



Research Article

Safety and Efficacy Outcomes of Off-Label Tenecteplase versus Alteplase for Acute Ischemic Stroke: Real-World Experience

Emily J Farina^{1*}, Gregory Kelly^{2,3}, Marc Sturgill², Deepali Dixit^{2,3}

¹Atlantic Health System, Morristown Medical Center, USA

²Ernest Mario School of Pharmacy, Rutgers, USA

³Robert Wood Johnson University Hospital, USA

*Corresponding author: Deepali Dixit, Ernest Mario School of Pharmacy, Rutgers, USA

Citation: Farina EJ, Kelly G, Sturgill M, Dixit D (2023) Safety and Efficacy Outcomes of Off-Label Tenecteplase versus Alteplase for Acute Ischemic Stroke: Real-World Experience. Int J Cerebrovasc Dis Stroke 6: 150. DOI: <https://doi.org/10.29011/2688-8734.100150>

Received Date: 28 April, 2023; **Accepted Date:** 04 May 2023; **Published Date:** 08 May, 2023

Abstract

Background: Tenecteplase offers several practical advantages over alteplase; recent comparative studies have demonstrated tenecteplase to be non-inferior to alteplase in terms of its safety and efficacy in acute ischemic stroke (AIS). We recently switched to Tenecteplase for AIS from alteplase and describe our real-world outcome data. **Objectives:** To compare the efficacy and safety of alteplase with tenecteplase for AIS. **Methods:** We conducted a retrospective study of patients' thrombolysis with alteplase or Tenecteplase from January 1st, 2021, to December 31st, 2021. Patients were included if they had received alteplase or tenecteplase within 4.5 hours of symptom onset. Patients with wake-up stroke were excluded. The primary outcome was a composite of bleeding-related adverse events. Secondary outcomes included door-to-needle (DTN) time, median 24-hour National Institute of Health Stroke Scale (NIHSS) score, discharge NIHSS score, and median discharge modified Rankin score (mRs). Data were assessed using the Mann-Whitney Rank Sum test and Chi-square test. **Results:** 62 patients were treated with Tenecteplase and 48 with alteplase. There was no difference in the primary outcome of bleeding-related adverse events. For the secondary outcome of DTN time, a significant difference was shown with tenecteplase compared to alteplase (32 minutes vs. 40 minutes, p=0.022). The other secondary endpoints were not statistically significant. **Conclusion:** There was no significant difference in safety endpoints between tenecteplase and alteplase. The efficacy endpoint of DTN time was greatly improved with tenecteplase.

Keywords: Stroke; Alteplase; Tenecteplase; Fibrinolytics; Thrombolytics

Introduction

Determining the etiopathological source of stroke is a cornerstone for correct secondary prophylaxis. The majority Each year in the United States, approximately 795,000 people experience an acute ischemic stroke [1]. Before the advent of contemporary strategies for management, mortality was about 10% [2]. Of the

people that survived, about 50% had moderate to severe neurologic deficits, and 25% had a disability requiring others' assistance [3]. The use of alteplase has substantially improved outcomes in patients presenting with AIS [4].

To date, alteplase is the only Food and Drug Administration (FDA) approved thrombolytic for the treatment of ischemic stroke; however, the literature suggests that alteplase leads to an incomplete and delayed reperfusion in patients with large vessel occlusion (LVO). Tenecteplase, another thrombolytic

agent, FDA approved only for use in ST-segment-elevation myocardial infarction, has practical advantages in administration as a single intravenous bolus compared to a bolus followed by a 60-minute infusion for alteplase, owing to more fibrin specificity and longer plasma half-life than alteplase. The aforementioned properties make tenecteplase an appealing alternative; single bolus thrombolytic has advantages over alteplase, shorter drug preparation, and administration time. Furthermore, Tenecteplase has a cost advantage; the average wholesale price of alteplase costs \$10,560.43 vs. \$7,463.50 for a single dose of tenecteplase [5].

