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Claire Mary Rose King

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The Thesis Committee for Claire Mary Rose King

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Cost Analysis: Switching from Alteplase to Tenecteplase for Management of Acute Ischemic Stroke

APPROVED BY

SUPERVISING

COMMITTEE:

Karen Rascati, Supervisor

James Wilson, Co-Supervisor

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Claire Mary Rose King

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Dedication

I would like to dedicate my thesis to my husband Alex, and son's Jaxson and Nash who gave me a purpose and never allowed me to give up.

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Abstract

Cost Analysis: Switching from Alteplase to Tenecteplase for Management of Acute Ischemic Stroke

Claire Mary Rose King, MSPS

The University of Texas at Austin, 2021

Supervisors: Karen Rascati and James Wilson

Background: Acute ischemic stroke (AIS) occurs due to obstructed blood flow into blood vessels to the brain and is considered a medical emergency. Thrombolytic therapy is the mainstay of AIS's acute management due to its benefit in improving neurological function within three months. Alteplase is a tPA approved for the treatment of AIS and is widely studied. Tenecteplase is another tPA approved for the treatment of Acute Myocardial Infarction (AMI) but not AIS. Although tenecteplase is not FDA-approved for AIS, it has theoretical advantages over alteplase, such as cost savings.

Methods: Estimated cost savings in the form of avoided costs due to a reduction in hospital days, ICU days, emergency department (ED) visits and tPA costs as a consequence of moving from the current standard of care (SoC), alteplase, to the new drug scenario, tenecteplase, for patients with AIS were analyzed based on hospital claims data.

Results: A total of 336 patients received alteplase (n = 166) or tenecteplase (n = 170) between August 2018 to August 2020. There was no significant difference in the hospital, ICU, inpatient and emergency department (ED) length of stay between the tenecteplase and alteplase groups. The estimated annual savings to Ascension for switching from tenecteplase to alteplase for the management of AIS was $563,001. The cost per patient was lower for patients treated with tenecteplase ($9,969) then alteplase ($13,054), resulting in a savings of $3,065 per patient.

Conclusions: Tenecteplase is less expensive, easier to dose and administer, and may have less adverse events such as bleeding complications than alteplase. Thus, hospitals should consider using tenecteplase rather than alteplase for thrombolysis of acute ischemic stroke.

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Chapter 1: Introduction

BACKGROUND

Acute ischemic stroke (AIS) occurs due to obstructed blood flow into blood vessels to the brain and is considered a medical emergency.[1] In the U.S., the prevalence of AIS is 3% of adults, or about 7 million Americans. Approximately 800,000 primary (first-time) and secondary (recurrent) strokes occur each year in the United States (U.S.), with roughly 75% being primary strokes. Of those who suffer from a primary stroke, approximately 87% are ischemic infarctions caused by blocked blood vessels, 10% are intracerebral hemorrhages caused by bleeding inside the brain, and 3% are subarachnoid hemorrhages caused by bleeding in the area that surrounds the brain.[2]

Several modifiable and non-modifiable risk factors apply to primary and secondary stroke. Modifiable risk factors can be managed. People with modifiable risk factors are at a low risk of stroke, since these can be changed with lifestyle modifications, or controlled with medical management.[2] Non-modifiable risk factors, which cannot be controlled or changed, put patients at a high risk of stroke.[2] Several major modifiable risk factors for AIS include hypertension, hyperlipidemia, diabetes mellitus, tobacco use, as well as antithrombotic therapy. Management of these risk factors helps prevent primary and secondary strokes.[3] Non-modifiable risk factors include age, sex, and race.[2] For example, stroke is 24% to 30% higher in men.[2] Individuals of Asian, African, and Latin American descent tend to have a higher frequency of stroke than those of European descent. Lastly, the incidence of stroke rapidly increases with age, doubling for each decade after the age of 55 years.[2]

The Food and Drug Administration approved the recombinant tissue-type plasminogen activator (tPA), alteplase, for AIS in 1996. It is the only FDA-approved

thrombolytic therapy for AIS in the U.S. Alteplase is an efficacious treatment for stroke and has been shown to improve outcomes.[4] Its safety and efficacy is reviewed in more detail later in this chapter. Additionally, significant emphasis is placed on early evaluation and thrombolysis with alteplase for the management of AIS. Delays in starting the infusion in the setting of AIS may result in lower serum concentrations, which could decrease thrombolysis effectiveness, leading to poor outcomes.[5] As a result, poor outcomes may increase health care costs to the patient and the health care system.

