Online August 29, 2023
Journal of Neuroendovascular Therapy 2023; 17: 232–242 DOI: 10.5797/jnet.ra.2023-0047

Review Article

Endovascular Therapy for Acute Stroke: New Evidence and Indications

Anurag Sahoo,[1] Mohamad Abdalkader,[1] Hiroshi Yamagami,[2] Xiaochuan Huo,[3] Dapeng Sun,[4] Baixue Jia,[4] Charlotte S. Weyland,[5] Francesco Diana,[6,7] Artem Kaliaev,[1] Piers Klein,[1] Jenny Bui,[1] Sami Al Kasab,[8] Adam de Havenon,[9] Osama O. Zaidat,[10] Wenjie Zi,[11] Qingwu Yang,[11] Patrik Michel,[12] James E. Siegler,[13] Shadi Yaghi,[14] Wei Hu,[15] and Thanh N. Nguyen[1]

Endovascular therapy (EVT) has revolutionized the treatment of acute ischemic stroke. In the past few years, endovascular treatment indications have expanded to include patients being treated in the extended window, with large ischemic core infarction, basilar artery occlusion (BAO) thrombectomy, as demonstrated by several randomized clinical trials. Intravenous thrombolysis (IVT) bridging to mechanical thrombectomy has also been studied via several randomized clinical trials, with the overall results indicating that IVT should not be skipped in patients who are candidates for both IVT and EVT. Simplification of neuroimaging protocols in the extended window to permit non-contrast CT, CTA collaterals have also expanded access to mechanical thrombectomy, particularly in regions across the world where access to advanced imaging may not be available. Ongoing study of areas to develop include rescue stenting in patients with failed thrombectomy, medium vessel occlusion thrombectomy, and carotid tandem occlusions. In this narrative review, we summarize recent trials and key data in the treatment of patients with large ischemic core infarct, simplification of neuroimaging protocols for the treatment of patients presenting in the late window, bridging thrombolysis, and BAO EVT evidence. We also summarize areas of ongoing study including medium and distal vessel occlusion.

Keywords endovascular therapy, large vessel occlusion, randomized clinical trial, large ischemic core, large core

Introduction

Endovascular therapy (EVT) has revolutionized the treatment of acute ischemic stroke (AIS). EVT is very effective in reducing the long-term disability with a number needed to treat (NNT) ranging from 2.6 to 3.0.[1,2] However, the global proportion of patients who receive this treatment remains low.[3,4] Although barriers such as cost, resources, and systems of care remain obstacles in many parts of the world,[5,6] providers are working on broadening the indications for this highly effective disability-saving treatment.[7] Published guidelines remain universally conservative in

[1]*Boston Medical Center, Boston University Chobanian and Avedisian School of Medicine, Boston, MA, USA*
[2]*Stroke Neurology, National Hospital Organization Osaka National Hospital, Osaka, Japan*
[3]*Cerebrovascular Disease, Beijing Anzhen Hospital, Capital Medical University, Beijing, China*
[4]*Interventional Neuroradiology, Beijing Tiantan Hospital, Beijing, China*
[5]*Neuroradiology, University Hospital RWTH Aachen, Aachen, Germany*
[6]*Interventional Neuroradiology, Vall d'Hebron University Hospital, Barcelona, Spain*
[7]*Vall d'Hebron Research Institute, Barcelona, Spain*
[8]*Neurology and Neurosurgery, Medical University of South Carolina, Charleston, SC, USA*
[9]*Neurology, Yale University, New Haven, CT, USA*
[10]*Neurology, Mercy Hospital, Toledo, OH, USA*
[11]*Neurology, Xinqiao Hospital of Army Medical University, Chongqing, China*
[12]*Neurosciences, Lausanne University Hospital, Lausanne, Switzerland*
[13]*Neurology, University of Chicago, Chicago, IL, USA*
[14]*Neurology, Rhode Island Hospital, Brown University School of Medicine, Providence, RI, USA*
[15]*Neurology, The First Affiliated Hospital of University of Science and Technology of China, Hefei, China*

Received: July 4, 2023; Accepted: July 25, 2023
Corresponding author: Thanh N. Nguyen. Boston Medical Center, Boston University Chobanian and Avedisian School of Medicine, 85 E Concord St, Boston, MA 02118, USA
Email: thanh.nguyen@bmc.org

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives International License.
©2023 The Japanese Society for Neuroendovascular Therapy

their recommendations with only minor variations in indications between guidelines. The 2021 Japanese stroke guidelines provide Grade A recommendations with a high level of evidence for EVT in patients with an internal carotid artery (ICA) or middle cerebral artery (MCA) M1 occlusion with an Alberta stroke program early computed tomography score (ASPECTS) of 6 or greater and National Institutes of Health Stroke Scale (NIHSS) score of 6 or greater in adult patients with a prestroke modified Rankin scale (mRS) score of 0–1, and a last known well (LKW) within 16 hours. Intravenous (IV) alteplase is recommended if eligible.[8,9] Other endovascular interventions or deviations from the above parameters were given lower levels of evidence. The American Heart Association/American Stroke Association Acute Stroke Guidelines and the European Stroke Guidelines from 2018 also have a similar level of recommendations with the addition of recommending advanced imaging for the late window.[10,11] Since the above guidelines, numerous clinical trials, and observational studies have been performed to ascertain whether patients outside these indications would benefit if treated by EVT.

