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DERLEME **REVIEW**

SHOULD WE GIVE OR NOT GIVE THROMBOLYTIC THERAPY BEFORE ENDOVASCULAR THERAPY?

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ABSTRACT

In acute ischemic stroke due to large vessel occlusion; endovascular interventions in which the clot is removed mechanically are gold standard treatments. According to the guidelines and the results of the studies carried out in previous years, current practice is; if the patient does not have contraindications, IV rtPA is initiated before endovascular treatment without loss of time. However, in recent years there is a tendency in the direction of taking patients directly into the angiography unit and randomized controlled studies comparing these two groups are gaining weight. For direct endovascular intervention of patients; results have also been obtained showing that it may not be worse than combined therapy in recent studies. In the light of current studies, it is not yet possible to make clear choices between both approaches. For this reason, it would be a more logical approach to consider each patient separately and to make the right choice on the basis of the patient.
Key Words: Acute ischemic stroke, endovascular therapy, thrombolytic therapy.

ENDOVASKÜLER TEDAVİ ÖNCESİNDE TROMBOLİTİK TEDAVİ VERELİM Mİ, VERMEYELİM Mİ?

ÖZET

Büyük damar oklüzyonunun neden olduğu akut iskemik inmede; pıhtının mekanik olarak çıkarıldığı endovasküler girişimler altın standart tedavilerdir. Önceki yıllarda yapılan çalışmaların sonuçlarına ve kılavuz bilgilerine göre günümüzdeki uygulama; eğer hastanın kontrendikasyonu yoksa zaman kaybına yol açmayacak şekilde endovasküler tedavi öncesinde IV rtPA başlanmasıdır. Ancak son yıllarda hastaların direkt anjiyografi ünitesine alınması yönünde eğilimler olup bu iki grubun karşılaştırıldığı randomize kontrollü çalışmalar ağırlık kazanmaktadır. Son çalışmalar içerisinde hastaların direkt olarak endovasküler müdahaleye alınmasının; kombine tedaviden daha kötü olmayabileceğini gösteren sonuçlar da elde edilmiştir. Mevcut çalışmalar ışığında henüz her iki yaklaşım arasında kesin seçimler yapmak mümkün değildir. Bu nedenle her hastayı ayrı ayrı ele alıp hasta bazında en doğru seçimi yapmak daha mantıklı bir yaklaşım olacaktır.
Anahtar Sözcükler: Akut iskemik inme, endovasküler tedavi, trombolitik tedavi.

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INTRODUCTION

Stroke is the leading cause of morbidity and the second leading cause of death in all populations. Every year, approximately 2.8 million people worldwide die as a result of an ischemic stroke. For this reason, it remains a significant public health problem today (1). In recent years, reperfusion therapies such as intravenous/intraarterial thrombolytic agents and endovascular therapy (EVT) are widely used as effective and safe methods in the treatment of ischemic stroke (2). Although the benefit of intravenous recombinant tissue-type plasminogen activator (IV rtPA) has been proven definitively in acute ischemic stroke patients consulted within the first 4.5 hours, acceptable reperfusion success is low in cases with large vessel occlusion (LVO)(3). For example; the reperfusion rate in terminal internal carotid artery occlusion is 6% (4).

The benefit and additional risk of using IV rtPA with EVT for acute ischemic stroke patients with large vessel occlusion remain unknown.

Our aim is to address the benefits and drawbacks of IV rtPA given before EVT in patients with acute ischemic stroke caused by LVO based on current literature evidence.

A CLOSE HISTORY OF ACUTE ISCHEMIC STROKE TREATMENT

What We Know About Thrombolytic Therapy

Following the publication of the NINDS (National Institute of Neurological Disorders and Stroke) report in 1995, systemic thrombolytic therapy using IV rtPA in the treatment of acute ischemic stroke became the gold standard procedure (5). However, due to its implementation within a narrow window, ineffectiveness in reducing mortality, and low effect on LVO, a more efficient treatment was needed (32-35%). The EMS (Emergency Management of Stroke) study was published in 1999 and the IMS II (Interventional Management of Stroke) study in 2007, and successful clinical results were obtained with IV rtPA (6,7).

