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Optimising Endovascular Stroke Care: From System-Level Transfer Strategies to Stent-Assisted Recanalization in Basilar Artery Occlusion

PhD thesis

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List of Abbreviations

AC - anterior circulation

ACA - anterior cerebral artery

AF - atrial fibrillation

AHA - American Heart Association

AI – artificial intelligence

AIC - Akaike Information Criterion

AIS - Acute ischemic stroke

aOR - adjusted odds ratio

ASPECTS - Alberta Stroke Program Early CT Score

BA - basilar artery

BAO - Basilar artery occlusion

BMT - Best medical treatment

CAD - coronary artery disease

CBF - cerebral blood flow

CBV - cerebral blood volume

CHADS-Vasc: Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke, Vascular disease

CI - confidence interval

CPP - cerebral perfusion pressure

CSC - comprehensive stroke center

CTA - Computed tomography angiography

DAPT - dual antiplatelet therapy

DMVO - distal and medium vessel occlusions

DR - delayed re-occlusion

DSA - digital subtraction angiography

DWI - Diffusion Weighted Imaging

ECASS - European Cooperative Acute Stroke Study

ESMINT – European Society of Minimally Invasive Neurological Therapy

ESO- European Stroke Organisation

ESUS - embolic stroke of undetermined source

eTICI – expanded Treatment in Cerebral Infarction

EVT - endovascular treatment

FLAIR - Fluid Attenuated Inversion Recovery

GBD - Global Burden of Disease, Injuries and Risk Factors

Gp - Glycoprotein

HI - hemorrhagic infarction

HR - hazard ratio

HTN - hypertension

ICA - internal carotid artery

ICAD - intracranial atherosclerotic disease

ICAS - intracranial atherosclerosis

IEL - internal elastic lamina

IQR - interquartile range

IV. - intravenous

LMWH - low molecular weight heparin

LVO - large vessel occlusion

MCA - middle cerebral artery

MeVO - medium vessel occlusion

MRI - magnetic resonance imaging

mRS - modified Rankin Scale

MSU - mobile stroke unit

MT - mechanical thrombectomy

mTICI - modified Treatment in Cerebral Infarction

NIHSS - National Institutes of Health Stroke Scale

NNT - number needed to treat

OR - odds ratio

PC - posterior circulation

PCA - posterior cerebral artery

PCIS - posterior circulation ischemic stroke

PH - parenchymal hematoma

PSC - primary stroke center

RACE - Rapid Arterial oCclusion Evaluation

RCT - randomized controlled trials

rtPA - recombinant tissue plasminogen activator

SCA – superior cerebellar artery

sICH - symptomatic intracranial hemorrhage

TOAST - Trial of Org 10172 in Acute Stroke Treatment

VA - vertebral artery

VB - vertebrobasilar

I. Introduction

Stroke is a leading cause of disability and death worldwide. According to the report of the Global Burden of Disease, Injuries and Risk Factors (GBD) study from 2021, both the incidence of stroke and the stroke-related mortality continue to increase.[1] The overall burden of cardiovascular diseases, including stroke, as measured by disability-adjusted life years, deaths, and economic costs, nearly doubled between 1990 and 2019[1,2] and stroke remains the second leading cause of death globally.[3] The increase was observed despite substantial declines in age-standardized stroke rates, particularly among individuals older than 70 years.[2]

Acute stroke is a medical emergency, characterized by the sudden onset of neurological symptoms that correspond to a vascular territory of the brain, retina or spinal cord. Acute ischemic stroke (AIS) accounts for the vast majority of all stroke cases (approximately 87%[4]) and arises when occlusion of a cerebral or cervical artery leads to neural hypoperfusion. When cerebral perfusion pressure (CPP) decreases, regional cerebral blood flow (CBF, 50-60 ml/100g/min under physiological conditions) can initially be preserved, as auto-regulatory mechanisms are able to compensate the flow by reflex arteriolar vasodilatation.[5] This maximal vasodilatation results in an increase in regional cerebral blood volume (CBV) to maintain CBF for a limited period. The effectiveness and duration of this compensatory response depend critically on the integrity of the collateral circulation within the affected vascular territory.

I.1. Significance of cerebral collateral circulation

The cerebral collateral system denotes the capacity of vascular networks to maintain CBF when conventional arterial routes are compromised by various aetiologies. When regional hypoperfusion occurs, existing anastomoses are capable of immediate flow diversion (primary collaterals), whereas other collateral routes require time to activate or develop (secondary collaterals). Primary collaterals refer to the circle of Willis, secondary collaterals include leptomeningeal, and anastomotic pathways from the external carotid artery branches.[6,7] The circle of Willis is incomplete in 50% of cases, while that prevalence is higher (50-80%) in stroke patients.[8,9] Whether collateral status can change during AIS is debated, although small studies suggest that collateral function may either improve or decline in some cases.[10] The gold standard in collateral imaging is digital

subtraction angiography (DSA) due to its high temporal and spatial resolution, but it is not eligible for routine assessment.[11] Computed tomography angiography (CTA) source images are most widely used, while this technique has some pitfalls concerning the timing of contrast bolus.[12] Therefore, multiphase CTA provides a more sensitive tool of assessment.[13] Some parameters derived from CT and magnetic resonance imaging (MRI) perfusion techniques indirectly provide information on collateral quality and function.[14] Visual assessment is most frequently applied, standardized grading scales are not yet available. The use of artificial intelligence (AI) is promising in this particular question.[15] Patients with acute large vessel occlusion (LVO) related to intracranial atherosclerotic disease (ICAD) have been reported to exhibit better collateral development than those with cardioembolic stroke,[16] which is consistent with the fact that chronic hypoperfusion due to large-artery atherosclerotic stenosis induces angiogenesis in the corresponding vascular territory.[17] Good collateral circulation is associated with a smaller volume of baseline infarct core, slower progression of infarction and smaller final infarct core, therefore lower Alberta Stroke Program Early CT Score (ASPECTS) on imaging.[18, 19] The longer the clot and the more proximal it is located, the poorer the collateral status.[20] Overall, the most powerful predictor of favorable clinical outcome after mechanical thrombectomy (MT) is the presence of good collateral circulation.

I.2. The penumbra concept

As CBF decreases either due to insufficient collateral circulation or due to exhaustion of autoregulation, it first reaches the threshold of 'oligemia', meaning no functional or morphological impairment. Then with further decrease of CBF, profound metabolic impairment is reached, called the 'ischemic penumbra' (30-40% of normal CBF)[5]. The term was first used by Astrup et al. in 1981[21], referring to a certain area of the brain with decreased perfusion leading to functional impairment and possibly irreversible damage without urgent restoration of CBF. Therefore, its resistance to ischemic changes is highly time sensitive.[22] With the progression of perfusion failure, surpassing the 10-12 ml/100g/min threshold, the affected tissue becomes unsalvable even with the quickest restoration of flow. That state is referred to as the 'ischemic core'. [23,24] One should remember, that these changes are highly variable and represent a dynamic process, depending on the duration and severity of decreased CPP.[25] Therefore, the CBF cutoff

values are rough measures, real life values are difficult to obtain even with advanced imaging techniques.[26] The aim of reperfusion therapies is to save the tissue at risk, the so-called penumbra. Due to its time sensitive nature, flow restoration should be performed the quickest possible way.

I.3. Stroke etiologies, focusing on LVO

Clinical stroke manifestations are determined by the location and volume of the affected brain tissue. The underlying pathophysiological mechanisms shape the pattern and severity of these symptoms, as well as the range of potential therapeutic options; therefore, it is crucial to investigate the possible aetiology of stroke already in the hyperacute phase. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification is widely used for division by its origin.[27] The five proposed groups are large artery atherosclerosis (LAA), small vessel occlusion, cardioembolism (CE), stroke of undetermined etiology and stroke of other determined etiology. Ischemic stroke risk factors, recurrence and survival were found to differ between TOAST subtypes, therefore the classification system contributes to therapeutic decision making in secondary prevention.[28] Although modified TOAST classifications were introduced, like SSS-TOAST and CCS, targeting to solve the problems of reliability and validity, the complexity of their algorithms led many experts to the application of the original TOAST due to its simplicity.[29] The primary goal of an etiological approach is to identify the best medical treatment (BMT) for each individual stroke cases to prevent recurrence.

A significant subgroup of AIS patients presents with LVO. There are some variabilities in the terminology and definitions, but large vessel most commonly refers to the terminal segment of internal carotid artery (ICA), the first and second segments of the anterior cerebral artery (ACA; A1, A2), the first and second segments of the middle cerebral artery (MCA; M1, M2), the V4 segment of the vertebral artery (VA), the basilar artery (BA) and the first and second segments of the posterior cerebral artery (PCA; P1, P2).[30,31]

Stroke cases due to LVO result in higher mortality and morbidity compared to other subtypes. LVO accounts for up to 46% of all AIS cases.[31,32] The rate of this subtype of stroke has been debated, as the definition of a cerebral large vessel is not uniform. Most of the large randomized controlled thrombectomy trials defined patients with LVO as occlusion of the terminal ICA or M1, some of these trials also enrolled cases of M2 and

A1 or A2 segment occlusions as well. The detection of a LVO is pivotal in the emergent management of AIS, as mechanical clot removal is feasible in this subgroup of patients and is associated with substantial improvements in functional outcome.

I.4. Historical evolution of reperfusion therapies

The NINDS trial, published in 1995, represented the first major milestone in reperfusion therapy for AIS, demonstrating that intravenous (iv.) recombinant tissue plasminogen activator (rtPA) administered within 3 hours of symptom onset improves clinical outcomes despite an increased risk of symptomatic intracranial hemorrhage (sICH).[33] This benefit was subsequently shown to persist up to 4.5 hours after symptom onset in the ECASS III trial published in 2008[34], and to extend even further in selected patients when guided by advanced neuroimaging.[35,36]

Mechanical clot removal in AIS patients was first performed by Gunnar Wikholm in 1994[37], later several devices and techniques were applied during the years in many centers, until the results of the first randomized controlled trials (RCT) were published in 2013, although with sobering results.[38,39,40] The so called 'unhappy' trials (Synthesis, MR-RESCUE and IMS-III) failed to demonstrate the superiority of MT over intravenous thrombolysis (IVT) in AIS with LVO. The weakness and criticism of these studies included the heterogeneity and out-dated profile of the used devices, the long period of inclusion and the small number of patients, inappropriate inclusion imaging and comparison of iv. tPA with endovascular treatment (EVT) alone.[41]

With the introduction of modern endovascular devices, especially stent retrievers, five randomized controlled trials published in 2015 showed that endovascular thrombectomy plus IVT is more effective and equally safe than standard medical therapy in patients with proximal anterior circulation (AC) LVO, marking a revolution in the treatment of AIS.[42,43,44,45,46] The meta-analysis of pooled individual patient data from MR-CLEAN, ESCAPE, REVASCAT, SWIFT PRIME and EXTEND IA trials was published by the HERMES collaboration group.[47] The primary outcome was the degree of disability measured on the modified Rankin Scale (mRS) at 90 days. The mRS is a clinical measure for disability that has been widely used for evaluating recovery after a stroke event and as a primary end point in RCTs. The scale consists of six categories, where 0 marks complete independence, 5 signifies a total bed-ridden state, while 6 refers to death.[48,49,50]

The pooled data demonstrated a lower risk of disability at 90 days in the mechanical thrombectomy group compared with the control group. Additionally, the efficacy of mechanical thrombectomy has been shown to be highly time dependent: the probability of achieving functional independence decreases by 7.7% with each hour of treatment delay, as demonstrated by the MR CLEAN investigators. These RCTs served as the basis for new recommendations in updated stroke guidelines (American Heart Association, AHA; European Stroke Organisation, ESO).[51,52] Partly as a consequence of the strict enrolment criteria, the therapeutic effect was remarkably large, with a number needed to treat of 2.6, indicating that for every 2.6 patients treated with MT, one achieves at least a one-point improvement on the mRS compared with standard therapy. Therefore the level of recommendations became very strong for a patient with AIS due to LVO within 6 hours of onset, if the occlusion affected the M1 segment of the MCA or the terminal segment of the ICA, if the ischemic core was small (ASPECTS $\geq$ 6 points), if the neurological symptoms were severe (National Institutes of Health Stroke Scale, NIHSS $\geq$ 6), if the symptom onset was within 6 hours and if the pre-stroke mRS was 0-1. With such a significant therapeutic power, many questions were raised about the multitude of patients excluded from treatment: later time window, large ischemic core, distal occlusion, posterior stroke, mild symptoms, less independent pre-stroke condition. Therefore, the subsequent years have been devoted to pushing the boundaries of MT.

Angiographic reperfusion in the five landmark thrombectomy trials was assessed using the modified Thrombolysis in Cerebral Infarction (mTICI) scale, which classifies reperfusion as follows: grade 0 indicates no reperfusion; grade 1 indicates antegrade reperfusion with minimal distal branch filling; grade 2a indicates reperfusion of less than 50% of the affected territory; grade 2b indicates reperfusion of at least 50% of the affected territory; and grade 3 indicates complete reperfusion.

I.4.1. Late time-window

In 2018, the results of the DAWN and DEFUSE 3 trials extended the MT window to 16–24 hours after symptom onset in selected patients with a small infarct core and either severe deficits or a substantial penumbra.[53,54] DAWN used a clinical-imaging mismatch approach, while DEFUSE 3 used perfusion imaging to identify patients with target mismatch; both trials showed markedly better functional outcomes without a major increase in sICH. Although these studies were practice changing, their complex imaging

criteria were difficult to apply routinely in the real-world management and may have been too restrictive given the large treatment effect. This is reflected in the "late window paradox", where the absolute gain in mRS 0–2 outcomes were larger in the late-window trials than in the early time-window HERMES study.[55] The MR CLEAN-LATE trial showed that a simpler selection strategy using non-contrast CT and CTA could also identify late-window patients who benefit from MT.[56] Even though sICH was somewhat more frequent, MT improved functional outcome without increasing mortality.