Large Core

Early randomized clinical trials focused on patients with a large vessel occlusion (LVO) and small regions of an established infarct ("core"). A pooled meta-analysis of these trials suggested that patients with ASPECTS 3–5 could benefit from thrombectomy.[12] However clinical equipoise remained in the absence of dedicated randomized controlled trial (RCT) data in this group and other data suggested higher symptomatic intracranial hemorrhage (sICH) rates.[13] With the release of large core RCTs including RESCUE-JAPAN LIMIT, ANGEL ASPECT, and SELECT 2, the evidence favors treating these patients with EVT,[14–17] and the TESLA trial showed a direction of benefit although the results did not achieve a statistical significance.[18] The RESCUE JAPAN trial examined patients with an ICA or M1 occlusion and an ASPECTS of 3–5 who were within 6 hours of LKW or had a diffusion weighted imaging (DWI)–FLAIR mismatch in the late window. The primary outcome of a mRS score of 0–3 favored the EVT group with 31% of patients achieving this compared to 12.7% in the medical management group (relative risk [RR] 2.43, 95% confidence interval [CI] 1.35–4.37, P = 0.002). Secondary outcomes of mRS scores 0–1 and 0–2 favored EVT but were not significant. There was significantly more intracranial hemorrhage (ICH) and numerically more sICH in the EVT group. Largely MRI-based selection and a Japanese population limited the generalizability of this study.[14] Subsequently, the ANGEL ASPECT and SELECT 2 trials confirmed the results of RESCUE-JAPAN LIMIT. ANGEL ASPECT enrolled patients with an ICA or M1 occlusion in China. The imaging criteria included patients with (1) ASPECTS 3–5, (2) ASPECTS 0–2 with infarct volumes of 70–100 mL on CT perfusion (CTP), or (3) ASPECTS of 5 or greater in the late window if infarct volume was 70 to 100 mL on CTP. Infarct volumes were calculated with MRI DWI or CTP. The trial was stopped early due to the evidence of the efficacy of EVT. The primary endpoint of an ordinal shift on the mRS score was in favor of EVT (odds ratio [OR] 1.37, 95% CI 1.11–1.69, P = 0.004). There were 30% of patients in the EVT group and 11.6% of patients in the medical management group who reached a mRS score of 0–2.[15] The probability of achieving a mRS score of 0–2 by 90 days was less than what was reported by the HERMES collaboration (which included patients treated with EVT having highly favorable preintervention imaging profiles)[1]; however, the magnitude of benefit with EVT over medical management is similar. SELECT 2 evaluated patients from America, Europe, Australia, and New Zealand with an ASPECTS of 3–5 or a CTP or MRI DWI infarct greater than 50 mL. This trial was also stopped early as there was a mRS shift in favor of the EVT group (OR 1.51, 95% CI 1.20–1.89, P <0.001). There were 20.7% of patients who reached a mRS score of 0–2, whereas only 7% of medical therapy patients reached this endpoint. sICH rates were not significantly higher in the EVT groups in all trials although RESCUE-JAPAN LIMIT and ANGEL ASPECT had numerically higher rates of sICH. RESCUE-JAPAN LIMIT and ANGEL ASPECT found significantly higher rates of any ICH.

Still, further questions need to be answered. In SELECT 2, a subgroup analysis showed that the presence of a core/penumbra mismatch did not mediate the treatment efficacy. Considering that core/penumbra hypothesis has been at the center of stroke treatment, these findings prompt the question of whether we are accurately assessing if the core/penumbra or acute stroke pathophysiology is more complex than just core/penumbra. Similarly, ASPECTS regions are not equal in their contribution to functional outcome. Subtle loss of gray–white differentiation and a well-circumscribed infarct result in a given region being scored as abnormal, but these two imaging patterns may respond to treatments differently.[19] Broocks et al. looked at this phenomenon with net water uptake (NWU), a measure that quantifies the level of hypodensity in an infarcted tissue.[20] They found

that a higher NWU or more hypodensity was associated with a decreased likelihood of a mRS score of 0–3 and that a successful recanalization mediated a treatment response only when NWU was low. Although they did not report the hemorrhage rates, it would also be interesting to see if the hemorrhage rates vary as well given the trends in the abovementioned RCTs. Lastly, as an ASPECTS of 3 to 5 is now an established target for mechanical thrombectomy and is likely cost-effective,[17,21,22] the question remains if there is a floor for the ASPECTS score and a response to recanalization.

Rescue Stenting

Approximately 10%–20% of stroke patients do not achieve successful recanalization after mechanical thrombectomy.[23,24] A common etiology for failed recanalization is intracranial atherosclerotic disease (ICAD) with higher rates of reocclusion.[25,26] Rescue therapy in this patient population comprised of rescue stenting (RS), angioplasty, or use of IV antiplatelet therapy to achieve vessel patency.[27,28] Hesitation in adopting this approach is related to stent thrombosis leading to reocclusion, bleeding with dual antiplatelet therapy or IV antiplatelet medication, and risk of vessel perforation. The level of evidence remains low with retrospective data and smaller studies. Mohammaden et al. retrospectively examined multicenter data of patients with M1 and M2 occlusions with a modified thrombolysis in cerebral infarction (mTICI) score of 0 or 1 after multiple passes.[29] They compared the outcomes in 499 patients and performed a propensity score matched analysis with 107 patients each in the RS and non-RS arm. In both analyses, the RS arms achieved a positive shift on the 90-day mRS as well as higher rates of functional independence at 90 days compared to non-RS arms. There was a lower 90-day mortality with similar rates of sICH in both groups.

Two meta-analyses evaluated the use of RS in patients with LVO.[30,31] In the larger analysis, the RS group was younger and had lower rates of IV alteplase. For studies that listed an ASPECTS, most included small core patients with median scores ranging from 8 to 9 except for one study. There was heterogeneity in the definition of EVT failure with 6 studies that defined failed EVT as a mTICI score of 0–2a, 4 studies as a mTICI score of 0–1, and 2 studies as reocclusion. The primary endpoint of functional independence was achieved more frequently in the RS group (41% vs. 21.1%, OR 3.27, 95% CI 2.08–5.16) with a substantial between-study heterogeneity. Including single-arm studies, the rate of successful reperfusion after RS was 87% (95% CI 82%–91%). sICH occurred at similar rates in both groups (8.5% vs. 11.7%, OR 0.85, 95% CI 0.59–1.20) with low-certainty evidence and very little between-study heterogeneity. Mortality at 90 days occurred less in the RS group (22.5% vs. 33.8%, OR 0.47, 95% CI 0.32–0.69). Subgroup analysis for anterior or posterior circulation stroke did not change the trend of the above results. However, the meta-analysis is at a high risk of bias considering mostly the retrospective data, missing outcome data, heterogeneity in regards to definitions of EVT failure, treatment approaches, and etiology of occlusions that limit the validity. Therefore, stent placement to achieve vessel patency is likely protective, but questions regarding optimal patient population, the definition of EVT failure, and when to proceed with stenting or balloon angioplasty, stent type, and type of antiplatelet therapy remain open.[32,33]

Bridging Thrombolysis

The question of the added benefit of intravenous thrombolysis (IVT) surfaced after the advent of the positive EVT trials. Potential advantages of skipping thrombolysis could be reduced cost, less bleeding complications, and hesitancy in interventions such as stenting, given the need for antiplatelet therapy after IVT. Between 2020 and 2021, six trials were published that evaluated the role of bridging IVT.

