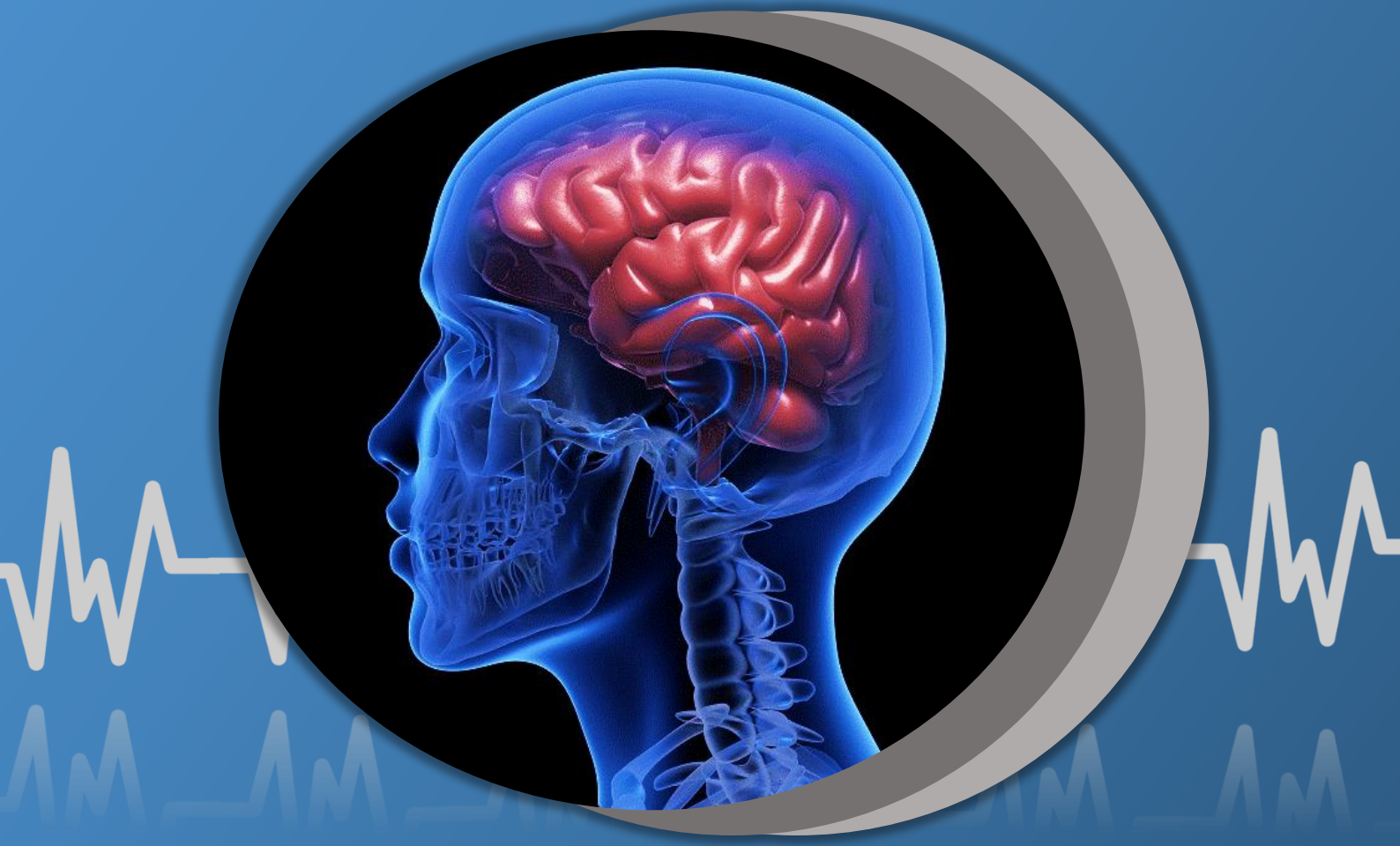
ROLE OF TENECTEPLASE IN BRIDGING THERAPY IN ACUTE ISCHEMIC STROKE



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Background and Objective of the Survey

Tenecteplase, a genetically engineered variant of tissue plasminogen activator (tPA), plays a pivotal role in bridging therapy for acute ischemic stroke (AIS). Bridging therapy involves the initial administration of intravenous thrombolytic agents followed by mechanical thrombectomy. Tenecteplase offers several advantages over the traditional tPA, alteplase, due to its pharmacological properties.

Tenecteplase has a higher fibrin specificity and longer half-life compared to alteplase, allowing it to be administered as a single bolus injection rather than a continuous infusion. This simplifies the administration process, which is crucial in the time-sensitive treatment of AIS. The single-dose administration can facilitate quicker treatment initiation, which is essential for minimizing the time to reperfusion and improving patient outcomes.

Clinical studies have demonstrated the efficacy and safety of tenecteplase in AIS, showing comparable or even superior results to alteplase in achieving early recanalization of occluded vessels. Its use in bridging therapy has been associated with higher rates of reperfusion prior to mechanical thrombectomy, potentially improving the success rates of subsequent endovascular procedures.

Moreover, tenecteplase's longer half-life and enhanced thrombolytic activity can maintain effective clot dissolution during the transition to mechanical thrombectomy. This sustained thrombolytic action increases the likelihood of vessel recanalization, which is critical for reducing the extent of brain damage and improving functional outcomes in stroke patients.

The objective of the survey is:

To evaluate the role of tenecteplase in bridging therapy in acute ischemic stroke

Methodology of the Survey

A survey was conducted to evaluate the role of tenecteplase in bridging therapy in acute ischemic stroke. A total of 100 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Introduction
- Pharmacokinetic Comparison
- Optimal Dose in Ischemic Stroke
- Recanalization and Reperfusion
- Early Neurological Improvement
- Neurological Functional Outcome at 90 Days
- Risk of Intracranial Hemorrhage
- CT Perfusion (CTP)/MR Mismatch Group
- Minor Stroke/Stroke Mimics Group
- Bridge Therapy with Mechanical Thrombectomy
- STEMI Clinical Trials
- Stroke Clinical Trials
- Early recanalization and reperfusion
- Early neurological improvement
- Three-month clinical outcome on modified Rankin Scale (mRS)
- Safety Outcomes
- Thrombolysis in the Later Time Window
- Late Time Window Ongoing Trials

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

Literature Review

Introduction[1]

In the global burden of disease study 2019, stroke ranked third among the main causes of disability-adjusted life-years. Of all strokes, >80% are ischemic strokes due to intracranial or extracranial vessel occlusion. Recanalization of occluded vessels in the ultra-early period is crucial to improving functional outcomes of patients with ischemic stroke. Hence, reperfusion therapy, especially intravenous thrombolysis, has been recommended as the first-line therapy of ischemic stroke in the current guidelines.

Clinical trials on recombinant tissue plasminogen activator (rtPA) have demonstrated its efficacy in ischemic stroke 20 years ago. In the very beginning, the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study, also known as the NINDS trial,4 proved the efficacy and safety of intravenous thrombolysis alteplase in the 3-h time window of ischemic stroke onset in 1995. The European Cooperative Acute Stroke Study III trial, also known as the ECASS III trial, extended the time window of alteplase to 4.5 h. The Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke (WAKE-UP) trial and the Extending the time for Thrombolysis in Emergency Neurological Deficits (EXTEND) trial showed that alteplase can be used in wake-up stroke, un-witnessed stroke, and unknown-onset stroke.

Tenecteplase (TNK) is a genetically engineered, mutant, tissue plasminogen activator that has shown a greater recanalization rate than alteplase in acute myocardial infarction as well as a lower risk of hemorrhagic events. Several clinical trials were conducted to test the efficacy and safety of TNK in reperfusion therapy for ischemic stroke. The 2019 American Heart Association/American Stroke Association Guidelines recommended 0.4 mg/kg TNK as an alternative to alteplase in patients with mild neurological impairment and no major intracranial occlusion. Moreover, 0.25 mg/kg TNK was recommended in the 2019 American Heart Association/American Stroke Association Guidelines in patients without contraindications for intravenous (IV) fibrinolysis who were also eligible to undergo mechanical thrombectomy. Considering the limited clinical trials on TNK, the class of recommendation and level of evidence are low (IIb, B-R). The 2021 European Stroke Organisation Guidelines recommended

0.25 mg/kg TNK over 0.9 mg/kg alteplase before mechanical thrombectomy within 4.5 h from stroke onset. However, the recommendation of TNK over alteplase was based on expert consensus recommendation with a weak strength of recommendation and low quality of evidence. In the real-world clinic, TNK is still used cautiously to treat ischemic stroke, and more clinical trials on TNK in ischemic stroke are needed. In this review, we summarize the clinical trials on TNK in ischemic stroke (Table 1).

Table 1: Clinical Trials on TNK in Ischemic Stroke

Name	**EXTEND IA TNK II**	**EXTEND IA TNK**	**NOR-TEST**	**ATTEST**	**TAAIS**	**Haley et al**
Year	**2020**	**2018**	**2017**	**2015**	**2012**	**2010**
Study design	PROBE	PROBE	PROBE	PROBE	PROBE	Multi-center, perspective randomized controlled trial
Dose	0.4 mg/kg 0.25 mg/kg	0.25 mg/kg	0.4 mg/kg	0.25 mg/kg	0.1 mg/kg 0.25 mg/kg	0.1 mg/kg 0.25 mg/kg 0.4 mg/kg
Time window	4.5h	4.5h	4.5h	4.5h	6h	3h
Imaging	ICA/MCA/ BA occlusion	ICA/MCA/ BA occlusion			CTA: intracranial vessel	

					occlusion; CTP: TTP≥core volume 20%, core volume≤20 mL	
Sample size	300	202	1100	96	75	112
Initial NIHSS	16 VS 17	17 VS 17	5.6 VS 5.8	12 VS 11	14.5 VS 14.6 VS 14	8 VS 10 VS 9 VS 13
90d mRS 0–1	49 VS 49%(p=0.69)	51 VS 43%(p=0.20)	64% VS 63%(p=0.52)	28% VS 20%(p=0.28)	54% VS 40%(p=0.25)	45.2% VS 48.4% VS 36.8% VS 41.9%
Symptomatic intracranial hemorrhage	PH2 36h: 1.3VS. 4.7% (p=0.12)	PH2 36h: 1 VS 1% (p=0.99)	ECASS III: 3 VS 2% (p=0.70)	ECASS III: 6% VS 8% (p=0.59) SITS-MOST: 2% VS 4% (p=0.50)	SITS-MOST: 4 VS 12% (p=0.33)	0% VS 6.5% VS 15.8% VS 3.2%
Mortality	15 VS 17% (p=0.35)	10 VS 18% (p=0.049)	5 VS 5% (p=0.68)	17% VS 12% (p=0.51)	8 VS 12% (p=0.68)	6.5% VS 22.6% VS

						15.8% VS 25.8%

Pharmacokinetic Comparison[1]

Because fibrin molecules bind to each other and form the skeleton of a thrombus, (Figure 1), it can be lysed through fibrinolysis. Tissue plasminogen activator (tPA) is generated in endothelial cells to convert plasminogen into plasmin. Plasmin breaks down the fibrin skeleton by converting fibrin into fibrinogen degradation products, and the thrombus is eventually dissolved to achieve recanalization of the occluded vessel.

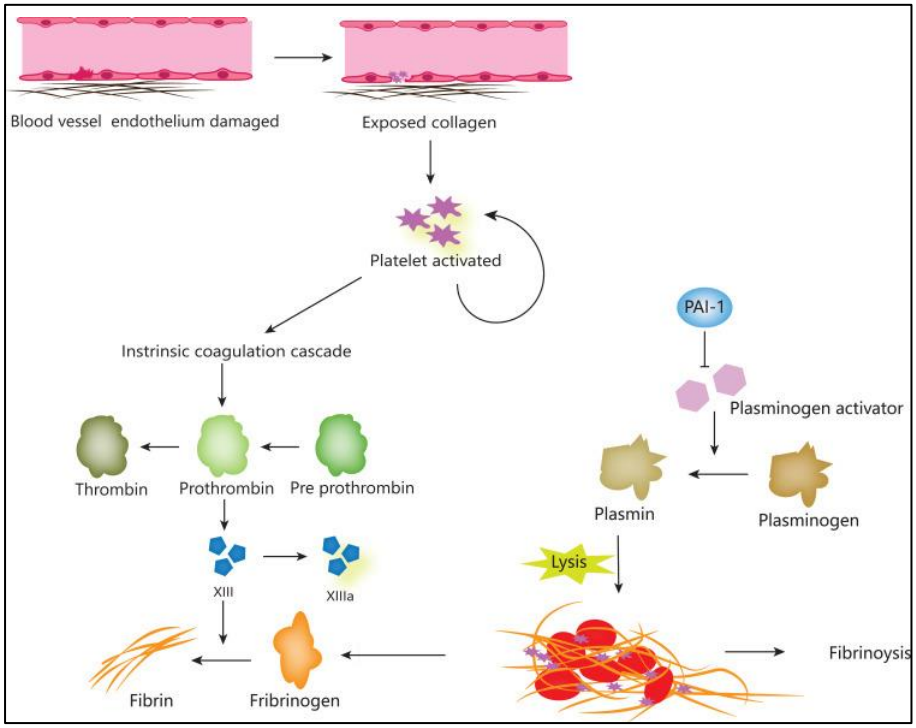

Figure 1: Mechanism of thrombosis.

