

Tenecteplase 0.25 mg/kg versus alteplase in acute ischaemic stroke: functional outcome, safety and thrombectomy

Research summary

The clinically relevant comparison is intravenous tenecteplase 0.25 mg/kg versus alteplase for excellent functional outcome, defined as modified Rankin Scale (mRS) 0–1 at approximately 90 days, and for symptomatic intracranial haemorrhage (sICH) and death. In the conventional thrombolysis window, the evidence supports tenecteplase as a **non-inferior alternative**, rather than establishing that it is consistently superior. In AcT, mRS 0–1 at 90–120 days occurred in 36.9% versus 34.8% with alteplase; the unadjusted risk difference was 2.1% (95% CI –2.6 to 6.9), meeting the prespecified –5% non-inferiority threshold. TRACE-2, in patients who were ineligible for or declined thrombectomy, and ATTEST-2 also found tenecteplase 0.25 mg/kg non-inferior to alteplase within 4.5 hours. A meta-analysis restricted to randomized comparisons of tenecteplase 0.25 mg/kg with alteplase found a modestly higher pooled odds of 90-day mRS 0–1 (OR 1.14, 95% CI 1.03–1.25); this pooled superiority signal should be distinguished from the non-inferiority conclusions of the individual phase 3 trials.

The 4.5–24-hour question is different. The late-window tenecteplase trials described here compared 0.25 mg/kg with placebo or standard medical treatment, not alteplase. TIMELESS did not demonstrate better 90-day clinical outcomes than placebo in perfusion-selected patients with large-vessel occlusion, most of whom underwent thrombectomy. TRACE-III found less disability than standard medical treatment in imaging-selected patients with large-vessel occlusion who did not have access to thrombectomy, while sICH appeared higher. These results inform whether tenecteplase may have a role in particular extended-window populations; they do not establish late-window non-inferiority or superiority *versus alteplase*. Differences in thrombectomy access and selection also prevent treating the two trials as interchangeable.

For patients proceeding to thrombectomy, the direct agent comparison is strongest for **early reperfusion**, not 90-day mRS 0–1. EXTEND-IA TNK found more reperfusion before thrombectomy and better functional outcome with tenecteplase than with alteplase when treatment began within 4.5 hours. ATTEST-2 reported a possible advantage in reperfusion on the first angiographic run among thrombectomy recipients, but noted substantially lower early recanalisation rates than in EXTEND-IA TNK. Thus, the reperfusion finding is clinically pertinent but should not be presented as a definitive, generalizable mRS 0–1 benefit across thrombectomy populations.

At 0.25 mg/kg, randomized-trial pooling has not identified a significant excess of sICH or all-cause death

versus alteplase: the respective estimates were OR 1.11 (95% CI 0.81–1.52) and OR 0.99 (95% CI 0.81–1.19). Confidence is strongest for the within-4.5-hour efficacy conclusion, more limited for uncommon safety events and thrombectomy-specific excellent outcome, and insufficient for a direct alteplase comparison at 4.5–24 hours. These conclusions are dose-specific: evidence involving tenecteplase 0.4 mg/kg should not be used to infer the safety of 0.25 mg/kg.

Bottom line

- **Within 4.5 hours:** Tenecteplase 0.25 mg/kg is non-inferior to alteplase for excellent functional outcome in multiple randomized trials; confidence is high for this conclusion.
- **Overall randomized comparison:** A dose-restricted meta-analysis found higher odds of 90-day mRS 0–1 with tenecteplase, OR 1.14 (95% CI 1.03–1.25) versus alteplase. This supports a possible modest advantage, not uniform trial-level superiority.
- **At 4.5–24 hours:** Evidence is indirect for the requested agent comparison because the reported randomized comparators were placebo or standard medical treatment, not alteplase; confidence in any *tenecteplase-versus-alteplase* conclusion is insufficient.
- **Before thrombectomy:** Randomized evidence supports more pre-thrombectomy reperfusion with tenecteplase in EXTEND-IA TNK; evidence for a consistent thrombectomy-specific increase in 90-day mRS 0–1 is less secure.
- **Safety at 0.25 mg/kg:** Randomized-trial pooling found no significant difference versus alteplase in sICH, OR 1.11 (95% CI 0.81–1.52), or all-cause death, OR 0.99 (95% CI 0.81–1.19); uncommon-event estimates remain less precise than the efficacy conclusion.
- **Guideline adoption:** The European Stroke Organisation, Australian living stroke guidelines, and the 2026 American Heart Association/American Stroke Association guidance support use of tenecteplase in specified early-window settings; their recommendations do not establish an alteplase comparison throughout the extended window.

Evidence at a glance

Source	Design	Population (n)	Comparison	Key result	Ref
Dose-restricted randomized-trial meta-analysis	Meta-analysis of 11 RCTs	Acute ischaemic stroke (7,546)	Tenecteplase 0.25 mg/kg vs alteplase	90-day mRS 0–1: OR 1.14 (95% CI 1.03–1.25) vs alteplase; sICH: OR 1.11 (95% CI 0.81–1.52) vs alteplase; all-cause death: OR 0.99 (95% CI 0.81–1.19) vs alteplase	

Source	Design	Population (n)	Comparison	Key result	Ref
AcT	Phase 3 randomized non-inferiority trial	Thrombolysis-eligible acute ischaemic stroke within 4.5 hours (1,577)	Tenecteplase 0.25 mg/kg vs alteplase	mRS 0–1 at 90–120 days: 36.9% vs 34.8%; unadjusted risk difference 2.1% (95% CI – 2.6 to 6.9), meeting the –5% non-inferiority threshold	
TRACE-2	Phase 3 randomized non-inferiority trial	Thrombolysis-eligible acute ischaemic stroke within 4.5 hours; ineligible for or declined thrombectomy	Tenecteplase 0.25 mg/kg vs alteplase	Tenecteplase was non-inferior to alteplase in this non-thrombectomy population	
ATTEST-2	Randomized non-inferiority trial	Acute ischaemic stroke within 4.5 hours	Tenecteplase 0.25 mg/kg vs alteplase 0.9 mg/kg	Tenecteplase was non-inferior to alteplase; an exploratory thrombectomy analysis suggested potentially higher reperfusion on the first angiographic run	
EXTEND-IA TNK	Randomized trial	Large-vessel-occlusion stroke treated within 4.5 hours before thrombectomy	Tenecteplase 0.25 mg/kg vs alteplase	More reperfusion before thrombectomy and better functional outcome with tenecteplase	
TIMELESS	Randomized placebo-controlled trial	Perfusion-selected large-vessel-occlusion stroke at 4.5–24 hours; most underwent thrombectomy	Tenecteplase vs placebo	No improvement in 90-day clinical outcomes versus placebo; sICH incidence was similar	
TRACE-III	Randomized trial	Imaging-selected large-vessel-occlusion stroke at 4.5–24 hours without access to thrombectomy	Tenecteplase 0.25 mg/kg vs standard medical treatment	Less disability and similar survival with tenecteplase; sICH appeared higher	
European Stroke Organisation, 2023	Guideline	Thrombolysis-eligible acute ischaemic stroke	Tenecteplase vs alteplase	For eligible patients treated before hospital arrival in a mobile stroke unit within 4.5 hours, suggests tenecteplase 0.25 mg/kg over alteplase 0.90 mg/kg (low evidence; weak recommendation)	
Australian living stroke guidelines, 2022 update	Guideline	Potentially disabling large-vessel-occlusion stroke meeting eligibility criteria within 4.5 hours	Tenecteplase or alteplase	Intravenous tenecteplase 0.25 mg/kg, maximum 25 mg, or alteplase 0.9 mg/kg, maximum 90 mg, should be administered	
American Heart Association/ American Stroke Association, 2026	Guideline	Eligible acute ischaemic stroke within the 4.5-hour thrombolysis window	Tenecteplase or alteplase	Endorses either intravenous agent in the 4.5-hour treatment window	

