	34(35)
Hypertension				No statistical difference	
Diabetes					

Table 4. Baseline characteristics of the different populations of the studies.

	MT patients (I, III)	MT patients (II)	MT patients (IV)	IVT patients (IV)
Excluded	25[1]	25[1]+20[2]	25[1]+38[3]	215[4]
Included	105	85	67	98
Total population	130	130	130	313

Table 5. The study populations and the excluded patients. 1) 8 patients had posterior circulation stroke, one patient had occlusion of the A3 segment and one of the M3 segment, and 15 patients had no clot visible in DSA (spontaneous dissolution of the clot). 2) 20 patients were treated with stent retrievers other than TREVO® 42 or Capture LP™ or a combination of different devices. 3) 38 patients in the MT group had onset-to-imaging times >3h. 4) 215 patients in the IVT group did not have an anterior circulation clot visible in CTA or had contraindications to IVT or had clots beyond the M2 segment or in ACA.

4.2.1 Mechanical thrombectomy patients (I,III)

The clinical and imaging data of 130 consecutive patients presenting anterior circulation stroke symptoms, admitted between January 2013 and December 2014

to Tampere University Hospital with an intention to perform MT, were collected. For population baseline characteristics and inclusion criteria please refer to Tables 4 and 5. A complete multimodal CT protocol was completed in 72 of the 105 patients (69%) who received MT, and incompleteness was mainly because CTP was not successfully performed for every patient. NECT and CTA were assessed for all patients. Based on CTA scans, thrombus location, clot burden score and collateral score were recorded. The median NIHSS at admission was 14.5 (interquartile range, IQR, 5) and slightly higher than expected among the M2 occlusion patients (Table 4). In two patients, evaluation of NIHSS was not possible because of sedation during transportation by the ambulance crew. Also the mean age was higher in the M2 occlusion group (Table 4). Sixty-six of the 105 patients (64%) received IVT; the remaining patients were denied of IVT because of contraindications (i.e., anticoagulation, wake-up strokes, history of recent surgery), and one was treated with MT without any previous r-tPA bolus. There was no statistically difference in mean time from onset of symptoms to imaging or in the mean time from onset to recanalization. The median duration of the intervention measured from groin puncture was also similar between the groups. The mRS score was missing for one patient who could not be reached.

4.2.2 Mechanical thrombectomy patients treated with TREVO® or Capture LP™ (II)

Clinical and imaging data of 85 consecutive patients who were treated with MT using solely TREVO® or Capture LP™ between January 2013 and December 2014 in the University Hospital of Tampere were collected. Forty-two patients (49%) were treated with TREVO®. For baseline characteristics and inclusion criteria, please refer to Tables 4 and 5. In the TREVO® group, there was a non-significant trend towards more patients with distal occlusions (the distal M1 or the M2 segments). CTP was successfully completed in 60 of the 85 patients (71%), of which 25 were in the TREVO® group (60%) and 35 were in the Capture LP™ group (81%).

4.2.3 Mechanical thrombectomy patients with onset-to-imaging time less than 3h (IV)

We prospectively collected and analyzed clinical and imaging data of 130 consecutive patients admitted to Tampere University Hospital from January 2013 to December 2014 because of acute ischemic stroke symptoms and who underwent clinical and imaging evaluation and proceeded to digital subtraction angiography (DSA) with an intention to perform MT. For baseline characteristics and inclusion criteria, please refer to Tables 4 and 5. CTP was successfully obtained from 42 patients (63%). NIHSS, CBV-ASPECTS, clot burden score and collateral score were collected (Table 4). In one case, NIHSS could not be reliably scored because the paramedic crew had sedated the patient during transportation. The mean time from onset of symptoms to imaging was 90 min (SD 44).

4.2.4 IVT Patients between January 2004 and December 2007 (IV)

A total of 313 anterior or posterior circulation ischemic stroke patients from January 2004 to December 2007 were treated with IVT only and had a 3-month follow-up after thrombolysis. There were 105 (37%) patients who met the inclusion criterion. Ninety-eight of the 105 patients remained in this group after patients with occlusions distal to the M2 segment were removed (Table 5). CTP was successfully obtained in 76 patients (77%). NIHSS upon admission, CBS, collateral score and CBV-ASPECT were collected (Table 4). The mean time from onset of symptoms to imaging was 90 min (SD 26). The median preictal mRS was 1. For the other baseline characteristics, please refer to Table 4.

4.3 Clinical variables

The baseline clinical characteristics included age, gender, clinical risk factors for ischemic stroke (hypertension, diabetes, coronary heart disease, atrial fibrillation) and time from symptom onset to initiation of IVT. These data were collected from the patient records. National Institutes of Health Stroke Scale (NIHSS) score at presentation, the times from symptom onset to imaging and to recanalization of the occluded vessel, the duration of the procedure, TICI grading evaluated via DSA at the end of the procedure, and procedural complications were prospectively

stored. Follow-up NECT and NIHSS scoring were performed for all of the patients 24 h after treatment.

The primary clinical outcome measure in all studies was the modified Rankin Scale (mRS), evaluated three months after stroke based on a follow-up visit with a neurologist or a phone interview with a neurologist. A mRS ≤2 was considered good clinical outcome. The primary technical outcome was the TICI score evaluated via DSA (I, II, IV). TICI > 2a was set as the threshold for good technical outcome.

4.4 Imaging parameters

CT scans were obtained using a 64-row multidetector CT scanner (General Electric LightSpeed VCT, GE Healthcare, Milwaukee, WI, USA). MR imaging at admission was not performed to any patient.

The parameters for brain NCCT were 120 kV with AUTO mA and SMART mA technique, noise index of 3.3, collimation of 4x5 mm, 40% adaptive statistical iterative reconstruction (ASIR), and rotation of 0.5 s. Images were obtained axially (0.625-mm-thick slices), and then, contiguous axial slices were reconstructed to a thickness of 5 mm and coronal slices to a thickness of 2 mm.

CTA was performed via a 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 of 9, 40% ASIR, collimation of 40x0.625 mm, rotation of 0.5 s, and pitch factor of 0.984. Seventy milliliters of contrast agent (iomeprol, 350 mg I/ml, IOMERON, Bracco, Milan, Italy) was administered via an antecubital vein with an 18-gauge cannula using a double-piston power injector at a flow rate of 5 ml/s followed by flushing with 50 ml saline. An automatic bolus triggered from the aortic arch was used.

CTP was performed using the parameters 80 kV, 250 mA, 50% ASIR, collimation of 8x5 mm, and rotation of 0.4s, and 272 slices covering a range of 80 mm were generated in 46 s using an alternating toggle table protocol to increase the z-axis coverage. Contiguous slices were reconstructed to a thickness of 5 mm at even intervals. The imaging range was positioned such that the ASPECTS level was covered. Forty milliliters of contrast agent (IOMERON 350 mg I/ml) was administered via an antecubital vein with an 18-gauge cannula using a double-

piston power injector at a flow rate of 5 ml/s followed by flushing with 40 ml saline.

Digital subtraction angiographic images were obtained using an Artis Z angiographic equipment (Siemens, Munich, Germany) with the parameters 102 kV, AUTOmA and SMARTmA.

4.5 Image analysis

NECT, CTA and CTP examinations were reviewed using dedicated medical imaging workstations. Parametric perfusion maps that included the mean transit time (MTT), cerebral blood flow (CBF), and cerebral blood volume (CBV) were generated with CT Perfusion 4 software (GE Healthcare, Milwaukee, WI, USA), which uses a deconvolution-based algorithm. The ACA was used as a source for the arterial input function (AIF), and the region of interest for the venous output function (VOF) was positioned in the superior sagittal sinus. CTA images were reviewed by examining both the raw data and the maximum intensity projection images. The Alberta Stroke Program Early CT Score (ASPECTS) was assessed from admission and follow-up NECT images and from MTT and CBV maps. The principles of the ASPECTS scoring of NECT and CTP maps are described in Section 2.2.2.1. The infarct core was estimated using the CBV map, and the full extent of the perfusion defect was interpreted from the MTT map. The presence of a perfusion defect was evaluated visually from the color-coded maps by comparing the appearance of the affected locus to that of healthy tissue in the contralateral hemisphere.

CTA was used to evaluate the site of the occlusion, the clot burden score, CTA-SI ASPECTS and the collateral score, as described in Sections 2.2.2.2 - 2.2.2.4. The location of the clot was recorded based on the most proximal position of the occlusion. The M1 segment was further divided in two parts of equal length, the proximal part designated M1P and the distal designated M1D.

The examinations were reviewed in the following order, paralleling the clinical workflow: NECT, CTA, and finally CTP. Two radiologists were assigned ASPECTS, CBS and CS. In cases when the scoring or the assignment differed, a consensus opinion was agreed on. The reviewers were blinded to the clinical data apart from the side and nature of the acute symptoms. One radiologist measured

final infarct volumes two times. The boundaries of the affected areas on NECT were determined visually. Volume was calculated by multiplying the measured area with the slice thickness.

4.6 Statistical analysis

The data were analyzed with SPSS version 21 (SPSS Inc., Chicago, IL). In all studies, group comparisons were performed by using Student's t-test, the Chi-squared test, Fisher's exact test, the Kruskal-Wallis test, and the Mann-Whitney U test where theoretically appropriate. Patients with collateral scores from 2 to 4 were regarded as having good collateral vessel filling. Patients who had three-month mRS≤2 were considered to have experienced good clinical outcome and those with mRS≤1 as excellent outcome. A p-value <0.05 was considered statistically significant.

Binary logistic regression modeling using good and excellent clinical outcome measures as dependent variables was repeated for different variables of interest in studies II and IV. In study II, mortality was also used as a dependent variable. In this study, admission NIHSS, age, gender, time from onset to recanalization, clinical risk factors of stroke, device selection, CBV-ASPECTS at admission, site of the occlusion and collateral score were examined as potential confounders and were first tested in univariate models with the dependent variables as described. Based on these results, multivariate models were devised. In study IV, binary logistic regression analyses were performed in order to control for the effect of differing average patient age, onset-to-imaging times and admission NIHSS between the MT and IVT-only groups for different sites of the occlusion. The calibration of the models was evaluated with the Hosmer-Lemeshow test, and discrimination was assessed with the *C* statistic. In study III, univariable and multivariable binary logistic regression analyses using poor clinical outcome as the dependent variable were performed, and the odds ratio (OR) with the 95% confidence interval (CI) were calculated for each covariate.

5 RESULTS

5.1 Impact of the site of the occlusion on technical and clinical outcomes (I-II, IV)

The impact of the site of the occlusion on technical and clinical outcomes was studied in the context of MT in the anterior circulation. Furthermore, we evaluated the efficacy of MT compared to that of IVT alone to clarify which treatment offered the highest potential benefit to the patient in different locations of the clot.

5.1.1 The site of the occlusion seems not to significantly affect clinical or technical outcomes of MT (I)

The patients who underwent MT during the study period were analyzed for possible differential technical and/or clinical outcomes based on the site of the occlusion. Thirty-seven patients (35%) presented with an occlusion of the ICA, of which only one was stented to treat stenosis of the proximal ICA during the MT procedure, 46 patients (44%) presented M1 segment occlusion, and 22 patients (21%) presented M2 segment occlusion. There was a trend towards patients having lower NIHSS at admission in the M2 group, but the difference was not statistically significant. The size of the perfusion defect in CBV maps was significantly larger in the ICA and M1 groups compared to the M2 group (median CBV-ASPECTS 7 vs. 7 vs. 9, *p=0.005*). The collateral score was also significantly higher, and the overall size of the perfusion defect, as described by MTT-ASPECTS, was smaller in the distal occlusion group. The time between the onset of symptoms and imaging was similar between groups.

The recanalization outcome was TICI 2b or 3 in 92 out of 105 cases (88%). Even though there was no statistically significant difference in the recanalization rates between the sites of occlusion, there was a trend towards a better result in the more proximal clot locations (TICI>2a: 87% in ICA, 94% in M1 and 77% in M2) although the CBS was significantly higher in the proximal locations. This was

mainly due to a lower number of patients with TICI 2b in the M2 group, as depicted in Figure 9. The ASPECTS score at 24 h NECT was significantly higher in the M2 group (7 vs. 8 vs. 9), which also translated into a smaller infarct volume in the control CT imaging. However, there was no significant difference between groups in the 3-month mRS. When excellent outcome (≤1) at three months was considered, we observed a trend towards achieving a better result in the more proximal locations (16 patients, 44% in the ICA group vs. 19 patients, 41% in the M1 vs. 5 patients, 23% in the M2, p=0.22) with just 1 patient having mRS=1 (5%) in the M2 group (Figure 10). Overall, 57 of the 105 patients (55%) experienced favorable clinical outcome (mRS≤2) at three months with no significant difference between groups. At 24 h, 20 of the 105 patients (19%) presented a hemorrhagic complication, of which 30% involved major space occupying PH2 or PHr2 hemorrhage. There was no difference in mortality or complication rates between the sites of the occlusion.

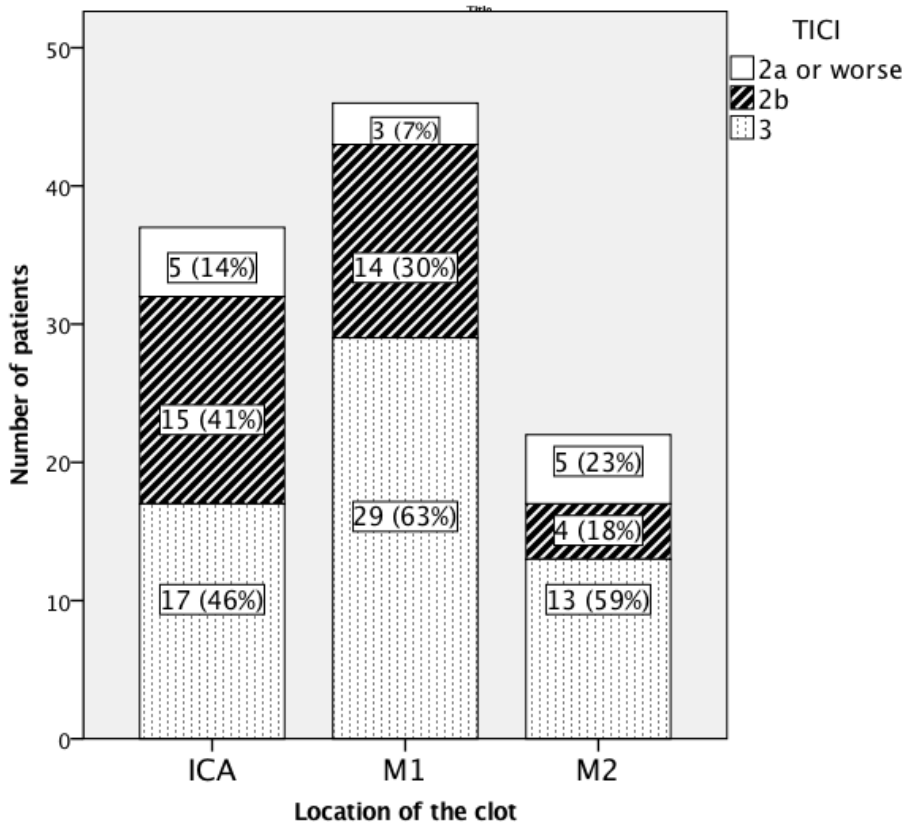


Figure 9. TICI scores by the thrombus location ICA: internal carotid artery, M1: middle cerebral artery segment 1, M2: middle cerebral artery segment 2. TICI: Thrombolysis In Cerebral Infarction.

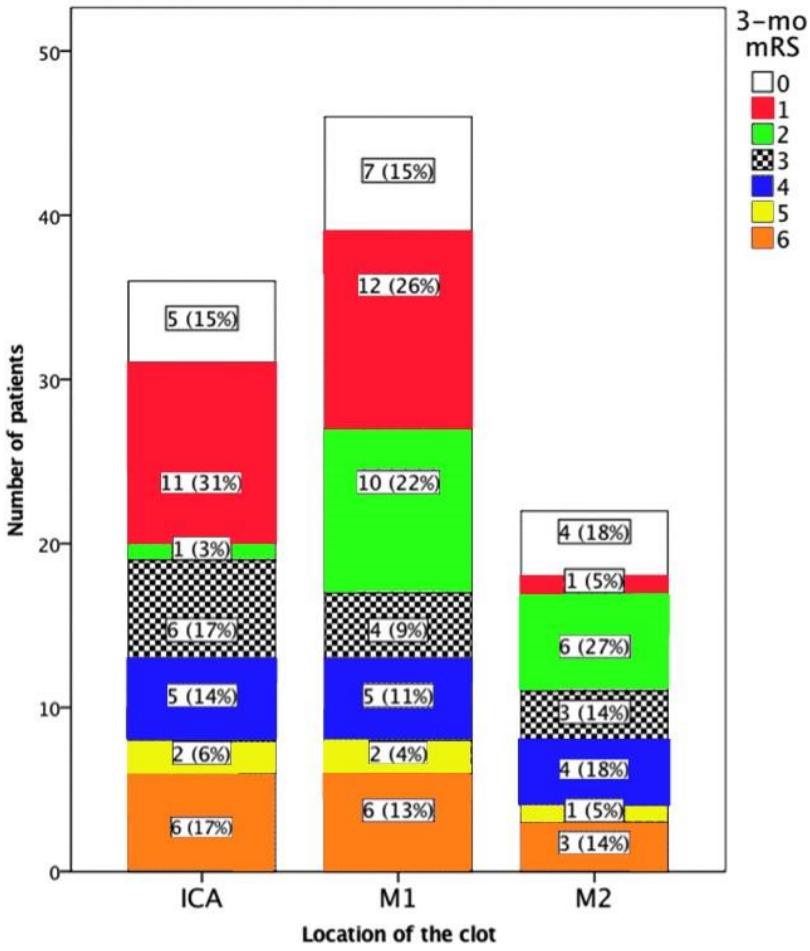


Figure 10. Three-month mRs by the thrombus location. ICA:internal carotid artery, M1:middle cerebral artery segment 1, M2: middle cerebral artery segment 2. mRS: modified Rankin Scale.

5.1.2 The clinical benefit of MT is highest for proximal large vessel occlusions (IV)

Continuing along the lines of location based analysis of study I, in study IV we further divided the M1 segment in to subsegments of equal length as proposed by Zaidat et al. [53]. This cut-off location was applied to classify large vessel

occlusions into proximal (ICA and M1P) and distal (M1D and M2). The performance of MT and IVT to treat hyperacute (<3h) stroke was compared in these two locations. There were 67 patients in the MT group and 98 patients in the IVT-only group. In the IVT-only group, there was a slightly larger proportion of distal thrombi, whereas in the MT group, the proximal location was predominant.

As expected from the distribution of clot locations in the two groups, the overall CBS was higher and perfusion defects depicted by MTT-ASPECTS was significantly smaller in the IVT-only group, which was reflected in a trend toward smaller CBV perfusion defects in the IVT-only group (median CBV-ASPECTS 7 vs. 8, p=0.10). The recanalization outcome was TICI 2b or 3 in 59 cases out of 67 (88%) treated with MT. Interestingly, the technical results were best in the proximal M1 segment (100% TICI 2b or 3) and worst in the most distal location, corresponding to 79% in the M2. The mean duration of the procedure was 34 min (SD 21 min). The mean onset-to-reperfusion time was 182 min (SD 57 min). The overall clinical outcomes in the two groups after three months were nearly equivalent: 56 % of patients in the MT group and 49% in the IVT-only group experienced good clinical outcome (mRS≤2)

However, there was a significantly larger number of patients who experienced excellent clinical outcome (mRS≤1) in the MT group (28 patients, 42% vs. 21 patients, 22%, p=0.005). Correspondingly, patients who received IVT-only had a significantly larger final infarct volumes in the follow-up NECT at 24 h (57 vs. 27ccm, p=0.005), even though they presented a higher percentage of distal occlusions. The two groups did not differ in mortality and hemorrhagic complication rates.

	Excellent outcome (mRS≤1)			Good outcome (mRS≤2)		
Clot location	**Odds ratio**	**CI 95%**	p_1	**Odds ratio**	**CI 95%**	p_2
ICA	9.0	0.9–89.8	0.06	4.9	0.77–31.5	0.09
proximal M1	n/a	n/a	n/a	11.9	1.6–90.1	0.02
distal M1	1.9	0.49–7.6	0.37	1.0	0.26–3.7	0.96
M2	0.51	0.07–3.7	0.50	0.30	0.05–1.9	0.20
ICA and proximal M1	28.0	3.4–233.8	0.002	6.0	1.9–18.3	0.002
distal M1 and M2	1.1	0.37–3.1	0.90	0.54	0.16–1.5	0.24

Table 6. Excellent and good clinical outcome in the MT group compared to the IVT-only group in different clot locations P_1, P_2: significance of the MT vs. IVT-only covariate in the binary logistic regression model, ICA:internal carotid artery, M1:middle cerebral artery segment 1, M2: middle cerebral artery segment 2, n/a not available because there were no patients with mRS=1 or better in the IVT-only group in the corresponding clot location.

We could not demonstrate any statistically significant difference in outcome between the two groups in the distal LVOs after controlling for the confounders. However, there was a trend toward better clinical outcome in the IVT-only group when M2 occlusions were evaluated. This difference was statistically significant (p=0.03) before accounting for confounding factors.