I.4.2. Large core

Historically, patients with large ischemic core, defined as ASPECTS 0–5 or an acute infarct volume ≥50 ml on advanced imaging[57], were excluded from EVT trials due to concerns about increased reperfusion hemorrhage and consequent higher disability and mortality.[47] When AC-LVO occurs, approximately 20% of patients presenting within 24 hours already has a large infarct core. Six recent randomised trials (RESCUE-Japan LIMIT, ANGEL-ASPECT, SELECT2, TESLA, TENSION, LASTE) now provide high-level evidence that, in AC occlusions with large infarct core (ASPECTS 2–5), MT significantly reduces disability and increases the likelihood of ambulation and functional independence compared with BMT, despite higher rates of ICH, but without increasing mortality.[58,59,60,61,62,63] One-year data from SELECT2 and TENSION further indicate sustained benefits in functional outcome, survival and quality of life, confirming that patients with large infarct core derive both short- and long-term benefit from EVT.[64,65]

I.4.3. Posterior circulation stroke with LVO

Basilar artery occlusion (BAO) has a highly heterogeneous clinical presentation, ranging from mild brainstem symptoms and sensory–motor deficits to severe levels of disturbance of consciousness. Reperfusion therapy is crucial, as untreated acute mortality reaches 90% of cases, and even with BMT the majority of patients never regain functional independence.[66,67] Early trials (BASICS, BEST) did not demonstrate benefit from EVT, largely due to recruitment challenges, inclusion of patients with mild deficits, and substantial crossover between treatment arms.[68,69] More recent trials with stricter imaging and clinical selection have shown clear clinical outcome benefit after MT. The ATTENTION trial, enrolling patients with limited ischemic changes (posterior circulation (pc) ASPECTS ≥ 6 or ≥ 8 depending on age) and stroke severity of NIHSS > 10, within 12 hours of symptom onset, found that MT nearly doubled the rate of

independent ambulation and almost tripled functional independence at 3 months, while significantly reducing mortality.[70] The BAOCHE trial confirmed these findings while using a longer time window (6–24 hours) and allowing milder deficits (NIHSS ≥ 6) but similarly limited ischemic burden: EVT more than doubled the odds of better neurological outcome, and lowered mortality probability by 25%, despite the increased sICH rates (6% vs 1%) and procedural complications.[71] A meta-analysis of these four trials provided high-level evidence that in BAO, MT within 24 hours of symptom onset significantly improves functional outcome (higher proportion of mRS 0–3) and reduces mortality, albeit with a higher sICH rate.[72]

I.4.4. Distal and medium vessel occlusion (DMVO / MeVo) stroke

Distal and medium vessel occlusions (DMVOs) represent a heterogeneous group of lesions with overlapping terminology in the literature and are defined differently by certain groups. The Distal Thrombectomy Summit Group focuses mainly on the size of arteries, defines medium vessel occlusions as of arteries 0.75–2.0 mm in diameter located beyond more than one bifurcation from the proximal vessel.[73] Ospel et al. proposed a different approach that includes clinical symptoms additionally to size and anatomy.[74] They suggested the term medium vessel occlusion (MeVO) in case of an affected arterial caliber ranging from 1 to 3 mm. In order to outweigh the potential risks associated with MT in a distal location, a clinical deficit criterion was added to the definition (NIHSS ≥5 or NIHSS <5 with disabling deficits). MeVos typically affect non-dominant M2 as well as M3–M4 segments of the MCA, A2–A4 (and occasionally A1) segments of the ACA, P2–P4 (and sometimes P1) segments of the PCA, and the major cerebellar arteries.[73,75]

Acute DMVOs are estimated to account for 25–40% of all AISs, and although the associated neurological deficits are often less severe than in LVO cases, they are frequently disabling, with 30–50% of patients remaining non-independent despite current therapies.[74] Advances in smaller stent retrievers and more flexible, atraumatic aspiration catheters have made EVT technically feasible in DMVOs, but at the cost of higher procedural risk and a smaller volume of salvageable brain tissue compared with LVOs.[76,77,78] Two RCTs (DISTAL and ESCAPE-MeVO) were published recently evaluating the efficacy and safety of MT in case of a MeVo, with the contribution of our team to the latter trial.[79,80] Both studies concluded neutral results: they could not report functional outcome benefit of MT over BMT for DMVO stroke patients, and they raised

safety concerns as well. Across these RCTs, and the related DISCOUNT trial, current randomized evidence indicates that routine thrombectomy for DMVO/MeVO stroke does not improve functional outcomes or reduce mortality compared with BMT, while increasing the rate of sICH and other safety concerns.[81,82] These findings support a more selective, trial-based or subgroup-focused approach rather than broad adoption of EVT for all MeVO patients. The therapeutic questions of MeVO are under further investigation in some ongoing trials (e.g. DISTALS, REVISAR).

I.5. Device evolution

Over the past two decades, MT has evolved from the first FDA-approved Merci Retriever to a wide array of modern stent retrievers, aspiration catheters, and adjunctive devices (aspiration systems, balloon guide catheters, etc.), resulting in markedly higher recanalization rates and faster, more complete cerebral reperfusion than earlier systems.[83,84] Landmark RCTs established stent retriever thrombectomy as standard of care in LVO stroke, while subsequent COMPASS and ASTER trials showed that contact aspiration is non-inferior in terms of clinical efficacy, albeit with frequent crossover to stent retrievers.[85,86] Randomized studies of combined techniques (ASTER2, VECTOR) have not demonstrated superiority in revascularization, clinical outcomes, or safety, thus, routine use of combined MT is currently not recommended.[87,88]

Balloon-guide catheters were proven to be able to arrest anterograde flow and permit flow reversal during MT, reducing clot fragmentation and distal embolization in-vitro, and observational studies have linked their use to less distal embolization, higher first-pass recanalization, improved reperfusion, shorter procedure times, and better clinical outcomes compared with conventional guide catheters.[89,90,91,92] However, the PROTECT-MT randomized trial contradicted these observational data, showing that balloon-guide–assisted MT did not improve distal embolization or recanalization, was associated with longer procedure duration and more catheter-induced vasospasm, and ultimately resulted in worse clinical outcomes than procedures performed with standard guide catheters.[93]

I.6. The key to improved outcomes: optimized cerebral reperfusion!

The clinical outcome of LVO stroke is largely dictated by how rapidly and reliably reperfusion can be achieved. This includes not only minimizing the time to restore antegrade flow but also ensuring that recanalization remains durable over time. Accordingly, optimizing outcomes requires parallel system-level and procedure-level strategies. At the system level, prehospital pathways and triage algorithms must be structured so that patients are directed without delay to centers capable of delivering EVT, thereby reducing onset-to-reperfusion times. At the procedural level, technical aspects of MT must be tailored to secure lasting vessel patency, which is particularly challenging in settings such as BAO due to underlying ICAD, where the propensity for re-occlusion is substantial. This overarching concept underpins the present work and informs the specific aims outlined in the following section.

I.7. Prehospital Triage and Transport Paradigms

I.7.1. Drip-and-ship vs. mothership models, workflow metrics and determinants

When AIS occurs, two main prehospital triage concepts are applicable upon where the patient is transported first, and which reperfusion treatment is available.[94] The *drip-and-ship* concept refers to the case when patients are transported first to the nearest primary stroke center (PSC), where rapid imaging and IVT can be given if indicated. If LVO is proven, the patient is then secondarily transferred to a comprehensive stroke center (CSC) for EVT. This model provides earlier IVT for many patients, uses local hospital network, and spares the capacities of CSCs from AIS cases without LVO. Its main disadvantage is the additional inter-hospital transfer time which can delay EVT, possibly worsen outcomes in LVO if door-in-door-out times are long.[95]

The *mothership* concept means that emergency medical transport services bypass the closest PSC and take the patient directly to the nearest CSC that can provide both IVT and EVT. The aim of this model is to minimize onset-to-groin and onset-to-recanalization times for patients who are candidates for MT. The main advantages of this paradigm are faster access to EVT for LVO patients due to the lack of secondary transfers, and better functional outcomes when extra travel time to the CSC is limited. On the downside, mothership may cause delay to IVT if the CSC is much farther, may overload CSCs and can be suboptimal when LVO probability is low or geography is unfavorable.[96]

I.7.2. Evidence comparing routing strategies

Observational and pooled data suggest that direct transfer to a CSC shortens AIS workflow times and improves outcomes after MT, while the underpowered TRIAGE-STROKE trial and a large meta-analysis also seemed to confirm these findings, in support of the *mothership* strategy.[97,98] However, the RACECAT randomized trial using the Rapid Arterial oCclusion Evaluation (RACE) prehospital triage score didn't demonstrate a functional outcome advantage for direct transfer, leaving the optimal prehospital pathway for patients with suspected LVO unresolved.[99] Although RACECAT is usually referred to as an RCT in support of the *drip-and-ship* approach, the trial was conducted in a mainly non-urban region, characterized by long transport distances and multiple referral stroke centers. In such a geographical location with such a logistical background, direct transfer did not improve clinical outcomes despite shorter workflow times, reflecting system-level limitations rather than a lack of therapeutic benefit. Applying these findings to densely populated regions with short transfer routes and high procedural capacity may therefore be misleading. Whether direct transfer can provide additional benefit in urban regions — especially in patients eligible for both IVT and EVT, who are frequently first directed to primary centers — remains an open question and a central focus of our investigation.

I.7.3. Guideline positioning and 'EVT first' concepts

Observational studies and meta-analyses suggest that mothership tends to result in better clinical outcomes in LVO patients, especially when additional transport time to a CSC is modest, but outcomes vary by region and logistical considerations.[100,101] Decision-analytic models suggest that *drip-and-ship* may be more beneficial when PSC workflows are fast and extra travel time to a CSC is long, while mothership is possibly favored when CSC is not significantly further, or PSC workflow systems are slower.[95,102] Current guidelines highlight the importance of adapting prehospital triage to local transport times, LVO estimation and communication systems, and hospital capabilities rather than generally favoring one model.[102]

I.7.4. Metropolitan system challenges

Metropolitan prehospital stroke systems face important logistical and organizational challenges in triage for AIS patients with suspected LVO.

- *Transport challenges*

Despite relatively short distances in a dense urban location, travel times may vary due to rush hours, local traffic and complex urban networks, making time predictions less reliable.[103] Notably, direct transferring of most stroke suspects to a CSC can add only a few extra transport minutes on average but may markedly increase patient volumes at the target centers.[104]

- *Capacity challenges*

Significant emergency room and intensive care unit occupancy at CSCs may delay imaging, as well as door-to-needle and door-to-groin times, challenging the importance of time savings from the *mothership* strategy. If too many mimics or mild strokes are transported to CSCs, these centers risk overcrowding and potential further delays for other time-dependent emergency cases. On the other hand, if secondary transport systems are frequently overwhelmed, therefore becoming highly time consuming, even with the overpacked CSC challenges, significant gain can be achieved in door-to-reperfusion times.[105]

- *Triage challenges*

Current prehospital LVO predicting scales have only moderate sensitivity and specificity, therefore in dense urban regions they generate considerable number of transfers to CSCs. For LVO prediction in case of AIS, numerous prehospital stroke scales have been introduced and validated. In a comparative analysis of eight prehospital stroke scales (RACE, LAMS, C-STAT, G-FAST, PASS, CPSS, CG-FAST, FAST-PLUS) the results proved that the RACE scale, the CG-FAST and the G-FAST scales were the best performing prehospital scales for LVO assumption.[106,107] The RACE scale is a simplified version of the NIHSS with a strong correlation and similar capacity to predict LVO likewise the NIHSS.[108] Modeling studies demonstrate that in metropolitan areas direct transport to CSCs tends to improve LVO patient access to EVT, at the same time it raises the number of non-LVO strokes arriving at CSCs.[109]

- *Network coordination and data transmission challenges*

Stroke centers within a metropolitan region require well-defined protocols for patient triage as well as dynamic updates when a hospital is overwhelmed. Real-time audio and visual communication, data and imaging transfer systems between emergency medical

services and stroke centers are still inconsistently implemented but are crucial to reduce delays and misrouting.[110]

- *Strategic challenges*

Modeling studies suggest that *mothership* performs acceptably in densely populated urban areas when CSCs are centrally located, while drip-and-ship strategy may still be preferable for more peripheral areas.[111,112]

I.8. Posterior Circulation Stroke and Basilar Artery Occlusion

Epidemiology and severity of BAO

Posterior circulation ischemic stroke (PCIS) refers to a neurological deficit resulting from the occlusion of one of the arteries of the vertebrobasilar (VB) system causing impaired perfusion in the brainstem, cerebellum, thalamus or occipital or parietal lobes. PCIS accounts for nearly 20% of all ischemic stroke cases, whereas BAO represents 1%. Out of all PCIS cases, BAO is reported as high as 27%, while 10% of all LVO stroke cases with a strong male predominance.[113,114] The clinical presentation of BAO is nonspecific, often with delayed onset and diagnosis leading to late treatment. Neurological symptoms range from mild diplopia, dysarthria, ataxia, paresthesia, or motor weakness to tetraplegia, hemianopia, anarthria, and impaired consciousness.[115] Poor outcomes are associated with advanced age, high baseline NIHSS score, prodromal minor stroke, longer treatment time, proximal occlusion location, prior PC stroke, and the clinical triad of depressed consciousness, tetraparesis, and pupillary abnormalities.[116] The overall morbidity and mortality rates are reported to be variable, although in case of a BAO, mortality can reach up to 90%, if left untreated.[117,118] Occlusions of the proximal and middle portions of the BA have been associated with more severe deficits and higher mortality rates compared with the occlusion of the distal one-third of the artery.[119,120] Proximal BAOs result from atherosclerotic disease, most commonly affecting older adults (sixth and seventh decades of life), while distal BAO due to embolism is more frequent in younger patients.[121,122]

Early neutral and later positive trials on BAO-EVT

Although MT is the standard of care for eligible AC strokes, high-quality evidence for PC cases has only recently become available. As noted above, two earlier trials (BASICS and BEST) failed to demonstrate superiority of EVT over best medical management.

BASICS was a randomized controlled, multicenter trial examining EVT versus standard medical care for BAO within 6 hours of stroke onset published in 2021. The primary outcome was the 90 days mRS score of 0 to 3. Symptomatic ICH within 3 days and 90-day mortality were observed as safety end-points. Outcomes did not differ significantly between the two groups, which was explained by poor recruitment and selection bias (29.2% of eligible patients were treated outside the trial, of which 79% received EVT, and 5% of the control arm patients crossed over to EVT).[68] BEST was also a multicenter RCT, based in China, EVT versus BMT for VB occlusion within 8 hours was assessed. The primary outcome was the 90 days mRS score of 0-3. The RCT was terminated early due to poor recruitment and significant crossover rates. In the intention-to-treat analysis, mRS score 0-3 at 90 days did not differ between the two groups. Although, per-protocol and as-treated analyses that accounted for crossover demonstrated more mRS score 0-3 with EVT, with similar 90-day mortality across groups.[69]

In 2022, two clinical trials have finally proven the superiority of EVT over BMT for BAO. ATTENTION, a multicenter RCT of 340 patients with BAO and NIHSS score ≥10 within 12 hours, randomized patients 2:1 to EVT plus BMT vs BMT alone. The pc-ASPECTS, a 10-point scale showing the involvement of the pons, midbrain, thalami, occipital lobes, and cerebellar hemispheres, was used for imaging selection. Primary outcomes (mRS score, 0–3 at 90 days) was found in 46% of cases with EVT versus 23% of patients on control arm. The mortality rate was also lower on the EVT arm (37% versus 55%), while higher sICH (5%) and procedural complications (14%) were reported. BAOCHE, another multicenter RCT, enrolled similar population, differing in their longer possible time window (treatment 6 to 24 hours after onset). The trial was halted early due to clear EVT superiority: mRS 0-3 was found to be 46% versus 24% in the control population, sICH rates of 6% versus 1% and mortality of 31% versus 42%.[70,71] These RCTs provide high-quality evidence to demonstrate that EVT in addition to BMT improving functional outcomes and reducing mortality in adults with a baseline mRS score of 0 to 1 presenting with an acute BAO and NIHSS score ≥10 within 24 hours of symptom onset.[123] This signifies a major advance for a clinical condition associated with very poor prognosis and limited treatment options. On the other hand, one of the important limitations of these results is that in the examined Chinese population ICAD accounts for almost half of stroke etiologies, limiting the applicability to other

populations. Additionally, due to the low recruitment rates of patients with mild symptoms (NIHSS<10), evidence remains insufficient to determine EVT effectiveness in this particular subgroup.[124]

Differences between AC and PC arteries

Anterior and posterior intracranial arteries differ in their histological structure, especially in elastin content, media thickness, and remodeling patterns. These differences may explain why atherosclerosis, stroke subtypes and aneurysms distribute differently between anterior and posterior circulation.[125,126,127]

- *Elastin content and internal elastic lamina (IEL)*

Arteries of the AC have significantly *thicker* elastin layers than those of the posterior fossa. Posterior circulation vessels therefore have a relatively thinner IEL, with less elastin content, which may endure less resistance to dilation and wall deformation processes.[125,127]

- *Media thickness and wall thickening with aging*

Posterior cranial arteries show greater wall and media thickening and more advanced aging than anterior arteries at comparable age groups. Histopathological analysis demonstrates more concentric intimal thickening and more significant loss of elastin in PC arteries, particularly in the BA.[127]

- *Plaque morphology in intracranial atherosclerosis*

The structural pattern of thicker IEL and thin or absent external elastic lamina influences how plaque components and calcification are scattered within the wall. Intracranial arterial plaques show the same basic components (fibrous cap, lipid or necrotic core, calcification, macrophage infiltration and neovascular density) as extracranial ones, but they generally lack features of complicated plaques. Low rates of intraplaque hemorrhage, neovascularization, luminal thrombus, macrophage infiltration and calcification were demonstrated. A post-mortem Chinese study found substantial heterogeneity in intracranial plaques by their location: VB arteries tended to show different plaque compositions and remodeling compared with carotid and middle cerebral arteries.[126,128] MCA and intracranial ICA plaques have been reported to be more advanced (more fibroatheromas) and had more frequent intraplaque hemorrhage and thrombus than VB lesions. The latter ones more frequently remained at an earlier stage (pathologic

intimal thickening, fibrous plaques) and showed fewer complicated plaque morphological changes. Altogether intracranial arterial wall may show a distinctive intracranial phenotype (less complicated plaques), but within the intracranial locations the differences are mostly in degree rather than morphology.[126]

- *Location of plaques and risk factors*

Anterior and posterior circulation intracranial atherosclerosis differ in plaque distribution patterns and in prevalence of traditional risk factors.[129] Intracranial ICA and MCA carry the greatest AC risk, whereas vertebral and basilar arteries are the key PC segments. In Asian populations, MCA involvement is predominant, basilar and vertebral plaques rank only behind ICA in their prevalence.[130] High resolution-MRI studies demonstrate that PC plaques are more likely to be diffusely distributed along the arterial segment (73.6% posterior vs 31.6% anterior for diffuse distribution; p=0.001).[131]Anterior-circulation plaques are more often focal, concentrated at specific high-risk regions such as the ICA syphon or M1 segment of the MCA.[132] Overall, AC ICAD tends to be a focal lesion in the intracranial ICA or MCA, while PC-ICAD dominantly involves vertebral and basilar segments with more diffuse, circumferential plaque distribution and a larger plaque burden for a given degree of angiographic stenosis.

