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Thrombolytic Therapy in Acute Ischemic Stroke: Consensus Statements, Insights, and National Clinical Practice Perspectives from the Turkish Stroke Expert Panel

Akut İskemik İnmede Trombolitik Tedavi: Türk İnme Uzmanlar Kurulu'ndan Uzlaşı Bildirileri, Kavramsal Yaklaşımlar ve Ulusal Klinik Uygulama Perspektifler

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ABSTRACT

Intravenous thrombolytic therapy (IVT) remains a foundational component in the management of acute ischemic stroke, utilized either as a standalone treatment or in combination with mechanical thrombectomy (MT). Over the past decade, clinical research has broadened the therapeutic landscape to include alternative thrombolytic agents administered across extended time windows, in some cases up to 24 hours, and for varied clinical indications. This evolution marks a clear departure from the historical reliance on alteplase within the narrow 4.5-hour treatment window, ushering in a new paradigm characterized by multi-agent flexibility, time-adjusted protocols, and indication-specific strategies. This guideline initiative was undertaken to systematically review recent high-quality evidence and propose updates to thrombolysis practices within Türkiye's stroke care framework. All phase 3 randomized controlled trials published in the past decade addressing "stroke" and "thrombolysis" were included. Employing the GRADE methodology, the evidence base was rigorously appraised. Where feasible, recommendations were grounded in direct evidence; where gaps persisted, meta-analyses of case-control studies and structured expert consensus were used. Overall, the quality of evidence supporting recommendations was determined to be high. An eight-member expert panel addressed 19 clinical questions spanning eight core PICO domains, resulting in 30 formal recommendations. Full consensus was reached on all but two items. Notably, tenecteplase at a dose of 0.25 mg/kg was unanimously favored over alteplase, based on its demonstrated non-inferiority and greater ease of administration. The most debated recommendations pertained to the preference for alteplase in mismatch positive (penumbral) patients lacking thrombectomy access, and the omission of IVT when groin puncture is feasible within 30 minutes, both of which were rejected by a 75% majority. Tailoring stroke treatment through individualized patient assessment remains essential. Further randomized controlled trials are needed to better define the role of thrombolysis in relation to mechanical thrombectomy—whether administered before, during, or after the intervention. Tenecteplase, in particular, offers encouraging potential to advance stroke outcomes within the context of Türkiye's clinical landscape.

Key words: Tenecteplase, alteplase, plasminogen activator, mismatch, stroke system of care.

ÖZ

İntravenöz trombolitik tedavi (İVT), akut iskemik inme yönetiminde tek başına ya da mekanik trombektomi (MT) ile kombine olarak uygulanan temel bir tedavi yaklaşımı olmayı sürdürmektedir. Son on yılda yapılan klinik araştırmalar, alternatif trombolitik ajanların daha geniş zaman pencerelerinde, bazı durumlarda 24 saate kadar ve farklı klinik endikasyonlarla uygulanmasını içerecek şekilde tedavi yelpazesini önemli ölçüde genişletmiştir. Bu evrim, yalnızca 4,5 saatlik dar bir zaman diliminde kullanılan alteplaz merkezli geleneksel yaklaşımdan belirgin bir kopuşa işaret etmekte; çoklu ajan esnekliği, zaman uyumlu protokoller ve endikasyona özgü stratejilerle tanımlanan yeni bir paradigma ortaya koymaktadır. Bu kılavuz girişimi, Türkiye'nin inme hasta/sistem yönetimi çerçevesinde tromboliz uygulamalarını güncellemek amacıyla, son on yılda yayımlanmış "inme" ve "tromboliz" kombinasyonunu ele alan tüm faz 3 randomize kontrollü çalışmaları sistematik olarak incelemek üzere başlatılmıştır. GRADE metodolojisi kullanılarak mevcut kanıtlar titizlikle değerlendirilmiştir. Mümkün olan durumlarda öneriler doğrudan kanıtlara dayandırılmış; kanıt boşluklarının bulunduğu alanlarda ise olgu-kontrol çalışmaları meta-analizleri ve yapılandırılmış uzman görüş raporları kullanılmıştır. Genel olarak, önerileri destekleyen kanıt düzeyinin yüksek olduğu söylenebilir. Sekiz kişilik uzman paneli, sekiz temel PICO alanını kapsayan 19 klinik soruyu ele alarak 30 uygulama önerisi geliştirmiştir. Bu önerilerden yalnızca ikisinde tam mutabakat sağlanamamıştır. Önerilerin başında "0,25 mg/kg dozundaki tenekteplaz, non-inferiority verileri ve uygulama kolaylığı nedeniyle oybirliğiyle alteplaza tercih edilmiştir" gelir. En fazla tartışılan öneriler ise, "trombektomi erişimi olmayan mismatch pozitif (penumbral) hastalarda alteplaz tercihinin uygunluğu" ve "kasık ponksiyonu 30 dakika içinde mümkünse İVT'nin atlanmasıyla" ilgiliydi, her iki öneri de %75 çoğunlukla reddedilmiştir. Yani, bu iki durumda da IVT uygulaması esastır. İnme tedavisinin kişiye özel hasta değerlendirmesiyle kişiselleştirilmesi hâlâ hayati önem taşımaktadır. Trombolizin mekanik trombektomiyle ilişkisini daha iyi tanımlamak için, müdahaleden önce, müdahale sırasında veya müdahaleden sonra uygulanması fark etmeksizin, daha fazla randomize kontrollü çalışmaya ihtiyaç vardır. Özellikle tenekteplaz, Türkiye'nin klinik durumu bağlamında inme sonuçlarını iyileştirme konusunda cesaret verici bir potansiyel sunmaktadır.

Anahtar kelimeler: Tenekteplaz, alteplaz, plazminojen aktivatörü, penumbral uyumsuzluk, inme yönetim sistemi.

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BACKGROUND

The fibrinolytic system plays a pivotal role in breakdown of intravascular thrombus by converting plasminogen into plasmin, which subsequently degrades fibrin clots.[1] In acute ischemic stroke, timely reperfusion is critical for minimizing neuronal damage, a principle summarized by the widely cited phrase "time is brain".[2,3]

Intravenous thrombolytic (IVT) therapy has consistently demonstrated efficacy in improving functional outcomes in acute ischemic stroke when administered within the appropriate therapeutic window.[4,5] Patients with moderate stroke severity, as defined by clinical scales such as the National Institutes of Health Stroke Scale (NIHSS)[6] appear to derive the greatest benefit from thrombolysis.[7]

The most significant adverse event associated with IVT is intracranial hemorrhage.[7] A meta-analysis of alteplase data found SITS-MOST[8]-defined symptomatic intracerebral hemorrhage (sICH) rate to be 3.7% in all patients and bleeding rates to be higher in lower NIHSS score groups, whereas they remained relatively stable (3-3.5%) for NIHSS ≥11, highlighting that larger infarcts carry a higher risk of hemorrhage.[7] Intensive blood pressure reduction (lower than 180/105 mmHg) following alteplase or lower dose alteplase use has not demonstrated consistent benefits in reducing hemorrhagic risk.[9-11] Currently, no intervention has been definitively proven to mitigate the risk of intracranial bleeding except for careful case selection.

IVT remains the cornerstone of acute ischemic stroke management, significantly improving the likelihood of functional independence when administered within the optimal time window. Its ability to dissolve thrombi rapidly helps restore cerebral perfusion, reducing long-term disability and improving survival rates.[12] While alteplase has long served as the standard of care, tenecteplase has emerged as a promising alternative, offering pharmacokinetic advantages and operational simplicity that may enhance real-world applicability.[12,13] Traditionally, the term "tissue-plasminogen activator" or "tPA" has been used to refer to alteplase; however, since it is no longer the only tissue plasminogen activator (tPA) in use, it is now important to use the specific agent's name instead. In this paper, we will refer to it as alteplase.

MAIN POINTS

- Mechanical thrombectomy remains the gold standard for treating acute ischemic stroke due to large vessel occlusion, with intravenous thrombolysis—preferably tenecteplase—recommended as adjunctive therapy unless contraindicated, even when rapid endovascular access is feasible.
- Patient selection is critical according to recommendations from clinical studies on endovascular treatment of patients with acute ischemic stroke.
- In the endovascular treatment of patients with acute ischemic stroke, not only technical success but also pre-hospital and emergency room organization and post-procedure follow-up are important.

METHODS

This study was conducted by a Scientific Board comprised 8 neurologists who are experts in management of acute ischemic stroke. Topics have been prioritized by the Board members who rated the importance of each topic on a scale from 1 to 10, and mean scores were calculated across all respondents. Selected topics were 'Use of alteplase for the management of acute ischemic stroke' and 'Use of tenecteplase for the management of acute ischemic stroke'. Eight relevant Population, Intervention, Comparator, Outcome (PICO) questions related to the selected topics were has been identified to guide the evaluation. Systematic reviews of the literature focused on randomized controlled trials (RCTs), meta-analyses and clinical guidelines published before March 2025 was conducted for each PICO question by all board members, and the quality of the evidence was assessed to develop evidence-based recommendations. Where available evidence was insufficient to support recommendations using the GRADE approach, expert consensus statements were provided. The recommendations were based on randomized controlled trials (RCTs), meta-analyses, and established clinical guidelines. For each PICO question, all Board members contributed to the evidence appraisal and formulation of recommendations. In cases where no RCTs were available, systematic literature reviews were conducted by each Board member to identify high-quality non-randomized studies. For each PICO question and each outcome, risk of bias was evaluated. The quality of evidence was graded as high, moderate, low, or very low, based on study design (randomized or observational), inconsistency of results, indirectness of evidence, imprecision of estimates, and risk of bias- according to GRADE methodology (but not using the GRADEpro tool) (Table 1).[14]

Table 1: Grade-definition*

Grade	Definition
High	High level of confidence that the estimate of the effect is close to the true effect
Moderate	Moderate level of confidence in the estimate of the effect. The available evidence is sufficient to support a conclusion, but further research may impact the level of confidence.
Low	Low level of certainty in the estimate of the effect. The available evidence is limited and the true effect may be substantially different from the estimate.
Very low	Very low level certainty. The available evidence is insufficient to support any firm conclusions.

*Adapted from reference[14]

EXPERT CONSENSUS

PICO-1: Key considerations in the clinical use of tenecteplase (TNK)

1.1. Is tenecteplase superior to alteplase in terms of pharmacological features and '*theoretical*' efficacy?

Analysis of available evidence

Pharmacological features: TNK is a third generation thrombolytic agent with 15-fold higher fibrin specificity, 80 fold higher PAI-1 (Plasminogen Activator Inhibitor-1) resistance than alteplase, slower clearance and longer plasma half-life than alteplase.[15] Individualized TNK dosage based on the patient's weight (15-25 mg) is administered as a single bolus over 5 seconds.[16]

Clinical efficacy and safety: TNK clinical trials demonstrated higher recanalization and reperfusion rates,[17] higher reperfusion rate before recanalization for large vessel occlusions and 'probably' lower intracranial hemorrhage.[18] The clinical data is discussed in detail in PICO 2 section.

Administration and logistics: TNK offers easier administration potentially providing easier interhospital transfers in addition to lower risk of under-dosing and administration errors, because it carries no risk of infusion interruption or delayed infusion initiation after the bolus.[19]

Guideline recommendations: European Stroke Organization (ESO) guidelines on intravenous thrombolysis for acute ischemic stroke was published in 2021.4 Within the following year, a number of randomized-controlled clinical trials (RCTs) comparing tenecteplase and alteplase have been reported. Taking these into account, a paper on the use of tenecteplase for patients with acute ischemic stroke of <4.5 h duration and who are eligible for IVT including evidence-based recommendations, have been published.[20] According to expert consensus statements, compared to alteplase (0.9 mg/kg), tenecteplase (0.25 mg/kg) is a safe and effective alternative (moderate evidence, strong recommendation) and preferred for patients with prehospital management with a mobile stroke unit (low evidence, weak recommendation) and for patients with large vessel occlusion (LVO) acute ischemic stroke (moderate evidence, strong recommendation). TNK may be favored over alteplase in view of comparable safety and efficacy data and easier administration.

Similarly, National Clinical Guideline for Stroke for the UK and Ireland, an online resource published in 2023, stated that: "Patients with acute ischemic stroke, regardless of age or stroke severity, in whom treatment can be started within 4.5 hours of known onset, should be considered for thrombolysis with alteplase or tenecteplase."[21]

In summary, stroke guidelines recommend tenecteplase as an effective and safe alternative to alteplase in acute ischemic stroke patients, and even favor tenecteplase (on the basis of easier adminisration and better outcomes in patient groups such as LVO acute ischemic stroke) (Table 2 and 3).[20,21]

Expert consensus statement

We are in full agreement for recommending tenecteplase 0.25 mg/kg to be favored over alteplase 0.9 mg/kg for patients with acute ischemic stroke of <4.5 hours duration on the basis of pharmacological features, clinical data and administration and logistic advantages and guideline recommendations.