At 24 h in the MT group, 14% of patients were diagnosed with a hemorrhagic complication. In 6% of patients, the resulting hematoma had a major space occupying effect. In the IVT group, a hemorrhagic complication was detected in 7 cases (7%), and a hemorrhage with a major space-occupying effect was detected in 3 patients (3%).

5.1.3 The technical outcome of MT is not significantly influenced by the selection of the stent retriever. (II)

The performance of two newer generation stent retrievers, TREVO® and Capture LP™, were compared overall and considering different sites of the occlusion. Proximal LVOs (ICA or M1P) and distal LVOs (M1D, M2 or M3) were analyzed separately. Twenty-seven patients (64%) in the TREVO® group and 15 (35%) patients in the Capture LP™ group had a proximal LVO (p=0.007). The TREVO® group had significantly more ICA occlusions (19 vs. 6, p=0.002), whereas there were more M2 occlusions in the Capture LP™ group (5 vs. 15, p=0.01). The technical outcome was TICI 2b or 3 in 77 out of 85 cases (91%), and there was no significant difference between the groups (93% vs. 88%, p=0.48), even though the TREVO® group presented lower CBS and more proximal occlusions. The recanalization rates were similar in both groups also when different clot locations were studied separately. The duration of the procedure (33 vs. 32 min, p=0.79) and the onset-to-reperfusion times (229 min vs. 243 min, p=0.55) were also similar. When proximal and distal occlusions were studied separately, no significant differences were found between the devices in these last two parameters. The infarct volume at 24 h was similar in the two groups except in the distal LVO population, for which patients in the TREVO® group had significantly larger infarct volumes (10.5 ccm vs. 1.2 ccm, p=0.04). Regarding the clinical outcome there was a trend toward more patients having excellent outcome (mRS≤1) in the Capture LP™ group in all comparisons (overall: 32% vs. 49%; proximal occlusions: 39% vs. 60%; distal occlusions: 20% vs. 57%; p-values 0.11-0.19).

A borderline significantly higher overall mortality (17% vs. 5%, p=0.07) and significantly more severe overall post-infarct edema based on the presence of COED2 or COED3 was found in the TREVO® group (25% vs 9%, p=0.05). At 24 h 19% of all patients presented a hemorrhagic complication with 5% exhibiting bleeding having a notable space occupying effect. The proportion of hemorrhagic complications was significantly higher in the distal LVOs in the TREVO® group (33% vs. 7%, p=0.04). In a binary logistic regression multivariate model with excellent outcome as the dependent variable, the device selection, the site of occlusion and the collateral score were statistically significant predictors, with Capture LP™ increasing the odds of excellent outcome more than five-fold (OR=5.2, 95% CI 1.5-17.3, p=0.008, Table 7). If good clinical outcome (mRS≤2) was instead chosen as the dependent variable, the device used was not a significant predictor. When proximal and distal LVOs were evaluated separately in regression models, device selection was a borderline significant predictor of excellent outcome (p=0.08 and p=0.07, correspondingly).

	Overall mRS at three months ≤1 (H-L = 0.84, C = 0.77)		
	Odds ratio	**CI 95%**	***p* value**
Clot location		-	0.002
ICA	ref	ref	-
M1	30.8	4.5 - 211.2	<0.001
M2	12.6	2.3 - 67.9	0.003
Favorable CS (2-4)	4.5	1.3 - 15.3	0.02
Device: Capture LP	5.2	1.5 - 17.3	0.008
Age	1.00	0.96 - 1.05	0.79

Table 7. Logistic regression analysis for excellent clinical outcome (all patients). Odds ratios are per year for age. H-L= Hosmer-Lemeshow significance, C=C statistic, CS=Collateral Score, ICA=internal carotid artery, ref=reference location.

5.2 Low CBV-ASPECTS is a predictor of poor clinical outcome in mechanical thrombectomy (III)

The predictors of poor clinical outcome were evaluated among patients treated with MT. Following exclusions, 105 patients were eligible for analysis. Ninety-two patients (88%) had TICI > 2a, which was considered the threshold of good technical result of MT. Among those patients, 38 (41%) experienced poor clinical

outcome despite successful recanalization. Overall, poor clinical outcome was seen in 47 of the 105 patients (45%). No statistically significant difference was found in the baseline characteristics or in the stroke risk factors between the poor and good outcome groups. High NIHSS at presentation was borderline significantly associated with worse outcomes (14 vs. 15.5, p=0.08). Not receiving IVT was correlated with poor outcomes (p=0.08). The main factor correlated with poor clinical outcome at 3 months was the size of the infarct core evaluated with the ASPECTS in the admission CBV perfusion maps. The score was significantly lower in the poor outcome group (9 vs. 7, p=0.01). This finding was also validated by univariate regression analysis, which showed that an increment of 1 ASPECTS point in the CBV map lowered the odds of poor outcome by a factor of 0.79 (95% CI=0.64 to 0.94, p=0.01). This finding did not change when only the successfully recanalized patients were evaluated (OR=0.74, 95% CI=0.6 to 0.9, p=0.004). Poor collateral circulation was also correlated to poor clinical outcome at 3 months: 73% of patients with CS=0 experienced poor clinical outcome (p=0.03). In univariable regression analysis, having CS=0 increased the odds of poor clinical outcome 4.4-fold (95% CI 1.27 to 15.5, p=0.02), and when only patients with a favourable reperfusion result (TICI>2a) were considered, the result was even more significant (p=0.009). A low CBV-APECTS score demonstrated a strong association with poor clinical outcome especially among those patients presenting moderate to severe strokes (NIHSS 8 or more, OR=0.82, 95% CI 0.68 to 1 p=0.05) or with malignant CS (0-1): OR=0.66, 95% CI 0.48 to 0.90 (p=0.009). No statistically significant difference was found among those with mild strokes or good CS. Finally, a binary logistic multivariate model using backwards likelihood method was devised with poor 3-month clinical outcome as the dependent variable. Lower CBV-ASPECTS (OR=0.77, 95% CI=0.63 to 0.95, p=0.01) and not receiving IVT (OR=3.2, 95% CI=1.1 to 9.4, p=0.04) emerged as the only statistically significant predictors of poor outcome in the final model.

6 DISCUSSION

Acute ischemic stroke is a common disease and its natural history, if no treatment is delivered, often leads to high-grade morbidity and mortality [1]. Even though the evolution of the disease condition is highly dynamic and somewhat unpredictable because of its dependence on multiple factors, such as pathophysiological aspects and promptness of treatment, evaluating the parameters that influence the clinical and technical outcomes is crucial. Studying the factors related to outcome facilitate improving our ability to administer more efficient therapies to those patients who will have the largest benefits from the treatment. The introduction of interventional radiology techniques with efficacies superior to intravenous thrombolysis (IVT) has amplified the need to refine our diagnostic methods to permit more precise risk stratification and treatment decision-making. Technical, clinical and imaging variables can predict the outcome of the patient and can provide important information on who would not be a good candidate for diverse revascularization therapies. While the overall superiority of MT with new generation stent retrievers over IVT has been largely demonstrated by numerous randomized trials [13-17, 245], it remains partly unclear if all patients with LVO and acute ischemic stroke symptoms benefit from MT or if there are subgroups to whom IVT could be the best first choice of treatment. Furthermore, it has not yet been unequivocally demonstrated whether different clot locations or device selection influence the result.

6.1 The effect of the occlusion site and the revascularization treatment type on the outcome of stroke

In **study I**, we evaluated the effect of the site of occlusion on the technical and clinical outcomes of patients presenting anterior circulation occlusion and who were treated with newer generation stent retrievers. In our study, a statistically significant difference in the technical and clinical outcomes in different clot location could not be demonstrated.

In recent randomized trials, the majority of the patients treated with MT had occlusion of the M1 segment, whereas far fewer patients had a clot in the M2 segment [13-17, 245]. Only some of these trials reported results that were stratified according to the location of the clot. In the ESCAPE trial, the clinical outcomes for different clot locations were comparable to our results. However, we had slightly better outcomes with ICA occlusions: the proportion of patients with mRS=0 at three months was 15% in our study vs. 13% in the ESCAPE study, mRS=1: 31% vs. 16%, and mRS=2: 17% vs. 22%, respectively. The finding was also similar when comparing to the results of the REVASCAT study. In particular, we had fewer patients who experienced a dismal outcome (mRS 5-6) in the ICA group (23% in our study vs. 46% in REVASCAT). In the recent THRACE study, outcomes with respect to the location of the clot were evaluated only for ICA and M1, where the M2 occlusions were included in the M1 group. Compared to this trial, our results were slightly better regarding ICA occlusions: mRS=0-2 47% in our study vs. 23% in the THRACE study. However, these differences may be partly due to longer average onset-to-recanalization times in these randomized trials and slightly better recanalization rates in our study. The overall recanalization rate in our study was 88% vs. 72% in ESCAPE, 66% in REVASCAT, and 69% in THRACE [13-17, 245].

Coutinho et al. collected the results from SWIFT, STAR and SWIFT PRIME trials and evaluated the technical and clinical outcomes in M1 and M2 occlusions [251]. They did not find any significant differences between the two locations in terms of technical or clinical outcomes, and even the complication rate was similar. Modified TICI >2a was seen in 85% of patients with M2 occlusion and excellent clinical outcome was achieved in 50% of patients, while in our study we observed TICI >2a in 77% of patients and mRS 0–1 in just 23% of patients. Further, Dorn et al. recently showed better technical and clinical outcome in patients presenting with distal clot, with a recanalization rate in of 76% for M1 occlusions and 93% for M2 occlusions. The proportions of patients with good clinical outcome at 3 months were 43% and 60%, respectively [252]. Unexpectedly, in our study, there were no significant differences in the 3-month clinical outcome among the different clot locations, despite significantly larger thrombus burden and worse collateral circulation in the more proximal occlusions. In contrary, there was a trend towards worse results in the M2 group when excellent clinical outcome (mRS≤1) was considered. Correspondingly, the recanalization outcomes were also slightly worse in the M2 population (77%). In contrast to the populations of Dorn

et al. and Coutinho et al., in our study the M2 occlusion group had more severe strokes (median NIHSS 14) than expected based on the literature [52]. In addition, compared with the other populations, there was a higher average age and a slight female predominance in the M2 group. Therefore, more symptomatic patients, patients with occlusions of multiple M2 branches and non-responders to IVT may have been selected for MT treatment in our population. Finally, the worse technical outcome may be due to increased tortuosity of the vessels, involvement of multiple vessel branches, a smaller proportion of patients who had received IVT, and a thrombus composition less amenable to MT and/or IVT [113, 253]. Nevertheless, the duration of the intervention was similar in all clot locations and total infarct volume after 24 h was smaller in the M2 group, as expected. However, this was not statistically significantly reflected in the 3-month clinical outcome.

These findings emphasize the importance and efficacy of MT for the proximal clot locations where IVT has been demonstrated to be less effective. However, the role of MT in more distal occlusions remains somewhat unclear.

We readdressed this problem in **study IV**, in which we compared our MT results with the findings from a historical population treated in our hospital with IVT only and limited the analysis to only those patients with the treatment decision made within 3 h from symptom onset. In the analysis, we divided the M1 segment in two subsegments – the proximal M1 and the distal M1, as suggested by a current consensus statement [53] – and classified occlusions proximal to this point of division as proximal LVOs and those distal to this point as distal LVOs.

We found that MT was close to equally effective in the treatment of both proximal and distal LVOs with more than 50% of patients experiencing good clinical outcome. While MT proved to be superior to IVT in the treatment of proximal occlusions (ICA and M1P), superiority of MT over IVT in more distal occlusions was not demonstrated.

Numerous studies have demonstrated the feasibility and efficacy of MT with newer generation stent retrievers in the M2 segment of the MCA, with reperfusion rates up to 93% and the proportion of good clinical outcome up to 60% [251, 252, 254, 255]. Four of the recent pivotal randomized trials on MT reported their results regarding occlusion of the M2 segment. In the MR CLEAN trial 91% of patients in the control group received IVT [13]. M2 occlusion was seen in 18 patients in the MT group and 21 patients in the control group. A subgroup analysis with M2

occlusion included in the stratification criteria was not reported. In the ESCAPE study 79% of patients in the control group were administered IVT [14]. Only six patients in the intervention group had an isolated M2 occlusion whereas patients with occlusion of all M2 segment arteries were pooled with M1 occlusions. The authors stated that the treatment effect (showing benefit from MT) was similar in the location-based subgroup analyses, but details were not provided. In the SWIFT PRIME trial, 18 patients had an M2 occlusion, 13 of whom were included in the intra-arterial intervention group and 5 in the control group corresponding to 53% and 40% of patients experiencing good clinical outcome, respectively [16]. In the REVASCAT study 78% of patients in the control group received IVT [15]. Ten patients in the MT group and 8 in the control group had an M2 occlusion. The clinical outcome for this clot location was not detailed. Neither of the abovementioned MT trials had a sufficient number of patients with an M2 occlusion to elucidate the best technique for distal occlusions. Recently, Goyal et al. published a meta-analysis of 5 randomized trials. When pooled together, there were 51 patients with an M2 occlusion in the MT population and 44 in the control population [207]. In this study, the direction of the effect favored MT but the adjusted OR was not significant (OR=1.28, 95% CI 0.51-3.21). Similar results were found in a meta-analysis of older studies (OR=1.5, 95% CI 0.8-3.0) [256].

In line with previous studies, our study also could not demonstrate superiority of MT over IVT (or vice versa) for the treatment of distal MCA occlusions. Interestingly, in our study, after adjusting for confounders, we observed a non-significant trend toward worse clinical outcome in the MT group, which was also observed when the M2 and the distal M1 segments were pooled together (Table 6). This could be explained by the lower NIHSS, indicating milder stroke in the IVT-only group (median NIHSS 10 vs. 14); however, the trend remained unchanged when patients with mild strokes (NIHSS<8) were excluded. Moreover, successful recanalization of an M2 segment occlusion with MT was achieved in 79% of subjects, which is comparable to the literature but not optimal. In our data, 77% of M2 occlusion patients treated with only IVT experienced good clinical outcome, a considerably higher proportion than in the IMS III trial (44.5%) [100]. This along with the somewhat suboptimal reperfusion rate in our MT group and the inclusion of patients with moderate and severe strokes to in the MT group likely led to a pessimistic estimation of the efficacy of MT. Notwithstanding, there is no indication in our data that MT would outperform IVT for the treatment of M2 occlusions in a hyperacute setting.

None of the randomized trials reported the distinction of a proximal and distal part of the M1 segment in their analysis. However, the IMS III trial used this characterization and 64% of subjects in the IVT-only arm compared to 55% in the endovascular arm had good clinical outcome of a distal M1 occlusion [100]. The difference was not statistically significant. According to a recent retrospective study 61% of subjects treated for a distal M1 occlusion with MT experienced good clinical outcome, and 44% had excellent outcome [257]. These findings are compatible with our results in that the efficacy of MT and IVT were roughly equivalent with nearly 60% of patients achieving good clinical outcome in both groups. When the M1 segment was analyzed as a whole, the result was borderline significant in favor of MT (OR=2.6, CI 95% 0.90-7.8, p=0.08). This is in line with the results of a recent meta-analysis considering that, in our study, two-thirds of the M1 occlusions were in the distal subsegment [207, 256].

Almost half of the patients in the MT group who had a proximal occlusion experienced excellent clinical outcome compared to only one patient (3%) in the IVT-only group. Thus, it appears that surviving an ICA or proximal M1 occlusion without any disability-causing neurological deficits essentially requires MT. This finding has potential implications, especially in the management of patients with low pre-stroke mRS (0-1) who are often younger patients in their working years.

We restricted our analysis to hyperacute strokes. The time window of IVT was extended to 4.5 h in 2008. The efficacy of IVT deteriorates rapidly in the first few hours resulting in a large number-needed-to-treat figure of 14.9 in the 3- to 4.5 h time window [258]. Considering the superior reperfusion rates of MT, one would expect the performance of MT to be at least at the level of IVT in the extended time window. Extrapolating from the results of a recent meta-analysis, this appears to be the case [207].

6.2 Influence of the device choice on technical and clinical outcomes

The superiority of newer generation stent retrievers over older devices in efficacy and safety has been established in previous studies [240, 242, 243]. Newer generation devices have different design features that potentially make them more suitable to certain anatomies and occlusion sites. In the literature, only few studies have evaluated the differences between newer generation devices. Roth et al. compared Solitaire AB/FR™ and Aperio™ in a porcine model [259]. They did not find any significant difference in technical success or in complications between the two devices. Another study, in a retrospective, non-randomized setup, compared TREVO® and Solitaire AB/FR™ [260]. Technical and clinical outcomes were similar in the two groups. Interestingly, there was a trend toward a larger number of symptomatic ICHs in the Solitaire group (4 vs. 0), but due to the small population (n=22) the difference was not statistically significant. Zaidat et al. compared the results of two post-marketing registries and found that the clinical performance of TREVO® is comparable to that of Solitaire AB/FR™ [261].

In accordance with the literature, there were also no significant differences between the two stent retrievers in technical and clinical outcomes in our study. Although, there was a higher clot burden and, thus, potentially more difficult thrombus removal in the TREVO® group, the average duration of the procedure and the technical results were similar. This may be because, in a distal position, the tortuous anatomy and the more difficult catheterization can influence the deployment and withdrawal of the stent, making the procedure more challenging and time consuming [113]. Moreover, the technical outcomes were also similar when proximal and distal occlusions were considered separately. This suggests that despite different target vessel profiles intended by the manufacturer, the devices perform similarly in large- and medium- sized vessels.

The 3-month clinical outcome was equivalent in both groups when functional independence (mRS≤2) was considered. However, in the univariate analyses there was a trend towards more patients having excellent outcome (mRs≤1) in the Capture LP™ group and higher mortality in the TREVO® group both overall and for different clot locations. These findings are likely partially due to larger perfusion defects in the admission CBV maps in the proximal occlusions, differences in stroke risk factors between the groups in the distal occlusions, and

consequently larger infarct volumes at 24 h, more hemorrhagic complications and significantly more severe post-infarct edema. However, in the multivariate analyses the device selection remained a significant or borderline significant predictor of excellent outcome. For distal clot locations this may reflect the actual superiority of Capture LP™, which is specifically designed in terms of size and flexibility of the system components to enable MT of more distal clots. However, only 6 patients in the TREVO® group had an M2 occlusion, which inherently has a higher potential for an excellent 3-month clinical outcome, thus adding uncertainty. However, the same trend could also be observed for the proximal occlusions in both the univariate and multivariate analyses.

These results have to be interpreted in the temporal and device specific context, i.e. only two stent retrievers were compared out of the many in market at the time of the study and currently. Further, the results may be influenced by the details of the MT procedure, for example aspiration from a balloon tipped guiding catheter as opposed to distal access catheter and the type of anesthesia.

6.3 Predicting the outcome of acute ischemic stroke independent of the type of the revascularization therapy

In **study III,** we evaluated which factors could influence the clinical outcome of patients presenting large vessel anterior circulation ischemic stroke to identify possible factors that predict poor outcome regardless of whether reperfusion is achieved. Many studies have focused on evaluating factors that predict good outcome, whereas fewer studies have primarily addressed factors related to poor clinical outcome at 3 months [180, 262-266]. Most of the setup have been evaluated factors associated with poor clinical outcome despite successful recanalization. In contrast, the goal of our study was to understand which factors, known at the time that the clinical decision to perform MT is made, could predict poor outcome. It appeared that these two approaches yield very similar results.

CBV-ASPECTS emerged as the most important imaging parameter in predicting the outcome in patients being evaluated for MT, while we could not demonstrate a significant difference in NECT-ASPECTS scores at admission between those with good and poor 3-month outcomes. The lack of sensitivity of NECT could be partly explained by the relatively short average onset-to-imaging times. The superior performance of CTP-CBV compared to NECT is in agreement with

previous results regarding both IVT and MT. [17, 173, 173, 180, 267-269, 269-271] As demonstrated in previous studies on IVT, a CBV-ASPECTS threshold of 7 or 8 best differentiates patients with good and poor outcomes [21, 184]. In our study, the median CBV-ASPECTS in the poor outcome group was 7. CBV-ASPECTS did not significantly predict poor clinical outcome among patients with mild strokes (NIHSS<8) or good collateral circulation (CS 2-4,) whereas low CBV-ASPECTS was significantly associated with poor outcome among those suffering from moderate or severe stroke and/or having poor collateral circulation. A mild stroke entails less extensive and severe ischemia, which considering a mean onset-to-imaging time of less than 3 h, translates into a small infarct core especially if an aggregating quantification method such as ASPECTS is used. Similarly, good collateral circulation is related to smaller infarct core in this short timeframe. In a recent meta-analysis, MT did not significantly improve the clinical outcome of patients with NIHSS<10 compared to IVT [207]. These findings imply that perfusion imaging in the context of MT can be targeted to specific subgroups (i.e. those with moderate or severe symptoms and/or poor collateral circulation in CTA), even if we believe that there likely is a benefit to routinely performing CTP in all patients presenting stroke symptoms and no bleeding in the initial NECT scan. CTP was still not performed or was of low quality in about 30% of acute stroke patients. Often the restless and least co-operating patients are those with more severe strokes. This problem may in the future be in part addressed with the development of imaging systems with faster scanning time and better movement artefact correction algorithms.