AMERICAN HEART ASSOCIATION (AHA) AIS GUIDELINES

Thrombolytic therapy is the mainstay of acute management for AIS due to its benefit in improving neurological function within three months. The American Heart Association (AHA) recommends intravenous (IV) alteplase for eligible patients with mild but disabling stroke symptoms who can be treated within 3 hours of symptom onset (COR: I; LOE: BR; Table 1.1). Intravenous alteplase may also be reasonable for patients treated within 3 to 4.5 hours of symptom onset. For severe stroke, IV alteplase is indicated within 3 hours of symptom onset.[6]

Although IV alteplase is recommended for the treatment of AIS, it is not recommended in some patients, including those with a mild non-disabling stroke even if they are within the recommended time window of 0 to 3 hours or 3 to 4.5 hours. It also should not be administered to patients with an active intracranial hemorrhage or a history of an intracranial hemorrhage or subarachnoid bleeding. Additionally, patients should not receive alteplase if they have had intracranial or intraspinal surgery, ischemic stroke, or severe head trauma within the last three months.[6]

The 2019 AHA Guidelines for management of AIS also state that it may be reasonable to choose IV tenecteplase (single IV bolus of 0.25 mg/kg, maximum 25 mg)

over IV alteplase in patients without contraindications for IV fibrinolysis (COR: IIb; LOE: B-R). The guidelines also recommend considering IV tenecteplase, administered as a 0.4 mg/kg single IV bolus, as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion (COR: I; LOE: B-R). This dose has not been shown to be superior or non-inferior to alteplase.[6]

Table 1.1 Treatment of AIS: IV Administration on Alteplase[6]

Infuse 0.9 mg/kg (maximum dose 90 mg) over 60 min, with 10% of the dose given as a bolus over 1 min.
Admit the patient to an intensive care or stroke unit for monitoring.
If the patient develops severe headache, acute hypertension, nausea, or vomiting or has a worsening neurological examination, discontinue the infusion (if IV alteplase is being administered) and obtain emergency head CT scan.
Measure BP and perform neurological assessments every 15 minutes during and after IV alteplase infusion for 2 hours, then every 30 minutes for 6 hours, then hourly until 24 hours after IV alteplase treatment.
Increase the frequency of BP measurements if SBP is > 180 mmHg or if DBP is > 105 mmHg; administer antihypertensive medications to maintain BP at or below these levels.
Delay placement of nasogastric tubes, indwelling bladder catheters, or intraarterial pressure catheters if the patient can be safely managed without them.
Obtain a follow-up CT or MRI scan at 24 hours after IV alteplase before starting anticoagulants or antiplatelet therapy.

BP – Blood Pressure; SBP – Systolic Blood Pressure; DBP = Diastolic Blood Pressure; CT – computed tomography; MRI – Magnetic resonance imaging

IV ALTEPLASE: SAFETY AND EFFICACY IN THE SETTING OF AIS

Alteplase is a tPA approved for the treatment of AIS. When introduced into systemic circulation at recommended doses, it binds to fibrin in a thrombus and converts the entrapped plasminogen to plasmin. This initiates local fibrinolysis. However, the conversion of plasminogen is limited in the absence of fibrin. Alteplase rapidly clears from the plasma with an initial half-life of fewer than 5 minutes. The most common side effect

of alteplase is bleeding. In clinical studies in patients with AIS, intracranial hemorrhage was higher in the alteplase treated group than in the placebo group. A dose-finding study suggested that doses greater than 0.9 mg/kg may be associated with an increased incidence of intracranial hemorrhage.[7]

Alteplase in the setting of AIS has been widely studied. Two placebo-controlled, double-blinded trials in patients with AIS led to the approval of alteplase in the U.S. Both studies enrolled patients with neurological deficient who could complete screening and begin study treatment within 3 hours from symptoms onset. Patients were randomized 1:1 to either the alteplase (0.9 mg/kg) or placebo group. Alteplase was administered as a 10% initial IV bolus over 1 minute, followed by the reminding dose administered as continuous IV infusion over 60 minutes.[7]

The first study enrolled 291 patients and evaluated neurological improvement at 24 hours after stroke onset. The primary endpoint was the proportion of patients with 4 points or greater improvement in the National Institutes of Health Stroke Scale (NIHSS) score or complete recovery. The level of stroke severity measured by the NIHSS system is no stroke (score of 0), minor stroke (score between 1 and 4), moderate stroke (score between 5 and 15), moderate to severe stroke (score between 15 to 20) and severe stroke (21 to 42). There was not a significant difference in the primary outcome between the treatment groups.[7]

The second study enrolled 333 patients and assessed clinical outcomes at three months. A favorable outcome (defined per scale in parenthesis) was defined as minimal or no disability using four stroke assessment scales: the Barthel Index (score of 95 or greater), the Modified Rankin Scale (score of 1 or less), the Glasgow Outcome Scale (score of 1), and the NIHSS (score of 1 or less). The results comparing alteplase and placebo-treated patients for the four outcomes together and individually are presented in Table 1.2. Depending on the scale, the favorable outcome of minimal or no disability occurred in at

least 11 per 100 more patients treated with alteplase than those receiving placebo. Study results demonstrated functional and neurological improvement within all four stroke scales.[7]

Lastly, alteplase is contraindicated in situations where the risk of bleeding is greater than the potential benefit. These situations include current intracranial hemorrhage, subarachnoid hemorrhage, active internal bleeding, intracranial or intraspinal surgery, severe head trauma within the past three months, presence of intracranial conditions that may increase the risk of bleeding, bleeding diathesis, and current severe uncontrolled hypertension.[7]