There are many studies supporting IV rtPA before endovascular treatment. In a study conducted by the HERMES collaborative group and comparing pooled data from five LVO index studies (MR CLEAN, ESCAPE, REVASCAT, EXTEND IA, SWIFT PRIME), the beneficial effect of tPA (mRS 0–1) was demonstrated in just 12.9 percent of stroke patients with LVO (8). A meta-analysis of 13 studies involving 1561 patients with large vessel occlusion found that after IV rtPA but before mechanical thrombectomy, 7% of patients with tandem lesions and 17% of those without tandem lesions had reperfusion (9). In the post-hoc analysis of ASTER randomized study, which included three hundred and eighty-one patients; The patients who underwent mechanical thrombectomy with 250 IV rtPA were compared with 131 patients who had only mechanical thrombectomy, and no difference was found between the 90th-day outcomes, reperfusion rates, 24th-hour NIHSS scores, and symptomatic intracerebral bleeding rates, however, mortality was found to be lower in the group receiving IV rtPA (10). Prospective, observational in a cohort of 485 patients; 348 patients who received IV rtPA and mechanical thrombectomy were compared with 137 patients treated with only mechanical thrombectomy, and success was reported as 35% in the combined therapy group and 22% in the mechanical thrombectomy group. In the same research, the low mortality rate in 3 months was shown as 14% in combined therapy and 32% in mechanical thrombectomy; It has been reported that successful reperfusion (Thrombolysis in Cerebral Infarction scale 2b-3) is superior to combined therapy, and there is no difference between the groups in terms of hemorrhagic complications (11).

In contrast to all of this data, there are also studies reporting the disadvantages of IV rtPA before endovascular treatment. In a 2010 analysis of the Calgary stroke program's computed tomography angiogram database, recanalization rates in large vessel occlusions with IV rtPA; 4.4% for the distal internal carotid artery, 32.3% for the middle cerebral artery M1 segment, 30.8% for the middle cerebral artery M2 segment, and 4% for the basilar artery (12). In a single-center retrospective study, 90 consecutive patients, 64 of whom were within the first 4.5-hour window, were compared as receiving endovascular treatment only (n=52) and receiving IV rtPA plus endovascular therapy (n=38); No difference was found in demographic characteristics, stroke severity, clot distribution, bleeding, mortality,

length of hospital stay, or clinical outcomes, but direct costs were significantly higher in those who received IV rtPA (13).

What We Know About Endovascular Treatment

Endovascular treatment is the mechanical removal or dissolution of a clot (aspiration, retrriever stents) in acute ischemic stroke caused by a large vessel occlusion.

Due to the limitations of thrombolytic therapy, IMS-3 (The Interventional Management of Stroke), MR RESCUE (Mechanical Retrieval and REcanalization of Stroke Clots Using Embolectomy), SYNTHESIS Expansion randomized controlled studies were published in 2013 and the superiority of EVT over thrombolytic therapy could not be demonstrated in these studies (14-16). In these three studies in literature published in two thousand and fourteen; It has been reported that negative results related to EVT may be associated with inadequate imaging, use of older generation thrombectomy devices, and delayed recanalization times (17).

However, studies published in 2014 and 2015 brought positive developments in terms of EVT. With the MR CLEAN (Multicenter Randomized Clinical trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) study and the ESCAPE (EndovascularTreatment for Small Core and Proximal Occlusion Ischemic Stroke), EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial), REVASCAT (Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours) and SWIFT PRIME (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment) studies published immediately after, EVT has been proven to be effective and reliable in acute ischemic stroke patients with proximal artery occlusion and has become the gold standard treatment method (18-22). In patients with acute ischemic stroke due to large vessel occlusion, in selected patients in the AHA/ASA guideline (A Guideline for Healthcare Professionals From the American Heart Association / American Stroke Association), EVT is recommended as class I, level of evidence A (2).

In these randomized controlled studies, in the first 6 hours, the combined application of thrombolytic therapy and EVT in anterior system LVOs were shown to be superior to standard thrombolytic therapy alone in the first 6 hours (18).