Findings

1. Is tenecteplase 0.25 mg/kg non-inferior to alteplase for 90-day mRS 0–1 in the overall acute ischaemic stroke population?

The randomized evidence supports **non-inferiority of intravenous tenecteplase 0.25 mg/kg to alteplase 0.9 mg/kg for excellent functional outcome** in patients with acute ischaemic stroke eligible for thrombolysis. AcT, a pragmatic phase 3 non-inferiority trial, reported mRS 0–1 at 90–120 days in 36.9% of tenecteplase recipients versus 34.8% of alteplase recipients: unadjusted risk difference 2.1% (95% CI –2.6 to 6.9), meeting its prespecified non-inferiority margin of –5%. TRACE-2 independently concluded that tenecteplase was non-inferior in a Chinese population eligible for intravenous thrombolysis but ineligible for, or declining, endovascular thrombectomy. ATTEST-2 likewise found tenecteplase 0.25 mg/kg non-inferior to alteplase 0.9 mg/kg in its randomized acute-stroke population. These concordant trial conclusions establish that a clinically important loss of efficacy, as defined by each trial’s non-inferiority criterion, was not demonstrated. **Non-inferiority does not itself establish superiority.**

For the requested 90-day mRS 0–1 endpoint, the dose-specific pooled estimate adds a distinct finding. A meta-analysis restricted to randomized comparisons of tenecteplase 0.25 mg/kg against alteplase included 11 trials and 7,546 patients; its pooled odds ratio for mRS 0–1 was 1.14 (95% CI 1.03–1.25) versus alteplase. That interval favours tenecteplase and excludes an odds ratio of 1. Nevertheless, the pooled result should be read alongside the trials’ differing eligibility criteria and primary analyses rather than as proof that every thrombolysis-eligible phenotype derives the same incremental benefit. In particular, AcT’s reported assessment was at 90–120 days, whereas the meta-analytic question is framed as outcome at 90 days.

What the pooled estimate represents

“Overall acute ischaemic stroke” is a synthesis across enrolled trial populations, not a single unrestricted clinical population. AcT used pragmatic thrombolysis eligibility, whereas TRACE-2 excluded patients planning thrombectomy and TASTE selected patients using a perfusion-imaging target mismatch. Thus, the pooled estimate spans different distributions of occlusion status, imaging characteristics and expected prognosis. It is most directly applicable to patients who resemble those enrolled in the contributing randomized comparisons; it is not an estimate of treatment effect in every presentation labelled acute ischaemic stroke.

Trial design also matters when interpreting the apparent difference between a positive pooled superiority estimate and individual non-inferiority conclusions. Non-inferiority trials ask whether a prespecified clinically unacceptable disadvantage can be excluded; a pooled superiority analysis asks whether an average advantage can be detected with greater precision. ATTEST-2 judged its results consistent with AcT but indicated that the magnitude of any day-90 advantage was smaller than earlier studies had suggested. TASTE was stopped early after results from other non-inferiority trials became available, and its findings in a perfusion-selected population were significant only in the per-protocol analysis. Neither

observation overturns non-inferiority, but both argue against describing superiority as a uniformly established result of the individual phase 3 trials.

The choice of dose is another explanation for apparently different summaries. An earlier randomized-trial meta-analysis combined tenecteplase regimens that included 0.25 mg/kg alongside other doses and found no statistically significant difference in excellent functional outcome: odds ratio 1.08 (95% CI 0.93–1.26) versus alteplase. That estimate answers a broader *tenecteplase-versus-alteplase* question, whereas the 11-trial estimate of 1.14 (95% CI 1.03–1.25) specifically addresses the requested 0.25 mg/kg regimen. The estimates are not inherently contradictory: their intervals overlap, and their included doses and trials differ. The dose-restricted synthesis is the more direct pooled comparison for this question.

Finally, endpoint definitions require attention before treating trial percentages or pooled estimates as interchangeable. The broader meta-analysis permitted “mRS 0–1, or no change from baseline” within its excellent-outcome definition. No change from baseline and an absolute mRS of 0–1 are not identical outcomes for a person with pre-stroke disability. The clearest conclusion is therefore that **tenecteplase 0.25 mg/kg is non-inferior to alteplase for excellent functional outcome in randomized thrombolysis-eligible populations**, with a dose-specific pooled 90-day mRS 0–1 estimate favouring tenecteplase. The evidence does not establish that this pooled advantage is constant across all trial eligibility profiles or baseline disability states.

2. Does that comparison differ for treatment within 4.5 hours versus 4.5–24 hours?

The apparent difference between the conventional and extended treatment windows is principally a difference in **what has been tested**, not an established change in the relative effect of tenecteplase and alteplase. Within 4.5 hours, randomized active-comparator trials support tenecteplase 0.25 mg/kg as a non-inferior alternative for functional outcome. From 4.5 to 24 hours, the randomized trials identified here compare tenecteplase with placebo or standard medical treatment in imaging-selected populations, rather than with alteplase. They therefore cannot establish non-inferiority, superiority, or inferiority to *alteplase* in that later window.

