Tenecteplase Versus Alteplase for Acute Stroke: Mortality and Bleeding Complications

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Study objective: Intravenous thrombolysis with alteplase has been the foundation of initial treatment of acute ischemic stroke for several decades. Tenecteplase is a thrombolytic agent that offers logistical advantages in cost and administration relative to alteplase. There is evidence that tenecteplase has at least similar efficacy and safety outcomes compared with alteplase for stroke. In this study, we compared tenecteplase versus alteplase for acute stroke in a large retrospective US database (TriNetX) regarding the following 3 outcomes: (1) mortality, (2) intracranial hemorrhage, and (3) the need for acute blood transfusions.

Methods: In this retrospective study using the US cohort of 54 academic medical centers/health care organizations in the TriNetX database, we identified 3,432 patients treated with tenecteplase and 55,894 patients treated with alteplase for stroke after January 1, 2012. Propensity score matching was performed on basic demographic information and 7 previous clinical diagnostic groups, resulting in a total of 6,864 patients with acute stroke evenly matched between groups. Mortality rates, the frequency of intracranial hemorrhage, and blood transfusions (as a marker of significant blood loss) were recorded for each group over the ensuing 7- and 30-day periods. Secondary subgroup analyses were conducted on a cohort treated from 2021 to 2022 in an attempt to determine whether temporal differences in acute ischemic stroke treatment would alter the results.

Results: Patients treated with tenecteplase had a significantly lower mortality rate (8.2% versus 9.8%; risk ratio [RR], 0.832) and lower risk of major bleeding as measured by the frequency of blood transfusions (0.3% versus 1.4%; RR, 0.207) than alteplase at 30 days after thrombolysis for stroke. In the larger 10-year data set of patients with stroke treated after January 1, 2012, patients receiving tenecteplase were not found to have a statistically different incidence of intracranial hemorrhage (3.5% versus 3.0%; RR, 1.185) at 30 days after the administration of the thrombolytic agents in patients. However, a subgroup analysis of 2,216 evenly matched patients with stroke treated from 2021 to 2022 demonstrated notably better survival and statistically lower rates of intracranial hemorrhage than the alteplase group.

Conclusion: In our large retrospective multicenter study using real-world evidence from large health care organizations, tenecteplase for the treatment of acute stroke demonstrated a lower mortality rate, decreased intracranial hemorrhage, and less significant blood loss. The favorable mortality and safety profiles observed in this large study, taken together with previous randomized controlled trial data and operational advantages in rapid dosing and cost-effectiveness, all support the preferential use of tenecteplase in patients with ischemic stroke. [Ann Emerg Med. 2023;■:1-9.]

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0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2023.03.022

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INTRODUCTION

Acute ischemic stroke remains a disease with a high burden on society. Every year, approximately 800,000 individuals in the United States have a stroke. More than 600,000 are first-time occurrences and 87% are ischemic infarctions.[1] Currently, the only Food and Drug Administration-approved medication for the treatment of acute ischemic stroke is alteplase, a recombinant tissue plasminogen activator.[2,3]

Alteplase has been the foundation of acute ischemic stroke therapy for decades, but alteplase has complicated dosing that requires an initial bolus and an hour-long infusion because of a short half-life of 5 minutes.[4] To mix alteplase, administer a bolus dose, and then administer an infusion, which may result in a considerable delay in receiving the complete therapeutic dose. In addition, this dosing strategy is labor-intensive and may contribute to treatment interruption or failure.[5,6] Decreasing the time to thrombolysis may improve neurologic deficits and decrease the risk of intracranial hemorrhage.[7]

Background

Thrombolytics work by increasing the conversion of plasminogen to plasmin after thrombosis occurs. This leads

Editor's Capsule Summary

What is already known on this topic

Tenecteplase is easier to administer and at least as safe and as efficacious as alteplase, but not FDA-approved for stroke therapy.

What question this study addressed

In this propensity-score-adjusted analysis of claims data, what are mortality, intracranial bleeding, and transfusion outcomes of tenecteplase and alteplase?

