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The impact of early imaging and reperfusion therapy tactics on radiological and clinical outcome in acute ischemic stroke

Summary of the Doctoral thesis for obtaining a doctoral degree (*PhD*)

Sector – Clinical Medicine
Sub-Sector – Radiology

Rīga, 2020

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Defence of the Doctoral thesis will take place online on 18 June 2020 at 15.00 using the Zoom platform

The Doctoral thesis is available in RSU Library and on RSU website: www.rsu.lv

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ABSTRACT

The Thesis "The impact of early imaging and reperfusion therapy tactics on radiological and clinical outcome in acute ischemic stroke" addresses one of the most topical current problems – diagnostics and active treatment of acute ischemic stroke. Acute ischemic stroke is one of the major causes of mortality and long-term disability in the world, having a significant social impact.

The aim of the Thesis was to evaluate the relationship between multimodal computed tomography (CT) diagnostic and active treatment tactics for acute ischemic stroke with radiological and clinical outcome. The study included 288 patients with acute ischemic stroke with major cerebral vascular occlusion.

The Thesis deals with less researched problems to date of active treatment of acute ischemic stroke in patients with large cerebral artery occlusion: use of isolated endovascular thrombectomy compared to the bridging therapy (intravenous thrombolysis with subsequent endovascular thrombectomy) and thrombolysis alone, also recanalization efficiency in the posterior circulation area. The Thesis provides evaluation of treatment complications and thrombectomy procedure parameters, for instance, number of attempts before recanalization and the duration of the procedure.

As a result of endovascular treatment, it is possible to reach a high degree of recanalization, which may not correlate with satisfactory clinical outcome; therefore, patient selection is vitally important, which can be improved using modern radiological examination, radiological evaluation. The Thesis evaluates such radiological criteria upon the choice of the treatment tactics and prognostication of the outcome as collaterals, stroke volume on ASPECTS scale, occlusion site, etc.

The study revealed statistically significantly better results in patients with endovascular treatment compared to patients undergoing isolated intravenous thrombolysis with occlusion of the large cerebral arteries. The results indicated that the clinical outcome of the bridging therapy (intravenous thrombolysis with subsequent endovascular thrombectomy) is similar to that of isolated endovascular thrombectomy, moreover without a significant increase in the number of complications. As a result of endovascular thrombectomy, patients with large cerebral artery occlusion in most cases reached a higher recanalization rate; furthermore, the risk of complications turned out to be low.

Early multimodal CT diagnostics is vitally important is patient selection for active treatment to obtain good late clinical outcome. Radiological parameters such as good collaterals and pre-defined infarct volume in CT perfusion on the ASPECTS scale ≥ 6 statistically significantly correlated with a better clinical and functional outcome, which has been affected by various factors, especially with successful recanalization and reperfusion.

The study includes recommendations in active treatment of acute ischemic stroke and screening of patients with known large cerebral artery occlusion and definition of the action algorithm.

CONTENTS

ABBREVIATIONS

AB	basilar artery (lat. *arteria basilaris*)
ACI	internal carotid artery (lat. *arteria carotis interna*)
ACM	middle cerebral artery (lat. *arteria cerebri media*)
ACP	posterior cerebral artery (lat. *arteria cerebri posterior*)
aICH	asymptomatic intracerebral haematoma
ASPECTS	Alberta Stroke Program Early CT Score
CBF	cerebral blood flow
CBV	cerebral blood volume
CI	cerebral infarction
CT	computed tomography
CTA	computed tomography angiography
CTP	computed tomography perfusion
DSA	digital subtraction angiography
ESO	European Stroke Organisation
EVT	endovascular thrombectomy
ICH	intracerebral haematoma
IVT	intravenous thrombolysis
MIP	maximum intensity projection
mRS	modified Rankin scale
MTT	mean transit time
NIHSS	National institutes of Health Stroke Score
OR	Odds Ratio
RCTs	randomised controlled trials
sICH	symptomatic intracerebral haematoma
SPKC	Centre for Disease Prevention and Control
TICI	thrombolysis in cerebral infarction

INTRODUCTION

Acute cerebral infarction or ischemic stroke (CI) is one of the main causes of mortality in the world; annually the disease affects approximately 16.9 million people in the world (Feigin et al. 2014). Latvia is located in the region characteristic with high incidence of stroke ~ 384/100,000 people. Over the last few years, increased mortality due to cerebrovascular disease has been observed. In 2017, mortality was acknowledged in ~ 279 cases per 100,000 inhabitants. However, mortality caused by CI over the last few years is in decline – 80.6/100,000 inhabitants, which might be connected to the rehabilitation possibilities and growth in the number of thrombolysis in the country (SPKC 2017; Feigin et al., 2014; Sousa et al., 2009).

Treatment of patients with strokes requires high costs from health and social care budget; therefore, society should be informed on how to recognise a stroke early and call for medical assistance since time is vital in the efficacy of the therapy (Saver, 2006; Ganesalingam et al., 2015).

Intravenous thrombolysis (IVT) long was known to have been the only officially recognised active treatment in patients with CI, who can be started on the therapy within 4.5 hours of the onset of the symptoms (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995; Powers et al., 2018a). Nevertheless, IVT efficiency in case of large cerebral artery occlusion is suboptimal, especially when the thrombus exceeds 8 mm in length, as is the case with internal carotid artery (ACI) occlusion (Riedel et al., 2011). Therefore, in recent years several studies have been conducted on the efficacy and benefits of endovascular thrombectomy (EVT) in cases when stroke has developed due to large cerebral artery occlusion.

In 2013, in several randomised controlled trials (RCTs) scientists sought to confirm the effectiveness of the EVT by assessing its safety and outcome in patients with large cerebral artery occlusion; however, efficiency was statistically insignificant (Broderick et al., 2013; Kidwell et al., 2013). The studies were heavily criticised for patient selection; therefore, new studies were urgently organised in different parts of the world, and between 2014 and 2016 several of those were already published (MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT, THERAPY, TRACE). In comparison to the studies published in 2013, all of these studies indicated statistically significant superior clinical outcomes in patients with large cerebral artery occlusion receiving EVT compared to those that received only IVT (Fransen et al., 2014; Goyal et al., 2015; Campbell et al., 2015a; Jovin et al., 2015; Mocco et al., 2016; Bracard et al., 2016). Since 2016, EVT has been officially approved as the first choice method for patients with CI with large cerebral artery occlusion in the anterior circulation area if IVT is contraindicated (Powers et al., 2018a; Fiehler et al., 2016).

Multimodal CT examination methods are most commonly included in the radiological diagnosis of acute ischemic stroke, which includes noncontrast CT, CT angiography (CTA), and CT perfusion (CTP). Noncontrast CT allows for differentiation of haemorrhagic and ischemic stroke, as well as assessment for early signs of stroke, such as hyperdense artery sign and brain tissue hypodensity (Tomura et al., 1988). CTA is vitally important, if the patient is a candidate for endovascular treatment since it allows for determination of occlusion level, assessment of collateral blood flow and vascular anatomy (Pulli et al., 2012). CTP allows early detection of hypoperfusion in the brain, which helps in differentiation of the occlusion site, especially if the CTA connection is not visible, and early detection of damaged tissue volume, specifying whether they correspond to a irreversible *core* lesion or a reversible *penumbra* type lesion in case of arterial recanalization (Lev et al., 2001; Radzina et al., 2013).

Nevertheless, various studies on topical issues in the treatment of acute ischemic stroke are still ongoing, for instance, wider time frame for active therapy, role and benefits of bridging therapy (IVT with subsequent EVT) compared to isolated IVT or EVT, effectiveness of alternative thrombectomy methods (Mocco et al., 2016).

The current study compared the efficacy and complications of bridging therapy (IVT with subsequent EVT), isolated EVT, and isolated IVT in acute CI treatment groups. Evaluation of the effectiveness of the EVT, procedural parameters has also been performed, for example, duration of thrombectomy, complications and recanalization rates and their impact on clinical outcome by mRS and NIHSS scales. The study also included analysis of comparison of radiographic screening criteria and their impact on clinical outcome by measuring parameters such as collaterals, occlusion site, and ischemic *core* lesion on the ASPECTS scale at hospital admission and in control studies.

1. TOPICALITY, NOVELTY AND PRACTICAL IMPLICATIONS OF STUDY

Despite many successful studies confirming the efficacy of IVT and EVT treatment, appropriate selection of patients prior to active revascularization therapy to achieve the most favourable clinical outcome remains a pressing issue, and radiology plays the leading role in primary patient screening.

A study comparing active treatment methods for acute ischemic stroke – intravenous thrombolysis and endovascular thrombectomy – in patients with major cerebral artery occlusion and analysing the combined use of both methods has been performed for the first time in Latvia. The results obtained in the bridging therapy for treatment of cerebral infarction are very significant, as there is still lack of research in its application not only in Latvia but worldwide as well.

As a result of the study, the data were obtained on imaging diagnostic criteria such as collaterals, and relationship between the extent of ASPECTS CTP ischemia and site of occlusion with radiological and clinical outcome. The study provides results on the efficacy of endovascular treatment regarding time until the onset of recanalization as well as efficacy of treatment based on a patient's age.

The study also provides data on procedural parameters of endovascular treatment, analysis of EVT methods, the number of attempts to achieve recanalization, duration of procedures, and impact on the outcome. The obtained results are applicable in clinical practice. The results on treatment efficacy at different sites of occlusion, including the efficacy of endovascular treatment in the posterior circulation area, are significant since this has been poorly studied in the world so far. Therefore, recommendations for active treatment of acute cerebral infarction in patients with large cerebral artery occlusion have been developed and an action algorithm has been defined.

Personal contribution

The author of the Thesis has participated in all parts of the study – planning of the study, collection of material, post-processing of CT data, statistical analysis, interpretation of the obtained results, literature research, preparation and translation of publications, theses, conference reports; is the author of images published in the study. This prospective cross-sectional study was approved by the Ethics Committee of Rīga Stradiņš University and the Science Department of Pauls Stradins Clinical University Hospital.

2. AIM, TASKS AND HYPOTHESIS OF STUDY

The aim of the study was to evaluate the relationship of multimodal CT diagnostic and active treatment tactics in patients with acute ischemic stroke and large cerebral artery occlusion, it's impact on radiological and clinical outcome.

Tasks of the study

1. Perform multimodal CT examinations to detect radiological criteria to be used in selection and outcome prognosis of cerebral infarction therapy in patients with major cerebral artery occlusion.
2. Compare efficacy and incidence of different types of reperfusion therapy (isolated intravenous thrombolysis, isolated endovascular thrombectomy and bridging therapy) in patients with acute ischemic stroke in the anterior circulation area.
3. Evaluate the effectiveness of isolated endovascular thrombectomy and bridging therapy in patients with acute cerebral stroke in the posterior circulation area and large cerebral artery occlusion.
4. Evaluate the influence of endovascular treatment procedure parameters (degree of recanalization, time of procedure and number of complications, recanalization attempts) on the clinical outcome.

