A Comparison of Acute Ischemic Stroke Functional Independence Rates between Mechanical Thrombectomy after Intravenous Thrombolysis versus Intravenous Thrombolysis alone

Nina Ngo

Core Elective

Arcadia University

July 20th, 2020

Abstract

Introduction
Strokes affect for than 17 million people annually and account for the second most common cause of death globally. Thrombotic and embolic ischemia account for 85% of all strokes. The standard of treatment for ischemic strokes was intravenous thrombolysis using tissue plasminogen activators (tPA) such as alteplase. However, with its many exclusion criteria, it is still only moderately efficacious for a small portion of ischemic stroke patients. Furthermore, IV thrombolytics are less effective in patients with larger clot burdens. The MR CLEAN study addressed the use of combining this therapy with several other adjunctive treatments in large vessel occlusion strokes. This study specifically analyzes whether combining it with mechanical thrombectomy would lead to a significantly higher rate of 90-day functional independence rate than those who only received IV thrombolytic therapy.

Methods
A literature search was conducted through various search engines including PubMed and EBISCO to look for large scale randomized control trials that compared these two treatment branches in patients with acute ischemic strokes. A total of 7 trials fit the inclusion and exclusion criteria and were critically analyzed.

Results
The 7 trials were individually analyzed to critique several common factors such as control for bias, blinding of researchers, inclusion and exclusion criteria, adherence to treatment time window, rate of 90-day functional independence and the primary safety outcome of 90-day mortality for both treatment branches. Shortcomings and advantages of each trial were also noted.

Discussion
Trials were then compared to each other to assess how each trial approached each of the above factors. Since the MR CLEAN trial interrupted many of the trials analyzed, some were unable to reach their targeted sample size which deemed two of the seven trial results inconclusive. Despite the early cessation of the trials, most of the trials did have significant results at the time of their conclusions. Those that were inconclusive, still had results that trended in support of the original hypothesis.

Conclusion
Through the comparison of the primary outcome measures and primary safety outcomes, there was a significant increase in 90-day functional independence rate in patients who received the combined therapy versus those who only received IV thrombolytics. There was not a significant difference in the 90-day mortality rate between the two groups. Based on this evidence, combinative therapy does have a place in the treatment of acute large vessel occlusion strokes.

Introduction

An ischemic stroke is defined as an episode of neurological dysfunction caused by focal cerebral, spinal or retinal infarct based on pathological, imaging or other evidence of ischemic injury in a defined vascular distribution.[1] Globally, with an annual rate of 17 million patients strokes are the second most common cause of death, after ischemic heart disease.[2,3] In 2017, strokes were the sixth leading cause of morbidity and was projected to rise to fourth place by 2020.[2] Stroke care and treatment has imposed considerable financial burdens on individuals and society alike. In the US, the total direct and indirect cost was reported to be $65 million in 2008 alone and is expected to rise along with the aging population of the US.[4]

Among all strokes, 85% are ischemic in nature, resulting from a thrombotic/embolic occlusion of a cerebral artery, impairing blood supply to a designated vascular distribution in the central nervous system. Occlusions could originate from plaques secondary to carotid artery disease, or embolic clots secondary to cardiac disorders like atrial fibrillation.[2] There are many other factors that would increase a patient's likelihood of having a stroke, including but not limited to age, sex, diabetes mellitus, smoking, poor dietary intake, obesity, and air pollution. One of the most prominent risk factors is hypertension.[3] Nearly half of all stroke-related mortality could be contributed to modifiable risk factors.[3] Given the high prevalence, economic burden, and morbidity and mortality; the aim of preventative treatment should be on controlling modifiable risk factors. Additionally, the goal of acute treatment of stroke is aimed towards achieving early reperfusion of ischemic brain tissue to improve functional outcomes and decrease mortality rates of affected patients.

Until 2015, the standard of treatment for ischemic strokes was intravenous thrombolysis using tissue plasminogen activators (tPA) such as alteplase. Although IV tPA has been proven to

be efficacious in some ischemic stroke patients, it had numerous exclusion and inclusion criteria that limited it use, such as a treatment window of less than 4.5 hours of symptom onset.[5,6] In patients that were unable to receive this treatment and were not reperfused, their prognosis and neurological deficits were generally poor. In 2014, the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), a large-scale randomized control trial compared the functional outcome of patients receiving endovascular or intra-arterial treatment (IAT), to those who did not receive IAT, showed a reduce in patient disability when treated with mechanical thrombectomy in addition to standard of care.[6] The MR CLEAN trial has been followed by similar studies with positive results, leading to a promising new treatment for ischemic strokes.[7]

Although MR CLEAN was a revolutionary study in the area of acute stroke management, its treatment arms were very generalized, in which their IAT group could have been treated with any combination of IV or IA tPA, mechanical thrombectomy, or both.[6] They compared this to those who did not receive any of these treatments at all. Therefore, it creates a discrepancy of which specific treatments in their IAT treatment arms were more efficacious compared to one another. Subsequent studies aimed to make this distinction between the various treatments. Since the gold standard at the time was IV thrombolysis with tPA, this research paper compares this treatment with the combination of IV thrombolysis plus the novel treatment of mechanical thrombectomy. This analysis reviews seven studies to compare two, more specific treatments. In patients presenting with acute ischemic strokes (within 6 hours), does the combination treatment of mechanical thrombectomy and intravenous thrombolytic provide a greater 90-day functional independence rate than intravenous thrombolysis alone?

Methods

A literature search was conducted in November 2019 on PubMed.gov using the terms "Stroke[Mesh] AND Thrombectomy [Mesh] AND Thrombolytic Therapy [Mesh]". The search was first limited by article type to include "Randomized Controlled Trial." Second, the search also had a publication date within 5 years (Nov 2014). This search yielded 12 results. This search was limited to those that were Mesh term indexed and thus would not include studies that were not yet indexed. Of the 10 articles, articles were excluded based on the following criteria: 1. Studies that involved systematic reviews or meta-analysis 2. Studies that did not compare duel therapy with individual therapy. 3. Studies that observed the effects of an individual therapy (intravenous thrombolysis or mechanical thrombectomy) 4. Treatment time was outside of 6 hours of symptom onset. These exclusion criteria were necessary to ensure that the studies only involved comparing a combination of two treatment versus an individual treatment of acute ischemic strokes. It was also imperative to use primary sources of randomized control trials. The exclusion criteria narrowed the results to 3. Furthermore, 2 additional studies that fit the above criteria were found when eliminating the article type filter.

Another search was conducted on EBSCO host using the terms "Stroke or Cerebrovascular accident or CVA" AND "mechanical thrombectomy" AND "Thrombolytic therapy" AND "Randomized Controlled trials or rtc or randomized control trials." Additionally, the exclusionary term "NOT meta-analysis or systemic review" was also used. The search was limited to a 5-year window, excluding publication dates prior to 2014. This search yielded 17 results. Of those results, studies or articles were excluded based on the criteria stated above, resulting in 2 articles.