What this study adds to our knowledge

Patients with stroke treated with tenecteplase had lower mortality rates and fewer blood products administered. Intracranial bleeding was similar.

How this is relevant to clinical practice

This study provides additional evidence that tenecteplase is a viable and potentially preferred alternative to alteplase.

to clot breakdown and ideally restored cerebral perfusion. Tenecteplase is another recombinant tissue plasminogen activator routinely used in the treatment of acute myocardial infarction that has begun to be used in the treatment of acute ischemic stroke. Several amino acid substitutions have given tenecteplase a longer half-life (18 minutes), 14-fold higher fibrin specificity, and an 80-fold higher resistance to plasminogen activator inhibitor-1 (PAI-1).[3,8] These characteristics of tenecteplase allow it to be administered as a single bolus dose and eliminate the need for a subsequent 1-hour intravenous infusion.[8]

The advantages of single bolus dosing compared with a combination of a bolus followed by intravenous infusion have contributed to a recent increase in the treatment of acute ischemic stroke with tenecteplase.[3,9-12] The feared side effects of treatment of acute ischemic stroke with thrombolytics is hemorrhagic conversion of an ischemic stroke into an intracranial hemorrhage or other clinically significant bleeding events. Multiple exclusion criteria exist to limit the possibilities of hemorrhagic conversion because it remains a potentially devastating complication.[4] Recent studies that compared tenecteplase with alteplase have suggested that tenecteplase might be more effective in breaking down a thrombus, and with lower risk of intracranial hemorrhage due to increased specificity.[9,11-13]

Thrombolysis in patients with acute ischemic stroke remains an off-label use for tenecteplase.[9] It has been used for years with FDA approval as a thrombolytic for ST-elevation myocardial infarction.[6] In the most recent stroke guidelines published by the AHA, it was given a grade IIb recommendation stating that it is reasonable to treat patients with acute ischemic stroke eligible for mechanical thrombectomy who present within 4.5 hours of symptom onset with a single intravenous bolus (0.25 mg/kg, maximum 25 mg).[4] There are clinical trials with varying doses of tenecteplase from 0.1 mg/kg to 0.5 mg/kg, with most studies using a dose of 0.25 mg/kg.[3,8,9,12-16] Tenecteplase doses that are more than 0.25 mg/kg are associated with a trend toward higher rates of intracranial hemorrhage.[8,17]

Because of the lower cost of tenecteplase,[18] ease of administration, and a trend toward benefit over alteplase, there has been a move to switch to tenecteplase as the primary thrombolytic for acute ischemic stroke.[12-14,16,19] Most recent studies have been meta-analyses combining different methodologies that have demonstrated the noninferiority of tenecteplase to alteplase for acute ischemic stroke. We sought to assess whether tenecteplase would offer an improved safety profile in comparison with alteplase in a large retrospective health care database of patients with acute ischemic stroke. We evaluated mortality, rates of intracranial hemorrhage, and the frequency of blood transfusions as a surrogate marker for other clinically significant bleeding in patients with stroke treated with tenecteplase versus alteplase.

METHODS AND MATERIALS

TriNetX is a global federated health research network providing de-identified access to retrospective electronic medical records (diagnoses, procedures, medications, laboratory values, and genomic information) from approximately 91 million patients in 54 large health care organizations within the United States. These are largely tertiary academic centers and their satellite facilities.[20] This study used the United States Collaborative Network to identify patients who were treated with tenecteplase and alteplase for acute stroke. Patient data were obtained from the TriNetX US Collaborative Network database on September 19, 2022. The following 2 cohorts were identified for this study: cohort (1) consisted of patients who were treated with tenecteplase for acute stroke and cohort (2) of patients with stroke treated with alteplase, both within 7 days of stroke diagnosis to capture any possibility of delayed stuttering neurologic symptoms or clinical decompensation that may not have initially received thrombolysis. The statistical analysis was completed on the TriNetX research platform. The variables included in the propensity score matching include the demographic and

preexisting conditions listed in the methodology. These conditions were chosen because they are the established risk factors for mortality. Most were significantly (statistically) different between the cohorts before propensity matching, but not different after matching.