Hypothesis of the study

1. The choice of the bridging therapy (intravenous thrombolysis with subsequent endovascular thrombectomy) for occlusion of large cerebral arteries increases the possibility of achieving a better clinical outcome when compared to single intravenous thrombolysis or endovascular thrombectomy.
2. The extent of ischemic damage defined by multimodal CT imaging varies dynamically with the efficacy of the therapy used, and early diagnostic results can be used to predict a potential outcome.

3. MATERIALS AND METHODS

3.1. Patient selection

Patients with acute ischemic stroke, hospitalised at Pauls Stradins Clinical University Hospital (PSCUH) between the period of March 2014 and October 2017, were included in the study. Patients with ischemic stroke in the anterior circulation area were included in the study, if EVT was performed within 8 hours of the onset of the symptoms; however, patients with ischemic stroke in the posterior circulation – if the EVT did not exceed 24 hours. Larger time frame in posterior circulation was selected due to high mortality because of basilar artery occlusion, and also due to undefined frame of time in the guidelines for the given area (Schonewille et al., 2005).

Patients who underwent a full multimodal computed tomography scan were included in the study, which involves non-contrast computed tomography of the brain, CT angiography and CT perfusion. To assess the radiological efficacy of the therapy, a follow-up radiographic examination was performed 24 hours after the treatment: assessing the extent of stroke on the ASPECTS scale and complications such as symptomatic and asymptomatic intracranial haemorrhage. Clinical data on patients' neurological status were obtained in cooperation with PSCUH Neurology Clinic, using the NIHSS and mRS neurological status assessment scales on admission and post-therapy (Brott et al., 1989; Broderick, Adeoye, and Elm, 2017). Patient medical records and extracts from the PSCUH Medical Archive were also used to obtain the required data. The long-term efficacy assessment was performed 90 days after the treatment, using the mRS scale, and the functional result in dynamics was evaluated.

3.1.1. Inclusion and exclusion criteria

One of the main inclusion criteria was occlusion of large cerebral arteries. Large blood vessels in this study were considered to be *arteria cerebri media*

(ACM) M1 segment, *arteria carotis interna* (ACI), or connection of both of these blood vessels, also called “Tandem” occlusion, as well as patients with *arteria basilaris* (AB) and or vertebral artery occlusion. The inclusion and exclusion criteria in the study are detailed in Table 3.1.

Table 3.1.

Patient inclusion and exclusion criteria in the study group

Inclusion criteria	**Exclusion criteria**
Occlusion of large cerebral arteries, AB, ACI, ACM M1 and in separate cases in M2 segment	Distal branch occlusion in M3 and M4 segments, chronic ACI connection with a new connection in the corresponding distal ACM M1 segment
Full multimodal CT examination has been performed, noncontrast CT, CTA, CTP, and has a noncontrast CT 24 h control exam	Full multimodal CT examination has not been performed
Neurological deficit NIHSS > 5	Neurological deficits NIHSS < 5
Age above 18, without a maximum age limit	Post-treatment problems with patient radiology images due to pronounced artifacts
EVT has been performed within 8 h of the onset of symptoms in a patient with anterior circulation artery occlusion, within 24 h in a patient with AB occlusion or in a patient with awakening stroke	Noncontrast CT examination shows already completed ischemia or haemorrhage

(AB – *arteria basilaris*, ACI – *arteria carotis interna*, ACM – *arteria cerebri media*, CT – computed tomography, CTA – CT angiography, CTP – CT perfusion, NIHSS – National Institute of Health stroke scale, IVT – intravenous thrombolysis)

Patients with CI in the anterior circulation area and large cerebral artery occlusion having received only isolated intravenous thrombolysis within 4.5 h were included in the control group. Assembling of the control group was possible because the EVT was not included in the guidelines at the start of the study.

3.1.2. Characteristics of patient groups

The study initially included 299 patients with a multimodal CT scan; however, 11 patients had to be excluded from the study due to technically inconclusive examination images. The most common cause was marked by movement artefacts or poor arterial contrast characteristic of hemodynamically unstable patients. During the study, 30 patients were enrolled in the control group, who due to various reasons received only isolated IVT, although they were found to have large cerebral artery occlusion.

The grouping of patients has been represented in Figure 3.1.

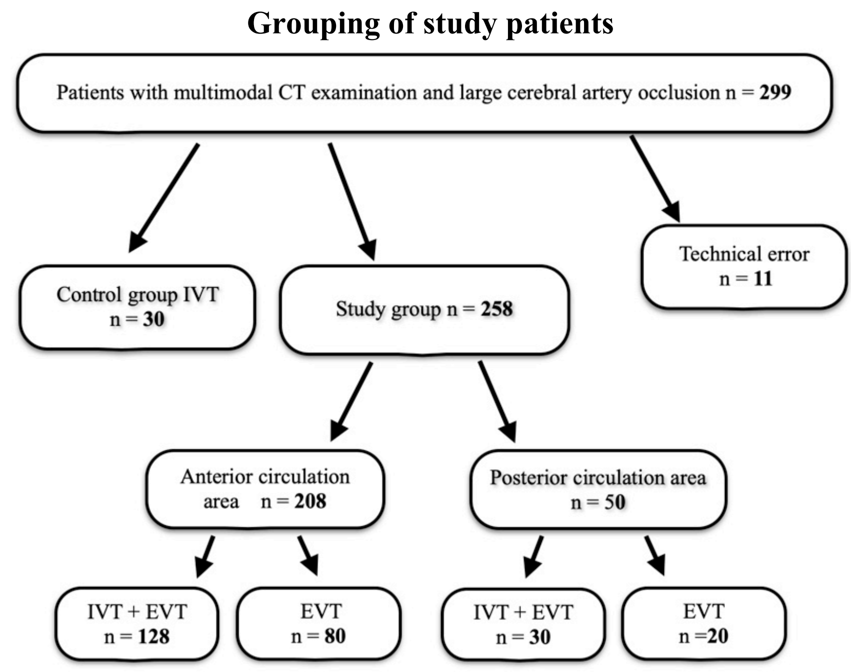


Figure 3.1. **Patient distribution across the study groups**
(EVT – endovascular thrombectomy, IVT – intravenous thrombolysis, CT – computed tomography)

Of the 288 patients selected, 132 (46 %) were male and 156 (54 %) female, patient age range – between 29 and 91 (mean age – 72, interquartile range 77–64) years.

According to age distribution, the majority of patients, 82 % (n = 237), were older than 61 years.

More than 60 % (n = 125) of the patients in the study group with ischemic stroke received endovascular treatment early, within 4.5 h, but more than 80 % of patients (n = 167) received treatment within 6 h. The distribution of patients included in the study until recanalization has been represented in Figure 3.2.

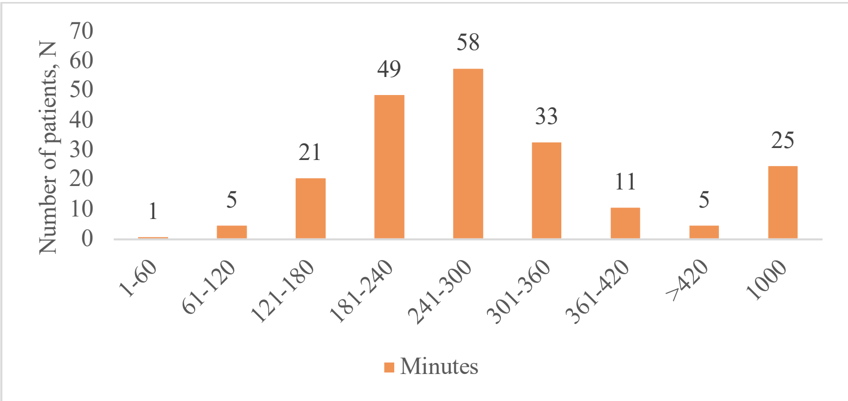


Figure 3.2. **Distribution of patients until recanalization**

Patients without known time of the onset of the disease and those with awakening stroke were also included in the study; overall this included 12 % of the patients (n = 25) with ischemic stroke in the anterior circulation area. The number of patients who had a stroke or had an unknown time of onset has been plotted against the 1000-minute section.

A patient database was created on a personal computer in *Microsoft Office Excel*. The following data were archived in the table: patient age and sex, date of examination, neurological evaluation of patients before and after treatment, and 90 days after treatment using the NIHSS and mRS scales, respectively.

The study summarises and analyses the following results: EVT procedure time and number of attemps before recanalization in DSA, site of occlusion, noncontrast CT finding, volume of collateral blood flow in CT angiography, CTP reversible *penumbra* and irreversible tissue volume *core* on the ASPECTS scale, complications and lethality.

3.2. Multimodal computer tomography examination

A multimodal CT examination was performed on all patients in the study with 64 rows of multilayer computed tomography equipment General Electric, starting the examination with noncontrast CT for the head, CT angiography (CTA) and CT perfusion (CTP). Noncontrast CT examination assessed for cerebral haemorrhage or pre-existing extensive ischemia, as well as the absence of any other cause of acute neurological deficits, for instance, intracranial oncological process (Mair and Wardlaw, 2014). In patients without bleeding or other abnormalities, examination was continued with CT angiography and CT perfusion examinations. Indirect stroke pointers – sign of hyperdense artery, loss of difference between gray and white matter – did not affect further investigations by CTA and CTP.

Noncontrast CT examination parameters: soft scalp tissue at the base of the skull with a 2.5 mm layer – 24 images. Soft scalp tissue with a 5 mm layer, 120 kv and 240 mA – 20 images.

CT angiography of intra- and extracranial blood vessels was performed, including the entire skull in the axial plane of the aorta after iodinated non-ionic intravenous contrast medium.

CT perfusion was performed from the base of the brain, including the posterior circulation area and the large hemispheres of the brain, including the majority of the brain. *AW CT Perfusion* 4D post-treatment programme was used for post-treatment of CT perfusion examinations (GE Healthcare, USA), with the help of which CTP maps were obtained to assess blood perfusion of brain tissue: MTT – mean transit time, CBV – cerebral blood volume, CBF – cerebral blood flow. The maps were used to differentiate the *core* area, which represents irreversible brain tissue ischemia or necrosis as well as the *penumbra* brain tissue showing potentially reversible brain tissue if recanalization is achieved over a period of time (Lui et al., 2010).

3.4. Endovascular thrombectomy and its procedural parameters

Endovascular thrombectomy was performed on DSA (digital subtraction angiography) RTG fluoroscopy control using *Siemens AXIOM Artis dBA/BA*. To avoid time delays, the procedure has been performed under local anesthesia for all patients wherever possible by puncture of femoral artery using Seldinger's method. In rare cases, the procedure was followed by sedation medication or general anesthesia in patients who were restless or had more severe status, for instance, in the case of basilar artery occlusion (Seldinger, 2008; Van den Berg et al., 2015).

