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In vitro-Testung eines Kathetermodells mit einer trichterförmig erweiterten Spitze zur Reduktion von Thrombusmigration unter Verwendung von verschiedenen Thrombuskompositionen für die mechanische Thrombektomie

In vitro Testing of a Funnel-tip Catheter Model to Decrease Clot Migration and to Evaluate Clot Effects in Mechanical Thrombectomy

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Vorgelegt von

Emily Sarah Payne
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I dedicate this thesis to my parents,

Hanna and Robert,

for their love and support.

Table of Contents

List of Abbreviations

ACA	anterior cerebral artery
ADAPT	A Direct Aspiration First Pass Technique
ADC	apparent diffusion coefficient mapping (MRI)
AHA	American Heart Association
AIS	acute ischemic stroke
ARR	absolute risk reduction
ASA	American Stroke Association
ASPECTS	Alberta Stroke Program Early CT Score
ASTER	The Contact Aspiration versus Stent Retriever for Successful Revascularization (trial)
ATLANTIS	Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (trial)
ATP	adenosine triphosphate
BA	basilar artery
BGC	balloon guide catheter
BMM	best medical management
CBF, rCBF	(regional) cerebral blood flow
CBV	cerebral blood volume
CG	control group
95% CI	95% confidence interval
cm	centimeter(s)
COMPASS	Aspiration thrombectomy versus stent retriever thrombectomy as first-line approach for large vessel occlusion (trial)
(c)CT	(cerebral) computed tomography
NCCT	non-contrast computed tomography
CTA	computed tomography angiography
CTP	computed tomography perfusion
d	diameter
DAC	distal access catheter
DALY	disease adjusted life years
DAWN	DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (trial)
DEFUSE-3	Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (trial)

DSA	digital subtraction angiography
DWI	diffusion-weighted imaging
ECASS	European Cooperative Acute Stroke Study
ENT	embolism in new territories
EPITHET	Echoplanar Imaging Thrombolytic Evaluation Trial
ESCAPE	Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (trial)
ESMINT	European Society for Minimally Invasive Neurological Therapy
ESO	European Stroke Organization
EVT	endovascular therapy/treatment
EXTEND-IA	Extending the Time for Thrombolysis in Emergency Neurological Deficits – Intra-Arterial (trial)
FAST	Face – Arms – Speech – Time
FAST	Forced Aspiration Suction Thrombectomy (technique)
FDA	Food and Drug Administration
FLAIR	fluid-attenuated inversion recovery
GBD	Global Burden of Disease (study)
GCS	Glasgow Coma Scale
h	hour(s)
HERMES collaboration	Highly Effective Reperfusion Using Multiple Endovascular Devices (meta-analysis)
HMCAS	hyperdense middle cerebral artery sign
IA r-proUK	intra-arterial recombinant prourokinase
IAT	intra-arterial thrombolysis/therapy
ICA	internal carotid artery
(s) ICH	(symptomatic) intracranial or intracerebral hemorrhage
ID	inner diameter
IG	interventional group
IST-3	Third International Stroke Trial
IU	international unit(s)
IV rt-PA/IVT	intravenous recombinant tissue-type plasminogen activator (= alteplase), intravenous thrombolysis
LVO	large vessel occlusion
MCA	middle cerebral artery; (segments: M1-MCA, M2-MCA)
(multi-) MERCI	Mechanical Embolus Removal in Cerebral Ischemia (trial; retriever)
min	minute(s)

ml	milliliter
ml/100g/min	milliliter per 100 grams per minute
MRA	magnetic resonance angiography
MR CLEAN	Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands
MRI	magnetic resonance imaging
MRP	magnetic resonance perfusion
mRS	modified Rankin Scale
MT	mechanical thrombectomy
mTICI	modified treatment in cerebral infarction (score)
MTT	mean transit time
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
NNH	number needed to harm
NNT	number needed to treat
OD	outer diameter
OR	odds ratio
P	p-value (level of significance)
PCA	posterior cerebral artery
PROACT	Prolyse in Acute Cerebral Thromboembolism (trial)
PROTECT	PRoximal balloon Occlusion TogEther with direCt Thrombus aspiration during stent retrieval thrombectomy (technique)
PWI	perfusion-weighted imaging
RACECAT	Transfer to the Local Stroke Center versus Direct Transfer to Endovascular Center of Acute Stroke Patients with Suspected Large Vessel Occlusion in the Catalan Territory (trial)
RCT	randomized controlled trial
REVASCAT	Randomized Trial of Revascularization with Solitaire FR Device vs. Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within 8 Hours of Symptom Onset (trial)
SAH	subarachnoid hemorrhage
SAVE	Stent retriever Assisted Vacuum-locked Extraction (technique)
Solumbra	SOLitaire and PenUMBRA (technique)
STRATIS	Systematic Evaluation of Patients Treated With Neurothrombectomy Devices for Acute Ischemic Stroke (registry)
SWI	susceptibility-weighted imaging

SWIFT	Solitaire With the Intention for Thrombectomy (trial)
SWIFT PRIME	Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment of Acute Ischemic Stroke (trial)
TG	treatment group
TIMI	thrombolysis in myocardial infarction score
TOF(-MRA)	time-of-flight angiography
TREVO	Thrombectomy Revascularization of Large Vessel Occlusion in Acute Ischemic Stroke (trial)

List of Figures

List of Tables

Zusammenfassung

Die mechanische Thrombektomie ist ein etabliertes Standardverfahren zur Behandlung von akuten cerebralen Gefäßverschlüssen im Rahmen des ischämischen Schlaganfalls und inzwischen bis zu 24 Stunden nach Symptombeginn indiziert. Dabei kann thrombotisches Material in bis zu 10% der Fälle in distale Territorien embolisieren. Eine Ursache hierfür ist die kleinere Öffnung von distalen Zugangskathetern in Relation zum größeren Thrombus- und Gefäßdurchmesser. Somit wird der Thrombus beim Zurückziehen des Stent-Retrievers in eine zu schmale Katheterspitze komprimiert und verformt. Bei Überschreiten des Elastizitätsmoduls kann der Thrombus entlang der Katheterspitze abgestreift werden und fragmentieren. Ein antegrader Fluss während der Prozedur kann zudem das Risiko einer Migration thrombotischen Materials in distale Territorien erhöhen.

Um die Rekanalisationsrate und damit die Effektivität der mechanischen Thrombektomie zu optimieren, wurde eine Kathermodell mit einer trichterförmig erweiterten Spitze entwickelt und mit einem Modell mit kleinerer Katheterspitze verglichen. Der größere Innendurchmesser (ID = 2,5 mm) der trichterförmigen Katheterspitze entspricht knapp dem aus Studien bekannten anatomischen Durchmesser des M1-Segmentes der A. cerebri media (2,7 ± 0,23 mm, Mittelwert ± 1 SD). Der Durchmesser der kleineren Katheterspitze (ID = 1,5 mm) ist vergleichbar mit dem Innendurchmesser herkömmlicher distaler Zugangskatheter.

In vitro wurde die mechanische Thrombektomie 80 Mal für jede Katheterspitze durchgeführt (N = 160), wobei zwei Stent-Retriever (Trevo XP ProVue 3/20 und 4/20 mm) und vier verschiedene Thrombusarten verwendet wurden (harte mechanisch hergestellte Chandler Loop Thromben versus weiche, statisch hergestellte Thromben, jeweils 0 bis 24 Stunden frisch versus 72 Stunden gealtert).

Es wurden eine Haupt- und eine Nebenthese definiert:

I. **Haupthese:** Eine trichterförmig erweiterte Spitze mit einem größeren Innendurchmesser könnte höhere Rekanalisations- und verminderte Thrombusabstreifungsraten als die kleinere Katheterspitze erzielen.
II. **Nebenthese:** Die Viskosität und Zusammensetzung verschiedener Thrombusarten hat einen Einfluss auf die Rekanalisationsrate. Dabei sollten harte, mechanisch hergestellte Thromben (Chandler Loop) weniger zur Fragmentierung neigen als weichere, unter statischen Bedingungen hergestellte Thromben.

Die Haupthese dieser Dissertation konnte verifiziert werden. Unabhängig von der Thrombusart und dem Stent-Retriever ergab sich für die trichterförmige Katheterspitze eine signifikant höhere Rekanalisationsrate von 70,0%, im Vergleich zu 30,0% für die kleinere Katheterspitze

(absolute Differenz 32; relative Differenz 57.1%; P < .001). Für die trichterförmige Spitze, konnte in der Hälfte der Fälle, bei der eine first-pass Rekanalisation nicht erreicht wurde, eine fehlende Interaktion des Stent-Retrievers mit dem Thrombus festgestellt werden. Dies trat doppelt so häufig bei Verwendung der härteren Thromben auf. In der anderen Hälfte der Fälle wurde der Thrombus entlang der trichterförmigen Spitze bei dem Versuch, diesen in den Katheter zu ziehen, abgestreift. Dies ereignete sich häufiger bei Verwendung von weicheren Thromben, die eher zur Fragmentierung neigten als die härteren Thromben. Ein Abstreifen thrombotischen Materials erwies sich als die häufigste Fehlerursache für die kleinere Katheterspitze und erreichte statistische Signifikanz (P < .05). Diesem Ergebnis liegt nahe, dass der kleinere Durchmesser der Katheterspitze, das Risiko einer Thrombusabstreifung erhöht.

Darüber hinaus zeigten die Ergebnisse, dass die Rekanalisationsraten von verschiedenen Thrombusarten beeinflusst wurden. Da das α-Signifikanzniveau im Voraus auf 5% festgelegt wurde und die Rekanalisationsraten der unterschiedlichen Herstellungsmethoden von Thromben knapp die statistische Signifikanz überschritten (P = .06), konnte unsere Nebenhypothese unter den statistischen Rahmenbedingungen nicht angenommen werden. Histopathologisch zeigten die härteren mechanisch hergestellten (Chandler Loop) Thromben einen signifikant höheren Fibrinanteil, eine gleichmäßigere Fibrinverteilung und ein retikuläres oder inselförmiges Fibrinmuster im Vergleich zu den weicheren statisch hergestellten Thromben. Da ein Chandler Loop Gerät die Blutgerinnung unter dynamischen Bedingungen simuliert, werden Blutzellen und Fibrin regelmäßig verteilt. Dagegen sind die Erythrozyten unter statischen Bedingungen ungleichmäßig verteilt und dichter konzentriert. Darüber hinaus konnten bei 0 bis 24 Stunden frischeren Thromben höhere Rekanalisationsraten als bei 72 Stunden gealterten Thromben erreicht werden. Der Unterschied der Rekanalisationsraten zwischen den Thrombusalterungszeiten (0 bis 24 Stunden versus 72 Stunden) wirkte sich stärker auf die härteren als auf die weicheren Thromben aus. Da Fibrin bei gealterten Thromben lytischen Prozessen unterliegt, sind die fibrinreichen, härteren Thromben möglicherweise anfälliger für Alterungsprozesse als die weicheren fibrinärmeren Thromben. Für die beiden Stent-Retriever mit unterschiedlichen Durchmessern wurde kein statistisch signifikanter Einfluss auf die Rekanalisationsrate nachgewiesen.

Zusammenfassend, unterstreicht dieses Forschungsprojekt die Überlegenheit einer größeren, trichterförmigen Katheterspitze im Vergleich zu der kleineren Katheterspitze, hinsichtlich verbesserter Rekanalisationsraten für die mechanische Thrombektomie. Dieser konzeptionelle Beweis legitimiert die Entwicklung eines trichterförmigen selbst-expandierenden Katheterprototypen, der erst kürzlich von uns patentiert wurde.

1 Introduction

1.1 Mechanical Thrombectomy in Stroke Treatment

Mechanical thrombectomy (MT) is the standard treatment for acute ischemic stroke in patients with large vessel occlusion and can be performed up to 24 hours after symptom onset. (1) Despite mean recanalization of 71%, rates for embolism in new territories of up to 8.6% have been reported. (2-4) Causes for this could be clot abruption during stent retrieval into the smaller opening of a standard distal access catheter, and antegrade blood flow via collaterals despite proximal balloon protection. (1-5) Standard distal access catheters often have a smaller opening diameter in relation to the larger-sized thrombus and vessel diameters. During stent retrieval into the narrow standard tip the thrombus might be compressed and deformed, thus increasing the risk of stripping and fragmentation at the tip. (6, 7) Therefore, a funnel-shaped tip was developed and tested to increase the rate of first-pass recanalization and to improve the safety and efficacy of mechanical thrombectomy. Furthermore, this research project aims to advance MT device technology. Using an experimental in vitro setup, this study compared the efficacy of a funnel-shaped tip with a standard tip in combination with different clot compositions for mechanical thrombectomy. Thus, this research project can be defined by a main hypothesis and a subordinate hypothesis:

1.2 Main Research Hypothesis

We hypothesize that a funnel-shaped tip, featuring a larger inner diameter (ID = 2.5 mm), would achieve higher recanalization rates than a smaller standard tip (ID = 1.5 mm) and would reduce the rate of clot abruption and stripping at the tip.

1.3 Subordinate Research Hypothesis

As recent studies have shown, thrombus-vessel and thrombus-device interaction are influenced by the viscosity and composition of different clot types. (6, 8, 9) Successful recanalization is associated with reduced friction and adhesion during stent retrieval. Certain clot types may be prone to fragmentation and may increase the risk of clot abruption at the tip during MT procedure. (6, 8) Therefore, the effects of four different clot types – prepared with mechanical (Chandler loop) versus static methods at two different clot aging times, 0 to 24 hours versus 72 hours – were evaluated comparing the funnel-shaped tip with a standard tip model. We hypothesize that different clot compositions could have an effect on the success of mechanical thrombectomy. In particular, the harder mechanically prepared clots should be less prone to fragmentation than the softer statically prepared clots. We would also expect 0 to 24-hour clots to achieve higher recanalization rates than the friable 72-hour aged clots.

2 Literature Review

2.1 Definition and Etiology of Stroke

By definition, stroke occurs as a sudden onset of neurological deficits. (10) Stroke can be classified by its heterogeneous etiology, severity, chronological sequence, symptomatology and morphology. In industrial countries, 80 to 85% of strokes are related to acute ischemia, while 5 to 20% are of hemorrhagic origin. Subtypes of hemorrhagic stroke include intracerebral hemorrhage (ICH) in 15% and subarachnoid hemorrhage (SAH) in 5 to 10% of all stroke cases. (10-13)

The main causes for acute ischemic stroke (AIS) are macroangiopathic and microangiopathic changes of the arterial vasculature. Macroangiopathy due to atherosclerosis triggers two thirds of all symptomatic strokes, while microangiopathy accounts for one third of all symptomatic strokes. According to the **ASCO** classification criteria, acute ischemic stroke can be divided into four different subtypes: 1) **A**therosclerotic stroke in 40 to 45% of cases, which is the most common type; 2) **S**mall vessel disease in 15 to 30% of cases; 3) **C**ardio-embolic disease in 15 to 25% of cases; and 4) **O**ther causes. (11) Furthermore, the TOAST classification (Trial of ORG 10172 in Acute Stroke Treatment) differentiates between acute ischemic stroke of other determined etiology and embolic stroke of undetermined source (ESUS), also denoted as cryptogenic stroke. (10-12)

Atherosclerotic vascular disease is the leading cause of acute ischemic stroke, which occurs in both intracranial and extracranial arteries, usually at bifurcation sites where blood turbulence triggers thrombus formation and atherosclerotic plaque rupture. Large vessel occlusion in the anterior circulation, in particular the middle cerebral artery, is the most frequent localization for acute ischemic stroke in the intracranial vasculature. (10, 11) The most frequent site of occlusion in the extracranial vasculature is the proximal internal carotid artery (ICA). (10, 14) In fact, 15% of all AIS cases in Germany are caused by carotid stenosis ≥ 50%, which can be measured by the NASCET (North American Symptomatic Carotid Endarterectomy Trial) method. (14)

Small vessel disease, which leads to microangiopathy in small cerebral arteries, can cause lacunar infarction with lesions < 1.5 cm. This commonly occurs in the lenticulostriate arteries, and involves the basal ganglia and internal capsule. Diabetes, hypertension, smoking and hyperlipidemia are risk factors that can induce lipohyalinotic changes, fibrosis and microatheromas. (10, 12)

The majority of territory infarctions are of embolic origin. By definition, an embolism does not occur at the site of occlusion, but forms at another location and is carried away with the

bloodstream. Atrial fibrillation increases the risk of acute cardioembolic stroke by 5 to 16-fold. (15) In atrial fibrillation, the atria and ventricles are no longer synchronized due to irritable atrial foci. This can cause blood to recirculate within the left atrium, hereby inducing blood clot formation. Other causes of acute cardioembolic stroke, which can be further classified as aseptic or septic, include: heart valve disease, prosthetic heart valves, acute myocardial infarction, coronary heart disease, congestive heart disease, dilated cardiomyopathy, sinus node dysfunction, atrial myxoma, endocarditis and atrial septal aneurysms. (10-12, 15)

Other causes of acute ischemic stroke are: acute vessel dissection, migraine-associated AIS, coagulopathies (e.g., hypercoagulability, thrombophilia, sickle cell anemia and polycythemia vera), rheumatic and inflammatory disorders (e.g., Takayasu's arteritis, polyarteritis nodosa, and systemic lupus erythematosus), as well as amyloid angiopathy, fibromuscular dysplasia, Moya-Moya syndrome and hereditary syndromes (e.g., CADASIL syndrome = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, Marfan syndrome, Ehlers-Danlos syndrome and Fabry syndrome). (11, 12, 15)

Assessing the etiology of stroke is essential for initiating medical procedures, for treating key comorbidities and risk factors such as atrial fibrillation or carotid stenosis, and for preventing the risk of reoccurrence.

2.2 Epidemiology, Relevance and Outcome

After ischemic heart disease, stroke ranks internationally as the second leading cause of death and the number three cause of disability. Thus, stroke is not only one of the most significant diseases confronting medical practitioners, but also impacting health care systems worldwide. (16-18) The Lancet's *Global Burden of Disease Study 2019* (GBD) (17) systematically quantifies the disease burden and epidemiological impact of 369 diseases and injuries, including stroke, in over 200 countries. Findings in the recent GBD 2019 annual stroke study indicated around 6.6 million stroke deaths, 12.2 million cases of stroke, as well as 143 (5.7%) disease adjusted life years (DALY) lost due to stroke globally. (19, 20) Although the GBD did not specify the subtype of stroke by percentage, it reported that intracerebral hemorrhage and acute ischemic stroke account for nearly an equal proportion of DALYs lost, whereas subarachnoid hemorrhage was a minor cause for DALYs lost. About 101 million cases of stroke were diagnosed worldwide in 2019. Women accounted for 56.4 million cases – more than half of the total – and men for 45.0 million cases. Despite a higher incidence of stroke in 2019, women showed a lower death rate than men: 73.5 out of 100,000 deaths versus 96.4 out of 100,000, respectively. (16, 17, 19)

In terms of age, data from the GBD 2016 reported similar stroke incidences for both men and women up to the age of 55. However, a noticeable deviation occurred from 55 to 75 years,

when men registered higher rates. After 75 years of age, the incidence of stroke for both men and women balanced out again, only to increase for women after 80 years and surpass the incidence for men. The overall lifetime risk of stroke for all adults from 25 years of age and above reached about 25%, representing an increase of more than 20% compared to 1990. (19)

Statistics by geographic region revealed that East Asia, Eastern Europe and Central Europe had the highest stroke rates, while Latin America reported the lowest rates in 2016. China, which is one of most densely populated nations, is burdened by its high incidence and mortality of stroke. In terms of deaths and DALYs lost, the burden of stroke caused by hemorrhagic stroke was more common for low-income and middle-income countries. In contrast, the overall incidence of acute ischemic stroke in industrialized countries reached 80 to 85%, which was higher than 15 to 20% for hemorrhagic stroke. (16, 19, 21)

Overall trends indicate that the incidence of stroke and stroke-related mortality is decreasing in high-income countries but increasing in low-income countries. This suggests that medical treatment, overall infrastructure and accessibility of stroke units are more advanced in industrialized countries. Additionally, prevention programs in these nations target the reduction of risk factors (such as arterial hypertension, atrial fibrillation, diabetes, obesity, smoking, alcohol abuse and hyperlipidemia) more effectively than in low and middle-income countries. Procedural mnemonics such as the FAST (Face – Arms – Speech – Time) criteria may increase consciousness within the population and enable fast-recognition patterns. This shows that the sociodemographic index has to be taken into account for evaluating epidemiology studies. Nevertheless, the overall prevalence (the absolute number of stroke patients including stroke-related disability) is continuously rising in high-income-countries. This rise can be attributed to demographic changes caused by population aging, despite innovative technological advancements in stroke research leading to lower mortality rates in high income countries. (16, 18, 19, 21, 22)

Germany’s stroke statistics indicate a similar development profile. According to the German Federal Statistical Office (Gesundheitsberichterstattung des Bundes (GBE); Deutsches Statistisches Bundesamt, Destatis), a total of 360,943 cerebrovascular cases were registered in 2019: including 256,965 (71.2%) cases of acute ischemic stroke, 33,951 (9.4%) cases of intracerebral hemorrhage and 10,667 (3.0%) cases of subarachnoid hemorrhage. About 282 out of 100,000 people suffered from acute ischemic stroke in 2019. With 15,115 AIS related deaths in 2019, acute ischemic stroke ranked 14th among the most frequent causes of death in Germany. Men had a higher incidence of acute ischemic stroke with 134,805 cases, compared to women with 122,160 cases. (23-25) Prevalence of stroke remained below 1% for patients under 55 years of age. In patients over 75 years, prevalence increased

disproportionately by more than 6% for both sexes. (26) Hospitalization periods for AIS treatment reached a mean duration of 12 days. In 2019, the German federal state of Rhineland-Palatinate registered 11,735 AIS incidents, with 660 AIS-related deaths. (25)

Given the high incidence and prevalence rates, overall cerebrovascular diseases are costing Germany about €10 billion annually, representing 3% of total health costs. (27) To meet these high healthcare demands, Germany operated 328 certified stroke units in 2019, including 117 centers qualified to provide endovascular treatment. (28) According to the German Stroke Society (Deutsche Schlaganfall-Gesellschaft, DSG) a total of 10,680 mechanical thrombectomies were performed in 2017, an increase of 1,828 compared to 2016. Statistics predict that 13,000 to 16,000 patients would benefit from mechanical thrombectomy yearly. (29) Furthermore, acute ischemic stroke is one of the leading causes of long-term disability in Germany. (18) About 700,000 stroke patients suffer from long-term impairments in daily activities. (15) According to stroke prognosis and outcome figures, case fatality rates generally reached about 15% after one month, 25% after one year, and 50% after five years. About 40% of patients who survived acute ischemic stroke initially recovered and regained their neurological abilities. Another 30% suffered from irreversible “deficits”, while the remaining 30% had serious disabilities requiring intensive professional care. The majority of patients recovered within the first 3 to 6 months following acute ischemic stroke. After this initial half-year period, the recovery process dissipated. Some 10% of strokes reoccurred after one year, 25% after five years, and 40% after ten years. This shows not only the significance of acute treatment, but also underscores the impairments caused by acute ischemic stroke. Consequently, post-care, follow-up and rehabilitation programs are indispensable. (21, 26)

In conclusion, these epidemiological statistics give valuable insight into the future challenges of acute ischemic stroke and its treatment. While AIS mortality and incidence rates are decreasing in high-income countries, the prevalence is expected to increase. According to the American Heart Association and the American Stroke Association (AHA; ASA), some 4% of adults in the United States are expected to experience an acute ischemic stroke by 2030. This will more than double the costs of treatment from about $72 billion in 2012 to $183 billion by 2030. (30) Germany is also expected to undergo a similar surge. (31) To keep up with capacity demands, it is vital to continue research and development in this rapidly advancing field of medicine.

2.3 Treatment of Acute Ischemic Stroke

2.3.1 Stroke Unit

According to stroke protocol, the first steps performed in a stroke unit are a rapid neurological assessment and initiation of non-contrast cerebral computed tomography (cCT). Currently, there are two standard treatments for treating acute ischemic stroke: mechanical thrombectomy and intravenous thrombolysis, which both can be used as standalone or combined treatments. If acute ischemic stroke is confirmed in neuroradiological imaging (CT protocol: CTP, CTA; see section 2.3.2 for specification), the clinician and interventionalist must then decide whether the patient is eligible to receive mechanical thrombectomy and/or intravenous thrombolysis. Mechanical thrombectomy can be performed up to 24 hours after AIS symptom onset, intravenous thrombolysis only within a 4.5 hour time window. The overall goal in the treatment of acute ischemic stroke is to stabilize and monitor the patient, to initiate reperfusion strategies as soon as possible, to prevent further complications and to improve clinical outcome. (1)

Treatment of acute ischemic stroke requires an intensive multidisciplinary approach involving emergency medicine, intensive care, clinical neurology, neuroradiology, neurosurgery and anesthesia. (32, 33) Expeditious prehospital assessment is vital. However, only 25% of patients actually arrive within 4.5 hours from AIS symptom onset. This accounts for why only 6% of all patients are qualified to receive thrombolytic treatment. Mnemonics like the FAST criteria recommended by the World Health Organization (WHO), as well as the Cincinnati Prehospital Stroke Scale and the Los Angeles Prehospital Stroke Screen, provide validated and standardized screening tools. (13) If one out of three criteria from the FAST screening tool are positive, then acute ischemic stroke is probable in over 70% of cases. (33, 34)

To qualify as a designated primary stroke unit, the unit must provide neuroradiological imaging such as cCT, in-house neurology or telemedicine neurology, administration of intravenous recombinant tissue-type plasminogen activator (intravenous thrombolysis = IV rt-PA = alteplase) and inpatient care. In addition, comprehensive stroke centers offer neuroendovascular and neurosurgical procedures. Checklists and stroke protocols in the emergency room provide a quick and standardized routine, enabling triage to become more efficient and less time-consuming. For this purpose, the AHA/ASA recommends time-based guidelines for managing acute ischemic stroke: door-to-physician time $\leq$ 10 min, door-to-stroke-team time $\leq$ 15 min, door-to-non-contrast-cCT initiation time $\leq$ 25 min, door-to-CT interpretation $\leq$ 45 min, door-to-needle time $\leq$ 60 min (time upon arrival in the hospital until the administration of IV rt-Pa), and a door-to-stroke-unit admission time $\leq$ 3 hours. (1, 32, 33, 35)

Initially, the patient should be assessed according to the ABCDE (Airway, Breathing, Circulation, Disability, Exposure/Examination) approach and the Glasgow Coma Scale (GCS). Intubation should be carefully considered in mentally altered patients with a GCS ≤ 8. Increased intracranial pressure, consequently leading to reduced consciousness, may be a sign of bulbar stroke. Vital signs such as oxygen saturation, respiratory rate, blood pressure, heart rate and temperature should be monitored closely at all times. Hypoglycemia and hyperglycemia are associated with poor clinical outcome. Therefore, the AHA/ASA recommends stabilizing blood glucose levels between 140 to 180 mg/dL. Oxygen saturation should be maintained above 94%. Hyperthermia (temperature > 38 °C) is also associated with higher mortality and poor outcome, as a result of increased permeability and neurological injury caused by inflammatory cytokines. An electrocardiogram should be performed to check for cardiac arrhythmias, in particular atrial fibrillation. (1, 32, 33, 36) After ruling out intracranial hemorrhage in cCT, eligibility criteria for thrombolytic treatment have to be carefully evaluated. This is achieved by assessing the patient's history. (13, 33)

1) When was the first onset of symptoms (time last seen normal) and how does that compare to the normal neurological baseline?
2) Has the patient received anticoagulation or any recent operations?
3) Has there been any occurrence of stroke and/or hemorrhage in the past?
4) Does the patient exhibit any bleeding disorders, comorbidities such as atrial fibrillation, malignancy, hypertension, diabetes, or neurological disorders?

Furthermore, transient ischemic stroke and stroke mimics, such as hypoglycemia, seizure, acute migraine and intoxication, should be ruled out. Intravenous thrombolysis may be administered only if the patient fulfills all the criteria. (13, 33, 36) To maintain cerebral blood flow (CBF) in acute ischemic stroke, hypovolemia and hypotension should be strictly avoided. The best outcome can be achieved with a systolic blood pressure between 140 to 180 mmHg, which is high enough to secure cerebral perfusion and low enough to prevent cerebral edema. If blood pressure persistently rises above 220/120 mmHg, antihypertensive medication (such as Labetalol, Nicardipine, Clevidipine, Hydralazine or Enalapril) should be administered. Before receiving intravenous thrombolysis, blood pressure should be lowered to < 185/110 mmHg to prevent intracranial hemorrhage. Administering fluids may help maintain sufficient blood pressure levels. It should be noted, that blood pressure treatment for hemorrhagic stroke differs greatly from that of acute ischemic stroke. For the treatment of hemorrhagic stroke a systolic blood pressure < 160 mmHg has to be strictly maintained to avoid further risk of hemorrhage. (33, 35, 36) The following stroke protocol (see Figure 1) summarizes the steps for initial treatment of acute ischemic stroke, including monitoring and stabilization the patient, as well as diagnostic workup and eligibility criteria for intravenous thrombolysis.

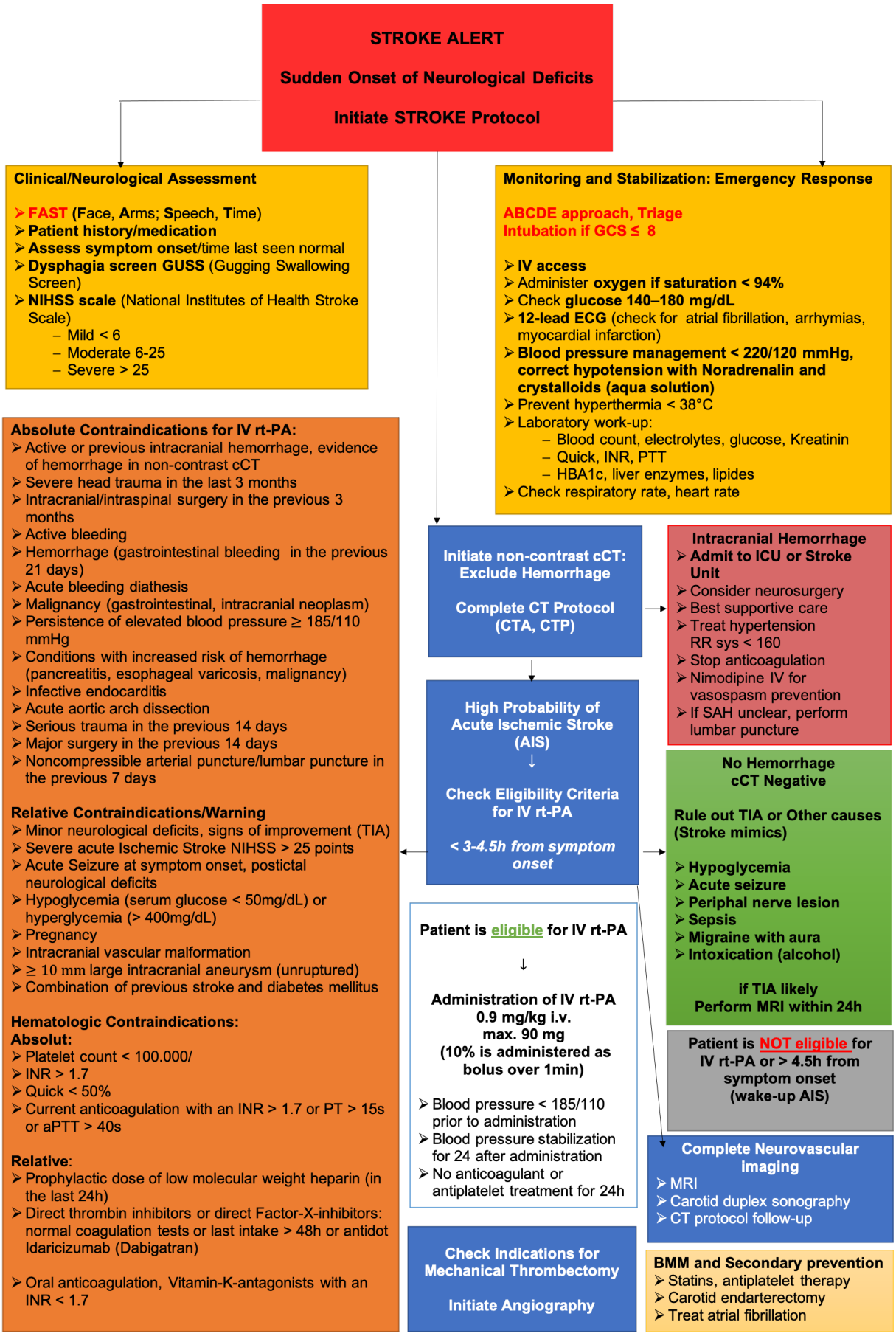


Figure 1. Stroke protocol, clinical assessment and flowchart: *Monitoring and stabilization; eligibility criteria for IV rt-PA. This chart was adapted from UpToDate. (37)*

After initial evaluation, monitoring and stabilization, the patient should receive a rapid neurological evaluation using the National Institutes of Health Stroke Scale (NIHSS). The NIHSS scale comprises 11 criteria (actually 13, if 1a, b, c are each counted): Ranging from 0 to 42 points, the scale designates < 6 points as mild, 6 to 25 points as moderate, and > 25 as severe stroke, (see Table 1). Thrombolysis is indicated when the NIHSS ranges between 6 to 22 points. (32, 33, 37)

Clinical Tool	**Criteria**	
NIHSS	1a	Orientation
	1b	Level of consciousness
	1c	Response to commands
	2	Best gaze
	3	Visual fields
	4	Facial palsy
	5	Motor arm
	6	Motor leg
	7	Limb ataxia
	8	Sensory function
	9	Best language (aphasia)
	10	Dysarthria
	11	Extinction and inattention (neglect)

Table 1. National Institutes of Health Stroke Scale (NIHSS)

Several scoring tools, essential for the evaluation of clinical trials, are summarized below. Frequently serving as a parameter for long-term functional outcome in clinical trials, the modified Rankin Scale (mRs) ranges from 0 to 6 points for evaluating the degree of disability in AIS patients after 90 days (see Table 2). Mechanical thrombectomy is considered successful when the mRS is ≤ 2, which means the patient is able to carry out his daily activities independently. (37)

The modified thrombolysis in cerebral infarction (mTICI) scale is an angiographic grading system to determine perfusion rates during and after recanalization (see Table 3), ranging from 0 (no reperfusion) to 3 (maximal reperfusion). Successful reperfusion is classified as an mTICI score $\geq$ 2b, meaning that reperfusion is restored in more than half of the occluded vessel or completely. According to the AHA guidelines, at least 75% of all patients receiving endovascular treatment should achieve mTICI grading scores of $\geq$ 2b. (37, 38)

	Grade	
mRs at 90 days	0	No symptoms
	1	No disability despite symptoms: the patient is able to carry out all daily activities independently
	2	Slight disability: the patient is unable to carry out all daily activities, but is able to look after his bodily needs without assistance
	3	Moderate disability: the patient requires assistance with daily activities, but is still able to walk without help
	4	Moderately severe disability: the patient requires assistance for looking after bodily needs and for walking
	5	Severe disability: the patient is incontinent, bedridden and is dependent on constant nursing care
	6	Exitus

Table 2. Modified Rankin Scale (mRS) at 90 days. *Adapted from UpToDate. (37)*

	Grade	
mTICI	0	No perfusion
	1	Minimal antegrade reperfusion past the initial occlusion site with reduced distal reperfusion
	2a	Antegrade reperfusion of less than half of the occluded target
	2b	Antegrade reperfusion of more than half of the previously occluded target artery
	3	Complete antegrade reperfusion of the previously occluded target artery and distal branches

Table 3. Modified Thrombolysis in Cerebral Infarction Scale (mTICI)

For evaluating efficacy in clinical trials, the mRS is employed as a primary long-term clinical endpoint parameter, while the mTICI scale serves as a secondary outcome parameter. (37, 39) Some older trials used the thrombolysis in myocardial infarction score (TIMI), an outdated grading tool to assess the amount of recanalization. (40) Predictive factors for acute ischemic stroke are depicted in Figure 2.

