Alteplase- and Tenecteplase-Related Errors and Risk Mitigation Strategies in the Treatment of Acute Ischemic Stroke: **A Study of Event Reports From 52 Hospitals**

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Abstract

Background: Alteplase and tenecteplase are thrombolytic agents used to treat patients with acute ischemic stroke (AIS). Despite the convenient bolus dosing of tenecteplase, its off-label use for AIS creates new patient safety challenges that are understudied.

Methods: The study was conducted in two parts. In Part I, we queried the Pennsylvania Patient Safety Reporting System (PA-PSRS) database for event reports involving alteplase and tenecteplase that were submitted between 2017 and 2022. Based on results from Part I, in Part II we narrowed the query to reports submitted in 2021–2022 and applied inclusion criteria to identify reports that described a medication error involving the use of alteplase or tenecteplase to treat AIS. In Part II, all reports were reviewed and coded for stages of the medication-use process, associated factors, and event type.

Results: Part I results (N=858) showed a decrease in reports of alteplase events and an increase in reports of tenecteplase events. In Part II (N=92), 52% of reports involved alteplase and 48% involved tenecteplase. *Wrong dose* was the most frequently coded event type for both medications at a combined 48%. Several tenecteplase-related events were attributed to unfamiliarity with the medication, confusion between indications, and incorrect use of the electronic health record (EHR) or failure to use the EHR, whereas many errors unique to alteplase occurred during the multistep calculation, preparation, and administration processes.

Conclusions: Safety events involving alteplase and tenecteplase in the treatment of AIS are diverse. We present a list of potential strategies to prevent and mitigate errors involving these high-alert medications and encourage providers to adopt those that are meaningful to their workflow and practice setting.

Introduction

Thrombolytics (i.e., fibrinolytics) are a class of medications that dissolve blood clots and maintain vascular patency.[1,2] Alteplase and tenecteplase are agents in this class that are currently available for the lifesaving treatment of serious conditions such as acute ischemic stroke (AIS), acute myocardial infarction (AMI), and pulmonary embolism (PE).[3,4]

Alteplase (Activase) is the first recombinant human tissue plasminogen activator approved by the U.S. Food and Drug Administration (FDA) and has been the drug of choice for intravenous thrombolysis since it appeared on the market in 1996.[5,6] It is the only agent within the class that is FDA-approved for AIS, AMI, and PE.[3] For the treatment of AIS, alteplase requires a weight-based dosing with a bolus administration followed by an infusion over one hour.[3]

Tenecteplase (TNKase) is a genetically engineered tissue plasminogen activator that has a faster onset of action, longer half-life, and greater specificity to fibrin than alteplase.[5-8] It has the additional advantages of a single bolus administration and a lower cost compared to alteplase.[9-11] Although currently FDA-approved to treat AMI only, tenecteplase also has been shown to be safe and effective in its off-label use to treat AIS.[12-17] Currently, the guidelines for early management of AIS by the American Heart Association and the American Stroke Association suggest tenecteplase as a reasonable alternative to alteplase, with a Class IIb level of recommendation.[18]

As a class, thrombolytics are considered high-alert medications, meaning that they could cause serious harm to a patient if used in error.[19] Alteplase and tenecteplase have been associated with several types of medication errors due to both medications having multidosing regimens, being commonly referred to by abbreviations, and being dispensed from the same care area to treat similar patient populations.[20-29] Between October 2000 and June 2014, the FDA received 21 reports of wrong-drug errors associated with tenecteplase.[6,30] In 2015, it issued an FDA Advise-ERR to warn against the confusion between alteplase and tenecteplase,[28] including the problems caused by using the abbreviation "TPA," which stands for "tissue plasminogen activator."[20-24,28,31] Despite the aforementioned risks and concerns, we are unaware of any studies that have explored and compared the full range of medication errors occurring with alteplase and tenecteplase during treatment of AIS. (One prior study explored only dosing errors[32] and another study explored only wrong-drug errors.[29])

The purpose of this two-part study is to measure the frequency of event reports in which either alteplase or tenecteplase was the medication prescribed, regardless of indication, and to further analyze medication errors that involved the treatment of AIS. Based on findings related to the stages of the medication-use process, associated factors, and event types, we aim to identify similarities and differences in the patient safety risks associated with these medications when used to treat AIS. We anticipate that the findings of this study will help staff across multiple disciplines identify gaps in their safety practices and develop strategies to mitigate risks associated with the use of alteplase and tenecteplase to treat AIS.