Treatment within 4.5 hours

The early-window evidence spans patients selected by routine thrombolysis criteria and more restricted imaging or treatment-pathway criteria. In the pragmatic AcT trial, excellent outcome at 90–120 days occurred in 36.9% of tenecteplase recipients versus 34.8% of alteplase recipients; the unadjusted risk difference was 2.1% (95% CI, –2.6 to 6.9), meeting its prespecified –5% non-inferiority margin. Its 90–120-

day assessment interval should not be silently equated with an outcome measured strictly on day 90. ATTEST-2 likewise found tenecteplase 0.25 mg/kg non-inferior to alteplase 0.9 mg/kg when administered within 4.5 hours of symptom onset. TRACE-2 found non-inferiority within 4.5 hours in a Chinese population eligible for intravenous thrombolysis but ineligible for, or declining, endovascular thrombectomy; that restriction matters when applying its result to the broader early-window population.

The pooled direction of effect is compatible with at least comparable excellent outcome, although a pooled result is not itself a time-window interaction test. A meta-analysis restricted to trials comparing tenecteplase 0.25 mg/kg with alteplase included 11 randomized trials and 7,546 patients and reported an odds ratio for mRS 0–1 of 1.14 (95% CI, 1.03–1.25) versus alteplase. Because that estimate pools trials rather than isolating a common late-window alteplase comparison, it must not be presented as the effect specifically within either side of the 4.5-hour boundary. Conversely, a meta-analysis that combined multiple tenecteplase doses found an overall excellent-outcome odds ratio of 1.08 (95% CI, 0.93–1.26) versus alteplase. Its mixed-dose estimate addresses a broader intervention than the 0.25 mg/kg comparison and does not overturn the dose-specific early-window non-inferiority trials.

Selection also affects how confidently the early result can be generalized. AcT tested thrombolysis-eligible patients in pragmatic practice; TRACE-2 excluded planned thrombectomy; and TASTE selected patients using a perfusion-imaging target mismatch profile. TASTE was stopped early after other non-inferiority results emerged, and its reported significant finding was confined to the per-protocol analysis. These differences are more informative than treating every early-window trial as a replicate in an identical population. They do not, however, create an active-comparator estimate for patients first treated after 4.5 hours.

Treatment from 4.5 to 24 hours

Late-window tenecteplase has been evaluated under substantially narrower eligibility conditions. TIMELESS enrolled patients with internal carotid or middle cerebral artery occlusion and salvageable tissue on perfusion imaging; most underwent thrombectomy. Tenecteplase initiated 4.5–24 hours after last known well did not improve 90-day clinical outcomes compared with placebo. That null result tests the *additional benefit of tenecteplase under that treatment strategy*, not whether tenecteplase performs better or worse than alteplase. TRACE-III, in contrast, enrolled Chinese patients with large-vessel occlusion and salvageable tissue who did not have access to thrombectomy. Tenecteplase 0.25 mg/kg given 4.5–24 hours after last known well resulted in less disability than standard medical treatment. Its favorable finding does not supply an alteplase comparison either. CHABLIS-T II similarly studied perfusion-selected Chinese patients with large- or medium-vessel occlusion against best medical treatment, rather than alteplase.

TIMELESS and TRACE-III should not be read as contradictory estimates of a single alteplase-relative effect. Their controls differed from alteplase, and their populations differed in access to thrombectomy; the late-window trials also required evidence of salvageable tissue and specified arterial occlusions, unlike a general population presenting within 4.5 hours. Moreover, onset-based eligibility in early trials and last-known-well-based eligibility in late trials are not interchangeable descriptions of elapsed biological ischaemic time, particularly for unwitnessed or awakening stroke. An outcome advantage against standard medical treatment in one selected late population and no added benefit against placebo in another can therefore coexist without demonstrating a treatment-by-time interaction between tenecteplase and alteplase.

Thus, the defensible window-stratified conclusion is **early-window non-inferiority to alteplase, with no direct late-window tenecteplase–alteplase verdict**. Neither the positive nor the neutral late-window trial result establishes a relative mRS 0–1 effect between the two thrombolytics at 4.5–24 hours, and extrapolating the early active-comparator result across that boundary would substitute biological plausibility for randomized comparative evidence.

3. Among patients proceeding to thrombectomy, how do early reperfusion, mRS 0–1, and safety compare?

In patients selected for endovascular thrombectomy (EVT) and treated within 4.5 hours, the clearest randomized signal favouring tenecteplase 0.25 mg/kg over alteplase 0.9 mg/kg concerns **reperfusion before the procedure**, rather than a demonstrated improvement in 90-day mRS 0–1. EXTEND-IA TNK randomized thrombolysis-eligible patients with a documented large-vessel occlusion who were planned for EVT; its prespecified comparison concerned reperfusion on the initial angiogram after intravenous treatment, before thrombectomy could restore flow. Tenecteplase produced more early reperfusion than alteplase, and the trial reported better functional outcome, but that functional finding should not be relabelled as a proven between-group difference specifically in mRS 0–1.

Early reperfusion and its clinical interpretation

Pre-thrombectomy reperfusion is a particularly relevant endpoint in this population: it isolates an effect of the intravenous drug before mechanical treatment, while successful EVT can subsequently reduce differences in final disability between drug groups. EXTEND-IA TNK therefore provides direct evidence that tenecteplase 0.25 mg/kg can outperform alteplase 0.9 mg/kg on an angiographic endpoint in selected EVT candidates treated within 4.5 hours. It does not follow that every EVT-eligible population will experience the same frequency—or the same clinical consequence—of reperfusion before arterial puncture.

ATTEST-2 reported some evidence of higher mTICI 2b–3 reperfusion on the first angiographic run with tenecteplase among participants undergoing EVT, but observed substantially lower early recanalisation rates than EXTEND-IA TNK. Its discussion reports **8% in ATTEST-2 and 10.5% in AcT, compared with around 20% in EXTEND-IA TNK**; the investigators identify differences in endovascular selection criteria as a possible explanation. These are rates across trial populations, not an estimate of the tenecteplase-versus-alteplase treatment effect within each population. The apparent discrepancy is consequently more informative about transportability of the early-reperfusion result than about whether the original randomized comparison was valid. Occlusion and thrombus characteristics are also plausible sources of variation, but an EXTEND-IA TNK analysis pooling patients assigned to tenecteplase **0.25 or 0.4 mg/kg** cannot be treated as a dose-specific estimate for 0.25 mg/kg.

Excellent outcome and safety after EVT

The angiographic advantage is not interchangeable with a demonstrated advantage in **90-day excellent outcome, mRS 0–1**, among patients proceeding to EVT. EXTEND-IA TNK's reported better functional outcome supports clinical interest in the early-reperfusion signal, but does not by itself establish the size of an mRS 0–1 effect. Nor does the angiographic observation in ATTEST-2 establish that its EVT subgroup attained more mRS 0–1 outcomes: the trial describes a possible first-run reperfusion difference while placing its lower recanalisation rates in the context of different EVT selection. For this subgroup, the defensible conclusion is thus stronger for *reperfusion before thrombectomy* than for a particular dichotomised 90-day disability endpoint.