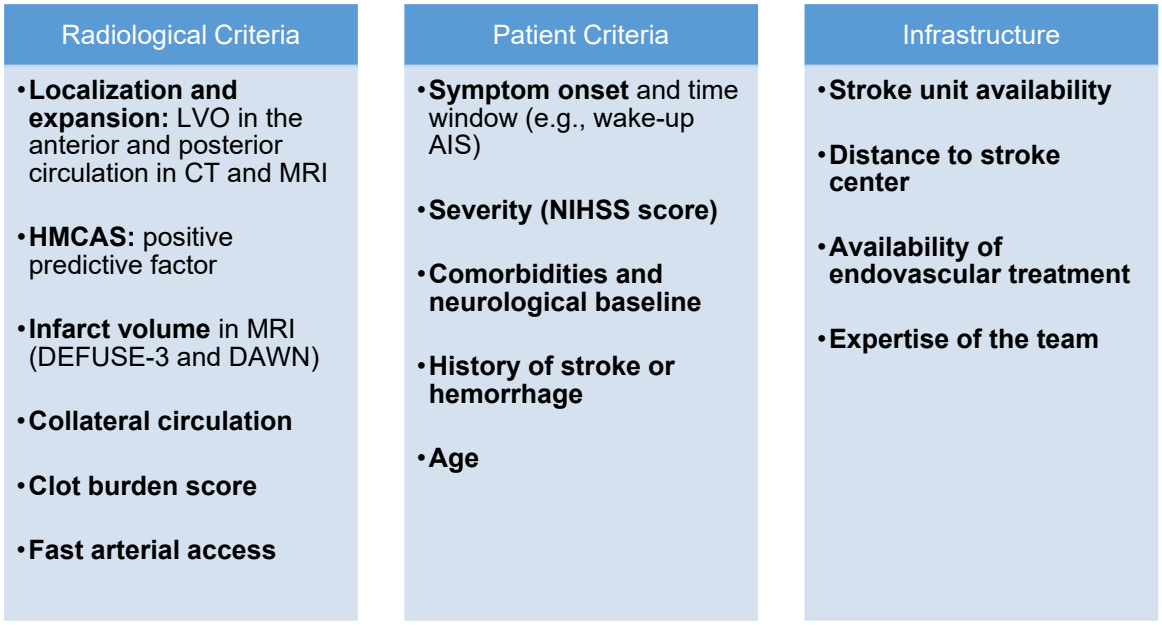


Figure 2. Predictive factors for acute ischemic stroke

2.3.2 Neuroradiological Imaging Modalities

Currently, there are two options for treating acute ischemic stroke: intravenous thrombolysis (IVT) to chemically dissolve the thrombus, and endovascular therapy (EVT) to mechanically remove the thrombus. The overall goal of treatment is to restore the perfusion of oxygen- and adenosine triphosphate-deprived (ATP) brain tissue. This is based on the dynamic Penumbra concept defined by Astrup in 1981 (see Figure 3). (41, 42) There are four main brain tissue types which can be quantified by the amount of regional cerebral blood flow (rCBF): the immediate infarct core, penumbra, oligemia and normal brain parenchyma. (41-43)

In the infarct core, brain tissue is irreversibly damaged and rCBF is severely reduced to a minimum of 10 to 12 milliliters per 100 grams per minute (ml/100g/min). (41, 43, 44) Due to the lack of perfusion, neurons in the infarct core are unable to maintain their cellular integrity. Consequently, the deprivation of oxygen and ATP leads to lactate acidosis and the disruption of ion gradients. This can induce cytotoxic and vasogenic edema, as well as increased permeability of the blood brain barrier. Finally, a cascade of apoptosis and necrosis is triggered. (15, 43-45)

The ischemic penumbra, which etymologically refers to a half-shadow or eclipse, is considered the “tissue at risk” with a rCBF ranging between 12 to 22 ml/100g/min. The ischemic threshold lies around 22 ml/100g/min. (41, 43) In this stage, neurons are dysfunctional but still potentially salvageable. This can only be achieved if the occlusion is resolved and sufficient rCBF is provided. Neuronal transmission terminates once rCBF reaches 16 to 18 ml/100g/min. (44) If diminished blood flow consistently remains below the threshold of function, neuronal death can

occur. Salvaging the penumbra by restoring perfusion is the key target of endovascular and thrombolytic treatment. (15, 43)

Oligemia is defined as brain tissue that is still functional despite hypoperfusion with rCBF levels of 22 to 60 ml/100g/min. (43) Recanalization may restore perfusion. However, there is no immediate risk of infarction. In comparison, the average rCBF is approximately 60 to 100 ml/100 g/min for intact brain parenchyma, 80 ml/100 g/min for gray matter and 20 ml/100g/min for white matter. (43, 46)

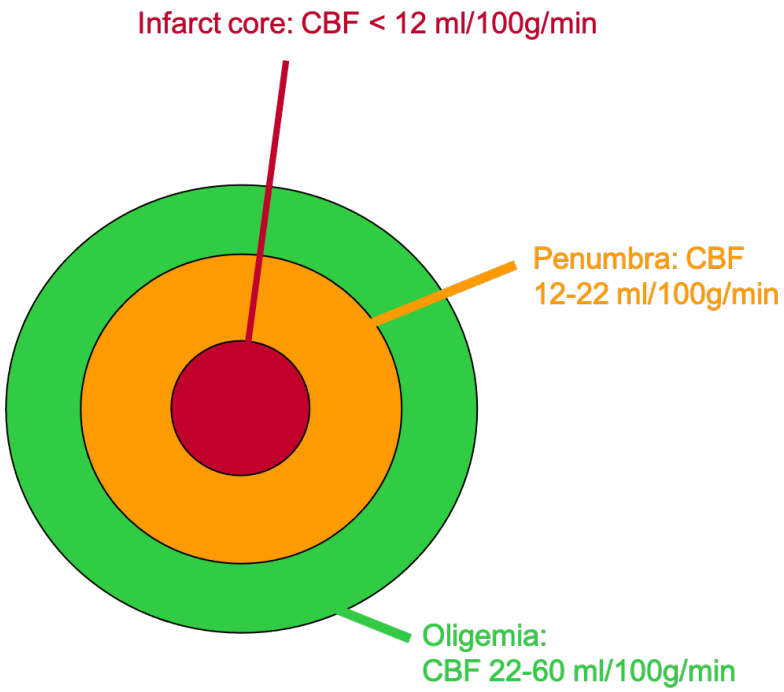


Figure 3. Infarct core, penumbra and oligemia

According to stroke protocol, non-contrast cerebral computed tomography (NCCT) has to be performed first to rule out hemorrhage and to determine whether the patient qualifies for IV rt-PA treatment. (36, 37) In the event of acute ischemic stroke, different neuroradiological imaging modalities can be used to determine the penumbra and to evaluate whether a patient qualifies for reperfusion treatment (eligibility criteria). Important imaging modalities available for this purpose include: cCT, computed tomography angiography (CTA), and computed tomography perfusion (CTP), which are part of the multimodal CT protocol. Alternative imaging modalities are: magnetic resonance imaging (MRI) involving MRA (magnetic resonance angiography), magnetic resonance perfusion (MRP), fluid-attenuated inversion recovery (FLAIR), susceptibility-weighted imaging (SWI), diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI) and time-of-flight angiography (TOF-MRA). (11)

There are different stages of ischemic stroke. Since the definition of each stage varies in scientific literature, the following classification is only one example of how ischemic stroke can be graded. Hyperacute ischemic stroke may occur within 0 to 6 hours from AIS symptom onset, acute ischemic stroke within 6 to 72 hours, early subacute stroke within 1.5 to 5 days, late subacute stroke within 5 days to 2 weeks and chronic ischemic stroke after 2 to 3 weeks. (47)

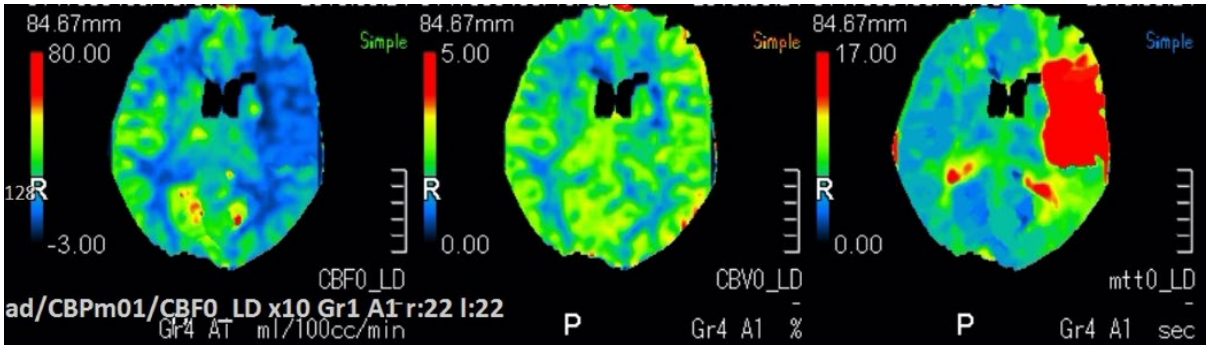
Early radiological signs of hyperacute ischemic stroke can be detected about 0 to 6 hours after symptom onset. These signs include loss of gray-white matter differentiation, cortical hypodensity due to cerebral swelling, effacement of sulci, and hyperdense occluded vessels such as the hyperdense middle cerebral artery sign (HMCAS). (10, 11, 43, 47) Within 12 to 24 hours of AIS symptom onset, brain tissue is demarcated, resulting in hypodense parenchyma due to cerebral edema. This can cause a secondary mass effect and compression of neighboring brain tissue. Subacute ischemic stroke, which develops days after symptom onset, is easy to mistake with normal brain tissue (isodense). After 2 to 3 weeks, the area of infarction is fully demarcated and hypodense (isodense to cerebrospinal fluid). In this chronic stage, gliosis replaces normal brain parenchyma. (10, 11, 47)

For further distinction, the Alberta Stroke Program Early CT Score (ASPECTS) calculates early ischemic changes in the MCA territory using two axial non-contrast cCTs. For this purpose, brain parenchyma is divided into 10 different regions: 7 cortical (including the insula and M1-M6 segments) and 3 subcortical regions (caudate, lentiform area and internal capsule) to assess the degree of infarction core volume within the MCA territory. (48) Starting from a total score of 10 points, 1 point is subtracted for every ischemic region. The lower the score, the higher the number of ischemic areas affected and the worse the outcome. (10, 11) According to the European Stroke Organization and the European Society for Minimally Invasive Neurological Therapy (ESO/ESMINT), patients with an ASPECTS score of ≥ 6 are qualified to receive endovascular treatment beyond 6 hours of AIS symptom onset. (1)

The success of mechanical thrombectomy can be rated clinically and radiographically before, during and after procedure. The predictors for successful mechanical thrombectomy before and during procedure are indicated by an ASPECTS score of ≥ 6, gaining fast access to the patient’s vasculature and high recanalization rates (≥ TICI 2b). Post-procedure indicators for MT success are long-term functional outcome rated as mRS at 90 days, and a low incidence of intracranial hemorrhage or embolism in new territories (ENT). (1, 49)

According to cCT protocol, computed tomography angiography (CTA) can be used to distinguish the site of occlusion, the clot length (clot burden score), and the collateral status. Magnetic resonance angiography (MRA) can be performed as an alternative to CTA. (43)

Computed tomography perfusion (CTP) and magnetic resonance perfusion (MRP) are key imaging modalities for assessing the penumbra. This is based on the perfusion mismatch of the infarct core and penumbra. In CTP, the passing of contrast agent enables perfusion deficits to be measured. Regarding the central volume principle, three parameters – cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time (MTT) – are relevant for mismatch assimilation (CBF = CBV/MTT). (50, 51) The CBF is outlined as the volume of blood flowing through 100 g of the brain tissue per minute (see above). The CBV refers to the volume of blood in one voxel, flowing within a specific area of the brain. Reference values for the CBV are 2.5 ± 0.4 ml/100g for grey matter and 1.7 +/- 0.4ml/100g for white matter. (52) The MTT is the time required for the contrast agent to be distributed from the cerebral arteries to the cerebral veins, from contrast injection to maximum contrast enhancement in a specific region of interest (ROI) – which takes 4 seconds for grey matter and 4.8 seconds for white matter. (51, 52) In the infarct core and penumbra, the MTT is prolonged because the contrast agent has to travel via collateral vessels, bypassing the occlusion site. The infarct core is distinguished by low CBF and CBV rates due to the diminished perfusion. In comparison, the CBF within the penumbra is slightly reduced, while the CBV is mostly sustained by intact autoregulatory mechanisms. In imaging, disparities between these three parameters (CBF, CBV, MTT) are visualized with a color scale ranging from red/yellow/green for the highest CBV and CBF values and blue/purple/black for the lowest values, in descending order. Color coding for the MTT is reversed. Prolonged time to perfusion is generally depicted in red, correlating with the infarct core and penumbra. A matched reduction of CBF and CBV defines the infarct core. The penumbra can be quantified by deducting the CBF from the CBV, which is defined as mismatch (see Figures 4 and 5). (10, 11, 51)



CBF *CBV* *MTT*

***Figure 4. Perfusion mismatch assimilation in CTP to demask the penumbra**. The different CBF, CBV and MTT parameters are shown from left to right. The CBF is reduced in the left MCA territory; the CBV is mostly retained; the MTT is prolonged.*

MRI is an alternative imaging modality that also enables early and high-sensitivity detection of acute ischemic stroke. A hyperintense signal can be detected in the T2-weighted image (MRI) after 6 hours of AIS symptom onset due to cerebral edema. The T1-weighted image is hypointense after 16 hours of symptom onset. Both cCT and MRI protocols are used for assessing wake-up strokes, as well as excluding stroke-mimics and determining the stage of infarction. Disadvantages of MRI include higher costs, limited availability and longer acquisition times. The exposure to radiation and the use of iodinated contrast agent are disadvantages of CTP. (10, 11, 51)

Diffusion-weighted imaging (DWI) is one of the most sensitive methods for detecting hyperacute ischemic stroke (0 to 6 hours). Hyperintensities due to restricted water molecule diffusion in the infarct core can occur within 3 to 30 minutes of AIS symptom onset. Vasogenic and cytogenic edema can be determined by comparing the DWI sequence to apparent diffusion coefficient (ADC) mapping. Both ADC mapping and DWI are generally included in MRI stroke imaging protocols. Due to the T2-shine effect (hyperintense signal) DWI cannot detect differences between vasogenic and cytogenic edema, in contrast to ADC mapping, which is able to quantify water diffusion. Vasogenic edema shows up as a hyperintense signal on ADC mapping compared to cytogenic edema (true diffusion disorder: e.g., infarct core), which is revealed as a hypointense signal. Contrast enhanced T1-weighted images are also early signs of infarction and are positive 0 to 2 hours after symptom onset. Susceptibility-weighted imaging allows early detection of the thrombus as a hypointense signal, commonly referred to as the susceptibility sign. (10, 11, 47, 51, 53) Enhanced visualization is possible with the fluid-attenuated inversion recovery sequence (FLAIR), which suppresses the cerebrospinal fluid signal due to a prolonged inversion recovery time. Hyperintensities in FLAIR can also be detected in the hyperacute stage. (10, 11, 47, 51, 53) Mass effect peaks in the subacute stage after 3 to 4 days, due to vasogenic edema. In the subacute stage, ADC mapping decreases in hypointensity, while DWI and T2-weighted images remain high. In the chronic stage, the mass effect is resolved and cystic encephalomalacia occurs: as indicated by mild hyperintense T2 signals, decreased DWI signals and hyperintense ADC signals. (10, 11, 47, 53)

In MRI, DWI-PWI-mismatch is used to assess the penumbra, thus facilitating the selection of patients who would benefit from endovascular treatment. The infarct core can be detected on diffusion-weighted imaging (DWI). Hypoperfused ischemic areas in the brain can be highlighted with perfusion-weighted imaging (PWI), thus exposing both the infarct core and penumbra. The volume of penumbra can be calculated by subtracting the DWI-demarcated infarct core from the PWI sequence (see Figure 5). DWI-PWI mismatch does not necessarily require contrast agent. The arterial spin labeling technique traces the magnetic features of protons in arterial blood without using contrast agent. (10, 11, 47, 53) Other PWI techniques

such as dynamic susceptibility contrast-enhanced MR perfusion and dynamic contrast-enhanced MR perfusion can be used to determine the penumbra. (54) The quantification of the penumbra has been made possible through advances in imaging technology in recent years. This has led to a reevaluation of guidelines and an extension of the time window for endovascular treatment up to 24 hours of AIS symptom onset (DAWN trial). The recent DAWN and DEFUSE-3 trials (see section 2.4.7) indicated that patients with a certain infarct core volume and/or mismatch ratio may benefit from mechanical thrombectomy. (55, 56)

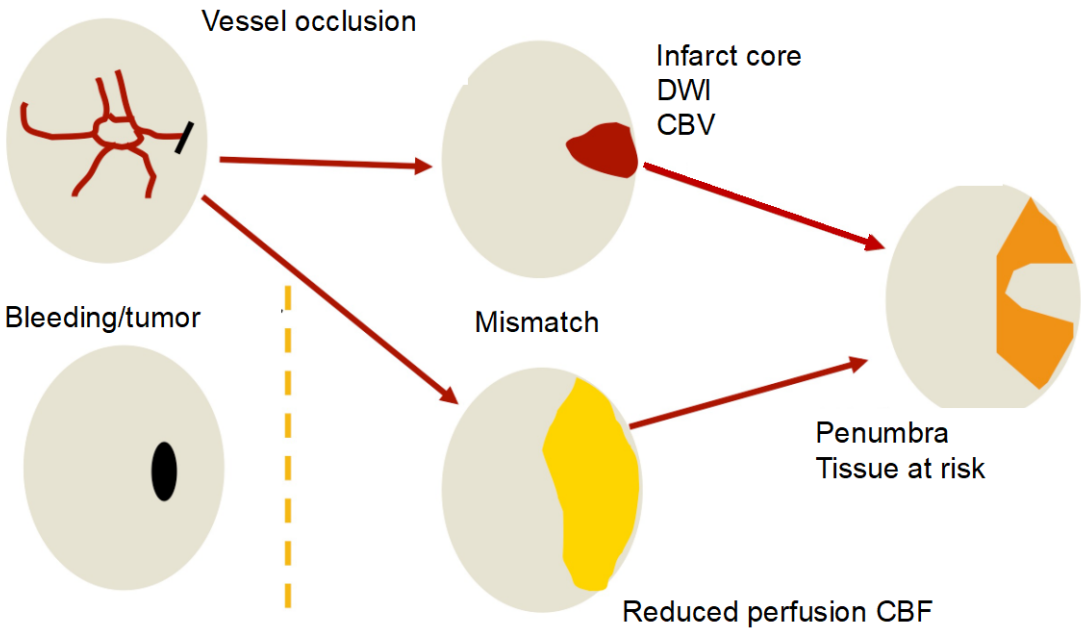


Figure 5. DWI-PWI-mismatch in MRI to determine the penumbra

2.3.3 Thrombolytic Treatment

Alteplase or IV rt-PA was first discovered in 1979. (57) According to the ASA and ESO/ESMINT guidelines, Alteplase is administered within a 4.5-hour time window of AIS symptom onset. Time is counted from when the patient was last seen normal. (1, 33) Alteplase is a genetically-modified derivative of tissue-type plasminogen activator, which is physiologically released from vascular endothelium cells. It dissolves the fibrin mesh of the thrombus by catalyzing the "conversion of plasminogen to plasmin", thereby inducing and enhancing the fibrinolysis process. (58) A dosage of 0.9 mg/kg per body weight, with a maximum dose of 90 mg, is infused intravenously. Initially, 10% of the dose is administered as a bolus for a 1 minute period, with the remainder infused over the next 60 minutes. (1) Before treatment, blood pressure must be held at < 185/110 mmHg to reduce the risk of intracerebral hemorrhage.

During and after treatment, blood pressure should be maintained at < 180/105 mmHg. Blood pressure should be monitored every 15 minutes for the first 2 hours, every 30 minutes for 6 hours, and then every hour for 16 hours. The outcome is dependent on the time window in which Alteplase is administered. (33) The indications and contraindications for receiving intravenous thrombolysis underlie strict eligibility criteria and are summarized in Figure 1 (Stroke Protocol).

Rescuing the penumbra is the overall goal of AIS treatment. However, the process of reperfusion is time dependent. Khatri et al., 2009 (59) investigated the effect of time dependency on the clinical outcome of patients with acute ischemic stroke, based on the data from the IMS I and II (Interventional Management of Stroke) trials. The IMS I and II trials compared combined intra-arterial and IV rt-PA treatment to standard IV rt-PA treatment, within 3 hours of symptom onset in patients with acute ischemic stroke. (59-61)

Figure 6 below shows the probability of achieving a good clinical outcome, rated as an mRS score of ≤ 2, in relationship to the time of reperfusion from symptom onset in minutes. After 280 to 310 minutes, the slope showed the steepest decline in clinical outcome. Notably, a perfusion delay of only 30 minutes – during a time window of approximately 280 to 310 minutes after symptom onset (4.5-5h) – caused a 10.6% decline in clinical outcome (see green bars in Figure 6). Considering that 2 million neurons are damaged every minute, a period of 30 minutes would result in a loss of 60 million neurons – hence the “time is brain” paradigm. (59)

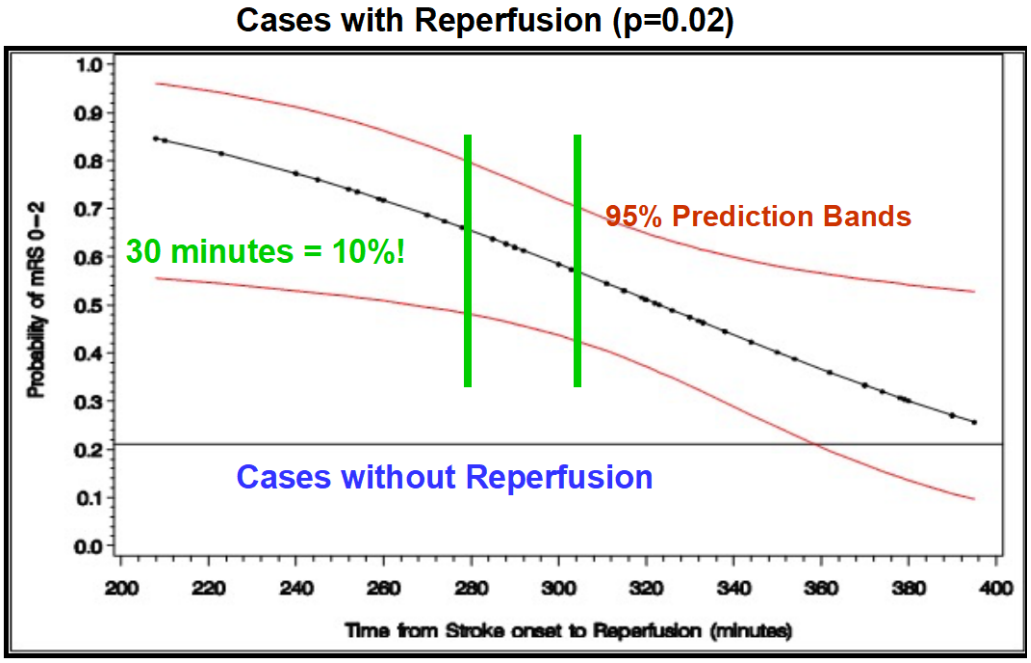


Figure 6. The success of reperfusion is time-dependent. *Adapted from Khatri et al., 2009* (59) *The graph shows the probability of improved functional outcome (mRS ≤ 2) in relation to time from stroke onset to reperfusion (in minutes).*

The use of intravenous thrombolysis for treating acute ischemic stroke was controversial for a long time. Due to smaller study designs, prolonged time windows, limited imaging techniques and outdated substances, thrombolytic medication did not seem beneficial. In particular, one study by Meyer et al., 1964 (62) compared the combined treatment of Streptokinase and Heparin versus Heparin treatment alone. This study demonstrated higher rates of mortality and intracerebral hemorrhage for the Streptokinase group. As a result, the use of Streptokinase was terminated. (57, 62)

The NINDS (National Institute of Neurological Disorders and Stroke) randomized controlled trial (RCT) marked a turning point in 1995. Due to the improved clinical outcome, NINDS established IV rt-PA as standard treatment for acute ischemic stroke. In 1996, the Food and Drug Administration (FDA) finally approved IV rt-PA as AIS treatment after 3 hours of initial symptom onset. Today, IV rt-PA is still the only approved thrombolytic drug for the treatment of acute ischemic stroke, although the efficacy of other substances with higher selectivity for fibrin (e.g., Desmoteplase and Tenecteplase) continues to be investigated (13, 57, 63, 64). Current research includes the ATTEST 2 (Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis), the TWIST (Tenecteplase in Wake-up Ischemic Stroke Trial), and the TASTE (Alteplase for Stroke Thrombolysis Evaluation) trials. (1)

Results from the NINDS trial showed that the odds for improved long-term functional outcome (measured by the global test statistic) were 1.7 times higher for the intravenous thrombolysis group within 3 hours of AIS symptom onset versus no treatment. While overall mortality rates remained the same, the rate of intracerebral hemorrhage increased by 6.4%. Intravenous thrombolysis led to an absolute increase in good functional outcome of 13%, calculated for a mRS ≤ 1. Thus, the number needed to treat (NNT) reached 8 when IV rt-PA was administered within 3 hours of AIS symptom onset. (13, 63, 65) The NNT is a statistical tool that describes how many patients have to be treated on average in order for one person to benefit. It is estimated as the inverted ratio of the absolute risk reduction (ARR). The lower the NNT, the more effective the treatment. (66) The results from NINDS outlined the efficacy of IV rt-PA within a 3-hour time window of AIS symptom onset. (13, 63, 65)

Further trials have investigated the efficacy of IV rt-PA. Compared to NINDS, subsequent trials extended the time window for IV rt-PA treatment from 3 to 6 hours of AIS symptom onset. Results indicated that the NNT increased by 1 for every 20-minute delay in treatment. This led to a reduction of functional outcome and reduced efficacy of IV rt-PA over time. (63) Moreover, a pooled meta-analysis showed that the odds ratio for improved outcome in favor of IV rt-PA versus no treatment incrementally decreased over time; reaching 2.81 for a time window of 0 to 90 minutes, 1.55 for 91 to 180 minutes, and 1.40 for 181 to 270 minutes. Thus, treatment

with IV rt-PA was nearly twice as effective within the first 1.5 hours compared to 1.5 to 3 hours after symptom onset. (67, 68)

Especially after the release of the ECASS-III (European Cooperative Acute Stroke Study), which specifically evaluated the efficacy of IV rt-PA between 3 and 4.5 hours of AIS symptom onset, higher rates of improved functional outcome (mRS $\leq$ 1) were recorded for the IV rt-PA treatment group compared to the placebo group. The NNT score reached 14 for an extended time window of 3 to 4.5 hours after symptom onset. Although the NNT almost doubled within the 1.5-hour delay in treatment compared to the original 3-hour time window for the NINDS trial, IV rt-PA was considered beneficial up to 4.5 hours after symptom onset. (65, 68) However, this does not mean that the administration of IV rt-PA should be delayed. On the contrary, the sooner treatment is initiated the better the outcome. Further trials investigated whether the time window for IV rt-PA could be extended if patients fulfilled certain imaging selection criteria (Wake-up Stroke, EXTEND, ECASS-IV and EPITHET trials). Although the results were mostly positive, reviews remain ambiguous due to premature termination. (69, 70)

The meta-analysis by Emberson et. al (71), published in the Lancet in 2014, analyzed data from a number of major stroke trials: including NINDS**,** ECASS I-III, ATLANTIS (Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke), EPITHET (Echoplanar Imaging Thrombolytic Evaluation), and IST-3 (Third International Stroke Trial). Results indicated that the overall improved long-term functional outcome, defined as mRS $\leq$ 1 at 3 months, outweighed the pooled risk of intracerebral hemorrhage of 6.8% for the treatment group (TG), compared to 1.3% for the control group (CG). This resulted in an NNT of 10 at 3 hours, an NNT of 20 at 4.5 hours, and an overall number needed to harm (NNH) of 18. Compared to the original 3 hours for the NINDS trial, this meta-analysis confirmed that the time window for IV rt-PA might be extended to 4.5 hours from symptom onset, regardless of age and stroke severity. However, the study also signified that the risks for IV rt-PA treatment beyond the 4.5-hour time window outweighed the benefits. Only 1 out of 50 patients showed improved clinical outcome, whereas 1 out of 18 patients were harmed with IV rt-PA treatment. (63, 70, 71) These results emphasize that efficacy of thrombolysis is time dependent. Based on this “window of opportunity”, ESO/ESMINT guidelines recommend IV rt-PA treatment up to 4.5 hours, which has now become the European standard. (1) However, to the best of our knowledge, the FDA has not extended the approval to use IV rt-PA beyond 3 hours. (57, 63, 72, 73). Table 4 and Figure 7 highlight the relation between good functional outcome and time dependency.

Time window	***TG** (IV rt-PA) **mRS ≤ 1 [in %]***	***CG** (no IV rt-PA) **mRS ≤ 1 [in %]***	***ARR = TG – CG***	***NNT** = $\frac{1}{ARR}$*	***OR** (95%-CI)*
0 to 3h	32.9%	23.1%	~ 10%	**10**	1.75 (1.35–2.27)
3 to 4.5h	35.3%	30.1%	~ 5%	**20**	1.26 (1.05–1.51)
> 4.5h	32.6%	30.6%	= 2%	**50**	1.15 (0.95–1.40)

Table 4. Efficacy of intravenous thrombolysis in relation to the time window after AIS symptom onset. *The primary outcome (in %) for both the treatment group (TG: IV rt-PA administration) and control group (CG: no IV rt-PA) is defined as a mRS ≤ 1 at 3 months. Other statistical tools such as the absolute risk reduction (ARR), the number needed to treat (NNT) and the odds ratio (OR) with the 95% confidence interval (95% CI) are presented for the different time windows. This table is based on data by Emberson et al., 2014 (71) and was adapted from UpToDate (70).*

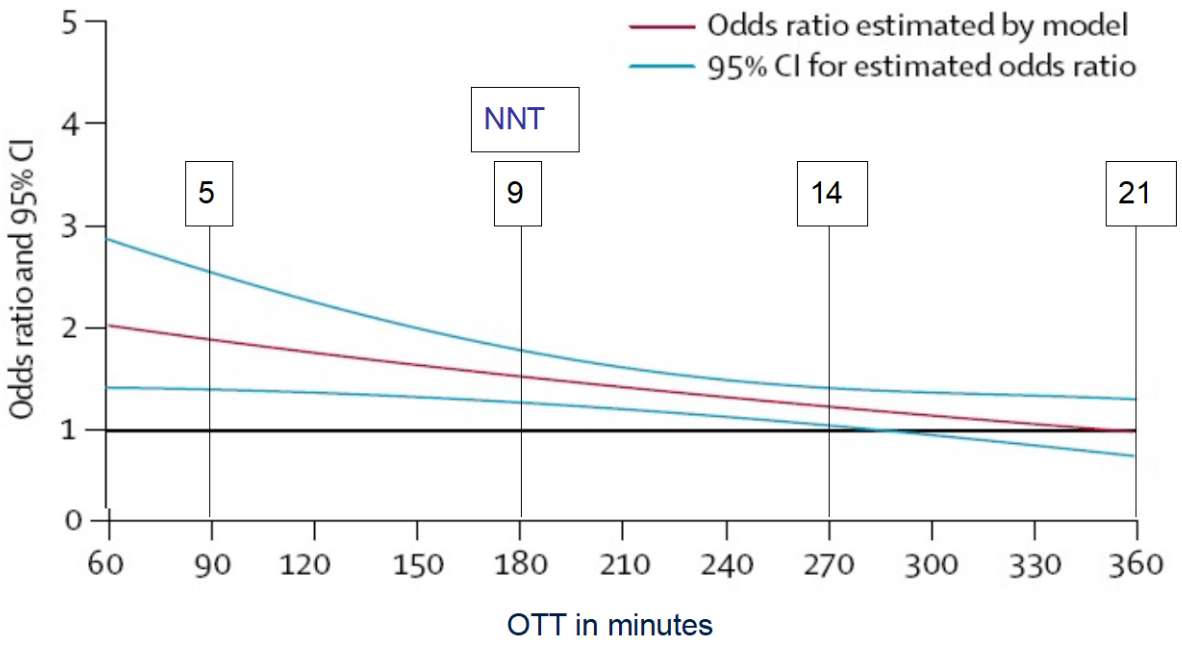


Figure 7. Time in relation to good outcome. *Onset to treatment time (OTT) in minutes in relation to functional outcome (NNT, OR and 95% CI). After 360 min (6h), the odds ratio (OR) declines to 1, showing no difference between the treatment group (IV rt-PA) versus control group (no IV rt-PA). The number needed to treat (NNT) increases over time while the odds for improved functional outcome decrease. The graph was adapted from Hacke et al., 2004, (67); and Lees et al., 2010, (74).*

The effectiveness of intravenous thrombolysis is also dependent on the thrombus length (see Figure 8). In a retrospective analysis, intravenous thrombolysis failed to dissolve thrombi > 8 mm long; while shorter thrombi < 5 mm in length were associated with higher recanalization rates. (75)

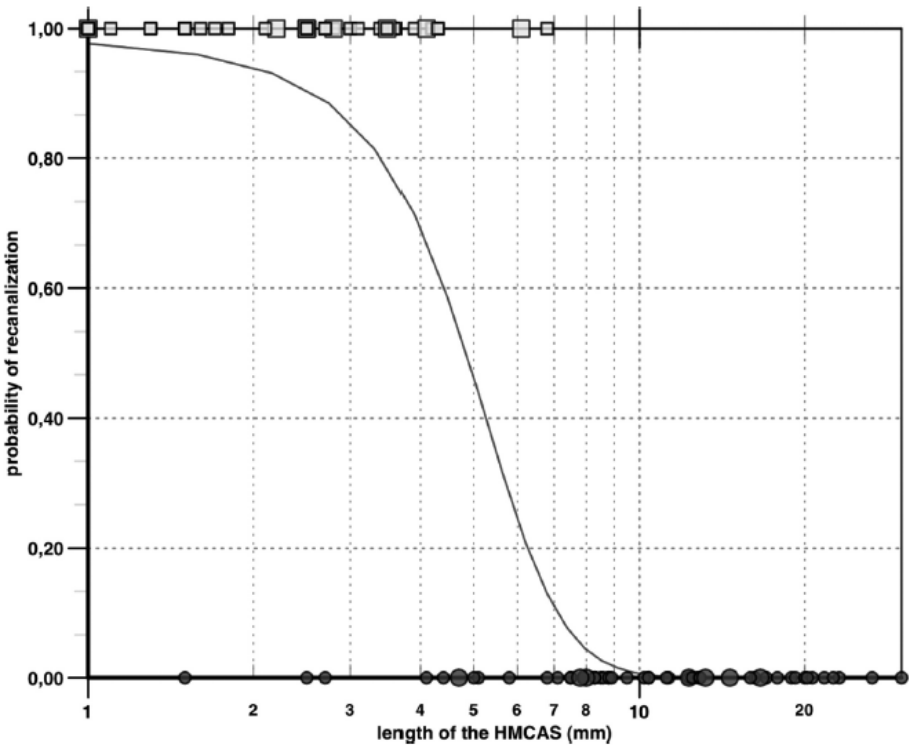


Figure 8. Effect of thrombus length on recanalization. *Recanalization rates drop < 1% for thrombi > 8.0 mm (length); from Riedel et al., 2011 (75).*

Post hoc analysis from the THERAPY trial (76) examined the effect of thrombus lengths ≥ 8 mm on mechanical thrombectomy, compared to intravenous thrombolysis alone. Patients were able to benefit from mechanical thrombectomy in combination with IV rt-PA compared to IV rt-PA alone. Longer thrombi registered worse clinical outcome after 90 days, a higher incidence of adverse events and prolonged recanalization times. Every 5 mm increase in thrombus length led to a 33% reduction in clinical outcome (mRS ≤ 2 at 90 days). Furthermore, mechanical thrombectomy succeeded in restoring reperfusion when intravenous thrombolysis failed to dissolve longer thrombi. This, however, does not mean that IV rt-PA and mechanical thrombectomy are used sequentially. Instead, it implies that mechanical thrombectomy is superior to IV rt-PA. (76) These results were confirmed by a retrospective study that measured the thrombus length in the M1-MCA territory, depicted as hyperdense middle cerebral artery sign (HMCAS) in non-contrast cCT. In 37.5% of cases, the HMCAS disappeared after administering intravenous thrombolysis when the thrombus length ranged between 10 to 20

mm. If the thrombus exceeded 20 mm, the HMCAS sign could only be resolved by endovascular treatment, which was used in conjunction to intravenous thrombolysis. (77)

As a primary guideline recommendation, IV rt-PA can be administered within a 4.5-hour time window after AIS symptom onset. However, there are a number of disadvantages to using IV rt-PA. Compared to mechanical thrombectomy, IV rt-PA showed lower recanalization rates and an increased risk of symptomatic intracerebral hemorrhage. Since mechanical thrombectomy achieves mean recanalization rates of 71% and numbers needed to treat (NNT) ranging from 3 to 5 versus 10 to 20 for IV rt-PA, endovascular treatment seems to be more beneficial than IV rt-PA alone. (3, 71, 78) Furthermore, a neurotoxic effect of IV rt-PA may impact the permeability of the blood-brain barrier and influence the N-methyl-D-aspartic-acid-(NMDA) receptor. (79) With a short half-life of five minutes, IV rt-PA has the disadvantage of requiring constant infusions to be administered. (57) Additionally, intravenous thrombolysis often fails to dissolve thrombi longer than 8.0 mm. Mechanical thrombectomy, in comparison, can dissolve thrombi longer than 20.0 mm. (75, 76) Importantly, the administration of IV rt-PA is restricted to a narrow time window of 4.5 hours and a very strict selection of eligibility criteria. Meanwhile, mechanical thrombectomy has become the standard treatment for acute ischemic stroke up to 24 hours after AIS symptom onset. To conclude, IV rt-PA can be used as a standalone treatment or as a combined bridging therapy alongside mechanical thrombectomy. (1)

2.4 Endovascular Treatment

2.4.1 Intra-arterial Thrombolysis

In the 1980s, time windows, eligibility criteria and dosages were not established for the treatment of acute ischemic stroke. Systemic thrombolytic therapy was not considered viable due to the recurrent risk of hemorrhage. Aiming to reduce systemic side effects, as well as combining diagnostic and interventional procedures simultaneously, clinical studies during the 1980s and 1990s examined the results of local fibrinolysis, also referred to as intra-arterial thrombolysis (IAT) for treating acute ischemic stroke. These trials marked the launch of endovascular therapy. (13, 80)

In his landmark 1982 clinical case study, renowned German Neuroradiologist Hermann Zeumer examined the effect of intra-arterial thrombolysis in basilar artery thrombosis – known for its high 60 to 80% mortality rate. In his case report, a 27-year old female was admitted to the hospital with prodromal neurological symptoms such as a severe headache, unilateral right-sided paresthesia and ataxia. The initial non-contrast cCT showed no signs of early infarction and a subarachnoid hemorrhage was excluded. Clinical worsening 24 hours later was characterized by somnolence, gaze paresis and downbeat nystagmus. An angiography

revealed a basilar artery occlusion. During angiography, intra-arterial thrombolysis with 200,000 international units (IU) of streptokinase was initiated via a vertebral artery catheter. In addition, 5000 IU heparin and 250 mg prednisolone were administered intravenously. During intra-arterial thrombolysis, angiography demonstrated a partial thrombus reduction in the basilar artery and a reperfusion of the communicating posterior arteries. After 24 hours, intra-arterial thrombolysis was repeated and revealed further reduction of the thrombus size. Clinical improvement was rated electrophysiologically (orbicularis oculi reflex, somatosensory evoked potentials, brain stem evoked response audiometry). Although a post procedure cCT showed a remaining hypodensity in the right side of the cerebellum, the patient recovered substantially. The significant improvement of clinical symptoms characterized the success of local fibrinolysis.