Table 1.2. Study 2 Efficacy Outcomes at Three-Months[7]

	Frequency of Favorable Outcomes[a]				
Analysis	Placebo n=165	Alteplase n=168	Absolute Differences (95% CI)	Odds Ratio[b] (95% CI)	p-Value
Barthel Index	37.6%	50.0%	12.4% (3.0, 21.9)	1.66 (1.07, 2.57)	0.02
Modified Rankin Scale	26.1%	38.7%	12.6% (3.7, 21.6)	1.79 (1.12, 2.87)	0.02
Glasgow Outcome Scale	31.5%	44.0%	12.5% (3.3, 21.8)	1.71 (1.09, 2.68)	0.02
NIHSS	20.0%	31.0%	11.9% (2.6, 19.3)	1.79 (1.06, 2.96)	0.02

a. Favorable outcome is defined as recovery with minimal or no disability
b. Value greater than 1 indicates odds of recover in favor of alteplase treatment

SHORTCOMINGS OF IV ALTEPLASE

Shortcomings of IV alteplase include delayed drug administration, dosing errors, and an increased risk of bleeding. Another drawback is the lack of appropriately trained or certified staff needed to correctly administer alteplase.

Due to alteplase's short half-life, a loading dose followed by continuous infusion is necessary to achieve adequate concentrations. Delays in drug administration are a concern with the alteplase dosing regimen. Delays result in lower serum concentrations, which can have a subsequent effect on clinical outcomes. One study investigated delays in alteplase administration and the effect on serum plasma concentrations of alteplase. It determined that administration of alteplase infusion > 5 minutes after initial bolus dose resulted in significantly decreased serum plasma concentrations of alteplase and concluded that alteplase infusion should be given immediately after the initial bolus does to maintain therapeutic plasma concentrations.[8] A second study conducted by Acheampong et al. observed the clinical outcomes associated with delays in alteplase bolus dose and continuous infusion. The study found that an infusion delays of > 8 minutes resulted in lower independent functional outcomes and higher mortality but the difference was not statistically significant, likely due to the small sample size.[9]

Additionally, dosing errors related to alteplase therapy for the management of AIS are documented in literature. The primary reason for dosing errors of alteplase is inaccurate weight records (recall that alteplase is dosed by weight). A single-center retrospective study found that the majority of patients evaluated had estimated weights used to dose alteplase. These patients were more likely to be obese, older, have impaired consciousness on admission, and have a longer door to needle times.[10] Another observational study based on a retrospective chart review also found that most patients who received alteplase were

dosed based on estimated weights, concluding that patients who were not weighed in the hospital had significantly greater NIHSS scores on admission and increased mortality.[11]

While alteplase has been shown to benefit some patients who presented with acute stroke symptoms within 4.5 hours, its administration increases the patients' risk of intracranial hemorrhage. The PRISMS trial was terminated before reaching its enrollment goals. However, it found that alteplase treatment did not improve neurologic outcomes at 90 days compared to aspirin for minor strokes.[11] Additionally, a study by Wee et al. found no benefit in administering alteplase to patients undergoing endovascular thrombectomy for acute stroke due to larger vessel occlusion as compared to thrombectomy alone.[11] However, this was based on a small sample of patients.

Lastly, many tertiary care facilities involve trained clinical pharmacists in stroke protocols. It has been shown that the involvement of a clinical pharmacist has reduced door-to-needle time significantly in the setting of AIS.[12] However, staffing of clinical pharmacists may not be feasible in smaller or rural hospitals. Also, the alteplase drip administration requires an IV pump, which not all emergency medical technicians are qualified to manage. This can cause a delay in dosing or complicate a patient's interfacility transfer.[12]

TENECTEPLASE FOR THE MANAGEMENT OF AIS

Tenecteplase is a tPA that has been approved for the treatment of Acute Myocardial Infarction (AMI), but not AIS. Currently, tenecteplase is undergoing a pilot evaluation as part of a study funded by the National Institutes of Health for AIS.[13] Although tenecteplase is not FDA-approved for AIS, it has theoretical advantages over alteplase. For example, it has greater fibrin specificity and a longer half-life than alteplase.[14] These pharmacologic differences allow tenecteplase to be administered as a bolus rather than a bolus followed

by continuous infusion. It should be noted that current evidence suggests that 0.25 mg/kg (maximum dose of 25 mg) is the optimal dose. Additionally, the use of tenecteplase does not require a pump, which would simplify the administration of thrombolytics.

Lastly, because the human nervous tissue is rapidly lost as stroke progresses there is a great deal of emphasis on achieving rapid door-to-needle times for thrombolytics. However, although the door-to-thrombolytic initiation time is important, and is generally tracked as a quality measure, the door-to-thrombolytic completion time may be more important to assess.[12] A patient who is given tenecteplase will have a one-hour faster door-to-thrombolytic completion time than if they were given alteplase.[12]

EFFICACY- IV TENECTEPLASE COMPARED WITH IV ALTEPLASE AFTER AIS

Five randomized controlled trials compared IV alteplase and IV tenecteplase for use in acute ischemic stroke. These studies evaluated improvements in neurologic function after an AIS.