Part I

Methods I

This study used the Pennsylvania Patient Safety Reporting System (PA-PSRS)[a], which is one of the largest patient safety databases in the world and contains more than 5 million event reports submitted by healthcare facilities across the state of Pennsylvania.[33,34] Each PA-PSRS report includes several structured fields (e.g., event date, patient age, patient gender, care area, facility type) as well as free-text narrative fields that the reporter can use to describe the safety event. Due to the unstructured nature of the free-text narrative fields, the quantity and quality of details may vary from one report to another.

For Methods I, we performed a query of the PA-PSRS database "Medication Error" category for reports submitted between January 1, 2017, and December 31, 2022, that used the keywords "alteplase," "tenecteplase," and spelling variations of their generic and brand names in the "Medication Prescribed" field. The objective of Methods I was to explore the extent of reported events involving the two medications, regardless of indication, and guide the design of the inclusion criteria for Methods II of the study.

Results I

Methods I generated a total of 858 reports, of which 92% (791 of 858) involved alteplase and 8% (67 of 858) involved tenecteplase (**Figure 1**). Tenecteplase-related reports had a frequency near zero from 2017 to 2020 and increased in 2021 and 2022, while the number of alteplase-related reports increased in 2018 and 2019 and decreased each year thereafter. As a result of these changes in frequency of reports, we targeted the 2021–2022 time period for further analysis in Methods II.

Part II

Methods II

Based on the findings from Results I, we chose to narrow the scope of Methods II to further examine the nature of events involving alteplase and tenecteplase in the treatment of AIS. As shown in **Figure 2**, we started with 301 reports from Methods I submitted to PA-PSRS in 2021–2022 and then applied the following inclusion criteria:

- The report described a medication error, which we defined as "any preventable behavior or condition directly involving alteplase or tenecteplase that created a potential for harm or caused harm to a patient" (adapted from the National Coordinating Council for Medication Error Reporting and Prevention definition[35])[b].
- Alteplase or tenecteplase was intended for the intravenous treatment of AIS[b].

[a]PA-PSRS is a secure, web-based system through which Pennsylvania hospitals, ambulatory surgical facilities, abortion facilities, and birthing centers submit reports of patient safety–related incidents and serious events in accordance with mandatory reporting laws outlined in the Medical Care Availability and Reduction of Error (MCARE) Act (Act 13 of 2002).[34] All reports submitted through PA-PSRS are confidential and no information about individual facilities or providers is made public.

[b]This criterion was verified through manual review of the event narrative in the report.

Figure 1. Results of Methods I Showing the Frequency of Event Reports Involving Alteplase and Tenecteplase Submitted Between 2017 and 2022 (N=858)