Additional randomized controlled trials comparing tenecteplase with alteplase are ongoing, but the existing trials and meta-analysis on Tenecteplase suggest a greater degree of early reperfusion of LVO and showed the efficacy and safety to be non-inferior to alteplase [6-10]. Several investigators out of New Zealand and other countries recently published their local experience with the off-label use of Tenecteplase for AIS and suggest comparable safety and outcomes to alteplase [11,12].

Current clinical practice guidelines for ischemic stroke include Tenecteplase 0.25 mg/kg dose as an alternative primarily for patients without contraindications for IV fibrinolysis eligible for thrombectomy [13]. On June 7, 2021, a level 1 trauma and comprehensive stroke center in New Jersey switched to Tenecteplase at a 0.25mg/kg dose for AIS except for wake-up strokes. This study compares the safety, efficacy, and DTN time of a newly implemented Tenecteplase protocol with alteplase for AIS.

Materials and Methods

Study Design

This study was a single-center retrospective study that received the Institutional Review Board (IRB) approval (approval code: Pro2021001569) on November 30th, 2021. The study site received approval for the conduct of this study with waivers of informed consent from the IRB.

Study Population

Patients who presented to the Emergency Department between January 1st, 2021, and December 31st, 2021, ≥ 18 years of age, received tenecteplase or alteplase for AIS within 4.5 hours of symptom onset were included in the study. Patients that received thrombolytic for wake-up stroke were excluded.

Data Collection

The data was extracted from the Hospital Stroke Center Database. Baseline demographics, comorbidities (previous

stroke or transient ischemic attack, atrial fibrillation/atrial flutter, hypertension, hyperlipidemia, coronary artery disease, diabetes, obesity, smoking, excessive alcohol use, migraines), admission NIHSS, 24-hour NIHSS, discharge NIHSS score, date of treatment, type of fibrinolytic, total dose, antiplatelet/anticoagulant use, hemorrhagic transformation, type of bleeding, in-hospital all-cause mortality, DTN time, and discharge Modified Rankin Scale score (mRs) were recorded. The 30-day mRs was not considered for this study due to low documentation. Functional independence was defined as mRs 0 to 2 at 30 days.

Outcome Measure

The primary outcome was to compare the adverse events between tenecteplase and alteplase. The secondary outcomes were DTN time, 24-hour NIHSS, discharge NIHSS, and discharge mRs.

Statistical Method

Demographic variables and study results are summarized using descriptive statistics. Categorical variables are presented as frequency and percentage (for nominal variables) and median and interquartile range (IQR) for ordinal variables. Continuous outcomes are presented as mean, \pm standard deviation (SD), median, and IQR in the case of outcomes that are not normally distributed.

Comparisons between the two patient cohorts employed a chi-square test for nominal variables and an unpaired Student t-test for continuous variables. A Mann-Whitney Rank Sum Test was used for ordinal and continuous variables that are not normally distributed. A P value less than 0.05 will be considered statistically significant for all comparisons.

Results

A total of 123 acute ischemic cases were reviewed. Of these, 48 received alteplase, and 62 patients received tenecteplase. Thirteen patients were excluded due to treatment with thrombolytics by wake-up stroke protocol. Figure 1 describes patient enrollment. Baseline characteristics, including demographics and comorbidities, are summarized in Table 1. The median age was (71.5 vs. 74 years) with the incidence of notable stroke risk factors including hypertension (82% vs. 73%), hyperlipidemia (39% vs. 38%), diabetes mellitus (39% vs. 27%) and obesity (69% vs. 72%) in the tenecteplase and alteplase group, respectively. None of the patients were on factor Xa inhibitors. One patient in the alteplase group was on dabigatran at baseline though nonadherent; the family confirmed the last dose was about four days ago. Of note, one patient in the tenecteplase group was on warfarin, but the INR was < 1.7 . The median NIHSS score at baseline was 6.5 in the Tenecteplase and 6 in the alteplase group.

Figure 1: Patient baseline characteristics.

