Thrombectomy outcomes in middle cerebral artery stroke among the patients at the University hospital of Split

Caap, Christopher

Master's thesis / Diplomski rad

2021

Degree Grantor / Ustanova koja je dodijelila akademski / stručni stupanj: **University of Split, School of Medicine / Sveučilište u Splitu, Medicinski fakultet**

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:171:429448

Rights / Prava: In copyright / Zaštićeno autorskim pravom.

Download date / Datum preuzimanja: **2024-03-28**

SVEUČILIŠTE U SPLITU
MEDICINSKI FAKULTET
UNIVERSITAS STUDIORUM SPALATENSIS
FACULTAS MEDICA

Repository / Repozitorij:

MEFST Repository

zir.nsk.hr

UNIVERSITY OF SPLIT

dabar
DIGITALNI AKADEMSKI ARHIVI I REPOZITORIJI

UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE

CHRISTOPHER CAAP

THROMBECTOMY OUTCOMES IN MIDDLE CEREBRAL ARTERY STROKE AMONG THE PATIENTS AT THE UNIVERSITY HOSPITAL OF SPLIT

DIPLOMA THESIS

Academic year: 2020/2021

Mentor:
Assist. Prof. Vana Košta, MD, PhD

Split, September 2021

Table of Contents

1. INTRODUCTION 1
1.1. Definition 2
1.2. Epidemiology 4
1.3. Clinical Presentation 4
1.4. Risk Factors 5
1.5. Primary and Secondary Prevention 8
1.6. Pathophysiology 8
1.7. Baseline and outcome measurements 10
1.8. Workflow, Diagnostic procedures, Stroke Algorithm 13
1.9.0. Acute treatment of stroke 14
1.9.1. Intravenous therapy 15
1.9.2. Endovascular therapy 16
2. OBJECTIVES 18
2.1. Aim of study 19
2.2. Hypothesis 19
3. MATERIALS AND METHODS 20
3.1. Study design 21
3.2. Measurements of the outcomes of the procedure 21
3.3. Ethical approval 21
3.4. Statistical analysis 21
4. RESULTS 22
5. DISCUSSION 27
6. CONCLUSION 31
7. REFERENCES 33
8. SUMMARY 40
9. CROATIAN SUMMARY 42
10. CURRICULUM VITAE 44

LIST OF ABBREVIATIONS:

ACA	Anterior Cerebral Artery
ACLS	Advanced Cardiovascular Life Support
AF	Atrial Fibrillation
AH	Arterial Hypertension
AHA/ASA	American Heart Association/ Acute Stroke Association
AIS	Acute Ischemic Stroke
ATP	Adenosine Triphosphate
BA	Basilar Artery
CNS	Central Nervous System
CPSS	Cincinnati Prehospital Stroke Scale
CKMB	Creatine Kinase Myocardial Band
CT	Computed Tomography
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
DTN	Door to Needle
EVT	Endovascular Therapy
GSC	Glasgow Coma Scale
ICA	Internal Carotid Artery
ICH	Intracranial Hemorrhage
ICP	Intracranial Pressure
IVT	Intravenous Therapy
LVO	Large Vessel Occlusion
MAP	Mean Arterial Pressure
MCA	Middle Cerebral Artery
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Score
mTICI	Modified Thrombectomy in Cerebral Infarction
NCCT	None Contrast Computed Tomography
NIHSS	National Institute of Health Stroke Score
PCA	Posterior Cerebral Artery

PFO	Patent Foramen Ovale
rt-PA	Recombinant Tissue Plasminogen Activator
TIA	Transient Ischemic Attack
TICI	Thrombolysis in Cerebral Infarction
TIMI	Thrombolysis in Myocardial Infarction
VA	Vertebral Artery
WHO	World Health Organization

First and foremost I would like to thank Assist. Prof. Vana Košta MD, PhD, for being there when I needed help and guiding me through the entire research project. For your patience support whenever I needed it. Thank you!

A special thanks to Marko Galić and Robin Andersen for helping me with the statistical analysis throughout this time.

For my friends and family for their continuous support that they have shown me throughout my years. Especially to my parents that have always been there for me, for which I will be forever grateful.

Finally, I would like to thank the University of Split School of Medicine for giving me the opportunity to complete my MD degree here in Croatia.

1. INTRODUCTION

1.1. Definition

Stroke is referred to as a major cause of disability and mortality worldwide and is defined as a neurological deficit caused by an acute focal injury of the central nervous system (CNS). Defined as by World Health Organization as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin" (1). This definition is obsolete according to the new definitions by American Heart Association/American Stroke Association (AHA/ASA) (Table 1) taking in to consideration of time and advancement in imaging, also excluding global disturbance of stroke (2). Produced by a sudden disruption in the blood flow to the brain caused by a thrombus in situ or embolus occluding an artery (ischemic stroke) or a burst artery causing bleeding in the brain tissue (hemorrhagic stroke). The vast majority of strokes (87 percent) are ischemic, with atherosclerosis and cardio-embolism as the most common initiates (3, 4).

Transient ischemic attack (TIA) was originally defined in 1975, this was later redefined with advancement in imaging and redefining duration and incorporating brain and vascular imaging. TIAs are episodes of a transient and localized vascular dysfunction that occur anywhere from 2 to 15 minutes but can persist up to a day (24 hours). TIAs do not cause any long-term brain damage, differentiating it from stroke (2).

There are three types of strokes: ischemic, hemorrhagic and silent. All types result in the same culprit. By causing a deficiency of nutrients, mainly oxygen and glucose, as well as cleansing the tissue of metabolites in the surrounding brain tissue due to decreased blood flow. Neurons will be affected and will die fast owing to their high energy requirement (4). Neurological function loss in various degrees, depending on the size and location of the damaged brain tissue, and might include paralysis on one side of the body, sensory abnormalities, decreased eyesight, speech and language impairments.

The clinical presentation varies according to the anatomical area affected in terms of which artery is occluded or ruptured. Defined as anterior and posterior circulation by Internal Carotid Artery (ICA) and Vertebral Artery (VA) respectively, connected collateral arteries are anterior and posterior communicating arteries, as a whole defined as the circle of Willis.

Table 1. Stroke definitions

	Definitions
CSN infarction	CNS infarction is brain, spinal cord, or retinal cell death attributable to ischemia, based on 1. "pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or" 2. "clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death, and other etiologies excluded. (Note: CNS infarction includes hemorrhagic infarctions, types I and II; see "Hemorrhagic Infarction.")"
Ischemic stroke	"An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction. (Note: Evidence of CNS infarction is as defined previously.)"
Intracerebral hemorrhage (ICH)	"A focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma. (Note: Intracerebral hemorrhage includes parenchymal hemorrhages after CNS infarction, types I and II - "Hemorrhagic Infarction.")"
Stroke caused by ICH	"Rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma."
Silent cerebral hemorrhage	"A focal collection of chronic blood products within the brain parenchyma, subarachnoid space, or ventricular system on neuroimaging or neuropathological examination that is not caused by trauma and without a history of acute neurological dysfunction attributable to the lesion."
Subarachnoid hemorrhage (SAH)	"Bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord)."
Stroke caused by subarachnoid hemorrhage	"Rapidly developing signs of neurological dysfunction and/ or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma."

Data are presented and taken directly from AHA/ASA Sacco *et al.* (4)

Legend: * CNS – Central nervous system, † ICH – Intracranial hemorrhage.

Collateral circulation interconnected mainly by the Circle of Willis and its communication arteries. Though only 40% of the population demonstrates a complete circle of

Willis, it functions as a circuit that give rise to alternative pathways in the event of a major vascular blockage (5). Weak collaterals had a greater rate of infarct development than those with strong collaterals (6). Anterior circulation is further divided into anterior cerebral artery (ACA) and middle cerebral artery (MCA) which both have further subdivisions. E.g, MCA is divided into M1-M3, M1 (horizontal segment) being the most proximal, M2 intermediate (sylvian segment) and M3 (cortical segment) the most distal. When a proximal part of any artery is occluded the stroke can be denoted as a large vascular obstruction (LVO).

1.2. Epidemiology

The WHO estimates that 17 million people die annually from heart disease and stroke. The reported incidence over a lifetime for developing stroke is one in six for acute ischemic stroke (AIS) is especially essential since stroke is the second most common cause of death worldwide and one of the most prevalent causes of neurological disability in the elderly (7, 8). Every year, stroke affects 1.1 million Europeans and kills 440 000 people (9). In 2017, the cost of a stroke was assessed to be € 45 billion, which included both direct and indirect expenses of treatment as well as lost productivity (10). According to WHO the estimate of stroke incidence in all EU nations the number of stroke incidence could rise from 1.1 million to over 1.5 million in 2025, near 37% increase (11).

Currently stroke incidence and fatality in high income countries are decreasing, owing to a reduction in risk factors and improved access to healthcare. However as stated earlier incidence is estimated to increase with the probable increase in age of the growing population in undeveloped countries (11).

1.3. Clinical Presentation

The clinical symptoms and signs depending on the placement of the occlusion or interruption in blood flow, the clinical picture changes accordingly to where the ischemic process takes place.