Similar to alteplase, TNK is also a 527-amino acid-modified human tissue plasminogen activator that contains the fibronectin finger, epidermal growth factor, kringle 1, kringle 2, and serine protease domains. However, three amino acids are substituted in TNK compared to alteplase: the substitution of threonine 103 with asparagine and glutamine 117 with asparagine has increased the half-life of TNK; the amino acid replacement in positions 296–299 has

enhanced its resistance to plasminogen activator inhibitor-1 (PAI-1) and potentiated fibrin specificity. The different biomolecular structure of TNK has given it more pharmacological advantages over alteplase (Table 2). The prolonged half-life enables TNK to be administered as a single intravenous bolus rather than a bolus and continuous infusion. The single bolus of TNK is more convenient for "drip and ship" cases. Moreover, poor fibrin selectivity of alteplase results in excessive systematic bleeding events and disintegration of the blood–brain barrier leading to post-stroke cerebral edema and hemorrhagic transformation. Alteplase also causes more damage to the fibrinolytic system than TNK and increases the risk of intracerebral hemorrhage.[7] Further, alteplase inhibits platelet aggregation and influences the coagulation process with an elevated risk of hemorrhagic events.[7] Therefore, theoretically, TNK is a better thrombolytic agent than alteplase with lower risk of side-effects when administrated intravenously in ischemic stroke patients.

Table 2: Pharmacokinetic Comparison Between Alteplase and TNK

	Fibrin Selectivity	PAI-1 Resistance	Half-Life Time	Platelet-Rich Thrombus Activity	BBB Damage	Fibrinogen Depletion	HDL-C Level Lowering	Thrombolytic Potency
Alteplase	Moderate	Low	4–8min	Low	Moderate	Moderate	Moderate	Low
TNK	High	Moderate	11–20min	High	Unknown	Low	Low	High

Abbreviations: PAI-1, plasminogen activator inhibitor-1; BBB, blood-brain barrier; HDL-C, high-density lipoprotein cholesterol.

Optimal Dose in Ischemic Stroke[1]

A pilot dose-escalation safety study was conducted to investigate the safety and efficacy of TNK in ischemic stroke patients (n=88) at four doses (0.1 mg/kg, 0.2 mg/kg, 0.4 mg/kg, 0.5 mg/kg). The occurrence of symptomatic intracranial hemorrhage (sICH) at TNK doses of 0.1 mg/kg, 0.2 mg/kg, and 0.4 mg/kg were lower than that of alteplase (0% vs 0% vs 0% vs 15%, respectively). A phase IIb, randomized, double-blind trial was conducted in 2010 to compare the three doses of TNK (0.1 mg/kg, 0.25 mg/kg, and 0.4 mg/kg) with alteplase. The trial was terminated prematurely because patient enrolment was very slow, with only 112 patients being finally enrolled. The dose of 0.4 mg/kg TNK was prematurely terminated considering its poor performance in both efficacy and safety; in terms of good outcome (combining major neurological improvement and symptomatic ICH), the 0.25 mg/kg TNK group had the highest

proportion (15/31, 48.4%), followed closely by the 0.1 mg/kg TNK group (14/31, 45.2%). By comparison, the rt-PA group had 41.9% (13/31) good outcomes. The difference between the 0.25 mg/kg and 0.1 mg/kg groups was not statistically significant because of the insufficient sample size after patient enrolment was terminated (n=112). Moreover, the study did not show conclusive results for an optimal dose of TNK in ischemic stroke.

The Tenecteplase VERSUS Alteplase for Acute Ischemic Stroke (TAAIS) trial enrolled patients with middle cerebral artery (MCA) occlusion on CTA and reversible penumbra on CTP (n=75) and showed the superiority of 0.25 mg/kg TNK over 0.1 mg/kg TNK among all the efficacy endpoints (mean rates of reperfusion at 24 h: 88.8% vs. 69.3%, P=0.006; complete recanalization at 24 h: 80% vs. 35%, P=0.002; median improvement in National Institutes of Health Stroke Scale score at 24 h: 11 vs. 7, P=0.0059; and mRS 0–1: 72% vs. 36%, P=0.011). However, no significant difference was detected in safety endpoints between the two doses of TNK (sICH: 4% vs. 4%, P=1.000). The TAAIS trial and another meta-analysis both implied that the optimal dosage of TNK in ischemic stroke may be 0.25 mg/kg, and this dosage was utilized in subsequent Phase II and Phase III trials including ATTEST (Alteplase vs. tenecteplase for thrombolysis after ischaemic stroke), TEMPO-1 (Tenecteplase–Tissue-Type Plasminogen Activator Evaluation for Minor Ischemic Stroke With Proven Occlusion), and EXTEND-IA TNK (Tenecteplase vs. Alteplase before Endovascular Therapy for Ischemic Stroke trial). The TEMPO-1 study also found that there were no serious drug-related adverse events in the 0.1 mg/kg TNK group. In the 0.25 mg/kg TNK group, there was one sICH (4%). Comparable risks of sICH were found between the 0.1 mg/kg TNK and 0.25 mg/kg TNK groups. Owing to a small sample size (n=100) and non-randomized study design, it was served as a safety and feasibility trial. The Norwegian tenecteplase stroke trial (NOR-TEST trial), a phase III trial with over 1000 enrolled patients, utilized 0.4 mg/kg TNK and failed to prove the superiority of TNK over alteplase on functional outcomes (mRS score 0–1 at 3 months: 64% vs. 63%, P=0.52). Safety outcomes were also similar between the TNK and alteplase groups (sICH: 3% vs. 2%, P=0.49; death within 3 months: 5% vs. 4%, P=0.49). The limitations of the NOR-TEST trial included a large proportion of TIA and stroke mimics (25%) and mild neurological impairment (median NIHSS score=4) that decreased its external validation. The EXTEND-IA TNK 2 trial failed to prove the superiority of 0.4 mg/kg TNK compared with 0.25 mg/kg TNK. Per another study, 0.25 mg/kg was the optimal dosage for patients undergoing bridge therapy. (intravenous thrombolysis [IVT]+mechanical thrombectomy [MT])

Recanalization and Reperfusion[1]

The TAAIS trial demonstrated that TNK was superior to alteplase in reperfusion at 24 h (79.3% vs 55.4%, P=0.004). The ATTEST trial failed to demonstrate the superiority of TNK over alteplase in reperfusion. The TAAIS trial only enrolled patients with a reversible penumbra on CTP and limited the percentage of hypoperfusion area volume (at least 20% greater than the infarct core lesion), whereas the ATTEST trial did not. While MR-DWI was used in most trials, the infarction core volume was measured via non-contrast CT in the ATTEST trial, which likely led to bias. The TEMPO-1 study, a prospective multicenter cohort study, showed that patients treated with 0.25 mg/kg TNK had a greater recanalization rate than those treated with 0.1 mg/kg TNK (52.17% vs 39.13%). TEMPO-1 enrolled patients with minor stroke (initial NIHSS score ≤5) owing to intracranial vessel occlusion and assessed the recanalization rate at 4–8 h from the administration of TNK, a timepoint earlier than those used in the TAAIS trial and ATTEST trial. Hence, the results from the TEMPO-1 study were more representative of patients with minor stroke. Although the ATTEST trial enrolled 104 patients, only 71 were included in the penumbra salvage analysis and 67 in the recanalization analysis, less than the sample size estimated to produce significant results on reperfusion and recanalization. A pooled analysis of the data from the TAAIS and the ATTEST trials showed that the recanalization rate of patients treated with TNK is greater than that of patients treated with alteplase, including the rate of complete (71% vs 42%, P<0.001) and partial (80% vs 57%, P<0.001) recanalization, indicating the superiority of TNK over alteplase in recanalization rate.

The EXTEND-IA TNK trial showed that more patients in the 0.25 mg/kg TNK group achieved substantial reperfusion (ie, restoration of blood flow to >50% of the involved territory or an absence of retrievable thrombus in the target vessel at the time of the initial angiographic assessment) than those in the alteplase group before thrombectomy, within 4.5 h after the onset of ischemic stroke (22% vs 10%, P=0.002); this indicated the superiority of TNK to alteplase in reperfusion and recanalization rate in ischemic stroke. TNK has demonstrated its superiority over alteplase in terms of recanalization rate and reperfusion in previously conducted clinical trials." Other imaging endpoints including infarct core volume and salvage tissue volume may warrant further investigations in future trials.

The reperfusion/recanalization rates among the TAAIS, ATTEST, and EXTEND-IA TNK trials were measured at different time points, and the trials also had different inclusion criteria. The reperfusion and recanalization rates were measured at 24 h after treatment in the

TAAIS trial. The percentage of penumbra salvage and recanalization were measured at 24–48 h post treatment in the ATTEST trial. In the EXTEND-IA TNK trial, the reperfusion and recanalization rates were measured at the initial angiography or 1–2 h post thrombolysis, earlier than the measurement time in the former two trials. The TAAIS trial enrolled patients with an NIHSS score≥4 and intracranial arterial occlusion in the anterior, middle, and posterior cerebral artery, within 6 h. The ATTEST trial enrolled all the patients within 4.5 h after the onset of ischemia. In the EXTEND-IA TNK trial, the patients were enrolled if they had cerebral vascular occlusion within 4.5 h after the onset of stroke and were eligible for mechanical thrombectomy within 6 h. Different time points of reperfusion/recanalization rates and number of enrolled patients may have led to bias in the results of the three trials.

Early Neurological Improvement[1]

While only the TAAIS trial defined a reduction of the NIHSS score as the primary endpoint, early neurological improvement is still considered an index to assess the efficacy of TNK. The TAAIS trial showed that patients in the TNK group had a greater reduction of NIHSS score than patients in the alteplase group, 24 h after thrombolysis (median NIHSS reduction: 8 vs 5, P<0.001), and the percentage of NIHSS score reduction ≥8 was higher in the TNK group than the alteplase group (64% vs 36%, P=0.02). The TAAIS trial was the first to identify a statistically significant difference between TNK and alteplase with respect to early neurological improvement in patients with thrombolysis. The ATTEST trial showed non-significantly greater NIHSS score reduction in the TNK group than the alteplase group at 24 h (3 vs 2, P=0.74). The ATTEST trial had a similar baseline NIHSS score as the TAAIS trial, but the difference of NIHSS score at 24 h between the TNK group and alteplase group was not significant. The underlying reason may be that all enrolled patients in the TAAIS trial had proven reversible ischemic penumbra on CTP, and after recanalization of the occluded vessels, the blood supply recovered in the ischemic penumbra and neurological function improved, thereby manifesting as a greater NIHSS score reduction. The NOR-TEST trial (0.4 mg/kg TNK) and EXTEND-IA TNK trial (0.25 mg/kg) showed similar results for early neurological improvement between TNK and alteplase (NOR-TEST: 42% vs 39%, P=0.97; EXTEND-IA TNK: 71% vs 68%, P=0.70). To date, accomplished trials have failed to demonstrate whether TNK is superior to alteplase with respect to early neurological improvement.

Neurological Functional Outcome at 90 Days[1]

The NOR-TEST trial is the only phase III trial among the TNK trials in ischemic stroke to investigate the efficacy of TNK in 90-day clinical outcomes, with mRS 0–1 defined as the primary endpoint. However, the NOR-TEST trial showed similar rates of mRS 0–1 at 90 days between the TNK and alteplase groups. Insufficient sample size in per-protocol analysis, lower baseline NIHSS score among the enrolled patients, and high rates of stroke mimics were likely hindrances in proving the difference between the TNK and alteplase groups on mRS score at 90 days. The TAAIS trial is the only clinical trial to demonstrate that patients treated with TNK had superior 90-d neurological functional outcomes than patients treated with alteplase (mRS 0–1: 72% vs 44%, P=0.02). The ATTEST trial showed a non-significantly higher percentage of mRS score 0–1 at 90 d in the TNK group than the alteplase group (28% vs 20%, P=0.28). A larger baseline infarction core volume was found in the TNK group compared with the alteplase group (TNK 32 mL vs alteplase 24 mL), and the final infarction core volume was larger in the TNK group than the alteplase group (total infarct volume at 24–48 h: 75 mL vs 66 mL, P=0.75), implying that patients in the TNK group had greater severity than those in the alteplase group. The EXTEND-IA TNK trial showed a non-significantly higher percentage of mRS score 0–1 in the TNK group (51% vs 43%, P=0.23), and the median mRS score at 90 d was also lower in the TNK group (2 vs 3, P=0.004) than the alteplase group, indicating that compared to alteplase, TNK could improve the functional outcomes in bridge therapy (IVT+MT). A pooled analysis of the EXTEND-IA TNK and EXTEND-IA TNK-2 trials (401 patients who received TNK vs 101 patients who received alteplase) showed the functional outcome difference favored TNK with a significant improvement in ordinal analysis of the mRS score (adjusted common odds ratio: 1.50, 95% CI: 1.01–2.22; P=0.04). Because TNK only proved superior in terms of the 90-day functional outcomes in some of the trials, the performance of functional outcomes of TNK and alteplase is still and it is still a debate.