What We Know About Bridging Therapy

In patients presenting with acute ischemic stroke who are eligible for thrombolytic therapy, the initiation of thrombolytic therapy first and then taking the patient into EVT is called bridging therapy. In addition to the positive effects of IV rtPA administration prior to endovascular intervention, such as early reperfusion, rupture of distal emboli, improved microvascular reperfusion, and impact on thrombi that are not reachable with mechanical instruments, it is believed to have negative effects, such as an increased risk of bleeding and a delay in initiation of endovascular intervention thrombus rupture, distal embolism, blood-brain barrier disruption (23-25). Advantages and disadvantages of bridging treatment over direct EVT are summarized in the Figure.

The negative outcome of the IMS III trial, which examined the delivery of intravenous thrombolytic therapy alone or with bridging EVT in a large-scale randomized series, raised questions about the future of this treatment option in the first place (26).

While it was observed that 100% of the patients included in the EXTEND-IA, SWIFT PRIME, THRACE, and THERAPY studies received IV rtPA; t was observed that 87% of patients in the EVT group in the MR CLEAN study, 68% in the REVASCAT study and 73% in the ESCAPE study received IV rtPA before the procedure. In this context, IV r-tPA should be administered to every patient who has no contraindications in line with the current acute ischemic stroke treatment principles, and appropriate patients should be directed to EVT. Current guidelines also recommend giving IV rtPA prior to EVT in patients eligible for thrombolytic therapy (2).

Studies that are aimed at improving the effectiveness of endovascular therapy and assessing each stage that may affect patients' positive outcomes have started to appear in the literature in recent years. SWIFT and STAR studies; These are two important prospective studies showing the effectiveness of EVT. In the year two thousand and seventeen, post-hoc analysis of patients who underwent only EVT and