A subsequent randomized comparison in EVT candidates found greater substantial reperfusion on initial angiography with tenecteplase 0.25 mg/kg and no significant difference in symptomatic intracranial haemorrhage within 24 to 36 hours or 90-day mortality. Its alteplase regimen, however, was **0.6 mg/kg**, not the 0.9 mg/kg comparator used in the principal trials. Its study-level pooled analysis reported an mRS 0–1 **risk difference of 0.030 (95% CI, 0.008–0.051)**, but combined trials using alteplase 0.9 mg/kg with that low-dose-alteplase trial. That estimate is not a clean pooled answer to the specified 0.25-versus-0.9 mg/kg question. Similarly, comparisons of tenecteplase followed by EVT with EVT alone address whether to give bridging thrombolysis, not which thrombolytic to choose.

No EVT-specific safety advantage of tenecteplase 0.25 mg/kg over alteplase 0.9 mg/kg is established by the direct early-window comparisons described here. Safety also requires attention to what happens *after* the first angiogram: an early reopening signal cannot be assumed to reduce symptomatic haemorrhage or mortality once patients undergo EVT. In the 0.25-versus-0.6 mg/kg Japanese comparison, the reported lack of a significant difference in symptomatic haemorrhage or mortality is reassuring for that regimen, but it cannot replace a safety estimate against standard-dose alteplase.

Finally, the late-window EVT setting should remain separate from this early-window head-to-head evidence. TIMELESS studied perfusion-selected patients treated 4.5 to 24 hours after last known well, most of whom underwent EVT, but randomized tenecteplase against **placebo**, not alteplase; it found no better clinical outcome with tenecteplase. It therefore neither overturns the early pre-thrombectomy reperfusion result nor establishes relative efficacy or safety against alteplase in late-window EVT candidates.

4. How do symptomatic intracranial haemorrhage, mortality, and other safety outcomes compare at 0.25 mg/kg?

At tenecteplase 0.25 mg/kg, randomized comparisons with alteplase have not demonstrated a statistically significant difference in symptomatic intracranial haemorrhage (sICH) or death. In a meta-analysis restricted to randomized trials comparing this tenecteplase dose with alteplase, sICH had an odds ratio (OR) of 1.11 (95% CI 0.81–1.52) and all-cause death an OR of 0.99 (95% CI 0.81–1.19), each for tenecteplase versus alteplase. These estimates support broadly similar *observed* safety, but their intervals do not establish equivalent risks: the sICH interval, in particular, remains compatible with a clinically consequential increase or decrease. The finding is consistent with the AcT trial's report of similar sICH at 24 hours and all-cause death within 3 months in the two treatment groups.

Interpreting the haemorrhage evidence

Dose restriction matters more for this safety question than for a general comparison of thrombolytic agents. An earlier randomized-trial meta-analysis pooled several tenecteplase doses and found no significant sICH difference from alteplase (OR 1.12, 95% CI 0.79–1.59); its estimate cannot be assigned specifically to 0.25 mg/kg. Similarly, a systematic review that combined interventional and observational evidence reported a relative risk of sICH of 0.89 (95% CI 0.65–1.23) for tenecteplase versus alteplase across its comparative studies. That estimate spans doses and study designs, so it provides context rather than a cleaner answer than the dose-restricted randomized analysis. The principal analyses therefore differ in eligibility and estimand, not in showing opposing, statistically established sICH effects.

The definition of sICH also differs among trials. A haemorrhage accompanied by neurological deterioration may be classified differently depending on the imaging and clinical criteria applied; consequently, apparently similar pooled results should not be read as proof that every haemorrhage subtype or ascertainment interval has the same risk. Prespecified time points require particular care: AcT assessed sICH at 24 hours, whereas other syntheses aggregate reported sICH outcomes under the definitions used by their constituent studies. Rare-event imprecision remains relevant even when an

aggregate comparison does not reach statistical significance.

The 0.25 mg/kg conclusion must not be extrapolated to 0.40 mg/kg. A dose-comparison network meta-analysis found a higher sICH rate with tenecteplase 0.40 mg/kg than with tenecteplase 0.25 mg/kg (RR 2.39, 95% credible interval 1.00–7.92). That is a comparison *between tenecteplase doses*, not an estimate of the haemorrhage effect of 0.25 mg/kg versus alteplase. It nevertheless helps explain why safety syntheses mixing doses are less directly applicable to the regimen under consideration.

Mortality and other adverse outcomes

The dose-restricted randomized estimate for all-cause death does not suggest an overall mortality difference (OR 0.99, 95% CI 0.81–1.19, tenecteplase versus alteplase). A broader safety meta-analysis reported a small increase in *overall* mortality with tenecteplase (RR 1.10, 95% CI 1.02–1.19), but not in mortality at 90 days (RR 1.03, 95% CI 0.89–1.18). Those findings should not be presented as a contradiction within the 0.25 mg/kg randomized evidence: the analyses differ in their included evidence and mortality time points, and the broader result does not isolate the dose-restricted trial comparison. The distinction between in-hospital, early and 90-day death is consequential in stroke, because these outcomes need not have the same distribution of causes.

Other potential complications include any intracranial haemorrhage, parenchymal haematoma, extracranial bleeding and angioedema. The earlier complications review assessed these outcomes, but its comparative sICH estimate incorporated mixed study designs and tenecteplase regimens. A broader meta-analysis reported no clear difference in parenchymal haematoma (RR 1.04, 95% CI 0.81–1.34, tenecteplase versus alteplase); that result should likewise not be treated as a dose-specific randomized estimate. Neither a nonsignificant pooled result for these less frequent events nor the overall sICH result excludes differences in individual bleeding phenotypes.

Safety evidence from the extended window answers a different causal question. TIMELESS compared late-window tenecteplase with placebo and reported similar sICH incidence, whereas TRACE-III compared it with standard medical treatment in patients largely without access to thrombectomy and reported an apparently higher sICH incidence. Neither trial directly estimates late-window *tenecteplase versus alteplase* safety; their differing comparators and selected populations preclude treating them as a head-to-head haemorrhage comparison. Thus, the most defensible safety conclusion for 0.25 mg/kg versus alteplase remains the dose-restricted randomized result: no demonstrated difference in pooled sICH or death, with uncertainty sufficient to preclude a claim of identical risk across treatment windows, stroke phenotypes or individual complications.