Risk of Intracranial Hemorrhage[1]

TNK has better fibrin selectivity and is less harmful to the coagulation process and blood-brain barrier than alteplase, thereby theoretically implying a lower risk of intracranial hemorrhage. The TAAIS and ATTEST trials showed that patients treated with TNK had similar risks of sICH (TAAIS: 4% vs 12%, P=0.33; ATTEST: 6% vs 8%, P=0.59) and parenchymal hematoma (TAAIS: 6% vs 20%, P=0.11; ATTEST: 2% vs 10%, P=0.12) as those

treated with alteplase. The EXTEND-IA TNK trial showed that TNK (0.25 mg/kg) and alteplase had the same risk for sICH (1% vs 1%, P=0.99) and similar risk for parenchymal hematoma (6% vs 5%, P=0.76) in the bridge therapy (IVT+MT). The occurrence of parenchymal hemorrhage type 2, the most severe type of intracranial hemorrhage after intravenous thrombolysis, was lower in the TNK group than the alteplase group (0% vs 6%), as observed in the ATTEST trial.

Similar mortality at the 90-d follow-up was noted between the TNK and alteplase groups in some of the accomplished clinical trials (TAAIS: 8% vs 12%, P=0.68; ATTEST: 17% vs 12%, P=0.51; NOR-TEST: 5% vs 5%, P=0.68)" and a meta-analysis (7.6% vs 8.1%). The EXTEND-IA TNK trial showed that TNK had comparable mortality with alteplase (15% vs 17%, P=0.35) in bridge therapy.

CT Perfusion (CTP)/MR Mismatch Group[1]

The TAAIS trial added CTP mismatch to its inclusion criteria and demonstrated the superiority of TNK over alteplase. A pooled analysis including data from the TAAIS and ATTEST trials showed that in patients fulfilling the target mismatch criteria, those treated with TNK had greater early neurological improvement (median NIHSS reduction: 6 vs 1, P<0.001); higher recanalization rates (90% vs 33%, P<0.001), greater 90-d functional outcome (mRS 0–1, OR: 2.33, 95% CI: 1.13–5.94, P=0.032); and lower risk of parenchymal hematoma (0% vs 21%, P=0.003) and sICH (0% vs 12%, P=0.04) than patients treated with alteplase. Patients fulfilling the target mismatch criteria were more likely to have an excellent functional outcome after thrombolysis with TNK than those who failed to fulfill the target mismatch criteria (mRS 0–1, OR: 2.33 vs 1.26, P=0.044). Another pooled analysis that enrolled data from the TAAIS and ATTEST compared the influence of DWI (diffusion weighted imaging)-NIHSS mismatch and CTP mismatch on 90d functional outcome. Patients fulfilling CTP mismatch were more likely to have excellent functional outcomes than those fulfilling the DWI-NIHSS mismatch (90-d mRS 0–1 OR: 2.33 vs 2.15). However, patients fulfilling either DWI-NIHSS mismatch or CTP mismatch were likely to have greater early neurological improvement (median NIHSS reduction: 7 vs 2, P=0.037), higher recanalization rate (41% vs 19%, P<0.001), and lower risk of parenchymal hematoma (7% vs 13%, P=0.044) than patients who fulfilled neither of the two target mismatch criteria.

A subgroup analysis of the NOR-TEST trial showed that among patients with DWI-fluid attenuated inversion recovery (FLAIR) mismatch, those in the 0.4 mg/kg TNK group had greater early neurological improvement than patients in the alteplase group (NIHSS reduction≥4: 87.5% vs 54.2%, P=0.027). However, selection bias cannot be neglected for the small sample size and low baseline NIHSS score in this subgroup study.

Taken together, the performance of TNK is superior to alteplase in patients fulfilling target mismatch criteria. Moreover, fulfilling the target mismatch criteria indicated salvable ischemic penumbra and a greater collateral status around the infarction core. Abundant collateral circulation and higher recanalization rate owing to intravenous TNK can save the reversible penumbra around the infarction core and improve functional outcome. However, the evidence favoring TNK in patients fulfilling target mismatch criteria was mainly generated from post-hoc analysis or subgroup analysis, except in the TAAIS trial. Phase III randomized controlled trials are awaited to produce results that are more robust to demonstrate the superiority of TNK over alteplase in patients fulfilling the target mismatch criteria.

Minor Stroke/Stroke Mimics Group[1]

The TEMPO-1 study enrolled patients with minor stroke (NIHSS≤5), wherein 76% of patients in the 0.25 mg/kg TNK group had excellent functional outcome (90-d mRS score 0–1). A post-hoc analysis that enrolled patients with NIHSS≤5 in the NOR-TEST trial compared the functional outcome of patients in the TNK group and alteplase group. Those in the TNK group had similar functional outcomes as the alteplase group (52.8% vs 57.1%, P=0.57). The difference was non-significant between TNK and alteplase after excluding the data of patients with stroke mimics (57.1% vs 60.6%, P=0.7). Therefore, further evidence on the efficacy of TNK in patients with minor stroke and future trials of TNK use in minor strokes is still warranted.

TEMPO-2 (A Randomized Controlled Trial of TNK-tPA vs Standard of Care for Minor Ischemic Stroke With Proven Occlusion) is an ongoing phase III trial comparing 0.25 mg/kg TNK versus standard medical treatment in minor strokes (NIHSS≤5). Their results may provide more evidence of the efficacy of TNK in patients with a low NIHSS score.

Studies on the safety of TNK in patients with stroke mimics are limited. A study that performed subgroup analysis on 181 patients with stroke mimics (functional, 30%; migraine, 17%;

seizure, 14%; without further specification, 13%; others, 26%) from the NOR-TEST trial showed that no patients had sICH after administration of TNK, indicating that TNK was safe in patients with stroke mimics.

Bridge Therapy with Mechanical Thrombectomy[1]

The Direct Intra-arterial Thrombectomy in Order to Revascularize Acute Ischemic Stroke Patients with Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals: a Multicenter Randomized Clinical Trial (DIRECT-MT) demonstrated that primary MT was non-inferior compared to bridging MT (IVT+MT) in ischemic stroke caused by large vessel occlusion in the anterior circulation. However, the DIRECT-MT trial could not neglect the value of intravenous thrombolysis in bridging MT because the non-inferior margin was very broad (0.8). Direct endovascular treatment versus standard bridging therapy in large artery anterior circulation stroke (DEVT) trial again proved the non-inferiority of primary MT over bridging MT. The following trials comparing primary MT with bridging MT are ongoing: Netherlands-No-Intravenous tPA (ISRCTN80619088); DIRECT-SAFE (A Randomized Controlled Trial of DIRECT Endovascular Clot Retrieval vs Standard Bridging Thrombolysis With Endovascular Clot Retrieval Within 4.5 Hours of Stroke Onset) in Australia and China; SWIFT DIRECT (Bridging Thrombolysis vs Direct Mechanical Thrombectomy in Acute Ischemic Stroke) in China; TESLA (Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke) in North America. However, all the trials that compared primary MT with bridge MT used alteplase as the thrombolytic drug. Whether bridging MT with TNK is superior to direct MT is still unknown and requires further investigation. Endovascular Treatment With Versus Without Intravenous Tenecteplase in Stroke (BRIDGE-TNK) is an ongoing phase III trial to compare TNK bridging MT versus primary MT in ischemic stroke caused by M1/M2 occlusion, and the results are awaited.

STEMI Clinical Trials[1]

Tenecteplase went into clinical trial comparisons with alteplase as a single bolus thrombolytic. Patients in the tenecteplase randomized trials in acute myocardial infarction also received heparin and aspirin co-administered with either lytic.[,–] The definitive Phase 3 double-blinded trial, ASSENT-2 found equivalent 30-day mortality (7%) in 16,949 patients randomized

between the two treatments. The tenecteplase group had significantly fewer non-cerebral bleeding complications (26% to 29%; P=0.0003), while showing no difference in the incidence of intracranial hemorrhage (0.9% in both groups). No differences were observed in the rates of reinfarction.

As primary percutaneous coronary intervention (PCI) became first line treatment of STEMI, tenecteplase treatment for STEMI was relegated to cases where PCI was not available in a timely fashion. ASSENT-4, a randomized trial of tenecteplase-facilitated PCI versus primary PCI in 1667 patients, found that rather than enhancing the effects of PCI, tenecteplase prior to PCI was associated with a higher rate of in-hospital major adverse events including in-hospital death, intracranial hemorrhage (1%), and reinfarction, despite more than twice as many patients in the tenecteplase group having an open infarct artery at the time of the first angiogram. This counterintuitive finding may have been due to the narrow window of potential benefit in STEMI (1–3 hours) which may have negated the restoration of flow effect on the ischemic myocardium. These patients were still exposed to the potential harm of thrombolysis, i.e. cerebral and myocardial hemorrhage, making the net effect unfavorable. The benefit/harm ratio may be different for stroke thrombolysis prior to thrombectomy.[–]

The Strategic Reperfusion Early After Myocardial Infarction (STREAM) trial compared pre-hospital intravenous tenecteplase (with concomitant antiplatelet and anticoagulant medicines) to primary PCI on arrival to a PCI-capable hospital, randomizing 1892 STEMI patients less than 3 hours from symptom onset who were unable to receive PCI within one hour of first medical contact. [–] Eighty percent of the pre-hospital patients were randomized to treatment in the ambulance, the remainder at a referring community hospital. Patients in the tenecteplase group (pharmaco-invasive strategy) that did not have evidence of reperfusion by 90 minutes after fibrinolytic treatment by electrocardiographic or clinical criteria were given rescue PCI, but otherwise had their coronary arteriogram 6–24 hours after randomization. The median time from symptom onset to start treatment was 100 minutes for pre-hospital tenecteplase group and 178 minutes for the primary PCI group. Reperfusion criteria at 90 minutes after treatment were met by 63.7% of the tenecteplase group, in 86% of whom Thrombolysis in Myocardial Infarction (TIMI) grade flow of 2 or 3 was later observed on non-urgent angiogram, indicating complete filling of the distal coronary arterial bed. In the primary PCI group, TIMI 2 or 3 flow on the initial angiogram was found in only 30.6%. The pre-hospital tenecteplase group reported nominally fewer (12.4% to 14.3%) primary clinical composite endpoint events of all-cause death, cardiogenic shock, congestive heart failure, and reinfarction at 30 days, however, there

were no significant differences on that outcome or on one-year all-cause mortality.[,] Early in the trial an excess of intracranial hemorrhage was observed in patients 75 years or older treated with the standard 0.5mg/kg dose of tenecteplase. The protocol was amended lowering the dose to 0.25 mg/kg for those 75 and older, and no further intracranial hemorrhages occurred in that age group.[–] The similarly designed STREAM-2 trial is comparing safety and efficacy of the pharmaco-invasive strategy at 0.25 mg/kg of tenecteplase to primary PCI in patients age 60 and greater.

Tenecteplase achieved regulatory approval in the US (TNKase; Genentech) and Europe (Metalyse; Boehringer Ingelheim) in the year 2000 as a tiered weight-based dose of 0.5 mg/kg to a maximum of 50 mg given as a 5–10 second bolus for the treatment of STEMI. Clinical trials of tenecteplase for pulmonary embolism, for catheter clearance,[,] and for ischemic stroke (see below) have also been reported, but these are not currently FDA approved indications. A version of tenecteplase is marketed as a biosimilar in India for both STEMI and stroke indications under different commercial names and different doses, but in vitro studies from Boehringer Ingelheim reported less purity and reduced thrombolysis with that version, questioning its status as a biosimilar.

Stroke Clinical Trials[2]

Dose Selection of Tenecteplase for Ischemic Stroke

Doses of tenecteplase from 0.1– 0.5 mg/kg have been tested in clinical trials of ischemic stroke and are summarized in Table 3. Haley and colleagues performed the initial studies with a planned maximum dose of 0.6 mg/kg, and 25-patient cohorts. At doses 0.1, 0.2 and 0.4 mg/kg there were no occurrences of the primary endpoint, symptomatic intracranial hemorrhage (sICH). The study was terminated at the 0.5 mg/kg tier after 2 of 13 patients had sICH. The follow-up Phase 2b/3 randomized double-blind trial compared standard dose alteplase (0.9mg/kg) to 3 doses of tenecteplase 0.1 mg/kg, 0.25 mg/kg and 0.4 mg/kg treated within 3 hours from stroke onset. Using a combined measure of early neurological improvement and sICH, the 0.4 mg/kg dose, which had sICH in 3 of 19 treated was eliminated as inferior. The trial was terminated prematurely for slow enrollment with no significant differences between the two viable doses and did not proceed to Phase 3. The Tenecteplase versus Alteplase for Acute Ischaemic Stroke (TAAIS), also referred to as the Australian-TNK trial, randomized patients with middle cerebral artery occlusion and penumbral mismatch on CT perfusion to 0.1

mg/kg or 0.25 mg/kg tenecteplase (n=25 per group) and observed significantly higher rates of early recanalization, reperfusion, and neurological improvement in the 0.25 mg/kg dose group along with better 90-day clinical outcome on the mRS of 0–1.