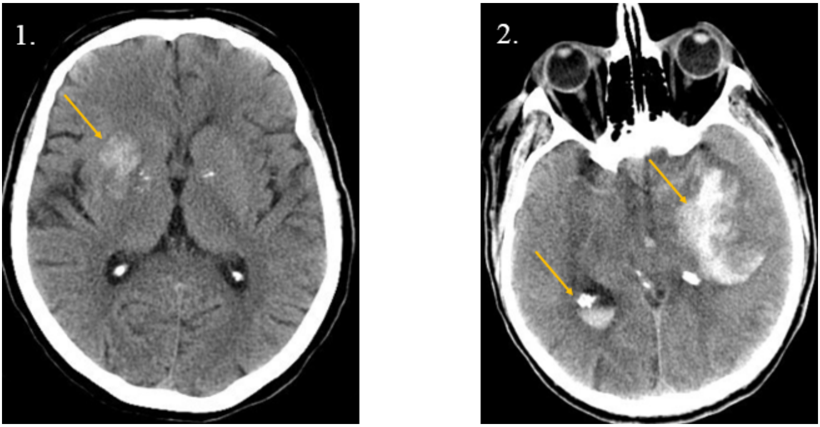
The most commonly used systems for thrombus extraction were *Solitaire* and *Trevo*. These are the latest generation systems that are also considered to be the most advanced since many studies have shown good clinical results (Fransen et al., 2014; Campbell et al., 2015b). In some patients, successful recanalization was achieved using a large caliber aspiration catheter (*penumbra system*), positioning it before the thrombus, sometimes also using proximal aspiration with a thrombectomy stent (Park, 2015).

The efficacy of thrombectomy was assessed immediately after the procedure by TICI classification. Good recanalization was rated as TICI 2b-3 but bad as 0-2 a/c.

All patients enrolled in the study had a control noncontrast CT scan 24 hours after the treatment. The control study evaluated the radiological efficacy of the treatment, analysing the extent of ischemia on the ASPECTS scale, which changes in dynamics after the treatment, compared to the originally defined damage to the ASPECTS CTP *core* and ASPECTS CTP *penumbra*.

3.5. Symptomatic and asymptomatic haemorrhages

One of the complications of the treatment was haemorrhage, which was evaluated in 24-hour control CT examinations. Symptomatic intracranial haemorrhage (ICH) was defined as extensive parenchymal haemorrhage when it occupied more than 30 % of the ischemic area with a mass effect and a 4-point or greater increase in neurological deficit according to the NIHSS scale (Kase et al., 2001) (sample has been represented in Figure 4.4). Asymptomatic haemorrhage was characterised by haemorrhagic imbibition without mass effect and without increase in NIHSS score (Kase et al., 2001). Total number of haemorrhages consisted of symptomatic and asymptomatic haemorrhages. Symptomatic and asymptomatic haemorrhages have been shown in Figures 3.3 and 3.4 obtained from the patients included in the study.



Figures 3.3 and 3.4. **Example of evaluating asymptomatic and symptomatic haemorrhage**
1 – asymptomatic haemorrhage on the right hemisphere in the basal nuclei;
2 – symptomatic haemorrhage with mass effect, right-sided dislocation of the middle structures and breakout to the cerebral ventricles (images from the author's archive)

3.6. Stroke volume evaluation – evaluation of ASPECTS and collaterals

The study used the ASPECTS (*Alberta stroke programme early CT score*) scale to measure stroke volume evaluating irreversible damage, upon admission to hospital in a noncontrast CT scan. Irreversible and potential reversible damage was assessed in the CTP study. Irreversible *core* damage was evaluated on noncontrast CT examination after 24 h using the ASPECTS scale. Statistical analysis of the data, to determine the potential to achieve a potentially good radiological and clinical outcome of stroke, is based on two estimates: ASPECTS ≥ 6 and ASPECTS ≥ 7; the possibility of achieving this in patients with lower ASPECTS scores was also analysed. An additional study modeled the potential risk for patients with good or bad outcomes, incrementing the ASPECTS scale by 1 point. A practical example of assessing stroke using the ASPECTS scale is shown in Figures 3.5 and 3.6.

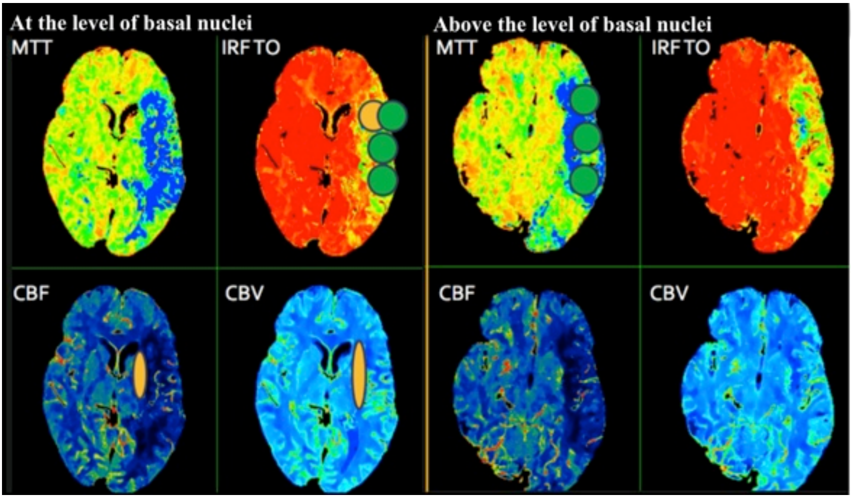


Figure 3.5. **A practical example of assessing stroke extent using the ASPECTS scale** (ASPECTS – Alberta stroke programme early CT score), (images from the author's archive)

Patient (72 years) with severe neurological deficits NIHSS 17, ACM M1 segment occlusion. MTT – mean transit time, CBF – cerebral blood flow, CBV – cerebral blood volume, IRF – impulse response function. At the basal ganglia level: ASPECTS *core*: insula and *n. lentiforme* 10 − 2 = 8 points (marked on CTP maps with orange circle). ASPECTS *penumbra*: M1+M2+M3+M4+M5+M6; 10 − 6 = 4 points (marked on the maps with a green circle), extensive, potentially reversible lesion, the patient is a good candidate for endovascular treatment. Control 24 h CT ASPECTS rating has been represented in in Figure 3.6.

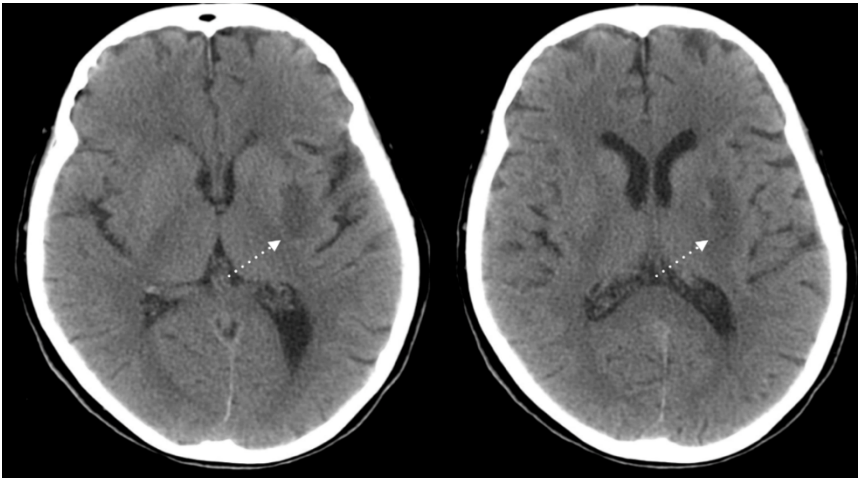


Figure 3.6. **Example of ASPECTS evaluation after endovascular thrombectomy,** 24-hour control in noncontrast CT scan (ASPECTS – Alberta stroke programme early CT score), (images from the author's archive)

Good clinical and radiologic outcome with mRS 1 at patient discharge. ASPECTS *core*: *n. lentiforme* 10 − 1 = 9. Wide *penumbra* area described in the above figure 3.6 without damage, complete reperfusion during endovascular thrombectomy with score TICI 3.

3.7. Collaterals

For the evaluation of collaterals, a modified (Tan et al., 2009) classification has been used in the study dividing collaterals into two groups – good and bad, as well as dividing them into four groups – good, medium and bad, in addition, distinguishing a special group – malignant collaterals. CTA collaterals were evaluated at optimum layer thickness (maximum intensity projection) – MIP = 45 to better evaluate the number and contrast of distal arteries in M3 and M4 branches of middle cerebral artery. Evaluation of collaterals and their examples in four groups have been presented in Figure 3.7.

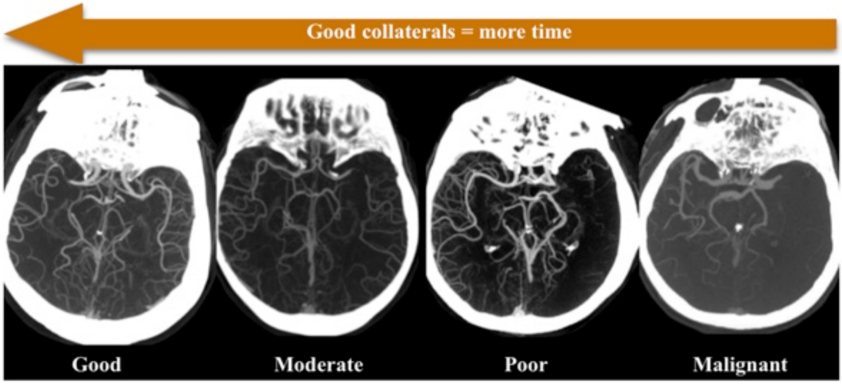


Figure 3.7. **Clinical example of collateral evaluation in each group**

Malignant: complete lack of collaterals compared to healthy hemosphere, poor: number and intensity of collaterals up to ≤ 50 % but above > 0 % collateralisation compared to whole ACM area. Intermediate collaterals: ≥ 50 % but < 100 % of occluded ACM area, good: number and intensity of collaterals 100 % or more relative to the opposite hemisphere of the brain (images from the author's archive).

Threshold level for good and poor collaterals was assumed to be ≥ 50 % relative to healthy hemisphare (Wufuer et al., 2018).

4. RESULTS

4.1. Evaluation of endovascular thrombectomy in patients with stroke in the anterior circulation area

Successful recanalization – TICI (2b-3) was achieved in 189 (91 %) patients with stroke in the anterior circulation area treated in the study, 89 % of the patients in the EVT group and 91 % in the bridging therapy group achieved recanalization. The results of recanalization and reperfusion are shown in more detail in Table 4.1.

Table 4.1.