As a result, Zeumer's team conducted additional case studies with intra-arterial thrombolysis, this time using a balloon catheter in the MCA-territory. Initial reperfusion, which was evaluated in digital subtraction angiography (DSA), and clinical outcome both improved despite hemorrhagic complications. Zeumer concluded that the success of recanalization was time-dependent. Additionally, an intra-arterial (IA) streptokinase dosage of 10,000 IU was considered sufficient to dissolve the thrombus and to avoid further risk of hemorrhaging. Due to high local concentrations, streptokinase may accumulate within the thrombus and create an "after lysis effect", meaning that the effects of fibrinolysis could continue hours after administering streptokinase. This was the basis for reducing the local dosage of intra-arterial thrombolysis. (81, 82) Another Zeumer study involved higher patient collectives (N = 137) with acute ischemic stroke in the anterior circulation. This study achieved recanalization in 74 out of 137 cases (54%; TIMI ≥ 2) and a good functional outcome of 35% (Barthel index > 90%). (83)

Zeumer's 1980s pioneering work with intra-arterial thrombolysis led to further research trials during the next decade. These included the North American PROACT (Prolyse in Acute Cerebral Thromboembolism) trials: the PROACT I, double-blinded multicenter randomized controlled trial, and the PROACT II, an open-label multicenter randomized controlled trial. During the PROACT II trial, a total of 180 patients with an occlusion in either the M1-MCA or M2-MCA received intra-arterial recombinant prourokinase (IA r-proUK) in combination with intravenous heparin for the interventional group, versus intravenous (IV) heparin alone for the control group within 6 hours of symptom onset. The PROACT II trial achieved a higher recanalization rate (TIMI ≥ 2), 66% for the interventional group versus 18% for the control group ($P < .001$). For the interventional group, recanalization was restored in 66% of the cases in PROACT II, compared to 57.7% in PROACT I – most likely due to the higher concentration of IA r-proUK administered, 9 mg versus 6 mg, respectively. Initially, high doses of heparin

were administered in PROACT I (100 IU/kg bolus plus 1000 IU/h for 4 hours) alongside IV rt-PA. Recanalization rates were higher for the high-heparin group compared to the low-heparin group in the PROACT I trial, 81.8% versus 40.0%, respectively (P = .051). However, noticeably higher rates of symptomatic hemorrhage occurred, 27.3% for the high-heparin group versus 6.7% for the low-heparin group. Due to the increased risk of intracerebral symptomatic hemorrhage s(ICH), the heparin dose was lowered (2000 IU bolus, 500 IU/h for 4 hours) for the remaining patients. The low-heparin-regimen was continued in the PROACT II trial. (78, 84-86) See Table 5 for a comparison of the PROACT I and II trials.

Trials	***PROACT I***	***PROACT II***
Study design	double-blinded multicenter RCT	open-label multicenter RCT
N (patients)	N = 40	N = 180
Occlusion site	MCA (M1, M2), ICA	MCA (M1, M2)
Time window	≤ 6 hours of symptom onset	≤ 6 hours of symptom onset
Interventional group (IG)	IA r-proUK 6 mg over 2 h (N = 26) + IV heparin High heparin (IG = 11; CG = 5) Low heparin (IG = 15; CG = 9)	IA r-proUK 9 mg over 2h (N = 121) + IV heparin (low)
Control group (CG)	IV heparin alone (N = 14)	IV heparin alone (N = 59)
Outcome parameters	***IG vs. CG***	***IG vs. CG***
Functional outcome	31% vs. 21%, *(P = .72)* (mRS ≤ 1 at 90 days)	40% vs. 25%, *(P = .04)* (mRS ≤ 2 at 90 days); NNT = 7
First-pass recanalization (TIMI ≥ 2)	58% vs. 14%, *(P = .02)* 82% high heparin vs. 40% low heparin, *(P = .05)*	66% vs. 18%, *(P < .001)*
Mortality at 90 days	27% vs. 43%, *(P = .48)*	25% vs. 27%, *(P = .80)*
Complications *sICH in 24 hours*	15% vs. 7%, *(P = .64)*	10% vs. 2%, *(P = .06)* NNH = 12

Table 5. Proact I and II trials. *Study design and outcome parameters. Note abbreviations (ICA = internal carotid artery; MCA = middle cerebral artery; mRS = modified Rankin scale; N = number; NNT = number needed to treat; NNH = number needed to harm; ns. = not specified; IA r-proUK = intra-arterial recombinant prourokinase; sICH = symptomatic intracerebral hemorrhage; RCT = randomized controlled trial; TIMI = thrombolysis in myocardial infarction score). (78, 84-86)*

Despite improved clinical outcome (mRS ≤ 2) in favor of IA r-proUK, the PROACT trials still remain the only randomized controlled trials that evaluated the efficacy of intra-arterial thrombolysis. Results were never confirmed in subsequent trials. Furthermore, the FDA failed to approve IA r-proUK, due to similar mortality and higher symptomatic intracerebral hemorrhage rates for the interventional group. Consequently, intra-arterial thrombolysis has been largely discontinued and is only occasionally used as adjunctive treatment to mechanical thrombolysis. Since then, endovascular technology has advanced incrementally and has achieved higher recanalization and efficacy rates. (78, 84-86)

2.4.2 Stent Retrievers

Officially approved by the FDA in 2004, the MERCI (Mechanical Embolus Removal in Cerebral Ischemia) retriever was the first MT device used in patients with acute large vessel occlusion. The efficacy of this corkscrew-shaped device was tested in the MERCI (Part I and II) and multi-MERCI prospective single-armed, non-randomized controlled trials. Patients with an NIHSS score of ≥ 8 and symptom onset ≤ 8 hours were considered eligible to participate in these trials. In comparison to Part I, the MERCI Part II trial enrolled a larger number of patients (N = 96 vs. 55, respectively), extended the follow-up time, and included patients with M2-MCA occlusions. (40, 87-89) The multi-MERCI trial used the same selection criteria as the MERCI Part I and II trials to ensure comparability, but included more patients who were ineligible for IV rt-PA. Only first-generation devices were employed in the MERCI Part I and II trials. Second-generation devices (MERCI Retriever X5, X6, L5) were allowed in the multi-MERCI trial. A balloon guide catheter (BGC) was also used to reduce the rate of distal embolization. (87-91)

The MERCI device achieved significantly higher recanalization rates (TIMI II/III) of 46% (intention-to-treat) for the MERCI, 60% for the MERCI in combination with intra-arterial treatment, and 68% for the Multi-MERCI trials. In addition, the rates for improved clinical outcome at 90 days (mRS ≤ 2) reached 27.7% for the MERCI and 36.0% for the Multi-MERCI trials. However, mortality rates were comparatively high: 43.5% for the MERCI versus 34.0% for the Multi-MERCI trials. In retrospect, it was concluded that the high mortality rates could also be attributed to a high baseline NIHSS score (median = 19) and an older age group (mean 68.1 ± 16.0). (13, 73, 88-91). Procedure-related complications using the MERCI device included vessel dissection, perforation, groin hemorrhage and thrombus fragmentation – which occurred in 7% of cases. (88) Interestingly, the dissipation of emboli to the ACA was reported in 3 out of 141 cases (2.1%). (90) The multi-MERCI trial did not specify the embolism in new territories rate (40), but counted this complication as a procedure-related adverse event (secondary endpoint parameter). In total, procedure-related adverse events reached 10% for the Multi-MERCI versus 5% for the MERCI. (89)

The development of second-generation devices marked a turning point for endovascular therapy. In 2010, high-volume comprehensive stroke centers in Europe started using non-detachable and self-expanding stent retrievers for off-label AIS treatment. Recanalization of the occlusion site was performed by expanding the stent retriever over the thrombus. (91-93) Initial reports indicated successful recanalization in nearly 80% of cases for self-expanding stents. (94, 95). In 2012, the FDA finally approved two MT devices: the Solitaire and Trevo stent retrievers. (91-93) These second-generation stent retrievers were tested in comparison to the MERCI device in two different randomized controlled trials: the TREVO 2 (Thrombectomy Revascularization of Large Vessel Occlusion in Acute Ischemic Stroke) and the SWIFT (Solitaire With the Intention for Thrombectomy) trials. (96, 97) Both of these trials chose similar eligibility criteria: initiating MT procedure within 8 hours of symptom onset, a NIHSS score $\geq$ 8 to $\leq$ 30, and patient inclusion if IV rt-PA treatment failed or was contraindicated. Despite slightly different scoring scales and study allocations, both trials equally demonstrated the superiority of stent retrievers to the first-generation MERCI device – in terms of higher recanalization, improved clinical outcome and reduced mortality rates. (89, 91, 93, 96, 97) The results of these studies are summarized in Table 6. The Trevo stent retriever (NNT = 6) reached higher recanalization rates than the Solitaire (NNT = 13). In contrast, the Solitaire surpassed the Trevo in terms of improved clinical outcome, significantly lower mortality rates and a reduced incidence of symptomatic intracerebral hemorrhage (sICH). It should be noted that both second-generation devices are considered first-line treatment in AIS and play a significant role in in today's endovascular treatment. (89, 91, 93, 96, 97)

Trials	***MERCI I + II***	***Multi-MERCI***	***Penumbra***	***TREVO 2***	***SWIFT***
Study design	prospective single-arm multicenter	prospective single-arm multicenter	prospective single-arm multicenter	multicenter RCT	multicenter RCT
N (patients)	151	177	125	178 (IG; N = 88) (CG; N = 90)	103 (IG; N = 58) (CG; N = 55)
Occlusion site	ICA, MCA, vertebrobasilar				
Time window	≤ 8 hours of symptom onset				
Devices	MERCI	MERCI	Penumbra System	Trevo (IG) vs. MERCI (CG)	Solitaire (IG) vs. MERCI (CG)
Outcome parameters				***IG vs. CG***	***IG vs. CG***
mRS ≤ 2 at 90 days	27.7% *(P < .0001)*	36.0% *(P < .001)*	25.0% *(P < .06)*	40% vs. 22% *(P = .01)*	58% vs. 33% *(P = .02)*
First-pass recanalization	46% (TIMI ≥ 2) *(P < .0001)*	68% (TIMI ≥ 2)	81.6% (TIMI ≥ 2)	86% vs. 60% (TICI ≥ 2) *(P < .0001)*	61% *vs.* 24% (TIMI ≥ 2) *(P = .0001)*
Mortality at 90 days	43.5% *(P = .01)*	34.0% *(P < .001)*	32.8% (P = .13)	33% vs. 24% *(P = .18)*	17% *vs.* 38% *(P = .02)*
sICH	7.8%	9.8% (P > .05)	11.2%	7% vs. 9% *(P = .78)*	2% vs. 11% *(P = .06)*
ENT	2.1% (ACA)	N = 1 (M3)	1.6%	ns.	ns.

Table 6. Comparison of first-generation and second-generation devices. *Study design and outcome parameters. Note abbreviations (CG = control group; ICA = internal carotid artery; IG = interventional group; MCA = middle cerebral artery; mRS = modified Rankin scale N = number; ns. = not specified; RCT = randomized controlled trial; sICH = symptomatic intracerebral hemorrhage; TIMI = thrombolysis in myocardial infarction score). (87, 89, 93, 96-99)*

2.4.3 Aspiration Devices

After the MERCI, the Penumbra System (catheter) became the second MT device to receive FDA approval for the treatment of AIS. Instead of ensnaring the thrombus with a coiled wire and retracting it into a microcatheter, the Penumbra catheter utilized vacuum aspiration to retrieve the thrombus. (99, 100) First developed in 2008, the Penumbra System featured a reperfusion catheter connected to an aspiration pump to enable continuous aspiration. To prevent clogging of the aspiration tips, subsequent Penumbra models contained a separator wire to break down the thrombus. (73, 99). Following aspiration thrombectomy step by step, the Penumbra catheter was maneuvered over a guidewire to the occlusion site and placed proximally to the thrombus. After reaching the site, the guidewire was removed and the separator was advanced via the reperfusion catheter to penetrate the thrombus. After applying aspiration (vacuum pressure), the thrombus was suctioned into the Penumbra catheter. Due to the proximal placement of the aspiration catheter to the thrombus, this technique is referred to as “contact aspiration”. (49, 101)

The multicenter single-arm Penumbra Pivotal Stroke Trial (99) tested the efficacy of the Penumbra catheter within an 8-hour time window from symptom onset. Independent of the occlusion site, the Penumbra catheter demonstrated a recanalization rate of 81.6% (TIMI ≥ 2) versus 68% for the Multi-MERCI. (49, 73, 91, 99) Despite higher recanalization rates, secondary functional outcome of 25.0% (mRS ≤ 2 at 90 days) and mortality rates of 32.8% at 90 days were still comparable to antecedent stroke cohorts. Additionally, the Penumbra catheter registered a higher rate of sICH (11.2%) within the first 24 hours of symptom onset, compared to the MERCI (7.8%). The Penumbra catheter and the MERCI retriever are both classified as first-generation devices because of their high rate of complications and relatively low functional outcome, despite increased recanalization rates. (49, 99)

One case study by Menon et al., 2011 (102) tested the Penumbra catheter on 27 patients. This study reported high recanalization rates of 85% (TIMI 2/3), but also the formation of distal emboli in 48% of the cases. Given the small case number, these results might be slightly distorted. However, the tendency for increased distal embolization remains. An explanation for this could be clot fragmentation, most likely induced by the separator during aspiration thrombectomy. (102)

Since the development of the first Penumbra catheter, aspiration device technology and techniques have advanced incrementally. The first aspiration thrombectomy improvement – known as the Forced Aspiration Suction Thrombectomy (FAST) technique – served as a bailout procedure, if revascularization did not succeed with the Penumbra separator. The FAST technique, which was first published in 2011, is a simplified procedure that requires

neither a separator nor an aspiration pump. Instead, forced manual aspiration was applied using a vacuum syringe. A balloon guide catheter was additionally used to reduce proximal antegrade flow. (49) Case studies showed that the FAST technique achieved high recanalization rates of 81.9% (mTICI score ≥ 2b) and improved functional outcome of 45.5% (mRS ≤ 2 at 90 days), compared to the original Penumbra catheter (25.0%, mRS ≤ 2 at 90 days). One disadvantage was the use of inflexible aspiration catheters, which were difficult to maneuver in tortuous vessels. (103)

Similar to FAST, the ADAPT Technique (A Direct Aspiration first Pass Technique) is a modified aspiration procedure that evolved in 2013. Aspiration can either be applied with an aspiration pump or manually; a separator is not required. Unlike FAST, the ADAPT technique relies on the latest updated versions of aspiration catheters (5 MAX or 5 MAX ACE Penumbra catheter), compared to the older aspiration device series (041 and 032 Penumbra catheters) used with FAST. Clot removal can be further facilitated by employing aspiration catheters with greater flexibility and an increased internal diameter. (49, 100, 104)

Published in 2014, the ADAPT-FAST (105) trial evaluated the efficacy of the ADAPT technique in 98 patients with large vessel occlusion in the distal ICA, proximal MCA (M1, M2) and basilar artery. The thrombus was aspirated using either 20 or 60 ml syringes, or the Penumbra aspiration pump. The procedure was initiated with a mean time of 8.5 hours after symptom onset. This has to be taken into account, since the extended time window further affects the outcome. Recanalization was restored in 78% of the cases (mTICI score ≥ 2b). Functional outcome at 90 days resulted in a mRS ≤ 2 in 40% of the cases. There was no significant difference in terms of recanalization for the different aspiration catheters (5 MAX 75%, 5 MAX ACE 82%, TICI score ≥ 2b). After three failed attempts for aspiration thrombectomy, a stent retriever bailout was initiated, reaching recanalization rates of up to 95%. However, the duration for this prolonged procedure ranged from an average of 31.4 minutes for the standalone ADAPT technique to 56.8 minutes for combined aspiration and stent retriever thrombectomy. Despite good functional outcome, complications such as distal embolization still remained high, registering 10%. In the study, all cases of distal emboli could be removed using aspiration or stent retrievers as a rescue strategy. (39, 105)

2.4.4 Intermediary Catheters/Distal Access Catheters

The development of the “Outreach Distal Access Catheter” (106) in 2010 has advanced aspiration device technology and MT procedure significantly. Distal access catheters (DACs) are also referred to as intermediary catheters. As the name implies, intermediary catheters feature a diameter size “intermediate” between a guiding catheter and a microcatheter. This size allows DACs to reach distal vessel territories. (106-108) Initially, DACs were developed

to support the MERCI device during clot retrieval. (106, 107) Varying in size and length, DACs are able to increase tracking and stability during mechanical thrombectomy. This facilitates navigation in tortuous vessels such as the ophthalmic artery. (107, 108)

DACs are characterized by their “flexible tip with increased shaft strength and axial load-bearing characteristics, as well as good hoop strength”. (106, 108) They are often integrated in a coaxial or triaxial system consisting of three components: a guiding catheter, an intermediary catheter and a microcatheter. These three components are inserted into one another, providing increased proximal stability and stiffness. By enabling improved angulation due to proximal stability, DACs are often used to guide the microcatheter to the target site. (106-108)

Guiding catheters with a flexible-tip (e.g., Neuron family) can also be used to achieve proximal stability. These devices feature a proximal stiff component, a transitional zone, and a flexible tip. Compared to a DAC, a flexible-tip guiding catheter provides a larger diameter and greater flexibility. One disadvantage is that the catheter can catch on tortuous vessels. This is referred to as the “ledge effect”, which often occurs in the ophthalmic artery. Flexible-tip guiding catheters that are deployed alone can be navigated up to the distal ICA, but not into more distal vessels. (106-109)

Traditionally, a microcatheter was maneuvered via a stiff guiding catheter without using a DAC. (107) However, vertical instead of horizontal vector forces (e.g., along the M1-MCA-segment to the internal carotid artery), can cause strain and twisting of the vessel. (108) DACs decrease the distance between the microcatheter and guiding catheter, thereby reducing friction and facilitating advancement through tortuous vessels. As a result, the strain on the vessel and the vertical vector forces are lowered, thereby minimizing the risk of vessel dissection and perforation. (106, 108) Therefore, the occlusion site can be reached more effectively and stent retriever placement and unsheathing can be targeted more precisely. Thus, DACs can be used to navigate a microcatheter containing a stent retriever. (106-108, 110) Due to the larger inner diameter and shorter length, DACs can also be directly deployed as clot aspiration catheters. (106-108)

Examples of DACs include the Penumbra 3 and 4 Max series, which were launched in 2012 and used in the M1 and M2-MCA segments. The larger 5 MAX device (distal inner diameter ID = 1.37 mm) is typically inserted in the proximal MCA segment and internal carotid artery using a coaxial technique. Compared to the original distal access catheters, these large-bore catheters have a greater internal diameter. Newer models, such as the ACE 064 (distal ID = 1.63 mm) and the ACE 68 (distal ID = 1.73 mm), have an even larger internal diameter, which enable increased suction or aspiration forces during clot retrieval. (100, 108, 110) A case study

by Kalia and Zaidat, 2009 (109) registered a 1.5-fold increase in flow during aspiration compared to the Penumbra catheter. Thus, aspiration can be applied more effectively making the procedure safer, faster and more cost-effective. (106, 109) The larger lumen of a DAC also makes it possible to apply greater amounts of contrast agents compared to when using a conventional aspiration catheter. (106, 108) However, one disadvantage of DACs is that the distal tip can lead to embolism in new territories. According to Balami et al., 2018 (4) ENT rates of “1 to 8.6% of cases for most RCTs and in 1 to 12.5% of cases for non-RCTs” have been registered. (2, 4) Along with direct aspiration thrombectomy for AIS treatment, DACs can be used for a wide range of neuroradiological interventions. These include treating arteriovenous malformations as well as embolization of aneurysms in tortuous vessels, because they provide increased proximal stability and thus control. DACs can also be used to treat intracranial atherosclerosis and vasospasms. (106)

2.4.5 Endovascular Techniques

Stent retriever and aspiration thrombectomy are both standard approaches for mechanical thrombectomy. Therefore, the question arises which method is superior? Two multicenter randomized controlled trials compared the efficacy of contact aspiration (ADAPT) to second-generation stent retrievers: the ASTER (Contact Aspiration versus Stent Retriever for Successful Revascularization) and the COMPASS (Aspiration thrombectomy versus stent retriever thrombectomy as first-line approach for large vessel occlusion) trials. To date, there are still no randomized controlled trials that compare these two approaches as standalone treatment. (111, 112)

The goal of the ASTER trial was to demonstrate the superiority of aspiration catheters versus second-generation stent retrievers. ASTER permitted a rescue strategy to be used after three failed attempts (switching or combined therapy). There was no statistically significant difference between aspiration and stent retriever devices. Aspiration devices recorded a slightly higher recanalization rate of 85.4% versus 83.1% for stent retrievers (mTICI score $\geq$ 2b; P = .53). However, stent retrievers achieved higher rates of mTICI 3 as first-line treatment in 35.5% of cases versus 28.7% for aspiration devices (P = .16). Furthermore, stent retrievers reached a slightly higher functional outcome of 50% (mRS score of ≤ 2) versus 45.3 % for aspiration devices (P = .38). Distal emboli were reported in 7/192 (3.7%) cases using ADAPT, and in 5/189 cases (2.7%) for stent retriever thrombectomy. (1, 112)

The COMPASS trial, published in *The Lancet* in 2019, was conducted as a multicenter, randomized open-label trial. This study showed similar results for aspiration and stent retriever thrombectomy: with mTICI $\geq$ 2b recanalization rates of 83.2% for aspiration devices versus

81.3% for stent retrievers (P = .75); improved functional outcome (mRS score of ≤ 2 at 90 days) of 52% for aspiration devices versus 49% for stent retrievers (P = .001); as well as similar mortality and complication rates. The trial mainly demonstrated non-inferiority of aspiration to stent retriever devices for mechanical thrombectomy. (1, 111)

According to the ESO/ESMINT guidelines, contact aspiration alone does not improve recanalization and functional outcome over stent retriever thrombectomy. Due to higher mTICI 3 rates, as well as higher NIHSS and improved ASPECTS scores after 24 hours, recommendations tend to favor stent retrievers over contact aspiration alone. Although results were not significant, mortality rates and procedure-related adverse events were higher for aspiration devices. (1) In conclusion, aspiration thrombectomy has been advanced in tandem with the development of stent retrievers and can be used as an alternative, or in combination with stent retrievers. Aspiration thrombectomy has the advantages of being simple, fast and inexpensive to perform compared to stent retriever thrombectomy. The disadvantages of aspiration catheters include higher rates of distal embolization, an increased number of attempts for bailout strategies, as well as lower TICI 3 rates. Aspiration devices and stent retrievers can be deployed sequentially or simultaneously. Numerous combined aspiration and stent retriever techniques have been reported in scientific literature. (49)

The “Bailout/Switching” technique relies on using both aspiration and stent retriever devices successively as a rescue strategy or bailout attempt. (49) As already mentioned, the ADAPT-FAST trial showed recanalization rates of up to 95% with additional stent-retrieval, when aspiration thrombectomy had failed after three attempts. (105) Furthermore, it is possible to switch from aspiration thrombectomy to stent-retrieval, and vice versa. (49)

In contrast to switching, the simultaneous use of aspiration and stent retriever thrombectomy is defined as the primary combined approach. A modified version of the primary combined approach, known as the Solumbra procedure, utilizes the Solitaire and Penumbra devices. This technique employs a triaxial system comprising a guiding catheter, intermediary DAC and stent retriever. Efficacy of the Solumbra technique remains unproven and its benefits are unclear. (100)

The PROTECT (PRoximal balloon Occlusion TogEther with direCt Thrombus aspiration during stent retrieval thrombectomy) technique is a modified version of Solumbra that includes a balloon guide catheter to enable proximal flow arrest and improved efficacy of distal aspiration. (110, 113)

When using the SAVE (Stent retriever Assisted Vacuum-locked Extraction) technique, only the proximal part of the stent retriever interacts with the thrombus. The distal two-thirds of the stent

retriever do not interact with the thrombus. This procedure aims to prevent thrombus loss during stent retrieval. The stent retriever and the aspiration catheter are both removed as a vacuum locked unit. (1, 113)

2.4.6 Efficacy of Mechanical Thrombectomy in Trials

In 2013, the *New England Journal of Medicine* published three randomized controlled trials that questioned the efficacy of mechanical thrombectomy: the IMS III (Interventional Management of Stroke III), the SYNTHESIS EXPANSION (Local Versus Systemic Thrombolysis Versus for Acute Ischemic Stroke), and the MR RESCUE (MR and Recanalization of Stroke Clots Using Embolectomy) trials. This was the first time that a randomized controlled study design directly compared endovascular treatment to standard IV-rtPA treatment. Because of severe limitations in their study design, all three trials failed to prove the superiority of mechanical thrombectomy versus standard IV rt-PA treatment. In particular, criticism focused on the unsystematic selection of patients and prolonged time windows (7 hours for IMS III, 8 hours for MR RESCUE) and outdated MT devices. All three trials utilized first-generation devices known for achieving lower recanalization rates and secondary outcome benefit, instead of deploying second-generation devices (see TREVO 2 and SWIFT trials above). Nowadays, first-generation devices have been rendered obsolete. Furthermore, large vessel occlusion was not specified as an eligibility criterion in the IMS III and SYNTHESIS EXPANSION trials, and the availability of CT angiography was restricted at the time. (13, 60, 114-117)

Conducted in 2014, the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) trial was as an open-label, phase III, randomized controlled trial employing second-generation stent retrievers. MR CLEAN is often referred to as a “pivotal” trial because it led to a paradigm shift in favor of MT procedure. (118)

The following five randomized controlled trials are often referred to as the **“**big five**”** in scientific literature:

1) MR CLEAN was the first trial in a randomized controlled setting to prove the efficacy of MT with second-generation stent retrievers, compared to standard treatment alone. Specifically, MR CLEAN compared the outcome of intra-arterial treatment within 6 hours of symptom onset as adjunctive treatment to standard treatment (standard patient care +/- IV rt-PA) alone. (73, 118) Because of MR CLEAN’s breakthrough results, four other trials were terminated early: (73, 91, 92)

2) ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times), (5)

3) SWIFT PRIME (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke), (119)

4) EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits – Intra-Arterial), and (120)

5) REVASCAT (Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within 8 Hours of Symptom Onset). (121)

All of the “big five” used neuroimaging techniques (CT and/or CTA, MRA) to select patients with large vessel occlusion in the anterior circulation, mainly located in the terminal internal carotid artery (ICA) and M1-segment of the middle cerebral artery (MCA). Second-generation stent retrievers were utilized in all five trials. (73) In particular, second-generation stent retriever devices were deployed in more than 80% of the cases in the MR CLEAN and ESCAPE trials. The remaining 20% received intra-arterial treatment. The other trials used stent retrievers as obligatory inclusion criterion. Most patients (in all five trials) received thrombolytic medication IV rt-PA before randomization. Implementing even stricter criteria, the EXTEND IA and SWIFT PRIME trials included only those patients who had received IV rt-PA before randomization. (5, 73, 118-121)

With a total of 500 patients selected, MR CLEAN randomized the largest number of patients and is considered the most extensive of all five trials. With only 70 patients, the EXTEND-IA trial had the lowest number of cases, selected from age 18 upwards. The median age for all five trials reached 68 years. The MR CLEAN, ESCAPE and EXTEND-IA trials did not set any upper age limits, while the SWIFT PRIME and REVASCAT trials only included patients from 18 to 80 years of age. The lowest limit for the NIHSS score differed greatly in all trials: ranging from 2 (MR CLEAN) to 8 (SWIFT PRIME). Pooled data from all five trials resulted in a baseline NIHSS score of 17. (5, 73, 118-121)

A time window of 6 hours from symptom onset to procedure time was implemented for the MR CLEAN, EXTEND-IA and SWIFT PRIME trials. In contrast, REVASCAT had an extended time frame of 8 hours and ESCAPE an even longer period of 12 hours. Despite the prolonged time windows, the median time from stroke onset to groin puncture ranged from 210 to 269 minutes in all five trials. (5, 73, 118-121)

Primary outcome was defined by an mRS score of ≤ 2 after 90 days. In the MR CLEAN trial, 32.6% of the patients achieved primary outcome, compared to 19.1% for the control group (OR 1.67, 95% confidence interval (CI), 1.21 to 2.30, $P < .05$). (118) The other four trials also reported a significant improvement in long-term functionality.

A meta-analysis from the HERMES (Highly Effective Reperfusion Using Multiple Endovascular Devices) collaboration (3) which was funded by Medtronic and published in *The Lancet* in 2016, summarized the results of the MR CLEAN, ESCAPE; EXTEND-IA, SWIFT PRIME and REVASCAT trials. According to the HERMES collaboration, an mRS score of ≤ 2 after 90 days was achieved in 46% of the cases for the interventional group (MT), compared to 26.5% of the cases for the standard group (Best medical care including IV rt-PA, if indicated); (OR 2.35; 95% CI 1.85 to 2.98; P < .0001). Thus, mechanical thrombectomy more than doubles the odds in favor of a higher functional outcome (3, 73) at 90 days. Furthermore, stent retrieval benefitted patients with prolonged time windows > 300 min, patients who were ≥ 80 years of age, and patients unable to receive IV rt-PA (adjusted OR 2.49; 95% CI 1.76 to 3.53; P < .001). Recanalization rates, defined as mTICI scores of ≥ 2b, ranged from a minimum of 58.7% (MR CLEAN) to a maximum of 88.0% (SWIFT PRIME). The mortality rate at 90 days decreased by 11.4% for the EXTEND-IA trial and 8.6% for the ESCAPE trial. However, mortality rates in the other trials remained similar for both the control and interventional groups. Additionally, there was no significant difference concerning complications such as sICH and parenchymal hematoma. (3, 73, 122)

In summary, all five trials confirmed the superiority of mechanical thrombectomy with stent retrievers versus standard IV rt-PA treatment alone. Moreover, these studies demonstrated that mechanical thrombectomy combined with IV rt-PA provides the best treatment in terms of safety and efficacy for AIS patients. This was highlighted by the low NNT scores, ranging from 3.2 (EXTEND IA) to 7.1. (MR-CLEAN). (73) In comparison, the NNT for IV rt-PA treatment alone, depending on the time window, ranks from 10 at 3 hours after AIS symptom onset to 50 beyond 4.5 hours after AIS onset. Thus, mechanical thrombectomy has become the state of the art treatment for AIS patients. (1) Table 7 compares the study designs and outcome parameters of the MR CLEAN, ESCAPE, EXTEND-IA, SWIFT-PRIME and REVASCAT trials.