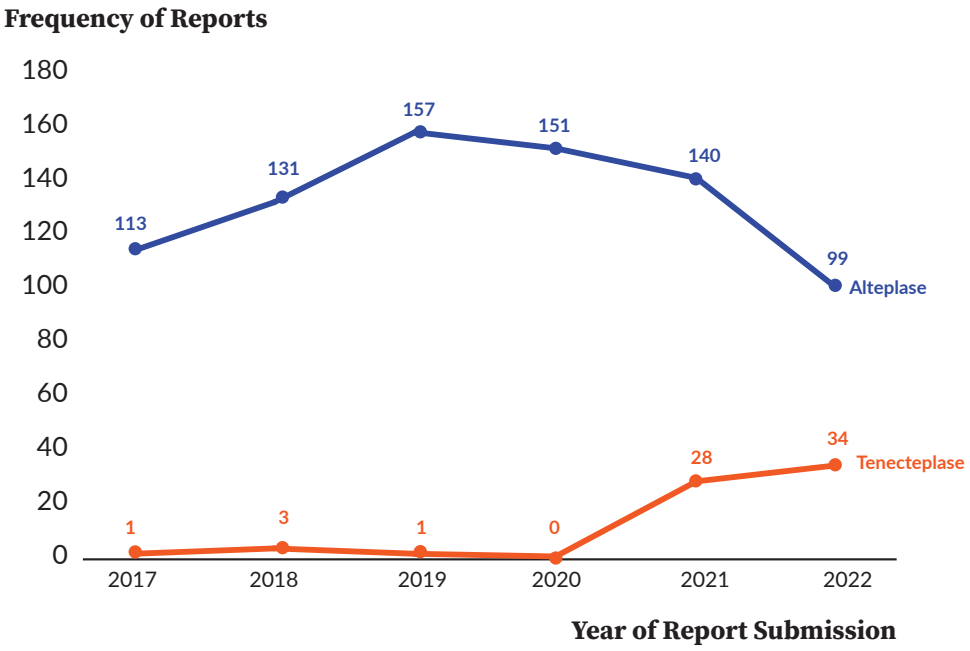
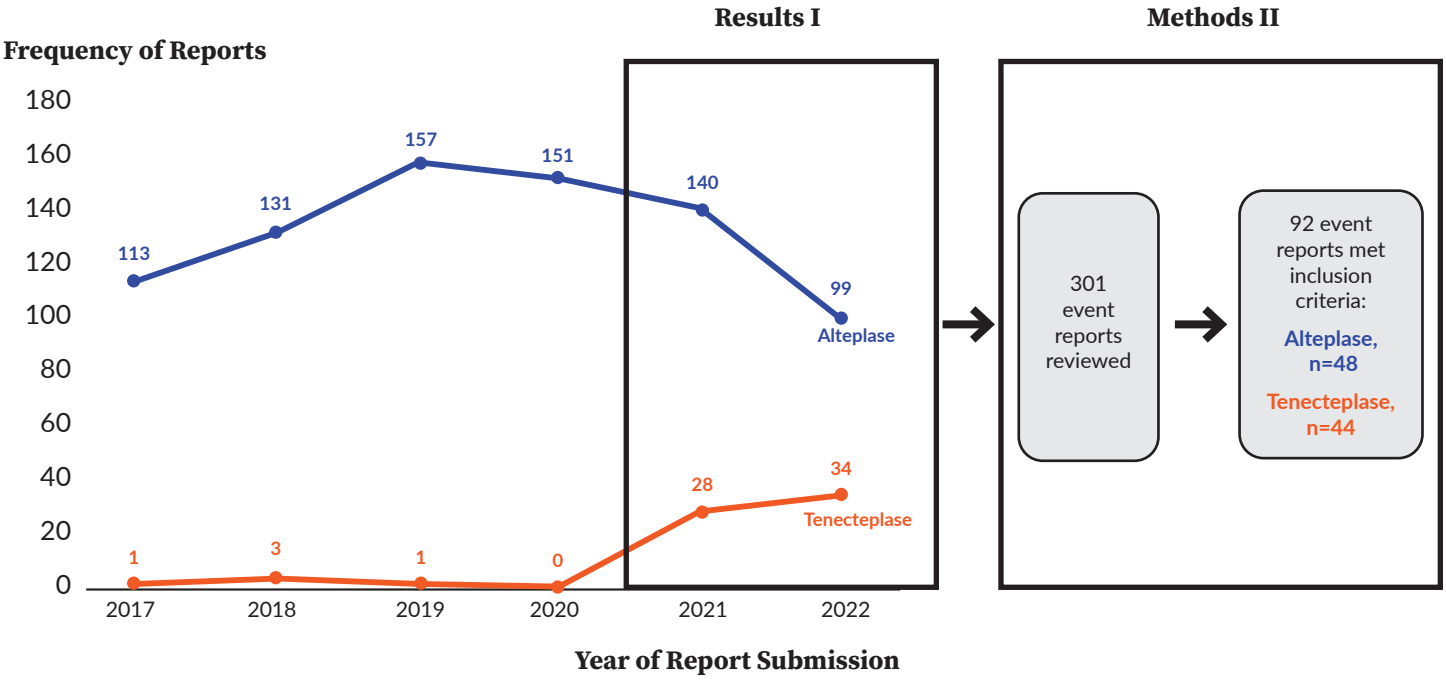


Figure 2. Identification of Relevant Event Reports for Inclusion in Part II of Study



Note: Results I had a total of 301 event reports that were submitted during 2021–2022. In Methods II, the 301 event reports were manually reviewed, and we found that 92 (alteplase n=48; tenecteplase n=44) met the inclusion criteria for analysis in Part II of the study.

