

Reperfusion therapy for acute ischemic stroke: Where we are and where to go

Siying Fan¹, Lu Yang¹, Xunming Ji²

¹Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing 100053, China;

²Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing 100053, China

INTRODUCTION

Acute ischemic stroke (AIS) is caused by the occlusion of a cerebral artery, resulting in an abrupt cessation of blood flow to the brain and posing a serious threat to human health. Over the past decades, significant progress has been made in reperfusion therapies for AIS. However, the issue of personalized therapy and time window is crucial and still needs to be evaluated according to the specific circumstances of the patient. Future research should focus on optimizing strategies, reducing treatment-related risks and improving clinical outcomes.

REPERFUSION THERAPY

AIS is caused by the occlusion of a cerebral artery, leading to an abrupt cerebral arterial blood flow cessation. Therefore, prompt restoration of blood flow, known as reperfusion therapy, is currently considered the first choice in the management of AIS. In recent years, studies have shown that intravenous thrombolytic therapy with alteplase can significantly improve clinical outcomes for patients with onset within 4.5 hours. More recent studies further showed that 0.25 mg/kg tenecteplase had no significant difference in clinical prognosis, incidence of symptomatic intracerebral hemorrhage, and mortality compared with 0.9 mg/kg alteplase, and 0.25 mg/kg tenecteplase was more convenient to administer. Suitable for use in mobile stroke units. A series of randomized controlled trials published in 2015 demonstrated the efficacy of endovascular thrombectomy using modern thrombectomy devices.^[1] Compared with standard medical treatment with intravenous thrombolysis alone, eligible AIS patients receiving thrombectomy

therapy showed significantly higher rates of successful recanalization without increased risk of symptomatic intracranial hemorrhage. In addition, the large-scale study in Japan (Rescue-Japan Limit) further expanded the suitable population for anterior circulation endovascular therapy, showing that endovascular therapy is also superior to drug-conservative therapy in highly screened patients with large cerebral infarction.

CEREBRAL PROTECTION

Over the past two decades, significant advances have been made in reperfusion therapies. However, the overall prognosis of patients treated with reperfusion therapy remains unsatisfactory. Neuroprotective therapy based on revascularization may become one of the measures to improve the current situation. Therefore, it is necessary to develop cerebral protection as an adjunct therapy, which may focus on two potential neuroprotective targets. One is to prevent or delay the conversion of salvageable tissue from the ischemic penumbra to the irreversible ischemic core, and another is to reduce the consequences of reperfusion injury in a variety of ways. The neuroprotective effect of pharmacological approaches designed to inhibit ischemic cascade pathways and non-pharmacological therapies, including hypothermia, normobaric hyperoxia, remote ischemic conditioning, cathodal transcranial direct current stimulation, and so on, have been fully evaluated in preclinical trials.^[2] With a further and deeper understanding of the mechanisms of cerebral protection, recent studies have focused more on the neurovascular unit (consisting of neurons, astrocytes, microglia, pericytes, and the

Address for Correspondence:
Xunming Ji, Department of Neurosurgery,
Xuanwu Hospital, Capital Medical
University, Beijing 100053, China.
Email: jixm@ccmu.edu.cn

Access this article online

Website:

www.intern-med.com

DOI:

10.1515/jtim-2025-0001

 Open Access. © 2025 The author(s), published by De Gruyter on behalf of Scholar Media Publishing.
 This work is licensed under the Creative Commons Attribution 4.0 International License.

endothelial lining of blood vessels) rather than targeting individual neurons in previous studies.^[3] The successful translation from laboratory conditions to clinical trials of the cerebral protection mentioned above is the current research hotspot to explore not only the safety and feasibility but also the efficacy of those novel and multi-targeted therapies when applied to the bedside.

ANTIPLATELET THERAPY

Advances in reperfusion therapy have significantly improved the rate of cerebral revascularization and clinical outcomes for AIS. However, a substantial proportion of patients treated with timely thrombolysis still experience persistent or recurrent neurological impairment. Apart from the direct causes, such as intracerebral hemorrhage and malignant edema, neurological worsening after thrombolysis is often attributed to ischemic stroke progression, which leads to worse outcomes and higher morbidity. Known as early neurological deterioration (END), this condition is primarily associated with the absence of early antiplatelet therapy. As END tends to peak within 24 hours of being admitted, antiplatelet therapy given at an early stage is particularly important.^[4] Current guidelines recommend the use of aspirin as monotherapy or for the intensification of antiplatelet therapy with clopidogrel plus aspirin.^[5] Studies on the effect of emerging agents such as tirofiban have also been conducted.^[6] The findings of the investigation are expected to address the issue of existing drug resistance and limitations of antiplatelet drug delivery.

MOBILE STROKE UNITS

The “Time is Brain” concept highlights the critical importance of initiating revascularization promptly in cases of ischemic stroke, with mobile stroke units playing a pivotal role in achieving this goal. Mobile Stroke Units, which are specialized ambulances equipped with CT scanners, point-of-care lab testing, and expert medical teams, enable on-site diagnosis and immediate treatment, thus shortening the window from stroke onset to intervention.^[7,8] Studies confirm that Mobile Stroke Units outperform traditional emergency services, primarily by significantly reducing the time to treatment, which is essential for prehospital intravenous thrombolysis. For endovascular thrombectomy, Mobile Stroke Units tend to serve as a reference to help triage and optimize the workflow for delivering therapy. Future directions may include incorporating neuroprotective agents and individualized management plans facilitated by enhanced imaging capabilities into mobile stroke units. However, as mobile stroke units gain traction, cost considerations and strategic deployment remain key, with a focus on ensuring coverage in high-incidence regions to maximize their

clinical benefits.

