Clinical aspects of endovascular treatment in acute ischemic stroke

<u>PhD Thesis</u>

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1. *Introduction*

Acute stroke is defined by WHO as a clinical syndrome of rapid onset of focal or global neurological deficits of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than a vascular origin. Stroke is the second leading cause of death and the first leading cause of permanent disability. About 87% of strokes are ischemic and 13% are hemorrhagic. Approximately 40,000-50,000 stroke cases (~45.4 stroke/10,000 people) occur annually in our country. Every second patient dies as a result of the disease (~25,000 people/year).

The circulatory demand of the human brain is supplied in parallel by four large arteries, the two internal carotid arteries (ICA) and the two vertebral arteries (VA). The connection between the vessels supplying the brain is provided by an anastomotic structure (circulus arteriosus cerebri of Willis) created at the base of the brain.

Acute ischemic stroke (AIS) usually begins with a severe focal hypoperfusion event. Although, the occurred ischemic brain damage can last for hours or days. The extent of the permanently damaged brain area depends on two main factors: the degree and duration of the ischemia. The part of the affected brain region, where the perfusion drops below the infarction threshold (8-10 ml/min/100g), is called the infarct core. The penumbra is a potentially salvageable area around the core region with reduced circulation.

Approximately 30% of ischemic strokes are caused by large vessel occlusion (LVO), which means the proximal part blockage of the cerebral vessels. Primarily the occlusions of the intracranial segment of the ICA, the middle cerebral artery (MCA) M1, M2, M3, the anterior cerebral artery (ACA) A1, A2, the posterior cerebral artery (PCA) P1, P2 segment, the VA and the basilar artery (BA) are considered as LVO, although the exact definition can slightly differ in different studies.

The primary aim of AIS treatment is to recanalize the blocked vessel as soon as possible. Until recently, the primary method of recanalization was the intravenous thrombolysis (IVT), that included a recombinant tissue plasminogen activator (rt-PA) applied in the systematic circulation to dissolve the clot causing vessel blockage. However, previous studies observed the recanalization effectiveness of IVT inversely correlates to the diameter of the occluded vessel and the length of the thrombi. Furthermore, recent randomized controlled trials (RCT) of mechanical thrombectomy (MT) have shown the efficiency and safety of endovascular treatment (EVT) in LVO of the anterior circulation. Current guidelines recommend (with IA evidence) the thrombectomy in properly selected stroke patients. In addition, the therapeutic time window can be extended to 24 hours in case of MT and to 9 hours in case of IVT after the stroke onset based on perfusion imaging results.

2. *Objectives and methods*

The primary aim of the presented studies was the examination of the current issues related to the application of MT:

1. Evaluating the effectiveness and safety of combined therapy (CT) (prior IVT before MT) and direct MT (dMT) in patients with LVO, and comparing the two methods.
2. Investigating the endovascular treatment of tandem occlusion (TO) of the anterior circulation with special regard to the comparison of the clinical parameters and outcomes of patients treated with acute carotid stent (ACS) or balloon angioplasty only (BAO) according to the balloon-assisted tracking (BAT) technique.
3. Assessing the prognostic impact of diabetes mellitus (DM) and admission hyperglycemia (aHG) on functional and clinical outcomes of AIS patients who underwent recanalization therapies. Moreover, we sought to investigate the potentially detrimental effect of these risk factors on outcomes with different recanalization techniques.

The demonstrated studies in my dissertation are based on retrospective analyses of prospective patient data from the STAY ALIVE Acute Stroke Registry. The registry has been active since November 2017, with over 1400 patients and the selection of the patients is still ongoing. The inclusion criteria in the studies slightly differed, but the common methodological characteristics of the investigated patient groups are presented in this chapter.

Patients with ischemic stroke who received recanalization treatment (IVT, MT) between November 2017 and December 2021 in the participating institutions (University of Debrecen, University of Pécs, University of Szeged) were primarily investigated. The research protocol was approved by the Hungarian ethics committee. All involved patients gave written consent to participate in our study, following the Good Clinical Practice (GCP) guidelines.