Table 3: Clinical trials comparing doses of tenecteplase

Trial Name	**Key Eligibility Criteria**	**Trial type**	**Enrollment**	**Primary Hypothesis / Outcome**	**Primary Outcome Results**	**Key Safety Outcomes**
Pilot Dose-Escalation Safety Study of Tenecteplase in Acute Ischemic Stroke	Time window: 0–3 hr NIHSS: NIHSS ≥ 1 Maximum age: none Vascular imaging: not reported Perfusion imaging: not reported Pre-stroke mRS: not specified	Phase: 1/2, dose-escalation safety study Randomized: No Blinded Treatment: No Blinded outcome assessment: Yes	88 total enrollment 0.1 mg/kg tenecteplase (n=25) 0.2 mg/kg tenecteplase (n=25) 0.4 mg/kg tenecteplase (n=25) 0.5 mg/kg tenecteplase (n=13)	Primary hypothesis: Tenecteplase is safe for acute ischemic stroke ≤ 3 hr from onset at doses that may be associated with improvement in clinical neurological outcome	0.1, 0.2, 0.4 mg/kg no symptomatic intracranial hemorrhages (ICHs) 0.5 mg/kg was closed after 2 of 13 patients (15%) had symptomatic ICH	See primary outcome results

				Primary outcome: symptomatic ICH within 36 hr		
TNK-tPA Evaluation for Minor Ischemic Stroke With Proven Occlusion (TEMPO-1)	Time window: 0–12 hr, ≤90 min of CT/CTA NIHSS: < 6 Maximum age: none Vascular imaging: Acute occlusion relevant to symptoms Perfusion imaging: not reported Pre-stroke mRS: Barthel Index ≥ 90 or mRS ≤ 1	Phase: 2, safety, feasibility Randomized: No, tiered Blinded treatment: No Blinded outcome assessment: No	50 total enrollment 0.1 mg/kg tenecteplase (n=25) 0.2 mg/kg tenecteplase (n=25)	Primary hypothesis: The treatment of minor stroke with intracranial occlusion with tenecteplase is safe and feasible. Primary outcome: Rate of expected serious adverse events	No serious drug-related adverse events in 0.1 mg.kg group In the 0.25 mg/kg group, one symptomatic ICH	Symptomatic ICH: 0.25 mg/kg group, 1/25 (4%) Mortality: 0.25 mg/kg group, 1/25 (4%)

Determining the Optimal Dose of Tenecteplase Before Endovascular Therapy for Ischaemic Stroke (EXTEND-IA TNK Part 2)	Time window: 0–4 hr NIHSS: none Maximum age: none Vascular imaging: Arterial occlusion on CTA of the ICA, M1, M2, or basilar artery Perfusion imaging: not reported Pre-stroke mRS: ≤ 3	Phase: 2 Randomized: Yes Blinded treatment: No Blinded outcome assessment: Yes	300 total enrollment 0.25 mg/kg tenecteplase (n=150) 0.4 mg/kg tenecteplase (n=150)	Primary hypothesis: Superior recanalization with 0.4 mg/kg vs 0.25 mg/kg Primary outcome: Substantial angiographic reperfusion (mTICI score = 2b/3) or absence of retrievable thrombus at initial angiogram	Reperfusion: no difference, 0.40 mg/kg tenecteplase, 29/150 (19.3%), 0.25 mg/kg tenecteplase, 29/150 (19.3%), adjusted RR, 1.03, [0.66–1.61]; P = 0.89	Symptomatic ICH: 0.40 mg/kg group - 7/150 (4.7%) and 0.25 mg/kg group - 2/150 (1.3%), unadjusted risk difference, 3.3% [−0.5%–7.2%]; RR = 3.50 [0.74–16.62]; P = 0.12 Mortality: 26/150 (17%) deaths in the 0.40 mg/kg group and 22/150 (15%) in the 0.25 mg/kg group

						(adjusted RR, 1.27 [0.77–2.11]; P = 0.35)

The tenecteplase dose 0.25 mg/kg to a maximum of 25 mg was most frequently used in subsequent stroke trials, however the Norwegian Tenecteplase Stroke Trial (NOR-TEST) used 0.4 mg/kg to a maximum of 40 mg and found comparable safety to alteplase in the largest cohort of tenecteplase-treated stroke patients yet published (n=549). To compare 0.25 mg/kg to 0.4 mg/kg the Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke Study (EXTEND-IA TNK) Part 2 randomized 300 patients with stroke due to acute large vessel occlusion prior to endovascular thrombectomy. Both dose groups had identical rates (19.3%) of substantial reperfusion on the initial angiogram and no statistical differences in clinical outcome, sICH or mortality, although the number of sICH events was higher in the 0.4 mg/kg group (7 to 2). The authors conclude that the higher dose does not confer a clinical advantage but may offer a margin of reassurance if a patient's weight is overestimated for the 0.25 mg/kg dose. A network meta-analysis of the five randomized trials of tenecteplase versus alteplase found better efficacy on clinical and imaging endpoints with the 0.25 mg/kg dose and fewer sICH with 0.1mg/kg relative to 0.4 mg/kg.

Early recanalization and reperfusion[2]

In TAAIS, patients with CT evidence of relevant intracranial occlusion and a penumbral pattern with mismatch of at least 20% and 20 mL were randomized to alteplase, 0.1 mg/kg tenecteplase, or 0.25 mg/kg tenecteplase within 6 hours from onset (n=25 per group). The study found significant benefit on the co-primary endpoint of better reperfusion (P = 0.004) in the pooled tenecteplase group, as well on secondary outcomes of partial or complete recanalization by 24 hours and infarct growth by 24 hours or 90 days. Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST) randomized patients with stroke based on non-contrast CT to 0.25mg/kg tenecteplase or alteplase within 4.5 hours from onset and acquired CTA and CTP to test the hypothesis of superior penumbral salvage with tenecteplase. Selection was not limited to patients with occlusion or mismatch, but relevant analyses were. No difference was

observed on the primary outcome of percent penumbral salvage at 24–48 hours after treatment (n=35, 36) nor on recanalization at that time (n=32, 35). EXTEND-IA TNK Part 1 was designed to test the primary hypothesis of non-inferiority of tenecteplase 0.25 mg/kg relative to alteplase in the 4.5-hour window for early reperfusion of an occluded internal carotid, middle cerebral or basilar arteries in patients eligible for endovascular thrombectomy. With a median time interval from the start of the intravenous lytic to the diagnostic angiogram of 54–56 minutes, substantial reperfusion of >50% or absence of a retrievable thrombus was found in 22% of patients randomized to tenecteplase relative to 10% of alteplase patients (P = 0.002 for non-inferiority and P = 0.03 for superiority). EXTEND-IA TNK Part 2 confirmed the high rate of early reperfusion (19.3%) with either 0.25 or 0.4 mg/kg dose.

Meta-analysis of these three trialsreported an overall benefit of tenecteplase on complete recanalization (30% to 15%, P = 0.04) but not on complete or partial recanalization (54% to 41%, P = 0.3). Pooled analyses of TAAIS and ATTEST patients found that among those meeting more stringent imaging selection criteria (absolute mismatch volume >15 mL, mismatch ratio >1.8, baseline ischemic core <70 mL, and volume of severely hypoperfused tissue <100 mL) the tenecteplase treated patients had significant benefit on median penumbral salvage, median infarct growth and complete recanalization relative to the control group.[,]

Early neurological improvement[2]

Criteria for major early clinical improvement varied across the 5 trials (Table 4), but they all involved a substantial improvement on the NIHSS by 24–72 hours. Only TAAIS found a difference between the two treatments, an advantage for the tenecteplase treated patients (P < 0.001). Meta-analysis reported an overall benefit on the proportion of tenecteplase-treated patients with early neurological improvement (45% to 41%, P = 0.05) with a greater benefit in those treated with 0.25 mg/kg.

Three-month clinical outcome on modified Rankin Scale (mRS) [2]

Among the 5 randomized comparisons, NOR-TEST was the largest and the only Phase 3 trial with 3-month mRS as its primary endpoint, testing for superiority of tenecteplase over alteplase. Randomizing approximately 1100 patients to either 0.4 mg/kg tenecteplase or standard dose alteplase, no differences were found on 3-month mRS, sICH or mortality, either

in the intention to treat or per protocol analysis, which eliminated the stroke mimics from consideration. The median NIHSS was 4, characteristic of a broad population of stroke, which skews toward mild. In a subset of 87 NOR-TEST patients with NIHSS ≥ 15, there was no difference in mRS or sICH, but the tenecteplase group had a higher rate of mortality at three months (P = 0.045). There were no differences between treatment arms in a subset of patients 80 years or older, or wake up strokes treated within 4.5 hour of symptom discovery.[,] NOR-TEST 2 is testing 0.4 mg/kg tenecteplase versus alteplase with a minimum NIHSS > 5.

In a planned secondary analysis of EXTEND IA TNK Part 1, patients receiving tenecteplase had a more favorable 3-month mRS on an adjusted ordinal logistic regression (P = 0.04) with 64% achieving functional independence (mRS 0–2) relative to 51% of alteplase treated patients (P = 0.06).

In a pooled analysis of patients from TAAIS and ATTEST, patients with target mismatch on perfusion CT (33 tenecteplase, 35 alteplase), treatment with tenecteplase was associated with better 3-month mRS of 0–1 (P = 0.032) than those treated with alteplase, whereas the entire pooled sample did not show a difference on 3-month mRS. Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation (TASTE) Trial (ACTRN12613000243718) is an ongoing Phase 3 trial selecting patients with demonstrated arterial occlusion and target penumbral pattern on imaging for randomization to 0.25 mg/kg tenecteplase or alteplase.

Burgos and Saver conducted a formal non-inferiority meta-analysis of the five randomized tenecteplase vs alteplase comparisons across the dose ranges of 0.1 mg/kg to 0.4 mg/kg, n = 1585. The primary analysis was non-inferiority on freedom from disability (mRS 0–1) at 3 months using a non-inferiority margin of 6.5%, as was used in a completed thrombolytic comparison randomized trial. More stringent non-inferiority margins, 5% and 1.3%, were also explored guided by surveys of stroke experts. Non-inferiority based on all analyzed thresholds was evidenced by rates of 3-month mRS 0–1 outcomes nominally higher with tenecteplase than alteplase, with 95% confidence intervals within all three non-inferiority margins. The corresponding P values for non-inferiority were < 0.0001, 0.0002, and 0.02, respectively (personal communication from Drs. Burgo, Gornbein, and Saver, May 16, 2020).

Ongoing large Phase 3 clinical trials randomizing 0.25 mg/kg tenecteplase or alteplase include the Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST-2) testing the superiority of tenecteplase, and Alteplase Compared to Tenecteplase in Patients With Acute Ischemic Stroke (AcT), which will test the non-inferiority of tenecteplase in real world practice.

Safety Outcomes

In total from the five trials, 24 of 828 tenecteplase patients experienced sICH (2.9%) as did 20 of 747 alteplase patients (2.7%). Mortality was 7.6% for tenecteplase and 8.2% for alteplase.[,] Thrombolytic complications of angioedema and extracranial bleeding have been reported for both tenecteplase and alteplase with no apparent differences in the rate of occurrence.

Thrombolysis in the Later Time Window[2]

Clinical trial evidence supported the benefit of intravenous alteplase over placebo patients treated greater than 4.5 hours from the time last known well, if they met imaging criteria. The criteria were either diffusion weighted imaging positive and FLAIR negative MRI, suggesting that the true duration of ischemia was likely to be less than 4.5 hours or the presence of a target penumbra on perfusion imaging. Some tenecteplase studies permitted enrollment of patients with time last known well greater than 4.5 hours. The TAAIS trial enrolled up to 6 hours, and NOR-TEST included wake-up strokes if time from symptom discovery to randomization was less than 4.5 hours and MRI criteria were met, but neither had specifically tested for efficacy in the later time window.

TNK-tPA Evaluation for Minor Ischemic Stroke With Proven Occlusion (TEMPO-1) gave 0.1 mg/kg or 0.25 mg/kg to sequential groups of 25 patients up to 12 hours from onset (median time to treatment of 208 minutes) in minor stroke (NIHSS < 6) due to proven arterial occlusion. The 0.25 mg/kg group had a higher rate of complete recanalization, which correlated with favorable 90-day mRS, and one sICH. TEMPO-2 is an ongoing Phase 3 trial randomizing similarly selected patients to 0.25 mg/kg versus standard of care anti-platelet treatment to test for benefit of tenecteplase on 90-day mRS.

Late Time Window Ongoing Trials[2]

Tenecteplase in Wake-up Ischaemic Stroke Trial (TWIST) is an ongoing Phase 3 trial randomizing to tenecteplase 0.25 mg/kg or standard care if patient can be randomized within 4.5 hours of awakening with the new stroke symptoms. TWIST uses only non-contrast CT for

imaging selection but will analyze whether CT angiography or CT perfusion identifies patients more likely to benefit from tenecteplase, as measured by mRS at 3 months.