Voting: 100% (8/8 members)

Table 2. Recommended dose and administration for tenecteplase and alteplase

	Tenecteplase[16]	Alteplase[22]
Dose for stroke indication	0.25 mg/kg	0.9 mg/kg
Administration	Bolus	%10 of total dose as bolus, then the rest as a 1-hour infusion.
Total duration	5 seconds	61 minutes
Maximum dose	25 mg	90 mg
Dose for AMI indication	0.5 mg/kg	1.1 mg/kg

Abbr: AMI, Acute Myocardial Infarction

Table 3. Advantages of tenecteplase over alteplase based on clinical data and expert opinions

Slower clearance and longer plasma half-life[15]
15-fold higher fibrin specificity and lower systemic fibrinolysis[15]
80 fold higher PAI-1 resistance[15]
Probability of lower intracranial hemorrhage[23]
Higher recanalization, reperfusion rates[24,25]
Higher reperfusion rate before recanalization for large vessel occlusions[26]
Easier administration- potentially lower risk of under-dosing and administration errors (no risk of infusion interruption or delayed infusion initiation after the bolus), easier inter-hospital transfers[19]

Abbr: PAI-1: Plasminogen activator inhibitor type 1

1.2. What should be the optimal IV tenecteplase dose for acute ischemic stroke?

Analysis of available evidence

Various doses of tenecteplase ranging from 0.1 to 0.5 mg/kg were studied in clinical trials.

In a phase 2B trial comparing tenecteplase (0.1 mg/kg or 0.25 mg/kg) with alteplase (0.9 mg/kg) in less than 6 hours after the onset of ischemic stroke, the higher dose of tenecteplase was found to be superior to the lower dose (and to alteplase) for all efficacy outcomes such as reperfusion and absence of serious disability at 90 days.[27]

NOR-TEST is a phase 3, randomized, open-label, blinded endpoint, superiority trial comparing tenecteplase (0.4 mg/kg; n=549) with alteplase (n=551) in stroke treatment (0-4.5 hours). Primary outcome, excellent functional outcome (modified Rankin Scale (mRS) score 0-1 at 3 months), was achieved by 354 (64%) patients in the tenecteplase group and 345 (63%) patients in the alteplase group (odds ratio (OR) 1.08, 95% CI 0.84–1.38; P=.52). sICH incidences were similar in both groups: 3% vs. 2%.[28]

NOR-TEST 2 is a phase 3, randomized, open-label, blinded endpoint, non-inferiority (3% margin) trial for stroke treatment (0-4.5 hours). 100 patients in tenecteplase (0.4 mg/kg) and 104 patients in alteplase groups were included in intention-to-treat (ITT) analysis. According to the primary outcome, favourable functional outcome defined as a mRS score of 0–1 at 3 months, superiority was not shown: Favorable functional outcome was observed in 32% of patients receiving tenecteplase whereas 51% of patients with alteplase (unadjusted OR: 0.45 [95% CI 0.25–0.80]; P=.0064). Incidences of any ICH (P=.0031), sICH (P=.061) and mortality (P=.013) were higher in tenecteplase group.[29]

The objective of the EXTEND-IA TNK Part 2 randomized clinical trial was to determine whether 0.40 mg/kg of tenecteplase safely improves reperfusion before endovascular thrombectomy (EVT) vs. 0.25 mg/kg in patients with LVO ischemic stroke. Greater than 50% reperfusion of the previously occluded vascular territory was achieved in 19.3% of the patients in the 0.40 mg/kg group vs. 19.3% in the 0.25 mg/kg group (adjusted risk ratio (aRR), 1.03 [95% CI, 0.66-1.61]; P=.89). These data demonstrate that a dose of 0.40 mg/kg, compared with 0.25 mg/kg, of tenecteplase did not significantly improve cerebral reperfusion.[18]

Another Phase IIB/III RCT comparing 0.1, 0.25, and 0.4 mg/kg tenecteplase with standard dose alteplase using 24-hour clinical outcome

based on efficacy (Major Neurological Improvement defined as improvement in NIHSS score of ≥8 points or an NIHSS score of 0 at 24 hours) and safety (risk of sICH), discarded 0.4 mg/kg dose as inferior due to higher sICH risk.[30]

In summary, 0.25 mg/kg dose has demonstrated better efficacy than 0.1 mg/kg. In addition, TNK 0.40 mg/kg dose has not significantly improved reperfusion and has shown negative results compared to 0.25 mg/kg (Table 2).

Expert consensus statement

We recommend against usage of high dose (≥0.40 mg/kg) or low dose (0.1 mg/kg) tenecteplase as data shows increased rates of hemorrhage and lower efficacy with these doses, respectively. We all agree that 0.25 mg/kg is the recommend dose for tenecteplase for treatment of acute ischemic stroke.

Voting: 100% (8/8 members)

PICO-2: Is tenecteplase more effective and safer than alteplase within the first 4.5 hours of acute ischemic stroke?

Analysis of available evidence

Tenecteplase (0.25 mg/kg) has demonstrated either non-inferiority or superiority compared with alteplase (0.9 mg/kg) within the first 4.5 hours of acute ischemic stroke in 5 RCTs (Table 4).

Five randomized controlled trials conducted between 2002 and 2004—namely AcT[31], TRACE-II[32], ATTEST2[19], TASTE[33], and ORIGINAL[34]—demonstrated that the third-month favorable functional outcome (mRS 0–1) was numerically higher among patients treated with tenecteplase (TNK) compared to those receiving alteplase. The absolute differences in favorable outcomes were 2.1% in AcT, 4% in TRACE[2], 2% in ATTEST[2], 2% in TASTE, and 2.4% in ORIGINAL.[19,31-34] Across all studies, tenecteplase met non-inferiority criteria relative to alteplase, although superiority was not established in the ATTEST2 trial.[19] Notably, there was no statistically significant difference in the incidence of symptomatic intracerebral hemorrhage (sICH) or overall mortality in the alteplase group (Table 4). [19,31-34]

A recent systematic review and meta-analysis including all available (eleven) RCTs that investigated efficacy and safety of TNK (0.25 mg/kg) compared with alteplase for the treatment of acute ischemic stroke within first 4.5 hours defined the primary outcome as the excellent functional outcome at 3 months (mRS score 0-1). Secondary outcomes were defined as good functional outcome (mRS score 0-2), reduced disability at 3 months (≥1-point reduction across all mRS scores), sICH and 3-month mortality. Pooled analysis comprised a total of 3788 patients treated with TNK and 3757 patients treated with alteplase. TNK was found to be associated with higher likelihood of excellent functional outcome (RR 1.05, 95% CI 1.01–1.10; P=.012; I2=0%; risk difference 2.95%; 95% CI 0.76%–5.14%; P=.008; I2=0%) and higher likelihood of reduced disability at 3 months (common odds ratio 1.10, 95% CI 1.01–1.19; P=.034; I2=0%). A similar good functional outcome (RR 1.03, 95% CI 0.99–1.07; P=.142; I2=28%) and similar rates of sICH (RR 1.12, 95% CI 0.83–1.53; P=.456; I2 = 0%) and 3-month mortality (RR 0.97, 95% CI 0.82–1.15; P=.727; I2=12%) was noted.[12]

According to the results of another meta-analysis including nine RCTs with a total of 2994 patients, compared with alteplase, TNK was associated with statistically significant increase in early vessel recanalization (n= 368, TNK vs. alteplase, OR: 2.07, 95% CI: [1.19, 3.59], I2= 0%) and increase in excellent recovery (n= 3548, TNK vs. alteplase, OR: 1.15, 95% CI: [1.01, 1.32], I2= 0%). Similar rates were observed for good recovery (n= 3486, TNK vs. alteplase, OR: 1.38, 95% CI: [0.89, 2.15], I2= 84%), early neurological improvement (n= 1686, TNK vs. alteplase, OR: 1.06, 95% CI: [0.87, 1.28], I2= 24%), poor recovery (n= 3548, TNK vs. alteplase, OR: 0.94, 95% CI: [0.81, 1.10], I2= 0%), sICH (n= 3567, TNK vs. alteplase, OR:1.06, 95% CI: [0.70,1.60], I2= 0%), PH2 (n= 3103, TNK vs. alteplase, OR: 1.26, 95% CI: [0.39,4.07], I2= 56%) and mortality (n= 3447, TNK vs. alteplase, OR: 0.99, 95% CI: [0.80, 1.23], I2= 33%).[17]

In summary, available scientific data that demonstrates tenecteplase (0.25 mg/kg) has non-inferior efficacy and probability of achieving better outcomes shown as better early recanalization, higher likelihood of excellent functional outcome and reduced disability at 3 months in addition to the similar safety profile compared with alteplase (0.9 mg/kg).

Expert consensus statement

We unanimously recommend tenecteplase over alteplase within the first 4.5 hours of acute ischemic stroke, in the light of available scientific data that demonstrates tenecteplase (0.25 mg/kg) has non-inferior efficacy (probably superior for some outcomes) and similar safety profile compared with alteplase (0.9 mg/kg), guideline recommendations, and considering easier administration (single bolus instead of 1-hour infusion) advantage.

Voting: 100% (8/8 members)

PICO-3: What is the efficacy of tenecteplase in patients with acute stroke due to cerebral large vessel occlusion?

Analysis of available evidence

There are three RCTs which investigated TNK in patients with acute stroke due to cerebral large vessel occlusion (LVO): EXTEND-IA TNK Part 126, TIMELESS35 and Eternal-LVO36 (Table 5).

EXTEND-IA TNK Part 1 was a RCT with non-inferiority and sequential superiority analysis. The study enrolled patients with ischemic stroke who had occlusion of the terminal internal carotid artery, basilar or middle cerebral artery, and who were eligible to undergo MT. 202 patients received either tenecteplase (0.25 mg/kg, n=101) or alteplase (0.9 mg/kg, n=101) within the first 4.5 hours. The primary outcome, defined as reperfusion of >50% of the involved ischemic territory or

Table 4. Phase III trials comparing tenecteplase 0.25 mg/kg with alteplase 0.9 mg/kg in acute stroke within the first 4.5 hours

Trial	Design	n	Results		
			Primary outcome (PO: mRS 0-1 at 90th day)		Other findings in TNK vs. alteplase groups, respectively
AcT[31] Canada (Menon, 2022)	Design: PROBE, non-inferiority [Margin: 5%] (Bridging to MT was included)	n=1577 22 centers	PO: 36.9% in TNK vs 34.8% in Alteplase Unadjusted risk difference=2.1% (CI: -2.6%-6.9%)	TNK was non-inferior	Median NIHSS: 9 vs. 10 sICH: 3.4% vs. 3.2% Mortality: 15.3% vs. 15.4%
TRACE-II[32] (Wang, 2023)	Design: PROBE, non-inferiority [Margin: 3.74%] (Patients who were eligible for MT were excluded.)	n=1430 53 centers China	PO: 62% in TNK vs 58% in Alteplase RR=1.07 (CI: 0.98–1.16)	TNK was non-inferior	sICH: 2% vs. 2% Mortality: 7% vs. 5%
ATTEST–2[19] (Muir, 2024)	Design: Randomized, non-inferiority and superiority	n=1858 40 centers UK	PO:44% in TNK vs 42% in Alteplase mRS-02: 68% in TNK vs 65% in Alteplase aOR=1.07 (CI 0.90-1.27, P<.001)	TNK was non-inferior but not superior (P=.43)	Median NIHSS=7 (IQR 5-13) sICH: 2% vs. 2%, Mortality: 8% vs. 8%
TASTE[33] (Parsons, 2024)	Design: PROBE, non-inferiority [Margin: 3%]	n=601 35 centers 8 countries	PO: 57% in TNK vs 55% n Alteplase (ITT) 59% in TNK vs 56% in Alteplase (Per-protocol)	TNK was non-inferior (per protocol) but non-inferiority was not met (ITT).	NIHSS =7 sICH: 3% vs. 2% Mortality: 7% vs. 4%
ORIGINAL[34] (Meng, 2024)	Design: PROBE, Non-inferiority	n=1489 55 centers China	PO: 72.7% in TNK vs 70.3% in Alteplase RR=1.03 (95%CIs, 0.97-1.09)	TNK was non-inferior	sICH: 1.2% vs. 1.2% Mortality: 4.6% vs. 5,8%

