PICO Search Assignment Worksheet **Name** Rachel Freundlich

Brief description of patient problem/setting:
74 y/o M was brought in to the ER by EMS due to left lower extremity hemiparesis, left sided facial droop, and aphasia. The stroke team was prepared in the ER when the patient arrived and immediately began a stroke assessment. The pt underwent non-contrast head CT and CTA which both revealed no hemorrhagic concerns. The neurologist present diagnosed the patient with an acute stroke and tenecteplase was given. I learned from the PAs in the room that while alteplase was previously given as an IV drip, tenecteplase is given as an IV push. I wondered if the quick delivery of tenecteplase might also be associated with ease of administration and, more importantly, a shorter door-to-needle time compared to alteplase.

Search Question:
Is tenecteplase associated with shorter door-to-needle time compared to alteplase when treating patients with an acute stroke?

Question Type: What kind of question is this?

☐Prevalence ☐Screening ☐Diagnosis
☐Prognosis ☒Treatment ☐Harms

Assuming that the highest level of evidence to answer your question will be meta-analysis or systematic review, what other types of study might you include if these are not available (or if there is a much more current study of another type)? **Please explain your choices.**

- If meta-analysis and systematic review are not possible to be used, I would look for randomized controlled trials to use due to their high quality of experiments which allow for control groups to be compared to the group receiving the treatment of interest. It also reduces bias which makes it a good study to use. However, it is important to note that blinding is not possible.
- A cohort study can also be used as it looks at the outcomes of two groups that received different treatment / interventions - in this case alteplase compared to tenecteplase.

PICO search terms:

P	**I**	**C**	**O**
Acute stroke	Tenecteplase	Alteplase	Reduced door to needle time
Ischemic stroke	TNK	TPA	Decreased door to needle time
stroke	TNKase	Tissue plasminogen activator	Shorter DTN

Cerebral occlusion			Shorter administration time
Cerebral infarction			

Search tools and strategy used:

Results found:

PubMed:

- Tenecteplase compared to alteplase door to needle time (Best Match) – 208
- Tenecteplase compared to alteplase door to needle time (Best Match, 5 years publication) – 144

Google Scholar:

- TNKase vs TPA door to needle time (Any time, sort by relevance) – 908
- TNKase vs TPA door to needle time (since 2020, sort by relevance) – 301

ScienceDirect:

- tenecteplase reduced door to needle time (any time, best match) – 206
- tenecteplase reduced door to needle time (since 2023, best match) – 20

- The first thing that I did when looking for articles was make sure to use search terms that I felt were generous enough to produce adequate search results as well as specific enough to provide articles that directly answered the question I wanted to answer. After adding filters to narrow down my search results to a number that I felt comfortable sifting through, I began reading the article titles. When an article caught my eye, I would click on it and see where the study took place. If the study was in America, I would read the abstract. I also prioritized studies with a higher level of evidence. With this process I was able to narrow down my articles to the three that I chose to include. I did keep in mind that because my question focuses on newer medical practice it was unlikely that I would be able to find meta analyses that addressed my question.

Results found:

Title: Tenecteplase Improves Door-to-Needle Time in Real-World Acute Stroke Treatment
Citation: Hall J, Thon JM, Heslin M, et al. Tenecteplase Improves Door‐to‐Needle Time in Real‐World Acute Stroke Treatment. *Stroke: Vascular and Interventional Neurology*. 2021;1(1). doi:https://doi.org/10.1161/svin.121.000102
Type of article: Retrospective Cohort

Abstract

Background: We report the interim results of a process improvement initiative at a comprehensive stroke center in which all tPA (tissue-type plasminogen activator)–eligible patients were given tenecteplase for acute ischemic stroke.

Methods: We retrospectively analyzed a prospectively maintained single-center registry of consecutive patients with acute ischemic stroke treated at our comprehensive stroke center emergency department or transferred for further care. Patients treated with alteplase (tPA) before the process improvement initiative (October 2019–April 2020) were compared with those treated with tenecteplase (May 2020–July 2021). The primary efficacy outcome was the Target: Stroke Phase II recommendation of door-to-needle (DTN) time ≤45 minutes. Backward stepwise logistic regression was used to estimate an independent effect of tenecteplase against DTN time ≤45 minutes. Two contemporaneous, negative controls (time to first emergency department antibiotic for patients who presented with infectious symptoms and door-to-groin puncture for thrombectomy) were evaluated to confirm DTN time was unrelated to emergency department and other stroke treatment throughput.

Results: Of the 113 included patients, 53 (47%) received tenecteplase. DTN time was significantly faster in patients treated with tenecteplase (median, 41 [interquartile range, 34–62] minutes versus 58 [interquartile range, 45–70] minutes; $P<0.01$), with no significant difference in symptomatic intracranial hemorrhage (2% versus 7%; $P=0.37$). Despite the higher proportion of tPA patients being transferred for care (with slower DTN time), tenecteplase remained independently predictive of DTN time ≤45 minutes (adjusted odds ratio, 3.96; 95% CI, 1.58–9.91). There was no difference in time to first emergency department antibiotic ($P>0.05$) or door-to-puncture ($P>0.05$) when similar periods were compared.