Lastly, a literature search was performed in Google Scholar using the search terms "thrombolysis" AND "tPA" AND "mechanical thrombectomy" AND "acute ischemic stroke" AND "Randomized control study" OR "cohort study." The search was further limited to publishing dates since 2015. This resulted in 630 results, which was too numerous. Therefore, a Google Scholar search of the previously found articles was done. "Related Articles" were then searched. Of those results, studies were excluded based on the criteria stated above to ensure that articles were either randomized controlled trials or cohort studies. The exclusionary criteria resulted in 3 articles. Of the 10 articles, randomized control trials were selected over cohort studies, and trials with greater number of participants were selected over those with fewer participants.

Results

Bracard S, Ducrocq X, Mas JL, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *The Lancet Neurology* . 2016;15:1138-1147. doi:10.1016/S1474-4422(16)30177-6.z

In the article by Bracard et al, "Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomized controlled trial" the article aimed to compare the standard of care, intravenous thrombolysis (IVT) with the combined therapy of IVT with mechanical thrombectomy (IVTMT) to determine the effects on functional independence at 3 months for moderate to severe, occlusive strokes of the proximal cerebral artery within 4 hours of onset of symptoms. The standard of care, intravenous administration of alteplase, a tissue plasminogen activator, improves the chances of good outcomes if administered within 4.5 hours of onset of symptoms. Endovascular treatments also increase the chance of successful and rapid recanalization. Thus, Bracard et al hypothesized that if the two treatments were used in

combination, it would result in quick administration and improved recanalization, thus improving the 3-month functional independence outcome. According to the article, previous studies comparing the two treatments did not show a benefit in the combined treatment. Although the authors note those previous studies had a number of limitations and drawbacks that their THRACE study aimed improved upon, such as; inability to use the most recent clot retrieval/aspiration devices available at the time, not using CT/MRA imaging in diagnosis and localization of emboli, or if they did use imagining, it was used in a manner than may have excluded those who would benefit from thrombectomy.

Bracard et al constructed a randomized controlled trial, conducted across 26 centers in France. The study estimated to show a 15% increase in the modified Rankin score of 0-2 in IVTNT group vs the IVT group at 3 months, with a power of 90% and p=0.05, estimating a 10% loss to follow-up rate, their enrollment target was 240 patients in each group. Their actual sample size was 414 patients. Although their sample size was less than their ideal goal, THRACE had a relatively large sample size compared to previous similar studies. Inclusion criteria were as follows; patients with acute ischemic stroke between ages 18-80 years; had a US National Institutes of Health Stroke Scale (NIHSS) score between 10-25; had an occlusion of the proximal cerebral artery confirmed by CT or MRA, could be administered IVT within 4 hours of onset, and if MT could be initiated within 5 hours of onset. The 414 patients were randomized by a computer analyst who was blinded to the institution and patient. Blinding of the investigators and patients was not feasible due to the nature of the intervention. They were randomized into the IVT group (n=208) or IVTMT group (n=204). 2 patients withdrew consent, in the IVT group, 2 patients were lost to follow-up and 4 had missing data. In the IVTMT group, 2 were lost to follow up and 2 had missing data. These 10 patients did not have substantial differences in

baseline clinical and imaging data compared to the 402 patients included in the primary analysis. Baseline characteristics of 412 patients did not differ between groups, although patients in the IVT group had higher proportions of diabetes (IVT 17% vs IVTMT 8%), hypertension (IVT 57% vs IVTMT 47%), and Hypercholesteremia (IVT 58% vs IVTMT 45%). There was no researcher or subject bias since the patients were randomized into groups within a rapid time frame (<20 minutes of IVT). Even though imaging was done before the patients inclusion into the trial, the imaging data showing the size of their ischemia zone did not affect the decision to include or exclude them. Additionally, patients were randomized within 20 minutes of receiving thrombolysis and thus the effects of thrombolysis were not known and did not affect which group they were placed into. Within the 2 groups; 8 of the patients in the IVT group eventually had thrombectomy due to poor clinical evolution; and within the IVTMT group 59 patients did not have thrombectomy due to significant clinical improvement (35 patients), partial or complete recanalization (18 patients), or violation of exclusion criteria (6 patients, had a history of surgery or presence of cervical carotid artery occlusion).

They measured their variable using modified Rankin score, estimated by a vascular neurologist, and NIHSS were used to assess at 24 hours, discharge or 7 days and at 3 months. Barthel index, an ordinal scale used to measure performance in activities of daily living, was assessed at 3 months. Their data management and statistical analysis were done by Inserm CIC-EC 1433, a research unit at a French Medical Research Institute, focusing on clinical epidemiology and methodological research in epidemiology and public health. They conducted a planned interim analysis after enrollment of 220 and used O'Brien-Fleming method to minimalize type I error (rejection of a null hypothesis). They conducted an unplanned interim analysis after the MR CLEAN results were released after 385 patients were enrolled. Differences

between the two groups were assessed with an unadjusted logistic regression. The modified Rankin scores were treated as a seven-category variable and analyzed with an ordinal logistic regression. They also did a prespecified subgroup analysis to determine the effect size of thrombectomy in the primary outcome variable by patient characteristics. Odds ratios and associated p values of each interaction term were estimated from separate logistic regression models across the prespecified subgroups and Alberta Stroke Program Early CT score (ASPECTS). Statistical analysis was done with SAS/STAT (version 9.3).

This study is cited as one of the largest studies to show that combined therapy increases the proportion of patients achieving functional independence at 3 months without a significant increase in mortality. Their study had a wide patient selection which better reflects the patient population seen in routine clinical practice. Lastly, due to their rapid randomization methods (within 20 minutes of IVT), they did not exclude fast responders to intravenous alteplase. Their study implicates that bridging therapy seems to be beneficial irrespective of sex, age, clinical severity, or intracranial location of the occlusion.

Saver JL, Goyal M, Bonafe A, et al. Stent-retriever Thrombectomy after Intravenous t-PA vs t-PA alone in Stroke. The New England Journal of Medicine. 2015;372:2285-2295 DOI: 10.1056/NEJMoa1415061

Saver et al aimed to investigate the efficacy and safety of stent retriever thrombectomy with intravenous thrombolysis compared to intravenous thrombolysis alone in the treatment of acute ischemic strokes. Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) trial was a multicentered, randomized, open clinical trial. Their trial included 39 centers in the United States as well as Europe. This design was appropriate since the best stroke treatment at the time was intravenous thrombolysis, thus patients would receive the

standard care with the prospect of additionally receiving a promising new treatment, stent retrieval thrombectomy. Randomization ensured no bias when choosing which patients would receive the tested treatment. The patients were randomized and allocated to one of two treatment groups, intravenous tPA plus stent retriever (intervention group) or intravenous t-PA alone (control group) on a 1:1 ratio. Four factors were considered during randomization of the treatment groups and a minimization algorithm was used to account for investigation site, baseline National Institutes of Health Stroke Scale (NIHSS) score, patient age, and site of occlusion.