Abbr: CI, Confidence Interval; IQR, interquartile range; ITT, Intention to Treat; mRS, Modified Rankin's Score; MT, Mechanical Thrombectomy; NIHSS, National Institutes of Health Stroke Scale; PO, Primary Outcome; PROBE, Prospective randomized open blinded end-point (Study); RR, Relative Risk; sICH, Symptomatic Intracranial Hemorrhage; TNK, Tenecteplase.

an absence of retrievable thrombus at the time of the initial angiographic assessment, occurred in 22% in tenecteplase vs 10% in alteplase group (incidence difference, 12%; 95% CI, 2 to 21; incidence ratio, 2.2; 95% CI, 1.1 to 4.4; P=.002 for non-inferiority; P=.03 for superiority). The trial was powered for non-inferiority, not for superiority, that was why the significance of superiority for reperfusion (primary outcome) was less robust. In this trial, tenecteplase also resulted in a better 90-day functional outcome compared to alteplase as shown with median mRS scores: 2 vs. 3 (common OR, 1.7; 95% CI, 1.0 to 2.8; P=.04). Incidence of sICH was similar in both groups (1%). Authors concluded that tenecteplase before thrombectomy was associated with a higher incidence of reperfusion and better functional outcome than alteplase.[26]

TIMELESS study investigated tenecteplase efficacy and safety compared to placebo in a different time frame to evaluate whether tenecteplase confers benefit beyond 4.5 hours. This multicenter, double-blind RCT involved patients with acute ischemic stroke who have evidence of occlusion of the MCA or ICA and salvageable tissue as determined on perfusion imaging. Results of tenecteplase (0.25 mg/kg) vs placebo administration within 4.5-24 hours after the last known to be well time (LKWT) were compared for the primary outcome of ordinal score on the mRS at 3 months. 77.3% of all patients subsequently underwent MT with similar ratios in both study groups. The median time between the time the patient was LKWT and randomization was approximately 12 hours vs 13 hours in tenecteplase and placebo groups, respectively. The median mRS score at 90 days was 3 in both groups. The adjusted common OR for the distribution of scores on mRS at 90 days for tenecteplase vs placebo was 1.13 (95% CI, 0.82-1.57; P=.45). Keeping in mind that the trial was not powered for conclusions from the subgroup analysis, it implied that tenecteplase may provide better results for patients with an occlusion of the M1 segment of the MCA: Adjusted common OR was 1.59 (95% CI, 1.00- 2.52) and the proportion of the patients with functional independence (mRS ≤2) at 90 days was 45.9% in tenecteplase group vs 31.4% in placebo group (adjusted OR: 2.03; 95% CI, 1.14-3.66). Mortality rates at 90 days (19.7% vs 18.2%) and the incidence of sICH (3.2% vs 2.3%) were also comparable. Investigators concluded that treatment with tenecteplase within 4.5- 24 hours after acute ischemic stroke with occlusions of the MCA or ICA did not result in better clinical outcomes than those with placebo.[35]

In the ETERNAL-LVO study[36], the results of which were announced at the International Stroke Conference 2025 but have not yet been published as a full text, no difference was found in the 90th day favorable prognosis between patients who had tissue salvageable with CTP within 0-6 hours and those who received TNK and standard treatment (mRS 0-1, 37% in TNK and 43% in standard treatment - 82% of whom received Alteplase, OR: 0.90, (Table 5). While an increase in sICH was observed in the TNK group, no change in mortality was detected.

Additional evidence was provided by the pooled analysis of clinical and imaging data obtained in ATTEST studies (phase II studies one of which demonstrated superiority of tenecteplase whilst the other showed no difference) that compared effect of tenecteplase on occlusion status at 24 hours post thrombolysis with the effect of alteplase, in total 146 patients with complete vessel occlusion. The analysis revealed greater recanalization at 24 hours (71% vs 43%, P<.001). Tenecteplase treatment for the patients with a TICI (Thrombolysis in Cerebral Infarction) 0/1 occlusion showed greater early clinical improvement (median NIHSS change 9 vs 1, P=.001) and higher rates of favorable 90-day outcomes (mRS 0–1: 49% vs 25%, OR 4.82, 95% CI, 1.02–7.84, P=.05). Furthermore, significantly lower risk for sICH was shown: 3% vs 7%, P=.02). These data indicate greater recanalization efficacy with tenecteplase vs alteplase, possibly being more evident in patients with complete vessel occlusions on baseline CT angiography.[25]

Table 5. TNK use in patients with acute cerebral large vessel occlusion

Trial	Design	n	Results		
			Primary outcome		Other findings in TNK vs. alteplase groups, respectively
EXTEND-IA TNK Part 1 (Campbell-2018)[26]	Design: PROBE, non-inferiority Followed superiority Time interval: 0-4.5 h Groups: TNK [0,25] vs Alteplase [0.9] (in mg/kg)	n=202 12 centers Australia and New Zealand	PO: Reperfusion: 12% [95%CI: 2-21, P=.002] advantage for Tenecteplase over Alteplase in thrombectomy angiography	TNK was superior	TNK vs tPA= 22% vs 10%, non-inferiority P=.002; Superiority aOR=2.6 (1.1–5.9), P=.02
TIMELESS (Albers-2024)[35]	Design: Randomized placebo control, double blind. Time interval: 4.5–24 hours MT ratio:77% Occluded arteries: M1/M2/ICA Groups: TNK [0,25] vs Placebo	n=458 112 centres USA, Canada	The median mRS at day 90 was 3 in both groups. aOR=1.13 (95%CI: 0.82-1.57) P=.45. mRS 0-2: 46% in TNK vs. 42.4% in Placebo. Subgroup analysis: TNK is successful in M1 occlusion. OR=1.59 (95%CI: 1.0-2.52) mRS-02: TNK 45.9% vs. Placebo: 31.4% (aOR=2.03; 95%CI, 1.14-3.66).	TNK is successful in M1 occlusion	Median NIHSS:12 sICH: 3.2% (TNK) vs 2.3% (Placebo) Death: 19.7% (TNK) vs18.2% (Placebo)
ETERNAL-LVO (Yogendurakumar-2025)[36]	Design: Non-inferiority Randomized controlled trial Time interval:0-6 h Groups: TNK[0.25] vs Standart treatment (Alteplase in 82%) All had CTP mismatch MT: 70% in both.	N=240 Australia, Canada*	PO: mRS at 90th day: 37% (TNK) vs %43 (Standard), OR:0.90 [95%CI, 0.67-1.21)	TNK is neural	Median NIHSS: 13 (TNK) vs 14 (standard) sICH: 4% vs 1%. Mortality: 9% vs 7%.

Abbr: aOR, Adjusted Odds ratio; CI, Confidence Interval; ICA, Internal carotid artery; ITT, Intention to Treat; M1, Middle cerebral artery M1 segment; M2, Middle cerebral artery M2 segment; mRS, Modified Rankin's Score; MT, Mechanical Thrombectomy; NIHSS, National Institutes of Health Stroke Scale; PO, Primary Outcome; PROBE, Prospective randomized open blinded end-point (Study); RR, Relative Risk; sICH, Symptomatic Intracranial Hemorrhage; TNK, Tenecteplase.*Number of centers was not stated in the presentation.

A systematic review and meta-analysis including 4 RCTs (ATTEST, Australian TNK, EXTEND-IA TNK and NOR-TEST) and a total of 433 patients compared tenecteplase at different doses to alteplase (0.9 mg/kg) for acute ischemic stroke patients with LVOs. Tenecteplase provided better outcomes as shown with higher odds of mRS scores of 0-2 (OR: 2.06; 95% CI, 1.15-3.69), successful recanalization (OR: 3.05; 95% CI, 1.73-5.40) and functional improvement defined as 1-point decrease across all mRS grades (common OR: 1.84; 95% CI, 1.18-2.87) at 3 months. Tenecteplase was found to confer similar outcomes with alteplase in terms of early neurological improvement and safety (sICH, any ICH, rates of mRS score 0-1 and all-cause mortality at 3 months). This meta-analysis provided additional evidence that tenecteplase is associated with significantly better recanalization and clinical outcomes compared with alteplase in acute ischemic stroke patients with LVO.[37]

In another meta-analysis of 1028 patients with acute stroke due to LVO extracted from 5 RCTs (AcT, ATTEST, Australian TNK, EXTEND-IA TNK and NOR-TEST), TNK was no different from Alteplase in terms of 90-day excellent neurological recovery (RR=1.18; 95% CI 1.00-1.40), good neurological recovery (RR=1.18; 95% CI 0.90-1.54) or successful reperfusion (RR=1.15; 95% CI 0.93-1.44), symptomatic intracerebral hemorrhage (RR=1.14; 95% CI 0.62-2.10) and mortality (RR=1.22; 95% CI 0.52-2.84). It was concluded that TNK is a good alternative to Alteplase.[38]

The efficacy of tenecteplase in the treatment of minor stroke, which has a large vessel occlusion but a mild clinical picture, has been investigated in TEMPO studies.[39,40] TEMPO-1 is a dose determination study and TNK was used in the first 12 hours in fifty acute stroke patients. The patients had NIHSS less than 5 and LVO on CT angiography. However, there was no well-evolved infarction on tomography. As a result, the successful recanalization rate was 39% with TNK 0.1 mg/kg, while this rate was 52% with TNK 0.25 mg/kg. The excellent outcome was 56% with TNK 0.1 mg/kg and 76% with TNK 0.25 mg/kg.40 The CT-based TEMPO-2 study announced in 2024 showed that TNK was no better in minor stroke patients with LVO within the first 12 hours. TEMPO-2 was stopped due to futility. And on the TNK side, there was an increase in the rate of bleeding [higher in TNK: RR 4.2 (0.9–19.7, P=.059)] and death [higher in TNK: aHR 3.8 (CI 1.4–10.2, P=.0085]. This study will be briefly reviewed again in the context of late-window thrombolytic therapy applications.[39]

Tenecteplase has been recommended as a reasonable alternative to alteplase in patients undergoing bridging therapy in the AHA Guidelines (IIb)[41] as well as ESO Guidelines[4,20] and National Clinical Guideline for Stroke for the UK and Ireland.[21]

As a summary, tenecteplase exhibited better effectiveness than alteplase in acute ischemic stroke with LVO within first 4.5 hours as shown with 12% higher recanalization rate; and the analysis revealed no significant differences between 0.25 and 0.4 mg/kg doses of tenecteplase: both doses provided >50% reperfusion in 19.3% of the patients.[26] Tenecteplase did not convey any benefit over placebo for acute ischemic stroke with LVO (except for probable benefit in M1 group) within the extended time window of 4.5-24 hours.[35,39]

Expert consensus statement

In full agreement, we suggest that tenecteplase (0.25 mg/kg) has better efficacy (12% higher recanalization rate in one study) compared to alteplase within the first 4.5 hours of acute ischemic stroke with LVO for bridging treatment (IVT before thrombectomy).

Voting: 100% (8/8 members)

We do not recommend usage of tenecteplase in extended time window (4.5-24 hours) as there is no sufficient evidence of benefit over placebo for the patients with acute ischemic stroke with LVO, except for probable benefit in M1 group.

Voting: 100% (8/8 members)

We recommend against routine intravenous thrombolysis in patients with mild stroke and intracranial large vessel occlusion within 4,5-24 hours of stroke onset based on CT alone.

Voting: 100% (8/8 members)

PICO-4: What is the impact of tenecteplase in acute ischemic stroke within 4.5–24 hours or with unknown time of onset?

Analysis of available evidence

Literature review revealed several trials investigating efficacy and safety of tenecteplase in treatment of acute ischemic stroke within 4.5-24 hour or wake up stroke (WUS) (Table 6).