Conclusions: Tenecteplase was associated with faster DTN time when compared with tPA in those with acute ischemic stroke. This can likely be attributed to the ease of single bolus administration of tenecteplase.

Key points:

- 113 patients were included in the study, 53 of which received tenecteplase and 60 patients received alteplase
- Patients that received alteplase between October 2019-April 2020 were compared to patients that received tenecteplase from May 2020-July 2021
- Door to needle (time that thrombolysis agent is given) for tenecteplase averaged at 41 minutes compared to 58 minutes when alteplase was given.
- Tenecteplase reduced the time from CT to drug given
- Time from arrival to CT did not differ significantly for patients that received tenecteplase compared to alteplase

Why I chose it:

I chose this article because it was published in the last 5 years and it attempts to answer the same question that I am interested in. While many articles include door to needle time in the outcomes they assess, it is not necessarily the main outcome that is being looked at in the research article. Therefore, I was excited to find this article. It is also important that it was conducted in the United States as the research is most applicable to the patients that I will be treating.

Title: Comparative safety of tenecteplase vs alteplase for acute ischemic stroke

Citation:
Flint AC, Eaton A, Melles RB, et al. Comparative safety of tenecteplase vs alteplase for acute ischemic stroke. *J Stroke Cerebrovasc Dis*. 2024;33(1):107468. doi:10.1016/j.jstrokecerebrovasdis.2023.107468

Type of article:
Retrospective Cohort Study

Abstract:
Introduction: Tenecteplase has been compared to alteplase in acute stroke randomized trials, with similar out- comes and safety measures, but higher doses of tenecteplase have been associated with higher hemorrhage rates in some studies. Limited data are available on the safety of tenecteplase outside of clinical trials.
Methods: We examined the safety measures of intracranial hemorrhage, angioedema, and serious extracranial adverse events in a 21-hospital integrated healthcare system that switched from alteplase (0.9 mg/kg, maximum dose 90 mg) to tenecteplase (0.25 mg/kg, maximum dose 25 mg) for acute ischemic stroke.
Results: Among 3,689 subjects, no significant differences were seen between tenecteplase and alteplase in the rate of intracranial hemorrhage (ICH), parenchymal hemorrhage, or volume of parenchymal hemorrhage. Symp- tomatic hemorrhage (sICH) was not different between the two agents: sICH by NINDS criteria was 2.0 % for alteplase vs 2.3 % for tenecteplase ($P = 0.57$), and sICH by SITS criteria was 0.8 % vs 1.1 % ($P = 0.39$). Adjusted logistic regression models also showed no differences between tenecteplase and alteplase: the odds ratio for tenecteplase (vs alteplase) modeling sICH by NINDS criteria was 0.9 (95 % CI 0.33 - 2.46, $P = 0.83$) and the odds ratio for tenecteplase modeling sICH by SITS criteria was 1.12 (95 % CI 0.25 - 5.07, $P = 0.89$). Rates of angioedema and serious extracranial adverse events were low and did not differ between tenecteplase and alteplase. Elapsed door-to-needle times showed a small improvement after the switch to tenecteplase (51.8 % treated in under 30 min with tenecteplase vs 43.5 % with alteplase, $P < 0.001$).
Conclusion: In use outside of clinical trials, complication rates are similar between tenecteplase and alteplase. In the context of a stroke telemedicine program, the rates of hemorrhage observed with either agent were lower than expected based on prior trials and registry data. The more easily prepared tenecteplase was associated with a lower door-to-needle time.

Key points:

- 1,931 patients with an ischemic stroke from October 2018-September 2020 received alteplase
- 1,758 patients received tenecteplase from October 2020 - July 2022
- Imaging was completed 24 hours after initial CT to identify if a hemorrhage was present
- Average door to needle time for alteplase was 33 minutes compared to 30 minutes for tenecteplase
- The percent of patients that received thrombolytic therapy within 60 minutes was 90.2% for alteplase and 92.4% for tenecteplase
- The percent of patients that received thrombolytic therapy within 45 minutes was 76.4% for alteplase and 79.8% for tenecteplase
- The percent of patients that received thrombolytic therapy within 30 minutes was 43.5% for alteplase and 51.8% for tenecteplase

Why I chose it:
I chose this article because it was published in 2023 which allows the research to be up to date. The use of tenecteplase is still developing and I like that it includes such recent data. This article is also based in the US which makes its information relevant. Lastly, although door to needle time was not the only outcome assessed in this paper, the article provides a helpful table which breaks down the mean difference in door to needle time between alteplase and tenecteplase as well as at 30, 45, and 60 minute divisions.

