Key Recent Papers in Acute Ischemic Stroke/ Large Vessel Occlusion

An overview of significant stroke and neurointerventional articles published in recent literature and summaries on their impact on the field.

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Endovascular treatment for stroke is a rapidly evolving landscape, with the publication of many new studies and trials in the past year. This article highlights five acute ischemic stroke/large vessel occlusion (LVO) studies and provides a summary of their findings and contribution to the greater stroke literature.

Noncontrast Computed Tomography vs Computed Tomography Perfusion or Magnetic Resonance Imaging Selection in Late Presentation of Stroke With Large-Vessel Occlusion (CLEAR Study)

Nguyen TN, Abdalkader M, Nagel S, et al. JAMA Neurol. 2022;79:22-31. doi: 10.1001/jamaneurol.2021.4082

SUMMARY

CLEAR is a multicenter retrospective study that examined different imaging modalities to select patients with LVO for treatment with mechanical thrombectomy (MT) in the extended window. The study included 1,530 patients across 15 sites and five countries. Patients who were included presented with a vessel occlusion in the internal carotid artery (ICA) or proximal middle cerebral artery (M1/M2 segments), a National Institutes of Health Stroke Scale (NIHSS) score ≥ 6, a prestroke modified Rankin Scale (mRS) of 0 to 2, and a time last seen well of 6 to 24 hours. Patients were categorized by imaging modality performed prior to treatment, which included noncontrast CT (NCCT) with CTA, CT perfusion (CTP), or MRI. The primary endpoint was the distribution of mRS score at 90 days.

Baseline factors were in favor of advanced imaging groups, with the NCCT group having higher presenting NIHSS; higher rates of hypertension, atrial fibrillation, and ICA occlusions; and presenting more frequently as transfers. Rates of intravenous (IV) thrombolysis were most common in MRI, followed by NCCT and then CTP. The median ASPECTS (Alberta Stroke Program Early CT Score) was 8 (IQR, 7-9) across the three groups. Shorter door-to-puncture times were observed for NCCT (median [IQR], 76 [50-107] min) compared with CTP (93 [72-118] min) and MRI (98 [78-135] min; $P < .001$).

Successful reperfusion, defined as modified treatment in cerebral infarction (mTICI) 2b or 3, was more common in the NCCT (88.9%) and CTP groups (89.5%) as compared with the MRI group (78.9%; $P < .001$). There

was no difference in 90-day ordinal mRS shift after adjusting for prespecified variables. The probability of an mRS of 0 to 2 at 90 days was similar between the NCCT, CTP, and MRI groups. Symptomatic intracranial hemorrhage (sICH) and mortality were similar across all groups.

IMPORTANCE OF FINDINGS

This study supports the notion that NCCT and CTA alone are comparable with advanced imaging (MRI or CTP) in selecting patients for MT in the late window. A potential concern in selecting patients with NCCT only in the late window is a possible increased risk of sICH due to a less conspicuous visualization or understanding of the precise boundaries of a patient's core/penumbra. However, functional outcomes in this study were similar when comparing NCCT to MRI/CTP. Safety outcomes also did not differ across groups.

The benefits of a simpler acute stroke imaging workflow could be of importance. Simplifying acute stroke imaging will increase access to MT. Advanced imaging with CTP or MRI has been thought to be critical in selecting the patients for clinical trials who would be most likely to benefit to prove that MT is a beneficial intervention in an advanced time window. However, this approach may risk overselecting patients in a real-world setting because the goal of imaging should be to identify patients who may benefit, not to only select patients with the highest chance of benefiting. Additionally, access to acute MRI or CTP is not available 24/7/365 in many stroke centers in the United States (particularly primary stroke centers) or globally, thus limiting access to MT. This paper supports a paradigm where only NCCT is required. Lastly, a simpler imaging paradigm allows for a faster workflow, with potential neuronal and cost savings.