DIRECT-MT evaluated 654 patients with ICA, M1, and M2 occlusions from 41 centers in China.[34] Among those, 326 patients did not receive bridging therapy and 328 received bridging therapy. The trial demonstrated non-inferiority with an adjusted common OR for a shift in the mRS score at 90 days of 1.07 (95% CI 0.81–1.40, P = 0.04) and a prespecified lower CI of 0.8 for noninferiority. A successful recanalization prior to thrombectomy occurred significantly more often in the alteplase group and numerically more often without a statistical significance after EVT in the alteplase group. Both sICH and procedural complications did not vary between groups. Limitations of the trial that biased against the bridging arm were a wide noninferiority margin, long door to IVT times resulting in short delays between IVT to groin puncture, possibly due to payment models and consent. The DEVT trial evaluated 234 patients across 33 centers in China with LVO in ICA and M1.[35] The trial was stopped early as the prespecified efficacy boundary was met on an interim analysis: 54.3% of patients in the direct EVT group reached the primary outcome of functional independence compared to 46.6% in

the bridging group (difference 7.7%, one-sided 97.5% CI −5.1% to ∞). This was within the prespecified noninferiority margin of 10%. No differences were noted in the safety measures of mortality and sICH. Like DIRECT MT, the presence of long door-to-IVT times with short IVT-to-EVT times and generous noninferiority margins were the limitations. The SKIP trial enrolled 204 patients in 23 stroke centers in Japan with ICA or M1 occlusions.[36] As per Japanese guidelines, bridging patients received a lower dose of 0.6 mg/kg of alteplase in contrast to the other trials. There were 59.4% of patients in the direct EVT group who reached the primary endpoint of functional independence compared to 57.3% in the bridging group (OR 1.09, one-sided 97.5% CI 0.63–∞) who did not meet the prespecified noninferiority margin of 0.74. Other secondary outcomes and sICH also did not differ. Longer door-to-IV thrombolysis times, usage of low-dose alteplase, and the start of IVT after an arterial puncture in 21.4% limit generalizability. DIRECT-MT, DEVT, and SKIP were all conducted in east Asian countries that are known to have higher percentages of ICAD, which may be less responsive to alteplase.[37]

The next 3 trials were conducted outside of Asia. MR CLEAN- NO IV enrolled 539 patients across 20 centers in the Netherlands, Belgium, and France with an occlusion of the ICA, M1, and proximal M2.[38] The adjusted odds ratio (aOR) for a shift in an mRS score was 0.84 (95% CI 0.62–1.15, P = 0.28) which was not non-inferior with a prespecified lower boundary for the CI set at 0.8. The two groups did not differ with respect to the secondary outcomes, mortality, or sICH. SWIFT-DIRECT included 408 patients across 48 centers in Europe and Canada with an occlusion of the ICA or M1.[39] The primary outcome of functional independence occurred in 57% of direct EVT patients compared to 65% of bridging patients (adjusted risk difference −7.3%, 95% CI −16.6 to 2.1). The lower limit of the one-sided 95% CI was −15.1%, which did not meet the prespecified noninferiority margin of 12%. Final recanalization occurred more often in the bridging group, and there was a trend toward more sICH and groin hematoma in bridging patients. DIRECT-SAFE evaluated 293 patients across 25 centers in Australia, New Zealand, China, and Vietnam with occlusions of the ICA, M1, and M2.[40] Patients were also allowed to receive IV tenecteplase. The primary outcome of functional independence occurring in 55% of the direct EVT group and 61% of the bridging group (difference 5.1%, two-sided 95% CI −16% to 5.9%) did not satisfy the noninferiority margin of 10%. Secondary and safety outcomes did not differ. In contrast to the above Asian trials, patients enrolled in Asia had more benefit from bridging than patients in Australia and New Zealand in DIRECT-SAFE. These studies led to an ESO-ESMINT guideline recommendation and SVIN Brief Practice Update to keep the bridging therapy.[41,42] They also performed a study-level meta-analysis that did not show noninferiority of direct EVT across a range of noninferiority margins and significantly reduced the successful recanalization rates with direct EVT. Data from the Improving Reperfusion strategies in Ischemic Stroke (IRIS) collaborative, a patient level meta-analysis of the 6 trials also did not show non-inferiority of direct EVT.[43]

Considering that patients in these trials largely had successful thrombectomies, the role of IVT in patients who do not achieve recanalization is less well understood. Faizy et al. looked at patients with ICA, M1, or M2 occlusion who went for EVT with an unsuccessful final recanalization (TICI 0-2a) in the German Stroke Registry. They performed propensity score matching to include 746 patients. A higher portion of patients in the bridging group had the primary outcome of functional independence at 18.2% compared to 11.3% in the EVT-only group (aOR 2.63, 95% CI 1.41–5.11, P = 0.003). The bridging group also had better secondary outcomes of mRS 0–3 as well as a shift in the overall mRS scores. A subgroup analysis favored bridging patients across the predefined subgroups. Bridging patients benefited within 4.5 hours after onset but not after 4.5 hours or with an unknown time of onset. Bridging patients also had more benefit with partial reperfusion rather than failed reperfusion. sICH was not different in both groups, whereas mortality occurred less often in the bridging patients. Importantly, the effect of IVT varies by the patient population, of which many were not included in the above trials. These trials examined mostly the anterior circulation occlusions presenting to a thrombectomy-capable center, and it is possible that the benefit of bridging thrombolysis will be more apparent in transfer patients. Posterior circulation occlusions, distal occlusions, and smaller thrombi are also more responsive to thrombolysis and the first two of the three locations were not well represented in the above trials.[44–46]

Investigators of the CHOICE randomized clinical trial randomized 121 patients with a successful recanalization (mTICI 2b-3) of an anterior or posterior LVO to intra-arterial alteplase (0.225 mg/kg) or placebo over 15–30 minutes and found a higher rate of the primary outcome (90-day mRS score 0–1) among patients treated with alteplase (59% vs. 40%, P = 0.047).[47] While most patients had

achieved technically successful recanalization with mechanical thrombectomy, the added benefit of intra-arterial alteplase argues for the importance of microcirculatory failure that remains present despite successful large vessel recanalization.