Patients were admitted mainly to the emergency department (ED) of the stroke centers or the hospitals of surrounding cities and were transferred to comprehensive vascular centers. Patients were examined immediately after admission based on the standard examination protocol (including medical history and recording of stroke risk factors, blood test, and electrocardiography) and the baseline National Institutes of Health Stroke Scale (NIHSS) which was assessed by a dedicated stroke neurologist. Every patient underwent cranial CT with stroke imaging protocol to evaluate the intra- and extracranial vessel status and to exclude intracranial bleeding events. The standard CT imaging protocol included a non-contrast CT scan, CT angiography, and in cases beyond 6 hours from the symptom onset CT perfusion was also performed. All investigated patients received recanalization therapy. In every eligible patient, standard IVT therapy was applied within 4.5 hours after symptom onset (according to the conventional criteria of IVT application). In addition, selected patients (based on the clinical and imaging data) underwent MT. The exact endovascular strategy was left to the decision of the neurointerventional specialist. The final mTICI scoring of 2b, 2c, or 3 (modified thrombolysis in cerebral infarction) was defined as successful recanalization. A control CT scan was performed after 24 hours (or if there was any sign of clinical deterioration) from stroke onset to assess the postprocedural intracranial status. The intracranial bleeding events were classified according to the European Cooperative Acute Stroke Study (ECASS II) classification. Symptomatic intracranial hemorrhage (sICH) was defined as parenchymal hematoma (PH1 and PH2) on the control imaging and associated with a 4 point increase of the NIHSS.

We recorded and investigated the following parameters: (a) demographic data; (b) vascular risk factors; (c) baseline, 24 hours, and 72 hours neurological status based on NIHSS (National Institutes of Health Stroke Scale) score; (d) imaging data (Alberta Stroke Program Early CT Score [ASPECTS]; multiphase CT-angiography [mCTA] collateral score); (e) time metrics, details of the recanalization treatment and complications.

The primary outcome was the modified Rankin Scale (mRS) score at 90 days with scores ranging from 0 (no symptoms) to 6 (death), mRS 0–2 is considered as a good functional outcome. Other analyzed outcomes included all-cause mortality at 90 days, successful arterial recanalization (TICI $\geq$ 2b), and symptomatic intracranial hemorrhage (sICH).

For the statistical data analysis, SPSS (version 26.0, IBM, New York, NY, USA) was applied. Normality was assessed with the Kolmogorov–Smirnov test. Quantitative data were expressed as the median and interquartile range (IQR) or the mean ± standard deviation (SD). Categorical variables were analyzed using chi-square or Fisher's exact test. Student t-tests or Mann–Whitney U tests were used to compare the continuous variables. Multivariable binary logistic regression analysis was performed to analyze the relationship between diabetes, aHG, and the investigated outcomes. For the adjustment of potential confounders, variables with a p-value <0.1 in the univariate analysis were entered into the multivariable logistic regression model. Statistical significance was considered as $p \leq 0.05$

3. Results and conclusions of our studies

3.1 The role of intravenous thrombolysis before mechanical thrombectomy in the treatment of large vessel occlusion strokes

In our first study, we evaluated and compared the safety and effectiveness of CT and dMT. We selected all patients with LVO of anterior circulation with the onset of symptoms within 4.5 hours and who underwent MT between November 2017 and August 2019 at the Department of Neurosurgery at the University of Pécs. Patients with any contraindication to IVT (according to the official guidelines) were primarily enrolled in the dMT group.

A total of 142 ischemic stroke patients due to LVO within 4.5 hours from the stroke onset were enrolled. The clinical characteristics of enrolled patients are summarized in Table 1. Direct thrombectomy occurred in 81 (57.0%) cases, and 61 (43.0%) patients received CT. The incidence of comorbidities (hypertension, diabetes mellitus, atrial fibrillation, ischemic heart disease) was significantly higher in the dMT group. The rate of successful recanalization (mTICI ≥ 2b) following MT (94.2% vs. 98.0%, p=0.318) and the number of sICH detected on the 24-hours control imaging (2.5% vs. 3.4%, p=0.757) did not differ significantly between the groups. In the 90-day follow-up, patients treated with CT achieved favorable functional outcome moderately more frequently (46.3% vs. 40.8%, p=0.542) with a slightly lower mortality rate (25.9% vs. 33.8%, p=0.343) compared to the dMT group. The correlations between the investigated outcomes and CT are shown in Table 2. There was no significant association between the outcomes and CT before and after the adjustment for potential confounders.

The results of our study confirm that combined recanalization treatment of intracranial large vessel occlusions within 4.5 hours moderately improves stroke outcomes and reduces mortality. Furthermore, CT did not significantly increase the incidence of sICH, supporting the recommendations of current guidelines.

