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REVIEW ARTICLE

Extended Windows in Acute Ischemic Stroke: What is the Time Limit?

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ABSTRACT

"Time is brain" has traditionally guided acute ischemic stroke (AIS) management, with intravenous thrombolysis generally restricted to 4.5 hours and mechanical thrombectomy (MT) historically limited to selected patients within 6 hours. Advances in neuroimaging and endovascular therapy have demonstrated that tissue viability may be more important than elapsed time alone. This review examines contemporary therapeutic windows for acute cerebrovascular events and discusses how imaging-based selection has expanded opportunities for reperfusion therapy. Tissue-based thrombolysis using diffusion-weighted imaging–fluid-attenuated inversion (DWI-FLAIR) recovery mismatch or perfusion imaging has enabled treatment of selected patients with wake-up or unknown-onset stroke and those presenting 4.5–9 hours after last known well. Emerging evidence with tenecteplase suggests potential benefit in highly selected patients with large-vessel occlusion presenting up to 24 hours. Trials have now established substantial benefit in appropriately selected patients presenting 6–24 hours after last known well. Recent trials have further expanded thrombectomy eligibility to selected patients with large ischemic cores. Treatment beyond 24 hours remains investigational.

Importantly, extended windows should not encourage treatment delays. Treatment decisions increasingly incorporate infarct-core size, collateral circulation, penumbral viability, occlusion site, clinical severity, pre-stroke functional status, and haemorrhagic risk. This paradigm is particularly relevant to resource-limited settings, where delayed presentation and interhospital transfer frequently prevent treatment within conventional windows. There is no single universal time limit for reperfusion therapy. The therapeutic window is increasingly determined by the interaction between time, tissue viability, and clinical factors, while earlier reperfusion remains preferable whenever feasible.

Key words: *Acute ischemic stroke, extended therapeutic window, mechanical thrombectomy, thrombolysis, wake-up stroke.*

INTRODUCTION

"Time is brain" has traditionally been the central principle of acute stroke management. For decades, the therapeutic window for intravenous thrombolysis in acute ischaemic stroke (AIS) was largely defined by the clock: treatment with alteplase was recommended within 4.5 hours of symptom onset, while mechanical thrombectomy (MT) was generally restricted to selected patients presenting within 6 hours.[1] However, advances in neuroimaging and endovascular therapy have fundamentally changed this paradigm. The modern approach recognises that chronological time alone does not determine tissue viability. Some patients continue to harbour substantial salvageable penumbra many hours after symptom onset, whereas others develop a large irreversible infarct rapidly.

The question is therefore no longer simply, "How many hours have elapsed?" but rather, "How much viable brain can be salvaged?" This transition from a *time clock* to a combination of *time, tissue and clinical clocks* has progressively expanded reperfusion therapy. The 2026 American Heart Association/American Stroke Association (AHA/ASA) guideline now explicitly incorporates extended-window intravenous thrombolysis, broader endovascular thrombectomy indications, large-core infarction and posterior-circulation stroke.[2]

From the 4.5-hour rule to tissue-based thrombolysis

For patients with disabling AIS presenting within 4.5 hours of symptom onset or last known well, intravenous thrombolysis (IVT) remains a cornerstone of treatment. The 2026 AHA/ASA guideline recommends either alteplase or tenecteplase at the appropriate dose in eligible patients, with treatment initiated as rapidly as possible. Importantly, additional advanced imaging should not delay IVT in otherwise eligible patients within the conventional window.[2]

The first major challenge to the rigid 4.5-hour boundary came from patients with wake-up or unknown-onset stroke. The WAKE-UP trial demonstrated that MRI diffusion-weighted imaging–fluid-attenuated inversion (DWI-FLAIR) mismatch could identify patients likely to have a relatively recent infarct despite an unknown onset time.[3] This provided the conceptual foundation for a tissue clock: treatment could be considered when imaging suggested that the brain was salvageable though the conventional time window implied otherwise.