Tenecteplase in Stroke Patients Between 4.5 and 24 Hours (TIMELESS) is an ongoing randomized, double-blind, placebo-controlled trial of tenecteplase 0.25 mg/kg in patients with large vessel occlusion (internal carotid or middle cerebral artery) with a target mismatch profile on MR or CT, similar to the criteria used in the DEFUSE 3 trial. Although planned thrombectomy is not required for eligibility, it is likely that the majority of subjects will be referred for mechanical recanalization therapy. The primary outcome will test difference on the mRS at 3 months.

CHinese Acute Tissue-Based Imaging Selection for Lysis In Stroke -Tenecteplase (CHABLIS-T) is an ongoing Phase 2 trial randomizing between 0.25 mg/kg and 0.32 mg/kg dose using similar imaging requirements as TIMELESS and assessing early favorable outcome (reperfusion at 4–6 hours or no sICH by 36 hours).

Abstracts on Tenecteplase

Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke[3]

Abstract

Background: Intravenous infusion of alteplase is used for thrombolysis before endovascular thrombectomy for ischemic stroke. Tenecteplase, which is more fibrin-specific and has longer activity than alteplase, is given as a bolus and may increase the incidence of vascular reperfusion.

Methods: We randomly assigned patients with ischemic stroke who had occlusion of the internal carotid, basilar, or middle cerebral artery and who were eligible to undergo thrombectomy to receive tenecteplase (at a dose of 0.25 mg per kilogram of body weight; maximum dose, 25 mg) or alteplase (at a dose of 0.9 mg per kilogram; maximum dose, 90 mg) within 4.5 hours after symptom onset. The primary outcome was reperfusion of greater than 50% of the involved ischemic territory or an absence of retrievable thrombus at the time of the initial angiographic assessment. Noninferiority of tenecteplase was tested, followed by superiority. Secondary outcomes included the modified Rankin scale score (on a scale from 0 [no neurologic deficit] to 6 [death]) at 90 days. Safety outcomes were death and symptomatic intracerebral hemorrhage.

Results: Of 202 patients enrolled, 101 were assigned to receive tenecteplase and 101 to receive alteplase. The primary outcome occurred in 22% of the patients treated with tenecteplase versus 10% of those treated with alteplase (incidence difference, 12 percentage points; 95% confidence interval [CI], 2 to 21; incidence ratio, 2.2; 95% CI, 1.1 to 4.4; P=0.002 for noninferiority; P=0.03 for superiority). Tenecteplase resulted in a better 90-day functional outcome than alteplase (median modified Rankin scale score, 2 vs. 3; common odds ratio, 1.7; 95% CI, 1.0 to 2.8; P=0.04). Symptomatic intracerebral hemorrhage occurred in 1% of the patients in each group.

Conclusions: Tenecteplase before thrombectomy was associated with a higher incidence of reperfusion and better functional outcome than alteplase among patients with ischemic stroke treated within 4.5 hours after symptom onset.

Tenecteplase vs. Alteplase for Acute Ischemic Stroke: A Systematic Review[4]

Abstract

Introduction: Thrombolysis for acute ischemic stroke (AIS) with alteplase is the currently approved therapy for patients who present within 4.5 h of symptom onset and meet criteria. Recently, there has been interest in the thrombolytic tenecteplase, a modified version of alteplase, due to its lower cost, ease of administration, and studies reporting better outcomes when compared to alteplase. This systematic review compares the efficacy of tenecteplase vs. alteplase with regard to three outcomes: (1) rate of symptomatic hemorrhage, (2) functional outcome at 90 days, and (3) reperfusion grade after thrombectomy to compare the efficacy of both thrombolytics in AIS METHODS: The search was conducted in August 2021 in PubMed, filtered for randomized controlled trials, and studies in English. The main search term was "tenecteplase for acute stroke."

Results: A total of 6 randomized clinical trials including 1675 patients with AIS was included. No one's study compared alteplase to tenecteplase with all three outcomes after acute ischemic stroke; however, by using a combination of the results, this systematic review summarizes whether tenecteplase outperforms alteplase.

Conclusions: The available evidence suggests that tenecteplase appears to be a better thrombolytic agent for acute ischemic stroke when compared to alteplase.

Tenecteplase vs. Alteplase for the Treatment of Patients with Acute Ischemic Stroke: A Systematic Review and Meta-analysis[5]

Abstract

Background: At present, studies regarding the efficacy and safety of tenecteplase for the treatment of patients with acute ischemic stroke (AIS) are still limited and inconsistent. The purpose of this systematic review and meta-analysis is to compare the efficacy and safety of tenecteplase with alteplase for the treatment of AIS patients.

Methods: Literature search was conducted in PubMed, Embase, and Cochrane Library up to May 10, 2022. Primary outcomes of this study included 90-day good outcome (defined as an mRS score of 0-2) and 90-day excellent outcome (defined as an mRS score of 0-1). Risk ratios (RRs) with 95% confidence intervals (95% CIs) were calculated using a random-effect model for each outcome.

Results: Fourteen studies with a total of 3537 patients were finally included in this meta-analysis. There was no statistical difference between patients receiving tenecteplase and those receiving alteplase in the rates of 90-day good outcome (RR 1.01; 95% CI 0.91-1.13; P = 0.79) and 90-day excellent outcome (RR 1.04; 95% CI 0.92-1.19; P = 0.50). Patients receiving tenecteplase might associated with higher incidence of early neurologic improvement compared with those receiving alteplase (RR 1.29; 95% CI 1.04-1.61; P = 0.02). In addition, no statistical difference was observed between the two groups in other outcomes.

Conclusion: This meta-analysis indicated that tenecteplase in AIS patients is as safe and effective as alteplase and might provide more benefit than alteplase. However, due to several inherent limitations of this study, more prospective studies should be conducted to confirm the above results.

Off-Label Use of Tenecteplase for the Treatment of Acute Ischemic Stroke: A Systematic Review and Meta-analysis[6]

Abstract

Importance: Tenecteplase is being evaluated as an alternative thrombolytic agent for the treatment of acute ischemic stroke (AIS) within ongoing randomized clinical trials (RCTs). In addition, nonrandomized clinical experiences with off-label use of tenecteplase vs alteplase for AIS treatment are being published.

Objective: To evaluate the available evidence on the safety and efficacy of intravenous tenecteplase compared with intravenous alteplase provided by nonrandomized studies.

Data sources: Eligible studies were identified by searching MEDLINE and Scopus databases. No language or other restrictions were imposed. The literature search was conducted on October 12, 2021. This meta-analysis used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was written according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) proposal.

Study selection: Nonrandomized studies (prospective or retrospective) comparing intravenous tenecteplase (at any dose) with intravenous alteplase in patients with AIS were included in the analysis.

Data extraction and synthesis: The crude odds ratios (ORs) and 95% CIs were calculated for the association of tenecteplase vs alteplase with the outcomes of interest and adjusted ORs were extracted if provided. Estimates using random-effects models were pooled.

Main outcomes and measures: The primary outcome was the probability of good functional outcome (modified Rankin scale [mRS] score, 0-2) at 90 days.

Results: Six studies were identified including a total of 1820 patients (618 [34%] treated with tenecteplase). Patients receiving tenecteplase had higher odds of 3-month good functional outcome (crude odds ratio [OR], 1.22; 95% CI, 0.90-1.66; adjusted OR, 1.60, 95% CI, 1.08-2.37), successful recanalization (crude OR, 2.82; 95% CI, 1.12-7.10; adjusted OR, 2.38; 95% CI, 1.18-4.81), and early neurological improvement (crude OR, 4.88; 95% CI, 2.03-11.71; adjusted OR, 7.60; 95% CI, 1.97-29.41). No significant differences were detected in 3-month excellent functional outcome proportions (mRS score 0-1; crude OR, 1.53; 95% CI, 0.81-2.91; adjusted OR, 2.51; 95% CI, 0.66- 9.49), symptomatic intracranial hemorrhage (crude OR, 0.97;

95% CI, 0.44-2.16; adjusted OR, 1.16; 95% CI, 0.13-10.50), or parenchymal hematoma (crude OR, 1.20; 95% CI, 0.24-5.95).

Conclusions and relevance: Evidence from nonrandomized studies suggests tenecteplase is as safe as alteplase and potentially associated with improved functional outcomes compared with alteplase. Based on these findings, enrollment in the ongoing RCTs appears to be appropriate.

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Survey Form

1. How familiar are you with the use of Tenecteplase in bridging therapy for AIS?

a) Very familiar

b) Somewhat familiar

c) Not very familiar

d) Not familiar at all

2. What are the primary benefits of Tenecteplase in bridging therapy for AIS, in your opinion?

a) Faster clot dissolution

b) Easier administration

c) Reduced risk of hemorrhage

d) Better patient outcomes

3. How does the mechanism of action of Tenecteplase compare to other thrombolytics in AIS?

a) More fibrin-specific

b) Less fibrin-specific

c) Same as others

d) Unsure

4. In what percentage of your AIS patients do you use Tenecteplase as part of bridging therapy?

a) 0-25%

b) 26-50%

c) 51-75%

d) 76-100%

5. What is your primary consideration when choosing Tenecteplase for bridging therapy in AIS?

a) Patient eligibility

b) Time from symptom onset

c) Severity of stroke

d) Institutional protocols

6. How often do you administer Tenecteplase before mechanical thrombectomy in AIS patients?

a) Always

b) Often

c) Sometimes

d) Rarely

7. What factors influence your decision to use Tenecteplase over other thrombolytics?

a) Patient's medical history

b) Efficacy data

c) Side effect profile

d) Cost considerations

8. How effective do you find Tenecteplase in improving outcomes for AIS patients?

a) Very effective

b) Effective

c) Moderately effective

d) Not effective

9. In your experience, how does Tenecteplase impact the need for subsequent interventions in AIS patients?

a) Reduces the need significantly

b) Reduces the need moderately

c) No impact

d) Increases the need

10. What is the average time to recanalization in AIS patients treated with Tenecteplase?

a) Less than 30 minutes

b) 30-60 minutes

c) 1-2 hours

d) More than 2 hours

11. How does Tenecteplase compare with Alteplase in terms of ease of administration?

a) Easier to administer

b) Similar ease of administration

c) More difficult to administer

d) No opinion

12. What are the most common adverse effects observed with Tenecteplase in AIS patients?

a) Bleeding complications

b) Allergic reactions

c) Hypotension

d) Nausea and vomiting

13. In your practice, what percentage of AIS patients receive Tenecteplase instead of Alteplase?

a) 0-25%

b) 26-50%

c) 51-75%

d) 76-100%

14. How would you rate the safety profile of Tenecteplase in AIS bridging therapy?

a) Excellent

b) Good

c) Fair

d) Poor

15. Do you have a specific protocol for the administration of Tenecteplase in your institution?

a) Yes, a detailed protocol

b) Yes, a general protocol

c) No, we follow case-by-case

d) Not sure

Survey Findings

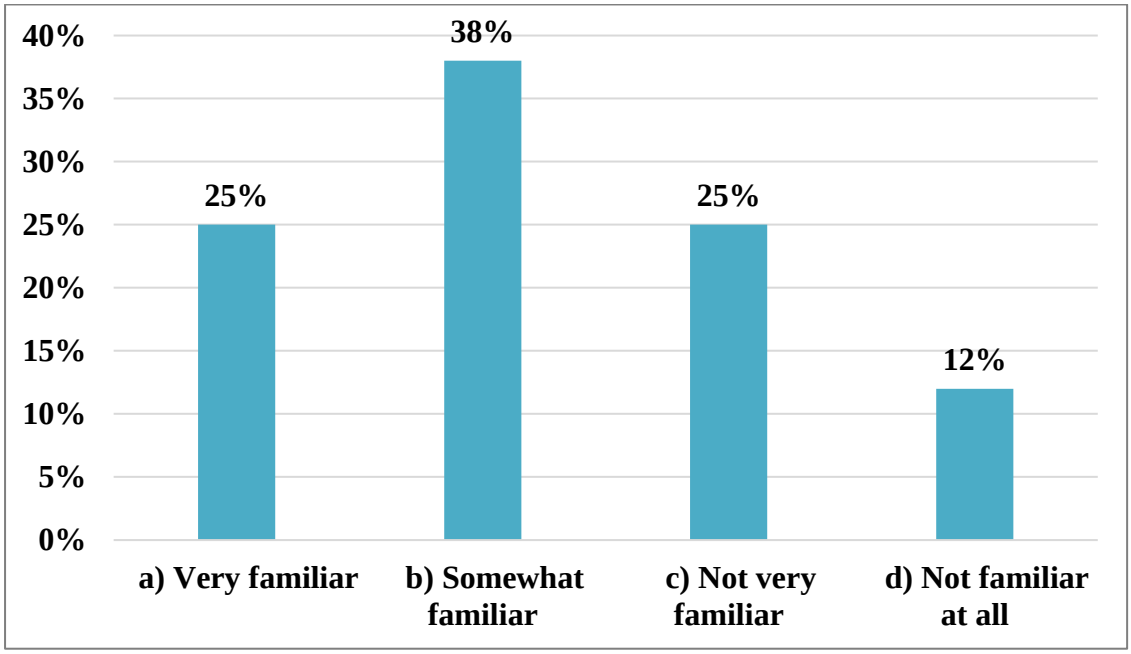
1. How familiar are you with the use of Tenecteplase in bridging therapy for AIS?

a) Very familiar

b) Somewhat familiar

c) Not very familiar

d) Not familiar at all



38% of doctors are somewhat familiar with the use of Tenecteplase in bridging therapy for AIS.