A subgroup analysis of NOR-TEST trial evaluated the efficacy and safety of tenecteplase (0.4 mg/kg) compared to alteplase (0.9 mg/kg) in patients with WUS (n= 40) who were included in the study based on DWI-FLAIR mismatch. The number of patients achieving good clinical outcome (mRS 0-1) were similar in both treatment groups (68.8% vs 65.2%, P=.82). Tenecteplase was associated with better early neurological improvement (87.5% of patients vs 54.2%, P=.027). No ICH or death was detected on MRI/CT 24-28 hours after thrombolysis.[42]

TWIST was an investigator-initiated, multi-center, open-label RCT that was conducted at 77 centers in ten countries between June 2017 and September 2021. The study used non-contrast CT to assess the effect of 0.25 mg/kg of tenecteplase (within 4.5 hours of awakening) on functional outcome in patients with ischemic WUS. The patients (n=578) were selected using non-contrast CT. Tenecteplase did not show better results in terms of functional outcome (primary outcome): Adjusted OR 1.18, 95% CI 0.88-1.58; P=.27. Rates of sICH 2% vs 1%), any ICH (11% vs 10%; adjusted OR 1.14, 0.67-1.94; P=.64) and mortality at 90 days were comparable in tenecteplase and placebo groups (10% vs 8%; adjusted HR 1.29, 95% CI 0.74-2.26; P=.37). However, the trial did not meet the required enrollment number (600) therefore it was not sufficient to produce definitive results.[43]

As previously discussed in PICO 3, TIMELESS compared tenecteplase (0.25 mg/kg) and placebo within 4.5-24 hours after the last known to be well LKWT in LVO (MCAO or TICAO). Patients were enrolled if they had evidence of salvageable brain tissue: Initial ischemic core volume <70 ml, ratio of the volume of ischemic tissue to the initial infarct volume (mismatch ratio) ≥1.8, absolute volume of penumbra (mismatch volume) ≥15 ml). The primary outcome was ordinal score on the mRS at 3 months. 77.2% of patients in tenecteplase group subsequently underwent thrombectomy (77.4% in placebo group). Median mRS score at 90 days was 3 in both groups. The adjusted common OR for the distribution of scores on mRS at 90 days for tenecteplase vs placebo was 1.13 (95% CI, 0.82-1.57; P=.45). Complete recanalization as assessed on 24-hour angiography by MRI or CT (secondary outcome) was improved by tenecteplase: 76.7% vs 63.9% (adjusted OR 1.89; 95% CI, 1.21-2.95). Safety analysis showed no significant difference in terms of sICH (3.2% vs 2.3%) or mortality rate at 90 days (19.7% vs 18.2%). The authors concluded that compared to placebo, tenecteplase did not improve outcomes in patients with MCAO or TICAO (most of whom underwent subsequent thrombectomy) within 4.5-24 hours after the last known to be well LKWT.[35]

TRACE-III, a RCT that evaluated tenecteplase without thrombectomy beyond 4.5 hours, involved patients with LVO (MCAO or TICAO) who had salvageable brain tissue as identified on perfusion imaging. Efficacy and safety of tenecteplase (0.25 mg/kg) was compared to standard medical treatment within 4.5-24 hours after LKWT, including after stroke on awakening and unwitnessed stroke. The study enrolled 516 patients in 58 centers in China. Less than 2% of all patients (4 in the tenecteplase group and 5 in the standard-treatment group) underwent rescue endovascular thrombectomy. Tenecteplase achieved significantly higher rate of the patients with no disability (mRS 0-1) at day 90: 33.0% vs. 24.2%; RR 1.37; 95% CI, 1.04-1.81; P=.03 (primary outcome). Incidence of sICH within 36 hours after treatment was 3.0% and 0.8%, with tenecteplase and standard medical treatment, respectively, whereas mortality rates at 90 days were comparable: 13.3% vs 13.1%. It was concluded that patients with acute ischemic stroke due to LVO, most of whom did not undergo endovascular thrombectomy, tenecteplase administered 4.5 to 24 hours after stroke onset provided less disability and similar survival as compared with standard medical treatment, and the incidence of sICH was found to be higher.[44]

Additional evidence was provided by another RCT, CHABLIS-T II, comparing tenecteplase 0.25 mg/kg with the best medical treatment for acute ischemic stroke due to LVO that presented 4.5-24 hours after the last known well is unknown (favorable penumbral profile identified via perfusion imaging: mismatch ratio >1.2, mismatch volume >10 mL, ischemic core volume <70 mL). The primary outcome was defined as the achievement of major reperfusion (restoration of blood flow of >50% of the involved ischemic territory) without sICH within 24-48 hours. Among the whole study population (n=224), 111 patients were randomized to receive tenecteplase and 113 patients to receive best medical treatment (23% of the whole population received alteplase) and 54.9% underwent thrombectomy. Tenecteplase was associated with 3-fold increase in the rate of achievement of major reperfusion: 33.3% vs 10.8% (aRR 3.0; 95% CI, 1.6-5.7; P=.001).

Table 6. Late (extended time) window* IV TNK thrombolysis Stroke studies

Trial	Design	n	Results		
			Primary outcome		Other findings in TNK vs. alteplase groups, respectively
TWIST (Roaldsen-2023)[43]	Design: PROBE Patients: WuS within 4.5 h of weakening NIHSS>2 or Aphasia Selection criteria: favorable Plain CT	n=578 77 centers (10 countries)	TNK 45%, Alteplase 38% aOR: 1.34 (0.95-1.88)**	Neutral	Median NIHSS: 6 vs 6 sICH: 2% vs 1% Mortality: 10% vs. 8%
TRACE–III (Xıong-2024)[44]	Design: PROBE Patients: Within 4,5-24 h With occlusion of ICA, MCA M1/M2 Plus positive mismatch	n=516 58 Centers China	TNK=33% vs. Placebo=24.2% OR=1.37 (1.04–1.81), P=.03	Positive	Median NIHSS: 11 vs. 10 sICH: 3% vs. 0.8% Mortality: 13.3% vs. 13.1%
TIMELESS (Albers-2024)[35]	Design: RCT, Double blind Patients: Within 4.5–24 h, With occlusion of M1/M2/ ICA and Positive mismatch [RAPID-AI®] Thrombectomy in %77	n=458 112 centers USA-Canada	Primary outcome: Median mRS at 90th day(3 in both) aOR=1.13 (0.82-1.57, p:0.45] mRS0-1 at 90th day: 32.3% (TNK)vs 26.6% (control).	Neutral	Median NIHSS: 12 vs. 12 sICH: 3.2% vs. 2.3% Mortality: 19.7% vs. 18.2%
CHABLIS-T II (Cheng-2025)[45]	Design: RCT, Double blind Patients: Within 4.5-24 h with favorable CTP Penumbral pattern with LAD or MeVO, MT in %54.9 (n=123)	TNK: n=111, Control:n=113	Primary outcome: Major reperfusion (>50%) without sICH at 24-48 h: 33.3% (TNK), 10.8%(Control) (aRR=3.0 [1.6-5.7], p:0.001) mRS0-1 at 90th day: 36.9% vs 36.3% [aRR: 1.1 (0.7-1.6)]	Positive	Median NIHSS: 9 vs. 9 sICH: 5.4% vs.4.4% Mortality: 10.6% vs. 10.6%

*Delayed time window (4.5-24 hours [h]) or wake-up stroke or stroke with unknown onset.

**Footnotes:TNK dose 0.25 mg/kg in all. The primary outcome in TWIST was mRS shift, which was not significant (OR=1.18 (0.88-1.58)[P=.27]).

Abbr: aOR, Adjusted Odds ratio; aRR, adjusted Relative Risk; CI, Confidence Interval; CT, Computed tomography; CTP, Computed tomography perfusion; ICA, Internal carotid artery; ITT, Intention to Treat; LVO, Large vessel occlusion; M1, Middle cerebral artery M1 segment; M2, Middle cerebral artery M2 segment; MeVO, Medium vessel occlusion; mRS, Modified Rankin's Score; MT, Mechanical Thrombectomy; mTICI, "Modified Thrombolysis in Cerebral Infarction"; NIHSS, National Institutes of Health Stroke Scale; PO, Primary Outcome; PROBE, Prospective randomized open blinded end-point (Study); RCT, Randomized Controlled Trial; sICH, Symptomatic Intracranial Hemorrhage; TNK, Tenecteplase; WuS, Wake up Stroke.

Recanalization rate was also significantly increased with tenecteplase: 35.8% vs 14.3% (aRR 2.5; 95% CI, 1.4-4.4; P=.002). The clinical outcomes at 90 days were not affected but this was revealed by sensitivity analysis. Clinical efficacy outcomes or rates of hemorrhagic transformation were similar n both groups. The study results indicated that tenecteplase increased reperfusion without sICH in patients with ischemic stroke selected by imaging in late-time window treatment.[45]

The HOPE trial presented at the 2025 International Stroke conference, which has not yet been published in full text, showed that among patients with LVO and MeVO with salvageable tissue on CT perfusion between 4.5 and 24 hours, the 90-day favorable prognosis (mRS 0-1) was higher in 186 patients receiving IV Alteplase than in 186 patients receiving standard therapy [40.3% vs. 26.3%, sRR=1.52 (1.14-2.02), P=.004]. sICH was significantly increased in the Alteplase group [3.8% vs. 0.5%, aRR:7.34 (1.54-34.84)], while there was no change in death (10.8% in both groups).[46]

Use of tenecteplase within extended time frame is off-label at this moment.[16]

Expert consensus statement

The evidence obtained from the studies investigating tenecteplase beyond 4.5 hours or between 4.5-24 hours is insufficient to draw conclusions.
Voting: 100% (8/8 members)

The data suggest that is it not convenient to select patients in this setting using CT.
Voting: 100% (8/8 members)

Patient selection based favorable perfusion-imaging profile (penumbra) may be appropriate for determining IVT with tenecteplase (same imaging criteria with alteplase).
Voting: 100% (8/8 members)

Tenecteplase (0,25 mg/kg) is a reasonable alternative over alteplase (0,9 mg/kg) for patients with penumbra selected based on advanced imaging (diffusion-perfusion mismatch positive) who are eligible for IVT and do not have access to endovascular thrombectomy. Further studies on alteplase are needed.
Voting: 75% in favor (6/8 members).

Based on lacking evidence regarding the patients with wake up stroke or stroke with unknown time of onset, use of tenecteplase is not recommended outside a clinical trial setting.
Voting: 100% (8/8 members)

PICO-5: What are the practical advantages and disadvantages of tenecteplase in clinical practice?

5.1. Would tenecteplase fully replace alteplase across all indications?

Expert consensus statement

Given the non-inferior efficacy (and probably superior in some metrics) compared to alteplase in, comparable safety and greater ease of use, we all agree that tenecteplase will fully replace alteplase across all stroke indications.

Voting: 100% (8/8 members)

5.2. Are the contraindications for tenecteplase and alteplase identical?

We reviewed exclusion criteria of the clinical trials of tenecteplase and alteplase and also product labels (Table 7).

Expert consensus statement

We all agree that contraindications for tenecteplase and alteplase are almost identical.

Voting: 100% (8/8 members)

Table 7. Contraindications of Activase® (Alteplase) and TNKase® (Tenecteplase) based on labels approved by U.S. Food and Drug Administration (FDA)[16,22]

TNKase contraindications	Activase contraindications
Active internal bleeding	Active internal bleeding
History of cerebrovascular accident	
Intracranial or intra-spinal surgery or trauma within 2 months	Recent intracranial or intraspinal surgery or serious head trauma.
Intracranial neoplasm, arteriovenous malformation, or aneurysm	Intracranial conditions that may increase the risk of bleeding.
Known bleeding diathesis	Bleeding diathesis.
Severe uncontrolled hypertension	Current severe uncontrolled hypertension
	Acute Ischemic Stroke: Current intracranial hemorrhage and subarachnoid hemorrhage

5.3. Does tenecteplase offer economic advantages over alteplase?

Analysis of available evidence

Several publications at the time of literature review analyzing comparison of cost effectiveness of tenecteplase vs alteplase, conducted in US, Australia (EXTEND-IA TNK) and China (TRACE II) pointed out that tenecteplase may carry significant economic advantages over alteplase:
The data from US revealed 3000 USD saving per treatment as a result of switching to tenecteplase over alteplase corresponding to 50% saving.Post hoc within-trial economic analysis of EXTEND-IA TNK from Australia showed that the substitution of IV alteplase with tenecteplase was associated with less additional lifetime cost (96.357 vs 106.304 Australian dollars) and greater benefits in the long term.[47] Analysis of TRACE-II trial data from China, also showed that the total cost of therapy was lower compared with tenecteplase vs alteplase (11255.45 vs 12094.25 Yuan).[32]

It is yet to be seen if the transition from alteplase to tenecteplase will be cost effective or improve key metrics (such as door-to-needle time, door-in-door-out time, and transport times) at a population level. However, given the ease of administration of tenecteplase (single bolus with no infusion monitoring requirement during intra-hospital or inter-hospital transfer) it is highly likely that it will help minimize dosing errors, streamline patient workflow, and potentially improve clinical outcomes. In this regard, from a health economics perspective, transitioning to tenecteplase may yield significant cost savings.

Expert consensus statement

Given the evidence showing within-trial and long term economic advantages, we recommend transition to tenecteplase over alteplase for the treatment of acute ischemic stroke.

Voting: 100% (8/8 members)

5.4. Does tenecteplase provide advantages in terms of ease of administration and logistics?

Analysis of available evidence

We evaluated ease of administration and logistics for both molecules based on prescribing information in the FDA-approved labels (Table 8).