Variables Coded

Each report that met inclusion criteria was coded with two sets of variables. The first set was coded by the reporter at the time of submission to PA-PSRS and included variables such as the event date, care area[c], facility type, and patient demographic information. The second set of variables consisted of the intended thrombolytic medication, near miss, clinical indication, stage of the medication-use process, associated factor, and event type. Each report was reviewed and manually coded by two researchers, and any discrepancies were discussed with a third researcher until consensus was reached. Our coding taxonomies for stage of the medication-use process, associated factor, and event type were developed using a deductive approach by adapting the PA-PSRS taxonomy and prior literature,[27,36,37] combined with an inductive approach to create additional codes where necessary.

Near Miss. The event was considered a near miss if it did not reach the patient (i.e., did not impact or interrupt patient care) due to chance or active intervention.

Clinical Indication. A clinical indication was defined as a medical condition or reason to prescribe the thrombolytic agent. Although all the prescribed thrombolytics included in the study were intended for AIS, we also coded clinical indications for which the medications were incorrectly ordered or dispensed. When not explicitly mentioned in the event details, the clinical indications for which the medication was intended, ordered, and dispensed were identified by examining the dose, consult type, methods used to prepare or administer the medication, and other contextual information provided in the report details.

Stage of the Medication-Use Process. See **Table 1** for definitions of the four stages of the medication-use process that characterize the chronological order of events and behaviors that typically occur in the acute care setting. We coded event reports according to the following four stages of the medication-use process: *Admission and screening, Prescribing and ordering, Verification and dispensing*, and *Administration*. We defined the stage as the point in the medication-use process at which a preventable behavior or condition likely contributed to the safety event (i.e., associated factor; see **Table 2**).

Associated Factor. An associated factor was defined as the preventable behavior or condition that likely contributed to the safety event. Based on the complexity of the safety event and details provided by the reporter, multiple associated factors may have been coded for a single report. When two or more reports shared the same associated factor, a standalone category of associated factor was formed. We identified 24 associated factors occurring across the four stages of the medication-use process. The associated factor *Other* contained reports that did not fit into a more specific category of associated factor for that stage. See **Table 2** for definitions of the 24 associated factors.

Event Type. An event type was defined as the actual or likely result of the associated factor. One event type was coded for each report. If the report lacked sufficient details or the event was a near miss and had the potential for multiple event types, the event was categorized as *Unable to determine*. See **Table 3** for definitions of the nine event types.

Data Analysis

We performed a descriptive analysis to explore the data and identify any phenomena or patterns that may not have been described in previous literature.[38] The analysis was conducted using tables and graphs to triangulate the relation among various combinations of variables. The goal with this type of analysis is to summarize data, describe patterns, and point toward possible causal mechanisms in a meaningful display that is helpful to the reader. The conclusions drawn from our analysis are not intended to establish causal relationships but rather to examine important dynamics between the coded variables, understand gaps in practice, and promote safe use of alteplase and tenecteplase to treat AIS.

Table 1. Definitions of Stages of the Medication-Use Process

Stage of the Medication-Use Process	Definition
Admission and screening	Patient is examined and assessed for indication of therapy with an IV thrombolytic. Patient information is collected to determine eligibility for treatment and documented in the EHR.
Prescribing and ordering	The prescriber uses clinical decision-making skills to select the appropriate medication and treatment regimen. The medication order, which can be verbal or electronic, is transcribed and entered into the EHR.
Verification and dispensing	The medication order is reviewed independently by a second provider for completeness, accuracy, and appropriateness. Following verification, the medication is prepared and dispensed from the pharmacy or the ADC.
Administration	The medication, which has been prepared to its ready-to-administer form, is given to the patient. Details of the administration are documented in the MAR.

Note: Stages of the medication-use process characterize the chronological order of events and behaviors that typically occur in the acute care setting.
ADC: Automated dispensing cabinet. EHR: Electronic health record. IV: Intravenous. MAR: Medication administration record.

[c]Within the PA-PSRS acute care database, there are 168 care areas for facilities to use to identify where events occur. Each of these care areas is then placed into one of 23 higher level care area groups.

