A comparative review of alteplase and tenecteplase in the management of acute ischaemic stroke

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Background: Acute ischaemic stroke is a major cause of mortality and long-term disability worldwide. Intravenous alteplase has long been the standard thrombolytic therapy; however, tenecteplase has emerged as a promising alternative because of its pharmacokinetic advantages and simplified administration.

Objective: To critically evaluate the efficacy and safety of tenecteplase compared to alteplase in the treatment of acute ischaemic stroke, with a focus on functional outcomes and risk of symptomatic intracranial haemorrhage.

Methods: A structured narrative review of 10 randomised controlled trials involving adult patients with acute ischaemic stroke was conducted. The primary outcomes were functional independence at 90 days, measured by the modified Rankin Scale (0–1) and the incidence of symptomatic intracranial haemorrhage within 36 hours. Studies included comparisons of standard-dose alteplase (0.9 mg/kg) with varying doses of tenecteplase, most commonly 0.25 mg/kg.

Results: Across the included trials, tenecteplase at 0.25 mg/kg demonstrated comparable and in some studies superior, efficacy to alteplase in achieving good functional outcomes. The incidence of symptomatic intracranial haemorrhage was similar between groups, with no significant increase observed with tenecteplase. Higher doses (0.4 mg/kg) were associated with increased bleeding risk and poorer outcomes.

Conclusions: Tenecteplase at 0.25 mg/kg is a safe and effective alternative to alteplase for acute ischaemic stroke thrombolysis. Its single-bolus administration and cost-effectiveness offer additional advantages, particularly in pre-hospital or resource-limited settings. Further large-scale blinded trials are warranted to confirm these findings and guide clinical practice.

Keywords acute ischaemic stroke, AIS, thrombolysis, intravenous alteplase, tenecteplase, symptomatic intracranial haemorrhage

Background

Acute ischaemic stroke (AIS) results from an abrupt interruption of blood flow to a specific region of the brain causing a neuroinflammatory response, typically because of an arterial occlusion instigated by a thrombus or embolus (Stoll and Nieswandt 2019; Campbell et al, 2020). This sudden lack of perfusion leads to a cascade of cellular events, including energy failure, excitotoxicity, oxidative stress and ultimately neuronal death. The resulting neurological deficits vary depending on the size and location of the infarct, but can include speech disturbance, hemiparesis and loss of consciousness.

Globally, AIS constitutes the majority of all stroke subtypes and remains a leading cause of adult disability and death. In the UK alone, there are more than 85 000 cases reported annually (Stroke Association, 2025). Prompt restoration of cerebral blood flow is critical to preserving viable brain tissue, encapsulated in the concept 'time is brain'. To this end, thrombolysis has become a cornerstone in the early management of AIS, aiming to rapidly dissolve the clot, restore perfusion and minimise the extent of irreversible damage (Royal College of Physicians (RCP) et al, 2023).

Thrombolysis, a treatment used to dissolve blood clots causing strokes, should be administered to approximately 20% of patients. However, in England and Wales, only 11–12% receive it, with hospital rates varying from 2% to 24% (Allen et al, 2022).

Alteplase, a recombinant tissue plasminogen activator (rt-PA), has been the standard thrombolytic therapy since the landmark National Institute of Neurological Disorders and Stroke (NINDS) trial in 1995, which demonstrated its clinical benefit when administered within a limited therapeutic window (NINDS; rt-PA Stroke Study Group, 1995). However, alteplase is not without limitations. Its pharmacokinetics include a short plasma half-life, necessitating continuous infusion over an hour. It also has only moderate efficacy in achieving arterial recanalisation and carries a well-documented risk of intracranial haemorrhage (Bhatia et al, 2010; Yeo et al, 2013). These shortcomings have spurred the investigation of alternative thrombolytics that may offer improved outcomes or greater logistical feasibility.

Tenecteplase, a genetically engineered variant of alteplase, introduces several pharmacological enhancements. It has a longer plasma half-life, higher fibrin specificity and is administered as a single intravenous bolus. These features not only simplify administration, particularly in pre-hospital and rural settings, but may also confer clinical advantages by accelerating reperfusion while potentially reducing bleeding risk (Nepal et al, 2018; Alamowitch et al, 2023). As such, tenecteplase is increasingly viewed as a compelling alternative in the acute management of AIS.

