Implementation of a Tenecteplase Protocol for Treatment of Acute Ischemic Stroke in a Health System

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Abstract

Purpose. Alteplase is the standard of care for intravenous thrombolytic treatment of acute ischemic stroke, but recent evidence suggests that tenecteplase may be as safe and efficacious. The purpose of this study was to evaluate the direct cost savings, safety, and efficacy outcomes following the implementation of a tenecteplase protocol for acute ischemic stroke in the emergency departments within a health system. *Methods.* A multicenter retrospective medical record review was performed for 4 months prior to protocol implementation on patients who received alteplase and for 4 months post-implementation on patients who received tenecteplase. The primary outcome was the direct cost difference associated with tenecteplase. Secondary outcomes included reduction in National Institutes of Health Stroke Scale 24 hours after thrombolytic therapy, door-to-needle time, symptom onset to intravenous thrombolysis time, incidence of adverse effects, and death. *Results.* Pre-implementation, 102 received alteplase and post-implementation, 117 received tenecteplase. Four months of utilization of tenecteplase resulted in direct cost savings of $209,476.80 for the health system, which translates to roughly $2,000 per patient. Reduction in the National Institutes for Health Stroke Scale were similar between the two groups with -3.96 in alteplase and -3.18 in tenecteplase (p = 0.952). Median door-to-needle time was 44.5 minutes in alteplase and 49 minutes in tenecteplase. Adverse events occurred in 19 patients in alteplase and 19 in tenecteplase (p = 0.573). Death occurred in 9 patients in alteplase and 14 patients in tenecteplase (p = 0.376). *Conclusion.* A tenecteplase protocol was successfully implemented in the healthcare system resulting in direct cost savings with no significant differences in adverse events.

Keywords: tenecteplase, alteplase, thrombolytics, acute ischemic stroke, cost savings

Introduction

Stroke ranked fifth among all causes of death in the year 2020 and is also a leading cause of long-term disability in the United States. Stroke also presents a large economic burden in the United States. In the United States from 2019 to 2020, the direct and indirect costs of stroke was $56.2 billion, with an estimated direct medical cost of $34.5 billion.

Alteplase is currently the only Federal Drug Administration (FDA)-approved thrombolytic for the treatment of acute ischemic stroke (AIS)[2]. While alteplase improves the chances of long-term functional outcomes from AIS, it has several limitations including a short half-life, a two-step dosing regimen comprised of an initial bolus followed by a one-hour continuous infusion, and ensuring the full dose was administered if transferred to a higher level of care. Tenecteplase is a recombinant tissue-type plasminogen activator that is more fibrin-specific and has a longer duration of action compared to alteplase. Tenecteplase's pharmacokinetic profile allows for easier administration as a single bolus injection, and potentially allows for improvement in door to needle times[3-5]. Compared to alteplase, dosing calculations for tenecteplase are simpler with no pump-related issues[6]. Tenecteplase is currently off-label for treatment of AIS; however, there are several studies published with updates to the American Heart Association stroke guidelines supporting the use of tenecteplase for AIS[3,5,6].

Current clinical evidence has shown tenecteplase to be noninferior to alteplase for the treatment of AIS and may have a safer side effect profile. The Burgos *et al*[3] meta-analysis of five randomized controlled trials found tenecteplase to be noninferior to alteplase for the treatment of AIS. The Katsanos *et al*[7] meta-analysis concluded that patients with large vessel occlusion receiving tenecteplase have three-fold higher odds of achieving successful recanalization and two-fold higher odds of having favorable clinical outcomes at three months compared to patients receiving intravenous alteplase. Previous trials that compared alteplase and tenecteplase looked at various outcomes, which included door-to-needle-time, change in the National Institutes of Health Stroke Scale (NIHSS) from baseline to 24 hours post thrombolytic, incidence of hemorrhagic conversion and adverse effects[2,8,9].

Transitioning to tenecteplase represented a potential cost minimization opportunity for the Mercy Health System compared to alteplase. This study was conducted at six hospitals within Mercy, which is a large health system consisting of more than 40 specialty and acute care/critical access hospitals. There was a roughly $2,000 direct cost difference for a 50 mg tenecteplase vial compared to a 100 mg alteplase vial. The purpose of this study was to retrospectively review the direct cost minimization, safety, and efficacy of implementing a tenecteplase protocol for the treatment of AIS.