It has been suggested that the type of anesthesia used during the thrombectomy procedure could significantly influence the patient outcome. The majorities of the studies reported in the literature are retrospective and shows better results with conscious sedation compared to general anesthesia [247-249]. In these studies patients who received conscious sedation had lower in-hospital mortality and lower rate of pneumonia, shorter hospital stays and the costs were also lower compared to patients who had general anesthesia. However, a recent randomized controlled trial, the SIESTA study, failed to demonstrate an advantage for the use of conscious sedation [232]. We did not directly address this problem in our studies. In our institution conscious sedation is preferred over general anesthesia, because it permits monitoring the neurological status of the patient, enables fast initiation of the intervention and allows a better blood pressure control.

6.4 Limitations

All the observational studies reported here have various limitations. A major limitation is the retrospective nature of the studies, although all the data were collected and recorded prospectively according to a preset protocol. The non-randomized design could have generated differences between groups, even though in all studies, the risk factor for stroke and the baseline characteristics were largely similar between groups. In study I, the uneven distribution of patients between different clot locations could have influenced the results; however, such a distribution reflects the clinical reality, with the largest number of proximal occlusions occurring in the M1 segment. In addition, there was a higher average age and a slight female predominance in the distal occlusion group. Additionally, in study II, because of non-randomization, there was an imbalance between groups, with a larger number of ICA occlusion patients in the TREVO® group. This difference in the selection of the device is probably due to operator preference and driven by device properties, namely, the sizes available at the time, flexibility, trackability, pushability, and maneuverability. The generalizability of the results is limited by the procedural details of the MT techniques used (out of many alternatives) and the comparison of only two stent retrievers. In study IV, there may have been a greater selection of patients with more severe symptoms for MT, especially for distal occlusions and conversely, those with milder symptoms may not have an invasive procedure. Patients who responded to IVT or experienced significant and sustained spontaneous resolution of symptoms between admission imaging and groin puncture (median interval 48 min) were not included in the MT group, whereas those with contraindications to IVT were obviously not in the IVT-only group. The latter reason explains why the proportion of patients with atrial fibrillation was larger in the MT group. However, all these biases act to diminish the perceived efficacy of MT in relation to IVT only. Finally, the small study population can be a limiting factor, diminishing the value of all subgroup analyses.

7 SUMMARY AND CONCLUSIONS

Driven by the recent technological advances in MT and the results of several randomized trials confirming the superiority of MT over older therapies for patients suffering from acute stroke due to anterior circulation LVO, this thesis investigated the role and effect of different clinical and imaging parameters on the technical and clinical outcomes of patients treated with MT. Moreover, this thesis aims to clarify the factors that could improve the treatment decision-making process and the evaluation of which patients may benefit most from MT.

The position of the clot is an established, independent factor that predicts the outcome of ischemic stroke. We found that the technical outcome seems not to be significantly dependent on the anatomical location of clot. Thus, the varying technical challenge of thrombectomy seems not to significantly contribute to the differential clinical outcome in the different anatomical locations of the clot. However, this finding may in part reflect the details of the MT technique used in our study. For proximal clot positions, MT is clearly superior to IVT, while these treatment modalities have no statistically significant difference in performance among patients with a distal occlusion. The division into proximal and distal M1 segments best indicates the cutoff where MT supersedes IVT. The findings reported here even suggest that surviving an ICA or proximal M1 occlusion without any disability-causing neurological deficits requires MT.

The selection between two popular newer generation stent retrievers did not have a significant effect on the technical and clinical outcomes. This implies that the decision of which device to use may be left to the operator based on his/her own judgment and experience of the individual devices.

CBV-ASPECTS is a robust predictor of poor clinical outcome at the time that the decision to use MT is made. It is more sensitive and precise than evaluations with NECT only. A low CBV-ASPECTS score, which is associated with a large infarct core, is a significant predictor of poor clinical outcome, especially in settings of poor collateral circulation and/or moderate or severe stroke. The status of

collateral circulation is also an important predictive factor, and non-existent collateral circulation at presentation is specifically related to poor clinical outcome.

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ORIGINAL COMMUNICATIONS

Stent Retriever Thrombectomy in Different Thrombus Locations of Anterior Cerebral Circulation

Cover title: Stent retriever thrombectomy in different thrombus locations of anterior cerebral circulation

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Abbreviations: ASPECTS = Alberta Stroke Program Early CT Score; CBV = cerebral blood volume; ICA = internal carotid artery; IV = intravenous; MCA = middle cerebral artery; MT = Mechanical thrombectomy; MTT = mean transit time; NIHSS = National Institutes of Health Stroke Scale; TICI = thrombolysis in cerebral infarction

Keywords: interventional radiology; ischemic stroke; mechanical thrombectomy; stent retriever

ABSTRACT

Background: Mechanical thrombectomy (MT) is a safe and efficient treatment for acute ischemic stroke in patients with proximal anterior occlusion and large penumbra. We evaluated the technical and clinical success of MT in relation to the location of the occlusion (internal carotid artery, M1 and M2 segments of the middle cerebral artery).

Methods: We prospectively reviewed 130 patients of whom 105 met the inclusion criteria. Baseline clinical, procedural and imaging variables, technical outcome (TICI, thrombolysis in cerebral infarction), 24h imaging outcome and three-month clinical outcome (mRS, modified Rankin Scale) were recorded. Differences between the groups were studied with statistical tests according to the type of the variable.

Results: There were 37, 46 and 22 patients in the internal carotid artery (ICA), M1 and M2 groups, respectively. TICI 2b or 3 was achieved in 92 cases (88%) with a non-significant trend towards a better recanalization outcome in the ICA and M1 groups. Overall, 57 of the 105 patients (55%) experienced favorable clinical outcome (mRS≤2) with no significant differences between the groups. Excellent outcome (mRS≤1) was seen in 40 patients (39%) and there proportionally more patients with excellent outcome in the ICA and M1 groups (ICA: 44%, M1: 41%, M2: 23% of patients, p=0.22).

Conclusions: There were no statistically significant differences in the technical or clinical outcomes between the different sites of occlusion (ICA, M1 or M2). There was a non-significant trend towards achieving excellent clinical outcome (3-month mRS≤1) more often and better recanalization results in the two more proximal locations.

INTRODUCTION

Mechanical thrombectomy (MT) is a safe and efficient treatment for acute ischemic stroke in patients with large penumbra and good collateral circulation as established by several recent randomized studies [1-6].

The success of the intervention depends among other factors on achieving the reperfusion of the ischemic brain tissue quickly after groin puncture. The technical success is usually measured using the Thrombolysis in Cerebral Infarction score (TICI) [7, 8].

According to previous studies the location and volume of the clot are critical determinants of the success in intravenous thrombolysis (IVT). The recanalization results are poor in proximal clot locations with a higher clot burden [9-11]. The location of the occlusion and the anatomy of the vessels can influence the recanalization rate and the clinical outcome also in MT. Vessel anatomy can have an effect on MT with extensive tortuosity and acute angles in the vessel bends being more difficult to treat [12]. These challenges have been partly addressed by newer generation retrievable stent-based MT devices which seem to be easier to use and have better technical and clinical outcomes compared to the older generation devices [13-16].

Our study aimed to evaluate the success of MT in different clot locations using the TICI score and the duration of the procedure as indicators of technical outcome and the 3-month modified Rankin Scale (mRs) as a measure of clinical outcome.

METHODS

Overview, participants and variables

We prospectively collected and analyzed the clinical and imaging data of 130 consecutive patients, who were admitted to Tampere University Hospital between January 2013 and December 2014 because of acute ischemic stroke symptoms and who underwent clinical and imaging evaluation and proceeded to digital subtraction angiography (DSA) with an intention to perform MT. The inclusion criteria were occlusion of the internal carotid artery (ICA) and/or the M1 or M2 segment of the middle cerebral artery (MCA) and MT with a stent retriever. 105 patients met these criteria. Eight patients were excluded because of posterior circulation stroke, one patient had occlusion of the A3 segment, and another in the M3 segment. In 15 cases thrombectomy was not performed either because the clot had dissolved or there was no access to the thrombus or only aspiration thrombectomy was done. MT was performed with different stent retrievers and sometimes with multiple devices. The initial imaging evaluation consisted of non-contrast-enhanced computed tomography (NCCT), CT angiography (CTA) and CT perfusion (CTP). 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 and proximal clot position in CTA. Patients that were referred to our institution from another hospital were re-evaluated with at least NCCT and CTA upon arrival. In the case of wake-up strokes, CTP was performed if no large infarct was seen in NCCT.

Baseline clinical characteristics included age, sex, and clinical risk factors for ischemic stroke (hypertension, diabetes, coronary heart disease, atrial fibrillation). This data was collected from the patient records. National Institutes of Health Stroke Scale (NIHSS) score at the presentation, time from symptom onset to imaging and recanalization of the occluded vessel, the duration of the procedure, TICI grading, and possible intraprocedural complications had been prospectively stored to a specifically devised questionnaire. A follow-up NCCT was performed 24h after MT.

Hemorrhagic complications and postinfarct oedema were classified according to SITS-MOST criteria [17].

Revascularization was evaluated with TICI, which was scored from the final DSA control runs of the intervention. The clinical outcome measure was mRS, evaluated three months after the stroke based on a follow-up visit to a neurologist or a phone interview by a neurologist. The imaging outcome measure was infarct volume evaluated 24h after the intervention.

Recanalization therapies

MT was performed using a bi-axial system consisting of an 8F or 9F guiding catheter with a tip balloon and coaxially a 0.021" micro-catheter or a tri-axial system consisting of an 8F guiding catheter, a distal access catheter through which a micro-catheter was inserted with the aid of a 0.014" micro-guidewire. The micro-catheter was navigated through the occluded segment of the artery and a suitable stent retriever was positioned trough 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 retriever devices were used based on the preference and judgment of the operator. TREVO® (Stryker Neurovascular/Concentric Medical, Mountain View, CA, USA) was used in 40 % of cases, CAPTURE LP™ (eV3/ COVIDIEN/Medtronic, Santa Rosa, CA, USA) in 40%, ERIC® (MicroVention, Tustin, CA, USA) in 9%, Aperio® (Acandis, Pforzheim, Germany) and REVIVE® (Codman &Shurtleff, Raynham, MA, USA) in 1% respectively and in 10% of cases multiple device types were used. The diameters of the devices used varied between 3mm and 6mm with a 4mm device being most commonly used. Intravenous thrombolysis (Actilyse® 0,9mg/kg, Boehringer-Ingelheim, Ingelheim, Germany) was administered as bridging therapy

based on the judgment of the attending stroke neurologist and possible contraindications. Actilyse® bolus was given on the CT table. If the delay from the symptom onset to groin puncture was expected to be minimal, e.g. in the case of an inpatient during office hours, IVT was not necessarily given. Patients coming from an outside hospital received IVT according to drip-and-ship protocol. Actilyse® drip was continued until groin puncture.

Imaging parameters

CT scans were obtained using a 64-row multidetector CT scanner (General Electric LightSpeed VCT, GE Healthcare, Milwaukee, WI, USA). Brain NCCT was performed using the parameters 120kV with AUTOmA and SMARTmA technic, noise index 3.3, collimation 4x5mm, 40% adaptive statistical iterative reconstruction (ASIR), and rotation 0.5s. Images were obtained axially (0.625mm thick slices) and then contiguous axial slices were reconstructed to the thickness of 5mm 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 100kV, AUTOmA and SMARTmA, noise index 9, 40% ASIR, collimation 40x0.625mm, rotation 0.5s, pitch factor 0.984. The contrast agent (iomeprol, 350mg 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 5ml/s using 70ml contrast agent followed by a 50ml saline flush. Automatic bolus triggering from the aortic arch was used. CTP was performed using the parameters 80kV, 250mA, 50% ASIR, collimation 8x5mm, and rotation 0.4s. 272 slices covering a range of 80mm were generated in 46s using alternating toggle table protocol to increase the z-axis coverage. Contiguous slices were reconstructed to a thickness of 5mm at even intervals. The contrast agent (IOMERON 350mg I/ml) was administered via an antecubital vein with an 18-G cannula using a double-piston power injector with flow rate of

5ml/s using 40ml of contrast agent followed by a 40ml saline flush. Digital subtraction angiographic images were obtained using the Artis Z angiographer (Siemens, Munich, Germany) using the parameters 102kV, AUTOmA and SMARTmA

Image analysis

NCCT, CTA and CTP examinations were reviewed using dedicated medical imaging workstations. Parametric perfusion maps – mean transit time (MTT), cerebral blood flow (CBF), and cerebral blood volume (CBV) – were generated with CT Perfusion 4 software (GE Healthcare, Milwaukee, WI, USA). CTA images were reviewed by examining both the raw data and maximum intensity projection images. The Alberta Stroke Program Early CT Score (ASPECTS) was assessed from admission and follow-up NCCT images, and MTT and CBV maps as described in our previous article [18]. CTA was used to evaluate the occlusion site, the Clot Burden Score (CBS) and the Collateral Score (CS) as described in our previous report [19]. 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 finally CTP, paralleling that of the clinical work flow. Two radiologists assigned ASPECTS, CBS and CS. In cases where the scoring or the assignment differed, a consensus opinion was agreed on. The reviewers were blinded to the clinical data apart from the side and nature of the acute symptoms. Final infarct volumes were measured by one radiologist. The boundaries of the affected areas were determined visually. Volume was calculated by multiplying the measured area with the slice thickness. Validation of the measurements including intraclass correlation coefficients (ICC) and Cohen's kappa values can be found in the above mentioned previous publications.

Statistics

The data was analyzed with SPSS version 21 (SPSS Inc., Chicago, IL). Group comparisons were performed by using the Student t-test, the Chi-squared test, the Fisher exact test, and the Mann-Whitney U test. Patients with Collateral Score from 2 to 4 were regarded as having good collateral vessel filling. Patients who had three-month mRS≤2 were considered to have experienced good clinical outcome and those with mRS≤1 excellent outcome. A TICI score >2a was considered a good recanalization result. A p-value <0.05 was considered statistically significant.

RESULTS

Population and baseline characteristics

The inclusion criteria were met by 105 patients with 37 patients (35%) presenting with an occlusion of the ICA, 46 patients (44%) had M1 segment occlusion and 22 patients (21%) had M2 segment occlusion.

The main baseline and admission imaging characteristics are summarized in Table 1. In two cases NIHSS could not be scored reliably because the paramedic crew had sedated the patient during transportation. In six cases the time of the onset of the symptoms was unknown (i.e. they were wake-up strokes). CTP was successfully obtained from 72 patients (69%). There were no significant differences between the groups in age or the other established stroke risk factors apart from there being significantly larger number of women in the M2 group (Table 1). There was a trend towards patients having lower NIHSS at admission in the more distal clot locations but the difference was not statistically significant. The size of the perfusion defect in CBV maps was significantly larger in the ICA and M1 groups compared to the M2 group (median CBV-

ASPECTS 7 vs 7 vs 9, respectively, p=0.005). Correspondingly, NCCT-ASPECTS scores at admission were significantly more favorable in the M2 occlusion group when compared to other sites (median NCCT-ASPECTS 9 vs 9 vs 10, respectively, p=0.04). Also the Collateral Score and the CBS were significantly higher and the overall size of the perfusion defect as described by MTT-ASPECTS smaller in the M2 group. There were no statistically significant differences in the onset-to-imaging times. Sixty-seven patients (63%) received IVT before the procedure with a slightly higher proportion in the ICA group (73%).

Technical outcome and the three-month clinical outcome

The recanalization outcome was TICI 2b or 3 in 92 out of 105 cases (88%, Table 2), with a non-significant trend towards better results in the ICA and M1 groups (87% vs 94% vs 77%, p=0.16, Table 2) even though these groups had a significantly larger clot burden (p<0.001, Table 1). The differing clot burden was not reflected in the duration of the intervention (35min vs 25min vs 32min, p=0.20, Table 2) nor the onset-to-recanalization times (242min vs 245min vs 210min, p=0.36, Table 2). There was a slightly larger proportion of patients in the M2 group who had low TICI (2a or worse) compared to the others groups. This was mostly due to a smaller number of patients with TICI 2b (Figure 1).

The distribution of the 3-month mRS scores in the ICA, M1 and M2 groups is depicted in Figure 2. The proportion of patients with different mRS scores is quite similar in the three sites of occlusion apart from there being only one patient with mRS=2 in the ICA group and only one patient with mRS=1 in the M2 group with correspondingly smaller proportions. However, the proportions even up when all the adjacent scores (mRS 0-3) are considered: 67% vs 72% vs 64% (Figure 2). Overall, 57 of 105 patients (55%) experienced favorable clinical outcome (mRS≤2) at three months with no significant difference between the groups (Table 2). However, excellent

outcome (mRS≤1) was seen in 40 patients (39%) and there was a trend towards more patients having excellent outcome in the ICA and M1 groups (16 patients, 44% vs 19 patients, 41% vs 5 patients, 23%, p=0.22, Table 2) with only 5% of patients having mRS=1 in the M2 group (Figure 3). However, the ASPECTS score at 24h was significantly higher in the M2 group (median ASPECTS 7 vs 8 vs 9, p=0.02, Table 2). In accordance, patients in the M2 group presented with smaller infarct volumes in the 24h follow-up NCCT (Table 2, p=0.03). There were 20 patients (19%) with parenchymal bleeding postoperatively and 21 patients (20%) suffered from post-infarct oedema graded COED 2 or 3, but no significant differences were found in the occurrence of these between the three clot locations. Also the mortality rates were similar with an overall three-month mortality of 14% (p=0.89, Table 2).

DISCUSSION

With the advent of the third generation stent retrievers, superior to the previous generation devices in efficacy and safety, and the results from recent randomized trials, the treatment of anterior circulation acute stroke is dramatically changing [1-6, 13-15]. We evaluated in an observational prospective study setup the technical and clinical outcome of MT, performed with the new generation devices, in different sites of the occlusion in patients presenting with acute anterior circulation stroke.

In the recent randomized trials, the majority of the patients treated with MT had occlusion of the M1 segment whereas far fewer patients had a clot in the M2 segment [1-5]. Only some of these trials reported their results stratified according to the location of the clot. In the ESCAPE trial the clinical outcomes in different clot locations were comparable to ours. However, we had slightly better outcomes with ICA occlusions: the proportion of patients with mRS=0 at three months was

15% in our study vs 13% in the ESCAPE study, mRS=1: 31% vs 16%, and mRS=2: 17% vs 22%, respectively. The finding was similar also when comparing to the results of the REVASCAT study. Especially, we had fewer patients that experienced dismal outcome (mRS 5-6) in the ICA group (23% in our study vs 46% in REVASCAT). However, these differences may be partly due to longer average onset-to-recanalization times in both of these randomized trials. Overall, considering the differences in study populations and delays, our results are compatible with those of these trials.

Whether occlusions distal to the M1 segment should be treated with MT is still an open issue. Unexpectedly considering the literature, in our study there were no statistically significant differences in the 3-month clinical outcome between the different clot locations despite significantly larger thrombus burden, worse collateral circulation and larger perfusion defects in the more proximal occlusions (Table 1). On the contrary, there was a trend towards worse results in the M2 group when attaining excellent clinical outcome (mRS≤1) was considered. Correspondingly, also the recanalization outcomes were somewhat poorer in the M2 group. These findings may be because patients in the M2 group had more severe strokes (median NIHSS 14) than expected from the literature [20]. In addition, there was higher average age and slight female predominance in the M2 group. There may be selection of more symptomatic patients, patients with occlusions of multiple M2 branches and non-responders to IVT into treatment with MT. Finally, the worse technical outcome may be due to increased tortuosity of the vessels, involvement of multiple vessel branches, a smaller proportion of patients that had received IVT, and a thrombus composition less amenable to MT and/or IVT. However, there were no statistically significant differences in the duration of the intervention between the three groups. The total infarct volume at 24h was, as expected, significantly smaller in the M2 group. This was not reflected in the 3-month clinical outcome. This may be due to quite small infarct volumes

also in the ICA and M1 groups and a relatively small number of patients in the M2 group (Table 2).

Taking together these findings, the good technical feasibility and the comparatively favorable outcomes in the more proximal anterior circulation (ICA and M1 segment) and the more complex picture in the M2 segment, these results highlight the importance of MT in the most proximal occlusions.

The major limitation of our study is the non-randomized design. Another limitation is the somewhat small study population, which decreases the value of subgroup analyses, and the uneven distribution of patients in thrombus locations. However, the latter reflects clinical reality with the largest number of proximal occlusions occurring in the M1 segment.

In conclusion, we did not find statistically significant differences in the technical or clinical outcomes between different locations of the clot in the anterior circulation (ICA, M1 or M2) despite significantly larger thrombus burden and worse collateral circulation in the more proximal sites. Interestingly, there was a trend towards achieving excellent clinical outcome (3-month mRS≤1) more often and better recanalization results in the two more proximal locations. These findings emphasize the importance and efficacy of MT in the proximal clot locations. MT in the M2 segment requires further research.

Conflict of Interest Disclosure Statement

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

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.