Symptomatic intracranial haemorrhage

Symptomatic intracranial haemorrhage represents a severe and potentially life-threatening complication of thrombolytic therapy in AIS. It is characterised by radiologically confirmed bleeding within the brain parenchyma or subarachnoid space, accompanied by neurological deterioration. Clinically, symptomatic intracranial haemorrhage may manifest as sudden worsening of consciousness, new focal deficits, or an abrupt rise in National Institutes of Health Stroke Scale (NIHSS) scores. The reported incidence of symptomatic intracranial haemorrhage following thrombolysis is approximately 2.9%, although rates can vary depending on patient selection and treatment protocols (Fekete et al, 2023). Several risk factors have been consistently associated with an increased likelihood of symptomatic intracranial haemorrhage, including older age, elevated blood pressure, hyperglycaemia and higher initial stroke severity scores (Derex and Nighoghossian, 2008). These factors underscore the importance of stringent patient selection when considering thrombolytic therapy.

In comparative trials of alteplase and tenecteplase, symptomatic intracranial haemorrhage serves as a critical safety endpoint. It is typically defined through a combination of neuroimaging evidence of new intracranial bleeding and corresponding clinical deterioration. This dual requirement ensures that only clinically meaningful events are classified as symptomatic intracranial haemorrhage, thereby enhancing the accuracy and reliability of safety assessments across studies (Rao et al, 2014). The consistent application of these criteria is essential for drawing valid conclusions about the relative safety of thrombolytic agents.

Aims

In response to growing evidence supporting tenecteplase as an alternative to alteplase in the treatment of AIS, this review critically examines the comparative efficacy and safety of both agents. Tenecteplase, a genetically modified form of alteplase with enhanced fibrin specificity and an extended half-life, has been associated with improved functional outcomes and a potentially lower risk of haemorrhagic complications. This review aims to evaluate the clinical benefits and limitations of tenecteplase relative to alteplase in AIS management, with particular emphasis on functional recovery and, based on outcomes reported in contemporary randomised controlled trials. Accordingly, the central research question is: in adult patients with AIS, how does tenecteplase compare to alteplase in terms of functional outcomes and the incidence of symptomatic intracranial haemorrhage.

Methods

This study was conducted as a structured narrative review of randomised controlled trials comparing intravenous tenecteplase and alteplase in the management of AIS. A structured search approach was used to identify relevant literature; however, the review

was not designed as a full systematic review with meta-analysis. Reporting was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to enhance transparency and reproducibility of the search and-selection process (Table 1) (Moher et al, 2009; Page et al, 2021). The review aimed to synthesise and compare available trial evidence relating to functional outcomes and the risk of symptomatic intracranial haemorrhage, rather than to generate pooled effect estimates.