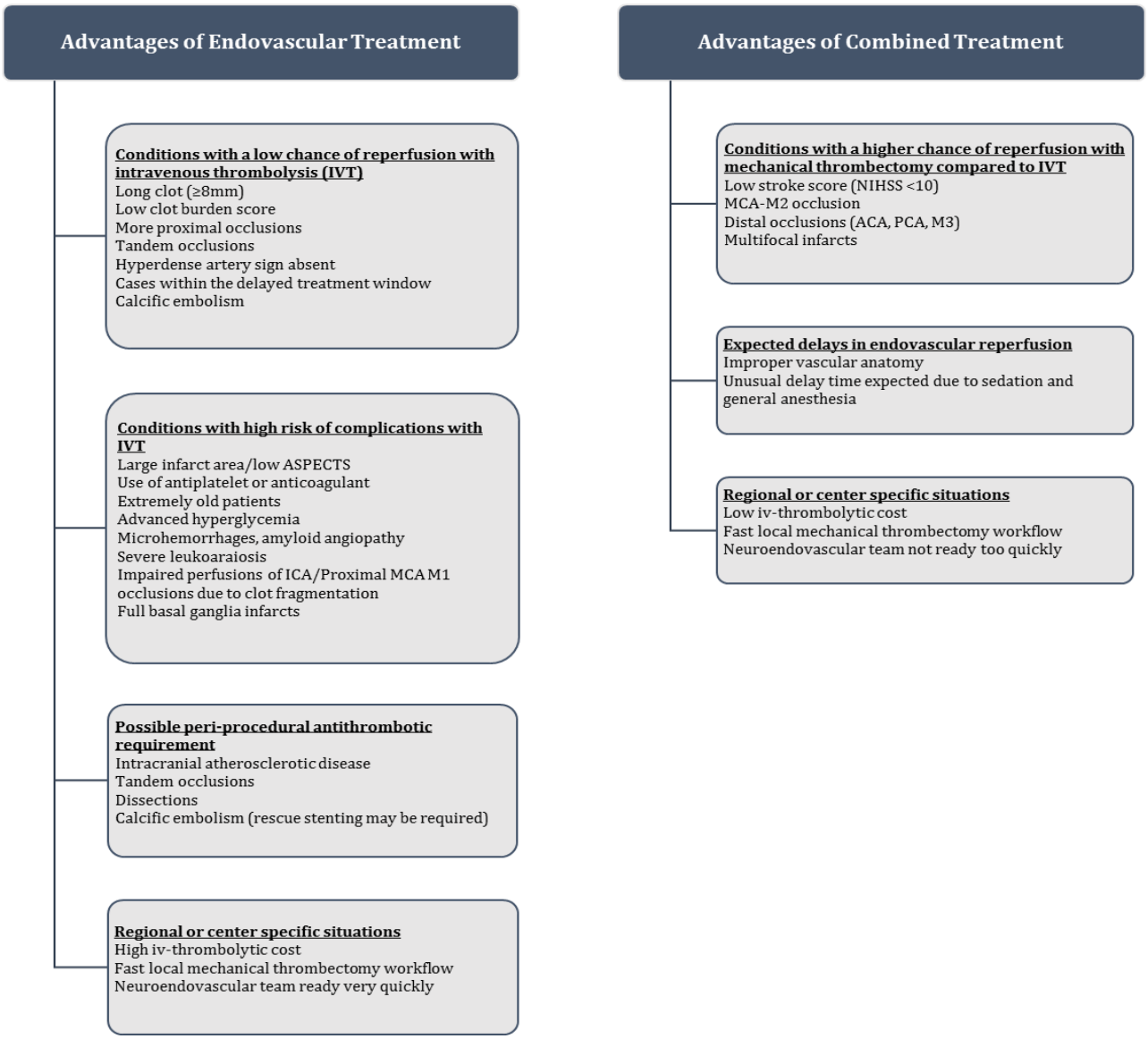

Figure. Endovascular treatment and advantages of combined therapy (27).

those who were applied to EVT after IV rtPA in these 2 studies were performed (28). In this analysis, 291 patients who underwent EVT were examined (160 patients in the combined group, 131 patients in the EVT group only). There was no substantial difference between the two groups in terms of symptom-inguinal time, number of procedures, successful recanalization, functional independence at 90th days, mortality within 90 days, symptomatic bleeding, and collateral embolism. As a result, it was commented that IV rtPA administration prior to EVT provided no clinical benefit.

The first meta-analysis was published by Phan et al. in 2017, with the increase in studies that compared patients who were taken to EVT directly and patients who were taken to EVT after IV rtPA before (4). In this meta-analysis, 12 studies with a total of 2615 patients were analyzed, and it was discovered that there was no substantial difference between the two groups in functional outcome, mortality within 90 days, symptomatic intracranial bleeding, and all other complications. While there were no statistically significant differences between the two groups, it was also noted that there was a trend in favor of good

clinical outcomes in the group receiving the combined therapy. In another meta-analysis published in 2018, in which five studies were examined, a total of 457 patients were examined (204 patients in the combined group, 253 patients only in the EVT group), and no difference was found between the groups between mortality and symptomatic bleeding. Although not statistically significant, a more positive trend was observed in the combined group in successful recanalization and good clinical outcomes at 3 months (29).

The majority of research and meta-analyses performed to date have been observational, with only a few randomized controlled trials examining the disparity between the two groups. The fact that IV rtPA is contraindicated (delayed duration, new surgery, high pre-stroke mRS score, bleeding disorders, comorbidity) among patients in the direct endovascular group is a significant factor influencing the findings in most studies. Patients with contraindications for thrombolytic therapy were not included in the DIRECT-MT (Direct Intraarterial Thrombectomy in Order to Revascularize Acute Ischemic Stroke Patients with Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals: a Multicenter Randomized Clinical Trial) study, and a total of 656 patients were randomized and was viewed as. The primary endpoint of the study was determined to be the mRS of 90th day, and statistical analysis revealed that the group that received direct EVT alone did not perform worse than the combined group.

Mortality within ninety days; While it was 17.7% in the group with endovascular intervention alone, it was 18.8% in the group treated with combined therapy. In the first angiographic imaging performed before the thrombectomy procedure, successful reperfusion was achieved at a rate of 2.4% in the direct endovascular intervention group, while this rate increased to 7.2% in the combined group in which IV rtPA was administered before. The combined group also had a higher rate of successful reperfusion after the procedure (84.5% - 79.4%). It was observed that the results were similar between the two groups for serious side effects, symptomatic and asymptomatic intracerebral hemorrhage during 90 days of follow-up. Similar results of EVT alone with combined treatment in terms of functional outcome were reported in the DIRECT-MT study (30).