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Eur.J.Neurol. 19: 1121-1127

Figure 1: TICI scores by the thrombus location

ICA:internal carotid artery, M1:middle cerebral artery segment 1, M2: middle cerebral artery segment 2. TICI: Thrombolysis In Cerebral Infarction.

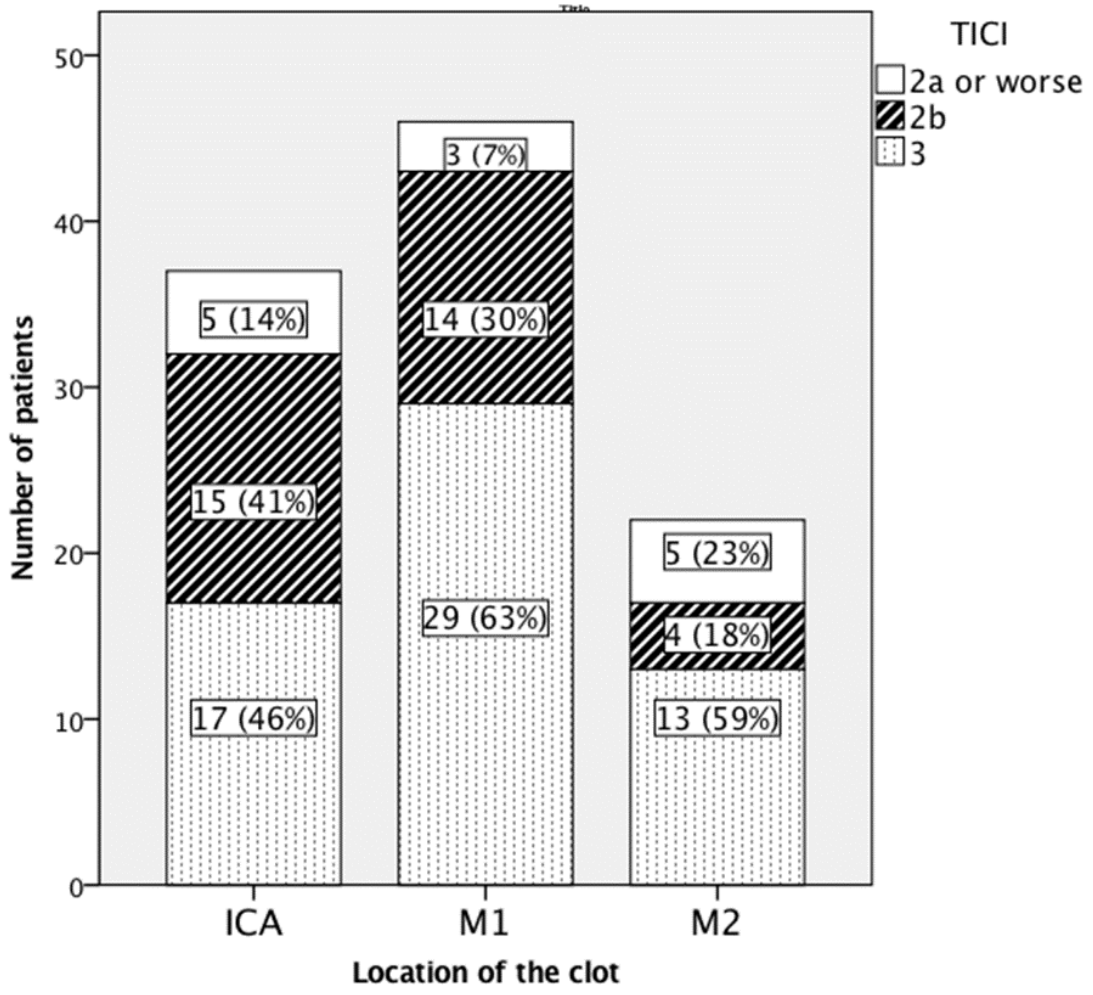
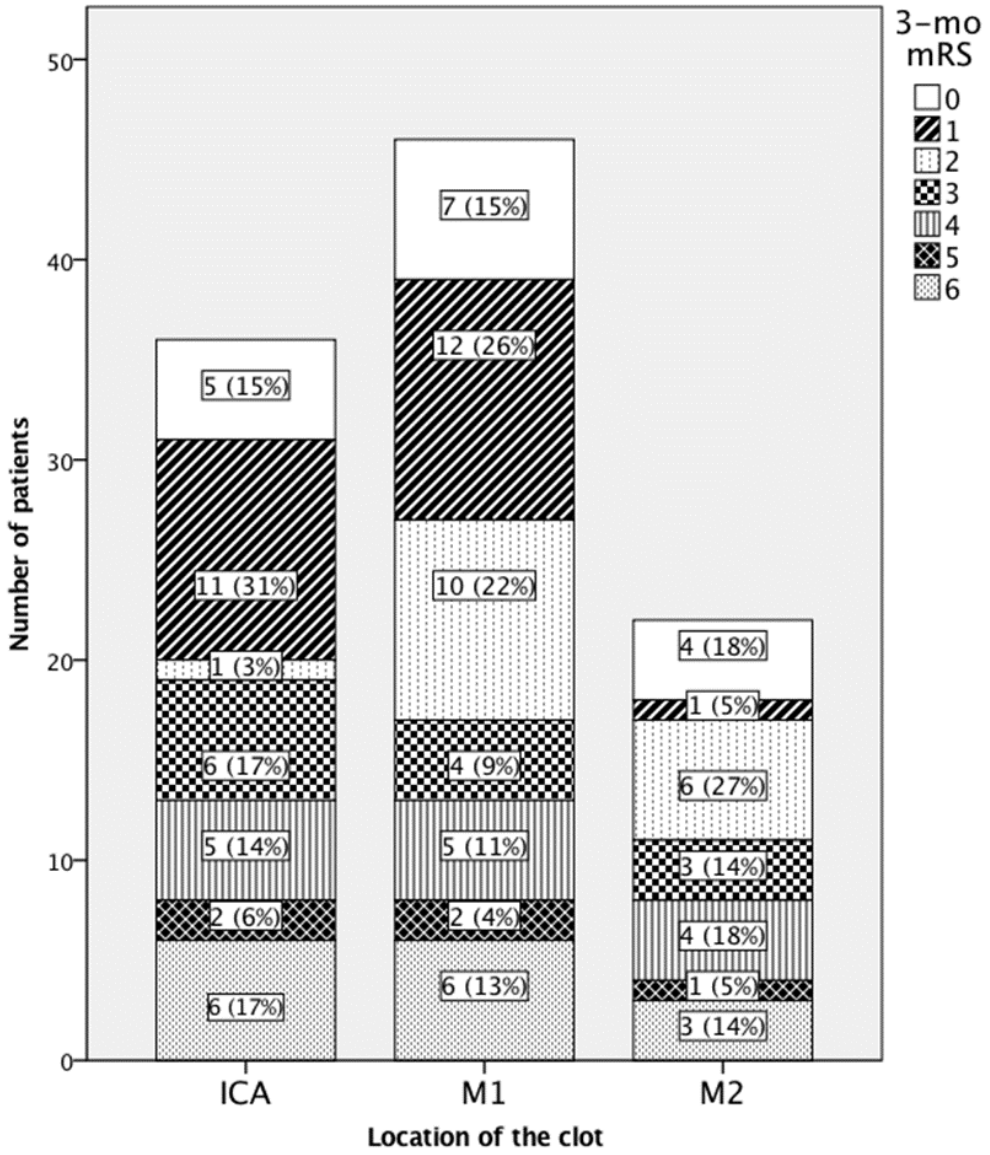


Figure 2: Three-month mRs by the thrombus location

ICA:internal carotid artery, M1:middle cerebral artery segment 1, M2: middle cerebral artery segment 2. mRS: modified Rankin Scale.



Characteristic	All patients (N=105)	ICA (N=37, 35%)	M1 (N=46, 44%)	M2 (N=22, 21%)	P_1
Age (y), mean (SD)	66.1 (11.2)	64.8 (10)	65.3 (12.8)	69.8 (9.3)	0.22
Female sex (%)	45 (43)	14 (38)	16 (35)	15 (68)	0.03
NIHSS before treatment, median (IQR)	14.5 (5)	15 (7)	14 (6)	14 (6)	0.7
Intravenous thrombolysis (%)	67 (65)	27 (73)	30 (65)	10 (45)	0.1
ASPECTS score at admission NCCT, median (IQR)	9 (3)	9 (2)	9 (3)	10 (1)	0.04
ASPECTS score at admission MTT, median (IQR)	2 (4)	1 (2)	2 (3)	5 (3)	<0.001
ASPECTS score at admission CBV, median (IQR)	7 (4)	7 (5)	7 (5)	9 (2)	0.005
Onset to imaging time (min), mean (SD)	154 (103)	150 (97)	160 (100)	148 (122)	0.88
Clot Burden Score, median (IQR)	6 (3)	3 (4)	6 (1)	8 (1)	<0.001
Collateral Score >1 n (%)	43 (41)	11 (32)	14 (29)	18 (82)	<0.001
Hypertension n (%)	46 (44)	16 (43)	21 (46)	9 (41)	0.93
Diabetes n (%)	18 (17)	4 (12)	10 (20)	4 (12)	0.42
Atrial fibrillation n (%)	54 (51)	18 (49)	25 (54)	11 (50)	0.87
Coronary artery disease n (%)	16 (15)	3 (9)	10 (20)	3 (14)	0.22

Table 1: Demographic and baseline and admission imaging characteristics of all patients by the thrombus location

P1: p-value between gourps, ICA:internal carotid artery, M1:middle cerebral artery segment 1, M2: middle cerebral artery segment 2, NIHSS: National Institutes of Health Stroke Scale, .ASPECTS: Alberta Stroke Program Early CT Score, NCCT: non-contrast-enhanced computed tomography, MTT: mean transit time, CBV: cerebral blood volume.

Characteristic	All patients (N=105)	ICA (N=37)	M1 (N=46)	M2 (N=22)	P_1
3-month modified Rankin Scale 0-2 (%)	57 (55)	17 (47)	29 (63)	11 (50)	0.32
3-month modified Rankin Scale 0-1 (%)	40 (39)	16 (44)	19 (41)	5 (23)	0.22
3-month mortality (%)	15 (14)	6 (17)	6 (13)	3 (14)	0.89
ASPECTS score at 24h CT, median (IQR)	7 (4)	7(4)	8 (4)	9 (2)	0.02
Total infarct volume at 24h (ccm), mean (SD)	35 (58)	46 (64)	36 (61)	15 (31)	0.03
Onset to recanalization time (min), mean (SD)	238 (103)	242 (97)	246 (110)	211 (99)	0.36
TICI 2b or 3 (%)	92 (88)	32 (87)	43 (94)	17 (77)	0.16
Duration of the intervention (min), median (IQR)	28 (27)	35 (34)	25 (24)	32 (21)	0.2
Hemorrhagic complication at 24h (%)	20 (19)	8 (22)	8 (18)	4 (18)	0.9
Major space-occupying effect PH2 or PHr2, (%)	6 (6)	1 (3)	3 (7)	2 (9)	0.56
Post-infarct oedema COED2 or COED3 (%)	21 (20)	9 (24)	7 (16)	5 (23)	0.62

Table 2: Technical and imaging outcome of all patients by the thrombus location

P1: p-value between gourps,, ICA:internal carotid artery, M1:middle cerebral artery segment 1, M2: middle cerebral artery segment 2, ASPECTS: Alberta Stroke Program Early CT Score, TICI: Thrombolysis In Cerebral Infarction score, PH: parenchymal hemorrhage, PHr: parenchymal hemorrhage remote, COED: cerebral oedema.

ORIGINAL RESEARCH

TREVO and Capture LP have equal technical success rates in mechanical thrombectomy of proximal and distal anterior circulation occlusions

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ABSTRACT

Purpose Mechanical thrombectomy (MT) is a proven method to treat large vessel occlusions in acute anterior circulation stroke. We compared the technical, imaging, and clinical outcomes of MT performed with either TREVO or Capture LP devices.

Methods There were 42 and 43 patients in the TREVO and Capture LP groups, respectively. Baseline variables, technical outcome (Thrombolysis In Cerebral Infarction, TICI), 24 hours imaging outcome, and 3-month clinical outcome (modified Rankin Scale, mRS) were prospectively recorded. The patients were stratified according to clot location, groups compared, and logistic regression models devised to study the effect of device selection on the clinical outcome.

Results The technical success rates were equal in both proximal (internal carotid artery and proximal M1 segment) and distal occlusions (distal M1 and M2 segments). The proportion of TICI 2b or 3 was 96% and 87% with TREVO and 87% and 89% with Capture LP (p=0.25 and p=0.80, respectively). Device selection did not significantly predict good clinical outcome (mRS ≤2) in either proximal or distal occlusions. In multivariate analysis, selecting Capture LP borderline significantly increased the odds of an excellent outcome close to sixfold both in proximal and distal occlusions (OR 6.7, 95% CI 0.82 to 53.7, p=0.08 and OR 5.7, 95% CI 0.88 to 37.8, p=0.07, respectively).

Conclusions TREVO and Capture LP perform equally well in proximal and distal occlusions in the anterior circulation when technical and good clinical outcome are considered. Capture LP may have a small advantage in reaching mRS ≤1 at 3 months. However, this needs to be confirmed in a randomized study.

INTRODUCTION

Recent randomized studies have established the efficacy and safety of mechanical thrombectomy (MT) as treatment for acute anterior circulation stroke in patients having a proximal vessel occlusion with substantial penumbra in perfusion imaging, a reasonably small infarct core, and adequate collateral circulation.[1–5]

There are a number of newer generation retrievable stent-based MT devices in the market. Among the more popular of these systems are TREVO ProVue (Stryker Neurovascular/Concentric Medical, Mountain View, California, USA) and Capture LP (eV3/ Covidien/Medtronic, Santa Rosa, California, USA). However, currently only a few studies have compared the different retrievable stent systems.

The TREVO Retriever is a thrombectomy device designed to optimize the integration of the clot, especially in intracranial proximal large vessel occlusions. It is a retrievable, hydrophilic coated, closed cell stent-like system. This device has conventional stent characteristics with optimized orientation of the struts, which aims at better thrombus incorporation. Capture LP is a laser-cut stent attached to a nitinol wire. The device is specially designed to fit in smaller microcatheters to allow thrombectomy in distal and more tortuous vessels.

Our study aimed to compare the efficacy and safety of two different newer generation stent retriever devices with different target vessel profiles —the TREVO Retriever and Capture LP—in the treatment of both proximal and distal occlusions in the anterior circulation.

METHODS

Overview, participants and variables

We prospectively collected and analyzed the clinical and imaging data of 130 consecutive patients who were admitted to Tampere University Hospital between January 2013 and December 2014 with acute ischemic stroke. Patients underwent clinical and imaging evaluation and proceeded to digital subtraction angiography with an intention to perform MT. The inclusion criteria for this study were occlusion of the internal carotid artery (ICA) and/or middle cerebral artery and MT with either TREVO or Capture LP. These criteria were met by 85 patients and 45 patients were excluded. Eight were excluded because they had posterior circulation stroke and one patient had an occlusion of the A3 segment of the anterior cerebral artery. In 15 cases thrombectomy with a stent retriever device was not performed either because the clot had dissolved, there was no access to the thrombus, or only aspiration thrombectomy was done. In 10 patients more than one device type was used and in 11 cases the device used was neither TREVO nor Capture LP.

The initial imaging evaluation consisted of non-contrast-enhanced CT (NCCT), CT angiography (CTA), and CT perfusion (CTP). 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 and

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clot position in CTA. ICA or proximal M1 segment occlusions were defined as proximal and distal M1 and M2 segment occlusions as distal occlusions. Patients who were referred to our institution from another hospital 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.

Baseline clinical characteristics included age, sex, time from symptom onset to imaging and to the initiation of intravenous thrombolysis (IVT), and clinical risk factors for ischemic stroke (hypertension, diabetes, coronary heart disease, atrial fibrillation). These data were collected from the patient records. The National Institutes of Health Stroke Scale (NIHSS) score at presentation, time from symptom onset to imaging and to recanalization of the occluded vessel, duration of the procedure, Thrombolysis in Cerebral Infarction (TICI) grading, and possible intraprocedural complications had been prospectively stored in a specifically devised questionnaire. A follow-up NCCT was performed 24 hours after MT. Hemorrhagic complications and post-infarct edema were classified according to SITS-MOST criteria.[6] The primary clinical outcome measure was the modified Rankin Scale (mRS), evaluated by a neurologist 3 months after the stroke based on a follow-up visit or a telephone interview.

Recanalization therapies

IVT (Actilyse 0.9 mg/kg, Boehringer-Ingelheim, Ingelheim, Germany) was administered as bridging therapy based on the judgment of the attending stroke neurologist and possible contraindications. According to the literature, IVT prior to MT is associated with a better clinical outcome.[7 8] The Actilyse bolus was given on the CT table. In one case an eligible patient did not receive the bolus because the onset to imaging time was less than 30 min and the patient was transferred directly to the angiographic suite. Patients coming from an outside hospital received IVT according to the drip-and-ship protocol. The Actilyse drip was continued until groin puncture. MT was performed using a biaxial system consisting of a 8 Fr guiding catheter with a tip balloon and coaxially a 0.021 inch microcatheter or a triaxial system consisting of a 8 Fr guiding catheter with a tip balloon, a distal access catheter through which a microcatheter was inserted with the aid of a 0.014 inch microguidewire. The microcatheter was navigated through the occluded segment of the artery and a suitable stent retriever device was positioned through the microcatheter to the site of the thrombus and deployed. The stent was left in place for up to 3 min 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. Two experienced (>5 years) neurointerventional radiologists (JS and J-PP), who had been trained to use both devices, performed the interventions. The selection of the device was eventually based on the preference of the operator. However, during half of the study time one device was the first choice over the other, during which periods 83% of the MTs were performed with TREVO and 84% with Capture LP, respectively. The TREVO device has been used for longer in our institution and the Capture LP device was available from spring 2013. This was why TREVO was the predominant device used in the earlier half of the investigation. Furthermore, it appears that Capture LP was preferred for more distal locations due to its lower profile which enables it to fit in smaller microcatheters. We used 4 mm×20 mm TREVO and 3 mm×23 mm or 4 mm×23 mm Capture LP devices.

Imaging parameters and image analysis

Details are given in online supplement 1.

Statistical analysis

The data were analyzed with SPSS V.23 (SPSS, Chicago, Illinois, USA). Group comparisons were performed using the Student t test, the χ^2 test, Fisher exact test, and the Mann-Whitney U test. Patients with a collateral score of 2–4 were regarded as having good collateral vessel filling. Patients who had 3-month mRS ≤2 were considered to have experienced a good clinical outcome and those with mRS ≤1 an excellent clinical outcome. Binary logistic regression modeling using these two outcome measures and mortality as the dependent variables was repeated for different variables of interest. Admission NIHSS, age, sex, time from onset to recanalization, clinical risk factors of stroke, device selection, cerebral blood volume (CBV) Alberta Stroke Program Early CT Score (ASPECTS) at admission, site of the occlusion and collateral score were examined as potential confounders and were first tested in univariate models with the dependent variables described above. Based on these results, multivariate models were devised. OR with 95% CI was calculated for each covariate. The calibration of the models was evaluated with the Hosmer-Lemeshow test and discrimination with the C statistic.

RESULTS

Population and baseline characteristics

The inclusion criteria were met by 85 patients with 42 patients (49%) in the TREVO group and 43 patients (51%) in the Capture LP group. In the TREVO group 27 (64%) patients had a proximal thrombus compared with 15 (35%) in the Capture LP group (p=0.007, figure 1). There was a significantly larger number of ICA occlusions in the TREVO group (19 vs 6, p=0.002) whereas there were more M2 occlusions in the Capture LP group (5 vs 15, p=0.01).

The main baseline and admission imaging characteristics are summarized for the whole population by device type and according to the site of the occlusion (proximal or distal) in tables 1 and 2. Nevertheless, in two cases NIHSS could not be scored reliably because the paramedic crew had sedated the patient during transportation. In six cases the time of the onset of the symptoms was unknown (ie, they were wake-up strokes). CTP was successfully completed in 60 of the 85 patients (71%), of which 25 were in the TREVO group (60%) and 35 in the Capture LP group (81%). In one case the 24-hour control

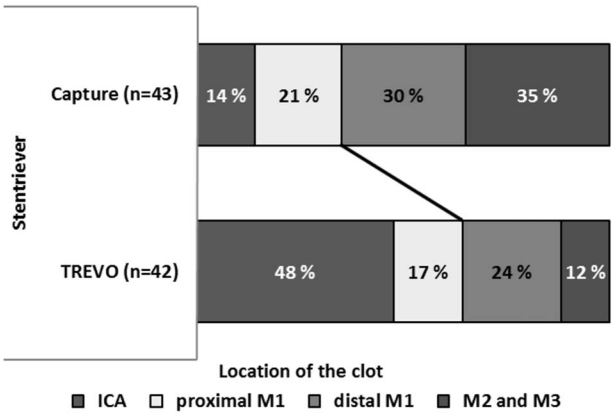

Figure 1 Site of the occlusion in the TREVO and Capture LP groups. ICA, internal carotid artery. The thick line indicates the division between proximal and distal occlusions.