1. Table Demographic data and clinical parameters between the study groups.

	dMT (n=81)	CT (n=61)	p-value
Age, years, mean (± SD)	69.9 (±12.1)	66.1 (±13.1)	0.081
Gender, female, % (n)	51.9 (42)	55.7 (34)	0.646
Baseline NIHSS score, median (IQR)	12 (9-18)	15 (11-18)	0.248
Onset-to-door time, minutes (IQR)	77 (44-113)	79 (54-111)	0.850
Hypertension, % (n), 5 MD	88.5 (69)	74.6 (44)	0.034
Diabetes mellitus, % (n), 12 MD	33.8 (26)	13.2 (7)	0.008
Hyperlipidemia, % (n), 46 MD	57.1 (32)	65.0 (26)	0.438
Atrial fibrillation, % (n), 10 MD	50.0 (37)	32.8 (19)	0.047
Ischemic heart disease, % (n), 35 MD	48.3 (29)	27.7 (13)	0.030
Systolic blood pressure, Hgmm, median (IQR)	140 (130-165)	150 (130-170)	0.442
Diastolic blood pressure, Hgmm, median (IQR)	80 (73-90)	82 (80-90)	0.156
Baseline glucose level, mmol/l, median (IQR)	7.1 (6.1-8.1)	6.9 (6.1-8.8)	0.877
ASPECTS, median (IQR)	9 (8-10)	9 (8-10)	0.968
Primary transport, % (n)	55.6 (45)	63.9 (39)	0.321
Onset-to-IVT time, minutes median (IQR)	-	135 (110-180)	-
Onset-to-revascularization time, minutes, median (IQR)	295 (225-372)	298 (225-341)	0.851
Symptomatic intracranial hemorrhage, % (n), 3 MD	2.5 (2)	3.4 (2)	0.757
Successful recanalization (mTICI ≥ 2b), % (n) 6 MD	94.2 (76)	98.0 (60)	0.318
30-day good functional outcome (mRS < 2), % (n)	34.7 (28)	43.6 (27)	0.307
90-day good functional outcome (mRS < 2), % (n)	40.8 (33)	46.3 (28)	0.542
30-day mortality (mRS 6), % (n)	22.2 (18)	23.6 (14)	0.851
90-day mortality (mRS 6), % (n)	33.8 (27)	25.9 (16)	0.343

Abbreviations: dMT, direct mechanical thrombectomy; CT, combined therapy; n, population size; SD, standard deviation; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; MD, missing data; BMI, body mass index; CRP, C-reactive protein; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; mTICI, modified thrombolysis in cerebral infarction

2. Table Correlations between the combined therapy and the investigated outcomes.

	Non-adjusted OR (95% CI)	Adjusted* OR (95% CI)
90-day good functional outcome	1.249 (0.611 - 2.550)	1.150 (0.495 - 2.670)
90-day mortality (mRS 6)	0.685 (0.313 - 1.499)	0.716 (0.283 - 1.812)
Successful recanalization (mTICI ≥ 2b)	2.954 (0.320 - 27.274)	1.828 (0.177 - 18.835)
sICH	1.739 (0.697 - 4.340)	1.727 (0.633 - 4.714)

*Adjusted: gender, age, baseline NIHSS score

Abbreviations: OR, odds ratio; CI, confidence interval; mRS, modified Rankin Scale; mTICI, modified thrombolysis in cerebral infarction; sICH, symptomatic intracranial hemorrhage

3.2 Comparing endovascular treatment methods in acute ischemic stroke due to tandem occlusion focusing on clinical aspects

Ischemic stroke (AIS) due to tandem occlusion (TO) is defined as a high-grade stenosis or occlusion of the extracranial segment of the ICA (EICA) associated with concurrent ipsilateral intracranial LVO along the anterior cerebral circulation (primarily in the terminal ICA (t-ICA) or MCA segment). According to the current guidelines, opening the EACI lesion should be considered with IIB evidence in addition to intracranial MT. Although, the appropriate EACI revascularization strategy, including the necessity of acute stent is still unclear.

In our second study, we investigated the EVT methods in TO of anterior circulation. We compared the clinical parameters and the outcomes of patients treated with ACS or BAO according to the BAT technique before the intracranial MT. The applied endovascular method was left to the discretion of the physician. In general, the anterograde approach (proximal-to-distal) was applied.