Between December 2012 and November 2014, 196 patients were recruited to the study across 39 sites. This is a moderate study size, however most studies examined thus far have been smaller in scope. Only few other studies in this field, such as A Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN) which included 500 patients, were able to recruit more patients for a randomized control trial. Each treatment group had 98 patients, with similar demographics. There were 3 patients who were lost to follow-up. The inclusion criteria included; patients between ages 18-85 with acute ischemic strokes with moderate-to-severe neurologic deficits, had intracranial internal carotid artery or first segment of the middle cerebral artery or both confirmed with imaging, were receiving or had received intravenous t-PA and were able to undergo endovascular thrombectomy within a 6 hour time window, and had no prestroke functional deficit. Exclusion criteria included but was not limited to history of stroke, renal failure, bleeding disorders, current pregnancy or lactation, or had uncontrolled hypertension (>185/>110).

SWIFT PRIME's primary study outcome measured the disability of patients at 90-days with the modified Rankin Scale (mRS). Their secondary efficacy outcomes included rate of

death at 90 days, rate of functional independence at 90 days, measured with the mRS, change in NIHSS score at 27 hours post-randomization, and rate of successful reperfusion at 27 hours, quantified as reperfusion of 90% or more of the initial perfusion-lesion volume via CT/MRI. Imaging was assessed by staff blinded to the treatment group of the patient. The mRS score is a common, reliable and comparable quantification of disability and functional independence across stroke studies. NIHSS scores are used to quantify the severity of strokes internationally and is a reliable method of measurement. Furthermore, while most studies evaluated their patients upon discharge and then at 90-days, the SWIFT PRIME study also evaluated patients at 30 days which improves their body of results and thus more reliable.

SWIFT PRIME employed a simultaneous success criterial to analyses the overall distribution of mRS scores at 90 days as well as the proportion of those who reached functional independence (mRS score between 0-2). They also used the Cochran-Mantel-Haenszel test to analyze the shift of the entire mRS score range. Saver et al hypothesized that the shift analysis would favor the intervention group over the control group. If both criteria were met, which it was, the study would be declared positive. Additionally, the dual success criteria were used to determine power and sample size. They planned five interim analyses for efficacy, futility and safety during their study. When preliminary results from the MR CLEAN and the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trials were reported, SWIFT PRIME conduced an earlier than planned analysis which revealed their efficacy boundary had been crossed. The predetermined efficacy boundary was that the proportion of patients who reached functional independence at 90 days was higher in the intervention group by a difference of 12%.

The current participating patients had reached a difference of 25%. Saver et al decided to halt the study in February of 2015.

Their primary outcome was reached for both pre-established criteria; patients in the intervention group had a favorable shift in their mRS scores at 90 days, with the intervention group having an interquartile range of 1-4, and the control group having an interquartile range of 2-5 ($p<0.001$). Their secondary outcomes were reflective of that shift as well, where 60% of the intervention group reached functional independence at 90 days, compared to 35% in the control group ($p<0.001$). The rate of functional independence in this trial was higher than that of the MR CLEAN (33%) but comparable to that in the ESCAPE trial (53%) and the Extending the Time for Thrombolysis in Emergency Neurological Deficits — Intra-Arterial (EXTEND-IA) trial (71%). The trials with higher rates all also emphasized earlier intervention times. Mortality at 90 days did not differ significantly between the two groups ($p=0.5$). Successful reperfusion at 27 hours was achieved in 83% of the intervention group and 40% of the control group ($p<0.001$). Rate of reperfusion was higher in this trial than previous studies, which the authors attributed to their homogenous patient population, and their regulatory use of homogenous treatment (their sites used the Solitaire stent retrievers only).

This study recognizes a few limitations it had during the trial. They had a homogenous cohort of patients who were able to be treated with intravenous t-PA, which has many contraindications and thus this population of patients does not accurately reflect all patients presenting with acute ischemic strokes. They recognized that further research would need to be done to determine the efficacy of stent retrieving thrombectomy procedures in other populations, such as those presenting past 6 hours of symptom onset, those who presented with “wake up” strokes or patients who had strokes due to a posterior circulation occlusion. Secondly, during the

study, the sites were continuously improving their program and workflow. Implementation of mechanical thrombectomy at other hospitals would require a substantial amount of resources and continuous improvements, which is not feasible for all hospitals. The trial was conducted primarily at tertiary care facilities with established stroke-intervention programs, experienced neurointerventionalists and trained staff. They acknowledge that the results they obtained would not be replicable at sites without these resources.

SWIFT PRIME showed that stent thrombectomy in addition to intravenous thrombolysis administration was an effective treatment for patients presenting with acute ischemic strokes due to large-vessel occlusions with small or moderate ischemic cores compared to the standard treatment of intravenous thrombolysis alone. In addition to this study, other similar studies such as EXTEND-IA, MR CLEAN, ESCAPE, THERAPY, show that mechanic thrombectomy concomitant with intravenous thrombolysis is a efficacious treatment for patients presenting with acute ischemic strokes.

Mocco J, Zaidat OO, Kummer RV, et al. Aspiration Thrombectomy After Intravenous Alteplase Versus Intravenous Alteplase Alone. Stroke. 2016;47(9):2331-2338. doi:10.1161/strokeaha.116. 013372.

Mocco et al designed the THERAPY (The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke) study to compare the 90-day functional independence of stroke patients who were either treated with intravenous alteplase concurrent with aspirational thrombectomy (IAT) or with intravenous alteplase alone. THERAPY was a multicenter prospective, randomized control trial, with blinded end point evaluation. Randomization was done on a 1:1 ratio. Independent blinded adjudicators

assessed the primary outcome measure, the 90-day modified Rankin Scale. All baseline and follow-up imaging and imaging outcome events were assessed by blinded neuroradiologists. Mocco et al calculated a projected sample size of 692 patients based on a 2-sided X^2 test with 80% power and an α of 0.05. The study was halted on February 13th, 2015 after the publication of MR CLEAN due to the concern that providing intravenous tPA alone would be unethical. Therefore, THERAPY was halted and ended with a sample size of 108; 53 patients were treated with intravenous alteplase alone, and 55 patients were treated with intravenous alteplase and aspirational thrombectomy. The eligibility criteria patients needed to meet in order to qualify for the study includes the following; 18-85 years old, have either an intracranial internal carotid artery or middle cerebral artery occlusion on CT angiography, with an NIHSS score of ≥8, and a clot length ≥8mm. Patients were excluded if they had >1 of 3 of the affected MCA territory with established infarction, cervical ICA stenosis/occlusion that required treatment prior to thrombectomy, and prestroke disability (mRS >1). The patients were similar in demographics, however notable differences included female sex (57% in intravenous alteplase group and 38% in IAT group), history of atrial fibrillation (49% versus 33%), smoking history (39% versus 60%), and intracranial ICA occlusions (23% versus 33%). Although notable, these differences were not statistically significant.