TABLE 7

Trials	*MR CLEAN*	*ESCAPE*	*EXTEND-IA*	*SWIFT PRIME*	*REVASCAT*	*THERAPY*	*THRACE*
Region	Netherlands	UK, US, Canada, S. Korea, Ireland	Australia, New Zealand	US, Europe	Spain	US	France
Number of centres	16	22	10	39	4	4	26
N (patients) ***N (CG/IA)***	500 (267/233)	315 (150/165)	70 (35/35)	196 (98/98)	206 (103/103)	108 (54/54)	412 (208/204)
BASELINE CHARACTERISTICS							
Age range in years	≥ 18	≥ 18	≥ 18	18-80	18-80	18-85	18-80
NIHSS range	≥ 2	> 5	n.s.	8-29	≥ 6	≥ 8	10-25
Control group (CG)	BMM (+/− IV rt-PA)	BMM (+/− IV rt-PA)	IV rt-PA	IV rt-PA	BMM (+/− IV rt-PA)	IV rt-PA	IV rt-PA
Intervention group (IG, IA)	IAT	IAT	Solitaire	Solitaire	Solitaire	Penumbra	MT
Use of stent retriever	81.5%	86.1%	100%	100%	100%	0%	n.s.
Time window	0-6h	0-12h	0-6h	0-6h	0-8h	0-4.5h	0-5h
Neurological inclusion criteria	n.s.	Barthel Index of ≥ 90	n.s.	mRS ≤ 2	mRS ≤ 1		
Neuroimaging techniques	CT/CTA	CT/CTA/ CTA Multi-phase for collaterals	CT/CTA/ CTP for mismatch	CT/CTA/ MRA/MRP/ CTP	CT/CTA/ MRA-DSA	CT/CTA	CT/CTA
Occlusion site	ICA, M1, M2, A1, A2	ICA, M1	ICA, M1, M2	ICA, M1, M2	ICA, M1	MCA	ICA, M1, M2, BA
Infarct core perfusion	n.s.	NCCT, CBV or CBF ASPECTS ≥ 6	Core < 70 ml, mismatch > 1.2	Core < 50 ml, mismatch > 1.8, NCCT ASPECTS ≥ 6	ASPECTS ≥ 7 (NCCT) ASPECTS ≥ 6 (DWI)	Clot length ≥ 8 mm	n.s.
AIS onset to puncture	260 min	241 min	210 min	224 min	269 min	226 min	255 min
Baseline NIHSS [Median (IQR)]; CG vs. IA	18 (14-22) vs. 17 (14-21)	17 (12-20) vs. 16 (13-20)	13 (9-19) vs. 17 (13-20)	17 (13-19) vs. 17 (13-20)	17 (12-19) vs. 17 (14-20)	n.s.	17 (13-20) vs. 18 (15-21)
Median ASPECTS CG/IA	9/9	9/9	n.s.	9/9	8/7	n.s.	n.s.
Patients with IV rt-PA CG/IA	91/87	79/73	100/100	100/100	78/68	100/100	100/100

Trials (continued)	*MR CLEAN*	*ESCAPE*	*EXTEND-IA*	*SWIFT PRIME*	*REVASCAT*	*THERAPY*	*THRACE*
Primary outcomes	mRS at 90 days	mRS at 90 days	Reduction in perfusion lesion vol., NIHSS ≥ 8 reduction or mRS ≤ 1 at day 3	mRS 0-2 at 90 days	mRS at 90 days	mRS at 90 days	mRS at 90 days
mRS ≤ 2 at 90 days % CG vs. IA	19.1 vs. 32.6, P < .05	29.3 vs. 53, P < .001	40 vs. 70, P = .001	35.5 vs. 60.2, P < .001	28.2 vs. 43.7	30.4 vs. 38	42.1 vs. 54.2
Improvement in mRS ≤ 2 at 90 days	13.5%	23.7%	31.4%	24.7%	15.5%	7.6%	12.1%
sICH risk (%); CG vs. IA	6.4 vs 7.7 P > .05	2.7 vs. 3.6 P > .05	5.7 vs. 0 P > .05	3.1 vs. 0 P = .12	1.9 vs. 1.9 P > .05	11.3 vs. 10.9	2 vs. 2 P = .71
Mortality (%); CG vs. IA	22.1 vs. 21 P > .05	19 vs.10.4 P = .04	20 vs. 8.6, P > .05	12.4 vs. 9.2 P > .05	15.5 vs. 18.4 P = .06	23.9 vs. 12	13 vs. 12 P = .70
Decrease in mortality at 90 days	1.1%	8.6%	11.4%	3.2%	2.9%	11.9%	1%
mTICI ≥ 2b	58.7%	72.4%	86.2%	88.0%	65.7%	n.s.	n.s.
Complete recanalization neuroimaging 24-27 h later; CG vs. IA	68/207 (33%) vs. 141/187 (75%)	n.s.	15/35 (43%) vs. 33/35 (94%)	21/52 (40%) vs. 53/64 (83%)	n.s.	n.s.	n.s.
Brain infarction volume at 24h (mean, 95% CI); CG vs. IA	79 mL (34-125) vs. 49 mL (22-96), P < .01	n.s.	n.s.	35 mL (0-407) vs. 32 mL (0-503), P = .09	39 mL (12-87) vs. 16 mL (8-59), P = .02	n.s.	n.s.
NNT	7.1	4.2	3.2	4.0	6.3	13.2	8.3

Table 7. Comparison of endovascular trials regarding the efficacy of mechanical thrombectomy. *This table was adapted from Bhaskar et al., 2018 (73). Study design and outcome parameters. Note abbreviations (ACA = anterior cerebral artery (A1, A2); ASPECTS = Alberta Stroke Program Early CT Score; BA = basilar artery; BMM = best medical management; CG = control group; CTA/CTP = computed tomography angiography/perfusion; DSA = digital subtraction angiography; DWI = diffusion-weighted imaging; IA(T) = intra-arterial treatment group; ICA = internal carotid artery; IG = interventional group; IV rt-PA = intravenous thrombolysis; MCA = middle cerebral artery (M1, M2); mRS = modified Rankin scale; MRA/MRP = magnetic resonance angiography/perfusion; mTICI = modified treatment in cerebral infarction; N = number; NCCT = non-contrast cerebral computed tomography; NIHSS = National Institutes of Health Stroke Scale; ns. = not specified; sICH = symptomatic intracerebral hemorrhage).*

2.4.7 Indications and Guidelines

Mechanical thrombectomy is recommended for patients with large vessel occlusion in the anterior circulation, specifically the ICA and M1-MCA segments. It has been debated whether mechanical thrombectomy in accordance with best medical management (BMM) would benefit patients with occlusions in the M2-segment. Among the “big five” trials, MR CLEAN and EXTEND IA both included M2-occlusions in their study design. Other trials such as EASI, PISTE and THRACE also followed this example. However, the number of patients was relatively small in the subgroup with M2-occlusions (total = 71/962; 7.4%). (1) A meta-analysis by Saber et al., 2018 (123) reviewed the efficacy of mechanical thrombectomy in M2-occlusions, indicating recanalization rates of 81% and improved long-term functional outcome of 59% (mRS score of $\leq$ 2 after 90 days). There was no difference between M1 and M2-occlusions, regarding recanalization rates (TICI 2b/3: 84.2% vs. 84.9%) and mortality rates (18.5% vs. 15.8%), respectively. However, it was suggested that the risk of symptomatic intracerebral hemorrhage was significantly higher for M2 than M1-occlusions (15% vs. 4.7%, respectively). In addition, there was no difference regarding recanalization rates and long-term functional outcome between stent retriever and aspiration devices in M2-occlusions. (1, 123) According to the ESMINT expert opinion, mechanical thrombectomy should be performed in M2-occlusions because most randomized controlled trials added M2-occlusions to their study design. (1) Due to the lack of randomized controlled trials until recently, it has been uncertain whether mechanical thrombectomy can benefit AIS patients with occlusions in the posterior circulation – such as the basilar artery, vertebral arteries and posterior cerebral arteries. (1, 33)

The efficacy of proximal balloon guide catheters (BGC) alongside mechanical thrombectomy has not been proven in a randomized controlled setting. However, a recent meta-analysis by Brinjikji et al., 2018 (124) comprised five non-randomized controlled trials (post-hoc SWIFT-Prime, post-hoc NASA registry, post-hoc-STRATIS registry, post-hoc TRACK registry and single-center retrospective trials), which examined the effect of proximal balloon protection on the MT success rate during stent retrieval. Using BGC resulted in a significant improvement of long-term functional outcome (59.7% for BGC vs. 43.8% for non-BGC, $P < .01$; mRS $\leq$ 2 at 90 days); an increase in first-pass recanalization (78.9% for BGC vs. 67.0% for non-BGC, $P < .01$; TICI 2b/3), and a reduction of mortality rates (13.7% BGC vs. 24.8% for non-BGC, $P < .01$; mortality endpoint not specified). In addition, overall procedure times were 20 minutes shorter. Moreover, it has been suggested that using proximal balloon protection during mechanical thrombectomy can significantly reduce the rate of distal embolization by establishing proximal antegrade flow arrest. (1, 124)

In the past, mechanical thrombectomy was performed within 6 hours after AIS symptom onset. Meanwhile, new research indicates that this time frame can be extended up to 24 hours, which has now become the new standard. (33, 37) In 2018, the *New England Journal of Medicine* published two multicenter, randomized controlled trials that investigated the efficacy of mechanical thrombectomy beyond the standard 6-hour time frame: the DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) and the DEFUSE-3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) trials. (55, 56, 125, 126) The DAWN trial expanded the time window for mechanical thrombectomy up to 24 hours after initial AIS symptom onset and the DEFUSE-3 trial up to 16 hours. (55, 125, 126) Patients who fulfilled imaging selection criteria and presented a large vessel occlusion in the ICA and proximal MCA (M1) were considered eligible to receive mechanical thrombectomy. The DAWN trial selected patients according to the infarct core volume, depending on the patient's age and NIHSS score. The DEFUSE-3 trial considered a larger infarct core than the DAWN trial (70 ml), but also evaluated the perfusion mismatch score (perfusion CT or MRI) and penumbra volume (15 ml) as eligibility criteria. (55, 56, 125, 126) Table 8 summarizes patient selection criteria and results of the DAWN and DEFUSE-3 trials.

Trials	***DAWN (126)***	***DEFUSE-3 (56)***
Inclusion criteria	➢ 80 years NIHSS ≥ 10 Infarct volume < 21 ml ➢ < 80 years NIHSS ≥ 10 Infarct volume < 31 ml ➢ < 80 years NIHSS ≥ 20 Infarct volume 31 ml to < 51 ml	➢ Infarct volume ≤ 70 ml ➢ Mismatch volume ≥ 15 ml (penumbra) ➢ Mismatch ratio ≥ 1.8 (penumbra/infarct core)
Region	US, Canada, Europe, Australia	US
Number of centers	26	38
N (patients)	206 (107 IG vs. 99 CG)	182 (92 IG vs. 90 CG)
Occlusion site	M1-MCA, ICA	M1-MCA, ICA
Time window	**6-24h of symptom onset**	**6-16h of symptom onset**
Neuroimaging techniques	CTP and MRI (DWI)	
Neuroimaging modalities	➢ Ischemic core volume ➢ Vessel occlusion site ➢ Mismatch volume is not a required inclusion criterion	➢ Ischemic core volume ➢ Vessel occlusion site ➢ Mismatch volume ≥ 15 ml ➢ Mismatch ratio ≥ 1.8
	Only Trevo stent retrievers	All FDA-approved devices allowed
	Funded by Stryker	Funded by the National Institute of Health
Outcome parameters		
	IG vs. CG	***IG vs. CG***
mRS ≤ 2 at 90 days	49% vs. 13%, posterior probability of superiority > .999; NNT = 3	45% vs. 17%, P < .001; NNT = 4
Mortality at 90 days	19% vs. 18%, P = 1.00	14% vs. 26%, P = .05
sICH	6% vs. 3%, P = .50	7% vs. 4%, P = .75

Table 8. The DAWN and DEFUSE-3 trials. *Study design and outcome parameters. (55, 56, 125, 126) Note abbreviations: (CG = control group; CTP = computed tomography perfusion; DWI = diffusion-weighted imaging; FDA = Food and Drug Administration; ICA = internal carotid artery; IG = interventional group; MCA = middle cerebral artery; MRI = magnetic resonance imaging; mRS = modified Rankin scale; N = number; NIHSS = National Institutes of Health Stroke Scale; NNT = number needed to treat; sICH = symptomatic intracerebral hemorrhage).*

Both trials were stopped prematurely after positive interim analysis. Results indicated that the time window can be extended beyond 6 hours, if strict perfusion imaging criteria are met to determine the remaining salvageable brain tissue. In both trials, the interventional group benefited from MT procedure achieving higher rates of long-term functional outcome, defined as mRS ≤ 2 at 90 days. The primary outcome was blinded for both trials. While overall 90-day mortality remained consistent for both the interventional and control groups in the DAWN trial, the DEFUSE-3 trial showed improved mortality rates for the interventional group. The rate of sICH did not differ greatly between the interventional and control group for both the DAWN and DEFUSE-3 trials. (125, 126)

Despite the evidence supporting extended time windows for mechanical thrombectomy, the ESMINT guidelines rate the recommendations as moderate. (1) Since most patients in both trials had experienced either a wake-up stroke or unwitnessed stroke, the actual time onset could not be assessed accurately; this includes 88% of patients for the DAWN trial and 64% for the DEFUSE-3 trial. It cannot be excluded that AIS occurred within the 6-hour time window. (1) In addition, not all stroke units are equipped with the necessary imaging tools to determine the eligibility. A recent retrospective study (127) indicated that out of 2,667 patients with AIS, only 1.1% of patients met both DAWN and DEFUSE-3 criteria; and 2.7% met either DAWN and/or DEFUSE-3 criteria. Furthermore, one-third of AIS patients who were considered eligible for DAWN were regarded as ineligible for DEFUSE-3. (127) This might bring into question the arbitrarily chosen imaging selection criteria and strict cut-off levels. Interestingly, the DAWN trial was funded by Stryker Neurovascular, (Kalamazoo, Michigan, USA) employing only TREVO stent retriever devices. This could have impacted the results; at this point a certain bias and commercial interest cannot be excluded. The DEFUSE-3 trial was sponsored by the National Institute of Health and employed all FDA-approved devices. In conclusion, mechanical thrombectomy within a 6 to 16-hour time window is a viable option and should be carefully considered, if eligibility criteria for DAWN and DEFUSE-3 are met (IA-recommendation according to the American Stroke Association) (33). Mechanical thrombectomy is also recommended 16 to 24 hours after symptom onset, if the DAWN criteria are fulfilled (IIa-BR recommendation). However, the number of patients who qualify is limited and not every stroke unit is properly equipped with the required imaging analysis software. (1, 33)

3 Materials and Methods

3.1 Catheter Model Setup

Through experimental research and in vitro model testing, a distal access catheter model – featuring a funnel-shaped tip – was compared to a standard cylindrically-shaped tip in terms of functionality and efficacy during simulated MT procedure. Two introducer sheaths were modified to create the funnel tip and standard tip catheter models (4 French (F) Radifocus Introducer II Standard Kit; TERUMO International Systems, Leuven, Belgium). For this purpose, the tapered tip of each sheath was removed. To develop the funnel-shaped tip, one sheath was manually dilated to a diameter of 2.5 mm with an awl. For the standard tip, the other sheath was cut to a diameter of 1.5 mm, comparable with commercially available DACs. (2)

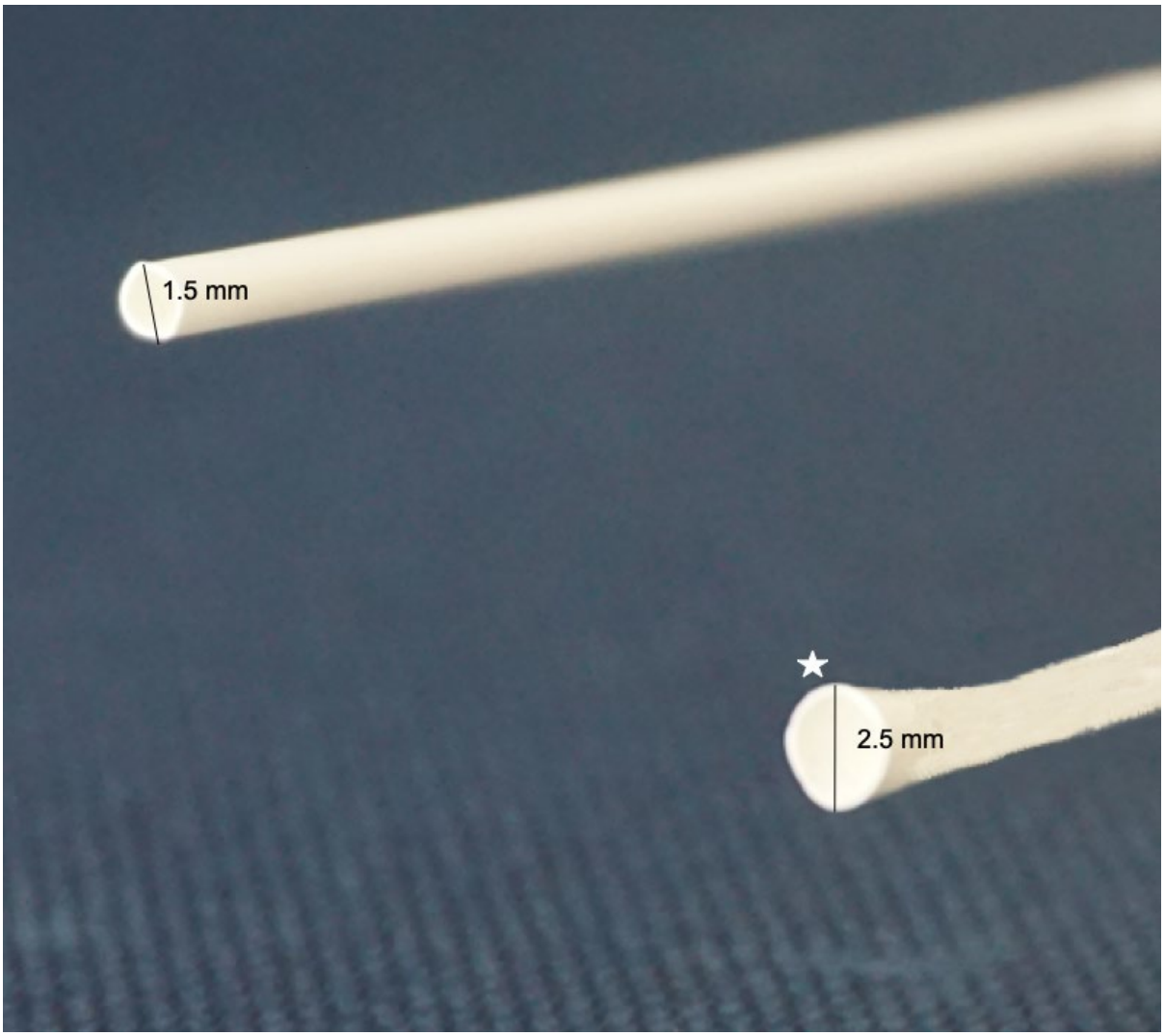


Figure 9. The funnel-shaped tip *(indicated by the asterisk)* ***features a larger opening diameter*** *(ID = 2.5 mm),* ***compared to the standard tip*** *(ID = 1.5 mm). Adapted from Tanyildizi et al. (2)*

3.2 MCA Model

Mechanical thrombectomy was performed in vitro using a MCA vasculature model of the M1-segment (inner tube diameter 3.0 mm, length 16 cm). The M1-MCA model was constructed from an IV line blood transfusion kit (CODAN, Medizinische Geräte GmbH & Co KG, Lensahn, Germany) and attached to the shortened 3 cm end of a 9 French introducer sheath for gaining access. (2) The location of the M1-segment is shown in the circle of Willis, Figure 10 below. Prior to each MT experiment, the model was flushed with 40% aqua-glycerol solution (Glycerin 85%; Caesar & Lorenz GmbH, Hilden, Germany) to simulate blood-like viscosity as a non-Newtonian fluid. (2, 128) The M1-MCA model is shown in Figure 11.

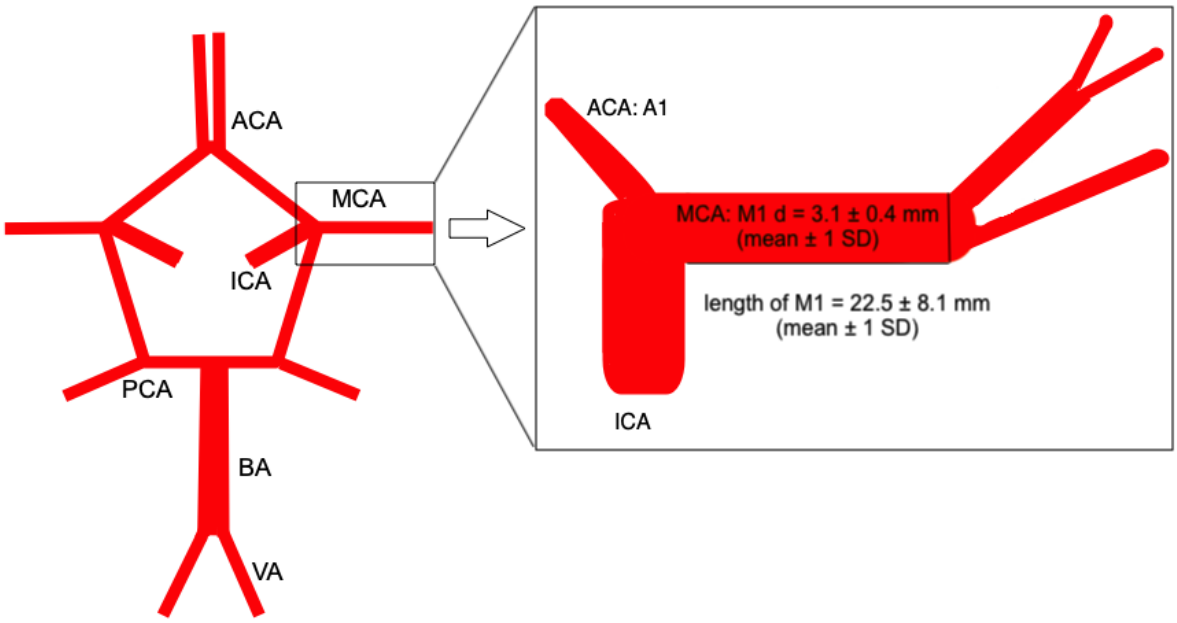


Figure 10. Circle of Willis and close-up of M1-segment of the middle cerebral artery. *The MCA model used for the experiments is based on the anatomical measurements of the M1-segment. The location of the M1-segment within the circle of Willis is indicated. The M1-MCA segment is schematically enlarged. ACA (anterior cerebral artery; ICA (internal carotid artery); PCA (posterior cerebral artery); BA (basilar artery); VA (vertebral artery).*

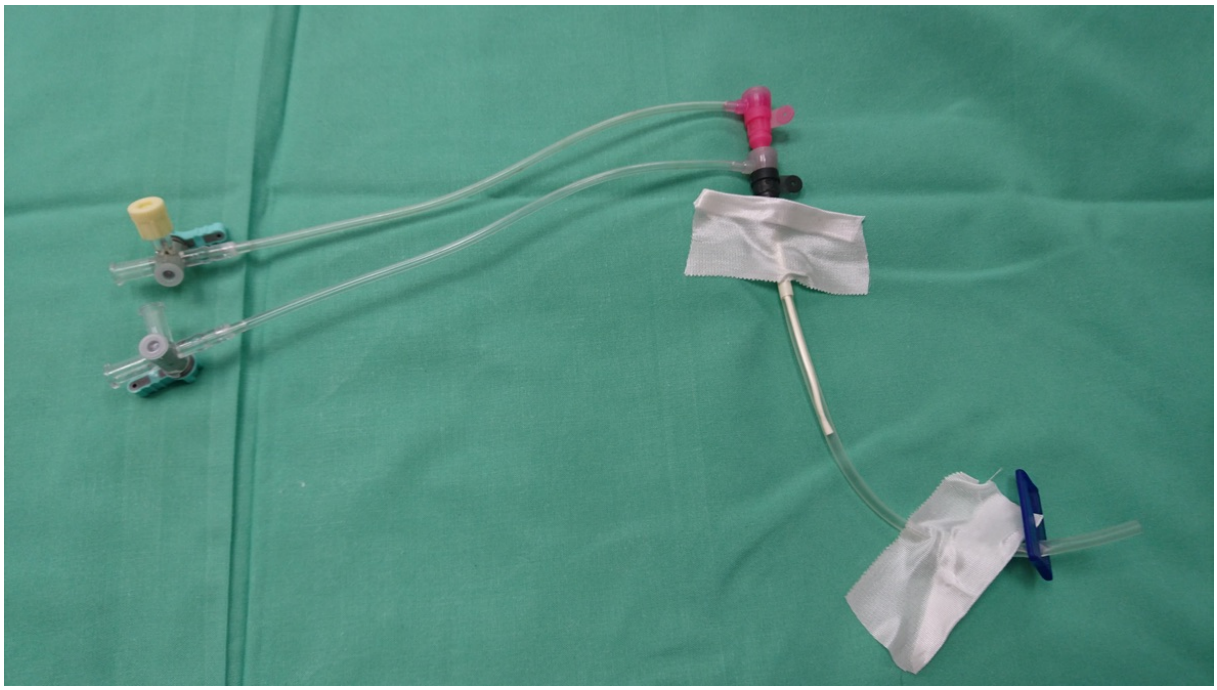


***Figure 11. MCA model of the M1-segment constructed from a PVC tube**. The funnel-shaped tip (4 French, pink sheath) is inserted into the MCA model (9 French, black sheath).*

3.3 Generation of Thrombus Material

Blood from five pigs was used to generate thrombi for the MT experiments and histopathological analyses. Research was conducted in accordance with all applicable international, national and/or institutional guidelines for the care and use of animals, including the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines. Specifically, the research project was examined by an ethical committee and approved (reference number 23 177-07/G 14-1-094) by the responsible local government authority (Landesuntersuchungsamt Rheinland-Pfalz, Germany), in accordance with the German Animal Welfare Act (Tierschutzgesetz). (2)

Venous whole blood was extracted before sacrificing the pigs, in accordance with the above mentioned animal welfare regulations and procedures. Polyvinyl chloride (PVC) tubes (clear PVC tubing, inner diameter 8.0 mm, outer diameter 12.0 mm; Thermo Scientific Fischer, Waltham, Massachusetts, USA) were half-filled with blood, and the ends of the tubes were connected using a silicone cuff. (2)

Two methods were employed for generating thrombi: mechanical preparation using a Chandler loop device (Chandler loop System, Neuffen, Germany) and clot preparation under static conditions. The Chandler loop simulated physiological blood circulation under dynamic conditions in a standardized setting. For this purpose, a temperature-controlled water basin was preheated to 38.5 °C. The PVC tubes containing porcine blood were placed in the loop cradle and rotated at 15 rpm (see Figure 12). (2) The “moving column of blood” (129, 130) coagulated after 20 to 30 minutes.

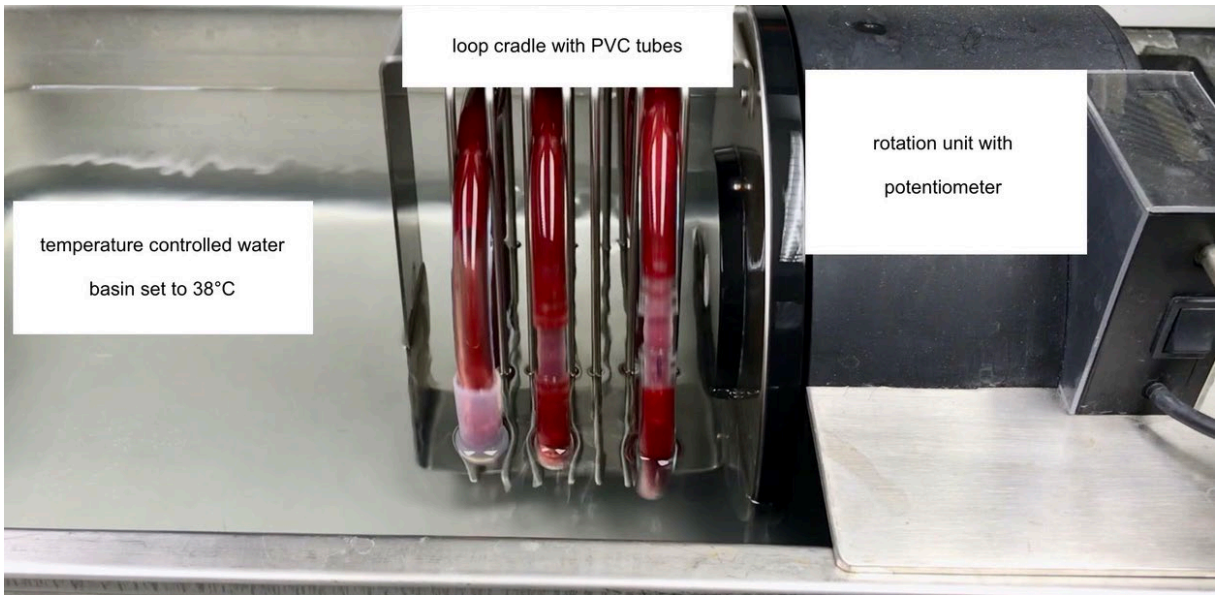


Figure 12. Mechanical preparation with a Chandler loop. *The PVC tubes are rotated at 15 rpm forming a “Moving column of blood”. (129, 130)*

Simultaneously, the thrombi processed under static conditions were prepared by hanging the PVC tubes vertically from a rod for 20 to 30 minutes at room temperature (see Figure 13).

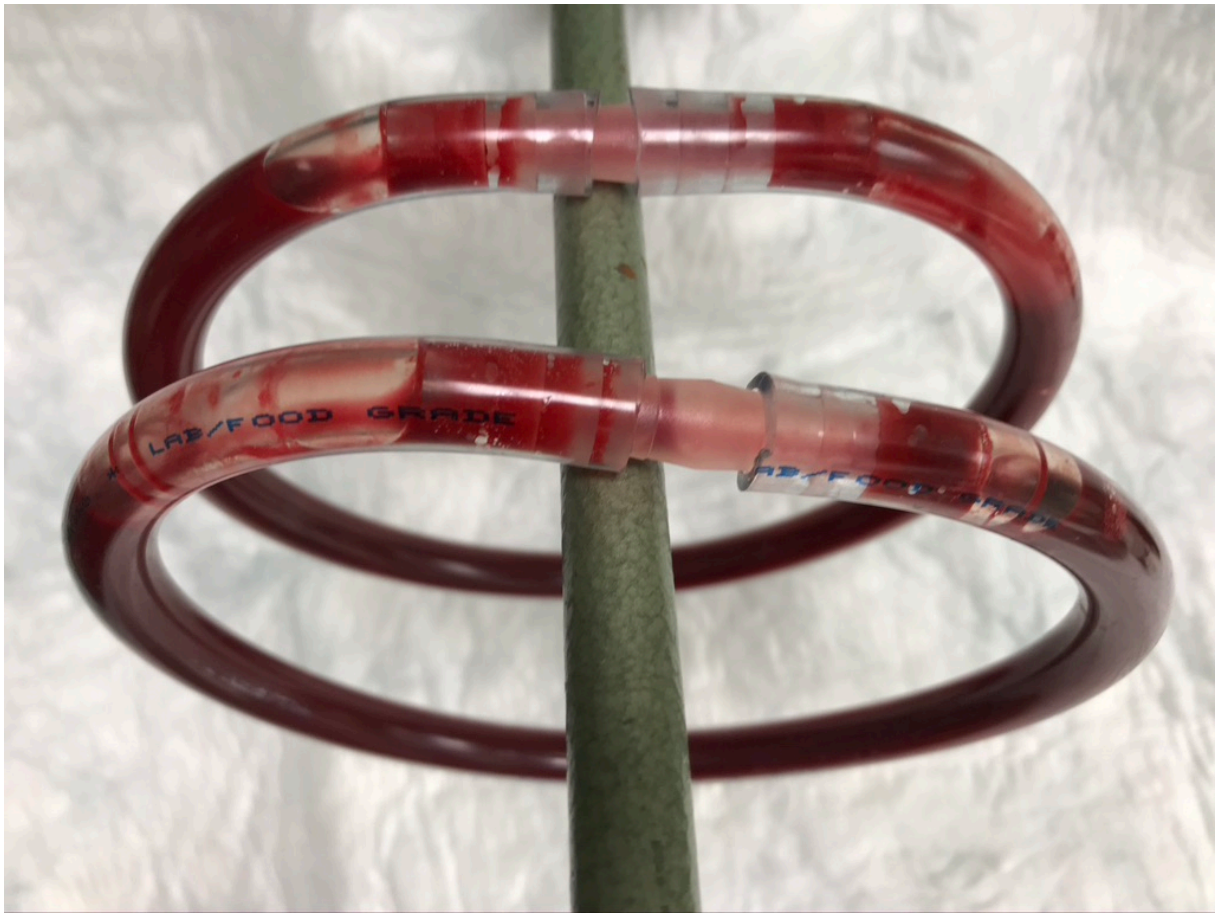


Figure 13. Thrombus preparation under static conditions

After blood coagulation within the PVC tubes, the clots from both preparation methods were removed from the tubes and refrigerated in saline solution at 10 °C. (2) Mechanical thrombectomy was performed either 0 to 24 hours or 72 hours after preparation of thrombi. Using an experimental in vitro setup, this study compared the efficacy of a funnel-shaped tip with a standard cylindrical tip in combination with four different clot types (mechanical vs. static preparation, 0 to 24h vs. 72h clot aging times) to assess the effect of different clot compositions on mechanical thrombectomy.

Prior to each experiment, the thrombi were cut equally into 20 mm long segments (see Figure 14 below).

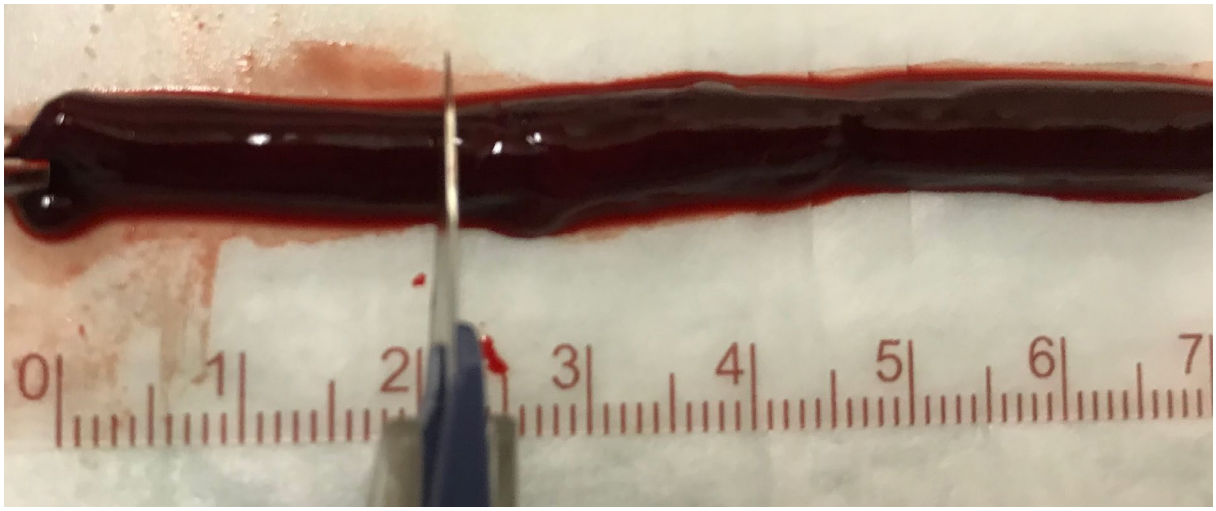


Figure 14. Dissection of thrombi into 20 mm segments.

3.4 Mechanical Thrombectomy Procedure

For each MT experiment, a fresh thrombus segment was positioned within the MCA model. Then, one of the catheter models (funnel-shaped tip; standard tip) was inserted at the proximal end of the thrombus. A microcatheter, containing one of the stent retrievers (Trevo XP Pro Vue 3/20 mm; Trevo XP Pro Vue 4/20 mm; Stryker, Kalamazoo, Michigan, USA), was introduced into the MCA model via the 9 French sheath and pushed through the thrombus. After penetrating the thrombus, one of the stent retrievers was slowly released out of the microcatheter over the thrombus. The stent retriever was deployed for 3 minutes, allowing the mesh to interact with the thrombus. Then, the stent retriever and the thrombus were slowly retracted into the model tip under aspiration using a vacuum pressure syringe (60 ml, VacLok, Vacuum pressure syringes; Merit Medical System). Aspiration was applied by turning the three-way stopcock attached to the vacuum pressure syringe, which was set in advance to a negative pressure at a volume of 40 ml. Mechanical thrombectomy was conducted using the primary combined approach, for both aspiration and stent retriever devices. (2) Experiments were performed under visual control using fluoroscopy and/or video monitoring. The experimental setup is depicted in Figures 15 and 16.

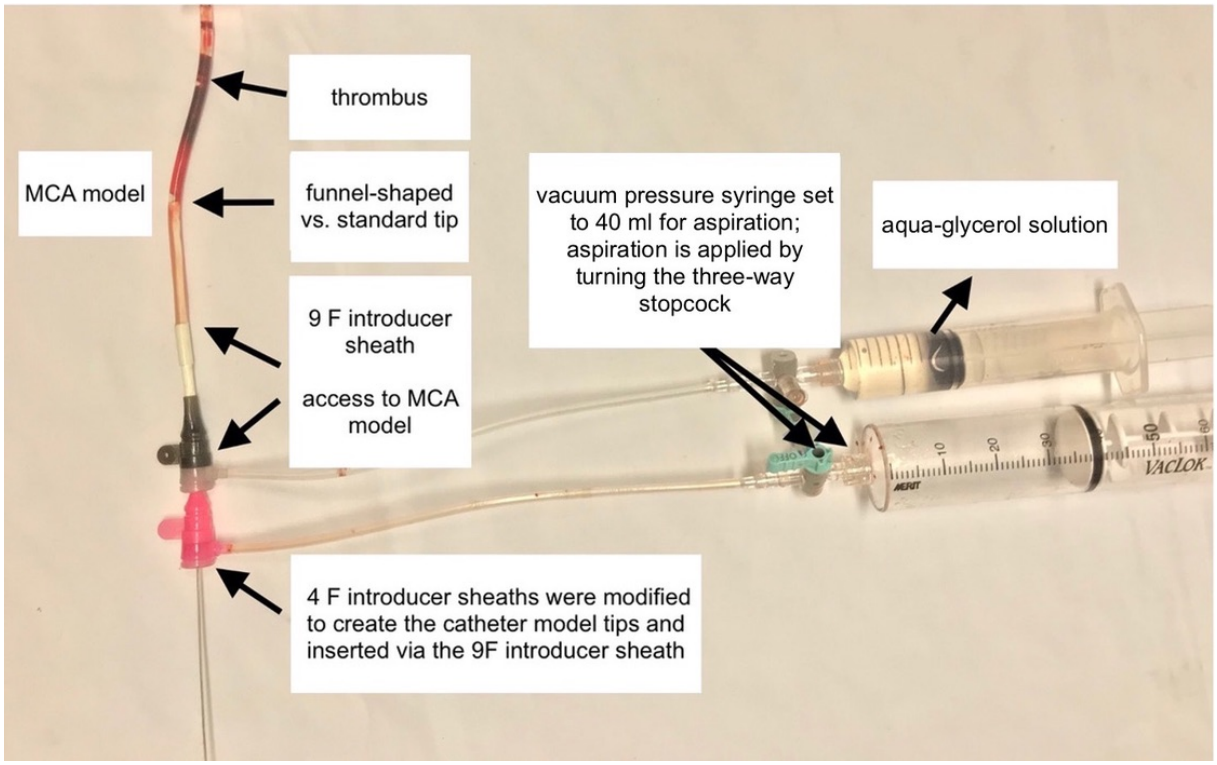


Figure 15. Experimental setup

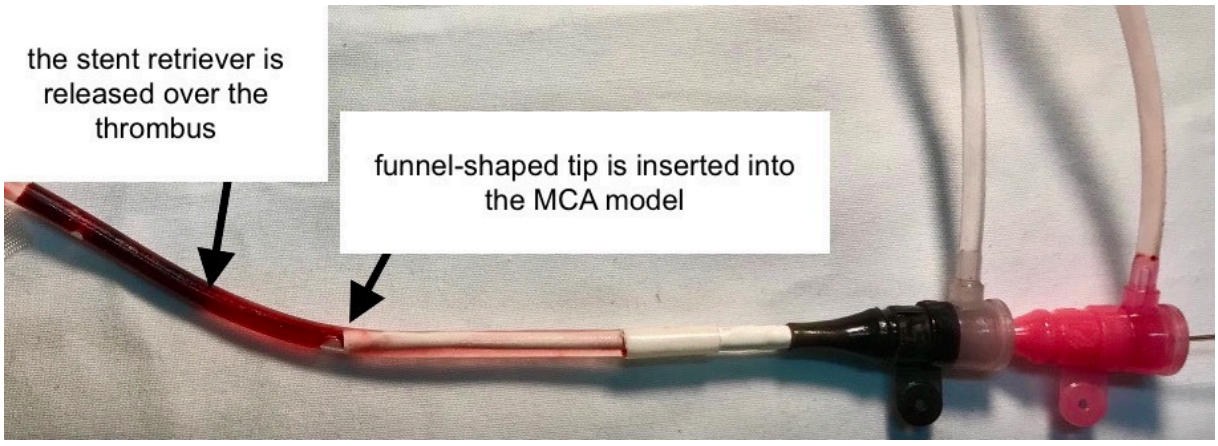


Figure 16. Close-up of the experimental setup during mechanical thrombectomy

The sequence of MT is shown in the fluoroscopy images below (Figure 17; Figure 18).

