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Comparison of newly introduced cerebral angiographic revascularization grading eTICI with the actual standard mTICI scale

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Hiermit erkläre ich, die Dissertation mit dem Titel "*Comparison of newly introduced cerebral angiographic revascularization grading eTICI with the actual standard mTICI scale*" eigenständig angefertigt und keine anderen als die von mir angegebenen Quellen und Hilfsmittel verwendet zu haben.

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TABLE OF CONTENTS

1 ABBREVIATIONS

ACA:	Anterior cerebral artery
ADAPT:	A direct aspiration first pass technique
AIS:	Acute ischemic stroke
BA:	Basilar artery
CI:	Confidence interval
CT:	Computed tomography
eTICI:	Expanded treatment in cerebral ischemia
EVT:	Endovascular treatment
FDCT:	Flat-detector computed tomography
FDCTA:	Flat-detector computed tomography angiography
IA:	Intra-arterial
ICA:	Internal carotid artery
ICC:	Intraclass correlation coefficient
IQR:	Interquartile range
IV:	Intra-venous
LVO:	Large vessel occlusion
MCA:	Middle cerebral artery
MDCT:	Multi-detector computed tomography
MDCTA:	Multi-detector computed tomography angiography
MDCTP:	Multi-detector computed tomography perfusion

MRI:	Magnetic resonance imaging
mRS:	Modified ranking scale
MT:	Mechanical thrombectomy
mTICI:	Modified treatment in cerebral infarction
NIHSS:	National Institutes of Health Stroke Scale
OD:	Odds ratio
PCA:	Posterior cerebral artery
r-tPA:	Recombinant tissue plasminogen activator
SAVE:	Stent retriever assisted vacuum-locked extraction
TICI:	Thrombolysis in cerebral infarction
TIMI:	Thrombolysis in myocardial infarction
UMG:	University of Medicine Göttingen

2 INTRODUCTION

Stroke represents a common pathology with potentially heavily debilitating or lethal consequences if untreated. The last two decades witnessed a remarkable development of therapeutic options for ischemic stroke, the most frequent subtype of cerebrovascular accident. Current therapeutic options include both medical treatment and minimally invasive mechanical thrombectomy. The goal of the latter, a new modality of interventional stroke therapy, is to revascularize ischemic yet not completely infarcted brain tissue via endovascular mechanical removal of the thrombus.

The progress in techniques and methods led to remarkable improvement of outcome in stroke patients (Balucani et al. 2016; Evans et al. 2017). Parallel to the evolution of interventional stroke treatment, there has been a development in revascularization grading, utilized to assess the success of mechanical embolectomy of large vessel occlusion. Several gradings are available and the most commonly adopted is the “modified treatment in cerebral ischemia” (mTICI). Although the mTICI scale represents a practical and relatively simple scale easily applied in everyday clinical practice, it shows a considerable lack of predictability of clinical outcome in middle to high percentages of revascularization of ischemic territory. In order to overcome this limitation we investigate a new angiographic revascularization grading, named “expanded treatment in cerebral

ischemia” (eTICI), and we compare the ability of the newly introduced eTICI to the mTICI angiographic revascularization grading in predicting the clinical neurological outcome and functional independence after endovascular treatment of large vessel occlusion in a real world cohort. Moreover, the influence of time on the angiographic outcome (eTICI) after endovascular treatment will be examined.

2.1 Stroke

2.1.1 Ischemic Stroke

Cerebrovascular disease can be best defined as an “acute neurologic dysfunction of vascular origin with sudden or rapid occurrence of symptoms and signs corresponding to the involvement of focal areas in the brain” (Goldstein et al. 1989).

Stroke is an extremely common pathology, representing the leading mortality cause in the female and the second after coronary artery disease in the male gender in industrialized nations (11 % of the total) (Allen and Bayraktutan 2008; Kalaria 2012; Arboix 2015). Cerebrovascular insult is furthermore the major reason of lost disability-adjusted life-years in adults in first world countries (Vidale and Agostoni 2017). Circa 90 % of patients affected by stroke present residual and permanent neurological deficits. About 30 % of these patients are so heavily affected, that they cannot return to their previous usual activities at the same degree of independence as before the cerebrovascular insult (Kalaria 2012; Arboix 2015). Stroke also represents an important etiology of mental impairment and dementia (Allen and Bayraktutan 2008; Arboix 2015).

2.1.2 Etiology and pathophysiology

Stroke is a multifactorial disease and several risk factors play a significant role in its etiology. These are typically classified in “non-modifiable” and “modifiable”. The first ones mainly include inherited diseases, gender and age, while the latter can be at least partially influenced by the lifestyle (diabetes mellitus, arterial hypertension, carotid stenosis, smoking and substance abuse including alcohol, dyslipidemia, obesity, metabolic syndrome among others) (Marrugat et al. 2007; Allen and Bayraktutan 2008; ESO 2008; Arboix 2015).

Two major subtypes of stroke can be distinguished: hemorrhagic (15 – 20 %) and ischemic stroke (80 – 85 %) (Lopez et al. 2006). The ischemic cerebrovascular accident is a very diverse pathological and clinical condition, accounting for several causes and a broad spectrum of neurological appearances. The majority of ischemic cerebrovascular accidents (almost 50 %) have an arterial thrombotic origin. Concerning the remaining half ca. 20 % have an embolic etiology, 5 - 10 % are watershed strokes (caused by cardiac insufficiency or severely low blood pressure), while the rest have different (such as tumor compression, cerebral venous thrombosis) or unknown origin (Hinkle and Guanci 2007). In a thrombotic cerebrovascular accident, an injury of the endothelium of the arteries supplying the brain leads to plaque and thrombus formation along the

injured vessel. The damage of the tunica intima activates the thrombocytes' adhesion and aggregation, followed by the coagulation cascade and eventually the development of a thrombus. The thrombotic formation may cause an arterial flow reduction, while the collateral circulation may maintain its function and compensate the flow drop. However, if the compensation of collateralization is insufficient or disrupted, brain perfusion is decreased or even abolished in the supply territory of the thrombosed artery, leading to cerebral ischemia and, if the process is not reversed, eventually cell death (Hinkle and Guanci 2007). In the event of an embolic stroke, an embolus originates outside the intracranial circulation and is then transported via the blood circulation to the brain, where it wedges within the cerebral arteries. An embolus often has a thrombotic origin (thromboembolus), detaching from an atherosclerotic plaque in the internal carotid artery. Emboli can moreover have a cardiac genesis (often because of cardiac arrhythmias or endocarditis) or a venous origin (deep vein thrombosis with thromboemboli moving from venous to arterial circulation through a patent foramen ovale) (Hinkle and Guanci 2007). Surgical and interventional procedures may cause fat, gas or thromboembolism, particularly during major surgery or endovascular procedures. Other less frequent etiologies of cerebrovascular insult comprise carotid dissection (Blum and Yaghi 2015) and the presence of coagulation disorders (Levine et al. 2004). Further

rarer yet clinically relevant etiologies are vasculitis, infectious diseases and intravenous substance abuse (Blank-Reid 1996).

Independently from its etiology, in the event of an ischemic cerebrovascular accident, a sudden interruption or relevant decrease in blood supply to a cerebral area occurs. The consequent glucose and oxygen deprivation impair the normal function of brain cells, which cannot perform aerobic metabolism and, unlike other tissues, are unable to switch to anaerobic metabolism due to the lack of any long-term energy storage, making the brain particularly vulnerable to ischemia. The adenosine triphosphate (ATP) supply is rapidly depleted (usually within 4 minutes), leading to loss of ability to maintain electrochemical gradients, impairment of disposal of metabolic waste, lipolysis, the arrest of protein synthesis and eventually cell death (Lee et al. 2000). Furthermore, solid evidence indicates that the blood supply and the lack of metabolites limitations are only a part of the equation in the cerebral damage due to ischemia. The brain's signaling pathways, which under normal conditions serve for physiological inter- and intracellular communication, can precipitate the effects of ischemia by exacerbating the energetic depletion and fostering the chemical pathways involved in neuronal and glial death (including but not limited to reactive oxygen species, inflammation, insufficiency of membrane pumps, activation of proteases, nucleases, lipases, caspases

and apoptosis) (Choi 1988; Obrenovitch and Richards 1995; Lee et al. 1999; Lee et al. 2000; Hinkle and Guanci 2007).

Comprehension of etiology/pathophysiology as well as of the rapid dynamics of the cerebral ischemic event contributed to the development of a “therapeutic timespan” for stroke treatment. Within the ischemic cerebrovascular bed, two major injury areas can often be distinguished: the infarct core and the “penumbra”, an area of surrounding ischemic, hypoperfused but not fully infarcted brain tissue, which can potentially be rescued via intra-venous or interventional treatment (Kaufmann et al. 1999; Yu et al. 2016). A higher volume of penumbra around a cerebral infarction indicates a greater volume of potentially salvageable brain tissue (Herholz and Heiss 2000).

2.1.3 Signs and symptoms

In the acute setting, a potential stroke is handled as a medical emergency. A precise anamnesis collected by the emergency physician or the neurologist is critical in order to identify the precise moment of onset of the ischemic event. Important information comprises a detailed description of the episode, relevant clinical and pharmacological anamnesis plus significant risk factors. Clinical neurological assessment of the patient in

acute care is usually supported by the “National Institutes of Health Stroke Scale” (NIHSS), allowing a relatively impartial quantification of the severity of the neurological deficits caused by a cerebrovascular accident. The NIHSS is structured as a checklist and allows the clinician a rapid yet precise assessment of the acute stroke patient, including consciousness, visual, motor, sensory and language functions (Goldstein et al. 1989; Goldstein and Samsa 1997; Richardson et al. 2006; Meyer and Lyden 2009).

Because of the sophisticated and highly differentiated anatomy and physiology of the encephalon, the manifestations of a stroke cover a wide spectrum and differ widely according to the artery and the cerebral vascular territory involved in the apoplectic event. A stroke involving the anterior and middle cerebral artery territorium causes, among others, motor or sensory deficits of the contralateral bodyside with variable involvement of the extremities (primary motor cortex in the precentral gyrus, premotor cortex, supplementary motor cortex, centrum semiovale and internal capsule). In a flow disturbance in the internal carotid artery symptomatic from both anterior and media territorium can occur in addition to amaurosis fugax or transmonocular blindness. Involvement of the posterior cerebral artery territorium typically causes ipsilateral hemianopsia or cortical visual impairment (optic radiation and visual cortex) plus eventually contralateral motor and sensory deficits (posterior

limb of the internal capsule). Considering the complexity of the brain stem, where numerous nuclei and white matter tracts are precisely organized in a rather restricted space, a stroke affecting the mesencephalon, pons or medulla oblongata usually manifests with a complex and variable constellation of signs and symptoms including hemi- or tetraparesis, sensory impairment in all extremities, eye movement disorders and diplopia, vertigo, tinnitus, nausea, vomiting and consciousness impairment. In addition, a variable involvement of the cranial nerves (III – XII) can manifest. A cerebellar apoplectic event affects coordination and causes limb and gait ataxia. Along with these symptoms, dominance plays an important role since the dominant encephalic hemisphere also controls the language. The left cerebral hemisphere is dominant in virtually all right-handed and ca. 60 % of left-handed individuals. An affection of a dominant left-brain hemisphere, in addition to the above cited ones, can cause impairment of different language functions, including aphasia (motor, sensory or mixed), apraxia, acalculia and agraphia. A stroke involving a nondominant hemisphere may cause neglect, dysarthria and ipsilateral gaze preference (Searls et al. 2012). A representation of the brain arterial vessels can be seen in ***figure 1***.

As mentioned above, about 90 % of patients suffering a stroke will present permanent sequelae, affecting their everyday life in various degrees. In order to assess and objectively quantify the impairment in common life

activities experienced by stroke patients the *modified Ranking Scale* (mRS) was originally introduced by Dr. Rankin in 1957 (Rankin 1957; Quinn et al. 2007; Quinn et al. 2008) and subsequently modified to its current form in the end of the 1980s (Farrell et al. 1991). The mRS classifies the disability in 7 degrees, spanning from 0 to 6 (No Symptoms – Death) (for details see ***table 1***).

2.1.4 Imaging

Considering the acute nature and the necessity of rapid treatment, neuroimaging represents a cornerstone in the work-up of stroke, supplying crucial information to the diagnosis and management of patients, particularly involving therapy in acute setting (NINDS 1995).

As of today, both magnetic resonance and computed tomography imaging can be used in stroke imaging. Both techniques offer the possibility to identify fully infarcted as well as ischemic brain parenchyma and most critically the capability of distinguishing between the two. The potential of detecting salvageable brain tissue is with state-of-the-art scanners almost equal in both techniques. Despite the radiation dose, imaging via CT is often preferred due to widespread availability of CT scanners and reduced scanning time. MRI is typically reserved for chronic cases or control

examinations in stroke patients although protocols, work-flows and standard operating procedures vary between different institutions (Vymazal et al. 2012). Clinical neurological and non-contrast CT data may not fully depict the extension or the gravity of a brain ischemia, particularly in the hyperacute phase (Dromerick and Reding 1995; Mohr et al. 1995; Fisher 1997). Therefore further imaging techniques are necessary to accurately evaluate possible acute stroke interventions (Mohr 1997), including a representation of the brain vasculature (CT-Angiography) or of the cerebral perfusion (CT-Perfusion), thus allowing to distinguish fully infarcted from ischemic and thus salvageable brain parenchyma.

In the Department of Diagnostic and Interventional Neuroradiology of the University of Medicine Göttingen, imaging in acute stroke is performed via multi-detector computed tomography (MDCT/ MDCT-Angiography/ MDCT-Perfusion) or flat-detector computed tomography (FDCT/ FDCTA) (Leyhe et al. 2017; Psychogios et al. 2017) as explained in detail in *Materials and methods, interventional treatment*. An example of acute stroke imaging can be seen in ***figure 2***.

2.2 Stroke treatment

2.2.1 Overview and intravenous therapy

Considering the burdening and often permanent consequences of an ischemic cerebrovascular event, adequate and prompt treatment is required on acute setting and is a key healthcare priority (Evans et al. 2017), thus promoting research to establish an effective therapy. Current therapeutic options for acute stroke include thrombolysis, such as with intra-venous recombinant tissue-type plasminogen activator and interventional treatment.

IV therapy for ischemic stroke with alteplase (trade names Activase and Actilyse) was first authorized by the US Food and Drug Administration in 1996, led by the conclusions of the clinical trial of the National Institute of Neurological Disorders and Stroke (National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group 1995). IV therapy played a major role in the establishment of stroke management. Stroke services "flourished around" intravenous thrombolysis, with the creation of specialized stroke units, dedicated workflows and operating procedures plus highly trained personal, both inside and outside the hospitals. Several attempts have been made to raise awareness in general population in

order to recognize a possible stroke, react promptly and consequently be able to rapidly receive adequate therapy (Goldstein 2014; Romano and Sacco 2015). These have been effectively summarized in the rather catchy slogan “Time is brain” (Saver 2006).