Recanalization and reperfusion scores on the TICI scale for patients with stroke in the anterior circulation area

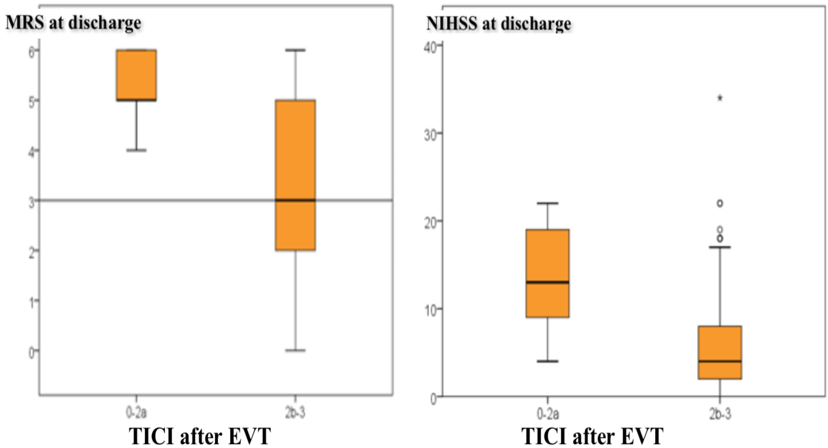
TICI according to EVT in the anterior circulation area	Number of patients, N (%)
0	**0**
1	**6** (3)
2a	**12** (6)
2b	**42** (20)
3	**148** (71)

(TICI – thrombolysis in cerebral infarction, EVT – endovascular thrombectomy)

In the complete reperfusion group, the median value for NIHSS was 4 and the interquartile range was 8–2; in contrast, in the group of incomplete reperfusion, the median value was 13 and the interquartile range was 19–9, $p < 0{,}001$, thus, the patient's neurological status was significantly better at discharge according to the NIHSS in the group of patients with complete recanalization and reperfusion.

The group of patients who did not achieve complete reperfusion had a higher post-treatment lethality (n = 6; 35 %) compared to patients who achieved complete reperfusion (n = 20; 11 %), $p < 0.001$.

Differences between mRS and NIHSS assessment in patients with complete and incomplete reperfusion have been more broadly represented in Figure 4.1 and 4.2.



Figures 4.1 and 4.2. **Comparison of complete and incomplete reperfusion treatment groups by NIHSS and mRS assessment in patients with stroke in the anterior circulation area**
(TICI – thrombolysis in cerebral infarction, NIHSS – National Institute of Health stroke scale, mRS – modified Rankin scale, EVT- endovascular thrombectomy)

The parameters analysed in the study showed positive dynamics after receiving endovascular reperfusion therapy. ASPECTS CTP *penumbra* median value increased by 2 points 24 h after the treatment, $p < 0.001$. Median values for NIHSS and mRS were also significantly better when comparing hospital admission data with the discharge data, $p < 0.001$. It should be noted that mRS scores continued to improve even after discharge from the hospital, reaching the median score after 2 to 3 months. This means that most patients were functionally independent at 3 months after hospitalisation with mild or minimal neurological deficits.

The results confirmed that EVT is an effective treatment method, and successful recanalization is vital for achieving a good clinical and radiological outcome after EVT.

4.2. Comparison of intravenous thrombolysis and endovascular thrombectomy groups in patients with stroke in the anterior circulation area

The bridging therapy (IVT with subsequent EVT) and isolated endovascular treatment groups showed statistically significantly better early functional outcome on mRS at baseline compared to the isolated thrombolysis group: rating mRS 0–2 respectively 29 % (n = 59) and 16 % (n = 5) of the patients, $p = 0.006$. When comparing the results in the treatment groups 90 days after onset of the disease, a favourable stroke outcome, consistent with mRS 0–2, was more common in the endovascular patient groups, in 40 % of the patients (n = 83), while in isolated thrombolysis group only 20 % (n = 6), $p < 0.001$. A more detailed comparison between treatment groups has been represented in Figures 4.3 and 4.4.

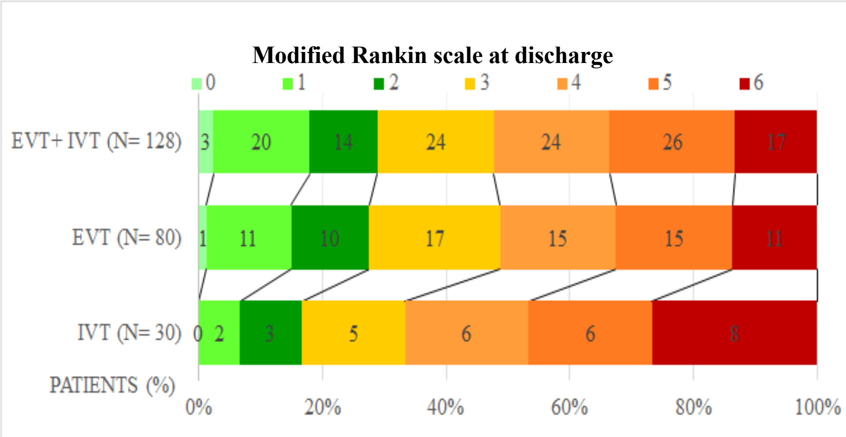


Figure 4.3. **Evaluation of modified Rankin scale at discharge in different treatment groups in patients with large cerebral artery occlusion in the anterior circulation area**

The graph shows the absolute numbers of patients with an mRS score ranging from 0 to 6: 0 – no symptoms; 6 – fatal outcome. (bridging IVT+ EVT – intravenous thrombolysis with subsequent endovascular thrombectomy, EVT - endovascular thrombectomy, IVT – intravenous thrombolysis)

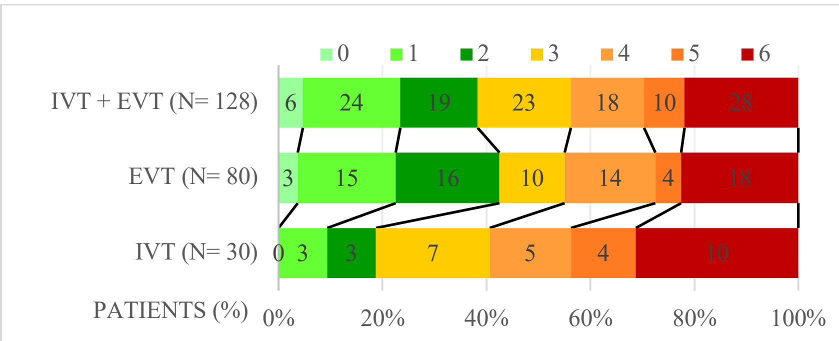


Figure 4.4. **Evaluation of modified Rankin scale 90 days after hospitalisation in different treatment groups in patients with large cerebral artery occlusion in the anterior circulation area**

The graph shows the absolute numbers of patients with an mRS score ranging from 0 to 6: 0 – no symptoms; 6 – fatal outcome. (bridging IVT + EVT – intravenous thrombolysis with subsequent endovascular thrombectomy, EVT – endovascular thrombectomy, IVT – intravenous thrombolysis)

In the isolated IVT group, the clinical outcome was not affected by the percentage of patients with good collaterals; in the isolated IVT group, 93 % (n = 28) of the patients, while in the endovascular treated group only 49 % (n = 102) of the patients had good collaterals, $p < 0.001$. The results reaffirm the importance of successful recanalization with reperfusion.

Statistically significantly higher patient mortality was observed in the isolated IVT group 90 days after treatment, 33 % (n = 10), compared to the endovascular group where mortality was 1/3 lower and equal to 22 % (n = 46), $p < 0.001$.

Endovascular treatment groups showed significantly better early and late functional outcome after treatment than patients with isolated IVT and known large cerebral vascular occlusion in the anterior circulation area.

4.3. Comparison of endovascular thrombectomy and bridging therapy groups in patients with stroke in the anterior circulation area

Comparing the bridging therapy group to isolated EVT, the first group results did not show statistically significantly better neurological outcome compared to isolated endovascular treatment after 90 days. The proportion of patients with a favourable outcome (mRS 0–2) in the isolated EVT group was 42 % (n = 34) and in the combined therapy group 39 % (n = 49), $p = 0.8$. The distribution of patients according to mRS score at discharge and after 90 days has been shown in Figures 4.3 and 4.4. The number of symptomatic ICHs did not differ significantly between groups. Symptomatic ICH were observed in 7 % (n = 6) of patients in the endovascular treatment group and 8 % in the bridging treatment group (n = 10).

There was a tendency to develop asymptomatic haemorrhages more frequently in the bridging therapy group (n = 20; 16 %) than in the isolated EVT group (n = 7; 9 %), p = 0.1. A broader comparison between isolated EVT and bridging therapy groups has been represented in Table 4.2.

Table 4.2.

Comparison of isolated endovascular thrombectomy and bridging therapy groups in patients with stroke in the anterior circulation area

Parameters	**Bridging therapy group (n = 128)**	**Endovascular thrombectomy group (n = 80)**	**p value**
Clot localisation: ACM M1, N (%) ACI, N (%)	**89** (70) **39** (30)	**68** (85) **12** (15)	0.012 0.012
Etiology of stroke: Cardioembolic, N (%) Aterothrombotic, N (%) Unknown, N (%)	**82** (64) **39** (31) **7** (5)	**39** (49) **30** (37) **11** (14)	0.037
Time to recanalization min Median (IQR)	**250** (301–220)	**265** (340–220)	0.878
EVT procedure time min Median (IQR)	**30** (50–20)	**35** (54–22)	0.713
Clot length mm Median (IQR)	**14** (17–11)	**13** (15–11)	0.122
Number of EVT attempts Median (IQR) 1 approach, N (%) > 1 approach, N (%)	**1** (2–1) **50** (52) **46** (48)	**1** (2–1) **30** (64) **17** (36)	0.21 0.184 0.184

(EVT – endovascular thrombectomy, ACM M1 – middle cerebral artery in M 1 segment, ACI – internal carotid artery, IQR – interquartile range)

In both patient groups (bridging therapy and isolated EVT), endovascular treatment was performed at similar times, both in terms of time to recanalization and duration of the procedure, $p > 0.05$. This helps to compare the results of the study groups after treatment as the groups are more homogeneous and statistically comparable.

Both treatment types (bridging therapy and isolated EVT) showed relatively similar clinical and radiological outcomes after treatment and had a low complication rate.

4.4. Evaluation of the efficacy of endovascular thrombectomy in patients with stroke in the posterior circulation area

Successful recanalization (TICI 2b–3) by EVT in the posterior circulation area was slightly less frequent compared to EVT results in the anterior circulation area, accounting for 86 % (n = 43).

In the posterior circulation area, patients had a statistically significantly better functional outcome at discharge than at baseline, according to mRS. The median mRS score at entry was 5 (interquartile dispersion 5–5), but at discharge it was likely to 3 (interquartile dispersion 4–2), $p < 0.001$. Meanwhile, 90 days after treatment, the median mRS value improved to 2 and the interquartile dispersion was 3–1, $p = 0.004$. Comparison of the broader mRS ratings at the time of treatment for posterior circulation has been shown in Figure 4.5.