Tenecteplase (TNKase®) is supplied as a 50 mg lyophilized powder in a single-dose vial, packaged with a separate 10 mL vial of sterile water for reconstitution to achieve a concentration of 5 mg/mL. The reconstituted solution may be refrigerated at 2-8°C and must be used within 8 hours. Tenecteplase is administered as a single IV bolus over 5 seconds, with weight-adjusted dosing of 0.25 mg/kg, not exceeding a maximum dose of 25 mg for acute ischemic stroke treatment.[16]

Alteplase (Activase®) should be reconstituted to a standard concentration of 1 mg/mL, where the volume (mL) to be administered equals the prescribed dose (mg). The diluted solution has been shown to remain stable for up to 24 hours at 2-8°C or 8 hours at 25°C. From a microbiological standpoint, the product should ideally be used immediately after reconstitution (though stability data support the above storage conditions).[22]

Expert consensus statement

We strongly support the view that tenecteplase demonstrates clinically meaningful advantages over alteplase, with clear implications for routine practice.

Voting: 100% (8/8 members)

Table 8. Logistics of use as determined by the FDA

	Tenecteplase (TNKase®)	Alteplase (Activase®)
Reconstitution	50 mg vial + 10 mL sterile water → 5 mg/mL	1 mg/mL concentration
Storage	Refrigerate at 2–8°C; use within 8 hours	Stability for 24 hours at 2–8°C or 8 hours at room temperature
Microbiological guidance	-	Use immediately per aseptic handling principles

5.5. Are the quality metrics for tenecteplase and alteplase administration completely equivalent?

Analysis of available evidence

We evaluated quality metrics for tenecteplase and alteplase administration including:

- efficacy metrics including time-to-treatment, door-to-needle time; reperfusion success; mortality and other outcomes (previously discussed in PICO 1-4 and PICO 5.6)
- safety metrics (bleeding risk, allergic reactions) (previously discussed in PICO 1-4), and
- practical metrics (discussed in PICO 5).

In addition to previous discussions that implicate tenecteplase being non-inferior (and probably superior in some metrics) compared to alteplase in terms of efficacy, safety and ease of use.

Expert consensus statement

We suggest that all of the quality metrics for tenecteplase and alteplase administration including efficacy, safety and ease of use metrics are completely equivalent.

Voting: 100% (8/8 members)

5.6. Are the quality metrics for tenecteplase and alteplase administration completely equivalent?

Analysis of available evidence

A 10-hospital network in US, which transitioned to tenecteplase (0.25 mg/kg) as the standard of care for IVT, conducted a prospective cohort study to analyze clinical outcomes and total costs and to identify whether tenecteplase reduced thrombolytic workflow times with noninferior clinical outcomes. Study cohort involved 234 patients who received tenecteplase and 354 patients who received alteplase. Favorable outcomes were defined as the composite of walking independently at discharge and discharge to home, and unfavorable outcomes included sICH, in-hospital all-cause mortality and discharge to hospice. In tenecteplase group, target DNT ("door-to-needle time") within 45 minutes for all patients was superior [41% vs 29%; aOR 1.85 (95% CI, 1.27-2.71); P=.001]. Also, target Door-in-Door Out (DIDO) time within 90 minutes was superior [37% vs 14%, aOR 3.62 (95% CI, 1.30-10.74); P=.02]. Favorable outcome possibility was noninferior (OR 1.26; 95% CI, 0.89-1.80) and unfavorable outcome was less likely: [7.3% vs 11.9 (aOR 0.77; 95% CI, 0.42-1.37)], however, this did not meet the pre-specified noninferiority criteria. Net benefit was greater [ratio of favorable/unfavorable: 37% vs 27%, P=.02] and median cost per hospital encounter was reduced (13.382 vs 15.841 USD; P<.001). The investigators concluded that switching to tenecteplase in routine clinical practice in a 10-hospital network was associated with shorter DTN and DIDO times, noninferior favorable clinical outcomes at discharge, and reduced hospital costs.[23]

A retrospective analysis of patients who received tenecteplase between July 2018 and February 2020 was conducted in several centers in New Zealand. The study aimed to compare the outcomes of the patients treated with tenecteplase (n=165) with those treated with alteplase (n=254). There were no significant difference between groups in terms of median age (75 vs 74 years), gender distribution (56% vs 60% male), median NIHSS scores (8 vs 10), median DNT (47 vs 48 minutes), onset-to-needle time (129 vs 130 minutes), rates of angioedema (2.4% vs 0.4%, P=.08) and 90-day functional independence (61% vs 57%, P=.47). However, sICH incidence was numerically lower in tenecteplase group [1.8% (95% CI, 0.4-5.3) vs 2.7% (95% CI, 1.1-5.7), P=.75].[48]

Another prospective study on transition to tenecteplase was conducted in New Zealand and investigated stakeholder opinion (including stroke and emergency clinicians, pharmacists, national regulatory bodies, and hospital legal teams) via pre- and post-implementation surveys, assessment of patient treatment rates, metrics, and clinical outcomes using data of patient who were treated between January 2018 and February 2021 (New Zealand National Stroke Registry data). The transition was supported by all survey responders and satisfaction was remained at 12 months post-implementation. The study found evidence of benefit and no evidence of harm. Patients treated with tenecteplase (n=555) had greater odds of a favorable mRS vs alteplase (n=283): aOR was 1.60 in shift and 2.17 in dichotomous analyses. Tenecteplase was also associated with shorter median DTN time (53 vs 61 minutes, P=.0002). No significant differences were identified with regards to rate of sICH (1.8% vs 3.4%; aOR 0.46), death by day 7 (7.5% vs 11.8%; aOR 0.46), and median needle to groin time for the 42 transferred regional patients (155 vs 200; P=.27) in tenecteplase vs alteplase groups, respectively.[49]

Expert consensus statement

We suggest that real-world data adds to the body of evidence obtained from randomized trials for transition to tenecteplase over alteplase: Comparable or shorter DTN/ DIDO times; noninferior favorable outcomes; comparable unfavorable outcomes (some data suggest improvement); comparable safety profile (except for potentially lower rates of sICH).

Voting: 100% (8/8 members)

PICO-6: Systemic thrombolysis before thrombectomy- why is it indispensable?

6.1. Should neurothrombectomy be performed after IV thrombolysis or should IV thrombolysis precede neurothrombectomy?

Analysis of available evidence

The literature search revealed 7 RCTs that assessed whether mechanical thrombectomy (MT) alone is non-inferior or superior to combined IVT plus MT within 4.5 hours of symptom onset in patients with LVO ischemic stroke: DEVT[50], SKIP[51], DIRECT-MT[52], MR CLEAN no-IV[53], SWIFT-DIRECT[54], DIRECT-SAFE[55] and BRIDGE-TNK[56]. The studies were published between 2020-2025. Except for two (MR CLEAN no-IV[53] and BRIDGE-TNK[56]), they were designed with a non-inferiority architecture. The main features and results of the studies are summarized in Table 9. Tenecteplase (0.25 mg/kg) was used in the BRIDGE-TNK study[56], TNK (13%) or Alteplase (83%) was used in the DIRECT-SAFE study[55], and standard-dose Alteplase (0.9 mg/kg) was used in all other studies except for the low-dose (0.6 mg/kg) used in the SKIP study.[51] Pre-treatment NIHSS was high as 15-19, therefore mRS<3 and mRS<2 dichotomizations were made in the outcome evaluation. Across two studies (DEVT[50] and SKIP[51]), the rate of good functional outcomes (mRS 0–2) decreased by 2.1% to 7.7% with pre-thrombectomy IV thrombolysis. Conversely, in the remaining four studies (DIRECT-MT[52], MR CLEAN No-IV[53], SWIFT-DIRECT[54], DIRECT-SAFE[55], and BRIDGE-TNK[56]), it increased by 0.4% to 8.8%. For excellent functional outcomes (mRS 0–1), three studies (DEVT[50], SKIP[51], MR CLEAN No-IV[53]) reported a reduction ranging from 0.7% to 6.5%, whereas the others (DIRECT-MT[52], SWIFT-DIRECT[54], DIRECT-SAFE[55], and BRIDGE-TNK[56]) observed gains of 3% to 7%. Successful recanalization rates improved by 3.1% to 5.1% in five studies (SKIP[51], DIRECT-MT[52], MR CLEAN No-IV[53], SWIFT-DIRECT[54], and BRIDGE-TNK[56]), with only the DEVT[50] trial reporting a 1.3% decrease. Symptomatic intracranial hemorrhage (sICH) was more frequent in patients receiving systemic thrombolytics prior to MT in all studies except MR CLEAN No-IV.[53] Regarding mortality, five studies (DEVT[50], SKIP[51], DIRECT-MT[52], DIRECT-SAFE[55], and BRIDGE-TNK[56]) showed slight increases ranging from 0.6% to 2.35%. In contrast, MR CLEAN No-IV[53] and SWIFT-DIRECT[54] reported lower mortality rates by 4.7% and 2.5%, respectively (Table 9).

Meta-analyses have been published including these studies. A total of 1166 control and 1170 intervention patients who participated in above-mentioned 6 studies (except BRIDGE-TNK56) were included in the Cochrane meta-analysis.[57] All studies showed high quality and low risk of bias in terms of outcome evaluation. As a result, it was observed that there was no difference between the IVT (thrombolysis before MT) and control (no-thrombolysis before MT) groups in terms of functional independence [risk ratio (RR)=1.03, 95% confidence interval (CI) 0.92 to 1.14]; excellent functional outcome [RR=0.99, 95% CI 0.92 to 1.05] and mortality [RR=0.94, 95% CI 0.78 to 1.14]. Asymptomatic intracranial hemorrhage [RR=1.13, 95% CI 1.00 to 1.29] tended to be higher in patients receiving IVT before MT (P=.06), while symptomatic intracranial hemorrhage did not increase with IVT (RR=1.20, 95% CI 0.84 to 1.70). There was a higher rate of successful revascularisation with IVT over control (RR 1.04, 95% CI 1.01 to 1.08). When evaluated in terms of complete recanalisation, the effectiveness of IVT becomes more obvious (RR=1.14, 95% CI 1.02 to 1.28).[57]

Table 9: Logistics of use as determined by the FDA

Study	DEVT trial[50]			SKIP[51]			DIRECT-MT[52]			MR CLEAN no-IV[53]			SWIFT-DIRECT[54]			DIRECT-SAFE[55]			Bridge-TNK[56]		
Country/ center number	China (n=33)			Japan (n=23)			China (n=41)			Netherlands, Belgium, France (n=20)			Europe, Canada (n=48)			Australia, New Zealand, China, Vietnam (n=25)			China (n=39)		
Design	Noninferiority margin -10%			OR=0.74			Lower limit of %95CI=0.8			Superiority (PROBE), cOR≤0.8			Noninferiority (PROBE) absolute 12%			Australia, New Zealand, China, Vietnam (n=25)			China (n=39)		
Groups	MT	Comb*	Difference %	MT	Comb*	Difference %	MT	Comb*	Difference %	MT	Comb*	Difference %	MT	Comb*	Difference %	MT	Comb*	Difference %	MT	Comb*	Difference %
n	116	118		101	103		327	329		273	266		201	207		146	147		272	278	
NIHSS	16	16		19	17		17	17		16	16		17	17		15	15		16	16	
mRS<3	54.3%	46.6%	7.7↓	59.4%	57.3%	2.1↓	36.4%	36.8%	0.4↑	49.1%	51.1%	2↑	56.7%	65.2%	8.5↑	54.8%	60.5%	5.7↑	44.1%	52.9%	8.8↑
mRS<2	37.9%	31.4%	6.5↓	40.6%	44.7%	4.1↑	24.5%	22.5%	2.0↓	16.1%	15.4%	0.7↓	40%	43%	3↑	42.5%	48.3%	5.8↑	27.9%	34.9%	7↑
TICI2b-3	88.5%	87.2%	1.3↓	90.1%	93.2%	3.1↑	79.4%	84.5%	5.1↑	78.7%	83.1%	4.4↑	91%	96%	5↑	89%	89%	0	94.1%	91.4%	2.7↓
sICH	6.1%	6.8%	0.7↑	5.9%	7.1%	1.2↑	4.3%	6.1%	1.8↑	5.9%	5.3%	0.6↓	1.5%	4.9%	3.4↑	2.7%	4.8%	2.1↑	6.7%	8.5%	1.8↑
Mortality	17.2%	17.80%	0.6↑	7.90%	8.7%	0.8↑	17.7%	18.8%	1.1↑	20.5%	15.8%	4.7↓	11%	8.5%	2.5↓	15.1%	16.3%	1.2↑	19.95	22.3%	2.35↑

*0.9 mg/kg; **0.6 mg/kg; ***tPA 0.9 mg/kg or TNK 0,25 mg/kg, ***TNK 0,25 mg/kg

Abbr: aOR, Adjusted Odds ratio; CI, Confidence Interval; Comb, Combined; cOR, corrected Odds ratio; mRS, Modified Rankin's Score; MT, Mechanical Thrombectomy; mTICI, "Modified Thrombolysis in Cerebral Infarction"; NIHSS, National Institutes of Health Stroke Scale; PROBE, Prospective randomized open blinded end-point (Study); sICH, Symptomatic Intracranial Hemorrhage.