IV therapy with r-tPA is still performed to this day within max. 4.5 hours from begin of the symptomatic, achieving however a low recanalization of the occluded vessel (< 30 % of patients) (Bhatia et al. 2010; Wardlaw et al. 2012). This therapeutic approach has also demonstrated reduced effectiveness in the recanalization of large intracranial arteries occlusions (distal internal carotid and basilar artery), with a positive clinical outcome (mRS 0 -2) in ca. 25 % of cases (Fischer et al. 2005; Rubiera et al. 2005). Relevant predictors of poor outcome with IV therapy are the length (Riedel et al. 2010; Riedel et al. 2011; Kamalian et al. 2013; Mishra et al. 2014) as well as the localization of the clot (Hirano et al. 2010; Saarinen et al. 2012). In particular patients with longer thrombi and/ or location in larger vessels (ICA, proximal MCA and BA) respond poorly to IV r-tPA. IV therapy presents further and well recognized limitations, including a limited time frame of administration (up to 4.5 hours) plus several contraindications due to the high bleeding risk (including coagulation disorders, bleeding diatheses, oral anticoagulation such as with sodium warfarin, recent bleeding, positive anamnesis for brain neoplasm or hemorrhage and surgery in the last 3 months among several others) (Jauch et al. 2013;

Berkhemer et al. 2015). This relative lack of effectiveness combined with the relevant limitations of application of the only approved therapy of the time contributed to the development of endovascular techniques for ischemic stroke.

2.2.2 Endovascular treatment

Intra-arterial stroke treatment comprises the pharmacological disaggregation of the clot via endovascularly applied thrombolytic drugs and the mechanical removal of the thrombus (Berkhemer et al. 2015). The first was introduced systematically during the late 1990s with an initial trial called PROACT: “Prolyse in Acute Cerebral Thromboembolism” (del Zoppo et al. 1998).

IA thrombolytic treatment consists in direct injection of thrombolytic agents in close proximity to the thrombotic occlusion under x-ray guidance. Although early randomized trials and subsequent meta-analyses (Lee et al. 2010) demonstrated a potential benefit of intra-arterial treatment with prourokinase (del Zoppo et al. 1998; Furlan et al. 1999) or urokinase (Ogawa et al. 2007), IV therapy was not administered in the control groups of these studies, making the validity of these results doubtful (Berkhemer et al. 2015). Furthermore the conclusions of recently conducted trials

investigating intra-arterial therapy with thrombolytic drugs (such as the IMS III, SYNTHESIS Expansion and MR RESCUE) have contributed to the uncertainty of significance of this approach (Broderick et al. 2013; Ciccone et al. 2013; Kidwell et al. 2013). As a result thrombectomy has widely superseded IA thrombolytic drugs as interventional treatment of ischemic stroke (Mehta et al. 2013; Berkhemer et al. 2015; Evans et al. 2017).

2.2.3 Mechanical thrombectomy

The goal of mechanical thrombectomy is to restore perfusion in ischemic brain parenchyma by means of endovascular mechanical removal of the thrombus, hence avoiding or limiting infarction of the tissue (Przybylowski et al. 2014). This is made possible by a vast assortment of dedicated interventional materials, as represented in ***figure 3*** (Raychev and Saver 2012). The first endovascular device (Merci Retrival System, MERCI) was approved for clinical application by the FDA in August 2004 (Felten et al. 2005). The MERCI and subsequent Multimeric trials demonstrated positive recanalization rates (60.8 and 69.5 % respectively) with good neurological outcome in 34 % of patients, using the Merci device plus thrombolytic therapy (IA/ IV) (Smith et al. 2005; Smith et al. 2008). These

encouraging results fostered the development of further techniques and materials, with the introduction of the Solitaire FR Revascularization Device and Trevo ProVue Retriever, so called “Stent-retrievers”. Their efficacy was put to test in 2012 in two different randomized trials, the SWIFT (Saver et al. 2012) and TREVO 2 (Nogueira et al. 2012). Both devices demonstrated a remarkably better recanalization compared with to MERCI. The Solitaire FR performance was as a matter of fact so remarkably superior to the MERCI (recanalization rate: 83 % vs 48.1 %, mortality rate at 3 months: 17.2 % vs 38.2 %), that the SWIFT trial was interrupted earlier than planned (Saver et al. 2012).

During the first half of the 2010 decade several new generation stent retrievers were tested. The results of nine randomized controlled trials were all issued in a rather short interval, representing a true milestone in interventional stroke treatment (Berkhemer et al. 2015; Campbell et al. 2015; Goyal et al. 2015; Jovin et al. 2015; Saver et al. 2015; Bracard et al. 2016; Mocco et al. 2016; Khoury et al. 2017a; Khoury et al. 2017b; Muir et al. 2017). The first published study has been the “Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischaemic Stroke” in the Netherlands. The so called “MR CLEAN” study demonstrated the clear superiority of thrombectomy vs. standard medical treatment as therapy of acute stroke with LVO in the anterior cerebral circulation (ICA/ MCA), improving functional independence at 90 days (evaluated with the mRS).

All the following, above cited studies confirmed the MR CLEAN results and were stopped earlier than planned because of manifest efficacy and/ or loss of principle of equipoise (Evans et al. 2017). The HERMES meta-analysis of the first five published studies („Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials“) was subsequently conducted and published in 2016 (Goyal et al. 2016). HERMES provided a significant amount of data, most importantly indicating that stroke patients treated with thrombectomy are more likely to achieve functional independence at 90 days (i. e. mRS 0–2, no symptoms to slight disability) in comparison with patients who received best medical treatment (46.0 % versus 26.5 %). IV r-tPA was administered to 83 % of patients in the thrombectomy population and 87 % of those in the control population. Remarkably no significant difference was observed between the two groups regarding mortality at 90 days or the risk of subarachnoid or intracerebral hemorrhage (Evans et al. 2017). Successive meta-analyses confirmed the results of the HERMES study (Bush et al. 2016; Rodrigues et al. 2016). The convincing evidence of these trials led to an update of stroke practice guidelines in North America (Powers et al. 2015; Casaubon et al. 2016; Powers et al. 2018) and in Europe as well (Wahlgren et al. 2016; White et al. 2017). The new recommendations indicate that thrombectomy should be performed in patients older than 18 years old with

an occlusion of the ICA or proximal MCA (M1 segment) within 6 hours of symptom onset (Powers et al. 2018).

A further meta-analysis of the five studies (Saver et al. 2016) demonstrated improved clinical outcome even with embolectomy carried out up to 7.3 hours after onset. In 2018 two further important randomized trials were published: DAWN and DEFUSE 3. These studies reported better outcomes for disability at 90 days with thrombectomy plus standard care compared to standard care alone in selected group of patients treated up to 24 and 16 hours after ischemic stroke onset respectively (Albers et al. 2018; Nogueira et al. 2018), although the greatest benefit can be achieved with recanalization within 2 hours after onset. Just as for IV r-tPA, rapid patient management and interventional treatment are key to achieving the best possible outcomes. Indeed the time factor (particularly from onset of symptoms to admission in the hospital and to recanalization) plays a major role in the probability in attaining a favorable neurological outcome after thrombectomy (Saver et al. 2016). As for intravenous therapy, efficient patient management and rapid interventional treatment are critical for the treatment success, since an extended interventional time above 60 minutes is linked with lower reperfusion percentage and an increased complications rate (Behme et al. 2014; Spiotta et al. 2014).

2.2.4 Devices and technique

In the last 15 years interventional neuroradiology witnessed a remarkable expansion of devices and techniques in order to achieve the primary goal of rapid and safe recanalization of large vessel occlusion and consequently restore the reperfusion of the brain.

Following the encouraging results of the randomized trials (Berkhemer et al. 2015; Campbell et al. 2015; Goyal et al. 2015; Jovin et al. 2015; Saver et al. 2015; Bracard et al. 2016; Mocco et al. 2016; Khoury et al. 2017a; Khoury et al. 2017b; Muir et al. 2017), the stent retriever became a frequently used device for mechanical thrombectomy (***figure 4***). Besides the main retrieving tool, numerous support equipment is available to the neurointerventionalist, including but not limited to balloon guide catheters, aspiration catheters and vacuum devices. Additionally, the different etiology/pathophysiology of the LVO (e. g. free-floating thrombus, single vs. tandem lesion, concurring arterial dissection), the thrombus type and anatomic variability of the patient may challenge the standard approach and require different techniques and materials (Evans et al. 2017).

During a standard procedure, after puncture of the common femoral artery under local anesthesia, a large (typically 8 French) guiding catheter is steered under x-ray guidance to the ICA ipsilateral to the occlusion. Through the guide catheter an intermediate catheter (commonly 5 or 6 Fr)

is positioned within the cerebral arterial circle, often in the distal segments of the ICA. A microcatheter (usually 0.018 inches) is then pushed past the thrombus under aspiration or with the assistance of a microguidewire (Maus et al. 2017; Maus et al. 2018). After reaching a satisfying set up, the microguidewire is carefully extracted and the stent retriever is deployed, unfolding around the clot, similarly to a stent, but unlike this one remaining attached to its wire. After a variable time, but usually 2-3 minutes, the stent retriever gets enmeshed with the thrombus. At this point the stent retriever gets retracted in the intermediate catheter under vacuum aspiration. The stent retriever- intermediate catheter system is then removed through the guide catheter and angiography series are performed in standard technique to assess the reperfusion of the brain territory (Evans et al. 2017; Maus et al. 2017; Maus et al. 2018). A summary of the main steps of a mechanical thrombectomy procedure can be found in ***figure 5***, while ***figure 6*** pictures a thrombus extracted with a stent retriever. As stated above, vessel conformation, the mechanism of the LVO, thrombus type and location might require a diverse approach as well as different techniques and materials.

The issue of anesthesia versus awake thrombectomy is still somewhat controversial. In two recent prospective, randomized studies (GOLIATH, General or Local Anesthesia in Intra-Arterial Therapy and ANSTROKE, Anesthesia During Stroke) no difference in terms of neurological outcome

where found when comparing general anesthesia to conscious sedation (Löwhagen Hendén et al. 2017; Simonsen et al. 2018). Our current approach (further discussed in *materials and methods, interventional treatment*) is to conduct endovascular treatment under conscious sedation with support from an anaesthesiologist. General anesthesia is only applied in cases of lack of consciousness to protect the airways or in the event of agitation of the patient, which might complicate the procedure or jeopardize its safety.

2.3 Revascularization scores

To categorize and standardize the success of the interventional treatment several grading systems have been used. All different grading systems classify the results of endovascular therapy based on the amount of revascularization of previously ischemic brain tissue (Zaidat et al. 2012). Historically the very first score utilized to assess cerebral reperfusion has been the “Thrombolysis in Myocardial infarction” (TIMI) scale, originally constructed to quantify the reperfusion of the myocardium after percutaneous coronary angioplasty (TIMI Study Group 1985; Gobin et al. 2004). A modified version of TIMI scale, named “Thrombolysis in Cerebral

Infarction" (TICI) grading, was introduced in 2003 by Higashida and colleagues and represented the first dedicated scale for cerebral reperfusion (see ***table 2***) (Higashida et al. 2003). Further several scales have been described, such as the AOL and the ACG (IMS II 2007; Bang et al. 2011). Currently the most utilized in clinical practice is the "Modified Treatment in Cerebral Infarction" score (mTICI), shown in ***table 3*** (Zaidat et al. 2013). In 2014 Almekhlafi and colleagues proposed an additional category to the mTICI scale, named mTICI2c (indicating a "near complete reperfusion except slow flow or few distal cortical emboli"), see ***table 4***. In their study they showed that mTICI2c reperfusions result in significantly better early neurological improvement compared to mTICI2b (Almekhlafi et al. 2014). These results were also validated by Tung and colleagues in 2017 (Tung et al. 2017). Recently Liebeskind and colleagues reexamined the data from the HERMES study utilizing a new 7-point eTICI score (Expanded Treatment in Cerebral Infarction) in relation to the prediction of functional outcome at 90 days. Their results indicated that increasing TICI grades were linked with better clinical outcomes (Liebeskind et al. 2019).

As techniques and expertise in interventional stroke therapy evolve and improve, so do the radiological and clinical outcomes. Most of the actual interventional outcomes are placed somewhere between 50 to 99 % of anterograde revascularization of the previously ischemic territory (Almekhlafi et al. 2014). Parallel to these developments there has been a

significant change in the definition of what should be considered a successful recanalization result, increasing the threshold from TICI 2a to TICI 2b (Jayaraman et al. 2013).

Although the mTICI represents a practical and relatively simple scale easily utilized in everyday clinical practice, it shows a considerable lack of predictability of clinical outcome in middle to high percentages of revascularization of ischemic territory (50 to 99 % of territory are graded all together TICI 2b, see ***table 3***). This wide spectrum of radiological results correlates therefore with an equally heterogeneous variety of clinical outcomes. In all likelihood a difference in almost 50 % of reperfused brain territory can have a marked impact on the neurological outcome of the patient. To imagine a scenario, the ICA supplies through the ACA and MCA ca. 72 % of the ipsilateral cerebral hemisphere (Zarrinkoob et al. 2015). In a distal ICA occlusion therefore up to 72 % of a brain hemisphere volume can become ischemic due to the thrombus, depending on the rate of collateralization. A successful revascularization with mTICI2b (50 – 99 %) could then mean a loss of 1 to 36 % of the volume of the cerebral hemisphere. It is intuitive to understand that the neurological outcome may vary considerably within this range (also being dependent on the localization of the infarction), yet the revascularization result would still be classified as mTICI2b.

So ultimately one of the major issues of mTICI scale is that mTICI2b is a very broad definition and de facto a rather imprecise grade covering 50-99 % of reperfused territory, lacking adequate predictability of clinical outcome (Kallmes et al. 2018). Even the newly introduced mTICI2c category does not solve this issue of the mTICI scale and has also shown unsatisfying inter-reader agreement, likely because of vague criteria (Tung et al. 2017). Numerous authors reported further limitations of the TICI scale, including internal inconsistencies (Kallmes 2012), confusing nomenclature (Tomsick 2007) and a substantial variability in the definition and application of the TICI scale in the literature (Fugate et al. 2013).

Despite the relative diffusion of the mTICI scale, the current heterogeneity in brain angiographic revascularization scores represents a relevant hindrance to the development in interventional treatment, not to mention the possible discrepancies in everyday clinical practice. Furthermore, the varied definitions within a certain scale plus a certain inaccuracy, and this holds true particularly for the mTICI score, might cause confusion to its application and interpretation, potentially affecting its predictive power regarding clinical outcome. Ideally an optimal grading system should demonstrate a good correlation with the clinical neurological outcome, simplicity and feasibility in the clinical practice and high inter-rater reproducibility (Zaidat et al. 2013). To date no revascularization score takes the effect of time into account, which probably represents a major

disadvantage. In a case with a particularly challenging and protracted intervention, successful angiographic recanalization might be achieved, yet a considerable amount of brain parenchyma may have meanwhile infarcted and poor neurological status would likely follow, thus likely resulting in a discrepancy between angiographic and clinical outcome.

2.4 Study design

In order to address these limitations we evaluate the novel angiographic revascularization grading, named “Expanded Treatment in Cerebral Infarction” (eTICI) in a real world cohort. The eTICI score is partially based and could be considered an expansion on the mTICI score (see ***table 5*** and ***6***). The eTICI score classifies the revascularization outcome in 7 grades (from 0 to 3). Grades 0 – 2a are equivalent to the similar grades on the mTICI scale. Angiographic revascularization outcomes with 50 to 99 % of anterograde revascularization of the previously ischemic territory, which are graded altogether grade 2b in the mTICI score, are divided in 3 grades in the eTICI score (in detail grade 2b50, 2b67 and 2c. The definition of eTICI2c differs from mTICI2c. See ***table 4***, ***5*** and **6**). Grade 3 defines complete reperfusion in the eTICI as well as in the mTICI scale.

In this study we examine the ability of the newly introduced expanded TICI (eTICI) compared to the modified TICI (mTICI) angiographic revascularization grading in predicting the favorable clinical neurological outcome and functional independence (Farrell et al. 1991) in patients with LVO after treatment with endovascular thrombectomy. Additionally, since time heavily affects the neurological outcome in acute ischemic stroke, the influence of the “time factor” on the angiographic results (also assessed with the eTICI scale) will be investigated.