35 studies (9117 patients) were evaluated in the latest meta-analysis published by Vidale et al. In March 2020 (31). There was no difference in gender, hypertension, diabetes mellitus, or arrival NIHSS between the two groups included in the analysis, but the combined treatment group had a higher age (69.5-68.7, p:0.013) and less concomitant atrial fibrillation (32-37.2, p<0.001) and shorter symptom-groin period (234-273, p0.001). The primary endpoint was functional independence on day 90 (patients with mRS<3 on the 90th day); it was observed that the group that obtained endovascular treatment after IV rtPA administration outperformed the group that received direct EVT (OR 1.44, 95% Cl 1.22-1.69, p0.001, p heterogeneity 0.001). In terms of successful recanalization rates, there was no significant difference between the two groups when only randomized controlled trials and observational retrospective studies were investigated; when observational prospective studies were reviewed, it was observed that the group treated with combined therapy had a higher rate of successful recanalization (OR 1.47; 95 % CI 1.16-1.87, p<0.01). While mortality rates within 90 days were higher in the direct EVT group (OR 1.38; 95% CI 1.09-1.75), there was no difference between the groups in symptomatic intracranial bleeding. As a result; despite the limited number of randomized controlled trials included in the meta-analysis is small, lower mortality and better clinical outcomes were found in the group of patients treated with combined therapy.

In the SKIP study published in January 2021; a total of 204 patients from 23 stroke centers in Japan were included in the study (32). All patients who presented within the first 4.5 hours and were qualified for IV rtPA were chosen. Alteplase treatment was given at 0.6 mg/kg. When the mRS 0-2 rates in the patient groups receiving direct EVT and combined therapy were compared at 3 months, the findings were found to be statistically similar (59.4%, 57.3%, respectively). There was also no significant difference in successful recanalization rates and mortality rates within 90 days between the two groups. Although any intracranial bleeding that occurred within 36 hours was more frequent in the combined therapy community (50% - 33.7%, p:0.02); there was no statistically significant difference in symptomatic intracranial bleeding rates (7%- 5.9%, p:0.78).

Another randomized controlled study published is the DEVT study (33). This study, like the SKIP study, was founded on the hypothesis that direct EVT has a similar impact to combined therapy. A total of 234 patients eligible for both IV rtPA (0.9 mg/kg) and EVT were included in the study from 33 stroke centers in China. Although 970 patients were scheduled to be included in this study, the study was terminated early due to efficiency was shown in the first interim analysis. After 90 days of follow-up, functional independence was observed with a rate of 54.3% in the group of patients who were taken directly to EVT, while this rate was found to be 46.6% in the group that received the endovascular intervention after IV rtPA (p:0.03 for noninferiority). There was no significant difference between the two groups in terms of symptomatic intracranial bleeding within 48 hours (6.1%- 6.8%) or mortality within 90 days (17.2%- 17.8%).

A very short time ago, the results of two more major studies were announced at the International Stroke Conference held online in March 2021. The first of these is the SHRINE (The Systemic Thrombolytic Randomization in Endovascular Stroke Therapy) analysis (34-35). Pool analysis was performed with the data of SKIP (Japan) and DEVT (China) study patients performed in the Asian population, and the noninferiority of direct EVT to combined therapy was investigated in patients with acute anterior circulation stroke eligible for IVT. Except for the doses of alteplase (SKIP: 0.6 mg/kg, DEVT: 0.9 mg/kg), the pool review of these studies whose designs are very close to each other; the primary outcome was functional independence at day 90 (mRS 0-2) with a noninferiority border of 0.85. This rate was 56.7% in the group of 217 patients who underwent direct EVT, 51.6% in the combined treatment group consisting of 221 patients, and noninferiority could not be demonstrated (OR 1.23 0.84-1.79) (p = 0.29).

The second study whose results are highly anticipated was MR CLEAN NO IV (36-37). Unlike the related DIRECT-MT analysis, it was performed in European centers (Netherlands, Belgium, and France) rather than Asia, and the primary outcome was determined as the superiority of direct EVT rather than the noninferiority of combined treatment. The superiority of direct EVT could not be shown in the primary result, 90th-day mRS change analyses, in this study, which involved 540 patients from the Western population who were eligible for both IVT and EVT (OR, 0.88 95% CI 0.65-1.19). Interestingly, when the groups were compared in terms of any hemorrhagic outcome, no significant difference was observed in the safety results, which suggests that the bleeding may be due to recanalization, not directly due to tPA.