Methods

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Study Locations. Mercy is a large health system with 44 acute care, critical access and specialty hospitals providing care across four states, including Arkansas, Kansas, Missouri, and Oklahoma. The six sites that implemented the tenecteplase protocol on November 30, 2022, included two level 1 comprehensive stroke centers with 24/7 in-person neurological response and four community hospitals and their associated stand-alone/critical access emergency departments that connected remotely with tele-neurologists for recommendations on patients presenting with AIS symptoms[9].

Pre-implementation Alteplase Protocol. At each Mercy location, neurological deficits were measured using the NIHSS. Baseline NIHSS scores were completed by the consulted neurologist, and the NIHSS scores at 24 hours were assessed by either a nurse, neurologist, or the attending physician. In the emergency department, if the consulted neurologist determined the patient to be eligible for intravenous thrombolysis the patient would receive alteplase. The standard dosing for alteplase for AIS was 0.9 mg/kg to a maximum of 90 mg with a 10% bolus followed by a 90% continuous infusion. The max bolus was 9 mg with a maximum dose of 81 mg for the continuous infusion dose. Mercy Hospital obtained 100 mg vials of alteplase, therefore no more than one vial of alteplase was used per patient.

Tenecteplase Protocol Standardization. From August 2022 to November 2022, several multidisciplinary teams across the health system consisting of pharmacists, neurologists, physicians, stroke coordinators and nursing supervisors collaborated on a health-system wide standardization initiative aimed at transitioning from alteplase to tenecteplase for treatment of AIS. The pharmacy and therapeutics committee and medication safety committee discussed safety concerns regarding the myocardial infarction dosage labeling on the tenecteplase manufacturer packaging. The health system decided that the tenecteplase for AIS kits would be stored in high alert medication bags in the Omnicell and would include a 10 ml syringe, 5 ml syringe, tenecteplase 50 mg vial, 10 ml sterile water for reconstitution, an 18-gauge needle, and a dosing and administration card for tenecteplase presented in figure 1. The protocol was implemented at six hospitals within the health system on November 30, 2022.

Post Implementation Tenecteplase Protocol. The standard workflow for assessing a patient utilizing the NIHSS score and determining eligibility for intravenous thrombolysis was the same for tenecteplase as it was for alteplase. The standard dosing of tenecteplase for AIS was a single bolus of 0.25 mg/kg with a maximum dose of 25 mg. Mercy Health System obtained 50 mg vials of tenecteplase, therefore no more than one vial was used per patient.

Study Design. This was a multi-center retrospective quality improvement study exempt from full Mercy Investigational Review Board (IRB) review spanning July 1, 2022, through March 31, 2023. This pre- and post-implementation quality improvement evaluation within a health system was designed to assess the impact of a protocol for tenecteplase for AIS on direct costs, safety, and efficacy. Pre-implementation data for alteplase administration was collected from July 1, 2022, through October 31, 2022, and post-implementation data was collected for tenecteplase administration from December 1, 2022, to March 31, 2023. A cost-minimization analysis was conducted over the study period, and direct costs of the intravenous thrombolytic vials were included in cost calculations. Drug product costs were determined from health system purchasing information.

Patients. Patients were included in the study if they were 18 years of age or older and received intravenous thrombolysis for AIS at the emergency departments within the six locations. There was no upper age limit and no restriction based on stroke severity assessed using the patient's NIHSS. Patients were excluded if they received a thrombolytic for an indication other than for AIS, or if they received an intravenous thrombolytic for AIS outside of the emergency department.

Data Collection. Data collected consisted of each patient's age, gender, weight, thrombolytic used and dosage, NIHSS at baseline and 24 hours post thrombolytic therapy, door-to-needle time, symptom onset to intravenous thrombolytic time, adverse events reported within 24 hours and incidence of death within 3 months of thrombolytic therapy.