Title: Prospective Observational Cohort Study of Tenecteplase Versus Alteplase in Routine Clinical Practice

Citation:
Warach SJ, Dula AN, Milling TJ, et al. Prospective Observational Cohort Study of Tenecteplase Versus Alteplase in Routine Clinical Practice. *Stroke*. 2022;53(12):3583-3593. doi:10.1161/STROKEAHA.122.038950

Type of article:
Prospective observational cohort study

Abstract
Background: A 10-hospital regional network transitioned to tenecteplase as the standard of care stroke thrombolytic in September 2019 because of potential workflow advantages and reported noninferior clinical outcomes relative to alteplase in meta-analyses of randomized trials. We assessed whether tenecteplase use in routine clinical practice reduced thrombolytic workflow times with noninferior clinical outcomes.
Methods: We designed a prospective registry-based observational, sequential cohort comparison of tenecteplase- (n=234) to alteplase-treated (n=354) stroke patients. We hypothesized: (1) an increase in the proportion of patients meeting target times for target door-to-needle time and transfer door-in-door-out time, and (2) noninferior favorable (discharge to home with independent ambulation) and unfavorable (symptomatic intracranial hemorrhage, in-hospital mortality or discharge to hospice) in the tenecteplase group. Total hospital cost associated with each treatment was also compared.
Results: Target door-to-needle time within 45 minutes for all patients was superior for tenecteplase, 41% versus 29%; adjusted odds ratio, 1.85 (95% CI, 1.27–2.71); *P*=0.001; 58% versus 41% by Get With The Guidelines criteria. Target door- in-door-out time within 90 minutes was superior for tenecteplase 37% (15/43) versus 14% (9/65); adjusted odds ratio, 3.62 (95% CI, 1.30–10.74); *P*=0.02. Favorable outcome for tenecteplase fell within the 6.5% noninferiority margin; adjusted odds ratio, 1.26 (95% CI, 0.89–1.80). Unfavorable outcome was less for tenecteplase, 7.3% versus 11.9%, adjusted odds ratio, 0.77 (95% CI, 0.42–1.37) but did not fall within the prespecified 1% noninferior boundary. Net benefit (%favorable– %unfavorable) was greater for the tenecteplase sample: 37% versus 27%. *P*=0.02. Median cost per hospital encounter was less for tenecteplase cases ($13 382 versus $15 841; *P*<0.001).
Conclusions: Switching to tenecteplase in routine clinical practice in a 10-hospital network was associated with shorter door-to-needle time and door-in-door-out times, noninferior favorable clinical outcomes at discharge, and reduced hospital costs. Evaluation in larger, multicenter cohorts is recommended to determine if these observations generalize.

Key points:

- A primary cohort of patients were treated at one of 10 Ascension Seton hospitals from September 2017 - December 2020
- 354 patients were treated with alteplase and 234 patients were treated with tenecteplase
- 41% of patients receiving tenecteplase had a door to needle time of <45 minutes compared to 29% of alteplase patients.
- With Get With the Guidelines (a hospital registry system aimed at improving stroke protocol) defined door to needle time, 58% of tenecteplase patients and 41% of alteplase patients received thrombolytic therapy within 45 minutes.

Why I chose it:

I chose this article because it listed door to needle time as one of its primary outcomes. I thought this article was particularly interesting because it included a hypothesis of the outcomes. The study was completed relatively recently and I appreciated that it looked at other outcomes such as risk of hemorrhage and other unfavorable outcomes as well. This study was conducted across 10 connected hospitals which I thought was interesting because this broadened the array of clinicians involved in the timeliness of giving thrombolytic therapy and increased the validity of its findings. Of course, a larger scale study is necessary to further validate the outcomes in this paper.

What is the clinical "bottom line" derived from these articles in answer to your question?

These articles all suggest that treatment with tenecteplase in comparison to alteplase is associated with reduced door to needle time. The first study reports that the average time to thrombolytic therapy upon arrival at the hospital was 41 minutes for tenecteplase and 58 minutes for alteplase. A similar finding is seen in the second article authored by Flint, et al. Their research concludes that tenecteplase had shorter door to needle time on average, 30 minutes compared to 33 minutes, as well as at the 60, 45 and 30 minute marks. Tenecteplase was given 51.8% of the time after 30 minutes compared to alteplase which was given 43.5% of the time. Lastly, the third article reports that 41% of patients received tenecteplase within 45 minutes of arrival compared to 28% of patients that received alteplase within 45 minutes of arrival. This research is critical in treating and improving the management of stroke patients. It is important to note that due to the relatively new use of tenecteplase in the treatment of strokes, there is limited high level evidence research that addresses reduced door to needle time. Understandably, much of the beginning research aimed to discern whether tenecteplase is as effective and safe as alteplase. As the research becomes clearer that tenecteplase is safe and effective, I look forward to seeing more research dedicated to answering the question that this PICO addresses.