Table 2. Definitions of Associated Factors

Stage	Associated Factor	Definition
Admission and screening	1. Weight incorrect or not collected	Patient's weight was inaccurate or unavailable.
	2. Medication history inaccurate	Patient's historical medication record or medication reconciliation was incorrect.
	3. Vital signs or lab values not assessed	Essential patient information needed for prescribing, administering, and monitoring of medication was unavailable or disregarded by the healthcare provider.
Prescribing and ordering	4. Order not placed in EHR	Medication order was not placed in the EHR in a timely manner.
	5. Order unclear or ambiguous	Components of the medication order were conflicting or confusing to the receiving healthcare provider.
	6. Order placed under wrong encounter or record in EHR	Medication order was entered under a previous encounter or in the wrong patient's record within the EHR.
	7. Order set available in EHR but not used	Prescriber failed to use the designated order set to place the medication order.
	8. Order misheard or misinterpreted	A verbal order was not heard or not interpreted as intended.
	9. Absence of warning or alert in EHR	Warning or alert did not display at the time of provider's computerized order entry.
	10. Knowledge and/or experience deficit	The event reporter attributed the event to the healthcare provider's lack of knowledge and/or experience.
	11. Order for incorrect indication	Medication order was placed for a wrong indication.
	12. Other	The report contained enough detail to determine that the *Prescribing and ordering* stage was involved in the safety event but lacked sufficient detail to identify an associated factor, or the identified associated factor did not fit into any of the aforementioned categories.
Verification and dispensing	13. Dosing information unavailable or incorrect	Dosing instructions provided in the medication kit or stroke protocol were not available or incorrect.
	14. Drug label wrong or missing	The drug label and/or its accompanying barcode was wrong or missing.
	15. Knowledge and/or experience deficit	The event reporter attributed the event to the healthcare provider's lack of knowledge and/or experience.
	16. Medication in ADC unstocked, inaccessible, or wrong	Intended medication in the ADC was unavailable, inaccessible, or incorrectly stocked.
	17. Wrong volume dispensed	The medication was prepared with a wrong volume, leading to a wrong dose or concentration of the final product.
	18. Medication delivery issues	The medication was not delivered or was delivered to the wrong location.
	19. Calculation error	The dose of the medication was incorrectly calculated and prepared during the dispensing stage.
	20. Other	The report contained enough detail to determine that the *Verification and dispensing* stage was involved in the safety event but lacked sufficient detail to identify an associated factor, or the identified associated factor did not fit into any of the aforementioned categories.
Administration	21. Medication administration not documented in MAR	Details of the medication administration were not documented in the MAR in a timely manner.
	22. Programming error with infusion pump	A programming error occurred with the infusion pump.
	23. Knowledge and/or experience deficit	The event reporter attributed the event to the healthcare provider's lack of knowledge and/or experience.
	24. Other	The report contained enough detail to determine that the *Administration* stage was involved in the safety event but lacked sufficient detail to identify an associated factor, or the identified associated factor did not fit into any of the aforementioned categories.

Note: Multiple associated factors could be coded for each event report. The associated factors *Calculation error, Knowledge and/or experience deficit*, and *Other* were identified across several stages and were counted individually per stage. ADC: Automated dispensing cabinet. EHR: Electronic health record. IV: Intravenous. MAR: Medication administration record.

Table 3. Definitions of Event Types

Event Type	Definition
Wrong dose	The dose ordered, dispensed, and/or administered differed from the dose originally intended by the prescriber and/or recommended by the published guidelines.
Delay of therapy	The medication was not given to the patient in a timely manner or within a period of time deemed acceptable by the reporting facility.
Patient not eligible	Medication was ordered, dispensed, and/or administered to the patient against known contraindications or lack of indication for therapy.
Wrong drug	The medication ordered, dispensed, and/or administered differed from the medication originally intended by the prescriber.
Wrong rate	The medication rate ordered and/or received by the patient was inconsistent with the rate originally intended by the prescriber and/or recommended by the published guidelines.
Wrong patient	The medication was ordered, dispensed, and/or administered to the wrong patient.
Extra dose	A duplicate dose was ordered, dispensed, and/or administered to the patient.
Omission of therapy	The patient did not receive the intended medication.
Unable to determine	The report lacked sufficient detail to identify an event type, or the event was a near miss and had the potential for multiple event types.

