Stroke: Vascular and Interventional Neurology

ORIGINAL RESEARCH

MARVEL: A Randomized Double-Blind, Placebo-Controlled Trial in Patients Undergoing Endovascular Therapy: Study Rationale and Design

Qingwu Yang, MD, PhD†; Changwei Guo, MD†; Chengsong Yue, MD†; Jie Yang, MD; Linyu Li, MD; Zhouzhou Peng, MD; Jinrong Hu, MD; Jiandi Huang, MD; Jiaxing Song, MD; Jiacheng Huang, MD; Weilin Kong, MD; Nizhen Yu, MD; Dahong Yang, MD; Xiang Liu, MD; Duolao Wang, PhD; Raul G. Nogueira, MD; Fengli Li, MD‡; Thanh N. Nguyen, MD‡; Wenjie Zi, MD‡

BACKGROUND: Steroids have pleiotropic neuroprotective actions including the regulation of inflammation and apoptosis which may influence the effects of ischemia on neurons, glial cells, and blood vessels. The effect of low-dose methylprednisolone in patients with acute ischemic stroke in the endovascular therapy era remains unknown. This trial investigates the efficacy and safety of low-dose methylprednisolone (2 mg/kg IV for 3 days) as adjunctive therapy for patients with acute ischemic stroke undergoing endovascular therapy within 24 hours from symptom onset.

METHODS: The MARVEL (Methylprednisolone as Adjunctive Therapy for Acute Large Vessel Occlusion: A Randomized Double-Blind, Placebo-Controlled Trial in Patients Undergoing Endovascular Therapy) trial is an investigator-initiated, prospective, randomized, double-blind, placebo-controlled multicenter clinical trial. Up to 1672 eligible patients with anterior circulation large-vessel occlusion stroke presenting within 24 hours from symptom onset are planned to be consecutively randomized to receive methylprednisolone or placebo in a 1:1 ratio across 82 stroke centers in China.

RESULTS: The primary outcome is the ordinal shift in the modified Rankin scale score at 90 days. Secondary outcomes include 90-day functional independence (modified Rankin scale score, 0–2). The primary safety end points include mortality rate at 90 days and symptomatic intracerebral hemorrhage within 48 hours of endovascular therapy.

CONCLUSION: The MARVEL trial will provide evidence of the efficacy and safety of low-dose methylprednisolone as adjunctive therapy for patients with anterior circulation large-vessel occlusion stroke undergoing endovascular therapy.

Key Words: adjunctive therapy ■ corticosteroids ■ endovascular therapy ■ methylprednisolone ■ randomized trial ■ trial protocol

The American Heart Association guidelines recommend endovascular treatment (EVT) for select patients with large-vessel occlusion with class IA evidence. The recanalization rate has improved to 80% to 94% with newer endovascular techniques.[1,2] As high recanalization rates have been achieved, research priorities

Correspondence to: Wenjie Zi, MD, Department of Neurology, Xinqiao Hospital, Army Medical University, No. 183 Xinqiao Main Street, Shapingba District, Chongqing 400037, China. E-mail: ziwenjie@126.com

†Q. Yang, C. Guo, and C. Yue are co-first authors.

‡W. Zi, T.N. Nguyen, and F. Li are co-senior authors.

Clinical Trial Registration Information: www.chictr.org.cn (Unique identifier: ChiCTR2100051729)

Stroke: Vascular and Interventional Neurology is available at: www.ahajournals.org/journal/svin

Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
BBB	blood–brain barrier
EVT	endovascular therapy
MARVEL	Methylprednisolone as Adjunctive Therapy for Large Vessel Occlusion (MARVEL): A Randomized Double-Blind, Placebo-Controlled Trial in Patients Undergoing Endovascular Therapy
mRS	modified Rankin scale
RESCUE-Japan LIMIT	Randomized Clinical Trial of Endovascular Therapy for Acute Large Vessel Occlusion With Large Ischemic Core

CLINICAL PERSPECTIVE

What Is New?

- We initiated a large, multicenter, double-blind, randomized clinical trial to give a high level of evidence of the efficacy of low-dose methylprednisolone, an intermediate-acting corticosteroid in patients with stroke who underwent endovascular treatment (EVT).

What Aare the Clinical Implications?