Posterior-circulation ICAD is associated with higher age (≥54 years), male sex and hypertension compared to AC patients. Diabetes mellitus shows stronger associations with vulnerable plaque features in the posterior than in the anterior circulation.[131]

- *Remodeling behavior*

Posterior arteries, especially the BA, show more concentric intimal thickening and diffuse wall enlargement consistent with chronic positive (outward) remodeling.[127] Anterior arteries often present eccentric plaques, which might produce focal stenosis earlier for a similar plaque burden.[126]

- *Significance for stroke mechanisms (AC vs PC)*

Posterior ICAD more often relates to local branch occlusion and hemodynamic compromise in small perforator territories, while AC-ICAD more commonly causes large artery embolism to cortical branches or flow-limiting ICA or MCA stenosis.[126]

Higher prevalence of ICAD

The risk of ICAD in Asian populations (which shows heterogenity between certain nations) has been reported to be higher compared to the Caucasian population, where extracranial atherosclerosis has been more frequent. ICAD-associated stroke in Asia has been shown to be between 33% and 56.3%.[133] ICAD has been reported to be responsible for up to 10% of all strokes in the United States. The Northern Manhattan Stroke Study showed that the annual incidence of ICAD is significantly higher in the Black and Hispanic population than in white patients. At the same time, cardiovascular risk factors should also be considered when evaluating racial differences.[134] ICAD is likely the most common stroke subgroup.[135,136] LAA has been reported as the proportionally more frequent etiology in PC than in AC, whereas CE has been over-represented in AC strokes.[137,138]

The MR CLEAN Registry evaluating PC-LVO strokes also found that in patients undergoing MT, LAA was the most frequent cause in the PC, followed by CE, dissection, and embolic stroke of undetermined source (ESUS).[139] When all ischemic strokes are included (not just LVO), several large registries show that both anterior and posterior strokes share similar main TOAST categories, though the proportions shift somewhat with more LAA and less atrial fibrillation (AF)-related CE in posterior stroke cases.[140]

ICAD-Related Occlusion and Procedural Challenges

- *Mechanisms of ICAD-related occlusion*

The pathomechanism of atherosclerosis starts with endothelial involvement by fatty deposits, then continuing with complex inflammatory processes, smooth muscle and connective tissue cell migration, ending up in forming a plaque.[141] When this process is ongoing in intracranial arteries, AIS can occur by different mechanisms. The first is when local thrombosis occludes the parent artery. The second option is artery-to-artery embolisation, when a plaque fragment occludes a downstream distal artery. The third way is progressive segmental stenosis of the artery leading to reduced distal blood flow causing perfusion deficit. And lastly a side branch occlusion, when the plaque obstructs the orifice of neighbouring smaller arteries, often perforators in BAO.[142]

- *Residual stenosis and re-occlusion*

Real-world data show that basilar stenosis is an independent risk factor for poor clinical outcomes compared to BAO of embolic origin.[143] Patients with BAO due to underlying

ICAD have a lower chance of successful recanalization and profit less from successful recanalization than those of embolic cases.[144] Atherosclerosis accounts for roughly 50% of all BAO cases and a significant number of them have tandem VB lesions.[145] Meta-analytic data demonstrates that anterior and posterior circulation intraprocedural re-occlusion occurs in about one-third of ICAD cases versus patients without ICAD (<5%).[146] In a BAO-specific cohort, delayed re-occlusion (DR, within 7 days on CTA or MRA) after successful MT occurred in 10% of cases and was independently associated with poor 90-day outcome on the mRS scale (adjusted OR of 5). Absence of mTICI 3 (OR=0.2) and non-use of a stent-retriever (OR=0.29) were independently associated with DR.[147] Residual stenosis represents both a technical challenge to durable reperfusion and a biological marker for probable re-occlusion, partly explaining the high rate of futile recanalization in BAO series.[153]

- *Rescue therapies*

Randomized clinical trials have failed to demonstrate the efficacy and safety of intracranial stenting in patients with symptomatic severe intracranial atherosclerosis (ICAS), therefore we lack evidence for optimal rescue strategy for failed recanalization or imminent reocclusion of intracranial arteries in these cases.[148,149,150,151,152] Landmark trials reported a higher rate of stroke or death within 30 days on the angioplasty and stenting plus BMT arm in the SAMMPRIS trial compared to the conservative arm.[168,153,154,155] Patients with ICAD related LVO were found to have longer procedure times, lower recanalization rates, and higher probability of reocclusion than those with embolic origin.[156] Observational and meta-analytic data suggest that in ICAD-related LVO intra-arterial glycoprotein (GP) IIb/IIIa inhibitors, balloon angioplasty and intracranial stenting can contribute to revascularization and improve outcomes comparable to non-ICAD cases, despite higher intraprocedural complication rates.[157,146] A systematic review of rescue therapies for ICAD-based LVO highlighted that balloon angioplasty plus tirofiban achieved high successful recanalization (approximately 87%) and acceptable rates of good functional outcome, supporting a strategy of aggressive vessel-modifying rescue treatment in selected residual-stenosis cases.[157]

BAO due to ICAD requires more complex interventional therapy, usually including stenting, and has been shown in recent studies to be associated with a worse outcome than embolic patients.[158,159] In VB ICAD cases more broadly, recent publications emphasize

that angioplasty and stenting are effective but carry significant periprocedural risk, therefore they advocate careful patient selection, meticulous periprocedural antithrombotic management and long-term risk factor control to prevent restenosis and re-occlusion.[160] Successful vessel recanalization is the key for improving the treatment outcomes of stroke, therefore different approaches attempt to reach durable arterial patency by the end of the intervention.[161]

1. Glycoprotein IIb/IIIa receptor inhibitor infusion

Tirofiban, eptifibatide and abciximab are the three GPIIb/IIIa inhibitors approved by the Food and Drug Administration.[162] Regarding recommendations for their use, including route of administration, dosage and duration in ICAD related LVO stroke events, we lack large RCTs, therefore high level evidence as well. In retrospective studies, results are controversial: some report no association with increased risk of hemorrhage, 3-month mortality or improved outcome, others report excellent outcomes, without an increased risk of intracranial hemorrhage. The association seems stronger in patients with severe stroke (NIHSS>5) and AC stroke.[163] Overall, hemorrhagic transformation is very uncommon in patients with PC stroke, and the use of tirofiban in this patient population is generally reported to be safe.[164] ICAD-related stroke patients may be even less prone to ICH due to the previous formation of collaterals, therefore ischemic preconditioning over time, resulting in a generally smaller infarct core compared to patients with other etiologies of LVO.

2. Balloon angioplasty only

To date, no RCTs have addressed this question. Only a few retrospective studies have evaluated patients treated with balloon angioplasty alone or balloon angioplasty combined with tirofiban for residual severe intracranial stenosis after successful clot removal, and their findings have been inconsistent.[165,166,167] The rationale behind avoiding stent implantation and try to reach luminal reconstruction with a balloon in the acute phase of AIS is to avoid the increased risk of hemorrhage caused by dual antiplatelet therapy (DAPT) and the in-stent thrombosis risk due to a lack of adequate preprocedural antiplatelet effect.[168] Therefore some authors propose balloon angioplasty first in case of a severe residual stenosis,[169] while others suggest that balloon angioplasty may lead to further intimal injury and increase the risk of vessel rupture, arterial re-stenosis, or reocclusion, occlusion of perforators and may be less durable than stenting.[189]

3. Rescue stenting for failed MT

Maingard et al. published a meta-analysis of 530 patient data from 2019 reporting that rescue stenting after failed MT results in significantly improved clinical outcomes compared with cases without stenting, without an increase in the rate of sICH, despite any additional use of antiplatelet drugs.[170] The SAINT trial has been the largest, though retrospective study of 499 patients, comparing the effect of rescue stenting, when recanalization attempts failed, to unsuccessful recanalization cases (mTICI 0–1). The stenting group proved to achieve higher rates of independence (35.1% vs. 7%; adjusted odds ratio [aOR], 6.33 [95% CI, 3.14–12.76]; $p < 0.001$) and lower mortality (28% vs. 46.5%; aOR, 0.55 [95% CI, 0.31–0.96]; $p = 0.04$) at 90 days. The number of sICH were comparable within groups (7.1% vs. 10.2%; aOR, 0.99 [95% CI, 0.42–2.34]; $p = 0.98$).[171] A subgroup analysis of the ANGEL-ACT prospective registry investigated the outcomes of rescue stenting in failed BA MT cases: 87.1% of the included 93 patients received rescue stenting with a 92.6% recanalization rate. Compared with the cases who did not receive rescue stenting, the stenting group had a higher rate of favorable 90 days clinical outcomes (mRS, 0–3: 16.7 vs. 51.9%; $p = 0.023$), a significantly lower mortality rate (58.3 vs. 18.5%; $p = 0.006$) and comparable rate of sICH. The most important independent predictors of poor outcome after rescue stenting were high NIHSS score (aOR 1.10; $p = 0.002$) and a low mTICI score after stenting (aOR 23.24; $p < 0.001$).[172]

4. Emergent stenting of ICAD after successful recanalization

Strong evidence supporting emergent stenting after successful MT is not available, as the data are limited to case series and cohort studies. In a meta-analysis, published by Li et al., among 1315 pooled patients, 261 underwent emergent stenting due to residual stenosis after MT. The successful recanalization rate was 88% (95% CI 84–92%), the rate of favorable outcomes was 52% (95% CI, 47–56%), with low rate of sICH (5%) and mortality (15%).[173]

- *Antiplatelet strategies*

Five RCTs were published to investigate the questions of different therapeutic approaches when symptomatic intracranial stenosis occurs. None of the CAVATAS, SAMMPRIS, VISSIT, VAST and VIST trials managed to demonstrate that interventional therapy would offer clinical outcome benefit over medical therapy alone. BMT remains the primary choice of treatment, consisting of aspirin and clopidogrel administered for

3 months.[174] In the SAMMPRIS trial, patients with BA stenosis accounted for 22.3% of the intervention group and BA stenting was reported to have a higher risk of periprocedural ischemic stroke (20.8% BA vs. 6.7% non-BA) compared to other vascular territories. There is no consensus regarding the management of patients with symptomatic ICAD, however, the affected patients who fail antithrombotic therapy have very high rates of recurrent TIA, stroke or death.[175,176]

Overall, we still lack high quality evidence on medical therapy too for symptomatic ICAD related BAO stroke cases, and there is still no consensus regarding the optimal antiplatelet drug of choice and its duration in such conditions. In a large interventional survey on current practices for patients with BAO due to ICAD, neurointerventionalists were intending to proceed to stenting, but there was no consensus on the choice of antiplatelet therapy before or after stenting. Most of them (92.3%) answered to use DAPT, and the most common DAPT choices were aspirin and clopidogrel or aspirin and a GPIIb/IIIa inhibitor. Further study is needed to understand the optimal antiplatelet regimen in the setting of acute stenting.[177] A potential periprocedural antiplatelet strategy for ICAD-related BAO stenting is loading with DAPT (aspirin plus clopidogrel) before or immediately after the procedure, followed by continuation of dual therapy for at least 3 months and subsequent long-term single antiplatelet therapy. There are also bridging strategies with GP IIb/IIIa inhibitors when oral DAPT is not yet active: iv. or intraarterial (ia.) tirofiban before, during, or immediately after stenting to prevent re-occlusion.

- *Ongoing trials addressing controversy*

Overall, BAO patients with underlying ICAD show lower technical success rate, less probability of good neurological outcome and higher intraprocedural and delayed re-occlusion of the treated artery.[178] In BAO studies, *first-pass angiographic success* (mTICI 2b-3) is one of the few treatment-related predictors of good outcome, due to possible endothelial injury and clot fragmentation leading to re-occlusion.[179]

Many questions are unsettled though: optimal thresholds for intervening on residual basilar stenosis (50, 70, or 90% with or without distal flow pattern assessment), the best rescue modality (GPIIb/IIIa alone, angioplasty, stenting or their combinations, type of stent) and optimal periprocedural antiplatelet therapy remain unsettled. Our current evidence is largely retrospective and heterogeneous, no RCT has yet specifically addressed rescue strategies in ICAD-related LVO cases. Available randomized data are

either: PC-EVT versus BMT (data including non-ICAD cases), or ICAD-related LVO in general (both AC and PC) or non-hyperacute intracranial stenosis.

The ANGEL-REBOOT multicenter, prospective RCT, published in 2024, randomized 348 patients with failed (eTICI 0–2a) or suboptimal (residual stenosis >70%) EVT to either bailout angioplasty or stenting versus no bailout intervention. This trial included mainly AC-LVO cases and was not restricted to BAO. In both treatment groups, tirofiban was used in the majority of cases. The median age of patients was 63 years, 74% were male, all participants were Chinese. There was no difference in the primary outcome (mRS score at 90 days) and the mortality rate was similar between the two groups (11% *vs* 10%). The interventional arm showed a higher risk of sICH and procedure-related arterial dissection. Overall, authors concluded that bailout angioplasty or stenting with this approach did not improve clinical outcome at 90 days, and caused more complications compared with standard therapy after unsuccessful recanalisation or when at risk of reocclusion after MT.[180] The IntraCranial Atherosclerosis Related Large-Vessel Occlusion Treated With Urgent Stenting (ICARUS) trial is an ongoing, prospective, international, multicenter randomized controlled study designed to evaluate the impact of early intracranial stenting on long-term clinical outcomes in patients with ICAD-related LVO. A total of 296 patients are planned to be randomized to either early intracranial stenting or conventional EVT, which may include additional stent-retriever or aspiration passes, intra-arterial antiplatelet administration, or termination of the procedure.[181] Angioplasty and/or stenting following successful mechanical thrombectomy for intracranial atherosclerosis-related emergent large vessel occlusive stroke (ASSET) is an ongoing, multicenter, prospective, randomised, open-label, blinded end-point, controlled clinical trial, evaluating the effectiveness and the safety of emergency balloon angioplasty and/or stenting in combination with BMT compared with BMT alone in ICAS-LVO stroke patients with successful recanalisation.[182]

In summary, there has been growing number of randomized data published about EVT versus BMT in BAO, about tirofiban or bailout angioplasty in LVO generally, but there is still no dedicated, adequately powered RCT that directly answers crucial questions on optimal rescue therapies in ICAD related BAO. The ICARUS and ASSET trials' results are expected to fill some of these knowledge gaps.