Chi-square test and Student's *t* test were used for univariate analyses. In addition, 1:1 propensity score matching was performed with listed comorbidities, and 1:1 matching was performed on the basis of propensity scores generated by using the greedy nearest neighbor algorithms using a caliper width of 0.1 pooled standard deviations. Balance on covariates was assessed using standardized mean difference, and absolute values of more than 0.1 were considered positive for residual imbalance. A 2-sided alpha of less than 0.05 was defined a priori for statistical significance. The TriNetX platform uses input matrices of user-identified covariates and conducts logistic regression analysis to obtain propensity scores for individual subjects. TriNetX randomizes the order of rows to eliminate bias resulting from the nearest neighbor algorithms. This study method has been previously validated.[20]

Patients with stroke aged 18 years or older of all ethnicities, races, and sexes were identified using the International Statistical Classification of Diseases, Tenth Revision (ICD-10) code I63 (Cerebral Infarction, 1.46 million cases total) who had received a diagnosis on or after January 1, 2012. Cohort (1) was defined as patients with stroke treated with tenecteplase (RxNORM:259280) within 7 days (30 health care organizations, 9,667 cases total). Cohort (2) was defined as patients with stroke treated with alteplase (RxNORM:8410) within 7 days.

To control for potentially confounding risk factors for the measured outcomes, propensity score matching was performed on the basis of age at stroke diagnosis, race, ethnicity, sex, hypertensive diseases (I10 to I16), diabetes mellitus (E08 to E13), acute kidney failure and chronic kidney disease (N17 to N19), overweight and obesity (E66), heart failure (I50), cardiac arrest (I46), and ischemic heart diseases (I20 to I25). The balanced cohort tool in TriNetX was used for matching.

Outcome analysis between the 2 cohorts was performed for the following 3 events: (1) death (vital status: deceased), (2) nontraumatic intracranial hemorrhage, and (3) blood transfusions (CPT:36430). Nontraumatic intracranial hemorrhage was defined as nontraumatic subarachnoid, ICD-10: I60; nontraumatic intracerebral hemorrhage, ICD-10: I61; or nontraumatic acute subdural hemorrhage, ICD-10: I62.01. Rates of blood transfusion were used as a marker of significant blood loss after thrombolytic administration. All tested outcomes occurred on or after the first day following the stroke diagnosis. Outcomes were measured across a period of 7 and 30 days after thrombolysis. Patients who had the outcome at the time of or before the designated time window were subsequently excluded from the analysis.

A review study showing no better efficacy and possible higher intracranial hemorrhage rates with a higher dose of tenecteplase was published and widely publicized in October 2020, and a randomized trial with similar conclusions was published May 2022.[8,17] To determine whether temporal treatment differences in dosing or other unanticipated variables affected the outcomes, we performed a subgroup analysis on October 11, 2022 of a smaller group of patients evenly propensity-matched by demographics and preexisting conditions. This cohort included patients with stroke treated with either tenecteplase or alteplase after January 1, 2021, who we posited were more likely treated with lower recommended doses of tenecteplase (0.25 mg/kg with a maximum of 25 mg). In this subgroup analysis, we evaluated the same 3 outcomes (death, intracranial hemorrhage, and blood transfusions) at 7 and 30 days after thrombolysis.

Univariate analysis was performed using the measure of association tool in TriNetX, which compares outcomes within the designated time frames for each cohort reported both as risk ratios (RRs), odds ratios, 95% confidence intervals (CIs) of these ratios, and risk difference. The final TriNetX data analyses were performed on September 19, 2022 and October 11, 2022, and we reported our outcomes as RRs with 95% CIs. The TriNetX platform provides access to aggregated counts and statistical summaries of de-identified patient records. No protected health information or personal data are available to the platform users; therefore, this project is exempt from the Institutional Review Board.