- This study represents a study protocol of a prospective multicenter, double-blind, placebo-controlled trial that was conducted at nearly 80 centers in China, which investigated the effects of intravenous methylprednisolone in patients who underwent endovascular therapy. If positive, this study could provide a significant change to the clinical management of patients with acute ischemic stroke who underwent endovascular therapy.

pivot toward neuroprotection to improve patient outcomes. Theoretically, neuroprotection can be achieved either by extending the longevity of the penumbral territory that could be salvaged, limiting hemorrhagic and edema risks with reperfusion, or attenuating the potential risks of reperfusion injury and related inflammatory cascade postreperfusion. Intercepting any of these pathways may help to decrease the risk of "futile recanalization," a term that describes patients who achieve satisfactory reperfusion but fail to achieve functional improvement.[3–10] Another term that has recently emerged in lieu of "futile recanalization" is "reperfusion without functional independence" because many of these patients can still have quality of life despite being in a state of dependency.[11]

Growing evidence indicates that the inflammatory responses following stroke are present throughout the brain and can worsen secondary brain injury.[12] Cerebral edema after ischemic stroke can be classified as cytotoxic or vasogenic edema. While most of the edema after ischemic infarction is vasogenic, cytotoxic edema can also occur due to cell membrane dysfunction. Several early phase I/II trials focused on adjunctive immune-targeted therapies to EVT have yielded promising results of reducing disability and death compared with control patients.[4,13,14]

While corticosteroids are widely used anti-inflammatory and immunosuppressive agents, their effect on stroke outcomes remains debated. Preclinical studies have shown that corticosteroids can reduce infarct area, regulate cerebral blood flow, stabilize the blood–brain barrier (BBB), and reduce angiogenic edema in animal models,[15–19] while clinical stroke studies have shown neutral results.[20] However, there was a call to reignite the study of corticosteroids in stroke, especially in the reperfusion era.[21,22] Several lessons are learned from prior studies. First, previous neutral studies used high doses and a long duration of corticosteroid, which may have led to more side effects. Second, the sample size of these trials was small and most included patients with "presumed ischemic stroke" were treated in an era where reperfusion was not effective. Davis and Donnan suggested that steroid therapy for stroke may have been discarded prematurely. Third, the last trial was published in 2001 by Ogun and Odusote.[23] To date, the evidence for the use of corticosteroids in stroke is limited. High-quality evidence is warranted to provide a definitive answer to the benefit or risk of adjunctive therapy of corticosteroids in patients with stroke. Fourth, EVT has transformed the treatment of patients with ischemic stroke with large-vessel occlusion. While 80%–90% of patients achieve reperfusion, approximately half of patients are disabled, and the mortality rate is estimated to be 15%.[24] Improving functional outcome, reducing disability and death for patients who have achieved reperfusion is an important frontier in stroke research.[25] Thus, adjuvant treatments are needed to complement recanalization therapies.[21,26] Fifth, the EVT damages the BBB and will lead to severe brain

edema and hemorrhagic transformation, which considerably contribute to neurological deterioration and death.[27,28] As corticosteroids have been observed to stabilize the BBB and prevent vasogenic edema, they may present a promising avenue for mitigating hemorrhagic transformation and brain edema.[28] Considering the reasons above, studies with adequate sample size are warranted to give a high level of evidence to prove or disprove the use of corticosteroids in the new reperfusion era.

We initiated the MARVEL (Methylprednisolone as Adjunctive Therapy for Large Vessel Occlusion: A Randomized Double-Blind, Placebo-Controlled Trial in Patients Undergoing Endovascular Therapy) trial to give a high level of evidence of whether use of low-dose methylprednisolone can benefit patients with stroke in the era of EVT in a large, multicenter, double-blind, randomized clinical trial.[29]

METHODS

Design

The MARVEL trial is a multicenter, prospective, randomized, placebo-controlled, double-blind clinical trial. This trial was registered at www.chictr.org.cn (ChiCTR2100051729). The trial was designed in compliance with the Declaration of Helsinki. The protocol was approved by the ethics committee of Chongqing Xinqiao Hospital, Army Medical University, and all participating centers. Data will be made available upon reasonable request to the corresponding author. This study included 82 stroke centers in China. The key criterion for a qualifying participating center is the performance of at least 30 mechanical thrombectomy procedures with the use of stent retriever or contact aspiration devices annually, and all participating neurointerventionalists should have >3 years' experience in neurointervention and performed at least 30 EVT procedures. The trial flowchart is depicted in the Figure. This study is planned to start in January 2022 and finish its enrollment in June 2023.