Altogether, we enrolled 101 patients with acute stroke due to TO who were treated by endovascular approach between November 2017 and December 2020 in the three participating institutions. EICA lesion was treated with ACS in 72 (71.3%) and BAO in 29 (28.7%) patients. The investigated parameters of the overall patient population and the patient groups are summarized in Table 3. The mean age was 67 ± 10 years and patients were predominantly male (61.4%). Patients treated with BAO were slightly older (70 ± 9 vs. 66 ± 10 years, $p = 0.054$), and had a higher prevalence of comorbidities such as hypertension (100.0% vs. 59.4%, $p < 0.001$). Intracranial occlusion site was tICA in 30 patients (29.7%), MCA M1 in 55 patients (54.5%), and MCA M2 in 16 patients (15.8%). The median baseline NIHSS score was 12 (IQR 9–16) with median ASPECTS 9 (IQR 8–9) and median mCTA 4 (IQR 3–4) points without significant differences. Thrombolysis before thrombectomy was administered in 27 patients (26.7%). Regarding the details of the intervention, the median symptom onset to arterial puncture time was 347 (IQR 230–655) minutes. The procedure time was slightly shorter in the BAO group (43, IQR 30–60 vs. 49, IQR 33–65, $p = 0.450$), however, the difference was not significant. Successful recanalization was achieved in 83.2% of the patients and was more frequent in the ACS group (86.1% vs. 75.9%, $p = 0.213$). Although, the rate of intraprocedural complications (9.7% vs. 3.4%, $p = 0.291$) and distal embolization (39.1% vs. 17.9%, $p = 0.043$) showed an upward trend toward acute stent treatment. Symptomatic hemorrhagic transformation was detected in 7 patients (6.9%), and there was a slightly higher occurrence

(8.3% vs. 3.4%, p = 0.382) in the group treated with ACS.

Fifty-two patients (53.6%) showed favorable outcome and 20 patients (20.6%) died during the 90-day follow-up. Four patients (4.0%) were lost to follow-up. In the ACS group, 37 (54.4%) patients achieved good functional outcome and 15 (51.7%) patients in the BAO group. The mortality rate at 90 days was slightly lower in patients who underwent BAO (13.8% vs. 23.5%, p = 0.278). There were no significant differences in the outcomes.

3. Table Distribution of demographics and clinical parameters between the groups.

	Overall population (n=101)	ACS (n=72)	BAO (n=29)	p-value
Age, years, mean (± SD)	67 (±10)	66 ± 10	70 ± 9	0.054
Gender, female, % (n)	38.6 (39)	34.7 (25)	48.3 (14)	0.206
Smoking, % (n) 36 MD	66.2 (43)	66.0 (31)	66.7 (12)	0.957
Alcohol consumption, % (n) 36 MD	38.5 (25)	38.3 (18)	38.9 (7)	0.965
Hypertension, % (n) 3 MD	71.4 (70)	59.4 (41)	100.0 (29)	<0.001
Diabetes mellitus, % (n) 4 MD	20.6 (20)	20.3 (14)	21.4 (6)	0.900
Hyperlipidaemia, % (n) 4 MD	45.4 (44)	42.6 (29)	51.7 (15)	0.411
Atrial fibrillation, % (n)	19.8 (20)	16.7 (12)	27.6 (8)	0.213
Previous stroke or TIA, % (n) 7 MD	18.1 (17)	19.4 (13)	14.8 (4)	0.601
Admission antiplatelet therapy, % (n) 9 MD	22.8 (21)	18.2 (12)	34.6 (9)	0.091
Admission anticoagulant therapy, % (n) 9MD	8.7 (8)	6.1 (4)	15.4 (4)	0.153
Baseline NIHSS score, median (IQR)	12 (9-16)	12 (9-16)	13 (9-16)	0.450
NIHSS score at 24 hours, median (IQR)	8 (4-13)	8 (4-13)	8 (6-11)	0.591
NIHSS score at 72 hours, median (IQR)	7 (4-11)	7 (4-10)	8 (6-11)	0.432
ASPECTS, median (IQR)	9 (8-9)	8 (8-9)	9 (8-9)	0.213
mCTA collateral score, median (IQR)	4 (3-4)	4 (3-4)	4 (3-4)	0.938
LVO site				
t-ICA, % (n)	29.7% (30)	29.2 (21)	31.0 (9)	0.853
MCA M1, % (n)	54.5% (55)	56.9 (41)	48.3 (14)	0.429
MCA M2, % (n)	15.8 % (16)	13.9 (10)	20.7 (6)	0.397
IVT, % (n)	26.7 (27)	25.0 (18)	31.0 (9)	0.535
Onset-to-groin puncture time, median (IQR)	347 (230-655)	360 (235-655)	310 (215-665)	0.838
Puncture-to-revascularization time, median (IQR)	47 (33-64)	49 (33-65)	43 (30-60)	0.450
Onset-to-revascularization time, median (IQR)	400 (275-725)	400 (275-725)	385 (270-680)	0.832
Successful recanalization rate (mTICI ≥ 2b), % (n)	83.2 (84)	86.1 (62)	75.9 (22)	0.213
First pass effect, % (n) 4 MD	53.6 (52)	55.1 (38)	50.0 (14)	0.650
Complications, % (n)	7.9 (8)	9.7 (7)	3.4 (1)	0.291
Distal embolization, % (n) 4 MD	32.0 (31)	39.1 (27)	17.9 (5)	0.043
Early stent thrombosis, % (n)	5 (5)	8.8 (5)	-	
sICH, % (n)	6.9 (7)	8.3 (6)	3.4 (1)	0.382
90-day good functional outcome, % (n) 4 MD	53.6 (52)	54.4 (37)	51.7 (15)	0.808
90-day mortality, % (n) 4 MD	20.6 (20)	23.5 (16)	13.8 (4)	0.278