In 2010, Haley et al. published results from a small, multicenter, randomized, double-blind trial of 112 patients with AIS within 3 hours of symptoms onset. They compared tenecteplase 0.1 milligrams per kilogram (mg/kg), tenecteplase 0.25 mg/kg, tenecteplase 0.4mg/kg, to standard-dose alteplase (0.9 mg/kg). The trial was terminated because of slow enrollment. Patients in the tenecteplase 0.4 mg/kg group had the lowest rate of good neurological outcomes at three months. There were no statistically significant differences among the other groups, but there was a trend towards higher percentages of patients having good neurologic outcomes in the tenecteplase 0.1 mg/kg (45.2%) and 0.25 mg/kg (48.4%) groups as compared to the alteplase group (41.9%).[15]

In 2012, Parsons et al. published a study that randomized 75 patients with AIS less than six hours after onset of symptoms to tenecteplase 0.1 mg/kg, tenecteplase 0.25 mg/kg,

or standard-dose alteplase. Twenty-five patients were enrolled in each group. Patients treated with tenecteplase had significantly greater reperfusion on imaging studies and clinical improvement (P <0.001) at 24 hours than the alteplase treated group. The higher dose of tenecteplase, in this case, the 0.25 mg/kg dose, had superior outcomes compared to those receiving alteplase for all efficacy outcomes, including serious disability, at 90 days (72 % vs. 40% with alteplase, P = 0.02).[16]

In 2015, Huang et al. published the results from a single-center, phase 2, prospective, randomized trial that compared tenecteplase 0.25 mg/kg to standard-dose alteplase for patients with AIS within 4.5 hours of symptom onset. A total of 104 patients were enrolled, with 52 assigned to each group. There was no difference between groups regarding the primary outcome of percentage penumbra salvaged, 68% in each group. Brain cells within the penumbra, a rim of mild to moderately ischemic tissue lying between tissue that is normally perfused and the area in which infarction is evolving, may remain viable for several hours but can die of reperfusion if not established during the early hours of symptom onset.[19] There were also no significant differences in secondary outcomes between groups. Still, the tenecteplase groups tended towards more early neurologic improvement at 24 hours (40% vs. 24%) and a higher percentage of good neurologic outcomes at 90 days (28% vs. 20%).[18]

In 2017, Logallo et al. published the results from a block-randomized study comparing tenecteplase 0.4 mg/kg and standard-dose alteplase for patients with suspected AIS within 4.5 hours or less of symptom onset or within 4.5 hours of awakening with symptoms. A total of 549 patients were randomized to the tenecteplase group, and 551 were randomized to the alteplase group. There were no differences between groups in the primary outcome of good neurologic outcome at 90 days (64% tenecteplase vs. 63% alteplase.[19] The primary outcome was excellent (0-1points) functional outcomes at 3

months measured by modified Rankin Scale (mRS). The mRS is used to measure the degree of disability in patients how have had a stroke, where a score of 0 means no symptoms at all and a score of 1 means no significant disability despite symptoms and the patient is able to carry out all usual duties and activities.

In 2018, Campbell et al. compared tenecteplase 0.25 mg/kg to standard-dose alteplase for patients with AIS symptoms for less than 4.5 hours before thrombectomy. There were 101 patients in each group. There was a statistically significant difference between groups regarding the primary outcome of reperfusion of greater than 50% of the involved ischemic territory or an absence of retrievable thrombus at the time of the initial angiographic assessment. This primary outcome was found in 22% of patients in the tenecteplase group as compared to 10% of those with alteplase. Patients in the tenecteplase also had superior functional neurologic outcomes at 90 days as compared to the alteplase group.[20]

Four meta-analyses have been conducted using the clinical trials described above. All of these meta-analyses reported no statistically significant differences regarding neurologic recovery, and none of the meta-analyses found a difference between tenecteplase and alteplase with regards to mortality.[23-26] However, the meta-analyses by Thelengana et al. and Kheiri et al. reported scientifically improved early neurologic improvement with tenecteplase[22,23]

In summary, five randomized controlled trials have found tenecteplase to be at least as effective or more effective than alteplase for neurologic improvement after acute ischemic stroke. Using the results of those five randomized controlled trials, four separate meta-analyses have been performed, and none of them concluded that alteplase is superior to tenecteplase.

SAFETY- IV TENECTEPLASE COMPARED WITH IV ALTEPLASE AFTER AIS

In addition to efficacy, the clinical trials described above also measured the rates of symptomatic and total intracerebral hemorrhage. Neither of the most recent meta-analysis found statistically significant differences in intracerebral hemorrhage rates between tenecteplase and alteplase, but there were trends toward less intracerebral hemorrhage with tenecteplase (OR 0.81; 95% CI 056 -1.17; p=0.26).[25] However, there is evidence that the 0.4 mg/kg dose of tenecteplase might lead to higher intracerebral hemorrhage rates compared to the preferred 0.25 mg/kg dose.