When a major vessel in the anterior circulation is occluded, symptoms appear on the opposite side of the body and correspond to the area supplied by this artery. The first branching artery in the anterior circulation is the ophthalmic artery (supply of the retina), hence occlusion of this artery can lead to vision loss or ‘amaurosis fugax’ (temporary loss of vision in one or both eyes). Second branching artery of the ICA is ACA, occlusion of the ACA can cause motor and sensory deficits in the contralateral limbs. The occlusion of the proximal part of its third

branch the MCA, will cause severe stroke presented with contralateral hemiparesis and hemisensory loss, visual field deficiency, hemineglect, dyslexia, dysgraphia, dyscalculia and (if in the dominant hemisphere) aphasia (12). A combination of all the above symptoms, as well as involvement of the face, arm, and leg, with or without homonymous hemianopia, may occur in the case of an ICA occlusion.

Posterior circulations base is formed by the basilar artery (BA), which is the merge of left and right vertebral arteries. BA then splits to form the posterior cerebral arteries (PCA) and supplies, occipital lobe, and cerebellum. Infarction in this area causes ataxia, nystagmus, facial numbness/weakness, vertigo, dysphagia, dysphonia, hemianopia, cortical blindness, hemisensory loss and hemiparesis. Because of the wide range of clinical symptoms that can accompany strokes in the vertebrobasilar area diagnosing them can be difficult, where if you perform CT scan they are usually normal (12).

Small vessel occlusions of subcortical infarcts (lacunar syndromes) origin from small branching arteries deep in the tissue. Probably often go past unnoticed but when symptomatic are called 'Lacunar syndromes'. Pure motor stroke (posterior limb of the internal capsule), pure sensory stroke (lateral thalamus), sensorimotor stroke (thalamo-capsular area), dysarthria clumsy hand syndrome (typically pons), and ataxic hemiparesis (posterior internal capsule, pons) are the most prevalent lacunar syndromes (and matching infarct locations) (12).

1.4. Risk Factors

There are two types of risk factors for stroke: modifiable and nonmodifiable. For both ischemic and hemorrhagic stroke, age, sex, genetics and race/ethnicity are non-modifiable risk factors (13). Identification of modifiable risk factors and evidence of the efficacy of risk reduction measures are required to reduce the burden of stroke in the community (13).

Incidence of stroke increases with age. Above 55 years of age, the risk of stroke doubles every decade (14). The incidence and prevalence of ischemic stroke has increased in the 20 to 54-year-old age range, rising from 12.9 percent in 1993/1994 to 18.6 percent in 2005 (15).

Age also has a role in the relationship between sex and stroke risk. Women have the same or higher risk of stroke as men at early ages, however the proportional risk is somewhat higher for males with increasing age. The increased risk of stroke in younger women is most likely due to risks associated with pregnancy and the postpartum period, as well as other hormonal variables such the use of hormonal contraceptives. Overall women suffer from strokes at a higher rate than males, owing to their greater life expectancy (14). The risk of stroke

increased by 9% per year in males and 10% per year in women, according to a study conducted in eight European countries (16).

Stroke racial discrepancies have been well-documented. When compared to their white counterparts, blacks have twice the risk of incident stroke and have a greater fatality rate associated with stroke (13). In some cohorts, Hispanic/Latino Americans are more likely to suffer a stroke (13). One reason for racial differences could be the higher prevalence of stroke risk factors, such as hypertension, obesity, and diabetes mellitus, among blacks, as demonstrated by the REGARDS study (Reasons for Geographic and Racial Differences in Stroke) (17).

The most evident potential modifiable risk factors, hypertension, atrial fibrillation (AF), diabetes mellitus (DM), lifestyle factors (obesity, physical activity, diet, alcohol consumption) and hyperlipidemia being among the most significant ones (18).

Hypertension is the most common culprit for ischemic stroke as well as the single most essential modifiable risk factor. From a low to a high blood pressure, the risk increases ten-fold. When hypertension is defined as a systolic blood pressure of 160 mm Hg and/or a diastolic blood pressure of 95 mm Hg, most estimations imply a relative risk of stroke of around four (19). Although hypertension is definitely significant in the elderly, its influence may diminish with age: the odds ratio is four at age 50 and one at age 90 (20).

The efficacy of antihypertensive treatment has been well established in clinical trials. In a summary of 17 treatment trials of hypertension throughout the world involving nearly 50 000 patients, there was a 38% reduction in all stroke and a 40% reduction in fatal stroke favoring systematic treatment of hypertension (19).

Hyperlipidemia relationship to stroke is complex. Increased total cholesterol is associated with a higher risk of ischemic stroke, while elevated high-density lipoprotein cholesterol is associated with a lower risk of ischemic stroke (13). Risk appears to vary by stroke subtype, with a higher risk between cholesterol levels and big artery ischemic stroke than other ischemic stroke subtypes (21). Total cholesterol, meanwhile, is inversely associated with hemorrhagic stroke, with hemorrhagic stroke risk increasing as total cholesterol decreases (13). Statins appear to lower the incidence of total and ischemic stroke in the general population. The evidence on lipids and intracerebral hemorrhage is further confused by the fact that some observational studies have reported no increased risk of intracerebral hemorrhage with statin medication, while others have (22).

Patients with diabetes mellitus have a twofold higher risk of stroke, and stroke accounts for 20% of diabetic fatalities. Stroke risk is also higher in prediabetics. As an independent risk

factor diabetes is associated with stroke. Each year the risk increases by 3%, and diabetes for more than 10 years triples the risk of stroke in diabetic patients (23, 24).

Aggressive hyperglycemia control in diabetics has not been demonstrated to reduce the risk of stroke and may even be detrimental. In the ACCORD study (Action to Control Cardiovascular risk in Diabetes) it was showed that when intensive glucose lowering measures were taken to reduce glycohemoglobin below 6% compared with liberalized goals of 7 to 7.9% there was no reduction in stroke, but rather a statistically significant raise in overall mortality in the intensively managed group. As goes for lipid lowering treatment (not harmful but no statistically improved outcome) (25).

Sedentary behavior, diet/nutrition, obesity and metabolic syndrome are all risk factors for stroke and other cardiovascular diseases. Physical inactivity has been linked to a variety of negative health outcomes, including stroke. Physically active people have a decreased risk of stroke and stroke mortality than sedentary people (26).

Cardiac disease of various entities although AF being the most notable and preventable cardiac precursor. With increasing age, the frequency and prevalence of AF rises. The incidence of AF increases with each decade of life beyond the age of 55 (27). When compared to sinus rhythm, AF is linked to an increased risk of mortality, stroke, and coronary events (28). AF is estimated to be responsible for almost half of all cardioembolic strokes. Nonvalvular AF was shown to be related with a threefold to fivefold higher risk of stroke in the Framingham Study (29).

Age, history of hypertension, prior transient ischemic attack or stroke, and diabetes were found as risk factors for stroke after combining data from five randomized controlled trials of antithrombotic treatment in AF. Patients younger than 65 who had none of these characteristics, on the other hand, had a low yearly stroke rate of 1%, according to the research, in the pooled analysis of AF studies, warfarin anticoagulation lowered the incidence of stroke by 68%. The annual rate of stroke in the control group was 4.5 percent, whereas it was only 1.4 percent in the warfarin group, resulting in a 3.1 percent absolute decrease ($P<.001$) (30).

Many scoring systems have been used for estimating the risk of stroke. The Framingham Stroke Risk Profile is a widely used score which combines stroke risk factors to estimate ten-year stroke risk. Predictors such as age, systolic blood pressure, antihypertensive therapy, DM, cigarette smoking, cardiovascular disease (CVD), AF and left ventricular hypertrophy is used to make this estimation (31).

A recent 22 nation case – control study (INTERSTROKE) showed that ten risk variables (hypertension, diabetes mellitus, cardiac causes, smoking, obesity, lack of physical

activity, alcohol, psychosocial stress, depression and hyperlipidemia) are linked to 90% of stroke cases. Intervention targeting these risk factors can lower the burden of stroke in risk groups (18).

1.5. Primary and Secondary Prevention

Primary and secondary prevention is oriented on lowering the risk of a first ever stroke and a recurrent stroke respectively. Primary prevention has the goal in mind of reducing the risk of first ever stroke. Primary prevention of ischemic stroke includes the reduction in modifiable risk factors mentioned above. Hypertension being the most notable modifiable risk factor, accounting for approximately one third of stroke in developed countries to two thirds of stroke in developing countries (32). As of for secondary prevention of stroke, includes treatment of all the previously mentioned risk factors from primary prevention, as well as the inclusion of eventual, closure of patent foramen ovale (PFO), carotid endarterectomy in symptomatic carotid stenosis (70-99%), therapy of insulin resistance and optimal treatment of intracranial stenosis (32). As the INTERSTROKE study showed a link between 90% of stroke cases to risk factors, primary and secondary prevention is of high priority (18).

1.6. Pathophysiology

The brain consumes 20% of the total oxygen consumed by the body, near completely for the metabolism of glucose, which is the sole substrate for the brain's energy metabolism under normal physiological conditions. When a vessel is obstructed, the delivery of oxygen to the cells is reduced owing to reduced blood flow, and the cells capacity to produce energy is compromised (33). Tissue of the brain is particularly susceptible to the consequences of ischemia due to its low respiratory reserve and continuous reliance on aerobic metabolism (34).