Abbreviations: TO, tandem occlusion; EVT, endovascular therapy; ACS, acute carotid stent; BAO, balloon angioplasty only; SD, standard deviation; IQR, interquartile range; MD, missing data; TIA, transient ischaemic attack; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; mCTA, multiphase CT angiography; LVO, large vessel occlusion; t-ACI, terminal segment of internal carotid artery; MCA, middle cerebral artery; MD, Missing data; IVT, intravenous thrombolysis; mTICI, modified thrombolysis in cerebral infarction; sICH, symptomatic intracranial hemorrhage; mRS, modified Rankin Scale

Furthermore, regression analysis showed that younger age (p = 0.049), lack of atrial fibrillation (p = 0.009), lower baseline NIHSS score (p = 0.033), and successful recanalization (p = 0.027) were associated with favorable functional outcome, while older age (p = 0.031), alcohol consumption (p = 0.025), higher NIHSS score at 24 hours (p = 0.010) and the presence of sICH (p = 0.034) were associated with 90-day mortality. Distal embolization did not prove to be an independent predictor of the investigated outcomes. Investigated predictors of the outcomes are summarized in Table 4.

4. Table Results of regression analysis.

	OR (95% CI)	p-value
mRS 0-2		
Age	0.945 (0.893 – 1,000)	0.049
Baseline NIHSS score	0.899 (0.815 – 0.991)	0.033
Atrial fibrillation	0.115 (0.023 – 0.589)	0.009
Successful recanalization (mTICI ≥2b)	5.806 (1.219 – 27,662)	0.027
Admission anticoagulant therapy	1.210 (0.091 – 16,080)	0.885
mRS 6		
Age	1.150 (1.013 – 1.307)	0.031
NIHSS score at 24 hours	1.256 (1.057 – 1.492)	0.010
Alcohol consumption	15,755 (1.413 – 175.730)	0.025
mCTA score	0.402 (0.149 – 1.088)	0.073
sICH	15.264 (1.228 – 189.710)	0.034

Abbreviations: OR, odds ratio; CI, confidence interval; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; mTICI, modified thrombolysis in cerebral infarction; mCTA, multiphase CT angiography; sICH, symptomatic intracranial hemorrhage

In conclusion, the endovascular treatment of EICA in addition to MT is safe and effective in tandem occlusion of the anterior circulation, regardless of the opening technique. Our results suggest that the balloon angioplasty alone method according to the BAT technique has a comparable good functional outcome rate in contrast to ACS, with moderately fewer hemorrhagic events and mortality rates,

3.3 The impact of diabetes mellitus and admission hyperglycemia on clinical outcomes after recanalization therapies for acute ischemic stroke

Diabetes mellitus (DM) and admission hyperglycemia (aHG) are important risk factors for AIS. The aHG occurs in 30–40% of patients with ischemic stroke, even if they do not have a history of diabetes. Potential detrimental mechanisms of elevated serum glucose include disruption of the blood-brain barrier, lactic acid accumulation in the ischemic area leading to more extensive infarction, and the inhibition of plasma fibrinolysis. Previous studies showed that aHG was correlated with lower reperfusion rates after intravenous thrombolysis. Furthermore, evidence is limited in patients with acute stroke who were treated with MT. The post hoc analysis of previous RCTs (SWIFT, MR CLEAN) found inconsistent results regarding the potential negative effect of elevated serum glucose values on clinical outcomes after thrombectomy.