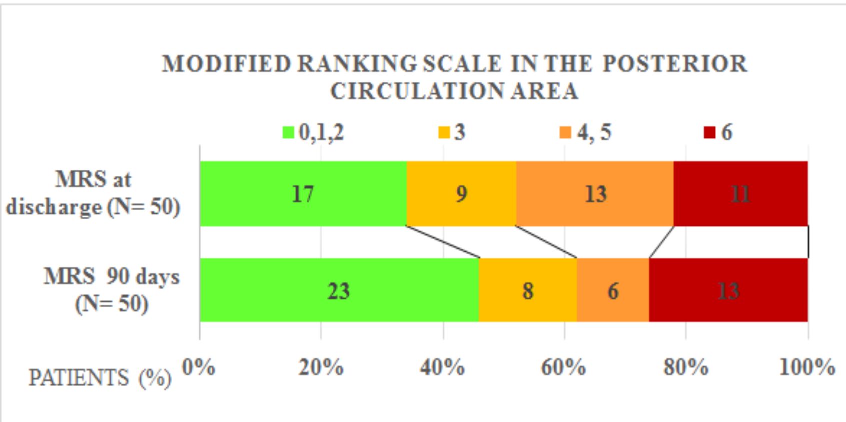


Figure 4.5. **Comparison of modified Rankin scale results for patients with stroke in the posterior circulation area at discharge and 90 days after hospitalisation**
The graph shows the absolute numbers of patients with a mRS score ranging from 0 to 6: 0 – no symptoms; 6 – fatal outcome. (mRS – modified Rankin scale)

The majority (n = 30; 60 %) of patients with stroke in the posterior circulation area received IVT with subsequent EVT, the other 20 patients received isolated EVT (40 %). Symptomatic ICH controls were relatively infrequent in CT examinations (n = 4; 8 %). In the bridging therapy group, the median time to recanalization was 280 min (interquartile range 370–240), it was slightly higher in the isolated EVT group similar to 320 min (interquartile range 390–240); however, without a statistically significant difference, p = 0.82. A higher procedure EVT time was observed in isolated EVT group with median time of 35 min and interquartile range 59–24, compared to the bridging therapy group in which the median time was 30 min and the interquartile range 43–20, p = 0.297. Overall mortality within 90 days after hospitalisation was relatively low, reaching 26 % (n = 13).

The results of the study showed a convincing, statistically significant improvement in patients after EVT in the posterior circulation area, with a high degree of recanalization and a low complication rate. Significantly better results were indicated in the group of patients who received IVT prior to endovascular therapy, which can only be partially explained by a statistically insignificant time frame for inclusion of patients in the EVT group.

4.5. Comparison of endovascular thrombectomy procedure parameters

The study analysed thrombectomy methods as the parameters of the procedure. Most often, a balloon catheter stent thrombectomy was used in the anterior circulation area (n = 118; 57 %), combination of stent thrombectomy with aspiration, (n = 75; 36 %), and thrombectomy with isolated aspiration – 7 % patients (n = 15). The median number of thrombectomy procedure attempts was 1 (interquartile range 2–1); moreover, the most commonly used stent type was *Solitaire*.

Complications of the procedure were evaluated in 136 patients immediately after the procedure. Complications included distal thromboembolic events, which occurred in 15 % of patients ($n = 21$), arterial dissections ($n = 4$; 3 %), arterial perforation and clinically significant intracerebral haemorrhage ($n = 6$; 5 %). Failed recanalization was not considered as a complication of the procedure. During thrombectomy, a minority of patients underwent extracranial stenting in ACI ($n = 24$; 16 %) or intracranial in ACM M 1 segment ($n = 4$; 3 %).

Shorter procedure time for endovascular treatment resulted in a statistically significant, moderate, negative correlation with ASPECTS 24 h control CT, respectively, smaller ischemia in control CT scan ($r = -0.309$, $p < 0.001$), as well as shorter procedure time resulted in a moderately strong, statistically significant correlation with better neurological outcome on the NIHSS scale ($r = 0.305$, $p < 0.001$) and also a better outcome on the mRS score at the end of therapy upon discharge ($r = 0.266$, $p < 0.001$).

In contrast, more than 1 thrombectomy attempt for reperfusion was statistically significant but poorly correlated with worse functional outcome by mRS upon discharge from hospital ($r = 0.186$, $p = 0.026$) and consequently extended the procedure $p < 0.001$. The duration of the procedure was statistically significant but also poorly correlated with the thrombus length ($r = 0.253$, $p = 0.003$) and with the total time to recanalization ($r = 0.304$, $p < 0.001$).

The graph of the number of endovascular thrombectomy attempts and functional outcome mRS have been represented in Figure 4.7.

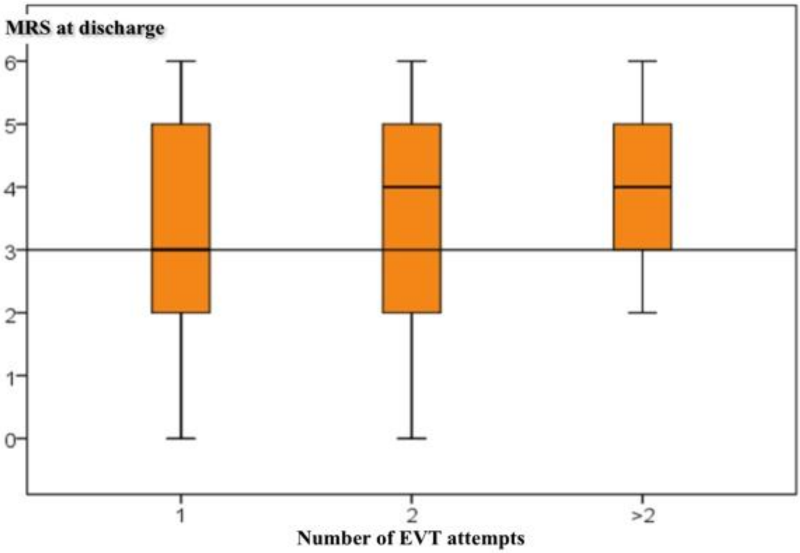


Figure 4.7. **Thrombectomy attempts versus neurological outcome (mRS) at discharge**
Reference line highlights a group of patients with moderate neurological deficits – mRS 3 (mRS – modified Rankin scale)

The procedural parameters of EVT analysed in the study significantly influenced the radiological and neurological outcome after thrombectomy. More than one thrombectomy attempt can be considered as an unfavourable marker, indicating that complete recanalization and reperfusion will not be achieved, leading to a significantly worse clinical outcome.

4.6. Efficacy of endovascular thrombectomy in the anterior circulation area in different age groups

In patients with expected benefit from endovascular treatment with major cerebral vascular occlusion, age was not included in the exclusion criteria of the study. Comparing clinical outcomes across age groups, patients aged 71 to 80 years showed relatively good post-treatment outcomes, the median value of

NIHSS was 6 and interquartile range 15–3, respectively (n = 87; 42 %). In patients older than 81 years, the median value of NIHSS was higher by one point – 7 and interquartile range 15–3 (n = 26; 12 %). There was no statistically significant difference between the age groups according to the NIHSS p = 0.684. An increase in median NIHSS at discharge was also observed with increasing age in each subsequent age group. Neurological outcome in different age groups has been represented in Table 4.3.

Table 4.3.

Results of endovascular treatment in different age groups on admission and discharge according to NIHSS

Age group years / N	**NIHSS at admission Median (IQR)**	**NIHSS at discharge Median (IQR)**
< 60 / (41)	**14** (18–10)	**5** (12–2)
60–70 / (54)	**17** (18–13)	**6** (12–3)
71–80 / (87)	**16** (12–19)	**6** (15–3)
> 80 (26)	**16** (12–20)	**7** (15–3)
p value	**0.31**	**0.684**

(NIHSS – National Institute of Health stroke scale, IQR – interquartile range)

The obtained data showed significant neurological improvement in all age groups after endovascular treatment in patients with large cerebral vascular occlusion, confirming the belief that age alone should not be a reason to exclude patients from potential endovascular therapy.

4.7. Effect of time on late functional outcome

Time to recanalization was important and statistically significantly associated with improved late functional outcome on the modified Rankin scale (mRS 0–2, AUC 0.657, $p < 0.001$) in the group of patients with anterior circulation occlusion. Patients who underwent recanalization within three hours of onset of symptoms exhibited a very high time specificity, equivalent to 91 %, to achieve a good functional outcome (mRs 0−2), but by 4.5 hours from the onset of symptoms this specificity dropped to 62 % and sensitivity was estimated at 65 %. Within six hours of the disease, specificity for achieving a good functional outcome (mRS 0–2) was only 16 %, albeit at high sensitivity, 96 %. In patients, 6 hours after the onset of symptoms the risk of adverse clinical outcome was 5 times greater (OR 5.68). The relationship specified in the study could indicate that factors other than revascularization time are more important 3 hours after the onset of symptoms. The relationship between time to recanalization and good late functional outcome on the modified Rankin scale is shown in Figure 4.8.

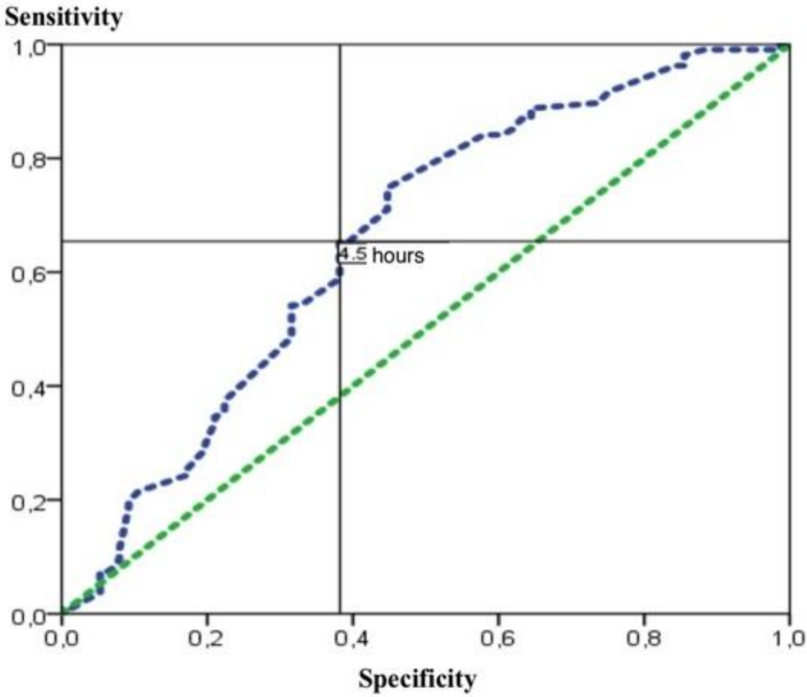


Figure 4.8. **ROC curve (time to recanalization and good late functional outcome (mRS))**
The ROC curve plots the relation of time with a good late result on the modified Rankin scale (mRS 0−2). (ROC − receiver operating characteristics; mRS – modified Rankin scale)

Shorter time to recanalization had a moderate yet statistically significant correlation with better functional outcome after treatment (mRS, $r = 0.263$, $p < 0.001$) and also the neurologic outcome upon discharge according to NIHSS ($r = 0,272$, $p < 0,001$).

Time to recanalization had a moderate, negative, statistically significant correlation ($r = – 0.299$, $p < 0.001$) with the numerical value of the ASPECTS scale, namely, patients with shorter time to recanalization had statistically significantly better neurological and radiological outcomes.

4.8. Estimation of the ASPECTS scale for predicting potential outcome

After treatment, in patients with relatively mild neurological deficits (NIHSS score 0–5), ASPECTS CTP *core* damage was minor, at admission it had a median value of 8 and interquartile range 9–7.

ASPECTS CTP *core* lesions had a significantly higher incidence at admission in the group with the lethal outcome, its median value was 7 and interquartile range 8–5, $p < 0.005$. There was also a statistically significant difference between survival and death groups when using the *Kruskall-Wallis* H test, $p = 0.003$.