RESULTS

We identified 90,866,059 patients in the TriNetX United States Collaborative Network from 54 academic medical centers/health care organizations. In cohort 1 of patients treated with tenecteplase for acute stroke, there were 3,432 patients identified (30 health care organizations, 9,667 cases total). In cohort 2 of patients treated with alteplase for stroke, there were 55,894 patients (50 health care organizations, 550,895 cases in total). After propensity score matching on basic demographic information and 7 previous clinical diagnostic groups associated with mortality, there were a total of 6,864 patients with acute stroke evenly matched between the tenecteplase and the alteplase groups.

Most of the demographic groups, except for sex (male/female) were statistically significant in differences between

the 2 cohorts before matching. All preexisting medical conditions controlled for were statistically different between the cohorts. After propensity matching, none of the demographic groups or preexisting medical conditions was statistically different between the cohorts. Table 1 presents the demographic characteristics in cohorts 1 and 2 before and after matching. Table 2 demonstrates preexisting conditions before and after propensity matching for the tenecteplase and alteplase cohorts. TriNetX reports infrequent events with outcomes that are 10 or more as 10; therefore, the difference between the 2 cohorts may have been slightly more for the Native American and Hawaiian demographic groups, where the number in the tenecteplase group is listed as 10.

A number of patients were excluded because they had an outcome at the time of or before the designated index event on the basis of what is recorded in the medical records. The risk analysis for the mortality outcome led to 58 patients excluded from cohort 1 (tenecteplase) and 45 patients from cohort 2 (alteplase). There were 1,106 patients excluded in cohort 1 and 643 patients in cohort 2 when calculating the risk of intracranial hemorrhage. In addition, 79 patients were excluded in cohort 1 and 162 patients in cohort 2 when calculating the frequency of blood transfusions. These exclusions are in part necessary when the outcome and index event occur within hours of each other because the TriNetX database does not always have the degree of granularity to distinguish which event occurred first. These exclusions are also necessary when the timing of an outcome diagnosis is uncertain.

In the 10-year data set at 7 days after thrombolytic therapy, the tenecteplase group demonstrated lower, but not statistically different, mortality rates (4.4% versus 4.7%; RR, 0.934; 95% CI, 0.751 to 1.63) and decreased rates of blood transfusions (0.3% versus 0.6%; RR, 0.488; 95% CI, 0.229 to 1.040). The rate of intracranial hemorrhages was comparable between cohorts at 7 days after tenecteplase versus alteplase (3.0% versus 2.3%; RR, 1.291; 95% CI, 0.925 to 1.802) (Table 3). Patients treated with tenecteplase had a lower mortality rate (8.2% versus 9.8%; RR, 0.832; 95% CI, 0.715 to 0.969) and lower risk of major bleeding as measured by the frequency of blood transfusions (0.3% versus 1.4%; RR, 0.207; 95% CI, 0.105 to 0.410) than alteplase at 30 days after thrombolysis

Table 1. Demographics before and after propensity score matching.

Before Propensity Score Matching						After Propensity Score Matching			
Cohort		Mean ± SD	Patients	% of Cohort	Standard difference	Mean ± SD	Patients	% of Cohort	Standard difference
1-TNK	Age at index, y	64.3 ± 14.5	3,432	100	0.075	64.3 ± 14.5	3,432	100	0.004
2-Alteplase		63.2 ± 14.4	55,894	100		64.2 ± 14.4	3,432	100	
1	Sex, Female		1,603	46.7	0.010		1,603	46.7	0.005
2			26,375	47.2			1,595	46.5	
1	Not Hispanic or Latino		3,161	92.1	0.514		3,161	92.1	0.005
2			40,964	73.3			3,166	92.2	
1	White		2,896	84.4	0.377		2,896	84.4	0.010
2			38,386	68.7			2,909	84.8	
1	Unknown Ethnicity		179	5.2	0.522		179	5.2	<0.001
2			12,702	22.7			179	5.2	
1	Black		315	9.2	0.302		315	9.2	0.004
2			11,004	19.7			319	9.3	
1	Unknown Race		176	5.1	0.169		176	5.1	0.017
2			5,324	9.5			163	4.7	
1	Hispanic or Latino		92	2.7	0.073		92	2.7	0.009
2			2,228	4.0			87	2.5	
1	Asian		29	0.8	0.056		29	0.8	<0.001
2			805	1.4			29	0.8	
1	American Indian or Alaska		10	0.3	0.032		10	0.3	<0.001
2	Native		275	0.5			10	0.3	
1	Native Hawaiian or Other		10	0.3	0.023		10	0.3	<0.001
2	Pacific Islander		100	0.2			10	0.3	