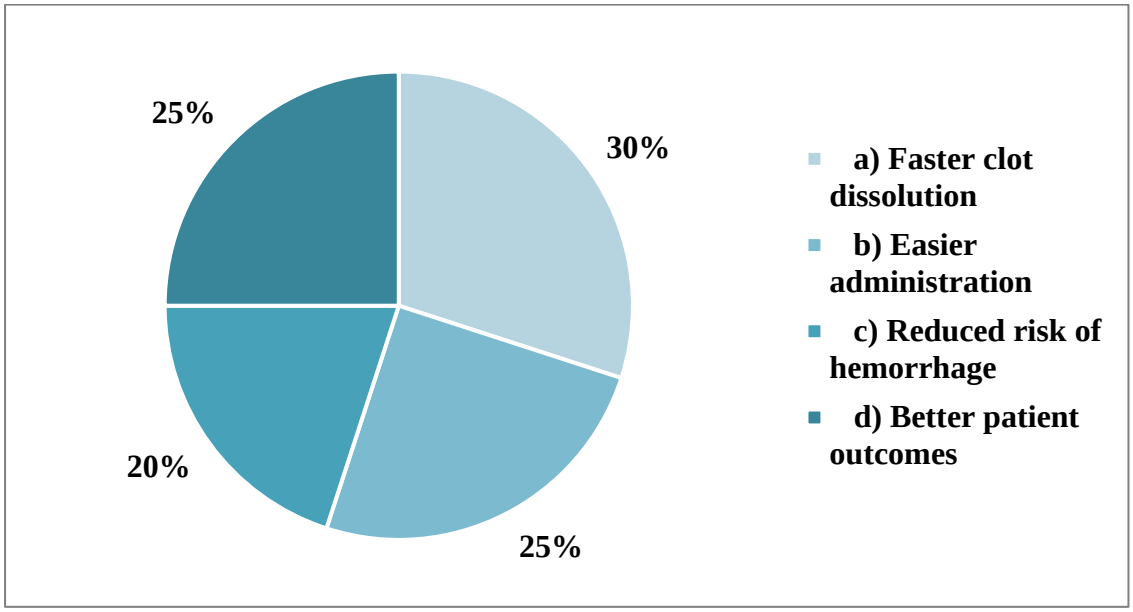
2. What are the primary benefits of Tenecteplase in bridging therapy for AIS, in your opinion?

a) Faster clot dissolution

b) Easier administration

c) Reduced risk of hemorrhage

d) Better patient outcomes



According to 39% of doctors, are the primary benefits of Tenecteplase in bridging therapy for AIS is faster clot dissolution.

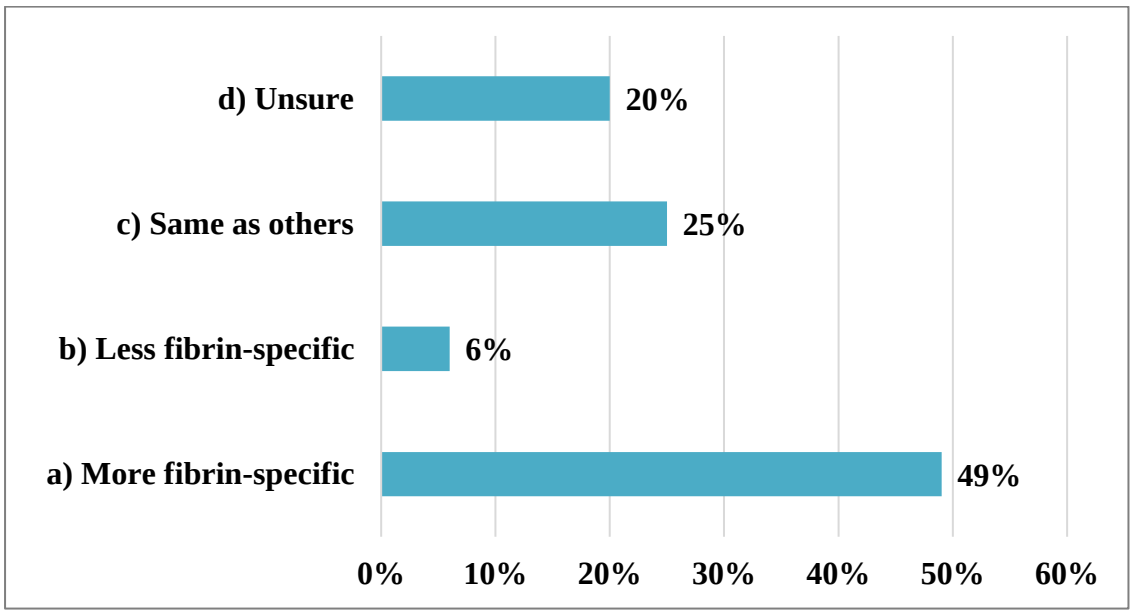
3. How does the mechanism of action of Tenecteplase compare to other thrombolytics in AIS?

a) More fibrin-specific

b) Less fibrin-specific

c) Same as others

d) Unsure



According to 49% of doctors, the mechanism of action of Tenecteplase is more fibrin-specific as compared to other thrombolytics in AIS

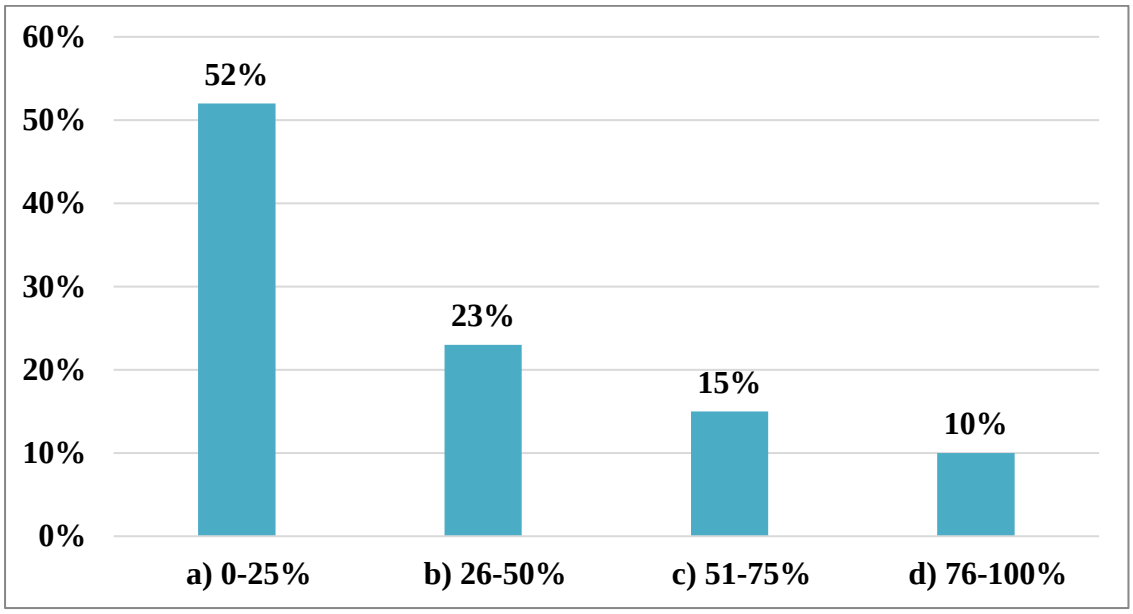
4. In what percentage of your AIS patients do you use Tenecteplase as part of bridging therapy?

a) 0-25%

b) 26-50%

c) 51-75%

d) 76-100%



Majority of doctors, 52%, use Tenecteplase as part of bridging therapy in0-25% of their AIS patients.

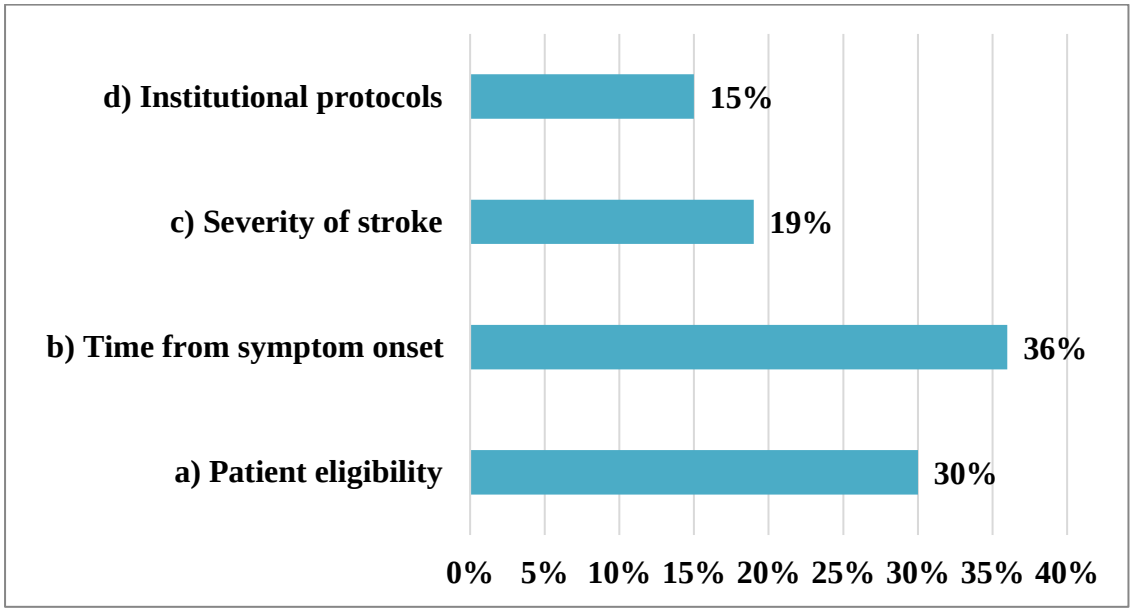
5. What is your primary consideration when choosing Tenecteplase for bridging therapy in AIS?

a) Patient eligibility

b) Time from symptom onset

c) Severity of stroke

d) Institutional protocols



When choosing Tenecteplase for bridging therapy in AIS, the primary consideration of 36% of doctors is time from symptom onset.

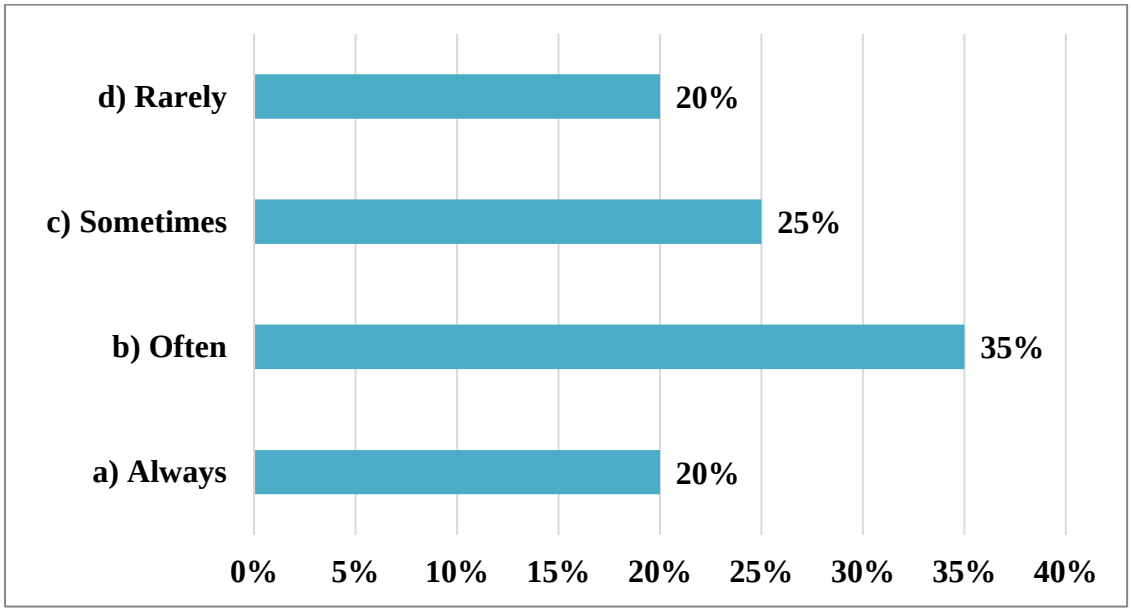
6. How often do you administer Tenecteplase before mechanical thrombectomy in AIS patients?

a) Always

b) Often

c) Sometimes

d) Rarely



35% of doctors often administer Tenecteplase before mechanical thrombectomy in AIS patients.