Thus, in patients (NIHSS score 0–5 at admission) with good neurological outcome after endovascular treatment CTP had less permanent brain damage or *core* on admission, according to the ASPECTS scale.

For data analysis, patients were categorized according to the NIHSS score and studied for the outcome based on ASPECTS CTP *core* score at admission. A significant difference was found when comparing NIHSS scores in patients with ASPECTS CTP ≤ 6 (large *core*) and ASPECTS ≥ 7 (small *core*), $p = 0.025$. Patients with ASPECTS ≥ 7 were much more likely to have a good clinical outcome according to NIHSS score of < 6 and significantly lower mortality.

To further clarify the potential benefit of endovascular therapy in patients with very large *core*, NIHSS scores were also analysed by grouping patients: ASPECTS ≤ 5 (significantly large *core*) and ASPECTS ≥ 6. In the large *core* group, mortality was discovered to be significantly lower, 38 % of patients had a good clinical outcome, and the groups were statistically significantly different, $p = 0.036$. When evaluating the major extent of irreversible ischemia with a potentially better outcome, groups with ASPECTS ≥ 7 had a statistically significant sign of good neurological outcome after treatment with a larger number of patients (p/Adjusted residuals = 2.5), as indicated in Table 4.4.

Table 4.4.

Comparison of neurologic outcome according to NIHSS scale with different ASPECTS CTP *core* distribution groups

NIHSS	**ASPECTS CTP *core* ≤ 6, N (%)**	**ASPECTS CTP *core* ≥ 7, N (%)**	**p/Adjusted residuals (>2)**
< 6	**16** (37)	**97** (59)	2,5
7– 15	**14** (32)	**41** (25)	−1
16– 41	**3** (7)	**12** (7)	0,1
Dead	**10** (23)	**15** (9)	– 2,5
Total	**43** (100)	**165** (100)	
p value	**p = 0,025**		
NIHSS	**ASPECTS CTP *core* ≤ 5, N (%)**	**ASPECTS CTP *core* ≥ 6, N (%)**	**p/Adjusted residuals (> 2)**
<6	**8** (38)	**105** (56)	1,6
7– 15	**4** (19)	**51** (27)	0,8
16– 41	**3** (14)	**12** (7)	– 1,3
Dead	**6** (29)	**19** (10)	– 2,5
Total	**21** (100)	**187** (10)	
p value	**p = 0,036**		

(ASPECTS – Alberta stroke program early CT score, NIHSS – National Institute of Health stroke scale, CTP – computed tomography perfusion)

4.9. Comparison of group collaterals

Good collaterals in endovascularly treated patients in the anterior circulation area were observed in 49 % of patients, (n = 102); in contrast, poor collaterals were observed in 51 % of patients, (n = 106). Depending on collaterals, subdividing the groups into two (each divided into two) four groups: only 28 % of patients (n = 58) had good collaterals, 41 % of patients – medium (n = 86), 28 % of patients – weak (n = 58) and 3 % of patients – malignant collaterals (n = 6).

Patients with good collaterals at discharge showed statistically significantly better clinical outcome at NIHSS assessment (p = 0.031) as well as better functional outcome at mRS (p = 0.005) compared to patients with poor collaterals. Comparison of good and poor collaterals in patients with occlusion of the anterior circulation after endovascular treatment has been represented in Table 4.5. In most patients, 65 % (n = 66) with mild neurological deficits, consistent with an NIHSS score of < 6, had good collaterals. However, the results indicated that nearly half of the patients, 44 % (n = 47) with poor collaterals, also achieved a good neurologic outcome at the time of discharge. This would be due to a number of side effects that also influenced the outcome, such as time to therapy and recanalization efficiency.

Table 4.5.

Number of patients with good and poor collaterals according to NIHSS rating

NIHSS at discharge	**Poor collaterals N (%)**	**Good collaterals N (%)**	**p/Adjusted residuals (> 2)**
≤ 6	**47** (44)	**66** (65)	2.9
7–15	**37** (35)	**15** (15)	− 3.5
16–41	**6** (6)	**9** (8)	0.9
Dead	**16** (15)	**12** (12)	− 0.5
Total	**106** (100)	**102** (100)	
p value	p = 0.031		

(ASPECTS – Alberta stroke program early CT score, NIHSS – National Institute of Health stroke scale, mRs – modifed Rankin scale)

When using good collaterals as a selection criterion for endovascular treatment, patients showed statistically significantly better clinical outcome compared to the group of patients with poor collaterals.

4.10. Comparison of ASPECTS and collaterals

In most patients, 90 % (n = 92) with good reversible ischemia, good collaterals were observed with CTP *core* at ASPECTS ≥ 7; however, in patients with ASPECTS CTP *core* ≤ 6, good collaterals were observed in almost 50 % of patients (n = 52) with a statistically significant difference between ASPECTS groups $p < 0.001$. Comparison of collaterals with ASPECTS CTP *core* ischemia has been represented in Table 4.6.

Table 4.6.

CTP comparison of collaterals and ASPECTS scale *core* ischemia volume

ASPECTS CTP *core*	**Poor collaterals (n = 106)**	**Good collaterals (n = 102)**	**p value**
ASPECTS *core* ≥ 7, N (%)	**52** (49)	**92** (90)	< 0.001
ASPECTS *core* ≤ 6, N (%)	**54** (51)	**10** (10)	< 0.001

(ASPECTS – Alberta stroke program early CT score)

The results confirm that patients with poor collaterals are more likely to have a larger irreversible ischemia on ASPECTS CTP *core*; consequently, the risk of extensive ischemia in the control CT (ASPECTS ≤ 6) is higher. Patients with poor collaterals were found to have a 7-fold greater risk of extensive ischemia after EVT than patients with good collaterals (OR 6.98).

4.11. Predicting potentially good functional outcome using multiple radiological criteria

Patients with various, including low ASPECTS CTP *core*, scores were included in the study (4–10). To achieve better treatment results, stricter radiological screening criteria need to be introduced.

Modeling the criteria for endovascular treatment, the outcomes of patients with irreversible *core* damage with ASPECTS CTP ≥ 7 on admission were analysed, and it was discovered that the favourable 3-month mRS score improved from 40 % to 59 % of patients (n = 98). Low mortality was also observed, in only 10 % of patients (n = 16). A more detailed assessment of the more stricter selection criteria is presented in Figure 4.9.

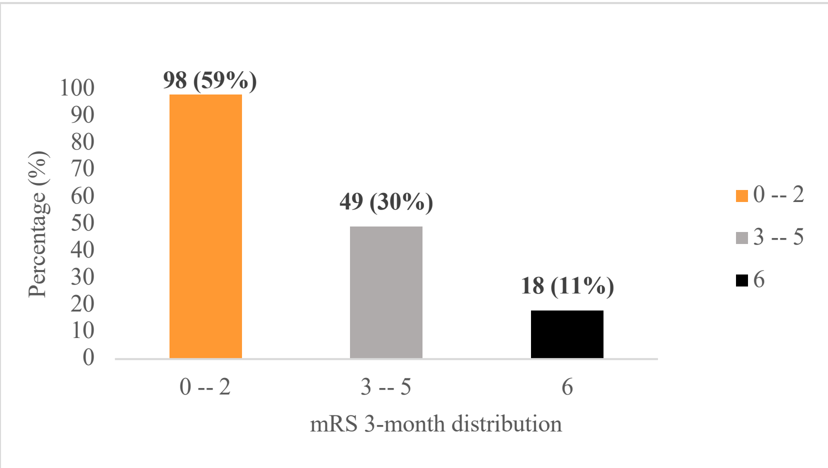


Figure 4.9. **MRS assessment 3 months after treatment in patients with ASPECTS CTP core ≥ 7**
(MRS – modified Rankin scale, ASPECTS – Alberta stroke program early CT score, CTP – computed tomography perfusion).

Analysing the potential risk for a good neurological outcome, two groups of patients were assessed. First, patients with good collaterals and ASPECTS CTP *core* score ≥ 7 were analysed. In these patients, the risk of achieving a good functional outcome in mRS was much higher (OR 4.651; CI: 95 %, 2.3–9.2) than in patients with large infarction *core* lesion and poor collaterals, $p < 0.001$.

Second, the outcome was analysed in a group of patients who also had good collaterals but lower ASPECTS CTP *core* score, ≥ 6. Similar even a slightly higher risk for good functional outcome (OR 4,738; CI 95 %, 2.4–9.5) was observed in patients with higher onset ischaemia, $p < 0.001$. Schematic representation of the data has been shown in Figure 4.10.

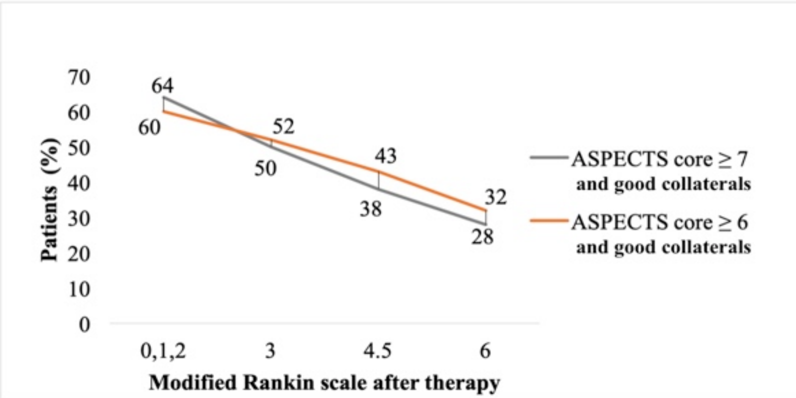


Figure 4.10. **Functional outcome (mRS) at discharge in different patient groups depending on ASPECT CTP *core* and collaterals**

Potential risk of functional outcome in two-way patient modeling with good collaterals and minor *core* ischemia; upon hospital admission. Results were evaluated by ASPECTS computed tomography perfusion evaluation (ASPECTS – Alberta stroke program early CT score)

The results of the study revealed that the best predictors of good neurological and radiological outcome after thrombectomy can be prognosticate considering two factors simultaneously: good collaterals and ASPECTS ≥ 7, as well as with ASPECTS scores ≥ 6.

4.12. Predicting potential neurological outcome after endovascular thrombectomy using ASPECTS CTP *core* assessment

To predict the potential functional outcome of mRS in patients undergoing endovascular thrombectomy, the magnitude of irreversible ASPECTS CTP *core* ischemia on perfusion maps was analysed and the potential risk for good or bad outcome was calculated for each ASPECTS scale from 1 to 10. The results are shown in Figure 4.11.

Data analysis showed that with a decrease in ASPECTS CTP *core* by each point, the risk of obtaining a moderate to poor functional outcome, corresponding to an mRS score of > 2, shows up to 1.3-fold increase (OR 1,3, CI: 95 %, 1.04–1.6). For example, in patients with an ASPECTS CTP *core* score of 2, the potential risk of a poor outcome after treatment exceeds 90 %, whereas the risk of potentially beneficial functional outcome was very low, at only 9 %. Conversely, in patients with ASPECTS CTP *core* rating 3, the potential risk of a poor outcome after therapy will be reduced to 89 % and the risk of a good outcome increased to 11 %. Analysing mortality rate, with the increase in ASPECTS CTP *core* volume with each point, the likelihood of fatal outcome after treatment increases by 1.3-fold. (OR 1,346, CI: 95 %, 1.06–1.7).

