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INFLUENCE OF THE THROMBECTOMY PARAMETERS ON THE EFFICACY IN THE ACUTE STROKE WITH LARGE VESSEL OCCLUSION TREATMENT

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UTICAJ PARAMETARA TROMBEKTOMIJE NA EFIKASNOST TRETMANA AKUTNOG ISHEMIJSKOG MOŽDANOG UDARA NAKON OKLUZIJE VELIKOG KRVNOG SUDA

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INFLUENCE OF THE THROMBECTOMY PARAMETERS ON THE EFFICACY IN THE ACUTE STROKE WITH LARGE VESSEL OCCLUSION TREATMENT

ABSTRACT

Background: Acute ischemic stroke (AIS) is an acute impairment of brain function caused by a central nervous system focal injury of a vascular origin. The cause is a sudden blockage of blood flow to the brain neural tissue caused by arterial occlusion. AIS is the second most common primary cause of death in Europe, accounting for 9% of deaths in men and 12% of deaths in women annually. Moreover, mortality within the first month after the incident is around 30%. Half of the survivors lose their independence in everyday life, as it is the leading cause of long-term disability. From a socio-economic point of view, AIS represents a major public health burden worldwide, mainly due to the high hospitality rate of severely disabled patients and consequently high costs of rehabilitation and medical care. The main goals of AIS treatment are the recanalization of occluded blood vessels and potential reperfusion of remained viable brain tissue. Until 2015, the only proven reperfusion technique was the application of recombinant tissue plasminogen activator (IV tPA) administered less than 4.5 hours from symptom onset. However, several randomized controlled trials (RCTs) promoted an endovascular treatment approach and proved that mechanical thrombectomy (MT) is safe and effective for the treatment of anterior circulation large vessel occlusion (ACLVO), in comparison with traditional AIS treatment. Although MT is currently an accepted standard of care, there are still a lot of pending questions to be clarified. For instance, issues about widening MT indications, best technique, practical organization, minimal required imaging, type of anesthesia, patient triage and transport, the best management of tandem occlusion (TO), and the influence of the clot composition on retrieval efficacy need to be additionally clarified in future. Another major issue is the applicability of RCTs results achieved in the well-organized centers and in \ highly-controlled settings, compared to a real-world situation, especially in developing country medical systems which are dealing with lack of trained personnel, shortage of appropriate financial and material support, lower basic health level of the population, etc. Therefore, this dissertation aimed to evaluate the influence of different thrombectomy parameters on the treatment of AIS in Belgrade and Toulouse cohort study populations.

Material and methods: This double center observational cohort study with the pragmatic care trial context for AIS patients treated with MT included data from 284 patients at Toulouse University prospective stroke registry and data from 82 patients at The Clinical Center of Serbia prospective stroke registry. Clinical and radiological data collection of treated cases were from January 2015 to January 2017 at Toulouse University center, and from January 2018 to January 2020 at The Clinical Center of Serbia. Moreover, additional collected data related to the anesthesia management during MT procedure in the Toulouse mono-center cohort were for the period from January 2014 until July 2016. The eligible cases were selected using the following inclusion criteria: (1) verified ACLVO by computed tomography (CT) angiography or magnetic resonance (MR) angiography; (2) MT initiated within the 6 hours from symptoms onset regardless of the use of intravenous recombinant tissue plasminogen activator (IV tPA). On the other hand, the exclusion criteria were as follows: (1) presence of intracranial hemorrhage (on MR or CT); (2) absence of the ACLVO; (3) small artery occlusion (distal from M2 division of the middle cerebral artery) or in the territory of posterior circulation (vertebrobasilar distribution); (4) MT initiated after 6 hours from symptom onset; (5) age below 18 years. From prospective stroke databases of both centers, several parameters were collected: clinical data (age, gender, pre-treatment National Institutes of Health Stroke Scale (NIHSS) score, side of occlusion, level of occlusion, use of IV tPA, and type of anesthesia), time metrics (time of stroke onset, time of arrival at the stroke center, time of imaging, time of arrival in the angio-suite, time of arterial puncture (AP) and time of recanalization/last image), imaging data (on MR or CT), the Alberta Stroke Program Early CT Score (ASPECTS) was calculated on

diffusion-weighted imaging (DWI) or CT to assess the extent of the ischemic core, endovascular treatment data and angiographic outcome on modified thrombolysis in cerebral infarction (mTICI) score, and safety and clinical outcomes (complications and intracranial hemorrhage, stroke severity measured on the NIHSS at 24h, the degree of disability assessed on modified Rankin scale (mRS) 3 months after discharge). Descriptive and analytical statistical methods were used in this study. All data were processed in SPSS 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) software package and R 3.4.2 (R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results: Overall rate of good clinical outcome (mRS 0-2) and mortality rate (mRS 6) were 49% and 18.3%, respectively. Pre-treatment NIHSS score was higher and DWI ASPECTS lower in the general anesthesia (GA) compared to conscious sedation/local anesthesia (CS/LA) group, with a significant difference on univariate regression analysis (p=0.001 and p=0.002 respectively). Median time from arrival in the angio-suite room-to-AP was 20 min (IQR=15-28) for GA compared to 15 min (IQR=10-21) for CS/LA (p=0.001), without significant differences in the investigated outcomes. Embolization into new vascular territories (ENT) was significantly higher for CS/LA on the univariate logistic regression (p=0.001). There was no difference in the outcomes between GA and CS/LA groups. Susceptibility vessel sign (SVS) + was associated with a higher rate of mTICI 2b/3 on univariate and multivariate-adjusted analysis [OR=2.48; 95% CI (1.05–5.74); p=0.03]. Day one clinical improvement was higher in the SVS+ compared to SVS- patients to the level of statistical significance on the multivariate regression analysis [OR=2.84; 95% CI, (−5.37 to −0.30); p=0.03]. Median time from arrival to the comprehensive stroke center (CSC) door to recanalization was 127.5 min (IQR=93-178) for higher NIHSS >5 compared to 157.0 min (IQR=131-255) for low NIHSS ≤5 patients significant on univariate analysis (p=0.049). ENT was significantly higher in the low NIHSS ≤5 group on the univariate analysis (p=0.05). Younger patients were significantly more frequent in the low ASPECTS ≤5 group. Median time from AP to recanalization was 43 min (IQR=27-65.5) for higher ASPECTS ≥6 compared to 58 min (IQR=31.5-87.5) for low ASPECTS ≤5 patients in the univariate analysis (p=0.040). There was a lower rate of good clinical outcome in low ASPECTS ≤5 at three months on multivariate analysis [OR=2.24, 95% CI (1.21-4.16); p=0.011), but MT achieved a substantial absolute rate of 33% of good clinical outcome. Tandem occlusion compared to non-TO patients had a longer median time from AP to recanalization 57.0 min (IQR=40-88) and 42 min (IQR=27-67) respectively (p=0.005). There was a statistically significant higher rate of good clinical outcome for TO patients at three months 66.0% vs 46.2% on multivariate analysis [OR=0.34, 95% CI (0.11-1.01); p=0.052], as well as lower mortality rate in TO group 18% compared to non-TO patients 19.9% on multivariate analysis [OR=0.48, 95% CI (0.25-0.95); p=0.034]. There was a tendency for a better outcome for the patients that received stenting of the extracranial lesion, but not to the level of statistical significance. All the onset time metrics were significantly shorter in favor of direct admission compared to indirect admission, including onset to recanalization that was 266 min for directly compared to 322 min for indirectly admitted patients (p<0.001). There was a significantly higher rate of hemorrhagic transformation and lower mortality rate in the indirect admission group on univariate analysis (p=0.003).

Conclusions: In the "real life" context, ACLVO strokes can be treated with MT under GA with angiographic and clinical results comparable to previously reported RCTs. Although GA was performed in patients with more severe stroke and associated with a delay for MT start times in the range of 5 to 10 minutes, there was no difference in recanalization rates and functional outcomes at 3 months compared to CS/LA. SVS represents an accessible and routine clinical biomarker associated with successful recanalization following thrombectomy and better short-term clinical improvement. There was no correlation between SVS+ and thrombus etiology. *Low NIHSS (NIHSS≤5) patients tend to be more observed and have treatment decisions postponed, with prolonged tome metrics to AP*. Mechanical

thrombectomy seems susceptible for ENT in these patients, but there was no difference in the primary and safety outcomes between high and low NIHSS patients. Low ASPECTS patients are younger and have prolonged AP to recanalization time. They have a lower chance for independence compared to higher ASPECTS patients. There was a higher rate of good clinical outcome and lower mortality in TO patients, assumably due to developed collateral circulation, without difference in symptomatic cerebral hemorrhage compared to non-TO patients. Acute implantation of the stent for the extracranial lesion seems to display a tendency for a better outcome, but it did not reach statistical significance. Although time metrics were overall longer and a rate of hemorrhagic transformation higher for the indirectly admitted patients, there was no overall difference in primary and safety outcomes compared to directly admitted patients. Compared to previously conducted RCTs, the overall higher mortality rate observed in the Belgrade cohort is due to the cohort exhibiting a significantly higher rate of mRS 6 at three months compared to the Toulouse cohort sample (15.1% vs. 29.3 respectively). The higher mortality in the Belgrade cohort sample is consistent with the results of the studies done in other middle-income and low-income countries.

Key words: Acute ischemic stroke, large cerebral vessel occlusion, mechanical thrombectomy, computed tomography, magnetic resonance imaging, ASPECTS, NIHSS, mRs, mTICI.

Scientific Field: Medicine
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UTICAJ PARAMETARA TROMBEKTOMIJE NA EFIKASNOST TRETMANA AKUTNOG ISHEMIJSKOG MOŽDANOG UDARA NAKON OKLUZIJE VELIKOG KRVNOG SUDA

SAŽETAK

Uvod: Akutni ishemijski moždani udar (AIMU) je akutno oštećenje moždane funkcije izazvano fokalnim oštećenjem centralnog nervnog sistema usled poremećaja cirkulacije krvotoka. Uzrok je iznenadni prekid krvotoka moždanog tkiva uzrokovan okluzijom arterijskog krvnog suda. AIMU je drugi najčešći pojedinačni uzrok smrti u Evropi, čineći 9% smrtnih slučajeva kod muškaraca i 12% smrtnih slučajeva kod žena svake godine. Štaviše, mortalitet u prvom mesecu nakon AIMU-a je oko 30%. Vodeći je uzrok trajnog invaliditeta, sa gubitkom sposobnosti za samostalni život. Sa socioekonomskog aspekta, AIMU predstavlja veliki socijalno-zdravstveni problem širom sveta, uglavnom zbog visoke stope hospitalizacije pacijenata sa teškom kliničkom slikom i posledičnih visokih troškova rehabilitacije i nege. Glavni ciljevi lečenja AIMU-a su rekanalizacija okludiranih krvnih sudova i posledična reperfuzija još uvek vijabilnog moždanog tkiva. Do 2015. godine, jedina dokazana reperfuziona terapija bila je intravenska aplikacija rekombinantnog tkivnog aktivatora plazminogena (IV tPA) primenjenog manje od 4,5 sata od pojave simptoma. Međutim, nekoliko randomiziranih kontrolisanih istraživanja (RCTs) promovisalo je endovaskularno lečenje, pri čemu je ustanovljeno da je mehanička trombektomija (MT) okluzije velikog krvnog suda prednje arterijske cirkulacije (ACLVO) sigurna i efikasna metoda u poređenju sa tradicionalnim tretmanom AIMU-a. Iako je MT trenutno prihvaćena kao standard lečenja za pacijente sa proksimalnom okluzijom prednje moždane cirkulacije, još uvek ima mnogo nerazjašnjenih pitanja. Na primer, proširenje indikacija za primenu MT, odabir optimalne tehnike, praktična organizacija rada, minimalno neophodna dijagnostika, vrsta anestezije, trijaža i transport pacijenta, adekvatan tretman tandem okluzije (TO), uticaj strukture tromba na efikasnost terapije, nepoznanice su koje u budućnosti treba dodatno razjasniti. Još jedno veoma važno pitanje je primenljivost rezultata RCTs postignutih u dobro organizovanim centrima i visoko kontrolisanim uslovima, u poređenju sa stvarnom situacijom na terenu, posebno u zdravstvenim sistemima zemalja u razvoju koji se bore sa nedostatkom obučenog osoblja, odgovarajuće finansijske i materijalne podrške, nižim osnovnim zdravstvenim nivoom populacije, itd. Stoga je ova doktorska disertacija imala za cilj da proceni uticaj različitih parametara trombektomije na efikasnost tretmana AIMU-a u ispitivanim populacijama pacijenata u Beogradu i Tuluzu.

Materijal i metod: Ova opservaciona kohortna studija sprovedena u dva istraživačka centra obuhvatila je podatke 284 pacijenta iz registra AIMU-a Univerziteta u Tuluzu i podatke 82 pacijenta iz registra AIMU-a Kliničkog Centra Srbije. Prikupljanje kliničkih i radioloških podataka lečenih pacijenata bilo je od januara 2015. godine do januara 2017. godine za Univerzitetski centar u Tuluzu, i od januara 2018. godine do januara 2020. godine za Klinički centar Srbije. Dodatno, prikupljani podaci koji se odnose na primenu različitih vidova anestezije tokom MT iz Univerzitetskog centra u Tuluzu odnose se na period od januara 2014. godine do jula 2016. godine. U studiju su uključeni pacijenti koji su ispunjavali sledeće kriterijume uključenja: (1) verifikovana ACLVO primenom kompjuterizovane tomografske (CT) angiografije ili magnetno rezonantne (MR) angiografije; (2) MT započeta u roku od 6 sati od pojave simptoma, bez obzira na primenu IV tPA. S druge strane, kriterijumi za isključenje bili su sledeći: (1) prisustvo intrakranijalnog krvarenja na (MR ili CT); (2) odsustvo ACLVO; (3) okluzija male arterije (distalno od M2 segmenta srednje velikomoždane arterije) ili u teritoriji zadnje cirkulacije (vertebrobazilarni sliv); (4) MT započet nakon 6 sati od pojave simptoma; (5) starost ispod 18 godina. Iz prospektivnih baza podataka o AIMU-u u oba istraživačka centra prikupljani su podaci o sledećim parametrima: klinički podaci (starost, pol, vrednost „National Institutes of Health Stroke Scale“ (NIHSS) skora pre tretmana, strana okluzije, nivo okluzije, upotreba IV tPA i vrsta anestezije), vremenski intervali (vreme početka AIMU-a, vreme dolaska u angio-salu, vreme dijagnostičkog snimanja, vreme dolaska u

specijalizovanu zdravstvenu ustanovu, vreme arterijske punkcije (AP) i vreme rekanalizacije/poslednje radiografije), podaci o radiološkoj dijagnostici (MR ili CT), „Alberta Stroke Program Early CT Score“ (ASPECTS) je određivan analizom na DWI ili CT kako bi se odredila veličina zone infarkta, podaci o endovaskularnom lečenju i angiografski ishod putem „modified thrombolysis in cerebral infarction“ (mTICI) procene, kao i bezbednosni i klinički ishodi (komplikacije, intracerebralno krvarenje, klinička težina moždanog udara određena NIHSS skorom nakon 24 sata i stepen invaliditeta procenjen putem „modified Rankin scale“ (mRS) tri meseca nakon otpusta). Za statističku obradu podataka u ovom istraživanju korišćene su različite deskriptivne i analitičke statističke metode. Svi podaci su obrađeni u SPSS 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) softverski paket i R 3.4.2 (R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Rezultati: Ukupna učestalost dobrog kliničkog ishoda (mRS 0-2) i mortaliteta (mRS 6) iznosila je 49% i 18.3% redom. NIHSS skor pre lečenja bio je veći a DWI ASPECTS niži u grupi pacijenata sa opštom anestezijom u poređenju sa sedacijom/lokalnom anestezijom, sa uočenom statistički značajnom razlikom u univarijantnoj regresionoj analizi (p=0.001 i p=0.002 redom). Medijana proteklog vremena od dolaska u angio-salu do arterijske punkcije (AP) iznosio je 20 minuta (IQR=15-28) u grupi pacijenata sa opštom anestezijom, u poređenju sa 15 minuta (IQR=10-21) koliko je iznosio u grupi pacijenata sa sedacijom/lokalnom anestezijom (p=0.001) bez statistički značajne razlike u praćenim ishodima. Embolizacija nove vaskularne teritorije (ENT) bila je značajno veća u grupi pacijenata sa sedacijom/lokalnom anestezijom primenom univarijantne logističke regresije (p=0.001). Znak hiperintenznog krvnog suda (SVS) bio je statistički značajno povezan sa većom učestalošću parametra uspešne rekanalizacije mTICI 2b/3, što je procenjeno pomoću univarijantne i multivarijantno prilagođene regresione analize [OR=2.8; 95% CI, (1.05–5.74); p=0.03]. Kliničko poboljšanje prvog dana bilo je veće u grupi pacijenata sa prisutnim SVS u poređenju sa grupom pacijenata sa odsutnim SVS, što je bilo značajno primenom multivarijantne regresione analize [OR 2.84; 95% CI, (-5.37 do -0.30); p=0.03]. Medijana vremena od dolaska u centar do rekanalizacije bila je 127.5 minuta (IQR=93-178) kod pacijenata sa NIHSS >5 u poređenju sa 157 minuta (IQR=131-255) za pacijente sa NIHSS ≤5 što se pokazalo značajno u univarijantnoj regresionoj analizi (p=0.049). ENT je bio značajno veći u grupi pacijenata sa NIHSS ≤5 procenjen univarijantnom regresionom analizom (p=0.05). Mlađi pacijenti bili su učestaliji u grupi ASPECTS skorom ≤5. Postojala je niža stopa dobrog kliničkog ishoda kod pacijenata sa ASPECTS skorom ≤5 nakon tri meseca procenjen multivarijantnom regresionom analizom [OR 2.24, 95% CI (1.21-4.16); p=0.011)], ali je primenom MT postignuta značajna apsolutnu stopu dobrog kliničkog ishoda od 33%. Medijana vremena od AP do rekanalizacije iznosio je 43 minuta (IQR=27-67) za pacijente bez TO u poređenju sa 57 minuta (IQR=40-88) kod pacijenata sa TO što se pokazalo značajnim primenom univarijantne regresione analize (p=0.005). Zabeležena je statistički značajna veća stopa dobrog kliničkog ishoda (mRS 0-2) za pacijente sa TO tokom tri meseca (66% u odnosu na 46.2%) primenom multivarijantne regresione analize [OR=0.34, 95%CI (0.11-1.01); p=0.052), kao i niža stopa mortaliteta u grupi pacijenata sa TO (18%) u odnosu na pacijente bez TO (19.9%) procenom multivarijantne regresione analize [OR=0.48, 95%CI (0.25-0.95); p=0.034]. Postojala je tendencija za bolji klinički ishod kod pacijenata kod kojih je učinjen stenting ekstrakranijalne promene, bez statističke značajnosti. Svi vremenski intervali od početka AIMU bili su znatno kraći u korist direktnog prijema, uključujući vreme od početka do rekanalizacije koji je iznosio 266 minuta (IQR=215-317) za direktni prijem u poređenju sa 322 minuta (IQR=277-364) za indirektno primljene pacijente (p<0.001). Zabeležena je statistički značajna veća stopa hemoragijske transformacije i niži mortalitet u grupi pacijenata sa indirektnim prijemom procenjeno univarijantnom regresionom analizom (p=0.003).

Zaključci: U kontekstu „svakodnevne prakse“ MT u terapiji ACLVO može se izvoditi pod opštom anestezijom sa angiografskim i kliničkim rezultatima koji su uporedivi sa ranije objavljenim rezultatima

randomizovanih istraživanja. Iako su pod opštom anestezijom tretirani pacijenti sa težom kliničkom slikom i odlaganjem početka MT u rasponu od 5 do 10 minuta, nije bilo razlike u stopama rekanalizacije i funkcionalnim ishodima nakon 3 meseca u odnosu na sedaciju/lokalnu anesteziju. Naše istraživanje je pokazalo da procena znaka hiperintenznog krvnog suda predstavlja pristupačan i rutinski klinički biomarker povezan sa uspešnom rekanalizacijom nakon trombektomije i boljim kratkoročnim kliničkim poboljšanjem. U ovom istraživanju nije uočena povezanost između prisustva znaka hiperintenznog krvnog suda i etiologije ugruška. Kod pacijenti sa vrednostima NIHSS skora ≤5 uočeno je produženo praćenje pacijenata i odlaganje AP. Takođe, prikazani rezultati ukazuju da su pacijenti sa NIHSS ≤5 skloni nastanku ENT-e, ali uopšteno gledajući nije bilo statistički značajne razlike u praćenim primarnim i bezbednosnim ishodima između posmatranih grupa. Uočeno je da su pacijenti sa vrednostima ASPECTS skora ≤5 mlađi i sa produženim vremenom od AP do rekanalizacije. U odnosu na pacijente sa ASPECTS skorom > 5 navedeni pacijenti imaju manje šanse za mogućnost samostalnog života. Zabeležena je statistički značajna veća stopa dobrog kliničkog ishoda i niži mortalitet za pacijente sa TO, najverovatnije zbog razvijene kolateralne cirkulacije, sa uporedivom stopom komplikacija kod pacijenata koji nisu imali TO. Takođe, uočena je i tendencija ka boljem ishodu kod pacijenata sa implantacijom stenta u nivou ekstrakranijalne lezije, koja nije dosegla nivo statističke značajnosti. Iako su vremenski pokazatelji bili sveukupno duži za indirektno primljene pacijente uz veću stopu hemoragijske transformacije, nije postojala razlika u primarnim i bezbednosnim ishodima u poređenju sa pacijentima koji su primljeni direktno. U ovom istraživanju uočena je veća ukupna stopa smrtnosti pacijenata u poređenju sa prethodno sprovedenim randomizovanim istraživanjima, najpre zbog beogradskog uzorka kohorte koji je imao veću učestalost mRS 6 na tromesečnom nivou u poređenju sa kohortnim uzorkom Tuluza (15.1% i 29.3 redom). Veći mortalitet beogradskog uzorka kohorte u skladu je sa studijama sprovedenim u zemljama srednje i niske platežne moći.

Ključne reči: Akutni ishemijski moždani udar, okluzija velikih cerebralnih krvnih sudova, mehanička trombektomija, magnetna rezonanca, kompjuterizovana tomografija, ASPECTS, NIHSS, mRs, mTICI

Naučna oblast: Medicina
Uža naučna oblast: Radiologija i nuklearna medicina
UDK:

CONTENTS

1. INTRODUCTION

1.1. Acute Ischemic Stroke – general considerations

1.1.1. Current status and future directions

Acute ischemic stroke (AIS) is a medical condition caused by large vessel occlusion (LVO) that has a poor prognosis if the arterial occlusion persists for a longer period. Until 2015, the only proven reperfusion therapy was administration of intravenous recombinant tissue plasminogen activator (IV tPA) less than 4.5 hours from symptom onset (1). IV tPA is a clot buster drug, that carries numerous limitations, including a strong time-dependency with short therapeutic window (2-4). Additionally, LVO is a proximal intracranial arterial occlusion with typically large thrombus burden, limiting the efficacy of IV tPA (5, 6). Successful revascularization results of IV tPA in patients with occlusions of the intracranial internal carotid artery (ICA) or the first segment of the middle cerebral artery (MCA) are poor and achieved only in 13 to 50% cases (7, 8).

Endovascular treatment (EVT) for acute ischemic stroke has evolved substantially since the beginning of the 21st century. The endovascular approach has already been successful for the treatment of cerebral aneurysms and vascular malformations of the head and spine; however, in regard to the treatment of AIS, the road was more challenging. Only after the publication of several positive multicenter randomized controlled trials (RCTs) in 2015 and 2016, carried out in CSC (Comprehensive Stroke Centers) located in different western countries, safety and efficacy of mechanical thrombectomy (MT) was proven. RCTs consistently showed that EVT in addition to best medical management (BMM) (which in the majority of cases included intravenous IV tPA) improved outcome after acute ischemic stroke compared to BMM alone, in patients with ACLVO (9-14). Thus, MT is currently the accepted standard of care for patients with proximal anterior circulation occlusions when performed with newer generation devices (in the RCTs stent retrievers were mainly used) (15). In the positive RCTs, more stringent imaging selection criteria and more efficient workflow than in previous trials, resulted in significantly reduced disability rates after AIS caused by ACLVO (9-13). The above-mentioned positive RCTs were SWIFT PRIME, REVASCAT, MR CLEAN, ESCAPE, EXTEND-IA, and THRACE which all confirmed the superiority of MT combined with the BMM in comparison to BMM alone (9-14). In patients with ACLVO, whether direct mechanical intervention is equally effective, superior or inferior to bridging thrombolysis with IV tPA, remains a matter of debate (16).

The HERMES collaboration was formed, which allowed patient-level data meta-analysis of previous RCTs that ascertained the benefit of endovascular intervention in a broader population compared to each trial (17). In the HERMES meta-analysis, the number of patients needed to treat (NNT) with endovascular therapy to change a patient from a higher level of disability to a lower level of disability was 2.6. Few fields in medicine have had such a strong therapeutic effect on patient's outcomes. For example, a coronary angioplasty for ST-elevation myocardial infarction (STEMI) compared to thrombolytics has a short-term mortality benefit with an NNT of 50 patients (18).

Overall, MT is effective irrespective of age, sex, and stroke severity at presentation. DAWN and DEFUSE-3 trials have shown that in selected cases the benefit of MT can last up to 24 hours (19, 20). Data from the HERMES collaboration show benefit with MT even in patients with large ischemic core (12, 21). Despite that, there is no published data from randomized trials on more distal occlusions; however, there is enough evidence from large size registries on MT to show that M2 occlusions are safe and effective (22). However, there are still a lot of pending questions to be clarified: MT indications; best technique; practical organization; minimal required imaging; type of anesthesia; patient triage and transport; best management of tandem occlusion; the influence of the clot composition on retrieval efficacy; and many more, which are on the way to be answered by new ongoing or pending RCTs.

Another important issue is the applicability of RCTs results achieved in developed, high-income countries, in the well-organized settings of RCTs, compared to a real-world situation, especially in

developing country medical systems. Problems with reimbursement, lack of trained personnel, financial and material constraints, low income and other organizational problems are some of the obstacles holding up MT optimization.

The ESNR scholarship allowed me to visit the Toulouse center in 2015, right after the release of the first positive RCTs and the beginnings of thrombectomy practice. During my stay, I have actively participated in the creation of a Toulouse center prospective thrombectomy registry, where I trained to perform MT. I published an article on the influence of the type of anesthesia on outcomes (23). In 2017, The European Society of Minimally Invasive Neurological Therapy (ESMINT) Stroke Scholarship allowed me to spend an additional year at the Toulouse center. During this period, I have continued training, gathering data for the database, and jointly evaluated the level of MT performance in the Toulouse center. As a result, we have published another article focused on the influences of clot type on thrombectomy outcomes (24). This double center cohort study aims to compare the patients treated with MT in the period of the first two years after establishment of the thrombectomy service in Toulouse in 2015 and Belgrade in 2018. The Toulouse biobank prospective database (DC2016-2804) officially opened 1 January 2015. A similar ongoing MT registry started in Belgrade 1 January 2018.

The goal of the Toulouse prospective database was to check if the result of thrombectomy, when performed by non-selected operators on a wide variety of different clinical situations of non-selected patients, would remain similar to the results of the main RCTs where operators and patients were highly selected. Indeed, in routine practice patients are not selected by inclusion/exclusion criteria but by clinical judgment and a common decision of both the neurologist and neurointerventionalist. Therefore, many treated patients would have been excluded from all the RCTs such as patients with: low ASPECTS ($\leq$ 5), low NIHSS score ($\leq$ 5), cervical occlusions without intracranial occlusion (tandem occlusion), distal occlusions (distal M2 and beyond), posterior circulation stroke, long delay after onset (>6 hours), and very old patients (>80, >90 years of age). It was then essential to confirm that widening the criteria for MT will not affect the benefit of the treatment in regard to the clinical evolution at three months.

The goal of the Belgrade prospective database was to check if the result of the main RCTs, all of them done in Europe or the USA, would remain valid in Serbia despite a less well-organized health care system, stroke unit network, and less access to rehabilitation care. There are, for example, two main differences between Belgrade and Toulouse: The pre-thrombectomy imaging is done by computed tomography (CT) instead of multimodal magnetic resonance imaging (MRI) and thrombectomy is predominantly performed under LA instead of GA. We aimed to show that MT is as efficient in avoiding dependency and death in developing countries compared to Western Europe and USA.

1.1.2. Epidemiology and socioeconomic impact

After heart disease, AIS is the second most common single cause of death in Europe, with more than one million deceased per year (25, 26). Mortality within the first month is around 30%, accounting for 9% of deaths in men and 12% of deaths in women each year (27, 28). Most of the people do not die from AIS and it is the leading cause of long-term disability, with loss of independence in one-third of the survivors (29). One of the patient's most frequent fears from stroke is not mortality, but to remain severely disabled, staying in the nursing home for the rest of their life, and being dependent on help from others.

From a socioeconomic point of view, stroke represents a major public health burden worldwide. It is a very common disease and it is estimated that one in three people was touched by stroke either as a patient or as a family member. Across Europe, the burden of stroke is unevenly distributed. The incidence and mortality in northern, western and southern countries remain lower, compared to the central and eastern parts of Europe (30-32). The total annual amount spent for stroke in Europe is estimated to be €45 billion (33). The distribution of the high cost of stroke (in euros): 20 billion spent for direct care, 9

billion for the loss of productivity, and 16 billion for informal care (26).

The tendency for decreased AIS incidence and mortality in developed countries may reflect both an improvement in risk factor control, as well as an improvement in life expectancy owing to reduced hypertension, hyperlipidemia and smoking reduction. In addition, an improvement in acute stroke care may have led to an overall reduction in the percentage of stroke hospitalizations. The importance of long-term therapeutic care after AIS cannot be stress enough, as many patients will improve in the rehabilitation period of the first month after stroke, but improvement can be extended years after stroke.

While there have been reports of reduction in AIS incidence and mortality in developed countries, the opposite was observed in low-to-middle income countries. In the last few decades, Central-Eastern European countries experienced an increase in stroke incidence and related mortality, with expected growth in the total number of AIS per year caused by the aging population, while on the other hand, there is a mild decline in stroke incidence in developed countries (34). The reasons for these differences are unclear; however, these patients are unlikely to have access to the same quality of acute stroke care and secondary stroke prevention measures as seen in higher-income countries (35). Furthermore, from the public health perspective, there is a need to monitor stroke burden on a global scale and compare burden between different countries and regions over time. Evidence-based approaches to organization and planning of stroke care and services require accurate on-going data on stroke incidence, prevalence, and outcomes. In developed countries, trends and projections relative to other major diseases should be calculated to adapt strategy of stroke care and optimize service developments. The countries with higher burden of stroke typically lack prospective stroke registries, and for the analysis multiple sources of regional and local information had to be extrapolated (36). As the data are not standardized, epidemiological analysis could be looked upon as exploratory. Because of substantial inequalities in stroke services between and within countries in Europe, research priorities and targets in stroke between 2018 and 2030 have been set (37).

Mechanical thrombectomy has proven to be one of the most powerful medical treatments, with NNT of around 2.5 (38). With this evidence of clinical effectiveness of MT, cost-effectiveness is also investigated from the economical point of view. Recent papers demonstrated not only cost effectiveness but also possible cost saving effects of MT (39, 40). The analyses suggested that although EVT was associated with higher costs, it also resulted in improved patient clinical condition. The higher hospital costs are later compensated in the nursing home and rehabilitation center. When data was stratified by age group, both cost-effectiveness and cost-saving was found for the patients who were less than 70 years old, while for the octogenarians and nonagenarians treatment was still cost effective (41).

Numerous challenges yet remain to be address. Clinicians and investigators are on the quest to uncover the underlying causes behind the many disparities in stroke burden and outcome observed in epidemiologic studies, to be able to design interventions that can improve stroke mortality and disability for all. It is critical for facilities to be transparent about their outcomes by collecting data on their performance measures and making them available for investigation and comparison.

In France, annual incidence of stroke is 2,000 per 1 million inhabitants (36). While the middle age of hospitalized patients remains stable around 74 years of age, augmentation is registered in the population over 85 years (42). Equally, a diminution is present in the population between 25 and 34 years and from 65 to 74 years. These changes could be explained with the extension of human lifespan, and better quality of life with the implementation of effective prevention strategies in the younger population. There is also a growing rate of incidence in the population younger of 65 years that comprises around 25% of cases, which is a negative trend worldwide (42).

In Serbia, the IS incidence is considerably higher compared to developed countries (43). Every year AIS affects around 30,000 people (36). Though there was a trend of cerebrovascular diseases mortality rate declining in last decade in Serbia, mortality rates remain exceedingly high (44). Specific characteristics of both centers are presented in Table 1.1 and are based on the burden of stroke report for

2017 (45).

Table 1.1. Specific characteristics of both centers

	Serbia	France
Population:	7,498,001	63,601,002
Incidence estimate (GBD 2015)	24,101 strokes/year, 172.1 strokes per 100,000 inhabitants annually age- and sex-adjusted	57,174 strokes/year, 46.7 strokes per 100,000 inhabitants annually age- and sex-adjusted
Prevalence estimate (GBD 2015)	106,001 strokes, 792.7 per 100,000 inhabitants age- and sex-adjusted	366,129 strokes, 349.0 per 100,000 inhabitants age- and sex-adjusted
Mortality (GBD 2015)	21,861 deaths due to stroke/year, 149.2 deaths per 100,000 inhabitants annually age- and sex-adjusted	47,671 deaths due to stroke/year, 31.5 deaths per 100,000 inhabitants annually age- and sex-adjusted
Healthcare system	National Health Service, free at point of use	National health insurance (national insurance contributions) covers all medical expenditure.
Healthcare cost of stroke:		Total € 1,973.2 million, € 30 per capita (26)
National strategy	in developing phase	The National Stroke Plan gave additional funding for patients treated in a stroke unit and treated with thrombectomy. Regional health agencies have a supervisory role with special responsibility for coordination between medical and social service.

1.1.3. Stroke care organization

Studies have consistently demonstrated that dedicated stroke wards in hospitals, known as Stroke Units (SU) are associated with better clinical outcomes as this is where stroke patients are admitted and what enables multi-professional teams to look after them. In 2003, an agreement was reached between the AHA/ASA and The Joint Commission regarding the process of certification for stroke care based on treating AIS with tPA (7). As a result, in 2004 Stroke Center Certification was implemented. In 2012 a two-level certification was proposed, including the standards concerning acute stroke care recommended by the Brain Attack Coalition (46). Consequently, two types of centers were differentiated: Primary Stroke Centers (PSC) and CSC. However, CSCs were required to ensure more extensive medical and surgical care such as the provision of 24/7 endovascular procedures. Stroke units fully complying with these requirements are certified by the European Stroke Organization (ESO). It is worth pointing out that there is a difference when it comes to designating the two types of centers. Namely, PSC is designated as an ESO Stroke Unit, while CSC is designated as an ESO stroke center. Both PSC and CSC provide patient admission for a few days. In 2015, after RCTs had confirmed that endovascular treatment (EVT)

substantially enhances clinical outcomes of AIS patients with anterior circulation LVO, European recommendations suggested the use of endovascular treatment in CSC (8–10). Regarding the imaging of stroke patients, the guidelines have increased the number of centers performing CT on a routine basis, with CTA available in a growing number of facilities. The ESO certification guidelines have also made MRI and more advanced imaging techniques compulsory for CSC (47).

Reasonable access to a primary stroke center or a center containing an SU or an SC varies between countries depending on the developmental level of transportation and road networks (11). Patients who do not have timely access to a primary stroke center may benefit from reaching out to a center with telemedicine support through a hub-and-spoke communication with a center providing stroke expertise. Telestroke is a mean aimed at providing stroke expertise to deprived areas without a dedicated SU and stroke care available. When applied with competence, it is a viable alternative option functioning remotely when it is not possible to receive in-person care. Moreover, it increases delivery of rtPA and is implemented within adequate standards. The AHA/ASA have issued policy statements to improve the status of telestroke activities, as well as the guidelines concerned with the practical aspects of the telestroke system (12-14). "Telethrombolysis" in patients suffering from stroke has been approved and certified as evidence level IIb2 based on the ESO guidelines (with level IA representing the highest level of evidence) (2).

Presumably, the quality of stroke care varies considerably across Europe. The latest studies show that:

1. In most European countries, access to SUs and delivery of IVT and EVT are far below the highest country rates and there are significant inequalities among and within different countries.
2. Only 7.3% of all acute ischemic stroke patients receive IVT, while only 1.9% receive EVT (3). Furthermore, there is a significant correlation between the number of stroke units per one million inhabitants and delivery rates of both IVT and EVT (15).