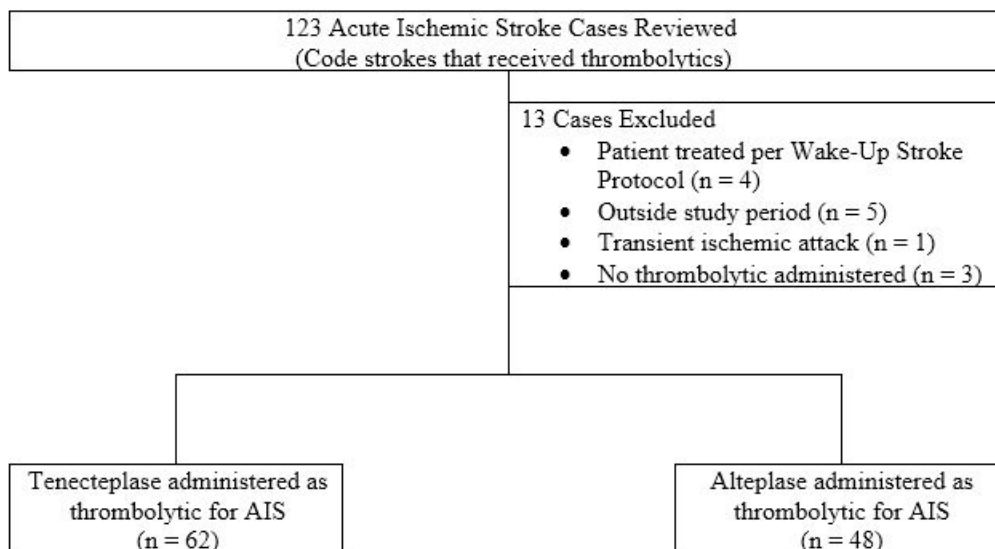


Table 1: Patient Baseline Characteristics

Baseline Characteristic	Tenecteplase (n = 62)	Alteplase (n = 48)
Age, Median (IQR)	71.5 (59-81)	74 (63.3-81)
Sex		
Male	30 (48.4)	22 (45.8)
Female	32 (51.6)	26 (54.2)
Race		
White	24 (38.7)	28 (58.3)
Black	9 (14.5)	8 (16.7)
Asian	10 (16.1)	6 (12.5)
Unknown	19 (30.6)	6 (12.5)
Past Medical History		
Previous stroke/TIA	14 (22.6)	13 (27.1)
Previous AFib/Aflutter	2 (3.2)	5 (10.4)
Hypertension	51 (82.3)	35 (72.9)
Hyperlipidemia	24 (38.7)	18 (37.5)
Coronary Artery Disease	10 (16.1)	6 (12.5)
Diabetes mellitus	24 (38.7)	13 (27.1)
Obesity	43 (69.4)	38 (79.2)

Smoking	2 (3.2)	3 (6.3)
Migraines	1 (1.6)	2 (4.2)
Home Medications		
Clopidogrel	6 (9.7)	9 (18.8)
Aspirin	26 (41.9)	17 (35.4)
Dabigatran	0	1 (2.1)
Warfarin	1 (1.6)	0
NIHSS at Presentation, Median (IQR)	6.5 (3.8-14)	6 (3-15)

Data presented as Number (Percent) unless otherwise noted

Table 2: Efficacy & Safety Outcomes.

Outcome	Tenecteplase (n = 62)	Alteplase (n = 48)	P-value for difference
Efficacy Outcomes			
Door to Needle Time (minutes), median (IQR)	32 (24-47.4)	40 (28.5-60)	0.022
NIHSS score at 24 hours, median (IQR)	3 (1-8)	4 (1-11.3)	NS
NIHSS score at hospital discharge, median (IQR)	2 (1-8)	2 (0-5)	NS
Modified Rankin Score at discharge, median (IQR)	2 (0-4)	3 (0.5-4)	NS
Safety Outcomes			
Hemorrhagic transformation	3 (4.8)	2 (4.2)	NS
Type of bleed			
Petechial	0	1 (2.1)	NS
ICH	1 (1.6)	0	
Unknown	2 (3.2)	1 (2.1)	NS
In-hospital death	2 (3.2)	3 (6.3)	NS