TNK, tenecteplase; *SD*, standard deviation.

Table 2. Diagnosis before and after propensity score matching.

Before Propensity Score Matching						After Propensity Score Matching		
Cohort	**ICD-10**	**Condition**	**Patients**	**% of Cohort**	**Standard difference**	**Patients**	**% of Cohort**	**Standard difference**
1-TNK	I10-I16	Hypertensive diseases	2,083	60.7	0.078	2,083	60.7	0.002
2-Alteplase			31,773	56.8		2,086	60.8	
1	E08-E13	Diabetes mellitus	1,202	35.0	0.091	1,202	35.0	0.007
2			17,196	30.8		1,191	34.7	
1	N17-N19	Acute kidney failure and chronic kidney disease	906	26.4	0.035	906	26.4	0.003
2			15,628	28.0		902	26.3	
1	E66	Overweight and obesity	776	22.6	0.040	776	22.6	0.006
2			11,726	21.0		768	22.4	
1	I50	Heart failure	614	17.9	0.058	614	17.9	0.005
2			11,263	20.2		607	17.7	
1	I46	Cardiac arrest	123	3.6	0.042	123	3.6	0.008
2			1,590	2.8		118	3.4	
1	I20-I25	Ischemic heart diseases	1,133	33.0	0.060	1,133	33.0	0.011
2			16,896	30.2		1,116	32.5	

ICD-10, International Statistical Classification of Diseases, Tenth Revision.

for stroke (Table 4). Patients receiving tenecteplase were not found to have a statistically different incidence of intracranial hemorrhage (3.5% versus 3.0%; RR, 1.185; 95% CI, 0.877 to 1.599) at 30 days after the administration of the thrombolytic agents in the 10-year data set (Table 4).

In a smaller subgroup analysis of 2,216 propensity-matched patients with stroke treated after January 1, 2021, with potentially lower doses of tenecteplase (2,216 patients—with 1,108 in each group). The findings at 7 days after thrombolytics trended toward the improved outcomes in mortality and intracranial hemorrhage but were not statistically different for mortality (3.1% versus 4.5% RR, 0.832; 95% CI, 0.452 to 1.071) or intracranial hemorrhage (1.4% versus 2.2%; RR, 0.634; 95% CI, 0.324 to 1.239) (Table 5). At 30 days, tenecteplase demonstrated statistically lower mortality rates (6.6% versus 8.9%; RR, 0.737; 95% CI, 0.549 to 0.989) and significantly decreased rates of intracranial hemorrhage (1.6% versus 3.2%; RR, 0.507; 95% CI, 0.278 to 0.924) relative to alteplase (Table 6). In addition, the number of blood transfusions as a marker of significant hemorrhage was too low in the tenecteplase group ($\leq$10) to analyze for both 7- and 30-day outcomes.

LIMITATIONS

A limitation of our study is that it is a retrospective cohort design, making it more difficult to demonstrate causality. Electronic databases of this type can also exclude health care organizations if they are temporarily offline at the time the search is performed. However, the size of our study—which was 4 times larger than any current meta-analysis, in conjunction with the propensity matching—gives it a higher power to identify the differences in outcomes between the groups of strokes treated with tenecteplase versus alteplase.

Table 3. Matched cohort tenecteplase versus alteplase outcomes at 7 days since January 1, 2012.