Inclusion criteria include:

1. Age ≥18 years
2. Presenting with acute ischemic stroke (AIS) with symptoms within 24 hours from time last known well
3. Baseline National Institutes of Health Stroke Scale≥6
4. Anterior circulation ischemic stroke was determined according to clinical symptoms and imaging examination
5. Baseline Alberta Stroke Program Early Computed Tomography Score≥3
6. Occlusion of the intracranial internal carotid artery, the M1 or M2 segment of the middle cerebral artery confirmed by computed tomography angiography, magnetic resonance angiography, or digital subtraction angiography
7. Planned treatment with EVT
8. Informed consent obtained from patients or their legal representatives

Exclusion criteria include:

1. Computed tomography or magnetic resonance imaging evidence of hemorrhage
2. Modified Rankin scale (mRS) score ≥2 before stroke onset
3. Pregnant or lactating women
4. Allergic to contrast agents or glucocorticoids
5. Participating in other clinical trials
6. Systolic blood pressure >185 mm Hg or diastolic pressure >110 mm Hg, refractory to antihypertensive drugs
7. Genetic or acquired bleeding diathesis, lack of anticoagulant factors, or oral anticoagulants and international normalized ratio >1.7
8. Blood glucose <2.8 mmol/L (50 mg/dL) or >22.2 mmol/L (400 mg/dL), platelets $<90\times10^9$/L
9. Arterial tortuosity precluding access with thrombectomy device
10. Bleeding history (gastrointestinal and urinary tract bleeding) in the past month
11. Chronic hemodialysis and severe renal insufficiency (glomerular filtration rate <30 mL/min or serum creatinine >220 μmol/L [2.5 mg/dL])
12. Life expectancy <6 months due to comorbidities
13. Follow-up is not expected to be completed
14. Intracranial aneurysm or arteriovenous malformation
15. Brain tumor with mass effect on imaging
16. Systemic infectious disease

Randomization

After confirming patient eligibility and receiving informed consent from patients or their legal representatives, randomization will be conducted through a web-based application (www.jinlingshu.com) stratified by participating centers. Eligible patients will be randomly assigned to either the methylprednisolone or control group in a 1:1 ratio. Patients enrolled in the trial will

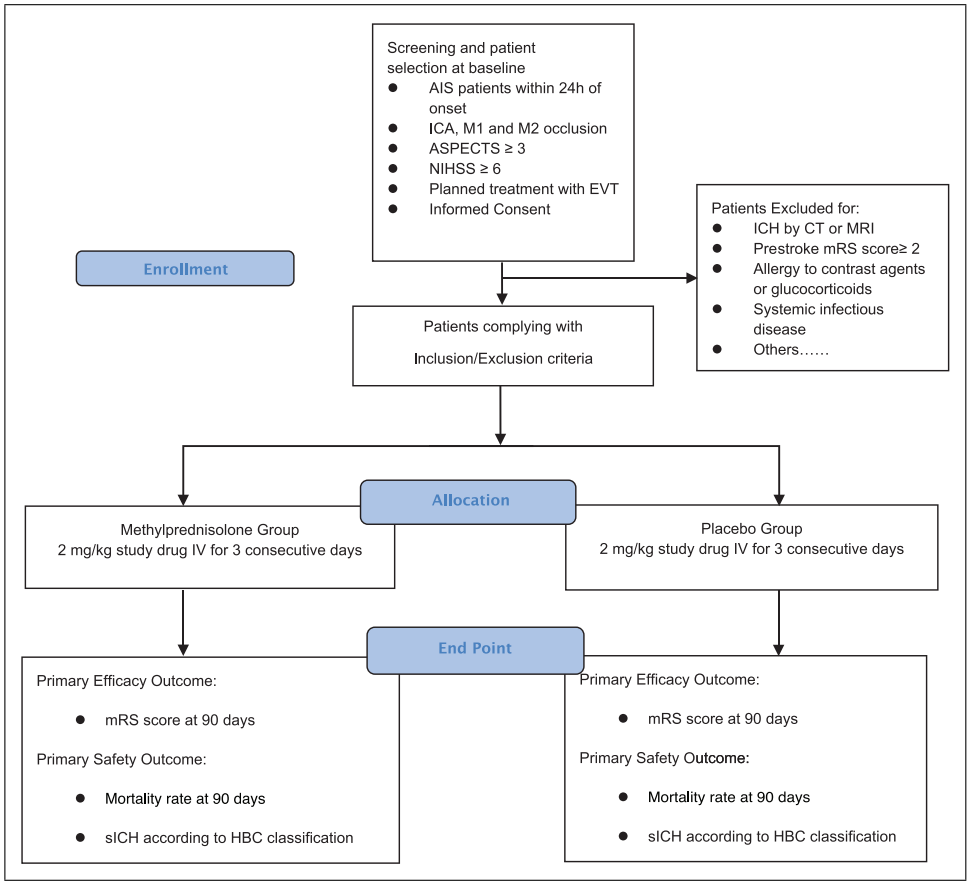

Figure. Study flowchart. AIS indicates acute ischemic stroke; ASPECTS, Alberta Stroke Program Early Computed Tomography score; CT, computed tomography; EVT, endovascular therapy; HBC, Heidelberg Bleeding Classification; ICA, intracranial carotid artery; ICH, intracranial cerebral hemorrhage; M1, first segment of the middle cerebral artery; M2, second segment of the middle cerebral artery; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Scale; and sICH, symptomatic intracranial hemorrhage.

receive masked medications corresponding to their assigned random serial number based on their enrollment time. Both trial personnel and patients will remain blinded to treatment assignment throughout the study.