II. Objectives

II.1. Primary Objectives

1. The impact of direct transport to EVT-capable centers

Our first objective was to examine the effect of the mothership concept on clinical outcome in urban areas — especially in patients eligible for both IVT and MT.

2. The role of rescue stenting in ICAD-related BAO

Thrombectomy in the PC is more prone to complications than in the AC, possibly due to the higher prevalence of ICAD in the posterior fossa as well as in cases of BAOs. The aim of our study was to analyse the effect of rescue stenting with high radial force coronary stent implantation in acute BAO with underlying stenosis on clinical outcome.

II.2. Secondary Objectives

Our secondary aims were to assess safety outcomes by transport paradigms and after rescue stenting, as well as to detect subgroup specificities and predictors of good clinical outcome.

III. Methods

III.1. Ethical approval

All procedures, including investigations, diagnostics, and treatments, were conducted in accordance with the Declaration of Helsinki and were approved by the institutional ethics committees of the National Institute of Clinical Neurosciences and Semmelweis University.

III.2. Study I: Direct Transport

Study setting, prehospital routing structure and patient selection for MT[197]

The *Central Hungarian Endovascular Stroke Registry* is a prospectively maintained regional database that includes all consecutive patients treated with MT for AIS in the Central Hungarian Region. In this area, a single CSC, the Department of Neurosurgery and Neurointervention of Semmelweis University (known as the National Institute of Clinical Neurosciences until January 2021, then as the National Institute of Mental Health, Neurology, and Neurosurgery until March 2024) provides all endovascular interventions for 11 PSCs, accepting additional referrals from neighboring areas as well. The present study was based on this registry, covering the period from January 2015 to December 2022. The analysis focused on the urban core of the Central Hungarian Region, defined as the area within a 60-minute ground transport radius of the CSC and comprising approximately 1.7 million inhabitants. The 60-minute threshold was selected based on the longest direct transport referral observed during the study period, in order to ensure a fair comparison between transport strategies. The catchment area was delineated using geospatial network analysis in QGIS version 3.x (QGIS Development Team, Open-Source Geospatial Foundation) with the ETRS89/EOV coordinate reference system (EPSG:23700). Input data were obtained from the Hungarian Central Statistical Office and OpenStreetMap. A 60-minute isochrone polygon representing the Monday 09:00 a.m. traffic conditions was generated and intersected with administrative boundaries to define the metropolitan service area (Figure 2A).

Emergency medical services and interhospital transfers were organized by the National Ambulance Service, a nationwide public provider operating under standardized, stroke-focused triage protocols. Hungary's publicly financed healthcare system offers universal coverage and full reimbursement for acute stroke care, which reduces socioeconomic disparities and supports comprehensive identification of stroke cases. Decisions regarding

whether patients with suspected LVO stroke should be transported directly to the CSC were made collaboratively by paramedics and the in-hospital stroke neurologist at the CSC. The RACE score was used by paramedics as a referral tool; however, no strict cutoff value was predefined, and any patient presenting with disabling neurological symptoms could be considered eligible for direct transfer. Patients with suspected ICH, such as those with gradually worsening symptoms, headache, or contralateral gaze deviation, were preferentially transported to the nearest hospital rather than to the CSC.

Patient selection for MT adhered to contemporary international guidelines in effect at the time of treatment. Prior to the publication of late time-window MT trials, patients presenting beyond 6 hours from symptom onset were treated if neuroimaging demonstrated a favorable profile, defined as an ASPECTS of at least 6. All patients with emergent LVO, premorbid mRS score 0–2, and an anticipated life expectancy greater than 6 months were considered eligible for MT. Posterior-circulation AISs were treated at the discretion of the neurointerventionalist. Patients with extensive early ischemic changes were only rarely selected for MT. Futile transfers were documented at the CSC in a dedicated log, which contained limited clinical information and focused primarily on the reasons for withholding thrombectomy.

Procedural techniques were adapted over time in line with advances in endovascular stroke therapy. In the early phase, MT was performed using stent-retriever devices (*Solitaire AB*, Medtronic, Irvine, CA, USA; or *Trevo*, Stryker Neurovascular, Fremont, CA, USA), in combination with proximal balloon-guide catheters for flow reversal using the *Cello* Balloon Guide Catheter (Medtronic, Irvine, CA, USA). Following publication of the results of ASTER trial, direct aspiration as a first-line approach became common practice in our center and was typically performed with the Sofia Aspiration Catheter (MicroVention, Aliso Viejo, CA, USA). Combined ("Solumbra") techniques, involving simultaneous distal aspiration and stent-retriever thrombectomy, were used at the discretion of the operator based on angiographic findings. In cases where ICAD or residual stenosis led to persistent vessel occlusion, rescue angioplasty or stenting was undertaken to achieve durable reperfusion. Periprocedural antiplatelet and anticoagulation regimens were individualized according to patient-specific risk profiles and institutional safety standards.

Outcome measures

Primary outcome was the functional outcome assessed at 90 days using the mRS, evaluated by certified stroke neurologists during outpatient visits or, when in-person assessment was not feasible, via structured telephone interviews. An mRS score of 0–2 was defined as functional independence and corresponded to a good clinical outcome, consistent with contemporary stroke trials. Vital status was ascertained through linkage with the National Health Insurance Fund of Hungary (NEAK), which provides complete nationwide health and mortality data.

Post-procedural ICH, evaluated as a secondary outcome, were classified according to the Heidelberg Bleeding Classification, distinguishing hemorrhagic infarction (HI1–HI2), parenchymal hematoma (PH1–PH2), and remote or extra-parenchymal hemorrhages (parenchymal, intraventricular, subarachnoid, subdural). Symptomatic ICH was defined as PH2 associated with a neurological worsening of more than 4 points on the NIHSS. All imaging was reviewed by expert radiologists in our CSC, based on 24-hour follow-up CT or MRI scans.

Symptom onset-to-admission time was defined as the interval between symptom onset (or last-known-well) and arrival at the CSC. The rate of reperfusion was evaluated on the final angiographic run using the mTICI scale, with successful reperfusion defined as mTICI 2b–3.

Statistical analysis

Continuous variables were summarized as medians with interquartile ranges, and categorical variables as counts with corresponding percentages. Between-group differences were assessed using the Mann–Whitney U test for continuous variables and the χ^2 test or Fisher's exact test, as appropriate, for categorical variables.

To evaluate whether primary transport independently predicted a favorable functional outcome (defined as mRS $\leq$2 at 90 days), we constructed a multivariable logistic regression model including age ($\geq$75 years), NIHSS ($\geq$6), sex, major comorbidities (hypertension, diabetes, atrial fibrillation, coronary and peripheral artery disease, hyperlipidaemia, malignancy), stroke territory, successful reperfusion (mTICI 2b–3), and use of IVT. Transport modality (primary vs secondary) was forced into all models as the main exposure variable. Covariates were retained in the final model according to their contribution to minimizing the Akaike Information Criterion (AIC). Missing covariate

data were imputed using subgroup-specific median values. As a sensitivity analysis, we performed 1:1 propensity score matching using nearest-neighbor matching without replacement, with a caliper of 0.2 standard deviations of the logit of the propensity score. The propensity model included baseline demographic and clinical characteristics as well as IVT use. Covariate balance after matching was evaluated using standardized mean differences.

Survival time was measured from the date of MT to death or last known follow-up; in surviving patients, follow-up was censored at the time of data extraction from the NEAK database. Kaplan–Meier methods were used to estimate cumulative survival, and inter-group differences were compared using the log-rank test. Among patients treated with combined IVT and MT, independent predictors of long-term mortality were examined using Cox proportional-hazards regression with AIC-based stepwise variable selection. The proportional-hazards assumption was verified both graphically and by inspection of Schoenfeld residuals. Results are reported as odds ratios (ORs) or hazard ratios (HRs) with 95% confidence intervals (CIs). Analyses were performed in Python 3.11 (Statsmodels v0.14, Lifelines v0.28) and cross-validated in R (survival and rms packages, version 3.5). Figures were generated using GraphPad Prism. Two-tailed $p < 0.05$ was considered statistically significant.

III.3 Study II: Basilar Occlusion and Rescue Stenting [183]

We retrospectively analyzed the data of our prospectively collected institutional stroke register in the National Institute of Clinical Neurosciences (former name, now Semmelweis University, Department of Neurosurgery and Neurointervention), a large volume, CSC with a catchment area of about 3 million inhabitants. We selected patients treated with BAO related stroke (Table 3). All included subjects were treated with MT over a 5 years' time period. We compared the characteristics of our stroke patients with or without ICAS involving the BA. Within the underlying stenosis-related occlusion group, we compared the cases treated by coronary stent implantation with conservatively treated patients allowing only MT and balloon dilatation in some cases in the latter group.

Inclusion criteria and procedural techniques

After neurological examination, BAO had to be confirmed by non-invasive imaging (either CTA or MRA). Patients within 12 hours from symptom onset were examined with CT and proceeded to MT if imaging did not indicate extensive ischemic hypodensity or

ICH. Beyond 12 hours of symptom onset and cases with unknown onset of symptoms were evaluated by MRI: a confirmed Diffusion Weighted Imaging (DWI) – Fluid Attenuated Inversion Recovery (FLAIR) mismatch in eloquent brain regions made patients eligible for EVT in this subgroup. All suitable patients for IVT received rtPA before MT.

Standard protocols for MT included using a balloon-guide catheter (*Cello* 8F, EV3 INC., Irvine, CA, USA), Trevo Pro 18" microcatheters (Stryker Neurovascular INC, Minneapolis, MN, USA) with dedicated intracranial Transend 14" microwires and three different types of commercially available stent retrievers: *Solitaire* (Medtronic INC, Dublin, Ireland), *Trevo* (Stryker Neurovascular INC, Minneapolis, MN, USA) and *Preset* (Phenox, Bochum, Germany). Five fully trained and experienced neurointerventional specialists performed the interventions, with a case number per operator of more than 30 MT per year. Direct aspiration first using the *Sofia* and *Sofia Plus* aspiration catheters (Microvention Terumo INC, Aliso Viejo, CA, USA) was chosen only in selected cases during the last two years of the study period. The vast majority of interventions were executed under general anesthesia.

Coronary stent implantation was applied for the subgroup of BAO patients with previously occluded, significant stenosis of the BA. Indication for stenting was left to the operator's decision. Significant stenosis was assessed upon DSA images: occlusion-underlying stenosis was defined as 50% or greater luminal narrowing at the site of the occlusion following MT, with the stenotic lesion persisting after ia. administration of 1 mg nimodipine through the guiding catheter (Figure 1).

As dedicated intracranial stents had questionable efficacy and had no indication for intracranial angioplasty, we decided to use bare metal coronary stents (BMS) (*Omega*, Boston Scientific INC, Marlborough, MA, USA) in our cohort. Upon deployment, stents were undersized by 0.5 mm to the distal reference diameter of the BA in order to prevent edge dissection, and the intended final diameter was reached by over-dilatation of the stent under roadmap control applying pressures defined on the device's label.

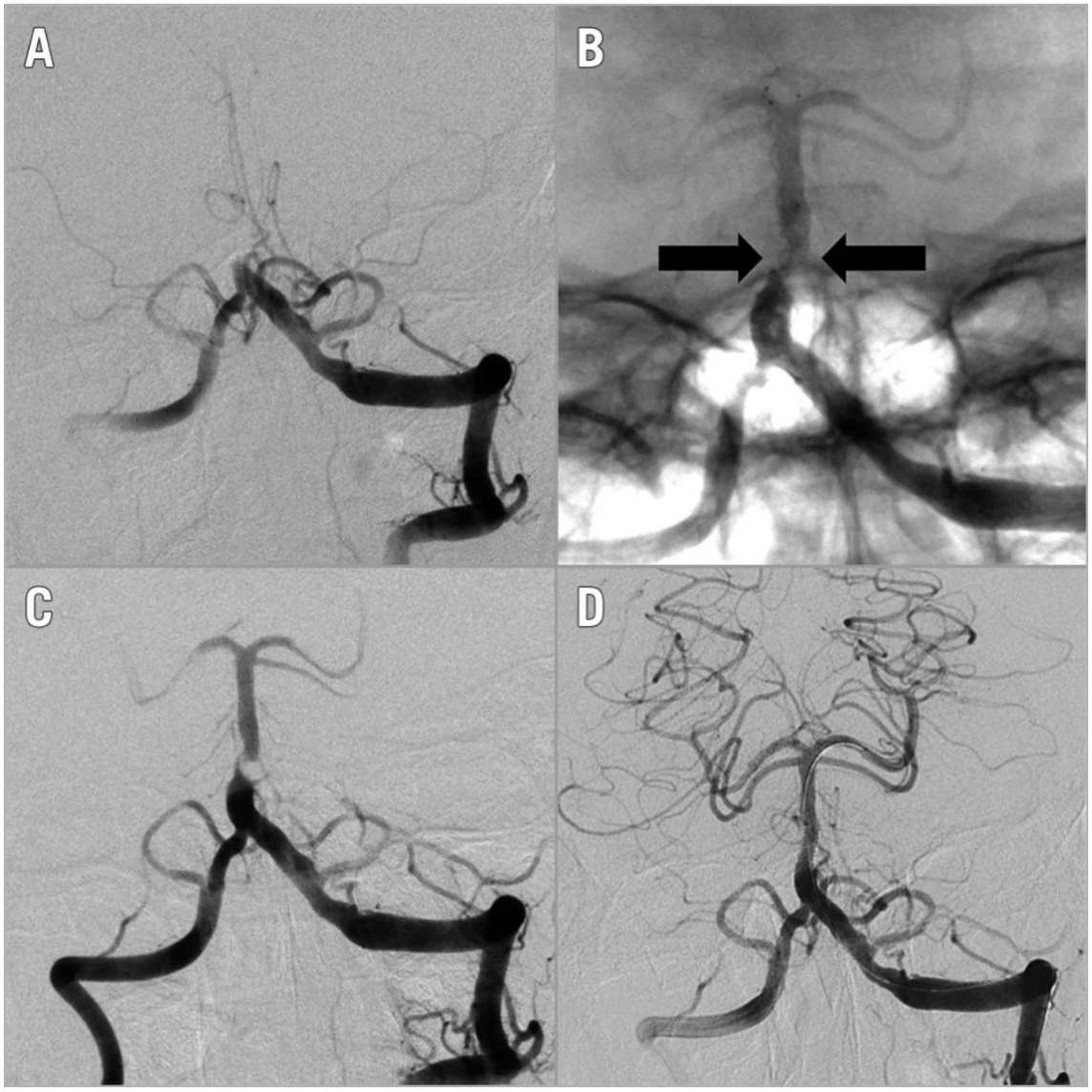


Figure 1. Stenting of the BA: Left vertebral angiogram proving BAO (A) with the deployed self-expandable stent retriever compressed (arrows) at the level of the occlusion (B), due to a flow limiting, high-grade stenosis (C). Successful recanalization of the occluded segment after balloon-expandable coronary stent implantation (D).[183]

Antiplatelet protocols

Patients having undergone BMS implantation received iv. unfractionated-heparin (UFH, 70 IU/kg) and iv. Aspirin (500 mg) perioperatively. If IVT was given prior to treatment, only additional Aspirin was given during the procedure. If the postoperative CT scan excluded intracranial hemorrhage, additional loading dose of clopidogrel (300 mg) was administered via a nasogastric tube. Those without stenting received secondary prevention therapy according to the current guidelines[51] without confirmed indication for anticoagulation, they were given Aspirin monotherapy and prophylactic LMWH. If large

ischemic lesion or hemorrhage was detected by the control imaging, the anti-thrombotic therapy was withheld according to recommendations.