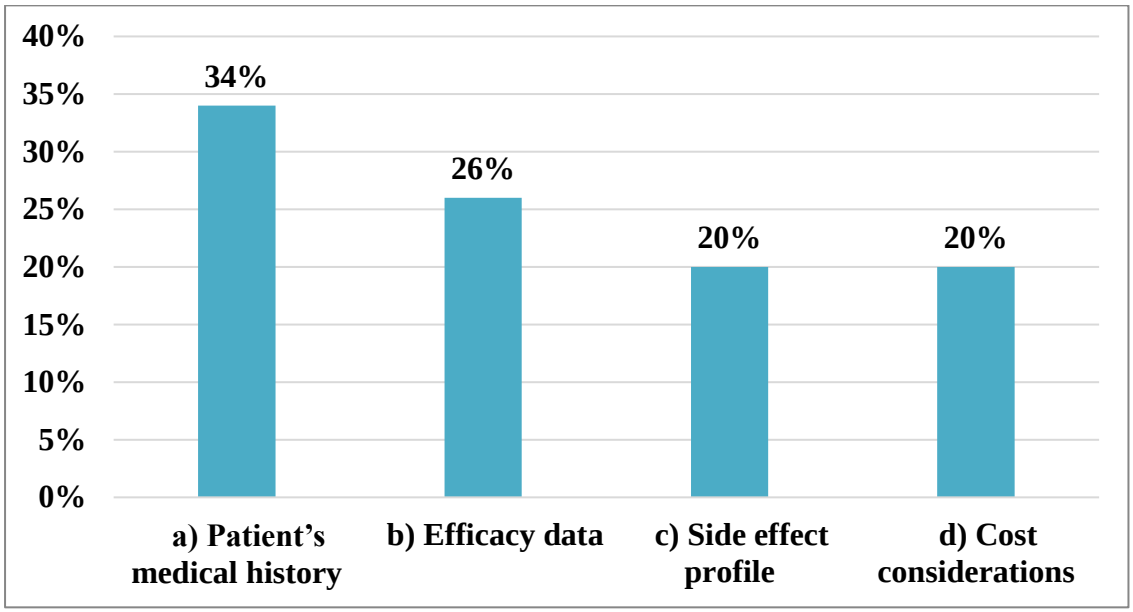
7. What factors influence your decision to use Tenecteplase over other thrombolytics?

a) Patient's medical history

b) Efficacy data

c) Side effect profile

d) Cost considerations



As per 34% of doctors, patient's medical history influences their decision to use Tenecteplase over other thrombolytics.

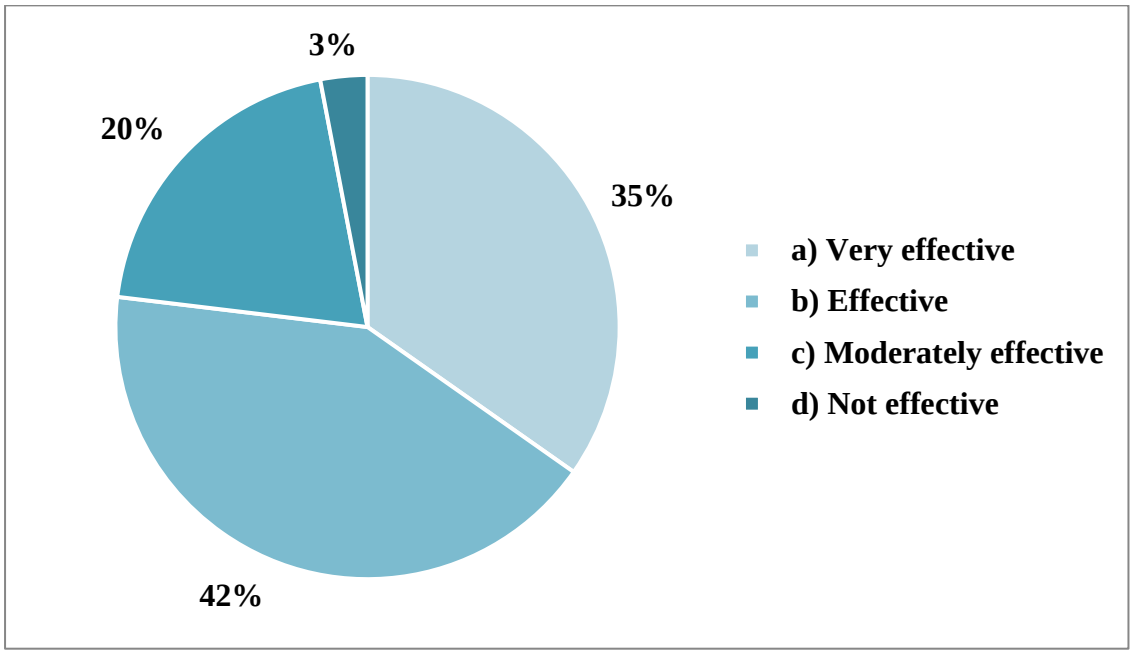
8. How effective do you find Tenecteplase in improving outcomes for AIS patients?

a) Very effective

b) Effective

c) Moderately effective

d) Not effective



42% of doctors find Tenecteplase effective in improving outcomes for AIS patients.

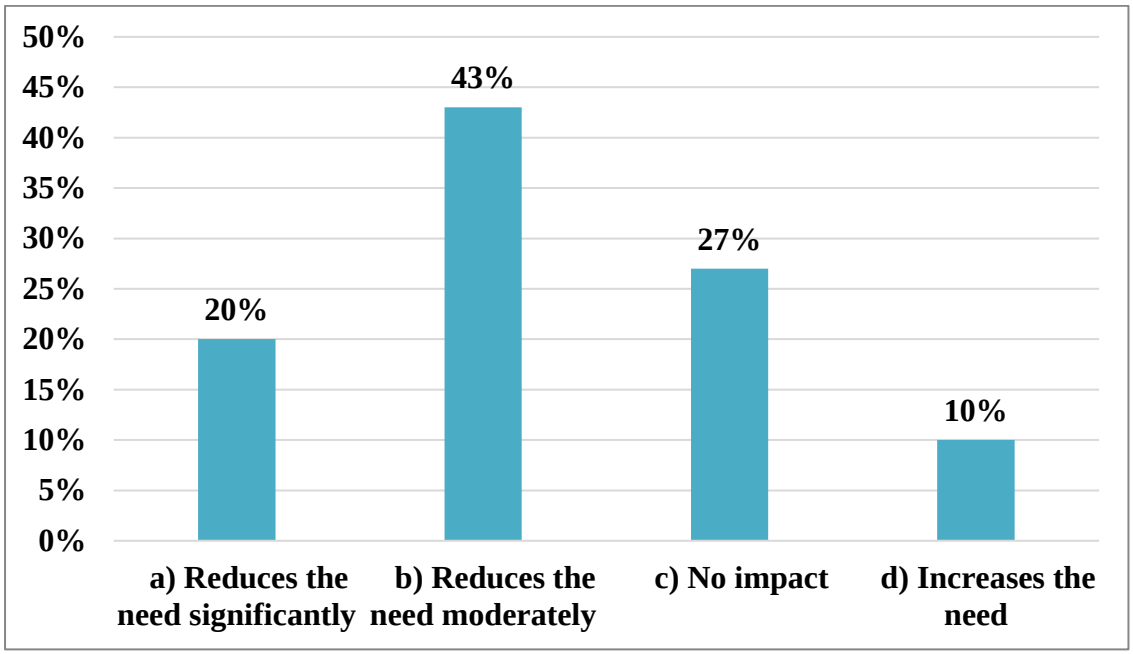
9. In your experience, how does Tenecteplase impact the need for subsequent interventions in AIS patients?

a) Reduces the need significantly

b) Reduces the need moderately

c) No impact

d) Increases the need



In the experience of 43% of doctors, Tenecteplase reduces the need for subsequent interventions in AIS patients moderately.

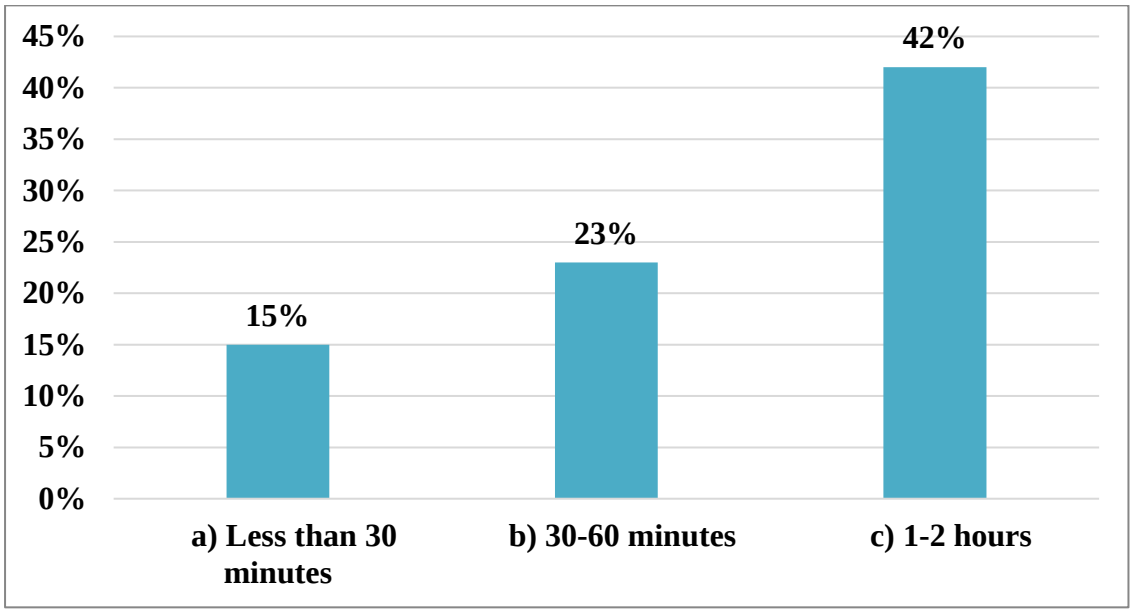
10. What is the average time to recanalization in AIS patients treated with Tenecteplase?

a) Less than 30 minutes

b) 30-60 minutes

c) 1-2 hours

d) More than 2 hours



42% of doctors consider the average time to recanalization in AIS patients treated with Tenecteplase is 1-2 hours.

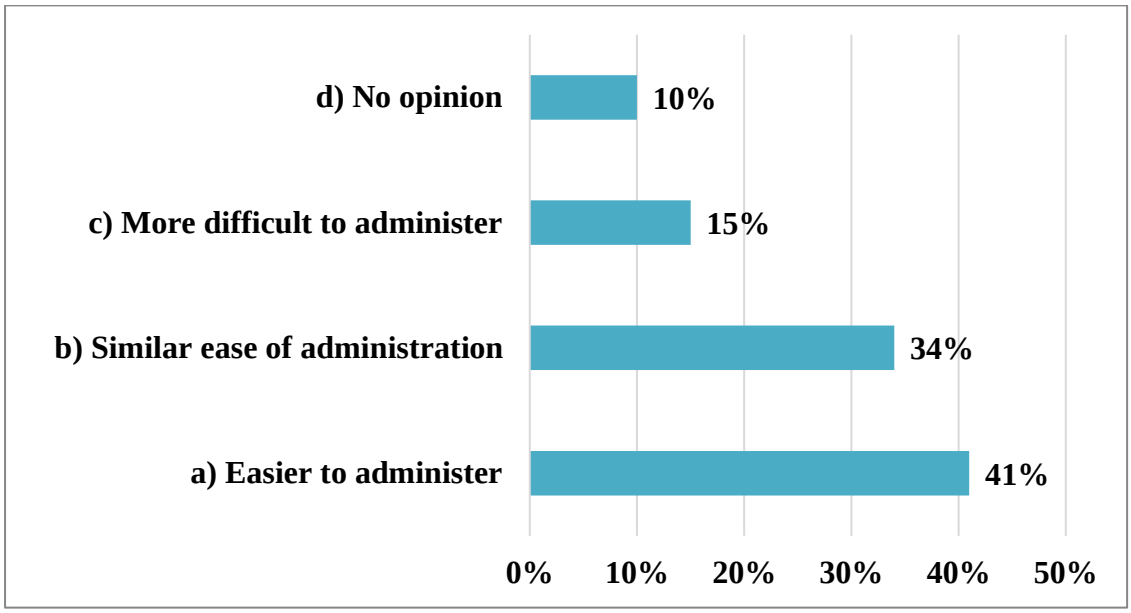
11. How does Tenecteplase compare with Alteplase in terms of ease of administration?

a) Easier to administer

b) Similar ease of administration

c) More difficult to administer

d) No opinion



As per 41% of doctors, Tenecteplase is easier to administer as compared to Alteplase.