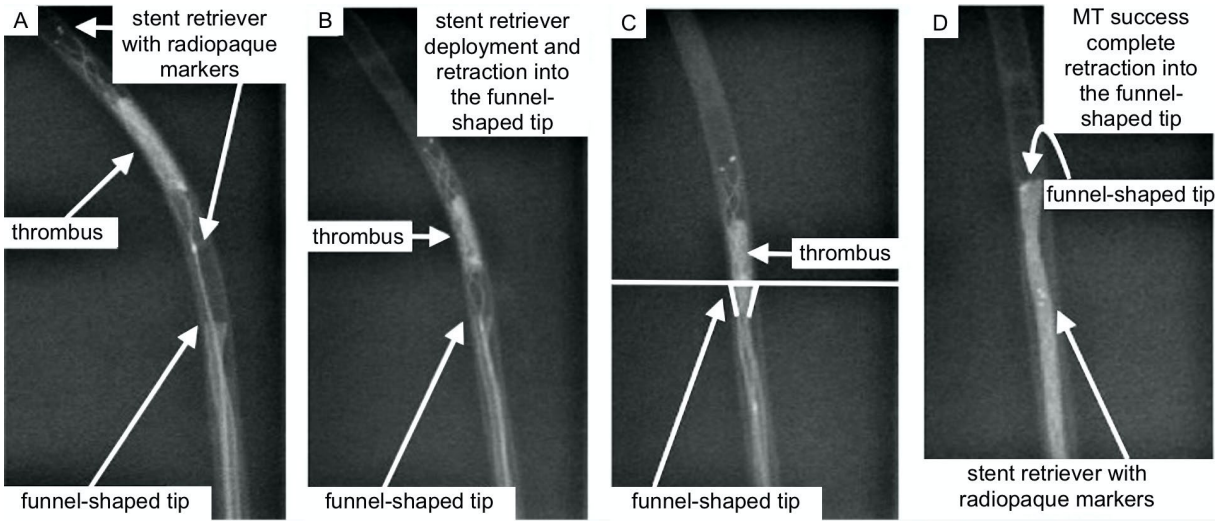


Figure 17. Fluoroscopy sequence. Mechancial thrombectomy (MT) performed with the funnel-shaped tip. *A (stent retriever release), B (stent retriever deployment); C (retraction into the funnel-shaped tip); D (MT success; complete clot removal). Adapted from Tanyildizi et al. (2)*

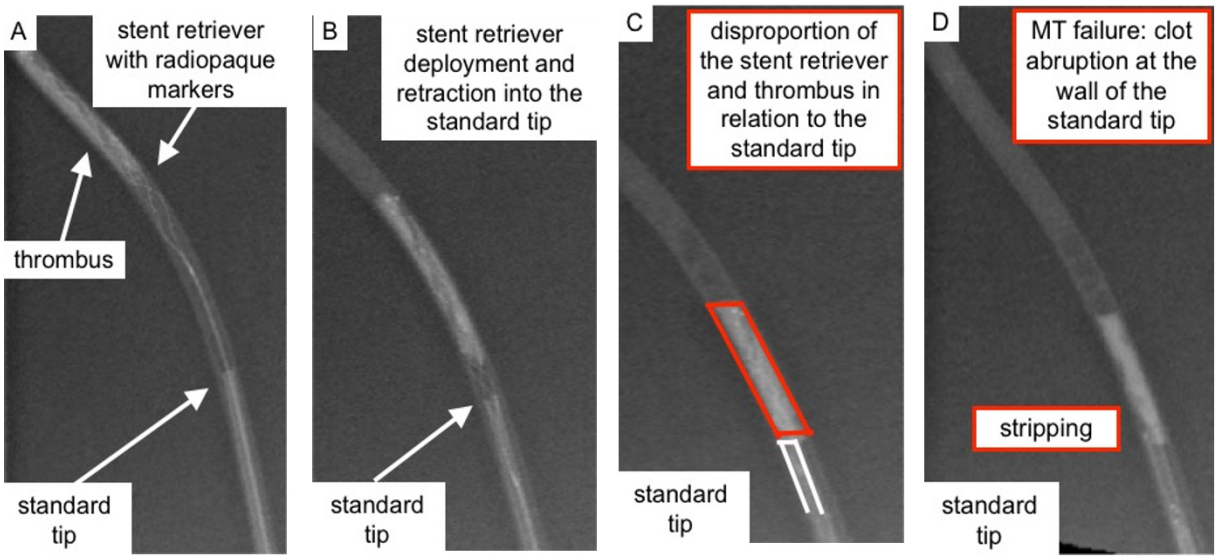


Figure 18. Fluoroscopy sequence. Mechanical thrombectomy (MT) performed with the standard tip. A (stent retriever release), B (stent retriever deployment); C (retraction into the standard tip); D (MT failure due to clot abruption at the tip). *Adapted from Tanyildizi et al. (2)*

The stent retriever and catheter model tips were removed out of the MCA model after every experiment, then cleaned and flushed for the next experiment (see Figure 19 below).

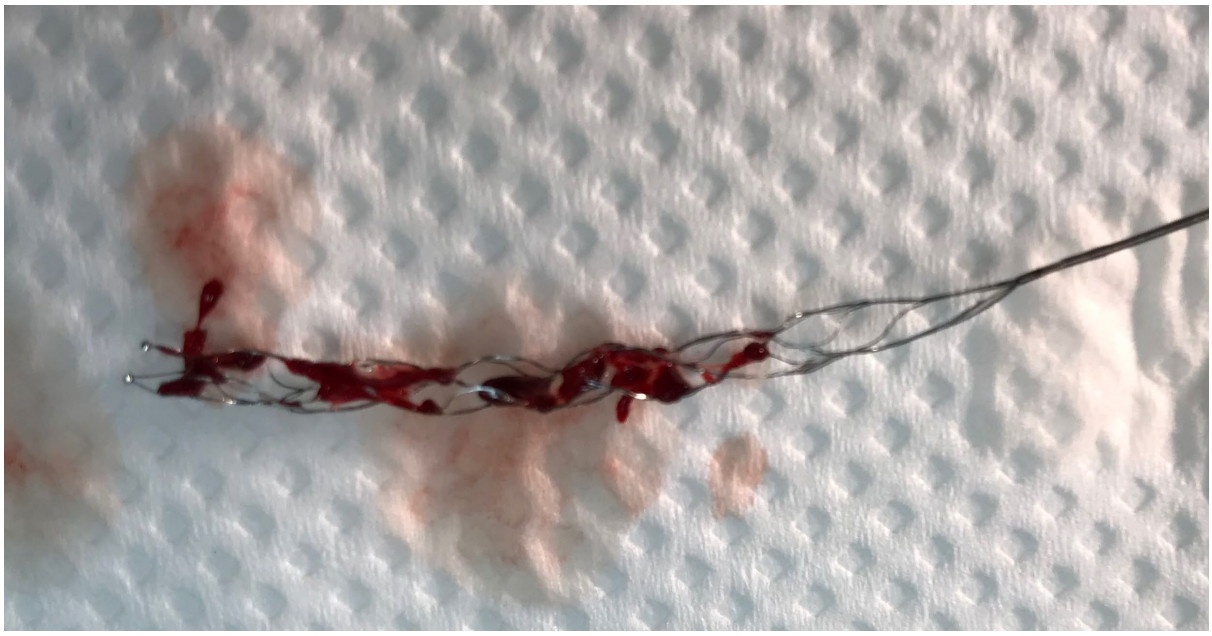


Figure 19. Stent retriever after removal

3.5 Histopathological Analyses

Histopathological analyses of fresh (0h) and aged (72h) thrombi, prepared with and without the use of a Chandler loop system, were performed after fixation of thrombi in 4% buffered formalin (Formaldehyde solution 4% buffered (PH 6.9); Merck KGaA, Darmstadt, Germany). The thrombi were stored in 50 ml polypropylene tubes (Cellstar Cellreactor Tube, 50 ml, PP, Greiner Bio-One International, Kremsmünster, Austria). Each tube was filled 1/3 with thrombi and 2/3 with formalin solution (see Figure 20). Time onset was defined as the removal of the thrombi from the PVC tubes.

Figure 20. Fixation of thrombi in 4% buffered formalin. *The tube was filled 1/3 with thrombi and 2/3 with formalin solution.*

After fixation, the thrombi were cut at 3 mm intervals. Following standard histopathological procedure, agar was heated in a microwave at 60 °C for two minutes until liquefied. The thrombus segments were then placed into the liquid agar for proper orientation and arranged sequentially the way they were cut. After the agar had cooled off, the solidification of the agar with its gel-like consistency held the thrombus segments in their position. The agar block with the embedded thrombi was cut into a square piece and placed into a standard tissue cassette (PrintMate, embedding cassette, Thermo Fisher Scientific, Waltham, Massachusetts, USA).

Generally, 6 thrombus segments were placed in one cassette, varying from 4 to 12 segments, depending on how much space was left in the cassette. The cassettes were then processed overnight in an automated tissue processor enabling dehydration and clearing. The tissue was then embedded in paraffin. The tissue blocks were sliced into 2 µm thick sections onto microscopic slides using a microtome, and stained with Masson trichrome (see Figure 21).

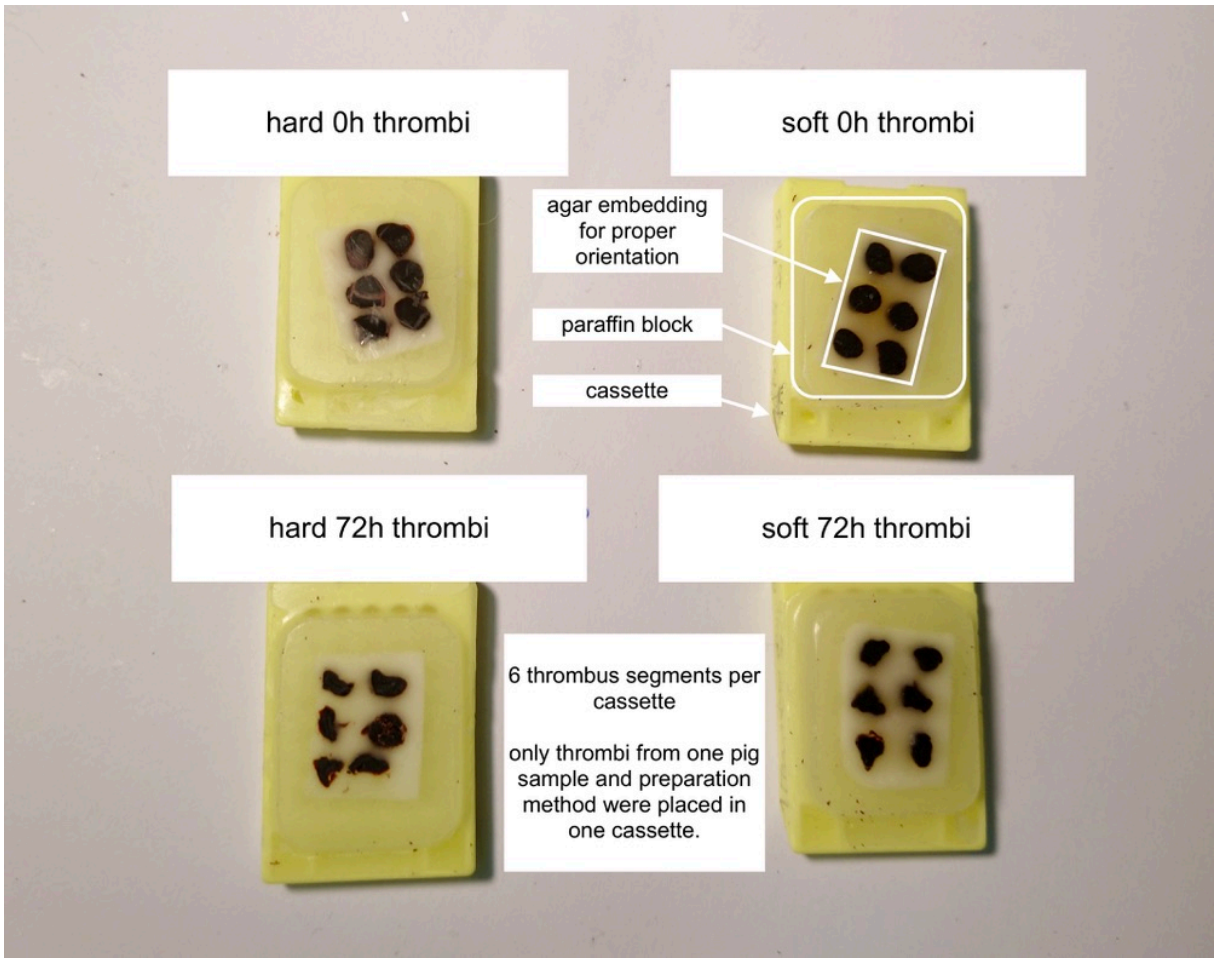


Figure 21. Histopathological processing. *The thrombus segments were cut at 3 mm intervals, placed in agar for proper orientation and embedded into paraffin. Samples of tissue cassettes for each clot type (hard clots: Chandler loop vs. soft clots: static preparation) are depicted.*

For enhanced visualization, the microscopic slides were scanned with Nanozoomer 2.0 HT (Hamamatsu), magnified 200-fold, and exported as TIFF files. To differentiate the exact fibrin distribution, pixel-by-pixel analysis was performed using Trainable Weka Segmentation Fiji plugin v3.2.27. (2, 131) To accomplish this, a training set of ten pictures cropped to 300 x 300 pixels was created and three classifiers were marked: fibrin, thrombus, and background. The classifier training process was repeated using a Hessian matrix filter in combination with a mean voxel distance calculation. (2, 131, 132) Images were further processed and transformed into grayscale images. A binary image with segmented particles, employing a noise tolerance value of 10, was generated. Two pathologists blinded to the sample groups (Chandler loop 0h; Chandler loop 72h; Static 0h; Static 72h) graduated each thrombus according to three different categories: fibrin pattern, distribution and outer fibrin rim. The category “fibrin pattern” was further specified as insular, reticular or no pattern. The distribution of fibrin was classified as

peripheral, central, both peripheral and central (regular), or irregular distribution, depending on the localization. The outer rim of fibrin (defined as circumferential layer of fibrin surrounding the thrombus) was divided into the subcategories total circumference of fibrin, focal or no rim. (2)

3.6 Statistical Analyses

For the MT experiments, statistical analyses were performed using Microsoft Excel 16.49 (Microsoft Inc., Redmond, WA) and GraphPad Prism 9.2 (GraphPad Software, Inc., San Diego, CA). The Pearson chi-square-test (X^2-test) was used to determine the statistical significance of categorial variables (contingency e.g., MT success; failure) involving an independent pair sample (e.g., funnel-shaped tip, standard tip). For histopathological analyses, SPSS Software 23.0 (IBM; New York, USA) was utilized. Multinomial logistic regression was used to assess the effect of independent variables (thrombus preparation and aging time) and their prediction of nominal outcome parameters (fibrin pattern, distribution and outer circumference). The p value threshold was set to $p < .05$ for all analyses. (2)

4 Results

4.1 Mechanical Thrombectomy Results

Mechanical thrombectomy (MT) was conducted 80 times for each catheter model (funnel-shaped; standard tip) using two stent retrievers (Trevo XP ProVue 3/20 mm; 4/20 mm) and four clot types (hard 0-24h; hard 72h; soft 0-24h; soft 72h), resulting in 10 procedures for each combination. The effects of two clot compositions (hard, mechanical preparation vs. soft, static preparation) and two clot aging times (0-24h vs. 72h) on mechanical thrombectomy were evaluated, resulting in 80 experiments for each clot composition and aging time. A total of 160 experiments were carried out. See Figure 22 for further differentiation.

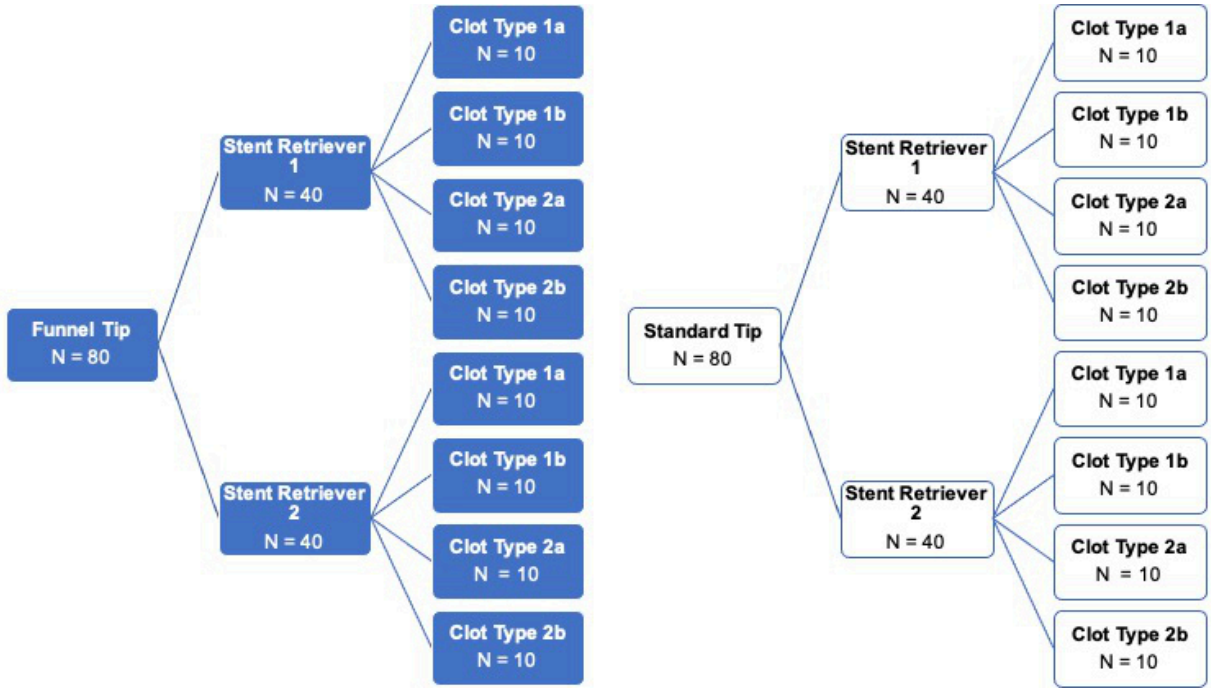


Figure 22. Flowchart of the MT experimental series. *Stent Retriever 1, Trevo XP ProVue Retriever 3 x 20 mm (Stryker); Stent Retriever 2, Trevo XP ProVue Retriever 4 x 20 mm (Stryker); Clot Type 1a, hard 0-24h; Clot Type 1b, hard 72h; Clot Type 2a, soft 0-24h; Clot Type 2b, soft 72h.*

The funnel-shaped catheter achieved successful first-pass recanalization in 56/80 (70.0%) cases, compared to the standard catheter with only 24/80 (30.0%) cases, regardless of the clot type and stent retriever (absolute difference, 32; relative difference 57.1%; $P < .001$), (see Figure 23 and Table 9).

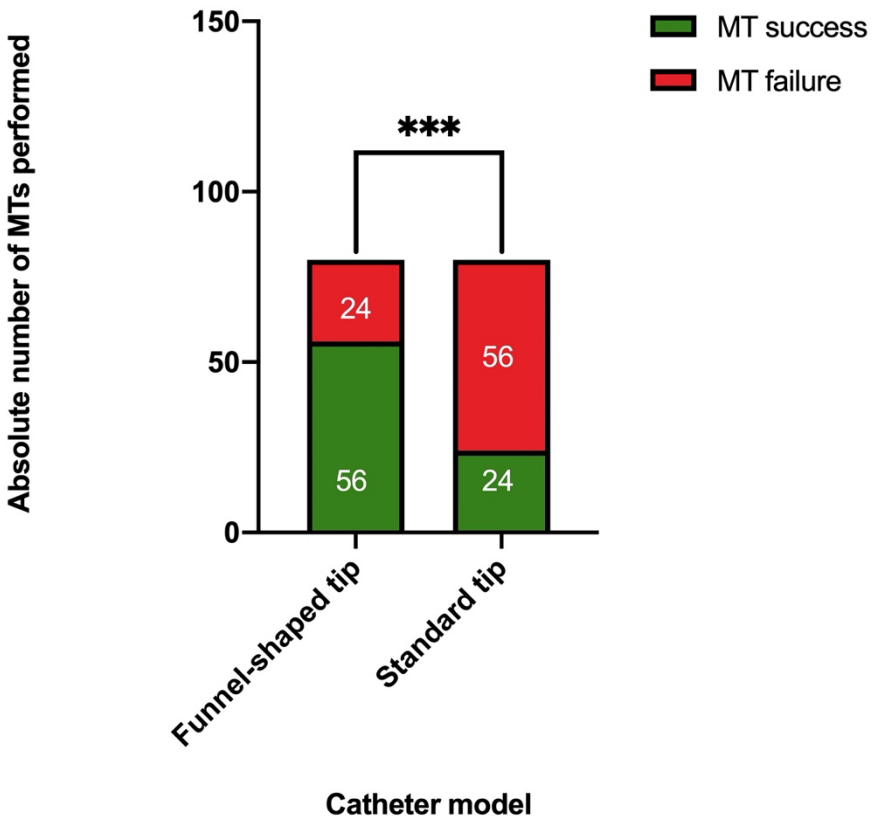


Figure 23. MT success rate for both catheter models. *The asterisk represents the level of significance (*** P < .001)*

	Catheter model		***Clot aging time***		***Clot composition***	
MT success rate	*Funnel-shaped*	*Standard*	*0-24h*	*72h*	*hard*	*soft*
N (success) / N (total = 80)	56/80 (70.0)	24/80 (30.0)	47/80 (58.8)	33/80 (41.3)	46/80 (57.5)	34/80 (42.5)
P value	*P < .001*		*P = .03*		*P = .06*	

Table 9. Summary of MT results. *Comparing two catheter models (funnel-shaped tip; standard tip); two clot aging times (0-24h vs. 72h) and two clot compositions (hard = mechanical preparation, Chandler loop vs. soft = static preparation) individually with the corresponding P values. MT success rate (in %).*

Failure causes for the funnel-shaped tip

The thrombus was lost in 11/24 (45.8%) MT failures before reaching the tip because the stent retriever failed to interact with the thrombus. Clot abruption at the tip caused 13/24 (54.2%) failures. Failure causes for both tips are shown in Figure 24.

Failure causes for the standard tip

Clot abruption at the standard tip led to 45/56 (80.4%) MT failures. The remaining 11/56 (19.6%) failures occurred after the stent retriever failed to interact with the thrombus during retraction, before reaching the tip.

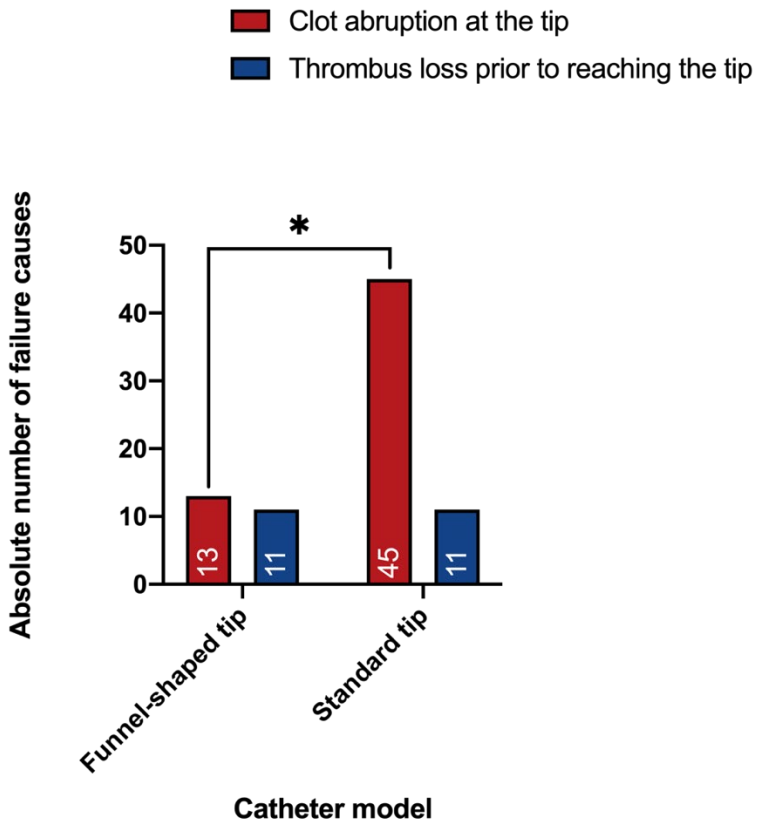


Figure 24. Causes of MT failure for both catheter models (funnel-shaped tip vs. standard tip). *The asterisk shows the level of significance (* P < .05).*

MT results for the different clot types

Mechanical thrombectomy performed with hard clots (Chandler loop, mechanical preparation) was successful in 31/40 (77.5%) cases for the funnel-shaped tip and 15/40 (37.5%) cases for

the standard tip (absolute difference, 16; relative difference, 51.6%; P < .05). Soft clots prepared under static conditions registered 25/40 (62.5%) successful MT cases for the funnel-shaped tip, and 9/40 (22.5%) successful MT cases for the standard tip (absolute difference, 16; relative difference, 64.0%; P < .05). (See Table 10). Regardless of the catheter tip, mechanical thrombectomy was successful in 46/80 (57.5%) cases for the hard clots (Chandler loop) and 34/80 (42.5%) cases for the soft clots (absolute difference 13; relative difference, 28.3%; P = .06). The recanalization rates for all clot types are shown in Figure 25 and in Tables 10 and 11.

Hard clots *N (success) / N (total)*	*Funnel-shaped tip*	*Standard tip*	*Funnel-shaped + Standard tips*	*P value*
0-24h	18/20 (90.0)	11/20 (55.0)	29/40 (72.5)	*P = .10*
72h	13/20 (65.0)	4/20 (20.0)	17/40 (42.5)	*P < .001*
0-24h + 72h	31/40 (77.5)	15/40 (37.5)	46/80 (57.5)	*P < .001*
P value	*P = .06*	*P = .02*	*P < .01*	

Hard clots total

N (success) / N (total) = 46/80 (57.5)

Table 10. MT results for both catheter models *(funnel-shaped tip; standard tip)* ***using hard clots*** *(mechanical preparation, Chandler loop) at different aging times (0-24h vs. 72h). MT success rate (in %).*

Soft clots *N (success) / N (total)*	*Funnel-shaped tip*	*Standard tip*	*Funnel-shaped + Standard tips*	*P value*
0-24h	13/20 (65.0)	5/20 (25.0)	18/40 (45.0)	*P = .03*
72h	12/20 (60.0)	4/20 (20.0)	16/40 (40.0)	*P* < .001
0-24h + 72h	25/40 (62.5)	9/40 (22.5)	34/80 (42.5)	*P* = .03
P value	*P = .74*	*P = .70*	*P = .65*	

Soft clots total

N (success) / N (total) = 34/80 (42.5)

Table 11. MT results for both catheter models *(funnel-shaped tip; standard tip)* ***using soft clots*** *(preparation under static conditions) at different aging times (0-24h vs. 72h). MT success rate (in %).*

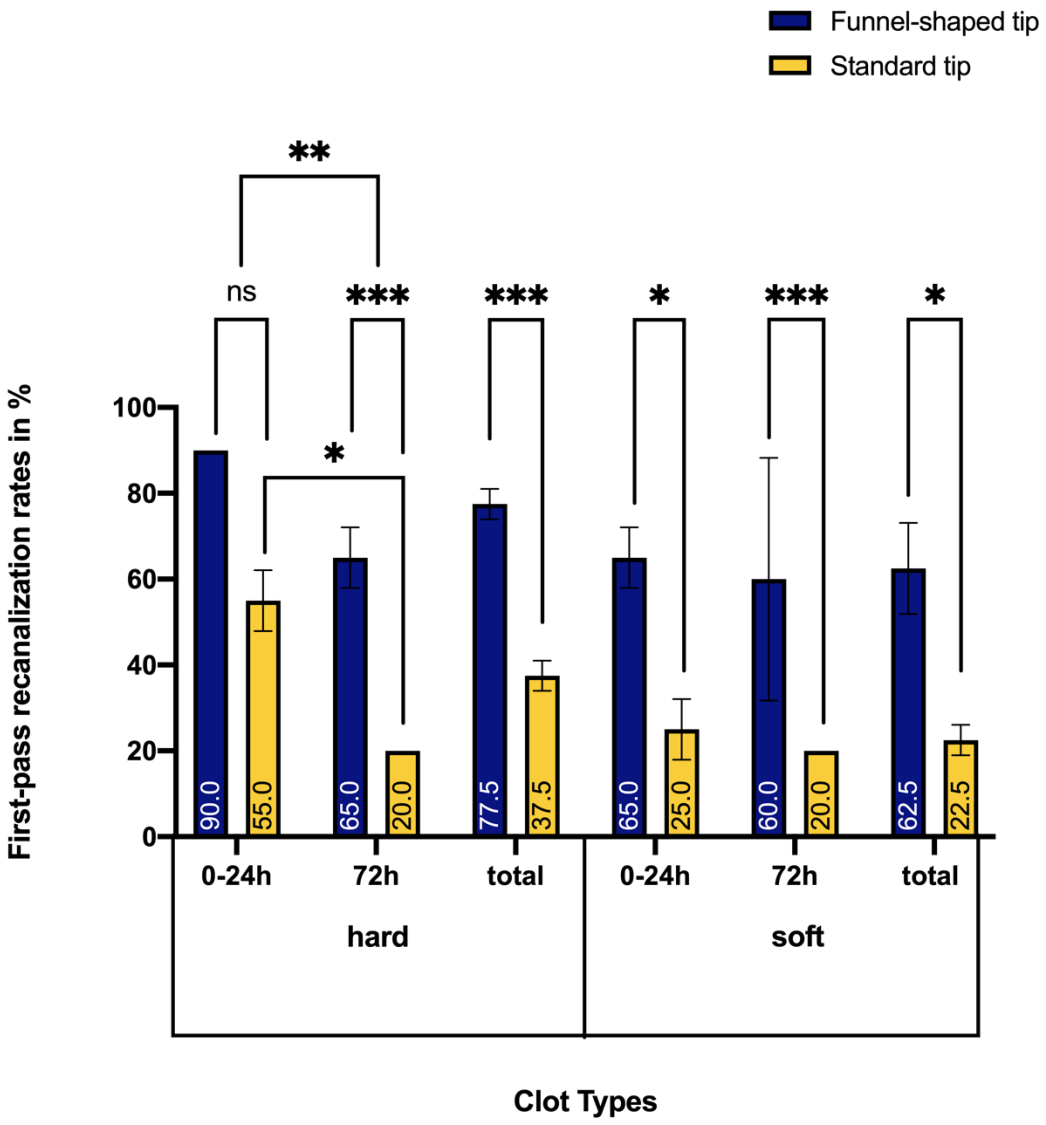


Figure 25. First-pass recanalization rates for four different clot types *(hard 0-24h; hard 72h; soft 0-24h; soft 72h). The asterisk symbols represent the levels of significance (ns = non-significant; * P < .05; ** P < .01; *** P < .001).*

MT failure causes using hard clots

For the funnel-shaped tip, thrombus loss before reaching the catheter tip during stent retriever retraction occurred in 6/9 (66.7%) cases when using hard clots (mechanical preparation, Chandler loop). In 3/9 (33.3%) cases mechanical thrombectomy failed due to clot abruption at the tip. For the standard tip, 21/25 (84.0%) failures resulted from clot abruption at the tip as the leading cause. In 4/25 (16.0%) cases the thrombus was lost before reaching the tip. There was no statistical significance regarding the failure causes for the different clot types for both preparation methods.

MT failure causes using soft clots

For the funnel-shaped tip, a total of 15/40 (37.5%) MT failures were registered when using soft clots prepared under static conditions. In 5/15 (33.3%) of these failures the thrombus was lost before reaching the tip, while 10/15 (66.7%) failures were caused by clot abruption at the tip. For the standard tip, 24/31 (77.4%) failures were associated with clot abruption at the catheter tip. The remaining 7/31 (22.6%) failures resulted from thrombus loss before reaching the tip. The distribution of MT failure causes for the different clot types are shown in Figure 26.

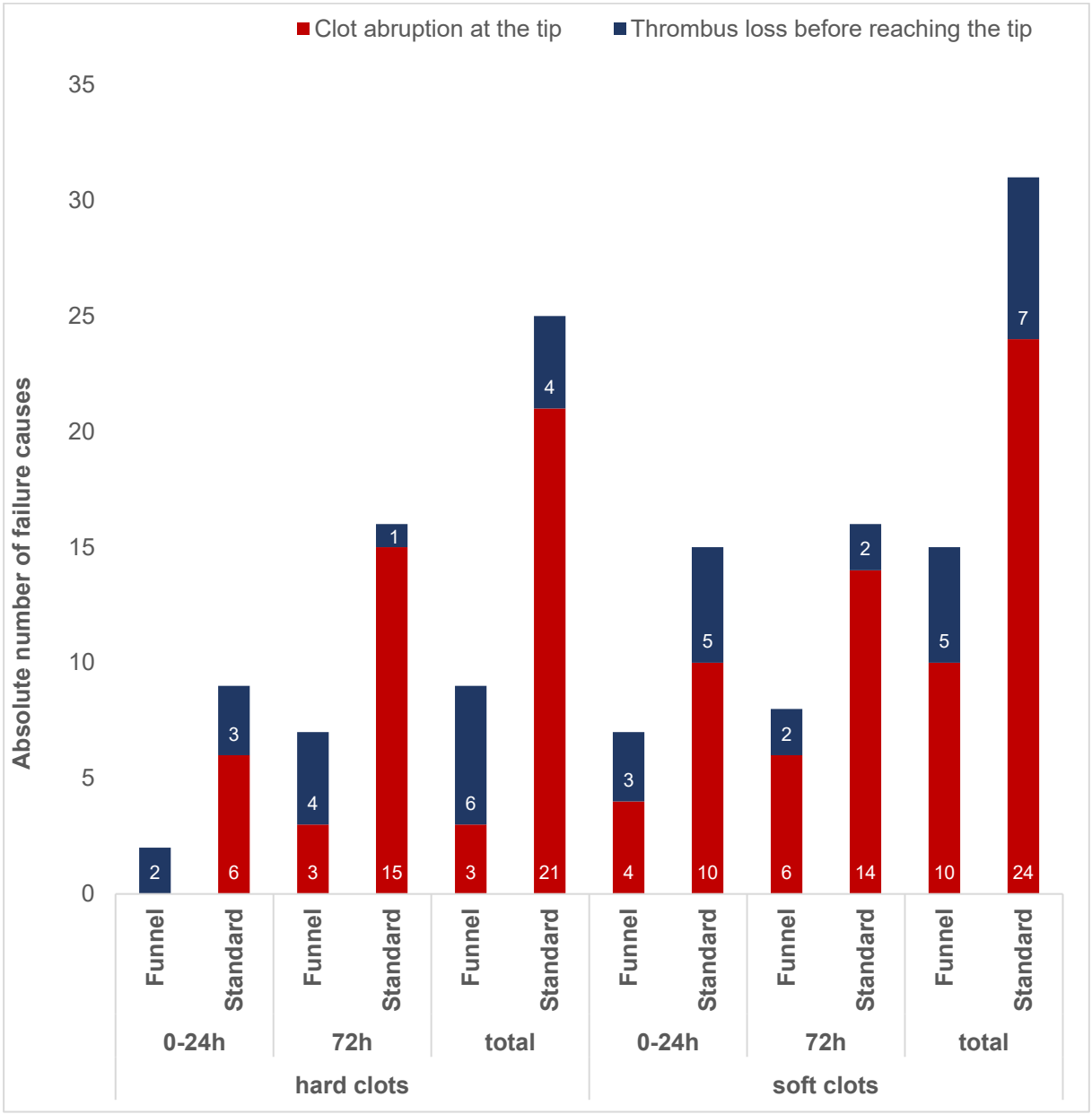


Figure 26. Distribution of failure causes for the different clot types*. There was no statistical significance regarding the failure causes for the different clot types.*

MT results for the different clot aging times

The funnel-shaped tip achieved 31/40 (77.5%) MT successes using 0 to 24-hour aged thrombi, in contrast to 25/40 (62.5%) MT successes for the 72-hour aged thrombi (absolute difference, 6; relative difference, 19.4%; P = .14). The standard tip attained 16/40 (40.0%) positive MTs for the 0 to 24-hour aged thrombi, versus 8/40 (20.0%) MT successes for the 72-hour aged thrombi (absolute difference, 8; relative difference, 50.0%; P = .05). Regardless of the thrombi preparation group and model tip, 0 to 24-hour aged thrombi achieved a greater MT success rate, totaling 47/80 (58.8%) positive MTs compared to 33/80 (41.3%) for the 72-hour aged thrombi (absolute difference, 14; relative difference, 29.8%; P < .05). The recanalization rates for the different clot aging times (0-24h vs. 72h) are shown in Table 12 and Figure 27.