Therefore our study aimed to assess the prognostic impact of DM and aHG on functional and clinical outcomes in stroke patients who underwent recanalization therapies. Moreover, we sought to investigate the potentially detrimental effects of these risk factors on outcomes according to the different recanalization techniques.

The total number of enrolled patients was 695 (45.0% female) who received recanalization therapies between November 2017 and January 2020 at the three participating stroke centers. Eighty-one percent of all patients (n=565) received IVT alone and MT was performed in 130 (19%) cases. The clinical characteristics of enrolled patients are summarized in Table 5. Diabetes was recorded in 182 (26.2%) patients. Poor functional outcome at 90 days was more frequent in diabetic patients (51.1% vs. 33.3%, $p < 0.001$) and they also had significantly higher mortality rate (21.9% vs. 11.6%, $p < 0.001$). In addition, intracranial bleeding events were detected in 25 (3.6%) patients and there was a higher incidence of sICH (7.8% vs. 2.2%, $p = 0.001$) in the DM group.

After adjusting for potential confounders, DM and aHG were independently associated with 90-day poor functional outcome (OR 2.02, 95% CI 1.31–3.11, $p = 0.001$; OR 2.09, 95% CI 1.39–3.14, $p < 0.001$), 90-day mortality (OR 2.45, 95% CI 1.35–4.47, $p = 0.003$; OR 2.42, 95% CI 1.37–4.28, $p = 0.002$) and sICH (OR 4.32, 95% CI 1.54–12.09, $p = 0.005$; OR 4.61, 95% CI 1.58–13.39, $p = 0.005$) (Table 6.).

Since the recanalization method, the presence of LVO and the stroke severity also differed between the enrolled patients we performed subgroup analysis to compare homogenous patient groups according to the recanalization therapies. Patients were predominantly treated with IVT alone (81.3%). Therefore, the characteristics of the patients were very similar in IVT alone group compared to the results of the overall population. Furthermore, DM and aHG were independently associated with the analyzed clinical outcomes.

5. Table Baseline and evaluated clinical characteristics of the overall population.

	Overall population (n=695)	DM (n=182)	non-DM (n=513)	p-value
Age, years, median (IQR)	69 (60-77)	71 (64-78)	67 (59-77)	<0.001
Gender, female, % (n)	45.0 (313)	46.7 (85)	44.4 (228)	0.599
Hypertension, % (n)	79.2 (548)	92.7 (166)	74.5 (382)	<0.001
Hyperlipidemia, % (n)	62.1 (394)	69.1 (114)	59.7 (280)	0.032
Atrial fibrillation, % (n)	17.5 (119)	23.0 (40)	15.6 (79)	0.027
Ischemic heart disease, % (n)	23.9 (157)	41.0 (68)	18.2 (89)	<0.001
Previous stroke or TIA, % (n)	22.0 (148)	29.2 (49)	19.6 (99)	0.009
Admission antiplatelet therapy, % (n)	37.4 (250)	55.4 (97)	31.0 (153)	<0.001
Admission OAC therapy, % (n)	11.1 (74)	15.8 (27)	9.5 (47)	0.025
Baseline NIHSS score, median (IQR)	7 (5-11)	7 (5-11)	7 (4-11)	0.964
BMI, kg/m^2	26.3 (23.3-31.1)	28.1 (25.5-33.2)	25.8 (23.0-29.5)	<0.001
ASPECTS, median (IQR)	10 (9-10)	10 (9-10)	10 (9-10)	0.372
mCTA collateral score, median (IQR)	5 (4-5)	5 (4-5)	5 (4-5)	0.112
Blood glucose, mmol/L, median (IQR)	6.6 (5.8-8.3)	8.7 (6.8-11.5)	6.4 (5.6-7.4)	<0.001
Admission hyperglycemia, % (n)	30.4 (201)	60.6 (103)	20.0 (98)	<0.001
Onset-to-door time, minutes, median (IQR)	85 (58-128)	89 (59-144)	83 (58-122)	0.075
Onset-to-puncture time, minutes, median (IQR)	52 (36-71)	52 (36-74)	52 (36-70)	0.965
Thrombolysis, % (n)	88.9 (618)	89.6 (163)	88.7 (455)	0.749
Mechanical thrombectomy, % (n)	18.7 (130)	18.1 (33)	18.9 (97)	0.817
sICH, % (n)	3.6 (25)	7.8 (14)	2.2 (11)	<0.001
90-day mRS ≤ 2, % (n)	62.1 (422)	48.9 (87)	66.7 (335)	<0.001
90-day mRS > 2, % (n)	37.9 (258)	51.1 (91)	33.3 (167)	<0.001
90-day mortality, % (n)	14.3 (97)	21.9 (39)	11.6 (58)	<0.001