In recent years, for pragmatic reasons, some of the primary stroke centers have set up an angio-suite and begun with EVT focusing primarily on MT which is usually not available around the clock. In 2018, a joint statement of a group composed of the European and American societies proposed three levels of stroke centers (48). The recommendations regarding the safest and most favorable conditions for practicing acute ischemic stroke intervention (AISI) were produced in line with current expert knowledge and evidence available. Ideally, all patients would be cared for at a Level 1 center. A Level 1 center provides comprehensive neuroendovascular care, as well as therapy, including comprehensive treatment of vascular diseases affecting the brain and spine (49). Nonetheless, not all patients have timely access to such a center due to geographical, traffic, and transportation conditions. For this reason, the group defined the recommendations on the minimum requirements for organizing stroke centers providing only MT for AIS, but not for other neurovascular diseases (a Level 2 center). Finally, some centers have an SU and offer IVT, but they do not provide endovascular stroke therapy (a Level 3 center). Together, Level 1, 2, and 3 centers form a network of a complete stroke care system.

It is highly recommended that the Level 2 center is organized in cooperation with a Level 1 center, so that they can pursue the objective of collaborative work with the Level 1 center for the following purposes: neurointervention training, continuous medical education, mortality and morbidity rounds, expertise advice either by tele-consultations or in-practice, a 24 hour, 7-day-per-week coverage, referrals, etc. (49).

1.2. The relevance of time in AIS treatment

Acute ischemic stroke caused by LVO is a neurologic emergency. Reperfusion can abort the progression of the infarction and is a key factor for favorable clinical outcomes. Initial experience suggested that the treatment benefit is highly time-sensitive (38). Conversely, more recent data suggests

that there exists a subgroup of the patient population with a high tolerance for ischemia, which continues to benefit from MT even at a late time window (19, 20).

After the NINDS trial on IV tPA, time became a vital factor in achieving favorable outcomes and an integral consideration in patient selection (50). Subsequently, complete stroke system service is focused to be time-efficient for the patient transfer, triage, and thrombolysis. Awareness of the impact of time delay on brain tissue loss was formulated by the phrase “time is brain”. In the absence of acute reperfusion therapy, there is an estimated loss of 2 million neurons per minute (51).

In 2015, five pivotal trials established MT as the standard of care for ACLVO strokes (9-13). Time from symptom onset to puncture ranged around 6 hours was a major criterion for patient selection. A HERMES individual patient-level data meta-analysis indicated that the benefit of EVT with BMM over BMM alone was not significant after 7.3 hours from stroke onset (38). The REVASCAT trial investigators demonstrated that for every 30-minute delay in reperfusion, the odds for achieving a good functional outcome decreased by 26% (52). Therefore, the time-dependent nature of stroke pathophysiology was evident in the setting of an LVO (Figure 1.1.). As supported by this data, the American Heart Association (AHA) and American Stroke Association (ASA) guidelines offered a class I level A evidence recommendation that MT should be performed up to 6 hours from stroke onset (15). This was supported by the ESO/ European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines (47).

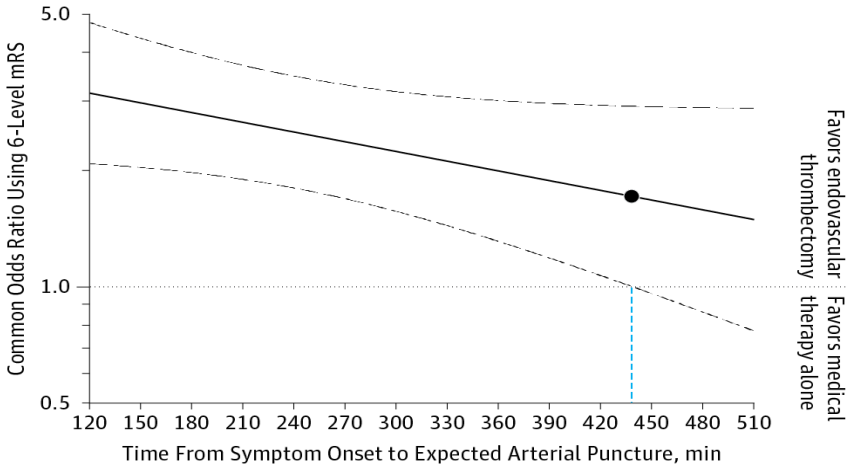

Figure 1.1. Association of time from symptom onset to expected time of endovascular thrombectomy procedure start (arterial puncture) with disability levels at 3 months. Modified according to the reference (38).

In 2017, the DAWN and the DEFUSE-3 trials proved that the time window of MT can be extended from 6 to 24 hours (19, 20). A key feature in these trials was patient selection with the use of advanced imaging, therefore favoring a tissue-based paradigm over the time-based paradigm, in the late time window. In 2018, the AHA/ASA updated guidelines, followed by the 2019 ESO/ESMINT guidelines, MT was recommended within up to 24 hours (47, 48). This data changed the relevance of time in patient selection for EVT.

1.2.1. The concept of penumbra and tissue clock

The penumbra is assigned as the region of almost or a half-shadow, in contrast to umbra or “shadow”. Its root is the Latin word *paene* "almost, nearly.” It has only a portion of the light coming from the source that is obscured by the occluding body. It represents the area between the umbra and outermost point of the light source, e.g. the Sun, and maybe noted during solar eclipse (Figure 1.2.) (53).

In ischemic stroke, penumbra represents ischemic brain area that is threatened by infarct due to low cerebral blood flow in the region of occluded artery and remains salvageable for an undetermined short time. The patient’s clinical deficit is a combination of infarct core and penumbra. Penumbra is characterized by loss of electrical function with an intact cell membrane. Rescue may be possible for these parts that are not yet infarcted, and tissue at risk is maintained vital mainly by the pial collateral circulation. Without reperfusion, the penumbral area will grow into the infarct core, with an individual pace.

The penumbra typically occurs when cerebral blood flow (CBF) drops below 20ml/100g/min Neuronal death starts at CBF below 10-12ml/100g/min. Increased infarct due to glutamate release, inhibition of ionic pumps and ATP depletion, all leading to the disruption of intracellular processes (Figure 1.3.) (54, 55).

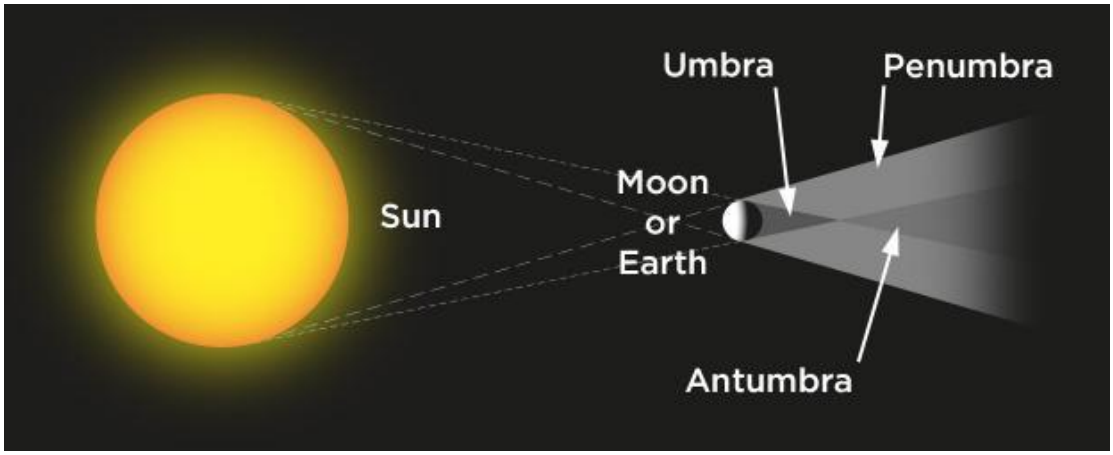

Figure 1.2. Penumbra - area between the umbra and the outer most point partially shadowed. Modified according to the reference (56).

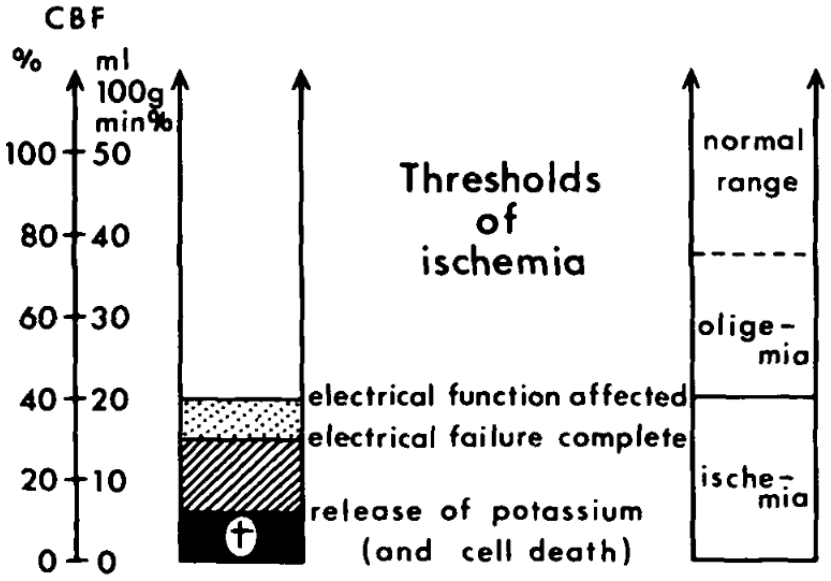

Figure 1.3. Ischemic thresholds for electrical failure and for release of cellular K+. Modified according to the reference (54).

The basic idea is to discriminate already infarcted from the salvageable brain tissue and select the patients that would not be treated, in order to avoid futile thrombectomy (Figure 1.4.). There are two important questions that must be asked: how much brain tissue is dead and is there a substantial amount of viable tissue left to save?

The question of the volume of the infarcted brain is primarily a safety profile, as the larger volume is believed to be related to increased risk for symptomatic intracranial hemorrhage (sICH). For IVT a non-contrast CT is sufficient to determine if a patient is eligible: if there is no hematoma and estimated infarct size is less than one third of the MCA territory (57). Similarly, cut off values of 50 and 70 cm^3 have been proposed for the infarcted volume (9, 13). If ASPECTS is used, a score ≤ 5 corresponds to a 70 cm^3 threshold volume and is considered a bad prognostic score (58).

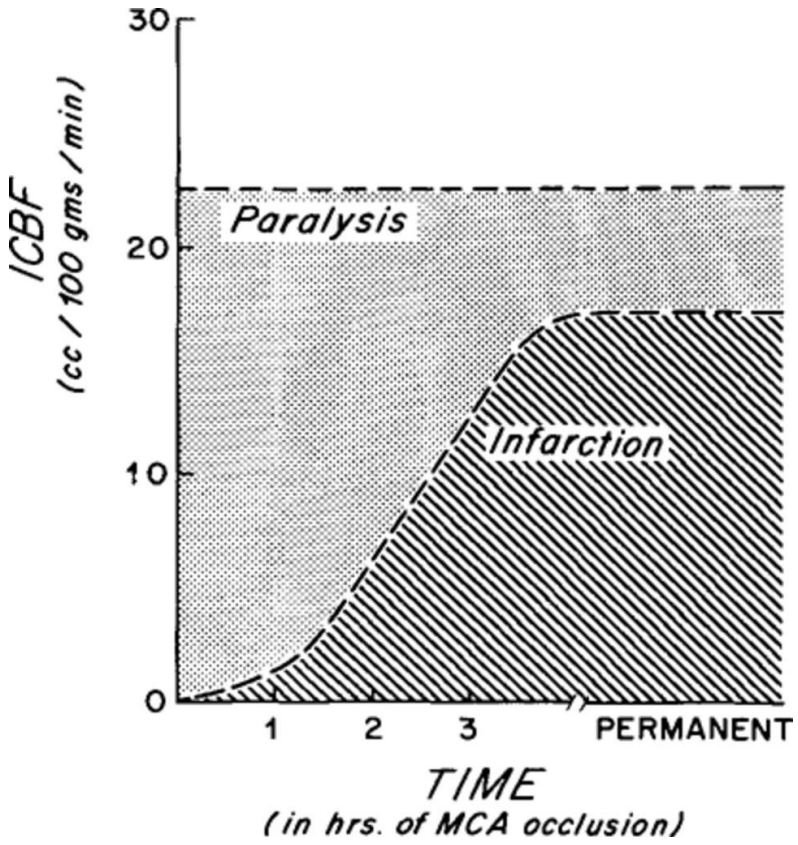

Figure 1.4. Thresholds of focal cerebral ischemia in awake monkeys. Modified according to the reference (55).

It seems that a more important question instead of how much brain tissue is dead, is whether there is a substantial amount of viable tissue that can be preserved, and a higher ratio of viable to unviable tissue. For this purpose, different mismatches are used, such as simpler clinical-imaging (i.e. ASPECTS) mismatch using non-contrast CT (NCCT), to more advanced imaging modalities like CT or MRI perfusion.

The basis for prolonged brain tissue survival, despite blockage in oxygen supply by the main artery, is mainly supplemental delivery by leptomeningeal (pial) collaterals. The MCA territory collateral supply is obtained through ipsilateral ACA and PCA. Such alternative arterial routes are developed on individual basis, leading to variability in time for complete infarct development. It is the result of genetic and environmental influence and in general, their existence is not predictable in advance. Only the patients with severe ICA stenosis or occlusion are a priori expected to have well-developed collateral circulation, as a result of vessel plasticity and adaptation to the gradual ICA closure. Carefully selected patients with long-lasting penumbral tissue due to well-developed collateral circulation, may benefit from MT even at very late time from the AIS onset (12, 19).

1.2.2. Heterogeneity in stroke pathophysiology

After the initial experience that suggested that the benefit of treatment is time-sensitive, recent data has shown that there is a subset of the population with high ischemic tolerance. This population continues to benefit from MT, even at a late time window. Almost linear dependency of the clinical outcome on procedural time metrics is an average estimation, and in reality, the speed of infarct growth

is different in different individuals. Roughly speaking, there exist two distinguished LVO stroke phenotypes: “fast progressors” and “slow progressors” of infarct growth (59, 60). For slow progressors time is less important since the ischemic core grows very slowly because they usually have well-developed pial collateral circulation that can maintain penumbral tissue for a longer period of time (60).

1.2.3. Time dependent neuroimaging

A time-based approach to patient selection is enforced by AHA/ASA guidelines (61). Derived from all the RCTs was a generalization that most LVO strokes in the 6-hour window have sufficient mismatch (viable penumbra), and advanced imaging is not required and may be potentially harmful in regard to time loss. Beyond 6 hours, advanced imaging (CT perfusion or MRI perfusion) is deemed to be necessary, as the proportion of LVO strokes with respectable penumbra/core mismatch is unknown (62, 63). Recent retrospective data suggests that simple NCCT could be sufficient in detecting patients with respectable penumbra using clinical/ASPECTS mismatch, even in a 24-hour window (63, 64).

1.2.4. Time dependent workflow

Recent studies demonstrated a correlation between a shorter time from onset to reperfusion and good clinical outcome after MT. A HERMES patient-level meta-analysis demonstrated that the clinical benefit of MT is highly time-dependent (38). The associations of a time delay with poorer outcomes were magnified in the time segment from the emergency department of the CSC arrival (at door) to reperfusion (Figure 1.5.). MR CLEAN registry demonstrated that for each hour delay in reperfusion there was a 7% decreased probability of a good outcome (65). The absolute difference in good outcomes between the endovascular and control groups revascularized within 2 hours of stroke onset was 33%, decreasing to 16.5% at 6 hours (38).

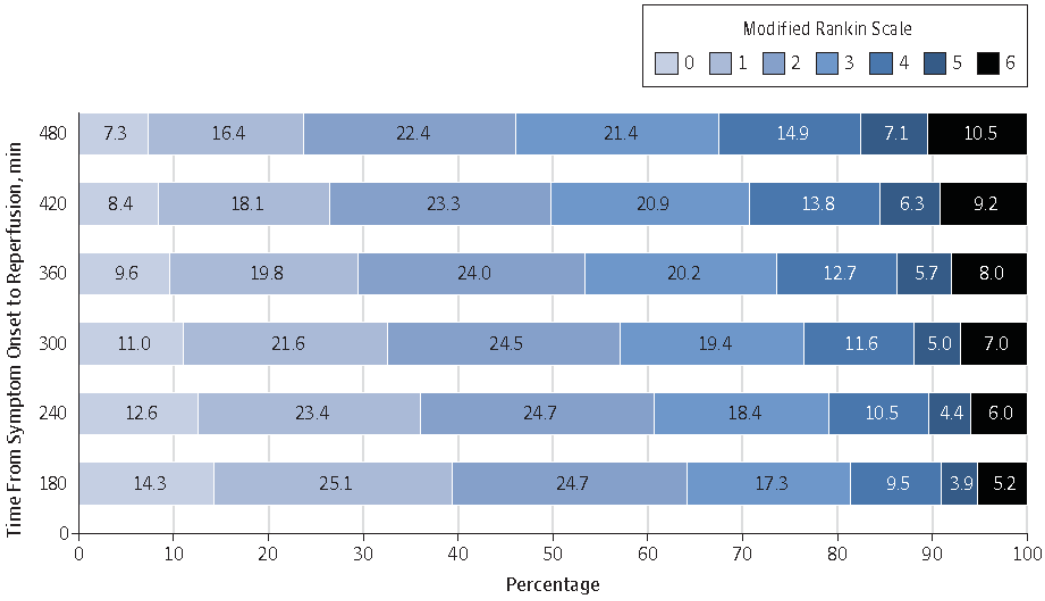

Figure 1.5. Odds ratio for less disability at 3 months in endovascular thrombectomy vs medical therapy alone groups by time to treatment. Modified according to the reference (38).

Every additional hour between imaging and arterial puncture was associated with a 26% reduction in the odds of the mTICI score 2b/3 reperfusion, and this time interval had the strongest association with final reperfusion (66). Once it is established that patient is a candidate for MT treatment, time dependency is much steeper because of the elimination of the ineligible patients from data analysis. For that reason, there is an importance of time dependency on future outcome regarding times from imaging studies. Though time to arterial puncture represents the efficacy of in-hospital patient displacement, time from imaging to AP is the most time-sensitive part of the workflow. For every 15 minutes, that the vessel is recanalized faster after patient arrival to EVT capable center, four out of 100 patients would have decreased disability (Table 1.2) (38).

Table 1.2. Number Needed to Treat, Benefit per Thousand, and Minutes Needed to Treat for faster reperfusion times. Modified according to the reference (38).

	Onset to reperfusion		ED arrival to reperfusion	
	Less disability	Functional independence	Less disability	Functional independence
Benefit per thousand per 15 min faster	16	9	39	25
NNBT per 15 min faster	62	112	26	40
Minutes faster needed to treat (MNT)	9	17	4	6

ED (Emergency department); Benefit per thousand (For every 15 minute faster achievement of substantial reperfusion, number of patients who would have improved outcomes among 1000 patients experiencing reperfusion); NNTB (Number needed to treat for benefit – the number of patients needed to have reperfusion achieved 15 minutes faster for 1 more patient to have a better outcome); MNT (Minutes faster needed to treat) –the number of minutes faster reperfusion needs to be achieved for 1 more reperfusion patient out of 100 to have a better outcome (lower 3 months disability by 1 or more grades on the mRS).

Around 15% of all patients have a large infarct core on the imaging study at presentation (ASPECTS ≤5) in the first 6 hours and only 4% in the first 3 hours from symptom onset, representing fast and super-fast progressors (67, 68). The 95% of the patients in the HERMES collaboration had a core/penumbra mismatch by SWITFT PRIME (DIFUSE 3) criteria, and 78% of patients had a large penumbra volume of >60ml (69).

1.2.5. Workflow optimization

Workflow optimization can be implemented with local adaptations, in any center offering EVT of stroke. Early activation of all team members is essential to obtain a time reduction of around 45 minutes and requires coordination with EMS and multidisciplinary protocols (70). In-hospital workflow is optimized by using parallel instead of sequential processing. Implementation of feedback on time intervals to the entire team on regular basis can have a time-saving effect of more than 1 hour (71-74). Evaluation of time metrics can simply be added to existing regular weekly or monthly meetings, or done by the other means of communications (email, mobile phone groups). One of the meta-analysis showed a difference in time to treatment effect of 26 minutes, with a total absolute risk difference of good functional outcome of 12%, which is higher compared to around 4% of absolute risk difference per hour as seen in the meta-analysis of five endovascular stroke RCTs (38). The same meta-analysis showed no difference in the rate of symptomatic intracranial hemorrhage, but significantly lower mortality among patients in the group with an optimized workflow. The organization of prehospital workflow is highly dependent on local conditions. Probability models were designed to predict the best transport model for

each scenario and region. One of them showed in a case of a transfer time superior to 45 minutes between the PSC and the CSC, and if the patient is close to a PSC, the drip-and-ship (indirect admission) paradigm is better than mothership (direct admission) (75). Under real-world conditions, in which PSC workflow is slower than ideal, the mothership strategy is favorable to the drip-and-ship model in all scenarios (76).

1.3. Indications for mechanical thrombectomy

Patient selection for MT is based on the criteria used in published RCTs, which were subsequently incorporated into international recommendations and guidelines. Since results of the aforementioned studies were published, MT became a part of ASA/AHA guidelines published in 2015. Summarizing AHA/ASA and ESO/ESMINT guidelines, a patient with a LVO occlusion of the ACI or MCA segment (M1), if the treatment can be initiated (arterial puncture) within 6 hours of symptom onset or last known well (LKW), is eligible for MT given they fulfill the following criteria: age 18 years or more, NIHSS score and ASPECTS 6 or above, and a baseline mRS score between 0 to 1 (Class I; Level A Evidence). Treatment is recommended with the use of a stent retriever and IV tPA for eligible patients (Table 1.3.) (15).

Table 1.3. Criteria for MT and unanswered questions and considerations

Criteria for MT (AHA/ASA)
Pre stroke mRS 0-1
ICA or M1 occlusion
≥ 18 years
NIHSS ≥ 6
ASPECTS ≥ 6
Treatment (i.e. arterial puncture) begun within 6 hours
MT unanswered questions and considerations:
Further extension of the time window
Low NIHSS
High NIHSS (large hypoperfusion volume)
Low ASPECTS (large volume core)
CS/LA vs. GA
IV tPA in addition to MT
Tandem occlusion (cervical ICA with distal embolus)
ACA and distal MCA occlusions (M2, M3, A1, A2, A3)
Posterior circulation

In the later time window (over 6 hours), patient selection is more complex. Based on the results of positive RCTs, AHA/ASA and ESO/ESMINT urged for the release of updated guidelines regarding early management of ischemic strokes. An extension of time window for MT to 16 (DEFUSE-3) and 24 hours (DAWN) was recommended (48). For the delineation of penumbral and infarcted core advanced neuroimaging is required, with CT perfusion (CTP) or MRI diffusion/perfusion studies with strict criteria defined for clinical-core mismatch by the DAWN trial, and target mismatch defined by the DEFUSE-3 trial (19, 20).

Based on new recommendations, more patients are now eligible for acute procedures and medications following stroke. Nonetheless, when AHA/ASA criteria are strictly employed for patient

selection eligibility of patients in the early and late extended time window criteria is only 11% and 9%, respectively (77, 78). The NNT in the HERMES, DAWN, and DEFUSE-3 trials were 5, 2.8, and 3.6, respectively (19-21). Limited eligibility (~10%) and large treatment effect (low NNT) suggests that strictly implementing AHA/ASA recommendations may be too restrictive and a larger population of patients can potentially benefit from EVT if more permissive criteria are applied. Although the guidelines do indicate uncertain benefits, MT may be reasonable for patients with AIS out of the recommended limitations. Latest analysis suggests benefit through all subgroups such as proximal or distal M2 segment, low ASPECTS and low NIHSS, including off-label criteria for delayed time thrombectomy compared to one applied in DAWN and DEFUSE-3 (Figure 1.6.) (19-21). Additional RCTs in the USA and Europe are already underway to determine the safety and efficacy of MT in patients with LVO outside current criteria.

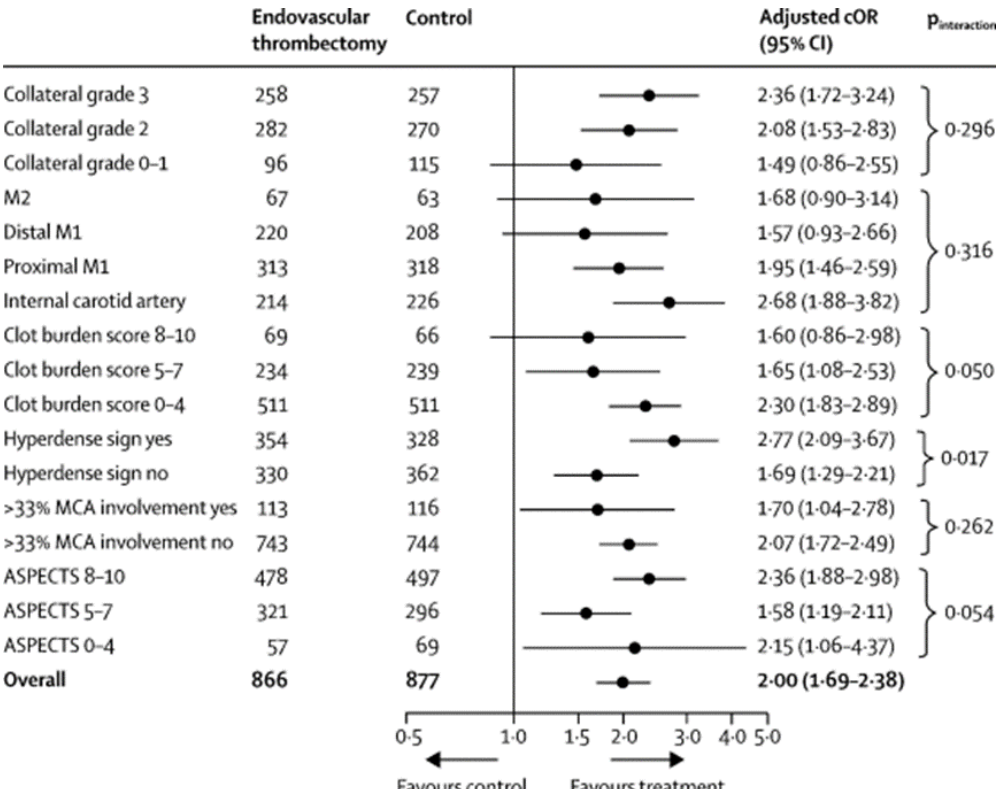

Figure 1.6. Imaging features, safety and efficacy of endovascular stroke treatment. Modified according to the reference (21).

Therefore, a strict application of these criteria severely hampers the overall impact of the treatment on the population as a whole (79, 80). Patients with aphasia have a major deficit and have NIHSS below 6. Others with fluctuating symptoms could be deprived if MT is denied or delayed. Center-specific patient-selection criteria may be broadened, depending on communication between the vascular neurologist, neuro-interventionist, and the patient and patient's family. At the current level of MT development, giving the grim prognosis of the disease, it is justified to try maximizing the benefit across all patients with LVO, and reduce overall disability due to stroke. This seems justified since the most fearful complication, sICH, was stable in all subgroup analysis of pooled patient RCTs data. In conclusion, we cannot do much harm by the procedure itself, the worst thing that could happen is futile

thrombectomy.

Additional special circumstances for MT include: dementia, thrombocytopenia, anticoagulation, terminal cancer (projected lifetime of ≤ 6 months), renal disease, aortic occlusion, and children. Considering AIS in children, there are not enough evidence for now. AHA/ASA recommendation: Stent retrievers "may be reasonable" in patients <18 years (Class II b, Level of Evidence C) (48).

1.4. Imaging of acute ischemic stroke

The selection of patients, who will benefit from reperfusion therapy, is one of the major concerns in reperfusion therapies. Since the advent of IV tPA brain imaging has been essential for stroke treatment decisions (50). The primary aim of imaging prior to fibrinolytic therapy is to support the diagnosis of AIS by the exclusion of hemorrhage as a cause of stroke, performed with NCCT or MRI. The second aim is to confirm no evidence of a large (more than one-third of MCA territory) completed stroke which is a relative and somewhat subjective criterion. For MT eligible patients who present in the first 6 hours need a non-contrast head CT to exclude hemorrhage, and CT/MR to screen for the LVO. Perfusion imaging is predominantly used for triaging patients eligible for MT beyond 6 hours from symptom onset.

1.4.1. Non-contrast brain imaging

Precise windowing of the NCCT images is essential to maximize the gray-white contrast, and correctly calculate the ASPECTS score (81). Default window presets are generally too wide (~80 Hounsfield unit (HU)) and sometimes set too high. Often quoted ideal stroke windows are window width (WW) of 35 HU window level (WL) of 35 HU, or WW of 40 HU and WL of 40 HU (82). However, it is suggested to always adjust window and level based on individual visual preferences. Many factors such as monitor grey scale values can affect the final output, and therefore it is better to rely on a window width and level that are individually comfortable in detecting the subtle grey-white differentiation (Figure 1.7.).

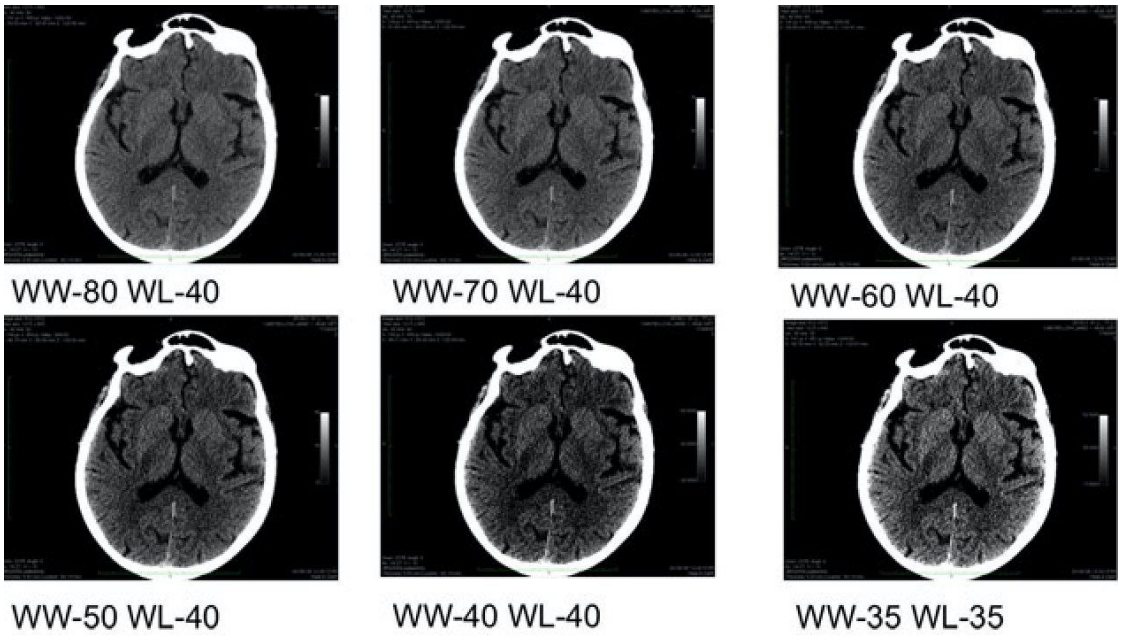

Figure 1.7. Different window level appearance on NCCT. Modified according to the reference (82).

Unilateral and asymmetric hyperdensity that can be found in any large vessel ("MCA hyperdense sign") may represent acute intravascular clot and should be further investigated with a CT angiography (CTA). Insular ribbon sign is an early AIS sign and represents loss of the grey-white differentiation in the external capsule/insula. It is important to look for the grey, white differentiation in all vascular territories, including the posterior cerebral artery (PCA) and the ACA. Identification of infarcted area is far more pronounced on DWI, compared to NCCT. Additionally, positive fluid-attenuated inversion recovery (FLAIR) imaging gives an indication of time elapsed from the AIS onset, which is especially valuable in unknown onset of symptoms. Positive T2* imaging gives good indication on thrombus burden and type of clot occluding the artery (83).

1.4.2. Infarct volume

Infarct volume is a strong independent predictor of a good outcome. However, it is not precise because there are patients with large infarct volume that will have good outcome and vice versa (Figure 1.8.) (84). Exclusion of these patients will be a loss of opportunity to help them. The proportion of low ASPECTS in the first 3 hours from symptom onset is around 4% and represents a population of super-fast progressors (68). In HERMES collaboration data analysis, a substantial penumbral volume of greater than 60cc was found in around 80% of the patients. The 95% of patients with perfusion on the baseline images had mismatch by DEFUSE-3 criteria (17, 20). HERMES study also demonstrated the benefit across a broad range of baseline imaging categories, including large infarcts (≥ 33% of middle cerebral artery territory or low ASPECTS score < 6), with an increased intracranial hemorrhage risk (21). In another study, investigators showed that while infarct volume is in general predictive of outcome, it is not that precise and could be misleading (84).

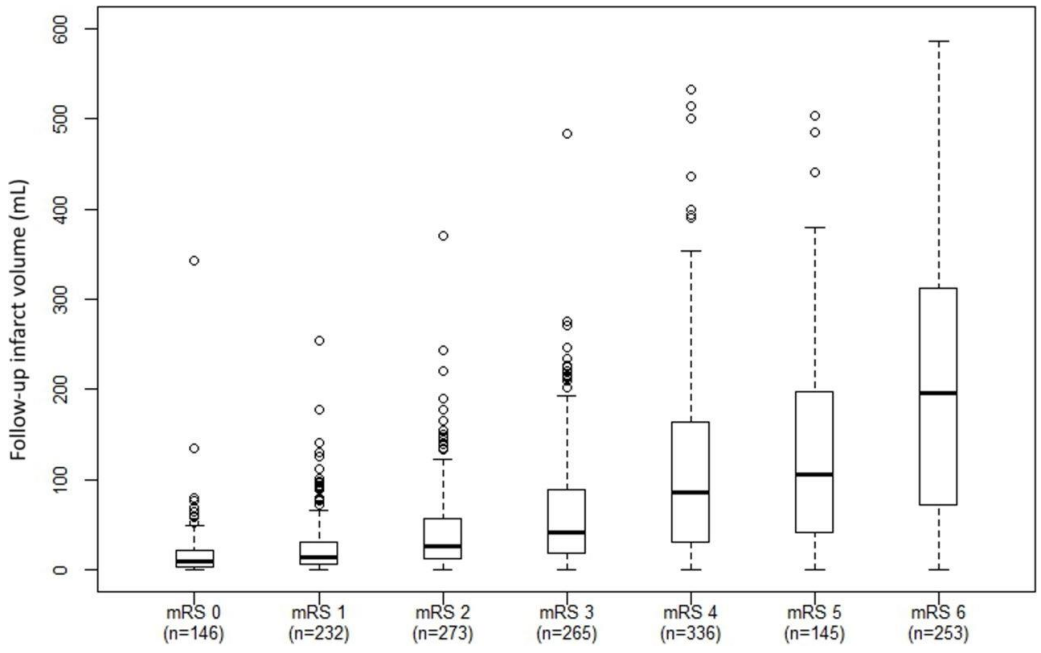

Figure 1.8. Follow-up infarct volume distribution per mRS score (infarct volume measured on NCCT at 24h after onset). Modified according to the reference (84).

1.4.3. The Alberta Stroke Program Early CT Score

The ASPECTS grading system is a 10-point scale used to steer decision making in the acute AIS (Figure 1.9) (85). Limitation of ASPECTS is restricted to MCA territory in the anterior circulation, and has a low inter- and even intra-reader variability (K= 0.13-0.32 and K= 0.04-0.47 respectively) (21). Another important limitation is the low sensitivity in the early period after stroke, as early cortical grey/white matter differentiation loss can be subtle and should be looked upon thoroughly. It is equally applied to MR diffusion imaging with the results even more precise than on NCCT. Furthermore, it is location dependent as ASPECTS 6 can be presented with moderate or severe neurological deficit. A further limitation is in the traditionally calculated on NCCT.