Subsequent trials using perfusion imaging further extended the window. An individual-patient-data meta-analysis incorporating EXTEND, ECASS-4 EXTEND and EPITHET demonstrated benefit (mRS 0-1 at 90 days) (adjusted odds ratio [OR] 1.86, 95% CI 1.15-2.99, p=0.011) from alteplase in selected patients presenting between 4.5 and 9 hours after onset or with wake-up stroke when advanced imaging identified salvageable tissue.[4] The benefit was accompanied by an increased risk of symptomatic intracranial haemorrhage adjusted OR 9.7, 95% CI 1.23-76.55, p=0.031), emphasising the need for careful patient selection.

The 2026 AHA/ASA guideline now gives a class 2a recommendation for IVT in selected patients with salvageable penumbra on automated perfusion imaging who are either 4.5–9 hours from last known well or awaken with stroke symptoms within 9 hours from the midpoint of sleep.[2]

Thus, for thrombolysis, the practical boundaries are no longer restricted to 4.5 hours.

How far can thrombolysis be extended?

The most striking development is the emergence of evidence for tenecteplase beyond 4.5 hours. The TRACE-III trial evaluated tenecteplase in patients with AIS caused by large-vessel occlusion presenting between 4.5 and 24 hours, selected using perfusion or diffusion imaging and with no immediate access to thrombectomy. The trial demonstrated improved functional outcomes with tenecteplase compared with standard medical therapy. However we must keep in mind that this was an open label trial and performed only in China.[5]

A subsequent 2025 meta-analysis of extended-window thrombolysis similarly suggested that thrombolysis between 4.5 and 24 hours may improve excellent functional outcome (RR 1.25; 95 % CI 1.11-1.41) without a significant increase in mortality or symptomatic intracranial haemorrhage in appropriately selected patients.[6]

These findings are important but should not be interpreted as establishing 24 hours as a universal thrombolysis window. Extended-window IVT remains highly dependent on imaging-defined salvageable tissue, vascular status, treatment availability and patient selection. The 2026 AHA/ASA guideline currently supports extended-window IVT particularly in the 4.5–9-hour window, while evidence for use of IV tenecteplase for upto 24 hours represents an evolving area rather than a blanket treatment recommendation for every late-presenting patient.[2,5]

Mechanical thrombectomy: the 6-hour boundary becomes 24 hours

The revolution in late-window treatment has been even more dramatic for endovascular thrombectomy. The DAWN trial demonstrated that patients with anterior-circulation large-vessel occlusion (LVO) presenting 6–24 hours after they were last known well could derive substantial benefit from thrombectomy when there was a mismatch between the severity of the clinical deficit and the size of the infarct core. Functional independence at 90 days was achieved in approximately 49% of thrombectomy-treated patients compared with 13% receiving standard care.[7]

DEFUSE 3 provided complementary evidence using perfusion-based selection. Patients presenting 6–16 hours

after last known well with ICA or proximal MCA occlusion, a small core and substantial perfusion mismatch had markedly better outcomes with thrombectomy than medical treatment alone. Functional independence was achieved in 45% versus 17% of patients.[8] These studies established that, in carefully selected patients, 6 hours is not an absolute biological deadline. Establishing the penumbra volume could extend treatment windows with effective functional improvement.

The 2026 AHA/ASA guideline therefore recommends thrombectomy for selected patients with anterior-circulation ICA or M1 occlusion presenting between 6 and 24 hours, including appropriately selected patients with Alberta Stroke Program Early Computed Tomography Score (ASPECTS) 3–5.[2] Importantly, the guideline also emphasises that advanced imaging should not become a reason for avoidable delay. The purpose of perfusion imaging is to identify patients likely to benefit—not to postpone reperfusion.[2]

The large-core revolution

Another major change is the recognition that a large established infarct does not necessarily mean "no thrombectomy." Recent randomised trials have challenged this assumption. SELECT2 demonstrated that thrombectomy improved functional outcomes in patients with large ischaemic cores presenting within 24 hours. However this trial also showed 18% of patients in the thrombectomy group had procedure related complications. One of the criticisms of this trial is that it was terminated early and the treatment effect could have been overestimated.[9] ANGEL-ASPECT similarly demonstrated improved outcomes with endovascular therapy in patients with large infarcts, although intracranial haemorrhage was more frequent.[10]

The 2026 guideline consequently supports thrombectomy in selected patients with larger established infarcts, including patients with ASPECTS 3–5 in the 6–24-hour window.[2] This is particularly important because large-core patients may represent a heterogeneous population. Some are rapid progressors with extensive irreversible injury, whereas others have substantial potentially salvageable tissue despite an apparently large core.