Clot aging time *N (success) / N (total = 40)*	Funnel-shaped tip	Standard tip	*P value*
0-24h	31/40 (77.5)	16/40 (40.0)	P = .02
72h	25/40 (62.5)	8/40 (20.0)	*P < .001*
P value for both aging times	*P = .14*	*P = .05*	P = .03

***Table 12. MT results for both catheter models** (funnel-shaped tip; standard tip) **for two clot aging times** (0-24h vs. 72h). MT success rate (in %).*

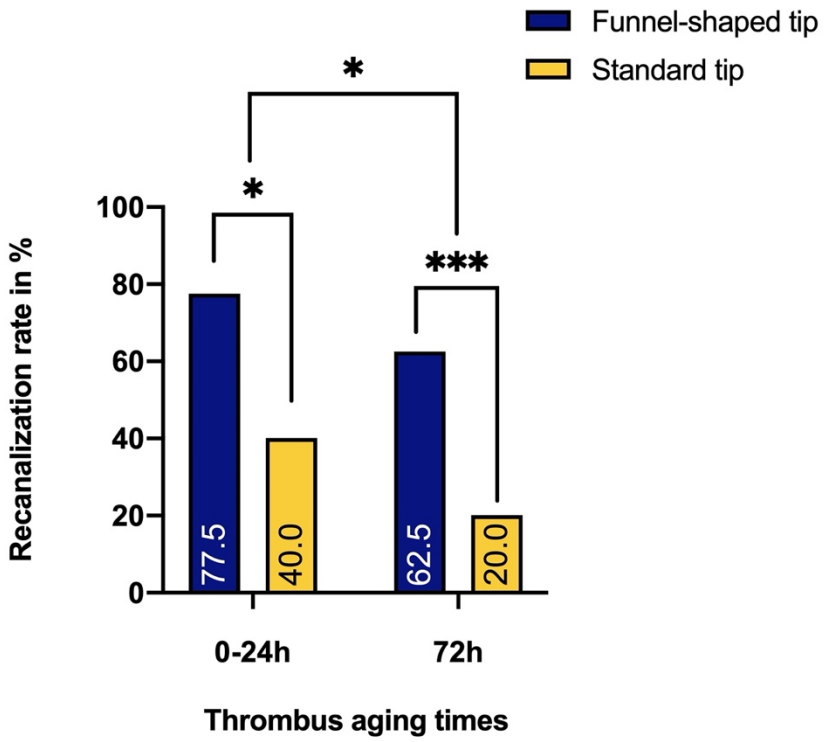


Figure 27. First-pass recanalization rates for different clot aging times. *The asterisk symbols indicate the levels of significance (* P < .05; *** P < .001).*

MT Results for the stent retriever types

Using the *Trevo XP ProVue Retriever 3 x 20 mm, m*echanical thrombectomy was successful 30/40 (75.0%) times for the funnel-shaped tip compared to 12/40 (30%) times for the standard tip (absolute difference, 18; relative difference, 60.0%; P < .001). Regarding the *Trevo XP ProVue Retriever 4 x 20 mm,* mechanical thrombectomy was successful in 26/40 (65.0%) times for the funnel-shaped tip versus 12/40 (30.0%) for the standard tip (absolute difference, 14; relative difference, 53.8%; P < .01). There was no significant difference in terms of improved recanalization rates regarding the size of the stent retriever. The smaller stent retriever Trevo XP ProVue Retriever 3 x 20 mm achieved a higher MT success rate of 30/40 (75.0%) for the funnel-shaped tip, versus the larger Trevo XP ProVue Retriever 4 x 20 mm which had 26/40 (65.0%) positive MTs (absolute difference, 4; relative difference, 10%; P = .33). In contrast, the standard tip showed no differentiation, with both retriever types recording 12/40 (30.0%) successful MTs. The *Trevo XP ProVue Retriever 3 x 20 mm* achieved an overall recanalization rate of 42/80 (52.5%) at first pass compared to 38/80 (47.5%) for the *Trevo XP ProVue Retriever 4 x 20 mm,* regardless of the tip *(*absolute difference, 4; relative difference, 9.5%; P = .53). MT results for the different stent retriever types are summarized in Table 13 and Figure 28.

Stent retrievers *N (success) / N (total = 40)*	Funnel-shaped tip	Standard tip	*P value*
Trevo XP ProVue Retriever *3 x 20 mm (Stryker)*	30/40 (75.0)	12/40 (30.0)	*P < .001*
Trevo XP ProVue Retriever *4 x 20 mm (Stryker)*	26/40 (65.0)	12/40 (30.0)	*P < .01*
P value for both stent retrievers	*P = .33*	*P = 1.00*	P = .53

Table 13. MT results for both catheter models *(funnel-shaped tip; standard tip)* ***using two stent retrievers*** *(Trevo XP ProVue Retriever 3 x 20 mm; Trevo XP ProVue Retriever 4 x 20 mm). MT success rate (in %).*

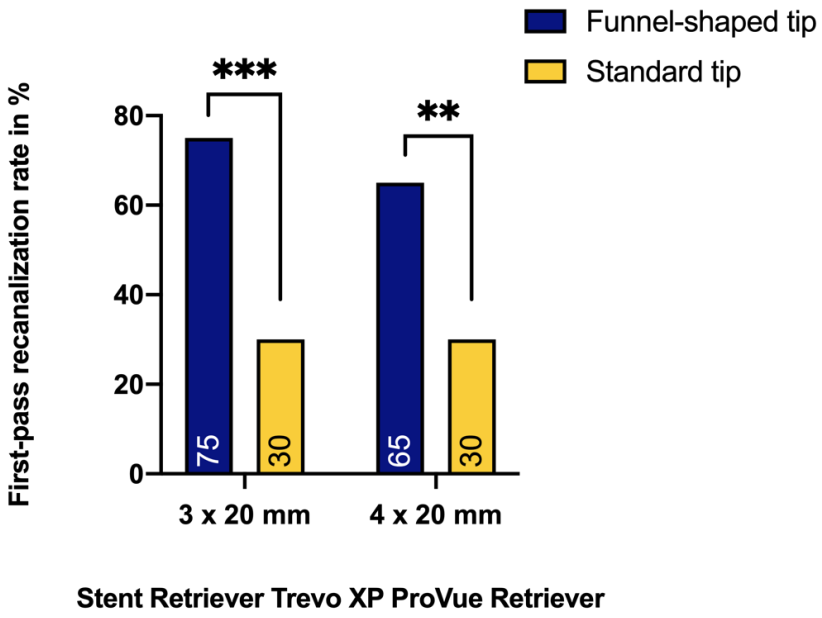


Figure 28. First-pass recanalization rates for two different stent retrievers. *The asterisk symbols represent the level of significance (** P < .01; *** P < .001).*

4.2 Results from the Histopathological Analyses

A total of 280 thrombus segments were included in the histopathological analyses. The thrombi were graduated according to three different categories: fibrin pattern, distribution and outer fibrin circumference. (See Materials and Methods, section 3.5. Histopathological Analyses for specification). Examples of different clot types are shown in Figure 29.

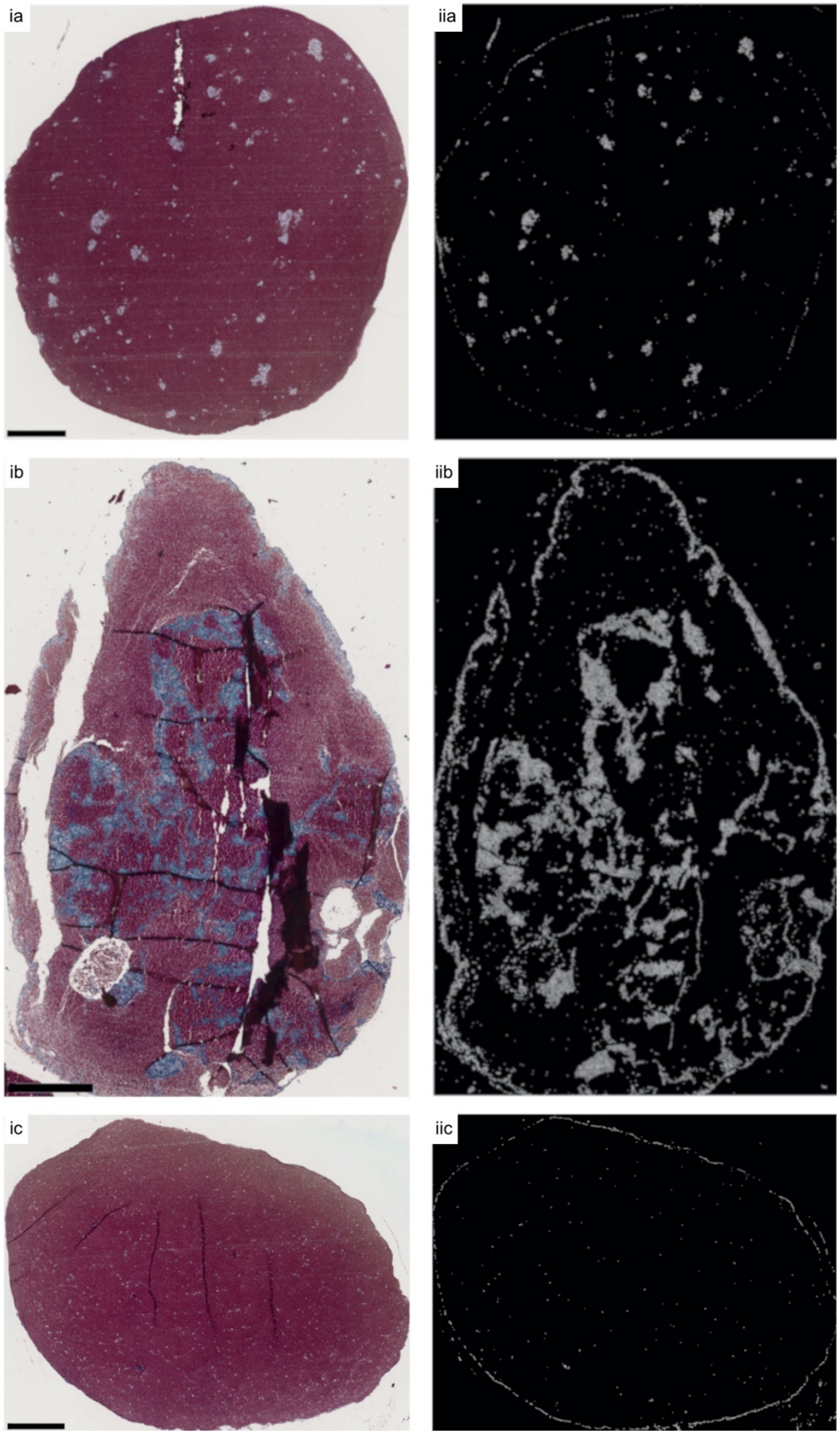


Figure 29. Thrombus graduation *before (i) and after (ii) segmentation calculation, grayscale image (ia, ib, ic. Masson-Goldner staining). All scale bars are set to 0.5 mm.*

a) An example of a hard 0-hour thrombus with an insular pattern (i, ii), a peripheral and central distribution of fibrin, and a total circumference of fibrin is demonstrated.

b) An example of a hard 72-hour thrombus with a reticulated pattern (i, ii), a peripheral and central distribution of fibrin, and a total circumference of fibrin is demonstrated.

c) An example of a soft 0-hour thrombus with the absence of a fibrin pattern (i, ii) is demonstrated. A total fibrin circumference is lacking. This thrombus type was predominant for the thrombi prepared under static conditions.

Histopathological results comparing hard versus soft clots

The harder clots (Chandler loop) displayed a reticular or insular fibrin pattern (total pattern: 83/107 vs. 32/173 cases, respectively; odds ratio, 15.2; 95% CI, 8.4 to 27.6; P < .05), and higher proportion and regular distribution of fibrin compared to the softer clots (static preparation), (total distribution: 56/107 vs. 20/173 cases, respectively; odds ratio (OR), 8.4; 95% CI, 4.6 to 15.3; P < .05). Comparing both clot aging times, an outer fibrin circumference was observed more frequently in the 72-hour aged clots than the 0-hour clots (circumference: 74/155 vs. 21/125 cases, respectively; odds ratio, 4.5; 95% CI, 2.6 to 8.0; P < .05). For further specification, see Table 14.

Histopathological results for the hard clots (0h + 72h)

Hard thrombi processed by a Chandler loop disclosed a fibrin pattern in 83/107 (77.6%) cases. The hard 0-hour thrombi had a fibrin pattern in 43/57 (75.4%) cases compared to the hard 72-hour aged thrombi with 40/50 (80.0%) cases. A regular distribution of fibrin was displayed in 56/107 (52.3%) of the thrombus segments, of which 26/57 (45.6%) could be attributed to the hard 0-hour thrombi and 30/50 (60.0%) to the hard 72-hour thrombi. An outer circumferential fibrin rim was found in 36/107 (33.6%) of the thrombus segments, with 19/107 (33.3%) for the hard 0-hour thrombi and 17/50 (34.0%) for the hard 72-hour thrombi. For further histopathological graduation, see Figure 30 and Table 14.

Histopathological results for the soft clots (0h + 72h)

Soft thrombi prepared under static conditions exhibited a fibrin pattern in 32/173 (18.5%) cases of which 6/68 (8.8%) cases belonged to the 0-hour soft thrombi and 26/105 (24.8%) cases to the 72-hour soft thrombi. A regular distribution of fibrin was present in 20/173 (11.6%) cases, with 3/68 (4.4%) cases for the 0-hour soft thrombi versus 17/105 (16.2%) cases for the soft 72-hour thrombi. An outer rim of fibrin was omitted (no rim) in 114/173 (65.9%) cases.

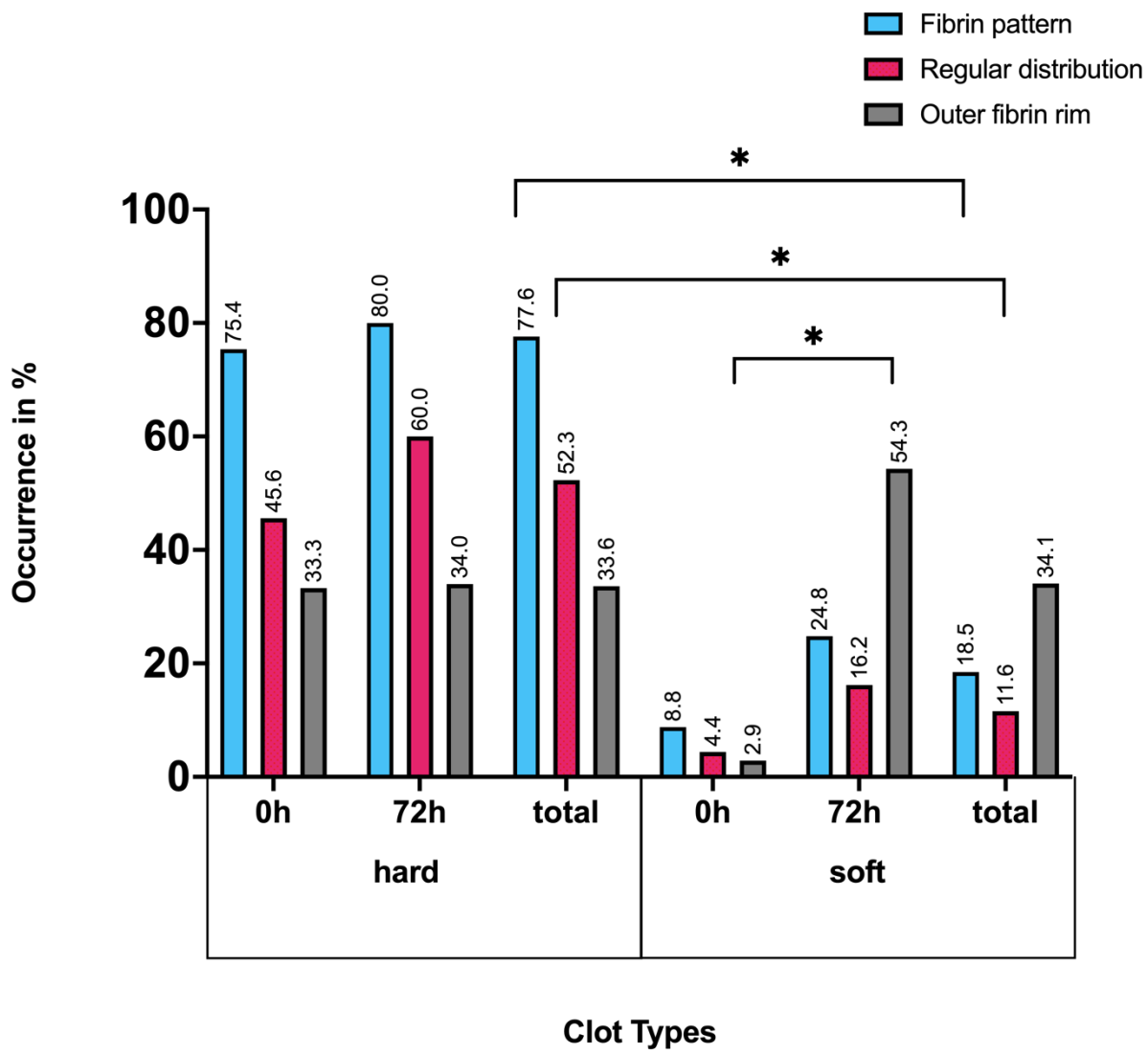


Figure 30. Histopathological analyses. *Percentage of thrombus segments presenting a regular fibrin distribution, a fibrin pattern and an outer fibrin rim. For simplification, the significance levels regarding the fibrin distribution and pattern were determined only for the total hard thrombi (mechanical preparation, Chandler loop) and total soft thrombi (static preparation) and within a preparation group, not for the individual clot types (* P < .05).*

Clot types	*Hard (Chandler loop)*			*Soft (static)*			*Aging times*	
	0h	**72h**	**0h + 72h**	**0h**	**72h**	**0h + 72h**	**0h**	**72h**
N_{Total}	57	50	107	68	105	173	125	155
Fibrin pattern absolute number of thrombus segments and amount (in %)								
Insular (a)	29 (50.9)	24 (48.0)	53 (49.5)	4 (5.9)	23 (21.9)	27 (15.6)	33 (26.4)	47 (30.3)
Reticular (b)	14 (24.6)	16 (32.0)	30 (28.0)	2 (2.9)	3 (2.9)	5 (2.9)	16 (12.8)	19 (12.3)
Pattern (a + b)	43 (75.4)	40 (80.0)	83 (77.6)	6 (8.8)	26 (24.8)	32 (18.5)	49 (39.2)	66 (42.6)
No Pattern (c)	14 (24.6)	10 (20.0)	24 (22.4)	62 (91.2)	79 (75.2)	141 (81.5)	76 (60.8)	89 (57.4)
Fibrin distribution absolute number of thrombus segments and amount (in %)								
Peripheral (d)	7 (12.3)	15 (30.0)	22 (20.6)	2 (2.9)	5 (4.8)	7 (4.0)	9 (7.2)	20 (12.9)
Central (e)	5 (8.8)	3 (6.0)	8 (7.5)	1 (1.5)	11 (10.5)	12 (6.9)	6 (4.8)	14 (9.0)
Central + Peripheral (f)	14 (24.6)	12 (24.0)	26 (24.3)	0 (0.0)	1 (1.0)	1 (0.6)	14 (11.2)	13 (8.4)
Regular (d + e + f)	26 (45.6)	30 (60.0)	56 (52.3)	3 (4.4)	17 (16.2)	20 (11.6)	29 (23.2)	47 (30.3)
Irregular (g)	31 (54.4)	20 (40.0)	51 (47.7)	65 (95.6)	88 (83.8)	153 (88.4)	96 (76.8)	108 (69.7)
Outer circumference absolute number of thrombus segments and amount (in %)								
Complete (h)	9 (15.8)	10 (20.0)	19 (17.8)	1 (1.5)	49 (46.6)	50 (28.9)	10 (8.0)	59 (38.1)
Focal (i)	10 (17.5)	7 (14.0)	17 (15.9)	1 (1.5)	8 (7.6)	9 (5.2)	11 (8.8)	15 (9.7)
Rim (h + i)	19 (33.3)	17 (34.0)	36 (33.6)	2 (2.9)	57 (54.3)	59 (34.1)	21 (16.8)	74 (47.7)
No rim (j)	38 (66.6)	33 (66.0)	71 (66.4)	66 (97.1)	48 (45.7)	114 (65.9)	104 (83.2)	81 (52.3)

Table 14. Histopathological analyses. *Absolute number of thrombus segments in reference to fibrin pattern, distribution and outer circumference.*

Fibrin pattern

Hard thrombi processed by a Chandler loop showed a fibrin pattern in 83/107 (77.6%) cases, including 53/107 (49.5%) thrombus segments with an insular pattern and 30/107 (28.0%) cases with a reticular pattern. In contrast, soft thrombi prepared under static conditions exhibited a fibrin pattern in 32/173 (18.5%) cases, of which 27/173 (15.6%) were insular and 5/173 (2.9%) were reticular. The occurrence of a fibrin pattern was predominantly found in the harder thrombi – one of the main differentiating factors compared to the softer thrombi (pattern: 83/107 vs. 32/173, respectively; odds ratio, 15.2; 95% CI, 8.4 to 27.6; $P < .001$). Reaching a level of significance, the occurrence of an insular pattern in relation to no fibrin pattern was 11.5 times more likely for the harder thrombi compared to the softer thrombi (odds ratio, 11.5; 95% CI, 6.1 to 21.7; $P < .05$). Furthermore, a reticular pattern in relation to no pattern was 35.2 times more likely for the harder thombi than for the softer thrombi (odds ratio, 35.2; 95% CI,

12.4 to 99.8; P < .05). There was no significant difference between the harder 0-hour and 72-hour thrombi groups: 75.4% of thrombus segments in the harder 0-hour thrombi group registered a fibrin pattern versus 80.0% for the harder 72-hour group (odds ratio, 1.3; 95% CI, 0.5 to 3.3; P = .54). The occurrence of a fibrin pattern for the clot types is shown in Figure 31.

The absence of a fibrin pattern predominated in the thrombi prepared under static conditions with a total number of 141/173 (81.5%) thrombus segments. The soft 0-hour thrombi displayed a significantly lower amount of thrombus segments with an insular pattern in 4/68 (5.9%) cases compared to the soft 72-hour aged thrombi with 23/105 (21.9%) cases, (odds ratio, 0.2; 95% CI, 0.1 to 0.7; P = .01). However, there was no significant difference in the occurrence of a reticular pattern for the soft 0-hour and 72-hour aged thrombi (odds ratio, 0.8; 95% CI, 0.1 to 5.2; P = .86). Regardless of the preparation method, the aging time of the thrombi, 0-hour versus 72-hour, did not affect the thrombi pattern structure to a statistically significant level (odds ratio, 0.9; 95% CI, 0.5 to 1.4; P = .57).

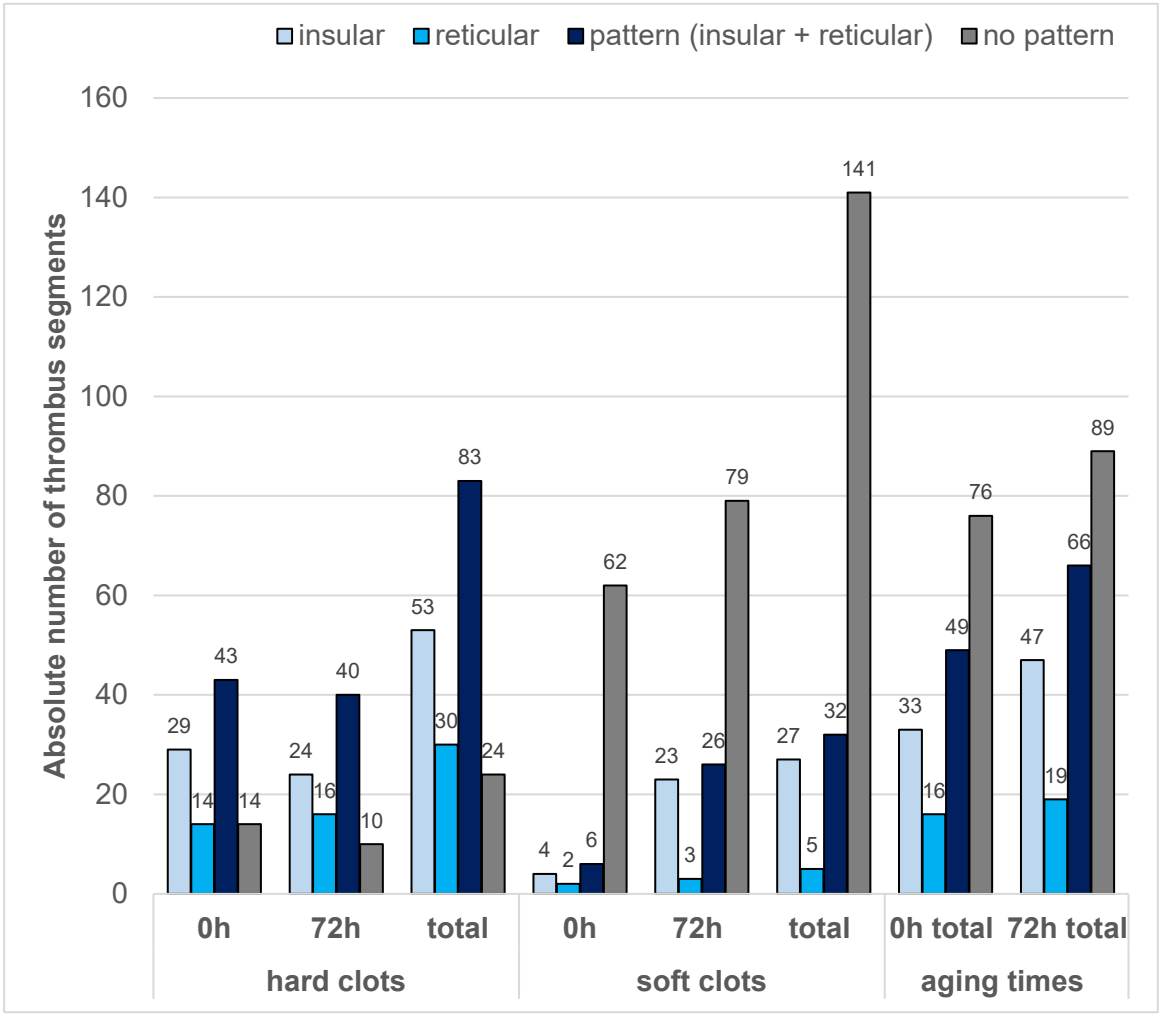


Figure 31. Fibrin pattern for different clot types.

Distribution of fibrin

For the hard thrombi (Chandler loop), a regular distribution of fibrin was displayed in 56/107 (52.3%) thrombus segments: with fibrin localized both centrally and peripherally in 26/107 (24.3%), peripherally in 22/107 (20.6%) and centrally in 8/107 (7.5%) cases. In comparison, softer thrombi prepared under static conditions presented a regular distribution of fibrin in 20/173 (11.6%) cases: displaying peripheral and central distribution in 1/173 (0.6%), peripheral distribution in 7/173 (4.0%) and central distribution in 12/173 (6.9%) cases. By means of multinomial logistic regression analysis, the odds in favor of a regular distribution of fibrin relative to an irregular distribution, were 8.4 times higher for the harder thrombi, compared to the softer thrombi, resulting in a significant difference between both groups. (odds ratio, 8.4; 95% CI, 4.6 to 15.3; $P < .05$). Therefore, the soft thrombi were predominantly marked by an irregular distribution of fibrin involving a total of 153/173 (88.4%) thrombus segments.

Comparing both preparation methods, a peripheral distribution relative to an irregular distribution of fibrin was 9.4 times more likely for the harder thrombi than the softer thrombi (odds ratio, 9.4; 95% CI, 3.8 to 23.4; $P < .05$). An even greater disparity was seen for a combined peripheral and central distribution of fibrin, relative to an irregular distribution, which was found 78.0 times more frequently in the harder thrombi compared to the softer thrombi. (odds ratio,78.0; 95% CI, 10.3 to 589.3; $P < .05$). Although the distribution of fibrin for the hard 0-hour versus 72-hour thrombi was comparable, a significantly higher peripheral distribution of fibrin for the hard 72-hour thrombi could be noted in 15/50 (30.0%) thrombus segments versus 7/57 (12.3%) for the hard 0-hour thrombi (odds ratio, 3.9; 95% CI, 1.3 to 11.7; $P < .05$). Soft 72-hour thrombi, registered a higher central fibrin distribution with 11/105 (10.5%) cases opposed to soft 0-hour thrombi with 1/68 (1.5%) cases (odds ratio, 0.1; 95% CI, 0.02 to 0.98; $P < .05$). Comparing the 0-hour versus 72-hour aged thrombi regardless of the preparation method (odds ratio, 0.7; 95% CI, 0.4 to 1.2; $P = .18$), no statistically significant difference could be determined between both groups. The fibrin distribution for the different clot types is shown in Figure 32.

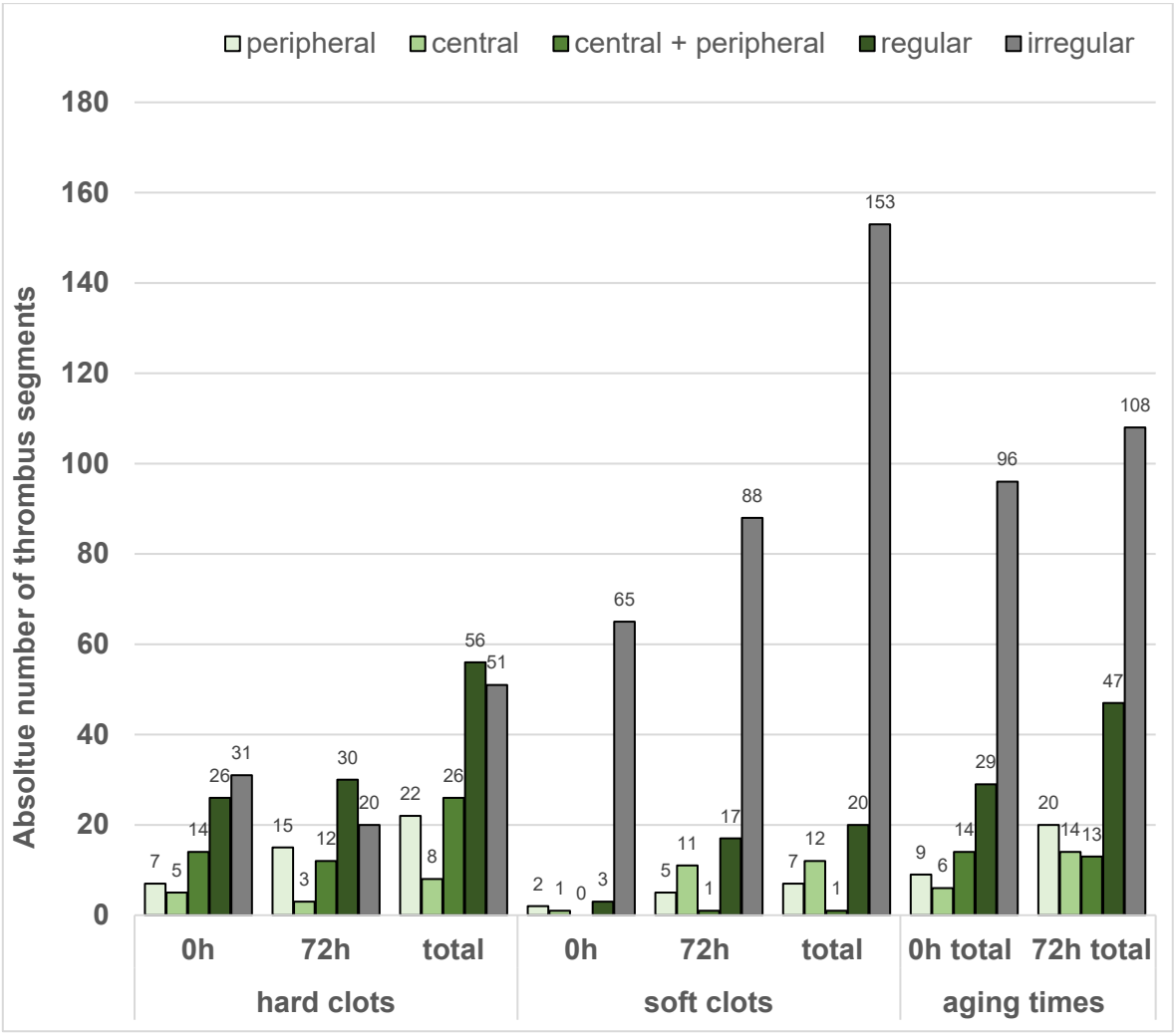


Figure 32. Distribution of fibrin for different clot types.

Outer circumferential fibrin rim

Comparing thrombi by aging times (for hard and soft thrombi combined), an outer fibrin circumference was observed more frequently in the 72-hour aged thrombi than in the 0-hour h thrombi (circumference: 74/155 vs. 21/125, respectively; odds ratio, 4.5; 95% CI, 2.6 to 8.0; P < .001). For the 72-hour aged group, 74/155 (47.7%) thrombus segments had a fibrin rim, of which 59/155 (38.1%) displayed a complete circumferential outer rim and 15/155 (9.7%) a focal outer rim.

For the 0-hour aged thrombi, the absence of an outer fibrin rim was predominant in 104/125 (83.2%) cases. Only 21/125 (16.8%) segments within the 0-hour group showed a fibrin rim, in which the outer rim of fibrin was complete in 10/125 (8.0%) or focal in 11/125 (8.8%) of the cases. Looking at aging times for the hard and soft clots, there was no significant difference

between hard 0-hour and 72-hour thrombi (Chandler loop) regarding outer fibrin rim. For the hard 0-hour thrombi, the fibrin circumference was localized more focally, compared to the hard 72-hour thrombi with a higher occurrence of a complete outer circumference. The soft 72-hour thrombi had a complete outer fibrin circumference in 49/105 (46.6%) cases and a focal outer rim in 8/105 (7.6%) cases, versus 1/68 (1.5%) cases for the soft 0-hour thrombi, respectively ($P < .05$). The outer circumference of fibrin for the different clot types is depicted in Figure 33.

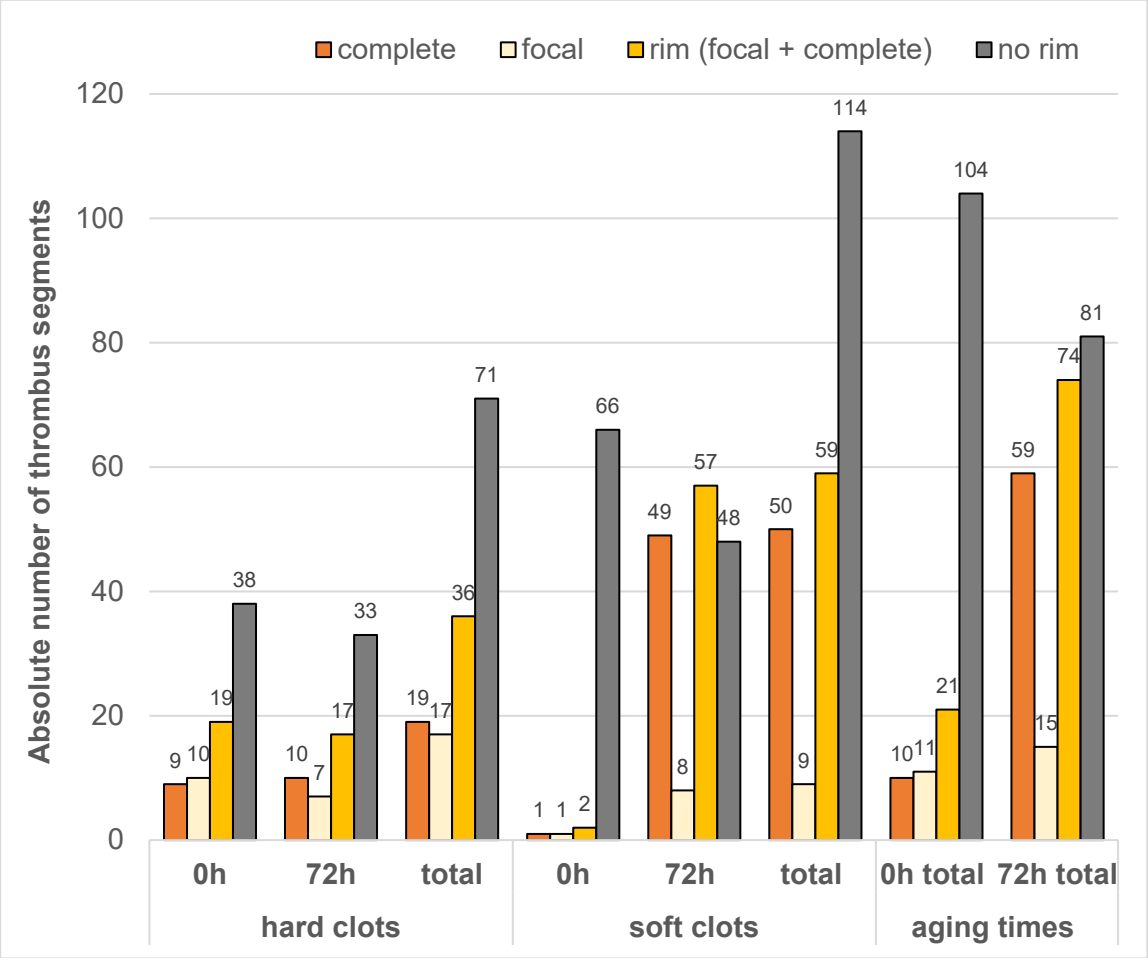


Figure 33. Outer fibrin circumference for different clot types.