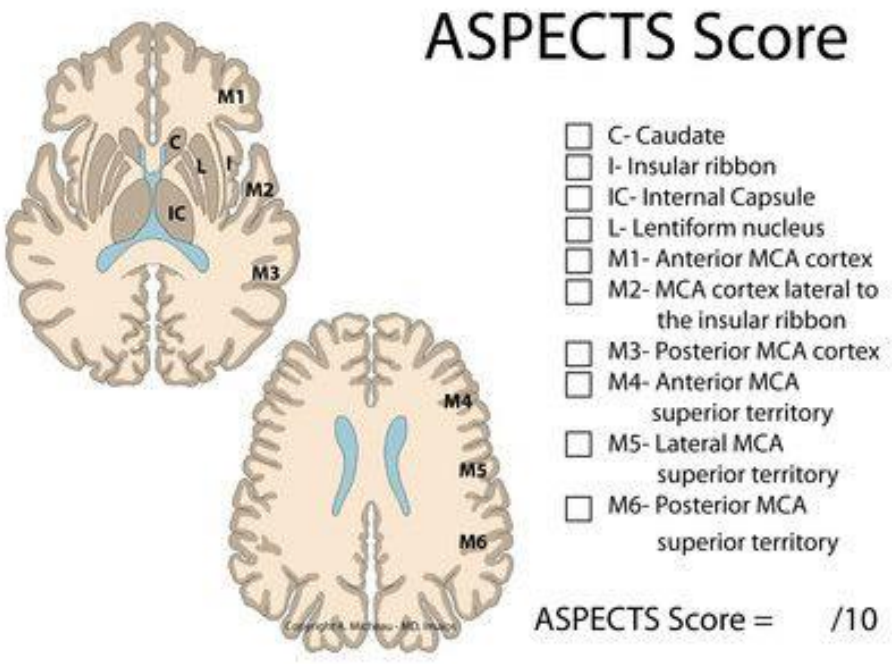

Figure 1.9. ASPECTS calculation chart. Modified according to the reference (86).

Early studies described ASPECTS as a good predictor of clinical outcome and sICH after IVT (82, 85, 87). The patients with early ischemic changes in over one-third of the MCA territory had a lower chance of good outcome after IV tPA with a threshold for high risk of ASPECTS ≤ 7 (88). ASPECTS < 7 roughly corresponds with an infarct volume of more than one-third of the MCA territory, most of the positive RCTs used ASPECTS to exclude patients (9, 10, 65). Correlation with MT functional outcome is less robust, compared to IVT (89). The score is limited to the anterior circulation, the template is unequally weighted, and correlation with lesion volume depends on lesion location. For the same ASPECTS there are different regions affected and hence different levels of disability. Moreover, faint hypodensity and well-established infarct are equally scored but could have different clinical outcome after depending on the level of neuronal loss. Thrombectomy studies rather pointed toward a linear relationship between ASPECTS and functional outcome (17). In the light of all the recent trials, the AHA/ASA guidelines changed in 2015, with MT becoming the standard of care for patients with LVO in the anterior circulation and an ASPECTS ≤6. Decision making should probably be age-adjusted, as negligible benefit has been achieved in those above 75 years of age (90). Conversely, younger patients who present early after the onset of symptoms have a higher likelihood of doing well despite having a

large infarct core (17). As most of the patients with low ASPECTS were under-represented in positive RCTs, it remained unknown if these patients could benefit from MT.

ASPECTS on MRI (DWI-ASPECTS) is found to be more accurate and is in practice somewhat lower than estimated on NCCT (91). For that reason, one-point lower ASPECTS was accepted if measured on MRI compared to CT (92).

In summary, despite its limitations, ASPECTS remains a simple, reliable and reproducible tool for prognosis assessment and treatment decision in acute stroke treatment. It will continue to be an important score for the management of patients with AIS, and the recently developed electronic assessment of ASPECTS (e-ASPECTS) that has been developed in order to avoid observer bias.

To optimize resources, many centers use only CT/CTA to select patients for MT based on the following criteria: ASPECTS score ≥6, NIHSS ≥6, presence of LVO, and time from stroke onset up to 6 hours. For wake-up and stroke cases beyond 6 hours from onset, most centers select patients for MT based on CTP or MRP mismatch findings. RAPID and OLEA perfusion software are designed and progressively used, for automated patient selection for MT (10, 19, 93). For wake-up stroke cases, most centers select patients for MT based on MRI findings (DWI/FLAIR mismatch).

1.4.4. Angiographic identification of large vessel occlusion

The advent and wide-spread availability of angiographic imaging enabled the identification of LVO and proper patient selection for MT (94, 95). The Interventional Management of Stroke (IMS) III trial failed to show a benefit for ET plus IV tPA over IV tPA alone, but the post hoc outcome analysis of the subset of patients selected by CTA demonstrated a benefit in favor of MT (96). As a result, all the seven positive pivotal ET trials used vascular imaging as an inclusion criterion, the large majority CTA, for the identification of ACLVO (15). Long CTA from the aortic arch is required to assess any obstacles in the large vessel catheterization (tortuosity, stenosis, and occlusion).

The first available way for the CTA or MRA interpretation is the source images. Another format for viewing is thick slab maximum intensity projections, where elongated vessels in the image plane are obtained when several millimeters of scan data are collapsed together. Finally, three-dimensional reconstructions are used for the angiographic analysis from various angles. The ability to distinguish the length of occlusion when the thrombus occludes the distal ICA is diminished, as there is often minimal flow into the internal carotid artery and the patent proximal ICA may appear occluded, simulating a TO (ICA pseudo-occlusion).

1.4.5. Perfusion imaging

Interest in identification of viable but ischemic tissue by perfusion imaging dates back to the 1990s, but it was not until more recent years that RCTs used perfusion imaging for the inclusion criteria, and demonstrated a benefit of revascularization. The DAWN and DEFUSE-3 trials selected patients in the late time window (> 6 hours) based on the ability of perfusion imaging to detect small core infarction or extensive areas of tissue at risk, respectively (19, 20). In these trials, investigators used an automated software platform RAPID (iSchemaView) with accurate and reliable perfusion and diffusion imaging processing on CT or MRI scanner. The results include the volume of core infarct (TMax exceeding 6 seconds), the penumbra and the mismatch ratio. The tissue at risk had to be at least 15 cc and the ratio of TMax to CT CBF had to be ≥ 1.8. Penumbral imaging analysis also was performed with the use of RAPID in the SWIFT PRIME and EXTEND-IA, trials that had the highest rates of favorable clinical outcomes following MT ever achieved (9, 13). Based on two late time window trials, AHA/ASA and ESMINT/ESO recommendations promoted perfusion imaging as necessary in the after-6-hour population.

A time-contrast (or susceptibility for MRI) curve is generated on a basis of time-resolved measurement of an intravascular arterial to venous flow (97). This curve is the source of most of the perfusion imaging data: Cerebral blood volume (CBV) is generated from a measurement of the area under the time-contrast curve; cerebral blood flow (CBF) is generated from the slope of the arrival curve; mean transit time (MTT) is calculated as the ratio of volume overflow; TMax is the time to peak contrast; time to drain (TTD) is a function of the washout curve. MTT, TMax, and TTD are all the parameters that reflect autoregulatory vasodilation and reduced blood mean transit time and are generally used for detection of the tissue at risk. However, these perfusion patterns are not specific for penumbral tissue and there can be some overlapping as some areas may be hypo-perfused but not ischemic (benign oligemia) while others may already be irreversibly directed towards necrosis (apoptosis) but are not yet projected as infarction (98).

In the real-world situation, by the visual assessment or simple calculations of the penumbra that is indicated by the perfusion–diffusion mismatch on MRI or perfusion CBF volume mismatch on CT. The precision of perfusion parameters for the definition of core infarction is time-dependent, with greater accuracy at later time points (99). However, there is definite value for perfusion imaging in early (≤ 6h) time-window (56). Identification of a larger perfusion defect can help in finding the exact LVO location, as M2 occlusions can sometimes be difficult to appreciate on CTA. Perfusion imaging can also help in reducing unnecessary utilization of expensive endovascular material by excluding the patients that will not benefit from MT (futile thrombectomy). This could be essential in the mid- and low-income countries where hospitals often face a problem of material shortage.

1.4.6. Future directions

In the future, fully automated software (RAPID; OLEA), will be in wide-spread use for the assessment of the infarct core, and prediction of outcome based on synthesis of all available data. Avoidance of repeated imaging is getting into practice to shorten time to revascularization. Though CTA to screen for LVO is important, even though many centers, including ours, routinely take transferred patients from outside hospitals directly to angiography. These patients already have NCCT taken on other hospital showing absence of hemorrhage and extensive ischemic demarcation, are generally ones with high NIHSS scores and that are approaching the 6-hour from AIS onset. Patients with hemiplegia, neglect and gaze deviation are sent directly to the angio-suite, as these are typical LVO occlusion signs. This practice shortens the door-to-revascularization time by avoiding repeat imaging in the ED.

1.5. Clinical considerations

1.5.1. Acute ischemic stroke etiology

Stroke as an acute impairment of brain function caused by central nervous system focal injury due to a vascular origin (100). The cause is a sudden disruption of blood flow to the brain neural tissue. Of two types of stroke, ischemic (a blocked artery) is by far the most common (85%), the second is hemorrhagic (a ruptured artery) that include cerebral and subarachnoid bleeding (15%) (101).

The most commonly used etiological classification Trial of Org 10172 in Acute Stroke Treatment (TOAST), denotes the five subtypes of ischemic stroke: 1) large-artery atherosclerosis (25%); 2) cardio-embolism (20%); 3) small-vessel occlusion (20%); 4) stroke of other determined etiology (5%); 5) stroke of undetermined etiology (30%) (102). The most common cause of atherosclerosis is anywhere from the aortic arch and extra-cranial head and neck vessels. In these settings, a ruptured plaque causes thrombosis in situ or the pieces of clot break loose end emboli blood vessels distally. In a prospective multicentric registry on 2637 individuals, cardioembolic stroke accounted for the half of the LVO patients (50.4%),

followed by large-artery atherosclerosis (25%), stroke of undetermined etiology (17.1%), and stroke of other determined etiology (7.1%) (103).

1.5.2. Stroke severity

Standardized clinical assessment scale directly quantifies the degree of neurological deficit, facilitates communication between medical practitioners, helps to triage patients for thrombolytic or mechanical intervention, identifies those at higher risk for complications such as sICH, and allows objective measurement of changing clinical status.

The most commonly used scoring system for assessment of the severity of neurologic deficits after AIS is the NIHSS (104). Initially used as a research tool, over time it has become an essential for clinical stroke quantification purposes. The NIHSS is valid for predicting infarct volume and can serve for a stroke severity quantification (105). The NIHSS is an excellent predictor of both short- and long-term outcome of AIS patients. A large prospective study on the data of Screening Technology and Outcomes Project in Stroke (STOPStroke), NIHSS score of > 10 demonstrated 81% positive predictive value for LVO (106, 107). In patients presented with NIHSS scores ≤10, about 90% of patients had no proximal LVO, but 55% of all patients did suffer from LVO, and would be indicated for MT (107). Formal stroke scores or scales such as the NIHSS that can be performed rapidly, that may be administered with accuracy and reliability by a broad spectrum of trained healthcare providers, have demonstrated utility and are recommended by the 2018 and 2019 stroke guidelines (47, 48, 61).

1. In patients harboring ACLVO with NIHSS score ≥ 6 thrombectomy is recommended (class I, level A).
2. MT may be considered on a case-by-case basis in patients with ACLVO and NIHSS score < 6 when associated with disabling symptoms (class II a, level B-NR). When treating these patients, complication and hemorrhagic rates should be kept below those reported in RCTs.

1.5.3. Stroke prognosis

Since the advent of MT, functional independence rates (mRS 0-2) 90 days after AIS due to LVO have significantly increased. A good outcome is found to be inversely related to the age, NIHSS score, sICH and ischemic core volume (10, 17). It is highly time-dependent, as functional independence is more pronounced in the early-time window (6-8 hours from LKW). Time importance exists but it is less profound in the late-time window (more than 8 hours from LKW), since the patient selection depends on penumbral mismatch and presence of salvageable brain tissue (59, 60). It is explained with progressive loss of brain tissue that it is a time-dependent process, previously quantified to be around 1.9 million neurons per minute. However, this is an average estimation and accumulating evidence suggests large individual variation. The rate of neuron loss in patients with LVO is highly variable, ranging from less than 35,000 (slow progressors) to more than 27 million (fast progressors) neurons per minute (108). The rate of developed collateral arterial supply to affected territory is probably the most differentiating factor of neuronal loss.

Successful recanalization (mTICI 2b/3) rate is an independent factor for a good functional outcome (109). It has been upgraded over time with technical advancements, reaching 80-85%. There still remains a group of patients (around 20%) in whom the thrombus cannot be removed using the current approaches. This subgroup represents one of the next challenges in the field of neurointervention. It is expected that with further refinement of the technique there will be higher quality recanalization using new devices and techniques. The first pass effect (FPE), defined as the achievement of complete recanalization (mTICI 3) after the first thrombectomy attempt, is an independent predictor of good outcome (110). As technology improves, FPE will be more frequently achieved. One of the major

complications are embolization in new territory (ENT), defined as emboli observed on postprocedural angiography within previously unaffected territories, and embolization in distal territory (EDT), defined as emboli seen within the territory of the vessel where the thrombus was originally located. They lead to increased procedure time and technical challenges. Fast penumbral tissue loss and an increase in ischemic volume are the result of both ENT and EDT respectively, leading to decreased likelihood of a good outcome (111, 112). While sICH is related to poor outcome, other intracranial bleedings like asymptomatic intracranial hemorrhage (aICH) and subarachnoid hemorrhage (SAH) usually do not affect the outcome if there is no obstructing intraventricular hematoma.

An important fact is that only 50% of patients with LVO who receive MT become functionally independent at 90 days follow up (Figure 1.10.) (109). This discrepancy of 30% versus the rate of recanalization, estimated to be around 80%, is indicative that the revascularization occurs too late for one-third of the patients. Significant efforts are made in preprocedural management to shorten times to arterial puncture. In this way, a patient who is treated in a timely manner that presents with a fast progressing infarct core could enter the good outcome group. Variability in angiographic and clinical outcomes in the recent randomized trials focused on MT gives an opportunity for further advancement in the field of more effective triage and treatment (slow versus fast progressors, clot composition).

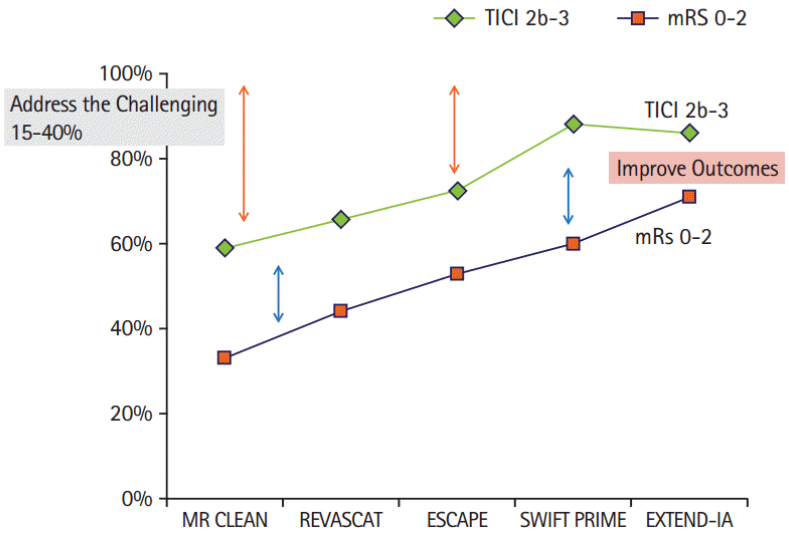

Figure 1.10. mTICI and mRS relation in major RCTs. Modified according to the reference (109).

1.5.4. Age and baseline severity

Before initiating transfer of a stroke patient, it is important to determine the baseline functional status. This is especially decisive for patients with pre-morbid conditions or those who are already hospitalized as their base functional status is unlikely to improve after MT. Additionally, successful recanalization less often translates into good outcomes for the patients with mRS of ≤ 2 including , amongst others, patients who are of age, have a history of a previous stroke, and cancer patients (109). These patients often do poorly with MT due to frailty, poor nutritional status, and slow rehabilitation seen in these patients. Approximately 10% of patients who develop AIS have a history of cancer (113). Most of these patients have a contraindication to IVT due to recent surgeries and in addition may present with a cancer-associated hypercoagulable condition.

Advanced age is being recognized as a strong and independent risk factor for a worse clinical

outcome after AIS (114). Some of the reasons are a higher rate of comorbidities and possible shorter time for conversion of ischemic penumbra to infarct core (115). Reduced neuroplasticity and neurological reserve, a lower rate of IV tPA administration and a more frequent arterial tortuosity are all additional factors that can further prolong the procedure (4, 116).

Elderly patients have been under-represented in RCTs, even though they account for over 30% of stroke admissions (117). Although those studies had no upper age limit, they enrolled only a small portion of octogenarians and even fewer nonagenarians. Safety and efficacy of EVT in the elderly compared to control were demonstrated in the HERMES collaboration, but with the inclusion of only 198 (15%) patients older than 80 years from a pooled total of 1,278 patients (17). The effect was found to be more pronounced as the odds ratio was higher in the ≥80 years group compared to the population younger than 80 years (3.68 vs 2.44). The benefit of EVT for LVO in the elderly becomes more relevant, as the numbers of aged patients are expected to increase with an aging population (118). Times from stroke onset to revascularization and mTICI results did not differ significantly by age as reported in the HERMES study (17). This suggests that the technical aspect of treatment is comparable to the less aged population, and does not contribute to age as a predictor of poorer clinical outcome. Conversely, clinical results were less favorable at 3 months follow up in the HERMES study. Favorable outcome was lower and mortality higher for patients aged ≥80 years that were randomized to not receive EVT and who received MT respectively.

A study of 79 patients aged ≥90 years with a LVO stroke in the anterior circulation, showed mTICI of 69.9%, sICH of 5.1%, independence at 3 months of 16%, and mortality at 90 days of 46.7% (119). Authors concluded that EVT in nonagenarians is linked to lower favorable outcome rates and higher mortality at 3 months compared to the less aged population. Therefore, MT in the elderly ≥80 did not show a similar benefit like seen in the younger population

A single-center study of 560 patients undergoing an ADAPT procedure included 108 patients aged >80, found that these patients were significantly less likely to achieve functional independence 90 days after the MT (120). 90-day mRS ≥4 in these age groups, included 65% of patients aged 75–85 and 70% of patients aged 85–95. Similar rates of 90-day mRS 6 in aged patients were found, including 35% of patients aged 75–85 and 45% of patients aged 85–95.

The authors of the study examined 30 patients ≥90 years old who were treated with MT. They observed a 70% mortality, and only 21% of the patients returned home after rehabilitation. (121). The study suggested that a final infarct volume <10cm^3 was a strong predictor of the patient returning home. The purpose of MT is to make the patients independent which otherwise if they were not treated would lead them to be dependent or even dead. Evaluation of stroke outcomes from the social perspective was performed in a recent study that evaluated it in terms of quality-adjusted life years (QUALY). Authors concluded that IV tPA was a better strategy compared to MT, with a difference of 0.83 QUALY (equivalent to 303 days of life in perfect health) (122). The authors highlighted that a better selection of the patients not benefiting from IV tPA, would optimize the selection of the patients for MT and improve the effectiveness of EVT.

To date, a meta-analysis of “real world” observational studies focusing on 90-day outcomes between patients ≥80 and those <80 years has been limited to small numbers undergoing EVT with older generation devices and/or intra-arterial therapies. Balance of the risk and benefit is important in the “real world” settings. The problems are ethical, socioeconomic, societal, etc. More careful decision-making among these patients is warranted, taking into consideration other risk factors for poor functional prognosis at 3 months.

All the available data demonstrates improved functional outcomes and reduced mortality rates for MT in elderly patients with LVO, compared to patients that did not receive EVT. Yet compared to the younger population, there is an overall lower likelihood of functional independence and higher mortality with EVT in the elderly.

To date, there are no RCTs focusing on patients ≥80 with EVT of LVO. MT is safe and beneficial in a smaller number of patients older than 80 years, and in general, should not be withheld from this population. There is no age limit, but rather a decision should be made a little more conservatively. Only patients who were independent before stroke should be considered for treatment.

1.6. Mechanical thrombectomy in clinical practice

1.6.1. General considerations

After the five positive RCTs in 2015, MT in addition to BMM has become the standard of care for patients with AIS with LVO (9-13). They demonstrated major benefits for patients treated with MT with BMM over BMM alone, with NNT of 3 to achieve any better functional outcome and NNT of 5 to reach functional independence (17). The degree of benefit is exceptional, and few therapies in medicine can approach that level of benefit. In those trials, unlike in previous, modern endovascular devices such as second-generation stent retrievers were utilized (Figure 1.11.). Due to clear statistical difference, many of the RCTs were closed for recruitment after interim analysis, before a pre-specified sample size was reached. Such premature trial termination carries the risk of overestimation of the treatment effect. Nonetheless, the benefit of MT is considered established, since RCTs demonstrated consistent benefit of MT with BBM over BMM alone, and a dose–effect relation (reperfusion rates vs. clinical outcome) (123). Outcome from MT are also found to be strongly time dependent ("time is brain").

As of today, nine RCTs of MT with classical inclusion criteria have been published: MR CLEAN, EXTEND IA, ESCAPE, SWIFT PRIME, REVASCAT, THRACE, THERAPY, PISTE, and EASI (9-14, 124-126). All of these trials recruited patients with AIS and proven LVO on vascular imaging (internal carotid artery, M1, M2) with or without tandem stenosis/occlusion, within a 6-hour period from stroke onset. Pooled risk ratio for functional independence in patients treated with MT with BMM versus BMM alone, favored the MT group in all the studies (Figure 1.12.) (47). Two of these trials featured an extended time window, up to 8 hours for REVASCAT and 12 hours for ESCAPE. Patients were randomized to MT plus BMM versus BMM alone, with intravenous thrombolysis (IVT) in both arms whenever indicated. In all of the trials, modern thrombectomy devices were used; second or third generation stent retrievers or contact aspiration catheters. After these studies were conducted, a plethora of questions to be answered were brought forth for different subgroups such as optimal anesthesia management, role of intravenous thrombolysis (IVT), stent retriever or aspiration technique, time management including transfer of the patients and extension of MT time window, treatment of patients with low NIHSS or low ASPECTS, best management of TO etc. The HERMES collaboration meta-analysis of individual patient data extracted from first five RCTs, was subsequently conducted for different subgroup analysis (17).

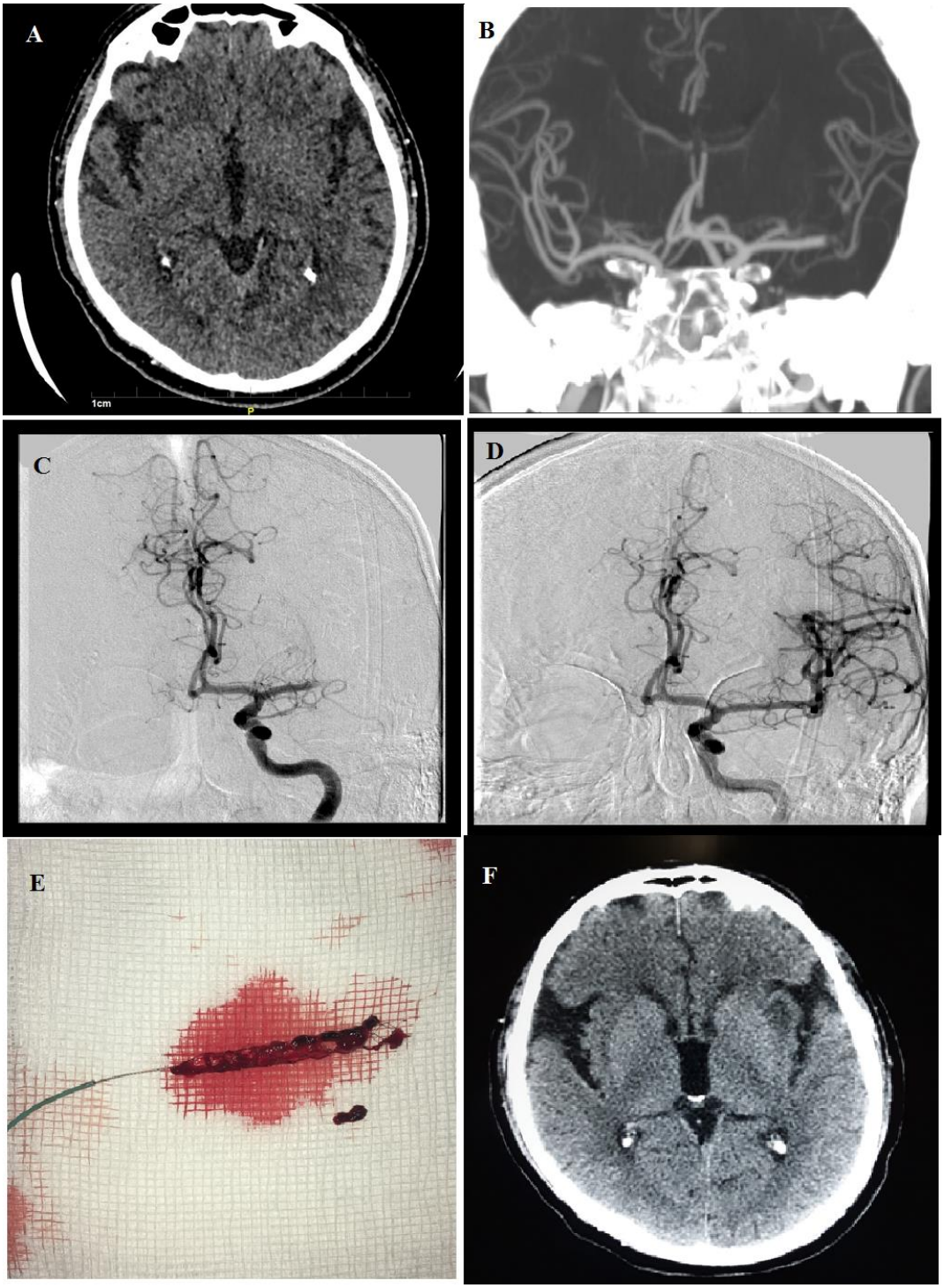

Figure 1.11. A 79-year-old male with NIHSS 9, ASPECTS 9 (A), and left M1 occlusion on CTA (B). Arterial puncture was initiated 4 hours and recanalization and recanalization achieved 4.35 hours after symptom onset. DSA confirmed existence of left sided M1 occlusion (C). DSA after the recanalization (D). Clot captured within the stent retriever mesh (E). Post 24-hour CT demonstrated small infarction at the level of insula (F). Day one NIHSS was 3, and 90 days mRS was 0.

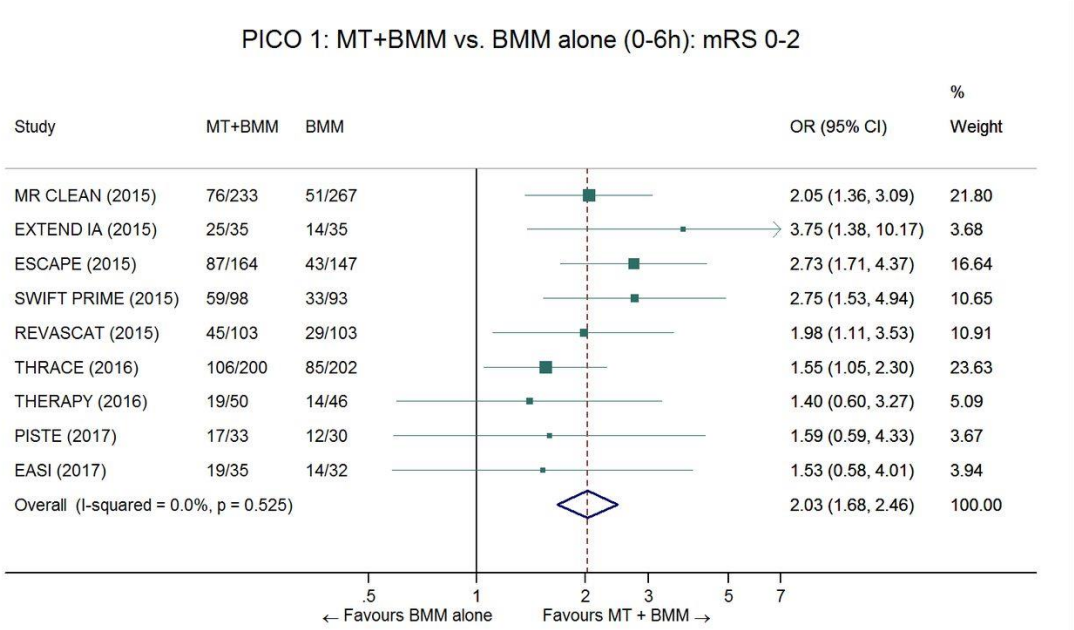

Figure 1.12. Pooled odds ratio for functional independence in patients treated with MT+BMM vs. BMM alone in the 0–6 h time window. Modified according to the reference (47).

The initial trials did not confirm the benefits for recanalization achieved outside 6-7 hours from AIS onset. Two recent RCTs, DAWN and DEFUSE-3, have demonstrated that MT, in highly selected patients with perfusion imaging, had beneficial effects for an extended time window from up to 16 (DEFUSE-3) or 24 hours (DAWN) after symptom onset or last seen normal (19, 20). In order to incorporate these findings, stroke guidelines have been updated where the potential time window for MT has now been extended to 24 hours (48). Subsequently, specifically designed RCTs attempt to evaluate conditions for optimal anesthesia management. Extending the scope of practice for MT to different subgroups of patients that were not yet directly or indirectly studied in existing clinical trials, are the current focus of ongoing and upcoming trials. These and other unresolved questions will be addressed later.

1.6.2. History

Premiere attempts in intra-arterial treatments of AIS have been done in the posterior circulation, as the mortality for the patients with basilar artery occlusion is extremely high. The first published focal treatment of basilar artery occlusion by intraarterial (IA) administration of streptokinase was done in 1982 and later published in an article with cohort of 65 patients presenting with acute basilar occlusion (127). The first of the AIS endovascular treatment RCTs, The Prourokinase in Acute Cerebral Thromboembolism (PROACT) trial, published in 1998, demonstrated a strong signal of clinical benefit with an elevated rate of symptomatic hemorrhage for IA thrombolysis (128). It was followed in 1999 by 186 patient PROACT-II study, which focused on MCA occlusion, and demonstrated that recanalization rates were greater in the IA r-proUK group compared to the controls (66% vs. 18%; $p < 0.001$) as were the rates of sICH within 24 hours of treatment (10% vs. 2%; $p = 0.06$) (129). Though there was an absolute difference of 15% in good clinical outcome in favor of IA treatment (40% vs. 25%) at 90 days follow up, the United States FDA (Food and Drug Administration) did not approve r-proUK or IA stroke therapy because of the small sample size and marginal statistical significance ($p = 0.043$). Despite the lack of FDA approval, PROACT-II was a turning point that launched the era of MT by redirecting the

industry towards construction of devices designed for mechanical clot extraction. The very early methods which consisted of attempts to fragment the clot in the brain were applied in the early 1990s, naming the procedure - MT. The first attempts of MT were done by attempts to fragment the clot and expose as much of its surface as possible to a fibrinolytic agent. The operators tried to utilize all of the material available on the shelf of the department: balloon, lasso, manual aspiration of the thrombus, low-energy ultrasound, and microcatheter/microwire manipulation. In the case series of angioplasty in nine patients after IA tPA failed to open the vessel, investigators reported 50% of failure and one vessel rupture complication (130). Acute intracranial stenting was attempted but was accompanied with elevated sICH risk due to antithrombotic management (131). Though these maneuvers were mostly unsuccessful, in the early 2000s, the first dedicated devices were introduced to the market. The Merci system and the Catch device were specifically designed for clot retrieval, along with many other devices with an innovative design that were never commercialized. The physicians started with first and second (with incorporated filaments) generation of the corkscrew like Merci device, that were first approved by the FDA in 2004. Recanalization rate increased from 50% using IA thrombolytic up to 68% using MERCI device, and had a lower rate (36%) of good clinical outcome compared to later positive RCTs done with newer generation stent retrievers (132). Technically speaking, these early devices had low tractability and exerted considerable retraction during the retrieval maneuver. In their attempt to reopen the arteries, these suboptimal vector forces superimposition during MT which was painful for the patient (requiring GA), and causing number of complications (dissection, perforation, straitening the vessel with perforator rupture and consequent SAH). In 2007, a new class of a neuro-thrombectomy device emerged in the form of suction thrombectomy. With this system, an aspiration catheter is navigated distally into contact with the thrombus and then the catheter's proximal end was attached to negative suctioning to aspirate and remove the intra-vascular clot. Continual vacuum aspiration is applied via a 50mL or 60mL syringe, or through an aspiration pump system. The original system used a continuous vacuum aspiration via −20 in/Hg aspiration pump. In this process, the olive tip "separator" was used to fragment the clot and facilitate aspiration. The greater stiffness and smaller catheter diameter resulted in insufficient suction power on the big clot and a downstream embolism. Aspiration trials demonstrated a good revascularization rate up to 80%, but achieved a 90-day mRS score of 0–2 in only 29%. Modern contact aspiration or A Direct Aspiration First Pass Technique (ADAPT) consists in achieving direct contact of the large bore aspiration catheter with the clot and pulling the clot into the guide catheter while applying continuous negative pressure. Contemporary large reperfusion catheters possess excellent navigability, efficacy, and safety profile (133). A new aspiration pump allows the generation of a near-perfect vacuum (over −29 in/Hg) with the use of alternating and intermittent aspiration.

The first thrombectomy done with modern technology was performed in 2003, and published as a technical report of MT with the Solitaire stent (134). It was originally dedicated for support during aneurysm coiling, with the unique design that allowed re-sheathing after complete deployment. As frequent in a new discovery, an accident with in-stent thrombosis that prevented re-sheathing of the stent revealed a possible new application of the Solitaire stent. The operator, lacking with any other option, simply retrieved the opened stent with the clot trapped between its metallic struts. The clot, stent in the microcatheter and whole system with the opened stent had to be retrieved along the vessels wall. Surprisingly, it was possible to achieve it, and the thrombus remained entangled within the stent struts and was able to be completely evacuated from the vessels. The physician recognized potential benefit and started repeating the maneuver for the clot occlusion cases. It was therefore realized that it was possible to use solitaire as a self-expanding stent to retrieve the clot, with low radial force and no trauma to the vessel wall. The stent was more navigable through a smaller microcatheter compared to the first-generation devices such as Merci, with a lower incidence of complications in the form of vessel dissection and perforation. Solitaire was the device that made a difference, and probably is the main reason for the success of 2015 RCTs. It enabled rate of mTICI 2b/3 revascularization of around 75% in the initial period

of its utilization (133). Patients were starting to rapidly improve clinically, often moving hemiplegic side of the body and talking after complete aphasia on the operating table. This effect was never seen before in patients with LVO stroke, which before had a straightforward natural course of disease.

Longer stent retrievers became available in 2015–2016. They would have advantages in cases of longer thrombi by providing a larger surface for device integration and uniform distribution of forces along the clot during traction. The longer device allows precise placement by decreasing the margin of error, and would enhance device grip distal to the clot increasing the chances of dragging the clot out if the primary binding to struts were to fail. Apart from the longer length, third generation devices have integrated radiopaque markers to optimize fluoroscopic visualization, and different cell design to optimize clot integration during retrieval. These improvements were associated with the higher rate of early (first-pass) mTICI 2b/3 reperfusion as compared to older-generation devices (133).

The SWIFT trial published in 2012, compared the Merci and Solitaire devices, and demonstrated superior successful recanalization (TIMI 2–3) (60.7% vs. 24.1%), good clinical outcome (mRS 0–2 at 90 days, 58.2% vs. 33.6%) and mortality (17.2% vs. 38.2%) with the Solitaire compared to Merci device respectively (135). Studies such as the Interventional Management of Stroke (IMS) I and the IMS II trials were negative (136). Despite the early advancements in MT, there was missing evidence to confirm clinical experience. About the time stent retrievers were being introduced to clinical practice, the first three RCTs on MT were released in 2013. IMS III, the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE), and Synthesis Expansion (SYNTHESIS) demonstrated no clinical improvement compared to IV tPA alone (96, 137, 138). Critical analysis of the study's design revealed that the inclusion criteria did not require the use of vascular imaging as a triage for the patients with LVO, meaning that the patients that would benefit the most from EVT could not be identified. The vast majority of the patients in these trials were imaged, triaged and treated using technologies that were obsolete at the time of their publication. By using mainly older generation devices, recanalization could not be fast and effective enough. Lack of successful revascularization in these three studies strongly limited extrapolation of the results to modern practice since at that time when the studies were done, newer generation of stent retrievers were already in widespread use in clinical practice. The pressure of these three negative trials directed the neurointerventional community to produce new, better designed trials, with the use of contemporary stroke treatment. In the pivotal RCTs, patients were enrolled if intracranial LVO of anterior circulation was angiographically confirmed and treatment initiated within the first 6 to 8 hours; depending on the study. All the patients received BMM and were treated with modern dedicated MT devices – mainly stent retrievers. Recanalization had to be achieved within the 90 minutes period form the angiographic confirmation of LVO. It took them less time to get the patients in the angio-suite, and shorter time to open up the vessel, compared to earlier devices that did not allowed a more aggressive approach. The same effect was seen in the group that did and did not received IV tPA. All the studies were stopped at the mid-point due to overwhelming efficacy, a year and a half from their launch. This demonstrated that they reached projected results twice as fast than initially expected.