Effect of Intra-Arterial Alteplase vs Placebo Following Successful Thrombectomy on Functional Outcomes in Patients With Large Vessel Occlusion Acute Ischemic Stroke: The CHOICE Randomized Clinical Trial

Renú A, Millán M, San Román L, et al; CHOICE Investigators. JAMA. 2022;327:826-835. doi: 10.1001/jama.2022.1645

SUMMARY

The CHOICE trial is a phase 2b, randomized, double-blind, placebo-controlled trial that looked at the efficacy of intra-arterial alteplase as an adjunctive therapy to MT. This study included 113 patients across seven stroke centers in Catalonia, Spain. Patients were included if they had an LVO in the anterior, middle, or posterior cerebral artery and MT resulted in successful recanalization, defined as ≥ 50% reperfusion. Patients were then randomly assigned to intra-arterial alteplase (0.225 mg/kg with maximum dose of 22.5 mg) or placebo infused after MT. The primary efficacy outcome was the proportion of patients with mRS of 0 to 1 at 90 days after adjusting for IV thrombolysis. Secondary efficacy outcomes included the proportion of patients with improved angiographic findings, an ordinal shift of mRS scores at 90 days, final expansion ratio of final infarct to initial ischemic tissue volume, infarct expansion ratio > 1, and infarction volume at 24 to 48 hours after stroke onset. Tertiary efficacy outcomes included Barthel Index of 95 to 100 at 90 days, proportion of ischemic worsening, and EQ-5D-3L at 90 days. Notably, the trial was stopped early due to limitation of placebo supply in the setting of COVID-19 and slow recruitment.

Baseline characteristics were similar between the two groups, including median ASPECTS, which was 9 and 10 in the alteplase and placebo groups, respectively. Forty-four percent of patients who received intra-arterial alteplase also had complete or near-complete reperfusion prior to infusion. The favorable outcome of an mRS score of 0 to 1 was achieved more often in the treatment group compared to the control group (adjusted risk difference, 18.4%; 95% CI, 0.3%-36.4%; $P = .047$). There were no differences in any of the secondary or tertiary outcome measures. There were also no differences in the safety measures, including sICH, evidence of hemorrhage on imaging, or mortality at 90 days.

IMPORTANCE OF FINDINGS

Despite high rates of successful revascularization in MT for stroke, a large proportion of patients still experience significant disability or mortality. The no-reflow phenomenon has been proposed as a possible explana-

tion, where revascularization of the large arteries during MT does not necessarily result in reperfusion of the microcirculatory system, thus leading to poorer outcomes. A similar phenomenon is seen in percutaneous coronary intervention in cardiology. Although the small sample size and early termination of the trial may limit the conclusion of the study, results of this trial suggest that intra-arterial thrombolysis may impact microcirculation in patients and result in better outcomes without increased rates of hemorrhage. The generalizability of safety to patients with larger cores is limited due to high pretreatment ASPECTS. Intra-arterial thrombolysis may also continue to exert an effect with any distal thrombi in patients with residual distal territory clot (ie, TICI 2b reperfusion). Although the trial will need to be replicated, it is the first positive clinical trial with regard to adjunctive therapy for MT in LVO stroke and provides support for the concept of the no-reflow phenomenon in stroke.

Endovascular Therapy for Acute Stroke With a Large Ischemic Region (RESCUE-JAPAN)

Yoshimura S, Sakai N, Yamagami H, et al. N Engl J Med. 2022;386:1303-1313. doi: 10.1056/NEJMoa2118191

SUMMARY

RESCUE-JAPAN is a multicenter, open-label, randomized controlled trial (RCT) that looked at the efficacy and safety of endovascular therapy in patients with LVO and large core infarct. There were 203 patients enrolled across 45 centers in Japan. Patients with an ICA or M1 occlusion, NIHSS score > 6, and ASPECTS 3 to 5 by CT or MRI were included, with most patients selected by MRI. If patients presented after 6 hours from last known well, a diffusion-weighted imaging (DWI) ASPECTS with FLAIR (fluid-attenuated inversion recovery) sequence showing no signal change was required, as this could be indicative of early infarction based on earlier work by Thomalla et al.[1]

Endovascular therapy was the tested intervention, and the technique was left to the discretion of the treating physician. Medical therapy was provided to both groups, including reduced-dose tissue plasminogen activator (tPA) per Japanese guidelines. The primary outcome was a 90-day mRS of 0 to 3. Secondary outcomes were an mRS of 0 to 2, an mRS of 0 to 1, an ordinal shift across 90-day mRS, and 48-hour improvement in NIHSS. Safety outcomes were sICH, any ICH, need for decompressive craniectomy, mortality, or recurrence of stroke.