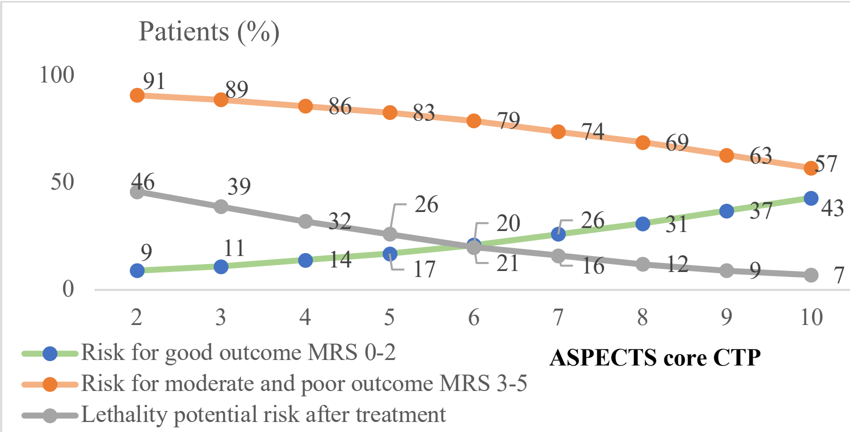


Figure 4.11. **Prognosis of potential functional outcome of patients depending on ASPECTS *core* CTP upon inpatient admission**

Schematic representation of potential risk outcomes for patients' reduction in ASPECTS *core* score on computed tomography perfusion by every point at hospitalisation, results are expressed as a percentage (ASPECTS – Alberta stroke program early CT score, mRS – modified Rankin scale)

The magnitude of irreversible core ischemia in ASPECTS CTP significantly influences late functional outcome and allows predicting potential outcome after endovascular treatment.

5. DISCUSSION

Intravenous thrombolysis (IVT) has long been the only guideline-approved active treatment option for patients with CI who can be started on therapy within 4.5 hours of the onset of symptoms (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995; Powers et al., 2018a). However, the efficacy of IVT in occlusion of large cerebral arteries is suboptimal, especially if the thrombus length is greater than 8 mm, such as the occlusion of the internal carotid artery (ACI) (Riedel et al., 2011). For this reason, the possibilities and benefits of endovascular treatment in cases of large cerebral artery occlusion have been actively explored in recent years.

In 2013, the authors of several randomised controlled trials (RCTs) published results on EVT in large cerebral artery occlusion. They analysed the efficacy and safety of the method; however, its efficacy was not proven (Broderick et al., 2013; Kidwell et al., 2013). For example, in a study by Broderick and colleagues (Broderick at al., 2013), after 90 days, a favourable functional outcome of 0–2 was seen in 40.8 % of patients in the EVT group and 38.7 % of patients in the IVT group, with no statistically significant differences between the groups.

Studies conducted in 2013 received very strong criticism of patient selection, leading to the publication of seven RCTs in response across the world between 2014 and 2016 including: MR CLEAN, ESCAPE, EXTEND–IA, SWIFT PRIME, REVASCAT, THERAPY, TRACE; this time statistically significantly better late clinical outcomes in the endovascular treatment group compared to the isolated IVT group were revealed in all of them (Fransen et al., 2014; Goyal et al., 2015; Campbell et al., 2015a; Jovin et al., 2015; Mocco et al., 2016; Bracard et al., 2016).

In the study by the author of the Thesis, significantly better results were observed in the EVT group compared to the isolated IVT group, namely, 41 %

of patients in the EVT group and only 17 % of patients in the IVT group had a favourable outcome, consistent with mRS 0–2. Treatment results were significantly different and better in the EVT group compared to the isolated IVT group. The reason for such results lies in the length of the occluded artery thrombus, which is crucial for the efficacy of isolated IVT, as Reedel and colleagues demonstrated in their study several years ago (Riedel et al., 2011).

Since 2016, EVT has been approved in the guidelines as the first choice method for patients with CI and major cerebral artery occlusion in the anterior circulation where IVT is contraindicated (Powers et al., 2018a; Fiehler et al., 2016). Since 2018, endovascular thrombectomy is also indicated in patients with large cerebral artery occlusion in the anterior circulation who are receiving intravenous thrombolysis (Powers et al., 2018a). Endovascular treatment is clearly regarded as a safe and effective treatment with a relatively low complication rate. In the given study, complications were observed in up to 9 % of patients, and data from other studies reported similar complication rates. The effectiveness of endovascular therapy depends on the degree of recanalization. In the current study, a high degree of recanalization was observed with up to 91 % of patients reaching the TICI 2b–3 in anterior circulation area, which was higher compared to *Mr Clean* study (Fransen et al., 2014) where recanalization was seen in a much smaller number of patients – only 59 %. The obtained results are similar to Extend IA study (Campbell et al., 2015a) in which 89 % of patients showed adequate, good recanalization. Extend IA study, likewise the given one, had stricter screening criteria for CT perfusion examinations and use of state-of-the-art thrombectomy devices.

Statistically significant clinical and functional improvements were observed in EVT groups as measured by the NIHSS and mRS scales, and there was a significant improvement in radiological parameters such as ASPECTS score and recanalization rate on the TICI scale when compared to pre- and post-treatment.

The bridging therapy, IVT with subsequent endovascular treatment was actively started after demonstrating the efficacy of EVT in the above RCTs in 2015 and 2016. Some of the studies also included patients with the bridging therapy, but this group was not analysed separately (Goyal et al., 2015; Saver et al., 2015). Due the lack of qualitative studies on the benefits of the bridging therapy versus isolated EVT, there is an ongoing debate as to whether patients with prescribed EVT have to undergo IVT prior to therapy. In several recently published studies, the bridging therapy was not considered superior since it did not show a better neurological outcome compared with isolated EVT (Chandra et al., 2016; Balodis et al., 2018; Ansaar et al. 2018; Tsivgoulis et al. 2016). However, scientific literature also reports on positive results in the bridging therapy, for example, in a meta-analysis published in 2017, better results were found in the bridging therapy groups with lower lethality. Interestingly, several studies included in the meta-analysis did not show any significant difference (Mistry et al., 2017).

The study included 128 patients who received the bridging therapy and demonstrated that it was an effective and safe method of treating CI, but failed to achieve a statistically significantly better rate or frequency of recanalization compared to isolated EVT groups (89 % versus 91 % of patients) or better functional outcome at mRS 0–2 (39 % versus 42 % of patients).

In the study, standard procedural parameters of the endovascular thrombectomy procedure were analysed by comparing isolated EVT and bridging therapy groups: number of runs to maximum recanalization and duration of the procedure. Complete recanalization and first-pass reperfusion was achieved in more than 50 % of cases in both the isolated EVT and the bridging therapy group, with no statistically significant difference.

Leker and colleagues (Leker et al., 2015) study indicated that patients receiving the bridging therapy on average required fewer EVT attempts and therefore a shorter procedure time. Other similar retrospective studies of the bridging therapy have not separately investigated the effect of thrombectomy procedure parameters on outcome. (Broeg-Morvay et al., 2016; Sallustio et al., 2013).

The question remains whether further analysis of thrombus structure, such as atherosclerotic or cardioembolic origin, could help predict the benefits of IVT before EVT. The structure of thrombi has been better studied through meta-analysis (Singh, Kaur, and Kaur, 2013), but it also does not give a clear answer, thus further research on the analysis of thrombus structure would be reasonable and practically useful. However, thrombus evaluation would require more early diagnostic magnetic resonance imaging, such as selective imaging of the thrombus and further evaluation of its structure, as well as a better understanding of thrombus fragmentation (Singh, Kaur, and Kaur, 2013; Gunning et al., 2018; Minnerup and Kleinschnitz, 2011).

Median time to recanalization was 250 minutes in the bridging therapy group and 265 minutes in the EVT group, so the difference between the groups was not statistically significant. It should be emphasised that similar time frames made the groups more homogeneous and more compatible. Given that the use of IVT is limited by a time frame of up to 4.5 h, such an average time between groups may be explained by the fact that the applied treatment algorithm does not expect an IVT treatment effect according to current Cerebral Infarction Treatment Guidelines (Powers et al., 2018a), but the patient is purposefully directed towards endovascular treatment. For comparison, a study by *Kass-Hout* and colleagues (Kass-Hout et al., 2014) showed that the median time to recanalization was longer in the bridging therapy group because of the expected treatment outcome after IVT, and then the patient was referred to EVT.

Analysing the frequency of complications between the groups in the current study, which mainly included symptomatic and asymptomatic ICH, it was discovered that 10 patients developed symptomatic ICH in the bridging treatment group and 8 patients in the isolated EVT group. Comparison of isolated EVT and bridging therapy groups reveals that no significant differences in the percentage of symptomatic ICH were found. On the one hand, such results demonstrate that both methods are equally safe as no greater risk of symptomatic ICH was observed in bridging therapy group when compared to other studies (Broeg-Morvay et al., 2016; Kass-Hout et al., 2014). However, comparing the incidence of asymptomatic ICH in another study (Broeg-Morvay et al., 2016) showed a statistically significantly higher risk in the bridging therapy group. It should also be taken into account that such patients would have further problems in initiating anti-aggregant and/or anticoagulant therapy after EVT due to the increased risk of intracranial haemorrhage. Thus it can be concluded that the study did not confirm that the bridging therapy was superior or, on the contrary, more dangerous than the isolated endovascular treatment.

RCTs that would provide additional information on the benefits of the bridging therapy would be desirable to compare the two groups. The authors of many other similar studies also express such thoughts (Coutinho et al., 2017; Gong et al., 2019). At least four RCTs are currently underway comparing the bridging therapy with isolated EVT (MR CLEAN IV in the Netherlands, SWIFT-DIRECT in Switzerland, DIRECT MT in China, DIRECT-SAFE in Australia), but the results are not available yet.

Cerebral infarction (CI) in the posterior circulation area with *a.basilaris* (AB) occlusion is highly lethal without recanalization; with conservative treatment, it reaches up to 90 %, while surviving patients develop severe, permanent disability (up to 65 % of cases; Schonewille et al., 2005). There is still lack of RCTs for AB endovascular treatment, with high mortality from conservative treatment being cited as the main cause, complicating patient randomisation. EVT with proven AB occlusion in CT angiography may achieve better results than conservative therapy. In several retrospective studies of the use of isolated IVT in AB occlusion, a good functional outcome, corresponding to an mRS score of 0–2, was found in 26 % of patients, but 40 % of patients had a fatal outcome (Van Houwelingen et al., 2016; Lindsberg et al., 2004).

Compared to other authors, the results obtained in the present study are different and better for both recanalization rates and survival. A high incidence of recanalization was observed with EVT in AB occlusion, up to 88 % of cases, and mortality at 90 days after treatment was much lower (n = 13; 26 %) than in the mentioned studies (Van Houwelingen et al., 2016; Lindsberg et al., 2004).