3 MATERIALS AND METHODS

3.1 Study population

The prospectively acquired database of the Department of Neuroradiology of the University of Medicine, Göttingen was retrospectively queried for all stroke patients who received interventional therapy for LVO between January 2015 and April 2017. LVO involving both the anterior (distal ICA, MCA) and posterior circulation (BA, PCA) were included in the study. We also enclosed cases which presented with concomitant cervical ICA affection (tandem lesions, including both subocclusive stenosis and occlusion) as well as occlusion exclusively of the proximal M2-segment of the MCA. No other in- or exclusion criteria were applied, resulting in a cohort of 225 patients.

After the evaluation of angiograms with the eTICI score was performed (see *2.3 Radiological assessment*), the patient cohort was screened for cases who underwent endovascular treatment of LVO in the anterior circulation and received successful recanalization (eTICI2b50 – eTICI3), which resulted in a second study population of 164 individuals.

All analyzed intra-arterial thrombectomies were performed prior to the 01.08.2017. The patient`s informed consent for medical treatment was

acquired in line with the institutional guidelines of the UMG. Ethics committee vote for the study was obtained (Application number **16/2/16**, **13/7/15An** and **7/5/19**). No individual-related data has been included in the study. No further questions regarding medical data or any data whatsoever were directed to the patients, their relatives or other hospitals.

3.2 Interventional treatment

Endovascular therapy was considered suitable for patients within 6 hours of onset of symptoms presenting with a large vessel occlusion and absence of an intracranial bleed. Imaging was performed by either multi-detector (MDCT/MDCT-Angiography. SOMATOM Definition AS 128-slices, Siemens Healthcare, Germany) or flat-detector computed tomography (FDCT/FDCTA. AXIOM Artis biplane, Siemens Healthcare) (Leyhe et al. 2017; Psychogios et al. 2017). Within the first 6 hours of symptom onset patients received EVT independently to the ASPECTS (Alberta Stroke Program Early CT Score) (Barber et al. 2000; Pexman et al. 2001). After 6 hours from onset of symptoms supplementary imaging via computed tomography perfusion (CTP) was conducted and exclusively cases with a CBV-CTP ASPECT (cerebral blood volume in CTP) score of 5 or more were considered eligible for EVT. Ancillary IV therapy with r-tPA

was delivered in conformity with the present German guidelines (DGN 2016). Intra-arterial r-tPA has never been administered in cases included in the study.

Patients transferred to the department of neuroradiology of the UMG from an external stroke center and potentially treatable with EVT, received imaging (MDCT/MDCTA or FDCT/FDCTA) before treatment to exclude an intracranial bleed and to assess the cerebral vascular status. All mechanical thrombectomies were performed in the neuroangiography suite of the Department of Diagnostic and Interventional Neuroradiology of the University of Medicine, Göttingen, equipped with an AXIOM Artis biplane angiographic imaging system (Siemens Healthcare). Most patients received EVT under conscious sedation while general anesthesia with intubation was necessary when psychomotor agitation or impairment of consciousness were present.

Mechanical thrombectomy was performed in the majority of cases using a standard tri-axial approach with either an 8F femoral long sheath (Destination Terumo Medical, Somerset, NJ, USA) or an 8F guiding catheter (VISTA Brite tip, Cordis, Milpitas, CA, USA), a 5 or 6F intermediate/aspiration catheter (Catalyst, Stryker Neurovascular, Kalamazoo, MI, USA or Penumbra ACE 64/68, Penumbra, Alameida, CA, USA), a microcatheter (Trevo pro 14/18, Stryker) and a stent-retriever (Trevo pro Vue 4x30mm, Stryker Neurovascular). Different thrombectomy

techniques were performed comprising “a direct aspiration first pass technique” (ADAPT) (Turk et al. 2014), Solumbra (Behme et al. 2016) and stent assisted vacuum locked extraction (SAVE) (Kowoll et al. 2016; Maus et al. 2017). From July 2015 on all patients were treated using solely SAVE (Maus et al. 2017; Maus et al. 2018). See ***figure 5*** for a detailed illustration of the SAVE technique. A balloon guide catheter was never utilized in the cases included in the study. The total of passes performed (i. e. thrombectomy maneuvers) was judged singularly in every case by the interventional neuroradiologist.

3.3 Radiological assessment

The angiographic imaging was retrospectively and independently examined by two readers with varied experience in interventional neuroradiology (I. Tsogkas > 5 years and R. Colla > 3 years), who were blinded to all clinical data. The amount of reperfusion of the ischemic territory was assessed in percentage analyzing postero-anterior as well as lateral view images of the final angiograms after EVT, based on the definitions of the eTICI scale. Regarding large vessel occlusions involving the posterior circulation, the quantification was similarly adapted to the correspondent supplying brain area and judged accordingly in every single

case. All images have been classified via mTICI score immediately after EVT and before further data was included into the data-base; both readers were blinded to these data as well. In cases with score disagreement the angiograms were reexamined by the same two readers in a collective meeting in order to attain a general agreement, therefore generating an additional harmonized body of data. This was then used for further analysis. The initial separate evaluation of the two readers was kept for calculation of the interclass correlation coefficient.

The 7-point scale eTICI is structured as follows: eTICI0 = 0 % = mTICI0; eTICI 1 = reduced clot without any reperfusion = mTICI1; eTICI2a = 1-49 % = mTICI2a; eTICI2b50 = 50-66 % = mTICI2b; eTICI2b67 = 67-89 % = mTICI2b; eTICI2c = 90-99 % = mTICI2b; eTICI3 = complete reperfusion = mTICI3 (see ***table 5*** and ***6***). An example of an ICA/MCA reperfusion grading from eTICI2a to eTICI2c (with mTICI2b divided into eTICI2b50, -2b67 and -2c) is given in ***figures 7-10***.

3.4 Clinical assessment

The ischemic stroke database of the Department of Neuroradiology of the UMG was interrogated for the following information: age, gender, time of symptom onset/ wake up, site of occlusion, baseline NIHSS, baseline

mRS, discharge NIHSS, discharge mRS, 90 days mRS, all intra hospital time points: admission, CT, tPA start, groin puncture, reperfusion and final angiogram. All neurological assessment data were collected and entered in the stroke database by an experienced vascular neurologist (I. Maier > 5 years or J. Liman > 10 years). Data at 90 days after ischemic stroke and EVT was acquired during a follow up examination of the patients by the same vascular neurologists. The two examining neurologists were blinded neither to the angiographic result of the interventional procedure nor to the precedent clinical data. Functional independence was designated as a 90-day mRS score of 0 to 2.

3.5 Statistical analysis

Statistical analysis was conducted with either SAS 9.4 (SAS, Wallisellen, CH) or Med Calc software (Med Calc, Ostend, Belgium). At the beginning of the analysis relevant population characteristics were examined. An overview of the results of that investigation can be found in ***table 7*** and ***10***. Analysis comparing eTICI with mTICI were conducted exclusively on cases of LVO in the anterior circulation (ICA and MCA). Regarding the comparison of mTICI2b with its eTICI equivalents (eTICI2b50, -2b67 and -2c) results of all patients were included in the examination. Receiver

Operating Characteristics (ROC) curves of eTICI and mTICI were obtained comparing good clinical outcome (mRS 0-2 at 90 days) versus unfavorable outcome (mRS 3-6 at 90 days) as dichotomized classification variables. The difference between the two ROC-curves (eTICI and mTICI) was then additionally tested applying the DeLong test comparing the area under the curves (AUC) (DeLong et al. 1988).

To assess if the subdivision of mTICI2b category into corresponding eTICI2b50, -2b67 and -2c subtypes could provide more precise prediction of clinical outcome, these two groups were tested concerning the difference in outcome (favorable: mRS 0 – 2 and unfavorable: mRS 3 – 6) with the Jonckheere-Terpstra test (Bewick et al. 2004). The Bonferroni correction for the p-value was added to control for the family-wise error rate (Ranstam 2016). Inter-rater agreement between neuroimaging readers was calculated with Cohen's Kappa (Cohen 1960) and interclass correlation coefficient (ICC) (Donner et al. 1998).

Concerning the analysis of the time factor, the clinical outcome at 90 days has been dichotomized in two categories (favorable outcome: mRS 0 – 2 and unfavorable outcome: mRS 3 – 6). The following time parameters were analyzed (admission to recanalization and groin puncture to recanalization) together with successful revascularization scores (eTICI2b50 to eTICI3) in the multiple logistic regression analysis (Sperandei 2014). In each of the two models p-values for eTICI grade, the

time frames and the patient's age were calculated. The influence of time on the angiographic results (assessed with the eTICI scale) and on the treatment outcome (good vs. poor outcome) was investigated using specific intercepts in the models. These models assume that the effect of time is constant for the scores of the eTICI scale (eTICI2b50 – 3) over time.

4 RESULTS

4.1 Large vessel occlusion

Collectively 225 patients were enclosed in the study. The median age was 76 (Interquartile range: 66-82) years, the NIHSS score at baseline was 16 (IQR: 10-20); 48.4 % were male and 51.6 % were female patients. The most common localization of LVO was the MCA (132/225, 58.7 %) followed by the ICA (64/225, 28.4 %); in 44 cases (44/225, 19.6 %) a tandem occlusion was present, simultaneously involving the ICA and the MCA. In a minority of cases the posterior circulation was affected: in 24 cases a BA occlusion (24/225, 10.7 %) and in 5 cases a PCA occlusion (5/225, 2.2 %) was treated (see ***table 7*** and ***figure 11***).

4.2 Reperfusion and clinical outcomes

The median time from arterial puncture to reperfusion was 50 min (IQR: 32-74). The degree of recanalization covered the whole range of the 7 points eTICI, varying from no reperfusion (eTICI0) to complete reperfusion of the previously ischemic territory (eTICI3). All angiographic views were adequate to the assessment of the results after mechanical

thrombectomy, so the grade of reperfusion could be evaluated in all the cases included in the study, resulting in 225 eTICI scores. Recanalization could not be achieved in 13 cases (13/225, 5.2 %), accounting for 9 cases of eTICI0 (9/255, 4 %) and 4 cases of eTICI1 (4/255, 1.8 %). In another 22 cases (22/225, 9,8 %) an eTICI2a result was obtained. In the remaining 84.4% of cases substantial perfusion was restored with eTICI2b50 (23/225, 10.2 %), eTICI2b67 (71/225 31.6 %), eTICI2c (46/225, 20.4 %) and eTICI3, i. e. complete reperfusion (50/225, 22.2 %), see ***table 7*** and ***figure 12***. A favorable clinical outcome (mRS 0-2 at 90days) was achieved in 88 cases (88/225, 39.1 %), see ***table 7*** and ***figure 13***. Clinical demographics, angiographic and procedural information of patients are summarized in ***table 7***.

Higher eTICI reperfusion grades are linked with better clinical outcomes (mRS at 90 days), particularly the higher the eTICI score is (i. e. greater reperfusion), the lower the mRS at 90 days tends to be (i. e. better neurological outcome). A higher revascularization score is related to a greater likelihood of achieving a good neurological outcome at 90 days (eTICI0: 0 %, eTICI1: 0 %, eTICI2a: 18 %, eTICI2b50: 17,39 %, eTICI2b67: 23,94 %, eTICI2c: 54,34 %, eTICI3: 76 %). A relatively wide distribution of neurological outcomes at 90 days stratified along all eTICI scores can nevertheless be observed, see ***table 8*** and ***figure 14***.

Concerning the analysis comparing eTICI scores with mTICI scores, ROC analysis with dichotomized mRS scores at 90 days (mRS 0-2) as outcome were calculated using the respective scores. Derived from the ROC-curve the AUC could be calculated leading to an AUC of 0.779 (95 % CI: 0.719-0.839) for eTICI and 0.740 (95 % CI: 0.683-0.797) for mTICI. Using the Youden-Index as criterion for optimal cutoff values, optimal cutoff for eTICI was achieved at eTICI2b67 with 75.9 % sensitivity (95 % CI: 67.86 % - 82.8 %) and a 71.6 % specificity (95 % CI: 60.98 % - 80.7 %) for favorable outcome. For mTICI a cutoff at mTICI2b with 89.7 % sensitivity (95 % CI: 83.44 % - 94.3 %) and 44.3 % specificity (95 % CI: 33.72 % - 55.3 %) was obtained (***figure 15***). Comparing AUC of both raters resulted in a p-value of 0.047.

Analyzing outcome differences of eTICI2b50, -2b67 and -2c scores in cases which were initially categorized as mTICI2b resulted in a significant association between increasing scores and growing probability of success (p=0.033). In the study cohort mTICI2b patients had a probability of 36 % for a favorable outcome, whereas the granulated success probabilities were 17 % for eTICI2b50; 24 % for eTICI2b67 and 54 % for eTICI2c (see ***table 9***).

4.3 Interrater reliability

Overall agreement (Cohen's Kappa) between raters was 0.706 (95 % CI: 0.645-0.769). Interclass correlation (ICC) within eTICI was 0.862 (95 % CI: 0.821-0.894).

4.4 Role of time

The screening of the initial patient cohort for cases of LVO in the anterior circulation who received EVT with successful recanalization (eTICI2b50 – eTICI3) produced a second study population of 164 patients. 45.1 % of these were male and the median age was 76 (IQR 66 – 82). The LVO involved the distal ICA in 31 % (51/164) and MCA in the remaining 69 % (113/164) of cases.

Median procedural times included the following results: admission to recanalization time: 97 minutes (IQR 76 – 116 min), admission to groin puncture: 47 min (IQR 29 – 63), groin puncture to recanalization: 47 min (IQR 31 – 66). Angiographic outcomes: 12.2 % (20/164) of cases obtained an eTICI2b50 result, 36.6 % (60/164) eTICI2b67, 23.2 % (38/164) eTICI2c and 28 % (46/164) eTICI3. The global of favorable outcome (mRS 0 – 2) was 42.7 % (70/164), subdivided in 15 % (3/20) for eTICI2b50, 18.3 % for

eTICI2b67 (11/60), 57.9 % (22/38) for TICI2c and 73.9 % (34/46) for eTICI3 (see ***table 10)***.

In the analysis of time of admission to vessel recanalization the p-values resulted overall in p=0.2281 (OR 0.994, CI: 0.984-1.004) and p=0.0161 (OR: 0.957, CI: 0.923-0.992) for patient's age. Concerning the investigation inside the eTICI scale, double grade correlation p-values were: p=0.5744 (eTICI2b50 vs. 2b67), p=0.0388 (eTICI2b50 vs. 2c), p=0.0012 (eTICI2b50 vs. 3), p=0.0366 (2b67 vs. 2c), p<0.0001 (2b67 vs. 3) and p=0.0731 (eTICI2c vs. 3). The odds change was calculated to be 0.9939 per minute and 0.9574 per year of age. For a complete report of p-values plus odd ratios of admission to recanalization see ***table 11*** – ***12*** and ***figure 16***.

In the evaluation of time of groin puncture to recanalization these p-values were calculated: for eTICI grades p<0.0001, overall p=0.1713 (OR 0.989, CI: 0.974-1.005) and for the age of the patient p=0.0139 (OR: 0.955, CI: 0.921-0.991). About the comparison within the eTICI scale, the following double grade correlation p-values emerged: p=0.5017 (eTICI2b50 vs. 2b67), p=0.0392 (eTICI2b50 vs. 2c), p=0.0016 (eTICI2b50 vs. 3), p<0.0001 (2b67 vs. 2c plus 2b67 vs. 3) and p=0.0933 (eTICI2c vs. 3). The odds change per minute was 0.9879 per minute and per year of age 0.9550. The exhaustive report of p-values, odd ratios and confidence

intervals of time from groin puncture to recanalization can be found in ***table 13*** - ***14*** and ***figure 17***.