Table 1 Demographic and baseline characteristics and outcome variables of all patients and by device selection

Characteristic	All patients (n=85)	TREVO (n=42)	Capture LP (n=43)	p_1 Value
Age (years), mean (SD)	66.0 (11.7)	67.6 (12.8)	64.2 (10.4)	0.19
Male sex (%)	46 (54)	20 (48)	26 (61)	0.24
NIHSS before treatment, median (IQR)	14 (6)	15.5 (6)	14 (8)	0.29
ASPECTS score at admission NCCT, median (IQR)	9 (2)	9 (4)	9 (3)	0.46
ASPECTS score at admission MTT, median (IQR)	2 (4)	2 (3)	3 (4)	0.18
ASPECTS score at admission CBV, median (IQR)	8 (4)	7 (4)	9 (5)	0.07
Onset to imaging time (min), mean (SD)	150 (100)	151 (100)	149 (101)	0.93
Clot burden score, median (IQR)	6 (4)	4.5 (3)	6 (2)	0.004
Collateral score, median (IQR)	1 (1)	1 (2)	1 (2)	0.20
Hypertension n (%)	37 (44)	20 (48)	17 (40)	0.45
Diabetes n (%)	15 (18)	9 (21)	6 (14)	0.37
Atrial fibrillation n (%)	44 (52)	23 (55)	21 (49)	0.56
Coronary artery disease n (%)	14 (17)	9 (21)	5 (12)	0.22
3-month modified Rankin Scale 0–2 (%)	50 (60)	23 (56)	27 (63)	0.53
3-month modified Rankin Scale 0–1 (%)	34 (41)	13 (32)	21 (49)	0.11
3-month mortality (%)	9 (11)	7 (17)	2 (5)	0.07
ASPECTS score at 24 hours CT, median (IQR)	9 (3)	8 (5)	9 (3)	0.11
Total infarct volume at 24 hours (mL), mean (SD)	31 (56)	39 (60)	23 (53)	0.19
Onset to recanalization time (min), mean (SD)	236 (102)	229 (96)	243 (109)	0.55
TICI 2b or 3 (%)	77 (91)	39 (93)	38 (88)	0.48
Duration of the intervention (min), mean (SD)	33 (22)	33 (24)	32 (19)	0.79
Hemorrhagic complication at 24 hours (%)	16 (19)	10 (25)	6 (14)	0.46
Major space-occupying effect (PH2 or PHr2, %)	4 (5)	3 (8)	1 (2)	0.27
Post-infarct edema COED2 or COED3	14 (17)	10 (25)	4 (9)	0.05

p_1=p value between TREVO and Capture LP groups.
ASPECTS, Alberta Stroke Program Early CT Score; CBV, cerebral blood volume; COED, cerebral oedema; MTT, mean transit time; NCCT, non-contrast-enhanced CT; NIHSS, National Institutes of Health Stroke Scale; PH2, parenchymal hemorrhage; PHr2, parenchymal hemorrhage remote; TICI, Thrombolysis In Cerebral Infarction.

imaging was not available and in three cases the exact duration of the procedure had not been recorded. In addition, one patient could not be reached by telephone or by other means for the 3-month mRS assessment. The differences between the groups in age, sex or other established stroke risk factors, NIHSS at admission, NCCT ASPECTS at admission, or the collateral circulation evaluated from admission CTA images were not significant. However, there was a non-significant trend towards more patients in the TREVO distal occlusion group being older and having coronary artery disease, atrial fibrillation, diabetes, larger clot burden and, correspondingly, worse collateral circulation and larger perfusion defects in the mean transit time (MTT) maps compared with the Capture LP distal occlusion group (table 2). Overall, the size of the perfusion defect in the CBV maps was borderline significantly larger in the TREVO group (ASPECTS 7 vs 9, p=0.07), but this trend was not seen when the proximal and distal occlusions were studied separately (tables 1 and 2). There were no significant differences in onset to imaging times in any of the three comparisons. Fifty-four patients (64%, 28 vs 26, p=0.55) received IVT before MT. IVT did not have a statistically significant impact on the 3-month clinical outcome. Otherwise, we noticed a trend towards good clinical outcome among patients treated with IVT compared with those not treated (34 vs 15, p=0.16).

Technical outcomes

Patients in the TREVO group had more proximal occlusions and a correspondingly significantly larger overall clot burden (p=0.004, table 1) and borderline significantly larger clot burden score (CBS) in the distal occlusion group. However, these differences were not reflected in technical success as measured by TICI (figure 2) or the duration of the procedure (33 vs 32 min, p=0.79, table 1). The technical outcome was TICI 2b or 3 in 77 out of 85 cases (91%, table 1) and there was no significant difference between the groups (93% vs 88%, p=0.48). Furthermore, there was no significant difference in the onset to recanalization times (229 min vs 243 min, p=0.55, table 1). When proximal and distal occlusions were studied separately, no significant differences were found between the devices in these three parameters (table 2).

Imaging and 3-month clinical outcomes

The distribution of the 3-month clinical outcome measured with mRS in the TREVO and Capture LP proximal and distal occlusion groups is shown in figure 3. Overall, 50 of the 85 patients (60%) had a favorable clinical outcome (mRS ≤2) at 3 months with no significant difference between the groups in any comparisons (tables 1 and 2). There was a trend towards more patients having an excellent outcome (mRS ≤1) in the Capture LP group in all comparisons (overall: 32% vs 49%; proximal occlusions: 39% vs 60%; distal occlusions: 20% vs 57%; p=0.11–0.19) and higher overall mortality in the TREVO group (17% vs 5%, p=0.07, tables 1 and 2). In accordance, patients undergoing surgery with TREVO had larger infarct volumes at 24 hours, a larger number of hemorrhagic complications, and significantly more severe post-infarct edema overall and in the distal occlusion group. No such significant differences or trends were found in the proximal occlusion group (tables 1 and 2). All major space-occupying hemorrhages were symptomatic with three occurrences (8%) in the TREVO group and one (2%) in the Capture LP group. One bleeding in the TREVO group was due to perforation of a lenticulostriate perforant

Table 2 Demographic and baseline characteristics and outcome variables of patients with proximal and distal occlusions by device selection

	ICA and proximal M1			Distal M1 and M2		
Characteristic	**TREVO (n=27)**	**Capture LP (n=15)**	**p_1Value**	**TREVO (n=15)**	**Capture LP (n=28)**	**p_2Value**
Age (years), mean (SD)	65.5 (14.0)	60.3 (9.3)	0.20	71.2 (10.0)	66.3 (10.5)	0.15
Male sex (%)	13 (48)	10 (67)	0.24	7 (47)	16 (57)	0.51
NIHSS before treatment, median (IQR)	16 (7)	14 (5)	0.87	15 (5)	13.5 (9)	0.31
ASPECTS score at admission NCCT, median (IQR)	8 (4)	8 (3)	0.81	10 (3)	9 (2)	0.96
ASPECTS score at admission MTT, median (IQR)	1 (2)	1 (2)	0.63	3 (3)	4 (5)	0.14
ASPECTS score at admission CBV, median (IQR)	5.5 (5)	8 (6)	0.24	8 (3)	9 (4)	0.66
Onset to imaging time (min), mean (SD)	159 (104)	143 (77)	0.62	137 (92)	152 (112)	0.65
Clot burden sore, median (IQR)	4 (3)	5 (3)	0.63	6 (2)	8 (3)	0.08
Collateral score, median (IQR)	1 (2)	1 (2)	0.36	1 (3)	2 (2)	0.11
Hypertension n (%)	15 (56)	7 (47)	0.58	5 (33)	10 (36)	0.88
Diabetes n (%)	4 (15)	2 (13)	0.90	5 (33)	4 (14)	0.14
Atrial fibrillation n (%)	12 (44)	8 (53)	0.56	11 (73)	13 (46)	0.09
Coronary artery disease n (%)	4 (15)	2 (13)	0.90	5 (33)	3 (11)	0.07
3-month modified Rankin Scale 0–2 (%)	15 (58)	10 (67)	0.57	8 (53)	17 (61)	0.64
3-month modified Rankin Scale 0–1 (%)	10 (39)	9 (60)	0.18	3 (20)	12 (57)	0.19
3-month mortality (%)	4 (15)	1 (7)	0.64	3 (20)	1 (4)	0.11
ASPECTS score at 24 hours CT, median (IQR)	8 (5)	8 (2)	0.92	8 (6)	9 (2)	0.04
Total infarct volume at 24 hours (ccm), median (SD)	4.7 (47)	2.8 (43)	0.90	10.5 (101)	1.2 (13.4)	0.04
Onset to recanalization time (min), mean (SD)	238 (106)	239 (88)	0.97	213 (76)	245 (121)	0.38
TICI 2b or 3 (%)	26 (96)	13 (87)	0.25	13 (87)	25 (89)	0.80
Duration of the intervention (min), mean (SD)	31 (24)	32 (25)	0.87	38 (25)	32 (16)	0.38
Hemorrhagic complication at 24 hours (%)	5 (20)	4 (27)	0.71	5 (33)	2 (7)	0.04
Major space-occupying effect (PH2 or PHr2, %)	0 (0)	1 (7)	0.38	2 (20)	0 (0)	0.04
Post-infarct edema COED2 or COED3	5 (20)	2 (13)	0.69	5 (33)	2 (7)	0.04

p_1=p value between TREVO and Capture LP proximal occlusion groups; p_2=p value between TREVO and Capture LP distal occlusion groups.
ASPECTS, Alberta Stroke Program Early CT Score; CBV, cerebral blood volume; ICA, internal carotid artery; MTT, mean transit time; NIHSS, National Institutes of Health Stroke Scale; TICI, Thrombolysis In Cerebral Infarction.

artery during catheterization. In addition, we incurred one unintended device detachment with Capture LP.

In a binary logistic regression multivariate model with mortality as the dependent variable and device selection, CBV ASPECTS at admission, NIHSS at admission, age, site of the occlusion (ICA vs non-ICA) and collateral score as covariates, CBV ASPECTS was the only significant predictor of mortality with each point increment decreasing the odds of dying by 0.59 (OR 0.59, 95% CI 0.36 to 0.97, p=0.04). When excellent outcome (mRS ≤1) was chosen as the dependent variable, the site of the occlusion, good collateral circulation, and the use of Capture LP statistically significantly predicted an excellent outcome (see online supplementary table 1). Admission NIHSS and CBV ASPECTS were left out of the model because they were not significant predictors in univariate analysis. Age was kept in the model for theoretical reasons. These three statistically significant variables were also the result of backward likelihood ratio method when all the six covariates of the first model were given as input. The use of Capture LP increased the odds of an excellent outcome fivefold (OR 5.2, 95% CI 1.5 to 15.3, p=0.008). When good clinical outcome (mRS ≤2) was chosen as the dependent variable instead, the device used was not a

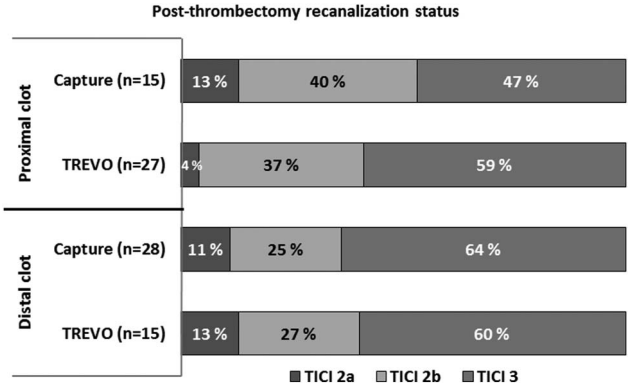

Figure 2 Recanalization outcome in the TREVO and Capture LP groups in proximal and distal occlusions. TICI, Thrombolysis In Cerebral Infarction.

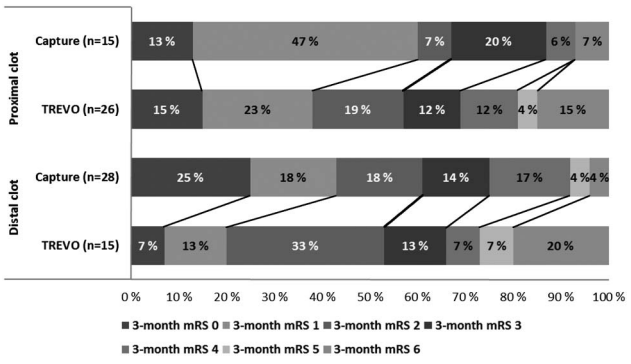

Figure 3 Clinical outcome in the TREVO and Capture LP groups in proximal and distal occlusions. The thick line indicates the division between functional independence (mRS ≤2, left hand side) and dependence (right hand side). mRS, modified Rankin Scale.

Table 3 Logistic regression analysis for excellent clinical outcome (proximal occlusions)

	Proximal occlusion mRS at 3 months ≤1 (H-L=0.08, C=0.83)		
	OR	95% CI	p Value
CBV ASPECTS	0.64	0.41 to 1.00	0.55
Favorable CS (2–4)	3.2	0.41 to 25.4	0.27
Device: Capture LP	6.7	0.82 to 53.7	0.08
Age	1.03	0.93 to 1.13	0.57

ORs are per year for age.
ASPECTS, Alberta Stroke Program Early CT Score; C, C statistic; CBV, cerebral blood volume; CS, collateral score; H-L, Hosmer-Lemeshow significance; mRS, modified Rankin Scale.

significant predictor. Regression models were devised with similar principles separately for proximal and distal clot locations (tables 3 and 4). In both these models device selection was a borderline significant predictor of an excellent outcome (p=0.08 and p=0.07, respectively).

DISCUSSION

MT with a stent retriever is an effective method to treat acute ischemic stroke in patients with a proximal vessel occlusion.[1–5 9] The superiority of newer generation devices over the older ones in efficacy and safety has been established in previous studies.[10–12] These newer generation devices have differing design features that potentially make them more suitable to certain anatomies and occlusion sites, as demonstrated in a recent article on stent retriever mechanical properties and effectiveness.[13]

In this report the radial force, radial pressure variation, and ability of the stent to adhere to the vessel wall during the retrieval were evaluated. The TREVO and Capture LP devices had comparable radial forces in small sizes and both experienced loss of contact with the vessel wall during retrieval. TREVO 4 mm×20 mm had a somewhat higher radial force, but during retrieval the authors observed severe loss in radial force and elongation of the device around angulated vessels.

We found only two studies in the literature that directly compared different newer generation stent retriever thrombectomy devices. Roth *et al*[14] conducted an experiment in a porcine model to compare Solitaire AB/FR and Aperio. They did not find any significant differences in the technical success rate or number of complications between the two devices. Another study compared, in a retrospective non-randomized set-up, the TREVO and Solitaire AB/FR devices.[15] There was a trend towards a larger number of symptomatic intracerebral hemorrhages in the Solitaire group (4 vs 0), but the difference was not statistically significant in this small population (n=22). Otherwise, no differences were found in either different aspects of technical success or clinical outcome. Zaidat *et al*[16] compared the results of two post-marketing registries and found that the clinical performance of TREVO was comparable to that of Solitaire AB/FR.

Table 4 Logistic regression analysis for excellent clinical outcome (distal occlusions)

	Distal occlusion mRS at 3 months ≤1 (H-L=0.66, C=0.75)		
	OR	95% CI	p Value
Clot burden score	0.64	0.41 to 1.00	0.05
Favorable CS (2–4)	1.4	0.32 to 6.5	0.64
Device: Capture LP	5.7	0.88 to 37.8	0.07
Age	0.99	0.93 to 1.06	0.74

ORs are per year for age.
C, C statistic; CS, collateral score; H-L, Hosmer-Lemeshow significance; mRS, modified Rankin Scale.

In our study no statistically significant differences were found between the TREVO and Capture LP groups in terms of age, sex, or the other established stroke risk factors. However, in the TREVO distal occlusion group there was a non-significant trend towards more patients being older and having more stroke risk factors and unfavorable admission imaging findings. Technical outcome was equivalent in the two cohorts in terms of recanalization results and procedure durations, even though there were more ICA occlusions and thus a higher clot burden in the TREVO group. The technical outcomes were also similar when proximal and distal occlusions were considered separately. This suggests that, despite different target vessel profiles by design, the devices perform similarly in large and medium sized vessels. As a general observation, the higher clot burden of the more proximal occlusions does not seem to convert into longer procedure times. This may be because of the extra time needed for more distal catheterizations and the more tortuous anatomy distally, which make both the withdrawal of the deployed device and aspiration technically more challenging.[17]

The 3-month clinical outcome was similar in both groups when functional independence (mRS ≤2) was considered. However, in univariate analyses there was a trend towards more patients having an excellent outcome (mRs ≤1) in the Capture LP group and higher mortality in the TREVO group, both overall and in different clot locations. These findings are probably in part due to larger perfusion defects in the admission CBV maps in the proximal occlusions, differences in stroke risk factors between the groups in the distal occlusions (older age, larger proportion of patients with coronary artery disease, atrial fibrillation and diabetes in the TREVO group), and consequently larger infarct volumes at 24 hours, more hemorrhagic complications and significantly more severe post-infarct edema. However, in multivariate analyses the device selection remained a significant or borderline significant predictor of excellent outcome. In the distal clot locations this may reflect actual superiority of the Capture LP device because it is specifically designed in terms of the size and flexibility of the system components to enable MT of more distal clots. However, only six patients in the TREVO group had an M2 occlusion, which inherently has a higher potential for excellent 3-month clinical outcome, which adds uncertainty to the findings. Yet, the same trend was also observed in the proximal occlusions in both univariate and multivariate analyses.

There was one case of mechanical failure with Capture LP, which led to permanent stent placement. There were no vessel perforations related to withdrawal of a deployed device.[18]

The major limitation of our study is the non-randomized design. Because of this there were significantly more ICA occlusions in the TREVO group and M2 occlusions in the Capture LP group. This difference in the selection of the device is probably due to operator preference and driven by device properties —namely, the sizes available at the time, flexibility, trackability, pushability, and maneuverability. This bias was controlled for by stratification based on clot location and by using multivariate techniques. The assignment of first choice periods in the device

selection during which 83% of the procedures were performed with the TREVO device and 84% with the Capture LP device, respectively, further offsets the bias. Another limitation was the somewhat small study population, which decreases the value of subgroup analyses.

In conclusion, TREVO and Capture LP perform equally well in proximal and distal occlusions in the anterior circulation when technical and good clinical outcome are considered. Capture LP may have a small advantage in reaching mRS ≤1 at 3 months. However, this needs to be confirmed in a randomized study or comparisons of large multicenter registries.

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Low Cerebral Blood Volume Identifies Poor Outcome in Stent Retriever Thrombectomy

Clinical Investigations

Cover title: Poor outcome in mechanical thrombectomy

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ABSTRACT

Background: Mechanical thrombectomy (MT) is an efficient treatment of acute stroke caused by large-vessel occlusion. We evaluated the factors predicting poor clinical outcome (3-month modified Rankin Scale, mRS>2) despite MT performed with modern stent retrievers.

Methods: We prospectively collected the clinical and imaging data of 105 consecutive anterior circulation stroke patients who underwent MT after multimodal CT imaging. Patients with occlusion of the internal carotid artery (ICA) and/or middle cerebral artery (MCA) up to the M2 segment were included. We recorded baseline clinical, procedural and imaging variables, technical outcome, 24h imaging outcome and the clinical outcome. Differences between the groups were studied with appropriate statistical tests and binary logistic regression analysis.

Results: Low Cerebral Blood Volume Alberta Stroke Program Early CT score (CBV-ASPECTS) was associated with poor clinical outcome (median 7 vs 9, p=0.01). Lower Collateral Score (CS) significantly predicted poor outcome in regression modelling with CS=0 increasing the odds of poor outcome 4.4-fold compared to CS=3 (95% CI 1.27-15.5, p=0.02). Lower CBV-ASPECTS significantly predicted poor clinical outcome among those with moderate or severe stroke (OR=0.82, 95% CI 0.68-1, p=0.05) or poor collateral circulation (CS 0-1, OR=0.66, 95% CI 0.48-0.90, p=0.009) but not among those with mild strokes or good collaterals.

Conclusions: CBV-ASPECTS estimating infarct core is a significant predictor of poor clinical outcome among anterior circulation stroke patients treated with MT, especially in the setting of poor collateral circulation and/or moderate or severe stroke.

Abbreviations: ASPECTS = Alberta Stroke Program Early CT Score; CBV = cerebral blood volume; COED = Cerebral oedema; CS = Collateral Score; ICA = internal carotid artery; IVT = intravenous thrombolysis; MCA = middle cerebral artery; MT = Mechanical thrombectomy; MTT =

mean transit time; NIHSS = National Institutes of Health Stroke Scale; TICI = Thrombolysis In Cerebral Infarction

Keywords: interventional radiology; ischemic stroke; mechanical thrombectomy; perfusion CT.

INTRODUCTION

Mechanical thrombectomy (MT) is an efficient treatment of acute stroke caused by large-vessel occlusion in patients presenting with favourable results in imaging evaluation [1-7]. Good clinical outcome, as signified by three-month modified Rankin score (mRS) ≤2, has been reported in roughly half of patients treated with MT despite high rates of successful reperfusion achieved with newer generation stent retrievers [3-7]. Thus, identification of patients with poor prognosis despite reperfusion is of central importance in improving the effectiveness of MT.