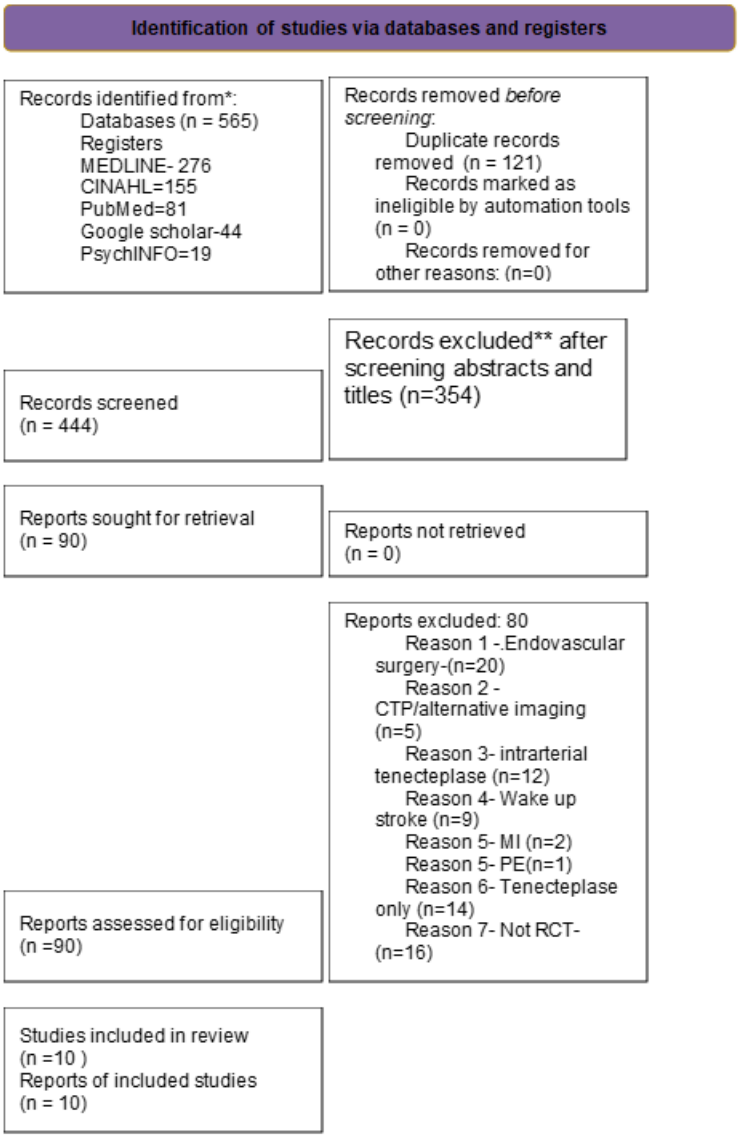

Table 1

Search strategy

A structured literature search was conducted across five electronic databases: PubMed, Medline, CINAHL, PsycINFO and Google Scholar. The search covered studies published

between January 2010 and July 2025, reflecting the period during which tenecteplase has been evaluated in AIS populations. Search terms included combinations of keywords and medical subject headings (MeSH), such as ‘tenecteplase’, ‘alteplase’, ‘AIS’, ‘AIS’ and ‘randomised controlled trial’, using Boolean operators (AND/OR) as appropriate. Searches were limited to English-language studies involving human participants aged 18 years and over. Reference lists of included articles were also hand searched to identify additional relevant studies.

Eligibility criteria

Studies were included if they met the following inclusion criteria: randomised controlled trials; adult patients (≥18 years) diagnosed with AIS; direct comparison of intravenous tenecteplase and alteplase; and reported at least one of the primary outcomes: functional independence at 90 days (defined as a modified Rankin Scale (mRS) score of 0–1) and incidence of symptomatic intracranial haemorrhage within 36 hours.

Exclusion criteria included: non-randomised studies, case reports or observational cohorts; studies involving non-ischaemic stroke populations; trials not reporting on either of the specified primary outcomes; studies focusing exclusively on bridging therapy or endovascular interventions without a separate intravenous thrombolysis comparison.

The primary outcomes were 90-day functional independence (mRS 0–1) and incidence of symptomatic intracranial haemorrhage within 36 hours. Some 10 studies met inclusion criteria, encompassing 5123 patients.

Data extraction and synthesis

Data from eligible studies were extracted into a pre defined spreadsheet, including study design, sample size, intervention details (dose and administration), outcomes (mRS, symptomatic intracranial haemorrhage) and trial settings. The primary outcomes of interest were:

1) Proportion of patients achieving functional independence at 90 days (mRS 0–1)
2) Incidence of symptomatic intracranial haemorrhage within 36 hours of thrombolysis.

Most included trials used tenecteplase at 0.25 mg/kg; however, variations in dosing (0.1 mg/kg and 0.4 mg/kg) were also captured, to reflect heterogeneity across studies.

Quality appraisal

Methodological quality of the included randomised controlled trials (RCTs) was assessed using the Critical Appraisal Skills Programme (CASP) checklist for randomised trials. The CASP tool was chosen for its structured and comprehensive approach to evaluating internal validity, relevance and applicability of trial findings. A separate CASP checklist was completed for each included study.

To complement this, the Cochrane Risk of Bias Tool was also used to further examine potential sources of bias, including randomisation, blinding, incomplete outcome data and selective reporting. Notably, the CASP checklist does not provide a numerical quality score, which aligns with recommendations from the Cochrane Handbook, as such scoring may over simplify complex methodological assessments (Higgins and Cochrane Collaboration, 2020).

