# Extended-Window IV Thrombolysis for Acute Ischemic Stroke

## Introduction

1. Acute ischemic stroke (AIS) requires rapid reperfusion to salvage the ischemic penumbra. Historically, IV thrombolysis with alteplase or tenecteplase was rigidly limited to ≤4.5 hours from symptom onset. The 2026 AHA/ASA guideline (Prabhakaran et al.) reflects a paradigm shift from a strictly time-based to a tissue-based selection model, expanding eligibility to selected patients up to 24 hours via advanced perfusion imaging.
2. Wake-up strokes and unwitnessed-onset strokes account for ~14–25% of all AIS presentations, leaving a large unmet need for patients who would otherwise be denied reperfusion under conventional time-window rules.
3. The extended-window strategy uses CT perfusion (CTP) or MRI (DWI/FLAIR mismatch or perfusion-diffusion mismatch) to identify salvageable penumbra. Imaging selection — not the clock — drives eligibility.
4. Extended-window thrombolysis benefit depends on three variables: (a) imaging modality used for selection (advanced perfusion vs. non-contrast CT); (b) presence of large vessel occlusion (LVO); and (c) whether endovascular thrombectomy (EVT) is also planned or accessible.
5. Both alteplase (0.9 mg/kg, max 90 mg, 10% bolus + 60-min infusion) and tenecteplase (0.25 mg/kg single bolus, max 25 mg) have been studied in the extended window. Tenecteplase's single-bolus administration confers logistical advantages, particularly during inter-facility transfer.
6. This pearl synthesizes the available randomized evidence — 6 landmark RCTs and 2 meta-analyses (n >2,800 patients combined) — to answer: which patients beyond 4.5 hours benefit, with which agent, and at what hemorrhagic cost?

## Pharmacology

| Pharmacology — Extended-Window IV Thrombolytics | | |
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| | **Alteplase (Activase®)** | **Tenecteplase (TNKase®)** |
| **Mechanism of Action** | Recombinant tissue plasminogen activator (tPA); converts plasminogen to plasmin, which lyses fibrin in the thrombus. | Genetically modified tPA variant (T103N, N117Q, KHRR 296-299AAAA mutations) — increased fibrin specificity, decreased PAI-1 inhibition, longer half-life. |
| **Dose (extended window)** | **0.9 mg/kg IV** (max 90 mg)<br>10% as bolus over 1 min; remainder infused over 60 min<br>Studied 4.5–9 hr (EXTEND), 4.5–24 hr (HOPE), wake-up via MRI mismatch (WAKE-UP) | **0.25 mg/kg IV bolus** (max 25 mg) over 5–10 sec<br>Single push — no infusion required<br>Studied 4.5–24 hr (TIMELESS, TRACE-III), wake-up via NCCT (TWIST — negative) |
| **Administration** | Reconstitute 50 mg or 100 mg vial with sterile water (no preservatives) | Reconstitute 50 mg vial with 10 mL sterile water → 5 mg/mL |

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| | Final concentration 1 mg/mL<br>Use within 8 hr of reconstitution; refrigerate if not used immediately | Use within 8 hr (room temp) or 24 hr (refrigerated)<br>Single IV push — major logistical advantage during transfer |
| **PK/PD** | Half-life: ~5 min (initial)<br>Hepatic metabolism<br>Fibrin specificity: moderate | Half-life: ~17–20 min (initial)<br>Hepatic metabolism<br>Fibrin specificity: 14× higher than alteplase; longer therapeutic effect |
| **Adverse Effects** | • **Symptomatic ICH**: 2.0–6.2% (extended window) vs. 0.4–0.9% placebo<br>• Systemic bleeding (GI, GU, surgical sites)<br>• Orolingual angioedema (~1–5%, esp. with ACEi)<br>• Hypotension during infusion | • **Symptomatic ICH**: 1.2–3.2% (extended window)<br>• Systemic bleeding (similar to alteplase)<br>• Orolingual angioedema (similar)<br>• Hypersensitivity (rare) |
| **Drug Interactions and Warnings** | Anticoagulants (DOACs, warfarin, heparin), antiplatelets — bleeding risk synergy<br>ACEi — angioedema risk<br>Recent surgery, GI bleed, intracranial pathology — absolute/relative contraindications per AHA/ASA criteria | Same anticoagulant/antiplatelet warnings<br>ACEi angioedema risk<br>Standard AHA/ASA absolute contraindications apply equally |
| **Compatibility** | Reconstitute with sterile water only (NOT saline initially)<br>Compatible with NS for further dilution if needed | Reconstitute with sterile water; compatible with NS post-reconstitution |
| **Comments** | Robust extended-window evidence in 4.5–9 hr (EXTEND), wake-up (WAKE-UP), and 4.5–24 hr (HOPE)<br>Standard infusion logistically more complex than tenecteplase | 2026 AHA/ASA guideline (Prabhakaran) endorses tenecteplase as a reasonable alternative to alteplase<br>Best evidence in extended window WITHOUT planned EVT (TRACE-III); minimal benefit when EVT is also performed (TIMELESS); wake-up evidence requires perfusion imaging, NOT NCCT (TWIST negative) |