Fast and effective recanalization of the occluded vessel with restoration of normal antegrade circulation has a crucial effect on the clinical outcome of acute stroke. However, it is not the only important factor [8, 9]. Multiple studies have mapped both clinical and imaging variables that predict favourable clinical outcome while those that directly address predictors of poor outcome in different settings are far fewer in number [9, 10, 10-13].

The objective of this investigation was to clarify which clinical and imaging variables predict poor clinical outcome (mRS>2) in patients with anterior circulation stroke who underwent MT.

METHODS

Participants and variables

The study was approved by the institutional review board. We prospectively collected and analysed 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 (DSA) with an intention to perform MT. The inclusion criteria for this study were occlusion of the internal carotid artery (ICA) and/or middle cerebral artery (MCA) up to the M2 segment, and MT with stent retriever. 105 patients met these criteria and 25 patients were excluded: eight patients because they had posterior circulation stroke, one patient had an occlusion of the A3 segment of the anterior cerebral artery and another of the M3 segment. In 15 cases thrombectomy with a stent retriever device was not performed because the clot had dissolved, there was no access to the thrombus or only aspiration thrombectomy was done. The baseline clinical characteristics included age, sex, clinical risk factors for ischemic stroke (hypertension, diabetes, coronary heart disease, atrial fibrillation), time from symptom onset to imaging and to initiation of IVT. This data was collected from the patient records. National Institutes of Health Stroke Scale (NIHSS) score at the presentation, time from symptom onset to imaging and to recanalization of the occluded vessel, the duration of the procedure, TICI (Thrombolysis in Cerebral Ischemia) grading evaluated with DSA at the end of the procedure, and procedural complications had been prospectively stored. A follow-up NCCT was performed 24h after MT. Haemorrhagic complications and post-infarct oedema were classified according to SITS-MOST criteria [14]. The clinical outcome measure was the modified Rankin Scale (mRS), evaluated three months after the stroke based on a follow-up visit to neurologist or a phone interview by neurologist. One patient could not be reached for this control.

Imaging protocol, clinical decision making and image analysis

The initial imaging evaluation consisted of non-contrast-enhanced computed tomography (NCCT), CT angiography (CTA) and CT perfusion (CTP). The selection of patients as candidates for MT was based on absence of extensive irreversible ischemic changes (frank hypodensity more than 1/3 of the MCA territory) and haemorrhage in NCCT, evaluation of the amount of salvageable tissue in CTP imaging and proximal clot position in CTA. The decision to proceed to MT was

multidisciplinary (stroke neurologist and neurointerventional radiologist). Patients referred to our institution from other hospitals were re-evaluated with at least NCCT and CTA 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. NCCT, CTA and CTP examinations were reviewed using dedicated medical imaging workstations. Parametric perfusion maps – mean transit time (MTT), cerebral blood flow (CBF), and cerebral blood volume (CBV) – were generated with the CT Perfusion 4 software that uses a delay insensitive deconvolution based algorithm (GE Healthcare). CTA images were reviewed by examining both the raw data and maximum intensity projection images. The Alberta Stroke Program Early CT Score (ASPECTS) was assessed from admission and follow-up 24h NCCT images, and from MTT and CBV maps as described in our previous article [15]. CTA was used to evaluate the occlusion site, the Clot Burden Score (CBS) and the Collateral Score (CS) as described in our previous report [16] and Table 1. 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 finally CTP, paralleling that of the clinical work flow. Two radiologists assigned ASPECTS, CBS and CS. In cases the scoring or the assignment differed, a consensus opinion was agreed on. The reviewers were blinded to the clinical data apart from the side and nature of the acute symptoms. One radiologist measured the final infarct volumes on the 24h NCCT. The boundaries of the affected areas were determined visually. Volume was calculated by multiplying the measured area with the slice thickness. Validation of the measurements including intraclass correlation coefficients (ICC) and Cohen's kappa values can be found in the above-mentioned previous publications.

Recanalization therapies

MT was performed with different stent retrievers and sometimes with multiple devices based on the judgment of the operator. We used a bi-axial system consisting of an 8F or 9F guiding catheter with

a tip balloon and coaxially a 0.021" micro-catheter or a tri-axial system consisting of an 8F guiding catheter, a distal access catheter trough which a micro-catheter was inserted with the aid of a 0.014" micro-guidewire. The micro-catheter was navigated through the occluded segment of the artery and a suitable stent retriever device was positioned trough 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 retriever devices were used based on the preference and judgment of the operator with size of the vessel and tortuosity of the vasculature as main selection criteria. The TREVO® device (Stryker Neurovascular/Concentric Medical, Mountain View, CA, USA) was used in 40 % of cases, CAPTURE LP™ (eV3/ COVIDIEN/Medtronic, Santa Rosa, CA, USA) in 40%, ERIC® (MicroVention, Tustin, CA,USA) in 9%, Aperio® (Acandis, Pforzheim, Germany) and REVIVE® (Codman &Shurtleff, Raynham, MA, USA) in 1% respectively and in 10% of cases multiple device types were used. Intravenous thrombolysis (Actilyse® 0,9mg/kg, Boehringer-Ingelheim, Ingelheim, Germany) was administered as bridging therapy to patients with no contraindications. The Actilyse® bolus was given on the CT table. If the delay from the symptom onset to groin puncture was expected to be minimal, i. e. in the case of an inpatient during office hours, IVT was not necessarily given. Patients coming from an outside hospital received IVT according to drip-and-ship protocol. Actilyse® drip was continued until groin puncture.

Imaging parameters

Please see online supplementary material.

Statistics

The data was analysed with SPSS version 23 (SPSS Inc., Chicago, IL). Group comparisons were performed by using the Student t-test, the Chi-squared test, the Fisher exact test, and the Mann-Whitney U test according to the type and distribution properties of the variable studied. Univariable and multivariable binary logistic regression analyses using poor clinical outcome as dependent variable were performed and odds ratio (OR) with 95% confidence interval (CI) were calculated for each covariate. Patients with Collateral Score from 2 to 4 were regarded as having good collateral vessel filling. Patients who had three-month mRS >2 were considered to have experienced poor clinical outcome. A TICI score >2a was considered a good recanalization result. A p-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

The inclusion criteria were met by 105 patients with 37 patients (35%) presenting with an occlusion of the ICA, 46 patients (44%) had an M1 segment occlusion and 22 patients (21%) had an M2 segment occlusion. The main baseline and admission imaging characteristics are summarized in Table 2. Poor clinical outcome was seen in 47 of 105 patients (45%). Ninety-two patients (88%) had TICI > 2a, which was considered the threshold of good technical result of MT. In this group, 38 patients (41%) experienced poor clinical outcome despite the successful recanalization. In two cases NIHSS could not be scored reliably because the paramedic crew had sedated the patient during transportation. In eight cases the time of the onset of the symptoms was unknown (i.e. they were wake-up strokes). CTP was successfully obtained from 72 patients (69%).

Predictors of poor 3-month clinical outcome

There were no significant differences between patients with poor and good clinical outcome in age, sex or other established stroke risk factors. Likewise, there were no statistically significant differences in the onset-to-imaging and recanalization times. The duration of the intervention was significantly longer in the mRS >2 group compared to the mRS ≤2 group (37min vs 23min, $p<0.001$, Table 3). The clot burden score (CBS) was similar in the two groups (Table 2). Patients with more severe strokes according to NIHSS at admission showed a trend towards worse 3-month clinical outcome ($p=0.08$, Table 2). The administration of intravenous thrombolysis (IVT) was more common in the good outcome group even though the difference was not statistically significant ($p=0.08$, Table 2). Fifteen (32%) patients in the poor outcome group succumbed to their illness.

The size of the infarct core as estimated from CBV parametric maps and quantified with ASPECTS was significantly larger in the poor outcome group (median CBV-ASPECTS 7 vs 9, $p=0.01$, Table 2). In univariable regression analysis, incrementing one ASPECTS point decreased the odds of poor outcome by a factor of 0.79 (95% CI=0.64 to 0.94, $p=0.01$, Table 4). The result was similar when only patients with a favourable reperfusion result (TICI>2a) were considered (Table 4).

Extremely poor collateral circulation (CS=0) was significantly associated with poor outcome with 73% of patients having no visible collateral circulation experiencing poor clinical outcome at three months ($p=0.03$, Table 2). Correspondingly, in univariable regression analysis including all patients, CS significantly predicted poor clinical outcome and having CS=0 increased the odds of poor outcome 4.4-fold (95% CI 1.27 to 15.5, $p=0.02$, Table 4) compared to having optimal collateral filling (CS=3). This association was even stronger if only those with successful reperfusion were considered (OR=6.5, 95% CI 1.6 to 26.4, $p=0.009$, Table 4).

When patients with moderate or severe stroke were evaluated (NIHSS 8 or more), lower CBV-ASPECTS significantly predicted poor clinical outcome (OR=0.82, 95% CI 0.68 to 1, $p=0.05$) whereas no significant difference was found among those with mild strokes. Similarly, when

restricting the analysis to patients with poor collateral circulation (CS 0-1), incrementing one CBV-ASPECTS point significantly decreased the odds of poor prognosis (OR=0.66, 95% CI 0.48-0.90, p=0.009) whereas no significant difference was found among those with good collaterals. Patients with reperfusion result TICI=2a or worse showed a trend to poorer outcome (OR=3.14, 95% CI=0.9-11. p=0.07, Table 4).

Finally, a binary logistic multivariable model using backwards likelihood method was devised with poor 3-month clinical outcome as the dependent variable and variables with p<0.1 in the univariable analysis included as covariates. Lower CBV-ASPECTS (OR=0.77, 95% CI=0.63 to 0.95, p=0.01) and not receiving IVT (OR=3.2, 95% CI=1.1 to 9.4, p=0.04) emerged as the only statistically significant predictors of poor outcome in the final model.

Imaging outcome

ASPECTS was markedly lower in the 24h-follow-up NCCT of patients with a mRS >2 (7 vs 9, p<0.001, Table 3). Correspondingly, the total infarct volume was larger among those with poor outcome (64 ccm vs 11 ccm, p<0.001, Table 3). Furthermore, the number of haemorrhagic complications and the extent of post-infarct oedema were significantly larger among these patients: the proportion of those with a haemorrhagic complication at 24 hours 14% vs 6% (p=0.01, Table 3), major space occupying haemorrhage type PH2 or PHr2 5% vs 2% (p=0.05), and post-infarct oedema grade COED 2 or 3 18% vs 2% (p<0.001).

DISCUSSION

Rapid and effective recanalization of the occluded vessel is a crucial predictor of good clinical outcome in the treatment of acute anterior circulation ischemic stroke [9, 12]. It is still unclear which patients with a large-vessel occlusion should be denied of MT because of poor prognosis regardless of the type of reperfusion therapy. A number of studies have focused on evaluating the

factors predicting good outcome, whereas fewer studies have primarily addressed the factors related to poor clinical outcome at 3 months [11, 17-21]. The setup of the majority of these studies has been the evaluation of factors associated with poor clinical outcome despite successful recanalization. In contrast, we studied all consecutive patients presenting with anterior circulation stroke who underwent MT with a goal to understand which factors that are known at the time of the clinical decision making to perform MT predict poor outcome. However, a subgroup analysis including only patients with successful recanalization revealed that these factors are essentially the same as in the entire study population. This finding was somewhat expected because of the high recanalization rate (88%).

Higher NIHSS score at admission signifying more severe stroke, proximal site of occlusion and absence of IVT treatment are closely associated with a poor 3-month outcome among patients undergoing MT [17, 19, 20]. In our study we saw similar trends but these findings were borderline statistically non-significant apart from the last. Interestingly, according to a meta-analysis of the five recent randomized studies that established MT as the treatment of choice in large-vessel occlusions, MT increased the odds of good clinical outcome regardless of IVT [2]. In our study also the location of the occlusion was not a significant predictor of outcome which can in part be due to worse recanalization outcomes among those with an M2 occlusion compared to those with more proximal occlusions [22]. Moreover, patients with an M2 occlusion had more severe strokes (median NIHSS 14) than expected from the literature [23] and somewhat higher average age (69.8 years vs. 64.8 and 65.3 years among patients with ICA and M1 occlusions, respectively). On the other hand, age was not significantly related to a poor outcome in our study. This may be because only a small number of patients in our study were 80 years of age or older, which has been demonstrated to be related to a poorer outcome. [17, 19]

There was no significant difference in NCCT-ASPECTS scores at admission between those with good and poor outcome. This needs to be interpreted in the context of relatively short average onset-

to-imaging times. However, where NCCT-ASPECTS lacks sensitivity, CBV-ASPECTS emerged as an important imaging parameter with lower scores predicting poor outcome (Table 2, Figure 1). This is compatible with previous results regarding both IVT and MT [4, 21, 24-29]. As demonstrated in previous studies on IVT a CBV-ASPECTS threshold of 7 or 8 best differentiates good and poor outcome. [15, 30] In our study the median CBV-ASPECTS in the poor outcome group was 7.

The status of the collateral circulation as measured with Collateral Score has been shown to be an important predictor of clinical outcome [31-33]. In our study having no visible collateral circulation at all (CS=0) was specifically related to poor outcome.

CBV-ASPECTS did not significantly predict poor clinical outcome among patients with mild strokes (NIHSS<8) or good collateral circulation (CS 2-4) whereas low CBV-ASPECTS was significantly associated with poor outcome among those suffering from moderate or severe stroke and/or having poor collateral circulation. A mild stroke entails less extensive and severe ischemia which considering the mean onset-to-imaging time of less than 3 hours translates into a small infarct core especially if an aggregating quantification method like ASPECTS is used. Similarly, good collateral circulation is related to smaller infarct core in this short timeframe. In a recent meta-analysis, MT did not significantly improve the clinical outcome of patients with NIHSS<10 compared to IVT [2]. These findings imply that perfusion imaging in the context of MT may be targeted to specific subgroups if not performed routinely to all patients presenting with stroke symptoms. This would also reduce the total radiation dose incurred in diagnostic imaging.

Our study has limitations. Firstly, as the formation of the MT cohort was clinically driven and thus non-randomized, there can be selection biases. Further, due to relatively small number of patients, subgroup analyses may be underpowered to detect small differences between the subgroups.

CONCLUSIONS

Clinical variables and NCCT at admission are lacking in precision in the detection of patients with poor prognosis regardless of MT. A low CBV-ASPECTS score associated with large infarct core is a significant predictor of poor clinical outcome among these patients especially in the setting of poor collateral circulation and/or moderate or severe stroke. Thus, perfusion imaging should be considered in the evaluation of acute anterior circulation stroke patients who are candidates to undergo MT.

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Figure 1: A 82-year old male with type 2 diabetes mellitus and chronic hypertension was brought to the emergency department because of right-sided hemiparesis. NCCT revealed minor ischemic changes (ASPECTS=9, only one level shown, Panel A). There was an occlusion of the left distal M1 segment in CTA (Panel B). CBV-ASPECTS was scored 7 and MTT-ASPECTS 5 (Panels D and E. White arrows indicate the boundaries of the lesion). Revascularization was achieved with MT (TICI=2b, Panel C). In the 24h control NCCT ASPECTS was 7. The 3-month mRS was 3 (Panel F).

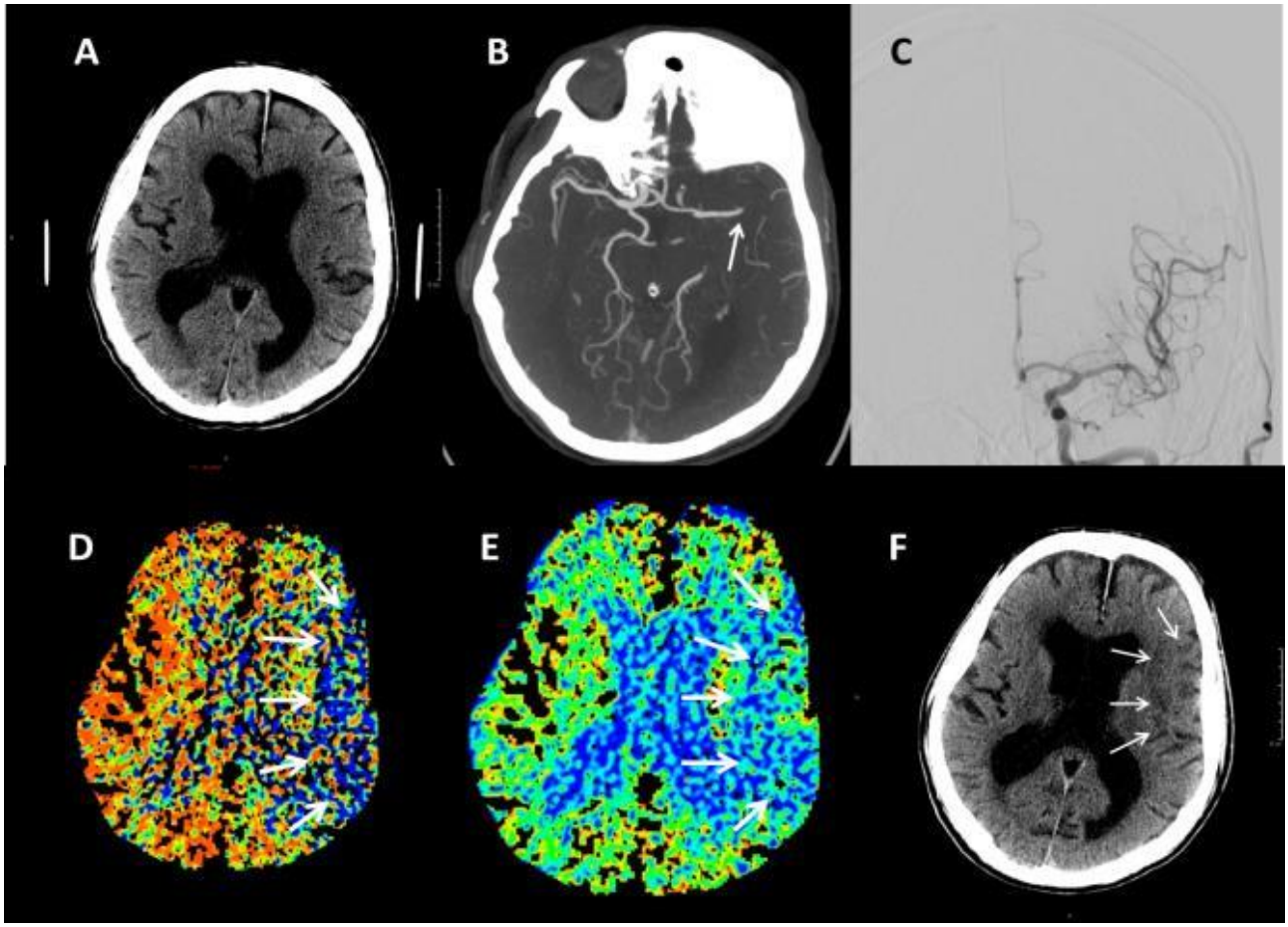

Table 1: Collateral Score

Collateral Score (CS) was evaluated from single-phase CTA using a modified score as defined by Souza et al. (2012). [34]

COLLATERAL SCORE	DEFINITION
0	Absent collaterals in > 50% of the MCA territory
1	Diminished collaterals in > 50% of the MCA territory
2	Diminished collaterals in < 50% of the MCA territory

3	Collaterals equals to the contralateral territory
4	Increased collaterals

Table 2: Demographic and baseline and admission imaging characteristics of all patients by the clinical outcome at 3 months

P1: p-value between groups, ICA:internal carotid artery, M1:middle cerebral artery segment 1, M2: middle cerebral artery segment 2, NIHSS: National Institutes of Health Stroke Scale, ASPECTS: Alberta Stroke Program Early CT Score, NCCT: non-contrast-enhanced computed tomography, MTT: mean transit time, CBV: cerebral blood volume.

Characteristic	All patients (N=105)	3-mo mRS ≤2 (N=57)	3-mo mRS >2 (N=47)	P_1
Age (y), mean (SD)	66(11)	65(12)	67(10)	0.45
Female sex (%)	45 (43)	24(42)	20(43)	0.96
NIHSS before treatment, median (IQR, N=103)	14.5(5)	14(9)	15.5(5)	0.08
Intravenous thrombolysis (%)	66(64)	40(70)	26(55)	0.08
Location of clot/occlusion				0.31
ICA	37(35)	17(30)	19(40)	
M1	46(44)	29(51)	17(36)	
M2	22(21)	11(19)	11(23)	
ASPECTS score at admission NCCT, median (IQR, N=72)	9(3)	9(2)	9(3)	0.58
ASPECTS score at admission MTT, median (IQR, N=72)	2(4)	3(3)	3(6)	0.24
ASPECTS score at admission CBV, median (IQR, N=72)	7(4)	9(3)	7(5)	0.01
Onset to imaging time (min), mean (SD, N=97)	154(103)	153(87)	157(111)	0.92
Clot Burden Score, median (IQR)	6(3)	6(3)	6(5)	0.72
Collateral Score = 0 n (%)	23(22)	6(27)	16(73)	0.03
Hypertension n (%)	46(44)	22(39)	23(49)	0.29
Diabetes n (%)	18(17)	8(14)	10(21)	0.33
Atrial fibrillation n (%)	54(51)	30(53)	23(29)	0.7
Coronary artery disease n (%)	16(15)	8(14)	8(17)	0.67

Table 3: Technical and imaging outcome of all patients by the clinical outcome at 3 months

P1: p-value between gourps, ICA: internal carotid artery, M1: middle cerebral artery segment 1, M2: middle cerebral artery segment 2, ASPECTS: Alberta Stroke Program Early CT Score, TICI: Thrombolysis In Cerebral Infarction score, PH: parenchymal haemorrhage, PHr: parenchymal haemorrhage remote, COED: cerebral oedema.