Imaging Modality

Although many of the landmark trials selected patients based on advanced imaging, particularly in the late window, this approach is not without its disadvantages: increased cost, increased time to acquire images, use of contrast, and decreased availability of advanced imaging capability.[6,48] As a result, there has been an influx of studies examining if simpler imaging paradigms may provide a benefit to our patients without harming them.[49]

The largest study was the CLEAR study, a multicenter, retrospective study that examined different imaging modalities to select patients for treatment with EVT in the late window.[50] The study included 1530 patients across 15 sites in 5 countries. Patients were included who presented with an occlusion in the ICA or proximal MCA (M1/M2 segments) and NIHSS score of 6 or more in the extended window of 6 to 24 hours from LKW. Patients were selected based upon non-contrast CT head (NCCT) with CTA, CTP, or MRI. The NCCT group had higher presenting NIHSS, higher rates of hypertension, atrial fibrillation, presented more frequently as transfers, and higher rates of ICA occlusion. Rates of IVT were most common in MRI followed by NCCT and then CTP groups. The median ASPECTS was 8 across all 3 groups. Significantly shorter door-to-puncture times were observed for the NCCT group as compared to those for the CTP and MRI groups. Successful reperfusion occurred significantly more often in the NCCT and CTP groups compared to that in the MRI group. The primary endpoint of distribution of mRS at 90 days did not differ between the groups after adjusting for the prespecified variables. The probability of functional independence and safety measures of sICH and mortality were also similar across groups. A meta-analysis combining 5 studies also found similar results with similar rates of functional independence and sICH.[51] They also found that the CTP group had lower rates of mortality and higher rates of recanalization. Katsanos et al. noted that due to the lack of patient-level data and retrospective nature of the data analyzed, it is possible that unbalanced baseline characteristics accounted for this difference.[52]

MR CLEAN-LATE was a randomized trial that enrolled patients not meeting DAWN and DEFUSE-3 criteria using CTA collaterals as a selection method for mechanical thrombectomy in the Netherlands.[53] Patients with ICA, M1, or M2 occlusions and presence of collateral flow on CTA divided into 3 grades were randomized into treatment with EVT or no treatment. Patients in the treatment arm had a better primary outcome with lower 90-day mRS scores (adjusted common odds ratio [cOR] 1.67, 95% CI 1.20–2.32). Dichotomized mRS trended in favor of EVT but was only significant for a mRS score of 0–3. sICH occurred more often in the EVT group, although in low numbers in both groups. Patients with weaker collaterals were associated with a stronger treatment effect.

Given the concerns of NCCT as a selection for EVT would lead to futile recanalization, reperfusion without functional independence,[54] and/or sICH, the positive large core thrombectomy data presented above provide reassurance that these concerns may not be relevant. ANGEL ASPECT and SELECT 2 used NCCT and CTP as a selection tool and found benefit in large core stroke as adjudicated by low ASPECTS. The benefits of a simpler acute stroke imaging workflow are also paramount. Only mandating NCCT as a screening tool could allow greater access to this disability-saving treatment in low-resource settings.[55–57] There is also the argument for a faster workflow with potential neuronal and cost savings. The risk of over-selection by CTP parameters and delays incurred with advanced imaging may place some patients at risk of being excluded or delayed from a potentially disability-sparing treatment.

Medium/Distal Vessel Occlusions

Although the data for intervention in large vessel occlusion are robust, the data for medium vessel occlusion (MeVO) are incomplete.[58–65] There is heterogeneity in the sites of occlusion as anterior cerebral artery (ACA), MCA, and posterior cerebral artery (PCA) occlusions have different clinical–anatomical considerations and it may be worthwhile to examine each arterial site separately.

Intervention in isolated ACA occlusions was evaluated by Meyer et al. in A2 to A4 occlusions with 110 patients after propensity score matching.[59] There were trends toward more large artery atherosclerosis as an etiology for the EVT group. There were no differences between the groups with respect to clinical or safety outcomes even when stratified by occlusion site, age, sex, occlusion site, NIHSS, and IVT, which may have been due to a low sample size. On multivariable analysis, improved reperfusion

scores were associated with good outcomes. Importantly, mechanical thrombectomy was safe and feasible in this site of occlusion. There was only 2% sICH observed and low rates of embolization to the new territory and vessel perforation. Moreover, NIHSS and mRS scores may not detect the disability related to neuropsychological deficits as seen in ACA occlusions, limiting conclusions about the functional benefit. A1 occlusions were not included in this study, but a retrospective study by Filioglo et al. found similar results on the subgroup analysis by location.[59,66]

Similar to ACA occlusions, PCA occlusions also were not included in the mechanical thrombectomy trials.[60,62,63,67,68] The Posterior Cerebral Artery Occlusion (PLATO) study evaluated EVT versus medical management in 1023 patients with PCA occlusions of the P1–P4 segments including fetal PCAs within 24 hours of a symptom onset.[61] Patients in the EVT arm had higher NIHSS scores, more proximal PCA occlusion, were treated in a later chronological year, had higher rates of mRS 0 at baseline, more often transfers, less diabetes, hyperlipidemia, and prior stroke. They also had a higher posterior circulation acute stroke early prognosis CT score (pc-ASPECTS) and perfusion mismatch. The primary endpoint of an ordinal mRS shift at 90 days did not differ between the EVT and medical management groups, but the coprimary endpoint of an early decrease in NIHSS by greater than or equal to 2 occurred more often in the EVT group. Secondary endpoints of early NIHSS improvement and vision improvement also occurred more often in the EVT group. There was a significantly higher rate of sICH and mortality in the EVT group. In adjusted analyses, there was a higher likelihood of excellent outcome of mRS 0–1 at 90 days in the EVT group. An adjusted analysis of a subgroup of patients treated with IVT also showed the same results except that the primary endpoint of decrease in NIHSS of greater than or equal to 2 was not significant. Like the ACA occlusion discussion, mRS places a larger emphasis on motor and language abilities, which may miss the benefit regarding the vision seen by treating PCA occlusions. These improvements in the vision may explain both the benefit regarding mRS score 0–1 at 90 days as well as the NIHSS improvements. The increased sICH and mortality trends do warrant caution and should be considered during the clinical decision making and weighed against the clinical deficit and possible functional gains.