Contents of Study Drug Kit

Each kit contains 12 bottles of drugs, and each bottle contains 40 mg of methylprednisolone sodium succinate or placebo (Chongqing Lummy Pharmaceutical Co., Ltd.). The medication kit and bottles are visually identical (including labeling, dosage form, size, and color), except for the identification number.

Treatment

After randomization, the study drug will be dissolved in saline with a dose of 2 mg/kg IV per day and administered immediately upon patient enrollment. The maximum dose is 160 mg IV. The study drug will be given for 3 consecutive days and then ceased. Gastrointestinal prophylaxis and hyperglycemia treatment will be administered per standard local protocols.

Study Schedule

Collection of data will include but not be restricted to patients' baseline characteristics, medical history, laboratory findings, stroke severity, and neurological deficits at time of treatment, pretreatment and post-treatment imaging findings, important time metrics, EVT characteristics, complications, presumed stroke causative mechanism, and functional outcomes at 90 days (Table).

Efficacy End Points

The primary end point is the distribution of the mRS (shift analysis) at 90 days after randomization.

The secondary end points include:

1. Proportion of mRS score of 0 to 4 at 90 days
2. Proportion of mRS score of 0 to 3 at 90 days

Table. Schedule of Assessments

	Visit (time in hours/days from treatment=V1)					
	Screening		Treatment		Follow-up	
			Visit 1[a]	Visit 2	Visit 3[b]	Visit 4
	Visit 0	Randomization	Study medication administration	(48–96 h)	(5–7 d)	(90±7 d)
Informed consent	X					
Demographic data	X					
Medical history	X					
Physical examination	X			X	X	
Prestroke mRS	X					
NIHSS	X			X	X	
mRS						X
EQ-5D						X
Previous medication	X					
Blood pressure and heart rate	X		X	X[c]	X	
Local laboratory result	X			X		
Pregnancy test[d]	X					
Brain CT/MRI plus CTA/MRA/DSA	X					
Brain CT/MRI scan[e]	X			X		
Inclusion/exclusion criteria	X					
Randomization		X				
Study medication			X			
Concomitant medication	X		X	X	X	X
12-lead ECG	X					
48-h monitoring			X[a]			
Adverse events			X	X	X	X

CT indicates computed tomography; CTA, computed tomography angiography; DSA, digital subtraction angiography; EQ-5D, EuroQol Five Dimensions Questionnaire ; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; mRS, modified Rankin scale; and NIHSS, National Institute of Health Stroke Scale.

[a]48-h monitoring in unit or equivalent unit including repeated measurements of blood pressure, heart rate, and body temperature.

[b]Or hospital discharge if <5 days.

[c]Every hour.

[d]Mandatory for women of childbearing potential.

[e]Also to be performed in any case of neurological deterioration during the first 96 h.

3. Proportion of mRS score of 0 to 2 at 90 days
4. Proportion of mRS score of 0 to 1 or return to premorbid mRS score at 90 days (for patients with mRS score >1)
5. National Institutes of Health Stroke Scale score at 5 to 7 days or at early discharge
6. European Quality Five-Dimension scale score at 90 days

Safety End Points

The safety end points include mortality rate at 90 days, symptomatic intracranial hemorrhage rate within 48 hours according to the Heidelberg Bleeding Classification,[30] the proportion of patients with any intracranial hemorrhage within 48 hours, or hemicraniectomy. The incidence of serious adverse events and corticosteroid-related adverse events (hyperglycemia, infection, and gastrointestinal hemorrhage) will also be recorded.

Data and Safety Monitoring Board

An independent data and safety monitoring board will be organized with 3 experts (including a neurologist, a neurointerventionist, and a biostatistician). Members of the data and safety monitoring board will not participate in the trial or be affiliated with the study sponsors. The data and safety monitoring board will meet annually and monitor trial progress. In addition, the data and safety monitoring board will review the incidence of serious adverse events to ensure patient safety.