Risk of bias assessment

Methodological quality of the included randomised controlled trials was assessed using the CASP checklist and the Cochrane Risk of Bias Tool. Overall, the included studies were judged to be of moderate-to-good methodological quality. Random sequence generation and allocation concealment were adequately reported in most trials, indicating a low risk of selection bias. Blinded outcome assessment was commonly used reducing the risk of detection bias, although several studies used open-label designs, which may have introduced performance bias.

Incomplete outcome data and selective reporting were generally low across studies, with primary outcomes consistently reported. However, variability in blinding procedures and early termination of some trials, particularly those evaluating higher doses of tenecteplase, were identified as potential sources of bias. Despite these limitations, the overall risk of bias was not considered sufficient to undermine the consistency of findings relating to functional outcomes and symptomatic intracranial haemorrhage.

Findings

A total of 5123 patients with AIS were included across the 10 studies identified (Table 1). Of these, 2446 patients received alteplase and 2677 received tenecteplase. Individual study sample sizes ranged from 75 to 1577 participants.

The therapeutic time window for thrombolysis across studies ranged from 3 to 6 hours following symptom onset. Most trials (TASTE-A, NOR-TEST 2, AcT, TRACE-2, EXTEND IA-TNK, ATTEST and NOR TEST) used a 4.5-hour window. In contrast, TRACE and Haley et al (2010) implemented a 3-hour window, while Parsons et al (2012) used a 6-hour window.

Regarding dosage, tenecteplase at 0.25 mg/kg was evaluated in eight trials. In addition, three trials included comparisons at 0.1 mg/kg and three trials assessed 0.4 mg/ kg. The alteplase dose of 0.9 mg/kg was consistently used as the control across all included studies.

Across trials, the primary outcomes measured were functional recovery, commonly defined as a modified Rankin Scale (mRS) score of 0–1 at 90 days, and the incidence of symptomatic intracranial haemorrhage within 36 hours post-thrombolysis.

During the literature search, additional studies were identified involving thrombolytic treatment for myocardial infarction (n=2) and pulmonary embolism (n=1); however, these were excluded as they were outside the scope of AIS management. Studies investigating bridging thrombolysis before endovascular intervention (n=20) and intra-arterial administration of tenecteplase (n=12) were also excluded because of insufficient data for direct comparison with intravenous monotherapy (Anadani et al, 2023).

Publication & year	Aim	Study characteristics	Inclusion / exclusion criteria	Control vs comparison	Funding / conflicts
AcT Menon et al. (2022)	Determine whether IV tenecteplase is non-inferior to alteplase	Multicentre, parallel-group open-label RCT; 1600 patients; 22 Canadian stroke centres	Adults ≥18; ≤4.5 h; CT/MRI confirmed AIS. Standard thrombolysis exclusions.	Alteplase 0.9 mg/kg vs Tenecteplase 0.25 mg/kg	Canadian Institutes of Health Research; no significant conflicts.
TASTE-A Bivard et al. (2022)	Comparison in Melbourne Mobile Stroke Unit	Prospective phase II open-label RCT; ~104 patients	Adults ≥18; ≤4.5 h; standard exclusions.	Alteplase 0.9 vs TNK 0.25	NHMRC Australia; no conflicts.
TRACE-2 Wang et al. (2023)	Tenecteplase versus alteplase	Phase III multicentre non-inferiority RCT; ~1430 patients	Adults ≥18; ≤4.5 h; standard exclusions.	Alteplase 0.9 vs TNK 0.25	Chinese national research funding; no conflicts.
TRACE Li et al. (2022)	Safety and efficacy	Phase II PROBE multicentre RCT; ~240 patients	Adults ≥18; ≤4.5 h; standard exclusions.	Alteplase 0.9 vs TNK 0.25	Chinese national funding; no conflicts.
NOR-TEST 2 Kvistad et al. (2022)	Management in Norway	Phase III blinded-endpoint RCT; ~208 patients	Adults ≥18; ≤4.5 h; standard exclusions.	Alteplase 0.9 vs TNK 0.40	Norwegian public funding.
EXTEND-IA TNK Campbell et al. (2020)	Reperfusion before thrombectomy	Phase III superiority RCT; ~300 patients	Large vessel occlusion; ≤4.5 h; mRS 0–1; NIHSS≥2.	Alteplase 0.9 vs TNK 0.25	NHMRC Australia; managed industry declarations.
ATTEST Huang et al. (2015)	Thrombolysis after stroke	Phase II RCT; 104 patients	Adults ≥18; ≤4.5 h; standard exclusions.	Alteplase 0.9 vs TNK 0.25	British Heart Foundation; UK Stroke Association.
NOR-TEST Logallo et al. (2017)	Management of acute stroke	Phase III RCT; ~1091 patients	Adults ≥18; excluded extensive hypodensity; standard exclusions.	Alteplase 0.9 vs TNK 0.40	Norwegian Research Council.
Parsons et al. (2012)	Randomised trial	PROBE RCT; 75 patients	Adults ≥18; ≤4.5 h; standard exclusions.	Alteplase 0.9 vs TNK 0.10/0.25	Australian NHMRC.
Haley et al. (2010)	Dose-escalation trial	Open-label Phase IIb/III; 112 patients	Adults ≥18; ≤3 h; standard exclusions.	Alteplase 0.9 vs TNK 0.1/0.25/0.40	NINDS/NIH.