Outcome definitions

Clinical outcome was evaluated on the mRS 90 days after treatment by certified stroke neurologists during outpatient visits. When subjects were unable to attend the outpatient clinic, mRS scores were assessed by telephone interviews. The long-term all-cause mortality data was acquired from the database of the National Health Insurance. Intracranial hemorrhages were classified according to the ECASS (European Cooperative Acute Stroke Study) II system[184]. The symptom onset-to-reperfusion time was defined as the interval between the onset of the AIS symptoms and the time of the DSA run following the last procedural step of MT. If the time of symptom onset was unknown, the time point the patient was last seen without symptoms was acknowledged as onset. Basilar artery angiography was performed from at least two perpendicular angles, as per protocol an antero-posterior and a lateral view. Arterial diameters and stenoses were quantified by a computerized analysis system (Advantage Workstation 4.6, General Electric, Chicago, Il, USA) on DSA images. Diameters at the level of the stenosis and at reference vessel segments distal to the lesion, as well as the grade of stenoses (%) were measured before and after angioplasty. The rate of achieved reperfusion was evaluated on the final angiogram by the operators using the mTICI scale. Successful reperfusion was defined as an mTICI grade of 2b-3.[185]

Statistical modelling

Baseline statistics for continuous measures were given as the *mean* with standard deviation or as the *median* with minimum and maximum values. For discrete data count (n/n) and percentages (%) were equally tabulated. Mann-Whitney's U test and Fisher's exact test, as appropriate, were used to compare clinical and imaging findings of the different patient cohorts. Survival probabilities were estimated by the Kaplan–Meier method, differences were evaluated by the Log-rank test. All tests were two-tailed with a CI of 95%, statistical significance was confirmed when p values were calculated to be <0.05. Statistical analyses were performed using the GraphPad Prism 6. Software (GraphPad Software Inc, San Diego, CA, USA).

IV. Results

IV.1 Direct Transport[197]

Baseline characteristics of the study population

Over the 7-year study period, 2,795 patients underwent EVT for emergent LVO within the Central Hungarian Region. Of these, 778 patients were referred from outside the 60-minute ground transport radius of the CSC and were therefore excluded from the present analysis. The remaining 2,017 patients, all residing within the densely populated urban inner catchment area, comprised the study cohort. Patients directly transported to the CSC represented 12% (242/2017) of our cohort (primary transfer group), whereas 88% (1775/2017) initially presented to one of the PSCs and were secondarily transferred to the CSC after confirmation of LVO, constituting the secondary transfer group.

The median onset-to-admission time was 101 minutes (range 7–1,071) in the primary transfer group and 240 minutes (range 40–1,411) in the secondary transfer group ($p < 0.0001$), demonstrating substantial difference between the two paradigms. The mean estimated travel distance from the referral site to the CSC was 13.2 km (interquartile range, IQR: 7-19 km) for the direct transfers, and 11.2 km (IQR 7–16,5 km) for secondary transfers, showing no significant difference between transfer strategies in this regard ($p = 0.28$) (Figure 2B).

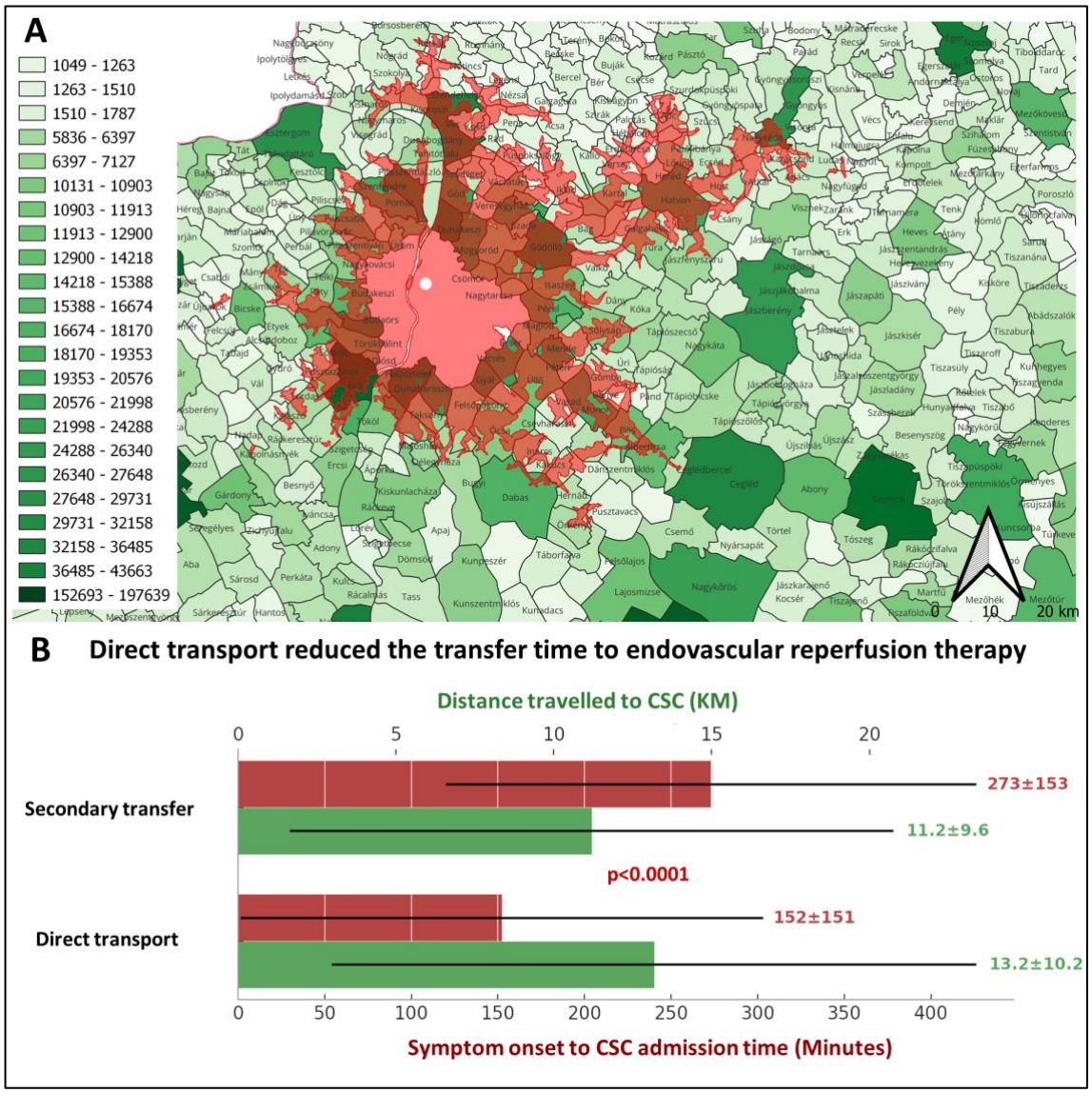


Figure 2A: Our analysis focused on the urban core of the Central Hungarian Region, defined as the area within a 60-minute ground transport radius of the CSC on a weekday (Monday) 9 am traffic conditions. The darker the color, the longer the transport time. **2B:** The mean onset-to-admission time was 152 minutes in the primary transfer group and 273 minutes in the secondary transfer group ($p < 0.0001$). The mean estimated travel distance from the referral site to the CSC was 13.2 km for the direct transfers, and 11.2 km for secondary transfers, showing no significant difference between transfer strategies ($p = 0.28$).[197] The color scales on the top left are marking population density (people/km^2).

The proportion of futile transfers, defined as patients referred for MT who ultimately did not undergo the procedure, therefore they were excluded from the study, was significantly higher in the direct transport group (32.96%, 119/361) compared with the secondary transfer cohort (23.62%, 549/2,324; $p = 0.0002$). The overall incidence of ICH on

admission to the CSC was 3.44% (23/668), with no significant difference between transfer strategies.

Most futile transfers were attributable to extensive early ischemic changes in the affected vascular territory. Additional reasons included spontaneous recanalization of the target vessel (15.71%, 105/668) and distal embolic migration of the occluding thrombus (21.26%, 142/668). In the direct transport subgroup, 53 patients received IVT alone upon arrival at the CSC without proceeding to thrombectomy.

Table 1. presents baseline characteristics of the study cohort. The primary and secondary transfer groups were broadly similar with respect to demographic, clinical, and angiographic parameters. Patients in the primary transfer group were slightly older than those in the secondary group (median 71 years range 16–95 vs 69 years range 10–99; $p = 0.044$), whereas stroke severity at admission was comparable (median NIHSS 15 in both groups; $p = 0.70$). The proportion of female patients did not differ significantly between groups (52% vs 49%; $p = 0.37$). The prevalence of vascular risk factors and comorbid conditions was comparable between the two groups. Posterior circulation occlusions were observed in 7.9% of patients in the primary transfer group and 11.3% of those in the secondary transfer group ($p = 0.12$). Carotid tandem lesions occurred in 15.3% and 17.3% of cases, respectively ($p = 0.47$). Successful reperfusion, defined as mTICI 2b–3, was achieved in 90.3% of primary transfer cases and 87.9% of secondary transfer cases ($p = 0.34$). A notable difference between groups was the significantly higher rate of IVT among secondary transfer patients (55.2% vs 45.5%; $p = 0.0048$). The 90-day functional outcome data were available for 75.6% of patients in the primary transfer group and 72.2% of those in the secondary transfer group ($p = 0.27$), indicating comparable completeness of short-term follow-up. One-year mortality status was ascertained in 98.8% of primary and 97.2% of secondary transfer patients ($p = 0.20$), providing a robust basis for long-term survival analyses. Overall, the two groups were well matched with respect to baseline clinical and angiographic characteristics, and follow-up completeness, supporting the validity of subsequent outcome comparisons.

Table 1. Baseline characteristics of patients			
Demographics			
	Direct Transport **n=242** (12%)	**Secondary Transfer** **n=1775** (88%)	**p=**
Age *Median (min, max)*	**71** **(16- 95)**	**69** **(10-99)**	**0.0444**
Female sex	52 % n=126	49 % n=868	0.3733
NIHSS on admission *Median (min, max)*	15 (1-37)	15 (0-43)	0.6978
Prehospital			
Onset to admission in minutes *Median (min, max)*	**101** **(7-1071)**	**240** **(40-1411)**	**<0.0001**
Co-morbidities			
Atrial Fibrillation	40.08% n=97	34.29% n=612	0.0846
Hypertension	75.62% n=183	77.24% n=1554	0.5691
Diabetes	24.38% n=59	24.90% n=442	0.6978
Hyperlipidemia	50.00% n=121	44.28% n=786	0.0985
Coronary artery disease	21.49% n=52	20.56% n=365	0.7354
Lower extremity PAD	8.68% n=21	10.31% n=183	0.4956
Malignancy	8.26% n=20	10.82% n=192	0.2637
Previous Stroke	14.88% n=36	13.41% n=238	0.5483
Angiographic findings			
Posterior circulation LVOs	7.85% n=19	11.32% n=201	0.1231
Carotid artery tandem lesions	15.29% n=37	17.30% n=307	0.4673
Reperfusion therapy			
mTICI 2b-3 grade reperfusion	90.34% n=215	87.89% n=1560	0.3354
IVT use	**45.45% n=110**	**55.15% n=979**	**0.0048**
Follow up			
Availability of 90 days mRS follow up	75.62% n=183	72.17% n=1281	0.2825
Availability of 12 months survival data	98.76% n=239	97.24% n=1726	0.1971

Outcome measures

A good functional outcome at 90 days was achieved in 50.3% of patients in the primary transfer group compared with 40.4% in the secondary transfer group, demonstrating significant difference between the groups ($p = 0.015$). This favorable shift across the full mRS spectrum indicates a consistent reduction in post-stroke disability among patients directly transported to the CSC (Figure 3).

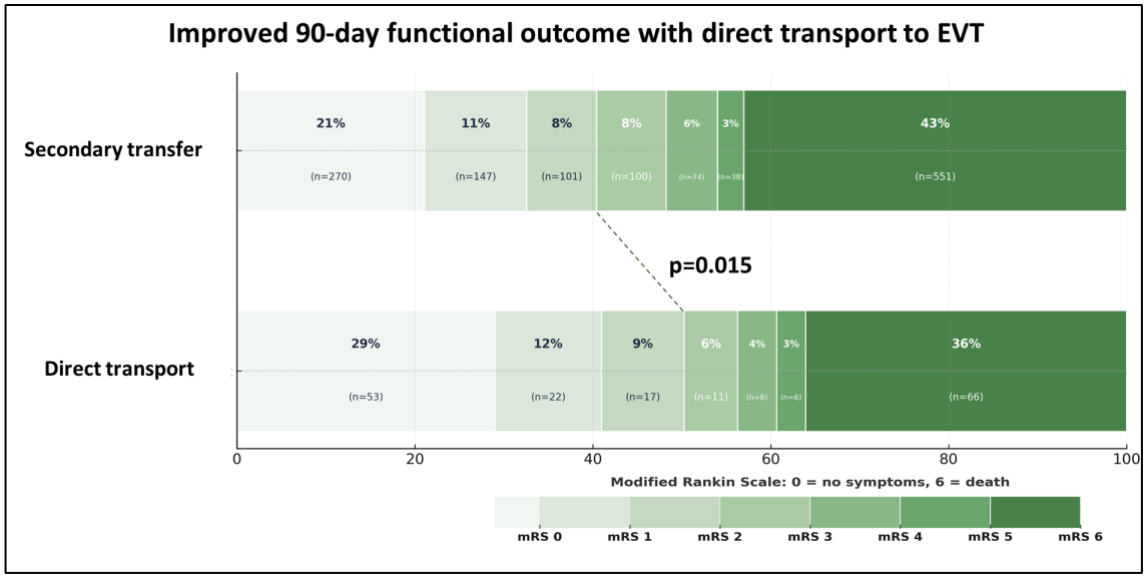


Figure 3. A good functional outcome at 90 days was achieved in 50.3% of patients in the primary transfer group compared with 40.4% in the secondary transfer group, showing significant difference between the two groups ($p = 0.015$).[197]

In a sensitivity analysis using 1:1 propensity score matching, all 242 patients who were directly transported for EVT were successfully matched to 242 secondary-transfer patients, achieving substantially improved baseline covariate balance. In this matched cohort, direct transfer remained significantly associated with higher odds of a good functional outcome at 90 days (OR 1.72, 95% CI 1.12–2.63; p = 0.013), supporting the robustness of the primary analysis. Among patients treated with IVT as well, good functional outcome occurred significantly more frequently after primary transfer (p = 0.046).