Abbreviations: DM, diabetes mellitus; IQR, interquartile range; TIA, transient ischaemic attack; OAC, oral anticoagulant; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; mCTA, multiphase CT angiography; sICH, symptomatic intracranial hemorrhage; mRS, modified Rankin Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment

6. **Table** Association of diabetes mellitus and admission hyperglycemia with clinical outcomes in the overall population.

	Diabetes mellitus				***Admission hyperglycemia***			
	Non-adjusted OR (95% CI)	p-value	Adjusted* OR (95% CI)	p-value	Non-adjusted OR (95% CI)	p-value	Adjusted* OR (95% CI)	p-value
90-day mRS 0-2	0.48 (0.34 – 0.68)	<0.001	0.50 (0.32 – 0.76)	<0.001	0.43 (0.30 – 0.60)	<0.001	0.48 (0.32 – 0.72)	<0.001
90-day mRS > 2	2.10 (1.48 – 2.97)	<0.001	2.02 (1.31 – 3.11)	0.001	2.35 (1.67 – 3.31)	<0.001	2.09 (1.39 – 3.14)	<0.001
90-day mortality	2.15 (1.37 – 3.36)	0.001	2.45 (1.35 – 4.47)	0.003	2.63 (1.68 – 4.14)	<0.001	2.42 (1.37 – 4.28)	0.002
sICH	3.80 (1.69 – 8.52)	0.019	4.32 (1.54 – 12.09)	0.005	4.50 (1.88 – 10.80)	0.001	4.61 (1.58 – 13.39)	0.005

*Adjusted: Age, Gender, Admission NIHSS score, Ischemic heart disease, C-reactive protein, IVT, Onset-to-door time

Abbreviations: OR, odds ratio; CI, confidence interval; mRS, modified Rankin Scale; sICH, symptomatic intracranial hemorrhage

A total of 130 patients (53.1% female) with LVO were treated with MT, and 33 of them (25.4%) had been previously diagnosed with diabetes. Patients with diabetes had higher baseline serum glucose levels (7.9 vs. 6.6 mmol/L, p = 0.001) and aHG was more common (59.3% vs. 25.3%, p = 0.001). There was no significant difference in the rate of successful recanalization (81.8% vs. 89.6%, p = 0.243), and intraprocedural complications (10.3% vs. 9.5%, p = 0.898). Although, intracranial bleeding events were more common (18.2% vs. 6.2%, p = 0.040) in patients with diabetes. The good functional outcome at 90 days was more frequent (43.3% vs. 24.2%, p = 0.046) in the non-DM patient group with a significantly lower 90-day mortality rate (21.6% vs. 39.3, p = 0.037).

There was unadjusted relative risk between DM, aHG, and 90-day poor functional outcome, 90-day mortality, and sICH (7. Table). Based on the results of the statistical analysis, DM and aHG were independently correlated with 90-day mortality (OR 3.72, 95% CI 1.04–13.34, p = 0.044; OR 3.76, 95% CI 1.11–12.76, p = 0.034) and hemorrhagic transformations (OR 12.45, 95% CI 1.73–89.60, p = 0.012; OR 7.36, 95% CI 1.26–44.18, p = 0.029). In addition, aHG was significantly associated with poor functional outcomes at 90 days (OR 6.99, 95% CI 1.98–24.72, p = 0.003). The presence of DM and aHG was not associated with successful revascularization (OR 0.39, 95% CI 0.09–1.67, p = 0.205; OR 0.42, 95% CI 0.09–1.97, p = 0.274) after MT.