Outcome	TNK (n = 3,432), %	Alteplase (n = 3,432), %	Risk Ratio (95% CI)
Mortality	4.4	4.7	0.934 (0.751, 1.163)
Intracranial hemorrhage	3.0	2.3	1.291 (0.925, 1.802)
Blood Transfusion	0.3	0.6	0.488 (0.229, 1.040)

CI, confidence interval.

Table 4. Matched cohort tenecteplase versus alteplase outcomes at 30 days since January 1, 2012.

Outcome	TNK (n = 3,432), %	Alteplase (n = 3,432), %	Risk Ratio (95% CI)
Mortality	8.2	9.8	0.832 (0.715, 0.969)
Intracranial hemorrhage	3.5	3.0	1.185 (0.877, 1.599)
Blood Transfusion	0.3	1.4	0.207 (0.105, 0.410)

CI, confidence interval.

Table 5. Matched cohort tenecteplase versus alteplase outcomes at 7 days since January 1, 2021.

Outcome	TNK (n = 1,108), %	Alteplase (n = 1,108), %	Risk Ratio (95% CI)
Mortality	3.1	4.5	0.696 (0.452, 1.071)
Intracranial hemorrhage	1.4	2.2	0.634 (0.324, 1.239)

CI, confidence interval.

TriNetX captures mortality and outcome data directly from the medical records of the healthcare organization. If a death or other outcome happened outside the healthcare organization, then that event would not be captured. However, most health care organizations are linked with national death registries. We are not provided information as to which healthcare organization link; therefore, some adverse outcomes may have remained unreported. We are also unable to determine with TriNetX whether a patient was transferred to a hospital not reporting data to TriNetX after treatment with either medication. This may have missed the capture of some outcomes.

Age, sex, race, hypertensive diseases, diabetes mellitus, acute and chronic kidney diseases, heart failure, ischemic heart disease, previous cardiac arrest, and overweight/obesity were selected as variables for 1:1 propensity score matching because they are the known risk factors for mortality. Although matching may have resulted in cohorts that are different in characteristics from the original cohorts, we believe that matching was necessary to control for variables that may affect the relationship between drug administration and death. It is important to note that although we selected multiple potentially confounding variables for matching, a variable that we did not include could have confounded the relationship between drug treatment and mortality.

TriNetX reports less than 10 outcomes as 10. For example, in this study, the number of patients in cohort 1 (patients treated with tenecteplase) who received blood transfusions within 30 days was found to be 10. However, the actual number of patients who got blood transfusions as a marker of significant bleeding could be anywhere from 1 to 10. This limitation does not affect the conclusions of this study, supporting the superiority of tenecteplase, as having any number less than 10 of cohort 1 patients who got blood transfusions would increase the risk-odds ratio of significant bleeding in the alteplase group over the tenecteplase group.

Table 6. Matched cohort tenecteplase versus alteplase outcomes at 30 days since January 1, 2021.

Outcome	TNK (n = 1,108), %	Alteplase (n = 1,108), %	Risk Ratio (95% CI)
Mortality	6.6	8.9	0.737 (0.549, 0.989)
Intracranial hemorrhage	1.6	3.2	0.507 (0.278, 0.924)

We used blood transfusion as an indirect marker of significant hemorrhage, although this cannot be determined to be as a result of thrombolytic administration. However, this outcome was investigated within 7 and 30 days of thrombolytic treatment, which should limit confounding by other secondary causes of hemorrhage.

The dosages of tenecteplase and alteplase are not documented in our database nor are the exact timings (within minutes) of drug administration. The dosing of tenecteplase has been thoroughly investigated, given some concern for the higher dosage (0.4 mg/kg) leading to the increased incidence of intracranial hemorrhage, in a small cohort of patients and one randomized trial.[10,17] Most patients in the previous meta-analyses for tenecteplase for stroke were treated with 0.25 mg/kg with a maximum of 25 mg,[9,12] and we recommend this dose. However, the inclusion of some patients treated with a higher dose of tenecteplase who were associated with a higher incidence of intracranial hemorrhage without a significant vessel opening benefit may have slightly skewed the intracranial hemorrhage rates in an unfavorable manner against tenecteplase in the 10-year data set.