TIME WINDOW

The current therapeutic window for thrombolysis in acute ischemic stroke remains limited to 3 to 4.5 hours after symptom onset.^[5] Expanding this time window allows more patients to benefit from intravenous thrombolysis. As an important solution to this envision, the “Tissue Clock Approach” achieved by advanced multimodal imaging widens the indication of intravenous thrombolysis, particularly with regard to the time window for the treatment. Ischemic penumbra refers to the brain area of reversible injury around focal ischemic necrosis tissue, and the imaging features of penumbra are different from ischemic core lesions. By leveraging the mismatch between various radiological markers during initial scans, clinicians can select eligible patients for thrombolysis, even beyond traditional time constraints. For patients with wake-up, stroke, or unclear symptom onset, identifying the onset time is challenging. Clinical trials confirmed that wake-up and other unknown onset patients could still benefit from alteplase if they meet the criteria of DWI-FLAIR mismatch, which is defined as an acute ischemic lesion on diffusion-weighted imaging but without high intensity on a fluid-attenuated inversion recovery.^[9] Ongoing trials continue to explore ways to extend the thrombolytic window safely. Additionally, research is investigating whether neuroprotective strategies could slow the growth of the infarct core, potentially preserving tissue viability longer, thus extending the therapeutic window.^[2]

THROMBOLYTIC AGENTS

Currently, the main thrombolytic agent used in clinical practice is recombinant tissue plasminogen activator (rt-PA). While rt-PA has addressed some limitations of earlier thrombolytic agents, such as poor fibrin selectivity and antigenicity, its strict time-dependence and the need for continuous infusion still limit its effectiveness. Therefore, thrombolytic agents need to be more diverse. Drugs showing higher recanalization rate, greater fibrin specificity, stable nature, fewer side effects, and easiness and feasibility of administration will become an ideal medication for reperfusion therapy, undoubtedly. The development of tenecteplase (TNK), nonimmunogenic staphylokinase, and recombinant human prourokinase (rhPro-UK) have shown non-inferiority of those novel thrombolytic agents to regular use of alteplase or similar safety outcome.^[10] Future research should focus on determining the optimal dosing regimens for these new agents and conducting large-scale studies to assess whether the observed benefits can be generalized to the broader patient population. These are important research gaps that remain to be addressed.

CONCLUSION

In summary, reperfusion treatment of AIS is making significant progress worldwide. However, the choice and timing of therapy still need to be evaluated on an individual basis according to the specific circumstances of the patient. Future research should focus on improving access to treatment, especially in low- and middle-income countries, and optimizing treatment strategies to reduce treatment-related risks. Through these measures, we can improve stroke outcomes worldwide by closing the treatment gap and ensuring that stroke patients worldwide have access to evidence-based medical care.

Acknowledgements

None.

Author Contributions

All authors were instrumental in the conception, implementation, and interpretations of this study. Siying Fan (First Author): Conceptualization, Writing—Original Draft; Lu Yang (First Author): Writing—Review and Editing; Xunming Ji (Corresponding Author): Conceptualization, Funding Acquisition, Supervision; Writing—Review and Editing.

Source of Funding

None.

Ethical Approval

Not applicable.

Informed Consent

Not applicable.

Conflict of Interest

No potential conflict of interest was reported by the

authors.

Use of Large Language Models, AI and Machine Learning Tools

None declared.

Data Availability Statement

No additional data is available.

REFERENCES

1. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, *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. Savitz SI, Baron JC, Yenari MA, Sanossian N, Fisher M. Reconsidering neuroprotection in the reperfusion era. *Stroke* 2017;48:3413-3419.
3. Lyden PD. Cerebroprotection for acute ischemic stroke: looking ahead. *Stroke* 2021;52:3033-3044.
4. Liu H, Liu K, Zhang K, Zong C, Yang H, Li Y, *et al.* Early neurological deterioration in patients with acute ischemic stroke: a prospective multicenter cohort study. *Ther Adv Neurol Disord* 2023;16:17562864221147743.
5. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, *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.
6. Zhao W, Li S, Li C, Wu C, Wang J, Xing L, *et al.* Effects of tirofiban on neurological deterioration in patients with acute ischemic stroke. *JAMA Neurology* 2024;81.
7. Fassbender K, Grotta JC, Walter S, Grunwald IQ, Ragoeschke-Schumm A, Saver JL. Mobile stroke units for prehospital thrombolysis, triage, and beyond: benefits and challenges. *Lancet Neurol* 2017;16:227-237.
8. Grotta JC, Yamal JM, Parker SA, Rajan SS, Gonzales NR, Jones WJ, *et al.* Prospective, Multicenter, Controlled Trial of Mobile Stroke Units. *N Engl J Med* 2021;385:971-981.
9. Thomalla G, Simonsen CZ, Boutitie F, Andersen G, Berthezene Y, Cheng B, *et al.* MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset. *N Engl J Med* 2018;379:611-622.
10. Tsigoulis G, Katsanos AH, Sandset EC, Turc G, Nguyen TN, Bivard A, *et al.* Thrombolysis for acute ischaemic stroke: current status and future perspectives. *Lancet Neurol* 2023;22:418-429.

How to cite this article: Fan S, Yang L, Ji X. Reperfusion therapy for acute ischemic stroke: Where we are and where to go. *J Transl Intern Med* 2025; 13: 1-3.