Posterior circulation: another 24-hour window

The concept of extended treatment is no longer restricted to anterior circulation stroke. In posterior circulation infarction, evidence for endovascular therapy has evolved from the neutral BEST[11] and BASICS[12] trials to the positive ATTENTION and BAOCHE studies. BEST and BASICS did not demonstrate a significant functional benefit from thrombectomy, with interpretation influenced by factors such as crossover, early termination, and heterogeneous patient selection. Subsequent trials adopted narrower eligibility criteria, selecting patients with clinically significant neurological deficits and limited established infarction, including imaging criteria such as a PC-ASPECTS ≥6. This more selective approach may have enriched the study populations for patients with substantial salvageable brain tissue and therefore contributed to the clearer treatment effects observed in ATTENTION and BAOCHE. For basilar artery occlusion, the ATTENTION and BAOCHE trials provided evidence supporting thrombectomy in appropriately selected patients presenting within 12 and 24 hours, respectively.[13,14]

BAOCHE enrolled patients with basilar artery occlusion presenting between 6 and 24 hours and demonstrated better functional outcomes with thrombectomy plus medical treatment than with medical treatment alone. However the procedure related complications and intracerebral hemorrhage rates were higher in the thrombectomy group.[14]

The 2026 AHA/ASA guideline now gives a strong recommendation for endovascular thrombectomy (EVT) in selected patients with basilar artery occlusion presenting within 24 hours, particularly those with NIHSS ≥10, prestroke mRS 0–1 and limited established posterior-circulation injury.[2] Thus, 24 hours has become an important treatment horizon for both anterior and posterior circulation thrombectomy, although the eligibility criteria differ.

There is increasing interest in thrombectomy beyond 24 hours in patients with persistent vessel occlusion and favourable imaging. Observational data have reported technically successful and clinically favourable outcomes in carefully selected patients treated beyond 24 hours, including patients fulfilling DAWN-like criteria.[15] However, these observations do not establish a new standard therapeutic window. Randomised evidence remains concentrated within 24 hours for most established indications.

Consequently, "24 hours" should not be interpreted as a biological cliff. It is better understood as the current evidence-supported boundary for routine guideline-based thrombectomy in selected patients. The underlying biological principle is more nuanced. Patients with robust collaterals may maintain viable tissue for many hours, whereas patients with poor collaterals may develop irreversible injury rapidly. Treatment benefit may be influenced by various factors (Table 1).

Table 1. Factors which may influence the treatment benefit of thrombectomy

1. Time from last known well
2. Infarct-core size
3. Collateral circulation
4. Penumbra and tissue viability
5. Occlusion site
6. Clinical severity
7. Pre-stroke functional status
8. Risk of reperfusion injury or haemorrhage

"Time is brain" still matters

The expansion of treatment windows must not create the misconception that delayed treatment is acceptable.

A major analysis of the DAWN trial demonstrated that the relationship between treatment delay and outcome remains complex even in the extended window.[16] Moreover, the 2026 AHA/ASA guideline explicitly recommends rapid evaluation and treatment even among patients eligible for 6–24-hour thrombectomy. Large-core patients may also include rapid infarct progressors, and therefore they should not be allowed to wait for unnecessary investigations or transfer delays.[2]

Unknown-onset and wake-up stroke

Wake-up stroke is a particularly important example of why the conventional clock is imperfect. The last-known-well time may be many hours earlier, but symptom recognition may occur only minutes before presentation. MRI DWI-FLAIR mismatch and CT/MR perfusion imaging can identify patients with a favourable tissue profile. The 2026 guideline explicitly incorporates imaging-selected wake-up stroke into extended thrombolysis recommendations.[2] Similarly, patients with LVO and unknown onset can be considered for thrombectomy using the same imaging and clinical principles applied to late-window patients.