This study did not investigate improvements in neurologic deficits, long-term neurologic outcomes, or reperfusion rates between these 2 treatment groups because limitations of the database prevented retrieval of these functional outcomes. However, previous meta-analyses published in 2022 have shown better revascularization rates and improved functional outcomes, by metrics such as the Modified Rankin Scale,[9,12] supporting the benefit of tenecteplase over alteplase for stroke.

Tenecteplase use is relatively novel relative to alteplase, which has been FDA-approved for acute stroke therapy since 1996. It is possible that some factors in treatment may have imbalanced the cohorts because of the recent increase in recommendations and use of tenecteplase for acute ischemic stroke. It is also much more likely that most tenecteplase use has been in recent years because the AHA guidelines endorsing tenecteplase use are relatively recent. However, we attempted to address this possibility of imbalance through the subgroup analysis of a more recent cohort that did not show marked differences in the outcomes. Other factors that we are unable to report that may influence results to include the number of large vessel occlusions that caused acute ischemic stroke in the cohort

because these are often treated with thrombectomy in addition to thrombolysis, which may then influence outcomes. In addition to temporal clustering with more tenecteplase use in recent times, there may exist an imbalance in which sites are using tenecteplase for acute ischemic stroke treatment (community versus large academic, rural versus urban) and factors present in that site imbalance may have altered the final outcomes of our study. The increased attention to stroke therapies and interventions in and of themselves in recent years may have lent a Hawthorne effect to patient care and altered outcomes.

DISCUSSION

In this multicenter, retrospective study, tenecteplase may demonstrate a better safety profile relative to alteplase in the treatment of acute nonhemorrhagic stroke with notably lower mortality rates and decreased bleeding complications, necessitating transfusions at 30 days after thrombolysis. Nonhemorrhagic patients with stroke treated with tenecteplase demonstrated comparable intracranial hemorrhage rates with those receiving alteplase in the 10-year data set but statistically lower rates in the 2021 to 2022 data set using a presumed lower dose of tenecteplase. Using TriNetX and the extensive collaborative network allowed an evaluation of the largest known sample size ($n =$ 6,864 after propensity matching) comparing tenecteplase and alteplase. Our 2021 to 2022 subgroup analysis is also larger than any other study currently in the literature. Other smaller meta-analyses have shown that tenecteplase is noninferior to alteplase in efficacy and adverse outcomes.[11,13,15,16]

Previous trials comparing alteplase with tenecteplase have shown mixed results but a trend toward favoring tenecteplase. The intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT) trial showed noninferiority of tenecteplase versus alteplase in a randomized controlled trial of 1,600 patients. The rates of intracranial hemorrhage and mortality were not notably different, and neurologic outcomes trended better in the tenecteplase group.[21] The NOR-TEST trial showed no significant difference between patients with stroke treated with the 2 thrombolytics, but most patients had a relatively low NIHSS stroke score, making it difficult to ascertain treatment effect.[16] Extend-IA tenecteplase showed a mortality benefit and more rapid occlusion resolution in a trial of patients with stroke and large vessel occlusion.[13] Part 2 of that trial showed no differences in the treatment of patients with large vessel occlusion with tenecteplase in a resolution of clot between 0.25 mg/kg and 0.4 mg/kg dosing.[14] Pooled analysis of data from this trial showed higher rates of reperfusion when tenecteplase was compared against alteplase. This outcome is significant given a previous study that was discontinued after a reported increased incidence (3/9 [16%] patients) of symptomatic intracranial hemorrhage with a higher dosage (0.40 mg/kg),[10] although as a result of the small number of patients in this study, their findings did not reach statistical significance. The follow-up randomized study, NOR-TEST, and NOR-TEST 2 confirmed that higher dosing of tenecteplase at 0.4 mg/kg results in unacceptably high intracranial hemorrhage rates.[17] A 2022 systematic review of nonrandomized trials comparing alteplase and tenecteplase totaling 1,820 patients showed no differences in Modified Rankin Scale of 0 to 2 or 0 to 1 at 90 days or intracranial hemorrhage rate. However, they showed faster recanalization of thrombus rates, more rapid improvement in neurologic status, and pooled analysis, suggesting an advantage of tenecteplase over alteplase.[9] A 2022 study showed no significant differences in hemorrhage rates or 90-day functional outcomes but did continue to show significant improvement in reperfusion rates of tenecteplase over alteplase.[21,12]