In light of the guidelines, the majority of recent studies were performed on patients who were taken to EVT following IV rtPA if there were no contraindications. In some of the studies, the patient group who received direct endovascular intervention without IV rtPA; patients for whom thrombolytic therapy is contraindicated due to comorbidity, new surgery, bleeding disorder, or time delay, and this affects the findings between the two classes. The DIRECT-MT, DEVT, SKIP, and MR CLEAN NO IV trials, on the other hand, have given a new perspective on the use of IV rtPA in patients who are eligible for EVT for acute ischemic stroke due to large vessel occlusion. These 4 studies are summarized in the Table. Results showed that admitting patients directly to the angiography unit was similar to combined treatment results. Although the suggestions arguing that patients can be taken to EVT directly without IV rtPA gain strength, it is not possible to separate these recommendations with sharp lines. The best option would be to treat each patient separately and make a decision based on the profit-loss ratio. In cases where the patient's referral to the angiography unit may be delayed, or in cases where the patient may be referred to an advanced stroke center from a center where no intervention can be rendered, it may be appropriate to continue preparations by starting IV rtPA. On the contrary, we believe that in an M1 occlusion of the middle cerebral artery that can be taken to an angiography unit without wasting time, the patient can be taken directly to the angiography unit without waiting for IV rtPA to start. The fact that these studies were carried out in Japan and China, i.e. in Asian populations where intracranial atherosclerosis is more prevalent, raises questions about applying the findings to the western population. Therefore, more studies including the western population are needed. Alteplase was used as an IV rtPA agent in the studies and a period of 1 hour is required as the application procedure of alteplase. Patients were compared with alteplase and tenecteplase before

Table. Summary of randomized clinical studies.

Study	Primary end goal	Characteristic	MT (n)	IVT + MT (n)	Primary end outcome
SKIP (32)	• Positive functional independence 90th day after stroke [mRS (0-2)] • Noninferiority target Odds ratio: 0.74	• Japan • Multicenter (23 centers) • (January 1, 2017 - July 31, 2019) • 18-85 years of age • ICA or MCA-M1 LVO (BT-A, MR-A) • IVT: (0.6 mg/kg) alteplase	101	103	• Odds: 1.09 • P=0.18 for noninferiority
	Primary end outcome (90th day mRS 0-2)		59 (57.3%)	60 (59.4%)	
DEVT (33)	• Positive functional independence 90th day after stroke [mRS (0-2)] • Noninferiority target Odds ratio: -10%	• China • Multicenter (33 centers) • (May 20, 2018 - May 02, 2020) • ≥18 years of age • Proximal anterior circulation LVO within the first 4.5 hours and patients eligible for IVT	116	118	• Odds: 1.36 • Odds (correcteda): 1.48 • P=0.003 for noninferiority
	Primary end outcome (90th day mRS 0-2)		63 (54.3%)	55 (46.6%)	
DIRECT-MT (30)	• 90th day mRS after stroke • Noninferiority target Odds ratio: 0.8	• China • Multicenter (41 centers) • (March 18, 2018 - October 19, 2019) • ≥18 years of age • ICA and/or MCA-M1/M2 proximal LVO (BT-A), patients admitted within the first 4.5 hours and eligible for IV-tPA • NIHSS ≥2 • IVT: (0.9 mg/kg) alteplase	326	328	• Common Odds ratio: 1.07 (0.81 - 1.40) • P=0.04 for noninferiority
	Primary end outcome (90th day mRS) Median (IQR)		3 (2-5)	3 (2-5)	
MR CLEAN NO IV (36-37)	• 90th day mRS after stroke	• Netherlands, Belgium, and France • Multicenter (20 centers) • ≥18 years of age • ICA and/or MCA-M1/M2 proximal LVO (BT-A), patients admitted within the first 4.5 hours and eligible for IV-tPA • NIHSS ≥2 • IVT: (0.9 mg/kg) alteplase		540	• Odds: 0.88 (95% CI 0.65-1.19) • Superiority could not be demonstrated
	Primary end outcome (90th day mRS 0-2)				