Basis of extended treatment timelines and radiological assessment

The conventional time-based approach to AIS treatment is increasingly complemented by a tissue-based approach, recognizing that the rate at which ischemic brain tissue progresses to irreversible infarction varies considerably among patients. This variation provides the biological basis for extending treatment beyond the conventional therapeutic windows in carefully selected patients. On NCCT, the principal initial objectives are to exclude intracranial hemorrhage and identify the extent of early ischemic change, often assessed using the ASPECTS. A relatively normal CT or limited early ischemic change suggests that substantial brain tissue may remain viable. CT angiography (CTA) can identify a LVO, while CT perfusion (CTP) provides an estimate of the infarct core and the surrounding hypoperfused but potentially salvageable penumbra. In simple terms, a small core with a larger region of delayed perfusion represents a "mismatch," indicating that viable tissue may persist despite a prolonged or unknown time from symptom onset. MRI provides a complementary approach: DWI becomes abnormal early with acute infarction, whereas corresponding FLAIR changes generally appear later. Thus, a DWI-positive/FLAIR-negative lesion ("DWI–FLAIR mismatch") may identify patients with a relatively recent stroke despite an unknown onset time. Similarly, DWI–perfusion mismatch represents a small established infarct surrounded by potentially salvageable tissue. These imaging patterns formed the basis for selection in trials such as WAKE-UP, EXTEND, DAWN and DEFUSE 3 and underpin current recommendations for selected patients presenting beyond conventional treatment windows. Importantly, advanced imaging should be interpreted alongside clinical findings and vascular imaging, and treatment should not be delayed unnecessarily when patients are otherwise eligible for early reperfusion therapy.[2,3]

Implications for resource-limited settings

The expansion of treatment windows is particularly relevant to low- and middle-income countries (LMICs), where delayed presentation and interhospital transfer frequently prevent treatment within conventional windows. Neurological complications are more frequent in LMICs and are associated with poorer outcomes. These challenges are further compounded by limited access to rehabilitation services, which are often rudimentary, inadequate, or entirely unavailable. However, extended windows should not become an excuse for inefficient stroke systems. Rather, they provide an opportunity to identify patients who remain treatable despite delayed arrival. A recent study which is relevant to the LMICs where MRI may not be available in many centres is the MR CLEAN – LATE study.[17] This study aimed to assess efficacy and safety of endovascular treatment for patients treated in the late window (6-24 h from symptom onset or last seen well) selected on the basis of the presence of collateral flow on CTA. The authors found that endovascular treatment was efficacious and safe for patients with ischaemic stroke caused by an anterior circulation large-vessel occlusion who presented 6-24 h from onset or last seen well, and who were selected on the basis of the presence of collateral flow on CTA. The selection of patients in the late window could be primarily based on the presence of collateral flow.[17] In LMICs, stroke systems should prioritise multiple aspects of stroke management (Table 2).

Table 2. Priorities of stroke systems in LMICs

1.	Rapid non-contrast CT and vascular imaging.
2.	Early identification of LVO.
3.	Streamlined transfer pathways to thrombectomy-capable centres.
4.	Access to automated or validated perfusion imaging where feasible.
5.	Protocols for wake-up and unknown-onset stroke.
6.	Tenecteplase pathways where evidence and local guidelines support its use, and
7.	Regional stroke networks linking primary hospitals with comprehensive stroke centres.

Importantly, advanced imaging should be used strategically. The 2026 guideline notes that advanced perfusion imaging is particularly useful in extended windows, but it is not mandatory for all early-window patients and should not delay treatment.[2] Table 3 provides resource-stratified approach to the management of AIS in the LMICs.

Table 3. Resource-stratified approach to the management of acute ischemic stroke (AIS) in LMICs