These results announced a paradigm shift that with the early identification of patients with LVO, the nearest IV tPA center should be bypassed, and the patient transferred to the nearest stroke center providing MT instead. In this way, the life-saving procedure can be delivered to the patient in a timely manner. In parallel, sicne the evolution of first-generation devices such as the Merci device to the third and fourth-generation devices, the aspiration technique advanced in the direction where larger bore reperfusion/intermediate catheters could be used alone and in combination with stent retriever. The new-generation large-bore distal-access catheters allowed direct aspiration of cerebral clots without breaking them up, thus reducing the chance of EDT and ENT. Using third generation stent retrievers in combination with the aspiration system allowed for recanalization rates of nearly 90% (133).

Over a period of 6 months, the publication of five randomized studies in 2015 dramatically changed AIS treatment. The MR CLEAN study was followed by a publication of four other RCTs –

ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA – done between December 2010 and December 2014 (9-13). MT with stent retrievers, became the new standard of practice for AIS treatment secondary to LVO. As a reaction to these positive RCTs, we witnessed a massive growth in regard to the number of thrombectomies performed annually, CSC, population education, all resulting in an increase in the capabilities to treat AIS that were not possible before. The result was an increase of MT by 30-40% per year, which was beginning of a global phenomenon. With respect to the indications from the RCTs, there was a tenfold increase in the number of MT treated patients.

However, there are still unresolved questions, but the as investigation advances further, the indications for MT are expanding. The evolution of endovascular devices has significantly improved procedural outcomes in MT. Technological advances are fast paced and multiple new aspiration catheters and stent retrievers (or retriever-like devices) are becoming available. The MT armamentarium includes a wide variety of stent retrievers and aspiration catheters that have eased MT. However, 20–30% of clots are still not retrievable with the current technologies (109). Clot-specific approaches may shape the future of device selection and technique utilization. The partnership of bioengineering and clinical research has rendered a wide variety of devices available for MT.

Identifying adjunctive techniques that could potentially result in improved outcomes for patients with LVO has become an issue of increasing importance. Although stent retrievers have demonstrated superior reperfusion rates as compared to the first-generation MERCI retriever in the 2012 trials (SWIFT and TREVO2), full reperfusion rates were achieved in a minority of patients (only 14% in TREVO2) (139). Potential contributing factors include the fact that a minority of patients were treated with balloon guide catheters (BGC) and adjuvant aspiration was performed with older-generation catheters.

1.6.3. Level of recanalization - mTICI classification

Based on cerebral angiography findings, several grading systems have been developed to describe the level of revascularization during neurointervention (140, 141). Thrombolysis in Myocardial Infarction (TIMI) and TICI are the most commonly applied grading systems. The TIMI grading system was originally designed for the assessment of coronary reperfusion rate during interventions for acute STEMIs. Subsequently, this grading system was modified to become the TICI scale, which was specifically designed for the intracranial circulation (142). In both systems, grading ranges from 0 (no recanalization/reperfusion) to 3 (complete recanalization/reperfusion), but TICI allows a more detailed description of partial recanalization.

In the modified mTICI scale, reperfusion ranges from none to minimal limited to the parent artery (TICI Grade 0 or 1), partial reperfusion of less than 50% beyond the occlusion site (TICI 2a), near-complete or more than 50% reperfusion beyond the occlusion site (TICI 2b), or complete reperfusion (TICI 3) (143). At the end of the endovascular procedure, technical efficacy was assessed by TICI rate. In all the pivotal RCTs, successful reperfusion was defined using the mTICI scale score of 2b or 3 corresponding to reperfusion of at least 50% of the affected vascular territory. Recently a novel distinction was created, 2c, which represents a near-complete recanalization with minor distal emboli (144).

1.6.4. Location of large vessel occlusion

The definition of an LVO is variable depending on the evolution of the reperfusion devices and the design of the studies investigating MT performance (145). One of the broad definitions depicts LVO as any arterial location that can be safely selectively catheterized with modern endovascular devices. Rigorous clinical trial data from the pivotal RCTs support MT in patients with intracranial and extracranial occlusions of the ICA, including tandem or isolated occlusion of the M1 segment of the

MCA (48). The cerebral territories supplied by distal vessels, although relatively small, can be significantly eloquent. For the patients with M2 occlusions that were underrepresented or excluded from previous pivotal RCTs, current data is insufficient for an evidence-based recommendation in favor of or against EVT (47). The same stands for ACA occlusion, which is reported only sporadically in the RCTs.

The EVT is a rapidly evolving field of medicine and newer endovascular devices enable operators to safely perform MT in small vessels. Although MT for distal occlusions has not been implemented as a standard of practice, it may be a valid option in patients outside the window for IV tPA or who fail to recanalize with IV thrombolysis alone.

ESMINT/ESO and AHA/ASA 2018 guideline recommendations:
1. In patients with occlusions of the ICA (including intracranial, cervical segments or TO) and M1 MCA thrombectomy is recommended [class I, level A].
2. There is an unclear benefit of thrombectomy in more distal segments, such as MCA M2/M3 or anterior cerebral artery. Thrombectomy of such patients should be considered on a case-by-case basis, and may be reasonable in some cases [class IIb, level B-NR].

1.6.5. Mechanical thrombectomy in distal vessels - M2 and beyond

A major point of debate is the effect of MT in patients with M2 occlusions. M2 occlusions were either excluded or an underrepresented in the large clinical trials. In a multicenter observational study of 65 patients, M2 occlusions were correlated to a good functional outcome in patients with NIHSS ≥9 (146). The recent analysis of non-randomized studies have demonstrated a clear improvement in imaging and clinical outcomes with successful MT reperfusion of M2 occlusions, while unfavorable results can be expected in up to 45% of untreated M2 occlusions (147, 148). Regarding pivotal RCTs, some trials enrolled such patients (MR CLEAN, EXTEND IA, PISTE, and THERAPY) (11, 13, 124, 125). Other trials (ESCAPE, SWIFT PRIME, REVASCAT, and THRACE) did not allow recruitment of these patients; however, they entered the studies mainly by misinterpretation of initial angiographic images as M1 occlusion, and later adjudicated as proximal M2 occlusions (9, 10, 12, 14). In the individual patient data from HERMES subgroup analysis showed that the number of patients with a M2 occlusion was 130, 67/818 (8%) in the MT with BMM and 63/828 (8%) in the BMM alone arms, respectively (17). There was a tendency in favor of MT group, though result did not reach the level of statistical significance. A similar safety profile was found in both arms. Additionally, in the subgroup of 90 days mRS 0-2 of patients with M2 occlusion, MT was associated with functional independence (adjusted OR=2.35, 95% CI 1.07 to 5.14, p=0.03). The direction of benefit favored EVT over the control for all of these subtypes of the M2 segment MCA occlusion, but the analysis of treatment effect modification was underpowered to show statistically significant efficacy of EVT.

From the beginnings of MT, a concern was raised that EVT is less effective in distal occlusions due to reduced stent retriever maneuverability in the small diameter and more tortuous vessels. Moreover, it has been proposed that MT is potentially unnecessary in these cases since distal vessels may recanalize with IV tPA, yielding good non-invasive outcomes (15). An isolated M2 segment occlusions are present in 9–38% of patients in large IVT series, thus accounting for 16–41% of all MCA infarctions (149). Since the M2 segment MCA occlusions affect a smaller part of the MCA territory compared to the ICA or M1 segment occlusions, it is assumed that infarct size will be comparably smaller and treatment effect modification will be seen in the lower levels of the mRS, and there will be less death and severe disabling infarcts even for the non-recanalized patients. The reperfusion rate and favorable clinical outcomes of the M2 occlusion after IV tPA ranges between 30.8% and 68.4% and between 48% and 81% respectively (149, 150). Although logistically IV tPA is a simple treatment that can be delivered efficiently, it is associated with a number of limitations. Speaking in favor of MT, there are many patients harboring M2

occlusions that are ineligible for IV tPA, or where IV tPA is ineffective. Proximal M2 MCA segment occlusions are usually as easily accessible for EVT as M1 segment MCA occlusions (145). It is not unusual that a M1 segment occlusion at baseline angiographic imaging turns into proximal M2 occlusion at procedural DSA, due to thrombus dislodgement and migration. Some dominant M2 segments supply blood to a large portion of the MCA territory. In fact, since M2 vessels could supply highly eloquent areas (e.g., motor cortex, supplementary motor area, Broca's area) MT for such patients is justifiable as persistent occlusion is linked to a severe disabling neurological deficit. Furthermore, the rate of distal emboli into new or same territories during intervention is 0.7–11%, making the ability to perform subsequent distal MT essential (151, 152). The recent availability of low-profile stent retrievers and reperfusion catheters enables operators to safely navigate to smaller vessels, with good MT outcomes and low morbidity and mortality. However, despite the development of new neurovascular devices, treatment of distal lesions can be challenging, and a careful risk-benefit assessment of the patient's condition is critical. It is advocated that the patients should be under GA during the navigation into distal vessels. With the use of small stent retrievers, a 60% of good functional outcome increasing to 82.4% (146, 153). At first, the use of ADAPT in distal vessels achieved functional independence in 59.4% of patients, proving this technique to be safe, in distal locations (154). Introduction of smaller catheters accomplished higher functional outcome in 83% of the cases (155).

The benefit of MT in more distal segments, such as MCA M3 or ACA, is unclear. MT of such patients may be reasonable in and considered on a case-by-case basis (156). Outcomes in MT for patients with distal vessel occlusion will improve with further development and miniaturization of dedicated devices and materials.

1.6.6. Complications in mechanical thrombectomy

After the multiple RCTs proved the benefit in MT with ACLVO, the volume of patients has dramatically increased since. For the neurointerventionalist performing the procedure is important to be familiar with the procedure related complications and bailouts to ensure a good outcome in most of the situations. Procedural complications can be broadly classified into access-site related (vessel/nerve injury, access-site hematoma, and groin infection), device-related (vasospasm, arterial perforation, dissection, device detachment/misplacement), embolization to new or target vessel territory, sICH, and SAH. Other unanticipated complications encompass post-operative hemorrhage, extra-cranial hemorrhage, medication (anesthetic/contrast) related, and pseudo-aneurysm formation. Safe practice and a high degree of the alert on the possibility of these complications are decisive for their prevention, rapid identification, and timely treatment. Immediate complications following IV tPA administration are angioedema and hemorrhagic transformation.

At an access site, the femoral artery has a sufficiently large caliber to accommodate for catheters that are typically used in MT, such as 8F or 9F BGC, 8F of 9F introducer sheaths. The same stands for the triaxial system (guide catheter or long guiding sheath, intermediate large-bore aspiration catheter, and microcatheter). The site-related hemorrhagic complications are more frequent with a larger size of the introducer sheaths at the access site. The majority of femoral artery dissections are self-limited, as the pulsatile arterial blood flow is opposite to the entry point of the intimal flap. On the other hand, continuous bleeding from a perforated femoral artery is one of the most feared complications. Retroperitoneal hematoma is an extension of a deep groin hematoma into the retroperitoneal space and considered to be a medical and surgical emergency. Before proceeding to endovascular or vascular surgery repair of the bleeding point, confirmation of blood extravasation is the first step. Bleeding is not always evident, and can be detected only in latest venous phases on CTA of the inguinal region and CT of the abdominopelvic region. In parallel, acute hypovolemia and shock have to be reversed, to avoid a catastrophic outcome. Radial artery access to the subclavian and vertebral arteries is relatively

straightforward which makes it an excellent alternative for the posterior circulation LVO. If complications at the access side occur, closure devices are not recommended.

For the device-related complications, extracranial or intracranial arterial dissection has been reported in the use of stent retrievers during MT in major trials in up to 4% of the cases (Table 1.4.). In most of the cases it is spontaneously healed, and in the cases of hemodynamic impairment and occlusion, is treated with acute stenting. By using second-generation devices, the rate of vessel perforation dropped by fivefold. Vascular perforation using MERCI device was 5.5–10% (139), and it occurred in 1-5% (1.7%) of RCTs using second and third generation devices. It is one of the most dangerous complications, which is associated with a high mortality if not addressed promptly and adequately. It can spontaneously resolve, but in most cases, temporary or permanent occlusion (balloon, coil, liquid embolic) of an injured artery is needed. If promptly stopped, there are no clinical consequences in most of the cases (157). Immediate head CT is mandatory and demonstrates the extent of the intracranial hemorrhage.

Table 1.4. Device-related complications reported in the RCTs using stent retrievers

	MR CLEAN	**SWIFT PRIME**	**ESCAPE**	**EXTEND IA**	**REVASCAT**	**DAWN**	**DEFUSE 3**
Embolism in a new territory	13/233 (5.6%)	N/A	N/A	2/35 (6%)	1/50 (2%)	4/107 (4%)	N/A
Perforation	2/233 (0.9%)	N/A	1/165 (0.6%)	1/35 (5%)	N/A	0/107 (0%)	1/92 (1%)
Dissection	4/233 (1.7%)	4/98 (4%)	1/165 (0.6%)	N/A	2/50 (4%)	2/107 (2%)	N/A
Vasospasm	N/A	N/A	N/A	N/A	N/A	N/A	1/92 (1%)

ENT has been reported in up to 6% of the major trials (9-14, 19, 20). It occurs during withdrawal of the thrombus via stent retriever and/or distal access catheter. It is one of the most debilitating complications, as the thrombus blocks the arteries that maintain collateral circulation. Application of BGC and constant aspiration on the catheters during retrieval maneuver are intended to prevent this complication. Extracranial or intracranial vasospasm is present in up to 6% of the endovascular treatment of AIS (9-14, 19, 20). It could be related to catheters or to the stent retriever withdrawal. In absence of spontaneous resolution, intra-arterial vasodilators are administrated.

ICH and SAH are common complications after MT, with the vast majority remaining asymptomatic. More concerning is symptomatic ICH or SAH that may obliterate the benefit of MT after the procedure. The reported rate of sICH ranges from 3.6% to 9.3% and the reported frequency of SAH ranges from 0.6% to 5.5% (157).

1.7. Challenges in mechanical thrombectomy

1.7.1 Intravenous treatment or not

For almost 20 years, IV tPA has been the only confirmed therapy for AIS (50). However, it is not clear whether there is a benefit from IV tPA prior to MT for AIS patients with an LVO in the anterior circulation. A new era in AIS treatment has begun since December 2014. RCTs have shown that endovascular clot retrieval in addition to BMM (with and without IV tPA) improves outcome in acute stroke ACLVO patients compared to BMM alone (9-14, 124, 125). Endovascular clot retrieval seems to be the main reason for the differences in outcome, since proportions of patients receiving IV tPA was well balanced between both groups (158). In the HERMES study of five RCTs, the treatment effect size of MT does not differ between patients receiving IVT and those treated with MT alone (17). Additionally, there is a multitude of observational studies reporting the successful reperfusion and functional outcome stratified according to IV tPA pre-treatment status. There is evidence that reperfusion rates of the ICA and M1 segment of the MCA occlusion may reach more than 80% after MT, while after IV tPA are low (158). It is then clear, that MT largely influenced the higher rates of good clinical outcome all of these trials, with little influence of bridging therapy.

There are several potential benefits from the administration of IV tPA prior to MT (i.e. bridging thrombolysis). IV tPA can be started earlier than MT. However, in clinical practice recanalization may not occur early enough to obviate the need for subsequent MT. A recent study analyzed early recanalization rates after IVT and prior to EVT in bridging patients (159). Recanalization rates before EVT in bridging patients were related to the occlusion site: 19 patients with ICA occlusions or 12 patients with M1 occlusions had to be treated with IV tPA prior to EVT in order to achieve one relevant recanalization before EVT. Conversely, the NNT for M2 occlusions was 6.20. In addition, recanalization rates were lower in mothership than in drip-and-ship patients: 3.8% vs. 7.3% for ICA occlusions, 5.9% vs. 12.8% for M1 occlusions, and 9.5% vs. 30.8% for M2 occlusions (159). Longer exposure time to IV tPA is probably the reason for higher recanalization rates in drip-and-ship patients compared to mothership patients.

IV tPA may improve recanalization and reperfusion rates of large thrombi aiding to mechanical clot retrieval by enzymatic digestions, making thrombi more friable and thus less difficult to extract (158). However, this possible positive effect is not confirmed by post hoc data analyses of recent RCTs (159, 160).

IV tPA may help lysis of small vessel thrombi inaccessible for thrombectomy devices. As described in previous publications, most distal branch occlusions are not present prior to MT. They commonly occur during main thrombus extraction, leading to incomplete reperfusions (161). However, the rate of patients who still have a running IV tPA infusion at the time of mTICI 2b reperfusion is low, limiting the potential benefit from IV tPA to engage distal emboli. Considering the median intervals from IV tPA to first reperfusion, IV tPA infusions have usually already disconnected when substantial reperfusion is achieved. Concentrations of circulating tPA has a short half-life in the human blood of 5-10 minutes, and concentrations at the end of the procedure may as well be relatively low.

On the other hand, IV tPA has multiple constraints: recanalization rates in patients with large thrombi are generally poor (6), and IV tPA increases the risk of symptomatic and asymptomatic ICH as well as the risk of systemic bleeding (50). In the RCTs on endovascular revascularization, hemorrhage rates were not higher in the MT group (9-14, 124-126). This suggests that most of the bleeding in the IV tPA arm and in the bridging thrombolysis arm were related to IV tPA rather than to MT (158). The bleeding risk of IV tPA may exceed the potential benefit, especially in patients with a high ICH risk after IVT, such as aged patients, patients with early infarct signs, microbleeds, extensive leukoaraiosis, high baseline NIHSS scores, and high baseline glucose values (162, 163).

The use of IV tPA is limited by its narrow therapeutic window, with steeply decreasing efficacy (164). Due to safety reasons and higher ICH risk, many patients with severe LVO strokes have absolute or

relative contraindications for IV tPA (i.e. wake-up strokes, high blood pressure (BP) borderline coagulation status, and high glucose levels, etc.) (158). Administration of antiplatelet agents and heparin are contraindicated for 24 hours after IV tPA, but potentially helpful after endovascular intervention and clearly indicated if the acute procedural stenting is necessary tPA increases the cost of treatment. If direct MT were equally effective as bridging thrombolysis, administration of IV tPA which is potentially inefficient for LVO patients would unnecessarily increase the cost of treatment. Moreover, IV tPA can cause some of the rare side effects, such as life-threatening orolingual angioedema. In the above-mentioned RCTs on endovascular reperfusion, hemorrhage rates were not higher in the mechanical group, suggesting that most of the bleeding in the IV tPA arm and in the bridging arm were related to IV tPA rather than to MT (159).

None of the RCTs have ever assessed whether direct MT in patients with AIS is equally effective as bridging thrombolysis (MT in combination with IV tPA). In a five RCTs patient-level pooled analysis of the HERMES collaboration, similar rates of functional independence and mortality at 3 months were observed between MT patients who received or not received IV tPA (Figure 1.13.) (17). However, patients with IV tPA contraindications were enrolled in direct MT group. In the two large registries outcome was similar in patients treated with MT alone and MT + IV tPA, where mRs 6 was lower in patients treated by MT than after bridging thrombolysis (Figure 1.14.) (16, 165). The organization of acute stroke management would change essentially if direct MT in patients with AIS would not be inferior to bridging thrombolysis. Direct MT would rather be the therapy of choice in stroke centers with endovascular facilities. However, whether pre-treatment with IV tPA for patients that arrive in stroke units with no capabilities for MT should be performed or whether they should directly be referred to stroke centers with endovascular facilities, is another matter of debate.

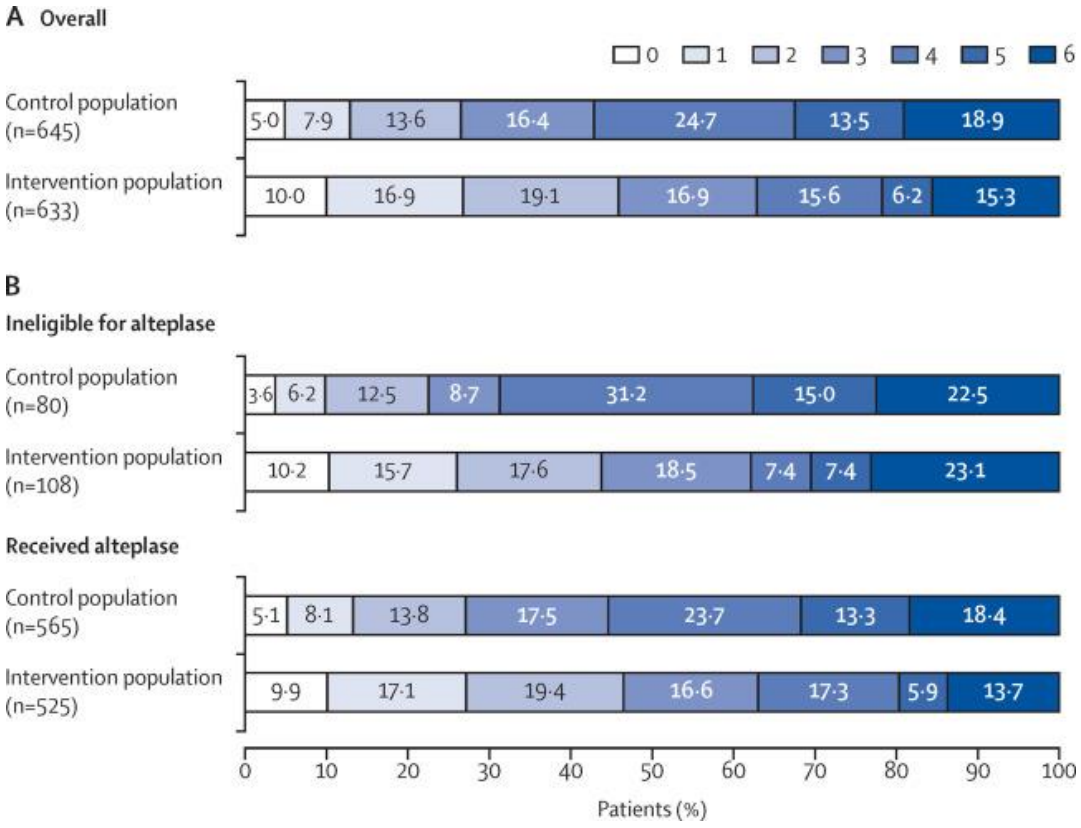

Figure 1.13. Distribution of mRS scores at 90 days: A) Overall population, B) According to IV tPA administration. Modified according to the reference (17).

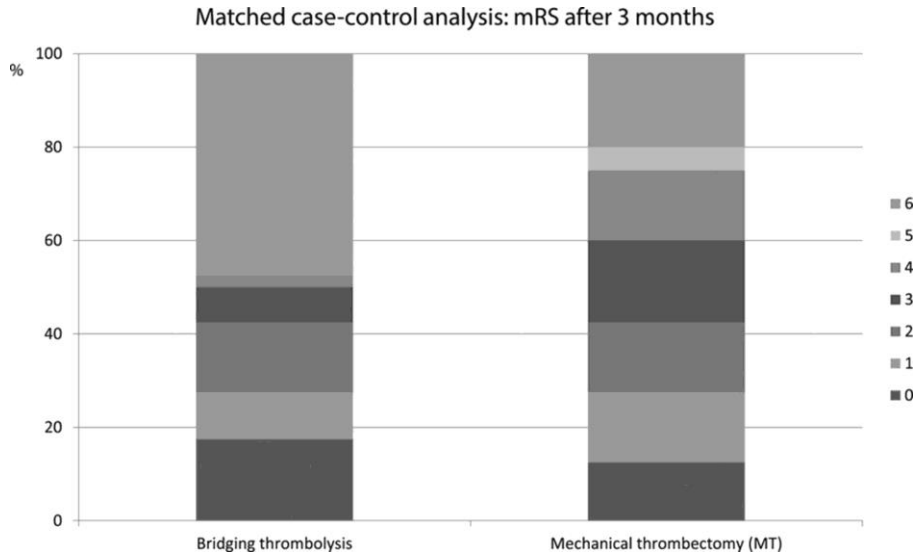

Figure 1.14. Matched case-control analysis: mRS after 3 months comparing bridging thrombolysis and MT. Modified according to the reference (16)

1.7.2. Best type of anesthesia

Anesthesia strategy has been a topic of great controversy and is largely driven by institutional and physician constraints. Anesthesia for MT can be divided into three administration methods, GA versus CS or LA without intubation. Potential disadvantages of GA include the increased delay in treatment time and the potential negative impact of anesthetic agents, such as a decrease and fluctuation of BP that could impair cerebral perfusion (166). General endotracheal anesthesia traditionally is widely used in neurointeventional procedures. Since EVT in neurovascular interventions requires the navigation of microcatheters and micro guidewires in the cerebral vasculature, road map images are accurately superimposed on the live fluoroscopic images, with the need for absolutes stillness during the procedure. Incorrectly advanced devices can lead to vessel perforation/dissection. Constant patient movement, agitation, and lack of cooperation (due to hemineglect -anosognosia) are common during MT performed under CS/LA. Many practitioners view GA as potentially advantageous over CS/LA in regard to elimination of the intraoperative movement, which in return shortens the intraoperative time and improves procedural safety with recanalization effectiveness. Intraprocedural monitoring of awake patients can be useful as any improvement or worsening of the clinical deficit can be evaluated and redirect treatment decision (reocclusion with worsening of the symptoms, complete recovery with one branch remaining occluded, deterioration in the case of intracranial bleeding). Lastly, GA has been associated with higher rates of respiratory complications secondary to aspiration and airway trauma, which can be avoided with immediate postprocedural extubation when eligible (167).

Exact reasons for the association of non-GA and good outcomes are unknown. Intraprocedural hypotension less likely occurs with non-GA than with GA (systemic BP <140 mmHg) (168). Significant BP variations typically occur during the induction and recovery phases of GA, which can compromise cerebral perfusion pressures especially in the penumbral area that has altered hemodynamic regulation (169). Inhaled anesthetic agents are associated with a higher risk of cerebral hypoperfusion, and general anesthetic agents can cause vasodilatation of the non-ischemic territories thus resulting in a steal phenomenon (170, 171).

The evidence for the ideal anesthesia management during MT for LVO is conflicting. Previous observational studies and post hoc analysis of RCTs, have demonstrated comparative revascularization rates and significantly improved clinical outcomes for CS/LA (38, 172-180). On the contrary, the only

three published single-center RCTs on anesthesia in MT (SIESTA, ANSTROKE, and GOLIATH) found only a marginal advantage of GA over CS (181-183).

However, a pooled data meta-analysis of these three RCTs demonstrated significantly higher rates of 90 days good functional outcome and higher recanalization rates for the GA over CS arm, with similar safety outcome rates (184). All three RCTs had important limitations, as they were single-center trials with a bias of local conditions. All the centers had dedicated, highly specialized anesthesia team, with control over procedural hypotension and 10-minute delay for the intubation. In many centers, availability of anesthesia is limited and this hampers the generalizability of these results. In both SIESTA and ANSTROKE trials there were also high rates of conversion to GA in the non-GA groups (14.2% and 15.6%, respectively), which is higher than the rate seen in previous RCTs (around 3%) (181, 182). This emergent endotracheal intubation could result in additional delays in care and complications. Many of the major concerns regarding the risks of non-GA (i.e., higher risk of wire perforation or vascular injury, risks of intraprocedural intubation, decreased procedural efficiency), have not been confirmed. So far, there is no conclusive evidence demonstrating any difference in procedure length of time, from onset to reperfusion, between GA or non-GA groups. The goal of this large data set was to study the real-world conditions affecting each type of anesthesia. Differences in outcomes for the anesthesia single center RCTs is presented in Table 1.5.

Table 1.5. Difference in outcomes for the anesthesia single center RCTs

	N	Prim. outcome	GA	CS	Diff	P value
SIESTA (181)	150	Change in NIHSS	-3.2 (-5.5 to -1.7)	-3.6 (-5.5 to -1.7)	-0.4 (-3.4 to – 2.7)	0.82
ANSTROKE (182)	90	mRS 0-2 at 90d	19 (42.2%)	18 (40.0%)	2.2%	1.0
GOLIATH (183)	128	Infarct growth on MRI (median)	8.2 ml	19.4 ml	11.2 ml	0.10

1.7.3. Type of clot

The rate of successful recanalization (mTICI 2b/3) after MT has ranged from 59% in MR CLEAN and up to 88% in EXTEND IA (11, 13). This demonstrates the impossibility for the extraction of all the thrombi, and 15-20% of the clots remain out of our reach for recanalization and analysis. The association between imaging characteristics of thrombi and technical and clinical outcomes has been the subject of studies, with the aim to predict difficulties and improve success of the recanalization therapies (185, 186). Different clot structures retrieved by MT and assessed by histopathological analysis, suggest that clot composition can have an impact on MT efficacy (187, 188). Thrombus with a high proportion/rate of red blood cells, are spontaneously hyperdense under CT and appear with low signal intensity, known as susceptibility vessel sign (SVS+), on T2*- gradient echo imaging (GRE) sequences (186, 189).

Spontaneously hyperdense clots are associated with successful recanalization: with a recanalization rate of 79% for spontaneously hyperdense clots and 36% in non-spontaneously hyperdense

clots (p=0.001) (185, 190). An SVS+ observed on MRI, in the early studies has been reported as not associated with successful recanalization (186, 189, 191, 192). Finally, the association between SVS+ and good clinical outcome has been reported in one study (193). The presence of an SVS+ could be predictive of the recanalization status (mTICI) and outcome (NIHSS day one) as well as stroke etiology (cardioembolic vs. non- cardioembolic), after MT (Figure 1.15.).

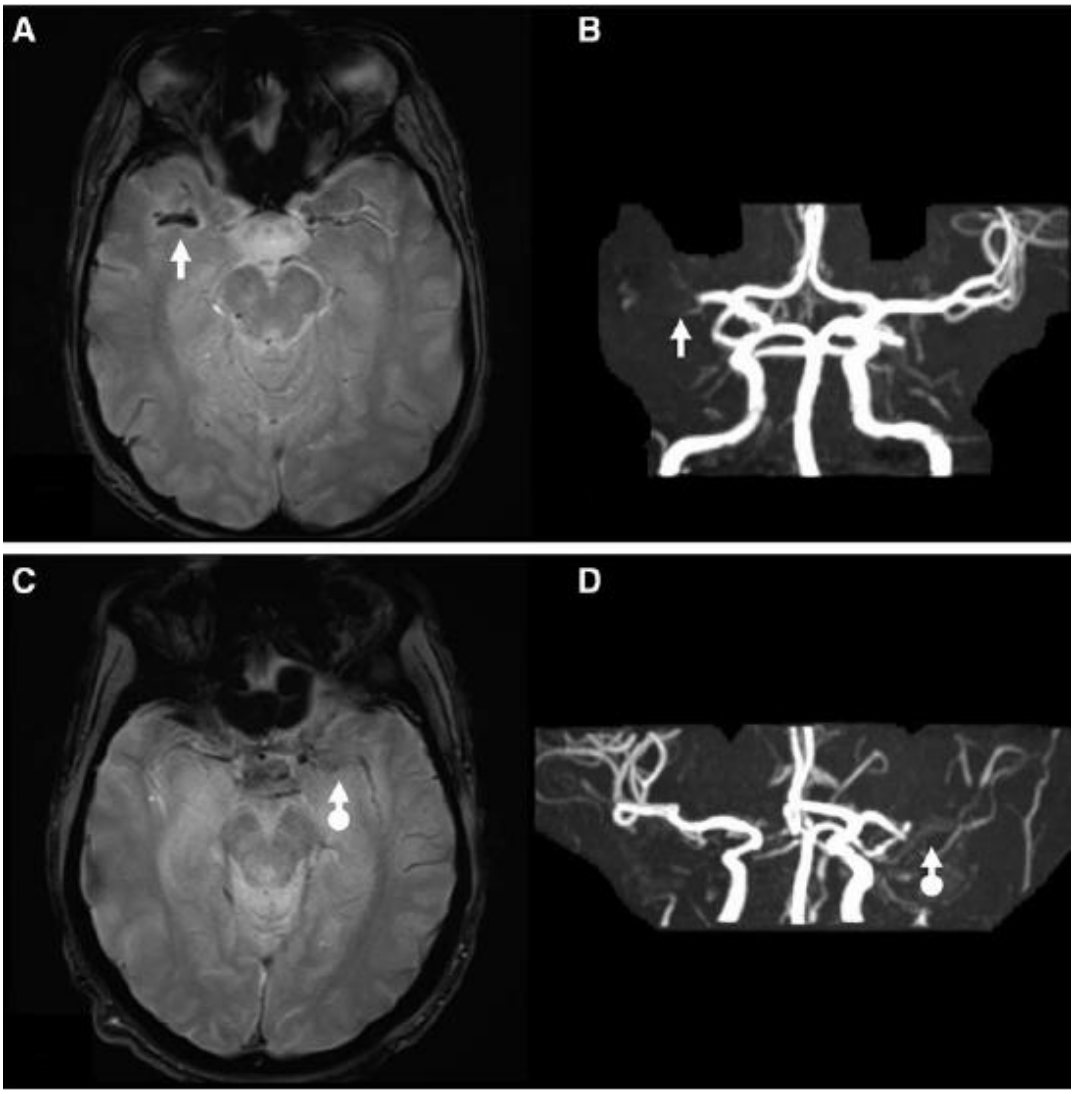

Figure 1.15. Examples of SVS + and SVS-. MRI of 2 patients presenting with (SVS)+ (A and B; white arrow) and SVS− (C and D; white arrow with dot). A and C, axial views of T2*- GRE imaging, (B and D) time of flight. Modified according to the reference (24).

1.7.4. Low ASPECTS (ASPECTS ≤ 5)

There is an ongoing debate of whether patients harboring a large ischemic core (ASPECTS 0-5) stroke at presentation may still benefit from MT, given the very poor natural history if managed by a BMM. Initial large medical trials using IV tPA set a clinical benefit threshold of ASPECTS 5 (Samurai - CT ALBERTA Score IV cohort) (194-196). In a lack of clear evidence of clinical benefit in the large infarct

core patient defined as ASPECTS 0-5, this population was excluded from most of RCTs involving MT. Consequently, patients with an LVO and a limited core volume defined as an ASPECTS > 5 were included in AHA Guidelines as the level 1A of evidence (48).

Despite the opened inclusion criteria in the study protocol, MR CLEAN, the median ASPECTS of the cohort was 9, the mean ASPECTS in SWIFT PRIME was 7, and in REVASCAT 7 (9-11). In SWIFT PRIME inclusion criteria were RAPID software volumetric core evaluation < 50 ml or ASPECTS 6-10, and a proven mismatch profile (9). In EXTEND-IA, prior randomization RAPID evaluation was performed in order to exclude large core infarct patients (13). Based on the initial protocol in REVASCAT, patients with ASPECTS ≤ 5 were equally excluded (10). Nonetheless, 25% of enrolled patients in REVASCAT had an ASPECTS 5 as revealed by the core lab. The ESCAPE trial included only 6% of the patients with CT ASPECTS < 6 (10). Recent data from the pooled HERMES meta-analysis of seven RCTs had a median ASPECTS 8 (IQR 7–9) in the patients treated with MT (21). HERMES pooled data analysis revealed 65 and 61 of 1764 patients underwent MT with an ASPECTS < 5 measured on MRI and on CT respectively. In the combined analysis of patients who had ASPECTS < 5 (n=126), the benefit of MT reached statistical significance in both MRI and CT arm (OR 2.15, 95% CI 1.06-4.37). Large hypodensity involving greater than 1/3 MCA territory, equally demonstrated benefit in MRI and CT group (OR 1.70, 95%CI 1.04-2.78).

Potential downsides of treating large strokes and low ASPECTS large vessel occlusion with thrombectomy outside current guidelines include patients with a higher risk of having a reperfusion hemorrhage or malignant edema, or simply doing a futile thrombectomy with a cost-effective downside (84). Several prospective registries showed that successful reperfusion was beneficial for low ASPECTS without increasing the risk of symptomatic hemorrhage (197, 198). In HERMES meta-analysis strong signals of benefit were found low APSECTS patients had increased risk for intracranial hemorrhage (21). The analyses suggest that symptomatic intracranial hemorrhage is four times more frequent in patients with ASPECTS 0–4 (21). The beneficial effect is nonetheless maintained across the entire spectrum of ASPECTS categories, which is explained by the fact that although patients with low ASPECTS tend to have poor outcomes overall, outcomes in medically treated patients with poor ASPECTS are even worse.