During a stroke the brain is not only depleted of oxygen, but also of glucose and all other nutrients, as well as interrupting the nutrient and waste exchange mechanism that is necessary for proper metabolism. As a result, a hypoxic - ischemic condition develops. Ischemia is a reduction in blood flow to tissues that limits sufficient oxygen, glucose, and other nutrients delivery. Ischemic stroke occurs when the blood supply to the brain is cut off completely or partially, depriving the tissue of nutrients (35). In acute ischemic stroke, the damaged area of the brain is shown to be electrically quiet yet metabolically active enough to maintain membrane potentials (36).

When a stroke is untreated, the average patient loses 1.9 million neurons every minute (of an average total of 22 billion) (37). According to a study from 2020 even though time is an important factor, treatment in selected patients have benefited of endovascular treatment up to 24 hours after stroke onset with an mRS at 90 days of 2 or less (38).

Individual variability in progression of infarct core and penumbra is apart from infarct size in partly hypothesized to time and collateral circulation. Where the variability is apparent from minutes to hours. Once obstruction of an artery appears, focal ischemia becomes evident within minutes. The areas of the brain that have the most severe degrees of blood flow reduction is referred to as the "ischemic core" and the surrounding area described as the "ischemic penumbra". Where the core has little but possible chance of recovery, the neurons in the core die within minutes, the penumbra's neurons are functionally damaged but even so viable. When perfusion is reestablished the neurons in the penumbra can recover, however if the perfusion does not return the penumbra collapses, brain cells die, and the lesion grow (36).

Cerebral perfusion pressure fluctuates throughout a wide range of mean arterial pressure (MAP) in healthy people, cerebral autoregulation is the brain circulation's natural capacity to maintain a steady blood flow (60 mm Hg to 150 mm Hg). This way a continuous blood supply can be met. Which is achieved through complex myogenic, neurogenic and metabolic processes. Intracranial vessels expand to maintain blood flow when a vessel is occluded, resulting in an increase in cerebral blood volume. Simultaneously, oxygen extraction from the blood rises until it reaches 100%, allowing metabolic cellular activity in the penumbra to continue, in part of collaterals (39, 40).

At cellular level ischemia eventually leads to mitochondrial failure, as the cellular energy storage is depleted, resulting in additional energy depletion and the potential for apoptotic cell death. Ischemia also results in a loss of potassium and ATP in the neurons, both of which are necessary for energy transfer. Energy deficiency does not cause rapid cell death, but occlusion for 5 – 10 minutes can result in permanent brain damage. Leading to a loss of ion gradient due to decreased function of ion pump function and rapid swelling of the neurons and glia (cytotoxic edema) (34).

On the other hand of cytotoxic edema there is excitotoxicity. Cell death caused by excitatory amino acid toxicity has a number of negative consequences, including disruption of cellular calcium homeostasis, production of free radicals and oxidative stress, activation of the mitochondrial permeability transition, secondary excitotoxicity, and activation of several transcription factors and their genes that can be deleterious for the cell (35).

Cytotoxic/cellular edema develops in minutes to hours and may be reversible. Characterized by swelling on the cellular elements within the parenchyma encompassing glia, neurons and endothelial cells due to insufficient ATP which leads to an imbalance within ions and osmotic effects within the cellular membrane (34) as well as oxygen free radicals. Whereas vasogenic edema taking effect by increased vascular permeability and taking its toll due to proteins and solutes transports into the brain parenchyma through the vascular endothelial wall. Resulting in increased extravascular volume with and increased intracranial pressure (ICP) (41).

1.7. Baseline and outcome measurements

There are a variety of scales and scores that can be used to assess the severity of a stroke as well as the effectiveness of treatment. The most important scales and scores utilized for assessment of stroke patients are National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) while thrombolysis in cerebral infarction (TICI) score is commonly used to describe the success of thrombectomy.

The NIHSS being the gold standard for stroke severity rating and also the most extensively used impairment rating scale in modern neurology, with over 500 000 healthcare professionals certified to use a web-based platform to administer it. Every vascular neurology department (prevention, acute therapy and recovery) requires a severity assessment (42). The NIHSS is composed of a 15-item scale that assesses level of consciousness, extinction/inattention, language, visual field, extraocular movement, limb/facial motor function, sensory loss, ataxia, dysarthria and aphasia (Table 2) (42). Selected scoring rules for NIHSS; score what you see, not what you think; score the first response, not the best response (except for item 9 best language); do not coach; for motor function count out loud (item 5 and 6) (42). Stroke severity is categorized into four categories based on the total scores in the NIHSS assessment: minor stroke (1-4 points), moderate stroke (5-15 points), moderate/severe stroke (16-20 points), and severe stroke (more or equal to 21 points). The NIHSS has also been found to be a strong predictor of neurological outcome (43). Furthermore, the NIHSS is correlated to the impaired brain volume and the placement of occlusion. Although the scale has a good association with the severity of an anterior circulation stroke, it may underestimate the severity of a posterior circulation stroke (44–46).

Table 2. National Institutes of Health Stroke Scale

NIHSS		
1a. Level of Consciousness (LOC)	0 = Alert; Keenly responsive 1 = Arouses to minor stimulation 2 = Requires repeated stimulation to arouse 3 = unresponsive, coma	
1b. Ask month and age	0 = Answers both correctly 1 = Answers one correctly 2 = Incorrect	
1c. 'Blinks eyes' & 'squeeze hands'	0 = Obeys both correctly 1 = Obeys one correctly 2 = Incorrect	
2. Horizontal extraocular movements	0 = Normal 1 = Partial Gaze Palsy 2 = Forced deviation	
3. Visual fields	0 = No visual loss 1 = Partial Hemianopia 2 = Complete Hemianopia 3 = Bilateral Hemianopia (Blind)	
4. Facial palsy	0 = Normal 1 = Minor 2 = Partial 3 = Complete	
5a. Left arm motor drift 5b. Right arm motor drift	0 = No drift 1 = Drift 2 = Can't resist gravity 3 = No effort against gravity 4 = No movement	Left Right
6a. Left leg motor drift 6b. Right leg motor drift	0 = Amputation / Joint fusion 0 = No drift 1 = Drift 2 = Can't resist gravity 3 = No effort against gravity 4 = No movement	Left Right
7. Limb ataxia	x = Amputation / Joint fusion 0 = No ataxia 1 = Present in one limb 2 = Present in two limbs	
8. Sensation	0 = Normal 1 = Partial Loss 2 = Severe loss	
9. Language/aphasia	0 = No aphasia 1 = Mild to moderate aphasia 2 = Severe aphasia 3 = Mute	
10. Dysarthria	0 = Normal articulation 1 = Mild to moderate alluring of words 2 = Near to unintelligible or worse	
11. Extinction/inattention	x = Intubated or other physical barrier 0 = No neglect 1 = Partial neglect 2 = Complete neglect	

In order to measure functional improvement and degree of disability several scoring systems have been developed over the years, the most common score used today is the modified Rankin Score (mRS). The mRS, an ordinal scale that evaluates the degree of disability during everyday life activities, as the primary endpoint evaluation in most endovascular treatment (EVT) studies (47). It is usually assessed three months following the stroke but can be used any time during treatment, often measured on arrival, discharge and follow up. It is composed of 7 groups, the scale goes from zero (no symptoms) to five (severe impairment), with a sixth category for death (Table 3). In general a mRS equal to or less than 2 is equivalent of a self-ambulant patient capable of taking care of one self and considered as a state of healthy recovered patient.

Table 3. modified Rankin Score

Grade	Description
0	No symptoms at all
1	No significant disability despite symptoms: able to carry out all usual duties and activities
2	Slight disability: unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability: requiring some help, but able to walk without assistance
4	Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, requiring constant nursing care and attention
6	Dead

With the advancement of treatment options in stroke, the Thrombolysis in Cerebral Infarction (TICI) score was created, which was based on the Thrombolysis in Myocardial Infarction (TIMI) grading scale, for evaluation of the success endovascular treatment (48). Later, a modified version (mTICI) was created with a change in the size of the target artery region demonstrating reperfusion. This change specifically intended to change 2a and 2b, where $x<2/3$ territory reperfusion and $x>2/3$ territory reperfusion were changed to $x<50\%$ and $x>50\%$ respectively (49). Shown in details in Table 4.