THERAPY measured their primary result with a 90-day modified Rankin Scale to assess the 90-day functional independence of patients post-treatment. This is a standard measurement of this variable, as other similar studies also used this criterion to assess the efficacy of their treatments. Secondary outcomes included using the mRS to measure the severity of 90-day disability, the proportion of patients with improvement of symptoms. Lastly, the 24-hour infarct

volume was measured using the Alberta Stroke Program Early CT score (ASPECTS). They used an intention-to-treat (ITT) analysis and a per-protocol (PP) analysis.

Since the study was halted, the results were not as definitive as originally planned. Functional independence at 90 days (mRS 0-2) was achieved in 38% of the IV+AT group versus 30% in the IV group with an odds ratio of 1.4 and p-value of 0.44 in the ITT analysis There was no significant difference in the primary safety outcome between the two treatment groups, 42% versus 48% respectively. With a p-value of 0.047, the per protocol analysis showed significant improvement in functional outcomes at 90-days for the IV+AT treatment group over the IV alone treatment group. Since the study was halted before completion, results did not reach enough significance as previously projected. However, the results did project a positive trend to confirm their hypothesis that aspirational thrombectomy would improve the clinical outcomes in patients who also received intravenous alteplase. THERAPY had results supporting favorable mRS scores for the IV+AT group that were comparable to previous similar studies like ESCAPE, EXTEND-AI, SWIFT PRIME. THERAPY differed from the other like studies above by using a different thrombectomy technique, aspirational thrombectomy and focused on treating clots greater than 8mm. They had successful reperfusion rates comparable to past studies as well.

Mocco et al recognized that their study did not reach its intended target sample size as a chief limitation to their study and informed readers to interpret their results with caution, noting its shortcomings. Thus, their small sample size led to an imbalance in their patient demographics despite randomization of the patients. They recognize that these imbalances could have affected their results significantly, most notably, the location of occlusions. However, they did account for these variables in their analysis. They also cited their focus on a very selective patient population as another limitation to their study. Overall, the study design itself was well thought

out, and comparable to previous studies. If the trial was not halted preemptively, they had results that trended towards a better 90-day functional independence rate for the IV+AT patient compared to the IV group.

Khoury NN, Darsaut TE, Ghostine JY, et al. Endovascular thrombectomy and medical therapy versus medical therapy alone in acute stroke: A randomized care trial. Journal of Neuroradiology . 2017;44(3):198-202. Doi:https://dio.org/10.1016/j. neurad.2017.01.126.

Khoury et al created a randomized care trial, Endovascular Acute Stroke Intervention (EASI), with the goal in mind to offer patients a promising but at the time, unproven, treatment of mechanical thrombectomy with standard care (intravenous thrombolysis), or standard care alone. Their primary hypothesis was that endovascular management with standard care would improve 90% functional independence of patients by 15% of their mRS score between 0-2, compared to those patients who received standard treatment alone.

The study had aimed to recruit 480 patients to demonstrate a 15% absolute difference to reach the primary outcome, accounting for 90% power and 10% rate of loss to follow up. This goal was not reached due to premature cessation of the trial by the Steering Committee after the release of the MR CLEAN trials. The EASI trial recruited 77 patients in 19 months between March 2013 and October 2014, before the study was halted considering the MR CLEAN publications. Patients were recruited from a single facility in Montreal, Canada. They allocated 40 patients into the thrombectomy group and 37 patients into the standard care group. Inclusion criteria were kept broad since other similar studies had trouble recruiting patients into their trials. Inclusion criteria included: being over age 18, NIHSS ≥ 8, onset of symptoms ≤ 5 hours, or presence of clinical-imaging mismatch, and suspected or proven occlusion of M1 and M2 segments of the MCA, supraclinoid ICA, or basilar artery. Vascular imaging was not mandated.

The exclusion criteria included: any established infarction or hemorrhagic transformation of the target symptomatic territory and co-morbidities associated with a poor 90-day outcome. No patients were lost to follow-up. Between the two groups, patient characteristics were similar.

The patients were randomized using a web-based application package on a 1:1 ratio to mechanical thrombectomy plus standard care or standard care alone. Randomization was done during IV thrombolysis or within 5 hours from time of symptom onset. This study notes that standard treatment includes IV thrombolysis, when appropriate, therefore not all patients in the trial received tPA. However, this does reflect real-life clinical decision making, as tPA has many contraindications and is not always utilized. This practice did reflect their best standards of care. Blinded data was provided to periodic review by an Independent Data Safety Monitoring Board. The primary outcome, 90-day functional outcome, was measured by achieving a score of 0-2 on the modified Rankin Scale mRS. This method is comparable to other trials studying acute ischemic strokes. The primary safety outcome quantified death at 90 days and symptomatic intracranial hemorrhage (sICH) at 24 hours. They also collected information of angiographic reperfusion TICI score and adverse events on secondary imaging to further evaluate safety outcomes. The trial used a single Fisher's exact test to compare the primary endpoint for efficacy between the two groups. Descriptive statistics were presented for intention-to-treat analysis and primary efficacy and safety endpoints are shown for prespecified subgroups.

The primary outcome of mRS score 0-2 at 90-days was reached in 20 out of 40 patients in the thrombectomy treatment group (95% confidence interval of 35-65%) and 14 out of 37 in the standard care treatment group (90% confidence interval of 24-54%). They also note 11 patients, and 9 patients died in the thrombectomy versus standard of care groups, respectively.

However, due to the premature cessation of the trial, they were unable to recruit the intended number of patients to provide statistically significant results.

The EASI trial aimed to improve on previous trials' shortcomings such as difficulty recruiting patients, patients were not guaranteed to receive standard care in timely fashion in other trials, and difficulty getting patients access to the most effective thrombectomy devices. They achieved these improvements by having a broader inclusion criterion, and by randomizing at the time of thrombolysis. Khoury et al notes that the pragmatic nature of the EASI trial, having a broad inclusion criterion, were more reflective of results obtained in clinical settings where thrombectomy utilization is more wide spread. Researchers sited no sources of financial bias as there was no funding for this study.

The size of the sample dampens the significance; however, the results were trending towards the original stated hypothesis where 90-day functional independence was more likely to be achieved in the thrombectomy plus standard care group versus standard care alone. Although the trial was prematurely halted, this trial adds to previous studies that concomitant treatment of thrombectomy with intravenous tPA is more beneficial than using intravenous tPA alone.

Campbell BCV, Mitchell PJ, Kleinig TJ, et al. Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection. The New England Journal of Medicine. 2015;372:1009-1018. DOI: 10.1056/NEJMoa1414792

Campbell et al designed this study to assess whether three factors, advanced imaging selection, newer thrombectomy devices and earlier time to intervention would impact outcomes of acute ischemic strokes. More specifically, they hypothesized patients with large vessel anterior circulation ischemic strokes would achieve higher revascularization rates and better functional

outcomes with the combined treatment of mechanical thrombectomy after administration of alteplase compared to patients who received only alteplase, the current standard of care.