The ability to administer tenecteplase more rapidly than alteplase has some implications for successful thrombectomy in the time of endovascular intervention for large vessel occlusion (LVO). Bolus dosing may allow patients to go for endovascular thrombectomy earlier with shorter times for vessel opening. One theoretical drawback is that bolus dosing tenecteplase does not provide the opportunity to stop the infusion whether the patient exhibits signs of developing intracranial hemorrhage. However, on the basis of our lower rates of intracranial hemorrhage in the 2021 to 2022 tenecteplase subgroup, this does not seem to be a clinically significant issue. This may reflect a broader treatment with thrombolytics in patients who may not have as severe infarcts or present with stroke mimics.

In this study, the rates of intracranial hemorrhage as a complication of intravenous administration of alteplase for stroke are comparable with those of other investigations of tenecteplase and alteplase, although we evaluated slightly different timeframes, and definitions of intracranial hemorrhage vary in these studies. We found rates of intracranial hemorrhage of 3.0% and 3.2% in the alteplase group at 30 days. The National Institute of Neurological Disorders and Stroke (NINDS) study found a 6% rate of symptomatic intracranial hemorrhage and a 3% rate of asymptomatic hemorrhage within 36 hours after alteplase administration. In addition, there were 2.7% more symptomatic hemorrhages in the subsequent 90 days.[22] A more recent randomized controlled trial, the AcT trial demonstrated a rate of intracranial hemorrhage of 3.2% in

the alteplase group, which is in line with our trial.[21] This may reflect a broader treatment with thrombolytics in patients due to increased health care focus on the treatment of acute ischemic stroke.

In summary, this large retrospective multicenter study using real-world evidence found tenecteplase to demonstrate an improved safety profile relative to alteplase in the treatment of acute nonhemorrhagic stroke. Tenecteplase demonstrated a decreased mortality rate, a lower risk of intracranial hemorrhage, and less significant hemorrhage, necessitating transfusions within 30 days of receiving the thrombolytics. In addition, tenecteplase is less expensive and much easier to administer than alteplase. These findings in conjunction with the previous meta-analyses showing better revascularization rates and more neurologic improvement with tenecteplase suggest that we should consider tenecteplase rather than alteplase as the primary thrombolytic drug for stroke.

Supervising editor: William J. Meurer, MD, MS. Specific detailed information about possible conflict of interest for individual editors is available at https://www.annemergmed.com/editors.

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Author contributions: LM, PH, GG, and DJ conceived the concept and design of the study. LM, PH, KP, GG, and DJ supervised the data collection. LM, PH, KP, MT, GG, HS, and DJ undertook data acquisition, analysis, or interpretation of data. GG, DJ, and LM provided statistical advice on study design and analyzed the data. LM, PH, KP, and MT drafted the manuscript, and all authors contributed substantially to its revision. LM takes responsibility for the paper as a whole.

Authorship: All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see *www.icmje.org*). The authors have stated that no such relationships exist. This study was conducted with the support of the Institute for Translational Sciences at the University of Texas Medical Branch, supported in part by a Clinical and Translational Science Award (UL1 TR001439) from the National Center for Advancing Translational Sciences, National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Publication dates: Received for publication October 18, 2022. Revisions received February 6, 2023, and March 9, 2023. Accepted for publication March 20, 2023.

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