The regression analysis permits a computation of the probability or reaching a certain outcome, in this case: log odds (probability of good outcome (mRS 0 – 2) / probability of poor outcome (mRS 3 – 6). In the model of the groin puncture to recanalization the likelihood of good outcome could be calculated as follows:

$$\textbf{log odds} = 5.3988 - (0.0108\ x\ groin\ to\ recan.time\ [min]\ ) - (0.0456\ x\ age\ [years]) - \ \alpha$$

α: correction factor of the eTICI scale

- eTICI3: 0.
- eTICI2c: 0.9434.
- eTICI2b67: 3.1095.
- eTICI2b50: 2.5662.

E. g. an 80 y. o. patient recanalized in 50 minutes (groin to recanalization) with an eTICI2c result would have a log odds for obtaining a good neurological outcome of:

$$\log odds = 5.3988 - (0.0108\ x\ 50) - (0.0456\ x\ 80) - \ \alpha$$

$$\log odds = 5.3988 - 0.54 - 3.648 - 0.9434$$

$$\log odds = 0.2674$$

The odds are: 1.31 and probability is: 0.57

In another example an 87 y. o. patient recanalized in 90 min. (groin to recanalization) with a eTICI2b50 result would have a log odds for achieving a good outcome of:

$$\log odds = 5.3988 - (0.0108\ x\ 90) - (0.0456\ x\ 87) - \ \alpha$$

$$\log odds = 5.3988 - 0.972 - 3.9672 - 2.5662$$

$$\log odds = -2.1066$$

The odds are: 0.122 and probability is: 0.11

In a further example a 65 y. o. patient recanalized in 35 min. (groin to recanalization) with an eTICI3 result would have a log odds for obtaining a good outcome of:

$$\log odds = 5.3988 - (0.0108\ x\ 35) - (0.0456\ x\ 65) - \ \alpha$$

$$\log odds = 5.3988 - 0.378 - 2.964 - 0$$

$$\log odds = 2.0568$$

The odds are: 7.821 and probability is: 0.89.

5 DISCUSSION

This is the first study which investigates the 7-point expanded Thrombolysis in Cerebral Ischemia score (eTICI) in a real world study population. The research group of Liebeskind and collegues retrospectively analyzed the HERMES angiography dataset using the eTICI score in their recent publication (Liebeskind et al. 2019). This analysis confirms the higher incidence of occlusions of the MCA, followed by the ICA and then the posterior circulation in ischemic stroke. A higher reperfusion score is linked to a greater probability of achieving a favorable neurological outcome at 90 days. The results of this study show overall several advantages of the expansion of the widely used and accepted mTICI and the application of the eTICI score. In the first instance the eTICI leads to a better overall outcome prediction as validated by ROC analysis. Secondly outcome stratification of eTICI2b50, 2b67 and 2c compared to mTICI2b resulted in more accurate prediction of good outcome at 90 days (mRS 0-2). In our cohort a significant increasing trend was observed between eTICI2b50 to eTICI2c results and the probability of good outcome with higher eTICI scores underlines the value of a more precise interpretation of angiographic result after mechanical thrombectomy. The results of this study confirm most of the conclusions of Liebeskind and colleagues when analyzing the HERMES data with the eTICI score. In

contrast to their findings, a statistically significant difference between eTICI2b50 and eTICI2b67 concerning the prediction of functional outcome at 90 days could not be determined. An increasing trend towards better neurological outcome in the eTICI2b67 versus the eTICI2b50 could nevertheless be found (23,94 % and 17,39 % respectively). This phenomenon could partially be due to the different number of patients in the cohort of the two studies (HERMES: 801 subjects, eTICI2b50 103 patients, eTICI2b67 218 patients. Present study: 225 subjects, eTICI2b50 23 patients, eTICI2b67 71 patients) (Liebeskind et al. 2019). Moreover the angiographic results after mechanical thrombectomy were substantially better in comparison to the ones of the HERMES study (In HERMES eTICI2b50-eTICI3: 75,4 % versus 84,4 % in the present study) (Liebeskind et al. 2019). This phenomenon might be a manifestation of the improving trend in mechanical thrombectomy over the past years, concerning both interventional techniques and speed of reperfusion. This hypothesis is corroborated by the recent results of Psychogios et al. and Maus et al. (Psychogios et al. 2017; Maus et al. 2018).

Furthermore, the eTICI score expands and implements the concepts proposed by Almekhlafi et al. and more recently by Tung et al. Both research groups suggested to add a supplementary category to the mTICI scale which indicates an almost complete reperfusion of the previously ischemic territory" named mTICI2c (Almekhlafi et al. 2014; Tung et al.

2017). Almekhlafi and colleagues showed that mTICI2c resulted in better clinical outcomes when compared to mTICI2b reperfusion. Tung's research group also found significant differences between early and 90 days neurological outcome when comparing patients with mTICI2c with patients having mTICI2b results. Remarkably, this was not observed when comparing mTICI3 with mTICI2c results (Tung et al. 2017). However, a noteworthy limitation of mTICI2c category is its somewhat unclear definition, being originally denominated as "near complete reperfusion except slow flow or few distal cortical emboli" (***table 4***). The eTICI scale overcomes this lack of precision by offering a clear percentage cutoff division to evaluate the grade of reperfusion for all its grades from 1 to 100 %, hence including the eTICI2c (90-99 % of the territory. See ***table 5*** and ***6***).

Determining clear percentage-cutoffs of the reperfused territory may not be easy in some cases and it might be influenced by the quality of the angiograms, but as shown in this study a distinction between three different mTICI2b grades (eTICI2b50 – 2c, 50-99 % of the previously ischemic territory) seems to be attainable in the everyday clinical setting. The initiating motive of the improvement of the angiographic scale in the above cited studies is the need to establish a more precise grading (see *introduction, revascularization scores*). A score which defines a "good" reperfusion result as an extremely broad area spanning from 51 to 99 %,

like mTICI2b does, is intrinsically weak in the predictive power of clinical outcome. More specifically in the current analysis 36 % of patients presenting with a mTICI2b result achieved a favorable neurological outcome at 90 days. When the mTICI2b category was granulated into three eTICI subgroups, a clear distinction of probability of outcome arose. In detail, 54 % of cases with an eTICI2c score reached a favorable neurological outcome at 90 days, while just ca. 17 % and 24 % of patients obtained a good outcome with an eTICI2b50 and eTICI2b67 result respectively (see ***table 9***).

Recently Kaesmacher et al. reported a significant difference in the rate of good neurological outcome comparing mTICI2b and mTICI2c/3 results, specifically 28.7 % vs. 46.5 % (p=0.008) (Kaesmacher et al. 2018). This research group also reexamined the database for thrombectomies where an initial mTICI2b outcome could be subsequently upgraded to mTICI2c/3, finding 28 cases where the revascularization and consequently the clinical outcome was improved. Remarkably no difference between the primary or secondary groups of mTICI2c/3 results could be observed.

Compared to an overall Cohen's Kappa of 0.609 and an ICC of 0.845 that were reached by the readers of the Tung group for mTICI grading and a Cohen's Kappa of 0.83 by the Liebeskind group, we calculated an overall Kappa of 0.706 and an ICC of 0.862. These data show a higher interrater agreement than in the results of Tung et al., possibly because of a clearer

definition of the grades of the eTICI compared to the mTICI scale. The novel score, being derived from the widely used mTICI score, appears very easy to implement and requires only minor changes in the daily routine of angiographic grading.

As stated above and confirming the results of Liebeskind's research group, higher eTICI scores reperfusion are associated with better clinical outcome, which represents a prerequisite for a model which includes the impact of the time factor. Both the admission to recanalization and the groin to recanalization time affect the probability of achieving a good outcome at 90 days (mRS 0 – 2) and this hold true for all successful eTICI reperfusion grades (eTICI2b50 - eTICI3). The longer the time to recanalization is, the lower the probability of attaining a favorable outcome is. This effect is more accentuated in high reperfusion scores (eTICI2c and eTICI3) and less pronounced in eTICI2b50 and eTICI2b67, although still noticeable (see ***figure 16*** and ***17***). A considerable distinction between eTICI2b50/eTICI2b67 and eTICI2c/3 groups in relation to the probability of reaching a good clinical outcome can be determined, further confirming the results of Tung's and Kaesmacher's groups. Significantly this study shows a circa 10 % difference in probability of achieving a good outcome at 90 days when comparing eTICI2c and eTICI3, reinforcing the importance of high revascularization results. This is in contrast with the

data reported by Tung et al., yet a different definition of eTICI2c/mTICI2c was used in the two studies, as stated above.

The model here presented might help to identify patients who might benefit from a further secondary improvement of the angiographic score, depending on age, time of groin puncture to actual recanalization and current eTICI revascularization score, thus increasing the probability of a favorable neurological outcome. For instance, younger patients with rapid interventions and an eTICI2b50/2b67 angiographic outcome would likely benefit from a proceeding in the intervention, with the goal of achieving a higher angiographic reperfusion grade and increasing the likelihood of a favorable neurologic outcome. As Kaesmacher's research group reported, a secondary angiographic improvement from a mTICI2b to mTICI2c/3 results leads to a benefit in clinical outcome. In the presented model patients with an eTICI2b50 or eTICI2b67 score which are improved to eTICI2c within 90 minutes of groin puncture to recanalization have an overall 50 % probability of achieving a favorable outcome. Likewise, this model could be of use in identifying cases where persisting in the intervention would not be convenient, despite a low revascularization grade, specifically in older patients with extended intervention times, considering the low chance of obtaining a favorable outcome. Additionally a higher number of stent retriever passes and a prolonged intervention time are linked with inferior recanalization percentages and greater rates

of complications, which must be considered in the evaluation of these patients as well (Behme et al. 2014; Spiotta et al. 2014).

This study presents several limitations. The first of them is represented by the retrospective evaluation of prospectively acquired data from a single center. The angiographic grading was blinded to the clinical outcome. However, the neurological assessment was not blinded to the angiographic result. Moreover, the radiological reviewers also performed or assisted some of the endovascular interventions, which might have affected their evaluation. We tried to mitigate this possible bias by blinding them to the clinical results as well as having them discuss eventual discrepancies of evaluation in a joint meeting. However, the imaging was not examined by an independent laboratory. Unlike others, we included cases with anterior as well as posterior circulation occlusion, since in our opinion all LVO cases need a reperfusion grading and we performed the grading according to the percentage definitions of eTICI regarding the downstream territory distal to the initial occlusion site. In this regard the eTICi score seems feasible for the assessment of LVO of the posterior circulation as well as for isolated proximal occlusions of a M2-segment of the MCA. Since the mTICI scale was not originally designed for the posterior circulation, this might have had an impact on our results. It is worth noticing that the regression analysis as well as the investigation of the time parameters was only performed for patients with an anterior

circulation stroke. The role of time was implied to be equal in the examined eTICI categories, which could possibly be an oversimplification, since the impact of time might vary depending on the volume of the initially reperfused territory. Another limiting factor of the eTICI is that the score does not include a categorization of large vessel occlusion site or of eloquent brain areas affected by the acute ischemic stroke. It is known that involvement of eloquent areas in stroke is a predictor of cognitive outcome (Munsch et al. 2016; Kallmes et al. 2018). These aspects might influence the outcome after mechanical thrombectomy and could represent interesting subjects of research in the future, perhaps leading to a score which includes the specific occlusion site or eloquent brain areas involved in the ischemic stroke, similarly to the Spetzler-Martin grading system in cerebral arteriovenous malformations (Spetzler and Martin 1986; Kallmes et al. 2018). More studies, ideally prospective, multicentric and including larger patient cohorts are necessary to validate the presented results.

Several international research teams are currently investigating the possibilities of using a flat-detector CT-perfusion (FDCTP) directly in the angiography suite (Yang et al. 2015). This could be used for the pre-interventional evaluation of stroke patients together with FDCT and FDCT-Angiography when transferred directly to the angiography suite as well as for intra- and immediate post-interventional assessment of brain perfusion. During the trombectomy procedure the interventionalist might perform a

FDCTP to assess the extent of reperfusion in real time, which might differ from the revascularization, for instance in the case of revascularization of already infarcted brain parenchyma. This might also guide the interventionalist in carrying on the thrombectomy, like in the eventuality of persisting perfusion deficit in eloquent brain areas despite a good revascularization grade. The assessment of brain perfusion directly after the procedure (through an ASPECTS-Score or a dedicated new score) might correlate to neurological outcome more precisely than an angiographic revascularization score.

6 CONCLUSIONS

Several recent randomized controlled trials have validated the major role of mechanical thrombectomy in the treatment of acute ischemic stroke. In summary, this study demonstrates the utility of the novel eTICI score, which expands the previous mTICI scale. This analysis shows that the eTICI score allows an overall better neurological outcome prediction compared to mTICI. Thereby granulation of the mTICI2b category into three more precise subdivisions (eTICI2b50, 2b67 and 2c) grants a more refined prediction of neurological outcome after thrombectomy of a large vessel occlusion compared to mTICI2b alone. This analysis also confirms the critical role of time in interventional stroke therapy and may provide a helpful tool in the management of patients with initial unfavorable angiographic score. Furthermore, this study corroborates that current endovascular reperfusion therapies allow for high recanalization rates and high rates of favorable clinical outcome. Moreover, higher degrees of recanalization of large vessel occlusion treated with mechanical thrombectomy result in greater neurological improvement and functional independence. Further multicentric trials may be necessary to investigate outcome prediction of the eTICI score on a larger cohort of patients as well as deepen our understanding of the role of time in interventional stroke treatment.

7 SUPPLEMENTS

7.1 Tables

Table 1. The modified Ranking Scale (mRS) (Quinn et al. 2007).

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

Table 2. The original TICI grading scale (Higashida et al. 2003).

TICI grades	Definitions
Grade 0	No reperfusion
Grade 1	Minimal reperfusion
Grade 2a	Only partial filling (less than 2/3) of the entire vascular territory
Grade 2b	Complete filling of all the expected vascular territory, but the filling is slower than normal
Grade 3	Complete reperfusion

Table 3. The mTICI revascularization score (Zaidat et al. 2013, Ginsberg 2016).

mTICI grades	Definitions
Grade 0	No reperfusion
Grade 1	Anterograde reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion
Grade 2a	Antegrade reperfusion of less than half (**1 – 49 %**) of the occluded target artery previously ischemic territory (e.g. in one major division of the middle cerebral artery and its territory)
Grade 2b	Antegrade reperfusion of more than half (**50 – 99 %**) of the previously occluded target artery ischemic territory (e.g. in two major divisions of the MCA and their territories)
Grade 3	Complete antegrade reperfusion (**100 %**) of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches

***Table 4*.** The mTICI revascularization score with the 2c grade (Almekhlafi et al. 2014).

Grade	mTICI	mTICI with 2c
0/1	No / minimal reperfusion	No / minimal reperfusion
2a	Partial filling < 50 % territory	Partial filling < 50 % territory
2b	Partial filling ≥ 50 % territory	Partial filling ≥ 50 % territory
2c	…	Near complete reperfusion except slow flow or few distal cortical emboli
3	Complete reperfusion	Complete reperfusion

Table 5. The newly introduced expanded Treatment In Cerebral Ischemia (eTICI) revascularization score.

eTICI score	Definition
eTICI0	No reperfusion
eTICI1	Reduced clot without reperfusion of distal branches
eTICI2a	**1 – 49 %** Anterograde reperfusion of the previously occluded target artery ischemic territory
eTICI2b50	**50 – 66 %** Anterograde reperfusion of the previously occluded target artery ischemic territory
eTICI2b67	**67 – 89 %** Anterograde reperfusion of the previously occluded target artery ischemic territory
eTICI2c	**90 – 99 %** Anterograde reperfusion of the previously occluded target artery ischemic territory
eTICI3	**100 %** Anterograde reperfusion of the previously occluded target artery ischemic territory

***Table 6*.** Comparison of the newly introduced eTICI with the mTICI revascularization score. The mTICI2b grade is divided in 3 grades (2b50, 2b67 and 2c) in the eTICI score.