Considering other adverse bleeding events associated with the administration of alteplase and tenecteplase. Three randomized controlled trials compared tenecteplase to alteplase for patients with acute coronary syndrome and reported major bleeding adverse events.[26-28] The assumption made here is that adverse events in patients with acute coronary syndrome are likely to be similar in patients diagnosed with AIS. The ASSENT-2 trial, which randomly assigned patients with acute myocardial infarction to alteplase or tenecteplase, found that patients who received tenecteplase had reduced rates of non-cerebral bleeding complications (26.43 vs. 28.95%, p= 0.0003).[26] A meta-analysis that included the ASSENT-2 trial and studies by Liang et al. and Binbrek et al. included 17,325 patients and found a statistically significant reduction in major bleeding with tenecteplase as compared with alteplase (RR 0.79; 95% CI 0.69-0.90; p=0.0002).[27-29]

In summary, no statically significant difference has been reported in the available literature in the rates of intracerebral hemorrhage for tenecteplase versus alteplase in patients diagnosed with AIS. The use of tenecteplase was also associated with lower rates of non-cerebral bleeding than alteplase.

COST- IV TENECTEPLASE COMPARED WITH IV ALTEPLASE AFTER AIS

AIS contributes to a large health care burden, accounting for 87% of all strokes, with an estimated 700,000 events annually, in the U.S.. This costs an estimated $22.8 billion in direct health care expenditures in the U.S. annually. By 2030, the direct health care costs are projected to grow to $18 billion.[30] Health care costs will continue to rise, and changing the way care is delivered to AIS patients is critical to mitigating financial outlays.

The usual dose of tenecteplase is less expensive than the usual dose of alteplase, both nationally and internationally, with one study from Nepal stating that alteplase is twice as expensive as tenecteplase ($450 for tenecteplase versus $1000 for alteplase).[31] According to Lexicomp (2021), in the United States, a 50 mg vial of tenecteplase costs $7,500, while a 100 mg vial of alteplase costs $10,500.[32] Given the doses of 0.25 mg up to 25 mg for tenecteplase and 0.9 mg/kg up to 90 mg for alteplase, it is evident that tenecteplase is the less expensive of the two tPAs.[33]

STUDY RATIONALE

Due to the evidence described above and the ease of administration of tenecteplase compared to alteplase, Ascension Texas facilities transitioned from alteplase to tenecteplase as the thrombolytic drug of choice for AIS management in September 2019. In addition to the safety and effectiveness of tenecteplase in AIS, it is also important to consider cost savings implications to a hospital system for using tenecteplase in place of alteplase for patients with AIS.

Chapter 2: Methodology

COST SAVINGS ANALYSIS

Study Objectives and Hypothesis

The aim of this study was to estimate the cost savings associated with the use of tenecteplase compared to alteplase in patients with AIS. The analysis focused on cost savings associated with the following endpoints: (1) Total Hospital days; (2) Intensive Care Unit (ICU) days; (3) Non-ICU hospital days (4) Emergency Department (ED) visits, and (5) Medication costs of tPAs.

The specific null hypotheses of these analyses included:

- $H_0$1.1: The difference in costs avoided for total hospital days between alteplase and tenecteplase cohorts is not statistically significant.
- $H_0$1.2: The difference in costs avoided for ICU days between alteplase and tenecteplase cohorts is not statistically significant.
- $H_0$1.3: The difference in costs avoided for Non-ICU days between alteplase and tenecteplase cohorts is not statistically significant.
- $H_0$1.4: The difference in costs avoided for ED visits between alteplase and tenecteplase cohorts is not statistically significant.
- $H_0$1.5: The difference in costs avoided for medication costs of tPAs between alteplase and tenecteplase cohorts is not statistically significant.

Study Design

Cost savings were estimated in the form of avoided costs for total hospital days, ICU days, Non-ICU days, emergency department (ED) visits and medication of tPA as a

consequence of moving from the current standard of care (SoC), alteplase to the new drug scenario, tenecteplase in the setting of AIS.

The analysis compared costs between two cohorts of patients at Ascension Texas facilities. The first cohort consisted of patients who were diagnosed with AIS and who were eligible to receive alteplase for AIS between September 1, 2018 and August 31,. 2019. The second cohort was made up of patients who were diagnosed with AIS and who received tenecteplase for AIS between September 1, 2019 and August 31, 2020. The same eligibility criteria were applied to both alteplase and tenecteplase per Ascension's AIS protocol. Patients were eligible to receive tenecteplase or alteplase within 4.5 hours of AIS symptom onset, but preferably within 3 hours of symptom onset. Patients with a greater risk of bleeding than potential benefits were not eligible to receive either therapy to treat acute ischemic stroke. These patients included those with current intracranial hemorrhage (ICH); subarachnoid hemorrhage; active internal bleeding; recent (within three months) intracranial or intraspinal surgery or serious head trauma; the presence of intracranial conditions that may increase the risk of bleeding (e.g., some neoplasms, arteriovenous malformations, or aneurysms); bleeding diathesis; or current severe uncontrolled hypertension. Subjects were excluded if they did not receive either medication or did not receive the full dose of either medication.