5 Discussion

5.1 Evaluation of Mechanical Thrombectomy Results

Mechanical thrombectomy, in combination with best medical management and intravenous thrombolysis, has become the standard treatment for acute ischemic stroke in patients with large vessel occlusion. Meanwhile, mechanical thrombectomy is performed up to 24 hours after AIS symptom onset. (1, 2) Recanalization rates of 71% (mTICI $\geq$ 2b) and improved functional outcome of 46% (mRS $\leq$ 2 after 90 days) have been achieved. Due to the 10% incidence of embolism in new territories for aspiration devices, endovascular treatment can be further improved. (3, 98, 105, 111) Proximal balloon protection can significantly reduce the rate of distal embolization by arresting antegrade blood flow. (124) However, the opening diameter of a standard distal access catheter is often smaller compared to the vessel and thrombus diameters. Thus, the thrombus might become elongated and compressed when entering the smaller tip during stent retrieval. This may cause stripping of the thrombus at the tip of the standard distal access catheter, resulting in clot fragmentation and migration. In addition, thrombus loss can occur due to failed interaction of the stent retriever with the thrombus before reaching the tip. (6, 7)

We developed a funnel-shaped tip model with a larger opening diameter to improve the efficacy of mechanical thrombectomy. The goal was to achieve higher first-pass recanalization rates by reducing unwanted effects like clot abruption at the catheter tip during stent retrieval. In vitro, this study compared a funnel-shaped tip with a larger inner diameter (ID = 2.5 mm) to a smaller standard tip (ID = 1.5 mm) in combination with different clot compositions. The opening diameter of the funnel-shaped tip corresponds to the anatomical diameter of the M1-MCA segment, measuring 2.7 ± 0.23 mm (mean ± 1 SD). (2, 133, 134) The smaller opening diameter of the standard tip relates to the inner diameter of customary distal access catheters. One example of a distal access catheter is the SOFIA catheter (MicroVention, Tustin, CA, USA), which is available in different sizes: 5F (ID 1.39 mm, 0.055 inch) or 6F (ID 1.78 mm, 0.070 inch). (2, 100)

According to recent scientific literature, 70 to 80% of acute large vessel occlusions are estimated to occur in the anterior circulation. (135) The MCA model used for the experiments is based on the anatomical measurements of the M1-segment (inner tube diameter 3.0 mm). The M1-segment is the most frequent site of large vessel occlusion in over 33% of cases, followed by the M2-segment in 27%, the internal carotid artery in 16.5%, the internal carotid artery and middle cerebral artery junction in 10.5%, and the anterior cerebral artery in less than 5% of the cases. (15, 136) Since ESO/ESMINT guidelines recommend mechanical

thrombectomy in the anterior circulation, we chose a diameter for our vasculature model based on a location site frequently accessed for mechanical thrombectomy.

Comparison of the funnel-shaped tip and standard tip

The proof-of-concept of the larger-sized funnel-shaped tip was validated by achieving significantly higher first-pass recanalization rates of 56/80 (70.0%) compared to 24/80 (30.0%) for the smaller standard tip, regardless of the stent retriever and clot type ($P < .001$). Evaluating the causes of MT failure is one advantage of an in vitro setting. (2) In addition to achieving significantly higher recanalization rates, the funnel-shaped tip showed a different distribution of MT failures. Thrombus loss before reaching the funnel-shaped tip accounted for half of these failures. The other half of the MT failures were caused by clot abruption at the funnel-shaped tip. Clot abruption at the tip proved to be the primary cause of MT failure for the standard tip and reached statistical significance ($P < .05$).

The thrombus was lost in 11/24 (45.8%) cases for the funnel-shaped tip, because the stent retriever failed to interact with the clot during retraction before reaching the tip. (2) This happened in 6/9 (66.7%) cases when using harder mechanically prepared thrombi (Chandler loop), and in 5/15 (33.3%) cases with softer thrombi prepared under static conditions. Thus, the likelihood of losing the thrombus during stent retrieval almost doubled for the harder thrombi compared to the softer thrombi. This would imply that the stent retriever interacted more strongly with the softer thrombi compared to the harder thrombi. In contrast, clot abruption at the funnel-shaped tip caused 13/24 (54.2%) failures. However, this mainly occurred when using softer friable thrombi instead of harder thrombi. Mechanical thrombectomy failed due to an abruption of clot material at the funnel-shaped tip in 10/15 (66.7%) cases for the softer thrombi, especially the 72-hour aged softer clots in 6/8 (75.5%) cases, compared to 3/9 (33.3%) cases for the harder thrombi. An explanation for this could be that the softer thrombi had a higher tendency of fragmenting during stent retrieval into the funnel-shaped tip.

For the standard tip, MT failure resulted from clot abruption at the tip in 45/56 (80.4%) cases, regardless of the clot type. Clot abruption occurred in 24/31 (77.4%) cases when using softer thrombi, versus 21/25 (84.0%) cases for the harder thrombi. There was no significant difference between both thrombi preparation methods when using the standard tip. These results would suggest that MT failure for the standard tip was primarily affected by the smaller diameter of the tip – not the clot type.

Procedural success depends on numerous factors: gaining quick and safe access to the patient's vasculature, location and accessibility of the occlusion site, collateral status of the patient, antegrade flow arrest, physical properties during procedure (e.g., aspiration and

retraction forces, pressure at the tip, vacuum pressure during aspiration, and the opening area of the tip, etc.), stiffness of the thrombus, interaction of the stent retriever with the thrombus, as well as device properties of the stent retriever and distal access catheter (e.g., diameter, material, design, flexibility and navigability). Looking at how MT procedure is performed helps us to understand how these factors might affect mechanical thrombectomy. Based on the primary combined approach, stent retriever assisted vacuum-locked extraction (SAVE) is a standard technique in mechanical thrombectomy that enables better interlock during aspiration. Access to the cerebral vasculature is gained by using a triaxial approach with a guiding catheter, distal access catheter and microcatheter. A microcatheter containing the stent retriever is pushed through the thrombus. After releasing the stent retriever out of the microcatheter over the thrombus, the microcatheter is removed. Only the proximal one third of the stent retriever interacts with the thrombus. The stent retriever is usually deployed for several minutes allowing it to interact with the clot. Then, a distal access catheter is navigated towards the thrombus. Aspiration is applied while pulling the proximal end of the stent retriever into the tip of the distal access catheter. Both the stent retriever and the aspiration catheter are removed together as a vacuum locked unit and pulled into the guiding catheter. (1, 137)

Different parameters must be taken into account to understand the physics of mechanical thrombectomy. In the following sections we will discuss and question the effects of physical properties such as force, pressure, radius, area, volumetric flow and thrombus elasticity on mechanical thrombectomy. Although this is a theoretical approach to MT procedure, it will allow us to analyze our results and compare them to recent scientific literature.

In theory, specific “retraction” or “impaction” forces as well as “aspiration forces” are required to pull part of the thrombus into the tip during stent retrieval. In mathematical terms, the retraction force can be defined as: *Force (F)* equals the *area* of the catheter opening multiplied by the *pressure* at the tip *(F = a · p)*. Because a catheter has a cylindrical shape, the cross-sectional area of the catheter must be circular. The circumference of any circular structure is proportional to the first power of the radius (*circumference* = $2\pi r$). The cross-sectional area of a catheter is proportional to the square of the radius and equals pi times the second power of the radius, or pi times the second power of the diameter divided by four. (138)

$$a = \pi r^2 = \frac{\pi d^2}{4} (a = area, r = radius, d = diameter)$$

The larger diameter of the funnel-shaped tip (ID = 2.5 mm) provides a greater opening area compared to the standard tip (ID = 1.5 mm). Thus, the opening area of our funnel-shaped tip is increased by a factor of 2.78.

$$\frac{\pi(2.5\ mm)^2}{4}\ funnel\ tip \text{ vs. } \frac{\pi(1.5\ mm)^2}{4}\ standard\ tip$$

$$\rightarrow (2.5\ mm)^2 = x\ (1.5\ mm)^2 \rightarrow x \sim 2.78$$

Assuming the *pressure (p)* at the tip remains constant, then the *retraction force* at the catheter tip during mechanical thrombectomy would increase by 2.78-fold. A high retraction force correlates with improved recanalization and MT success.

$$F = a \cdot p = \pi r^2 \cdot p$$

Adhesion and interaction of the thrombus with the vessel wall determine the *force of friction* $F_{friction}$. In turn, the *force of friction* counteracts the *force of retraction* in the opposite direction (see Figure 34). This occurs when the thrombus slides along the vessel wall during stent retrieval. The *force of friction* equals the *contact force* $F_{contact}$ multiplied by the *frictional coefficient c.* The *force of friction* runs parallel to the vessel length, in contrast to the *contact force* which runs perpendicular to the vessel length. The *frictional coefficient* is specific for the type of material and depends on the composition of the thrombus. (138)

$$\rightarrow F_{friction} = F_{contact} \cdot c \qquad (138)$$

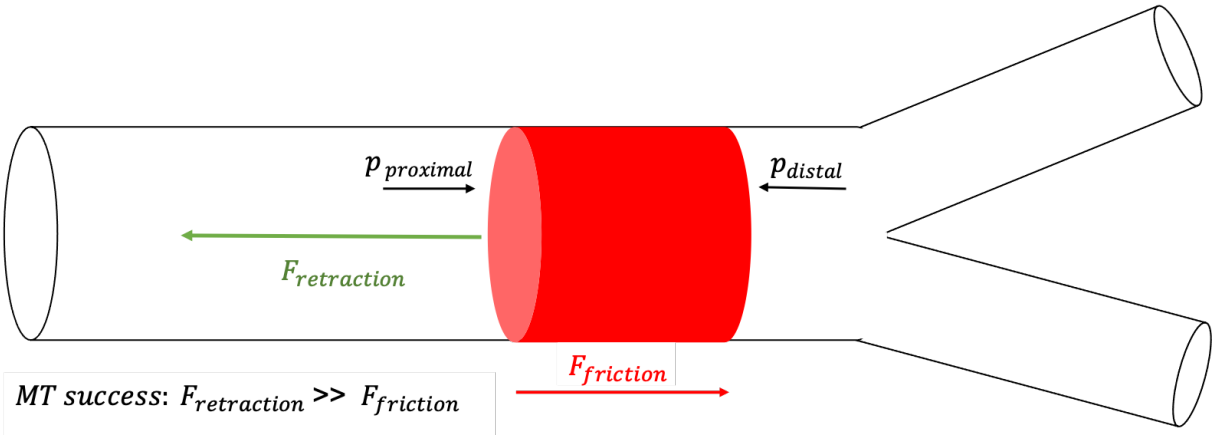


Figure 34. Forces involved in mechanical thrombectomy. *The force of retraction is counteracted by the force of friction. A pressure gradient (proximal and distal pressure) builds up across the thrombus. Based on a diagram from Yoo and Andersson, 2017 (6)*

By varying different parameters of the "*F = a · p"* equation, physical properties may be altered to improve the success of mechanical thrombectomy. In accordance with this equation, the *force of retraction* is proportional to the first power of the *pressure* and to the second power of the *radius* (f $\propto p; r^2$). The relationship between the *radius* and the *force of retraction* is exponential. Thus, the radius has a greater effect on the *force of retraction* than *pressure* does. Although the pressure gradient across the thrombus ($p_{proximal} + p_{friction} - p_{distal}$) might vary due to fluctuations in systemic blood pressure and might be further impacted by retrograde collateral blood flow, the influence of pressure on mechanical thrombectomy can be rated as

secondary. The same would apply to the aspiration or vacuum pressure during mechanical thrombectomy. Regardless of the internal diameter, most aspiration catheters transmit similar maximum vacuum pressures ranging from -26 to -28 inHg (~ 660 mmHg to 711 mmHg), which are measured relative to the ambient atmospheric pressure at sea level (29.9 inHg ~ 760 mmHg ~ 1 atm). We, therefore, assume that the vacuum pressure at the tip remains relatively constant during mechanical thrombectomy, which is also referred to as “static suction”. (138, 139) Under this assumption, the aspiration and retraction forces are mainly affected by the larger diameter and opening area of the funnel-shaped tip, not by the pressure at the tip.

Interestingly, a newly developed technique has been reported in scientific literature, which alternates the vacuum pressure during aspiration thrombectomy. Compared to applying constant or static vacuum pressure, this cyclic aspiration method uses oscillating vacuum pressure up to a maximum frequency of 6.3 Hz to induce “cyclic changes in force” resulting in clot instability or “fracture”. In vitro, this was achieved by connecting a three-way stop valve between the aspiration pump and aspiration catheter “to establish open continuity between the vacuum source” and an aspiration medium (e.g., air or water) at the catheter tip. (140) This method showed improved recanalization and faster clearing rates in favor of cyclic aspiration. How this method could affect the rate of distal emboli in vivo is still unclear. (140)

To conclude, the purpose of the funnel-shaped tip (see Figure 35) is to facilitate mechanical thrombectomy as follows:

1) Local antegrade blood flow is arrested by “sealing” the vessel lumen with the larger-sized tip. Thus, the risk of clot overlap and abruption at the funnel-shaped tip during stent retriever interaction is reduced. The larger opening of the funnel-shaped tip enables better stent retriever retraction and interlock during aspiration.

2) Due to the larger diameter of the funnel-shaped tip, the cross-sectional opening area of the tip is enlarged by a factor of 2.78-fold (area is proportional to the square of the radius → $a \propto r^2$). Both the thrombus and the catheter tip have similar cross-sectional areas. During aspiration, the contact area between the thrombus and catheter opening is greater than for the standard tip. Assuming that the pressure remains constant at the tip, higher aspiration and retraction forces can be applied along the cross-sectional area of the thrombus. *($F \uparrow = a \uparrow \cdot p$).* This should increase the likelihood of complete clot removal.

3) Resistance and shear forces during stent retrieval are lower when using the funnel-shaped tip compared to the standard tip. Due to the disproportionately larger size of the self-expanding stent retriever and the thrombus, in relation to the smaller opening of the standard tip the stent retriever and thrombus are compressed and deformed when entering the narrow standard tip. (2) This intensifies the shear forces at the standard tip, ultimately increasing the risk of stripping

and fragmentation. In contrast, the funnel-shaped tip reduces the risk of thrombus deformation and compression at the tip due to its larger opening. By increasing the contact area between the funnel-shaped tip and thrombus, the "strain σ" on the thrombus is decreased ($\sigma \downarrow = \frac{F}{a\uparrow}$). The retraction force, acting on the thrombus, is equally distributed to a larger contact area between the funnel-shaped tip and thrombus. Thus, the risk of clot rupture and fragmentation is reduced. Another factor that could influence MT success is the force of friction, which opposes the force of retraction. The force of friction, however, depends on the "stickiness" of the thrombus and the clot composition. (6)

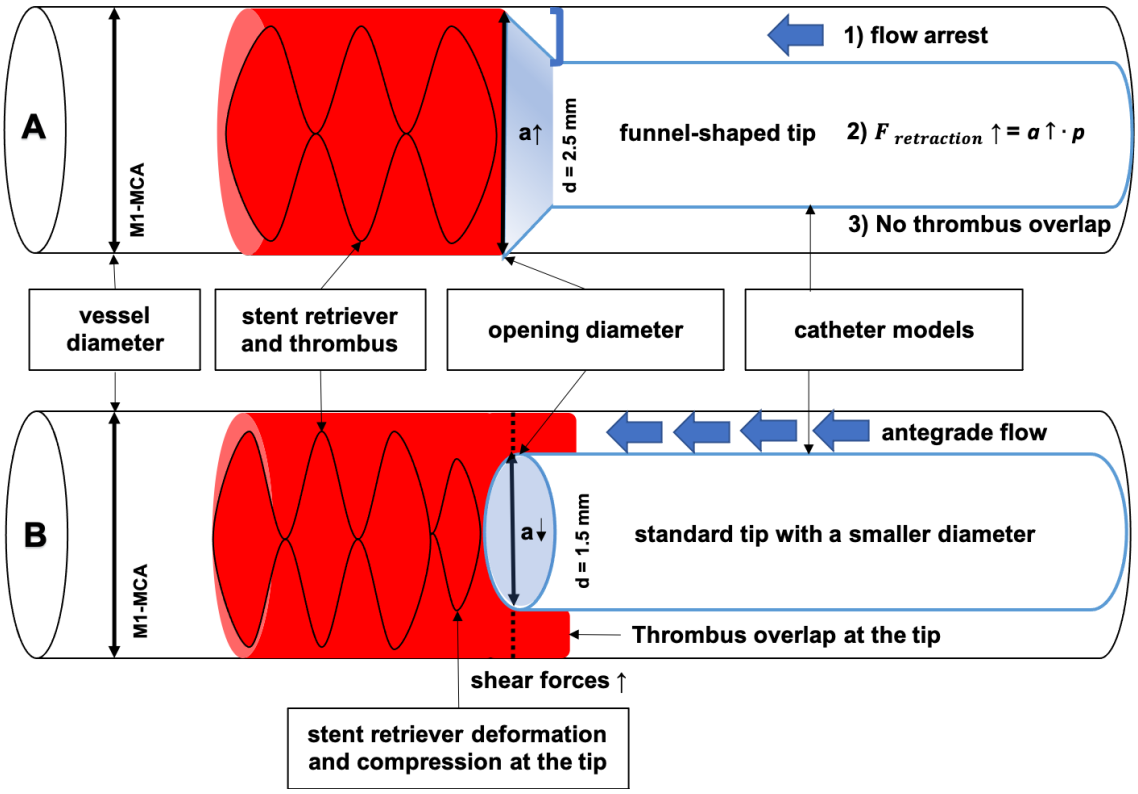


Figure 35. Physical properties of the funnel-shaped tip (A) compared to the standard tip (B) *during stent retriever retraction into the tip. p = pressure, F = force, a = area, d = diameter. The dimensions of the diagram are schematic and not to scale.*

Development and efficacy of the funnel-shaped prototype

The funnel-shaped tip model used in the underlying study was constructed from a modified introducer sheath with a manually dilated tip. This simplified catheter model was developed to test the proof-of-concept of a funnel-shaped opening with a larger internal diameter, in comparison to a standard tip for mechanical thrombectomy. At the time of the experiments, the actual funnel-shaped prototype was still being developed and was only recently patented. Our research work has been funded by Germany's Federal Ministry for Economic Affairs and

Energy (Bundesministerium für Wirtschaft und Energie) under its WIPANO (Wissens- und Technologietransfer durch Patente und Normen) sponsoring program (WIPANO grant number: 03THW13K02), primarily for developing and patenting the funnel-shaped prototype. (2)

The prototype (see Figure 36 below) is a modified distal access catheter (DAC) that features a self-expanding flexible Nitinol mesh and radiopaque markers for visualization. It is covered with polytetrafluoroethylene (PTFE), known for its flexibility and low coefficient of friction. (141) Due to the self-expanding structure, the modified DAC can expand and adapt to different vessel diameters to induce local antegrade flow arrest. Differing from the funnel-shaped tip model used in this study, the larger diameter of the “actual” prototype not only expands around the tip but continues over a length of 2 to 3 cm. This allows the catheter to adapt to the vessel diameter over a longer distance, thereby increasing distal stability and facilitating stent retrieval. The prototype fits into a guiding catheter. The guiding catheter encloses the funnel-shaped prototype, preventing it from expanding before reaching the target vessel. Thus, the prototype is released at the occlusion site. The prototype is also large enough to accommodate a stent retriever, and a microcatheter up to an inner diameter of 2.4 F (0.08 mm).

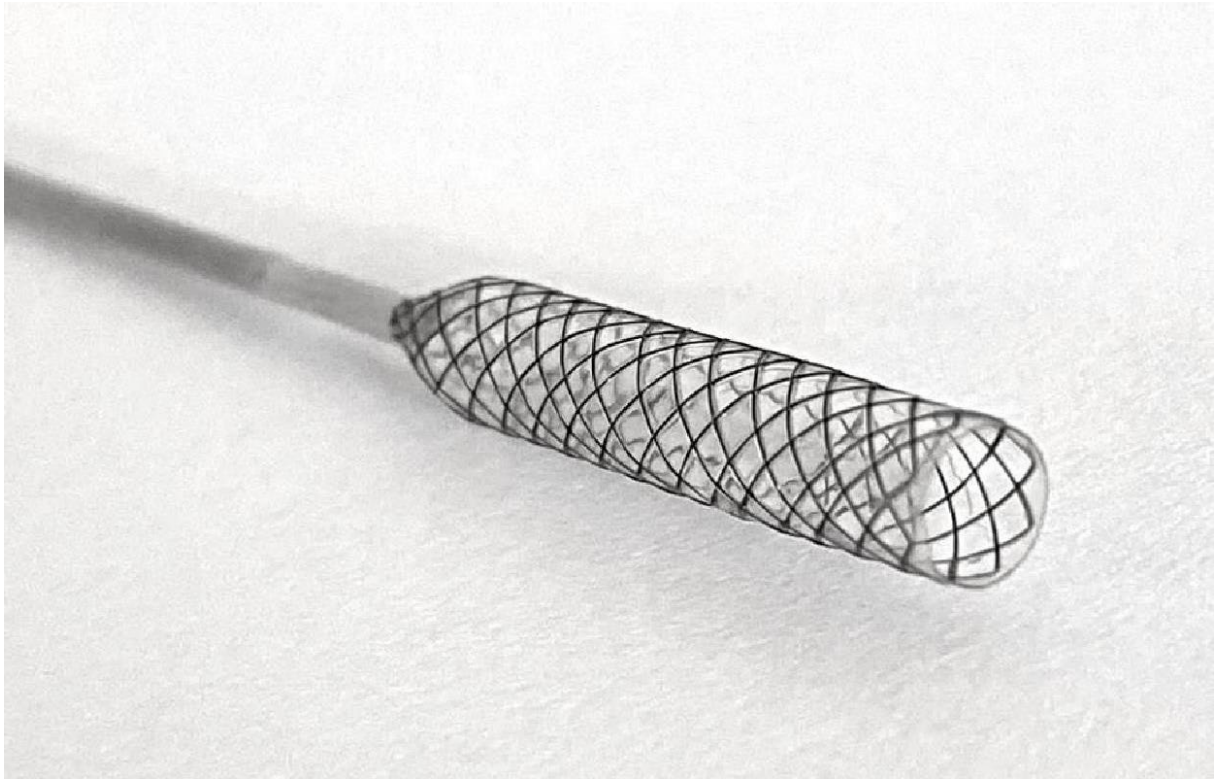


Figure 36. The flexible tip of the prototype catheter is 2.4 cm long. *The prototype consists of a flexible nitinol mesh and is covered with polytetrafluoroethylene (PTFE).*

The proof-of-concept for the funnel-shaped tip was validated in the preliminary study and the underlying study. (2) Due to the simplified experimental setup, the underlying study did not examine the navigability of the funnel-shaped model. Therefore, the tortuosity of the vasculature was not considered. However, the prototype was recently tested in a third experimental study, which reconfirmed the results of both the underlying and preliminary studies. In fact, the funnel-shaped prototype tested in the third study reached even higher recanalization rates of 95% versus 75% for the standard DAC. The third study also evaluated the navigability of the prototype, achieving first-pass recanalization 10/11 (91%) times. Further in vivo research is in progress to determine the efficacy of the funnel-shaped tip. Initial results are already promising.

Comparison of other funnel-shaped devices and aspiration devices for MT

Other funnel-shaped catheters have been developed independently of our project: such as the Lazarus Device (Lazarus Effect, Medtronic Neurovascular, Campbell, California, USA), (142) and the Advanced Thrombectomy System (ANCD; R&D, Anaconda Biomed, Barcelona, Sant Cugat del Vallès, Spain). (2, 7) Compared to our funnel-shaped tip, the Lazarus device does not induce local flow arrest. Instead, a self-expanding funnel-shaped nitinol mesh is released over a guide catheter to enclose the stent retriever during retraction, forming a protective sheath. (113, 142) The ANCD, which is technically similar to our funnel-shaped tip, also initiates local flow arrest during mechanical thrombectomy. (7) Both the Lazarus and ANCD funnel-shaped devices registered high recanalization rates of 80% and 94%, respectively. (7, 113, 142) A small clinical trial for the Lazarus device (N = 20) reported recanalization rates of 95% (mTICI $\geq$ 2b), with no occurrence of embolism in new territories. (143)

The R^4Q (MIVI Neuroscience, Inc., Eden Prairie, Minnesota, USA) is a newly designed distal access catheter. The name is etymologically derived from Hagen-Poiseuille's equation which states that the fourth power of the radius r^4 is proportional to the volumetric flow Q. Although the R^4Q device does not have a funnel-shaped tip, it is similarly based on the principle of an increased internal diameter for improving mechanical thrombectomy. Under normal circumstances, the standard distal access catheter is inserted through a guide catheter, thereby decreasing the internal diameter of the guide catheter and reducing the aspiration force. However, the R^4Q utilizes a control wire so that a maximum internal lumen diameter of the guide catheter is available for aspiration during mechanical thrombectomy. The proximal internal diameter of the guide catheter is relatively "enlarged" because the control wire "replaces the proximal three-quarters" (144) of the distal access catheter (see Figure 37). Thus, the R^4Q distal access catheter is only released at the distal end of the guide catheter over a control wire. (144) Results from in vitro experiments indicated higher aspiration forces. (104,

144) In contrast to our funnel-shaped tip, the R^4Q system does not initiate local antegrade flow arrest and therefore poses the risk of clot abruption and embolism in new territories. This was underscored by a recent retrospective clinical trial, in which the R^4Q device achieved first-pass recanalization rates of 91% (mTICI ≥ 2b), but still recorded an embolism in new territories rate of 3%. (144)

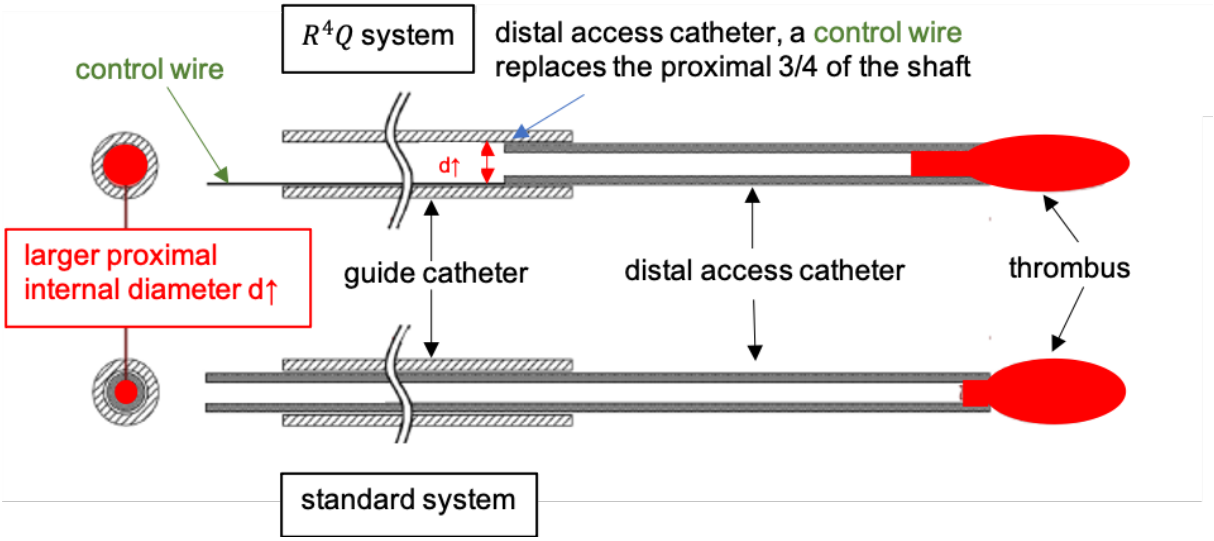


Figure 37. R4Q aspiration catheter with a guide wire, compared to a standard aspiration catheter. *This schematic diagram was adapted from Long et al., 2019 (104) and has been modified for this thesis.*

Some scientific literature states that an increase in diameter for aspiration devices would result in an increase of volumetric flow during aspiration (e.g., R^4Q catheter). (104, 109, 144) This hypothesis is based on Hagen-Poiseuille's law, which postulates that the volumetric flow is dependent on the fourth power of the radius. By doubling the radius, the volumetric flow would increase by 16-fold.

$$Q = \frac{\pi r^4 \Delta P}{8 \eta L}$$

Hagen-Poiseuille's law *(Q = volumetric flow rate, π = pi, r = inner radius, ΔP = pressure drop, η = liquid viscosity, and L= length of the tube*). (104)

We question and doubt the relevance of volumetric blood flow on mechanical thrombectomy and consider this hypothesis to be wrong. A thrombus arrests blood flow by occluding the vessel. During aspiration, the thrombus clogs the catheter like a cork or plug. As a result, there is no volumetric flow. In addition, Hagen-Poiseuille's law only applies to Newtonian fluids with

laminar flow properties. However, thrombus material is highly viscous and condensed. Therefore, the relationship between radius and volumetric flow is irrelevant for mechanical thrombectomy. (104, 139) Instead, we hypothesize that a larger proximal internal diameter at the tip would lead to an increase in aspiration or suction forces. As previously mentioned, aspiration forces are proportional to the second power of the radius (f $\propto r^2$).

5.2 Mechanical Properties of the Thrombus

A blood clot has a homogenous structure due to a random distribution of blood cells. In contrast, a thrombus has a heterogenous structure with distinct areas of agglutinated platelets. For simplification, the medical terms thrombus and clot, which are often referred to synonymously in scientific literature, are used interchangeably in this thesis. (145)

How do the viscoelastic properties of the thrombus influence the success of mechanical thrombectomy and what are the effects of mechanical thrombectomy on the thrombus. Similar to a cork or plug, a thrombus can arrest blood flow at the occlusion site. During stent retrieval a retraction force acts on the cross-sectional area of the thrombus (→ "stress") by directing and pulling the thrombus into the catheter tip. Consequently, the thrombus is strained and elongated (→ "strain"). Thus, stress and strain are two physical properties acting on the thrombus during mechanical thrombectomy. According to Hooke's law, which applies to the elasticity of materials, *stress* σ and *strain* ε are proportional to one another → ($\sigma \propto \varepsilon$). *Stress* σ is the external force divided by the *area* of an elastic material → $\sigma = \frac{F}{a} \left[\frac{N}{m^2}\right]$ (F = force, a = area, N = Newton, m^2 = square meters). Deformation of an elastic material results from *strain* ε caused by an external force. Strain is defined as the *change of length* Δl divided by the *original length* l_0 of an elastic material → $\varepsilon = \frac{\Delta l}{l_0}$ $[dimensionless]$. (146, 147) The relationship between stress σ and strain ε is mathematically defined by Young's modulus of elasticity E → $E = \frac{\sigma}{\varepsilon}$ ($\sigma \propto \varepsilon$). The higher the modulus of elasticity, the stiffer the material and the greater the resistance against elastic deformation. (148) The relationship between these parameters is expressed in Hooke's law.

$$\sigma = \frac{F}{a} = E \cdot \frac{\Delta l}{l_0} \quad \left[\frac{N}{m^2}\right]$$

Hooke's law (σ = mechanical stress, ε = strain, F = force, a = area, change of length Δl, original length l_0). (146, 147, 149)

Therefore, the question arises whether a thrombus is an elastic material? By definition, a thrombus is a polymer with viscoelastic properties. This means that the thrombus has both the viscosity of a fluid and the elasticity (or stiffness) of a spring. (150, 151) An elastic material is able to return to its original state after mechanical deflection. In contrast, a viscous material is

irreversibly deformed by force due to its plasticity. Fibrin determines the elastic and mechanical properties of a thrombus. Biomolecular analyses have indicated that the α-helical coiled-coil region of fibrin functions like an elastic spring. Therefore, the elasticity of a thrombus is dependent on the amount of fibrin. (151) Fibrin content is reported to be higher at lower hematocrits, resulting in a greater modulus of elasticity. (150) Thus, harder clots with higher levels of fibrin and lower levels of erythrocytes show greater stiffness than softer erythrocyte-rich clots. (152) In particular, calcified cholesterol-rich thrombi consist of hard atherosclerotic plaque material which causes rigidity. This leads to reduced interaction with the stent retriever and subsequent low recanalization rates. (153, 154) Erythrocyte-rich clots, on the other hand, are characterized by their viscosity and capability to deform. (154)

Young's modulus of elasticity for highly retracted human clots is estimated to be 3.21 ± 1.97 kPa, similar to that of porcine clots (5.33 ± 0.92 kPa). Clot elasticity can be measured by using ultrasound-based shear wave elasticity imaging. In general, clots associated with higher reperfusion rates contain denser concentrations of erythrocytes with intermingled areas of fibrin. In contrast, clots with lower recanalization rates have a greater porosity due to increased spaces in the fibrin network and lower density of erythrocytes. Interestingly, a higher thrombus porosity facilitates IV rt-PA diffusion. This could explain why mildly retracted clots are more receptive to IV rt-PA treatment. (155)

How do strain and stress affect the thrombus and the fibrin network during mechanical thrombectomy? When there is too much strain, the thrombus can no longer return to its original state and may rupture. In this case, the change in length ($\Delta l \uparrow$) from the original length (l_0) leads to irreversible deformation (viscous properties of the thrombus). This happens when the threshold of elasticity, meaning the resistance of the thrombus to elastic deformation, is crossed. In this case, the relationship between strain and stress is no longer proportional – also referred to as strain stiffening. (146-149, 151) During stent retriever retraction into a narrow standard tip, the thrombus becomes elongated and deformed. If the elasticity threshold of the thrombus is exceeded, the thrombus may rupture or "break". This principle may be applied to fibrin fibers. Fibrin determines the structural integrity or ability of blood clots to form a three-dimensional scaffold. In general, the fibrin density increases during clot retraction causing the fibrin network to "shrink". Mechanical forces, as well as thrombolysis, may induce the formation of cracks in the thrombus. These physical defects and cracks make the thrombus more susceptible to rupturing. (155) Thus, strain can also be defined as the variation of the thrombus crack length (Δl). Every increase in strain results in an increase in fiber density at the crack. Hydrophobic protein interactions may occur and lead to fluid loss in the hydration layer, eventually causing volume loss and negative compressibility of the thrombus. At a certain stress level when maximal forces are acting on the thrombus, fibrin monomers are unfolded and displaced. At this point, fibrin fibers are "overstretched" and lose their capacity

for densification and stiffening. (156) At the molecular level, α-helices within the coiled-coil region of fibrin fibers lose their structure and convert into β-sheets. (151) Consequently, the structural integrity of the blood clot is damaged. (2) As soon as the clot ruptures, the forces acting on the thrombus drastically decline and “strain” energy is released. The structural integrity or rupture resistance of the thrombus is associated with the ability of the clot to contract or retract. This is a material property that is dependent on the clot composition. Harder elastic clots with a high modulus of elasticity are more resistant to rupturing than softer friable clots. Clots with lower densification and compaction abilities, are exposed to higher shear forces during stent retrieval. As a result, the clots are more prone to rupture. Thus, clot composition and geometry play a pivotal role in the pathogenesis of clot rupture and embolism in new territories. (156)

5.3 Comparison of Clot Compositions

This study analyzed the effects of different clot compositions on mechanical thrombectomy, comparing softer thrombi prepared under static conditions to harder mechanically prepared thrombi (Chandler loop). In this research project, harder clots showed a higher tendency towards improved recanalization compared to softer clots. Recent publications have investigated the effect of clot composition on mechanical thrombectomy. (6, 7, 157) According to Duffy et al., 2017 (158), clots processed under static conditions, similar to softer clots from this study, displayed erythrocyte dominance and low-fibrin content. In correlation, the histopathological findings of this study showed significantly lower levels of fibrin, an absence of fibrin pattern, and an irregular fibrin distribution for softer clots ($P < .05$). Due to the coagulation of blood under static conditions, erythrocytes were unevenly distributed and more densely concentrated. In contrast, harder mechanically prepared clots from this study exhibited a reticular or insular fibrin pattern and a higher regularity of fibrin compared to softer clots. Characterized by their firmness and elasticity, harder Chandler loop clots had a fibrin-dominant pattern with intermingled clusters of erythrocytes and cellular components. (158) Since a Chandler loop simulates blood flow under dynamic conditions, blood cells and fibrin are regularly distributed. Research literature states that “white” fibrin-rich thrombi are associated with reduced recanalization rates due to a higher coefficient of friction, as well as increased stiffness and elasticity. Furthermore, it was suggested that the force of friction is higher when thrombi contain less than 20% erythrocytes (erythrocyte threshold). This can be explained by the inability of harder fibrin-rich thrombi to retain moisture. The high fibrin content could account for an increased adhesion and resistance along the vessel wall, thereby impeding mechanical thrombectomy. (6-8, 152)

Numerous studies indicated that softer erythrocyte-rich thrombi were related to higher recanalization rates, but showed a greater tendency of fragmentation than harder fibrin-rich

thrombi. Accordingly, softer thrombi from this study were found to be more susceptible to fragmentation, resulting in higher rates of clot abruption at the tip. This can be explained by a lack of structural integrity due to the absence of a fibrin pattern. (6-8) Although this research project registered higher recanalization rates for the harder “fibrin-rich” thrombi compared to the softer “fibrin-low” thrombi (P = .06), the results remained at the verge of statistical significance. One explanation why harder fibrin-rich clots registered higher recanalization rates than softer clots could be that this study did not quantify the erythrocyte, thrombocyte, leucocyte and fibrin amount. This was beyond the scope of our research project. Therefore, it is unclear whether harder thrombi exceeded the erythrocyte threshold of 20% associated with a reduced force of friction and increased recanalization. (6-8) Since the significance level was set at α = 5%, our secondary hypothesis could not be accepted under the statistical framework. To avoid a statistical error of the first type, we therefore adhere to the null hypothesis that there was no statistically significant difference between the harder and softer thrombi in terms of improved recanalization.