The study was aptly named Extending the Time of Thrombolysis in Emergency Neurological Deficits – intra-Arterial (EXTEND-IA) trial. EXTEND-IA was a multicentered, prospective, randomized control trial with a blinded endpoint. They selected 70 patients from 10 centers across Australia and New Zealand.

Inclusion criteria for the selection of patients included, eligibility of the use of tPA, CT angiography comfirmed occlusion in the ICA or MCA, and patients needed to have a baseline of functional independence (mRS score between 0 and 2). There was no age restriction for this study. Patients were identified as tPA eligible candidates, underwent CT angiography, and administered alteplase. Within a median time of 30 minutes, patients were randomized on a 1:1 ratio into the standard of care group (receiving no adjuvant treatment in addition to the alteplase), or the endovascular therapy group (the Solitaire FR stent retriever was used as the main thrombectomy device). Physicians and the clinical team were not able to be blinded to the treatment course. However, staff and subsequent clinicians who collected data points 24 hours and 90 days were blinded to the patients' treatment course.

In the endovascular therapy group, 8 patients did not undergo thrombectomy due to lysis of the thrombus prior to initiating treatment, clinical deterioration or improvement. No patients had dropped out of the study. Baseline characteristics of age, sex, comorbidities, were similar between the two treatment groups.

The coprimary outcomes the study measured included reperfusion and early neurologic improvement. Reperfusion was defined as the percentage reduction in perfusion-lesion volume between the initial CT angiogram imaging and those at 24 hours. Early neurological

improvement was defined as a reduction of at least 8 points on the NIHSS score at 3 days. The secondary outcomes included mRS score at 90 days, functional independence defined as mRS score between 0 and 2 at 90 days, mortality for any reason, symptomatic intracranial hemorrhage, defined as parenchymal hematoma type 2 within 36 hours of treatment and an NIHSS score increase of 4 from baseline. These were all valid methods of measuring each respective variable, as other similar studies have used identical or similar methods.

On October 31, 2014, The study was suspended from recruiting patients after the MR CLEAN trials were published. The study had already had a prespecified stopping boundary and began to analyze the intention-to-treat population with the Holm's step-down procedure. The data showed the endovascular therapy group was efficacious and the data and safety monitoring board halted the trial accordingly. The intention-to-treat analysis compared median reperfusion percentage between the two groups, adjusting for arterial occlusion, which acted as the primary analysis. They also used a logistic regression to compare differences between groups.

The coprimary results were significant demonstrating that endovascular therapy produced increased reperfusion at 24 hours ($p<0.001$) and greater early neurological recovery at 3 days ($p=0.002$). The secondary outcomes also demonstrated that endovascular therapy lead to a greater percentage of functional independence at 90 days (mRS score 0-2, 71% vs 40%, $p=0.01$). The study also compared the outcomes of patients' with various reperfusion rates. Patients with >90% reperfusion rates had improved functional outcomes ($p<0.001$), increased independence ($p<0.001$) and excellent outcomes ($p<0.001$) over patients with <90% reperfusion rates. Additionally, there was no significant difference in mortality between the two treatment groups.

In comparison with past studies such as MR CLEAN, EXTEND-IA initiated faster and more complete reperfusion rates with their use of CT angiography and streamlining patients.

EXTEND-IA showed a greater magnitude of clinical benefit than their predecessor MRCLEAN, which they attribute to the factors above. EXTEND-IA notes their use of CT angiography to exclude significantly large strokes may also have contributed to their greater clinical magnitude since it eliminated patients who had strokes with a low probability of a good outcome and higher probability of complications and adverse effects. They recognized this aspect as a strength since it was a factor to help select patients who would have optimal benefits from the potential treatment.

The study had few limitations that rooted from the its early cessation, including the inability to perform subgroup analysis and that early termination could potentially overestimate the study's effects. EXTEND-IA also acknowledges the use of volume-based criteria for quantifying the infarct and penumbra region does not take the location of the stroke into account. The note that further research would need to investigate thrombectomy benefits on more distal occlusions, later time windows and if the type of device or variable technique could influence the outcome.

Generally, EXTEND-IA improved on the research design of its predecessors, MR CLEAN and Intervention Management of Stroke 3 (IMS-3). It emphasized streamlining the treatment timeline, using more advanced technology, such as the CT angiogram in conjunction with programs that quantified ischemic areas, as well as newer stent-retrieval devices like Penumbra FR, and controlled for variable between groups well. Although it had a small sample population, the results were significant enough, along with those of MR CLEAN, to stop the trial early. This study adds significant data to support the use of thrombectomy devices in stroke management.

Muir KW, Ford GA, Messow CM, et al. Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. *J Neurol Neurosurg Psychiatry.* 2016;88:38-44. doi:10.1136/jnnp-2016-314117.

Muir et al's study aimed to determine chiefly whether intravenous thrombolysis (IV) alone or IV with adjuvant mechanical thrombectomy (MT) would achieve modified Rankin Score (mRS) of <2 at 90 days for patients presenting with acute ischemic stroke with large artery occlusive anterior circulation stroke confirmed on simple imaging, CT angiography (CTA). They wanted to investigate whether results seen in large RCTs were feasible in a country that was not as familiar to MT as a standard of treatment, such as the UK.

PISTE was a multicenter randomized controlled trial which recruited 65 patients between April 2013 and April 2015. They estimated that a sample size of 400 patients per group based on projected results, with 80% power, p=0.05 and a conservative 10% absolute increase in independent recovery. They were only able to recruit 65 patients within the above timeframe on account of their trial was suspended early after review of the MR CLEAN study data. Patients were randomized 1:1 using an interactive voice-response system managed by the Robertson Centre for Biostatistics, University of Glasgow. 32 patients were selected to receive IVT, and 33 patients were chosen for IVT with adjuvant MT. Patients were included based on the following; 18 years old, presentation with acute supratentorial ischemic stroke, if IVT could be initiated within 4.5 hours of onset of symptoms, and if CTA or MRA showed occlusion of anterior circulation. Patients were excluded if they have contraindications for IVT, life expectancy was limited to 90 days, if they had chronic extracranial ICA occlusion or with extensive early hypodensity on CT. Patients were also sorted into the intention -to-treat (ITT) population which

consisted of all patients who were randomized in the trial, and a per-protocol population, consisting all patients in the ITT population who did not have any major protocol violation, which excluded 6 patients. They noted that in the MT group, patients were generally older, female, had more severe strokes, had a higher prevalence of vascular risk (diabetes atrial fibrillation) and a higher proportion had prestroke impairment on estimated mRS. Also, a higher proportion had good collateral score and favorable ASPECT scores. During statistical analysis, odds ratios were adjusted for those factors accordingly. In the IVT group, 2 patients were lost to follow up at 90 days. The study design and methodology were appropriate given that they had planned to conduct a much larger study than what resulted. They followed similar guidelines and procedures as the other large RCTs. Despite the early termination, their study was still able to produce favorable results seen in the larger RCTs.