In multivariable logistic regression, adjusting for major comorbidities, age ≥ 75 years, baseline stroke severity (NIHSS ≥ 6), use of IVT, and posterior circulation stroke

location, primary transfer remained an independent predictor of favorable functional outcome (OR 1.74, 95% CI 1.25–2.42; p = 0.0011).

Hemorrhagic transformation patterns were similar between the two transfer groups (Table 2). Hemorrhagic infarction (HI1–HI2) occurred in 11.2% of patients in the primary transfer group and 14.7% in the secondary transfer group (p = 0.36), findings that are more consistent with the natural course of LVO stroke than with treatment-related complications. Parenchymal hematoma was infrequent, with no significant differences between groups: PH1 occurred in 2.9% vs 5.0% and PH2 in 3.3% vs 3.7% of primary and secondary transfers, respectively (both p > 0.19 and > 0.99). Subarachnoid hemorrhage, typically representing a small, angiographically visible but clinically mild consequence of MT, was observed in 7.9% vs 8.2% of cases (p > 0.99). Other bleeding patterns, including remote parenchymal, intraventricular, and subdural hemorrhage, were rare and evenly distributed between the two groups (Figure 4).

A modest increase in the overall rate of ICH was observed in the secondary transfer group compared with the primary transfer group (28.3% vs 21.9%; p = 0.038), likely attributable to the higher use of IVT in this cohort (55.1% vs 45.5%). Among patients who received both IVT and EVT, however, rates of any ICH, including all subtypes, no longer differed significantly between transfer strategies, suggesting that the excess hemorrhage was driven by treatment modality rather than by transport paradigms.

Table 2. Intra-cranial bleeding complications			
	Direct Transport	**Secondary Transfer**	**p=**
Heidelberg class 1a: **Hemorrhagic Infarction 1** *(Scattered small petechiae. no mass effect)*	5.37% n=13	6.87% n=122	0.4920
Heidelberg class 1b: **Hemorrhagic Infarction 2** *(Confluent petechiae. no mass effect)*	5.79% n= 14	7.77% n=138	0.3014
Heidelberg class 1C: **Parenchymal Hematoma 1** *(Hematoma within infarcted tissue, occupying <30%, no substantive mass effect)*	2.89% n= 7	5.01% n= 89	0.1957
Heidelberg class 2: **Parenchymal Hematoma 2** *(Hematoma occupying 30% or more of the infarc ted tissue. with obvious mass effect)*	3.31% n=8	3.66% n=65	>0.9999
Heidelberg class 3a: **Remote Hematoma** *(Parenchymal hematoma remote from infarcted brain tissue)*	0.41% n=1	0.11% n=2	0.3186
Heidelberg class 3b: **Intraventricular hemorrhage**	0.83% n=2	2.48% n=44	0.1630
Heidelberg class 3c: **Subarachnoid hemorrhage**	7.85% n=19	8.17% n=145	>0.9999
Heidelberg class 3d: **Subdural hemorrhage**	0.00% % n=0	0.06% % n=1	>0.9999
Any Intra-Cranial bleed (cumulative # and %)	**21.90% n= 53**	**28.28% n= 502**	**0.0383***

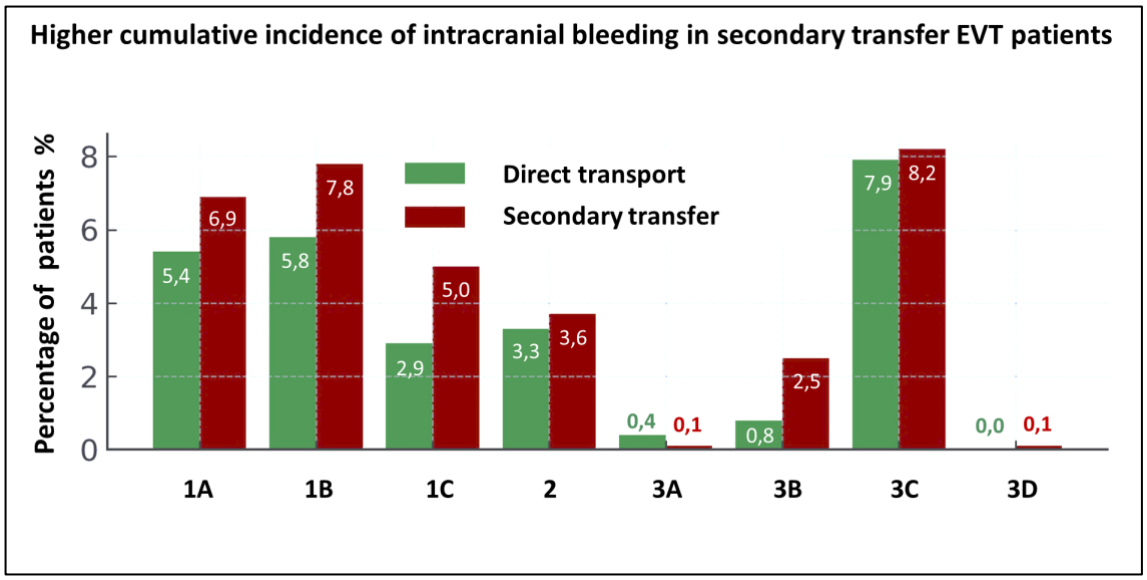


Figure 4. Hemorrhagic infarction 1 and 2 (1A, 1B) occurred in 11.2% of patients in the primary transfer group and 14.7% in the secondary transfer group (p = 0.36). Parenchymal hematoma (1C, 2) was infrequent, with no significant differences between groups: PH1 occurred in 2.9% vs 5.0% and PH2 in 3.3% vs 3.7% of primary and secondary transfers, respectively (both p > 0.19 and > 0.99). Subarachnoid hemorrhage (3C) was observed in 7.9% vs 8.2% of cases (p > 0.99). Other bleeding patterns, including remote parenchymal (3A), intraventricular (3B), and subdural hemorrhage (3D), were rare and evenly distributed between the two groups.[197]

Due to the observed differences in IVT use and the corresponding variation in ICH rates, the impact of transfer strategy on survival was further explored in a data-driven subgroup analysis restricted to patients who received both IVT and EVT (n = 1,110). In this subgroup of patients, Kaplan–Meier analysis demonstrated significantly better survival after primary transfer compared with secondary transfer (log-rank p = 0.0262) (Figure 5A). The median follow-up for mortality assessment was 12.2 months (IQR 7.8–18.4 months). In multivariable Cox regression adjusted for age ≥ 75 years, baseline NIHSS ≥ 6, successful reperfusion (mTICI 2b–3), and major comorbidities, primary transfer remained an independent predictor of improved survival (HR 0.67, 95% CI 0.47–0.95; p = 0.026) (Figure 5B). This association persisted after stepwise AIC-based variable selection (HR 0.69, 95%, CI 0.49–0.97; p = 0.034). Adverse prognostic factors included advanced age, higher baseline NIHSS scores, diabetes, hypertension, and coronary artery disease.

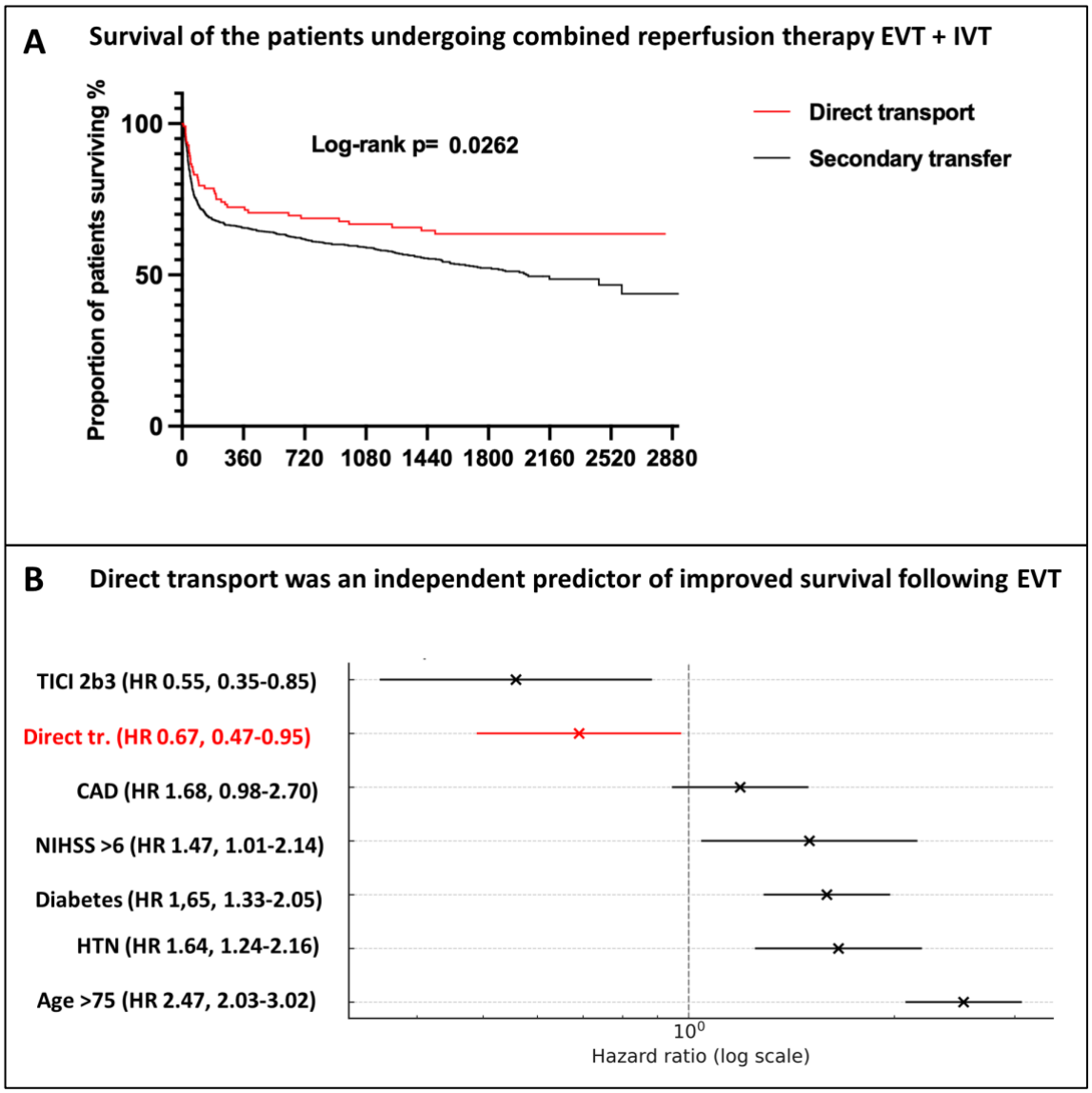


Figure 5A: patients who received both IVT and EVT, Kaplan–Meier analysis demonstrated significantly better survival after primary transfer compared with secondary transfer (log-rank p = 0.0262). The median follow-up for mortality assessment was 12.2 months (IQR 7.8–18.4 months). **5B:** In multivariable Cox regression adjusted for age ≥ 75 years, baseline NIHSS ≥ 6, successful reperfusion (mTICI 2b–3), and major comorbidities, primary transfer remained an independent predictor of improved survival (HR 0.67, 95% CI 0.47–0.95; p = 0.026).[197]

IV.2 Results – EVT in Basilar Artery Occlusion with or without stenting[183]

Between January 2014 and February 2019, over a period of five years, 92 patients were treated with MT due to BAO in our institution. One of our patients had two successful MTs in six months. One patient was excluded from our study due to loss to follow-up, therefore we finally included 91 cases in our analysis (98.9%, 91/92). The median

mortality follow-up time was 83 days (minimum 1, maximum: 1,050). The median symptom onset-to-reperfusion time was 398 (173; 1,650) minutes. Successful reperfusion (mTICI 2b-3 flow) was reached in 79.12% (72/91) of our cases. General anesthesia was induced during interventions in 83.52% (76/91) of all cases. Intravenous thrombolysis was used in 45.05% (41/91) of enrolled cases. Functional independence (mRS 0-2) at 90 days was achieved in 32.22% (29/90) of cases. The mortality rate at 3 months was 32.22% (29/90). Subarachnoid hemorrhage occurred in 7.69% (7/91), while sICH was detected in 2.20% (2/91) of our patients.

We dichotomized our cohort according to the presence or lack of occlusion-underlying stenosis. The baseline clinical and procedural characteristics of our subjects are listed in Table 3. Significant BA stenosis was diagnosed during MT in 45.05% (41/91) of our patients. Forty-one cases of BAO with underlying stenosis were characterized by a strong male predominance (92.68 % vs 50.00% p = 0.0001), and presented in a higher number of proximal BA segment occlusions (51.22% vs 26.00% p=0.0171), classified according to the Archer-Horenstein system.[186] Patients without ICAD (n=50) had higher median CHA2DS2-Vasc scores (3 vs. 2 p=0.0231)[187] supporting the proposed embolic origin of stroke in this subgroup of patients. Patients with ICAD related BAO had an increased risk of all-cause mortality (HR: 2.021; p=0.0417), compared to the patients without stenosis (Figure 7A). The two groups were comparable according to their age, risk factors, prestroke mRS scores and severity of stroke symptoms. The rate of general anesthesia, technical approach and the number of passes were also similar in the compared populations. All available validated predictive factors of EVT outcome in the PC were assessed, and significant differences were demonstrated in two parameters: the median symptom onset-to-reperfusion times were significantly higher (451.0 minutes vs 375.0 minutes; p=0.0020), and the rate of successful reperfusion (65.85% vs. 90.00%; p=0.0084) was significantly lower in the BAO patients with ICAS. We found no significant difference in the rate of hemorrhagic complications.

Table 3. Baseline clinical and procedural data of BAO cases				
		BAO W/o ICAS *n=50/91; 54.95%*	**BAO with ICAS** *n=41/91;43.95%*	**p =**
Median age (min; max) in years		64.0 (24.0; 84.0)	59.5 (39.0;89.0)	0.3571
Male gender		**50.00 % (25/50)**	**92.68% (38/41)**	**0.0001**
Hypertension		74.00% (37/50)	87.80% (36/41)	0.1189
Diabetes		22.00% (11/50)	29.27% (12/41)	0.8113
Atrial Fibrillation		30.00% (15/50)	14.63% (6/41)	0.1325
Median CHADS-VASC score (min; max)		**3 (1; 6)**	**2 (1; 6)**	**0.0231**
Vertebro-basilar tandem occlusion		18.00% (9/50)	9.76% (4/41)	0.3696
Systemic thrombolysis		48.00 % (24/50)	41.46% (17/41)	0.6723
*Median admission NIHSS (min; max)		17 (6; 43) *(n=40)*	20 (5; 36) *(n=34)*	0.9634
Occlusion site	Distal to SCA	**26.00% (13/50)**	**0.00% (0/41)**	**0.0002**
	Mid segment	48.00% (24/50)	48.78% (20/41)	1.0000
	Proximal to AICA	**26.00% (13/50)**	**51.22% (21/41)**	**0.0171**
General anesthesia		78.00% (39/50)	90.24% (37/41)	0.0790
Stent retriever passes		1 (1; 7)	2 (0;3)	0.1187
Direct aspiration first pass		16.00% (8/50)	4.88% (2/41)	0.1072
mTICI 2b-3 reperfusion rate (%)		**90.00% (45/50)**	**65.85% (27/41)**	**0.0084**
Onset-to-reperfusion time median (mins)		**375.0 (173.0; 1170.0)**	**451.0 (231.0; 1650.0)**	**0.0020**

Door-to-reperfusion time (mins)	**92.0 (17.0; 321.0)**	**160 (28.0; 1371.0)**	**0.0016**
Subarachnoid hemorrhage	10.00% (5/50)	4.88% (2/41)	0.4515
All intra-cranial hemorrhage	12.00% (6/50)	2.44% (1/41)	0.1234
Perforator-segment related infarct	60.00% (30/50)	73.17% (30/41)	0.2664
Median mortality follow-up (months)	**157.0 (1.0; 1056.0)**	**45.0 (1.0; 1000.0)**	**0.0390**
mRS 0-2 at 3 months	40.00 % (20/50)	26.83% (11/41)	0.2664
Hospital stay at the comprehensive stroke center (days)	6.0 (1.0; 56.0)	5.0 (1.0;30.0)	0.6770

Coronary stent implantation was performed in 18 out of the 41 cases presenting with ICAD related BAO. If IVT was not applied, peri-procedural iv. UFH loading dose was given, with early, post-procedural administration of DAPT. Without randomization process, the decision to perform stent placement was left entirely to the operators' discretion. Technical success of coronary stent implantation was achieved in all attempted cases.