## Overview of Evidence — Extended-Window IV Thrombolysis

| Author, year | Design / sample size | Intervention & comparison | Outcome |
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| Thomalla G, 2018 (WAKE-UP) | Multicenter RCT (n = 503 adults with wake-up stroke / unknown onset) | MRI DWI/FLAIR mismatch selection (suggesting <4.5 hr from onset)<br>Alteplase 0.9 mg/kg IV vs. placebo<br>Patients planned for EVT excluded | mRS 0–1 at 90 days: 53.3% vs. 41.8% (adjusted OR 1.61, 95% CI 1.09–2.36; p = 0.02; NNT = 9)<br>sICH: 2.0% vs. 0.4% (NS)<br>Mortality: 4.1% vs. 1.2% (NS)<br>Trial terminated early due to funding cessation — established MRI-guided |

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| | | | thrombolysis for unknown-onset stroke |
| Ma H, 2019 (EXTEND) | Multicenter, double-blind RCT (n = 225 adults, 4.5–9 hr or wake-up) | Automated CTP or MRI mismatch selection<br>Alteplase 0.9 mg/kg IV vs. placebo | mRS 0–1 at 90 days: 35.4% vs. 29.5% (adjusted RR 1.44, 95% CI 1.01–2.06; p = 0.04; NNT = 17)<br>sICH: 6.2% vs. 0.9% (RR 7.22; p = 0.05)<br>90-day mortality: 11.5% vs. 8.9% (NS)<br>Terminated early after WAKE-UP published; first RCT to show late-window IV alteplase benefit by perfusion imaging |
| Campbell BCV, 2019 (IPD meta) | Individual patient data meta-analysis of EXTEND, ECASS4-EXTEND, EPITHET (n = 414) | Perfusion-imaging-guided alteplase 4.5–9 hr or wake-up vs. placebo / standard care | mRS 0–1 at 90 days: 36% vs. 29% (adjusted OR 1.86, 95% CI 1.15–2.99; p = 0.011)<br>sICH: 5% vs. <1%<br>Mortality not significantly different<br>Confirms perfusion-guided extended-window alteplase benefit across pooled cohorts |
| Roaldsen MB, 2023 (TWIST) | Multicenter open-label RCT (n = 578 adults with wake-up stroke) | Non-contrast CT (NCCT) selection only — no perfusion imaging<br>Tenecteplase 0.25 mg/kg single bolus vs. no thrombolysis | mRS shift at 90 days: NEGATIVE (adjusted OR 1.18; NS)<br>sICH: 2% vs. 1% (NS)<br>Mortality: 10% vs. 8% (NS)<br>Established that NCCT alone is INADEQUATE for wake-up stroke selection — perfusion imaging required |
| Albers GW, 2024 (TIMELESS) | Multicenter, double-blind, placebo-controlled RCT (n = 458 adults, 4.5–24 hr) | LVO (MCA or ICA) + perfusion imaging-evident salvageable tissue<br>Tenecteplase 0.25 mg/kg IV vs. placebo<br>77.3% subsequently underwent EVT | mRS at 90 days: median 3 in BOTH groups (adjusted common OR 1.13, 95% CI 0.82–1.57; p = 0.45)<br>sICH: 3.2% vs. 2.3% (NS)<br>Mortality: 19.7% vs. 18.2% (NS)<br>NEGATIVE for adjunctive tenecteplase when EVT is planned and accessible |
| Xiong Y, 2024 (TRACE-III) | Multicenter, open-label, blinded-endpoint RCT (n = 516 adults, 4.5–24 hr, China) | LVO + perfusion-evident salvageable tissue, NO planned EVT (<2% rescue)<br>Tenecteplase 0.25 mg/kg IV vs. standard medical therapy | mRS 0–1 at 90 days: 33.0% vs. 24.2% (RR 1.37, 95% CI 1.04–1.81; p = 0.03; NNT ≈ 11)<br>sICH within 36 hr: 3.0% vs. 0.8% (RR 3.82; p = 0.06)<br>90-day mortality: 13.3% vs. 13.1% (NS)<br>Established late-window tenecteplase benefit in non-EVT settings — the practice-changing finding for centers without EVT capability |
| Zhou Y, 2025 (HOPE) | Multicenter, open-label RCT (n = 372 adults, 4.5–24 hr, China) | CTP or MRI mismatch selection; NOT planned for EVT<br>Alteplase 0.9 mg/kg IV vs. standard medical care | mRS 0–2 at 90 days: 40% vs. 26% (adjusted RR 1.52, 95% CI 1.14–2.02; p = 0.004; NNT = 7)<br>sICH: 3.8% vs. 0.51% (adjusted RR 7.34; p = |