5. Which guideline bodies have adopted 0.25 mg/kg tenecteplase on the basis of these trials?

The European Stroke Organisation (ESO), the American Heart Association/American Stroke Association (AHA/ASA), and Australia's living stroke guidelines have adopted tenecteplase as an intravenous thrombolytic option in defined acute ischaemic stroke populations. Their recommendations should be read by **dose, treatment window, and thrombectomy eligibility**, rather than as an unrestricted endorsement of tenecteplase whenever alteplase might be considered.

Treatment within 4.5 hours

The ESO's expedited recommendation supports tenecteplase **0.25 mg/kg** as an alternative to alteplase **0.90 mg/kg** for patients eligible for intravenous thrombolysis within 4.5 hours. It separately advises against tenecteplase **0.40 mg/kg** in this population. For eligible patients managed prehospital in a mobile stroke unit, ESO specifically *suggests* 0.25 mg/kg tenecteplase over alteplase 0.90 mg/kg, grading that recommendation as weak and the supporting evidence as low certainty. The dose distinction matters: evidence or recommendations concerning 0.40 mg/kg must not be carried over to the regimen established in the principal 0.25 mg/kg trials.

The **2026 AHA/ASA early-management guideline** endorses either tenecteplase or alteplase during the 4.5-hour thrombolysis window, citing international non-inferiority trials and the potential practical advantages of tenecteplase. Its accompanying summary emphasises prompt treatment of eligible patients with disabling deficits regardless of NIHSS score, without requiring advanced imaging selection within that window. This is a substantive change from the earlier, narrower AHA/ASA position, under which tenecteplase **0.25 mg/kg** could be considered for large-vessel occlusion as a Class IIb alternative. The later recommendation accommodates routine early-window use rather than limiting consideration to the pre-thrombectomy large-vessel-occlusion phenotype.

Australia's living stroke guidelines give a more explicitly phenotype-specific recommendation: in patients with **potentially disabling ischaemic stroke due to large-vessel occlusion** who meet the stated eligibility criteria, either tenecteplase **0.25 mg/kg, maximum 25 mg**, or alteplase **0.9 mg/kg, maximum 90 mg**, should be administered up to 4.5 hours after last known well. Thus, the Australian recommendation identifies both the dose and the large-vessel-occlusion population; it should not be quoted as though that particular wording applied to every thrombolysis-eligible stroke. Canadian Best Stroke Practices also updated its acute-stroke recommendations following the Canadian AcT trial, which is part of the clinical basis for adoption of 0.25 mg/kg tenecteplase.

These positions differ chiefly in **scope and timing of guideline revision**, not in a claim that tenecteplase

has proved clinically superior across all early-window patients. The ESO expedited process and the Australian large-vessel-occlusion recommendation reflect a more delimited evidence base, including the pre-thrombectomy EXTEND-IA TNK comparison; the later AHA/ASA position follows larger pragmatic, non-inferiority comparisons in broader thrombolysis-eligible populations. AcT, TRACE-2, and ATTEST-2 enrolled different clinical populations—particularly in whether thrombectomy was planned or excluded—so a recommendation applying broadly to early intravenous thrombolysis and one specifying large-vessel occlusion need not have identical wording.

Thrombectomy and the extended window

For an otherwise eligible patient proceeding to thrombectomy **within 4.5 hours**, the ESO and Australian positions permit use of the **0.25 mg/kg** regimen rather than treating a thrombectomy plan as a reason to default automatically to alteplase. The rationale includes the direct tenecteplase-versus-alteplase comparison before thrombectomy in EXTEND-IA TNK. This is an endorsement of a choice of *bridging thrombolytic* in eligible patients, not a recommendation to substitute intravenous thrombolysis for indicated endovascular treatment, or a resolution of whether bridging treatment is necessary in every thrombectomy candidate.

The **4.5–24-hour interval requires a separate decision framework**. Neither the ESO early-window recommendation nor the cited AHA/ASA 4.5-hour endorsement establishes routine tenecteplase–alteplase interchangeability throughout that later interval. Late-window trials selected patients by vascular and perfusion imaging, and the cited TIMELESS and TRACE-III comparisons tested tenecteplase against placebo or standard medical treatment, **not against alteplase**. The British and Irish Association of Stroke Physicians' consensus document takes a qualified position: tenecteplase *might be a reasonable alternative* in wake-up stroke or presentation beyond 4.5 hours when advanced imaging demonstrates salvageable tissue, subject to its stated exclusions; it also considers a service-wide switch from alteplase to tenecteplase reasonable. That consensus language is deliberately narrower than an unselected late-window recommendation. It should not be presented as proof, from a direct randomised comparison, that 0.25 mg/kg tenecteplase and alteplase have equivalent functional outcomes or safety at 4.5–24 hours.

In consequence, the established guideline adoption is strongest and clearest for **0.25 mg/kg tenecteplase within 4.5 hours**. Whether a particular recommendation includes all eligible early-window strokes or specifies large-vessel occlusion depends on the issuing body; late-window use remains contingent on imaging-defined eligibility and the precise recommendation being applied.

Guidelines

The **European Stroke Organisation (ESO)** expedited recommendation supports tenecteplase 0.25 mg/kg in place of alteplase 0.9 mg/kg for intravenous thrombolysis within 4.5 hours, including in patients with large-vessel occlusion who are candidates for endovascular thrombectomy. Its dose-specific distinction is important: ESO recommends *against* tenecteplase 0.40 mg/kg in otherwise eligible patients treated within 4.5 hours (**low-certainty evidence; strong recommendation**). For eligible patients managed prehospital in a mobile stroke unit, ESO *suggests* tenecteplase 0.25 mg/kg over alteplase 0.90 mg/kg (**low-certainty evidence; weak recommendation**). The mobile-stroke-unit recommendation should not be read as evidence of superior 90-day outcome across all treatment settings.

The **2026 American Heart Association/American Stroke Association (AHA/ASA)** acute ischaemic stroke guideline endorses either tenecteplase or alteplase for eligible patients in the 4.5-hour intravenous-thrombolysis window. Thus, its stated position permits either agent rather than expressing ESO's preference for tenecteplase. The available guideline summary does not assign a recommendation class or level of evidence to that specific choice, so none is inferred here. **Australian living stroke guidelines** likewise state that patients with potentially disabling ischaemic stroke due to large-vessel occlusion who meet their eligibility criteria should receive either intravenous tenecteplase 0.25 mg/kg, maximum 25 mg, or alteplase 0.9 mg/kg, maximum 90 mg, up to 4.5 hours after last known well; the published summary does not specify a class or evidence grade for this recommendation. The **British and Irish Association of Stroke Physicians** supports consideration of a service-level switch to tenecteplase and describes selected wake-up or later-presenting patients with advanced-imaging evidence of salvageable tissue as possible candidates. That consensus position is more permissive than a claim that tenecteplase has been shown non-inferior to alteplase throughout the extended window.