Reperfusion	mTICI	eTICI
No reperfusion	0	0
Reduced clot without reperfusion	1	1
1 – 49 %	2a	2a
50 – 66 %	**2b**	**2b50**
67 – 89 %	**2b**	**2b67**
90 – 99 %	**2b**	**2c**
100 %	3	6

Table 7. Clinical demographics, angiographic and procedural information of patients for the eTICI analysis (Behme et al. 2019).

Item	Median (IQR) or n (%)
Age	76 (66-82)
Initial NIHSS	16 (10-20)
Male gender	109 (48.4 %)
Female gender	116 (51.6 %)
Site of occlusion	
Internal carotid artery (ICA)	64 (28.4 %)
Middle cerebral artery (MCA)	132 (58.7 %)
Tandem lesions (ICA + MCA)	44 (19.6 %)
Basilar artery	24 (10.7 %)
Posterior cerebral artery (PCA)	5 (2.2 %)

Procedural information	
Groin to recanalization time, min	50 (32-74)
eTICI0 (mTICI0)	9 (4 %)
eTICI1 (mTICI1)	4 (1.8 %)
eTICI2a (mTICI2a)	22 (9.8 %)
eTICI2b50 (mTICI2b)	23 (10.2 %)
eTICI2b67 (mTICI2b)	71 (31.6 %)
eTICI2c (mTICI2b)	46 (20.4 %)
eTICI3 (mTICI3)	50 (22.2 %)
Neurological outcome at 90days	
mRS0	26 (12 %)
mRS1	32 (14 %)
mRS2	30 (13 %)
mRS3	27 (12 %)
mRS4	31 (14 %)
mRS5	22 (10 %)
mRS6	57 (25 %)

Table 8. Classification of eTICI categories respectively to the clinical outcomes (measured with mRS at 90 days) for all patients of the study.

	mRS 0	**mRS 1**	**mRS 2**	**mRS 3**	**mRS 4**	**mRS 5**	**mRS 6**
eTICI 0	0/9 (0 %)	0/9 (0 %)	0/9 (0 %)	0/9 (0 %)	0/9 (0 %)	2/9 (22,2 %)	7/9 (77,8 %)
eTICI 1	0/4 (0 %)	0/4 (0 %)	0/4 (0 %)	0/4 (0 %)	1/4 (25 %)	1/4 (25 %)	2/4 (50 %)
eTICI 2a	1/22 (4,5 %)	2/22 (9 %)	1/22 (4,5 %)	0/22 (0 %)	5/22 (22,8 %)	5/22 (22,8 %)	8/22 (36,4 %)
eTICI 2b50	2/23 (8.7 %)	1/23 (4.3 %)	1/23 (4.3 %)	1/23 (4.3 %)	7/23 (30.4 %)	4/23 (17.4 %)	7/23 (30.4 %)
eTICI 2b67	5/71 (7 %)	8/71 (11.3 %)	4/71 (5.6 %)	19/71 (26.8 %)	15/71 (21.1 %)	7/71 (9.9 %)	13/71 (18.3 %)
eTICI 2c	8/46 (17.4 %)	7/46 (15.2 %)	10/46 (21.7 %)	4/46 (8.7 %)	2/46 (4.3 %)	1/46 (2.2 %)	14/46 (30.4 %)
eTICI 3	10/50 (20 %)	14/50 (28 %)	14/50 (28 %)	3/50 (6 %)	1/50 (2 %)	2/50 (4 %)	6/50 (12 %)

Table 9. Probability of good outcome at 90 days according to mTICI2b versus eTICI2b50-2c (Behme et al. 2019).

	mRS=0,1,2	**mRS=3,4,5,6**	**% (mRS=0,1,2)**
mTICI2b	44	78	36,06 %
eTICI2b50	4	19	17,39 %
eTICI2b67	17	54	23,94 %
eTICI2c	25	21	54,34 %

Table 10. Demographics, angiographic and procedural information of patients for the time analysis of the eTICI scale (reproduced with permission of "Springer Nature").

Item	**Median (IQR) or n (%)**
Age	76 (66-82)
Initial NIHSS	16 (10.5-20)
Male gender	74 (45.1 %)
Site of occlusion	
Internal carotid artery (ICA)	51/164 (31 %)
Middle cerebral artery (MCA)	113/164 (69 %)
Procedural information	
Admission to recanalization	97 min (76 - 116)
Admission to groin puncture	47 min (29 - 63)
Groin puncture to recanalization time	47 min (31 - 66)
eTICI2b50	20 (12.2 %)
eTICI2b67	60 (36.6 %)
eTICI2c	38 (23.2 %)
eTICI3	46 (28 %)
Neurological outcome at 90days	
mRS 0 - 2	70 (42.7 %)
mRS 3 - 6	94 (57.3 %)
Favorable outcome (mRS 0 - 2)	
eTICI2b50	3/20 (15 %)
eTICI2b67	11/60 (18.3 %)
eTICI2c	22/38 (57.9 %)
eTICI3	34/46 (73.9 %)

Table 11. Statistical analysis of admission to recanalization time (pt. 1) (Behme et al. 2019, reproduced with permission of "Springer Nature").

Comparison (eTICI)	p-value	Odds ratio	Lower CI	Upper CI
2b50 vs. 2b67	0.5744	1.569	0.326	7.546
2b50 vs. 2c	0.0388	0.2	0.043	0.928
2b50 vs. 3	0.0012	0.0073	0.015	0.358
2b67 vs. 2c	0.0366	0.127	0.043	0.374
2b67 vs 3	<0.0001	0.073	0.015	0.358
2c vs. 3	0.0731	0.367	0.123	1.098

Table 12. Statistical analysis of admission to recanalization time (pt. 2). The variables are the time of admission to recanalization and the patient's age (Behme et al. 2019, reproduced with permission of "Springer Nature").

Variable	p-value	Odd-ratio	Lower-CI	Upper-CI	Change per min.
Admin. to rec.	0.2281	0.994	0.984	1.004	0.9939
Age	0.0161	0.957	0.923	0.993	0.9574

Table 13. Statistical analysis of groin puncture to recanalization time (pt. 1) (Behme et al. 2019, reproduced with permission of "Springer Nature").

Comparison (eTICI)	p-value	Odds ratio	Lower CI	Upper CI
2b50 vs. 2b67	0.5017	1.722	0.974	1.005
2b50 vs. 2c	0.0392	0.197	0.042	0.923
2b50 vs. 3	0.0016	0.077	0.016	0.379
2b67 vs. 2c	<0.0001	0.115	0.039	0.34
2b67 vs 3	<0.0001	0.045	0.014	0.143
2c vs. 3	0.0933	0.197	0.042	0.923

Table 14. Statistical analysis of groin puncture to recanalization time (pt. 2). The variables are the time of groin puncture to recanalization and the patient's age (Behme et al. 2019, reproduced with permission of "Springer Nature").

Variable	p-value	Odd-ratio	Lower-CI	Upper-CI	Change per min.
Groin to rec.	0.1713	0.989	0.974	1.005	0.9879
Age	0.0139	0.955	0.921	0.991	0.9550

7.2 Figures

Figure 1. The arterial circulation of the brain. The right temporal pole and a portion of the right cerebellar hemisphere have been removed (Gray 1918. Fig. 516. Public domain image).

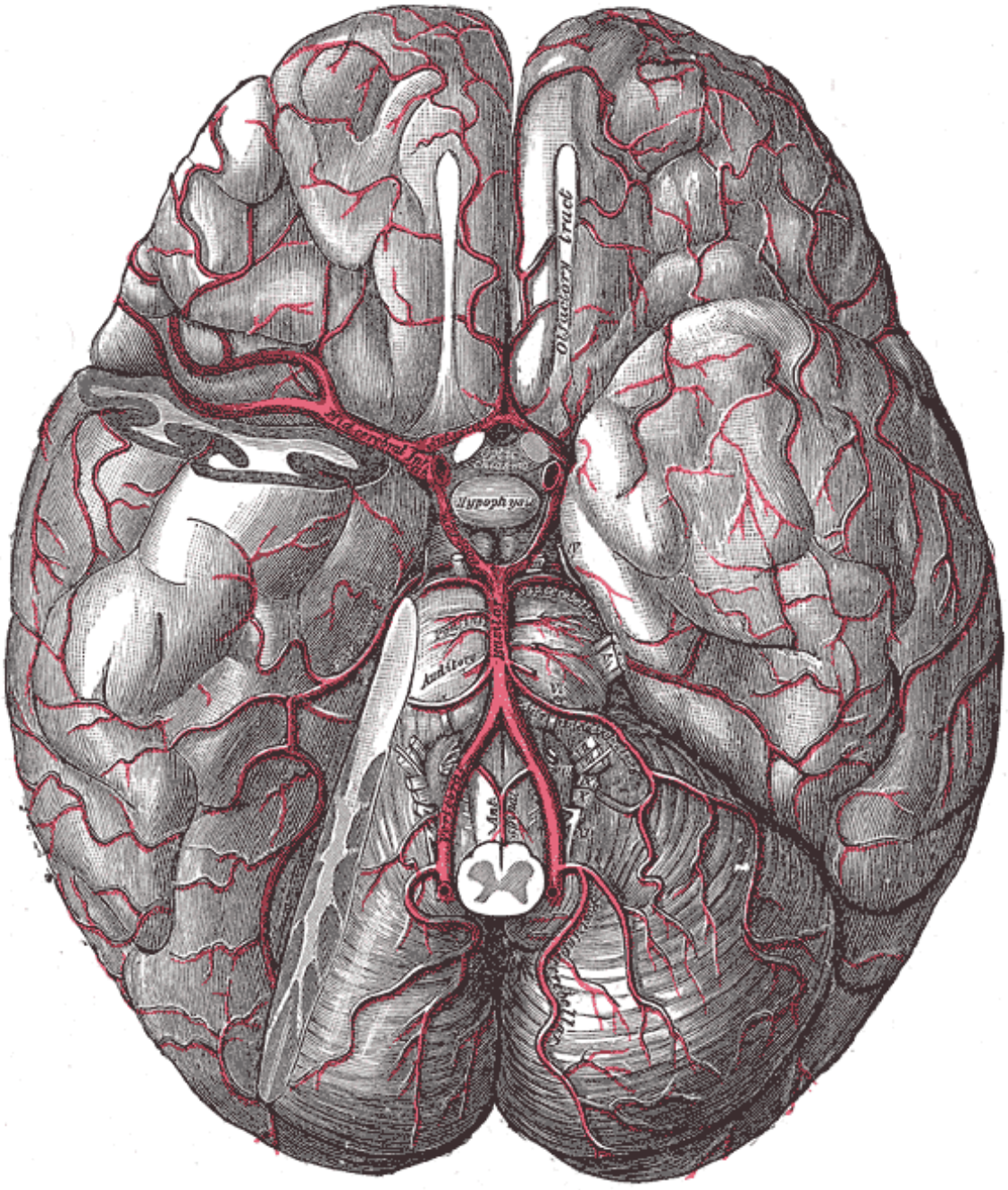


Figure 2. A typical imaging of a patient affected by acute ischemic stroke with spiral computed tomography. A 79 years old patient presented with global aphasia and right-sided hemiparesis. A: The non-contrast CT shows no early signs of infarction. B: In the maximum intensity projection (MIP) reconstruction of the CT-Angiography can be seen the abrupt cessation of contrast flow within the proximal portion of the middle cerebral artery (MCA), as an indirect sign of thrombotic occlusion. C: The CT-Perfusion depicts a CBF/CBV mismatch and a reduction of the other hemodynamic parameters, a sign of brain ischemia.

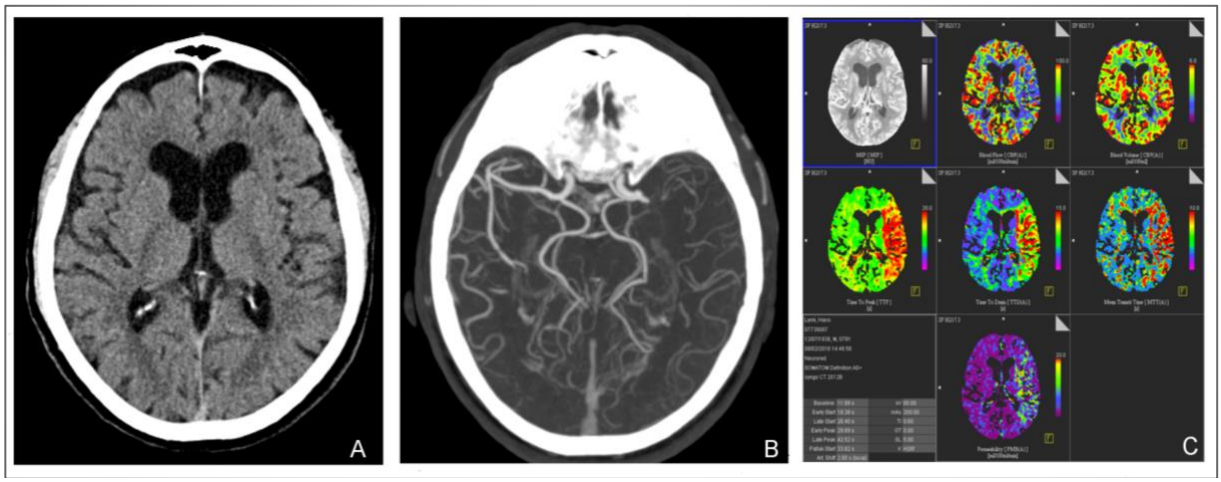


Figure 3. Graphic representation of the evolution of major techniques and devices in mechanical thrombectomy (Spiotta et al. 2015. Reproduced with permission of "BMJ Publishing group Ltd.").