Like much of the other RCT studies, they mainly assessed the functional independence of patients at 90 days using the modified Rankin Scale, which were assessed by a site staff who was blinded to the patients' treatment allocation groups. They compared the primary outcome of mRS <2 at 90 days between IVT group and IVT+MT group, using a logistic regression adjusting for the minimization factors including, age, NIHSS scores, time to rtPA and study site. mRS distribution was analyzed using proportional odds logistics regression instead of logistic regression. Their significant level for the primary analysis was 0.05. They used R foundation for Statistical Computing version 3.0.1. Due to their small sample size, their primary outcome was not statistically significant, but they did find that their secondary outcomes, showed significantly greater likelihood of complete functional recovery (mRS 0-1) at 90 days for those with IVT+MT compared to IVT alone. This finding is concurrent with the findings of larger RCT studies.

In comparison to other RCT studies, PISTE was the only trial which followed a policy of proceeding as rapidly as possible to intervention on the basis of CTA confirmation, whereas other studies like MR CLEAN and REVASCAT, delayed endovascular treatment to assess the effects of IVT or had additional imaging requirements (ESCAPE, EXTEND-IA, SWIFT-Prime). Additionally, PISTE wanted to investigate whether MT could be feasibly undertaken in the UK where MT and interventional management of stroke had been uncommon, save for a small number of specialized centers. This is another study that examines if results seen in large RCTs are replicable in countries without well-organized regional or national networks, such as in the Netherlands, where MR CLEAN was conducted or Spain, where REVASCAT was conducted.

Cabral NL, Conforto A, Magalhaes PS, et al. Intravenous rtPA versus mechanical thrombectomy in acute ischemic stroke: A historical cohort in Joinville, Brazil. *eNeurologicalSci.* 2016;5:1-6. doi:10.1016/j.ensci.2016.04.002.

Considering several landmark studies testing the efficacy of endovascular treatments of ischemic strokes, Cabral et al recognized that these new treatments would translate to significant challenges, particularly in low- and middle-income countries (LMIC). Cabral et al aimed to compare the results of large randomized clinical controlled studies to those results seen in the "real-world," specifically in Joinville, an industrialized city in Southern Brazil. They hypothesized that the 3-month functional outcomes of patients treated with intra-arterial thrombectomy (IAT) and intravascular thrombolysis (IVT) would be better than those patients who were treated with IVT alone.

Cabral et al conducted a retrospective cohort study, registering 82 patients in the IVT group and 31 patients in the IAT group. The cohort data was extracted from the Joinville Stroke Registry. They chose 83 patients in the IVT group between the years 2009 and 2011 (during which time

standard of care was to administer IVT within 4.5 hours of symptom onset), and 31 patients in the IAT group between the years 2012 and 2014 (at which time patients were treated with both IVT and endovascular catheterization with a Solitaire FR device up to 6 hours after symptom onset). Their inclusion criteria are listed as follows; no small artery strokes or lacunar syndrome, NIHSS score above 10, and above age 18 years old. They did not include imaging as an inclusion criterion since there was no angio-CT data between 2009-2011. Thus, they did not have any imaging-based patient selection bias. They noted that the IAT group were significantly younger (average age of the IAT group, 63 vs average age of the IVT group, 71 years), had a higher education level, slightly higher prevalence of atrial fibrillation, and clinically more severe strokes. To control for the standard of care and demonstrate that it was well balanced over time, they compared 546 consecutive patients, who had the same inclusion criteria, with ischemic strokes who did not receive IVT or IAT.

They used an NIHSS score upon admission which is a standardized quantification of stroke symptoms. For their primary results they used the modified Rankin score to assess functional independence at 30 days and at 90 days. However, they note that for the 90-day time point, they had a trained nurse, who was blinded to the patients treatment, surveyed the patients or their family via telephone. They recognized that this is not an ideal method due to low reliability. They evaluated the differences between the two groups with x^2 tests, t-tests, or the Mann-Whitney U tests when appropriated. Characteristics with a $p<0.05$ were included in the multivariate logistic model. Odds ratios were adjusted by logistic regression for age, educational level, atrial fibrillation, NIHSS at admission and OCSP classification. Their primary results were measured by the modified Rankin scale at 30 days and 90 days post intervention. Their results were significant at 30 days (48% of the IAT group scoring mRS:0-2 vs 31% of the IVT group)

and at 90 days (55% in the IAT group vs 37% in the IVT group). After odds adjustment, the IAT group still had favorable outcomes. They used the statistical Package for Social Sciences, version 17.0.

The study design was appropriate for a cohort study of this caliber, given the limited resources and access to care that Joinville had at the time. Their circumstances reflected what they deemed as "real-life" and accomplished their goal of comparing RCT studies with "real-life" situations. This study offers a perspective that is realistic in most of the world as Brazil is a middle-income country. They do note that more studies done in low-income countries need to be performed. With modified Rankin scores, they were able to compare their results with those of the larger randomized control trials previously published prior to this study. In the comparison, they found that the clinical stroke severity, proportion of IVT use in mechanical thrombectomy, successful reperfusion rate, and proportion of independent patients and device complications of their study were similar to the results of the RCTs. However, their cohort had a higher proportion of symptomatic hemorrhage and mortality in the IVT group. To explain this, they cited that the IVT group had a higher instance of patients with lower educational and economic status, who are often the patient population with lower survival rates and greater stroke severity. They also reasoned that patients in observational studies generally have more severe presentations and more comorbidities and complications than those selected for experimental studies. These results are directly applicable to my clinical question as they fit the inclusion criteria above. Yet it is an interesting perspective on the accessibility and practicality of implementing mechanical thrombectomy in LMICs. These results bolster the body of evidence built by randomized control trials that were recently published. This cohort shows that the benefit of combined therapy is replicable in low- and middle-income countries.

Discussion

Overall, the studies analyzed had very well thought out experimental designs that were similar and comparable to each other. Generally, their inclusion and exclusion criteria had common factors such having patients over the age of 18, diagnosis of ischemic stroke, with or without imaging, specific large vessel occlusion site and definitive treatment windows. Table 1 shows a comparison of study designs for the seven studies analyzed above.

All but 1 trial were RCT which is the optimal study of choice given that it eliminates most conscious and subconscious bias from studies. All the RCT had participants randomly assigned to treatment groups via a computer program eliminating any possible selection bias practitioners and study designers might have had in the treatment placement step.

Except for Bracard et al (THRACE) and Cabral et al, the majority of the studies did not achieve their initial intended sample size, largely due to the release of the MR CLEAN trial. Although the MR CLEAN trial provided significant evidence in favor of using combination therapy, they tested a variety of combination therapies, whereas the studies analyzed here examined the effects of the specific combination of IV thrombolytics with mechanical thrombectomy versus IV thrombolytics alone. Those studies with larger sample sizes (Bracard et al, Saver et al) saw a statistically significant results, adding to the body of evidence the MR CLEAN trial and other similar trials provided. Those that did not recruit their full sample size still had trending results supporting published data.