Table 4. mTICI

modified Treatment in Cerebral Ischemia	
Grade 0:	No perfusion
Grade 1:	Antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion
Grade 2a:	Antegrade reperfusion of less than half of the occluded target artery previously ischemic territory
Grade 2b:	Antegrade reperfusion of more than half of the previously occluded target artery ischemic territory
Grade 3:	Complete antegrade reperfusion of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches

Legend: * mTICI – modified Thrombolysis in Cerebral Infarction

1.8. Workflow, Diagnostic procedures, Stroke Algorithm

Identifying patients with stroke symptoms and bringing them to the hospital on time is crucial. According to the Stroke American heart association advanced cardiovascular life support (ACLS) protocol: First step in stroke algorithm is the contact with emergency medical services. Prehospital workflow starts with ambulance personnel and ACLS. Maintain a patent airway and cardiovascular status should be continuously assessed and monitored to rule out underlying conditions. Personnel who should be educated not only on symptom recognition, but also to assess the stroke and collect any other relevant data, such as last known well (in order to align with treatment time gated intervals), previous medical history, and comorbidities. A task often performed through third person interview (family or witness). Prehospital work can include fast tests such as the Cincinnati prehospital stroke scale (CPSS) for facial droop, abnormal arm and abnormal speech as well as scales such as Glasgow Coma Scale (GCS), NIHSS and mRS from the ambulance personnel. This helps identifying patients with plausibility of stroke. During transport it is imperative to measure, apart from performing CPSS or any of the like, measurements of blood pressure and to check blood glucose since hypoglycemia can mimic stroke to a certain degree. When stroke is suspected the hospital should be notified in order to prepare CT for a faster door to needle (DTN) approach (50). In large metropolitan areas, special stroke ambulances are equipped with CT scans with point of care laboratories in the vehicle to reduce the time to needle even further (51).

Intrahospital workflow, to reduce DTN times, emergency departments must have a well-established process for the treatment of AIS. Prior to recombinant tissue Plasminogen Activator (rt-PA) administration, a comprehensive series of events must occur. The neurologist will continue ACLS and gather all necessary data of time of onset of symptoms, time of hospital arrival, suspicion of anterior/posterior and left/right circulation in accordance with the NIHSS, risk factors, previous illnesses, medications and other relevant data mentioned above. Additional lab data required should contain a battery of electrolytes, hemoglobin, white blood cell differential, thrombocytes, creatinine, CRP, coagulation parameters and creatine kinase myocardial band (CKMB), troponin and lipid status as in special circumstances. With as little delay as possible a non - contrast computer tomography (NCCT) or magnetic resonance image (MRI) should be done to visualize the event of stroke signs, notify the stroke team, as well as for the event of bleeding and other contraindications for i.v. treatment. A brief explanation of rt - PA eligibility and safety weighed against risks with treatment for patient and/or family. After which therapy should be started as soon as possible in eligible patients (50).

With a CT scan that does not show any signs of bleeding or any other contraindications to therapy, when LVO is confirmed, the angiography team for neuro – intervention team should be notified as soon as possible and the patient should be transferred in angio suite and prepared for mechanical thrombectomy (52).

1.9.0. Acute treatment of stroke

Current guidelines in Croatia for treatment of AIS is as followed by AHA/AIS journals from 2019 an update of the 2018 guidelines for Early Management of Acute Ischemic Stroke (52). Current treatment of acute ischemic stroke is based on two treatment options that are often used in combination. As thrombolysis by rt – PA by dissolving the clot in an antegrade fashion, or/and by thrombectomy by various instruments but the two main purposes of aspiration or stent retrieval. Aspiration exerts its effect in a proximal fashion to the obstruction by suction and stent in a distal approach but piercing the stent and retrieving the clot in a net like structure.

1.9.1. Intravenous therapy

For ischemic stroke patients who come within 4.5 hours after the beginning of the stroke, in the absence of contraindications, intravenous therapy (IVT), with alteplase, to dissolve the blood clot is standard of care (53). Alteplase transforms plasminogen to plasmin, a proteolytic enzyme that lyses both fibrin and fibrinogen. Despite the danger of early symptomatic cerebral bleeding, intravenous thrombolysis using a recombinant tissue plasminogen activator (r-tPA) of a standard dose of 0.9 mg/kg, increases independent survival for 18 months (52, 54). Even though used in institutes earlier the treatment of LVO first proved its efficacy by the PROACT 1 and 2 trials that were conducted in 1995 and 1998 respectively (55). IVT is known to be less successful in individuals who have a LVO of the proximal intracranial arteries in the anterior circulation compared to distal small artery occlusions (56).

Even though iv alteplase is gold standard for all patients with AIS, a population of ischemic stroke patients, estimates of eligibility for alteplase vary from 6 to 8% of all strokes, with somewhat higher estimates in cross - sectional studies. The inclusion criteria for alteplase are: diagnosis of ischemic stroke with measurable neurologic deficit, with onset of symptoms within 4.5 hours and age above 18. Of the exclusion criteria there are many but the most notable is delay in presentation to medical services (52, 57, 58).

Current recommendation is that treatment begins within 4.5 hours since last known well the earlier the therapy is started, the better the outcome (59). Absolute contraindications to alteplase are several, the most notable are, intracranial hemorrhage (ICH) proven by imaging, history of prior ICH, severe uncontrolled hypertension (185/110 mmHg), serious head trauma within the last three months, hypo- or hyper- glycemia (<2.7, >22.2 mmol/L), thrombocytopenia (<100.000/mm3), coagulopathy and its treatment (52, 60). Relative contraindications for treatment with alteplase for AIS are mild or improving stroke symptoms (judged as NIHSS equal to or less than 4), severe stroke and coma (variably defined as NIHSS$\geq$25), major surgery or recent MI, recent hemorrhage within last 14 days (60).

Major complication and most common side effect of alteplase include symptomatic cerebral hemorrhage, severe systemic hemorrhage, and angioedema, that affect around 6, 2, and 5% of patients respectively (61). Regardless of these side effects the outcome for patients treated regardless of age, stroke severity, and despite risk of fatal intracranial hemorrhage, the treatment has proven better benefit than harm when introduced within 4.5 hours of the onset of AIS (53).

1.9.2. Endovascular therapy

The measures taken during stroke today are based on five trials that were concluded during 2015. During which the safety and efficacy of endovascular treatment for proximal anterior ischemic strokes, in absence of any exclusion criteria, was established. These trials namely, ESCAPE, REVASCAT, EXTEND-IA, MR CLEAN and SWIFT PRIME, came to the same conclusion during the use of intraarterial therapy. With the use of various retrievable intraarterial stents used for thrombectomy, they all had similar results measured as a significant increase in the rate of functional independence (mRS equal to or less than 2) at 30 days. The ESCAPE trial measured a significant lower mortality rate as well the previously mentioned mRS score, however neither of the four other studies came to this conclusion. Symptomatic intracerebral hemorrhage occurred at a slightly increased interval compared to the control groups in all studies, although not deemed substantial in either (62–66).

Endovascular thrombectomy was recommended for patients up to six hours following the beginning of symptoms. Reducing time to therapy is supported by all data (67). Due to differences in collateral circulation, new research shows that certain patients with favorable imaging with a considerable delay between symptom onset and therapy (up to 24 hours) may still benefit from intervention (67). To offer this therapy to eligible stroke patients as promptly as possible, well-organized care systems are required. Thrombectomy/embolectomy treatment is achieved by intraarterial approach through femoral artery. By setting a port to the artery, the use of guidewires conjoined with direct imaging with contrast we can visualize the arterial occlusions in real time. The guidewire is left in place as the use of stent retrievers or aspiration devices (distal approach or proximal approach, respectively) are used to extract the clot. This approach is a more effective treatment option for patient than alteplase alone, and more effective together with IVT. The efficacy and safety of endovascular treatment (stent retriever) within 6 hours after symptoms of stroke appeared, measured by mRS 0 to 2 at 30 days, was first proved by the MR CLEAN trial in 2015. The same year the ESCAPE trial showed that endovascular therapy was beneficial only for proximal occlusion (62). The rate of functional independence (modified Rankin score, 0 to 2) was 13.5 percentage points higher in favor of the intervention (32.6 percent vs. 19.1 percent) (66). After which EVT became gold standard in developed countries.

In accordance with the AHA/AIS guidelines from 2019 in absence of any contraindications, patient above age of 18, minimal prestroke disability, occlusion of internal

carotid or proximal MCA, NIHSS equal to or more than 6, as well as initiate treatment within 6 hours of last known well should be treated immediately (52).

2. OBJECTIVES

2.1. Aim of study

The main purpose of this study was to evaluate the early outcome of patients with stroke caused by medial artery occlusion after endovascular treatment – thrombectomy. The aim was also to determine whether there are some predictors of good outcome and to compare our results with already published data.

2.2. Hypothesis

1. The early outcome of Endovascular Stroke Therapy (EVT) is better in patients that have previously received intravenous thrombolysis.
2. EVT in lower volume centers is not that effective as described in clinical trials.
3. Previous comorbidities (cardiovascular diseases, hypertension, diabetes etc.) as well as previous medical treatment (antiplatelets, anticoagulants and statins) will have an impact on the success of thrombectomy and on the early functional improvement.

3. MATERIALS AND METHODS

3.1. *Study design*

A retrospective cohort study was carried out. Patients were selected based on the inclusion criteria of having a MCA stroke in University Hospital Split, Department of Neurology, during 2020.

Data was collected from journals from the department, a total of 90 patients were enrolled and one was excluded due to missing data.

3.2. *Measurements of the outcomes of the procedure*

To measure the outcome of thrombectomy success and early functional outcome of patients we used TICI-score, MRS and NIHSS. Good outcome was defined as TICI 2b and or 3, mRS ≤ 2 and NIHSS < 5.