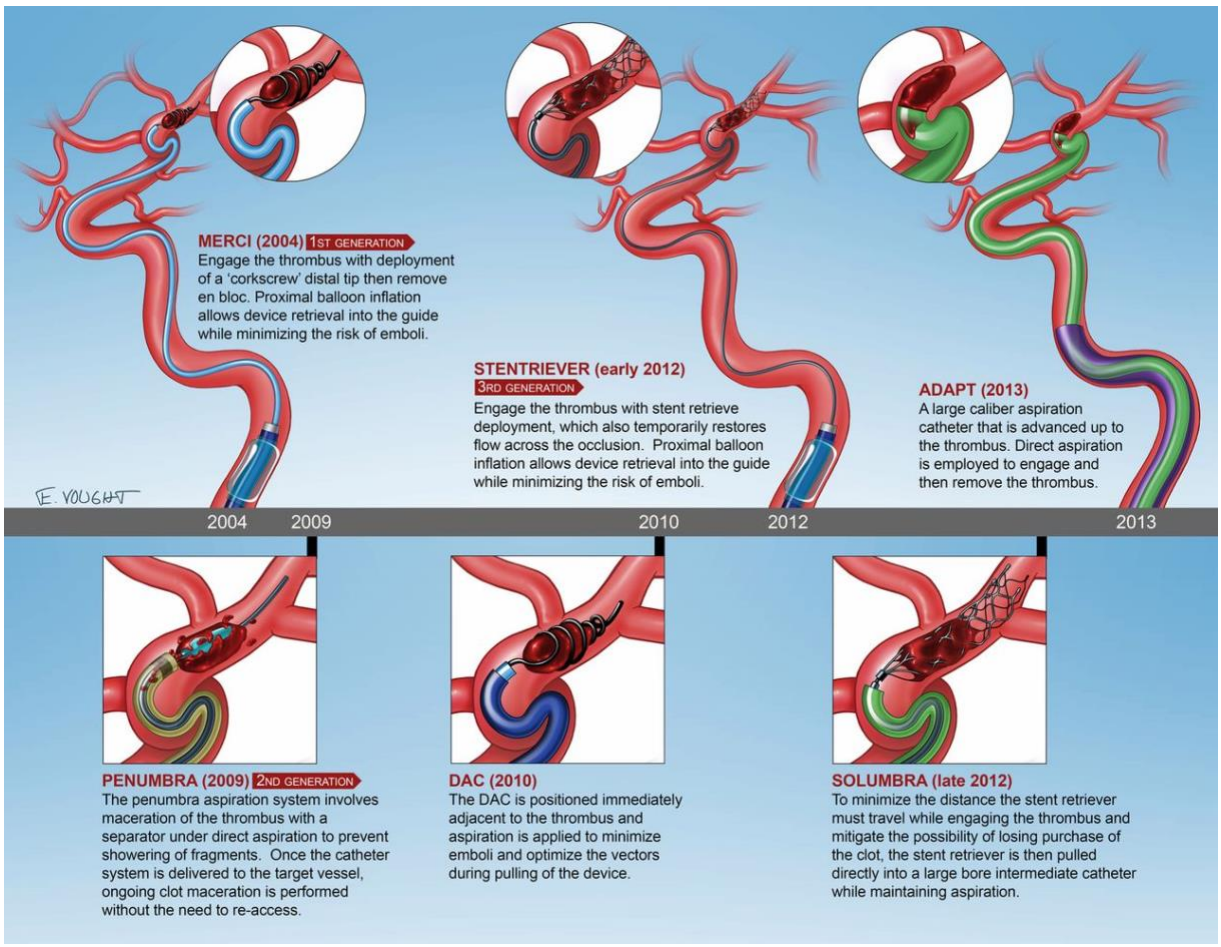


Figure 4**.** The Solitaire FR stent retriever device (Castaño et al. 2016. Reproduced with permission of "BMJ Publishing Group Ltd.").

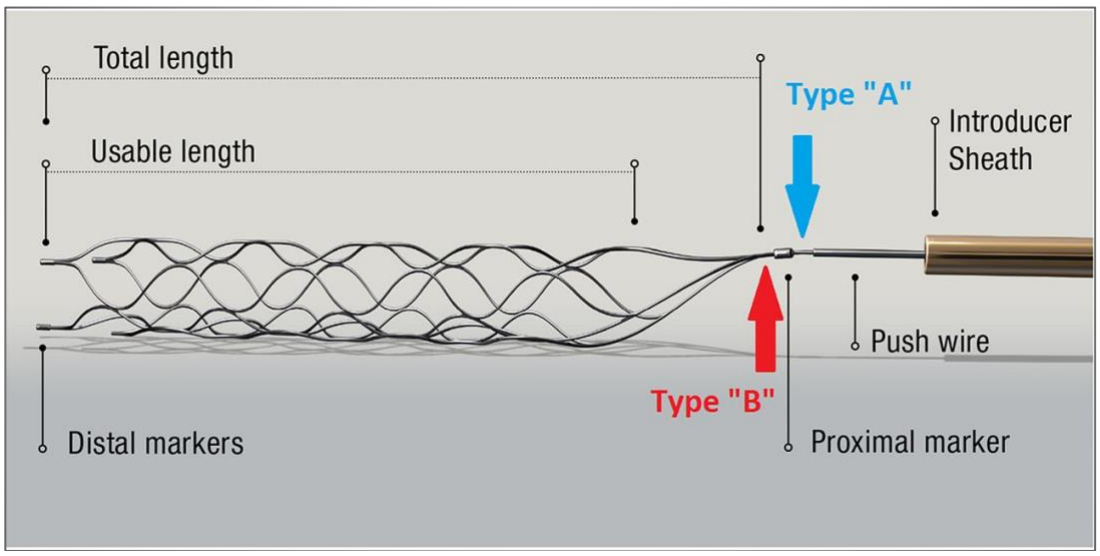


Figure 5. Representation of the Stent retriever Assisted Vacuum-locked Extraction technique (SAVE). A: Initial angiogram shows an occlusion of the right middle cerebral artery (MCA). B: A 4 x 30 mm stent retriever (Trevo ProVue, Stryker Neurovascular, Kalamazoo, MI, USA) placed distally and across the thrombus (along the proximal third, white arrow). C, D and E: The aspiration catheter is advanced distally under continuous aspiration, until a wedge position is achieved. After the unit retrieval process, posterior-anterior and lateral angiograms (F and G) show the successful reperfusion of the right MCA-territorium. H: Thrombus incorporated in the proximal/ middle portion the stent retriever with a clot fragment caught by the distal end of the device (Maus et al. 2017. Reproduced with permission of "Springer Nature").

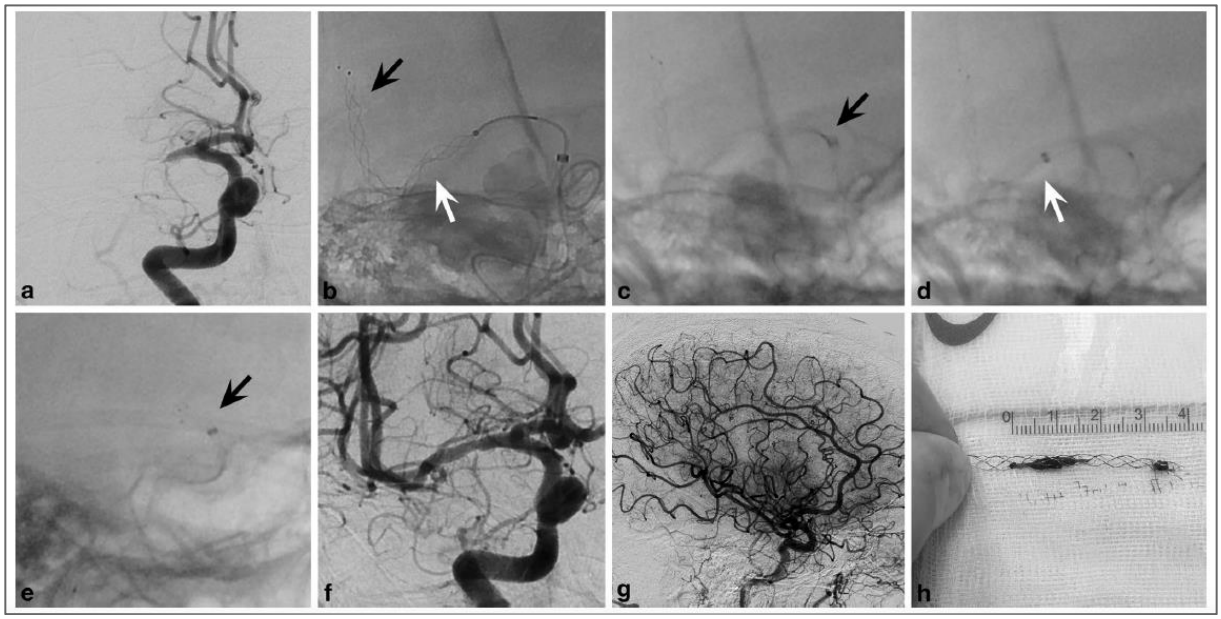


Figure 6. A large thrombus extracted with a stent retriever and partially incorporated in the distal portion of the device (Papanagiotou and White 2016. Reproduced with permission of "Elselvier").

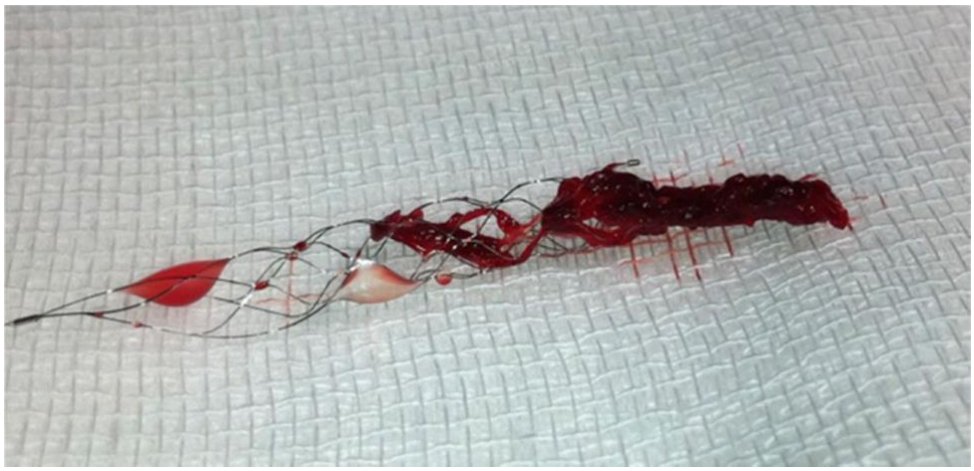


Figure 7. Lateral and posterior-anterior (PA) views of large vessel occlusion (LVO) and eTICI2a (mTICI2a) reperfusion results. A and B show a right-sided, proximal occlusion of the middle cerebral artery (MCA). After mechanical thrombectomy (C and D) the distal portion of the right MCA remains occluded, while reperfusion of the right anterior temporal artery and of the right medial lenticulostriate arteries can be appreciated, rated as eTICI2a (mTICI2a).

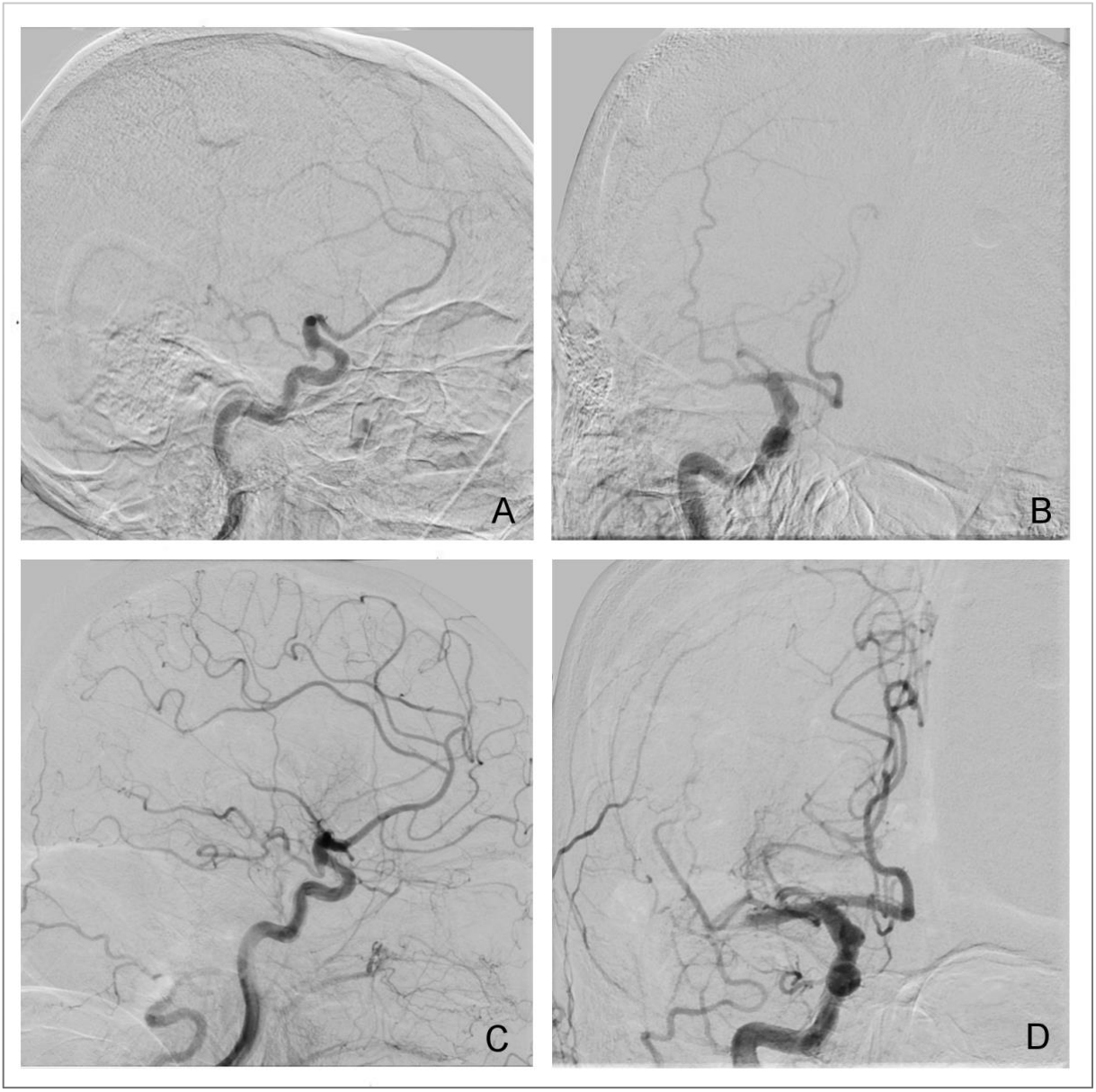


Figure 8*.* Lateral and posterior-anterior (PA) views of large vessel occlusion (LVO) and eTICI2b50 (mTICI2b) reperfusion results. A and B show a left-sided, proximal occlusion of the middle cerebral artery (MCA). Lateral and PA-views (C and D) after recanalization depict residual fronto-parieto-temporal occlusions in the left MCA-territorium, rated as eTICI2b50 (mTICI2b). Please note that, since the LVO involves the left MCA, only the left MCA-territorium (and therefore not the anterior cerebral artery vascular territory) must be evaluated with eTICI.