[a]Adjusted for age, Admission NIHSS (National Institutes of Health Stroke Scale), ASPECTS (Alberta Stroke Program Early CT Score), Occlusion side, Baseline-Randomization time values
Abbreviations: MTMechanical thrombectomy, IVTIntravenous thrombolysis ICA: Internal Carotid Artery MCA: Middle Cerebral Artery LVO: Great Vessel Occlusion, mRS: modified Rankin Score, SKIP: The Randomized Study of EVT With Versus Without Intravenous Recombinant Tissue-Type Plasminogen Activator in Acute Stroke With ICA and M1 Occlusion, DEVT: Effect of Endovascular Treatment Alone vs Intravenous Alteplase Plus Endovascular Treatment on Functional Independence in Patients With Acute Ischemic Stroke The DEVT Randomized Clinical Trial, DIRECT-MT: Endovascular Thrombectomy with or without Intravenous Alteplase in Acute Stroke, MR CLEAN NOTE IV: Intravenous Thrombolysis Followed by Endovascular Thrombectomy versus Direct Endovascular Thrombectomy.

endovascular intervention in the EXTEND-IA TNK study, and the reperfusion rate in the tenecteplase group was found to be 2-fold higher (22% - 10%, p: 0.002). With the increase in the use of tenecteplase due to its effectiveness and its short duration, studies, and guideline recommendations will probably reshape, and combined treatment recommendations will perhaps gain weight (ClinicalTrials.gov (# NCT02937194)) (38).

Randomized controlled trials (SWIFT DIRECT "NCT03192332," DIRECT-SAFE "NCT034949201") would be more influential in determining the clinical approach.

CONCUSION

The aim in the treatment of acute ischemic stroke is to quickly and completely open the blocked vessel. Because successful recanalization

directly affects the clinical outcome. When all literature data are examined, the majority of researches and guidelines in previous years indicate that initiating thrombolytic therapy in eligible patients before EVT improves the outcome. However, recent research has shown that putting patients straight into EVT is not a very wrong practice and does not result in major changes in outcomes. However, data are not yet sufficient to make definitive recommendations. When making a decision, we believe that considering each patient separately in light of current studies and making a decision based on the suitability of the conditions is the best approach.

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. Circulation 2015; 131(4): e29-e322.
2. Powers WJ, Rabinstein AA, Ackerson T, 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 Association. Stroke 2019; 50(12): e344-e418.
3. Mazighi M, Serfaty J-M, Labreuche J, et al. Comparison of intravenous alteplase with a combined intravenous–endovascular approach in patients with stroke and confirmed arterial occlusion (RECANALISE study): a prospective cohort study. The Lancet Neurology 2009; 8(9): 802-809.
4. Phan K, Dmytriw AA, Maingard J, et al. Endovascular thrombectomy alone versus combined with intravenous thrombolysis. World neurosurgery 2017; 108: 850-858. e2.
5. Disorders NIoN, Group Sr-PSS. Tissue plasminogen activator for acute ischemic stroke. New England Journal of Medicine 1995; 333(24): 1581-1588.
6. Lewandowski CA, Frankel M, Tomsick TA, et al. Combined intravenous and intra-arterial r-TPA versus intra-arterial therapy of acute ischemic stroke: Emergency Management of Stroke (EMS) Bridging Trial. Stroke 1999; 30(12): 2598-2605.
7. Investigators IIT. The interventional management of stroke (IMS) II study. Stroke 2007; 38(7): 2127-2135.
8. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet North Am Ed 2016; 387(10029): 1723-1731.
9. Tsivgoulis GAH, Schellinger PD, Kohrmann M, et al. Successful reperfusion with intravenous thrombolysis preceding mechanical thrombectomy in large-vessel occlusions. Stroke 2018; 49(1): 232-235.
10. Gariel F, Lapergue B, Bourcier R, et al. Mechanical thrombectomy outcomes with or without intravenous thrombolysis. Stroke 2018; 49(10): 2383-2390.
11. Ferrigno M, Bricout N, Leys D, et al. Intravenous recombinant Tissue-Type plasminogen activator. Stroke 2018; 49(6): 1377-1385.
12. Bhatia R, Hill MD, Shobha N, 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(10): 2254-2258.
13. Rai AT, Boo S, Buseman C, et al. Intravenous thrombolysis before endovascular therapy for large vessel strokes can lead to significantly higher hospital costs without improving outcomes. J Neurointerv Surg 2018; 10(1): 17-21.
14. Broderick JP, Palesch YY, Demchuk AM, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. New England Journal of Medicine 2013; 368(10): 893-903.
15. Kidwell CS, Jahan R, Gornbein J, et al. A trial of imaging selection and endovascular treatment for ischemic stroke. New England Journal of Medicine 2013; 368(10): 914-923.
16. Ciccone A, Valvassori L, Nichelatti M, et al. Endovascular treatment for acute ischemic stroke. N Engl J Med 2013; 368: 904-913.
17. Qureshi AI, Abd-Allah F, Aleu A, et al. Endovascular treatment for acute ischemic stroke patients: implications and interpretation of IMS III, MR RESCUE, and SYNTHESIS EXPANSION trials: a report from the Working Group of International Congress of Interventional Neurology. Journal of vascular and interventional neurology 2014; 7(1): 56.
18. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015; 372: 11-20.
19. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. New England Journal of Medicine 2015; 372(11): 1019-1030.
20. Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. New England Journal of Medicine 2015; 372(11): 1009-1018.
21. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. New England Journal of Medicine 2015; 372(24): 2296-2306.
22. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. New England Journal of Medicine 2015; 372(24): 2285-2295.
23. Desilles J-P, Loyau S, Syvannarath V, et al. Alteplase reduces downstream microvascular thrombosis and improves the benefit of large artery recanalization in stroke. Stroke 2015; 46(11): 3241-3248.
24. Fischer U, Kaesmacher J, Mendes Pereira V, et al. Direct mechanical thrombectomy versus combined intravenous and mechanical thrombectomy in large-artery anterior circulation stroke: a topical review. Stroke 2017; 48(10): 2912-2918.
25. Flint AC, Avins AL, Eaton A, et al. Risk of distal embolization from tPA (tissue-type plasminogen activator) administration prior to endovascular stroke treatment. Stroke 2020; 51(9): 2697-2704.
26. Khatri P, Yeatts SD, Mazighi M, et al. Time to angiographic reperfusion and clinical outcome after acute ischaemic stroke: an analysis of data from the Interventional Management of Stroke (IMS III) phase 3 trial. The Lancet Neurology 2014; 13(6): 567-574.
27. Nogueira RG, Tsivgoulis G. Large vessel occlusion strokes after the DIRECT-MT and SKIP trials: is the alteplase syringe half empty or half full? Stroke 2020; 51(10): 3182-3186.