Results

To facilitate comparison across studies, key trial characteristics and outcome measures are summarised in Table 2. This table provides a concise overview of tenecteplase dosing strategies, therapeutic time windows, primary functional outcomes and rates of symptomatic intracranial haemorrhage), allowing patterns in efficacy and safety to be readily identified across trials. Detailed methodological characteristics of individual studies are presented separately in Table 1.

All 10 studies included RCTs reporting functional outcomes at 90 days using the mRS. Across the ten studies, tenecteplase was consistently shown to be either non-inferior or, in some cases, superior to alteplase in achieving good functional outcomes (mRS 0–1). Additionally, the incidence of symptomatic intracranial haemorrhage was generally comparable between the two agents.

In the AcT trial (2022), a large multicentre, non inferiority study, 51% of patients treated with tenecteplase achieved mRS 0–1 at 90 days compared to 47.5% in the alteplase group, with similar symptomatic intracranial haemorrhage rates of 2.9% versus 3.3%, respectively.

The TASTE-A trial (2022), conducted within a mobile stroke unit framework, found tenecteplase to be equally effective in promoting functional independence, with both agents reporting an identical symptomatic intracranial haemorrhage rate of 2%.

Similarly, TRACE (2022) and TRACE-2 (2023) demonstrated non-inferiority of tenecteplase at a dose of 0.25 mg/kg, with functional outcomes and haemorrhagic complications closely matching those observed with alteplase.

In the EXTEND-IA TNK (2020) trial, which focused on early reperfusion before endovascular intervention, tenecteplase achieved numerically higher rates of functional independence (mRS 0–1 in 55% vs 44% with alteplase), although this trial was not powered to detect differences in long-term outcomes.

In contrast, findings from NOR-TEST (2017) and NOR-TEST 2 (2022), which used a higher tenecteplase dose of 0.4 mg/kg, indicated poorer functional outcomes and an increased incidence of symptomatic intracranial haemorrhage. These results suggest a potential dose-dependent risk profile, reinforcing the need for caution at higher doses.

Finally, Parsons et al (2012) and Haley et al (2010) explored multiple dosing strategies of tenecteplase. Both trials concluded that the 0.25 mg/kg dose provided the most favourable balance between efficacy and safety. Trials investigating the 0.4 mg/kg dose were either inconclusive or terminated early because of safety concerns.