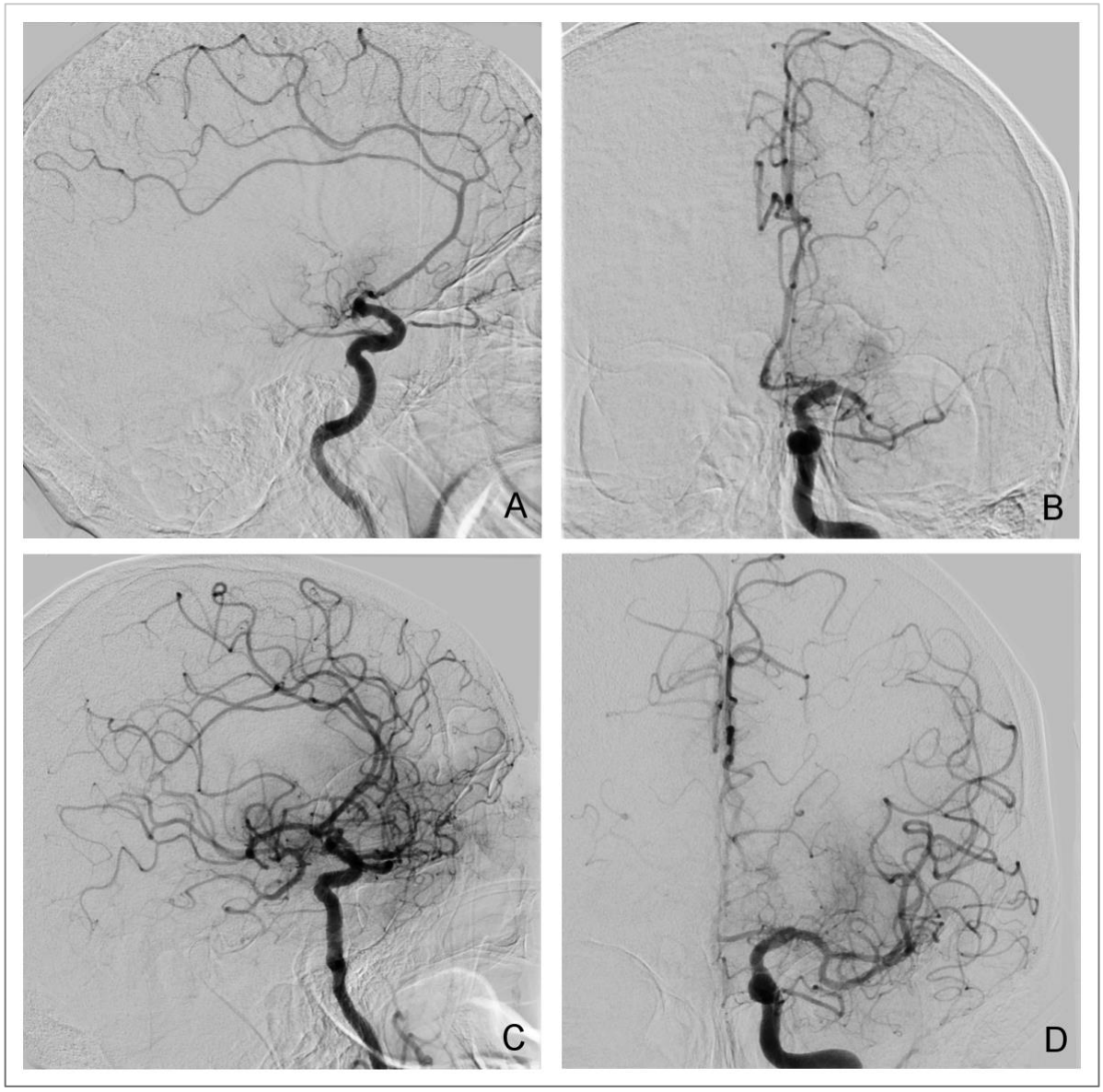


***Figure 9*.** Lateral and posterior-anterior (PA) views of large vessel occlusion (LVO) and eTICI2b67 (mTICI2b) reperfusion results. A and B show a left-sided, distal occlusion of the internal carotid artery (ICA). Lateral and PA-views (C and D) after recanalization depict residual frontoparietal occlusions in the left anterior- and media-territorium, rated as eTICI2b67 (mTICI2b). Please note that, since the LVO involves the left ICA, both the left middle and anterior vascular territory must be included in the eTICI evaluation.

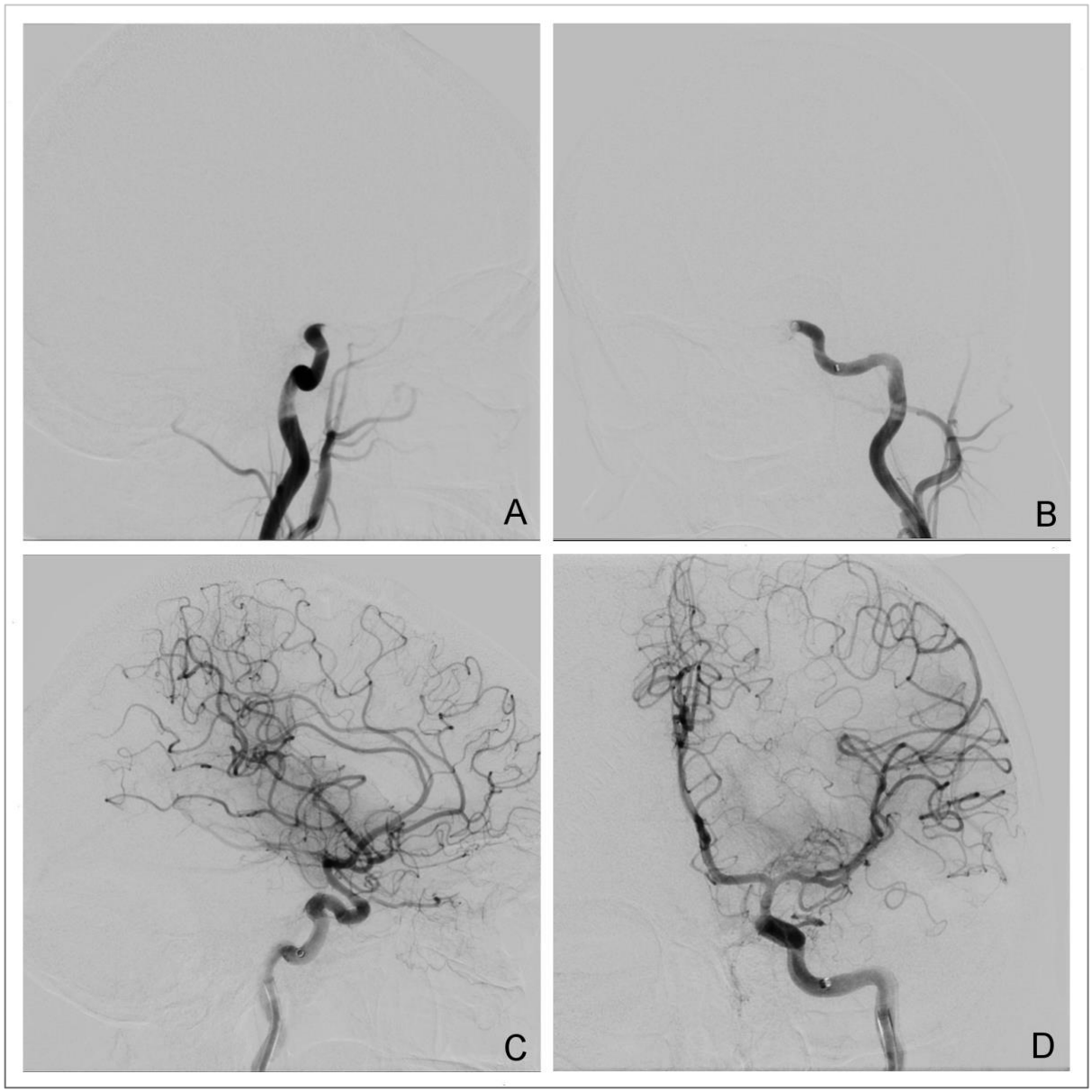


Figure 10. Lateral and posterior-anterior (PA) views of large vessel occlusion (LVO) and eTICI2c (mTICI2b) reperfusion results. A and B show a distal occlusion of the right internal carotid artery (ICA). In the lateral and PA-views (C and D) after recanalization only very small, distal parietal branches do not fill with contrast medium. The result was rated eTICI2c (mTICI2b). As noted before, since the LVO involves the right ICA, both the right anterior and media vascular territory must be evaluated in the eTICI analysis.

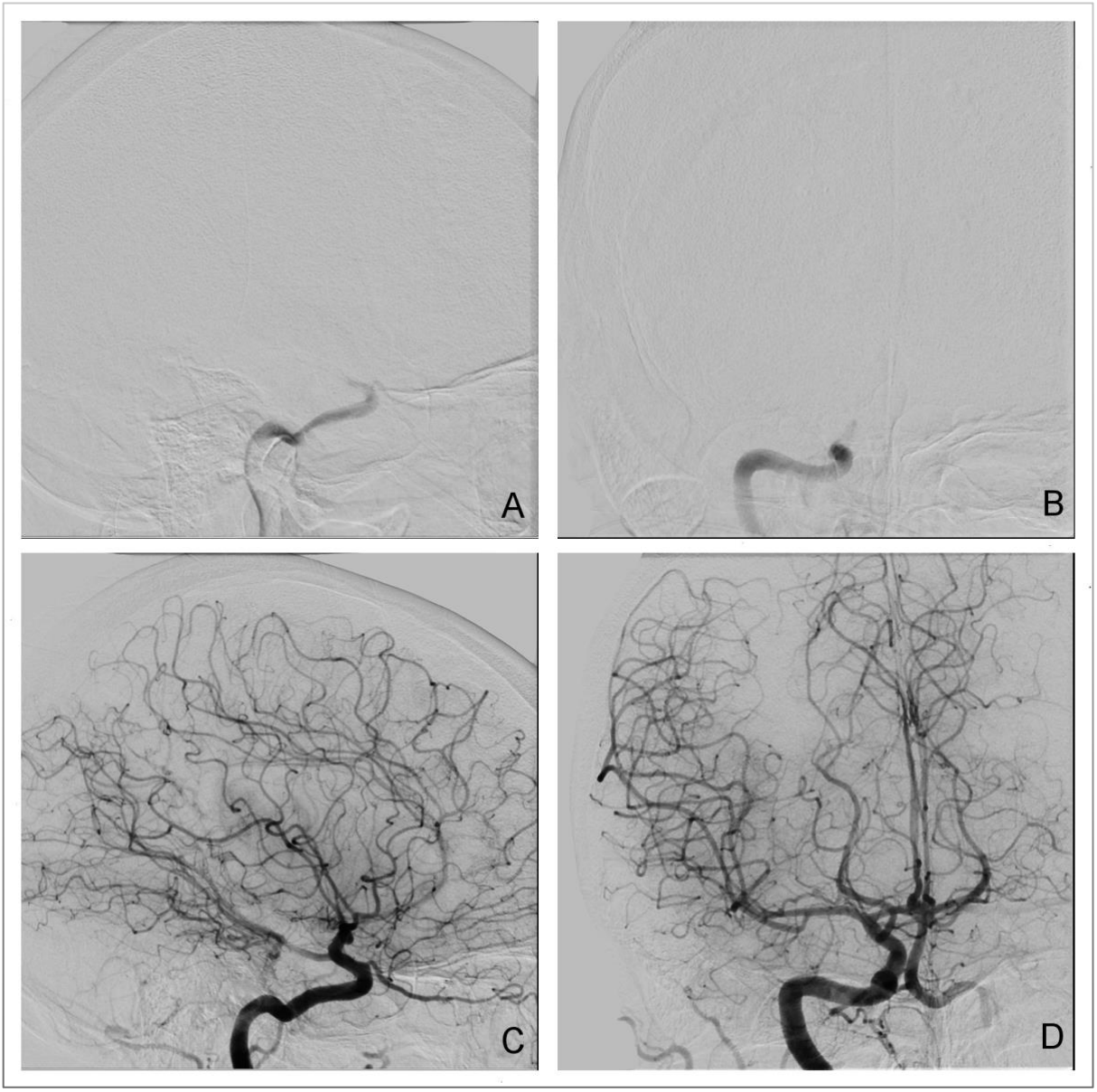


Figure 11. Circle chart illustrating the distribution of the large vessel occlusions (LVO) included in the study. The majority of the LVO were located in the anterior circulation (ICA, MCA and tandem lesions), while thrombotic occlusions of proximal vessels of the posterior circulation (Basilar artery and PCA) represented ca. 13 % of the LVO.

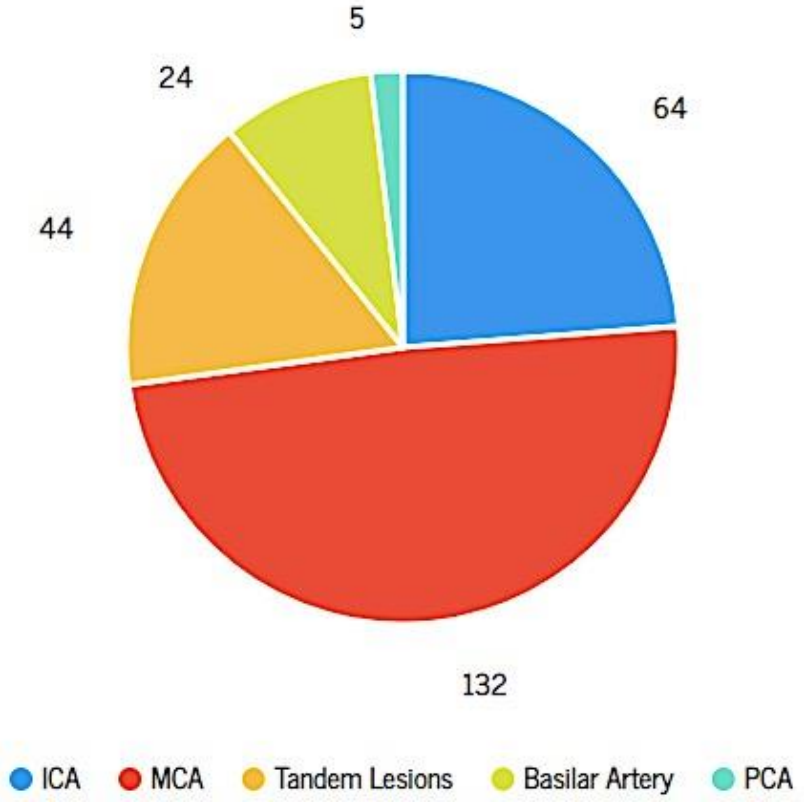


Figure 12. Bar chart depicting reperfusion outcomes classified with the eTICI scale. Reperfusion of 50 % or more of the previously ischemic territory was achieved in more than 84 % of cases. Complete reperfusion was achieved in almost one fourth of the patients (22.2 %). Reperfusion of 50-99 % of ischemic territory (eTICI2b50, eTICI2b67 and eTICI2c) accounts to ca. 62 % of cases.

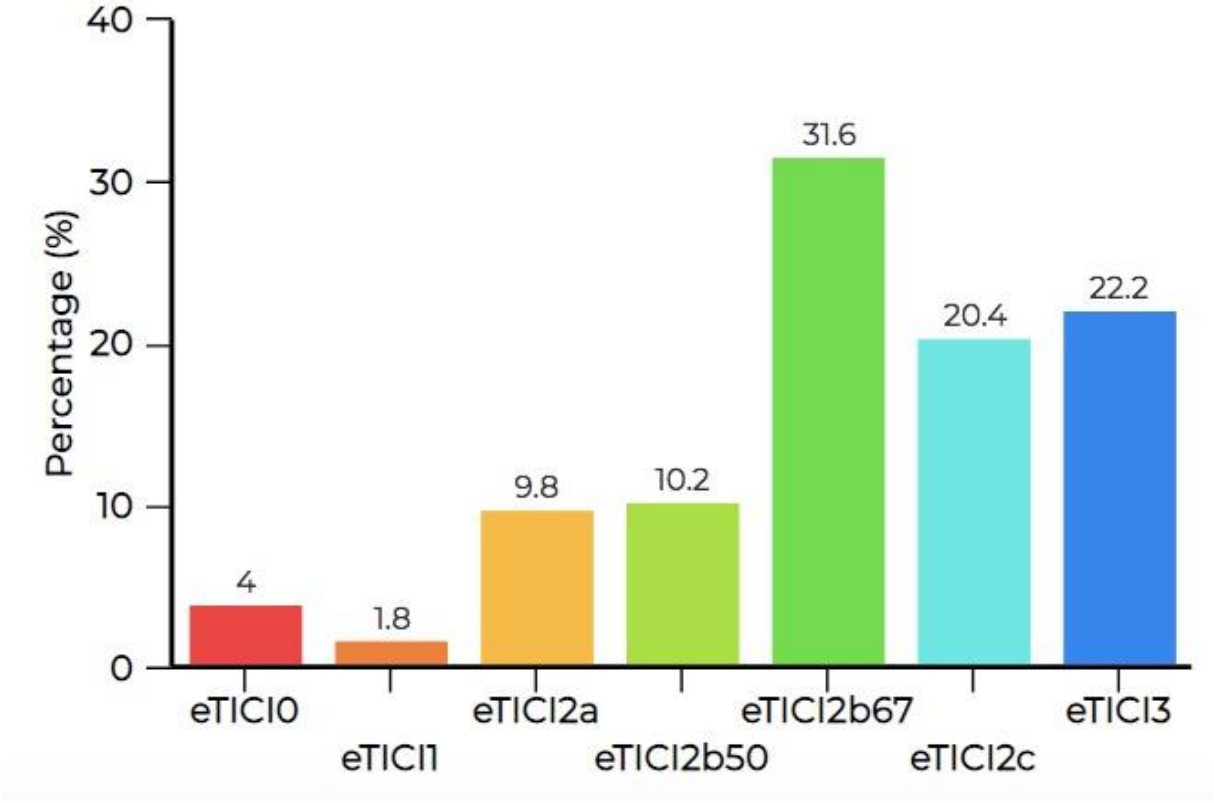


Figure 13. Bar chart representing the neurological outcome after mechanical thrombectomy, measured with modified Ranking Scale (mRS) at 90 days. Favorable outcome (mRS 0-2) was achieved in ca. 39 % of patients.