Between 2010 and 2014, more than 15 studies on the treatment of EVT in the posterior circulation have been published (Mokin et al., 2016; Singer, Berkefeld, Nolte, Bohner, Haring et al., 2015; Balodis et al., 2016), including meta-analysis (Gory et al., 2016) with a total of 312 patients treated, and 42 % of them had a good clinical outcome of mRS 0–2 compared to 46 % in the current study. Recanalization in the above studies was achieved in 81 % of patients and in *Van Houwelingen* and colleagues (Van Houwelingen et al., 2016) up to 89 %, while the overall complication rate was low at around 4 % (Gory et al., 2016). Possibility of recanalization in AB occlusion is greater if IVT treatment is timely initiated (Lindsberg and Mattle, 2006; Pfefferkorn et al., 2010). In the current study, successful recanalization was achieved in 88 % of patients, which is considered a good outcome.

However, despite the use of recent treatment, the outcome after acute AB occlusion is still poor in a large proportion of patients, partly due to larger time frames in the EVT group, mainly because of late admission to hospital.

Clinical and radiological outcome after EVT in patients with AB occlusion using advanced thrombectomy devices has improved. Given the already existing research on the treatment of AB occlusion, the authors of several publications and the author of the current study wonder whether RCT for endovascular treatment of AB occlusion is really necessary. According to the researchers of the current study, endovascular treatment for AB occlusion is a standard of care and should be used routinely in all eligible patients.

Numerous selection criteria exist and those have been described in several stroke treatment guidelines that have been updated several times in recent years, most recently for endovascular treatment and published in 2019 (Turc, Bhogal, Fischer, Khatri, Lobotesis, Mazighi, Schellinger, Toni, De Vries et al., 2019). The large number of guidelines can be explained by very active research in the treatment of stroke, especially analysis of various selection criteria.

Time in the treatment of acute ischemic stroke is very important. On the one hand, the time limit of IVT is traditionally considered to be 4.5 h (Hacke et al., 2008; Troke and Roup, 1995); on the other hand, shorter illness times do not allow us to be "slower" in decision making, because shorter time to treatment is proportional to greater chance of saving brain tissue and obtaining a better result after treatment (Saver, 2016). In the current study, the median time to arterial recanalization was 260 minutes, and the shorter median time to recanalization statistically significantly correlated with a better clinical outcome, with 91 % of patients achieving a good outcome in a time frame of up to 3 h. In addition, time in our study statistically significantly correlated with lower ischemia volume in control CT examinations.

The time frame as a criterion for EVT treatment is not as strict as for IVT. In recent studies, doctors rely more heavily on radiological diagnosis in later hours since, for example, if good collaterals are available, it can give more time so the patient may also receive significant treatment benefits from EVT within 8 and 10 hours after the onset of the disease (Turc, Bhogal, Fischer, Khatri, Lobotesis, Mazighi, Schellinger, Toni, De Vries et al., 2019; Albers et al., 2017;

Nogueira et al., 2017). However, the latest RCTs available (DEFUSE-3 and DAWN) allow for a better understanding of EVT application in a time frame of 6 to 24 hours (Albers et al., 2017; Nogueira et al., 2017). Studies have shown that patients with extensive *penumbra*-like lesions, as demonstrated by MRI or CTP, can achieve statistically significant clinical improvement compared to controls. Although not a large patient group (109 patients enrolled in the DAWN Multicentre RCT), it does allow for analysis and the ability to apply endovascular treatment and improve outcomes for a larger number of patients, particularly when patients are transported from a hospital where no endovascular treatment is available.

Comparison of functional late outcome with other RCTs that did not undergo CTP examination: MR CLEAN (33 % of patients), REVASCAT (44 % of patients), and ESCAPE (53 % of patients) suggest that more detailed patient selection may improve clinical outcome and avoid untargeted and expensive endovascular treatment (Carrera and Wintermark, 2017).

Using ASPECTS scale on CTP is much more effective than noncontrast CT examination because of its very low diagnostic sensitivity in the early hours. Pearson and colleagues already in 2007 described the more effective gains in ASPECTS for evaluating CTP within the first 6 hours (Parsons et al., 2007). Several studies have demonstrated superior clinical and radiological outcomes in patients with good collaterals, especially if considered in combination with an ASPECTS CTP score ≥ 7 for *core* ischemia (Yagri et al., 2014; Liebeskind and Sanossian, 2012). Modelling stricter radiological selection criteria for therapy (good collaterals and ASPECTS CTP *core* ≥ 7, and separately with a score ≥ 6), in the current study an unexpectedly slightly higher potential risk for a favourable outcome was observed with an ASPECTS score of ≥ 6 with OR 4.7 to OR 4.6.

Modeling stricter radiological selection criteria for therapy with ASPECTS CTP *core* score ≥ 7, the current study already showed a good late functional outcome of mRS 0–2 in most patients – 60 %. Similar data were obtained in the EXTEND-IA study defining stricter early radiological selection criteria (Campbell et al., 2015a). In contrast to the results of Yagri et al. (Yagri et al., 2014), the current study also showed significant improvement in patients with higher *core* ischemia at the time of hospitalisation (ASPECTS CTP ≥ 6).

If the patient has good collaterals, this gives extra time by delaying irrveresible ischemia in hypoperfused brain tissue. Blood circulation is primarily through the Circle of Willis, but also through collaterals from the external and internal carotid arteries, and additionally from leptomeningeal collaterals (Hossmann, 2006). Patients with good collaterals showed a statistically significantly better outcome according to mRS and NIHSS scoring, for example, the mRS score 0–2 was observed in 40 % of patients with good collaterals but only in 16 % of patients with poor collaterals. Patients with poor collaterals also had a 6.9-fold higher risk of extensive ischemia after treatment, despite the success of recanalization, indicating the need for multiple selection criteria to achieve a good clinical outcome. The referenced ESO ESMINT 2019 guidelines recommend that good and moderate collaterals should be considered as criteria for endovascular treatment, especially in the late hours (6–24 h) after the onset of symptoms (Turc, Bhogal, Fischer, Khatri, Lobotesis, Mazighi, Schellinger, Toni, De Vries et al., 2019).

5.1. Limitations of the study

There were a number of limitations to this study: no patient randomisation, patients' inclusion in the bridging therapy or the isolated EVT group was determined by a variety of factors including contraindications to IVT, as well as an individual physician's experience and availability of the necessary equipment. It is not known how much this has affected the results, but given similar time frames to recanalization in both groups and the design of similar studies, the two groups are comparable and give a measurable result.

In control CT examinations, asymptomatic ICH are sometimes difficult to distinguish from enhanced contrast accumulation after recanalization. This could be more precisely differentiated in the MR examination, but at the initial stage of the present study, the MR examination was not available.

Although widely used in clinical practice, the ASPECTS scale has several disadvantages. One is the variety of artefacts that make it difficult to evaluate CT and CTP images, especially in the posterior circulation area, and it is not very clear how much brain tissue from each area should be damaged to count as an affected region (Barber et al., 2000). Noncontrast CT examination may have difficulty in differentiating acute ischemia from chronic ischemia, and it is difficult to assess the effect of the ASPECTS scale with extensive changes in the periventricular cerebral white matter. The use of the ASPECTS scale is limited by proximal ACI occlusion with acute ischemia also in the ACA bleeding area and unfavourable variants of the Circle of Willis with ischemia in the posterior cerebral artery (ACP) bleeding area (Barber et al., 2000). ASPECTS scale might be difficult to use in patients with chronic ischemia and suspicion of new infarction within the same area especially if the patient has had neurological deficits before the new event (Puetz et al., 2009; Schröder and Thomalla, 2017).

Unfortunately, several collateral gradation systems and their evaluation methods are available in practice, which makes it difficult to compare research results (Bang, Goyal, and Liebeskind, 2015).

In the field of endovascular treatment, several methods of mechanical thrombus removal are currently being used in clinical practice, making it difficult to compare them. The methods are often incompatible in the different centers where EVT is carried out. It can be explained by possessing greater experience working with one of the methods. In some cases, several methods, such as stent thrombectomy and aspiration, are used to achieve recanalization.

5.2. Recommendations

1. Patients with major cerebral artery occlusion (ACI, AB, ACM M1 segment) demonstrated by computed tomography angiography should not wait for the treatment results of intravenous thrombolysis, but should be directed to endovascular thrombectomy without undue delay. The use of intravenous thrombolysis in major cerebral artery occlusion should not delay the initiation of endovascular therapy when indicated and available.
2. Intravenous thrombolysis prior to endovascular therapy is recommended in all patients, unless there is a contraindication, especially when endovascular therapy is not immediately available or if the patient is being transferred from an inpatient setting where endovascular treatment is not available.
3. For patients potentially undergoing any treatment modality such as intravenous thrombolysis and/or endovascular thrombectomy, a multimodal CT examination including noncontrast computed tomography, computed tomography angiography, and perfusion of computed tomography is recommended to differentiate permanently damaged brain tissue, stroke-like conditions and provide additional information for endovascular treatment.
4. Active treatment options are indicated for patients with large cerebral artery occlusion and ASPECTS CTP *core* ≥ 6 and good collaterals, whereas patients with ASPECTS CTP *core* < 6 and poor collaterals should be critically evaluated.
5. For patients with basilar artery occlusion, endovascular therapy should be considered as a standard of medical care. It is applicable in routine work to all eligible patients without waiting for treatment effect after intravenous thrombolysis.

6. For endovascular thrombectomy no maximum age of treatment should be determined, since patients over 80 years of age may also benefit from an endovascular thrombectomy.
7. Achieving successful recanalization in patients after endovascular therapy, in patients with extensive, potentially reversible (*penumbra*-like) lesions, is vital for achieving good late clinical outcome. The time to the initiation of therapy should be minimised.

CONCLUSIONS

1. The study showed that it is more expedient to perform patient screening for revascularization using two criteria simultaneously – ASPECTS CTP *core* value and collateral characterisation. Patients with good collaterals and with an ASPECTS CTP *core* threshold of at least 6 were found to have a favourable late clinical outcome in significantly more patients.
2. Patients with a shorter time to recanalization had statistically significantly better not only neurological but also radiologic outcome after treatment, and the risk of adverse clinical outcome in patients above 6 hours since the onset of symptoms increased by more than 5-fold.
3. In patients with ischemic stroke in the anterior circulation area, endovascular therapy proved to be a more effective and safer method compared to isolated intravenous thrombolysis. The clinical and radiological outcome of the bridging therapy involving intravenous thrombolysis with subsequent endovascular thrombectomy was similar to that of isolated endovascular therapy, with no significant increase in complication rates.
4. The study confirms that endovascular therapy in the posterior circulation in patients with large cerebral artery occlusion is safe and effective, and when combined with intravenous thrombolysis, was superior to isolated endovascular thrombectomy.
5. A favourable clinical and radiological outcome is significantly associated with successful recanalization; however, the timing of the thrombectomy procedure and the number of recanalization attempts also significantly influence the outcome. If the number of thrombectomy attempts is more than one, the likelihood of a suboptimal outcome increases.

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