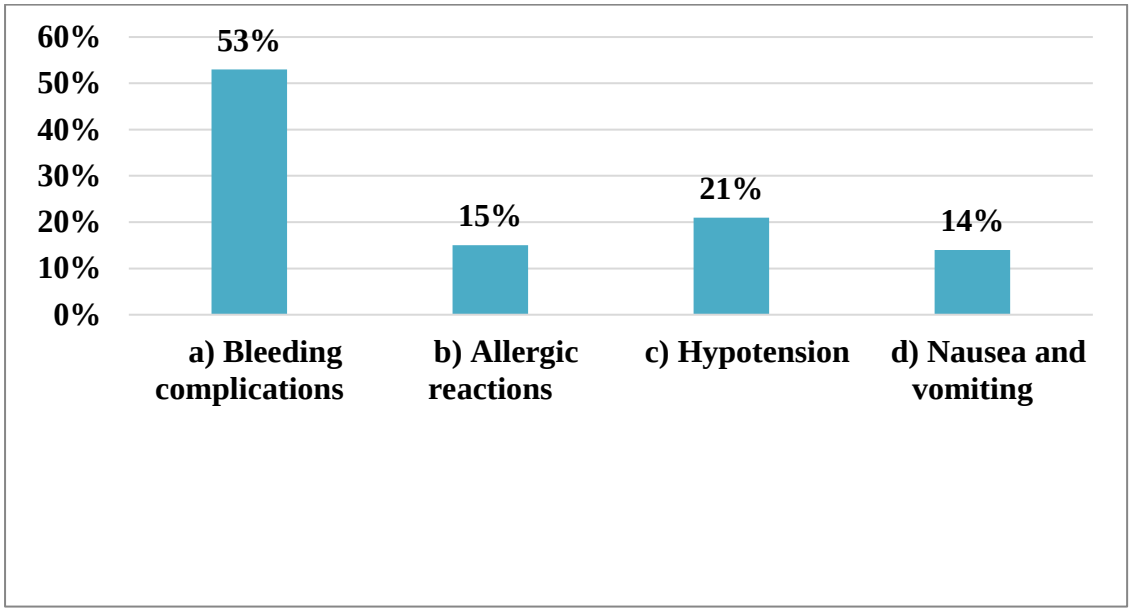
12. What are the most common adverse effects observed with Tenecteplase in AIS patients?

a) Bleeding complications

b) Allergic reactions

c) Hypotension

d) Nausea and vomiting



According to 53% of doctors, the most common adverse effects observed with Tenecteplase in AIS patients is bleeding complications.

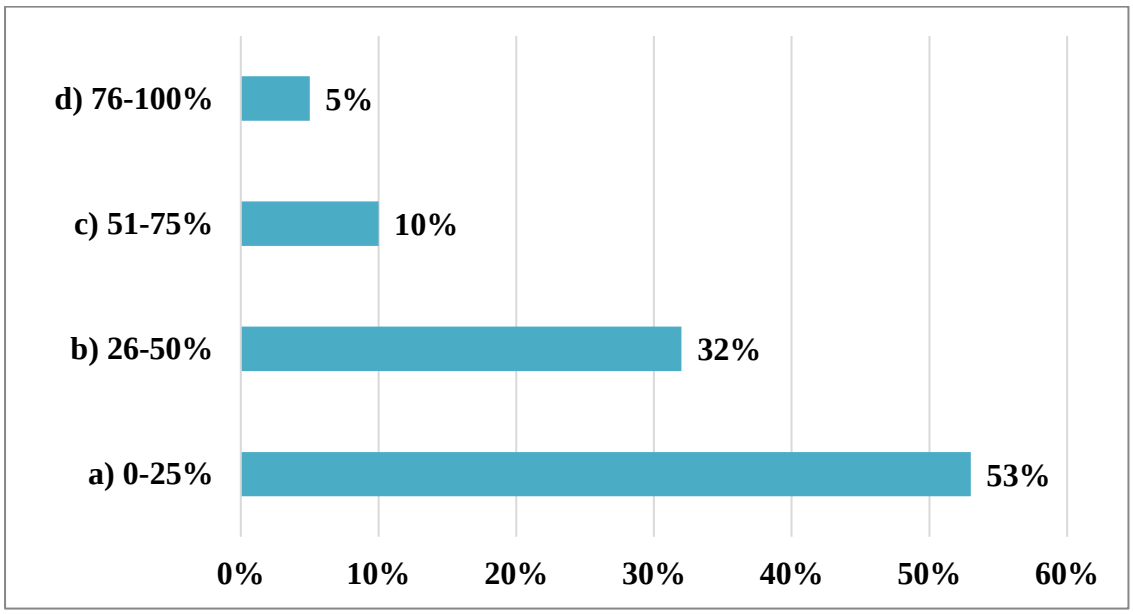
13. In your practice, what percentage of AIS patients receive Tenecteplase instead of Alteplase?

a) 0-25%

b) 26-50%

c) 51-75%

d) 76-100%



In the clinical practice of 53% of doctors, 0-25% of AIS patients receive Tenecteplase instead of Alteplase.

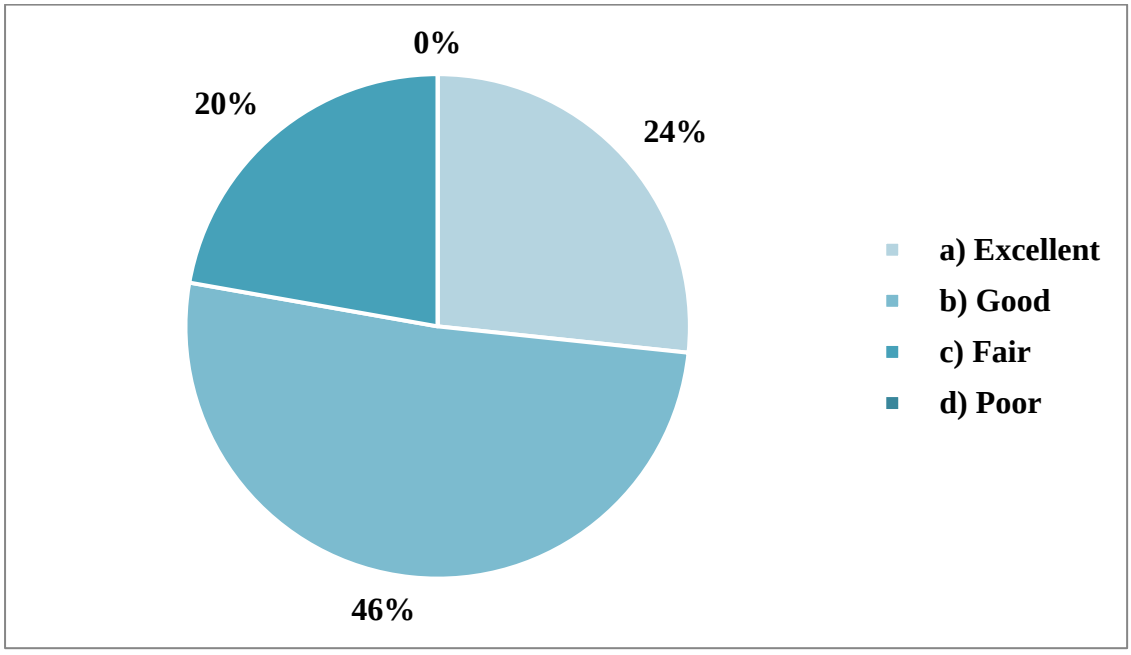
14. How would you rate the safety profile of Tenecteplase in AIS bridging therapy?

a) Excellent

b) Good

c) Fair

d) Poor



46% of doctors rate the safety profile of Tenecteplase in AIS bridging therapy as good.

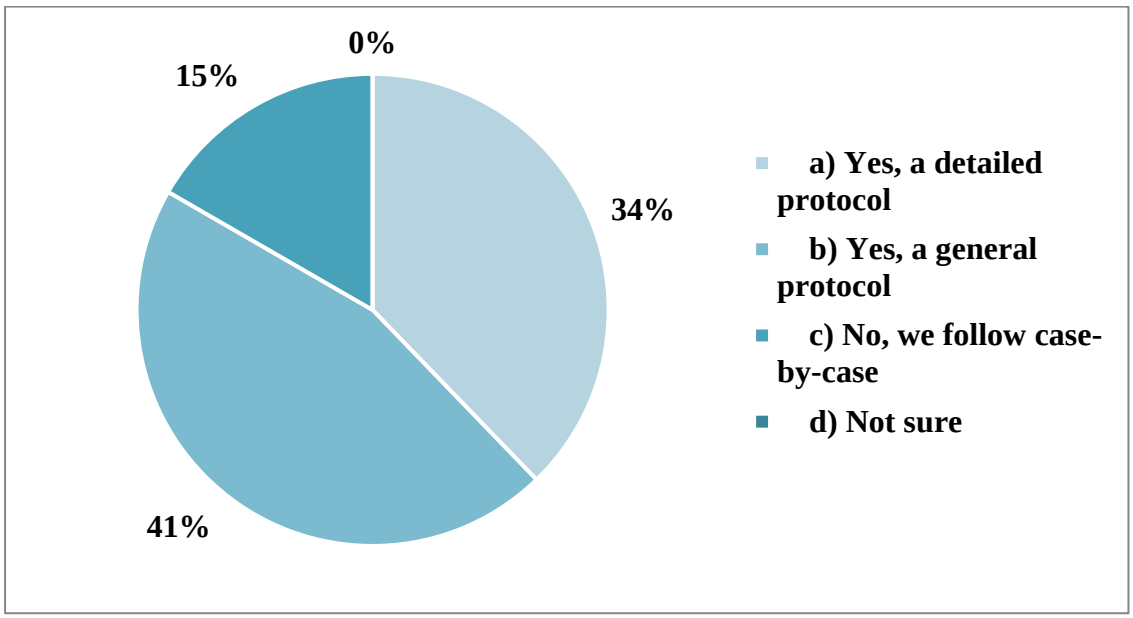
15. Do you have a specific protocol for the administration of Tenecteplase in your institution?

a) Yes, a detailed protocol

b) Yes, a general protocol

c) No, we follow case-by-case

d) Not sure



According to 41% of doctors, they have a general protocol for the administration of Tenecteplase in your institution.

Summary

- 38% of doctors are somewhat familiar with the use of Tenecteplase in bridging therapy for AIS.
- According to 39% of doctors, are the primary benefits of Tenecteplase in bridging therapy for AIS is faster clot dissolution.
- According to 49% of doctors, the mechanism of action of Tenecteplase is more fibrin-specific as compared to other thrombolytics in AIS
- Majority of doctors, 52%, use Tenecteplase as part of bridging therapy in0-25% of their AIS patients.
- When choosing Tenecteplase for bridging therapy in AIS, the primary consideration of 36% of doctors is time from symptom onset.
- 35% of doctors often administer Tenecteplase before mechanical thrombectomy in AIS patients.
- As per 34% of doctors, patient's medical history influences their decision to use Tenecteplase over other thrombolytics
- 42% of doctors find Tenecteplase effective in improving outcomes for AIS patients.
- In the experience of 43% of doctors, Tenecteplase reduces the need for subsequent interventions in AIS patients moderately.
- 42% of doctors consider the average time to recanalization in AIS patients treated with Tenecteplase is 1-2 hours.
- As per 41% of doctors, Tenecteplase is easier to administer as compared to Alteplase.
- According to 53% of doctors, the most common adverse effects observed with Tenecteplase in AIS patients is bleeding complications.
- In the clinical practice of 53% of doctors, 0-25% of AIS patients receive Tenecteplase instead of Alteplase.
- 46% of doctors rate the safety profile of Tenecteplase in AIS bridging therapy as good.
- According to 41% of doctors, they have a general protocol for the administration of Tenecteplase in your institution.

Consultant Opinion

Market Opportunities:

- Since only 38% of doctors are somewhat familiar with using Tenecteplase in bridging therapy for AIS, there is a significant opportunity for educational programs and training sessions. Pharmaceutical companies can sponsor workshops and seminars to increase awareness and familiarity among healthcare professionals.
- Continued investment in research to further validate the benefits of Tenecteplase, particularly its faster clot dissolution and fibrin-specific mechanism of action, can strengthen its position in the market.

Value for Healthcare Professionals:

- Providing robust clinical data and updated guidelines on the use of Tenecteplase in AIS can help healthcare professionals make informed decisions. Clear protocols and evidence-based practices can enhance confidence in using Tenecteplase.
- Developing decision-support tools that incorporate patient history and time from symptom onset can assist doctors in determining when to use Tenecteplase.

Adverse Effect Management:

- Given that 53% of doctors observe bleeding complications as a common adverse effect, establishing stringent monitoring and safety protocols can mitigate risks. Providing comprehensive guidelines on managing these complications can improve patient safety.
- Educating patients about the potential side effects and the importance of reporting any unusual symptoms promptly can help in early detection and management of adverse effects.

Withdrawal Management:

- For patients transitioning from Tenecteplase to other treatments or interventions, clear strategies and protocols should be in place to ensure continuity of care and minimize withdrawal-related issues.

Market Positioning:

- Emphasize the advantages of Tenecteplase, such as faster clot dissolution and its fibrin-specific action, in marketing materials. These benefits should be communicated clearly to healthcare professionals.
- Conduct and publish comparative studies showing the efficacy and safety of Tenecteplase versus Alteplase to reinforce its advantages.

Personalized Treatment Decisions:

- Develop individualized treatment protocols that consider patient-specific factors such as medical history, time from symptom onset, and likelihood of bleeding complications. This approach can enhance the effectiveness of Tenecteplase in AIS treatment.
- Establish clear criteria for selecting patients who are most likely to benefit from Tenecteplase, ensuring optimal outcomes.

Improving Patient Outcomes:

- Implement systems to track patient outcomes after Tenecteplase administration. Collecting and analyzing this data can help refine treatment protocols and improve overall patient care.
- Encourage a multidisciplinary approach involving neurologists, emergency medicine specialists, and interventional radiologists to ensure comprehensive care for AIS patients.

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Developed by:

Weston Medical Education Foundation of India

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