Trial (Year)	Tenecteplase Dose	Alteplase Dose	Time Window	Primary Functional Outcome	sICH Outcome
AcT (2022)	0.25 mg/kg	0.9 mg/kg	≤4.5 h	mRS 0–1 at 90 days: 51% (TNK) vs 47.5% (ALT)	2.9% vs 3.3%
TASTE-A (2022)	0.25 mg/kg	0.9 mg/kg	≤4.5 h	Functional independence non-inferior	2% vs 2%
TRACE-2 (2023)	0.25 mg/kg	0.9 mg/kg	≤4.5 h	Non-inferior functional outcome	Comparable
TRACE (2022)	0.25 mg/kg	0.9 mg/kg	≤4.5 h	Similar mRS outcomes	No significant difference
EXTEND-IA TNK (2020)	0.25 mg/kg	0.9 mg/kg	≤4.5 h	mRS 0–1: 55% vs 44%	Similar
ATTEST (2015)	0.25 mg/kg	0.9 mg/kg	≤4.5 h	No significant difference	Comparable
NOR-TEST (2017)	0.40 mg/kg	0.9 mg/kg	≤4.5 h	Inferior outcomes with TNK	Increased
NOR-TEST 2 (2022)	0.40 mg/kg	0.9 mg/kg	≤4.5 h	Worse functional outcomes	Increased
Parsons et al. (2012)	0.1 / 0.25 mg/kg	0.9 mg/kg	≤6 h	Best outcomes at 0.25 mg/kg	Acceptable
Haley et al. (2010)	0.1–0.4 mg/kg	0.9 mg/kg	≤3 h	Dose-finding study	Dose-dependent

Discussion

Recent clinical guidance in the UK has already reflected the growing evidence base supporting tenecteplase in AIS. The National Institute for Health and Care Excellence (NICE) (2024) and the RCP (RCP et al, 2023) now recognise tenecteplase as an acceptable alternative to alteplase in selected patients, particularly those with large vessel occlusion within the recommended therapeutic window. Rather than challenging this position, the present review aims to contextualise these recommendations by synthesising trial-level evidence on functional outcomes, dosing strategies and safety profiles, with particular emphasis on the consistency of findings across RCTs.

Collectively, the evidence supports tenecteplase at a dose of 0.25 mg/kg as non-inferior to alteplase in the management of AIS. Across multiple trials, this dose was associated with comparable or superior functional outcomes without an increased risk of symptomatic intracranial haemorrhage. A key advantage of tenecteplase lies in its single-bolus administration, which simplifies delivery, particularly in pre-hospital settings and during inter-facility transfers (Abuelazm et al, 2023).

In contrast, higher dosing (0.4 mg/kg) has been linked to poorer clinical outcomes and elevated bleeding risk, reinforcing the importance of dose optimisation. Consistent with these findings, the European Stroke Organisation now recommends tenecteplase 0.25 mg/ kg for AIS patients with large vessel occlusion within 4.5 hours of symptom onset (Alamowitch et al, 2023).

Cost-effectiveness is another significant consideration. In resource-limited settings, the lower cost of tenecteplase, combined with its ease of administration, may enhance access to thrombolytic therapy and streamline stroke pathways (Nepal et al, 2018).

Tenecteplase also offers pharmacological advantages. Its longer half-life allows for bolus dosing, and its increased resistance to plasminogen activator inhibitor-1 may enhance fibrinolytic efficacy. These properties could support earlier reperfusion and potentially improved outcomes in selected patient populations.

However, several limitations across the reviewed studies must be acknowledged. Some trials were open-label, increasing the risk of performance and detection bias. Additionally, a number of studies had small sample sizes or were terminated early, which may skew the interpretation of safety and efficacy data. Furthermore, many trials excluded patients with pre-existing disabilities (mRS>2), limiting generalisability to more complex or frail populations.

Future research should focus on expanding inclusion criteria to reflect real-world AIS populations and further evaluating tenecteplase in diverse clinical contexts, including pre-hospital thrombolysis and telemedicine-enabled stroke care. Head-to-head trials comparing dosing strategies would also help to refine the optimal therapeutic window for tenecteplase, with the evidence clearly favouring the 0.25 mg/kg dose.

Conclusions

Tenecteplase at a dose of 0.25 mg/kg appears to be a safe, effective and practical alternative to alteplase for thrombolysis in AIS. Across multiple trials, it demonstrated comparable or superior functional outcomes with no significant increase in the risk of symptomatic intracranial haemorrhage. Given its pharmacological advantages, ease of administration and cost-effectiveness, tenecteplase may represent a favourable replacement for alteplase in many clinical settings. However, further large-scale, blinded randomised trials are warranted to confirm these findings and inform future clinical guidelines.

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