Sample Size Estimates

We assume cumulative proportion of favorable functional outcome (mRS score, 0–2) of 50% and 43% in the methylprednisolone and placebo groups, respectively.[31,32] The steering committee estimated a

7% difference in improved outcomes with steroids, indicating an odds ratio of 1.33. To demonstrate a 7% absolute difference with a type 1 error α of 0.05 (2-tailed) with a power of 80% (β, 20%), a sample size of 1588 patients would be needed (794 patients per treatment group). To take into account a 5% attrition rate, a total of 1672 patients is required (836 per treatment group).

Statistical Analysis

The primary effect variable will be the generalized odds ratio.[33] The secondary outcomes and safety outcomes will be analyzed using generalized linear models. The treatment effect will be estimated adjusted for the following prognostic variables age, baseline National Institutes of Health Stroke Scale score, prestroke mRS score, baseline Alberta Stroke Program Early Computed Tomography Score score, use of intravenous thrombolysis, time from onset to randomization, and occlusion location. Primary data analyses will be based on the intention-to-treat principle. The per-protocol analyses will also be performed as supplemental analyses. All statistical analyses will be performed using SAS version 9.4 (SAS Institute) and R version 4.3.0 (R Foundation for Statistical Computing). The trial results will be reported following the Consolidated Standards of Reporting Trials guidelines for reporting randomized trials.

DISCUSSION AND SUMMARY

The MARVEL trial is planned to involve 1672 patients, which is nearly 4-fold higher than the Cochran review of 466 patients. Evidence-based treatments to salvage the penumbral tissue invariably involve restoring blood flow as early as possible.[34] Revascularization strategies including intravenous thrombolysis and EVT are recommended in select patients by multiple neuroscience organizations.[1,35,36] However, while the early recanalization rate is estimated to be achieved in >80% in patients with EVT, about half of patients do not achieve functional independence.[11,24,37] Several studies indicated that modulating the immune system could be a target to close this gap in patient outcomes.[13,38,39]

Inflammatory mechanisms after stroke are now increasingly considered prime targets for stroke therapy since immune signals and their mediators can have both detrimental and beneficial effects at different stages of the disease process.[12,38] Several proof-of-concept trials have demonstrated that immune modulators were effective in patients with AIS undergoing EVT.[3,4,13,40] Adjunctive therapies are now being increasingly considered to complement EVT. Shi's team suggested that fingolimod may be a potential treatment for patients with ischemic stroke. The phase Ib/IIa APRIL (A Double-Blind, Placebo-Controlled, Randomized, Phase Ib/IIa Clinical Study of Aptoll for the Treatment of Acute Ischemic Stroke) trial investigated a DNA aptamer, Aptoll, which is an antagonist of toll-like receptor, as an adjunctive therapy to EVT. The results were promising, indicating reduction in disability and death at 90 days.[14] However, the high cost and limited availability of this treatment restrict its widespread application.

Corticosteroids, being widely used and easily accessible anti-inflammatory and immunosuppressive agents, have demonstrated their ability to reduce the area of infarction in animal models. It has been suggested that corticosteroids can restore the overall structure and improve the tightness of the BBB.[16,41] Besides, several studies also suggested that use of corticosteroids in a transient middle cerebral artery occlusion model can improve cerebral blood flow and reduce the infarct volume.

However, the use of corticosteroids in clinical practice remains a subject of debate, as evidence for its benefit in patients with AIS remains sparse.[19] A Cochrane review on steroids for AIS evaluated 8 trials with 466 patients.[20] There was bias in the selection of patients with "presumed ischemic stroke." Besides, in past corticosteroid treatment trials, conducted before the advent of mechanical thrombectomy as a treatment option, it is likely that many patients failed to reperfuse; the candidate adjuvant treatments were tested in the more challenging setting of permanent rather than transient brain ischemia and thus failed to show benefit in clinical trials. The Stroke Treatment Academic Industry Roundtable suggested testing the neuroprotective agents in the new EVT era when the reperfusion rate can be up to 90%. One key strength of this study was that the design of this study largely matched the primate model of transient middle cerebral artery occlusion, in which the corticosteroids showed its effect, rather than the permanent middle cerebral artery occlusion.