3.3. *Ethical approval*

The Ethical committee of the University Hospital Split approved this research (Reference: 500-03/21-01/41). All data and rights of patients were protected in accordance with ethical standards of Croatian laws and World Medical Association Helsinki declaration 1964-2013.

3.4. *Statistical analysis*

The results were analyzed using IBM SPSS Statistics for Windows 26 (IBM Crop, 2019). Qualitative data were expressed as whole numbers and percentage while quantitative data were expressed as mean ± standard deviation or mean and interquartile range. For categorical variables frequencies are shown. Pearson coefficients of correlation were computed between continuous variables and Phi coefficients of correlation were computed between categorical variables, as well as t-tests. The significance of all tests was set to 0.05 or 0.01.

4. RESULTS

This study included 90 patients with acute ischemic stroke in ACM territory. One patient was excluded due to missing data. The inclusion criteria being endovascular treatment of stroke in anterior (MCA) circulation. The patients in this study were hospitalized at the University Hospital Split during the year 2020. The mean age of the participants was 77.2±8.6, with a minimum of 43 and maximum of 90 years. Patients showed an almost even gender distribution 48 women (53.9%) and 41 men (46.1%). The participants showed a mean systolic blood pressure of 147±25 and diastolic of 82±13 mm Hg. Almost all (94%) of them had at least one while 59 patients (66.3%) had multiple comorbidities. Hypertension is being the most common one (65.2%) while diabetes mellitus and atrial fibrillation were found in 23.6 and 22.5% of patients, respectively. Prior therapy with antiplatelet, anticoagulant and statins were used in roughly 20% of the patients. Table 5 shows more detailed description of the sample. Complications as brain hemorrhage or hospital infection was observed in 29 (32.6%) and 53 (60.9%) patients, respectively.

Table 5. Previous treatment and comorbidities (N=89)

Variable	Yes (%)	No (%)
Antiplatelet	21 (23.6)	68 (76.4)
Anticoagulant	16 (18)	73 (82)
Statins	18 (20.2)	71 (79.8)
Diabetes mellitus	21 (23.6)	68 (76.4)
Arterial hypertension	58 (65.2)	31 (34.8)
Atrial Fibrillation	20 (22.5)	69 (77.5)
Carcinoma	10 (11.2)	79 (88.8)
Other diseases	65 (73)	24 (27)
Previous stroke	13 (14.6)	76 (85.4)
Confirmed infection on admission	3 (3.4)	86 (96.6)
Without previous illness	5 (5.6)	84 (94.4)

Data are presented as number of participants or as number (%)

Descriptive parameters of the participants are described in Table 6. The mRS and NIHSS data were gathered on admission and discharge. Median NIHSS score at admission was 14.1±5.0 and the mean mRS score at admission was 4.1±0.77. While median NIHSS and mRS on discharge were 7.16±4.19 and 3.94±1.83 respectively. For the impact of thrombectomy on early

outcome we used the difference of the NIHSS and or mRS at admission and discharge. The total number of patients that died during the hospitalization after thrombectomy procedure was 31 (34.8%). These patients were not included in analysis for the outcome of thrombectomy measured by NIHSS while they were included in those measured by the mRS. There was a statistically significant difference in NIHSS change, the NIHSS at discharge was significantly lowered and reached statistical significance compared with the NIHSS at the arrival (t-test, t=5.883, df=45, P<0.01). There was also a statistically significant difference in mRS between admission and discharge (t-test, t=36.515, df=55, P<0.01).

The overall mean time to hospital arrival was 156±161.6 minutes, with the highest time being 1080 minutes and 20 minutes as the shortest measured. Door to thrombectomy time had a mean of 44.3±31.7 minutes. Which gave a total mean of stroke onset to needle time of 200.3 minutes. Thrombectomy outcome had a negative correlation measured against thrombectomy duration (-0.540, *P=0.01*). However, door to thrombectomy time did not significantly affected the outcome of treatment measured through NIHSS difference (*0.204, P=0.16*) as well as mRS difference (-0.014, *P=0.909*).

Table 6 Patients NIHSS and mRS (N=89, for all but NIHSS discharge and difference)

Variable	Mean	SD	Minimum	Max
mRS admission	4.4	0.77	1	5
mRS difference	-0.44	1.92	-4	5
mRS discharge	3.94	1.83	1	6
NIHSS Admission	14.1	4.98	4	28
NIHSS difference (N=56)	6.85	4.48	0	23
NIHSS disscharge (N=56)	7.16	4.19	0	17

Data is presented as numerical values.

Legend: * mRS – modified Rankin Score, † NIHSS – National Institute of Health Stroke Scale

Within the study group, during the thrombectomy, aspiration was used in 82 (94.3%) patients and is thereby the most common EVT utilized, 20 (22.5%) patients had previously been given thrombolysis. Stent retriever was never used solely, but always second to or together with

aspiration and never utilized together with thrombolysis. Successful recanalization after thrombectomy, measured as TICI 2b or 3, was achieved in 69% (N=62). Figure 1 shows thrombectomy outcome in our study population. Complete recanalization was achieved in most (64%) of all participants. For nine patients both the aspiration and stent retrieval were used, 33% of patients in this group had a successful recanalization. Out of the patients that received both thrombolysis and EVT, 17 (77.3%) out of the 22 patients had a successful recanalization. Graph 1 shows a detailed description of the samples thrombectomy outcome measured by TICI.

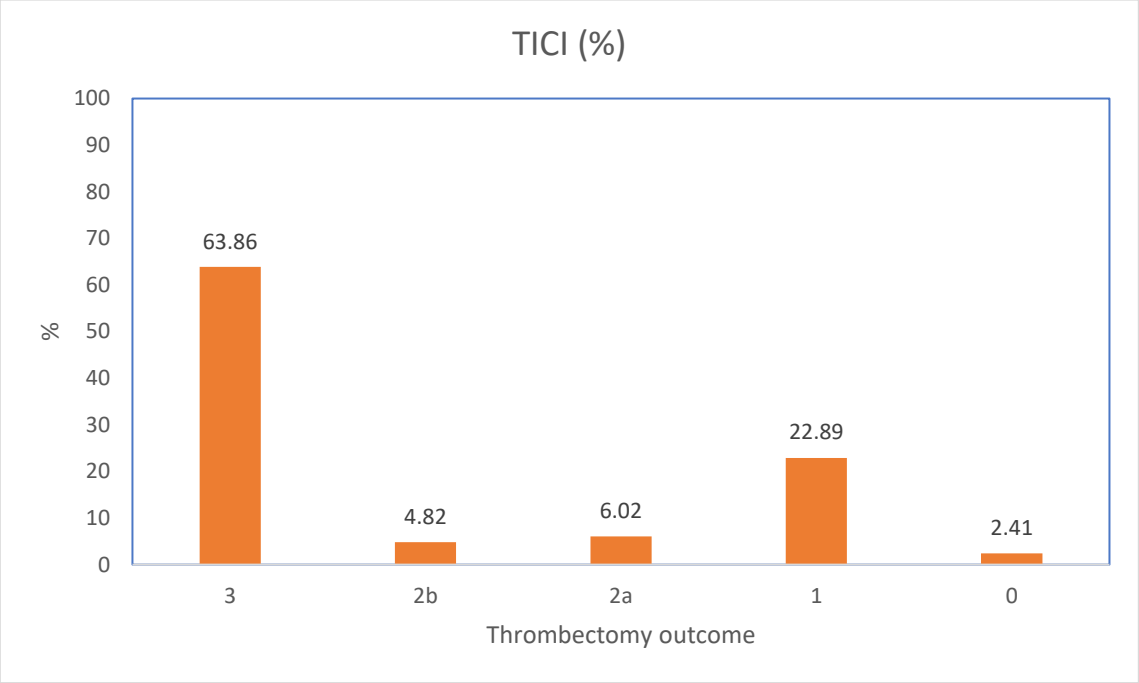


Figure 1. Thrombectomy outcome as thrombectomy in cerebral infarction score (N=89) Data is representing thrombectomy outcome in patients after performed EVT.

To examine the relationship between used comorbidities, previous treatments (anticoagulants, statins and/or antiplatelets), thrombectomy outcome and clinical outcome phi-coefficients of correlations were computed. A low negative correlation between previous anticoagulant treatment, thrombolysis and thrombectomy outcome (-0.252, *P=0.05* and -0.252, *P=0.05* respectively) was found. Participants who were using anticoagulants before admission had a better thrombectomy outcome. There was no significant correlation observed between thrombolysis and brain hemorrhage. There was a low positive correlation between the worse outcome in patients on previous anticoagulant treatment (0.271, *P=0.05* and 0.271, *P=0.05 respectively*), i.e, patients treated with anticoagulants experienced to have a higher NIHSS and/or mRS score on discharge.