It is also found that low ASPECTS is most likely age dependent (199). These patients have more severe NIHSS, delayed arterial puncture time, present late (more likely wake-up stroke) and are more likely to have an internal carotid artery occlusion compared to those with higher scores (ASPECTS 0–3: 50%; ASPECTS 4–5: 40.4%; ASPECTS 6–10: 22%).

As previously described in REVASCAT or HERMES pooled data analysis, LVO patients with a large stroke volume may belong to a “fast progressor” profile (10). This profile of patients is particularly sensitive to time metrics and has narrowed the treatment time window. In the patient population that is not selected on mismatch, the time-dependent benefit of thrombectomy declines in a steeper fashion and procedures initiated beyond 7.3 hours from time last known well, no longer demonstrate clinical benefit in a predictive way.

Three ongoing RCTs are aiming to answer this question:

1. TESLA (200): Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke (NCT03805308). The trial aims to test the effectiveness of MT compared to medical management in patients with moderate and large baseline infarcts core (NCCT ASPECTS 2-5) and to better define the upper threshold of infarct volume for treatment eligibility. Furthermore, the investigators aim to stratify subgroups of patients with large baseline infarcts to assess magnitude of treatment benefit.
2. LASTE (201): Large Stroke Therapy Evaluation (NCT03811769). The LASTE protocol is designed to assess the efficacy and safety of MT for patients with a large infarct volume defined by a score ASPECTS ≤ 5 in the acute phase of cerebral infarction less than 7 hours from symptoms onset. It will enroll 450 participants. The LASTE hypothesis states that MT may still be beneficial for the patients harboring a large ischemic core stroke at presentation, compared to management by a standalone medical therapy.
3. TENSION (202): Efficacy and Safety of Thrombectomy in Stroke with Extended Lesion and Extended

Time Window (NCT03094715). The primary objective of the trial is to establish the safety and effectiveness of MT (versus medical management) in the treatment of AIS patients with extended core lesions defined by an ASPECTS 3-5 and in an extended time window (≤ 12 hours or unknown time of symptom onset). The goal is to randomize 714 subjects.

1.7.5. Low NIHSS (NIHSS ≤ 5)

The best management of patients harboring LVO but presenting with minor and mild stroke symptoms has not yet been determined by recent RCTs. The vast majority, roughly two-thirds of all strokes, have NIHSS ≤ 5 (203). Of them, 10–20% harbor LVO with having a tenfold higher chance for subsequent deterioration compared to non-LVO patients. Published data suggests that the long-term natural outcome of this population may be less than optimal, but due to a lack of severe deficits, patients are rarely considered for acute medical or EVT. Though there is low mortality of 1.3%, at discharge, 30.3% of patients are unable to ambulate independently, and 29.4% could not return directly home (204). Furthermore, identification of LVO is infrequently found during the first presentation, as initial workup rarely includes vessel imaging due to mild symptoms. In addition, in the settings of low NIHSS, the question is raised whether the LVO represents a secondary process from an underlying lesion, such as severe atherosclerotic plaque or dissection, which makes procedure more complicated.

Official AHA/ASA guidelines for MT suggest a cutoff of NIHSS ≥ 6. The question is then should we perform MT in a patient with LVO and NIHSS < 6. The natural history of the disease is less benign than previously assumed, with a significant risk for long-term disability. Some of these patients will worsen without MT, with the uncertainty of how many. One study demonstrated that without thrombolysis or MT treatment, 22.7% of patients with LVO and a low NIHSS score deteriorated within 24 hours, 33.3% deteriorated during the hospital stay, and 41.4% deteriorated within 3 months, with a mortality rate of 6.7% (205). Another analysis showed that three out of eight (37.5%) patients with mild symptoms, LVO, and no treatment demonstrated infarct expansion, as opposed to one out of 31 (3.2%) patients without LVO (OR, 18; 95% CI, 1.6–209; p = 0.02) (206). A large European observational cohort found that one-third of mild stroke patients with LVO did not have a successful recovery (207). The use of IV thrombolysis has been rare in this patient population, possibly due to the presumed benign course of the disease. In addition, IV tPA has been shown to be less effective in treating proximal LVO (8). A North American retrospective multicenter study noted favorable outcomes (mRS 0–2) at 3 to 6 months in patients who underwent MT versus BMM (93% vs 69.2%; p = 0.04), based on a 26-pair matched analysis (208). There was a statistical tendency for a lower NIHSS score at discharge (p= 0.04) and a favorable NIHSS score shift (p = 0.03) after MT compared to BMM. Independence rates also increased at discharge (p = 0.03) and at 3-month follow-up (p = 0.04). Parenchymal hemorrhage was spotted in 7.7% of matched patients. In another multicentric retrospective cohort, investigators found no difference between MT and BMM in low NIHSS LVO, but deeper analysis suggested that BMM patients with very mild stroke (NIHSS 0–3) had better 90 days outcome and safety profiles (209). Conversely, patients treated with MT had a tendency for a more frequent favorable outcomes in the group of NIHSS 4-5.

Another question is whether the MT is as efficient if done at the time of the clinical worsening as if performed initially before the neurological decline. Additionally, if MT is done what is the risk of worsening the situation in a patient with a very low NIHSS especially in case of more distal migration of the thrombus during and post-thrombectomy. This is a patient population that could not afford to have a complication given their mild presenting disability; however, the probability of spontaneous ICH in small infarct core is lower. These low NIHSS patients with LVO are most probably “slow progressors” harboring well developed collateral circulation. In low NIHSS patients with low fluctuation for a longer period of time, more conservative approach is advocated.

As there have been no published RCTs, investigating the efficacy of MT for LVO with low

NIHSS scores, there is a strong demand for better understanding of this stroke subtype and to identify safe and efficient treatment strategies.

Two ongoing RCTs are aiming to answer this question:

1. MOSTE (210): Minor Stroke Therapy Evaluation (NCT03796468). The study aims to evaluate acute MT in LVO stroke with minor symptoms (NIHSS < 6) in patients last seen well < 24 hours from the symptom onset, and is planed too include 824 participants.
2. ENDOLOW (211): Endovascular Therapy for Low NIHSS Ischemic Strokes (NCT04167527). This study will randomize 175 participants, with aim to test the hypothesis that ischemic stroke LVO patients presenting ≤ 8 hours of onset and with low baseline NIHSS scores (0-5) will have better 90 days clinical outcomes with immediate MT compared to immediate standalone BMM.

1.7.6. Tandem occlusion

Acute TO is not rare, comprising up to 20% of major strokes in the anterior circulation. They represent an obstruction or occlusion of the extracranial ICA, with concomitant occlusion of ICA terminus (ICA T) or MCA (212, 213). Untreated acutely symptomatic ICA occlusion causes severe neurological morbidity in up to 70% and mortality up to 55% (214).

TOs were always an issue for the recanalization treatment modalities even before the advent of MT. Proximal block of flow results in minimal interaction of IV lysis with a clot, which is effective in only around 9% of TO (215). Furthermore, the ineffectiveness of IV lysis is attributed to potentially large clot burden, due to stagnant blood between proximal ICA stenosis/occlusion and distal embolus. Quite often, a large clot cannot progress into the M1 segment but is stuck in the ICA T, which is demonstrated on CTA with a cutoff of crossflow via anterior communicating artery. This low recanalization rate with IV lysis is accompanied with a high rate of unfavorable outcome in around 80% of cases (213, 216).

Seven recently published positive RCTs, excluded patients with isolated cervical ICA occlusion. Furthermore, patients with TOs were systematically excluded from most of these RCTs, due to treatment complexity and the fact that in the trials stenting of the ICA was considered as a major adverse event (217). Therefore, statistical interpretation in this subgroup was lacking sufficient power. The largest cohort is of the MR CLEAN trial (33%), while others reported 12% to 18% (218). Two of the eight trials excluded TO patients from their study data (9-14, 124-126). It was even uncertain if the number of patients designated as TO is overestimated. The reason could be a high possibility of false positive detection, as ICA T occlusion can mimic cervical occlusion due to flow stagnation in the cervical segment. Though combined thrombectomy and carotid stenting are routinely performed in many centers for TO, no prospective data is available concerning the efficacy and the safety of stenting in AIS thrombectomy reperfusion.

There are two major questions regarding the treatment of TO:

1. How to approach TO: no treatment, stenting, and PTA (percutaneous transluminal angioplasty), PTA alone?

2. Which lesion to treat first: intracranial or extracranial?

Etiologically cervical occlusion could be one of these four lesions: atherosclerotic, dissection, large thrombus, and/or arterial web. Management strategy can be different depending on the type of extracranial lesion. Recent AHA/ASA guidelines have stated that there are no definitive conclusions about the optimum treatment approach for the TO (61). ESO-ESMINT recommendations suggested that no definitive answer could be provided, apart from that patients with high-grade cervical ICA stenosis

or occlusion can be treated with intra-procedural stenting if unavoidably needed, with very low quality of evidence (47). Retrospective data analysis collected from 18 institutions, showed no significant difference in all outcomes comparing treatment of atheromatous and dissecting cervical lesion in tandem stroke (219). Eighteen international comprehensive stroke centers recently performed an individual patient data pooled analysis of more than 450 patients with TO harboring carotid stenosis ≥ 90% NASCET or complete occlusion (220). Better reperfusion rates were observed in the acute stenting of extracranial ICA (mTICI 2b/3 and mTICI 3) (220, 221). There was a tendency for a good clinical outcome at 90 days without safety issues (ICH at 24 hours and mRs 6 at 90 days) (220-222). Recent meta-analysis of case series demonstrated higher reperfusion rates after acute stenting and thrombectomy of (223). Considering all of the available evidence, chronic cervical lesions should probably be treated with a stent, after cranial vessel recanalization.

The primary question regarding stenting of the cervical lesion for TOs, is the risk of bleeding associated with medication. Probably all complications that occur are due to excessive medication, which elevates the risk for bleeding after reperfusion. There is no definitive answer to what the best treatment approach is, which is therefore left to the discretion of the operator or the institution's preferences.

There is also a concern whether stent implantation in the acute settings affects treatment success and clinical outcome for these patients, especially considering the necessity of mono or dual antiplatelet therapy in the setting of AIS. The optimal pharmacological protocol is not yet defined. Overmedication is presented in dual anti-aggregation that is started too early. Cervical stents have a lower risk for thrombosis, 10 – 15%, with aspirin alone. Usually, 300-500 mg aspirin IV is administered followed by a Plavix loading dose after the first 24 hours given that there is no hemorrhage on the follow-up CT (224). Glycoprotein IIb-IIIa inhibitors can also be used as a first-line medication (bolus followed with continuous infusion), while dual antiplatelet therapy is initiated in a delayed fashion at 12-24 hours post-procedure (225, 226).

The major question is whether or not both lesions should always be treated? Equally, there is a controversy regarding which lesion should be addressed first (extracranial or intracranial). Different approaches have been used, including:

1. No treatment of cervical lesion: MT of intracranial occlusion without attempted treatment of the cervical ICA in the acute settings, with elective cervical segment treatment (stenting or endarterectomy),

2. Anterograde approach (from neck to brain): angioplasty and/or stenting of the cervical lesion first, followed by intracranial MT,

3. Retrograde approach (from brain to neck): treatment of the intracranial occlusion with MT first, followed by treatment (angioplasty and/or stenting) of the cervical ICA occlusion.

Different lesions have a different recurrence rate, making different management approaches necessary. Etiologically based treatment strategies and adopted approaches for each type of cervical occlusion, will be the subject of future RCTs.

1. TITAN (227): Thrombectomy In Tandem occlusions (NCT03978988). The study is designed to demonstrate the superiority of the combined use of intracranial MT and extracranial carotid stenting compared to intracranial thrombectomy alone on the mTICI 3 rate at the end of the endovascular procedure in patients with AIS due to TO.

1.7.7. Transport paradigm

Studies have consistently demonstrated that high volume centers are associated with improved patient outcomes. Rates of complications and morbidity for open surgical and endovascular procedures are decreased in high-volume centers (228). Accordingly, higher-volume stroke centers are associated with better functional outcomes in comparison to low-volume centers. For improved clinical outcomes, it is better to transport LVO patients directly to the CSC with bypassing the PSC (in most situations) or ensure rapid workflow in PSC with door-in-door-out (DIDO) of <40 minutes (229).

Therefore, an effort was made to produce clinical examination for LVO prediction with sufficiently high sensitivity and specificity that would allow pre-notification and direct transfer of the patient to the EVT capable center (230, 231). Such protocols have already demonstrated significant reduction in time variables including treatment times (232). In the future, class 1 evidence from RCTs, will be challenging to translate into real life situations as every CSC has their own geographic and demographic differences specific to each region. Modeling studies showed that triage protocols should, therefore, be based on regional characteristics and individual likelihood of LVO (75, 233-235).

Mathematical analysis can be applied and yield best solutions for each region's in different settings. Different strategies are developed for different local settings. Different centers can be on call on different days, offering MT in a synchronized way. This scenario reduces the number of teams that are on call and hospital overload, while maintaining the case volume for each center and preventing hospital overload. Likewise, same interventional teams can be on call for different EVT centers on different days. This is a drip-and-drive concept, where the neurointerventionalist is shipped to PSC to perform intervention, became popular in the urban areas of highly populated cities. Significant time reduction can be acquired with this concept, reported time gain for onset to recanalization is 2 hours and CT to arrival (transport time) is 1 hour (236).

Today development of a collaborative stroke care network is implemented in regional settings connecting CSC with many PSC, and general hospitals with telemedicine supported IVT. All three types of hospital allow IVT administration, and only CSC is capable of offering MT (recently some of the PSC have been approved to perform endovascular treatment for AIS only). The major question today is should emergency service (EMS) transport, bypass the patients (some or all) with high suspicion for LVO going directly to a CSC. The concepts are also known as "mothership" (directly admitting) versus "drip-and-ship (transferred patients) (237)." The possibility of identifying LVO patients in prehospital settings with sufficient diagnostic accuracy is a matter of debate. The advantages of the mothership strategy are that the bypass of PSC can be as or more effective than a strategy of IVT in PSC and then secondary transfer to CSC. Secondary transport in LVO would result in treatment delay and worsen the clinical outcome. Waste of time especially in the fast progressors patient profile, could have a major impact and result in futile MT. On average, there is a loss of 120 minutes for the LVO patients by going to the PSC (38).

The true impact of IVT in LVO is unknown, combined MT and IVT (HERMES) had the same efficacy as MT alone (DAWN, DEFUSE-3) (17, 19, 20). Disadvantages are at a risk of delay of transport for many eligible patients, which will be denied of early effective IVT, or will not receive it as the time window exceeds. In reality, there also exists a problem of exceeding the capacity of CSC in case of inappropriate bypass or futile transfer. The fact that MT alone is effective enough in the case LVO, has not yet been confirmed by RCTs. The largest registry, STRATIS, demonstrated that rapid identification of LVO occlusion and direct routing to EVT capable centers for patients with severe stroke may improve clinical outcomes (238).

In the early time window, patients with ACLVO strokes transferred patients did poorly compared to direct admissions in the SWIFT PRIME trial and the STRATIS registry (52% vs 60%; $P = .02$) (17, 238). STRATIS prospective, single-arm observational registry of 984 patients showed that outcomes similar to those observed in clinical trials could be achieved in a real-world setting (239). Clinical

outcomes were worse in the transfer group with 52.2% (213/408) compared to the direct group with 60.0% (299/498) achieving functional independence (OR 1.38, 95%CI 1.06-1.79; p=0.02). There was no difference in mortality rate between the two groups and IV tPA did not affect 90 days outcomes. Seven RCTs in the pooled data HERMES analysis showed that the rate of successful reperfusion (mTICI 2b/3) at the end of the procedure decreased, as time elapsed after arrival at the stroke endovascular center .(38) In the intervention arm, every additional hour between arrival at the EVT capable center and arterial puncture was associated with a 22% reduction in the odds of mTICI 2b/3 reperfusion (Figure 1.16.). No such difference was observed in a late time window (DAWN trial), between the transfer and direct admission patients (53% vs 46%; *P* = .44) (240). This suggests that early time window criteria (CT ASPECTS ≥ 6) include both slow and fast progressors, compared with the stricter criteria of DEFUSE-3 and DAWN, selecting exclusively slow progressors in the late time window.

Relative delay in reperfusion in the early time window (≤ 6 hours) among transfer patients who represent a combination of fast and slow progressors (selected by CT ASPECTS) had a higher "penalty of time" compared with mostly slow progressors (late window patients selected by CT perfusion or MRI). A penalty of time includes time delays caused by the transfer of patients, as well as less efficient intrahospital workflow including time spent on advanced neuroimaging and post-image acquisition software processing.

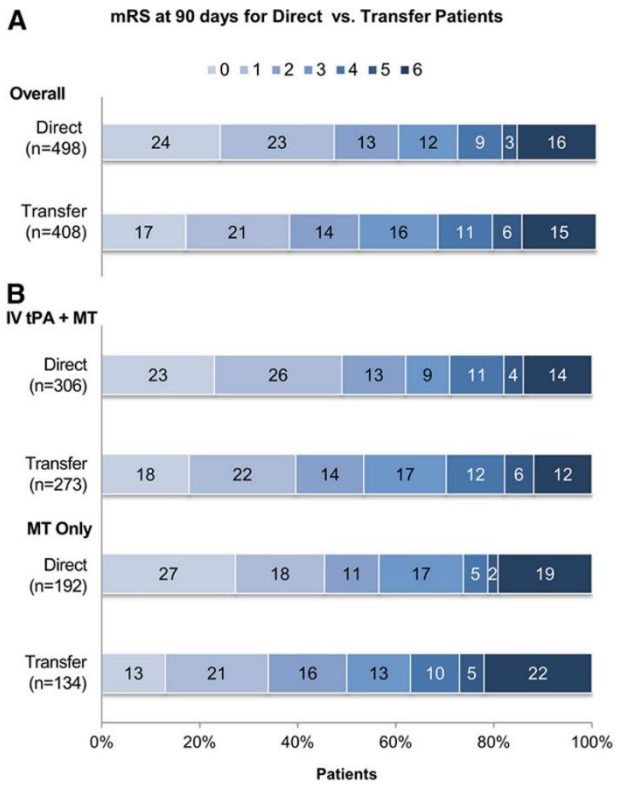

Figure 1.16. Unadjusted clinical outcomes at 90 days based on mRS, presented as percentage of the total. A, All patients, divided by direct admission (top) vs. interhospital transfer (bottom). B, Comparison of outcomes based on mRS between direct and transfer divided into patients who received IV tPA before MT (top) and those who underwent MT alone (bottom). There is a significant difference between the 2 groups. Modified according to the reference (238).

Regional prehospital triage is nowadays a mandatory strategy for shortening recanalization times. EVT centers tend to be located in urban areas, sometimes preventing quick access for all patients due to traffic difficulties. There are four options for EMS triage:

1. IS due to LVO (time-sensitive)
2. IS due to not-LVO (time-sensitive)
3. Hemorrhagic stroke (ICH not time-dependent)
4. IS mimics (not time-dependent)

Whether we can properly select the patients with high suspicion of LVO in prehospital settings, and how to do it adequately, is a matter of debate. High NIHSS is a sufficient predictor for LVO (47, 48, 61). Nonetheless, there are patients with high NIHSS with other etiologies such as stroke mimics (tumors, etc.), intracranial hemorrhage and small vessel ischemic stroke. There exist many prehospital/hospital stroke severity scores, designed to identify LVO (241). As there is no proof of their accuracy, an independent AHA/ASA committee has been selected to assess the diagnostic accuracy of LVO prediction instruments (242). The analysis suggested that no score predicted LVO with high sensitivity (60%) or specificity (≤90%) which points out the risk of false-positive and negative results. In the REVASCAT trial, around 60% of patient had LVO according to prehospital RACE score, and it was later confirmed for just half of the patients (10). This data emphasizes the problem with non-perfect prehospital stroke scales (243). There is insufficient evidence that one LVO prediction instrument is better than the others are. Nonetheless, their use is advocated in an unselected population-wide strategy, until better solution is found.

In many countries, paramedical services play a pivotal role in prehospital management. They are certified and well trained in prehospital stroke scales assessment and protocols. In France, specific training of paramedic staff and standardized protocols do not exist. However, there is an emergency and transportation phone regulated service. This service features stroke alert, triage, and decision of the best possible transport and destination given the patient's condition and expected duration of transfer. Other transfers mainly private or fire brigades. In Serbia phone triage and transport are done mainly by the EMS. In Belgrade, there is centralized public EMS that provides transport for the entire population.
One of the bypass hospital criteria are high suspicion of LVO (sudden onset and unilateral hemiplegia, stroke score scales) together with:
1. Known contraindication for IVT
2. Unknown onset time (proven efficacy of MT for wake-up stroke (DEFUSE-3, DAWN)
3. Geography – similar (≤ 10 minutes) transport time between CSC and PSC or estimated arrival to PSC ≥ 3.5 hours after onset time

Time-sensitive procedures such as organ harvest have used physician and/or entire team transport to a target facility, to improve time to procedure. In the regions with large distance gaps between CSC and lack of trained personnel, other solutions may be necessaire. The drip-and-drive concept is related to shifting neurointerventionalist and not the patient to the low volume center with angio-suite with MT material, trained personnel, fully equipped stroke unite and neurology department. In this strategy, MT is performed in a PSC, by the trained team imported from large volume CSC. Relevant times to recanalization can be significantly reduced compared to drip-and-ship concept (236). This is a low cost, high quality strategy, with time-saving parallelization of process. Helicopter transport of neurointerventional team is a recommended logistical option, where rationale and funding can be provided (244). Probability models for ideal transportation options were mapped with map visualizations are developed in recent years. They demonstrate that a PSC, that is in close proximity to a CSC remains significant only when the PSC is able to achieve a door-to-AP time reduced to ≤30 minutes. Therefore, only for the longer distance from CSC patients benefit from going to PSC (237).

The prehospital triage is of highest importance to reduce the onset to recanalization time. The

question remains whether a patient with an acute stroke should be first addressed to a stroke unit without thrombectomy facility to receive IV tPA or on the contrary, should be directly sent to a comprehensive stroke unit for thrombectomy. Direct admission to a CSC will reduce a lot the time to thrombectomy but will delay the time to IV tPA.

Two ongoing RCTs are aiming to answer this question:

1. RACECAT (245): Direct transfer to an endovascular center compared to transfer to the closest stroke center in acute stroke patients with suspected LVO (NCT02795962). The goal is to evaluate the hypothesis that direct transfer to an endovascular stroke center, compared to transfer to the closest local stroke center, offers a better outcome in the distribution of the mRs scores at 90 days in AIS patients with clinically suspected LVO identified by Emergency Medical Services (EMS). The RACE scale will be used as a prehospital screening tool to identify acute stroke patients with suspicion of LVO. Upon candidate identification, EMS will contact a stroke neurologist on call using a prehospital telestroke system who will confirm inclusion criteria and will allocate the subjects to a specific intervention per a pre-established temporal sequence. Allocation will account for 3 strata: time band (two groups of 12 hours), territory (metropolitan versus provincial area) and weekday (working versus weekend day).

As well, when a patient directly arrives in the comprehensive center to receive a thrombectomy the question is whether brain imaging should be done (CT, CTA, CTP, MRI, MRA) or if on the contrary the patient should be sent directly to the angio-suite to save time. Acute LVO strokes, requiring MT, are currently being managed through the radiology department before being transferred to the angiography room. However, younger patients with severe neurological deficits have demonstrated even greater benefits from recanalization as the symptom onset-to-reperfusion time is shortened to less than 1 hour. A recent pilot study has shown a benefit in reducing management delays with direct admission to the angiography room and subsequently in increasing functional independence at 3 months.

2. DIRECTANGIO (246): Effect of direct transfer to angio-suite on functional outcome in severe acute stroke (NCT03969511). The aim is to demonstrate the superiority of the direct angio-suite transfer versus the standard management, in terms of 3-month functional independence, in patients ≤ 60 years old with acute large-vessel stroke in 200 participants.

1.7.8. Applicability of the RCTs results in real-world settings

After the RCTs proved the benefit of MT in ACLVO, one of the major challenges is the implementation of the MT in real-world settings and translation of the results into clinical practice. Another question is, will the treatment effect be preserved in the reality of healthcare systems outside of first-world countries, as all the RCTs were done in Europe and the USA. Efficacy of thrombectomy in patients outside the criteria used in RCTs was addressed in several studies (247-249). Socioeconomic disparities are an issue reported even in developed countries (250). In developing countries, stroke-related mortality is much higher for ischemic and hemorrhagic strokes (65.1 and 71.8 per 100,000 people respectively) (32). Restricted funding, a high number of patients and a shortage of special expertise are the major problems for the implementation of evidence-based stroke management (IVT and MT), especially in developing countries. Social inequalities are reflected in health accessibility, which is a hallmark of middle-income countries (251). For example, majority of the population (75%) in Brazil, medical care is provided by the public national health system. For the remaining 25%, healthcare is provided by the private sector via private insurance. IV tPA was available in public hospitals in Brazil seventeen years after its approval in Europe (2012), while private hospitals did have it in the offer as a treatment about in the same period as in developed countries (2001). For the implementation of MT in real-world settings, it is necessary to overcome financial, logistical and political barriers.

The question is why the effect of MT might be different in lower resource countries? Clinical outcome is an interplay of many variables, one of them being the premorbid status of the patient.

Vulnerable population with higher overall morbidity-mortality from cardiovascular, chronic and malignant diseases is characteristic ow low-income countries. In prehospital faze, medical care and public awareness are not at a sufficient level of organization. Delayed presentation is one of the major challenges in the management of AIS in developing countries. Prolongations in diagnosis, transfer, and patient triage are common, issuing more time to arrival in the hospital. Problems with hospital infrastructure (difference in available angio-suite technology, un-adopted relation between angio-suite and diagnostic machine) and shortage of materials, different training of neurointerventionalists, with the shortage of trained staff raise difficulties to logistics organization. Equally, there are differences in the post-procedural level of care in and out of the hospital. Lack of access to rehabilitation centers after discharge, and lack of access to specialized medical care after primary rehabilitation, attribute to different clinical outcome. Therefore, by comparing clinical outcomes of one treatment method in high and low-income countries, there are multiple variables to be considered.

In most developing countries, IV tPA administration remains below 1% (36). In Serbia, less than 4% of all stroke patients receive IV tPA in the emergency setting (36). The same or worse is all across the countries in Balkan and Eastern European countries (252-254). In some countries of Asia and Latin America with asymmetric growth, availability of IVT and MT is troubled by parallel private and public health systems (251, 255, 256). The majority of patients cannot afford the treatment in private hospitals, and it is not available in public hospitals. Due to their socialistic political history, EVT in Central and Eastern European countries primarily remains in the public hospital domain for the time being.

It seems that the overwhelming efficacy of endovascular reperfusion is preserved, despite the many limitations encountered in the public healthcare system of low- and middle-income countries. Official governmental entities along with the Ministry of Health play a major role in managing resources, even more in countries with less unevenly developed healthcare system. Besides practical training in high patient volume centers, for overcoming a lack of special expertise to a larger population of LVO patients, telemedicine-assisted treatment was designed in the late 1990s. The results of RCTs can be transferred to the reality of countries that do not have the same degree of medical support system, which confirms the standpoint that MT should be available to them all regardless of socioeconomic status. The question of whether the results of these trials may apply as well to developing countries is addressed by at least two studies:

1. EAST (257): Endovascular therapy for acute ischemic stroke trial (NCT02350283). To evaluate the safety and efficacy of Solitaire thrombectomy in Chinese patients with acute stroke within 12 hours of symptom onset in 225 patients.
2. RESILIENT (258): Endovascular Treatment with stent-retriever and/or thrombo-aspiration vs. best medical therapy in acute ischemic stroke in Brazil (NCT02216643). This study results have already been presented and has shown similar results to the previous seven RCTs showing that in developing countries the thrombectomy is as efficient as in Europe and USA.

2. RESEARCH GOALS

The objective of this dissertation is to analyze the impact of contemporary MT on stroke outcome, in the initial period after the establishment of a stroke center, and the applicably of the results of RCTs in real-world settings, especially in developing countries. In this study, the activity of two CSC was analyzed, one in Toulouse University Hospital Pierre Paul Riquet, in France and second in the Belgrade University Hospital Clinical Center of Serbia. This is an analysis of two big regional CSC with already established interventional neuroradiology practice and experienced physicians and staff, in the first two years of practicing MT.
Research goals of the dissertation are:

1. Evaluation of MT efficacy depending of two types of anesthesia (GA vs. CS/LA)

2. Evaluation of clot removal efficacy (time mTICI2b/3, mTICI rate, time from arterial puncture to revascularization, number of attempts) depending in the clot origin and MRI characteristics

3. Mechanical thrombectomy outcomes evaluation for all the patients regardless of NIHSS and ASPECTS score, especially for the NIHSS ≤5 and ASPECTS ≤5

4. Assessment of the type of lesions where carotid stenting is indicated during MT

5. Evaluation of the impact of time variables and the way of transferring the patient on primary (recanalization and complication rate) and secondary (three-month morbidity and mortality) outcomes

3. MATERIAL AND METHODS

3.1. Ethical consideration

The Belgrade part of the study was thoroughly reviewed and approved by the Ethical Committee of Faculty of Medicine, University of Belgrade (29/XII-14). Observational retrospective studies according to the French legislation (articles L.1121–1 paragraph 1 and R1121–2, Public Health Code) do not require an ethics committee approval to use data for an epidemiologic study.

3.2. Study Design

This is a double center cohort study with the pragmatic care trial context for AIS patients treated with MT. For this observational study, the Toulouse University prospective stroke registry and Clinical Center of Serbia prospective stroke registry were used. Clinical and radiological information of cases treated in the Toulouse University Hospital Pierre Paul Riquet between January 2014 and January 2019 and the cases treated in the Emergency Center at Clinical Center of Serbia between January 2018 and January 2019 were retrospectively reviewed. The objectives of the proposed study are to follow the evolution of MT in two big CSC, and to assess the level of care in the first years after the implementation of the procedure. The Toulouse University center is the referring hospital for a region spanning 45,000 km^2 with a catchment area of almost 3 million inhabitants. Eleven PSC and SU refer patients to Toulouse center for MT. The Belgrade Clinical Center of Serbia is the referring hospital with a catchment area covering the population of around 2.5 million. Two CSC (in the days when not on call) and six PSC referred patients to Belgrade center for MT.

For the overall comparison of the first two years of the centers MT activities began from the year 2015 after the publication of positive RCTs. Periods for data collection are: from January 2015 to January 2017 for the Toulouse University center; from January 2018 to January 2020 for Clinical Center of Serbia. Moreover, additional collected data related to the management of anesthesia during MT procedure from the Toulouse mono-center cohort, are for the period from January 2014 until July 2016.

The eligible cases were selected using the following inclusion criteria: (1) verified ACLVO by CT or MR angiography; (2) MT initiated within the 6 hours from symptoms onset regardless of the use of IV tPA. However, additional inclusion criteria were used for the clot type assessment for the Toulouse cohort: (1) MRI established acute anterior circulation ischemic stroke including good quality DWI, time of flight (TOF) and susceptibility-weighted imaging (T2*-GRE).

On the other hand, the exclusion criteria were as follows: (1) presence of intracranial hemorrhage; (2) absence of the ACLVO on diagnostic; (3) medium and small artery occlusion (distal from M2 division) or in the territory of posterior circulation (vertebrobasilar distribution); (4) MT initiated after 6 hours from the symptom onset; (5) age below 18 years.

3.3. Multidisciplinary management

In both centers, a stroke neurologist evaluated all patients with suspected AIS and calculated NIHSS. The NIHSS is a 11-item neurologic examination stroke scale, each of which scores a specific ability between a 0 and 4 (104, 259). For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. Scoring range is from 0-42 points. The higher the number, the greater the stroke severity. NIHSS of 0 represents no stroke symptoms, 1-4 minor stroke, 5-15 moderate stroke, 16-20 moderate to severe, 21-42 severe stroke. Brain MRI or CT with a standardized stroke protocol was performed to exclude bleeding and confirm the diagnosis of stroke and the level of the arterial occlusion. Time from symptom onset was determined for all patients. For patients with wake-up stroke, the time from symptom onset was the time since the patient was last known well. IV tPA was used within the first 4.5-hours post-stroke onset except in known cases

of contraindication. In both centers, the decision whether to perform MT was jointly made by both the stroke neurologist and the interventionist. An experienced interventionist per the European guidelines on stroke treatment and institutional protocols performed MT (260, 261).

General anesthesia was used in most of the cases by intubation and mechanical ventilation using intravenous induction with etomidate and suxamethomiun followed by the use of sufentanil and a volatile agent (sevoflurane). Conscious sedation consisted of intravenous midazolam and sufentanil without intubation. Local anesthesia consisted of percutaneous local injection at the site of arterial puncture access, of the procaine hydrochloride 2%. Arterial BP was controlled to avoid a decrease of more than 20% of the baseline values, by using intravenous phenylephrine if necessary. Excessive BP (over 180 mmHg) was lowered by using intravenous bolus of urapidil.

Patients initially admitted to a primary stroke unit ("drip-and-ship" patients), underwent an initial CT or MRI in the first center. Following teleconsultation with the vascular neurologist, patients were transferred to our centers with or without IV tPA for MT. Once in our center, if the NIHSS score was the same or worse, the patient was immediately transferred to the angiosuite. If the NIHSS score had improved (> 4 points), another MRI or CTA was performed. MT was performed by stent retrievers or direct aspiration. If endotracheal (GA) anesthesia was used, at the end of the procedure patients were extubated, if possible, in the angio-suite and transferred to the recovery room and the stroke intensive care unit.

3.4. Clinical data

From prospective stroke databases in the both centers, we collected the patient's baseline demographics, and clinical and imaging information including: age, pre-treatment NIHSS, side of occlusion, level of occlusion, use of IV tPA, and type of anesthesia. Time metrics are all recorded including time of stroke onset, time of arrival at the stroke unit, time of imaging, time of arrival in the angio-suite, time of arterial puncture and time of recanalization/last image. Day one improvement is calculated as NIHSS pre-treatment – NIHSS at day one. A NIHSS 24 hour increase of 4+ point was defined as neurological deterioration. Early neurological improvement was defined as NIHSS 0-2 at 24 hours. For the purpose of clot evaluation, stroke etiology subtype is classified using the classification of the TOAST (The most commonly used etiological classification Trial of Org 10172 in Acute Stroke Treatment) that denotes five subtypes of ischemic stroke: 1) large-artery atherosclerosis; 2) cardio-embolism; 3) small-vessel occlusion; 4) stroke of other determined etiology; 5) stroke of undetermined etiology (102). Patients were then dichotomized in cardio-embolic and non-cardio-embolic strokes.

3.5. Imaging data

In Toulouse University Center, MRI is the standard modality for LVO ischemic stroke and treatment decisions. Three different MRI machines are available 24/7 (3T Skyra, Siemens, Erlangen, Germany; 3T Achieva, Philips, Andover, USA; 1.5T, Optima MR350, General Electric Medical System, Boston, USA), along with two CT machines (Optima CT660 128 slice, General Electric Medical System, Boston, USA; Discovery 750 HD 128 slice, General Electric Medical System, Boston, USA). In addition, drip-and-ship patients underwent an MRI or a CT in a remote hospital. In Toulouse CSC, when possible and if no contraindications existed, acute strokes are evaluated by MRI. On MRI, the diagnosis of acute ischemic stroke is confirmed on DWI and the occlusion of the intracranial anterior circulation artery is assessed using TOF imaging. The MRI imaging protocol takes 10 minutes and includes DWI, TOF MRA, T2*- gradient echo (GRE), FLAIR, gadolinium cervical angiography and perfusion. In cases of contraindication to MRI, CT and CTA scans are performed.

In the Clinical Center of Serbia, CT is the standard modality for LVO ischemic stroke and

treatment decision. Two different CT machines are available (Aquilion prime 128-slice, Toshiba, Tokyo, Japan; BrightSpeed 16-slice, General Electric Medical System, Boston, USA). The absence of intracranial bleeding and the presence of ischemic lesion is confirmed on NCCT, and the occlusion of the intracranial blood vessel is assessed using CTA. In addition, drip and ship patients did undergo a CT in a remote hospital.

The Alberta Stroke Program Early CT Score was calculated on DWI (DWI ASPECTS) or CT (CT ASPECTS) to assess the extent of the ischemic core. ASPECTS is a 10-point scale, where MCA territory is divided in 10 areas (caudate nucleus, lentiform nucleus, insular ribbon, internal capsule and six m territories) each accounted for one point. Final ASPECTS is calculated by taking off one point from 10 for every region that is affected (85, 86). Aspect of 10 represents no ischemic changes present on CT or DWI.