Data presented as Number (percent) unless otherwise noted
NS = not significant

Table 2 describes safety and efficacy outcomes. The primary composite outcome of bleeding-related adverse events occurred in three patients (4.8%) in the tenecteplase group and two patients (4.2%) in the alteplase group. The types of intracranial hemorrhage (ICH) were further divided into petechial hemorrhages, parenchymal hematomas, and ICHs of unknown type. One patient in the tenecteplase group experienced a parenchymal hematoma, and 2 patients experienced ICHs of an unknown type. In the alteplase group, one of the ICHs was a petechial hemorrhage, and the other was unknown. The ICH that occurred in the three patients, labeled as unknown, was not explicitly stated in the neurology progress notes with inconclusive radiographic evidence. Median DTN was 32 minutes (IQR 24-47.4) and 40 minutes (IQR 28.5-60) in the Tenecteplase and alteplase groups, respectively. The median NIHSS score at 24-hours was 3 (IQR 1-8) in the tenecteplase group and 4 (IQR 1-11.3) in the alteplase group. At the time of hospital discharge median NIHSS score was 2 in both groups. Median mRs at discharge was 2 (IQR 0-4) in the tenecteplase group and 3 (IQR 0.5-4) in the alteplase group. In hospital-death occurred in 2 patients (3.2%) in the tenecteplase group and 3 patients (6.3%) in the alteplase group.

Discussion

Tenecteplase is an attractive option for thrombolysis in AIS, considering its ease of preparation and administration. Adoption of tenecteplase for AIS has been slow due to the scarce data availability. Trials evaluating tenecteplase for AIS are heterogeneous, with varying doses, study populations, and outcomes investigated [6,8,9,10,14-16,17]. This is one of the first US studies to examine the use of tenecteplase for AIS outside of a controlled trial.

We observed a similar incidence of bleeding-related adverse events between alteplase and tenecteplase. Bleeding incidence with the use of tenecteplase for AIS has been previously published with significant variation, likely influenced by heterogeneity in dosing and study populations [6,8-10,14-17]. Most published studies evaluate primarily symptomatic intracranial hemorrhage (sICH), with incidences reported between 0-15.8% with tenecteplase and 1-12% with alteplase [8,10,14,15,17]. The highest incidences of sICH with tenecteplase have been reported with 0.4 mg/kg (0 -15.8%) and 0.5 mg/kg (15%) doses [8,10,14,15]. Concerns regarding dose-dependent bleeding have influenced many adopters of tenecteplase for AIS, including our system to utilize 0.25 mg/kg dose across all thrombolytic eligible AIS despite American Heart Association/American Stroke Association guideline recommendation for 0.4 mg/kg for non-large vessel occlusions [13]. The largest randomized trial of tenecteplase for AIS, the NOR-TEST trial, observed low rates of sICH at 3% with 0.4 mg/kg compared to 2% with alteplase [8]. The low rate of sICH in the NOR-TEST trial remains controversial; the trial included participants with a lower baseline NIHSS score of 4. Most clinical trials evaluating tenecteplase for AIS have required advanced imaging (CTA/CTP/MRI/MRA) with confirmation of LVO for study inclusion [6,8-10,17]. These requirements contrast with routine stroke care in which only a non-contrast CT head is recommended before administering thrombolytics [13]. While it is unclear if the requirement of advanced imaging and confirmed LVO influences the incidence of bleeding, this concern has also delayed the adoption of tenecteplase for AIS. Our results suggest that tenecteplase dosed at 0.25 mg/kg has similar rates of intracranial hemorrhage as alteplase.