In the meta-analysis conducted by Turc et al, which considered the 6 randomized trials mentioned above, the chance of functional independence (mRS ≤ 2) increased by 1.9% (95% CI -5.9% to 2.1%) with IVT before MT. In addition, similar to the Cochrane meta-analysis, it was shown that successful recanalization was increased relatively by 0.72 (95% CI 0.57 to 0.92) without an increase in symptomatic intracerebral hemorrhage (RR=0.77, 95% CI 0.52 to 1.13).[58]

The advantages and disadvantages of systemic thrombolytic therapy before mechanical thrombectomy are summarized in the Table 10. The studies, meta-analyses and listed advantages led the experts representing ESO and ESMINT to recommend positively the indication of pre-MT IVTin acute stroke with anterior LVO.[58]

Expert consensus statement

With high level of evidence we suggest that IVT should be administered to every patient with a valid indication, provided that IVT does not cause a delay in MT.

Voting: 100% (8/8 members)

Although the supporting evidence is limited and not universally endorsed by experts, we firmly oppose the recommendation to omit intravenous thrombolysis (IVT) in patients for whom mechanical thrombectomy (MT) is considered highly feasible, recanalization is expected within 30 minutes, and direct referral for angiography including potential stenting is planned. We advocate that IVT should be administered prior to any interventional procedure in cases with acute stroke.

Voting: 75% (6/8 members)

There is no data on whether IVT should be continued or discontinued after achieving TICI 2B or better recanalization.

Voting: 100% (8/8 members)

Table 10. Advantages of IVT before neurothrombectomy

Advantages	Disadvantages
Improvement in collateral circulation due to distal microthrombolysis	Increased risk of systemic and cerebral hemorrhage
Reperfusion of distal occlusions (such as M3, M4, A2)	tPA-induced orolingual angioedema (occurs less frequently with TNK)
Facilitation of thrombectomy due to clot softening: fewer passes, more/faster recanalization	Procedural risks arising from withholding antiplatelets/anticoagulants after alteplase
Possibility of a "drip-and-ship" approach	Delays in mechanical thrombectomy at low-volume centers (a potential alteplase-specific delay that is not observed with TNK)
Reduction in new territory infarcts caused by MT	New infarcts in the same territory due to clot fragmentation or migration
Complete avoidance of mechanical thrombectomy (approximately 10% with Alteplase, 20% with Tenecteplase)	Increased cost

Abbr: A2, Anterior cerebral artery A2 segment; M3, Middle cerebral artery M3 segment; M4, Middle cerebral artery M4 segment; MT, Mechanical Thrombectomy; TNK, Tenecteplase; tPA, Tissue plasminogen activator.

6.2. Is the decision to use IVT before MT time-dependent?

Analysis of available evidence

To assess the benefits and risks of systemic thrombolytic therapy in patients undergoing mechanical thrombectomy, two critical time intervals must be considered alongside other factors.

The first is the interval from symptom onset to the initiation of intravenous thrombolytic therapy (called as 'Symptom-to-needle-time' [SNT]), which is typically limited to 4.5 hours, irrespective of subsequent MT. The IRIS meta-analysis evaluated the impact of this time interval on clinical outcomes, revealing that each hour of delay in IVT administration resulted in an adjusted odds ratio of 0.84 [95% CI, 0.72-0.97], indicating a statistically significant decline in benefit.[59] The efficacy of IVT combined with MT diminished progressively as the delay from symptom onset to thrombolysis increased. The absolute risk reduction for achieving a modified Rankin Scale (mRS) score of 2 or less was estimated at 9% (95% CI, 3-16%) at 1 hour, 5% (95% CI, 1-9%) at 2 hours, and 1% (95% CI, -3-5%) at 3 hours. After 2 hours and 20 minutes, IVT ceased to significantly enhance the benefit of subsequent MT, and by 3 hours and 14 minutes post-symptom onset, its effect was neutralized. These findings suggest that the need for IV thrombolytic therapy diminishes over time in patients undergoing MT, paralleling the trend observed in those not receiving thrombectomy. However, early administration yields the greatest benefit, reinforcing the principle that "time is brain" even in this bridging approach. Importantly, the IRIS analysis confirms this trend, but it would be incorrect to conclude that IVT is ineffective for acute strokes presenting between 3 and 4.5 hours; thus, it should not be withheld in such cases.

Across all seven studies, "the needle-to-groin time" (time interval between initiation of parenteral thrombolytic therapy and groin puncture) was shorter than expected for optimal systemic thrombolytic therapy efficacy.[60] In five trials (DIRECT-MT, MR CLEAN–NO IV, SWIFT-DIRECT, DIRECT-SAFE, BRIDGE-TNK), the median needle-to-groin time was under 30 minutes. In all studies, the median needle-to-groin interval was shorter than 1 hour. During this brief window, spontaneous recanalization rates varied between 0–2.8% in patients directly undergoing MT and 1–7% in those receiving IVT. In three studies (DIRECT-MT, DIRECT-SAFE and BRIDGE-TNK), the increase in recanalization before MT was significant. When all of the seven studies were analyzed together, the increase was 1.6% in the direct MT group and 4.6% in the pre-MT IVT group and increase was highly significant (P<.001). This very short duration may contribute to heterogeneity across studies (Table 11). Additionally, higher recanalization rates might be expected in IVT-treated patients before MT in a Drip-and-Ship model setting. However, the fundamental clinical principle remains: "Do not delay thrombectomy in eligible patients to assess IVT effects and proceed with MT without waiting."

Table 11: Time metrics and pre-MT recanalization rates in randomized controlled trials investigating the effect of IV thrombolytic therapy before mechanical thrombectomy

	DEVT trial[50]		SKIP[51]		DIRECT-MT[52]		MR CLEAN no-IV[53]		SWIFT-DIRECT[54]		DIRECT-SAFE[55]		BRIDGE-TNK	
	EVT	Combined	EVT	Combined	EVT	Combined	EVT	Combined	EVT	Combined	EVT	Combined	EVT	Combined
DNT*		61 (49-81)		55 (38-71)		59 (45-78)		31 (24-44)		55 (38-71)		64 (47-87)	-*	-*
DGT	101 (80-135)	105 (80-132)	75 (60-90)	80 (63-101)	84 (67-105)	85.5 (70-115)	63 (50-78)	64 (51-78)	75 (60-90)	80 (63-101)	87(65-113)	101 (75-127)	-*	-*
NGT		44		24 (15-35)		26.5		28 (20-41)		24 (15-35)		37		16 (1.5-35)
Successful reperfusion before EVT	2 (1.7%)	2(2.6%)	0 (0%)	1 (1%)	8 (2.4%)	23 (7%)*	2.8%	3.7%	2 (1%)	8 (4%)	1 (%1)	9 (%6)	3(1.1%)	17 (6.1%)
	No difference, P=.986		No difference, P=1.0		Significantly higher OR=0.33 (95%CI: 0.14-0.74)		No difference aOR: 0.79 (95%CI: 0.42-1.47)		Risk difference -2.9% (95%CI: -6,0-0.3%, P=.077		Significantly higher, P=.0125		Significantly higher, aRR: 5.19 (95%CI: 1.5-17.8)	

*Symptom-randomization and randomization-needle times are given in this study. Time duration in minutes.

**calculated fron the manuscript tables.

Abbr: aOR, adjusted odds ratio, aRR, adjusted risk ratio; DNT, Door-to-Needle time=Arrival to intravenous alteplase; DGT, Door to groin time=Arrival to arterial puncture; NGT, Needle to groin time; EVT, (Neuro)Endovascular treatment; Combined (Systemic thrombolysis prior to mechanical thrombectomy).

Expert consensus statement

With full consensus, we strongly suggest that the decision to use IVT before MT should not be time-dependent for the patients eligible for IVT. Despite that it is established that IVT shows the greatest benefit within the 1st hour after symptom onset, there is no clear evidence showing relation between absence of benefit in extended time frames.

Voting: 100% (8/8 members)

6.3. Should IV thrombolysis be administered before large-core thrombectomy?

Analysis of available evidence

This question was not addressed by RCTs. We reviewed meta-analyses performed on observational studies.

The first meta-analysis included 13 studies (n=1717) comparing functional outcomes with and without IVT after MT and was systematically searched until October 10, 2023 to investigate the effect of IVT before MT on outcomes in large-core acute ischemic stroke. The pooled rate of functional independence in the group receiving IVT+MT was significantly higher than in those receiving MT alone: 26% vs. 18% (OR=1.55, 95% CI: 1.13–2.12, P=.006). Subgroup analysis showed that IVT+MT increased the likelihood of functional independence in retrospective studies (OR=1.97, 95% CI: 1.47–2.63, P<.001). Non-Asian patients benefited from IVT+MT for functional independence (OR=2.04, 95%CI: 1.48-2.81, P<.001), while Asian patients did not benefit (OR=1.45, 95%CI: 0.90-2.35, P=.13). The pooled sICH rate tended to be higher in the IVT+MT group compared to EVT: 16% vs. 11%, but the difference was not statistically significant (OR=1.42, 95%CI: 0.83-2.41, P=.20). The authors concluded that IVT before MT may increase the probability of functional independence in non-Asian patients with large ischemic cores.[61]

Another meta-analysis investigating the role of bridging IVT with alteplase before MT for ASPECTS ≤ 5 included five high-quality studies (n=2124, 41% received bridging IVT) published up to November 2023. There was no difference in 90-day functional independence (mRS 0-2) and independent ambulation (mRS 0-3) between the bridging IVT and EVT alone groups (adjusted OR=1.19 (95% CI: 0.68-2.09) and 1.18 (95% CI: 1.00-1.39, P=.05), respectively). The two groups showed no difference in recanalization success, any ICH or sICH, and mortality. These results were interpreted that bridging IVT may provide similar functional and safety outcomes compared with MT alone in LVO patients with baseline ASPECTS≤5.[17]

In the third meta-analysis including three studies, the rate of mRS 0-2 at the third month was found to be higher in large-core patients who received IVT before MT (RR=1.48, 95%CI: 1.27, 1.72, P<.001). EVT plus IVT was also better for mRS 0-3 level outcome (RR: 1.25, 95%CI: 1.11, 1.41, P=.003). In addition, EVT+IVT also produced better results in terms of early neurological recovery at 24 and 36 hours (RR: 1.16, 95%CI: 1.01, 1.34, P=.03). There was no difference between the two groups in terms of sICH, but mortality was lower in those who received EVTplus IVT.[62]

Expert consensus statement

We suggest that LVO does not change the strategy for decision making regarding bridging treatment and we recommend IVT to be used before MT when indicated for the treatment of acute ischemic steoke with large vessel occlusion.

Voting: 100% (8/8 members)

Clinicians should keep in mind that there is only very limited number of studies on this topic, the results of which show wide confidence intervals reflecting some of the patients may benefit from IVT before MT. However, at the moment, there is no reliable criteria to identify those patients. More evidence is needed to draw clear conclusions and recommendations.

Voting: 100% (8/8 members)

6.4 Would a reduced IV alteplase dose prior to large-core thrombectomy offer any advantage?

Analysis of available evidence

This question has not been the subject of RCTs either. A meta-analysis of 5 observational studies published between 2017 and 2022 compared the clinical outcomes of bridging low (mainly 0.6 mg/kg) with standard dose (0.9 mg/kg, reference group) alteplase in acute stroke patients with LVO and found no difference in functional independence at 90 days (OR=1.02; 95% CI, 0.58-1.80), successful recanalization rate (OR=1.35; 95% CI, 0.68-2.67), incidence of sICH (OR=0.36; 95% CI, 0.10-1.36), and mortality (OR=0.64; 95% CI, 0.27-1.54).[63]

Expert consensus statement

There is very limited evidence to draw any precise conclusions and additional well-designed prospective studies are required. The limited data suggest that use of low dose alteplase would not produce improved clinical outcomes for bridging treatment of acute ischemic stroke with large vessel occlusion.

Voting: 100% (8/8 members)

PICO-7: Intra-arterial thrombolytic therapy in acute ischemic stroke

7.1. Is intra-arterial thrombolytic therapy alone a successful approach in acute ischemic stroke?

There are several relatively earlier RCTs that have investigated the efficacy and safety of local (or selective intra-arterial [IA]) thrombolytic therapy in patients with acute ischemic stroke.