Outcomes and Data Analysis. The primary outcome of this study was the direct cost minimization associated with the transition to utilizing tenecteplase for AIS. For cost minimization categories direct cost savings was calculated by the difference between the purchase price of alteplase compared to tenecteplase multiplied by the total number of patients in the study period. For Mercy health System, a 100 mg vial of alteplase costs $8,414.90 compared to $6,624.50 for a 50 mg vial of tenecteplase. Secondary efficacy and safety outcomes included changes in baseline NIHSS to 24 hours post thrombolytic, door-to-needle time, symptom onset to intravenous thrombolysis time, incidence of adverse events and death. Door-to-needle time was defined as the time between patient arrival to the emergency department and the time intravenous thrombolytic was administered. Outcomes were limited to 24 hours based on time frames studied in previous trials. Safety events beyond the initial 24-hour time period would be difficult to determine if it were directly caused by the study drug or by other factors from hospitalization. Descriptive statistics were used to present baseline characteristics and outcomes and was presented as mean (standard deviation) and median (interquartile range). For safety outcomes, incidence of bleeding was categorized utilizing the Global Utilization of

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Streptokinase and t-PA for Occluded Arteries (GUSTO) scale of bleeding, with severe or life-threatening bleeding defined as intracranial hemorrhage or requiring substantial hemodynamic compromise requiring treatment; moderate bleeding defined as requiring blood transfusion, but not resulting in hemodynamic compromise, and mild bleeding defined as does not meet other criteria[11]. Baseline characteristics of age and weight were analyzed utilizing independent t-tests. The differences in the NIHSS, door-to-needle time, and symptom onset to intravenous thrombolytic time were analyzed with the use of the Mann-Whitney U test. The differences in adverse events and incidence of death were analyzed utilizing a chi-square test or fisher's exact test, as appropriate. The alpha level for significance was set at <0.05. The analysis of outcomes was not adjusted for multiple comparisons and should be interpreted as exploratory. Sample size was not calculated because this study included all eligible patients for assessing protocol implementation.

Results

Baseline Characteristics. A total of 234 patients received an intravenous thrombolytic at the six hospitals, of which, fifteen patients were excluded for being treated outside of the emergency department or receiving intravenous thrombolytic for an alternative indication (Figure 2). A total of seven patients in alteplase and twelve patients in the tenecteplase group were lost due to follow up for transferring for thrombectomy, lack of coverage or leaving against medical advice (Figure 2). Of the 219 patients that met inclusion criteria, 102 received alteplase and 117 received tenecteplase. Baseline characteristics are presented in Table 1. The mean age was 68 years old and the mean NIHSS at baseline was 8.8 in tenecteplase and 7.9 in alteplase (p = 0.347). There was a statistical difference in median time from symptom onset to intravenous thrombolytic, with 144 minutes in tenecteplase and 125 minutes in alteplase (p = 0.0396). There was no statistical difference in the level of care provided to patients, with 55 in the alteplase and tenecteplase group receiving care provided by tele-neurologists and 47 in the alteplase group and 62 in the tenecteplase group receiving care from in-person neurologists (p=0.307).

Outcomes. Utilizing tenecteplase over four months resulted in a $209,476.80 direct cost savings for the health system. Reduction in NIHSS at 24 hours was not statistically significant with -3.18 in tenecteplase and -3.96 in alteplase (p = 0.952). The average door to needle time in the tenecteplase group was 61 minutes and 52 minutes in alteplase (p = 0.278). Other efficacy outcomes are reported in Table 2.

Safety. Overall adverse events were similar between the two groups with 19 in the tenecteplase group and 19 in the alteplase group (p = 0.573) (Table 3). The number of post- thrombolytic severe bleeding was similar between groups, with 10 in tenecteplase and 11 in alteplase (p = 0.546). Severe bleeding included intracranial hemorrhagic conversion and a single instance of an expanding already present intracranial hemorrhage. There was no difference between mild bleeding, with 7 in tenecteplase and 1 in alteplase (p = 0.0704). Mild bleeding included gingival bleeding, hematemesis, hematuria, hematoma, and lip bleeding. Death occurred in a total of 23 patients, 9 patients who received alteplase compared to 14 patients who received tenecteplase (p = 0.376). Death due to stroke complications was statistically significant, 8 in the tenecteplase group and 1 in the alteplase group (p = 0.0391). Reasons for death due to stroke complications included patients whose family's withdrew care and patients that transitioned to hospice or comfort care and died. In the tenecteplase deaths due to stroke complications, the mean symptom onset to intravenous thrombolytic time was 298.6 minutes and the mean baseline NIHSS was 18.25. In comparison, tenecteplase survivors had a mean symptom onset to intravenous thrombolysis of 178.1 minutes and a mean baseline NIHSS of 8.28. Other safety outcomes are reported in Table 3.