The highest quality data for medium and distal MCA occlusions are from the HERMES meta-analysis of the early window trials. In a cohort of M2 occlusions, functional independence was greater for patients treated with EVT.[64] Most of the cohort had proximal and dominant or codominant MCA occlusions and the benefit was understandably larger for these subgroups. A study level meta-analysis by Loh et al. pooled 15 studies with 2252 patients with medium or distal vessel occlusions.[69] Herein, 72.1% patients had M2 MCA occlusion, 23.7% had PCA occlusion, and 4.2% had ACA occlusion. They found no significant difference for functional independence between the EVT and MM groups. However, they noted a substantial heterogeneity and publication bias on their funnel plot in favor of medical management. No difference was noted in the excellent functional outcome but with a substantial heterogeneity and no significant publication bias. Safety outcomes of sICH and mortality also did not differ. A subgroup analysis of patients receiving EVT with intra-arterial thrombolysis primary or in addition to mechanical thrombectomy showed no difference in the rates of functional independence but significantly increased rates of the excellent functional outcome in comparison to medical management. The patients receiving mechanical thrombectomy alone did not differ in functional independence or the excellent functional outcome in comparison to medical management. There were no differences in the outcomes by an occlusion location. They also looked at the studies that focused on the patients presenting with mean or median NIHSS score <6 and found that the EVT group had a lower likelihood of functional independence and significantly higher rates of sICH compared to medical management. When looking at the studies with only mean or median NIHSS score >6, they found that the EVT group had a greater likelihood of excellent outcome with no differences in functional or safety outcomes.

The common theme in the above studies is that relevant endpoints should be reconsidered when looking at the efficacy of intervention in MeVOs or distal vessel occlusions that are specific to the site of arterial occlusion. Either a higher bar for an efficacy endpoint in mRS should be considered or possibly another endpoint for ACA or PCA occlusions where the mRS may not weigh the deficit accurately. Although intervention appears overall safe, there are some subgroups such as PCA or MCA occlusions with a low NIHSS where there are safety concerns and the presenting symptoms should be weighed against these risks. Further randomized trial data via the DISTAL, ESCAPE-MeVO, DISCOUNT, DISTALS, and DUSK trials will help further inform this space.

Basilar Artery Occlusion

Although the landmark positive EVT trials included anterior circulation LVO patients only, the natural course of basilar artery occlusions (BAOs) made this lesion a logical EVT target. The BEST and BASICS trials were the two neutral trials looking at EVT in BAO.[70,71] The trial results were met with skepticism due to concerns about the patient selection, high crossover rates and treatment outside the trial, as well as personal clinical experience with the natural course and treatment response of BAO.[72–78] Subsequently, two RCTs, ATTENTION and BAOCHE, confirmed the benefit of EVT in BAO.[79,80]

The ATTENTION trial was a multicenter RCT of EVT in patients with a BAO presenting with a NIHSS >10, an estimated time of BAO within 12 hours. Angioplasty and stenting were used in 40% of patients in addition to thrombectomy. The primary outcome of mRS score of 0–3 occurred more often in the EVT group (RR 2.1, 95% CI 1.5–3.0, P <0.001). All secondary clinical outcomes favored the EVT group. sICH occurred significantly more often in the EVT group but mortality was less in the EVT group. The BAOCHE trial was a RCT in China looking at EVT in patients presenting 6 to 24 hours from LKW with a presenting NIHSS ≥10 and pc-ASPECTS ≥6. Intracranial angioplasty or stenting after failed thrombectomy was performed in 55% of the EVT arm. The primary outcome of mRS score of 0–3 occurred more often in the EVT group (adjusted rate ratio 1.81, 95% CI 1.26–2.60, P <0.001). sICH was numerically higher in the EVT arm and mortality occurred less often in the EVT arm. For many, the ATTENTION and BAOCHE trials confirmed what many clinicians knew[74] and provided a high quality evidence for EVT in BAO.[45]

In patients with BAO and mild deficit, the benefit is uncertain, where trial data were underpowered to show a difference as shown by a subgroup meta-analysis of patients with NIHSS <10.[45] The Nationwide Inpatient Sample of patients admitted with BAO in the United States showed more discharges to home in the EVT group as compared to patients who were medically managed.[81]

Conclusion

After the initial neutral mechanical thrombectomy trials in stroke, subsequent trials were restrictive to provide the proof of concept for mechanical clot retrieval in stroke. Therefore, guidelines are conservative in their recommendations, in keeping with the trial eligibility criteria.[56] However, maximizing the number of patients who can be helped necessitates that we broaden our criteria for interventions and update our guidelines.[56,82] Given the low NNT of EVT in stroke, broadening our criteria may dilute the overall effect of EVT but reach a greater number of patients overall that will benefit. We must also search for optimizing first-pass effect[83–85] and adjunctive therapies to help maximize the benefit of EVT.[47,86–92] EVT has changed the stroke treatment landscape and the stroke literature is now flourishing with new studies. We provide a summary of select studies representing the newest evidence that may inform decisions outside of the typical indications for EVT in an AIS.

Disclosure Statement

Dr. Thanh Nguyen reports advisory board of Idorsia. All the other authors report no other conflict of interest.

References

1) 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* 2016; 387: 1723–1731.
2) Jovin TG, Nogueira RG, Lansberg MG, et al. Thrombectomy for anterior circulation stroke beyond 6 h from time last known well (AURORA): a systematic review and individual patient data meta-analysis. *Lancet* 2022; 399: 249–258.
3) Nguyen TN, Qureshi MM, Klein P, et al. Global impact of the COVID-19 pandemic on stroke volumes and cerebrovascular events: a 1-year follow-up. *Neurology* 2023; 100: e408–e421.
4) Nogueira RG, Abdalkader M, Qureshi MM, et al. Global impact of COVID-19 on stroke care. *Int J Stroke* 2021; 16: 573–584.
5) Mai DT, Dao XC, Luong NK, et al. Current state of stroke care in Vietnam. *Stroke Vasc Intervent Neurol* 2022; 2: e000331.
6) Nguyen TN, Klein P, Berberich A, et al. Late window imaging selection for endovascular therapy of large vessel occlusion stroke: an international survey. *Stroke Vasc Intervent Neurol* 2023; 3: e000595.
7) Nguyen TN, Castonguay AC, Siegler JE, et al. Mechanical thrombectomy in the late presentation of anterior circulation large vessel occlusion stroke: a guideline from the Society of Vascular and Interventional Neurology Guidelines and Practice Standards Committee. *Stroke Vasc Interv Neurol*. Epub ahead of print November 30, 2022.
8) Yamagami H, Hayakawa M, Inoue M, et al. Guidelines for mechanical thrombectomy in Japan, the fourth edition, March 2020: a guideline from the Japan Stroke Society, the Japan Neurosurgical Society, and the Japanese Society for Neuroendovascular Therapy. *Neurol Med Chir* 2021; 61: 163–192.