Patients with hospital infections had tendency to have a prolonged hospital stay (0.399, *P=0.01*), as well as worse clinical outcome determined by NIHSS (0.285, *P=0.05*). Previous comorbidities DM (0.204, *P=0.059* and 0.147, *P=0.279* for mRS and NIHSS respectively*)*, arterial hypertension (0.018, *0.865 and* 0.142, P=0.298), AF (0.142, *P=0.*19 and 0.109, *P=0.*432), hyperlipidemia (-0.172, *P=0.11* and 0.109, *P=0.401)*, carcinoma (-0.195, *P=0.07* and -9.25, *P=0.063*), previous stroke (0.164, *P=0.129* and 0.018, *P=0.*895)) or antiplatelet treatment (-0.027, *P=0.802* and -0.162, *P=0.234))* as well as way of performing the thrombectomy (aspiration (0.196, *P=0.071* and 0.229, *P=0.092*), stent (0.2, *P=0.064* and 0.204, *P=0.136*)) or occurrence of brain hemorrhage (0.092, *P=0.396* and 0.148, *P=0.275*) did not show any significant correlation on mRS or NIHSS at the discharge.

Comparing different treatment modalities of EVT to TICI score there was no significant correlation between aspiration and thrombectomy outcome, however a low negative correlation was found between the use of a stent retriever and thrombectomy outcome (-0.220, *P=0.05*). When thrombectomy was performed without stents patients had a better thrombectomy outcome. There was no statistical significance between the use of thrombolysis and NIHSS or mRS at discharge (0.068, *P=0.616* and 0.018, *P=0.87 respectively*). Thrombectomy outcome showed a none significant negative correlation weighed against NIHSS at discharge (-0.134, *P=0.094*). Participants with better thrombectomy outcome have better clinical outcome (-0.220, *P=0.05*) operationalized as mRS.

5. DISCUSSION

Thrombectomy is being the gold standard of care for acute ischemic stroke since 2015, when several randomized clinical trials such as “MR CLEAN” (66), “REVASCAT” (64) and “ESCAPE” (38) proved its efficacy. Before EVT, 60 to 80% of patients with a proximal occlusion in the anterior circulation died within 90 days after start of stroke or did not achieve functional independence despite alteplase therapy (66). With thrombectomy, good clinical outcome at 90 days (mRS equal to 2 or less) was obtained in 33 and 44% in the intervention group and 19 and 28% in the control group of the MR CLEAN, and REVASCAT respectively (64, 66).

In our study we wanted to see whether the results of EVT in our hospital are comparable with those achieved in big multicentric studies and we wanted to see whether there are any factors that could predict the outcome of treatment. Among our 89 patients the success of EVT (TICI 2b and 3) was obtained in 57 (64%) participants and good clinical outcome at discharge was obtained in 22 (24.7%) of participants. Which is in accordance with other studies e.g, “MR CLEAN”, “ESCAPE” and “REVASCAT”(68–70). The slight decrease in good clinical outcome could be due to the mRS was gathered at discharge and not at 90 days.

Most of our patients, despite the thrombectomy outcomes, had significantly improved degree of disability or dependence in daily activities measured by significantly lower mRS at the discharge. Also, there was a significant difference in NIHSS change, as well as mRS change when both variables were compared against each other on admission and discharge.

No correlation was found between thrombectomy outcome and discharge NIHSS. Part of it could be in the fact that the mortality was high and data for NIHSS of some patients were missing so almost 40% of our patients were excluded from this analysis. Still, if we look at the NIHSS in the ESCAPE study when data were gathered 24 hours after the intervention mean NIHSS was 6 (3-14 interquartile range) that is quite comparable with our results where mean was 7 ± 4.

Significantly worse thrombectomy outcome with the utilization of stent retrievers in our study may be unexpected according to previous studies in which stent retrievers were the modality of choice (38, 64–66). The explanation is probably in the fact that in our hospital aspiration is used as a first line treatment and swapped to stent retriever when it is not successful. This means a longer duration of thrombectomy as well as unfavorable anatomical position or composition of clot. Along with similar studies made with the use of stents may have different results due to the previously given thrombolysis in majority of participants from MR CLEAN and ESACPE, and none within our study population (38, 66).

Though the number of patients in our study that have received intravenous thrombolysis before EVT was small (N=20, 22.5%) they had better early outcome which is in quite concordance with the results from MR CLEAN and ESACPE (68). In our study 77.3% of our patients who received thrombolysis had a TICI 2b or 3, compared to the 64% for overall. In MR CLEAN and ESACPE good recanalization was achieved in 58.7 and 72.4% of patients, respectively (69, 70). That is the reason why it is recommended that these two treatments should be utilized together if the patients are eligible for thrombolysis.

The mortality rate in our study was 34.8% that was substantially higher than that in the MR CLEAN or ESCAPE studies, where it was 10 and 21% respectively. Possible explanation for that could be in different treatment modalities, difference in the amount of patients who received thrombolysis, as well as amount of infections

With all above mentioned we can make some assumptions that EVT in lower volume centers is a bit less effective than as described in clinical trials. This could be due to more ideally picked patients, less hospital infections, and the follow up measured at 90 days instead of at discharge.

In our study we did not find that any of previous comorbidities (AH, DM, AF, previous stroke, hyperlipidemia, carcinoma, confirmed infection on admission or without previous illness) could be a predictor of better or worse clinical outcome at discharge. Only comorbidity that gave significant results for correlation with thrombectomy outcome was AF (-0.231, *P=0.036*), participants with atrial fibrillation seemed to have worse thrombectomy outcomes.

Previous studies have shown that hypertension, previous stroke, hemorrhagic stroke as well as combining comorbidities were increasing bad outcomes (71) and were the independent predictors for stroke mortality (72). Potential explanation for our results could be again in the small sample size and different timing of data gathering.

Out of the treatments given prior to hospitalization we found slight but statistically significant impact of anticoagulants on early thrombectomy outcome. Patient on previous anticoagulant treatment had worse thrombectomy outcome and increased NIHSS and or mRS on discharge. Our results are not in accordance with previously published data by Johnsen *et al.* (73) where oral anticoagulants given prior to hospitalization for stroke were linked with reduced 30 - day mortality rate and a less severe stroke. Possible explanation for our results could be in the fact that most of our patient on anticoagulants could not receive thrombolysis and again the sample of patients was very low (N=16, 18%).

Our patients on statins and antiplatelet prior to stroke were not found to have any significant correlation with clinical outcome for better or for worse. However Jonsson *et al.* (74)

showed that use of statins was moderately strong but statistically nonsignificant predictor of good outcome (multiple- adjusted odds ratio 1.42, 95% CI 0.90 to 2.22). In concordance with our study this could indicate that statins are safe to use in regard to its protective effects.

A study on antiplatelet use and ischemic stroke performed by Sanossian *et al.* (75) gave the results that antiplatelet increased likelihood of a good discharge outcome measured by mRS and also had an association with lower admission median NIHSS. Though in our study we didn't get any significant correlation of antiplatelets on NIHSS or mRS, they should be utilized whenever they are needed.

Our patients with hospital infection (60.9%) had a low but significantly prolonged hospital stay. MR CLEAN study had a hospital infection rate of pneumonia and other infections in intervention group of a total of 17.6% (10.7 and 6.9% respectively). Reason for this increase in hospital infection could be due to hospital protocol where all patients eligible for thrombectomy are given urinary catheter. More data would be needed in order to make definite conclusions.

Limitations of our study is that it is retrospective, monocentric and the sample size is small. Also, we were using mRS and NIHSS at the discharge while most of other studies were using these scales for the outcome assessments 90 days after stroke that makes our results a little bit harder to compare.

Anyhow, we believe that our study is important because this way we can objectively judge the outcomes of thrombectomy in our hospital and find the things that can be improved and in that way provide even better treatment for our patients.

6. CONCLUSION

With our study we can conclude that:

1. EVT is providing good clinical outcome for patient with acute stroke caused by MCA occlusion
2. Thrombolysis improves thrombectomy outcome when given to patients prior to EVT.
3. EVT in lower volume centers is little bit less effective than described in clinical trials
4. Previous comorbidities and medical treatment do not have an impact on the success of thrombectomy nor on early functional improvement, except for anticoagulants and atrial fibrillation which have a negative impact on both.