These positions are largely compatible once their scope is kept distinct. ESO expresses a preference for **0.25 mg/kg** within the conventional window; AHA/ASA and the cited Australian recommendation allow a choice between agents. None of those positions establishes a tenecteplase-versus-alteplase 90-day mRS 0–1 advantage for treatment at 4.5–24 hours.

Certainty and limitations

Certainty is **highest for tenecteplase 0.25 mg/kg versus standard-dose alteplase in patients eligible for intravenous thrombolysis within 4.5 hours**. Several phase 3 randomised comparisons contribute direct evidence, and the dose-specific synthesis of 11 trials, comprising 7,546 participants, reported a higher pooled frequency of 90-day mRS 0–1 with tenecteplase: OR 1.14 (95% CI 1.03–1.25) versus alteplase. That estimate supports at least non-inferiority in the populations studied, but a pooled superiority signal should not be treated as a uniform effect across trials or clinical phenotypes. In AcT, the excellent-

outcome proportions were 36.9% with tenecteplase and 34.8% with alteplase, an unadjusted risk difference of 2.1% (95% CI -2.6 to 6.9); this met its prespecified -5% non-inferiority margin without establishing superiority. TRACE-2 directly addressed eligible Chinese patients who were ineligible for, or declined, thrombectomy, whereas ATTEST-2 recruited a broader early-window thrombolysis population. Those differences matter when transporting a pooled estimate to patients with an occlusion proceeding to thrombectomy.

The pooled result also depends on **dose discipline**. A synthesis combining tenecteplase doses reported no statistically significant difference from alteplase for excellent 90-day outcome, OR 1.08 (95% CI 0.93–1.26), but that estimate is not interchangeable with an analysis restricted to 0.25 mg/kg. Conversely, the later dose-specific estimate of OR 1.14 (95% CI 1.03–1.25) versus alteplase should not be interpreted as proof that every constituent trial, imaging-selection strategy, or thrombectomy subgroup benefits to the same degree. The principal phase 3 trials were open-label, although blinded endpoint assessment limits bias in mRS ascertainment; deviations from intended interventions remained a concern in five trials assessed in the dose-specific synthesis. Non-inferiority also depends on each trial's prespecified margin and analysis population, not simply on a nonsignificant difference between treatments.

Certainty is substantially lower for an alteplase-relative conclusion at 4.5–24 hours, for a structural reason rather than just imprecision: the prominent extended-window randomised trials tested tenecteplase against placebo or standard medical treatment, not alteplase. TIMELESS evaluated perfusion-selected patients, most of whom underwent thrombectomy, and did not find better 90-day clinical outcomes with tenecteplase than placebo. TRACE-III studied perfusion-selected large-vessel occlusion largely without access to thrombectomy and found less disability than with standard medical treatment, with symptomatic intracranial haemorrhage appearing higher. CHABLIS-T II likewise compared tenecteplase with best medical treatment in an imaging-selected extended window. Their differing thrombectomy access, imaging criteria and controls can explain differing treatment effects; none resolves whether tenecteplase 0.25 mg/kg is non-inferior to **alteplase** for 90-day mRS 0–1 when administered 4.5–24 hours after last known well.

For patients **proceeding to thrombectomy within 4.5 hours**, EXTEND-IA TNK provides direct randomised evidence that tenecteplase improves pre-thrombectomy reperfusion relative to alteplase in its selected large-vessel-occlusion population. Confidence that the *magnitude* of this early-reperfusion advantage generalises to all thrombectomy pathways is lower: ATTEST-2 observed substantially lower initial-angiogram reperfusion rates than EXTEND-IA TNK and identified differences in endovascular selection as a plausible explanation. Early angiographic reperfusion is clinically relevant but is not itself the requested 90-day mRS 0–1 endpoint. Neither this evidence nor extended-window tenecteplase-versus-placebo evidence establishes a common tenecteplase-versus-alteplase effect across early and late thrombectomy pathways.

For **safety at 0.25 mg/kg**, the dose-specific randomised-trial synthesis found no statistically significant difference versus alteplase in symptomatic intracranial haemorrhage, OR 1.11 (95% CI 0.81–1.52), or all-cause death, OR 0.99 (95% CI 0.81–1.19). These intervals permit clinically relevant differences in either direction; absence of statistical significance is not evidence of identical risk. A broader synthesis of interventional and observational studies, including different tenecteplase doses, estimated symptomatic intracranial-haemorrhage RR 0.89 (95% CI 0.65–1.23) versus alteplase, but its mixed designs and doses make it less direct for the specified 0.25 mg/kg randomised comparison. Definitions of symptomatic haemorrhage also varied among trials, further limiting comparisons of absolute rates across studies. Overall, the evidence supports a well-tested early-window alternative with no demonstrated major safety penalty at 0.25 mg/kg; it does **not** support extending the same comparative certainty to 4.5–24 hours or assuming a proven functional advantage in every patient proceeding to thrombectomy.

Clinical reasoning

1. Define the decision and the standard of comparison. The relevant decision is whether to give intravenous tenecteplase 0.25 mg/kg rather than alteplase 0.9 mg/kg to an otherwise thrombolysis-eligible patient with acute ischaemic stroke. The leading clinical endpoint is excellent functional outcome, modified Rankin Scale (mRS) 0–1 at approximately 90 days; symptomatic intracranial haemorrhage (sICH) and death are essential counterweights. This is not a single decision across all presentations. Treatment within 4.5 hours, treatment from 4.5 to 24 hours, and treatment before planned endovascular thrombectomy (EVT) differ in eligibility, imaging selection and the comparisons actually tested. In particular, evidence that tenecteplase benefits a late-window patient *compared with no thrombolytic* does not establish that it is better than, or non-inferior to, alteplase in that window.

For the conventional thrombolysis window, the standard is a prespecified non-inferiority comparison against alteplase, interpreted alongside the direction and precision of the 90-day mRS 0–1 estimate and safety outcomes. AcT reported mRS 0–1 in 36.9% of tenecteplase recipients versus 34.8% of alteplase recipients, an unadjusted risk difference of 2.1% (95% CI –2.6 to 6.9), meeting its prespecified –5% non-inferiority threshold. TRACE-2, conducted among patients who were ineligible for or declined EVT, and ATTEST-2 also concluded that tenecteplase 0.25 mg/kg was non-inferior to alteplase within 4.5 hours. Non-inferiority permits tenecteplase to be selected as an alternative; it does not mean that every trial demonstrated superior clinical recovery.