Growing evidence has shown that the patients undergoing EVT were associated with disruptions of the BBB, leading to severe brain edema and hemorrhagic transformation.[27] These complications considerably contribute to neurological deterioration and death.[28] As corticosteroids have been observed to stabilize the BBB and prevent vasogenic edema, they may present a promising avenue for mitigating hemorrhagic transformation and brain edema.[28] Targeting patients with brain edema after EVT might bring hope for patients with AIS, especially those who suffered from a large infarct within an extended time window.[19]

Since The RESCUE-Japan LIMIT (Randomized Clinical Trial of Endovascular Therapy for Acute Large Vessel Occlusion With Large Ischemic Core), ANGEL-ASPECT

(Study of Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients With a Large Infarct Core), and SELECT2 (A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke) trials have expanded the use of EVT to treat patients with large infarct cores.[6,7,10] This study includes broad imaging eligibility criteria such as a baseline Alberta Stroke Program Early CT Score score≥3, consistent with recent evidence to treat patients with small and large infarct cores. Additionally, this study aims to investigate the effect of corticosteroids on patients experiencing high severity of stroke disease events associated with high morbidity and death.

However, this study has some limitations. First, all patients enrolled in this trial were from China, and the results might not generalize well to patients of other ethnicities Second, this study included only patients with anterior large-vessel occlusion, and patients with acute basilar occlusions should be further studied.

The MARVEL randomized trial enrolled the first patient on February 9, 2022. When completed, this trial will provide pivotal data for assessing the efficacy and safety of early adjunctive low-dose methylprednisolone with EVT for patients with AIS.

ARTICLE INFORMATION

Received August 2, 2023; Accepted December 13, 2023

Affiliations

Department of Neurology, Xinqiao Hospital, Army Medical University, Chongqing, China (Q.Y., C.G., C.Y., J.Y., L.L., Z.P., J.H., J.H., J.S., J.H., W.K., N.Y., D.Y., X.L., F.L., W.Z.); Global Health Trials Unit, Liverpool School of Tropical Medicine, Liverpool, UK (D.W.); UPMC Stroke Institute, Departments of Neurology and Neurosurgery, University of Pittsburgh School of Medicine, PA (R.G.N.); Department of Neurology and Radiology, Boston Medical Center, Boston, MA (T.N.N.)

Acknowledgments

None.

Sources of Funding

The author(s) disclose receipt of the following financial support for the research, authorship, or publication of this article: This clinical trial is sponsored by (1) Chongqing Lummy Pharmaceutical Co., China, (2) National Natural Science Foundation of China (No. 82090040, 82071323), and (3) Army Medical University Clinical Medical Research Talent Training Program No. 2018D004. The sponsors had no role in the study design, data collection, analysis, and interpretation, and in drafting and submitting this article.

Disclosure

Dr Nogueira reported receiving consulting fees for advisory roles with Anaconda, Biogen, Cerenovus, Genentech, Imperative Care, Medtronic, Phenox, Prolong Pharmaceuticals, and Stryker Neurovascular and having stock options for advisory roles with Astrocyte, Brainomix, Cerebrotech, Ceretrieve, Corindus Vascular Robotics, Vesalio, Viz-AI, and Perfuze. Dr Nguyen reported advisory board membership with Idorsia and Brainomix and data and safety monitoring board for SELECT2, Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke (TESLA), Workflow Optimization to Reduce Time to Endovascular Reperfusion for Ultra-fast Stroke Treatment (WE-TRUST), and Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST2). All other authors declare no potential conflicts of interest with respect to the research, authorship, or publication of this article.