Controversially, some studies define Chandler loop clots as erythrocyte-rich (soft clots). (157) In this research project, however, harder Chandler loop clots are classified as fibrin-rich because they contain lower amounts of erythrocytes and higher amounts of fibrin, relative to softer clots developed under static conditions. This underscores that “hard” and “soft” are relative and subjective terms that describe the quality of thrombi not the quantity (i.e., in terms of cell distribution, degree of softness and hardness). There are no specific benchmarks or cut-offs delineating the qualitative and quantitative characteristics of thrombi.

Furthermore, the methodology for generating harder fibrin-rich versus softer erythrocyte-rich thrombi differs greatly in scientific literature. Soft friable clots can be prepared by thrombin-induced clotting in combination with fibrinogen. Stiff elastic clots analogous to hard fibrin-rich clots can be generated by adding fibrinogen and calcium phosphate apatite. Barium sulfate is known to further reduce the elasticity of blood clots. (152, 153) Another study reported that harder fibrin-rich clots were generated by citrating human blood and storing it for 24 hours. After aspirating the plasma, buffy coat and erythrocytes, blood was recalcified and stored for another 72 hours. (157) Other studies processed erythrocyte-rich clots by centrifuging whole blood and mixing fixed ratios of citrated plasma with erythrocytes to generate specific erythrocyte concentrations. (158) The underlying study, however, used whole blood without additives to simulate in vivo thrombi as realistically as possible. This demonstrates that there are many preparation methods for processing soft and hard clots. Standardized protocols for clot generation are lacking. Therefore, it is difficult to compare our soft and hard clots to those described in scientific literature.

The underlying study evaluated mechanical clot preparation using a Chandler loop versus preparation under static conditions. Developed in 1958 by A.B. Chandler, the Chandler loop device was first used as an “in vitro thrombotic coagulation” method to investigate hemorheological effects and hemodynamics of blood clots. (130, 159) Similar biochemical and morphological qualities were reported for Chandler loop and in vivo thrombi. Electron microscopy displayed upstream agglutinated thrombocyte-rich “white heads” and downstream erythrocyte-rich “red tails” for both Chandler loop and in vivo thrombi. Higher concentrations of plasminogen activator inhibitor-1 (PAI-1) were found in the thrombocyte-rich “head” of the thrombus. Since PAI-1 is physiologically released from α-granules of thrombocytes, the resistance towards thrombolysis is higher in the thrombocyte-rich “head” than in the erythrocyte-rich “tail” of the Chandler loop thrombus. Due to the similarities between Chandler loop and human thrombi, the Chandler loop device is rated as a validated and reproducible procedure for preparing in vivo-like thrombi. (145, 160-162) Furthermore, Robbie et al., 1997 (162) emphasized that thrombi generated under static conditions are a “poor model” for clot generation. One explanation is that the concentration of PAI-1 in clots processed under static conditions is a hundred times lower than in Chandler loop thrombi. If the concentration of PAI-1 is lower, the degradation of fibrin is enhanced – resulting in increased fibrinolysis and lower concentrations of fibrin for the softer thrombi prepared under static conditions. High concentrations of plasminogen activator inhibitor are associated with an increased inhibition of fibrinolysis. This could be one of the reasons why harder Chandler loop thrombi contain higher amounts of fibrin and have a stabler structure. (162)

Clot structure is not only relevant for MT success, but also has an impact on clinical and radiological procedures. Computed tomography (CT) is used to assess clot length, location and volume. By quantifying the Hounsfield Units (HU) of a thrombus, additional information on clot composition may be gained. (152) Clot density depends mainly on the erythrocyte concentration. Softer erythrocyte-rich thrombi, with a mean erythrocyte proportion of 47%, can be detected as hyperdense middle cerebral artery sign (HMCAS) in non-contrast cerebral CT in 30% of patients with M1-occlusions, and as blooming artefact in the gradient echo sequence (MRI). This is frequently regarded as a positive predictor for mechanical thrombectomy. (8, 10, 163, 164) Thus, softer erythrocyte-rich clots are associated with shorter intervention times and higher first-pass recanalization rates, compared to harder fibrin-rich clots. (152) Although fibrin-rich clots are hypodense in non-contrast CT relative to erythrocyte-rich clots, they show a higher uptake of contrast agent. (164)

The clot composition may also give insights regarding clot formation, origin and pathogenesis. Clot formation is a complex process resulting from primary and secondary hemostasis. Primary hemostasis is caused by platelet activation, adhesion and aggregation. Secondary hemostasis involves the coagulation cascade. Thrombus compositions differ under high-flow and low-flow

conditions in the vessels. Traditionally, clots formed in the arterial system (high-flow system) are caused by primary hemostasis and are platelet-rich. Harder fibrin-rich clots, on the other hand, are suspected of having a venous or cardiac origin (low-flow system), deriving mainly from secondary hemostasis. (165) This traditional view is perhaps an oversimplification because primary and secondary hemostasis occur simultaneously under high-flow and low-flow conditions. Recent studies have suggested that arterial and cardiac emboli both showed a mixed “red” and “white” clot structure. However, a red erythrocyte-rich pattern was predominantly found in “arterial” thrombi. (165)

According to Madjidyar et al., 2020 (157), MT success not only depends on the “right” clot type, but also on the “correct” technique. (157, 166-168) The ADAPT technique was reported to be more effective using softer erythrocyte-rich clots, while stent retrievers in conjunction with balloon guide catheters (BGC) were more successful with harder fibrin-rich clots. (157) Since our research project relied on the primary combined approach involving both aspiration and stent retriever thrombectomy, different MT techniques should also be investigated in future studies to evaluate the efficacy of our modified prototype.

5.4 Comparison of Clot Aging Times

According to scientific literature, clots can be classified by their aging times: up to 24 hours for a fresh clot; 1 to 5 days for a lytic clot, and greater than 5 days for an organized clot. A fresh thrombus has multiple layers of blood cells intermingled with fibrin to create a stable structure. This differs from a lytic thrombus with areas of colliquation necrosis that cause instability. An organized thrombus is characterized by remodeling processes with capillary vessel ingrowth. Aged clots may also contain higher amounts of leucocytes. (165) Evaluating how clot aging times may affect mechanical thrombectomy, fresher (0-24h) aged clots achieved significantly higher recanalization rates than aged (72h) clots in this study (P = .03). (126) Aged clot material may restructure and degrade, becoming more condensed due to fluid loss. Additionally, the higher density could increase friction during retraction and therefore impede stent retrieval (8, 126, 165). There was a greater difference in the recanalization rates for the harder 0 to 24-hour and 72-hour clots compared to the softer 0 to 24-hour and 72-hour clots. Since fibrin may dissolve over time and become lytic, the harder fibrin-rich clots could be more affected by the aging time in terms of stability than the softer fibrin-low clots. Structural disparities were also found for the different aging times within the two preparation groups (hard thrombi vs. soft thrombi). In histopathological terms, the harder 72-hour thrombi had a higher peripheral distribution of fibrin compared to the harder 0-hour thrombi with a more central distribution. The higher peripheral concentrations of fibrin could have impacted mechanical thrombectomy due to a higher coefficient of friction, which is associated with lower recanalization rates. The 0-hour versus 72-hour harder thrombi did not have significant differences in terms of fibrin

pattern and outer fibrin rim. However, a comparison of the aging times for the softer thrombi revealed a predominance of an outer fibrin rim in the 72-hour clots. The outer fibrin rim could have caused increased friction and adhesion forces between the thrombus and vessel wall. This might be one of the reasons why the softer 72-hour thrombi had the lowest recanalization rates in this study.

5.5 Comparison of Stent Retrievers

MT experiments for this research project were conducted using two different stent retrievers (*Trevo XP ProVue Retriever, 3 x 20 mm* and *4 x 20 mm),* with matching lengths but varying diameters. (2) The stent retrievers also had the same length as the clots used for the experiments (clot length 20 mm). The smaller Trevo XP ProVue Retriever 3 x 20 mm achieved a slightly higher MT success rate for the funnel-shaped tip than the larger Trevo XP ProVue Retriever 4 x 20 mm. MT results for the standard tip were the same for both stent retrievers. These results support our hypothesis that larger distal access catheters improve the efficacy of mechanical thrombectomy. If the thrombus and stent retriever are larger in relation to the catheter tip (e.g., when using the smaller standard tip), then the risk of clot abruption and fragmentation at the tip would be higher. Due to diminished clot-stent retriever apposition, thrombus material might slide through the struts of the larger stent retriever when entering the smaller tip. Thus, oversizing of the stent retriever and material stiffness are associated with thrombus loss and stripping at the tip. In contrast, a smaller stent retriever would “fit” easier into a larger-sized DAC (e.g., funnel-shaped tip) during stent retrieval and would interact better with the thrombus. (168)

Furthermore, the interaction between the clot and stent retriever can be influenced by different clot compositions. Machi et al., 2017 (168) found that fibrin-rich “white” thrombi (larger than 6 mm) would roll and slide towards the tip of the stent retriever during retraction, due to insufficient clot incorporation into the mesh. (166, 168) This was caused by the increased stiffness of the fibrin-rich thrombi compared to the “red” erythrocyte-rich thrombi. As a result, higher compression forces were required to release the stent retriever over the fibrin-rich clot. Thus, the devices were not able to expand fully. However, “red” erythrocyte-rich thrombi – comparable to softer thrombi used in this study – were found to interact more strongly with the stent retriever mesh, but showed a higher incidence of fragmentation and distal embolization. In particular, softer 72h aged clots in the underlying study yielded increased MT failure rates for the larger stent retriever due to instability and fragmentation. Recanalization for both “red” and “white” clots could be improved by applying constant pressure and distal aspiration during mechanical thrombectomy.

Stronger radial forces during stent retriever expansion are associated with greater clot stent retriever apposition, thus enabling better interaction with the clot. Why is the radial force relevant for mechanical thrombectomy? The radial force expands outwards against the compression forces of the artery. Because the radial force is indirectly proportional to the vessel diameter, it increases in smaller vessels (e.g., M2-segment of the MCA compared to the M1-segment). High radial forces are associated with increased recanalization rates, but pose a higher risk of vessel wall damage. In addition, there is a “chronic outward force” that continuously expands when the vessel is relaxed. It depends on the material properties of the device. The radial force is also relevant for aspiration devices, such as our funnel-shaped tip. Attaining a sufficient radial force without damaging the vessel endothelium is essential to ensure safety of mechanical thrombectomy. (169)

The smaller stent retriever achieved higher recanalization rates although the MT success rate was not statistically significant for both stent retrievers (P= .53). These findings correlate with results from other trials. According to Yang et al., 2017 (170), stent retrievers with a smaller diameter had higher recanalization rates, shorter procedure times, and greater flexibility and deliverability for navigation in tortuous distant vessel territories, especially atherosclerotic vessels. However, stent retrievers with a smaller diameter also did not have a statistically significant effect on the reperfusion rate, as found in our study.

Recent studies indicated that MT success depends on the length of the stent retriever, rather than its diameter. (170-172) Reports on finding the “right” stent retriever length are contradictory. Some studies recommended a longer stent retriever (171, 172), while others a shorter stent retriever (173), depending on the clot burden score and the site of occlusion. (173) A retrospective analysis from the STRATIS (Systematic Evaluation of Patients Treated With Neurothrombectomy Devices for Acute Ischemic Stroke) registry rated longer stent retrievers (e.g., 40 mm) – due to their larger surface area – as independent predictive factors for improved first-pass recanalization (mTICI $\geq$ 2b), compared to shorter stent retrievers (e.g., 20 mm). Although long-term clinical outcome at 90 days (mRS $\leq$ 2 after 90 days) and final revascularization did not differ significantly, longer stent retrievers were associated with lower rates of clot fragmentation. (172) A further study found that radiopaque devices and local aspiration were independent predictors for improved first-pass recanalization. That is why we employed stent retrievers that contained one proximal and three distal radiopaque markers, as well as platinum wires for optimal visualization. (171) Self-expanding stent retrievers with a closed-cell configuration are generally used in distal vessels for mechanical thrombectomy, due to their flexibility in tortuous areas and their ability to interact with clots in the cerebral vasculature. (174) In accordance with recent scientific literature, we waited 3 minutes after releasing the stent retriever before retraction. This waiting period is considered a predictive

factor for improving first-pass recanalization and reducing distal embolization rates. This enables the stent retriever to capture the clot and integrate it into the mesh. (175)

In conclusion, most research trials examining stent retriever size for mechanical thrombectomy followed a retrospective design. This makes it difficult to determine the causality between MT success and stent retriever diameter and length. (170-173) To the best of our knowledge, randomized controlled trials that compare the optimal size of stent retrievers for mechanical thrombectomy have never been conducted because it would be unethical to randomize the stent retriever size in advance. Our study relied on the variation of the internal opening diameter as the main factor for comparing the funnel-shaped tip and the standard tip models. Therefore, we selected two stent retrievers with different diameters for our study design, instead of stent retrievers with different lengths.

5.6 Limitations: Evaluation of Material and Methods

Comprehensive preliminary results are essential for supporting development of a prototype, which in turn depends on third-party funding to complete and certify the device for the medical industry. To investigate the proof-of-concept of the modified funnel-shaped tip under standardized conditions, this study relied on a simplified and low-budget experimental setup using basic equipment for mechanical thrombectomy. The M1-MCA model was built from a single PVC tube. Therefore, collateral flow conditions were not considered. In addition, the M1-MCA-model did not take the tortuosity of the MCA-vasculature into account, making it difficult to determine the navigability of the funnel-shaped tip. Based on recommendations from other experimental studies, we used an aqua-glycerol solution to simulate blood-like viscosity. For simplification, our experiments were also performed without using a circulation flow pump. This meant that cerebral flow conditions could not be simulated. Thus, blood-like viscosity had no relevance for our MT experiments. (128)

The actual prototype was still being developed at the time of our experiments. Therefore, we utilized a simplified catheter model. Only the tip of the funnel-shaped model had a larger diameter. In comparison, the larger diameter of our prototype continues over a length of 2 to 3 cm. The inflexibility of our funnel-shaped tip (compared to the prototype) resulted in reduced wall-device apposition. The catheter tip might have been compressed and constricted during insertion into the MCA-model. Thus, the catheter tip model had to be manually dilated with an awl after every experiment. This might have led to an underestimation of the results for the funnel-shaped tip model. Under real life conditions, this limitation will no longer be valid, since the self-expanding prototype will be released at the occlusion site. Due to the basic equipment and simplified MCA model, mechanical thrombectomy was considered successful when the stent retriever and thrombus were fully retracted into the tip. For financial reasons, the stent

retrievers were reused numerous times, which might have decreased the ability of the stent retriever to interact with the thrombus. A performance bias in this study cannot be excluded, because the interventionalist could not be blinded during the MT procedures.

The limited availability of porcine blood restricted the number of experiments conducted for this study. Porcine whole blood, which is reported to have coagulation properties comparable to human blood, was used for generating thrombi for both histopathological and MT analyses. (176, 177) Despite the similarity of clot strength for both porcine and human blood clots, thromboelastographic findings from other studies indicated a lower platelet and higher fibrinogen clot contribution to clot firmness for porcine blood. Although the clot formation time was reported to be shorter, the clotting time was prolonged. The clot formation time is measured from clot initiation up to reaching a clot firmness of 20 mm, while the clotting time is defined as the onset of clot coagulation. In addition, porcine blood has a higher clot lysis index than human blood (measured after 30 minutes), which could affect the stability of clot structure. (176) Hypercoagulation, which is attributed to porcine blood, remains controversial in scientific literature and may influence clot composition and viscoelasticity during MT procedure. (176, 177) Furthermore, microscopic analyses showed that porcine clots contain a higher fibrin density despite having thinner fibrin fibers. Thus, porcine clots are associated with increased stiffness. This might have led to a reduction in recanalization rates compared to human clots. Although the effects of IV rt-PA on clot composition were not tested in this study, porcine clots were found to be less responsive to IV rt-PA. (155)

Testing homogenous clots under standardized laboratory conditions is another limitation of this study. In comparison, clinical clots from stroke patients reportedly have irregular and heterogenous compositions. (165) Although this study only employed one constant clot size and did not investigate the full range of clot compositions, the goal was to achieve results highlighting the comparative differences of the two catheter models. Furthermore, it should be noted that the clot structure from AIS patients is still relatively undefined and difficult to determine accurately. Additional studies should consider examining the impact of fibrinolytic agents on MT procedure and clot structure. Although an in vitro study design is a legitimate tool for initially testing the proof-of-principle of the funnel-shaped tip and evaluating MT failure causes, it has definite limitations. Further in vivo research is essential to evaluate the efficacy of the funnel-shaped prototype under cerebral flow conditions. At this point, it is unclear how the funnel-shaped tip might affect the vessel endothelium.

5.7 Future Outlook: Improving Acute Ischemic Stroke Treatment

Treatment of acute ischemic stroke can be improved at multiple levels. Many scientific and technological innovations impacting society in general are increasingly finding application in medicine. Key trends include digitalization, artificial intelligence, robotics, data analytics, imaging and biotechnology. Demographic changes and new service concepts will also affect medicine and spur further enhancements. The aging population in many countries will require new health prevention and awareness campaigns, products and services. More resources are flowing into medical research to adapt leading-edge technologies to the medical and healthcare industry. Improving in vitro models for research purposes and standardization will also benefit medicine. This will foster further development of new endovascular devices as well as pharmaceuticals for acute ischemic stroke. Further standardization of stroke protocols and checklists would improve stroke treatment. (178)

Endovascular devices

Mechanical thrombectomy is a rapidly advancing field of medicine. In particular, new endovascular devices (aspiration catheters and stent retrievers), procedures and techniques will further increase the safety and efficacy of mechanical thrombectomy. Aspiration devices are trending towards larger internal luminal diameters. Thus, large-bore distal access catheters (e.g., AXS Catalyst 7, SOFIA 6F plus) are increasingly being introduced. Enhancements to distal access catheters are focused on improving navigability and trackability, greater tip flexibility and proximal stability, as well as decreasing the rate of distal embolization. Technical enhancements for aspiration catheters include funnel-shaped devices like our prototype, as well as the ANCD and Lazarus devices. Furthermore, stent retriever technology continues to develop. Newly designed stent retrievers provide special cage and basket configurations for trapping different clot types and for reducing the rate of clot fragmentation. The push and fluff technique, which is used for closed-cell stent retrievers, has been developed to retrieve hard thrombi. Instead of using the standard unsheathing technique, the stent retriever is pushed into the clot during deployment, resulting in higher radial forces. A higher radial force allows the stent retriever to expand and interact better with the clot. A list of recently developed devices is shown in Table 15. (6, 49, 73, 110)

Redefining eligibility criteria and updating neuroradiological imaging technology

Faster and more specified patient selection can be achieved by redefining eligibility criteria and adapting imaging selection criteria. Neuroradiological imaging techniques are being developed and updated (e.g., redefining infarct volumes and mismatch ratios; see DAWN and DEFUSE-3 trials). The TESLA (Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke) trial is currently assessing and redefining infarct volumes for

radiological imaging. The goal is to examine cut-off scores and upper limits of infarct volume to improve the eligibility criteria for mechanical thrombectomy. Patients with a moderate to large infarct volume (ASPECTS score 2-5) in the anterior circulation are treated with mechanical thrombectomy in conjunction with best medical management and IV rt-PA, versus IV rt-PA alone. (179) Other trials such as the ENDOLOW (Endovascular Therapy for Low NIHSS Ischemic Strokes) and MOSTE (Minor Stroke Therapy Evaluation) trials are investigating the efficacy of mechanical thrombectomy in patients with low NIHSS scores. (1)

Basilar artery occlusions

Acute basilar stroke is known for its poor prognostic outcome. For a long time, it was unclear whether patients with basilar artery occlusions would be able to benefit from mechanical thrombectomy. This question was previously addressed in the BASICS (Basilar Artery International Cooperation Study) registry. However, there were no randomized controlled trials for the treatment of acute basilar stroke until recently. The first randomized controlled trial for basilar stroke was published in May 2021 in the *New England Journal of Medicine*. A total of 300 patients with symptomatic basilar occlusions were divided into two study groups (within a 6-hour time window after symptom onset) to evaluate the efficacy and safety of mechanical thrombectomy versus best medical management alone. Although mortality rates could be lowered when using endovascular therapy, there was no significant difference in favor of mechanical thrombectomy. Interestingly, patients over 70 years of age profited more from endovascular therapy than younger patients. The low power of the clinical trial was considered a limitation. Therefore, clinical trials with larger patient samples are required to verify these results. Finding the best treatment for patients with basilar artery occlusion still remains a challenge. (73, 180, 181)

Medications and therapies

Treatment of acute ischemic stroke can be further improved by launching new medications and establishing secondary prevention therapies. Some of these medications are investigational or off-label treatments. Examples of medications and therapies include: Elezanumab, immune modulator dimethyl fumarate, as well as allogeneic human stem cell treatment. The MOST (Multi-arm Optimization of Stroke Thrombolysis) trial is currently evaluating whether anticoagulants (such as Argatroban or Eptifibatide) administered alongside IV rt-PA will improve functional outcome at 3 months compared to the placebo group. (110, 182-184) Other studies such as the GOLIATH (The General or Local Anaesthesia in Intra-arterial Therapy), anSTROKE (Sedation Versus General Anaesthesia for Endovascular Therapy in Acute Stroke - Impact on Neurological Outcome) and SIESTA (Sedation vs. Intubation for Endovascular Stroke Treatment) single-center trials compared the effects of

conscious sedation versus anesthesia during mechanical thrombectomy. Although these trials favored general anesthesia over conscious sedation, results were not statistically significant. Due to limitations in the trial design, further multicenter randomized controlled trials are needed to clarify this question. (1)

Digitalization, telemedicine and stroke unit logistics

Digitalization in all areas of society is accelerating worldwide. This trend has been intensified by the global COVID-19 pandemic and the resulting surge in networked computing and communications for work, business, education, services and healthcare. In recent years, the German federal government has been moving ahead with digitalizing healthcare with a range of E-Health initiatives including the Electronic Health Card, E-Health Law, the National Health Portal (Das Nationale Gesundheitsportal) and the German Telemedicine Portal (Deutsches Telemedizinportal). (178) Optimizing logistics, procedures and infrastructure of stroke centers will help increase availability of AIS treatment (e.g., patients in rural areas), especially to meet the high demands of an aging population in many countries. Advances in telemedicine will also enable a faster assessment of acute ischemic stroke in the future. Many German federal states have set up telemedicine networks for AIS treatment. In April 2016, Rhineland-Palatinate established a network of 6 supraregional stroke units called the Telemedicine Stroke Network Rhineland-Palatinate or TemeS RLP (Telemedizinisches Schlaganfallnetzwerk Rheinland-Pfalz). These designated stroke units alternate in providing 24-hour on-call stroke expertise to participating hospitals in the network. The duty stroke expert is linked via video conferencing to remotely assist with patient examination and treatment. While we are only in the infancy of telemedicine, far greater capabilities are expected to emerge for telemedicine networks around the world. (185)

In accordance with the “time is brain” paradigm, quick referral to a specified stroke center is absolutely essential. There are two options for transferring patients with AIS symptoms to a stroke unit. The first option, called the “Direct Ship” paradigm, requires the patient to be transferred to an endovascular certified stroke center that provides mechanical thrombectomy. The second option calls for transferring the patient to a primary stroke center that provides best medical management as well as intravenous thrombolysis. In the latter case, eligible patients receive IV rt-PA as bridging therapy, before transfer to an endovascular certified stroke center. This is called the “Drip and Ship” paradigm. The RACECAT trial (Transfer to the Local Stroke Center versus Direct Transfer to Endovascular Center of Acute Stroke Patients with Suspected Large Vessel Occlusion in the Catalan Territory) compared the “Direct Ship” to the “Drip and Ship” paradigm. The goal was to determine whether transferring patients directly to an endovascular stroke center led to higher functional outcome. For this purpose,

the RACE (Rapid Arterial Occlusion Evaluation) scale was set to ≥ 5 in advance for assessing the likelihood of a large vessel occlusion in a prehospital setting. Results from the RACECAT trial indicated that “Direct Ship” was not superior to “Drip and Ship”. However, this does not mean that the “Drip and Ship” paradigm should delay treatment. (1, 186-188)

TABLE 15	***Mechanism***	***Recanalization***	***ENT***	***Trial***
Aspiration catheters				
Advanced Thrombectomy System *(ANCD, R&D, Anaconda Biomed, Barcelona, Sant Cugat del Vallès, Spain), (7)*	Self-expanding funnel-shaped tip with a large distal ID + distal flow arrest	94% (mTICI ≥ 2b)	0%	in vitro
ARC *(Medtronic, Irvine, California, USA),* ***(110, 189)***	Intracranial support catheter; high distal ID/OD ratio: distal ID (0.061 inch), distal OD (0.069 inch), improved trackability and navigability in tortuous vessels, greater tip flexibility;	98% (mTICI ≥ 2b) 49% (mRS score ≤ 2 at 90 days)	5%	clinical trial (N = 41)
AXS Catalyst 6/Cat 6 & AXS Catalyst 7/Cat 7 *(Stryker, Kalamazoo, Michigan, USA*), **(189, 190)**	Cat 6 ID (0.060 inch) at the tip Cat 7 ID (0.068 inch) at the tip flexible distal zone and a supportive proximal shaft, good trackability in tortuous vessels	For the Cat 6: 84% (mTICI ≥ 2b) 47% (mRS score ≤ 2 at 90 days) trials for the Cat 7 are still in progress	< 1%	clinical trial (N = 107)
ClearLumen *(Walk Vascular, Irvine, California, USA),* **(110, 191)**	The device combines thrombus aspiration and fragmentation; by injection of high-pressure saline jets inside the catheter tip, providing continuous aspiration; FDA approval for myocardial infarction	95% (TIMI ns.)	5%	clinical trial, prospective single-center trial (N = 20)
Lazarus Funnel *(Lazarus Effect, Campbell, California, USA),* (110, 142, 143)	Funnel-shaped nitinol mesh enclosing the stent retriever during retraction, forming a protective sheath	80% (in vitro) 95% (in vivo) (mTICI ≥ 2b)	0%	in vitro; clinical trial (N = 20)
Mi-Axus *(MIVI Neuroscience Inc. Eden Prairie, MN, USA),* (110)	DAC with a proximal 6F lumen and distal 5F opening to improve distal trackability	ns.	ns.	ns.
R^4Q aspiration catheter *(MIVI Neuroscience Inc. Eden Prairie, MN, USA),* ***(144, 192)***	Guiding catheter with a larger proximal ID (0.090 inch). The proximal three-quarters of the aspiration catheter are replaced with a control wire	91% (mTICI ≥2b) 44% (mRS score ≤ 2 at 90 days)	3%	clinical trial (N = 32)
SOFIA 6F Plus *(MicroVention Terumo, Tustin, California, USA),* **(189, 193)**	Large bore DAC with lumen ID (0.070 inch); provides a soft distal tip and torquable shaft; high navigability; can be used as aspiration device or concomitantly with a stent retriever	96% (mTICI ≥2b) 49% (mRS score ≤ 2 at 90 days)	5%	clinical trial (N = 85)

Stent retrievers				
Nimbus *(Cerenovus, Irvine, CA, USA),* **(194-196)**	Geometric clot extractor (GCE), consists of a proximal spiral section, which interacts with the thrombus and a distal barrel section. The struts have a pinch-pull configuration. The device was developed to retrieve thrombectomy-resistant clots. Can be used in the anterior and posterior circulation.	100% (TICI 3) GCE vs. 7.7% (TICI 3) Solitaire (SR), (P < .0001); average N of passes: 2.15 GCE vs. 3 SR; 66% FPE for the GCE after SR failure (P < .005)	ENT 7.7% (GCE) vs. 15.4% (SR)	in vitro (2017/2018), (194); launched Oct. 2020, post marketing study currently running (196)
EmboTrap II *(Neuravi/Cerenovus, Miami, FL, USA),* **(197)**	Open outer cage with a lower radial force; inner stent with a high radial force used as a flow channel; closed distal end; recommended for various clot types	80% (mTICI ≥2b) 52% FPE (mTICI ≥2b) 67% (mRS score ≤ 2 at 90 days)	6.6%	ARISE II, 2015 – 2017 European clinical trial (N = 227)
Embolus Retriever with Interlinked Cages (ERIC) *(MicroVention Terumo, Tustin, California, USA),* **(198)**	Interlinked wire cages to facilitate thrombus integration; comes in adjustable lengths and different numbers of cages	82% (mTICI ≥ 2b) 50% (mRS score ≤ 2 at 90 days)	< 1%	clinical trial (N = 183)
Golden Retriever *(Amnis Therapeutics, Or Akiva, Israel),* (6)	Cage formation expanding from a microwire; clinical trials planned at the Karolinska institute in Stockholm, Sweden	ns.	ns.	ns.
Tigertriever *(Rapid Medical, Yoqneam, Israel),* **(199)**	Flexible distal tip; the struts are connected at the crossing points; strong radial force, adjustable diameter	85% (mTICI ≥ 2b) 24% FPE (mTICI 3) 39% (mRS score ≤ 2 at 90 days)	5.9%	clinical trial (N = 61) retrospective trial
ThrombX Retriever *(TXR; ThrombX Medical Inc., Santa Clara, California, USA),* (152)	Stent retriever composed of two laser-cut nitinol baskets to trap the thrombus, tested with fibrin-rich clots	90% (mTICI ≥ 2c)	ns.	in vitro (N = 40)

Table 15. List of recently developed MT devices. *Without any claim to completeness. This table summarizes various recently developed aspiration catheters and stent retrievers. Some of these devices are investigational and have not yet received FDA approval. Note abbreviations: ARISE (Analysis of Revascularization in Ischemic Stroke with EmboTrap); BGC = balloon guide catheter; DAC = distal access catheter; FPE = first pass effect; GCE = Geometric Clot Extractor; ID = internal diameter; N = number; ns = not specified; OD = outer diameter; SR (Solitaire Retriever).* (6, 7, 110, 152, 189, 190, 192-199)

6 Conclusion

Mechanical thrombectomy is the standard treatment for patients with acute large vessel occlusion up to 24 hours after AIS symptom onset. Embolism in new territories and clot abruption at the tip of a distal access catheter can occur in up to 10% of cases. To improve the outcome of mechanical thrombectomy, we compared a catheter model with a funnel-shaped tip featuring a larger diameter to a catheter model with a standard-sized tip. Mechanical thrombectomy was performed 80 times for each catheter model (N = 160), using two different stent retrievers (Trevo XP ProVue 3/20 mm and 4/20 mm) and four different clot types (hard vs. soft thrombi, 0-24h vs. 72h aging times).

A significantly higher first-pass recanalization rate of 70% was observed for the funnel-shaped tip versus 30.0% for the standard tip, regardless of the clot type and stent retriever (absolute difference, 32; relative difference 57.1%; $P < .001$). In addition, the rate of clot abruption at the tip was reduced and reached statistical significance ($P < .05$). Thus, our main research hypothesis could be validated. Clot abruption at the tip was the leading cause of failure for the standard tip, while failure causes for the funnel-shaped tip varied. The stent retriever failed to interact with the clot before reaching the funnel-shaped tip in 45.8% of the cases. This occurred mainly when using harder thrombi. The other 54.2% of the failures were caused by stripping of thrombus material at the funnel-shaped tip, especially when using softer thrombi. Softer thrombi were found to be more susceptible to fragmentation during stent retrieval due to the absence of a fibrin pattern and a lack of structural integrity.

Consequently, results indicate that MT success rates were influenced by different clot compositions. Harder thrombi showed a tendency towards improved recanalization compared to softer thrombi ($P = .06$). Since the significance level was set at $\alpha = 5\%$ in advance and the recanalization rates of the different clot types fell short of statistical significance, our secondary hypothesis could not be accepted. Thus, we adhere to our null hypothesis that there was no statistically significant difference between the harder and softer thrombi in terms of improved recanalization. One explanation could be that harder thrombi contained enough erythrocytes to exceed the erythrocyte threshold of 20%. This is associated with a reduced force of friction and improved recanalization. However, quantifying the erythrocyte concentration of thrombi was beyond the scope of our research study. For future in vitro MT procedure and clot analyses, fixed concentrations of erythrocytes are recommended, as well as using different MT techniques.

Histopathological analyses indicated that harder mechanically prepared thrombi (using a Chandler loop) presented a significantly higher proportion of fibrin, a more regular fibrin distribution, and a reticular or insular fibrin pattern relative to softer thrombi prepared under

static conditions. A Chandler loop simulates blood flow under dynamic conditions. Therefore, blood cells and fibrin are regularly distributed. Under static conditions, erythrocytes are unevenly distributed and more densely concentrated. In addition, the 0 to 24-hour thrombi achieved significantly higher recanalization rates than 72-hour aged thrombi. Aged thrombus material may restructure and degrade, becoming more condensed due to fluid loss. This could increase friction during stent retrieval. The difference in recanalization rates between the clot aging times (0-24 hours vs. 72 hours) was greater for the harder fibrin-rich thrombi than the softer erythrocyte-rich thrombi. Since fibrin may dissolve over time, the harder fibrin-rich thrombi may be more susceptible to the aging time than the softer fibrin-low thrombi. The occurrence of an outer fibrin rim was observed more frequently in the 72-hour aged thrombi, particularly the softer 72-hour thrombi which showed the lowest recanalization rates of all clot types. The two stent retrievers *(Trevo, XP ProVue Retriever 3 x 20 mm* and *4 x 20 mm),* which varied in diameter, had no statistically significant effect on the MT success rate.

To conclude, this research project underscores the added value of using a catheter with a larger-sized tip for mechanical thrombectomy. Thus, a prototype with these characteristics was recently patented by our work group. Further in vitro and in vivo testing of our prototype is currently running and has already indicated promising results.

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9 Curriculum Vitae

Personal Details

Emily Sarah Payne

Date of Birth	05/15/1996
Place of Birth	Wiesbaden, Germany
Citizenship	German, Canadian

Work Experience

Aug. 23 – Sep. 21, 2018 Mar. 12 – Apr. 14, 2019	**Student assistant and clinical training** in Emergency Medicine at Englewood Community Hospital under supervision of Dr. Frank Novy (MD), Florida, U.S.A.
Sep. – Dec. 2018	**Student Assistant** at a GP's office, Dr. med. Frank Emmermann, Wackernheim, Germany
Oct. 2016 – Feb. 2017	**Student Assistant** at the Institute of Functional and Clinical Anatomy, University Medical Center of the Johannes Gutenberg University, Mainz, Germany

Education

2014 – 2021	**Faculty of Medicine, Johannes Gutenberg University, Mainz, Germany** 3. Medical State Examination on 05/11/2021 2. Medical State Examination on 04/17/2020 1. Medical State Examination on 08/30/2016
2006 – 2014	**High School, Maria Ward Schule, Mainz, Germany** German Abitur (A-levels, Baccalaureate equivalent) on 03/21/2014
2002 – 2006	**Primary School, Paul-Maar-Schule, Floersheim, Germany**