When comparing efficacy outcomes, including NIHSS score at 24 hours, NIHSS score at hospital discharge, and mRS at hospital discharge, we did not observe a significant difference between tenecteplase and alteplase. Most studies evaluating tenecteplase for AIS have been designed to demonstrate non-inferiority to alteplase. Phase II trials of tenecteplase for AIS are heterogeneous in efficacy measures with mixed results [6,15,17]. The TAAIS and EXTEND-1A trials reported greater reperfusion and improvement in NIHSS with tenecteplase compared to alteplase; however, the ATTEST and TNK-S2B trials observed no significant differences in functional status at 3 months and percent penumbra salvaged respectively [6,9,10,15,17]. The NOR-TEST trial evaluated a primary outcome of a proportion of patients

achieving mRS score of 0-1 at 3 months. It showed no significant difference between tenecteplase 0.4 mg/kg or alteplase 0.9 mg/kg [8]. As previously discussed, there are several concerns with the applicability of available data to routine stroke care. In addition to varying tenecteplase doses, most trials required advanced imaging (CTA/CTP/MRI/MRA) with confirmation of large vessel occlusion for study inclusion [6,8-10,17]. The selection of patients with imaging-confirmed LVO limits generalizability to routine stroke care, where most patients receive thrombolytics before confirmation or in the absence of LVO. While our study was not powered to detect differences in efficacy outcomes, our findings are consistent with those of the NOR-TEST trial, with no significant differences observed in efficacy outcomes. Although underpowered, our results provide necessary data evaluating the efficacy of tenecteplase in routine stroke care and suggest that tenecteplase dosed at 0.25 mg/kg is similarly efficacious as alteplase for AIS.

Our study observed a significant reduction in DTN time amongst patients receiving tenecteplase compared to alteplase; shorter DTN times have been associated with improved neurologic outcomes [13]. Our results suggest that tenecteplase may be expected to reduce DTN times compared to alteplase. Many factors, including institutional operational factors such as the location of thrombolytic preparation, influence DTN times. Pharmacists at our institution respond to all stroke codes and prepare thrombolytics at the bedside. The difference in DTN time may be smaller than expected, given the relatively small difference in time needed to prepare alteplase and tenecteplase at the bedside. Greater differences in DTN time may be expected in institutions where thrombolytic preparation may be decentralized with the transition to tenecteplase. Our results suggest that in routine stroke care, tenecteplase may reduce DTN times. However, the study was not powered to detect differences in efficacy outcomes that may result from reduced DTN times.

Limitations

Although our study provides valuable insights, there are limitations for consideration. Retrospective design, recall bias, missing information, and lack of follow-up may have affected the robustness of collected data. Our study relied on monitoring and imaging as part of routine care, which may have resulted in undetected bleeding. However, we expect that clinically significant bleeds were captured. Similarly, our assessment of thrombolytic efficacy was limited to information documented in the electronic medical record. Though we captured the NIHSS and mRS score at 24 hours and at discharge, we were unable to evaluate long-term differences in efficacy, such as mRS at 3 months. It is difficult to predict whether efficacy outcomes would differ between hospital discharge and at 3 months; however, our available data suggest no difference in efficacy consistent with the findings of the NOR-TEST trial [8]. Lastly, our findings are limited by sample size. Given the scarcity of US data evaluating tenecteplase, a one-year study period was selected. While our sample size is limited, our data assesses tenecteplase in routine stroke care. Future studies

should expand upon the data provided in this study, including the evaluation of tenecteplase in larger numbers of patients receiving routine stroke care.

Conclusions

Our study detected no significant difference in safety endpoints between tenecteplase and alteplase, which is consistent with the current literature. The efficacy endpoint of DTN time was reduced with tenecteplase compared to alteplase, as expected, due to the ability to bolus-only tenecteplase. Tenecteplase was successfully implemented at our stroke center, and according to other studies, institutions can safely transition from alteplase to tenecteplase as a thrombolytic of choice for AIS.

Article Summary

Why is this topic important?

This topic is important because recent comparative studies have demonstrated the noninferiority of tenecteplase to alteplase for acute ischemic stroke, and findings suggest tenecteplase may have a superior safety profile. Ease of preparation and administration of tenecteplase can potentially prevent medication errors and improve the door to thrombolytic time.

What does this study attempt to show?

This real-world study compares the efficacy and safety of a newly implemented tenecteplase protocol with alteplase for acute ischemic stroke.

What are the key findings?

Our study demonstrated no difference between alteplase and tenecteplase regarding bleeding-related adverse events. Our door-to-needle time was significantly reduced with tenecteplase compared to alteplase.