For the study of clot evaluation, the presence or absence of the SVS was retrospectively assessed on T2*-GRE. The acquisition parameters of the T2*-GRE sequences on the three machines are described (Table 3.1).

Table 3.1. The acquisition parameters of the T2*-GRE sequences on the three machines

T2*	**TR**	**TE**	**Flip angle**	**slice**	**Intersection gap**
Siemens, Skyra	730 ms	14,8 ms	20°	5 mm	1 mm
Philips, Achieva	790 ms	16 ms	20°	4 mm	0 mm
General Electric, Optima MR350	400 ms	18 ms	20°	5 mm	1 mm

3.6. Susceptibility vessel sign evaluation

Two independent investigators did susceptibility vessel sign assessment: one junior neuroradiologist with 5 years of experience, and one senior neuroradiologist with more than 10 years of experience. To evaluate the presence (SVS+) or absence (SVS-) of SVS, they used DWI, T2*-GRE and TOF sequences. “SVS+” was defined on T2*-GRE as a decreased signal within a vessel exceeding the size of the homologous contralateral artery diameter (Figure 3.1). The intra-rater and inter-rater agreements for SVS+ or SVS- was assessed using the Kappa coefficient and its 95% confidence interval.

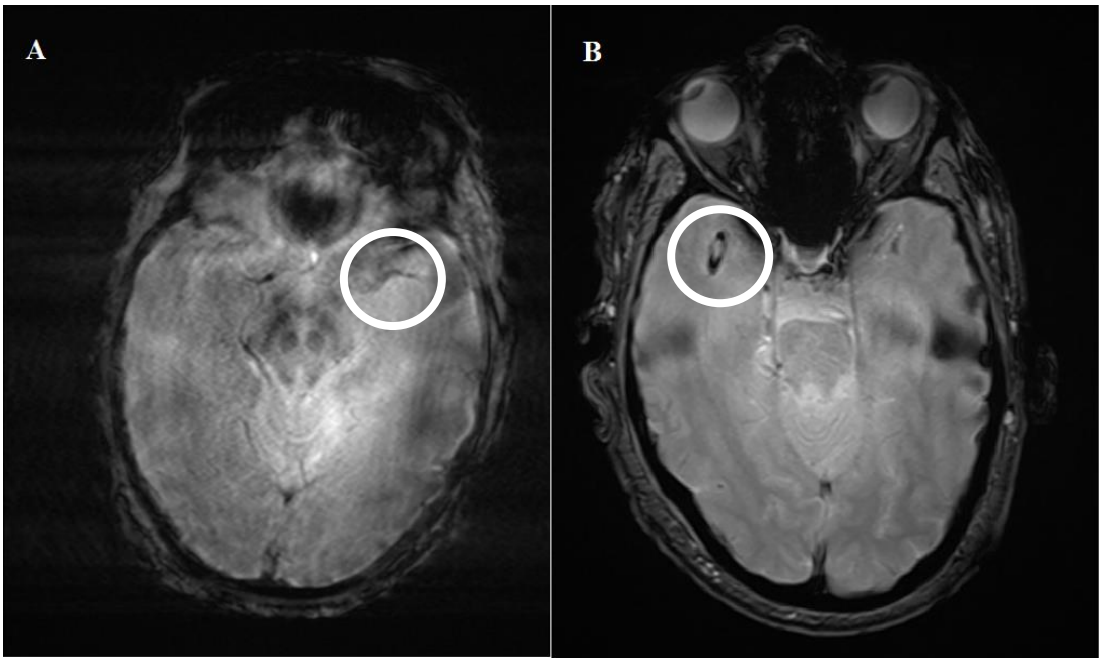

Figure 3.1. (A) CVS – Clot; (B) CVS + Clot.

3.7. Endovascular treatment data and angiographic outcome

In the Toulouse University Center, all endovascular procedures were performed on a biplane system (AlluraClarity 20/10; Philips Healthcare, Best, the Netherlands) by experienced interventionists. In Clinical Center of Serbia, all endovascular procedures were performed on a monoplane system (Artis zee 20; Siemens, Erlangen, Germany) by experienced interventionists. The level of vessel occlusion was confirmed on the initial angiogram. The final recanalization grade was assessed using the mTICI score as previously described (142, 262). Successful revascularization was defined as mTICI 2b/3, corresponding to reperfusion of at least 50% of the affected vascular territory.

3.8. Safety and clinical outcomes

For all Toulouse CSC cases a cone beam CT was performed right after procedure at the angio-suite to assess possible intracranial bleeding. For the Belgrade CSC cases a CT was performed right after procedure, if there was any suspicion for intracranial bleeding. In all cases, a follow-up 24-hour MRI or CT was performed, and any existence of a hemorrhagic transformation noted. In the case of clinical deterioration additional CT or MRI imaging was performed. Hemorrhagic transformation was classified on imaging studies as radiographic hemorrhagic infarction (HI) and parenchymal hematoma (PH) (263). More graduated distinction was used in our study: hemorrhagic infarction type 1 (HI1) defined by small petechiae along the margins of the infarction, and hemorrhagic infarction type 2 (HI2) defined by more confluent petechiae within the infarction area, both without mass effect; parenchymal hematoma type 1 (PH1) defined by one or more blood clots occupying 30% or less of the infarcted area with a mild mass effect, and parenchymal hematoma type 2 (PH2) defined by blood clots in more than 30% of the infarcted area with a clinically significant mass effect (264). Safety outcomes were sICH and mortality at 3 months.

Symptomatic intracranial hemorrhage was determined according to ECASS III criteria, as any parenchymal hemorrhage on postinterventional brain CT or MRI, accounting for clinical deterioration in NIHSS score increase of ≥ 4 points or leading to death within 24 hours from treatment as previously described (4). Asymptomatic intracranial hemorrhage encompassed all remaining non-symptomatic intracranial hemorrhages. Clinical outcomes were stroke severity measured on NIHSS score at 24 hours, and the degree of disability assessed on mRS 3 months after discharge. Change in NIHSS score of stroke severity from baseline to 24 hours after intervention was notified, patients with major early neurological recovery at 24 hours are defined as NIHSS reaching 0–2. Clinical outcome at three months after procedure was estimated by mRS (265, 266). The mRS is a 6-level scale ranging from 0 (without any neurological deficit) to 6 (death). Good clinical outcome after 90 days was defined as mRS ≤ 2 (functional independence). Poor clinical outcome is defined as mRS 3-6.

3.9. Statistical analysis

Descriptive and analytical statistical methods were used in this study. From the descriptive ones, the following were used: absolute and relative numbers (n, %); measures of central tendency (arithmetic mean, median); measures of variability (standard deviation, percentiles). From the analytical statistical methods, tests for difference examination were used: parametric (t test, ANOVA); nonparametric (Chi-square test, Fisher's test of exact probability, Mann-Whitney U test, Kruskal-Wallis test). The choice of the test depended on the type of data and the distribution. Parametric methods were used in a situation where the distribution was normal, while nonparametric methods were used in a situation where the distribution was not normal. The normality of the distribution was examined on the basis of descriptive parameters, tests of the normality of the distribution (Kolmogorov-Smirnov and Shapiro-Wilks test) and graphical methods (histogram, boxplot, QQ plot). Logistic regression analysis, univariate and multivariate, was used to assess significant predictors of the dependent binary variables. In multivariate analysis the adjusted cofounders for type of anesthesia were center, gender, ASPECTS ≤ 5, left side LVO, complication, ENT, number of passes, and time onset to recanalization; for the type of clot composition and origin were age, IV tPA, baseline NIHSS, and TICI for the NIHSS ≤ 5 were complication, ENT, and time onset to recanalization; for the ASPECTS ≤ 5 were center, age 80+, type of anesthesia, ICA T, number of passes, and time onset to recanalization; for the TO were gender, age 80+, wake up stoke, left side LVO, and time onset to recanalization; for the way of admission were complication, failure, and time onset to recanalization. The results are presented in tables and graphs.

All data were processed in SPSS 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) software package and R 3.4.2 (R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

4. RESULTS

4.1. PATIENT BASELINE CHARACTERISTICS

Patient baseline characteristics for the entire population are detailed in Table 4.1. In the study period of first two years in both centers, 366 MT were performed for ACLVO stroke, 284 in Toulouse (77.6%) and 82 (22.4%) in Belgrade. Among the 366 cases, 194 (53%) were male and 172 (47%) female. Wake-up stroke was present in 39 (10.7%) of patients. Overall, 128 (35.0%) patients were transferred to our center from another regional stroke unit (drip-and-ship). ASPECTS was calculated on DWI in 224 patients (61.2%) and on CT in 142 (38.8%). In regard to the thrombus location, there was a balanced proportion of left and right hemispheric stroke.

Table 4.1. Patient baseline characteristics

Center	Toulouse no. (%)	284 (77.6)
	Belgrade no. (%)	82 (22.4)
Male sex no. (%)		194 (53)
Age (yrs.) mean, (SD)		68.8 (14)
Age 80+ no. (%)		95 (26)
NIHSS median, (IQR)		18 (14-21)
NIHSS ≤ 5 no. (%)		12 (3.3)
Pre-stroke mRS score no. (%)	0	317 (86.6)
	1	39 (10.7)
	2	7 (1.9)
	3	3 (0.8)
Wake-up stroke no. (%)		39 (10.7)
Direct admission no. (%)		238 (65)
Diagnostic modality no. (%)	CT	142 (38.8)
	DWI	224 (61.2)
ASPECTS median, (IQR)	CT	10 (8-10)
	DWI	7 (5-8)
ASPECTS ≤ 5 no. (%)		68 (19.1)
IV tPA n, (%)		194 (53)
Left side LVO no. (%)		188 (51.4)
Tandem no. (%)		50 (13.7)
Anesthesia no. (%)	GA	239 (65.3)
	CS	50 (13.7)
	LA	77 (21)
Number of pass no. (%)		
	1	156 (42.6)
	2+	210 (57.4)
mTICI no. (%)		307 (83.9)??
2b/3		207 (83.9)
2a/1		26 (7.1)
0		33 (9.0)
sICH at 24h no. (%)		11 (3)
NIHSS at 24h median, (IQR)		10 (5-19)
3-month mRS score no. (%)	0	80 (21.9)
	1	53 (14.5)
	2	46 (12.6)
	3	52 (14.2)
	4	45 (12.3)
	5	23 (6.3)
	6	67 (18.3)

no, number of patients; SD, standard deviation; IQR, interquartile range (percentile 25-75);

4.2. MECHANICAL THROMBECTOMY IN RELATION TO ANESTHESIA MANAGEMENT

Patient characteristics for the entire population, GA and CS group are detailed in Table 4.2. Among the 366 cases, 239 (65.3%) were performed under GA and 127 (34.7%) under CS/LA. Patients were predominantly treated in under GA in Toulouse 234 (97.9%) compared to Belgrade 5 (2.1%) ($p<0.001$). Patients treated under CS/LA comprised 50 (39.4%) and 77 (60.6%) patients from Toulouse and Belgrade respectively. Overall, 128 (35%) of patients were transferred to our centers from another regional stroke unit (drip and ship), 88 (36.8%) in GA and 40 (31.5%) in CS. Pre-treatment NIHSS score was higher in the GA group, with a significant difference on univariate regression analysis ($p=0.001$). DWI ASPECTS was found to be significantly lower in GA group in univariate regression analysis ($p=0.002$). There was a higher proportion of patients in low ASPECTS (ASPECTS≤5) the GA group 61 (26.5%) than in CS/LA group 7 (5.6%) ($p<0.001$). Significantly higher proportion of M2 occlusion was found in CS/LA than in GA patients (26.8% vs 14.2%, $p=0.003$). IV tPA was significantly higher in GA compared to CS/LA group ($p<0.001$).

Table 4.2. Patient characteristics in subgroups related to anesthesia management

		Anesthesia		*P* value
		GA	CS/LA	
Center no. (%)	Toulouse	234 (97.9)	50 (39.4)	<0.001[a]
	Belgrade	5 (2.1)	77 (60.6)	
Male sex no. (%)		120 (50.2)	74 (58.3)	0.141[a]
Age (yrs.) mean, (SD)		71 (62-80)	70 (60-79)	0.341[d]
Age 80+ no. (%)		65 (27.2)	30 (23.6)	0.458[a]
NIHSS median, (IQR)		19 (16-22)	15 (11-20)	0.001[c]
NIHSS ≤ 5 no. (%)		7 (2.9)	5 (3.9)	0.759[b]
Wake-up stroke no. (%)		28 (11.7)	11 (8.7)	0.367[a]
Direct admission no. (%)		151 (63.2)	87 (68.5)	0.309[a]
Diagnostic modality median, (IQR)				
	CT ASPECTS	9 (8-10)	10 (8-10)	0.478[c]
	DWI ASPECTS	6 (5-7)	7 (6-8)	0.002[c]
ASPECTS ≤ 5 no. (%)		61 (26.5)	7 (5.6)	<0.001[a]
IV tPA n, (%)		156 (65.3)	38 (29.9)	<0.001[a]
Left LVO no, (%)		129 (54)	59 (46.5)	0.171[a]
A1 no. (%)		3 (1.3)	0 (0)	0.554[b]
A2 no. (%)		3 (1.3)	2 (1.6)	1.000[b]
ICA T no. (%)		62 (25.9)	29 (22.8)	0.513[a]
M1 no. (%)		148 (61.9)	66 (52)	0.066[a]
M2 no. (%)		34 (14.2)	34 (26.8)	0.003[a]
Tandem no. (%)		33 (13.8)	17 (13.4)	0.911[a]

no, number of participants; SD, standard deviation; IQR, interquartile range (percentile 25-75); [a] Chi Square test; [b] Fisher Exact test; [c] Mann-Whitney U test; [d] Student's t-test.

4.2.1. Procedure time metrics in subgroups related to anesthesia management

Table 4.3. displays the time metrics in the GA and CS/LA groups. Median time from arrival in CSC door to arterial puncture (AP) was 78 min (IQR=45-97) for GA compared to 96 min (IQR=49-137) for CS/LA in the univariate regression analysis (p<0.001). Median time from arrival in the angio-suite room to AP was 20 min (IQR=15.0-28.0) for GA compared to 15 min (IQR=10-21) for CS (p=0.001). Times door to recanalization and door to image were significantly better for GA compared to CS (p=0.002 and p<0.001 respectively).

Table 4.3. Procedure time metrics in subgroups related to anesthesia management

	Anesthesia		*P* value**
	GA	CS/LA	
Time Onset - Door CSC (min)*	135 (80-214)	133 (66-195)	0.273
Time Onset - IVT (min) *	135.5 (107-180)	132.5 (105-165)	0.332
Time Onset - AP (min) *	221 (170-280)	240 (190-292)	0.078
Time Door CSC - AP (min) *	78 (45-97)	96 (49-137)	<0.001
Time Image - AP (min) *	81 (58-139)	89 (63-126)	0.944
Time Room - AP (min) *	20 (15-28)	15 (10-21)	0.001
Time Door CSC - Recanalization (min) *	121 (91-163)	148 (97-207)	0.002
Time Room - Recanalization (min) *	68 (50-95)	67 (42-94)	0.185
Time AP - Recanalization (min) *	283 (222-335)	295 (243-344)	0.699
Time Onset – Recanalization (min) *	283 (222-335)	295 (243-344)	0.146
Time Door CSC - Image (min) *	23 (16-31)	35 (25-59)	0.146

* All variables are presented as median (percentile 25-75); ** Mann-Whitney *U* test; min, minutes.

4.2.2. Technical characteristics of procedure in subgroups related to anesthesia management

Median number of passes was 2 (IQR=1-3) in the global population and in both groups. There was a higher number of first pass successful recanalization, performed under GA (45.2%) versus CS/LA (37.8%) (p=0.173).

4.2.3. Procedural and post-procedural complications in subgroups related to anesthesia management

Procedural and post-procedural complications are given in Table 4.4. Only embolization into new vascular territories (ENT) was significantly higher in CS on the univariate logistic regression (p=0.001). At 24 hours, sICH was significantly more frequent in GA compared to CS/LA group (p=0.046) as did overall hemorrhagic transformation rate (p<0.001).

Table 4.4. Procedural and post-procedural complications in subgroups related to anesthesia management

		Anesthesia		
		GA	CS/LA	*P* value
Overall complication no. (%)		32 (13.4)	27 (21.3)	0.051 [a]
ENT no. (%)		10 (4.2)	17 (13.4)	0.001 [a]
Vessel dissection/perforation no. (%)		3 (1.3)	5 (3.9)	0.132 [b]
Procedural ICH no. (%)		2 (0.8)	0 (0)	0.546 [b]
SAH no. (%)		3 (1.3)	4 (3.1)	0.242 [b]
IVH no. (%)		0 (0)	0 (0)	-
Hemorrhagic transformation	HI1	30 (12.6)	2 (1.6)	
at 24h no. (%)	HI2	24 (10)	5 (3.9)	<0.001[c]
	PH1	21 (8.8)	5 (3.9)	
	PH2	16 (6.7)	6 (4.7)	
PH2 at 24h no. (%)		16 (6.7)	6 (4.7)	0.450 [a]
sICH at 24h no. (%)		11 (4.6)	0 (0.0)	0.046 [b]

no, number of participants; [a] Chi Square test; [b] Fisher Exact test; [c] Mann-Whitney *U* test;

4.2.4. Technical and clinical outcomes in subgroups related to anesthesia management

Technical and clinical outcomes are provided in Table 4.5. There was a tendency for higher rate of mTICI 3 in the CS/LA group (p=0.093). No significant differences in the rate of successful recanalization (mTICI 2b/3) was found. 24 hours post-treatment NIHSS was 11 (IQR=6-21) for GA compared to 10 (IQR=4-16) for CS/LA (p=0.005). There was a tendency of higher mortality in the GA group (p=0.177).

Table 4.5. Technical and clinical outcomes in subgroups related to anesthesia management

	Anesthesia		*P* value
	GA	CS/LA	
mTICI 2b/3 no. (%)	41 (17.2)	18 (14.2)	0.460 [a]
Failure in attempted MT (mTICI 0) no. (%)	21 (8.8)	15 (11.8)	0.355 [a]
NIHSS score 24h median, (IQR)	11 (6-21)	10 (4-16)	0.005 [b]
NIHSS 24h 0-2 no. (%)	30 (12.6)	22 (17.3)	0.219 [a]
NIHSS 24h increase 4+ no. (%)	26 (10.9)	13 (10.2)	0.839 [a]
3-month mRS 0-2 no. (%)	114 (47.7)	65 (51.2)	0.526 [a]
3-month mRS 6 (mortality) no. (%)	39 (16.3)	28 (22)	0.177 [a]

no, number of participants; [a] Chi Square test; [b] Mann-Whitney *U* test;

4.2.5. Results related to anesthesia management from Toulouse mono-center cohort.

This was prospective single-center, observational study conducted from January 1, 2014 until the July 1, 2016. Study enrolled 303 consecutive anterior circulation LVO patients treated by MT that was initiated within 6 hours from symptom onset.

4.2.5.1. Patient baseline and overall characteristics of Toulouse mono-center cohort

Patient characteristics for the entire population, GA and CS group are detailed in Table 4.6. In the study period, among the 303 cases, 263 (86.8%) were treated under GA and 40 (13.2%) under CS. Mean age was 67.5 (SD = 15.3) years. Pre-treatment NIHSS score was significantly higher in the GA group on univariate (p=0.049) but was not significant on multivariate (p=0.586) regression analysis. ASPECTS was estimated on DWI in 80.2% patients, and was found to be significantly lower in GA group in multivariate regression [OR=0.52, 95% (CI 0.28-0.99); p=0.045]. In regard to the thrombus location, left hemispheric stroke was more frequently present in GA patients (57.8% vs 35%) in multivariate regression analysis [OR=5.16, 95% CI (1.18-22.51); p=0.029].

Table 4.6. Patient baseline and overall characteristics from Toulouse mono-center cohort in subgroups related to anesthesia management

	Anesthesia			*P* value
	CS	GA	Total	
No.	40	263	303	
Age median, (IQR)	73 (24.8)	70 (20.5)	71 (21)	0.336 [d]
Onset NIHSS median, (IQR)	15.5 (10)	18 (7)	18 (7)	0.030 [c]
Pre mRS 0 no. (%)	36 (90)	223 (85)	259 (86)	0.383 [a]
Pre mRS 1 no. (%)	4 (10)	30 (11)	34 (11)	0.792 [a]
DWI ASPECTS median, (IQR)	7 (1)	7 (3)	7 (0)	0.013 [c]
CT ASPECTS median, (IQR)	9 (2.5)	9 (2)	9 (2)	0.639 [c]
NIHSS median, (IQR)	16.5 (9.3)	19 (6.5)	18 (7)	0.049 [c]
IV tPA no. (%)	20 (50)	176 (66.9)	196 (64.7)	0.045 [a]
LVO left-side occlusion no. (%)	14 (35.0)	152 (57.8)	166 (54.8)	0.008 [a]
M1 no. (%)	21 (53)	117 (44)	138 (46)	0.343 [a]
M2 no. (%)	7 (18)	29 (11)	36 (12)	0.238 [a]
ICA T no. (%)	8 (20)	56 (21)	64 (21)	0.852 [a]
Cervical ICA no. (%)	1 (2.5)	12 (4.6)	13 (4.3)	0.548 [a]
Tandem no. (%)	3 (8)	47 (18)	50 (17)	0.099 [a]

no, number of participants; IQR, interquartile range (percentile 25-75); [a] Chi Square test; [b] Fisher Exact test; [c] Mann-Whitney U test; [d] Student's t-test.

4.2.5.2 Procedure time metrics of Toulouse mono-center cohort

Table 4.7 displays the time metrics in the GA and CS groups. Median time from arrival in our hospital (door) to AP was 83 min for GA compared to 72 min significant in the univariate (p=0.032), but not in the multivariate analysis (p=0.170). Median time from arrival in the angio-suite to AP was 20 min) for GA compared to 15 min for CS, which was significant in the multivariate analysis [OR=1.14, 95% CI (1.02-1.26); p=0.017].

Table 4.7. Procedure time metrics of Toulouse mono-center cohort in subgroups related to anesthesia management

	Anesthesia			*P* value**
	CS	GA	Total	
Onset to IV tPA (min)*	136 (55)	150 (64)	148 (62)	0.186
Onset to AP (min)*	216 (139)	240 (125)	240 (127)	0.286
Door CSC to AP (min)*	72 (50)	83 (65)	80 (60)	0.170
Room to AP (min)*	15 (10)	20 (14)	20 (13)	0.017
Onset to recanalization (min)*	280 (123)	305 (121)	305 (122)	0.755
Door CSC to recanalization (min)*	115 (82)	133 (79)	132 (81)	0.127
Room to recanalization (min)*	70 (54)	73 (47)	72 (48)	0.472
AP to recanalization (min)*	45 (45)	42 (35)	42 (37)	0.806

* Data are presented as median and interquartile range (percentile 25-75); ** Mann-Whitney *U* test; min, minutes.

4.2.5.3 Technical characteristics of procedure of Toulouse mono-center cohort

Median number of passes was 2 (IQR=1-3) in both groups. There was a significant difference in the number of third pass successful attempts performed under GA versus CS (15% vs 32%) in univariate (p=0.023), but the effect was not transferred on multivariate regression analysis (p=0.555).

4.2.5.4. Procedural and post-procedural complications of Toulouse mono-center cohort

Post-procedural complications are detailed in Table 4.8. ENT was significantly higher in CS on the univariate (p=0.010) but not on the multivariate analysis (p=0.999). There was no statistical difference in symptomatic and asymptomatic hemorrhages between groups.

Table 4.8. Procedural and post-procedural complications and clinical outcomes of Toulouse mono-center cohort in subgroups related to anesthesia management

	Anesthesia			
	CS	GA	Total	*P* value
	40	263	303	
SAH no. (%)	0	3 (1.1)	3 (1)	0.497 [b]
Intracranial vessel perforation no. (%)	1 (2.5)	2 (0.8)	3 (1)	0.300 [a]
Cervical carotid dissection no. (%)	1 (2.5)	3 (1.1)	4 (1.3)	0.482 [a]
ENT no. (%)	4 (10)	6 (2)	10 (3)	0.031 [a]
sICH at 24h no. (%)				
HI1	0	2 (0.8)	2 (0.7)	0.580 [b]
HI2	0	3 (1.1)	3 (1.0)	0.497 [b]
PH1	0	5 (1.9)	5 (1.7)	0.379 [b]
PH2	0	3 (1.1)	3 (1.0)	0.497 [b]
SAH	1 (2.5)	1 (0.4)	2 (0.7)	0.123 [b]
Total	1 (2.5)	14 (5.3)	15 (5.0)	0.443 [a]
aICH at 24h no. (%)				
HI1	3 (7.5)	23 (8.7)	26 (8.6)	0.793 [a]
HI2	4 (10.0)	20 (7.6)	24 (7.9)	0.601 [a]
PH1	3 (7.5)	24 (9.1)	27 (8.9)	0.736 [a]
PH2	0	10 (3.8)	10 (3.3)	0.071 [b]
SAH	0	2 (0.8)	2 (0.7)	0.580 [b]
Total	10 (25.0)	79 (30.0)	89 (29.4)	0.514 [a]

no, number of participants; [a] Chi Square test; [b] Fisher Exact test; [c] Mann-Whitney U test; [d] Student's t-test.

4.2.5.5. Technical and clinical outcomes of Toulouse mono-center cohort

Primary and secondary outcomes are provided in Table 4.9. No significant differences were detected in the rate of mTICI 2b/3, NIHSS at 24 hours, and three months good clinical outcome and mortality rate.

Table 4.9. Clinical outcomes of Toulouse mono-center cohort in subgroups related to anesthesia management

	Anesthesia			
	CS	GA	Total	*P* value
mTICI no. (%)				
2b/3	32 (80)	209 (79.5)	241(79.5)	0.938 [a]
2a/1	5 (12.5)	31 (11.8)	36 (11.9)	0.896 [a]
0	3 (7.5)	23 (8.7)	26 (8.6)	0.793 [a]
Total	40 (100)	263 (100)	303 (100)	
NIHSS day1 median, (IQR)	11 (13.3)	12 (16)	12 (15)	0.102 [a]
3-month mRS 0-2 no. (%)	22 (58)	135 (53)	157 (54)	0.568 [a]
3-month mRS 6 (mortality) no. (%)	4 (11)	42 (16)	46 (16)	0.347 [a]

no, number of participants; [a] Chi Square test; [b] Fisher Exact test; [c] Mann-Whitney U test; [d] Student's t-test.

4.3. MECHANICAL THROMBECTOMY IN RELATION TO CLOT COMPOSITION AND ORIGIN

Baseline characteristics are detailed in Table 4.10. Of 180 patients, SVS was detected in 137 (76%) patients (SVS+), and missing in 43 (24%) patients (SVS-). Fifteen patients had an MRI at the admission to the PSC, 12 (80%) of them had SVS+ and 3 (20%) had SVS-. Location of the clot was MCA in 118 patients (65%), in the M1 segment 92 (51%), and the M2 segment 26 (14%). Terminal ICA was occluded in 28 patients (16%). Tandem occlusion was present in 34 (19%) (M1=18, M2=6, terminal ICA= 10) patients. For SVS+ or SVS- Kappa inter-rater agreement was K=0.71 with a 95% CI (0.59-0.82).

Table 4.10. Patient characteristics and time metrics related to clot aspect on T2*

	SVS + N=137 (%)	SVS - N=43, (%)	Total N=180	*P* value
Age (yrs.), mean (SD)	67.4(15.7)	70.7(6.5)	68.2(15.9)	0.12 [d]
NIHSS, mean (SD)	16.7(6.4)	16.9(6.0)	17(6.3)	0.72 [c]
Tandem, no. (%)	30 (21.9)	4 (9.3)	34 (18.9)	0.07 [a]
Intracranial clot location (tandem included)				
ICA T	29 (21.2)	9 (20.9)	38 (21.1)	
M1	81 (59.1)	29 (67.4)	110 (61.1)	0.46 [a]
M2	27 (19.7)	5 (11.6)	32 (17.8)	
IV tPA no. (%)	92 (67.2)	26 (60.5)	118 (65.6)	0.42 [a]
Time onset-image, median (IQR)	129 (90–171)	128 (76–178)	129 (89–172)	0.65 [c]
Time AP-recanalization, median (IQR)	43 (30–66)	61 (29–96)	45 (29–79)	0.3 [c]
Time onset-recanalization, median (IQR)	269 (219–340)	281 (217–347)	273 (217–344)	0.91 [c]

no, number of participants; SD, standard deviation; IQR, interquartile range (percentile 25-75); [a] Chi Square test; [b] Fisher Exact test; [c] Mann-Whitney U test; [d] Student's t-test.

4.3.1. Susceptibility vessel sign and stroke etiology

Cardio-embolic etiology was present in 100 (56%). Over the 100 cardio-embolic clots, 77 (77%) were SVS+ and 23 (23%) SVS -. Of the non-cardio-embolic clots 80 (44%), 60 (80%) were SVS+ and 20 (25%) SVS- on T2*. Univariate analysis showed no association between SVS and cardio-embolic mechanism of cerebral infarction [OR=1.12, 95% CI (0.56-2.22); (p=0,75)].

4.3.2. Susceptibility vessel sign and technical outcome

Successful recanalization (mTICI 2b/3) was accomplished in 147 (82%) patients, with a rate of 85% (117/137) in SVS+ group, and 69% (30/43) in cases of SVS- group. mTICI 2b/3 was associated with a higher rate of SVS+ on univariate and multivariate adjusted analysis [OR=2.48; 95% CI, (1.05–5.74); p=0.03]. IV tPA preceded MT in 118 procedures (66%). The use of IV tPA was significantly associated with successful recanalization in univariate adjusted analysis with [OR=2.49; 95% CI (1.11-5.64); p=0.03), but without statistical significance on multivariate adjusted analysis (p>0.05). Median number of passes was 2 (IQR=1-3) in both groups.

4.3.3 Susceptibility vessel sign and clinical outcome

Time to recanalization was associated with good outcome on univariate analysis (p=0.002), but the significance was not present in the multivariate analysis. Day one clinical improvement (pre-treatment NIHSS – NIHSS at 24 hours) was higher in the SVS+ group with median of 6 (IQR=3) compared to SVS- patients with a median of 1 (IQR=0) (p=0.01), which was significant on the multivariate regression analysis [OR=2.84; 95% CI, (−5.37 - −0.30); p=0.03]. No difference was found at three months regarding the rate of good clinical outcome (mRS 0-2) and mortality (mRS 6).

4.4. MECHANICAL THROMBECTOMY IN RELATION TO NIHSS AND ASPECTS

4.4A. Low NIHSS ≤ 5

Patient characteristics for the entire population, in the low and higher NIHSS group are detailed in Table 4.11. Among the 366 cases, 354 (96.7%) had NIHSS of >5, and 12 (3.3%) had NIHSS of ≤5. When comparing the centers, the majority of low NIHSS patients were estimated on DWI and treated in Toulouse; 10 (3.5%), while in Belgrade, 2 (2.4%) patients were diagnosed on CT. Of the 12 patients with low NIHSS, 3 (25%) patients were transferred from another regional stroke unit (drip and ship). As expected, pre-treatment NIHSS score was significantly lower in the NIHSS ≤5 group with median of 3 (IQR=3-4.5) compared higher NIHSS group with median of 18 (IQR=14-21). DWI ASPECTS was found to be significantly higher in NIHSS ≤5 group in univariate analysis (p=0.015). Concerning the thrombus location, there was a statistically significant predominance of treated low NIHSS in the patients with the left side ACLVO on univariate (p=0.006). There was a statistical difference for less frequent ICA T (p= 0.043) occlusion and more frequent M2 occlusion on univariate analysis (p=0.012).

Table 4.11. Patient characteristics in subgroups related to NIHSS score value

			NIHSS		*P* value
			≤5	>5	
Center no. (%)	Toulouse		10 (83.3)	274 (77.4)	1[b]
	Belgrade		2 (16.7)	80 (22.6)	
Male sex no. (%)			8 (66.7)	186 (52.5)	0.335[a]
Age (yrs.) mean, (SD)			62.8 (14)	69 (14)	0.910 [d]
Age 80+ no. (%)			1 (8.3)	94 (26.6)	0.198 [b]
Anesthesia no. (%)		GA	7 (58.3)	232 (65.5)	0.759 [b]
		CS/LA	4 (41.7)	122 (34.5)	
Wake-up stroke no. (%)			1 (8.3)	38 (10.7)	1[b]
Direct admission no. (%)			9 (75)	229 (64.7)	0.533 [b]
Diagnostic modality median, (IQR)					
	CT ASPECTS		10 (10-10)	10 (8-10)	0.127 [c]
	DWI ASPECTS		8 (7-9)	7 (5-7)	0.015 [c]
ASPECTS ≤ 5 no. (%)			1 (8.3)	67 (19.5)	0.475 [b]
IV tPA n, (%)			6 (50)	188 (53.1)	0.832[a]
Left LVO no, (%)			11 (91.7)	177 (50)	0.006 [b]
A1 no. (%)			0 (0)	3 (0.8)	1 [b]
A2 no. (%)			0 (0)	5 (1.4)	1 [b]
ICA T no. (%)			0 (0)	91 (25.7)	0.043 [b]
M1 no. (%)			6 (50)	208 (58.8)	0.564 [b]
M2 no. (%)			6 (50)	62 (17.5)	0.012 [b]
Tandem no. (%)			3 (25)	47 (13.3)	0.217 [b]

no, number of participants; SD, standard deviation; IQR, interquartile range (percentile 25-75); [a] Chi Square test; [b] Fisher Exact test; [c] Mann-Whitney U test; [d] Student's t-test.

4.4A.1 Procedure time metrics in subgroups related to NIHSS score value

Table 4.12 displays procedure time metrics in subgroups related to NIHSS score value. Median time from arrival to the CSC door to AP was 80 minutes (IQR=45-110) for the higher NIHSS compared to 95 minutes (IQR=86-139.5) for the low NIHSS patients (p=0.051). Median time from arrival to the CSC door to recanalization was 127.5 minutes (IQR=93-178) for higher NIHSS compared to 157.0 minutes (IQR=131-255) for low NIHSS patients significant on univariate analysis (p=0.049).

Table 4.12. Procedure time metrics in subgroups related to NIHSS score value

	NIHSS		*P* value**
	≤5	>5	
Time Onset - Door CSC (min)*	125.5 (47.5-150)	135 (75-210)	0.208
Time Onset - IVT (min) *	162.5 (105-180)	135 (107-180)	0.701
Time Onset - AP (min) *	236 (167.5-283.5)	226 (175-283)	0.863
Time Door CSC - AP (min) *	95 (86-139.5)	80 (45-110)	0.051
Time Image - AP (min) *	73 (64.5-104)	82.5 (60-137)	0.562
Time Room - AP (min) *	20.5 (13.5-23.5)	20 (12-25)	0.991
Time Door CSC - Recanalization (min) *	157 (131-255)	127 (93-178)	0.049
Time Room - Recanalization (min) *	66 (60-131)	68 (47-94)	0.221
Time AP - Recanalization (min) *	41.5 (38-117.5)	45 (27-69)	0.158
Time Onset – Recanalization (min) *	322 (208-259)	287 (229-336)	0.522
Time Door CSC - Image (min) *	23.5 (19.5-29.5)	26 (19-40)	0.400

* All variables are presented as median (percentile 25-75); ** Mann-Whitney *U* test; min, minutes.

4.4A.2 Technical characteristics of procedure in subgroups related to NIHSS score value

Median number of passes was 2 (IQR=1-3) in the global population and in both groups. There was a no difference in a number of first pass successful recanalization performed.

4A.3 Procedural and post-procedural complications in subgroups related to NIHSS score value

Procedural and post-procedural complications are detailed in Table 4.13. Regarding overall complications, there was a tendency for higher frequency in the low NIHSS group (33.3%), compared to higher NIHSS (15.5%). ENT was significantly higher in the low NIHSS group on the univariate (p=0.05). At 24 hours, sICH was significantly more frequent in the low NIHSS compared to the higher NIHSS group (p=0.046).