IA Prourokinase (Pro-UK) was tested in the PROACT II ("Prolyse in Acute Cerebral Thromboembolism II") study, which can be called the prototype of contemporary stroke studies, and demonstrated the potential benefit of IA pro-UK. It was a multicenter, open-label RCT conducted at 54 centers in the USA and Canada between 1996 and 1998. 180 patients with acute (<6 hours) MCA occlusion were randomized to receive 9 mg IA proUK plus heparin (n=121) or heparin alone (n=59). The study showed that 40% of patients treated with r-proUK and 25% of control patients had a mRS of 0-2 (P=.04). Mortality rates were similar (25% vs. 27%), while r-proUK had a higher recanalization rate (66% vs. 18%, P<.001). The incidence of sICH within 24 hours was also higher in the r-proUK group (10% vs. 2%, P=.06).[64] In the PROACT II trial, the microcatheter was positioned immediately within and adjacent to the thrombus to allow for direct infusion of the thrombolytic agent into the clot.[64] The technique aiming to evenly distribute alteplase around a thrombus was shown to lead to better reperfusion rates and clinical outcomes.[65]

In the phase-1 EMS (Emergency Management of Stroke Bridging Trial) trial, IA Alteplase was used in 17 patients and compared with the combination of IV alteplase and intraarterial alteplase applied in 18 patients. The combination has been noted to increase mortality. Although the study demonstrated combined IV and IA treatment provided better recanalization, it was not associated with improved clinical outcomes.[66]

The SYNTHESIS Expansion study compared 181 acute (first 4.5 hours) patients who received IA alteplase plus MT with 181 patients who received IV alteplase alone and found no difference in favorable prognosis (mRS 0-1) between the two groups (30.4% in EVT and 34.8% in IV alteplase, respectively). There was no difference in the rate of sICH occurring within the first 7 days (6% in both groups), serious adverse events, or deaths.[67]

IA thrombolytic therapy is now rarely used as a stand-alone procedure; MT is preferred as a more effective recanalization technique. IA thrombolysis can be performed in specific situations such as inability to reach the occlusive clot due to technical and anatomical reasons such as due to excessive tortuosity 68, inability to retrieve the clot and distal embolism including those occurring during embolectomy.[68,69] When clots cannot be retrieved using mechanical thrombectomy techniques, thrombolytic agents may be administered locally—either into or around the thrombus—though a standardized consensus on this practice has yet to be established.[70,71]

Expert consensus statement

MT is preferred over intra-arterial thrombolysis with higher efficacy for recanalization. Indications for intra-arterial thrombolysis is the same with MT. However, it is no longer used as a single procedure except for rare incidences:

1. When the thrombus is inaccessible for mechanical recanalization (e.g. due to excessive tortuosity)
2. to treat distal embolization, including those occurring during embolectomy
3. as a rescue procedure following failed mechanical thrombectomy.

Voting: 100% (8/8 members)

7.2. Should intra-arterial (local) thrombolytic therapy be administered after successful thrombectomy?

Seven RCTs assessed the effect of intra-arterial thrombolysis following successful thrombectomy.

The local application of thrombolytic agents following successful thrombectomy has been investigated in seven studies, summarized in Table 12. The agents and dosages used included alteplase at 0.225 mg/kg (CHOICE[72], PEARL[73]); tenecteplase ranging from 0.03125 to 0.125 mg/kg—specifically, 0.0625 mg/kg in ATTENTION-IA[74] and POST-TNK[75], 0.125 mg/kg in ANGEL-TNK[76,77], and both 0.03125 and 0.0625 mg/kg in DATE[78]; and 100,000 units of urokinase in POST-UK[79]. All patients were treated within the first 24 hours of symptom onset. Notably, PEARL[73] and DATE[78] were presented at the 2025 International Stroke Conference but have not yet been published. While ATTENTION-IA[74] included posterior circulation occlusions, the remaining studies treated anterior cerebral vessels, including the ICA and M1/M2 segments of the MCA. In the CHOICE[72] and PEARL[73] studies, patients also received intravenous alteplase before MT.

In three studies—CHOICE[72], ANGEL-TNK[76,77], and PEARL[73]—the administration of thrombolytics (alteplase or tenecteplase) following successful mechanical thrombectomy was associated with a statistically significant improvement in favorable outcomes: an increase of 18.6% in CHOICE[72] (P=.047), 14.1% in ANGEL-TNK[76,77] (P=.002), and 14.6% in PEARL[73] (P=.01). While the remaining studies also reported higher rates of favorable outcomes in the thrombolytic-treated groups, these differences did not reach statistical significance. Importantly, post-thrombectomy thrombolytic therapy did not result in significant changes in rates of symptomatic intracranial hemorrhage or mortality (Table 12).

Expert consensus statement

We agree that current evidence is insufficient to recommend use of local thrombolytic use following successful thrombectomy.

While it may be considered in some cases, the current evidence is only positive for alteplase and tenecteplase, however, this finding requires further validation due to a wide confidence interval, and results for other agents are negative. Therefore, we cannot recommend this approach at this time.

Voting: 100% (8/8 members)

Table 12. Studies Evaluating the Impact of Intra-Arterial Thrombolytics Following Successful Mechanical Thrombectomy [72-79]

Trials	CHOICE	ATTENTION-IA	POST-TNK	POST-UK	ANGEL-TNK	PEARL	DATE
	Alteplase 0.225 mg/ kg	Tenecteplase 0.0625 mg/kg	Tenecteplase 0.0625 mg/kg	Urokinase 100,000 IU	Tenecteplase 0.125 mg/kg	Alteplase 0.225 mg/kg	Tenecteplase 0.03125 and 0.0625 mg/kg
Location	ICA, M1, M2	BA, VA, P1	ICA, M1, M2	ICA, M1, M2	ICA, M1, M2	ICA, M1, M2	ICA, M1, M2
eTICI	eTICI-2b50-3	eTICI-2b50-3	eTICI-2c-3	eTICI-2c-3	eTICI-2b50-3	eTICI-2b50-3	eTICI-2b50-3
IVT	Yes	No	No	No	No	Yes	No
Early IV APT	No	Allowed	Allowed	Allowed	No	Allowed	Not-stated
Pefusion imaging	No	No	No	No	Yes	No	No
Time window	24h	24h	24h	24h	4,5-24h	24h	24h
Follow-up angiogram	Yes	No	No	No	No	No	No
Active, n	61	104	269	267	126	163	46 and 46
Placebo, n	52	104	271	267	129	159	65
90th day mRS 0-1	59% vs 40.4% 18.4% [0.3%-36.4%] P=.047	34.6% vs 26.0% aOR= 1.36 [0.92-2.02] P=.12	49.1% vs 44.1% aOR=1.15 [0.97-1.36] P=.11	45.1% vs 40.2% aOR=1.13 [0.94-1.36] P=.19	40.5% vs 26.4% 1.44 [1.06-1.95] P=.002	44.8% vs 30.2%, RR: 1.45 [1.08-1.96] P=.01	0.03125 vs control: 37% vs 33.8% (P=.50) 0.0625 vs control: 43.5% vs 33.8% (P=.55)
sICH	0% vs 3.8% -3.8% [-13.2 to -2.5%]	8.3% vs 3.1% aHR=3.09 [0.78-12.20]	6.3% vs 4.4% aHR=1.43 [0.68-2.99] P=.35	4.1% vs 4.1% aHR=1.05 [0.45-2.44] P=.91	5.6% vs 6.2% 0.95 [0.36-2.53] P=.92	4.3% vs 5.0% RR: 0.85 [0.43-1.69] P=.67	7.1% (TNK 0.03125) vs 9.1% (TNK 0.0625) vs 25% (TNK 0.125)
Mortality	8% vs 15% -%7.2 [-%19.2-%4.8]	27.9% vs 26.9% aOR=1.13 [0.73-1.74]	16.0% vs 19.3% aHR= 0.75 [0.50-1.13] P=.16	18.4% vs 17.3% aHR=1.06 [0.71-1.59] P=.77	21.45 vs 21.7% HR:0.99 [0.62-1.58] P=.39	17.2% vs 11.3% HR: 1.60 [0.88-2.89] P=.12	Not-stated

Abbr: aOR, Adjusted Odds ratio; APT, Anti-platelet treatment; CI, Confidence Interval; cOR, corrected Odds ratio; eTICI, "Extended Thrombolysis in Cerebral Infarction", HR, Hazard ratio; ICA, Internal carotid artery; IVT, Intravenous thrombolytic therapy, M1, Middle cerebral artery M1 segment; M2, Middle cerebral artery M2 segment; mRS, Modified Rankin's Score; MT, Mechanical Thrombectomy; mTICI, "Modified Thrombolysis in Cerebral Infarction", NIHSS, National Institutes of Health Stroke Scale; PROBE, Prospective randomized open blinded end-point (Study); RR, Relative risk; sICH, Symptomatic Intracranial Hemorrhage.

7.3. What should be the dosage of the drug used in intra-arterial thrombolytic therapy?

The recommended dose for intraarterial thrombolytic therapy varies depending on whether systemic thrombolytic agents have been administered before intraarterial therapy or not, and whether MT is successful or not, that is, complete recanalization is achieved or not (resistant thrombectomy) (Table 13).

Expert consensus statement

Based on these unstandardized data, no consensus could be derived regarding the recommended dosage of intra-arterial alteplase.

Voting: 100% (8/8 members)

Table 13. Dosing of thrombolytic agents in intra-arterial application

IVT timing	Dose and administration method
Stand alone (IAT without prior IVT)	According to original intra-arterial thrombolysis protocols 20 mg of alteplase is diluted in 50 mL of normal saline (final concentration: 1 mL = 0.4 mg tPA). However, the dosage is not standardized, most widely used dosage range is 2-20 mg. Different doses between 22 and 69 mg were studied. Even the IA dose of 0.9 mg/kg used in the SYNTHESIS-Extension study appears to be safe.67 Usually 40 mg tPA is administered over 2 hours. Initial bolus of 5 ml is followed by 45 mL/h infusion in the first hour and 50 mL/h in the second hour. Thrombus resolution is checked via super-selective angiograms every 15 min until thrombus resolves or maximum total dose of 40 mg is reached.[80]
After previous full dose of IVT	Usually used IA Actilyse dose is 20 mg. After5 mg initial bolus, 45 mL Actlyse infusion is continued over 1 hour. Control super-selective angiograms are performed every 15 minutes until thrombus resolution or a maximum total dose of 20 mg is reached. The combination of full-dose IVT followed by thrombectomy or IAT at a dose of 20 mg given over 1 hour appears to be safe. IAT at a dose of 69 mg given over previous IVT has also been reported to be safe.[81]
After previous successful MT	According to the CHOICE trial, the tPA dosing was: Alteplase 0.225 mg/kg (maximum 22.5 mg), administered over 15–30 minutes in patients with TICI 2b–3 reperfusion.72 In the ATTENTION-IA and Post-TNK studies, local tenecteplase at a dose of 0.0625 mg/kg (maximum 6.25 mg) was applied to the posterior circulation vessels for 15 seconds proximal to the remaining thrombus (if still present) or distal to the origin of the main pontine perforator branches.[74,75]

PICO-8: Will the adoption of tenecteplase in Türkiye positively impact acute ischemic stroke management and treatment systems?

Analysis of available evidence

"Directive on Health Services to be Provided to Patients with Acute Stroke", which came into effect in Türkiye on July 18, 2019, has played a crucial role in expanding stroke treatment accessibility despite the aging population and increasing stroke burden.[82,83] Over the years, nearly 200 stroke centers and units have been established, ensuring that 90% of the country now has access to thrombolytic and thrombectomy treatments.[84] According to NeuroTek Study, a point prevalence study performen in Türkiye, 12% of hospitalized stroke patients received systemic thrombolytics, while 8% underwent mechanical thrombectomy, with functional recovery and symptomatic cerebral bleeding rates remaining acceptable.[85]

However, significant delays in "door-to-needle time" remain a key challenge. NeuroTek reports an average DNT of 66±49 minutes, with door-to-groin times for thrombectomy at 103±90 minutes[85], while "the Turkish National Intravenous Thrombolysis Registry" records an average DNT of 69.5 (32.5) minutes.[86] Efforts to reduce these delays include a potential shift to tenecteplase,[87,88] which offers bolus administration, reduced need for nurse monitoring of infusion, and cost-effectiveness,[87,89] though evidence remains inconsistent.[90]

Additionally, drip-and-ship protocols face logistical issues with Actilysis's 1-hour infusion, particularly since ambulances transporting stroke patients from peripheral hospitals to stroke centers are staffed only by health technicians, limiting the ability to manage complications during thrombolysis. By using tenecteplase as a bolus, pre-hospital thrombolytic confusion is eliminated, improving stroke management efficiency and streamlining treatment authorization in transport settings.[91]

Expert consensus statement

We strongly agree that the adoption of tenecteplase in Türkiye will positively impact acute ischemic stroke management and treatment systems.
Voting: 100% (8/8 members)

We anticipate increased utilization (more patients who are eligible will actually receive IVT), as well as improved effectiveness of IVT treatment (by eliminating the challenges associated with alteplase infusion logistics, removing the need for monitoring during administration, and offering ease of administration).
Voting: 100% (8/8 members)

On top of efficacy and safety data and ease of use, potential cost-saving with tenecteplase may be a contributing factor.
Voting: 100% (8/8 members)

CONCLUSIONS

This expert consensus statement was developed to assess the indications for tenecteplase and extended-window thrombolysis—both of which remain unapproved by health authorities in Türkiye—and to establish national standards for clinical application. A total of 19 recommendations were formulated across eight PICO questions (Table 14).