Discussion

The successful transition to tenecteplase from alteplase for the treatment of AIS within a large health system required months of preparation from several multidisciplinary teams and different medical departments.

Four months of utilizing tenecteplase for AIS resulted in a substantial cost savings for the health system. For Mercy health System, a 100 mg vial of alteplase costs $8,414.90 vs $6,624.50 for a 50 mg vial of tenecteplase. No differences were observed in the study for changes in NIHSS score after intravenous thrombolysis. No differences were observed in overall adverse effects. No differences were observed in overall death, but an increase in death in tenecteplase due to stroke complications was observed, which resulted from patients transitioning to comfort care or hospice and withdrawing care.

The increase in deaths due to stroke complications in the tenecteplase group could be explained by the longer symptom onset to intravenous thrombolysis time and the higher mean NIHSS in those eight patients. The mean symptom onset to intravenous thrombolysis time of these eight patients was outside of the recommended 3-4.5-hour symptom onset window to intravenous thrombolysis[5]. In the tenecteplase group, fourteen patients (11.96%) received intravenous thrombolysis outside of the 4.5-hour window. In two of these patients, the consulted neurologist documented that they were hypertensive requiring blood pressure control prior to intravenous thrombolysis. The consulted neurologist documented the reasoning for administering tenecteplase in the other twelve patients as utilizing the Extend Trial and the Wake-Up Trial to support the use of tenecteplase outside of the 4.5-hour window. The Extend Trial found that the use of

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alteplase in patients presenting within 4.5 and 9 hours after onset of stroke symptoms resulted in no or minor neurological deficits compared to placebo[12]. Currently, it remains uncertain whether tenecteplase is of benefit outside of the 4.5-hour window and in patients with wake-up stroke. The Wake-Up Trial showed that patients with wake-up stroke and treated with tenecteplase within 4.5 hours of awakening was not associated with better functional outcome at 90 days as compared to the control group[13]. To determine the efficacy of tenecteplase in this patient population, more research into the use of tenecteplase for AIS outside of the 4.5-hour symptom onset window and in wake-up stroke patients need to be conducted.

There were several limitations to this retrospective data analysis, including the variability in practice at the different hospitals within the health system. Within the health system, some hospitals utilized tele-neurology for recommendations on patients who presented with AIS symptoms, whereas other hospital locations had code stroke teams, with an on-site neurologist, pharmacist, and stroke nurse present at all code stroke alerts. A few of the hospitals within the health system are Level 1 stroke centers that offer mechanical thrombectomies for patients, while other hospitals do not offer this and had to transfer patients for thrombectomies when appropriate. There was a potential for a reporting bias of adverse effects due to the off-label use of tenecteplase for AIS. The researchers did not calculate a sample size to power the study, so the results are meant to be exploratory results. This retrospective data analysis was the limited number of patients in a limited study time period.

Conclusion

A successful transition to a tenecteplase protocol for AIS required multidisciplinary teams to collaborate to conduct medication safety and operation evaluations. The implementation of a tenecteplase protocol for AIS resulted in substantial direct cost savings for the Mercy health system. No significant differences in adverse events and incidence of overall death were observed between the pre-implementation alteplase group and the post-implementation tenecteplase group. Tenecteplase recipients experienced a higher incidence of death due to stroke complications.

Conflicts of Interest: We declare no conflicts of interest or financial interests that the authors or members of their immediate families have in any product or service discussed in the manuscript, including grants (pending or received), employment, gifts, stock holdings or options, honoraria, consultancies, expert testimony, patents, and royalties.

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Figure 1. Tenecteplase for Acute Ischemic Stroke: Reconstitution and Administration Dosing Card

Tenecteplase for Acute Ischemic Stroke: Reconstitution and Administration

1. WITHDRAW 10 mL of sterile water using a 10 mL syringe.

Use only the diluent provided in this kit

2. INJECT 10 mL sterile water into the TNKase (Tenecteplase) vial, directing the diluent at the powder. Slight foaming is common.

3. GENTLY SWIRL until contents are completely dissolved. **DO NOT SHAKE.** Reconstitution should be complete in approximately 1 minute. Solution should be colorless or pale yellow and transparent. USE UPON RECONSTITUTION.