Baseline characteristics were similar between groups. Notably, a vast majority of patients were triaged based on MRI-calculated ASPECTS (88% in the treatment group and 87% in the control group), and only eight patients in both groups combined had an ASPECTS of 0 to 2. The primary outcome of favorable mRS (0-3) occurred more frequently in the endovascular therapy group than in the medical care group (31% vs 12.7%; relative risk [RR], 2.43; 95% CI, 1.35-4.37; $P = .002$). In terms of secondary outcomes, the ordinal shift favored the endovascular group (common odds ratio [OR], 2.42; 95% CI, 1.46-4.01), and a higher percentage of endovascularly treated patients had early neurologic improvement within 48 hours (RR, 3.51; 95% CI, 1.76-7.00). There were no differences in mRS score 0 to 1 or 0 to 2. ICH occurred more frequently in the endovascularly treated group (RR, 1.85; 95% CI, 1.33- 2.58), but other safety measures, including sICH, did not differ.

IMPORTANCE OF FINDINGS

This is the first trial to offer insight into endovascular treatment of large core. The patients in this trial who underwent MT saw a benefit at 90 days, with an impressive 18.3% greater number of patients in the treatment group reaching mRS 0 to 3 without increased sICH. It is important to highlight that the majority of patients were selected with MRI (ie, with a DWI-FLAIR mismatch representative of early window patients). MRI ASPECTS would be lower compared to CT ASPECTS, which runs the risk of enrolling moderate-sized cores. However, the rates of mRS 0 to 2 were low (14% and 8% in the treatment and control groups, respectively) compared to historical studies, which likely signifies that the population was large core patients.

Safety and Efficacy of Aspirin, Unfractionated Heparin, Both, or Neither During Endovascular Stroke Treatment (MR CLEAN-MED): An Open-Label, Multicenter, Randomized Controlled Trial

van der Steen W, van de Graaf RA, Chalos V, et al; MR CLEAN-MED investigators. Lancet. 2022;399:1059-1069. doi: 10.1016/S0140-6736(22)00014-9

SUMMARY

MR CLEAN-MED is a multicenter, open-label, randomized trial that looked at the efficacy and safety of procedural IV aspirin or unfractionated heparin (UFH) during endovascular treatment of stroke. There were 628 patients enrolled across 15 centers in the Netherlands. Patients with an occlusion in the intracranial ICA, M1, or proximal M2 who were last seen normal within 6 hours and had an NIHSS ≥ 2 were included. Patients were then randomly assigned to receive either IV aspirin or no aspirin and randomly assigned to receive moderate-dose UFH, low-dose UFH, or no UFH. Both treatments had to be started after groin puncture and completion of IV thrombolysis but before closure of the puncture site. The primary outcome was an ordinal shift of mRS at 90 days. The trial was stopped prematurely due to safety concerns in the treatment arms.

Of the 628 patients, 310 (49%) of patients were allocated to receive aspirin and 332 (53%) were allocated to receive UFH at either a low (87%) or moderate (13%) dose (allocation to aspirin and UFH were independent of each other); 538 (86%) of patients had MT, while the remaining underwent digital subtraction angiography only, catheterization, or no endovascular procedure. Acute carotid stenting and percutaneous angioplasty were performed in 5% and 7% of patients and were balanced across treatment groups when accounting for the early stoppage of moderate-dose UFH. There was no effect of aspirin or low- and moderate-dose UFH treatment on the primary outcome. Moderate-dose UFH–treated patients had significantly worse outcomes compared to no UFH (adjusted OR [aOR], 0.42; 95% CI, 0.18-0.99). UFH-treated patients had a higher chance of complete recanalization (NTM1) compared to those treated without UFH (aOR, 1.95; 95% CI, 1.13-3.35). All other comparisons for secondary outcomes showed no differences. Patients receiving aspirin had higher rates of sICH than patients not receiving aspirin (OR, 1.95; 95% CI, 1.13-3.35), and patients receiving UFH had higher rates of sICH than those not receiving UFH (OR, 1.98; 95% CI, 1.14 -3.46). sICH and mortality were not higher for the low-dose UFH group; although there was a trend favoring treatment without heparin, both parameters were higher in the moderate-dose UFH group. No interaction between treatment groups on primary functional or safety outcome was noted.

IMPORTANCE OF FINDINGS

This is the first published randomized trial to look at periprocedural antiplatelet or heparin treatment in endovascular therapy for stroke. Observational studies have suggested that periprocedural use of antiplatelets or heparin may be helpful for procedural efficacy, complication rates, or outcomes. This trial did not show functional or procedural benefits for aspirin at the risk of increased rates of sICH. The same was seen in the heparinized group, but complete recanalization was seen more often in the heparinized group—in addition to functional benefit in a subgroup of patients treated earlier from symptom onset. Further studies will need to look at different time thresholds or doses, but for now, the routine use of periprocedural aspirin or heparin should be cautioned against.