Outcomes Measured, Definitions, & Data Source

Outcomes and their definitions are found in Table 2.1. The data source for all outcomes measured was Ascension's electronic medical record (EMR) data. Index hospitalizations were defined as the encounter in which the patient was diagnosed with an acute ischemic stroke and received alteplase or tenecteplase. Hospital readmissions were defined as any inpatient stay within 30 or 60 days after the index hospitalization discharge date. Costs estimates per unit of utilization were estimated from previously published literature. Costs were adjusted to 2021 US dollars using the Medical CPI index for all cost except medication costs. Medication costs were reported in 2021 prices.

Table 2.1. Outcome definitions, and data source.

Outcomes measured	**Definition**
Readmissions avoided	The change in the readmission rate at 30 and 60 days from the discharge date of the index admissions, calculated by subtracting the percentage of patients who were readmitted in the tenecteplase group from the percentage readmitted in the alteplase group.
Inpatient Hospital Days Avoided	The change in the inpatient hospital days, calculated by subtracting the average number of inpatient hospital days for patients in the tenecteplase group from the average number of inpatient hospital days in the alteplase group
ICU Days Avoided	The change in ICU days, calculated by subtracting the average number of ICU days for patients in the tenecteplase group from the average number of ICU days in the alteplase group
Non-ICU Days Avoided	The change in non-ICU days, calculated by subtracting the average number of non-ICU days for patients in the tenecteplase group from the average number of non-ICU days in the alteplase group.
Emergency Department Hours avoided	The change in ED hours, calculated by subtracting the average number of ED hours for patients in the tenecteplase group from the average number of ED hours in the alteplase group
Index Admission Costs	The sum of all costs accrued by the patient for the index admission, which includes inpatient, emergency department, and medication costs.

ICU- Intensive Care Unit; ED – Emergency Department

Costs Definitions, Data Sources, and Estimates

Cost definitions and data sources are found in Table 2.2. Estimates of each unit costs are found in Table 2.3.

Table 2.2. Costs Saving Analysis - Costs Definitions and Data Sources

Costs	**Definition**	**Data Source**
Average Total Inpatient Cost	The sum of all costs accrued by the patient while admitted for an inpatient stay, divided by the number of patients. Sum of ICU and non-ICU costs.	Simpson et al. 2012[34] Kramer et al. 2017[35]
Average ICU Cost	The sum of all costs accrued by the patient while admitted in the ICU, divided by the number of patients. Used to estimate total healthcare costs for the encounter.	Kramer et al. 2017[35]
Average Non-ICU Cost	The sum of all costs accrued by the patient while admitted in the non-ICU, divided by the number of patients. Used to estimate total healthcare costs for the encounter.	Simpson et al. 2012[34]
Average Emergency Department (ED) Cost	The sum of all costs accrued by the patient while admitted in the ED, divided by the number of patients. Used to estimate total healthcare costs for the encounter.	Simpson et al. 2012[34]
Average Medication Costs	The sum of all tPA costs accrued by the patient while admitted for an inpatient stay, divided by the number of patients. Used to estimate total healthcare costs for the encounter.	Red Book (AWP, 2021)[36]
Total Health Care Cost	The sum of all costs accrued by the patient for the index admission, which includes inpatient, emergency department, and medication costs, divided by the number of patients	Simpson et al. 2012, Red Book (AWP, 2021)[34,36]

Table 2.3. Costs Saving Analysis - Costs Estimates for Inputs

Cost Input	**Tenecteplase ($)**	**Alteplase ($)**
Tenecteplase (50 mg vial; 2021)[36]	$7,462.63	Not applicable
Alteplase (100 mg vial; 2021)[36]	Not applicable	$10,560.43
Hospital, cost per event -adjusted to 2021 costs		
Non-ICU day[34]	$4,699,16	
ICU day[35]	$18,969.48	
ED Visit[34]	$1,951.12	

STATISTICAL ANALYSIS FOR COST SAVINGS ANALYSIS

Descriptive statistics were performed with continuous variables described using means with standard deviations (SD) or medians with interquartile ranges (IQR) and categorical variables described in frequency with percentages. An $\alpha < 0.05$ was used as the threshold for statistical significance. Data processing, cleaning, and analysis were conducted using Microsoft Excel. This study was approved by the Institutional Review Boards of the University of Texas and Ascension.

Chapter 3: Results

OVERVIEW

Based on the EMR records for Ascension's Texas facilities, 166 patients received alteplase between September 1, 2018 and August 31, 2019, while 170 patients received tenecteplase between September 1, 2019 and August 31, 2020.