9) Miyamoto S, Ogasawara K, Kuroda S, et al. Japan Stroke Society Guideline 2021 for the treatment of stroke. *Int J Stroke* 2022; 17: 1039–1049.
10) 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: e344–e418.
11) Turc G, Bhogal P, Fischer U, et al. European Stroke Organisation (ESO) - European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines on mechanical thrombectomy in acute ischaemic stroke endorsed by Stroke Alliance for Europe (SAFE). *Eur Stroke J* 2019; 4: 6–12.
12) Román LS, Menon BK, Blasco J, et al. Imaging features and safety and efficacy of endovascular stroke treatment: a meta-analysis of individual patient-level data. *Lancet Neurol* 2018; 17: 895–904.
13) Meyer L, Bechstein M, Bester M, et al. Thrombectomy in extensive stroke may not be beneficial and is associated with increased risk for hemorrhage. *Stroke* 2021; 52: 3109–3117.
14) Yoshimura S, Sakai N, Yamagami H, et al. Endovascular therapy for acute stroke with a large ischemic region. *N Engl J Med* 2022; 386: 1303–1313.
15) Huo X, Ma G, Tong X, et al. Trial of endovascular therapy for acute ischemic stroke with large infarct. *N Engl J Med* 2023; 388: 1272–1283.
16) Sarraj A, Hassan AE, Abraham MG, et al. Trial of endovascular thrombectomy for large ischemic strokes. *N Engl J Med* 2023; 388: 1259–1271.
17) Li Q, Abdalkader M, Siegler JE, et al. Mechanical thrombectomy for large ischemic stroke: a systematic review and meta-analysis. *Neurology* 2023 Jun:10.1212/WNL.0000000000207536.
18) Zaidat OO, AlKasab S, Sheth SA, et al. The TESLA trial: thrombectomy for emergent salvage of large anterior circulation ischemic stroke. *Stroke Vasc Intervent Neurol* 2023; 3: e000787.
19) Abdalkader M, Siegler JE, Lee JS, et al. Neuroimaging of acute ischemic stroke: multimodal imaging approach for acute endovascular therapy. *J Stroke* 2023; 25: 55–71.
20) Broocks G, Meyer L, Elsayed S, et al. Association between net water uptake and functional outcome in patients with low ASPECTS brain lesions: results from the I-LAST study. *Neurology* 2023; 100: e954–e963.
21) Pan Y, Huo X, Jin A, et al. Cost-effectiveness of endovascular therapy for acute ischemic stroke with large infarct in China. *J Neurointerv Surg* 2023; 16: jnis-2023-020466. [Epub ahead of print]
22) Starikova N, Raty S, Strbian D, et al. Endovascular thrombectomy for anterior circulation large vessel occlusion stroke: an evolution of trials. *Semin Neurol* 2023; 43: 397–407.
23) Haussen DC, Al-Bayati AR, Mohammaden MH, et al. The Society of Vascular and Interventional Neurology (SVIN) mechanical thrombectomy registry: methods and primary results. *Stroke Vasc Intervent Neurol* 2022; 2: e000234.
24) Zaidat OO, Castonguay AC, Gupta R, et al. North American Solitaire Stent Retriever Acute Stroke registry: post-marketing revascularization and clinical outcome results. *J Neurointerv Surg* 2018; 10(Suppl 1): i45–i49.
25) de Havenon A, Zaidat OO, Amin-Hanjani S, et al. Large vessel occlusion stroke due to intracranial atherosclerotic disease: identification, medical and interventional treatment, and outcomes. *Stroke* 2023; 54: 1695–1705.
26) Oliveira R, Correia MA, Marto JP, et al. Reocclusion after successful endovascular treatment in acute ischemic stroke: systematic review and meta-analysis. *J Neurointerv Surg* 2022; 3: jnis-2022-019382. [Epub ahead of print]
27) Huo X, Sun D, Chen W, et al. Endovascular treatment for acute large vessel due to underlying intracranial atherosclerotic disease. *Semin Neurol* 2023; 43: 337–344.
28) Gao F, Tong X, Jia B, et al. Randomised study of bailout intracranial angioplasty following thrombectomy for acute large vessel occlusion (ANGEL-REBOOT): protocol of a multicentre randomised controlled trial. *Stroke Vasc Neurol* 2023; 19: svn-2023-002433. [Epub ahead of print]
29) Mohammaden MH, Haussen DC, Al-Bayati AR, et al. Stenting and angioplasty in neurothrombectomy: matched analysis of rescue intracranial stenting versus failed thrombectomy. *Stroke* 2022; 53: 2779–2788.
30) Rodriguez-Calienes A, Vivanco-Suarez J, Galecio-Castillo M, et al. Rescue stenting for failed mechanical thrombectomy in acute ischemic stroke: systematic review and meta-analysis. *Stroke Vasc Intervent Neurol* 2023; 3: e000881.
31) Almallouhi E, Murad MH, Chalhoub R, et al. Rescue endovascular treatment of patients with emergent large vessel occlusion attributed to intracranial atherosclerosis: a systematic review and meta-analysis. *Stroke Vasc Intervent Neurol* 2023; 3: e000510.
32) Klein P, Herning A, Drumm B, et al. Basilar artery occlusion thrombectomy technique: an international survey of practice patterns. *Stroke Vasc Intervent Neurol* 2023; 3: e000642.
33) Krishnan K, Nguyen TN, Appleton JP, et al. Antiplatelet resistance: a review of concepts, mechanisms, and implications for management in acute ischemic stroke and transient ischemic attack. *Stroke Vasc Intervent Neurol* 2023; 3: e000576.
34) Yang P, Zhang Y, Zhang L, et al. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med* 2020; 382: 1981–1993.
35) 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: 234–243.