4. INSPECT the solution visually for particulate matter or discoloration. **WITHDRAW** the appropriate volume of solution based on patient weight using the **5 mL syringe**. Discard solution remaining in the vial.

5. PRECIPITATION may occur when TNKase (Tenecteplase) is administered in an IV line containing dextrose. *To prevent precipitation, flush a dextrose-containing line with a saline-containing solution* prior to and following single-bolus administration of TNKase.

6. ADMINISTER as an intravenous BOLUS over 5 seconds.

Dose: 0.25 mg/kg
Use actual body weight to calculate dose
Draw up dose in **5 mL syringe**
Maximum dose: 25 mg

Tenecteplase for STROKE Dosing Table

Weight (kg)	Dose (mg)	Vol. to Admin (mL)
38 to 41.9 kg	10 mg	2 mL
42 to 45.9 kg	11 mg	2.2 mL
46 to 49.9 kg	12 mg	2.4 mL
50 to 53.9 kg	13 mg	2.6 mL
54 to 57.9 kg	14 mg	2.8 mL
58 to 61.9 kg	15 mg	3 mL
62 to 65.9 kg	16 mg	3.2 mL
66 to 69.9 kg	17 mg	3.4 mL
70 to 73.9 kg	18 mg	3.6 mL
74 to 77.9 kg	19 mg	3.8 mL
78 to 81.9 kg	20 mg	4 mL
82 to 85.9 kg	21 mg	4.2 mL
86 to 89.9 kg	22 mg	4.4 mL
90 to 93.9 kg	23 mg	4.6 mL
94 to 97.9 kg	24 mg	4.8 mL
98 kg or greater	25 mg	5 mL

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Figure 2: Trial Profile
Screening log of all patients who received a thrombolytic