7. Table *Association of diabetes mellitus and admission hyperglycemia with clinical outcomes in the MT population.*

	Diabetes mellitus				***Admission hyperglycemia***			
	Non-adjusted OR (95% CI)	p-value	Adjusted* OR (95% CI)	p-value	Non-adjusted OR (95% CI)	p-value	Adjusted* OR (95% CI)	p-value
90-day mRS 0-2	0.40 (0.16 – 0.99)	0.050	0.62 (0.18 – 2.15)	0.449	0.13 (0.05 – 0.38)	<0.001	0.14 (0.04 – 0.51)	0.003
90-day mRS > 2	2.51 (1.01 – 6.27)	0.050	2.32 (0.54 – 10.00)	0.259	7.72 (2.66 – 22.40)	<0.001	6.99 (1.98 – 24.72)	0.003
90-day mortality	2.52 (1.04 – 6.07)	0.040	3.72 (1.04 – 13.34)	0.044	3.39 (1.39 – 8.26)	0.007	3.76 (1.11 – 12.76)	0.034
sICH	3.37 (1.01 – 11.31)	0.049	12.45 (1.73 – 89.60)	0.012	4.07 (1.11 – 14.89)	0.034	7.36 (1.26 – 44.18)	0.029
mTICI ≥ 2b	0.52 (0.17 – 1.57)	0.249	0.39 (0.09 – 1.67)	0.205	0.61 (0.19 – 1.90)	0.392	0.42 (0.09 – 1.97)	0.274

*Adjusted: Age, Gender, Admission NIHSS score, Ischemic heart disease, IVT, Onset-to-door time, Recanalization status

Abbreviations: OR, odds ratio; CI, confidence interval; mRS, modified Rankin Scale; sICH, symptomatic intracranial hemorrhage; mTICI, modified thrombolysis in cerebral infarction

Our results revealed that DM and hyperglycemia on admission were correlated with poor clinical outcomes at 90 days in acute stroke patients regardless of the recanalization method. The variables were also associated with sICH after recanalization therapies. However, successful arterial recanalization was not correlated with DM or aHG after the thrombectomy.

4. Summary

The results of our first study confirm the recommendations of the current guidelines and suggest that combined therapy should perform in large vessel occlusions within 4.5 hours from the stroke onset since these patients achieved more frequent favorable functional outcome and the 90-day mortality rate is also moderately lower. In addition, the usage of IVT before thrombectomy does not increase significantly the rate of symptomatic hemorrhagic transformation.

Furthermore, our studies have demonstrated the efficacy and safety of endovascular treatment in the therapy of patients with tandem occlusion. Our results suggest that carotid stent implantation in the acute phase can potentially be substituted - in a properly selected patient population - by balloon angioplasty only method according to the BAT technique.

In the last presented study, we have demonstrated an independent association between diabetes mellitus, admission hyperglycemia and 90-day poor functional outcome and mortality. There was a significant connection between the same variables and the appearance of symptomatic intracranial hemorrhage. Although, successful arterial recanalization was not associated with DM and aHG in patients who underwent MT.

5. Scientometrics

Scientific papers number: 4

Cummulative impact factor: **10.461** (based on the 2021 Journal Citation Reports)

Impact factor of the publications related to the present thesis: **7.210**

1. Kalmar PJ, Tarkanyi G, Karadi ZN, Bosnyak E, Nagy CB, Csecsei P, Szapary L. A mechanikus thrombectomiát megelőző intravénás thrombolysis szerepe az akut agyi nagyérelzáródások kezelésében. Ideggyógyászati Szemle, 2022, 75(01-02), 23-29. **IF:0.708**

2. Kalmar PJ, Tarkanyi G, Nagy CB, Csecsei P, Lenzser G, Bosnyak E, Karadi ZN, Annus A, Szegedi I, Buki A, Szapary L. Comparing Endovascular Treatment Methods in Acute Ischemic Stroke Due to Tandem Occlusion Focusing on Clinical Aspects. Life (Basel). 2021 May 20;11(5):458. **IF:3.251** (Citations: 4)

3. Kalmar PJ, Tarkanyi G, Karadi ZN, Szapary L, Bosnyak E The Impact of Diabetes Mellitus and Admission Hyperglycemia on Clinical Outcomes After Recanalization Therapies for Acute Ischemic Stroke: STAY ALIVE National Prospective Registry. Life 2022, 12, 632. **IF:3.251** (Citations: 4)

Other publication:

Tarkanyi G, Tenyi A, Hollos R, Kalmar PJ, Szapary L. Optimization of Large Vessel Occlusion Detection in Acute Ischemic Stroke Using Machine Learning Methods. Life (Basel). 2022 Feb 3;12(2):230. **IF:3.251** (Citations: 2)

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