ICAD-related BAO patients were split according to the treatment approach, and the two subgroups were proved to be comparable upon their distribution of gender, risk factors, the rate of IVT and procedural parameters. Baseline characteristics of this subgroup are summarized in Table 4. Despite the non-randomized nature of our study, among the baseline characteristics, we found significant difference only in the age of the ICAD related BAO patients: stented ones were slightly older (63.5 years vs. 56.0 years; p=0.0290). In two cases, the operator decided to emplace low radial force self-expandable stent devices. Due to the fundamentally different device structure and characteristics, these two patients were excluded from our analysis. The symptom onset-to-reperfusion times, the number of stent retriever passes, the number of complications leading to ICH, the rate of perforator-segment related infarcts, as well as the final successful (mTICI 2b-3) reperfusion rates of the two treatment strategies were proved to be statistically non-significant.

Despite the comparable baseline and procedural parameters of the patient subgroups, we found significant differences in the outcomes of the treatment strategies. The proportion of patients with residual BA stenosis was significantly lower among those who underwent stenting than among those who did not (14.7% vs 81.0%; p<0.0001) (Figure 6A). Less severe residual stenosis was associated with improved functional outcome (p=0.0266) (Figure 6B). The restenosis less than 30% target has been recommended by previous authors.[188]

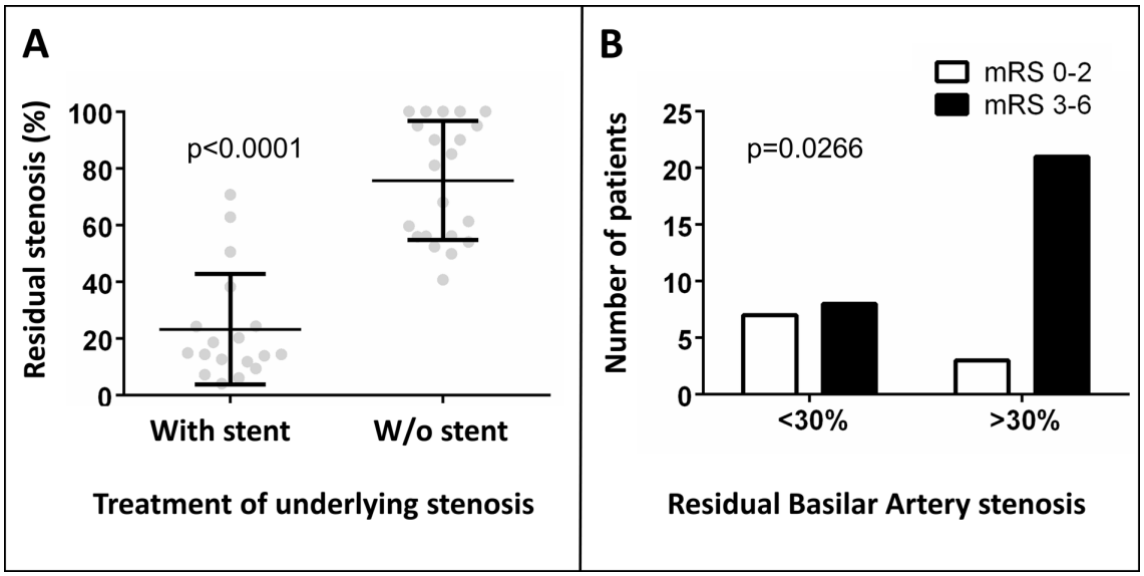


Figure 6A: Patients with ICAD-related BAO underwent stenting had a significantly lower proportion of residual BA stenoses than those who did not undergo stenting (14.7% vs 81.0%; p<0.0001). Error bars represent the means with standard deviation. **B:** Less severe residual stenosis was associated with improved functional outcome (p=0.0266).[183]

Stented patients presented with lower median NIHSS score at discharge (11.5 vs. 26.0; p=0.0057) and improved functional outcome at 90 days (mRS 0-2: 44.4% vs. 9.5%; OR: 7.6; p=0.0250) (Figure 8). Peri-procedural use of DAPT was administered more frequently in stented BAO patients (94.44% 17/18 vs 9.52% 2/21; p<0.0001). Most importantly, our stented subgroup demonstrated a significantly lower rate of overall mortality (HR: 4.163; p=0.0026) (Figure 7B).

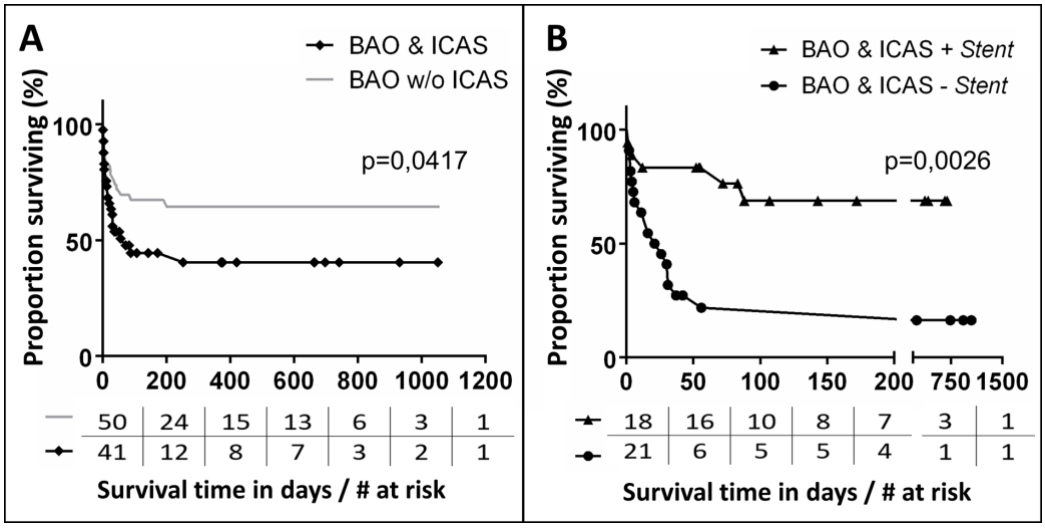


Figure 7. Overall survival of patients following EVT for BAO. A: Survival curve shows different overall survival for the BAO patients with (black curve with diamonds) or without (gray line) baseline ICAS (p=0.0417). **7B:** Survival of BAO-ICAS patients treated with or without stenting demonstrates that stented patients (curve with triangles) had better overall survival (p=0.0026). The tables under each survival curve show the number of patients at risk for each time interval.[183]

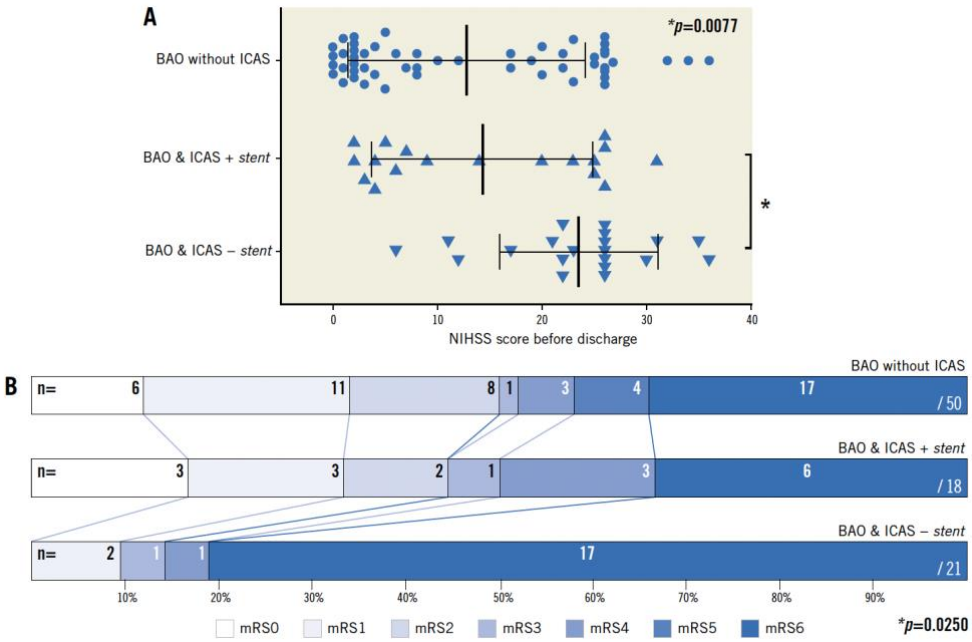


Figure 8. Functional outcomes following stent implantation. A: discharge NIHSS values are shown for each patient. The star (*) indicates the significantly (p=0.0077) worse discharge status of the BAO patients with stenosis treated without stenting. Bars represent the means with standard deviation. **B:** The horizontal bars in the lower panel represent the distribution of mRS values of the three patient groups at three months follow up. The star (*) highlights the significantly (p=0.0250) worse functional outcome of ICAD-related BAO patients treated without stents.[183]

Table 4. Comparative analysis by treatment strategy of BAO patients with underlying ICAS			
	W/o stent *n=21/39; 53.85%*	**With stent** *n=18/39; 46.15%*	**p =**
Median age (min; max) in years	**56.0 (45.0; 89.0)**	**63.5 (40.0; 74.0)**	**0.0290**
Male gender	95.23% (20/21)	88.89% (16/18)	0.5864
Diabetes mellitus	28.57% (6/21)	33.33% (6/18)	1.0000
Atrial Fibrillation	14.29% (3/21)	16.67% (3/18)	1.0000
History of Coronary artery disease	19.05% (4/21)	16.67% (3/18)	1.0000
Systemic thrombolysis	33.33% (7/21)	38.89% (7/18)	1.0000
Patient selection by DWI- FLAIR mismatch	14.29% (3/21)	22.22% (4/18)	0.6825
General anesthesia	95.24% (20/21)	83.33% (15/18)	0.3183
Number of stent retriever passes (min; max)	2.0 (1; 3)	1.5 (0; 3)	0.5496
Balloon (pre)dilatation	14.29% (3/21)	11.11% (2/18)	1.0000
Onset to reperfusion time in minutes (min; max)	455.0 (231; 1005)	445.0 (245; 1650)	0.7329
Successful reperfusion (mTICI 2b-3)	57.14% (12/21)	72.22% (13/18)	0.5043
Subarachnoid hemorrhage	4.76% (1/21)	5.56% (1/18)	1.0000
sICH	0.00% (0/22)	0.00% (0/20)	n. a.
Infarction of perforator bearing segments	85.71% (18/21)	61.11% (11/18)	0.1406
Residual BA stenosis (%)	**81.0 (40.7; 100.0)**	**14.7 (4.0; 70.7)**	**<0.0001**
Use of DAPT within 24 hours of EVT for BAO	**9.52% (2/21)**	**94.44% (17/18)**	**<0.0001**
NIHSS score at discharge	**26.0 (6; 36)**	**11.5 (2; 31)**	**0.0077**
mRS 0-2 at 3 months	**9.52% (2/21)**	**44.44% (8/18)**	**0.0250**
Median stent size in mm (min,max)	**n.a.**	**3(2.5; 3.5) x 12(8.0; 20.0)**	**n.a.**

V. Discussion

V.1. Interpretation of direct transport related findings

To our knowledge, this study provides the first real-world, comprehensive assessment of transport system challenges for patients with LVO-related AIS in the Eastern–Central European region, a socioeconomically relatively homogeneous area representing a substantial proportion of the European population. The principal finding is a significant functional and survival benefit associated with direct transport for MT within a 60-minute urban catchment area, most pronounced among patients treated with combined IVT and EVT. This analysis also represents, to our knowledge, the first observation of a potential mortality advantage linked to prehospital transfer strategy in a large, real-world endovascular stroke cohort. Furthermore, direct transfer independently predicted better 90-day functional outcome after adjustment for age, stroke severity, and comorbidities. The two transport modality groups were well matched with respect to demographics, comorbidities, and rates of successful reperfusion, allowing a clearer attribution of outcome differences to the prehospital routing strategy. Consistent with our findings, the TRIAGE-STROKE trial reported similarly balanced baseline characteristics and demonstrated a substantial time advantage for direct transport, shortening onset-to-groin puncture times by approximately 35 minutes, whereas PSC-first routing primarily expedited IVT initiation. Although TRIAGE-STROKE was underpowered, it showed a nonsignificant trend toward better functional outcomes with direct transport. Our results parallel this observation: time savings achieved by bypassing PSCs translated into more favorable 90-day functional outcomes, underscoring that streamlined prehospital routing - and particularly faster access to MT - can meaningfully influence post-stroke recovery.

Our findings may appear to contradict the RACECAT trial, which did not demonstrate a significant difference in neurological outcomes between prehospital transport strategies, however, RACECAT was conducted primarily in rural regions, where long transport distances and heterogeneous access to CSCs likely attenuated the potential benefit of direct routing approach. Another key factor underlying the neutral results of RACECAT was the high rate of futile long-distance transfers of patients with unrecognized ICH, a mechanism of harm that is less relevant over short urban transport distances. In our practice, joint real-time triage by paramedics and in-hospital stroke neurologists enabled bedside identification of clinical signs suggestive of hemorrhage, which helped to

minimize unnecessary transfers of patients with ICH to the CSC. As a result, the proportion of hemorrhagic strokes among transferred patients could be kept at a reasonably low level. Subgroup analyses of the RACECAT trial showed that outcomes after secondary transport were highly dependent on the quality of in-hospital stroke care, particularly door-in–door-out times at primary stroke centers, underscoring the importance of continuous workflow monitoring and targeted optimization of critical process steps when necessary. As a potential alternative to primary centers with only moderate performance, mobile stroke units (MSU) have been shown to accelerate diagnosis and treatment, further shortening time to reperfusion and avoiding unnecessary long-distance transfers of patients with ICH.[189]

In our cohort, patients receiving combined IVT and EVT presented within the early therapeutic time window, therefore this pattern suggests that the observed survival benefit of direct transfer is likely driven by more rapid and effective reperfusion among fast progressors, who in the secondary transfer pathway were frequently routed first to PSCs. Although this approach is in line with current ESO–ESMINT recommendations[52], which prioritize rapid thrombolysis at the nearest stroke unit, such detours may postpone definitive EVT and thereby diminish the overall therapeutic benefit. Interestingly, the most recent AHA stroke guideline explicitly acknowledges the persistent challenges of prehospital destination triage and, departing from earlier guidance favoring transport to the nearest thrombolysis-capable center, now recommends taking local system performance into account and considering direct transport to the closest endovascular thrombectomy–capable hospital when rapid interhospital transfer cannot be reliably ensured[124]. Our findings are consistent with this updated perspective.