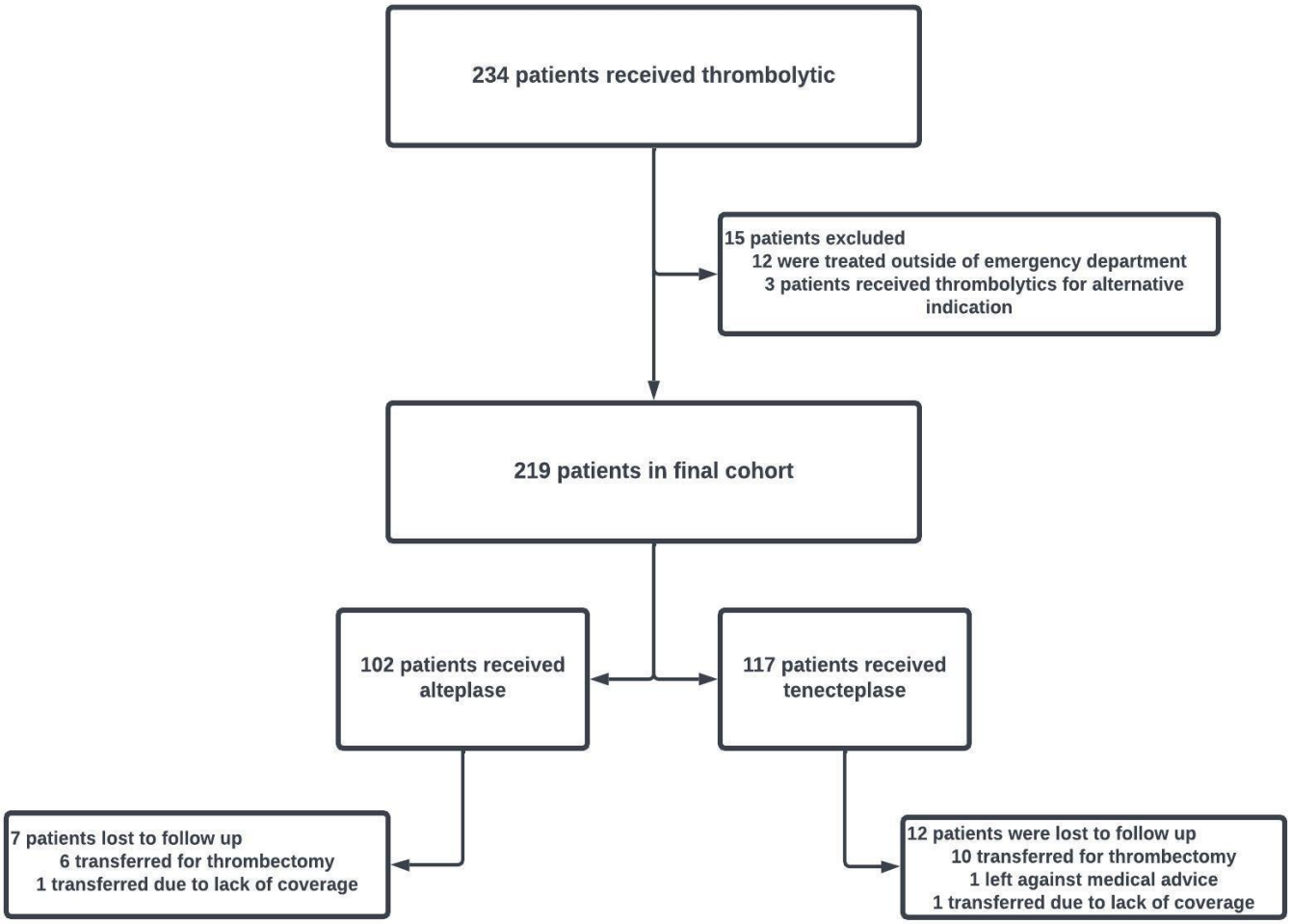

Table 1. Demographic and Clinical Data for Study Cohorts

Characteristic	Alteplase (n =102)	Tenecteplase (n = 117)	p-value
Age -year	69 ± 16.96	67 ± 16.38	p = 0.617
Gender – male No. (%)	50 (51)	65 (54)	p= 0.334
Weight (kg)	85 ± 22.33	90 ± 28.26	p = 0.139
Baseline NIHSS	7.9 ± 6.28	8.8 ± 7.07	p = 0.347
Median time from stroke onset to initiation of intravenous thrombolytic - minutes[b]	125 (85.25, 180.5)	144 (106.75, 205.25)	p=0.0396
Neurology Service Type			
Tele-neurology	55	55	p = 0.307
In-person neurology	47	62	p= 0.307

Abbreviations: NIHSS, National Institutes for Health Stroke Scale
[a]all data are mean (SD) unless otherwise indicated
[b]Reported as median and interquartile range

Table 2. Efficacy Outcomes in Patients Treated with Thrombolytic for Acute Ischemic Stoke Before and After Protocol Implementation

	Alteplase (n = 102)	Tenecteplase (n = 117)	p-value
24 Hour NIHSS	3.5 ± 6.18	5.2 ± 8.72	p = 0.704
Change in NIHSS	- 3.96 ± 5.41	-3.18 ± 8.43	p = 0.952
Median Door to Needle Time – minutes[b]	44.5 (34, 68)	49 (33, 76.25)	p=0.278

Abbreviations: NIHSS, National Institutes for Health Stroke Scale
[a]all data are mean (SD) unless otherwise indicated
[b]Reported as median and interquartile range

Table 3. Safety Outcomes in Patients Treated with Thrombolytic for Acute Ischemic Stoke Before and After Protocol Implementation

	Alteplase (n = 102)	Tenecteplase (n = 117)	p-value
Adverse Events			
Total	19	19	p = 0.573
Angioedema	7	3	p = 0.194
Bleeding[a]	12	17	p = 0.546
Severe Life Threatening	11	10	p = 0.575
Moderate	0	0	n/a
Mild	1	7	p = 0.0704
Death			
Total	9	14	p = 0.376
Hemorrhagic Conversion	4	2	p = 0.201
Stroke Complications	1	8	p = 0.0391
Other causes[b]	4	4	p = 1.00

[a]Severity of bleeding defined by the Global Utilization of Streptokinase and t-PA for Occluded Arteries (GUSTO) scale of bleeding, with severe or life-threatening bleeding defined as intracranial hemorrhage or requiring substantial hemodynamic compromise requiring treatment; moderate bleeding defined as requiring blood transfusion but not resulting in hemodynamic compromise; mild bleeding as defined as does not meet other criteria.
[b]Other causes of death included pneumonia, pulmonary embolism, heart failure complications, cardiac arrest, and unknown

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