DEMOGRAPHICS

The demographic characteristics for the population under study are depicted in Table 3.1. The mean (standard deviation, SD) age of the tenecteplase cohort was 65 years (SD 16) and 59% were male. The mean (SD) age of the alteplase cohort was 66 years (18 SD), and 54% were male. A majority of patients who received tenecteplase (62%) and alteplase (66%) were white. With respect to insurance type, almost half of patients in the tenecteplase cohort (48%) were Medicare beneficiaries, where less in the alteplase cohort (41%) were Medicare beneficiaries.

As expected, hypertension, dyslipidemia, diabetes, and obesity/overweight diagnoses were the four leading comorbid conditions for both populations (Table 3.1). Additionally, 15% and 16% of patients in the tenecteplase and alteplase cohorts, respectively, had a history of a prior stroke.

Table 3.1 Patient Demographic Characteristics by Anti-thrombolytic Therapy

	Alteplase N = 166	**Tenecteplase N = 170**
Age (years) , Mean (SD)	66 (18)	65 (16)
Gender, n (%)		
Female	77 (46)	70 (41)
Male	89 (54)	100 (59)
Race, n (%)		
White	110 (66)	106 (62)
Black	23 (14)	13 (8)
Asian	2 (1)	1 (1)
American Indian	0 (0)	1 (1)
Other	32 (19)	49 (29)
Insurance Type, n (%)		
Medicare	68 (41)	81 (48)
Non-Medicare	73 (44)	62 (36)
Missing	25 (15)	27 (16)
Comorbidities, n (%)		
Dyslipidemia	62 (37)	97 (57)
Family History of Stroke	10 (6)	20 (12)
Obesity/Overweight	55 (33)	90 (53)
Diabetes	40 (24)	66 (39)
CAD	28 (17)	32 (19)
Prior MI	26 (16)	26 (15)
Afib/flutter	32 (19)	29 (17)
Heart Failure	15 (9)	13 (8)
Renal insufficiency	9 (5)	10 (6)
Dementia	0 (0)	5 (3)
Hypertension	101 (61)	107 (63)
Smoker	21 (13)	29 (17)
Depression	17 (10)	23 (14)
Drug/Alcohol Abuse	11 (7)	14 (8)
Previous Stroke	37 (22)	39 (23)

RE-ADMISSION, THROMBECTOMY, AND DISCHARGE DISPOSITION

With respect to readmissions, 9% of patients were readmitted within the first 30 days and 4% were readmitted within 60 days after discharge in the tenecteplase group. In

the alteplase group, 8% of patients were readmitted within the first 30 and 1% were readmitted within 60 days after discharge. (Table 3.2)

With respect to discharge disposition associated with the primary admission, a majority of patients were discharged home in the tenecteplase (40%) and alteplase (43%) cohorts, followed by discharge to another health care facility (34% and 33%, respectively) or acute care facility (21% and 18%, respectively). (Table 3.2)

A small proportion of patients who were admitted for AIS received a thrombectomy during the primary admission for the tenecteplase cohort (15%) and the alteplase cohort (16%). Primary admission is defined as the admission in which the patient was diagnosed with AIS. (Table 3.2)

Table 3.2: Thrombectomy, Re-admission, and Discharge Disposition

	Alteplase N = 166	**Tenecteplase N = 170**
Thrombectomy, n (%)		
Yes	27 (16)	25 (15)
Re-admission, n (%)		
Re-admission (0-60 days)	16 (10)	22 (13)
Re-admission (0-30 days)	14 (8)	16 (9)
Re-admission (31-60 days)	2 (1)	6 (4)
Discharge Disposition		
Home	71 (43)	68 (40)
Hospice	2 (1)	4 (2)
Acute Care Facility	30 (18)	36 (21)
Other Health Care Facility	54 (33)	58 (34)
Expired	8 (5)	3 (2)
Left Against Medical Advice	2 (1)	1 (1)

COST SAVINGS ANALYSIS

There were no significant differences in the hospital, ICU, inpatient or emergency department (ED) length of stay between the tenecteplase and alteplase groups (Table 3.3).

Cost were calculated for each group. The estimated annual savings to Ascension based on switching from tenecteplase to alteplase for the management of AIS was $563,001. The cost per patient was lower for patients treated with tenecteplase ($9,969) then alteplase ($13,054). The per patient savings is $3,086 (Table 3.4) almost entirely due to a reduction of medication costs.

Table 3.3 Healthcare Utilization Outcomes

3	Alteplase N = 166	Tenecteplase N = 170	P-value
Hospital LOS Total days (mean, SD)	7.0 (5.4)	7.0 (5.7)	0.672
ICU LOS, days (mean, SD)	3.5 (3.7)	3.9 (4.3)	0.214
Non-ICU inpatient LOS, days (mean, SD)	3.6 (4.0)	3.1 (3.3)	0.287
Emergency Department LOS, hours (mean, SD)	3.2 (1.7)	3.4 (1.6)	0.161
Emergency Department visits, n (%)	165 (99%)	168 (99%)	-
Vials used, n (%)	166 (100%)	170 (100%)	-