Table 4.13. Procedural and post-procedural complications in subgroups related to NIHSS score value

		NIHSS		
		≤5	>5	*P* value
Overall complication no. (%)		4 (33.3)	55 (15.5)	0.110 [b]
ENT no. (%)		3 (25)	24 (6.8)	0.050 [b]
Vessel dissection/perforation no. (%)		3 (1.3)	5 (3.9)	0.132 [b]
Procedural ICH no. (%)		0 (0)	2 (0.6)	1[b]
SAH no. (%)		0 (0)	7 (2)	1[b]
IVH no. (%)		0 (0)	0 (0)	-
Hemorrhagic transformation	HI1	3 (25)	29 (8.2)	
at 24h no. (%)	HI2	0 (0)	29 (8.2)	0.449[c]
	PH1	0 (0)	22 (6.2)	
	PH2	0 (0)	22 (6.2)	
PH2 at 24h no. (%)		0 (0)	22 (6.2)	1 [b]
sICH at 24h no. (%)		2 (16.7)	9 (2.5)	0.046 [b]

no, number of participants; [b] Fisher Exact test; [c] Mann-Whitney *U* test;

4.4A.4. Technical and clinical outcomes in subgroups related to NIHSS score value

No significant differences in the rate of successful recanalization was detected. 24 hours post-treatment NIHSS was 4.5 (IQR=0.5-12.5) for low NIHSS ≤5 group, compared to 11 (IQR=5-19) for NIHSS >6 group (p=0.031). For the low NIHSS ≤5 there was a statistically significant higher rate of 24-hour NIHSS 4+ points worsening (p=0.005), but overall higher rate of good clinical outcome at three months 83.3% vs 47.7% on univariate analysis (p=0.018). The rate of good outcome at three months (mRS 0-2) was significantly higher in low NIHSS ≤5 group (p=0.018). Technical and clinical outcomes are provided in Table 4.14.

Table 4.14. Technical and clinical outcomes in subgroups related to NIHSS score value

	NIHSS		*P* value
	≤5	>5	
mTICI 2b/3 no. (%)	11 (91.7)	296 (83.6)	0.699 [a]
Failure in attempted MT (mTICI 0) no. (%)	1 (8.3)	3 (9.9)	1 [a]
NIHSS 24h median, (IQR)	4.5 (0.5-12.5)	11 (5-19)	0.031 [b]
NIHSS 24h 0-2 no. (%)	5 (41.7)	47 (13.3)	0.018 [c]
NIHSS 24h increase 4+ no. (%)	5 (41.7)	34 (9.6)	0.005 [c]
3-month mRS 0-2 no. (%)	10 (83.3)	169 (47.7)	0.018 [c]
3-month mRS 6 (mortality) no. (%)	1 (8.3)	66 (18.6)	0.703 [c]

no, number of participants; [a] Chi Square test; [b] Mann-Whitney *U* test; [c] Fisher Exact test.

4.4B. Low ASPECTS ≤ 5

Among the 366 cases ASPECTS was calculated on 356 patients, 288 (80.9%) had higher ASPECTS of >5, and 68 (19.1%) had low ASPECTS of ≤5. Comparing the centers, majority of low ASPECTS patients were estimated on DWI 64 (22.5%), while 4 (4.8%) patients were diagnosed on CT. Overall, 66 (97.1%) low ASPECTS patients were collected from Toulouse, and 2 (2.9%) from Belgrade (p<0.001). Younger patients were significantly more frequent in the low ASPECTS group, while there was no difference regarding the threshold of 80 years of age. There was a statistical difference for more frequent ICA T (p=0.014) occlusion and less frequent M2 occlusion in the low ASPECTS compared to higher ASPECTS group (p=0.008), on univariate analysis. Patient characteristics for the entire population, low and higher ASPECTS group are detailed in Table 4.15.

Table 4.15. Patient characteristics in subgroups related to ASPECTS score value

			ASPECTS		*P* value
			≤5	>5	
Center no. (%)	Toulouse		66 (97.1)	208 (72.2)	<0.001[a]
	Belgrade		2 (2.9)	80 (27.8)	
Male sex no. (%)			34 (50)	157 (54.5)	0.502 [a]
Age (yrs.) mean, (SD)			64.5 (15)	69.6 (13.8)	0.007 [d]
Age 80+ no. (%)			13 (19.1)	80 (27.8)	0.244 [a]
NIHSS ≤5 no. (%)			1 (1.5)	11 (3.8)	0.475 [b]
NIHSS median, (IQR)			16 (9-24)	9 (4-17)	<0.001 [c]
Anesthesia no. (%)		GA	61 (89.7)	169 (58.7)	<0.001[a]
		CS/LA	7 (10.3)	119 (41.3)	
Wake-up stroke no. (%)			10 (14.7)	28 (9.7)	0.231[a]
Direct admission no. (%)			49 (72.1)	187 (64.9)	0.263 [a]
Diagnostic modality median, (IQR)					
	CT ASPECTS		4 (3.5-4.5)	10 (8-10)	-
	DWI ASPECTS		4 (4-5)	7 (6-8)	
IV tPA n, (%)			38 (55.9)	150 (52.1)	0.572 [a]
Left LVO no, (%)			34 (50)	150 (52.1)	0.757 [a]
A1 no. (%)			1 (1.5)	2 (0.7)	0.472 [b]
A2 no. (%)			1 (1.5)	4 (1.4)	1 [b]
ICA T no. (%)			24 (35.3)	61 (21.2)	0.014 [a]
M1 no. (%)			41 (60.3)	170 (59)	0.848 [b]
M2 no. (%)			5 (7.4)	61 (21.2)	0.008 [a]
Tandem no. (%)			9 (13.2)	41 (14.2)	0.831 [a]

no, number of participants; SD, standard deviation; IQR, interquartile range (percentile 25-75); [a] Chi Square test; [b] Fisher Exact test; [c] Mann-Whitney U test; [d] Student's t-test.

4.4B.1. Procedure time metrics in subgroups related to ASPECTS score value

Table 4.16 displays the time metrics in subgroups related to ASPECTS score value. Median time from arrival in angio-suite to recanalization was 66 min (IQR=47-91.5) for higher ASPECTS compared to 76.5 minutes (IQR=51-102) for low ASPECTS patients (p=0.057) in the univariate analysis. Median time from AP to recanalization was 43 minutes (IQR=27-65.5) for higher ASPECTS compared to 58 minutes (IQR=31.5-87.5) for low ASPECTS patients (p=0.040) in the univariate analysis. Median time from arrival to the CSC door to image was 27.0 minutes (IQR=19-41) for higher ASPECTS compared to 23 minutes (IQR=15-33) for low ASPCECTS patients significant on univariate analysis (p=0.043).

Table 4.16. Procedure time metrics in subgroups related to ASPECTS score value

	ASPECTS		*P* value**
	≤5	>5	
Time Onset - Door CSC (min)*	120 (80-210)	135 (75-210)	0.690
Time Onset - IVT (min) *	144.5 (115-173)	135 (105-180)	0.722
Time Onset - AP (min) *	209 (168-280)	228.5 (176-281)	0.288
Time CSC - AP (min) *	80 (45-96)	83 (48.5-115)	0.241
Time Image - AP (min) *	70 (57.5-117)	84.5 (60-135)	0.177
Time Room - AP (min) *	20.5 (13.5-25)	20 (12-25)	0.629
Time Door CSC - Recanalization (min) *	131.5 (98-177)	130 (95.5-180)	0.830
Time Room - Recanalization (min) *	76.5 (51-102)	66 (47-91.5)	0.057
Time AP - Recanalization (min) *	58 (31.5-87.5)	43 (27-65.5)	0.040
Time Onset – Recanalization (min) *	288 (222-338)	284 (231-338)	0.954
Time Door CSC - Image (min) *	23 (15-33)	27 (19-41)	0.043

* All variables are presented as median (percentile 25-75); ** Mann-Whitney *U* test; min, minutes.

4.4B.2. Technical characteristics of procedure in subgroups related to ASPECTS score value

Median number of passes was 2 (IQR=1-3) in the global population and in both groups. There was a tendency for lower rate of the first pass successful recanalization in low ASPECTS group 22 (32.4%) compared to higher ASPECTS 129 (44.8%) group (p=0.062).

4.4B.3. Procedural and post-procedural complications in subgroups related to ASPECTS score value

Procedural and post-procedural complications are detailed in Table 4.17. There was no statistical difference in hemorrhagic or other complications between groups. There was a tendency for higher frequency of hemorrhagic transformation in low ASPECTS group, compared to higher ASPECTS (p<0.001). There was no statistical difference in sICH between groups.

Table 4.17. Procedural and post-procedural complications in subgroups related to ASPECTS score value

		ASPECTS		
		≤5	>5	*P* value
Overall complication no. (%)		11 (16.2)	47 (16.3)	0.977 [a]
ENT no. (%)		5 (7.4)	22 (7.6)	0.936 [a]
Vessel dissection/perforation no. (%)		1 (1.5)	7 (2.4)	1 [b]
Procedural ICH no. (%)		0 (0)	2 (0.7)	1[b]
SAH no. (%)		1 (1.5)	6 (2.1)	1[b]
IVH no. (%)		0 (0)	0 (0)	-
Hemorrhagic transformation	HI1	10 (14.7)	22 (7.6)	
at 24h no. (%)	HI2	12 (17.6)	17 (5.9)	<0.001[c]
	PH1	7 (10.3)	18 (6.3)	
	PH2	5 (7.4)	16 (5.6)	
PH2 at 24h no. (%)		5 (7.4)	16 (5.6)	0.569 [b]
sICH at 24h no. (%)		3 (4.4)	7 (2.4)	0.411 [b]

no, number of participants; [b] Fisher Exact test; [c] Mann-Whitney *U* test;

4.4B.4. Technical and clinical outcomes in subgroups related to ASPECTS score value

There was a tendency for the higher rate of mTICI 2b in the low ASPECTS group. No significant differences in the rate of mTICI 2b/3 was detected. NIHSS at 24 hours was significantly higher for the low ASPECTS (p<0.001). The rate of NIHSS 0-2 at 24 hours is significantly lower in ASPECTS ≤5 group 4/68 (5.9%), compared to higher ASPECTS 46/287 (16.0%) (p=0.031). There was a lower rate of good clinical outcome in low ASPECTS at three months 53.1% vs 35.3% on multivariate analysis [OR=2.24, 95% CI (1.21-4.16); p=0.011].

There was a tendency for higher mortality in low ASPECTS group on multivariate analysis on multivariate analysis [OR=1.89, 95% CI (0.88-4.03); p=0.100]. Technical and clinical outcomes are provided in Table 4.18.

Table 4.18. Technical and clinical outcomes in subgroups related to ASPECTS score value

	ASPECTS		*P* value
	≤5	>5	
mTICI 2b/3 no. (%)	54 (79.4)	245 (85.1)	0.252 [a]
Failure in attempted MT (mTICI 0) no. (%)	6 (8.8)	28 (9.7)	0.821 [a]
NIHSS 24h median, (IQR)	16 (9-24)	9 (4-17)	<0.001 [b]
NIHSS 24h 0-2 no. (%)	4 (5.9)	46 (16)	0.031 [a]
NIHSS 24h increase 4+ no. (%)	9 (13.2)	29 (10.1)	0.453 [a]
3-month mRS 0-2 no. (%)	24 (35.3)	153 (53.1)	0.008 [a]
3-month mRS 6 (mortality) no. (%)	15 (22.1)	47 (16.3)	0.262 a

no, number of participants; [a] Chi Square test; [b] Mann-Whitney *U* test; [c] Fisher Exact test.

4.5. MECHANICAL THROMBECTOMY IN RELATION TO TANDEM OCCLUSION

Among the 366 cases, 50 (13.7%) had diagnosed TO at presentation. Comparing the centers, in Toulouse center comprised 38/50 (76.0%) of TO patients and Belgrade there were 12/50 (24.0%). The mean age was lower in the TO group (64.2) compared to non-TO group (69.5) (p=0.001), and there was a significantly lower ratio of aged patients in TO group 4/50 (8.0%) compared to 91/225 (28.8%). Overall, 15 (32.0%) patients with TO were transferred to our center from another regional stroke unit (drip and ship), compared to 113 (35.8%) in non-TO patient group. There was a tendency for lower pre-treatment NIHSS score in the TO group (p=0.100). Concerning the thrombus location, there was a statistically significant predominance of treated patients with TO in the patients with the left side ACLVO on univariate (p=0.011). Patient characteristics for the analyzed subgroups group are detailed in Table 4.19.

Table 4.19. Patient characteristics in subgroups related to the presence of tandem occlusion

			Tandem		*P* value
			No	Yes	
Center no. (%)	Toulouse		246 (77.8)	38 (76)	0.771[a]
	Belgrade		70 (22.2)	12 (24)	
Male sex no. (%)			161 (50.9)	33 (66)	0.048 [a]
Age (yrs.) mean, (SD)			70 (14.3)	64 (11.7)	0.001 [d]
Age 80+ no. (%)			91 (28.8)	4 (8)	0.002 [a]
NIHSS ≤5 no. (%)			9 (2.8)	3 (6)	0.217 [b]
NIHSS median, (IQR)			18 (14-21)	16.5 (11-20)	0.100 [c]
Anesthesia no. (%)		GA	206 (65.2)	33 (66)	0.911[a]
		CS/LA	110 (34.8)	17 (34)	
Wake-up stroke no. (%)			37 (11.7)	2 (4)	0.101[a]
Direct admission no. (%)			203 (64.2)	35 (70)	0.427 [a]
Diagnostic modality median, (IQR)					
	CT ASPECTS		10 (8-10)	10 (9-10)	0.170 [c]
	DWI ASPECTS		7 (5-8)	6 (5.5-7)	0.886 [c]
ASPECTS ≤ 5 no. (%)			59 (19.3)	9 (18)	0.831 [a]
IV tPA n, (%)			162 (51.3)	32 (64)	0.094 [a]
Left LVO no, (%)			154 (48.7)	34 (68)	0.011 [a]
A1 no. (%)			3 (0.9)	0 (0)	1 [b]
A2 no. (%)			5 (1.6)	0 (0)	1 [b]
ICA T no. (%)			78 (24.7)	13 (26)	0.841 [a]
M1 no. (%)			185 (58.5)	29 (58)	0.942 [a]
M2 no. (%)			60 (19.0)	8 (16.0)	0.614 [a]

no, number of participants; SD, standard deviation; IQR, interquartile range (percentile 25-75); [a] Chi Square test; [b] Fisher Exact test; [c] Mann-Whitney U test; [d] Student's t-test.

4.5.1. Procedure time metrics in subgroups related to the presence of tandem occlusion

Table 4.20 displays the time metrics in the global population and in the TO and non-TO groups. Median time from arrival in the CSC door to recanalization was 124 minutes (IQR=92-178.5) for non-TO compared to 151 minutes (IQR=114-180) for TO patients (p=0.062). Median time from arrival to the angio-suite room to recanalization was 65.0 minutes (IQR=47-91.5) for patients without TO compared to 79.5 minutes (IQR=62-109) for patients with TO significant on univariate analysis (p=0.003). Median time from AP to recanalization was 42 min (IQR=27-67) for patients without TO compared to 57 minutes (IQR=40-88) for patients with TO significant on univariate analysis (p=0.005).

Table 4.20. Procedure time metrics in subgroups related to the presence of tandem occlusion

	Tandem		*P* value**
	No	Yes	
Time Onset - Door CSC (min)*	133.5 (74.5-210)	138.5 (77-201)	0.802
Time Onset - IVT (min) *	135 (105-180)	142.5 (115-191)	0.523
Time Onset - AP (min) *	226 (179-285)	232 (168-280)	0.652
Time Door CSC - AP (min) *	82 (45-111)	81 (59-111)	0.655
Time Image - AP (min) *	82.5 (60-138)	80 (56-110)	0.198
Time Room - AP (min) *	20 (12-25)	20 (13-30)	0.323
Time Door CSC - Recanalization (min) *	124 (92-179)	151 (114-180)	0.062
Time Room - Recanalization (min) *	65 (47-91.5)	80 (62-109)	0.003
Time AP - Recanalization (min) *	42 (27-67)	57 (40-88)	0.005
Time Onset – Recanalization (min) *	285 (230-337)	297 (219-370)	0.542
Time Door CSC - Image (min) *	26 (18-40)	27.5 (21-37)	0.676

* All variables are presented as median (percentile 25-75); ** Mann-Whitney *U* test; min, minutes.

4.5.2. Technical characteristics of procedure in subgroups related to the presence of tandem occlusion

Median number of passes was 2 (IQR=1-3) in the global population and in both groups. There was a no difference in a number of first pass successful recanalization. There was a statistical difference for less frequent failure in attempted MT (mTICI 0) in TO on univariate analysis (p= 0.042).

4.5.3. Procedural and post-procedural complications in subgroups related to the presence of tandem occlusion

Procedural and post-procedural complications are detailed in Table 4.21. At 24 hours, sICH was significantly more frequent in the TO compared to the non-TO group (p=0.050).

Table 4.21. Procedural and post-procedural complications in subgroups related to the presence of tandem occlusion

		Tandem		
		No	Yes	*P* value
Overall complication no. (%)		50 (15.8)	9 (18)	0.697 [a]
ENT no. (%)		21 (6.6)	6 (12)	0.237 [b]
Vessel dissection/perforation no. (%)		7 (2.2)	1 (2)	1 [b]
Procedural ICH no. (%)		1 (0.3)	1 (2)	0.255 [b]
SAH no. (%)		6 (1.9)	1 (2)	1[b]
IVH no. (%)		0 (0)	0 (0)	-
Hemorrhagic transformation	HI1	28 (8.9)	4 (8)	
at 24h no. (%)	HI2	21 (6.6)	8 (16)	0.216 [c]
	PH1	20 (6.3)	6 (12)	
	PH2	21 (6.6)	1 (2)	
PH2 at 24h no. (%)		21 (6.6)	1 (2)	0.335 [a]
sICH at 24h no. (%)		7 (2.2)	4 (8.0)	0.050 [a]

no, number of participants; [a] Chi Square test; [b] Fisher Exact test; [c] Mann-Whitney *U* test;

4.5.4. Technical and clinical outcomes in subgroups related to the presence of tandem occlusion

There was no difference in the rate of successful recanalization. There was a statistically significant higher rate of good clinical outcome (mRS 0-2) for TO patients at three months 66.0% vs 46.2% on multivariate analysis [OR=0.34, 95% CI (0.11-1.01); p=0.052]. There was statistically significant lower mortality rate in TO group 4/46 (18%) compared to non-TO patients 63/253 (19.9%) on multivariate analysis [OR=0.48, 95% CI (0.25-0.95); p=0.034]. Technical and clinical outcomes are provided in Table 22 and 23.

Table 4.22. Technical and clinical outcomes in subgroups related to the presence of tandem occlusion

	Tandem		*P* value
	No	Yes	
mTICI 2b/3 no. (%)	263 (83.2)	44 (88)	0.394 [a]
Failure in attempted MT (mTICI 0) no. (%)	35 (11.1)	1 (2)	0.042 [c]
NIHSS 24h median, (IQR)	11 (5-19)	10 (40-20)	0.762[a]
NIHSS 24h 0-2 no. (%)	44 (14)	8 (16)	0.703 [a]
NIHSS 24h increase 4+ no. (%)	32 (10)	7 (14)	0.414 [a]
3-month mRS 0-2 no. (%)	146 (46.2)	33 (66)	0.009 [a]
3-month mRS 6 (mortality) no. (%)	63 (19.9)	4 (8)	0.043[a]

no, number of participants; [a] Chi Square test; [b] Mann-Whitney *U* test; [c] Fisher Exact test.

Table 4.23. Technical and clinical outcomes in subgroups related to related to the treatment modality of tandem occlusion

	Tandem treatment				
	No	Stent	PTA	Stent + PTA	*P* value*
3-month mRS 6 (mortality) no. (%)	2 (11.1)	0 (0)	1 (16.7)	1 (4.8)	0.594
3-month mRS 0-2 no. (%)	12 (66.7)	5 (83.3)	2 (33.3)	15 (71.4)	0.355
PH2 at 24h no. (%)	1 (5.6)	0 (0)	0 (0)	0 (0)	0.588
Overall complication no. (%)	2 (11.1)	0 (0)	3 (50)	4 (19)	0.139

no, number of participants; PTA, balloon angioplasty; * Fisher Exact test;

4.6. MECHANICAL THROMBECTOMY IN RELATION TO PATIENT ADMISSION - TRANSPORT PARADIGM

Among the 366 cases, 338 (65.0%) were directly admitted, and 128 (35.0%) were admitted indirectly through a secondary center (drip-and-ship). When comparing the centers, the majority of indirectly admitted patients were treated in Toulouse; 114 (89.1%), while in Belgrade, 14 (10.9%) patients were admitted through a secondary center. There was a tendency for a higher median pre-treatment NIHSS score in the indirectly admitted group (p=0.080). CT ASPECTS was found to be significantly lower in the indirect admission group in univariate analysis (p=0.016). There was no statistical difference regarding thrombus location. Patient characteristics for the entire population regarding the way of admission are detailed in Table 4.24.

Table 4.24. Patient characteristics in subgroups related to the way of admission.

			Admission		*P* value
			Direct	Indirect	
Center no. (%)	Toulouse		170 (71.4)	114 (89.1)	<0.001[a]
	Belgrade		68 (28.6)	14 (10.9)	
Male sex no. (%)			130 (54.6)	64 (50)	0.398 [a]
Age (yrs.) mean, (SD)			68.3 (14.7)	69 (12.7)	0.510 [d]
Age 80+ no. (%)			59 (24.8)	36 (28.1)	0.488 [a]
NIHSS ≤5 no. (%)			9 (3.8)	3 (2.3)	0.553 [b]
NIHSS median, (IQR)			18 (13-21)	19 (15-22)	0.080 [c]
Anesthesia no. (%)		GA	151 (63.4)	88 (68.8)	0.309[a]
		CS/LA	87 (36.6)	40 (31.3)	
Wake-up stroke no. (%)			22 (9.2)	17 (13.3)	0.233[a]
Diagnostic modality median, (IQR)					
	CT ASPECTS		10 (8-10)	9 (8-10)	0.016 [c]
	DWI ASPECTS		6 (5-8)	7 (6-7)	0.467 [c]
ASPECTS ≤5 no. (%)			49 (20.8)	19 (15.8)	0.263 [a]
IV tPA n, (%)			120 (50.4)	74 (57.8)	0.177 [a]
Left LVO no, (%)			128 (53.8)	60 (46.9)	0.207 [a]
A1 no. (%)			2 (0.8)	1 (0.8)	1 [b]
A2 no. (%)			4 (1.7)	1 (0.8)	0.661 [b]
ICA T no. (%)			57 (23.9)	34 (26.6)	0.581 [a]
M1 no. (%)			138 (58)	76 (59.4)	0.797 [a]
M2 no. (%)			46 (19.3)	22 (17.2)	0.616 [a]

no, number of participants; SD, standard deviation; IQR, interquartile range (percentile 25-75); [a] Chi Square test; [b] Fisher Exact test; [c] Mann-Whitney U test; [d] Student's t-test.

4.6.1. Procedure time metrics in subgroups related to the way of admission

Table 24 displays the time metrics in subgroups related to the way of admission. Median time from onset to arrival in first hospital was 90 minutes (IQR=57-140) for directly compared to 75 minutes (IQR=46-120) for indirectly admitted patients (p=0.023). Median time from onset to IVT was 149 minutes (IQR=105-180.5) for directly compared to 130 minutes (IQR=107-170) for indirectly admitted patients (p=0.070). Time from admission to CSC to recanalization was significantly shorter for the indirectly admitted patients (p<0.001). All the other onset time metrics were significantly shorter in favor of direct admission including onset to recanalization that was 266 minutes (IQR=215-317) for directly compared to 322 minutes (IQR=277-364) for indirectly admitted patients (p<0.001).

Table 4.25. Procedure time metrics in subgroups related to the way of admission.

	Admission		*P* value**
	Direct	Indirect	
Time Onset - Door first hospitalization (min)*	90 (57-140)	75 (46-120)	0.023
Time Door - Door (min)*	- (-)	145 (125-172)	-
Time Door first hospital - AP (min)*	96 (77-126)	185 (160-220)	<0.001
Time Onset - Door CSC (min)*	90 (57-140)	222.5 (196.5-270)	<0.001
Time Onset - IVT (min) *	149 (105-181)	130 (107-170)	0.070
Time Onset - AP (min) *	203.5 (158-255)	275 (228-312)	<0.001
Time Door CSC - AP (min) *	96 (77-126)	37 (29.5-50)	<0.001
Time Image - AP (min) *	68.5 (54-89)	155 (118.5-181)	<0.001
Time Room - AP (min) *	18 (11-25)	20 (15-28.5)	0.024
Time Door CSC - Recanalization (min) *	157 (121-204)	84 (65.5-115)	<0.001
Time Room - Recanalization (min) *	69 (47-99)	65.5 (50-87)	0.305
Time AP - Recanalization (min) *	49 (27-78)	41 (29-60)	0.059
Time Onset - Recanalization (min) *	256 (277-364)	322 (277-364)	<0.001
Time Door CSC - Image (min) *	26.5 (19-40)	20 (14-40)	0.282

* All variables are presented as median (percentile 25-75); ** Mann-Whitney *U* test; min, minutes.

4.6.2. Technical characteristics of procedure in subgroups related to the way of admission

Median number of passes was 2 (1-3). There was no difference in a number of passes and first pass successful recanalization.

4.6.3. Procedural and post-procedural complications in subgroups related to the way of admission

Procedural and post-procedural complications are detailed in Table 4.26. Regarding overall complications, there was a tendency towards lower complication rate (p=0.167) and lower unsuccessful MT attempt in indirect admission (p=0.186), but without statistical significance. There was a statistically significant higher rate of hemorrhagic transformation in the indirect admission group on univariate analysis (p=0.003).

Table 4.26. Procedural and post-procedural complications in subgroups related to the way of admission

		Admission		
		Direct	Indirect	*P* value
Overall complication no. (%)		43 (81.9)	16 (12.5)	0.167 [a]
ENT no. (%)		19 (8)	8 (6.3)	0.545 [a]
Vessel dissection/perforation no. (%)		7 (2.9)	1 (0.8)	0.270 [b]
Procedural ICH no. (%)		1 (0.4)	1 (0.8)	1[b]
SAH no. (%)		7 (2.9)	0 (0)	0.101[b]
IVH no. (%)		0 (0)	0 (0)	-
Hemorrhagic transformation	HI1	16 (6.7)	16 (12.5)	
at 24h no. (%)	HI2	17 (7.1)	12 (9.4)	0.003[c]
	PH1	13 (5.5)	13 (10.2)	
	PH2	12 (5)	10 (7.8)	
PH2 at 24h no. (%)		12 (5)	10 (7.8)	0.288 [a]
sICH at 24h no. (%)		4 (1.7)	7 (5.5)	0.056 [b]

no, number of participants; [a] Chi Square test; [b] Fisher Exact test; [c] Mann-Whitney *U* test;

4.6.4. Technical and clinical outcomes in subgroups related to the way of admission

There was statistically significant lower mortality rate in indirect admission group 16/128 (12.5%) compared to direct admission group 51/238 (21.4%) on univariate, but not on multivariate regression analysis [OR=0.52, 95% CI (0.27-1.03); p=0.062]. Technical and clinical outcomes are provided in tables 4.27 and 4.28.

Table 4.27. Technical and clinical outcomes in subgroups related to the way of admission

	Admission		*P* value
	Direct	Indirect	
mTICI 2b/3 no. (%)	38 (16)	21 (16.4)	0.913 [a]
Failure in attempted MT (mTICI 0) no. (%)	27 (11.3)	9 (7)	0.186 [a]
NIHSS 24h median, (IQR)	10 (4-18)	10.5 (6-19.5)	0.762 [c]
NIHSS 24h 0-2 no. (%)	34 (14.3)	18 (14.1)	0.941 [a]
NIHSS 24h increase 4+ no. (%)	28 (11.8)	11 (8.6)	0.342 [a]
3-month mRS 0-2 no. (%)	116 (48.7)	63 (49.2)	0.930 [a]
3-month mRS 6 (mortality) no. (%)	51 (21.4)	16 (12.5)	0.035 [a]

no, number of participants; [a] Chi Square test; [b] Mann-Whitney *U* test; [c] Fisher Exact test.

Table 4.28. Single center rate of mortality related to the way of admission

			Admission		*P* value
			Direct	Indirect	
Center	Toulouse	3-month mRS 6 (mortality) no. (%)	29 (17.1)	14 (12.3)	0.271 [a]
	Belgrade	3-month mRS 6 (mortality) no. (%)	22 (32.4)	2 (14.3)	0.215 [b]

no, number of participants; [a] Chi Square test; [b] Fisher Exact test;

5. DISCUSSION

In the “real life” context, ACLVO strokes can be treated with MT under GA with angiographic and clinical results comparable to the previously reported RCTs, concluding that there was no difference in recanalization rates and functional outcomes at 3 months compared to CS/LA. We demonstrated that SVS represents an accessible and routine clinical biomarker associated with successful recanalization following thrombectomy and better short-term clinical improvement. Also, there was no correlation between SVS+ and thrombus etiology. Our findings indicated that low NIHSS ≤5 patients tent to be more observed and treatment decision postponed, with prolonged tome metrics to AP. In addition, low ASPECTS patients are younger and have prolonged AP to recanalization time. They have a lower chance for independency compared to higher ASPECTS patients. There was higher rate of good clinical outcome and lower mortality in TO patients, assumably due to developed collateral circulation, with the higher rate of sICH compared to non-TO patients. Acute implantation of the stent for the extracranial lesion seems to display a tendency for better outcome, but it did not reach statistical significance. Although time metrics were overall longer for the indirectly admitted patients, there was no overall difference in primary and safety outcomes compared to directly admitted patients. Overall higher mortality rate compared to previously conducted RCTs. is due to the Belgrade cohort sample that had significantly higher rate of mRS 6 at three months compared to Toulouse cohort sample (15.1% vs. 29.3 respectively). Higher mortality in Belgrade cohort sample is coherent with the results of the studies done in other middle-income and low-income countries.

The appropriate anesthetic modality for MT procedures has been the subject of continuous discussion. There have been several reports strongly suggesting CS or LA as the suitable solution, since it is perceived equally safe as GA and it has led to more favorable clinical outcomes at the 3-month follow-up (173-178). In addition, it has been postulated that there is a possibility of GA nullifying the beneficial effects of MT (179). Three recently published RCTs (SIESTA, ANSTROKE, GOLIATH) investigated the associations between GA and CS, and early neurological improvement (181-183). There was no evidence to claim CS/LA was superior in comparison with GA. In fact, the findings indicated that GA had a slight advantage over CS/LA (181, 182, 267).

In Toulouse mono-center cohort study, GA patients comprised 87% of all participants, which is considerably higher when compared to the recent RCTs (9-14). The policy in Toulouse CSC is that CS/LA should be reserved for the patients who are clinically less severe. The differences in baseline NIHSS, pre-treatment NIHSS and DWI-ASPECTS (higher stroke volume), as well as the discrepancy in left side LVO strokes between the GA and CS/LA groups were in accordance with this policy. Even though this indicates an obvious bias towards CS/LA patients, it should be pointed out there was no difference found in 3-month clinical outcomes. The policy in the Belgrade CSC is that CS/LA is preferred anesthesia modality (93.9% of the patients), and GA should be reserved for the patients who are clinically severe. In combined our Toulouse-Belgrade double-center cohort study, where GA patients comprised 65.3%, a same tendency for more severe neurological deficit in GA group was found compared to CS/LA group of patients. The first five RCTs had lower rates of GA compared to CS/LA, from 9% (ESCAPE) to 36% (SWIFT PRIME) (9-13)

The mean time from onset to IV tPA was 2 hours and 28 minutes. When compared to all previously reported multicentric RCTs, this mean time was higher, except for THRACE, probably because of rapid randomization (<20 minutes after IV tPA initiation) which allowed enrollment in the study the patients that received IV tPA closer to time window limit (9-14, 124-126). On the other hand, this mean time was lower in the GA group in our study when compared to the GA group of HERMES pooled data (180). A retrospective study from the pre-trial cohort of the centers which took part in the MR CLEAN trial, and a meta-analysis performed by Brinjikji *et al*. detected longer procedural times for the GA group as opposed to the non-GA group (14, 179). The present study has detected a loss of time ranging from 5 to 10 minutes in the GA group in time-to-AP metrics. Nevertheless, this was eventually neutralized by making procedural times shorter. The room-to-recanalization times were approximately

the same in both groups. Finally, GA did not cause postponements of recanalization, which is in line with the SIESTA trial findings (181). Other RCTs have also reported postponements when it comes to beginning the procedure, which was compensated by shorter procedural times in the GA group of patients (38, 180). Surprisingly longer door-to-recanalization and door-to-AP times in the times for the CS/LA group compared to GA group noticed in our Toulouse-Belgrade double-center cohort study, are biased by overall significantly longer times in the Belgrade part of the cohort where CS/LA is preferred that comprises 56% of all CS/LA patients

In spite of the prolonged onset-to-IV and onset-to-AP times in the Toulouse mono-center cohort study, GA was perceived as the standard anesthetic modality with successful recanalization rates (mTICI 2b/3: 79.5%), favorable clinical outcomes (3-month mRs 0-2: 54%), and the mortality rate of 16%, which is in accordance with the positive parameters recently published in the RCTs (9-13). These prolonged times are similar to the times in the CS/LA group reported in previous observational studies (173-178). Campbell *et al.* performed a meta-analysis which showed substantially worse clinical outcomes in the GA group of patients in comparison with the group of patients not treated under GA (180). It should be emphasized that patients from above mentioned observational studies were conducted in the centers without uniform anesthesia protocols and in which a non-GA practice prevails. The findings of the present study are coherent with the results of the primary and secondary endpoints of the GOLIATH, ANSTROKE, and SIESTA which have provided some evidence in favor of GA (181-183). For instance, even more favorable functional outcomes in the GA group have been indicated by SIESTA, though as a secondary endpoint (181). Although our results are consistent with the findings obtained via the SIESTA trial recanalization rate (mTICI 2b/3 GA: 65%, CS: 62%) and clinical outcome (3-month mRs 0-2 GA: 37%, CS: 18%), our study has demonstrated even higher success rate of recanalization (mTICI 2b/3 GA: 79.5%, CS: 80%) and better clinical outcomes (3-month mRs 0-2 GA: 53%, CS: 58%) in GA group.

No statistical differences were observed in overall procedural and post-procedural complications between the GA and CS/LA groups and the rates recorded were similar to those reported in other RCTs (9-13). There was higher rate of sICH in the GA Toulouse-Belgrade double-center cohort study, which can be attributed to higher rate of more severe patients in GA group. As all of the sICH were in the GA group and mostly from the HI1 and HI2 categories, results could be biased by the imaging technique used in Toulouse (MRI) that can depict subtle HI bleedings that would sometimes not be registered on CT. The percentage of ENT of 3-4% is lower in comparison with the percentages reported in other RCTs (9-13). Unequivocally, this can be attributed to a significant difference in GA rate. Moreover, the number of 3rd stent retriever passages necessary to ensure full recanalization was significantly lower in the case of the procedures performed under GA. Even though, no conclusive explanation can be provided to account for these results, they could indicate that MT performed under GA is swifter, safer, and more expeditious.

Thus, a potentially negative influence on the outcome for GA in the previous studies, could be accounted for by a possible drop in arterial BP during GA, which can be avoided with available dedicated anesthesia team (168, 268). Similar high infarct volumes were detected both in the GA group and in the control group in the MR CLEAN subgroup analysis (269, 270). It can be assumed that this occurs due to the missing cerebral autoregulation mechanisms in the collateral circulation. This renders the penumbra region highly vulnerable to fluctuations in arterial BP (54). To prevent large fluctuations, the BP values were strictly maintained within a range during the peri-procedural period. This was a practice we incorporated it in the workflow in Toulouse, which is in the line with SIESTA trial protocol (181). Still, additional factors including hands-on clinical experience and availability of anaesthesiology teams in high volume centres might have led to the dissimilarities among the studies.

The current study has demonstrated that SVS+ is associated with a higher rate of mTICI 2b/3 and favorable clinical improvement on Day One (pre-treatment NIHSS – Day One NIHSS) following MT. Since the superiority of MT over IV tPA was confirmed, all interventionists performing the procedure

have been able to notice that thrombi have different macroscopic appearances and colors (varying from black to red or white), and that some thrombi may be very easily retrieved, while others require several passes, or cannot be removed, whatsoever. Various publications dealing with the histopathological analyses of thrombi retrieved by MT have reported different values of red blood cells (RBC), fibrin, or platelets (187, 188). Computed tomography and MRI represent valuable tools in terms of analyzing thrombi prior to MT procedures as they can provide predictive biomarkers and make them accessible within clinical routine prior to MT (271). With respect to thrombus appearance on CT, several studies have linked hyperdense appearance of a thrombus on CT to RBC rich-clots (188, 190). Furthermore, it has been reported that successful recanalization has been accomplished in 79% of hyperdense thrombi, but in no more than 36% of non-hyperdense thrombi (185). Therefore, RBC rich thrombi appear denser on CT and seem to be easier to retrieve.