7. REFERENCES

1. Tunstall-Pedoe H. The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. 1988;41.
2. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJB, Culebras A, et al. AHA / ASA Expert Consensus Document An Updated Definition of Stroke for the 21st Century. Stroke. 2013;44:2064–89.
3. Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, et al. Heart disease and stroke statistics - 2006 Update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. AHA/ASA Circulation. 2006;113:85-151.
4. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American heart association/American stroke association. Stroke. 2013;44:2064–89.
5. Krabbe-Hartkamp MJ, Van Der Grond J, De Leeuw FE, De Groot JC, Algra A, Hillen B, et al. Circle of Willis: Morphologic variation on three-dimensional time-of- flight MR angiograms. Radiology. 1998;207:103–12.
6. Vagal A, Aviv R, Sucharew H, Reddy M, Hou Q, Michel P, et al. Collateral clock is more important than time clock for tissue fate a natural history study of acute ischemic strokes. Stroke. 2018;49:2102-7.
7. Seshadri S, Beiser A, Kelly-hayes M, Kase CS, Au R, Kannel WB, et al. The lifetime risk of stroke estimates from the framingham study. Stroke. 2015;37:345–51.
8. Who.int [Internet]. WHO methods and data sources for country-level causes of death 2000-2019. [updated 2020 dec; cited 2020 sep]. Available from https://www.who.int/.
9. Wafa HA, Wolfe CDA, Emmett E, Roth GA, Johnson CO, Wang Y, et al. Burden of stroke in europe. Stroke. 2020;51:2418-27.
10. Wilkins E, Wilson L, Wickramasinghe K, Bhatnagar P, Leal J, Luengo- Fernandez R, et al. European cardiovascular disease statistics 2017 edition. EHN. 2017;5
11. Truelsen T, Begg S, Mathers C. The global burden of cerebrovascular disease. EHN. 2001
12. Murphy SJX, Werring DJ. Stroke: causes and clinical features Key points. Medicine (Abingdon). 2020:48;9:561–6.
13. Boehme AK, Esenwa C, Elkind MS V. Stroke risk factors, genetics , and prevention. Circ res. 2017;120:472–96.
14. Roger L, Go AS, Lloyd-jones DM, Benjamin EJ, Berry JD, Borden WB et al. Executive summary: heart disease and stroke statistics — 2012 Update A Report From the American

Heart Association. AHA/ASA Stroke. 2012;125:188–97.

15. Kissela BM, Khoury JC, Alwell K, Moomaw CJ, Woo D, Adeoye O et al. Age at stroke: temporal trends in stroke incidence in a large, biracial population. Neurology. 2012;79:1781–7.
16. Asplund K, Karvanen J, Giampaoli S, Jousilahti P, Niemelä M, Broda G et al. Relative risks for stroke by age, sex, and population based on follow-up of 18 European populations in the MORGAM Project. Stroke. 2009;40:2319–26.
17. Howard VJ, Cushman M, Pulley L, Gomez CR, Go RC, Prineas RJ et al. The reasons for geographic and racial differences in stroke study: objectives and design. Neuroepidemiology. 2005;25:135–43.
18. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet. 2010;376:112–23.
19. MacMahon S, Rodgers A. The epidemiological association between blood pressure and stroke: implications for primary and secondary prevention. Hypertens Res. 1994;17:23-32.
20. Whisnant JP. Effectiveness versus efficacy of treatment of hypertension for stroke prevention. Neurology. 2000;3:279–302.
21. Tirschwell DL, Smith NL, Heckbert SR, Lemaitre RN, Longstreth WTJ, Psaty BM et al Association of cholesterol with stroke risk varies in stroke subtypes and patient subgroups. Neurology. 2004;63:1868–75.
22. Hackam DG, Austin PC, Huang A, Juurlink DN, Mamdani MM, Paterson JM, et al. Statins and intracerebral hemorrhage: a retrospective cohort study. Arch Neurol. 2012;69:39–45.
23. Banerjee C, Moon YP, Paik MC, Rundek T, Mora-McLaughlin C, Vieira JR, et al. Duration of diabetes and risk of ischemic stroke: the Northern Manhattan Study. Stroke. 2012;43:1212–7.
24. Sui X, Lavie CJ, Hooker SP, Lee D-C, Colabianchi N, Lee C-D, et al. A prospective study of fasting plasma glucose and risk of stroke in asymptomatic men. Mayo Clin Proc. 2011;86:1042–9.
25. Margolis KL, O'Connor PJ, Morgan TM, Buse JB, Cohen RM, Cushman WC, et al. Outcomes of combined cardiovascular risk factor management strategies in type 2 diabetes: the ACCORD randomized trial. Diabetes Care. 2014;37:1721–8.
26. Zhou M, Zhu L, Wang J, Hang C, Shi J, et al. The Inflammation in the Gut After

Experimental Subarachnoid Hemorrhage. 2007;108:103–8.

27. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA et al. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA. 1994;271:840–4.
28. Aronow WS, Banach M. Atrial fibrillation: The new epidemic of the ageing aorld. J Atr Fibrillation. 2009;1:154.
29. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991;22:983–8.
30. Howard VJ, Cushman M, Pulley L, Gomez CR, Go RC, Prineas RJ et al. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med. 1994;154:1449–57.
31. Wolf PA, Agostino RBD, Belanger AJ, Kannel WB. Probability of stroke: A risk profile from the framingham study. 2015;22:312–9.
32. Diener HC, Graeme J, Hankey MD. Primary and secondary prevention of ischemic Stroke and cerebral hemorrhage. JACC. 2020;75:1804-18.
33. Heiss W-D. The ischemic penumbra: correlates in imaging and implications for treatment of ischemic stroke. The Johann Jacob Wepfer award 2011. Cerebrovasc Dis. 2011;32:307–20.
34. Deb P, Sharma S, Hassan KM. Pathophysiologic mechanisms of acute ischemic stroke: An overview with emphasis on therapeutic significance beyond thrombolysis. Pathophysiol Off J Int Soc Pathophysiol. 2010;17:197–218.
35. Bretón RR, César J, Rodríguez G. Excitotoxicity and oxidative stress in acute ischemic Stroke. 2012;1
36. Murphy TH, Li P, Betts K, Liu R. Two-photon imaging of stroke onset in vivo reveals That NMDA-receptor independent ischemic depolarization is the major cause of rapid reversible Damage to dendrites and spines. J Neurosci. 2008;28:1756–72.
37. Saver JL. Time is brain-quantified. Stroke. 2006;37:263–6.
38. Kim BJ, Menon BK, Kim JY, Shin D-W, Baik SH, Jung C, et al. Endovascular treatment after stroke due to large vessel occlusion for patients presenting very late from time last known well. JAMA Neurol. 20211;78:21–9.
39. Jordan JD, Powers WJ. Cerebral autoregulation and acute ischemic stroke. Am J Hypertens. 2012;25:946-50.
40. H S Maruks. Cerebral perfusion and stroke. J Neurol Neurosurg Psychiatry. 2004;75:353–62.

41. Klatzo I, Sciences N, Disorders C. Pathophysiological aspects of brain edema. Acta Neuropathologica. 1987;72:236-39.
42. Lyden P. Using the National Institutes of Health Stroke Scale. Stroke. 2017;48:513-19.
43. Glymour MM, Berkman LF, Ertel KA, Fay ME, Glass TA, Furie KL et al. Lesion characteristics, NIH stroke scale, and functional recovery after stroke. AJPMR. 2007;86:725–33.
44. Linfante I, Llinas RH, Schlaug G, Chaves C, Warach S, Caplan LR. Diffusion-weighted imaging and national institutes of health stroke scale in the acute phase of posterior-circulation stroke. JAMA. 2016;58:621-28.
45. Heldner MR, Zubler C, Mattle HP, Schroth G, Weck A, Mono M, et al. National institutes of health stroke scale score and vessel occlusion in 2152 Patients with acute ischemic stroke. Stroke. 2013;44:1153–7.
46. Inoa V, Aron AW, Staff I, Fortunato G, Sansing LH. Lower NIH Stroke Scale Scores are required to accurately predict a good prognosis in posterior circulation stroke. Cerebrovasc Dis. 2014;37:251–5.
47. van Swieten JC, Koudstaal P J, Visser M C, Schouten H J and van Gjin J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19:604–7.
48. Higashida RT, Furlan AJ, Roberts H, Tomsick T, Connors B, Barr J et al. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. Stroke. 2003;34:109-37.
49. Ims T, Trial II. The interventional management of stroke (IMS) II study. Stroke. 2007;38:2127-35.
50. Jauch EC, Cucchiara B, Adeoye O, Meurer W, Brice J, Chan YYF et al. Part 11: Adult stroke: 2010 american heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2010;122:818–28.
51. Audebert H, Saver J L, Starkman S, Lees, Endres M. Prehospital stroke care new prospects for treatment and clinical research. Neurology. 2013;81:501-8.
52. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke a guideline for healthcare professionals from the American Heart Association/American Stroke A. Vol. 50. Stroke. 2019;50:344–418.
53. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay , age , and stroke severity on the eff ects of intravenous thrombolysis with

alteplase for acute ischaemic stroke : a meta-analysis of individual patient data from randomised trials. Lancet. 2014;384:1929-35.