Level of healthcare facility	Typical available resources	Key actions for suspected AIS	Reperfusion strategy	Imaging and investigations	Referral/ transfer priorities
Rural/primary hospital	Basic emergency care; limited laboratory and imaging facilities; usually no thrombolysis or thrombectomy	Rapid recognition of stroke; establish time last known well; ABCs; check glucose; establish IV access; assess neurological severity; avoid hypotension, hypoxia and hypoglycaemia; determine eligibility for urgent transfer	Do not delay transfer while waiting for investigations that are unavailable or unlikely to change management. Thrombolysis may be considered only if appropriate imaging, trained personnel and protocols are available	Non-contrast CT if available; otherwise arrange urgent transfer to a facility capable of stroke imaging and reperfusion	Early notification and rapid transfer to the nearest appropriate stroke-capable centre; send clinical information, time of onset, medications and available imaging
Regional/ district hospital	Emergency services; CT often available; basic laboratory support; limited stroke expertise; usually no thrombectomy	Follow a standardized stroke pathway; determine eligibility for reperfusion; obtain urgent brain imaging; manage airway, glucose, temperature and blood pressure appropriately	IV thrombolysis may be provided if trained personnel, imaging and protocols are available; otherwise expedite transfer	Non-contrast CT ± vascular imaging depending on availability; basic laboratory tests should not unnecessarily delay treatment	Transfer patients with large-vessel occlusion (LVO) or suspected LVO to a thrombectomy-capable centre; establish pre-transfer communication
Stroke/ thrombolysis-capable centre	CT, trained stroke team, thrombolysis capability; may have CTA; limited or no endovascular service	Rapid stroke assessment and imaging; establish stroke severity and eligibility for reperfusion; initiate evidence-based acute stroke care	IV thrombolysis in eligible patients within the appropriate time window; consider mechanical thrombectomy pathways for suspected LVO	NCCT + CTA where available; advanced perfusion imaging according to local capability and treatment window	Patients eligible for thrombectomy should be transferred rapidly to an endovascular-capable centre if MT is unavailable locally
Comprehensive stroke centre / thrombectomy-capable centre	24/7 stroke expertise; CT/CTA; MRI/perfusion where available; neurointerventional and neurocritical-care services	Full acute stroke pathway including reperfusion, neurocritical care, management of complications and multidisciplinary care	IV thrombolysis when indicated; mechanical thrombectomy for eligible patients with LVO, including appropriately selected patients presenting in extended time windows	NCCT/CTA with advanced imaging where appropriate; imaging selection should be adapted to available resources and treatment window	Definitive treatment, monitoring and complication management; initiate early rehabilitation and secondary prevention

AIS, acute ischemic stroke; ABC, airway, breathing and circulation; CT, computed tomography; CTA, CT angiography; LVO, large-vessel occlusion; MT, mechanical thrombectomy; NCCT, non-contrast CT.

A practical time-window framework for management of AIS is shown in Table 4.

Table 4. A practice time- window framework for intravenous thrombolysis or endovascular thrombectomy.

Clinical situation	Current evidence-supported window
Eligible AIS for IVT	≤4.5 h
Wake-up/unknown onset, imaging-selected IVT	Selected patients; tissue-based rather than clock-based
Perfusion-selected IVT	4.5–9 h in selected patients
Anterior circulation LVO, early-window EVT	≤6 h
Anterior circulation LVO, late-window EVT	6–24 h in selected patients
Selected large-core LVO	Up to 24 h in appropriate patients
Basilar artery occlusion	Up to 24 h in selected patients
EVT beyond 24 h	Investigational/individualised; not a routine guideline window

AIS, acute ischemic stroke; IVT, intravenous thrombolysis; LVO, large vessel occlusion; EVT, endovascular thrombectomy.

CONCLUSIONS

The therapeutic window for acute cerebrovascular intervention has evolved from a rigid clock-based paradigm to a time–tissue–clinical paradigm. The most important conceptual change is that there is no single universal time limit. For thrombolysis, the established extended window currently reaches approximately 9 hours in selected patients, while emerging evidence is pushing tenecteplase toward 24 hours in highly selected patients. For thrombectomy, 24 hours is the current evidence-supported late window for selected patients, but treatment beyond 24 hours remains an evolving area. The time limit is increasingly determined by the amount of salvageable brain rather than the clock alone—but the earlier reperfusion is achieved, the better the chance of preserving functional brain. The future of stroke treatment will likely involve increasingly sophisticated identification of the individual biological treatment window, potentially extending therapy beyond today's conventional 24-hour boundary while simultaneously shortening treatment delays for those who arrive early.

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During the preparation of this manuscript, the author used ChatGPT (OpenAI) to assist with language editing and improving the clarity and readability of the manuscript. The author critically reviewed and edited all AI-assisted content and takes full responsibility for the accuracy, originality, and integrity of the final manuscript.

CONFLICT OF INTEREST

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