Endovascular Treatment for Acute Basilar Artery Occlusion: A Multicenter Randomized Controlled Trial (ATTENTION)

Nogueira R. Presented at: European Stroke Organisation Conference (ESOC) 2022; May 4, 2022; Lyon, France.

SUMMARY

ATTENTION is a multicenter, prospective RCT with open-label treatment and blinded-outcome assessment. The trial enrolled 340 patients across 36 comprehensive stroke centers in China. Patients aged ≥ 18 years with a presenting NIHSS ≥ 10 within 12 hours of last known well, a visualized basilar artery occlusion on CTA/MRA, and posterior circulation ASPECTS > 8 were included. The

intervention was endovascular therapy (including MT using stent retrievers or thromboaspiration, balloon angioplasty, stent deployment, intra-arterial thrombolysis [recombinant tPA or urokinase], or a combination of the mentioned interventions) in addition to best medical management. The primary outcome was an mRS of 0 to 3 at 90 days. Secondary outcomes included an ordinal shift of mRS at 90 days, mRS of 0 to 2, NIHSS at 24 to 72 hours or at 5 to 7 days after intervention or discharge, EQ-5D-5L, and Barthel Index at 90 days. Safety outcomes were sICH and mortality from all causes within 90 days. Secondary outcomes also included recanalization at 24 to 72 hours by CTA, ICH, and volume of infarction.

Baseline characteristics were similar between groups. A majority of patients (82.8%) underwent MT with aspiration alone or a combined technique with aspiration and stent retriever. There were 93.3% of patients with an mTICI score ≥ 2b. Patients who underwent endovascular therapy had higher rates of mRS 0 to 3 (RR, 2.1; 95% CI, 1.5-3). All secondary clinical outcomes were significantly more favorable in the endovascular therapy group ($P < .001$). Mortality occurred less often in the endovascular therapy group (RR, 0.7; 95% CI, 0.5-0.8). sICH occurred more often in the endovascular therapy group (risk difference, 5.3%; 95% CI, 2.3%-8.2%).

It is worth mentioning that the BAOCHE trial (NCT02737189) aimed to assess endovascular therapy (MT with Solitaire [Medtronic] with or without adjunctive manual aspiration; balloon angioplasty and/or stenting of the vertebral artery or basilar artery at the discretion of the interventionalist) versus best medical management in acute basilar artery occlusion stroke in patients presenting in the 6- to 24-hour time window.[2] In BAOCHE, favorable outcomes (defined as mRS 0-3 at 90 days) were 46.4% in the endovascular group versus 24.3% in the best medical management group, with an aOR of 2.92 (95% CI, 1.56-5.47; $P = .001$). These results support the concept that endovascular therapy for late-presenting patients with basilar occlusion stroke has similar efficacy compared to endovascular therapy for patients with early acute basilar artery occlusion stroke and to the anterior circulation late-window trials. The rate of sICH in BAOCHE was also similar to the early window anterior circulation trials, and this increase of ICH did not translate to higher risks for unfavorable outcomes.

IMPORTANCE OF FINDINGS

The ATTENTION and BAOCHE trials are the first trials to show efficacy of endovascular therapy in basilar artery occlusion up to 24 hours from stroke onset. Prior to these trials, the BEST and BASICS trials were the two major RCTs to compare endovascular therapy to medical management specific to basilar artery occlusion. Both trials yielded neutral results. However, high crossover rates, treatment outside the trial, and patient selection in BEST and BASICS may have complicated the final results. ■

1. Thomalla G, Cheng B, Ebinger M, et al; STIR and VISTA Imaging Investigators. DWI-FLAIR mismatch for the identification of patients with acute ischaemic stroke within 4·5 h of symptom onset (PRE-FLAIR): a multicentre observational study. Lancet Neurol. 2011 Nov;10:978-986. doi: 10.1016/S1474-4422(11)70192-2
2. Jovin T. O217 Basilar artery occlusion Chinese endovascular trial (BAOCHE). Presented at: European Stroke Organisation Conference (ESOC) 2022; May 6, 2022; Lyon, France.

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