Table 3.4 Total and Per Patient Healthcare Costs

	Alteplase N=166	Alteplase Per patient	Tenecteplase N = 170	Tenecteplase Per patient	Cost Difference
Hospital Cost Total	$ 84,371	$508	$ 90,427	$532	$ 6,056
ICU Cost	$ 67,156	$405	$ 75,286	$443	$ 8,131
Non-ICU Inpatient Cost	$ 17,216	$104	$ 15,141	$89	$ (2,075)
Emergency Department Cost	$ 329,604	$1,986	$ 335,597	$1,974	$ 5,993
tPA Medication Cost	$ 1,753,031	$10,560	$ 1,268,647	$7,463	$ (484,384)
Total	$ 2,167,007	$13,054	$ 1,694,671	$9,969	$ (472,336)

Chapter 4: Discussion

Readmissions are common among AIS patients. In this study, 8% to 9% of patients with AIS were readmitted within 30 days of the primary admission. This is much lower than reported readmission rates by Johnson et al.[39] Johnson et al. reported higher readmission rates of 25% and 39% within 30 days for commercial and Medicare patients, respectively.[39] However, it should be noted that this study did not compare rates between tenecteplase and alteplase, only between Medicare and commercial beneficiaries diagnosed with AIS, it included all patients regardless of insurance status. There could be many reasons for the difference in readmission between our study and that reported in Johnson et al. First is that patients could have been readmitted to another health system and therefore they would not be captured in our study EMR database. Second, is that Johnson et al. may have included more severely ill patients then the current study.

Gao et al. estimated that the use of tenecteplase rather than alteplase across the United States for eligible large vessel stroke patients (69,165 patients per year) would save $366 million USD in acute hospital costs (including avoided thrombolysis and thrombectomy for the first 3 months), with an additional $435 million USD in savings over the lifetime.[38] The current study demonstrated cost savings of tenecteplase over alteplase in patients with ischemic stroke. This was almost entirely due to the reduction of tPA medication costs. Tenecteplase at stroke dosage is less expensive than alteplase. Additionally, our study showed a non-significant reduction in thrombectomy procedures for the tenecteplase cohort versus the alteplase cohort (15% vs. 17%). However, there may be cost savings associated with reduction in in thrombectomy in patients treated with

tenecteplase. Gao et al. reported additional costs savings associated with a reduction in the requirement for thrombectomy procedure in 1 in 10 patients treated with tenecteplase over alteplase.[38]

Although this study did not find any significant differences in units of health-care resource utilization, both short- and long-term health care resources utilization and costs associated with acute ischemic stroke have been reported elsewhere. Johnson et al. reported mean all-cause costs for commercial and Medicare patients the year following an AIS were $61,354 and $44,929, respectively.[41] A large share (50-55%) of these costs occurred more than 30 days after the index admissions. During 31 to 365 days following the admission for AIS, costs were largely attributed to services delivered in the outpatient setting (83% - 85% for AIS related costs; commercial and Medicare, respectively). The cost drivers were increased utilization of various outpatient services, such as outpatient hospital visits, office visits, and rehabilitative therapy. Outpatient services were not incorporated in our study, but it is possible that similar cost savings would accrue.[39]

LIMITATIONS

This study had a number of limitations. First, there may be additional costs associated with treatment of either alteplase or tenecteplase that were not included in this analysis, such as outpatient costs and administration costs. Only costs during the index inpatient stay were included in this analysis. Additionally, and as mentioned above, tenecteplase has greater fibrin specificity and a longer half-life than alteplase. Due to these pharmacologic differences, tenecteplase is administered as a bolus, where alteplase is administer as a bolus followed by a continuous infusion. Also, the administration of

alteplase requires an IV pump, as well as a nurse, technician or pharmacist who is qualified to manage IV pumps. Therefore, the cost associated with the time to administer and to monitor may be different among each tPA and may result in additional costs. This could possibly affect the estimated costs savings associated with the use of tenecteplase. Second, national average costs for non – ICU days and ED visits were based on 2012 Medicare data and inflated to 2021 costs. Third, the costs associated with the avoidance of a dosing error, incident of bleeding and/or recurring episode of stroke were not included in the analysis. Although the costs of treating adverse events could be similar between the two therapies, depending the on the incidence of bleeding, it is important to include the costs within the impact analysis for creditability purposes. Additionally, any reimbursements offered by pharmaceutical manufacturers to the hospital system were not included in the benefit analysis.

Chapter 5: Conclusion

Previous studies have shown that tenecteplase is as effective as alteplase with regards to neurologic improvement after treatment of acute ischemic stroke. Additionally, tenecteplase is less expensive, easier to dose and administer, and may have less adverse events such as bleeding complications than alteplase. Our study used real-world outcomes to estimate differences in healthcare utilization and costs between tenecteplase and alteplase cohorts and found that differences in health care utilization were small and not statistically significant, but costs were about $3,000 lower for the tenecteplase cohort, largely due to the lower cost of the tPA. Thus, hospitals should consider using tenecteplase rather than alteplase for thrombolysis of acute ischemic stroke.

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