Occlusion sites were selected based on the most common large vessels where thrombi/emboli would lodge, which included ICA, MCA, and Basilar artery. No studies chosen for this analysis specifically examined other large vessel occlusions such as those in the posterior

circulation. Therefore, it is recognized that this is an area of study which needs to be researched further.

The time window for intervention chosen for this analysis was mainly limited to a little longer than the treatment window of IV thrombolytics (3-4.5 hours) as it was involved in both treatment branches. Therefore, 6 hours was chosen for the latest intervention time to more critically examine the effects of the treatment branches for acute strokes. However, it is recognized that stroke can be clinically diagnosed later than this time window, such as the case with "wake-up strokes." Therefore, further research would need to be done to examine these treatments, especially mechanical thrombectomy alone on late presentation strokes and for those that do not meet the treatment criteria for IV thrombolytics.

The type of mechanical thrombectomy was nonselective in these studies and were limited by the available resources at each clinical site. The two main types of mechanical thrombectomy were stent retrievers and aspiration. The focus of these studies was whether mechanical thrombectomy with IV thrombolytics would be more efficacious. Differences between the different types and models of machines would need to be studied further, which have only started to be examined in recent years as this technology becomes more widespread and accessible. Each study had their own sets of primary, secondary and even tertiary outcome measures and safety outcomes, however the ones examined here are 90-day functionality measured by the modified Rankin Scale = 0 to 2, and mortality at 90 days, respectively.

Table 2 demonstrates the validity assessment of each study in respect to assessing control of selection and performance bias, blinding of staff, time window for intervention, and intention to treat analysis.

In all the RCT studies, selection bias was eliminated due to the nature of having a computer program randomly assign eligible patients into treatment branches. In Cabral et al, this was not possible as it was a retrospective study, thus they selected patients for each treatment based on who fit their inclusion and exclusion criteria and which treatments they already had.

In all the studies examined, performance bias as controlled for through statistical analyses that controlled for patient factors such as age, comorbidities, sex etc. In all the studies these factors were controlled for and did not have a significant impact on the outcomes of the studies.

Due to the nature of the treatments, the clinical staff performing mechanical thrombectomies and administering IV thrombolytics were not blinded. However, data, analytic staff, radiologists, clinical surveyor staff were blinded to the patients and treatments in the data collection and analytical processes. Some studies like Khoury et al, had data blinded and reviewed by an Independent Data Safety Monitoring Board. While other studies, Saver et al Mocco et al, blinded radiologists to the patients' treatments. Bracard et al did not mention blinding staff or radiologists in their study therefore there was inadequate evidence to assess this factor for their study.

Time window for intervention, quantified as less than 6 hours, was deemed adequate if they IV thrombolytics with or without mechanical thrombectomy was used within 6 hours. All of the studies analyzed met this criterion.

Intention-to-treat analysis was performed in most studies. Cabral et al did not complete this as it was a retrospective analysis.

Table 3 shows a comparison of study results. Five out of the seven studies examined had significant results, showing a higher percentage of patients with 90-day functional independence in the combination treatment branches compared to those in the IV thrombolytic branch. Five

studies were suspended after the release of the MR CLEAN trial and therefore did not recruit their target number of patients for each treatment branch. Although, even at their early end points, many of the trails still had significant primary and secondary results. Only Mocco et al and Khoury et als' studies resulted in inconclusive data because of this factor. However, these studies were amassing data that trended towards the efficacious use of mechanical thrombectomy in the treatment of acute ischemic strokes. Therefore, the use of this combination of treatments is promising in the field of acute stroke management.

In examining the primary safety concern for these trials, most of them did not find a statistically significant difference in 90-day mortality between the two treatment groups. Therefore, the addition of mechanical thrombectomy in these patients did not add significant risk compared to those treated with just IV thrombolytics. Mocco et al, and Khoury et als' studies were inconclusive due to the early interruption of their trials.

Conclusion

Strokes are one of the leading causes of death and disability throughout the world, therefore further innovation in treatment is imperative to the health and wellbeing of millions around the world each year. Given the significant results of these studies demonstrating the benefits of combination therapy of IV thrombolytics and mechanical thrombectomy versus IV thrombolytics alone and the similar rates of mortality between the two treatment groups, it is worth discussing implementing this treatment into clinical practice. However, there are many limitations to consider before implementation, such as the financial resources and the need for highly trained practitioners and staff needed to effectively utilize this technology needed. Considering this, it may only be feasible to implement this treatment in specialized stroke centers at this time. However, the geographical range of the chosen article above, from Brazil, France,

Netherlands, United States, United Kingdom to Australia and New Zealand, gives hope that this technology will soon become more accessible as healthcare and technology evolves and become more widespread.

Additionally, mechanical thrombectomy has its limited uses as well. Chiefly it can only be used for large vessel occlusions, thus small vessel occlusions like lacunar stroke patients would not benefit from this approach. Further research would need to be done to address if and how mechanical thrombectomy could be used for small vessel strokes.

The patients in these studies were chosen chiefly based on clinical presentation, whether they had an ischemic stroke, if the clot burden was large enough to implement mechanical thrombectomy and if they were within the inclusion and exclusion criteria of IV thrombolytics. These criteria only apply to a very small portion of patients with ischemic strokes; therefore this limits the portion of patients this could be efficacious for. Another possible option for treatment of strokes could be using mechanical thrombectomy without IV thrombolytics for patients presenting past 4.5 hours or for those that do not fit the IV thrombolytics criteria. This treatment is currently being researched as well.

With the current data presented in these studies, combination therapy of IV thrombolytics plus mechanical thrombectomy does provide a greater 90-day functional independence rate in acute ischemic stroke patients than IV thrombolytics alone without increasing the risk of mortality.

References

1. Sacco RL, Kasner SE, Broderick JP, et al. An Updated Definition of Stroke for the 21st Century. *Stroke*. 2013;44(7):2064-2089. doi:10.1161/str.0b013e318296aeca.

2. Aghamiri H, Paybast S, Lima BS, Mansoori B. New Advances in Acute Ischemic Stroke Management: Review Article. *International Clinical Neuroscience Journal* . 2020;7(2):55-60. doi:10.34172/icnj.2020.02.

3. Avan A, Digaleh H, Napoli MD, et al. Socioeconomic status and stroke incidence, prevalence, mortality, and worldwide burden: an ecological analysis from the Global Burden of Disease Study 2017. *BMC Medicine* . 2019;17(191). doi:10.1186/s12916-019-1397-3.

4. Demaerschalk BM, Hwang H-M, Leung G. US Cost Burden of Ischemic Stroke: A Systematic Literature Review. *The American Journal of Managed Care*. 2010;16(7):525-533. https://www.ajmc.com/journals/issue/2010/2010-07-vol16-n07/ajmc_10demaerschalkburdn _525.

5. Tawil SE, Muir KW. Thrombolysis and thrombectomy for acute ischaemic stroke. *Clinical Medicine*. 2017;17(2):161-165. doi:10.7861/clinmedicine.17-2-161.