2. Match the trial population to the clinical setting before applying the result. The broad early-window trials are most informative when a patient satisfies ordinary intravenous-thrombolysis criteria. TRACE-2 is particularly informative for patients not proceeding to EVT because that was built into its enrolment criteria; it should not, by itself, determine the preferred bridging drug for a thrombectomy candidate. Conversely, EXTEND-IA TNK directly randomised patients with an occlusion who were planned for

thrombectomy and received thrombolysis within 4.5 hours. Its finding of greater reperfusion before the procedure with tenecteplase is directly relevant to that pathway, but its selected population and angiographic endpoint do not replace the broader trials' estimate of 90-day mRS 0–1 in all thrombolysis-eligible strokes.

The pooled, dose-specific estimate helps put individual results in perspective. A meta-analysis of 11 randomised trials involving 7,546 patients reported higher odds of 90-day mRS 0–1 with tenecteplase 0.25 mg/kg than with alteplase: OR 1.14 (95% CI 1.03–1.25). That modest pooled advantage is compatible with the non-inferiority conclusions of the large individual trials; it should not be presented as a clinically decisive superiority finding for every stroke subtype or treatment pathway. Earlier pooling across several tenecteplase doses found no statistically significant difference in excellent outcome, OR 1.08 (95% CI 0.93–1.26), which is a different dose question and should not be substituted for the 0.25 mg/kg estimate.

3. Balance functional benefit against haemorrhage and death. The dose-specific randomised-trial meta-analysis reported sICH OR 1.11 (95% CI 0.81–1.52) and all-cause death OR 0.99 (95% CI 0.81–1.19) for tenecteplase versus alteplase. Neither estimate establishes a safety advantage. In particular, the sICH interval remains compatible with an increase as well as a decrease; “no statistically significant difference” is not proof that haemorrhagic risks are identical. A broader synthesis of interventional and observational comparisons reported an sICH relative risk of 0.89 (95% CI 0.65–1.23), but its mixture of study designs and tenecteplase regimens makes it less decisive for this dose-specific randomised choice. The benefit–harm judgement is therefore that tenecteplase 0.25 mg/kg preserves the established early-window functional-outcome benefit expected of a thrombolytic strategy relative to alteplase, without a demonstrated difference in sICH or mortality *between the two drugs*—not that either treatment is free of serious bleeding risk.

Dose discipline matters to that judgement. Results from higher-dose tenecteplase regimens cannot be treated as safety estimates for 0.25 mg/kg. A dose-comparison network meta-analysis found higher sICH with tenecteplase 0.40 mg/kg than with 0.25 mg/kg, RR 2.39 (95% credible interval 1.00–7.92). The European Stroke Organisation (ESO) recommends against 0.40 mg/kg for otherwise eligible patients presenting within 4.5 hours. At the bedside, an order for “tenecteplase” without a verified stroke dose is consequently an incomplete treatment decision.

4. Separate the thrombectomy question from the late-window question. For an early-window patient proceeding to EVT, the direct drug comparison supports considering 0.25 mg/kg tenecteplase before the procedure. EXTEND-IA TNK found more reperfusion before thrombectomy and better functional outcome with tenecteplase than with alteplase in its selected trial population. ATTEST-2, however, described much lower early-recanalisation rates in its EVT subgroup than those reported in EXTEND-IA TNK, with differences in endovascular selection offered as a possible explanation. A higher probability of

reperfusion on the first angiogram is biologically and operationally valuable, but it is not a guarantee of mRS 0–1 for an individual patient. Nor does a tenecteplase-versus-alteplase comparison answer whether thrombectomy should proceed or whether thrombolysis should be omitted altogether.

The extended window requires a more fundamental change in inference. TIMELESS compared tenecteplase with placebo in perfusion-selected patients treated 4.5 to 24 hours after they were last known to be well; most underwent EVT, and tenecteplase did not improve clinical outcome compared with placebo. TRACE-III compared tenecteplase with standard medical treatment in perfusion-selected patients with large-vessel occlusion who did not have access to EVT. It found less disability with tenecteplase, similar survival, and an apparently higher incidence of sICH. CHABLIS-T II likewise studied imaging-selected extended-window large- or medium-vessel occlusion against best medical treatment, not alteplase. These trials address whether to *add tenecteplase* to a particular late-window care pathway. Their different EVT access and selection criteria help explain why they should not be collapsed into an apparent late-window tenecteplase-versus-alteplase result.

5. Translate the comparison into an action. For an otherwise eligible patient within 4.5 hours, first establish disabling symptoms, last-known-well time, brain imaging findings, haemorrhage exclusions, relevant anticoagulant exposure and other thrombolysis contraindications. Then determine vessel status and EVT eligibility without allowing drug selection to delay an indicated thrombectomy pathway. Where tenecteplase is chosen, use the studied stroke regimen of 0.25 mg/kg, maximum 25 mg, rather than a higher tenecteplase regimen; the standard alteplase comparator is 0.9 mg/kg, maximum 90 mg. The single-bolus administration of tenecteplase can simplify interfacility transfer, but workflow convenience is a reason to prefer one *evidence-supported* regimen over another, not a reason to relax eligibility or dosing checks.

After either thrombolytic, follow the same vigilance for neurological deterioration, intracranial haemorrhage, systemic bleeding and airway complications, and reassess promptly if symptoms worsen. Record the functional outcome at the intended follow-up rather than inferring it from early vessel opening. In a late-window presentation, establish the imaging-defined target, occlusion and EVT pathway before considering thrombolysis; do not use the early-window non-inferiority result as an automatic authorisation to substitute tenecteplase for alteplase from 4.5 to 24 hours. Contemporary American Heart Association/American Stroke Association guidance endorses either agent in the 4.5-hour thrombolytic window, while Australian living-guideline recommendations include tenecteplase 0.25 mg/kg or alteplase for eligible patients with potentially disabling large-vessel-occlusion stroke within that window.

6. Check the facts that could reverse the choice. The decisive checks are the reliably established last-known-well time; whether the deficit is disabling; pretreatment imaging for haemorrhage, established infarction and any required late-window tissue selection; the presence and site of a treatable occlusion; whether EVT is indicated and available; and contraindications to fibrinolysis, particularly relevant

anticoagulant use and bleeding risk. A patient who fails thrombolysis eligibility should not receive tenecteplase merely because it is easier to administer. A patient eligible for EVT should not have EVT delayed to see whether tenecteplase works. Two recurrent interpretive errors are to describe pooled non-inferiority as proof of a large individual benefit, and to describe placebo- or standard-care-controlled late-window trials as head-to-head evidence against alteplase.