REFERENCES

1. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, 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.
2. Haussen DC, Al-Bayati AR, Mohammaden MH, Sheth SA, Salazar-Marioni S, Linfante I, Dabus G, Starosciak AK, Hassan AE, Tekle WG, et al. The Society of Vascular and Interventional Neurology (SVIN) Mechanical Thrombectomy Registry: methods and primary results. *Stroke*. 2022;2:e000234.
3. Hernández-Jiménez M, Martín-Vílchez S, Ochoa D, Mejía-Abril G, Román M, Camargo-Mamani P, Luquero-Bueno S, Jilma B, Moro MA, Fernández G, et al. First-in-human phase I clinical trial of a TLR4-binding DNA aptamer, ApTOLL: safety and pharmacokinetics in healthy volunteers. *Mol Ther Nucleic Acids*. 2022;28:124-135.
4. Hernández-Jiménez M, Abad-Santos F, Cotgreave I, Gallego J, Jilma B, Flores A, Jovin TG, Vivancos J, Molina CA, Montaner J, et al. APRIL: a double-blind, placebo-controlled, randomized, Phase Ib/IIa clinical study of ApTOLL for the treatment of acute ischemic stroke. *Front Neurol*. 2023;14:1127585.
5. Olthuis SGH, Pirson FAV, Pinckaers FME, Hinsenveld WH, Nieboer D, Ceulemans A, Knapen R, Robbe MMQ, Berkhemer OA, van Walderveen MAA, 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.
6. Huo X, Ma G, Tong X, Zhang X, Pan Y, Nguyen TN, Yuan G, Han H, Chen W, Wei M, et al. Trial of endovascular therapy for acute ischemic stroke with large infarct. *N Engl J Med*. 2023;388:1272-1283.
7. Sarraj A, Hassan AE, Abraham MG, Ortega-Gutierrez S, Kasner SE, Hussain MS, Chen M, Blackburn S, Sitton CW, Churilov L, et al. Trial of endovascular thrombectomy for large ischemic strokes. *N Engl J Med*. 2023;388:1259-1271.
8. Tariq S, Sah RG, Chan L, Rajashekar D, McTaggart R, Butcher K, Aviv R, Swartz R, Field T, Tarpley J, et al. Recanalization following Endovascular treatment and imaging of PErfusion, Regional inFarction and atrophy to Understand Stroke Evolution-NA1 (REPERFUSE-NA1). *Int J Stroke*. 2020;15:343-349.
9. Hill MD, Goyal M, Menon BK, Nogueira RG, McTaggart RA, Demchuk AM, Poppe AY, Buck BH, Field TS, Dowlatshahi D, et al. Efficacy and safety of nerinetide for the treatment of acute ischaemic stroke (ESCAPE-NA1): a multicentre, double-blind, randomised controlled trial. *Lancet*. 2020;395:878-887.
10. Yoshimura S, Sakai N, Yamagami H, Uchida K, Beppu M, Toyoda K, Matsumaru Y, Matsumoto Y, Kimura K, Takeuchi M, et al. Endovascular therapy for acute stroke with a large ischemic region. *N Engl J Med*. 2022;386:1303-1313.
11. Seker F, Qureshi MM, Mohlenbruch MA, Nogueira RG, Abdalkader M, Ribo M, Caparros F, Haussen DC, Mohammaden MH, Sheth SA, et al. Reperfusion without functional independence in late presentation of stroke with large vessel occlusion. *Stroke*. 2022;53:3594-3604.
12. Shi KB, Tian DC, Li ZLG, Ducruet AF, Lawton MT, Shi FD. Global brain inflammation in stroke. *Lancet Neurol*. 2019;18:1058-1066.
13. Tian DC, Shi K, Zhu Z, Yao J, Yang X, Su L, Zhang S, Zhang M, Gonzales RJ, Liu Q, et al. Fingolimod enhances the efficacy of delayed alteplase administration in acute ischemic stroke by promoting anterograde reperfusion and retrograde collateral flow. *Ann Neurol*. 2018;84:717-728.
14. Hernandez-Jimenez M, Abad-Santos F, Cotgreave I, Gallego J, Jilma B, Flores A, Jovin TG, Vivancos J, Hernandez-Perez M, Molina CA, 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;80(8):779–788.