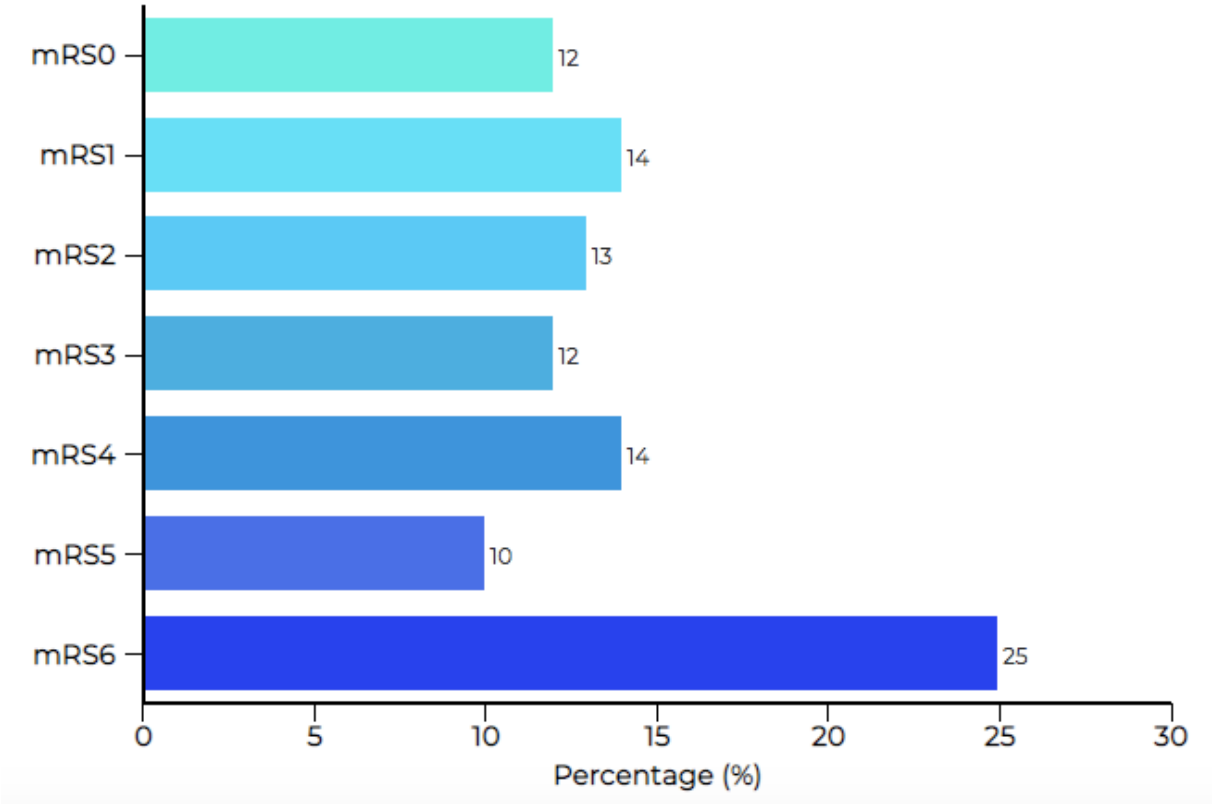


Figure 14. Graphic representation of neurological outcome (mRS at 90 days) after thrombectomy, depending on revascularization score, evaluated with the eTICI scale. Several distinctive trends can be observed. Most importantly with the improvement of the revascularization outcome (eTICI0 to 3), a progressive higher percentage of favorable outcome (mRS 0 – 2) can be achieved.

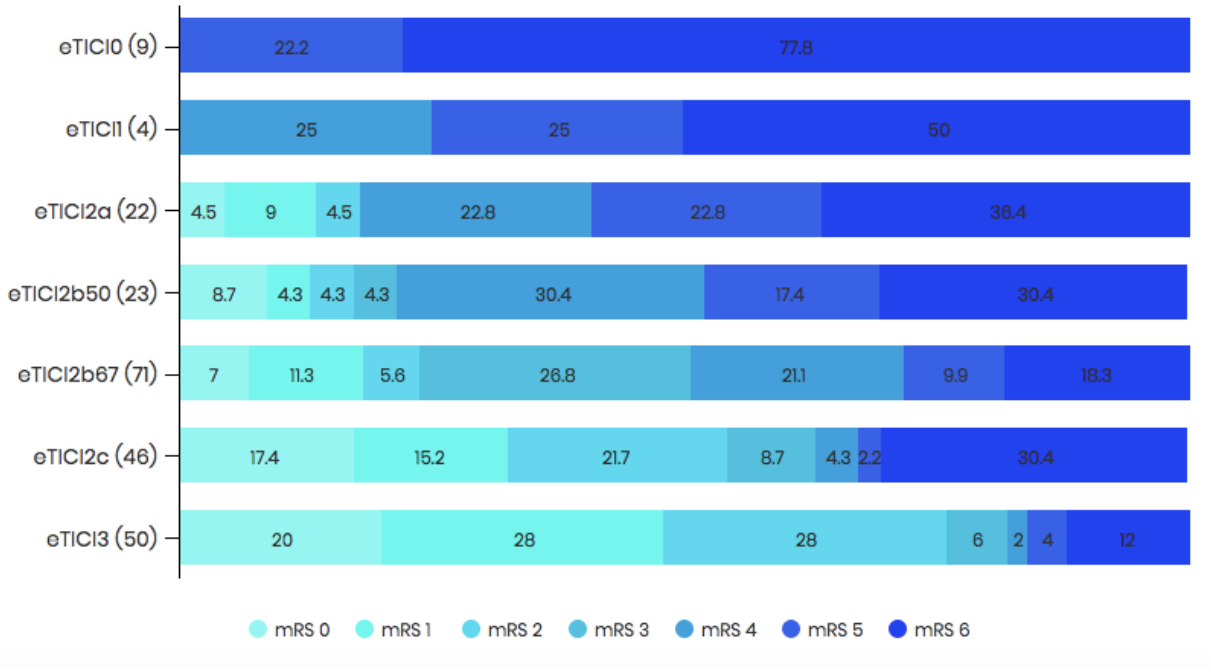


Figure 15. Receiver operating characteristic (ROC) curve for eTICI and mTICI. Comparison of both ROC curves for the prediction of good functional outcome (mRS 0 – 2) at 90 days (Behme et al. 2019).

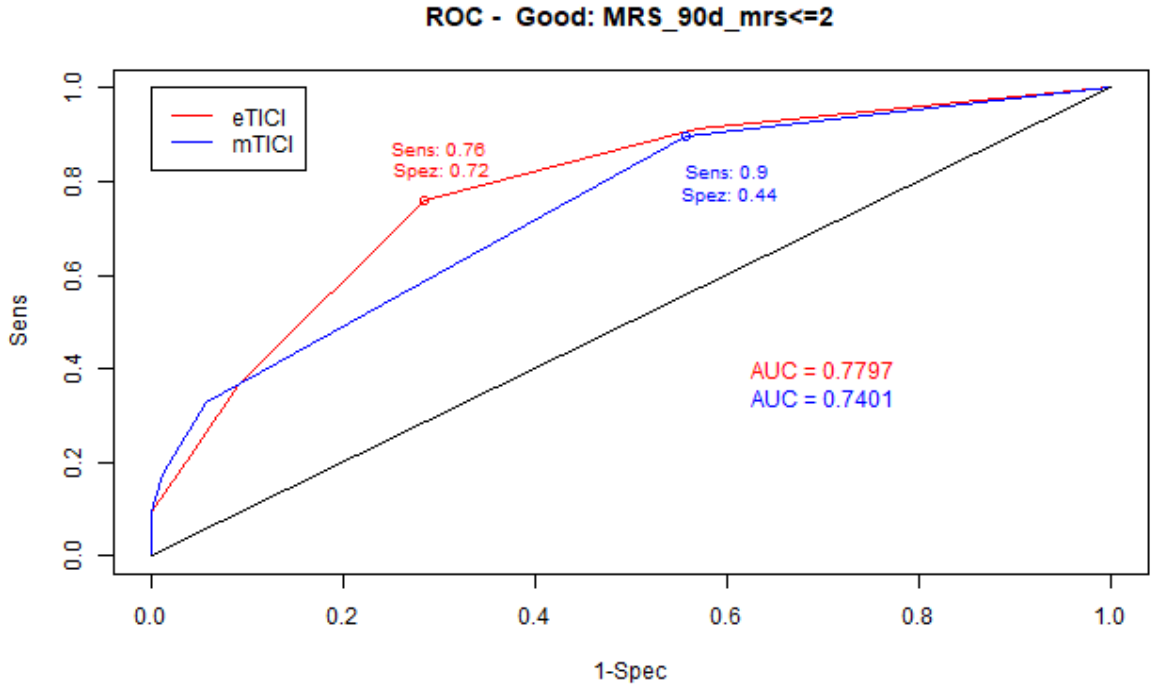


Figure 16. Analysis of time of admission to recanalization A: probability of achieving good outcome according to angiographic reperfusion grade, measured with eTICI. The x-axis shows the admission to recanalization time (in minutes) while the y-axis displays the probability of good outcome at 90 days (mRS 0-2). B: Log odds for attaining a good outcome at 90 days (mRS 0-2) depending on eTICI reperfusion grade. x-axis: time in minutes, y-axis: log odds (Behme et al. 2019, reproduced with permission of "Springer Nature").

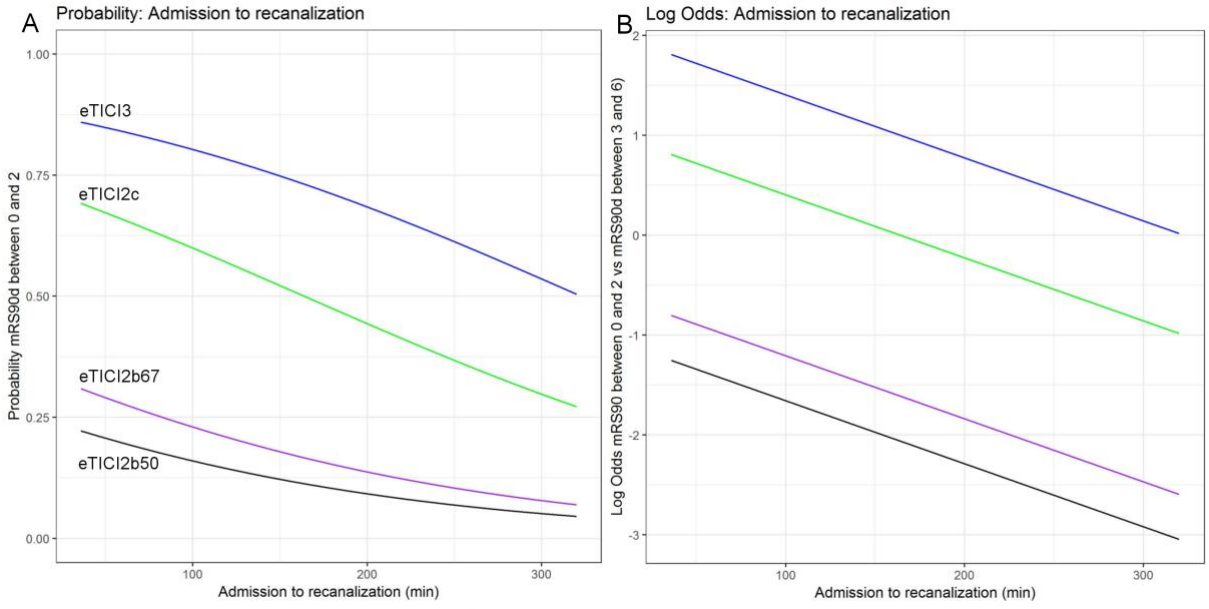
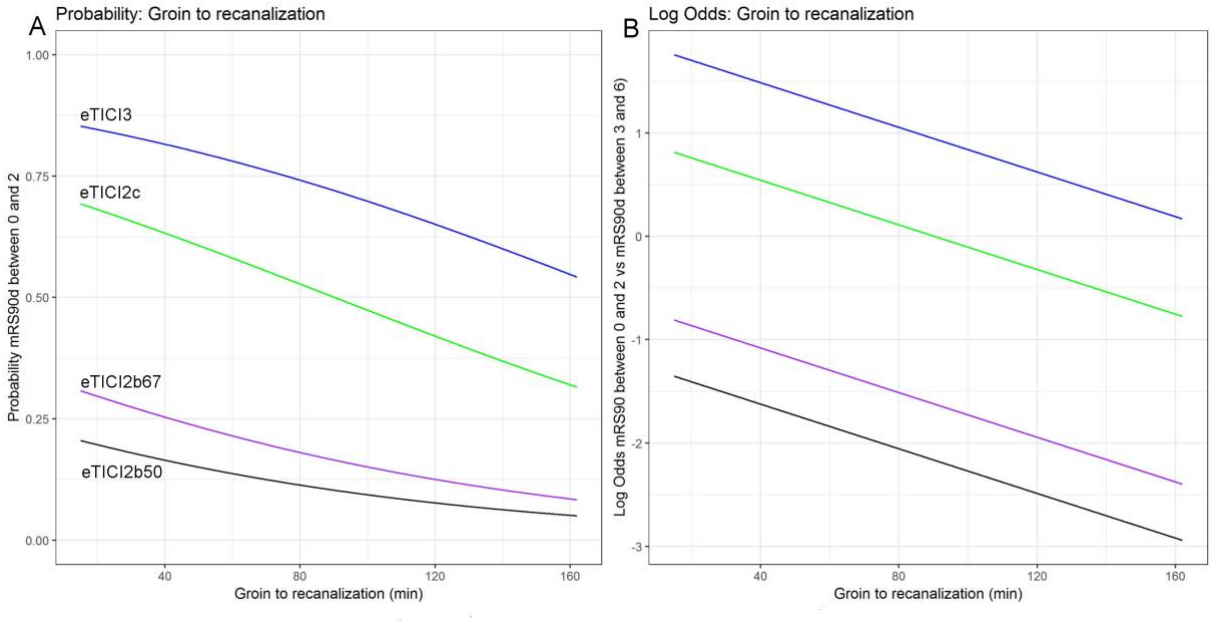


Figure 17. Analysis of time of arterial groin puncture to recanalization A: probability of achieving good outcome (mRS 0-2 at 90 days, y-axis) according to eTICI grade (colored lines) and depending on the groin to recanalization time (x-axis). B: Log odds for attaining a good outcome at 90 days (mRS 0-2) depending on eTICI reperfusion grade (colored lines). x-axis: time in minutes, y-axis: log odds (Behme et al. 2019, reproduced with permission of "Springer Nature").



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