Illustrative scenario: A patient with disabling acute ischaemic stroke is otherwise eligible for intravenous thrombolysis within 4.5 hours, and no EVT target is identified. Tenecteplase 0.25 mg/kg is a reasonable alternative to alteplase 0.9 mg/kg: AcT met its non-inferiority criterion for excellent outcome, and the dose-specific pooled comparison favours tenecteplase modestly without establishing a difference in sICH or death.

Illustrative scenario: Change only the vessel finding: the same early-window thrombolysis-eligible patient has an occlusion for which EVT is planned. The drug comparison now includes the prospect of reperfusion before arterial access, for which EXTEND-IA TNK favoured tenecteplase. Give an eligible bridging thrombolytic without delaying thrombectomy; do not interpret early angiographic reperfusion as assurance of an excellent 90-day outcome.

Illustrative scenario: Change only the treatment time: a patient with a large-vessel occlusion and favourable perfusion imaging is assessed from 4.5 to 24 hours after last known well. The decision is no longer governed by early-window tenecteplase–alteplase non-inferiority. Determine EVT access and apply late-window imaging and treatment criteria: TIMELESS did not show clinical benefit over placebo in a population in which most underwent EVT, whereas TRACE-III found less disability against standard medical treatment where EVT was unavailable, with an apparent sICH increase. Neither trial establishes late-window equivalence to alteplase.

What this means in practice

Within 4.5 hours, tenecteplase 0.25 mg/kg is an evidence-supported alternative to alteplase 0.9 mg/kg for an otherwise thrombolysis-eligible patient with acute ischaemic stroke. This is principally a conclusion of non-inferiority, not a promise of better recovery for an individual patient. In the phase 3 AcT trial, excellent functional outcome was reported in 36.9% with tenecteplase versus 34.8% with alteplase; the unadjusted risk difference was 2.1% (95% CI –2.6 to 6.9), meeting that trial's prespecified –5% non-inferiority margin. TRACE-2 reached a non-inferiority conclusion in patients who were ineligible for or declined thrombectomy, and ATTEST-2 also found tenecteplase 0.25 mg/kg non-inferior within 4.5 hours. A subsequent meta-analysis restricted to trials comparing tenecteplase 0.25 mg/kg with alteplase found a pooled advantage for 90-day mRS 0–1, OR 1.14 (95% CI 1.03–1.25), but that pooled superiority signal

should not be substituted for a demonstrated benefit in every clinical or imaging subgroup. The 2026 American Heart Association/American Stroke Association guidance endorses either agent in the 4.5-hour thrombolysis window; Australian living guidance likewise includes both agents for eligible patients with potentially disabling large-vessel-occlusion stroke.

If thrombectomy is planned within the early window, give the choice of thrombolytic its appropriate place alongside—not instead of—rapid endovascular treatment. EXTEND-IA TNK directly compared tenecteplase 0.25 mg/kg with alteplase before thrombectomy and found greater reperfusion and better functional outcome with tenecteplase in its selected trial population. That result is particularly relevant when selecting a bridging thrombolytic, but its reperfusion advantage should not be treated as certain across all thrombectomy pathways: ATTEST-2 described substantially lower early recanalisation rates than EXTEND-IA TNK and raised differences in endovascular selection as a possible explanation. A trial comparing tenecteplase with the 0.6 mg/kg alteplase regimen used in Japan informs that setting, but is not a direct comparison with standard-dose alteplase 0.9 mg/kg. A bolus regimen can simplify administration during transfer, yet operational convenience must not be mistaken for proof that intravenous treatment obviates thrombectomy.

Do not extend the early-window tenecteplase-versus-alteplase conclusion to 4.5–24 hours. Late-window trials tested tenecteplase against placebo or standard medical treatment, rather than alteplase, in populations selected by vascular and perfusion imaging. TIMELESS did not find a better 90-day clinical outcome with tenecteplase than placebo in its imaging-selected population, most of whom underwent thrombectomy. TRACE-III instead found less disability with tenecteplase than standard medical treatment in imaging-selected patients with large-vessel occlusion who generally did not have access to thrombectomy, while symptomatic intracranial haemorrhage appeared more frequent. These results address different treatment pathways; neither establishes that tenecteplase is superior, non-inferior, or equally safe relative to alteplase throughout the late window.

Safety should be interpreted at the **0.25 mg/kg dose and for the patient population under consideration.** The dose-specific randomized-trial meta-analysis found no statistically significant difference in symptomatic intracranial haemorrhage, OR 1.11 (95% CI 0.81–1.52), or all-cause death, OR 0.99 (95% CI 0.81–1.19), versus alteplase. These intervals do not exclude clinically important differences in uncommon harms. Estimates that combine tenecteplase doses or observational and interventional studies answer a broader safety question and should not override dose-specific randomized evidence. In particular, 0.4 mg/kg should not be treated as interchangeable with 0.25 mg/kg: the European Stroke Organisation recommends against 0.4 mg/kg for eligible patients presenting within 4.5 hours.

Open questions

The most consequential unresolved comparison is **tenecteplase 0.25 mg/kg versus alteplase in a defined late-window population**. A sufficiently powered, blinded-endpoint randomized trial would need common imaging eligibility criteria, prespecified last-known-well intervals, and separate strata for patients proceeding to thrombectomy and those managed without it. It should assess 90-day mRS 0–1 alongside the full disability distribution, with consistently defined symptomatic intracranial haemorrhage and mortality. Without a common comparator and treatment pathway, a favourable late-window result against standard care cannot establish relative efficacy against alteplase, and a neutral result against placebo in a predominantly thrombectomy-treated population cannot settle the no-thrombectomy question.

For thrombectomy candidates, it remains uncertain which occlusion sites, clot characteristics, imaging profiles and treatment intervals reproduce the early reperfusion advantage seen in EXTEND-IA TNK, and how often reperfusion before angiography translates into 90-day mRS 0–1 rather than merely changing the procedure performed. Prospectively powered interaction analyses within randomized tenecteplase-versus-alteplase trials—with uniform assessment of the first angiogram—would be more decisive than comparing reperfusion percentages across trials with different selection and transfer pathways. Analyses of thrombus characteristics can generate such hypotheses, but cannot by themselves establish a clinically useful rule for choosing the drug.

Finally, pooled safety equivalence is not proof of equivalence for rare bleeding outcomes or every high-risk subgroup. Larger dose-specific randomized datasets, harmonised haemorrhage definitions and prespecified analyses by imaging profile and thrombectomy status would narrow that uncertainty. Until then, the strongest actionable claim remains non-inferiority of **0.25 mg/kg tenecteplase** to standard-dose alteplase for appropriately selected early-window thrombolysis—not a universal efficacy or safety advantage across doses, time windows and reperfusion pathways.