MRI enables a reliable visualization of thrombi by utilizing SVS (272). Kim and Liebeskind have shown that SVS+ thrombi have higher amounts of RBC (42 to 48%) compared to SVS- (1.9 to 23%) (186, 271). There have been several investigations into the predictive value of SVS+ for recanalization (186, 271). A similar method was applied in all of these studies, i.e. a double-blinded retrospective analysis of MRI images, with access to DWI and T2*-GRE for one, and access to all MRI sequences for the others, which was the case in our study, as well. In addition, a few recent studies have combined SVS and advanced imaging techniques such as T2* mapping used by Bourcier *et. al.*, and three-dimensional measurements of thrombi used by Kang *et al.* (193, 273).

The present analysis has revealed a similar ratio of SVS+ (76%) compared to 73% of SVS+ reported in the so far largest cohort (191). Nevertheless, the publication based on the smallest cohort of 30 patients has reported a lower percentage of SVS+ (53%), which could be accounted for by the difference in the magnetic fields of the MRI devices (1.5T vs. 3T in our study) and/or by the smaller cohort (186).

Despite previously published Kappa for SVS+ being superior to our interrater agreement, our interrater agreement was still adequate [Kappa =0.71 with a 95% CI (0.59-0.82)] (191, 192). For the purpose of this study, "SVS+" was defined on T2* as a decreased signal within a vessel surpassing the size of the homologous contralateral artery diameter. The majority of the inconsistencies in the results of the two analysts were noted when the clot appeared as hypointense in T2*, but its size did not surpass the size of the corresponding contralateral vessel.

Surprisingly, three previous publications established no association between SVS+ and TICI 2b/3 after MT (186, 273, 274). Having investigated this in a cohort of 30 patients, Bourcier *et al.* concluded that successful recanalization was achieved in 73% of SVS+ and in 27% of SVS- (p=0.01) (192). Kang *et al.*, found no association between the SVS volume and recanalization status [OR=1.00; 95%CI (0.99-1.00)] (273).

Our findings indicate that SVS+ is correlated with a higher rate of successful recanalization (85% in case of SVS+ vs. 69% in case of SVS-). So far, no study has assessed the predictive value of SVS+ for clinical improvement on Day One. Our research suggests that SVS+ is associated with a higher NIHSS at 24h improvement after MT, with a median of minus 6 points in SVS+ versus median minus 1 point in SVS- (p=0.01). One publication has reported that SVS+ represents a predictive factor of favorable clinical outcome (mRS 0-2) at 3 months [OR=8.7; 95%CI (1.1-69.4); p=0.04] (193).

The predictive value of SVS and stroke subtype has already been explored. Two studies with a percentage of cardioembolic stroke of 42% and 64% respectively, established an association between SVS+ and cardioembolic stroke subtype (273, 275). As opposed to this, a meta-analysis showed no correlation between thrombus hyperdensity on CT and stroke subtype (189). In our series, we relied on the classification of the TOAST to determine the stroke subtype (102). Finally, in our study, 56% of cases belonged to cardioembolic-strokes, which is in line with the previously quoted publications (273, 275). Despite the largest cohort of patients and similar statistical data analysis, we did not find any

significant correlation between the presence of SVS and stroke-subtype. In our judgement, this comes as no surprise as it is very likely that cardio-embolic thrombi related to atrial fibrillation or patent foramen ovale and septum aneurysm may have very different compositions depending on how long they remained in the heart prior to migrating to the brain and the anticoagulant or antiplatelet treatment received.

One retrospective study has evaluated the influence of reperfusion on the functional outcome after MT (276). The selected patient population was dichotomized based on minor (NIHSS ≤ 3) and mild strokes (NIHSS <8) (277-279). The study has indicated that the functional outcome in minor-to-mild stroke patients with LVO is highly affected by the reperfusion status obtained by MT. Along with better reperfusion grades, the excellent outcome (mRS 0-1) rate improved. No successful recanalization was observed in 34.6% of patients who experienced excellent outcomes in comparison with 61.7% of patients with mTICI 2b reperfusion, and 78.5% patients with mTICI 3 reperfusion. A relatively small cohort study encompassing 33 patients has reported that in patients who suffered a minor stroke and underwent MT afterwards, the clinical outcome was mainly favorable, in 42.4% and 63.6% of patients excellent and favorable clinical outcomes were observed (280). In addition, a small-scale study, which included a group of 10 patients (MT) and another group of 22 patients (medical group), has concluded that there is a possibility of MT resulting in a shift towards a lower NIHSS at discharge in comparison with BMM only (the excellent outcome rate, MT=70% vs. BMM=55%) (281). Similarly, an analysis based on STOPStroke and GESTOR cohorts, which included 30 patients (MT) and 88 patients (medical group) suggests that MT seems to correlate with a favorable shift of NIHSS at discharge when it comes to patients who present with very mild stroke symptoms (NIHSS score ≤5) and LVO strokes (281). Improved rates of functional independence at discharge and long-term follow-up have been recorded (282). Moreover, a retrospective study comprising 378 patients who suffered minor strokes in the anterior circulation reported that there were 54 patients (14.2%) in whom large-vessel occlusions were confirmed (208). Mechanical thrombectomy was immediately performed in 8 out of these 54 patients (14.8%). Also, in 6 out of 54 patients (11.1%) MT was performed after early neurologic deterioration, while the remaining patients received standard thrombolysis solely. Successful recanalization rates did not differ significantly in the two groups of patients who underwent MT (75% vs. 100%). In the present study, the patients treated with MT whose NIHSS score was ≤ 5 achieved mTICI 2b reperfusion in 83.3% of cases, whereas mTICI 3 reperfusion was achieved in 8,3% of cases (mTICI 2b/3 91.6%), which is consistent with previous studies (208, 282). There was no significant difference in the mTICI 2b/3 rates between higher and low NIHSS patients treated with MT. In our study we found a predominance of treated low NIHSS in the patients with the left side ACLVO, significant on univariate but not significant on multivariate analysis. This tendency was previously observed and could be related to the fact that the minor AIS of the left hemisphere is associated with more debilitating neurological deficit such as speech difficulties and dominant (if right sided) hand palsy (278, 281, 283). Median time from arrival to the CSC door to recanalization was 30 minutes longer for the higher NIHSS compared to the low NIHSS cohort. This is mostly influenced by the door to AP time, which can be explained by hesitation while reaching the decision for MT, especially as there was no difference in the door-to-imaging time. This time delay of MT until neurological deterioration for the low NIHSS patients was reported in previous studies and is present in around 30% of the NIHSS ≤5 cases (208, 281, 284).

A previously mentioned retrospective study showed that outcome rates based on the mRs 0–1 were higher in the patients who underwent thrombectomy immediately, i.e. 75% as opposed to 33.3% in the case of patients who underwent delayed thrombectomy, and 55% in the group of patients who received thrombolysis only (208). No sICH was detected in any of these groups. A multicenter cohort study was carried out in four CSC and encompassed 301 patients who suffered either minor or mild arterial ischemic strokes with LVO in the anterior circulation. The study applied two therapeutic approaches, i.e. urgent MT (170 patients) associated with BMM, and BMM (131 patients) which was combined with MT only if worsening was detected. The mRS score ranging from 0–1 at 3 months was

used as a stepping stone to determine the rate of excellent outcome, which represented the main endpoint (285). The age of the patients who underwent urgent MT was lower; they more frequently received intravenous thrombolysis, and the door-to-imaging time was shorter in these patients. However, in the BMM group, there were 24 patients (18.0%) who experienced neurologic worsening and, therefore, underwent rescue MT. In total, in 64.5% of cases excellent outcome was accomplished, and there was no difference found between these two groups. With regard to the treatment effect size, a stratified analysis abased on major subgroups was conducted and it did not reveal any heterogenous data. To sum up, the patients who suffered minor-to-mild strokes with LVO had excellent and favorable functional outcomes at 3 months and the ratio was similar in the group of patients who underwent urgent MT in the group of patients who underwent delayed MT associated with BMM. Therefore, it is argued that in patients with minor-to-mild stroke symptoms and proximal arterial occlusion in the anterior circulation successful recanalization enables favorable functional outcomes at 3 months. In our study, in the low NIHSS group 83.3% of patients experienced good clinical outcome in comparison with 47.7% of patients in the higher NIHSS group, and there was a significant difference observed. Both major clinical improvement and worsening at 24 hours, NIHSS were significantly higher in the NIHSS $\leq$ 5 group. Regarding a safety issues, In our research there was a high sICH rate compared to other studies, however all these bleedings were of the HI1 level, and therefore clinical worsening of 4 points is probably not related to the bleeding itself but rather to the late clinical deterioration typical for the low NIHSS patients with LVO (208, 284). However, there was a tendency for 30 to 40 minutes slower door-to-AP, and AP-to-recanalization time in the low NIHSS group compared to the higher NIHSS group. This can be explained by hesitation while reaching the decision in favor of MT, especially as there was no difference in the door-to-imaging time.

One of the major issues is whether MT should be performed to treat ACLVO patients who present with ASPECTS ranging from 0 to 5. A few prospective studies have emphasized the potentially beneficial role of MT with regard to treating LVO cases with large baseline core (low ASPECTS score) (197, 276, 286). What is arguable, nonetheless, is the interrater reliability as well as the accuracy of the measured ASPECTS, which casts doubt on the validity of these results. Furthermore, the SAMURAI registry has already acknowledged the possibility of DWI overestimating the core (194). This is in accordance with the fact that there was a higher number of patients with positive outcomes who had ASPECTS 5 according to DWI-ASPECTS score in comparison with CT. It should be pointed out that there is a difference between CT-ASPECTS and DWI-ASPECTS. The former was developed for non-contrast CT, whereas the latter was developed for its MRI counterpart which demonstrates increased sensitivity of diffusion when it comes to diagnosing AIS. In principle, the DWI-ASPECTS is one point lower than the CT-ASPECTS score (47). It is argued that, if attainable, CT perfusion imaging or MR perfusion imaging should be obtained up to 6 hours following presentation in case of patients whose ASPECTS score is lower. This approach is considered useful for the decision-making process regarding different treatment options. Demeestere *et al.* observed no significant difference between the preciseness of ASPECTS or CT perfusion in terms of identifying ischemic stroke patients using DWI lesion of $\geq$70mL (89). Yet, CT perfusion with a core volume of 50 mL proved to be more precise than ASPECTS with an optimal cut-off point of <7 (89). In the present study, the overall median CT-ASPECTS score was 10, while the overall median DWI-ASPECTS score was 7, showing a substantial difference in the precision of the estimation. Nevertheless, there was no difference in the median low ASPECTS score which was 4 for both CT–ASPECTS and DWI-ASPECTS.

Being a prospective, multi-center, non-randomized, and observational registry, STRATIS has offered insights into the patients who were registered even though they were not within the guidelines (287). According to this registry, ASPECTS 0–5 is in correlation with a decreased functional outcome, whereas patients with ASPECTS 0–3 face even lower prospects for favorable outcome (10%) with the mortality rate being 60% (288). In addition, patients with the ASPECTS score 4–5 had a favorable

clinical outcome (in 33% of cases) with the mortality rate being 23%. Concerning the correlation of age with low ASPECTS ≤5, patients over 75 years did not have much benefit (mRS 0–2: 0%, mortality: 58%). In our series, younger patients were significantly more frequent in the low ASPECTS ≤5 group, while the number of ≥ 80 years of age patients was balanced. The majority of the low aspect patients had MT under GA. For the subgroup of patients with ASPECTS 4-5, the prospective database ETIS showed the rate of positive outcome of 34% (289). In the prospective cohort analysis RECOST, MT patients presenting with ASPECTS 0-5 had a 0-2 mRS score of 34% compared to 9% of positive outcome in the BMM arm (286). Additionally, recent data from the pooled HERMES meta-analysis shows a tendency for favorable clinical outcome in patients with low ASPECTS (21). Nevertheless, the number of patients with ASPECTS 0–4 was rather low in this meta-analysis 57/856 (7%) in the MT plus BMM as opposed to 69/862 (8%) in the BMM arm, without reaching statistical significance regarding favorable outcome [adjusted OR=2.72, 95%CI (0.89-8.33)] (47). None of the 11 patients who had ASPECTS 0–2 in the MT plus BMM arm became functionally independent. Newer reports suggest that these patients undergoing thrombectomy have a higher chance of achieving good functional outcomes and a lower chance of mortality or hemicraniectomy (17, 286). One prospective study argues that in patients with ASPECTS 4 and 5 functional independence (mRS 0-2) was restored in no more than 25% of patients at 90 days, especially if reperfusion was accomplished (197). Even though successful recanalization was correlated with a more favorable outcome, the reperfusion rates were greater in the group of patients whose ASPECTS score was 6-10, the AP to reperfusion time was greater, there was a higher incidence of perioperative complications, the patients were younger (probably owing to a lack of collaterals), and they more often had combined intracranial and proximal occlusion. In our study, functional independence was significantly lower in the low ASPECTS group comprising 35% of this group compared to 53% in the higher ASPECTS group, which is coherent with previous studies (21, 286, 289). There was an absolute difference of 8% when it comes to low ASPECTS in a younger population, without reaching statistical significance. Regarding LVO location, low ASPECTS patients had ICA T more frequently and M2 occlusions less frequently, which is consistent with the volume of the territory affected. Though we present study found no difference in successful recanalization rates low ASPECTS ≤5 group, AP-to-recanalization time was 15 minutes longer, and there was a tendency for lower rate of the first pass successful recanalization, which could be interpreted as the result of a more difficult intervention.

Although infarct volume is generally predictive of clinical outcome, it is not perfectly accurate. In other words, there are patients with a large core volume with excellent outcomes, and there are those with small infarct volume and poor clinical outcomes (84). In HERMES meta-analysis strong signals of benefit were found for a whole patient population regardless of large infarct core volume or absence of collaterals, though low ASPECTS patients were in greater risk of intracranial hemorrhage (21). The findings have revealed four times more frequent sICH in patients with ASPECTS 0–4, regardless of their age, baseline stroke NIHSS, or administration of IV tPA (21). However, a beneficial effect was still present in these patients. Our study at least provides reassurance regarding the safety of MT for these groups of patients as it has demonstrated that successful recanalization did not result in a significant augmentation of sICH for the large infarct core, which has also been suggested by other studies (197).

Data from EVT randomized controlled trials are limited regarding TO and acute stenting of the cervical part of ICA. In the 2015 endovascular trials, acute stenting was performed in only a small portion of patients (REVASCAT trial 18% of patients; ESCAPE trial 17% of patients; MR CLEAN trial 30% of patients) (10-12). As an early experience, reported 30% of TO in the MR CLEAN trial (11). Other reports presented lower and more realistic rate of TO (12-18%) (10, 12). Our cohort comprised 13.7% of TO. A post hoc analysis of MR CLEAN showed that additional cervical ICA occlusion (148 of 500 patients) has reduced OR favoring EVT from 1.85 (1.26-2.72) to 1.43 (0.78-2.64), corresponding to a non-significant result in the TO subgroup (11). On the other hand, the REVASCAT trial TO was also analyzed (55 patients), showed significant improvement after endovascular treatment compared to BMM, and not

significantly different from isolated intracranial occlusion (10). HERMES pooled data meta-analysis showed a similar statistical shift in favor of MT (17). Another recent meta-analysis showed no significant treatment result and outcome difference comparing TO with isolated LVO (290). Recanalization rate of 81% (95% CI, 73-89) and favorable outcome 44% (95% CL, 33-55) were comparable or even better to similar series with non-TO. Equally, mortality of 13% (95% CL, 8-20) and sICH of 7% (95% CL, 2-13) were no different to other single LVO series. In the present study, the successful recanalization rate (88%) was without difference compared to non-TO LVO. It was previously suggested that dense fibrin-rich clots were the main reason for the failure of IVT and MT (291). Fibrin-rich thrombi exert increased friction which makes them more resistant to mechanical force (109, 292, 293). A study of 88 thrombi showed a marked difference regarding the source of the embolic stroke (294). Whilst thrombi from cardioembolic LVO and valvular disease were fibrin rich and dense, thrombi derived after the CEA and the LVO stroke originated from the large artery atherosclerosis are erythrocyte rich and more friable. This could explain our findings of less frequent TICI 0 in TO compared to non-TO patients in the present study. The rate of sICH was higher in the TO compared to the non-TO group. Favorable outcome was significantly more frequent (95% CL, 0.25-0.95) and mortality less frequent (95% CL, 0.11-1.01) in the TO group. The reason could be found in the assumingly better collateral circulation in TO patients, which is in correlation with the level of stenosis and chronicity of the atherosclerotic ICA disease as the most common of four TO subtypes (around 75%) (218, 295). In one study, investigators found a correlation between collateral status and level of ICA stenosis but without difference in functional 90-day outcome (296). The higher sICH rate in our study in the TO group (8%) is comparable with previously published evidence (290, 297). Acute stenting in some series described high rates of intracerebral hemorrhage, which can be related to the use of antiplatelets therapy if acute stenting is performed (298, 299). Conversely, STRATIS registry did not show a difference in the sICH between stented and non-stented TO cohorts (218). Overall high mortality for the single vessel LVO of 19.9%, that is mainly driven by the Belgrade part of the cohort (29.3%), compared to the Toulouse part of the cohort (15.1%).

Investigators found a high risk for a recurrent stroke rate of 2.7-11.5% within the first 14 days, for acute symptomatic carotid stenosis waiting for CEA (300). Dissection recurrence is very low in the first 6 months under anticoagulant therapy, around 2% (301). Other observation trials find the risk of recurrent carotid dissection of 2% in the first month and 1% annually. Recommended endovascular treatment of internal carotid dissection-related TO stroke is the distal-to-proximal recanalization strategy, with a conservative approach and ICA stenting only in circle of the Willis insufficiency (302). ESCAPE trial investigators reported outcome for 30 TO patients, with better outcome (still statistically non-significant) in the treated compared to non-treated extracranial lesion group (65% vs 54% 0-2 mRS at 3 months) (303). The latest systematic review and meta-analysis showed similar treatment results and outcomes compared to isolated ELVO (290). Other prospective (non-randomized) registries comparing stenting, PTA alone, and MT alone demonstrated recanalization rates and clinical outcomes (statistically non-significant) in favor of stenting (304, 305). The STRATIS registry demonstrated the best results in the stenting group (287). PTA treated patients demonstrated the worst outcomes compared to the other two options (218). Finally, a recent meta-analysis of 33 studies and 1102 patients with TO, showed that 78% of patients had mTICI 2b/3, with good neurological clinical outcome in nearly 50% of patients and mortality and sICH of 15% and 8% respectively (297). However, TITAN investigators demonstrated stenting of the extracranial carotid steno-occlusion was associated with better reperfusion rates and a tendency for better clinical outcomes (220-222). In our series, we found no statistical difference between thrombectomy without treatment of cervical lesion and stented group, although there was an absolute augmentation of good outcome in the stenting group of 10% to 15% (with or without PTA) versus conservative treatment or PTA alone. In accordance with previously published data, the patients with PTA alone had a tendency a lower rate of good outcome, with higher absolute mortality rate, but these results also did not reach statistical significance.

The association between time from the onset of symptoms to the start of the endovascular procedure and disability level at 3 months is well-documented. According to the HERMES study, it is estimated that providing emergency department door–to-reperfusion time was 15 minutes shorter; there would be 39 patients with less-disabled outcome at 3 months and additional 25 patients who would be likely to gain functional independence (mRS 0-2) per every 1000 patients who have achieved substantial endovascular reperfusion (38). Drip-and-ship and mothership are the two transportation options available to the patients who are not located within the catchment areas of EVT centers (242). Although stroke patients suspected of LVO may benefit from direct prehospital transportation as this means they are immediately transported to an intervention center and time to EVT is, therefore, shorter, it is necessary to consider the potentially detrimental effects of postponing IVT. However, it is known that the chances of LVO reperfusion with IV tPA is very low (5). Recent RCTs have marked inter-hospital transfer as one of the main causes of treatment delay (306, 307). Over the years, stroke treatment paradigms concentrated on transporting patients to the closest IVT-capable hospital. The patient is transferred to a center equipped for EVT once LVO has been confirmed by means of the diagnostic workup. This is known as the drip-and-ship paradigm. Nonetheless, based on a registry analysis, it has been argued that the drip-and-ship approach postpones treatment and reduces the chances of restoring functional independence in everyday practice (238).

The findings of the largest multicenter observational study STRATIS are in favor of the mothership concept owing to inter-hospital transfer being associated with significant treatment delays and lower chances of good outcomes(238). Furthermore, this study reported that when the drip-and-ship approach was applied, additional 110 minutes were required to reach a CSC. Analysis of workflow and time-to-treatment conducted within the SWIFT Prime showed that additional 96 minutes were needed when the same paradigm was used (308). Several other studies have demonstrated there was a one-hour delay when the drip-and-ship method was applied, while the absolute mRS reduction was 10% (306, 309). Other researchers have reported the same discrepancies in the time intervals (310, 311). However, RCTs findings may not accurately represent daily practice due to selection bias, time to randomization, etc. After the positive RCTs on MT, the STRATIS Registry was launched and was comprised of 984 patients from the United States of America (238). The authors found that directly admitted patients had shorter time intervals, which is in accordance with the results of our study. The distances between the hospitals in the rural areas of the USA are much greater compared to densely populated European regions or large cities (312-314). The whole experience may be completely different for stroke patients located in more densely populated regions with short distances between the centers and well-organized systems of transportation. A previous small-scale study carried out in a region with short distances between the centers included only one primary stroke center and one intervention center (315). This study demonstrated that clinical outcomes were more favorable in the group of patients with shorter time intervals.

In the present study, we aimed to assess how inter-hospital transfer affects time to treatment and functional outcomes in routine clinical practice. In Toulouse, all the PSC refer patients from the near-by cities. Belgrade is a densely populated city, with a short distance between the centers. The emergency department is within a 60-minute reach for the majority of the population. One of the two CSC that predominantly refers patients (when they are not on-call) is 10 minutes away from the Belgrade CSC. Therefore, our results are likely to be representative of the logistics related to acute stroke treatment in densely populated areas. The mean direct transfer time to CSC was 90 minutes, whereas the mean indirect transfer time was 222 minutes, which was delayed compared to the previous reports (316). There were significantly longer time intervals observed between the onset of symptoms (or LKW) and the start of treatment. In comparison with directly admitted patients, treatment of patients who were transferred was delayed by 70 minutes on average. In these two groups of patients, the difference in time from first presentation to AP was comparable with the differences in other time metrics including onset-to-

recanalization time. All the time metrics were significantly in favor of direct admission except for CSC door-to-imaging time (no difference) and onset-to-IVT time, which was shorter in the case of indirect transfer.

In Venema *et al.* series, initial treatment of transferred patients more commonly included IVT (316). This could be elucidated by the fact that patients who are not eligible for IVT due to the time passed are usually transported directly to an intervention center. The same study reported that transferred patients had proximal occlusions (ICA, ICA-T, and proximal M1) more frequently in comparison with directly admitted patients, probably due to a hesitation for sending more distal occlusion to the MT capable center. Present study series has shown balanced numbers of different LVO sites, including M2 occlusion, even though previous studies have reported that, in principle, such occlusions react favorably to IVT (317).

Surprisingly enough, despite the difference of approximately 1.5 hours, in the present study there was no difference in the rates of good outcomes (mRS 0-2) between directly or indirectly admitted patients. A recent systematic review demonstrated no clinical difference between two way of admission, supporting our results (318). Even more, a higher mortality rate was detected in the direct admission group compared to indirect admission group. This can be interpreted in terms of overall high mortality in our double-center cohort, driven by the Belgrade cohort sample. However, absolute difference in favor of indirect admission remains in the case of both centers separately. Another observation that might be explained by the selection mechanism at the intervention center is that existing pre-stroke disability (mRS >0) was less frequently detected in transferred patients. This suggests that patients with favorable characteristics are more likely to be transferred to an intervention center. Additionally, imaging characteristics and pre-treatment NIHSS were slightly less favorable in the case of transferred patients.

Despite all of the issues encountered, publications from developing countries have reported MT outcomes that are similar to those reported within large-scale trials. Several studies have addressed the effectiveness of thrombectomy in patients outside the criteria used in RCTs (247-249). The findings of a study conducted by Cabral *et al.* have indicated that functional independence was restored in a higher number of patients treated with MT plus IV tPA in comparison with the group of patients who received only IV tPA (319). Moreover, Cabral *et al.* carried out a study called JOINVASC to assess 200 thrombectomies performed over the course of six years (i.e. 2012-2018). A total of 80% of these cases was in the public national health system. It is worth pointing out that 50% of patients achieved good clinical outcomes (mRS 0–2) at 90 days (unpublished data). A recently published case series, which included 161 patients from Brazil and 531 patients from Poland, has reported successful recanalization (mTICI 2b/3) in 76% and 64.6% of cases, with the sICH rates of 6.8% and 7.2%, a 3-month mRS ≤2 36% and 31.4%, and the overall mortality rate of 23% and 22.0%, respectively (320, 321). What should be highlighted is the fact that all the values were comparable with RCTs except for a significantly higher mortality rate. The Brazilian RESILIENT trial demonstrated similar findings (322). Namely, the trial included 221 randomized patients (111 MT vs. 110 in the non-interventional arm), mRS score at 90-days displayed superiority for MT [adjusted OR=2.28; 95% CI (1.41-3.7) p=0.001] with NNT of 6.6 (323). Functional independence (mRS ≤2) at 90-days was 35%; with the lower difference in mortality rate compared to previous RCTs (33% in the medical arm and 24% in the MT arm). Conversely, one of the largest treatment effect size in severe dependency/death rate was detected - mRS 5-6 (bedridden and incontinent, death) 46% in the control arm vs. 30% in the MT arm. As few as 12 patients experienced procedure-related complications. In the present series high mortality (18.3%) was largely driven by the Belgrade cohort sample mortality (29.3%) compared to Toulouse cohort sample mortality (15.1%) (OR 2.07, 95% CI 1.07-3.99; p=0.031). The rate of functional independence at 3 months was comparable comparing Belgrade and Toulouse cohort sample (42.7% vs. 50.7% respectively). For example, in Brazil, there are no such entities as nursing homes, so patients are referred directly from one hospital to another. On the other hand, there is rehabilitation logistics in Belgrade. Yet, the patients are often sent home after

a month of rehabilitation which could explain these results, along with the lower average health level of the population.

Reduced treatment times and better functional outcomes have been associated with increased experience, which is manifested through increased numbers of cases treated with EVT (324). The steady reduction of workflow times in the process of the optimization is a well-documented process (316). Taking the initial admission to the hospital (door) as a reference point, the authors reported mean door-to-AP time 149-187 minutes in transferred patients, while it was 97-123 minutes in the group of directly transported patients (316). The in-hospital workflow times detected in the MR-CLEAN trial (the Netherlands) were nearly 1h longer in comparison with this study (65). More interventions are required in order to complement the process of managing patient transfer. For instance, the following solutions have been described as helpful in reducing times to treatment: holding the initial ambulance primary stroke center until it has been decided whether a patient is an eligible candidate for EVT, streamlining transfer-related protocols, enhancing cloud-based image sharing, and transporting transfer patients directly to the angio-suite (238, 325-327).

Compared to Toulouse, the Belgrade center did not have previous experience with MT in the early implemental phase. Conversely, three out of four physicians trained for MT were formed at the same University Center in Toulouse. The results obtained at Belgrade and Toulouse center are comparable regarding the good recanalization rates mTICI 2b/3 (87% vs. 82%). Times from room-to-AP and AP-to-recanalization are also comparable despite the fact that interventions in Belgrade were conducted in cardiology angio-suite with a cardiological C-arm machine. Other intrahospital time metrics are significantly longer in the Belgrade cohort sample, including the CSC-to-AP time that was 125 minutes in Belgrade and 80 minutes in Toulouse. Assumably, the reason is inexperience and the lack of personnel in the entire chain of activities, while in Toulouse MT, along with other neurointerventional procedures, are done in the same facility and in the same angio-suite.

6. CONCLUSIONS

1. In the “real life” context, MT for ACLVO strokes can be performed under GA with angiographic and clinical results comparable to previously reported randomized clinical studies. When it comes to recanalization rates and functional outcomes at the 3-month follow-up, there was no difference observed, even though the procedure was performed under GA in the case of more severe strokes. General anesthesia was associated with a delay for MT start times in the range of 5 to 10 minutes, however there was no delay for final recanalization time metrics. Finally, immobility as a result of GA enabled more precise procedures, lower ENT and minimized the chance of third-pass retrieval.
2. Our study demonstrates that SVS is an accessible routine clinical biomarker associated with successful recanalization after thrombectomy and better clinical improvement at Day One post stroke onset. Our series shows no correlation between the SVS+ and thrombus origin and etiology.
3. Low NIHSS ≤5 patients tent to be more observed and treatment decision postponed, with prolonged time metrics to AP. There was a tendency for higher rate of ENT in these patients, but finally there was no difference in the primary outcomes between high and low NIHSS patients. Low ASPECTS patients are younger and have prolonged AP to recanalization time. They have a lower chance for independency compared to higher ASPECTS patients, but nonetheless MT achieved substantial absolute rate of 33% of good clinical outcome.
4. There was higher rate of good clinical outcome and lower mortality in TO patients, assumably due to developed collateral circulation, with higher rate of sICH compared to non-TO patients. Acute implantation of the stent for the extracranial ICA lesion seems to display a signal of benefit compared to conservative treatment or balloon dilatation only, but it did not reach the level of statistical significance in the present study.
5. Although time metrics were overall longer for the indirectly admitted patients, there was no overall difference in primary and safety outcomes compared to directly admitted patients. Overall, there was a higher mortality rate for direct admission patients compared to indirect admission patients and previously conducted RCTs. This is due to the fact that the Belgrade cohort sample had a significantly higher rate of mRS 6 at three months compared to the Toulouse cohort sample.

7. LITERATURE

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LIST OF ABBREVIATIONS

ACA: anterior cerebral artery
ACLVO: anterior circulation large vessel occlusion
ADAPT: a direct aspiration first pass technique
AHA: American Heart Association
aICH: asymptomatic intracerebral hemorrhage
AIS: acute ischemic stroke
AISI: acute ischemic stroke intervention
ASA: American Stroke Association
ASPECTS: Alberta Stroke Program Early CT Score
BGC: balloon guide catheters
BMM: best medical management
BP: blood pressure
CBF: cerebral blood flow
CBV: cerebral blood volume
CS: conscious sedation
CSC: comprehensive stroke center
CT: computed tomography
CTA: CT angiography
CTP: CT perfusion
DIDO: door-in-door-out
DWI: diffusion-weighted imaging
ED: emergency department
EDT: embolization in distal territory
EMS: emergency service
ENT: embolization in new territory
ESMINT: The European Society of Minimally Invasive Neurological Therapy
ESO: European Stroke Organization
EVT: endovascular treatment
FDA: Food and Drug Administration
FLAIR: fluid-attenuated inversion recovery
FPE: first pass effect
GA: general anesthesia
HERMES: The Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke trial
HI: hemorrhagic infarction
HT: hemorrhagic transformation
HU: Hounsfield unit
IA: intra-arterial
ICA T: internal carotid artery terminus
ICA: internal carotid artery
IV tPA: intra-venous recombinant tissue plasminogen activator
IVT: intravenous treatment
LA: local anesthesia
LKW: last known well
LVO: large vessel occlusion
MCA: middle cerebral artery
MR: magnetic resonance

mRS: modified Rankin scale score
MT: mechanical thrombectomy
mTICI: modified Thrombolysis in cerebral infarction score
MTT: mean transit time
NCCT: non-contrast CT
NIHSS: National Institutes of Health Stroke Scale core
NNT: number of patients needed to treat
PCA: posterior cerebral artery
PH: parenchymal hematoma
PSC: primary stroke center
QUALY: quality-adjusted life years
RBC: red blood cells
RCTs: randomized controlled trials
SAH: subarachnoid hemorrhage
sICH: symptomatic intracerebral hemorrhage
STEMI: ST-elevation myocardial infarction
SU: stroke unit
SVS: susceptibility vessel sign
T2*-GRE: T2* gradient echo imaging
TIMI: thrombolysis in myocardial infarction
TO: tandem occlusion
TOAST: Trial of Org 10172 in Acute Stroke Treatment
TOF: time of flight
TTD: time to drain
WL: window level
WW: window width

BIOGRAPHY

Dr. Ivan Vukašinović was born on November 11, 1974 in Belgrade. In 1995 he enrolled at the Faculty of Medicine, University of Belgrade, and graduated in 2005 with an average mark of 7.37. In September 2009, he enrolled in postgraduate academic residency program in the field of Neurosurgery at the Faculty of Medicine, University of Belgrade. He completed his final thesis entitled "Endovascular Techniques for Treating Vertebrobasilar Aneurysms" and received the highest mark in 2010. In November 2011, he enrolled in the PhD program in Radiology at the Faculty of Medicine, University of Belgrade. Since November 2011 he has been employed at the Department of Neuroradiology within the Center for Radiology and MRI at the Clinical Center of Serbia. He completed his residency program in Radiology in October 2014.

In 2013, Dr. Vukašinović received a grant from the French government to spend three weeks at the University Hospital in Toulouse, France. Having obtained a grant from the European Society of Neuroradiology, in 2015 he completed a 3-month professional development training in the field of Interventional Neuroradiology at the University Hospital in Toulouse, France. In 2017, he was awarded a grant to complete a year-long professional development training in endovascular treatment of acute ischemic stroke at the University Hospital in Toulouse, France. The grant was provided by the European Society of Minimally Invasive Neurological Therapy (ESMINT). His mentor was Prof. Dr. Christophe Cognard. In 2019, he was accepted as the fellow of the European Board of Neurointervention (EBNI). On behalf of the Team for mechanical thrombectomy of the University Hospital Clinical Center of Serbia, his mentor Doc. Ercegovac and him received City of Belgrade award for the 2019.

Dr. Vukašinović has authored and co-authored ten professional and scientific publications indexed in the CC/SCI database, as well as two book chapters. He is a member of the Serbian Medical Chamber, the Serbian Medical Society, and the European Board of Neurointervention. He is currently the Secretary of the Serbian Society of Neuroradiology.

Прилог 1.

Изјава о ауторству

Потписани-а Иван Д. Вукашиновић

број индекса RN 5/11

Изјављујем

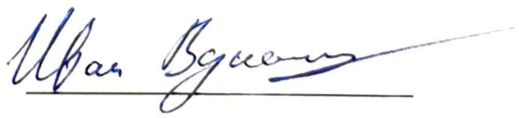
да је докторска дисертација под насловом:

„Утицај параметара тромбектомије на ефикасност третмана акутног исхемијског можданог удара након оклузије великог крвног суда“

- резултат сопственог истраживачког рада,
- да предложена дисертација у целини ни у деловима није била предложена за добијање било које дипломе према студијским програмима других високошколских установа,
- да су резултати коректно наведени и
- да нисам кршио/ла ауторска права и користио интелектуалну својину других лица.

Потпис докторанда

У Београду, 10.05.2021. године.



Прилог 2.

Изјава о истоветности штампане и електронске верзије докторског рада

Име и презиме аутора Иван Д. Вукашиновић

Број индекса RN 5/11

Студијски програм Докторске академске студије

Наслов рада Утицај параметара тромбектомије на ефикасност третмана акутног исхемијског можданог удара након оклузије великог крвног суда

Ментор Professor Christophe Cognard, Доц. др Марко Ерцеговац

Потписани/а Иван Д. Вукашиновић

Изјављујем да је штампана верзија мог докторског рада истоветна електронској верзији коју сам предао/ла за објављивање на порталу **Дигиталног репозиторијума Универзитета у Београду.**

Дозвољавам да се објаве моји лични подаци везани за добијање академског звања доктора наука, као што су име и презиме, година и место рођења и датум одбране рада.

Ови лични подаци могу се објавити на мрежним страницама дигиталне библиотеке, у електронском каталогу и у публикацијама Универзитета у Београду.

Потпис докторанда

У Београду, 10.05.2021. године.

Прилог 3.

Изјава о коришћењу

Овлашћујем Универзитетску библиотеку „Светозар Марковић“ да у Дигитални репозиторијум Универзитета у Београду унесе моју докторску дисертацију под насловом:

„Утицај параметара тромбектомије на ефикасност третмана акутног исхемијског можданог удара након оклузије великог крвног суда“

која је моје ауторско дело.

Дисертацију са свим прилозима предао/ла сам у електронском формату погодном за трајно архивирање.

Моју докторску дисертацију похрањену у Дигитални репозиторијум Универзитета у Београду могу да користе сви који поштују одредбе садржане у одабраном типу лиценце Креативне заједнице (Creative Commons) за коју сам се одлучио/ла.

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