54. Wardlaw JM, Murray V, Berge E, Zoppo G, Sandercock P, Lindley RL et al. Recombinant tissue plasminogen activator for acute ischaemic stroke : an updated systematic review and meta-analysis. Lancet. 2012;379:2364–72.
55. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. JAMA. 1999;282:2003–11.
56. Bhatia R, Hill MD, Shobha N, Menon B, Bal S, Kochar P et al. Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action. Stroke. 2010;41:2254–8.
57. Ringleb PA, Schellinger PD, Schranz C, Hacke W. Thrombolytic therapy within 3 to 6 hours after onset of ischemic stroke useful or harmful? Stroke. 2002;33:1437-41.
58. Demaerschalk BM, Demchuk AM, Fugate JE, Grotta JC, Khalessi AA, Levy EI, et al. AHA / ASA Scientific statement scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke. Stroke. 2016;47:581–641.
59. Lees KR, Emberson J, Blackwell L, Bluhmki E, Davis SM, Donnan GA, et al. Effects of alteplase for acute stroke on the distribution of functional outcomes a pooled analysis of 9 trials. Stroke. 2016;47:2373-9.
60. Fugate JE, Rabinstein AA. Absolute and relative contraindications to IV rt-PA for acute ischemic stroke. Neurohospitalist. 2015;5:110-21.
61. Miller DJ, Simpson JR, Silver B. Safety of thrombolysis in acute ischemic itroke : A review of complications, risk Factors, and newer technologies. Neurohospitalist. 2015;1:138–47.
62. Jovin TG, Willinsky RA, Sapkota BL, Dowlatshahi D, Frei DF, Kamal NR et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. NEJM. 2015;372:1019–30.
63. Pereira VM, Albers GW, Cognard C, Cohen DJ, Hacke W, Ph D, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. NEJM. 2015;372:2285–95.
64. Jovin T.G, Chamorro A, Cobo E, de Miquel M.A, Molina CA, Rovira A et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. NEJM. 2015;372:2296-306.
65. Yan B, Dowling RJ, Parsons MW, Oxley TJ, Wu TY, Brooks M, et al. Endovascular

therapy for ischemic stroke with perfusion-imaging selection. NEJM. 2015;372:1009–18.

66. Berkhemer OA, Fransen PSS, Beumer D, van den Berg LA et al. A randomized trial of intraarterial treatment for acute ischemic stroke MR CLEAN. NEJM. 2015;372:11-20.
67. Rehani B, Ammanuel SG, Zhang Y, Smith W, Cooke DL, Hetts SW et al. A new era of extended time window acute stroke interventions guided by imaging. The Neurohospitalist. 2020;10:29–37.
68. Berkhemer OA, Fransen PSS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015;372:11–20.
69. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372:1019–30.
70. Berkhemer OA, Majoie CBLM, Dieppl DWJ, MR CLEAN investigators. Endovascular therapy for ischemic stroke. N Engl J Med. 2015;372:2363–6.
71. Goldstein LB, Samsa GP, Matchar DB, Horner RD. Charlson index comorbidity adjustment for ischemic stroke outcome studies. Stroke. 2004;35:1941–5.
72. Russell JBW, Charles E, Conteh V, Lisk DR. Risk factors, clinical outcomes and predictors of stroke mortality in Sierra Leoneans: A retrospective hospital cohort study. Ann Med Surg. 2020;60:293-300
73. Johnsen SøP, Svendsen ML, Hansen ML, Brandes A, Mehnert F, Husted SE. Preadmission oral anticoagulant treatment and clinical outcome among patients hospitalized with acute stroke and atrial fibrillation: A nationwide study. Stroke. 2014;45:168–75.
74. Jonsson N, Asplund K. Does pretreatment with statins improve clinical outcome after stroke? A pilot case-referent study. Stroke. 2001;32:1112–5.
75. Sanossian N, Saver JL, Rajajee V, Selco SL, Kim D, Razinia T, et al. Premorbid antiplatelet use and ischemic stroke outcomes. Neurology. 2006;66:319-23.

8. SUMMARY

Objectives: The aim of our study was to investigate if EVT for acute stroke caused by occlusion of MCA is as efficient in low volume centers as it is in clinical trials. Furthermore, to identify whether any previous comorbidities or treatments have an impact on clinical outcome or thrombectomy outcome within the population of the University Hospital Split, in Croatia.

Materials and methods: A retrospective cohort study was carried out during 2020 of Neurology department in University Hospital Split. All data was acquired from the archives of the Neurology department, all patients treated with EVT for occlusion of MCA were included. A total of 90 patients of varied age, gender, previous health condition and treatments. Data collected was analyzed with IBM SPSS Statistics for Windows 26 (IBM Corp, 2019), for which t-tests and phi coefficient of correlation were used.

Results: The mean age for the patients was 77±9 years, with a span of 43 to 90 years. Selected patients showed an even gender distribution of 54% female and 46% male, of whom 94% had at least one comorbidity. Prior therapies as antiplatelet, anticoagulant or statins were utilized in roughly 20% of our study population. Good thrombectomy outcome (TICI 2b or 3) was achieved in 64% of our patients. There was a statistically significant difference in NIHSS and mRS between admission and discharge (t-test, $P<0.01$, $t=5.883$, $df=45$ and $t=36.515$, $df=55$ respectively). The good thrombectomy outcome significantly decreases the mRS at the discharge (-0.220, $P<0.01$). The NIHSS was also decreased but it did not reach the statistical significance (-0.134, $P=0.094$). There was a low negative correlation between the use of stent retriever and thrombectomy outcome (-0.220, $P=0.05$). Patients where thrombolysis was utilized prior to EVT had a better early outcome; TICI 2b or 3 was obtained in 77.3% of participants. No previous comorbidities or treatments, except the use of anticoagulants, had impact on thrombectomy or clinical outcome. Patient on anticoagulants had worse thrombectomy (-0.251, $P<0.05$) and clinical outcome (mRS discharge 0.217, $P<0.05$ and NIHSS discharge 0.271, $P=0.043$).

Conclusion: Even though EVT is slightly less effective than described in clinical trials, using EVT is effective in improving clinical outcome, for patients with MCA occlusion. Previous comorbidities and treatments do not affect the diseased, except for anticoagulants.

9. CROATIAN SUMMARY

Ciljevi: Cilj naše studije bio je istražiti je li endovaskularno liječenje akutnog moždanog udara uzrokovanog okluzijom MCA u svakodnevnoj praksi jednako učinkovito kao i u velikim kliničkim studijama. Također smo željeli istražiti je li ikakvi prethodni komorbiditeti ili terapija imaju utjecaja na ishod trombektomije kod bolesnika liječenih u Kliničkom bolničkom centru Split.

Materijali i metode: Retrospektivno kohortno istraživanje provedeno je u Klinici za neurologiju KBC-a Split. Svi podaci dobiveni su iz arhive Klinike. Uključeni su svi pacijenti koji su tijekom 20202.g. liječeni EVT zbog okluzije MCA. Obrađeni su podaci ukupno 90 bolesnika različite dobi, spola, s različitim komorbiditetima i prethodnim terapijama. Analiza podataka napravljena je programom IBM SPSS statistika za Windows 26 (IBM Corp, 2019), korišteni su t-tests i fi koeficijent korealcije.

Rezultati: Prosječna dob pacijenata je 77±9 godina, raspon od 43 do 90. Pedeset i četiri posto pacijenata su bile žene. Bar jedan komorbiditet imalo je 94% pacijenata. Prethodnu antiagregacijsku, antikoagulantnu ili terapiju statinima imalo je 20% bolesnika. Dobar ishod trombektomije (TICI 2b ili 3) postignut je kod 64% pacijenata. Razlika između NIHSS-a i mRS-a pri prijemu i otpustu bila je značajna (t-test, P<0.01, t=5.883, df=45 and , t=36.515, df=55). Dobar ishod trombektomije značajno snižava mRS pri otpustu (-0.220, *P<0.01*). Snižava i NIHSS ali bez dosezanja statističke značajnosti (-0.134, *P=0.094*). Zamijećena je Blaga negativna korelacija između ishoda trombektomije i korištenja *stent retrivera* (-0.220, *P=0.05*). Bolesnici kojima je prije EVT ordinirana tromboliza imali su bolji ishod trombektomije; TICI 2b ili 3 postignut je kod 77.3% bolesnika. Nikakvi prethodni komorbiditeti ili terapija, izuzev antikoagulantne, nisu imali utjecaja na ishod trombektomije ili klinički ishod. Bolesnici koji su bili na prethodnoj antikoagulantnoj terapiji imali su lošiji ishod trombektomije (-0.251, *P<0.05*) i lošiji klinički ishod (mRS pri otpustu 0.217, *P<0.05* i NIHSS pri otpustu 0.271, *P=0.043*).

Zaključak: iako je učinak EVT nešto lošiji nego što je opisano u velikim kliničkim studijama upotreba EVT je učinkovita metoda u liječenju akutnog ishemijskog moždanog udara uzrokovanog okluzijom MCA i značajno poboljšava klinički ishod liječenja ovih bolesnika. Prethodne bolesti i terapija ne utječu na ishod liječenja izuzev prethodne antikoagulantne terapije.

10. CURRICULUM VITAE

Personal information

Name:	Christopher Caap
Date and place of birth:	February 13th, 1990, Varberg Sweden
Citizenship:	Swedish
Address:	Knut Porses v.14 43244, Varberg Sweden
E-mail:	Christopher.caap@gmail.com

Education:

2015-2021 University of Split School of medicine, Split, Croatia.

2013-2014 Malvern House London, London, England

Clinical work experience:

01/2021 – 03/2021 – Clinical Observer, Hallands Hospital Varberg, Varberg, Sweden

06/2019 – 07/2019 – Clinical Observer, Neptunus Kliniken Varberg, Varberg, Sweden

Work experience:

07/2009 – 08/2016 – Chef, John's place, Varberg

11/2012 – 08/2013 – Chef, Le Petit Danois, Val D'isere

11/2010 – 05/2012 – Waiter, Doudoune, Val D'isere

07/2009 – 05/2010 – Military Service, Sweden

Languages:

Swedish (mother tongue)

English (C1)