	All patients (N=105)	3-mo mRS ≤2 (N=57)	3-mo mRS >2 (N=47)	P_1
ASPECTS score at 24h CT, median (IQR)	7 (4)	9(3)	7(6)	<0.001
Total infarct volume at 24h (ccm), mean (SD)	35 (58)	11(24)	64(73)	<0.001
Onset to recanalization time (min), median (IQR)	238 (103)	205(112)	235(187)	0.52
TICI 2b or 3 (%)	92 (88)	53(93)	38(81)	0.06
Duration of the intervention (min), median (IQR)	28 (27)	23(20)	37(27)	<0.001
Haemorrhagic complication at 24h (%)	20 (19)	6(10)	14(30)	0.01
Major space-occupying effect PH2 or PHr2, (%)	6 (6)	1(2)	5(11)	0.05
Post-infarct oedema COED2 or COED3 (%)	21 (20)	2(4)	18(40)	<0.001

Table 4: Univariate logistic regression analysis of poor clinical outcome at 3 months (mRs>2) in all patients and successfully reperfused patients (TICI>2a)

P1: p-value in overall population, P2: p-value in succesfully recanalized patients, ASPECTS: Alberta Stroke Program Early CT Score, CBV: cerebral blood volume, CS: Collateral Score, ICA: internal carotid artery, M1: middle cerebral artery segment 1, M2: middle cerebral artery segment 2, NCCT: non-contrast-enhanced computed tomography, NIHSS: National Institutes of Health Stroke Scale, MTT: mean transit time, TICI: Thrombolysis In Cerebral Infarction score

	All patients			Successfully reperfused		
Characteristic	Unadjusted OR	95% CI	P_1	Unadjusted OR	95% CI	P_2
Age (y)	1.01	(0.98 to 1.05)	0.45	1.02	(1 to 1.1)	0.3
Female sex	1.02	(0.47 to 2.22)	0.96	0.9	(0.4 to 2)	0.7
NIHSS before treatment	1.07	(0.99 to 1.17)	0.097	1.1	(1 to 1.2)	0.09
Intravenous thrombolysis	0.48	(0.22 to 1.08)	0.08	1.7	(0.7 to 4)	0.24
Location of clot/occlusion						
ICA	REF		0.32			0.55
M1	0.53	(0.22 to 1.3)	0.15	0.6	(0.2 to 1.5)	0.26
M2	0.9	(0.31 to 2.59)	0.84	0.7	(0.2 to 2.4)	0.57
ASPECTS score at admission NCCT	0.96	(0.75 to 1.22)	0.74	0.9	(0.7 to 1.15)	0.34
ASPECTS score at admission MTT	0.96	(0.78 to 1.16)	0.68	0.9	(0.7 to 1.08)	0.2
ASPECTS score at admission CBV	0.79	(0.64 to 0.94)	0.01	0.74	(0.6 to 0.9)	0.004
Onset to imaging time (min)	1	(1 to 1)	0.83	1	(1 to 1)	1
Clot Burden Score	0.95	(0.8 to 1.11)	0.51	1	(0.8 to 1.2)	0.74
Collateral Score (CS)						
CS 3	REF		0.05			0.06
CS 0	4.44	(1.27 to 15.5)	0.02	6.5	(1.6 to 26.4)	0.009
CS1	0.93	(0.33 to 2.68)	0.9	2	(0.6 to 6.76)	0.26
CS2	1.212	(0.35 to 4.15)	0.76	1.64	(0.4 to 6.76)	0.5
Onset to reperfusion	1	(1 to 1.01)	0.39	1	(1 to 1.01)	0.5
TICI 0-2a	3.14	(0.9 to 11)	0.07	-	---	-
Total infarct volume (ccm) at 24h	1.03	(1.02 to 1.05)	<0.001	1.03	(1.01 to 1.05)	<0.001
Hypertension	1.53	(0.7 to 3.3)	0.3	2.2	(0.9 to 5.1)	0.08
Diabetes	1.66	(0.6 to 4.6)	0.33	1.8	(0.6 to 5.3)	0.3
Atrial fibrillation	0.86	(0.4 to 1.87)	0.71	0.77	(0.3 to 1.8)	0.5
Coronary artery disease	1.26	(0.4 to 3.7)	0.68	0.9	(0.26 to 2.8)	0.8

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Original Paper

Internal Carotid Artery and the Proximal M1 Segment Are Optimal Targets for Mechanical Thrombectomy

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Keywords
Intravenous thrombolysis · Ischemic stroke · Mechanical thrombectomy · Revascularization · Stent retriever

Abstract
Background and Purpose: Mechanical thrombectomy (MT) is an established treatment of acute anterior circulation stroke caused by large vessel occlusion (LVO). We compared the clinical outcome (3-month modified Rankin Scale, mRS) in hyperacute (<3h from the onset of symptoms) ischemic stroke between an MT and an intravenous thrombolysis (IVT) cohort in proximal (ICA and the proximal M1 segment of the middle cerebral artery) and distal (the distal M1 and the M2 segment) LVOs. ***Methods:*** We prospectively reviewed 67 patients who underwent MT with newer-generation stent retrievers. The IVT cohort consisted of 98 patients who received IVT without MT. We recorded baseline clinical, procedural and imaging variables, technical outcome, 24-h imaging outcome, and the clinical outcome. Differences between the groups were studied with theoretically appropriate statistical tests and binary logistic regression analysis. ***Results:*** The proportion of patients who had a proximal LVO and experienced good (mRS ≤2) or excellent (mRS ≤1) clinical outcome was significantly larger in the MT group (62 vs. 7%, $p < 0.001$; 47 vs. 3%, $p < 0.001$, respectively). In a regression model including relevant confounding variables, good clinical outcome was seen significantly more often among patients with proximal occlusions (OR = 6.0, CI 95% 1.9–18.3, $p = 0.002$). In a similar model, no statistically significant differences were observed in patients with more distal occlusions. ***Conclusions:*** MT is superior to IVT in achieving good clinical outcome in hyperacute anterior circulation stroke in the most proximal occlusions (ICA and proximal M1 segment). In the distal M1 and M2 segments neither of these therapies clearly outperforms the other.

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Introduction

Mechanical thrombectomy (MT) is a safe and efficient treatment for acute ischemic stroke caused by large vessel occlusion (LVO) with sufficiently small infarct volume on admission imaging as established by several recent randomized studies [1–5]. Based on these trials there is convincing evidence that MT yields better results compared to revascularization with intravenous thrombolysis (IVT) only if the occlusion is located in the distal internal carotid artery (ICA) including the different conformations carotid I, L and T, or the M1 segment of the middle cerebral artery (MCA). It is still unclear if MT outperforms IVT in the M2 segment because of the small number and heterogeneousness of patients with M2 occlusions in the randomized trials and other previous research [6–8]. Further, according to a recent recommendation and previous reports, the proximal and distal halves of the M1 segments should be examined separately because these vessel subsegments have differing properties that seem to influence the potential for good clinical outcome and the efficacy of revascularization therapies [8–12].

We compared the clinical outcome measured with 3-month modified Rankin Scale (mRS) in hyperacute (<3 h from the onset of symptoms) ischemic stroke between an MT and an IVT cohort in different sites of occlusion: ICA, the proximal M1 (M1P), the distal M1 (M1D), and the M2 segment of the MCA. The first two sites were considered proximal LVOs and the latter two distal LVOs.

Methods

Overview, Participants, and Variables

We prospectively collected and analyzed the clinical and imaging data of 130 consecutive patients, who were admitted to Tampere University Hospital from January 2013 to December 2014 because of acute ischemic stroke symptoms and who underwent clinical and imaging evaluation and proceeded to digital subtraction angiography (DSA) with an intention to perform MT. The inclusion criteria were occlusion of ICA (the intracranial part with possible extension to the extracranial part) and/or the M1 or M2 segment of the MCA, MT with a stent retriever, and onset-to-imaging time 3 h or less. Sixty-seven patients met these criteria. An anterior circulation occlusion IVT-only cohort was used as a control group. This cohort has been extensively characterized in our previous report [12]. Ninety-eight from 105 patients remained in this group after patients with occlusions distal to the M2 segment were removed. The IVT-only cohort includes all patients treated with IVT from 2004 to 2007 for anterior circulation stroke and who had a clot visible in CT angiography (CTA). Starting from 2008 with the advent of the first generation MT devices we began to treat selected patients with MT. By 2012, we had established a stroke protocol where all anterior circulation stroke patients being evaluated for IVT were also evaluated for MT if there was a clot visible in CTA. The inclusion criteria to treat LVO (ICA and the M1 and M2 segments) with MT paralleled those of IVT apart from the time limit from the onset of symptoms that was <12 h with MT, and therapy-related differences in contraindications. The prestroke mRS was required to be ≤2. In the current study, only onset-to-imaging times <3 h were included to maintain congruence with the IVT-only cohort.

The initial imaging evaluation consisted of non-contrast-enhanced computed tomography (NCCT), CTA, and CT perfusion (CTP). CTP could be dropped to save time at discretion of the attending neurologist. The selection of patients as candidates for MT was based on absence of extensive irreversible ischemic changes (frank hypodensity spanning more than one-third the volume of MCA vascular territory) and hemorrhage in NCCT, presence of a proximal clot in CTA, and evaluation of the amount of salvageable tissue in CTP imaging (if available).

Baseline clinical characteristics included age, sex, and clinical risk factors for ischemic stroke (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 imaging and recanalization of the occluded vessel, the duration of the procedure, the Thrombolysis in Cerebral Infarction (TICI) score, and possible complications had been prospectively stored to a specifically devised questionnaire. A follow-up NCCT was performed 24 h after revascularization. Hemorrhagic complications and cerebral edema (COED) were classified according to the SITS-MOST criteria.

Reperfusion was evaluated with TICI, which was scored from the final DSA control runs of the intervention. The clinical outcome measure was mRS, evaluated 3 months after the stroke based on a follow-up visit to a neurologist or a phone interview by a neurologist. The imaging outcome measure was infarct volume evaluated 24 h after the intervention.

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee. For this type of study, formal consent is not required.

Revascularization Therapies

MT was performed using a bi-axial system consisting of an 8-Fr or 9-Fr guiding catheter with a tip balloon and coaxially a 0.021″ micro-catheter or a tri-axial system consisting of an 8-Fr guiding catheter, a distal access catheter through which a micro-catheter was inserted with the aid of a 0.014″ micro-guidewire. The micro-catheter was navigated through the occluded segment of the artery, and a suitable stent retriever was positioned trough the micro-catheter to the site of the thrombus and deployed. The stent was left in place for 4 min and then retrieved and at the same time the guiding or the intermediate catheter was aspirated forcefully. The same procedure was repeated until satisfactory circulation was restored. Different stent retrievers were used based on the preference and judgment of the operator. TREVO® (Stryker Neurovascular/Concentric Medical, Mountain View, CA, USA) was used in 40% of cases, CAPTURE LP™ (eV3/COVIDIEN/Medtronic, Santa Rosa, CA, USA) in 40%, ERIC® (MicroVention, Tustin, CA, USA) in 9%, Aperio® (Acandis, Pforzheim, Germany) and REVIVE® (Codman & Shurtleff, Raynham, MA, USA) in 1%, respectively, and in 10% of cases multiple device types were used. The diameters used varied from 3 to 6 mm with a 4-mm device being most commonly used. IVT (Actilyse® 0.9 mg/kg, Boehringer-Ingelheim, Ingelheim, Germany) was administered based on the judgment of the attending stroke neurologist and possible contraindications. Actilyse® bolus was given on the CT table. Actilyse® drip was continued until groin puncture or full dose.

Imaging Parameters

The imaging parameters are characterized in the Appendix.

Image Analysis

The details of image analysis and validation of the measurements are described in the Appendix.

Statistics

The data were analyzed with SPSS version 20 (SPSS Inc., Chicago, IL, USA). Group comparisons were performed by using the Student *t* test, the χ^2 test, the Fisher exact test, and the Mann-Whitney U test. Binary logistic regression analyses using good and excellent clinical outcomes as dependent variables were performed in order to control for the effect of differences in NIHSS and, when analyzing proximal LVOs, the presence of coronary artery disease and/or atrial fibrillation, or when analyzing distal LVOs, the presence of chronic hypertension, the onset-to-imaging time and the clot burden score between the MT and IVT-only groups. These variables were selected based on the results of univariate analyses and theoretical considerations. Odds ratio (OR) with 95% confidence interval (CI) was calculated for each covariate. Patients who had 3-month mRS ≤2 were considered to have experienced good clinical outcome and those with mRS ≤1 excellent outcome. Occlusions in ICA and/or M1P were defined as proximal and those in M1D and M2 segment as distal. A p value <0.05 was considered statistically significant.

Results

Baseline Characteristics

The inclusion criteria were met by 67 patients in the MT group and 98 patients in the IVT-only group. In the MT cohort 38 patients were excluded because of onset-to-imaging time (time to treatment decision making) longer than 3 h; 8 patients had posterior circulation strokes, 1 patient had occlusion of the A3 segment of the anterior cerebral artery, and another clot in the M3 segment. In 15 cases, MT was not performed either because the clot had dissolved or there was no access to the thrombus. The baseline and admission imaging characteristics for all patients and both groups are summarized in the Appendix. In one case,

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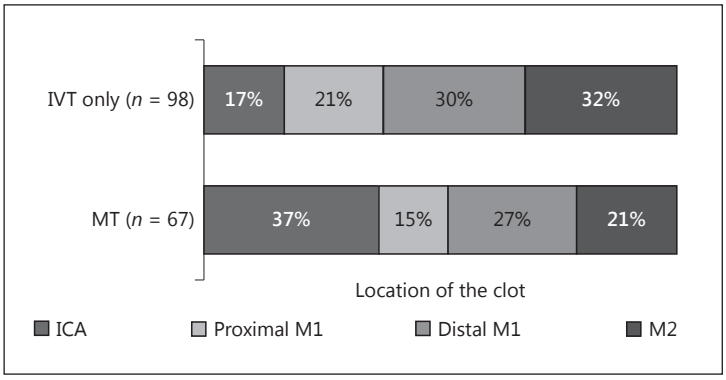

Fig. 1. Clot locations in the MT and IVT-only groups. ICA, internal carotid artery; M1, middle cerebral artery segment 1; M2, middle cerebral artery segment 2.

NIHSS could not be scored reliably because of sedation during transportation. CTP was successfully obtained from 42 patients (63%) in the MT group and 76 patients (77%) in the IVT-only group. The reperfusion outcome was TICI 2b or 3 in 59 out of 67 cases (88%). The results were nonsignificantly above average in the M1P segment (100%) and worse in the M2 segment (79%). The median duration of the procedure was 30 min (IQR 28 min) and the median onset-to-reperfusion time was 180 min (IQR 75 min). The median interval between admission imaging and groin puncture was 48 min (IQR 50 min). The distribution of locations of the clots is depicted in Figure 1. The proportion of patients with distal thrombi was larger in the IVT-only group (48 vs. 62%). Thus, proximal (ICA and M1P) and distal (M1D and M2) LVOs were studied separately.

Among those with proximal LVOs, there were no significant differences between the groups in age or the other established stroke risk factors apart from there being significantly larger number of atrial fibrillation in the MT group and ischemic heart disease in the IVT-only group (Table 1). Those who received only IVT had significantly smaller lesions on mean transit time (MTT) maps.

Among those with distal LVOs, the strokes were less severe in the IVT-only group based on NIHSS, and the clot burden and the sizes of the perfusion defects on MTT maps were correspondingly significantly smaller (Table 1). There were no statistically significant differences in onset-to-imaging times.

Outcomes in Different Sites of Occlusion

The distributions of the 3-month mRS scores in both groups in different sites of occlusion are depicted in Figures 2 and 3. The proportion of patients who had a proximal LVO and experienced good or excellent clinical outcome was significantly larger in the MT group (62 vs. 7%, $p < 0.001$; 47 vs. 3%, $p < 0.001$, respectively; Tables 2, 3). The results were similar when ICA and M1P occlusions were analyzed separately. Binary logistic regression analyses with good or excellent clinical outcome as dependent variables were performed to control for potential confounding variables. MT increased the odds of good clinical outcome 6-fold among patients with proximal LVOs (OR = 6.0, CI 95% 1.9–18.3, $p < 0.001$; Table 2). Again, the results were similar with borderline significance when ICA and M1P occlusions were analyzed separately (OR = 4.9, CI 95% 0.77–31.5, $p = 0.09$; and OR = 11.9, CI 95% 1.6–90.1, $p = 0.02$, respectively) or excellent clinical outcome was the outcome measure (OR = 28.0, CI 95% 3.4–233.8, $p < 0.001$; Table 3). Mortality was significantly higher in the IVT-only group (12 vs. 32%, $p = 0.04$; Table 1). Those who received IVT-only to treat a proximal LVO had almost triple the mean infarct volume (35 vs. 96 cm^3, $p = 0.003$; Table 1) at 24 h. Linked to the larger infarct volumes, these patients more often suffered from COED grade 2 or 3 postinfarct edema (24 vs. 53%, $p = 0.01$; Table 1).

Table 1. Baseline and admission imaging characteristics and the clinical and imaging outcomes of patients with proximal and distal large vessel occlusions in the MT and IVT-only groups

Characteristic	ICA and proximal M1 segment			Distal M1 and M2 segments		
	MT (n = 35)	IVT only (n = 38)	p_1	MT (n = 32)	IVT only (n = 60)	p_2
Age, years	67.4±9.4	65.7±15.2	0.64	68.4±10.4	70.7±12.8	0.21
Male sex	18 (51)	27 (71)	0.09	12 (38)	28 (47)	0.51
NIHSS before treatment	14.5 [5]	17.5 [7]	0.12	14 [6]	11 [10]	0.01
ASPECTS score at admission NCCT	9 [2]	9 [3]	0.66	10 [1]	10 [2]	0.68
ASPECTS score at admission MTT	1 [2]	3 [4]	0.001	3.5 [(5]	6 [3]	0.04
ASPECTS score at admission CBV	6.5 [6]	7 [5]	0.43	8.5 [(3]	8 [3]	0.53
Onset to imaging time, min	94 [79]	87 [40]	0.22	75 [58]	92 [31]	0.04
Clot burden score	4 [3]	4 [2]	0.27	6 [2]	8 [3]	0.01
Collateral score	1 [2]	1 [3]	0.91	2 [2]	2 [2]	0.90
Hypertension	20 (57)	22 (58)	0.95	15 (47)	40 (67)	0.08
Diabetes	3 (7)	8 (21)	0.14	7 (22)	8 (13)	0.38
Atrial fibrillation	19 (54)	12 (32)	0.05	18 (56)	25 (42)	0.20
Coronary artery disease	6 (17)	16 (42)	0.01	5 (16)	18 (30)	0.21
ASPECTS score at 24-h CT	8 [4]	4 [5]	0.001	9 [3]	8 [4]	0.17
Total infarct volume at 24 h, cm^3	4.5 [45.7]	59.4 [153.1]	0.001	2.5 [24.3]	8.3 [38.7]	0.32
Hemorrhagic complication at 24 h	5 (15)	4 (11)	0.73	4 (13)	3 (5)	0.23
Major space-occupying effect (PH2 or PHr2)	2 (6)	2 (5)	0.93	2 (6)	1 (2)	0.28
Postinfarct edema COED2 or COED3	8 (24)	19 (53)	0.01	6 (19)	10 (17)	0.78
Three-month mortality	4 (12)	12 (32)	0.04	4 (13)	2 (3)	0.18

Data are presented as mean ± SD, n (%), or median [IQR]. P1, P2: p values between groups; ASPECTS: Alberta Stroke Program Early CT Score; CBV, cerebral blood volume; COED, cerebral edema; MTT, mean transit time; NCCT, non-contrast-enhanced computed tomography; NIHSS, National Institutes of Health Stroke Scale; PH, parenchymal hemorrhage; PHr, parenchymal hemorrhage remote.

There were no statistically significant differences in clinical outcome between the MT and IVT-only groups when distal LVOs were considered after controlling for confounders (Tables 2, 3). However, there was a trend toward patients treated with MT for an M2 occlusion more often experiencing unfavorable clinical outcome (Fig. 3; Tables 2, 3). This difference was statistically significant (p = 0.03) before confounding was accounted for.

Sixty-three percent (42 of 67) of the patients who underwent MT received IVT before the procedure. Twenty-six of these (62%) experienced good clinical outcome compared to 12 patients (48%) among those without IVT (p = 0.27).

Discussion

We compared the 3-month clinical outcome of MT performed with third-generation stent retrievers and IVT only in the treatment of hyperacute ischemic stroke in different sites of occlusion: ICA, the M1P, the M1D, and the M2 segments of the MCA. Our study confirms the findings of the recent randomized trials [1–5, 13, 14] that MT is clearly superior to IVT in the treatment ICA and M1P occlusions (proximal LVOs). Only 12 and 24%, respectively, of patients who received only IVT experienced good clinical outcome (mRS ≤2) compared to 54 and 80% among those treated with MT. However, we did not find a significant difference in favor of either revascularization therapy in the treatment of M1D or M2 occlusions (distal LVOs).