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| | | | 0.01)<br>90-day mortality: 11% vs. 11% (identical)<br>Most recent extended-window alteplase RCT — confirms benefit out to 24 hr with perfusion imaging in non-EVT pathway |
| Wang Z, 2026 (meta) | Meta-analysis of 4 RCTs (n = 1,278) — late-window tenecteplase 4.5–24 hr | Tenecteplase vs. placebo or standard care<br>Subgroup analysis by EVT vs. non-EVT cohort | Overall mRS 0–1: OR 1.34 (95% CI 1.06–1.71; p = 0.02)<br>Recanalization: OR 3.30 (p = 0.001)<br>sICH and mortality NOT significantly elevated<br>Subgroup: non-EVT cohort OR 1.46; EVT-permitted cohort no functional benefit (recanalization only) |

## Conclusions

- **Imaging selection — not the clock — defines extended-window eligibility.** Advanced perfusion imaging (CTP or MRI mismatch) is REQUIRED. Non-contrast CT alone is insufficient (TWIST negative).
- **Alteplase has robust extended-window evidence: WAKE-UP (MRI mismatch), EXTEND (4.5–9 hr CTP/MRI), and HOPE (4.5–24 hr CTP/MRI in non-EVT pathway).** NNT ranges 7–17 for excellent functional outcome.
- **Tenecteplase's extended-window benefit hinges on EVT access:** TRACE-III (no EVT pathway) showed clear benefit (mRS 0–1: 33% vs. 24%); TIMELESS (EVT-eligible LVO) showed no functional benefit when added to thrombectomy. The Wang 2026 meta-analysis confirms this dichotomy.
- **sICH risk is increased ~3–7× in the extended window vs. placebo,** but 90-day mortality is consistently NOT increased in any of the 6 landmark RCTs. Functional benefit outweighs hemorrhagic cost when patients are selected by perfusion imaging.
- **Centers WITHOUT immediate EVT access:** extended-window IV thrombolysis (alteplase or tenecteplase) is the most impactful intervention. Endorsed by the 2026 AHA/ASA guideline (Prabhakaran).
- **Centers WITH EVT access for LVO:** prioritize EVT; do not delay thrombectomy for late-window IV thrombolysis without clear added benefit (TIMELESS).
- **Tenecteplase is preferred for extended-window thrombolysis when imaging supports it,** given single-bolus logistics, faster transfer-friendly administration, and equivalent safety to alteplase across the evidence base.

## References


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