15. Espinosa A, Meneses G, Chavarría A, Mancilla R, Pedraza-Chaverri J, Fleury A, Bárcena B, Pérez-Osorio IN, Besedovsky H, Arauz A, et al. Intranasal dexamethasone reduces mortality and brain damage in a mouse experimental ischemic stroke model. *Neurotherapeutics*. 2020;17:1907-1918.
16. Altamentova S, Rumajogee P, Hong J, Beldick SR, Park SJ, Yee A, Fehlings MG. Methylprednisolone reduces persistent post-ischemic inflammation in a rat hypoxia-ischemia model of perinatal stroke. *Transl Stroke Res*. 2020;11:1117-1136.
17. Slivka AP, Murphy EJ. High-dose methylprednisolone treatment in experimental focal cerebral ischemia. *Exp Neurol*. 2001;167:166-172.
18. Limbourg FP, Huang Z, Plumier JC, Simoncini T, Fujioka M, Tuckermann J, Schütz G, Moskowitz MA, Liao JK. Rapid nontranscriptional activation of endothelial nitric oxide synthase mediates increased cerebral blood flow and stroke protection by corticosteroids. *J Clin Invest*. 2002;110:1729-1738.
19. Norris JW. Steroids may have a role in stroke therapy. *Stroke*. 2004;35:228-229.
20. Sandercock PAG, Soane T. Corticosteroids for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2011;2011(9):CD000064.
21. Savitz SI, Baron J-C, Yenari MA, Sanossian N, Fisher M. Reconsidering neuroprotection in the reperfusion era. *Stroke*. 2017;48:3413-3419.
22. Davis SM, Donnan GA. Steroids for stroke: another potential therapy discarded prematurely? *Stroke*. 2004;35:230-231.
23. Ogun SA, Odusote KA. Effectiveness of high dose dexamethasone in the treatment of acute stroke. *West Afr J Med*. 2001;20:1-6.
24. Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, Davalos A, Majoie C, van der Lugt A, de Miquel MA, 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.
25. Nie X, Leng X, Miao Z, Fisher M, Liu L. Clinically ineffective reperfusion after endovascular therapy in acute ischemic. *Stroke*. 2023;54:873-881.
26. Lyden P, Buchan A, Boltze J, Fisher M, Ansari S, Broderick JP, Campbell BCV, Chaisinanunkul N, Chen C, Grotta JC, et al. Top priorities for cerebroprotective studies – a paradigm shift: report from STAIR XI. *Stroke*. 2021;52:3063-3071.
27. Shi ZS, Duckwiler GR, Jahan R, Tateshima S, Szeder V, Saver JL, Kim D, Sharma LK, Vespa PM, Salamon N, et al. Early blood-brain barrier disruption after mechanical thrombectomy in acute ischemic stroke. *J Neuroimaging*. 2018;28:283-288.
28. Ng FC, Churilov L, Yassi N, Kleinig TJ, Thijs V, Wu TY, Shah DG, Dewey HM, Sharma G, Desmond PM, et al. Microvascular dysfunction in blood-brain barrier disruption and hypoperfusion within the infarct posttreatment are associated with cerebral edema. *Stroke*. 2022;53:1597-1605.
29. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. *Nat Rev Immunol*. 2017;17:233-247.
30. von Kummer R, Broderick JP, Campbell BC, Demchuk A, Goyal M, Hill MD, Treurniet KM, Majoie CB, Marquering HA, Mazya MV, et al. The Heidelberg Bleeding Classification: classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke*. 2015;46:2981-2986.
31. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Davalos A, Majoie CB, van der Lugt A, de Miquel MA, 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.
32. Zi W, Wang H, Yang D, Hao Y, Zhang M, Geng Y, Lin M, Wan Y, Shi Z, Zhou Z, et al. Clinical effectiveness and safety outcomes of endovascular treatment for acute anterior circulation ischemic stroke in China. *Cerebrovasc Dis*. 2017;44:248-258.
33. Churilov L, Arnup S, Johns H, Leung T, Roberts S, Campbell BCV, Davis SM, Donnan GA. An improved method for simple, assumption-free ordinal analysis of the modified Rankin scale using generalized odds ratios. *Int J Stroke*. 2014;9:999-1005.
34. Baron JC. Protecting the ischaemic penumbra as an adjunct to thrombectomy for acute stroke. *Nat Rev Neurol*. 2018;14:325-337.
35. Liu L, Chen W, Zhou H, Duan W, Li S, Huo X, Xu W, Huang L, Zheng H, Liu J, et al. Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of clinical management of ischaemic cerebrovascular diseases. *Stroke Vasc Neurol*. 2020;5:159-176.
36. Nguyen TN, Castonguay AC, Siegler JE, Nagel S, Lansberg MG, de Havenon A, Sheth SA, Abdalkader M, Tsai JP, Albers GW, 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*. 2023;3:e000512.
37. de Rueda ME, Parrilla G, Manzano-Fernandez S, Garcia-Villalba B, Zamarro J, Hernandez-Fernandez F, Sanchez-Vizcaino C, Carreon E, Morales A, Moreno A. Combined multimodal computed tomography score correlates with futile recanalization after thrombectomy in patients with acute stroke. *Stroke*. 2015;46:2517-2522.
38. Planas AM. Role of immune cells migrating to the ischemic brain. *Stroke*. 2018;49:2261-2267.
39. Yang J, Jin Z, Song J, Guo C, Xie D, Yue C, Kong W, Hu J, Luo W, Liu S, et al. Futile recanalization after endovascular treatment in patients with acute basilar artery occlusion. *Neurosurgery*. 2023;92:1006-1012.
40. Wang A, Jia B, Zhang X, Huo X, Chen J, Gui L, Cai Y, Guo Z, Han Y, Peng Z, et al. Efficacy and safety of butylphthalide in patients with acute ischemic stroke: a randomized clinical trial. *JAMA Neurol*. 2023;80(8):851–858.
41. Espinosa A, Meneses G, Chavarria A, Mancilla R, Pedraza-Chaverri J, Fleury A, Barcena B, Perez-Osorio IN, Besedovsky H, Arauz A, et al. Intranasal dexamethasone reduces mortality and brain damage in a mouse experimental ischemic stroke model. *Neurotherapeutics*. 2020;17:1907-1918.