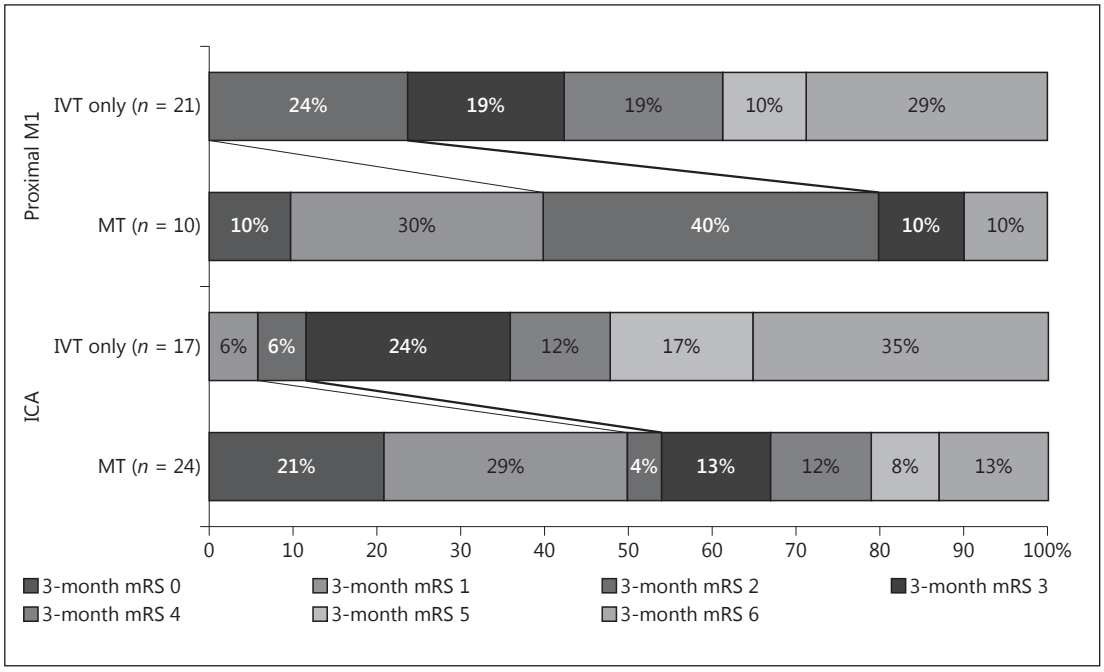

Fig. 2. The distribution of 3-month modified Rankin Scale (mRS) in the MT and IVT-only groups in proximal occlusions. The thick line indicates the division between functional independence (mRS ≤2, left hand side) and dependence (right hand side) and the thin line demarcates those with excellent clinical outcome (mRS ≤1, left hand side).

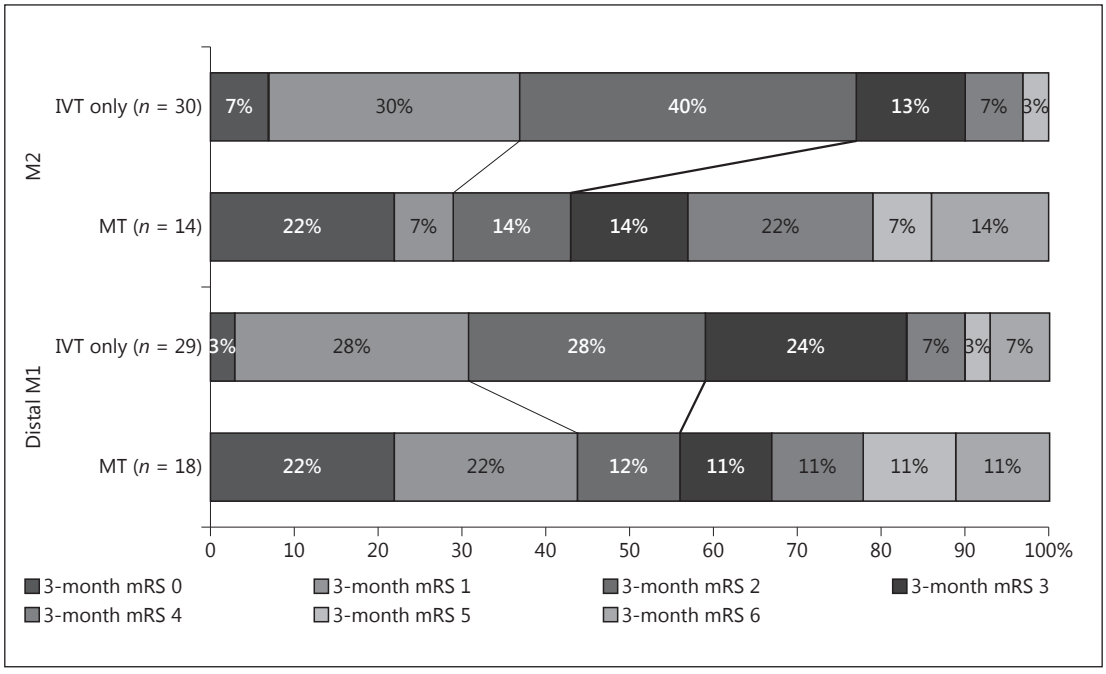

Fig. 3. The distribution of 3-month modified Rankin Scale (mRS) in the MT and IVT-only groups in distal occlusions. The thick line indicates the division between functional independence (mRS ≤2, left hand side) and dependence (right hand side), and the thin line demarcates those with excellent clinical outcome (mRS ≤1, left hand side).

Table 2. Good clinical outcome in the MT and IVT-only groups

Clot location	MT mRS ≤2	IVT only mRS ≤2	p_1	Odds ratio	95% CI	p_2
ICA	13 (54%)	2 (12%)	0.008	4.9	0.77–31.5	0.09
Proximal M1	8 (80%)	5 (24%)	0.006	11.9	1.6–90.1	0.02
Distal M1	10 (56%)	17 (59%)	0.84	1.0	0.26–3.7	0.96
M2	6 (43%)	23 (77%)	0.03	0.30	0.05–1.9	0.20
ICA and proximal M1	21 (62%)	7 (18%)	<0.001	6.0	1.9–18.3	0.002
Distal M1 and M2	16 (50%)	40 (69%)	0.12	0.54	0.16–1.5	0.24

P1, *p* value between groups; P2, significance of the covariate in binary logistic regression model; CI, confidence interval; ICA, internal carotid artery; M1, middle cerebral artery segment 1; M2, middle cerebral artery segment 2.

Table 3. Excellent clinical outcome in the MT and IVT-only groups

Clot location	MT mRS ≤1	IVT only mRS ≤1	p_1	Odds ratio	95% CI	p_2
ICA	12 (50%)	1 (6%)	0.005	9.0	0.9–89.8	0.06
Proximal M1	4 (40%)	0	0.007	n.a.	n.a.	n.a.
Distal M1	8 (44%)	9 (31%)	0.35	1.9	0.49–7.6	0.37
M2	4 (29%)	11 (37%)	0.73	0.51	0.07–3.7	0.50
ICA and proximal M1	16 (47%)	1 (3%)	<0.001	28.0	3.4–233.8	0.002
Distal M1 and M2	12 (38%)	20 (34%)	0.82	1.1	0.37–3.1	0.90

P1, *p* value between groups; P2, significance of the covariate in binary logistic regression model; CI, confidence interval; ICA, internal carotid artery; M1, middle cerebral artery segment 1; M2, middle cerebral artery segment 2.

A current consensus statement recommends that the M1 segment should be divided into proximal and distal subsegments [9]. None of the recent randomized trials reported this distinction in their published analyses. In the earlier IMS 3 trial, 64% of subjects in the IVT-only arm compared to 55% in the endovascular arm had good clinical outcome of an M1D occlusion [8]. The difference was not statistically significant. According to a recent retrospective study, 61% of subjects treated for M1D occlusion with MT experienced good clinical outcome and 44% had excellent outcome [10]. These findings are in alignment with our results (Fig. 3). When we analyzed the whole M1 segment, MT borderline significantly improved the outcome (OR = 2.6, CI 95% 0.94–7.2, $p = 0.07$). This is compatible with the results of recent meta-analyses [14, 15].

The feasibility and efficacy of MT of the M2 segment has been demonstrated in a few studies [6, 7, 16]. Successful reperfusion rates range from 78.5 to 93.3%, and up to 60% of patients achieved good clinical outcome. Four of the 5 recent randomized trials reported results on the M2 segment. In the ESCAPE study, 79% of patients in the control group received IVT [3]. Only 6 patients in the intervention group had an isolated M2 occlusion and patients with occlusion of all M2 segment arteries were pooled with M1 occlusions. The authors state that the treatment effect (showing benefit from MT) was similar in location-based subgroup

analyses but details are not provided. The SWIFT PRIME trial had 18 patients with an M2 occlusion [5]. Thirteen of them were in the MT and IVT group, and 5 in the IVT group with 53 and 40% experiencing good clinical outcome, respectively. The difference was not statistically significant. In the REVASCAT study, 78% of patients in the control group received IVT [4]. Ten patients in the MT group and 8 in the control group had an M2 occlusion whose clinical outcome was not detailed. In the MR CLEAN trial, 91% of patients in the control group were administered IVT [1]. Eighteen patients in the MT group and 21 patients in the control group had an M2 occlusion. A subgroup analysis of M2 occlusions was not reported. A meta-analysis of these trials has been published recently [14]. Pooled together, there were 51 eligible patients with an M2 occlusion in the MT group and 44 in the control group. The direction of the effect favored MT but the adjusted OR was not significant (OR = 1.28, 95% CI 0.51–3.21). Another meta-analysis of somewhat older studies reported similar results (OR = 1.5, 95% CI 0.8–3.0) [15].

The recanalization rate of an M2 segment occlusion with MT was 79% in our study, which is comparable to the literature but not optimal. After adjusting for confounders, there was a nonsignificant trend toward worse clinical outcome in the MT group which was observed also when the M2 and M1D segments were analyzed together (Table 2). The M2 occlusion patients in the IVT-only group had milder strokes compared to the MT group (median NIHSS 10 vs. 14). However, the trend remained unchanged when patients with mild strokes (NIHSS <8) were excluded (data not shown). The reported recanalization rates of M2 occlusions with IVT are reasonably high at 44–79% and correspondingly the clinical outcomes better compared to proximal LVOs [8, 17–19]. In our data, 77% of M2 occlusion patients treated with only IVT experienced good clinical outcome (Fig. 3), a considerably higher proportion than in the IMS 3 trial (44.5%) [8]. This along with the somewhat suboptimal reperfusion rate in our MT group and selection of moderate and severe strokes to the MT group probably leads to too pessimistic an estimate of the efficacy of MT. That withstanding, there is no indication in our data that MT would outperform IVT in the treatment of hyperacute M2 occlusions. A very recent multicenter retrospective analysis comparing modern endovascular therapy with best medical management reported a substantial (OR 3.2, CI 2–5.2, $p < 0.001$) advantage in favor of endovascular therapy [20]. However, this result is not directly comparable to ours because not all patients were treated with MT in the endovascular group and IVT in the medical management group. Further, patients presenting up to 8 h from the onset were included in the study.

Almost half of the patients in the MT group who had proximal LVO experienced excellent clinical outcome compared to only 1 patient (3%) in the IVT-only group. Thus, it appears that surviving an ICA or M1P occlusion without any disability-causing neurological deficits essentially requires MT. This has potential implications especially in the management of patients with low prestroke mRS (0–1).

We restricted our analysis to hyperacute strokes. The time window of IVT was extended to 4.5 h in 2008. The efficacy of IVT deteriorates rapidly in the first few hours resulting in a sizeable number-needed-to-treat figure of 14.9 in the 3- to 4.5-h time window [21]. Considering the superior reperfusion rates of MT, one would expect the performance of MT to be at least at par with IVT in the extended time window. Extrapolating from the results of a recent meta-analysis, this appears to be the case [14].

Our observational study has several limitations: a major limitation is its retrospective nature, although the data for both groups were collected and recorded prospectively according to a preset protocol. There may be a selection of patients with more severe symptoms to MT especially in distal occlusions, and conversely those with milder symptoms may have been denied an invasive procedure. Patients that responded to IVT or experienced significant and sustained spontaneous resolution of symptoms between admission imaging and groin

puncture were not included in the MT group, whereas those with contraindications to IVT were obviously not in the IVT-only group. The latter is the reason why the proportion of patients with atrial fibrillation was larger in the MT group. However, all these biases act to diminish the perceived efficacy of MT in relation to IVT only. Further, the somewhat small study population decreases the value of subgroup analyses. Patient level data on prestroke mRS were available only in the IVT-only group (the median mRS was 1). Several different stent retrievers or a combination of them were used in varying proportions in different clot locations based on the preference of the operator, which may lead to a bias between the proximal and distal LVOs. However, there were no significant differences in technical success between the two main devices that were used [22]. Finally, the technical details (primary stent retriever thrombectomy with a balloon-tipped guiding catheter) limit the generalizability of the results.

In conclusion, our study shows that MT is superior to IVT in achieving good clinical outcome in the treatment of hyperacute anterior circulation stroke in the most proximal occlusions, i.e. ICA or the M1P segment. In the distal M1 segment or the M2 segment, neither of these therapies clearly outperforms the other.

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Appendix

Imaging Parameters

In the MT cohort, the CT scans were obtained using a 64-row multidetector CT scanner (General Electric LightSpeed VCT, GE Healthcare, Milwaukee, WI, USA). Brain NCCT was performed using the parameters 120 kV with AUTOmA and SMARTmA technic, noise index 3.3, collimation 4 × 5 mm, 40% adaptive statistical iterative reconstruction (ASIR), and rotation 0.5 s. Images were obtained axially (0.625-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, AUTOmA and SMARTmA, noise index 9, 40% ASIR, collimation 40 × 0.625 mm, rotation 0.5 s, pitch factor 0.984. 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 s. 272 slices covering a range of 80 mm were generated in 46 s 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-gauge 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. DSA images were

obtained using the Artis Z angiographer (Siemens, Munich, Germany) using the parameters 102 kV, AUTOmA and SMARTmA.

In the IVT cohort, imaging was performed using two different multidetector scanners: General Electric LightSpeed 16-row (GE Healthcare, Milwaukee, WI, USA) and Philips Brilliance 64-row (Philips, Cleveland, OH, USA). Brain NCCT was performed using the parameters 120 kV, 430 mAs, collimation 12 × 1.25 mm, rotation 1.5 s (64-row) or 120 kV, 320 mAs, collimation 16 × 1.25 mm, rotation 1 s (16-row). Contiguous slices were reconstructed to the thickness of 5 mm in the whole scanning range (64-row) or to the thickness of 5 mm in the skull base and 7.5 mm in the supratentorial region (16-row). CTA was performed using a scanning range extending from the C2-vertebra to the vertex of the skull. The imaging parameters were 120 kV, 212 mAs (using dynamic tube current modulation), collimation 64 × 0.625 mm, rotation 0.75 s, pitch factor 0.923 (64-row) or 120 kV, 160 mAs, collimation 16 × 0.625 mm, rotation 0.8 s, pitch factor 0.938 (16-row). Contiguous slices were reconstructed to the thickness of 0.9 mm with a 0.45 mm overlap (64-row) or to the thickness of 1.25 mm (16-row). The contrast agent (iobitridol, Xenetix 350 mg I/mL; Aulnay-sous-Bois, France) was administered through an antecubital 18-gauge cannula using a double-piston power injector with a flow rate of 4 mL/s using 70 mL of contrast agent followed by a 50 mL saline flush. Manual bolus triggering was used. CTP was performed using the parameters 80 kV, 200 mAs (effective), collimation 32 × 1.25 mm, rotation 0.4 s (64-row) or 80 kV, 200 mAs, collimation 8 × 2.5 mm, rotation 1 s (16-row). 120 slices covering a range of 80 mm were generated in 55 s using an alternating toggle table protocol (64-row), or 200 slices covering a range of 20 mm were generated in 50 s with a stationary gantry position (16-row). Contiguous slices were reconstructed to the thickness of 10 mm (64-row) or to the thickness of 5 mm (16-row) at even time intervals. The imaging range was positioned so that the ASPECTS levels (the level of the basal ganglia and the supraganglionic level) were always covered. The rest of the 80 mm range (64-row) was positioned both cranial and caudal to the ASPECTS planes with the exact balancing depending on the clinical presentation. The contrast agent (Xenetix 350 mg I/mL) was administered through an antecubital 18-gauge cannula using a double-piston power injector with a flow rate of 5 mL/s using 60 mL of contrast agent followed by a 40 mL saline flush.

Image Analysis

NCCT, CTA, and CTP examinations were reviewed using dedicated medical imaging workstations. Parametric perfusion maps – mean transit time (MTT), cerebral blood flow (CBF), and cerebral blood volume (CBV) – were generated with the CT Perfusion 4 software that uses a delay insensitive deconvolution-based algorithm (GE Healthcare). CTA images were reviewed by examining both the raw data and maximum intensity projection images. The Alberta Stroke Program Early CT Score (ASPECTS) was assessed from admission and follow-up 24-h NCCT images and from MTT and CBV maps, and CTA was used to evaluate the occlusion site, the Clot Burden Score (CBS) and the Collateral Score (CS) as described in previous reports [23, 24]. The location of the clot was recorded based on the most proximal position of the occlusion. The M1 segment of the MCA was divided in two parts of equal length: the proximal and the distal half as described previously (M1P and M1D, respectively) [25]. The examinations were reviewed in the order NCCT, CTA, and finally CTP, paralleling that of the clinical work flow. Two radiologists assigned ASPECTS, CBS, and CS. In cases where the scoring or the assignment differed, a consensus opinion was agreed on. The reviewers were blinded to the clinical data apart from the side and nature of the acute symptoms. One radiologist measured the final infarct volumes. The boundaries of the affected areas were determined visually. Volume was calculated by multiplying the measured area with the slice thickness. TICI was evaluated and recorded prospectively to a questionnaire by the interventional neuroradiologist that performed the procedure. Intraclass correlation coefficients (ICC) between staff radiologists and an experienced neuroradiologist were calculated for ASPECTS assignments in a test sample (n = 20): ICC_{NCCT} = 0.86, ICC_{MTT} = 0.79, ICC_{CBV} = 0.73, and $ICC_{NCCT\ 24\ h}$ = 0.93. Median interobserver agreement indices for areas and volumes were $AREA_{MTT}$: 68%, $AREA_{CBV}$: 90% and $VOLUME_{INFARCT}$: 80%. ICC for CS was 0.87. Cohen's kappa was 0.94 for the location of the clot and 0.68 for the collateral score (0.90 after dichotomization 0–1 vs. 2–4).

Results

Baseline and admission imaging characteristics and the clinical and imaging outcomes of all patients and patients in the MT and IVT-only groups

Characteristic	All patients (n = 165)	MT (n = 67)	IVT only (n = 98)	p_1
Age, years	68.5±12.4	67.9±9.7	68.9±13.8	0.60
Male sex	85 (52)	30 (45)	55 (56)	0.18
NIHSS before treatment	13.5 [9]	14 (5)	14 (9)	0.26
ASPECTS score at admission NCCT	10 [2]	9 (2)	10 (2)	0.34
ASPECTS score at admission MTT	4 [4]	2 (4)	5 (4)	<0.001
ASPECTS score at admission CBV	8 [3]	7 (4)	8 (4)	0.10
Onset to imaging time, min	90±34	86±64	90±34	0.58
Clot burden score	6 [4]	6 (4)	6 (4)	0.03
Collateral score	1 [3]	1 (2)	2 (3)	0.58
Hypertension	97 (59)	35 (52)	62 (64)	0.16
Diabetes	26 (16)	10 (15)	16 (16)	0.81
Atrial fibrillation	74 (45)	37 (55)	37 (38)	0.04
Coronary artery disease	45 (27)	11 (16)	34 (35)	0.01
Three-month modified Rankin scale 0–2	84 (52)	37 (56)	47 (49)	0.34
Three-month modified Rankin scale 0–1	49 (30)	28 (42)	21 (22)	0.005
Three-month mortality	22 (13)	8 (12)	14 (14)	0.67
ASPECTS score at 24-h CT	7.5 [5]	8 (3)	7 (5)	0.007
Total infarct volume at 24 h, cm^3	45±75	27±52	57±85	0.005
Hemorrhagic complication at 24 h	16 (19)	9 (14)	7 (7)	0.18
Major space-occupying effect (PH2 or PHr2)	7 (4)	4 (6)	3 (3)	0.44
Postinfarct edema COED2 or COED3	43 (26)	14 (21)	29 (30)	0.20

Data are presented as mean ± SD, n (%), or median [IQR]. p_1, p value between groups; ASPECTS, Alberta Stroke Program Early CT Score; CBV, cerebral blood volume; COED, cerebral edema; MTT, mean transit time; NCCT, non-contrast-enhanced computed tomography; NIHSS, National Institutes of Health Stroke Scale; PH, parenchymal hemorrhage; PHr, parenchymal hemorrhage remote.

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