How is patient care impacted?

Management of acute ischemic stroke is time-sensitive; tenecteplase offers similar efficacy and safety, and practical advantages compared to alteplase. This may impact improved clinical benefits for our patients.

References

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, et al. (2020) American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2020 Update: A Report from the American Heart Association. *Circulation* 141: e139-e596.
2. Carandang R, Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, et al. (2006) Trends in incidence, lifetime risk, severity, and 30-day mortality of stroke over the past 50 years. *JAMA* 296: 2939-2946.
3. Kelly-Hayes M, Beiser A, Kase CS, Scaramucci A, D'Agostino RB, et al. (2003) The influence of gender and age on disability following ischemic stroke: The Framingham study. *J Stroke Cerebrovasc Dis* 12: 119-126.
4. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (1995) Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 333: 1581-1587.
5. Wolters Kluwer Clinical Drug Information I (2023) Lexi-Drug: Tenecteplase average wholesale price. <https://www.wolterskluwercli.com/lexicomp-online/database/>
6. Parsons M, Spratt N, Bivard A, Campbell B, Chung K, et al. (2012) A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. *N Engl J Med* 366: 1099-1107.
7. Kvistad CE, Næss H, Helleberg BH, Idicula T, Hagberg G, et al. (2022) Tenecteplase versus alteplase for the management of acute ischaemic stroke in Norway (NOR-TEST 2, part A): A phase 3, randomised, open-label, blinded endpoint trial. *Lancet Neurol* 21: 511-519.
8. Logallo N, Novotny V, Assmus J, Kvistad CE, Altheheld L, et al. (2017). Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): A phase 3, randomised, open-label, blinded endpoint trial. *Lancet Neurol* 16: 781-788.
9. Campbell BCV, Mitchell PJ, Churilov L, Yassi N, Kleinig T, et al. (2018). Tenecteplase versus alteplase before thrombectomy for ischemic stroke. *N Engl J Med* 378: 1573-1582.
10. Campbell BCV, Mitchell PJ, Churilov L, Yassi N, Kleinig TJ, et al. (2020) Effect of intravenous tenecteplase dose on cerebral reperfusion before thrombectomy in patients with large vessel occlusion ischemic stroke: The EXTEND-IA TNK part 2 randomized clinical trial. *JAMA* 323: 1257-1265.
11. Zhong CS, Beharry J, Salazar D, Smith K, Withington S, et L. (2021) Routine use of tenecteplase for thrombolysis in acute ischemic stroke. *Stroke* 52: 1087-1090.
12. Mahwesh k, Gommans J, Kleinig T, Lallu B, Tyson A, et al. (2021) Switching to tenecteplase for stroke thrombolysis. *Stroke* 52: e590-e593.
13. Powers W, Rabinstein A, Ackerson T, Adeoye OM, Bambakidis NC, et al. (2019) Guidelines for the early management of patients with acute ischemic stroke: 2019. Update to the 2018 guidelines. *Stroke* 50: e344-418.
14. Haley EC Jr, Lyden PD, Johnston KC, Hemmen TM (2005) TNK in Stroke Investigators. A pilot dose-escalation safety study of tenecteplase in acute ischemic stroke. *Stroke* 36: 607-612.
15. Haley EC Jr, Thompson JL, Grotta JC, Lyden PD, Hemmen TH, et al. (2010) Tenecteplase in stroke investigators. Phase IIB/III trial of tenecteplase in acute ischemic stroke: Results of a prematurely terminated randomized clinical trial. *Stroke* 41: 707-711.
16. Coutts SB, Dubuc V, Mandzia J, Kenney C, Demchuk AM, et al. (2015) TEMPO-1 Investigators. Tenecteplase-tissue-type plasminogen activator evaluation for minor ischemic stroke with proven occlusion. *Stroke*. 2015 46: 769-774.
17. Huang X, Cheripelli BK, Lloyd SM, Kalladka D, Moreton FC, et al. (2015) Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): A phase 2, randomised, open-label, blinded endpoint study. *Lancet Neurol*. 14: 368-376.