A recent individual participant meta-analysis of direct transport trials reported increased rates of ICH with only uncertain functional benefit from combined IVT and EVT,[190] which is consistent with our observation of more frequent ICH in the secondary transfer group. Taken together, these observations suggest that upfront IVT may confer limited additional benefit in urban systems with otherwise rapid access to MT, particularly when it prolongs overall transport time. In such settings, a selective or “rescue” thrombolysis strategy - reserving fibrinolytic therapy for cases with angiographic or clinical evidence of incomplete reperfusion - may be more appropriate. This concept is supported by the CHOICE trial, which demonstrated improved 90-day outcomes with intra-arterial rtPA

administered after successful MT, without an associated increase in hemorrhagic complications.[191] Thus, in metropolitan stroke networks, a thrombectomy-first strategy with selective add-on thrombolysis may offer the most favorable balance between efficacy and safety, although this approach has yet to be evaluated in large, randomized clinical trials.

Limitations and generalizability

The principal limitation of this single-center observational study is the absence of randomization, which inherently weakens the causal inference that can be drawn from our findings. Exclusion of patients who recanalized at the PSC or on arrival at the CSC may also have influenced the results, although the number of such cases was small. Incomplete follow-up for functional outcome represents an additional potential source of bias; however, follow-up completeness was similar between groups, and one-year mortality data were almost entirely available, permitting valid between-group comparisons and a robust assessment of survival.

Regarding time metrics, in-hospital workflow data from PSCs, such as door-in–door-out times, were not systematically recorded, precluding a detailed analysis of the entire stroke care pathway. Our results are therefore most applicable to densely populated urban stroke networks characterized by a single CSC and relatively slow PSC workflows, and are less generalizable to rural regions or settings with long transport distances. Finally, although the COVID-19 pandemic overlapped with the study period, its impact on LVO stroke management has been reported as minimal in prior large-scale studies and is unlikely to have substantially altered our main conclusions.[192]

V.2. Interpretation of ICAD and Rescue Stenting Findings

Our high-volume, single-center, retrospective study of 91 consecutive BAO cases treated with EVT demonstrated a 32.2% rate of good functional outcome (mRS 0–2) and a 32.2% mortality rate at 3-month follow-up. Although our findings were published in 2020, prior to the ATTENTION and BAOCHE trials, our results are statistically consistent with these RCTs in terms of procedural efficacy and safety. Because good functional outcome was defined differently in recent BAO trials (mRS 0–3) than in our study (mRS 0–2), direct comparison of the results is challenging and explains the lower rate of our cohort (32.2% vs. 46% in ATTENTION and 46% in BAOCHE). Mortality rates were 37% and 31% in the mentioned RCTs respectively, while our data showed 32.2%. We observed no

differences in sICH rates across the studied subgroups. These findings suggest that early initiation of DAPT was safe in most patients, irrespective of prior IVT.

We identified underlying BA stenosis in 45.05% (41/91) of our cases, which is comparable to the proportion of ICAD-related BAOs (40%) reported in the ATTENTION trial conducted in China, suggesting that the prevalence of ICAD-related BAO may be similar in our region. We demonstrated a significant impact on the prognosis of ICAD patients undergoing EVT. The reason for the difference in outcome was probably the significantly higher onset-to-reperfusion time and the significantly worse quality of reperfusion in cases with ICAD, both differences may be explained by the technical challenges of revascularization in the presence of steno-occlusive atherosclerotic plaques. Distinct clinical presentation and dynamics may also contribute to slower diagnosis in such cases, therefore longer onset-to-reperfusion times. Our findings demonstrate that specific rescue therapy may neutralize the negative effects of the presence of ICAD in case of a BAO. Lee et al. have reported an equally high clinical outcome success rate of MT in BAO patients with or without ICAD, however in 8 out of their 15 stenotic cases operators have used early aggressive treatment with stent implantation and DAPT, and almost all ICAD patients (13/15) underwent at least balloon angioplasty of the steno-occlusive plaque following MT.[193] Although our observations that ICAD-related BAO patients have worse clinical outcomes after MT than those without stenosis may appear to contradict these findings, procedural differences between the studies may explain the divergent conclusions; in our cohort, early aggressive therapy in the stented subgroup resulted in a treatment effect comparable to that observed in BAO patients without ICAD who underwent EVT. While the difference in outcomes in our study was primarily attributable to the high mortality of stenotic patients treated without stenting and DAPT, the optimal treatment strategy for occlusion-underlying stenosis in BAO is still uncertain. The choice of antiplatelet therapy seems to have crucial importance even in the very early phase following MT in BAO patients with ICAD. In a non-randomized cohort, Kang et al. found that tirofiban combined with bail-out balloon angioplasty resulted in rates of successful reperfusion comparable to those achieved with upfront angioplasty, with or without stent implantation.[194] However, current AIS guidelines do not endorse the use of GPIIb/IIIa inhibitors in stroke patients previously treated with IVT, necessitating alternative pharmacological strategies in a large proportion of cases[124]. However, the

optimal duration of DAPT is difficult to define, given the potentially fatal consequences of stent thrombosis and hemorrhagic complications.

The indication for stenting symptomatic BA stenosis remains highly controversial, as optimized medical therapy with DAPT (aspirin and clopidogrel) demonstrated superior safety and clinical outcomes compared with DAPT plus self-expandable Wingspan stenting (Stryker Neurovascular Inc., Minneapolis, MN, USA) in the SAMMPRIS randomized controlled trial.[161] Similar conclusions were published following the early termination of the VISSIT trial, favoring BMT over the use of balloon-expandable Pharos™ Vitesse™ Neurovascular Stent System (Johnson & Johnson, New Brunswick, NJ, USA).[166] After the publication of the SAMMPRIS and VISSIT trials, which focused exclusively on intracranial arteries, several concerns were raised regarding study design and device selection. Notably, patients with BA stenosis accounted for only 22.3% of the SAMMPRIS cohort, and the VISSIT investigators did not disclose the number of patients with BA stenosis. As a result, it is difficult to extrapolate the findings of these trials to questions concerning the optimal treatment strategy for ICAD-related BAO. The ANGEL-REBOOT trial did not demonstrate that stenting improves 90-day functional outcome after unsuccessful recanalization; however, it is not directly comparable with our cohort, as the RCT predominantly included AC strokes and tirofiban was administered in most cases.

Observational data consistently indicate that BAO carries a much higher risk of adverse outcome than non-occlusive BA stenosis. Mechanical thrombectomy may augment the thrombogenicity of underlying atherosclerotic plaques in the BA, increasing the risk of thrombotic re-occlusion, in a manner similar to that seen after balloon dilatation in coronary interventions. We selected bare-metal coronary stents for our patients after taking into consideration the high risk of hemorrhage, the tortuous vascular anatomy, and the generally short lesion length. Our decision appeared to be safe, as we did not observe an excess of bleeding complications or perforator territory infarctions, consistent with previous reports of this off-label technique in the treatment of symptomatic ICAS.[195]

Due to our knowledge, our study was the first analysis to demonstrate that coronary stent implantation in BAO was effective not only in increasing the final luminal diameter at the occlusion site, but was also associated with improved neurological outcomes and increased survival. We found that patients with less than 30% residual stenosis after

stenting had a significantly higher likelihood of functional recovery. We assume that, in the stented cohort, the therapeutic benefit primarily resulted from more complete restoration of blood flow in the BA, and that potential perforator occlusions did not substantially affect clinical outcomes. In addition, the early initiation of DAPT may also have contributed to the observed clinical benefit.

Interestingly, the rates of successful end-of-procedure reperfusion (mTICI 2b–3) did not differ significantly between ICAD-related BAO patients treated with or without adjunctive stenting. However, the version of this cerebrovascular anatomy-based scale that we used primarily captures side-branch occlusions and does not adequately reflect potential flow limitations caused by residual stenotic segments. A more contemporary grading system, the expanded TICI (eTICI) scale,[196] provides more granular subcategories of successful reperfusion; in particular, the 2c category denotes distal slow flow with complete opacification of all side branches and distal vessels on angiography. Our analysis was conducted in 2020, and therefore the preceding 5-year period was evaluated using the then-standard mTICI scale rather than the eTICI classification. Based on our findings, a dedicated scoring system for the assessment of reperfusion success in the PC would be important to develop, due to the unique pathophysiologic characteristics of this vascular territory.

The most important limitations of our study are the retrospective design and the lack of randomization.

VI. Conclusions

In our single-center research program, we examined two critical, highly time-sensitive components of contemporary LVO stroke care workflow: prehospital transport strategies in an urban setting and endovascular rescue therapeutic options for BAO cases caused by ICAD. Based on a real-world cohort from an Eastern–Central European region with relatively homogeneous socioeconomic characteristics, we found that direct transport to a CSC within a 60-minute urban catchment area was associated with a *significant functional and survival benefit*, particularly among patients treated with combined IVT and EVT, and that this benefit persisted after adjustment for age, baseline stroke severity, and comorbidities. These findings underscore that optimizing the earliest phase of stroke care pathway - prehospital routing - can meaningfully influence 90-day neurological outcomes in LVO-related AIS cases and may even confer a mortality advantage in routine clinical practice. Within this streamlined systems-of-care framework, our second investigation focused on technically and pharmacologically challenging ICAD-related BAOs, in which first-line MT may fail or result in early re-occlusion. In this high-risk subgroup, rescue stenting with coronary stents emerged as a feasible endovascular escalation strategy, achieving satisfactory reperfusion and supporting clinically acceptable outcomes in patients who otherwise face limited therapeutic options, and consequently unfavorable functional conditions.

By integrating these complementary observations, our work highlights that both macro-level organization of stroke systems (direct CSC transport in urban regions) and micro-level procedural decision-making (timely rescue stenting in refractory ICAD-related BAO) are pivotal levers for improving both clinical and radiological prognosis along the entire LVO stroke care workflow. Taken together, our results advocate for regionally tailored prehospital triage models that prioritize rapid access to thrombectomy-capable centers in urban areas, alongside the availability of advanced rescue techniques for complex PC disease, to maximize functional recovery and survival in patients with LVO stroke.

Although our conclusions are drawn from non-randomized data, the real-world design and large sample size provide important insights for the management of LVO-related stroke, particularly given the current absence of randomized trials offering high-level evidence for prehospital triage of LVO-AIS patients across different geographical settings

and for rescue therapies in complex ICAD-related BAO cases. The ongoing ICARUS and ASSET trials are expected to address several remaining knowledge gaps regarding the optimal perioperative management of ICAD underlying occlusive lesions, including potentially in the particularly dreaded subgroup of BAO. To the best of our knowledge, there is currently no ongoing large RCT designed to address the controversies surrounding prehospital and interhospital transfer strategies for patients with LVO-AIS. Therefore, our reports provide valuable contributions to the stroke literature.

Since January 2022, an electronic stroke (e-stroke) platform managed by Brainomix has been implemented across the entire Hungarian stroke network, enabling immediate image transfer between PSCs and CSCs and thereby facilitating communication and decision-making for patients with AIS who are eligible for EVT. Brainomix is an FDA-cleared and CE-marked suite of applications that uses AI algorithms to support decision-making in CT interpretation in cases of AIS. One of its key modules, e-ASPECTS, automatically quantifies the ASPECTS score, estimates infarct volume, and detects LVOs as well as hyperdense lesions on non-contrast CT. The e-CTA module assesses collateral circulation and detects LVOs on CT angiography, whereas e-CTP estimates ischemic core and penumbra volumes and calculates the mismatch ratio on CT perfusion imaging. By January 2026, a nationwide video-consultation system between emergency medical services and in-hospital stroke neurologists had been established, with the specific aim of improving the accuracy of stroke recognition and severity assessment in the prehospital setting so that, based on real-time visual evaluation, patients with suspected LVO can be transported directly to a CSC rather than the nearest PSC. In addition, from December 2026, the first MSU in Hungary is planned to be deployed in the Central Hungarian Region, with the goal of further reducing door-to-needle times. In parallel with the stepwise implementation of these system-level interventions, we are continuously monitoring their impact on patient outcomes. The current analysis of our pre-2022 cohort will serve as a benchmark for future comparisons with patients treated under these newer strategies, supported by the e-stroke platform, video-based prehospital referral, and MSU services. Consequently, our studies not only help to fill existing evidence gaps in stroke care but also represent an initial step in evaluating the effects of large-scale organizational changes within the Hungarian stroke network.

VII. Summary

The overarching aim of our research program has been to address key controversies in both macro-level stroke systems of care and micro-level procedural workflows, with the goal of improving clinical outcomes across the entire stroke treatment pathway. Our CSC is among the leading expert institutions in the Eastern-Central European region, owing to the highest regional patient volume and extensive experience in stroke management.

We synthesized the findings of two studies to provide this integrated perspective. In our analysis of the impact of direct transport in a densely populated urban region served by a single CSC, we observed significantly improved functional outcomes and survival among patients transported according to a mothership paradigm within a 60-minute urban catchment area, particularly in those treated with combined IVT and EVT. Direct transfer independently predicted a more favorable 90-day clinical outcome after adjustment for age, baseline stroke severity, and comorbidities.

In the BAO cohort, patients with ICAD–related BAO had a higher risk of all-cause mortality compared with those without stenosis. Symptom onset-to-reperfusion times were significantly longer, and rates of successful reperfusion were significantly lower, in BAO patients with underlying ICAS, while rates of hemorrhagic complications did not differ significantly between groups. Among patients with ICAD-related BAO, treatment strategy was also associated with outcome. Those undergoing stent implantation in the BA had a significantly lower rate of residual basilar stenosis than patients treated without stenting, lower NIHSS scores at discharge, and better 90-day functional outcomes. Moreover, the stented subgroup exhibited a significantly lower rate of overall mortality.

Although our robust database is retrospective and non-randomized, its results and analyses meaningfully enrich the international literature on LVO-AIS management, as neither optimal prehospital routing strategies nor the ideal treatment of ICAD-related BAO are yet well established. Collectively, our findings provide important complementary pieces of evidence toward two major determinants of functional outcome in LVO stroke: reducing onset-to-reperfusion times in the prehospital phase through appropriate routing of patients with suspected LVO and achieving durable reperfusion in cases of BAO of atherosclerotic etiology.

VIII. References

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IX. Bibliography of the candidate's publications

List of publications – related to the thesis

1. **Orosz P**, Kővári Z, Mészáros H, Bata ÁH, Kis B, Pásztor M, Böjti PP, Erőss L, Szikora I, Merkely B, Berentei Z, Kornfeld Á, Kondor M, Nardai S. Direct Transport to a Comprehensive Stroke Center May Offer Outcome Benefits in Metropolitan Thrombectomy Networks. *J Stroke*. 2026 Jun 30. doi: 10.5853/jos.2025.06758. Epub ahead of print. PMID: 42374979. **IF: 8.6**
2. Nardai S, Kis B, Gubucz I, Berentei Z, Vajda Z, **Orosz P**, Nagy A, Óváry C, Nagy Z, Szikora I. Coronary stent implantation for acute basilar artery occlusion with underlying stenosis. *EuroIntervention*. 2020 Dec 18;16(12):e1021-e1028. **IF: 6.534**

List of publications – not related to the thesis

1. **Orosz P**. The role of new oral anticoagulants in cerebrovascular diseases. *Neuropsychopharmacol Hung*. 2015 Dec; 17(4):183-90. Hungarian. **IF: 0.59**
2. **Orosz P**, Szőcs I, Várallyay Gy, Zsigmond I, Rudas G, Bereczki D, Vastagh I. Uncommon extradural lesion causing spinal canal compression – juxtafacet cyst *Orvostudományi Értesítő*; 2015, 88 (1): 29–32. Hungarian. **IF: 0**
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