The panel recognizes the favorable pharmacological profile and ease of administration of tenecteplase compared to alteplase (PICO 1). It was concluded that tenecteplase 0.25 mg/kg may be preferred over alteplase 0.9 mg/kg within the initial 4.5 hours of acute ischemic stroke (PICO 1). Nonetheless, the current approved indication for alteplase remains valid (PICO 2). Tenecteplase has demonstrated non-inferiority to alteplase, and all established quality criteria for alteplase use are equally applicable to tenecteplase (PICO 5).

Tenecteplase is further favored in patients with large vessel occlusion undergoing mechanical thrombectomy, as it can be administered as a bolus and has shown greater recanalization rates (PICO 3). Systemic thrombolytics (tenecteplase or alteplase) should be administered in all bridging cases, including patients eligible for immediate MT (<30 minutes), as omitting systemic thrombolysis is not considered good clinical practice. The dosing and clinical standards for IV thrombolysis remain unchanged in MT candidates (PICO 6).

Table 14. Summary of expert opinions

PICO	Expert consensus statement	Vote
PICO-1. Key considerations in the clinical use of tenecteplase (TNK)		
1.1. Is tenecteplase superior to alteplase in terms of pharmacological features/ 'theoretical' efficacy?	We are in full agreement for recommending tenecteplase 0.25 mg/kg to be favored over alteplase 0.9 mg/kg for patients with acute ischemic stroke of <4.5 hours duration on the basis of pharmacological features, clinical data, administration and logistics advantages and guideline recommendations	Voting: 100% (8/8 members)
1.2. What should be the optimal IV tenecteplase dose for acute ischemic stroke?	We recommend against usage of high dose (≥0.40 mg/kg) or low dose (0.1 mg/kg) tenecteplase as data shows increased rates of hemorrhage and lower efficacy with these doses, respectively. We all agree that 0.25 mg/kg is the recommended dose for tenecteplase for treatment of acute ischemic stroke.	Voting: 100% (8/8 members)
PICO-2. Which thrombolytic agent should be preferred within the first 4.5 hours of acute stroke treatment: Tenecteplase or alteplase?		
2.1. Is tenecteplase more effective and safer than alteplase within the first 4.5 hours of acute ischemic stroke?	We unanimously recommend tenecteplase over alteplase within the first 4.5 hours of acute ischemic stroke, in the light of available scientific data that demonstrates tenecteplase (0.25 mg/kg) has non-inferior efficacy (probably superior for some outcomes) and similar safety profile compared with alteplase (0.9 mg/kg), guideline recommendations, and easier administration (single bolus instead of 1-hour infusion).	Voting: 100% (8/8 members)
PICO-3. Efficacy of tenecteplase in acute cerebral large vessel occlusion		
3.1. What is the efficacy of tenecteplase in patients with acute stroke due to cerebral large vessel occlusion?	In full agreement, we suggest that tenecteplase (0.25 mg/kg) has better efficacy (12% higher recanalization rate in one study) compared to alteplase within the first 4.5 hours of acute ischemic stroke with LVO for bridging t-treatment (IVT before thrombectomy).	Voting: 100% (8/8 members)
	We do not recommend usage of tenecteplase in extended time window (4.5-24 hours) as there is no sufficient evidence of benefit over placebo for the patients with acute ischemic stroke with LVO, except for probable benefit in M1 group.	Voting: 100% (8/8 members)
	We recommend against routine intravenous thrombolysis in patients with mild stroke and intracranial large vessel occlusion within 4,5-24 hours of stroke onset based on CT alone.	Voting: 100% (8/8 members)
PICO-4. Extended time window use of tenecteplase in acute ischemic stroke		
4.1. What is the impact of tenecteplase in acute ischemic stroke within 4.5-24 hours or with unknown time of onset	The evidence obtained from the studies investigating tenecteplase beyond 4.5 hours or between 4.5-24 hours is insufficient to draw conclusions.	Voting: 100% (8/8 members)
	The data suggest that is it not convenient to select patients in this setting using CT.	Voting: 100% (8/8 members)
	Patient selection based favorable perfusion-imaging profile (penumbra) may be appropriate for determining IVT with tenecteplase (same imaging criteria with alteplase).	Voting: 100% (8/8 members)
	Tenecteplase (0.25 mg/kg) is a reasonable alternative over alteplase (0.9 mg/kg) for patients with penumbra selected based on advanced imaging (diffusion-perfusion mismatch positive) who are eligible for IVT and do not have access to endovascular thrombectomy.	Voting: 75% (6/8) in favor
	Based on lacking evidence regarding the patients with wake-up stroke or stroke with unknown time of onset, use of tenecteplase is not recommended outside a clinical trial setting.	Voting: 100% (8/8 members)
PICO-5. What are the practical advantages and disadvantages of tenecteplase in clinical practice?		
5.1. Would tenecteplase fully replace alteplase across all indications?	Given the noninferior efficacy (and probably superior in some metrics) compared to alteplase in, comparable safety and greater ease of use, we all agree that tenecteplase will fully replace alteplase across all stroke indications.	Voting: 100% (8/8 members)
5.2. Are the contraindications for tenecteplase and alteplase identical?	We all agree that contraindications for tenecteplase and alteplase are almost identical.	Voting: 100% (8/8 members)
5.3. Does tenecteplase offer economic advantages over alteplase?	Given the evidence showing economic advantages within-trial and in long term, we recommend transition to tenecteplase over alteplase for the treatment of acute ischemic stroke.	Voting: 100% (8/8 members)
5.4. Does tenecteplase provide advantages in terms of ease of administration and logistics?	We strongly support the view that tenecteplase demonstrates clinically meaningful advantages over alteplase, with clear implications for routine practice.	Voting: 100% (8/8 members)

5.5. Are the quality metrics for tenecteplase and alteplase administration completely equivalent?	We suggest that all of the quality metrics for tenecteplase and alteplase administration including efficacy, safety and ease of use metrics are completely equivalent.	Voting: 100% (8/8 members)
5.6. Do real-world data support tenecteplase in randomized trials?	We suggest that real-world data adds to the body of evidence obtained from randomized trials for transition to tenecteplase over alteplase: Comparable or shorter DTN/ DIDO times; noninferior favorable outcomes; comparable unfavorable outcomes (some data suggest improvement); comparable safety profile (except for potentially lower rates of sICH).	Voting: 100% (8/8 members)
PICO-6. Systemic thrombolysis before thrombectomy- why is it indispensable?		
6.1. Should neurothrombectomy be performed after IV thrombolysis or should IV thrombolysis precede neurothrombectomy?	With high level of evidence we suggest that IVT should be administered to every patient with a valid indication, provided that IVT does not cause a delay in MT.	Voting: 100% (8/8 members)
	Although the supporting evidence is limited and not universally endorsed by experts, we firmly oppose the recommendation to omit intravenous thrombolysis (IVT) in patients for whom mechanical thrombectomy (MT) is considered highly feasible, recanalization is expected within 30 minutes, and direct referral for angiography including potential stenting is planned. We advocate that IVT should be administered prior to any interventional procedure in cases with acute stroke.	Voting: 75% (6/8 members)
	There is no data on whether IVT should be continued or discontinued after achieving TICI 2B recanalization.	Voting: 100% (8/8 members)
6.2. Is the decision to use IVT before MT time-dependent?	With full consensus, we strongly suggest that the decision to use IVT before MT should not be time-dependent for the patients eligible for IVT. Despite that it is established that IVT shows the greatest benefit within the first hour after symptom onset, there is no clear evidence showing relation between absence of benefit in extended time frame.	Voting: 100% (8/8 members)
6.3. Should IV thrombolysis be administered before large-core thrombectomy?	We suggest that LVO does not change the strategy for decision making regarding bridging treatment and we recommend IVT to be used before MT when indicated for the treatment of acute ischemic stroke with large vessel occlusion.	Voting: 100% (8/8 members)
	Clinicians should keep in mind that there is only very limited number of studies on this topic, the results of which show wide confidence intervals reflecting some of the patients may benefit from IVT before MT. However, at the moment, there is no reliable criteria to identify those patients. More evidence is needed to draw clear conclusions and recommendations.	Voting: 100% (8/8 members)
6.4. Would a reduced IV alteplase dose prior to large-core thrombectomy offer any advantage?	There is very limited evidence to draw any precise conclusions and additional well-designed prospective studies are required. The limited data suggest that use of low dose alteplase would not produce improved clinical outcomes for bridging treatment of acute ischemic stroke with large vessel occlusion.	Voting: 100% (8/8 members)
PICO-7. Intra-arterial thrombolytic therapy in acute ischemic stroke		
7.1. Is intra-arterial thrombolytic therapy alone a successful approach in acute ischemic stroke?	MT is preferred over intra-arterial thrombolysis with higher efficacy for recanalization. Indications for intra-arterial thrombolysis is the same with MT. However it is no longer used as a single procedure except for rare incidences: 1- When the thrombus is inaccessible for mechanical recanalization (e.g. due to excessive tortuosity) 2- to treat distal embolization, including those occurring during embolectomy 3- as a rescue procedure following failed mechanical thrombectomy.	Voting: 100% (8/8 members)
7.2. Should intra-arterial (local) thrombolytic therapy be administered after successful thrombectomy?	We agree that current evidence is insufficient to recommend use of local thrombolytic use following successful thrombectomy. While it may be considered in some cases, the current evidence is only positive for alteplase and tenecteplase, however, this finding requires further validation due to a wide confidence interval, and results for other agents are negative. Therefore, we cannot recommend this approach at this time.	Voting: 100% (8/8 members)
7.3. What should be the dosage of the drug used in intra-arterial thrombolytic therapy?	Based on these unstandardized data, no consensus could be derived regarding the recommended dosage of intra-arterial alteplase.	Voting: 100% (8/8 members)
PICO-8. Would national approval and reimbursement of tenecteplase improve stroke care in Türkiye?		
8.1. Will the adoption of tenecteplase in Türkiye positively impact acute ischemic stroke management and treatment systems?	We strongly agree that the adoption of tenecteplase in Türkiye will positively impact acute ischemic stroke management and treatment systems.	Voting: 100% (8/8 members)
	We anticipate increased utilization (more patients who are eligible will actually receive IVT), as well as improved effectiveness of IVT treatment (by eliminating the challenges associated with alteplase infusion logistics, removing the need for monitoring during administration, and offering ease of administration).	Voting: 100% (8/8 members)
	On top of efficacy and safety data and ease of use, potential cost-saving with tenecteplase may be a contributing factor.	Voting: 100% (8/8 members)

Abbr: CT, Computerized tomography; DIDO, Door-in-door-out time; DTN, Door to needle time; IV, Intravenous; IVT, Intravenous thrombolysis; LVO, Large vessel occlusion; MT, Mechanical thrombectomy; sICH, Symptomatic intracranial hemorrhage; TICI, Thrombolysis in cerebral infarction; WUS, Wake up stroke.

The panel does not endorse systemic thrombolysis based solely on non-contrast CT in late-presenting (4.5–24 hour) or wake-up strokes. While not routine, thrombolysis may be considered in selected patients with salvageable penumbra on CTP or MRP (PICO 4), and further research is encouraged. Routine recommendations for adjunct intra-arterial thrombolysis following successful MT or in isolated LVO are premature pending more evidence (PICO 7). Lastly, tenecteplase may offer advantages for Türkiye's stroke care system by shortening Door-to-needle/Door-In-Door-Out times, eliminating infusion monitoring during transport, and offering comparable clinical outcomes to alteplase, with potential cost efficiencies (PICO 8).

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