28. Coutinho JM, Liebeskind DS, Slater L-A, et al. Combined intravenous thrombolysis and thrombectomy vs thrombectomy alone for acute ischemic stroke: a pooled analysis of the SWIFT and STAR studies. JAMA neurology 2017; 74(3): 268-274.
29. Kim CH, Jeon JP, Kim S-E, et al. Endovascular treatment with intravenous thrombolysis versus endovascular treatment alone for acute anterior circulation stroke: a meta-analysis of observational studies. Journal of Korean Neurosurgical Society 2018; 61(4): 467.
30. Yang P, Zhang Y, Zhang L, et al. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. New England Journal of Medicine 2020; 382(21): 1981-1993.
31. Vidale S, Romoli M, Consoli D, et al. Bridging versus direct mechanical thrombectomy in acute ischemic stroke: a subgroup pooled meta-analysis for time of intervention, eligibility, and study design. Cerebrovascular Diseases 2020; 49(2): 223-232.
32. Suzuki K, Matsumaru Y, Takeuchi M, et al. Effect of mechanical thrombectomy without vs with intravenous thrombolysis on functional outcome among patients with acute ischemic stroke: the SKIP randomized clinical trial. JAMA 2021; 325(3): 244-253.
33. Zi W, Qiu Z, Li F, et al. Effect of endovascular treatment alone vs intravenous alteplase plus endovascular treatment on functional independence in patients with acute ischemic stroke: the DEVT randomized clinical trial. JAMA 2021; 325(3): 234-243.
34. https://eventpilotadmin.com/web/page.php?page=IntHtml&project=ISC21&id=135
35. https://www.medscape.com/viewarticle/947987#vp_2
36. https://eventpilotadmin.com/web/page.php?page=IntHtml&project=ISC21&id=398
37. https://www.medscape.com/viewarticle/947774?src=soctw 210323 mscpedt news mdscp endovasculartreatment&faf=1
38. Campbell BC, Mitchell PJ, Churilov L, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. New England Journal of Medicine 2018; 378(17): 1573-1582.

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