6. Fransen PS, Beumer D, Berkhemer OA, et al. MR CLEAN, a multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands: study protocol for a randomized controlled trial. *Trials*. 2014;15(343). doi:10.1186/1745-6215-15-343.

7. Evans MRB, White P, Cowley P, Werring DJ. Revolution in acute ischaemic stroke care: a practical guide to mechanical thrombectomy. *Practical Neurology*. 2017;17(4):252-265. doi:10.1136/practneurol-2017-001685.

8. Jadhav AP, Desai SM, Kenmuir CL, et al. Eligibility for Endovascular Trial Enrollment in the 6- to 24-Hour Time Window. *Stroke*. 2018;49(4):1015-1017. doi:10.1161/strokeaha.117.020273.

9. Bracard S, Ducrocq X, Mas JL, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *The Lancet Neurology* . 2016;15:1138-1147. doi:10.1016/S1474-4422(16)30177-6.z

10. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever Thrombectomy after Intravenous t-PA vs t-PA alone in Stroke. The New England Journal of Medicine. 2015;372:2285-2295 DOI: 10.1056/NEJMoa1415061

11. Mocco J, Zaidat OO, Kummer RV, et al. Aspiration Thrombectomy After Intravenous Alteplase Versus Intravenous Alteplase Alone. Stroke. 2016;47(9):2331-2338. doi:10.1161/strokeaha.116. 013372.

12. Khoury NN, Darsaut TE, Ghostine JY, et al. Endovascular thrombectomy and medical therapy versus medical therapy alone in acute stroke: A randomized care trial. Journal of Neuroradiology . 2017;44(3):198-202. Doi:https://dio.org/10.1016/j. neurad.2017.01.126.

13. Campbell BCV, Mitchell PJ, Kleinig TJ, et al. Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection. The New England Journal of Medicine. 2015;372:1009-1018. DOI: 10.1056/NEJMoa1414792

14. Muir KW, Ford GA, Messow CM, et al. Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. *J Neurol Neurosurg Psychiatry.* 2016;88:38-44. doi:10.1136/jnnp-2016-314117.

15. Cabral NL, Conforto A, Magalhaes PS, et al. Intravenous rtPA versus mechanical thrombectomy in acute ischemic stroke: A historical cohort in Joinville, Brazil. *eNeurologicalSci.* 2016;5:1-6. doi:10.1016/j.ensci.2016.04.002.

Appendix

Table 1: Comparison of study design. Combination treatment vs. IV thrombolytic

Study	Design	Total N (IVT/CT)	Occlusion site	Time window for intervention	Mechanical Thrombectomy Device Type	Primary Outcome Measure	Primary Safety Outcome
Bracard (THRACE)	RCT	412 (208/204)	ICA, MCA, Basilar A.	<5 hours from onset	Stent-retriever, Aspiration	mRS = 0-2 at 90 days	Morality at 90 days
Saver (SWIFT PRIME)	RCT	196 (98/98)	ICA, MCA	<6 hours from onset	Stent-retriever	mRS = 0-2 at 90 days	Morality at 90 days
Mocco (THERAPY)	RCT	108 (54/54)	ICA, MCA,	<4.5 hours from onset	Aspiration	mRS = 0-2 at 90 days	Morality at 90 days
Khoury (EASI)	RCT	77 (37/40)	ICA, MCA, Basilar A.	<5 hours from onset	Stent-retriever, Aspiration	mRS = 0-2 at 90 days	Morality at 90 days
Campbell (EXTEND-IA)	RCT	70 (35/35)	ICA, MCA	<6 hours from onset	Stent-retriever	mRS = 0-2 at 90 days	Morality at 90 days
Muir (PISTE)	RCT	65 (32/33)	ICA, MCA	<4.5 hours from onset	Stent-retriever, Aspiration	mRS = 0-2 at 90 days	Morality at 90 days
Cabral et al	RCS	113 (82/31)	ICA, MCA, Basilar A.	<6 hours from onset	Stent-retriever	mRS = 0-2 at 90 days	Morality at 90 days

Key: **THRACE**: THRombectomie des Artères CErebrales, **SWIFT PRIME:** Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment, **THERAPY:** The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke, **EASI**: Endovascular acute stroke intervention, **EXTEND-IA**: Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial, **PISTE**: Pragmatic Ischaemic Thrombectomy Evaluation, **RCT**: Randomized Control Trial, **RCS**: Retrospective Cohort Study, **CT**: Combination treatment) **IVT**: Intravenous therapy, **ICA**: Internal Carotid Artery, **MCA**: Middle Cerebral Artery, **rtPA**: recombinant tissue plasminogen activator, **NIHSS**: National Institutes of Health Stroke Scale, **mRS** = 0-2 at 90 days: modified Rankin Scale score of 0-2 at 90 days

Table 2: **Validity Assessment.** Combination treatment vs. IV thrombolytic

Study	Selection Bias	Performance Bias	Blinding	Time window for intervention (<6 hrs)	Intention to treat analysis
Bracard (THRACE)	A	A	I	A	A
Saver (SWIFT PRIME)	A	A	A	A	I
Mocco (THERAPY)	A	A	A	A	A
Khoury (EASI)	A	A	A	A	A
Campbell (EXTEND-IA)	A	A	A	A	A
Muir (PISTE)	A	A	A	A	A
Cabral et al	I	A	A	A	I

Key: **A**: Adequate, assessment/measure (ie. blinding, intention to treat analysis) was completed and used appropriately through the study, **I**: Inadequate evidence, assessment/measure was not completed or discussed in the study. **Selection Bias** is considered adequate if the study randomized patients as they were placed into their treatment groups. **Performance Bias** is adequate if patient factors (ie. comorbidities, age, sex) were adjusted for in the study's statistical analysis. **Blinding** is considered adequate if the study blinded the analysis process and/or data collection after treatment (ie. staff member was blinded to the treatment group when collecting the mRS score of the patients at 90 days). **Time window for intervention** is adequate it patients began treatment within 6 hours of symptoms onset. **Intention-to-treat analysis** is adequate if it was performed in each respective study.

Table 3: Comparison of Results. Combination treatment vs. IV thrombolytic

Study	IVT mRS = 0-2 at 90 days	Combination Treatment mRS = 0-2 at 90 days	IVT Mortality at 90 days (%)	Combination Mortality at 90 days (%)
Bracard (THRACE)	S	S	NS	NS
Saver (SWIFT PRIME)	S	S	NS	NS
Mocco (THERAPY)	I	I	I	I
Khoury (EASI)	I	I	I	I
Campbell (EXTEND-IA)	S	S	NS	NS
Muir (PISTE)	S	S	NS	NS
Cabral et al	S	S	NS	NS

Key: **IVT**: Intravenous therapy, **S**: Significant ($p<0.05$), **NS**: Not Significant ($p>0.05$), **I:** inconclusive due to interruption of trial