36) 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: 244–253.
37) Qiu Z, Yuan J, Xie D, et al. Abstract 100: Endovascular treatment with intravenous tirofiban or alteplase versus endovascular treatment alone for acute ischemic stroke with large vessel occlusion: a pooled analysis of the DEVT and Rescue BT trials. *Stroke*, https://www.ahajournals.org/doi/abs/10.1161/str.54.suppl_1.100 (2023).
38) LeCouffe NE, Kappelhof M, Treurniet KM, et al. A randomized trial of intravenous alteplase before endovascular treatment for stroke. *N Engl J Med* 2021; 385: 1833–1844.
39) Fischer U, Kaesmacher J, Strbian D, et al. Thrombectomy alone versus intravenous alteplase plus thrombectomy in patients with stroke: an open-label, blinded-outcome, randomised non-inferiority trial. *Lancet* 2022; 400: 104–115.
40) Mitchell PJ, Yan B, Churilov L, et al. Endovascular thrombectomy versus standard bridging thrombolytic with endovascular thrombectomy within 4·5 h of stroke onset: an open-label, blinded-endpoint, randomised non-inferiority trial. *Lancet* 2022; 400: 116–125.
41) Turc G, Tsivgoulis G, Audebert HJ, et al. European Stroke Organisation - European Society for Minimally Invasive Neurological Therapy expedited recommendation on indication for intravenous thrombolysis before mechanical thrombectomy in patients with acute ischaemic stroke and anterior circulation large vessel occlusion. *Eur Stroke J* 2022; 7: I–XXVI.
42) Masoud HE, de Havenon A, Castonguay AC, et al. 2022 Brief Practice Update on intravenous thrombolysis before thrombectomy in patients with large vessel occlusion acute ischemic stroke: a statement from Society of Vascular and Interventional Neurology Guidelines and Practice Standards (GAPS) Committee. *Stroke Vasc Intervent Neurol* 2022; 2: e000276.
43) Fischer U. On behalf of the Improving Reperfusion strategies in Ischemic Stroke (IRIS). Direct mechanical thrombectomy versus bridging therapy - cumulative study-level meta-analysis of the DIRECT-MT, MR CLEAN-NOIV, DEVT, SKIP and SWIFT DIRECT randomized controlled trials. *Eur Stroke J* 2021; 1. [Epub ahead of print]
44) Nguyen TN, Fischer U. Treatment effect of intravenous thrombolysis bridging to mechanical thrombectomy on vessel occlusion site. *Stroke* 2022; 53: 17–19.
45) Abdalkader M, Finitsis S, Li C, et al. Endovascular versus medical management of acute basilar artery occlusion: a systematic review and meta-analysis of the randomized controlled trials. *J Stroke* 2023; 25: 81–91.
46) Strbian D, Sairanen T, Silvennoinen H, et al. Intravenous thrombolysis of basilar artery occlusion: thrombus length versus recanalization success. *Stroke* 2014; 45: 1733–1738.
47) Renú A, Millán M, San Román L, et al. 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. *JAMA* 2022; 327: 826–835.
48) Kaiser DPO, Abdalkader M, Berberich A, et al. Acute shortage of iodinated contrast media: implications and guidance for neurovascular imaging and intervention. *Neuroradiology* 2022; 64: 1715–1718.
49) Miao J, Sang H, Li F, et al. Effect of imaging selection paradigms on endovascular thrombectomy outcomes in patients with acute ischemic stroke. *Stroke* 2023; 54: 1569–1577.
50) Nguyen TN, Abdalkader M, Nagel S, et al. Noncontrast computed tomography vs computed tomography perfusion or magnetic resonance imaging selection in late presentation of stroke with large-vessel occlusion. *JAMA Neurol* 2022; 79: 22–31.
51) Kobeissi H, Ghozy S, Adusumilli G, et al. CT perfusion vs noncontrast CT for late window stroke thrombectomy: a systematic review and meta-analysis. *Neurology* 2023; 100: e2304–e2311.
52) Katsanos AH, Catanese L, Shoamanesh A. To use perfusion imaging or not in patient selection for late window endovascular thrombectomy? That is the question. *Neurology* 2023; 100: 1039–1040.
53) Olthuis SGH, Pirson FAV, Pinckaers FME, et al. Endovascular treatment versus no endovascular treatment after 6-24 h in patients with ischaemic stroke and collateral flow on CT angiography (MR CLEAN-LATE) in the Netherlands: a multicentre, open-label, blinded-endpoint, randomised, controlled, phase 3 trial. *Lancet* 2023; 401: 1371–1380.
54) Seker F, Qureshi MM, Möhlenbruch MA, et al. Reperfusion without functional independence in late presentation of stroke with large vessel occlusion. *Stroke* 2022; 53: 3594–3604.
55) Nguyen TN, Klein P, Berberich A, et al. Late window imaging selection for endovascular therapy of large vessel occlusion stroke: an international survey. *Stroke Vasc Interv Neurol* 2022; 000595.
56) Nguyen TN, Raymond J, Nogueira RG, et al. The problem of restrictive thrombectomy trial eligibility criteria. *Stroke* 2022; 53: 2988–2990.
57) Roushdy T, Aref H, Kesraoui S, et al. Stroke services in Africa: what is there and what is needed. *Int J Stroke* 2022; 17: 972–982.
58) Sun D, Liu R, Huo X, et al. Endovascular treatment for acute ischaemic stroke due to medium vessel occlusion: data from ANGEL-ACT registry. *Stroke Vasc Neurol* 2022; 8: 51–58.
59) Meyer L, Stracke P, Broocks G, et al. Thrombectomy versus medical management for isolated anterior cerebral artery stroke: an international multicenter registry study. *Radiology* 2023; 307: e220229.

60) Berberich A, Finitsis S, Strambo D, et al. Endovascular therapy versus no endovascular therapy in patients receiving best medical management for acute isolated occlusion of the posterior cerebral artery: a systematic review and meta-analysis. *Eur J Neurol* 2022; 29: 2664–2673.

61) Nguyen TN, Qureshi MM, Strambo D, et al. Endovascular versus medical management of posterior cerebral artery occlusion stroke: the PLATO study. *Stroke* 2023; 54: 1708–1717.

62) Strambo D, Bartolini B, Beaud V, et al. Thrombectomy and thrombolysis of isolated posterior cerebral artery occlusion: cognitive, visual, and disability outcomes. *Stroke* 2020; 51: 254–261.

63) Herweh C, Abdalkader M, Nguyen TN, et al. Mechanical thrombectomy in isolated occlusion of the proximal posterior cerebral artery. *Front Neurol* 2021; 12: 697348.

64) Menon BK, Hill MD, Davalos A, et al. Efficacy of endovascular thrombectomy in patients with M2 segment middle cerebral artery occlusions: meta-analysis of data from the HERMES Collaboration. *J Neurointerv Surg* 2019; 11: 1065–1069.

65) Nguyen TN, Abdalkader M, Qureshi MM, et al. First-line stent retriever versus contact aspiration or combined technique for endovascular therapy of posterior cerebral artery occlusion stroke: the PLATO study. *Stroke Vasc Intervent Neurol*, in press.

66) Filioglo A, Simaan N, Honig A, et al. Outcomes after reperfusion therapies in patients with ACA stroke: a multicenter cohort study from the EVATRISP collaboration. *J Neurol Sci* 2022; 432: 120081.

67) Abdalkader M, Sahoo A, Dmytriw AA, et al. Mechanical thrombectomy of the fetal posterior cerebral artery. *Stroke Vasc Intervent Neurol* 2021; 1: e000115.

68) Abdalkader M, Sahoo A, Shulman JG, et al. Acute occlusion of the fetal posterior cerebral artery: diagnosis and management paradigms. *Neuroradiol J* 2021; 0: 19714009211019383.

69) Loh EDW, Toh KZX, Kwok GYR, et al. Endovascular therapy for acute ischemic stroke with distal medium vessel occlusion: a systematic review and meta-analysis. *J Neurointerv Surg* 2022; jnis-2022-019717.

70) Liu X, Dai Q, Ye R, et al. Endovascular treatment versus standard medical treatment for vertebrobasilar artery occlusion (BEST): an open-label, randomised controlled trial. *Lancet Neurol* 2020; 19: 115–122.

71) Langezaal LCM, van der Hoeven EJRJ, Mont'Alverne FJA, et al. Endovascular therapy for stroke due to basilar-artery occlusion. *N Engl J Med* 2021; 384: 1910–1920.

72) Nguyen TN, Strbian D. Endovascular therapy for stroke due to basilar artery occlusion: a BASIC challenge at BEST. *Stroke* 2021; 52: 3410–3413.

73) Puetz V, Lutsep HL, Nguyen TN. Endovascular therapy for basilar artery occlusion: among the first to conceptualize, last to prove. *Stroke* 2023; 54: 905–908.

74) Drumm B, Banerjee S, Qureshi MM, et al. Current opinions on optimal management of basilar artery occlusion: after the BEST of BASICS survey. *Stroke Vasc Intervent Neurol* 2022; 2: e000538.

75) Huo X, Klein P, Raynald, et al. Perceptions on basilar artery occlusion management in China versus other countries: analysis of the after the BEST of BASICS (ABBA) survey. *J Stroke Cerebrovasc Dis* 2022; 31: 106804.

76) Alemseged F, Nguyen TN, Alverne FM, et al. Endovascular therapy for basilar artery occlusion. *Stroke* 2023; 54: 1127–1137.

77) Alemseged F, Nguyen TN, Coutts SB, et al. Endovascular thrombectomy for basilar artery occlusion: translating research findings into clinical practice. *Lancet Neurol* 2023; 22: 330–337.

78) Räty S, Nguyen TN, Nagel S, et al. What is the evidence for endovascular thrombectomy in posterior circulation stroke? *Semin Neurol* 2023; 43: 345–355.

79) Tao C, Nogueira RG, Zhu Y, et al. Trial of endovascular treatment of acute basilar-artery occlusion. *N Engl J Med* 2022; 387: 1361–1372.

80) Jovin TG, Li C, Wu L, et al. Trial of thrombectomy 6 to 24 hours after stroke due to basilar-artery occlusion. *N Engl J Med* 2022; 387: 1373–1384.

81) Patel K, Taneja K, Obusan MB, et al. Real-world outcomes for basilar artery occlusion thrombectomy with mild deficits: the national inpatient sample. *Stroke* 2023; 54: 2031–2039.

82) Klein P, Huo X, Chen Y, et al. Specialist perspectives on the imaging selection of large vessel occlusion in the late window. *Clin Neuroradiol* 2023: 1–11.

83) Zaidat OO, Castonguay AC, Linfante I, et al. First pass effect: a new measure for stroke thrombectomy devices. *Stroke* 2018; 49: 660–666.

84) Huo X, Sun D, Nguyen TN, et al. First-pass effect of mechanical thrombectomy for anterior circulation large vessel occlusion: incidence, predictors, and clinical impact. Insight from the ANGEL-ACT registry. *J Neurosurg* 2023: 1–8.

85) Mokin M, Primiani CT, Castonguay AC, et al. First pass effect in patients treated with the trevo stent-retriever: a track registry study analysis. *Front Neurol* 2020; 11: 83.

86) Kaesmacher J, Bellwald S, Dobrocky T, et al. Safety and efficacy of intra-arterial urokinase after failed, unsuccessful, or incomplete mechanical thrombectomy in anterior circulation large-vessel occlusion stroke. *JAMA Neurol* 2020; 77: 318–326.

87) Liu L, Li W, Qiu J, et al. Improving neurological outcome for acute basilar artery occlusion with sufficient recanalization after thrombectomy by intraarterial tenecteplase (INSIST-IT): rationale and design. *Eur Stroke J* 2023; 8: 591–597.

88) Hu H-Z, Qiu J, Li W, et al. Rescue thrombolysis for medium vessel occlusion (RESCUE-TNK): rationale and design of a phase 2 randomized trial. *Front Neurol* 2023; 14: 1154736.
89) Hernández-Jiménez M, Abad-Santos F, Cotgreave I, et al. Safety and efficacy of ApTOLL in patients with ischemic stroke undergoing endovascular treatment: a phase 1/2 randomized clinical trial. *JAMA Neurol* 2023. [Epub ahead of print]
90) Wang A, Jia B, Zhang X, et al. Efficacy and safety of butylphthalide in patients with acute ischemic stroke: a randomized clinical trial. *JAMA Neurol* 2023. [Epub ahead of print]
91) Zhao Z-A, Qiu J, Wang L, et al. Intra-arterial tenecteplase is safe and may improve the first-pass recanalization for acute ischemic stroke with large-artery atherosclerosis: the BRETIS-TNK trial. *Front Neurol* 2023; 14: 1155269.
92) Sang H, Xie D, Tian Y, et al. Association of tirofiban with functional outcomes after thrombectomy in acute ischemic stroke due to intracranial atherosclerotic disease. *Neurology* 2023; 100: e1996–e2006.