Note: Each of the 92 event reports was coded with one event type.

Results II

Based on Methods II, we identified 92 event reports (alteplase n=48; tenecteplase n=44) that met inclusion criteria for Part II of our study. These 92 reports are a subset of the sample from Part I of the study.

Demographics

A total of 52 Pennsylvania hospitals submitted at least one report describing an event that was included in our study. Of these, 31 hospitals submitted one report (60%, 31 of 52), 10 hospitals submitted two reports (19%; 10 of 52), and 11 hospitals submitted three or more reports (21%; 11 of 52). More than half of the reports (57%, 52 of 92) were submitted by facilities with more than 300 beds. The "Emergency Department" care area group was identified as the location in majority of reports (71%, 65 of 92). Based on the 92 reports, patient age was an average of 67 years and a median of 68 years (range: 14 to 98 years, 25th percentile: 55 years, 75th percentile: 81 years).

Medication

As shown in **Figure 3**, 52% of the reports involved alteplase (48 of 92) and 48% involved tenecteplase (44 of 92) as the intended medication for AIS. Of the total reports, near misses accounted for 42% (39 of 92) and occurred with an almost equal distribution between the two medications (alteplase 51%, 20 of 39; tenecteplase 49%, 19 of 39). An event attributed to a wrong indication was described in six reports; in five tenecteplase-related events, the indication was confused for AMI, and in one alteplase-related event, the order was incorrectly placed for PE.

Stage of the Medication-Use Process

Figure 4 and **Figure 5** show the distribution of each stage of the medication-use process involved by intended medication. Alteplase-related events occurred with a more similar frequency across the four stages (range of 12 to 14 reports), while the frequency of tenecteplase-related events was highly variable across the four stages (range of 5 to 26 reports). Across both medications, the *Prescribing and ordering* stage was associated with the highest frequency of total events (40 of 92 reports).

Associated Factor and Stage of the Medication-Use Process

Table 4 shows the frequency of associated factors by stage and intended medication. Associated factors were not mutually exclusive, resulting in a total of 120 associated factors that were coded across 92 reports. Seventy-four percent (68 of 92) of reports had one associated factor, 22% (20 of 92) had two associated factors, and 4% (4 of 92) had three associated factors coded. The associated factors we identified most frequently across all reports were *Weight incorrect or not collected* (13%, 15 of 120) and *Order not placed in EHR* (9%, 11 of 120). *Knowledge and/or experience deficit*, when combined across all stages of the medication-use process, was also coded frequently (10%, 12 of 120).

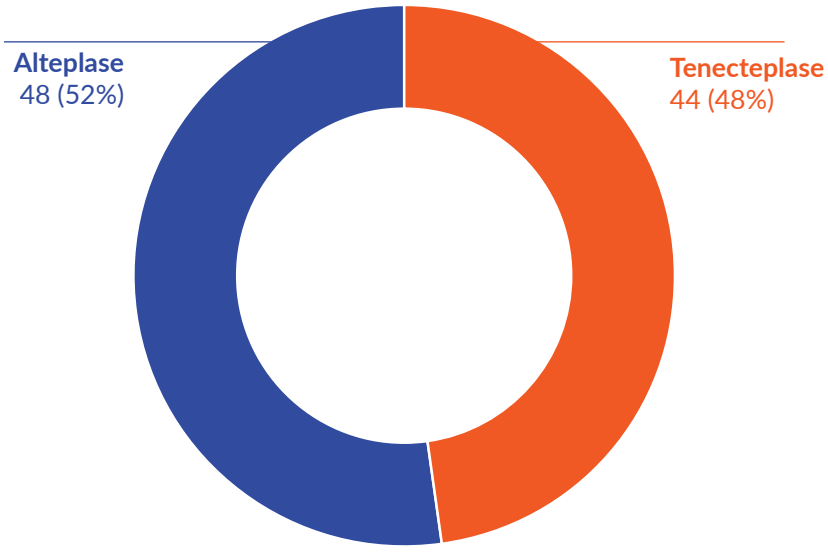
Admission and Screening

Across all associated factors, 16% (19 of 120) occurred during *Admission and screening*. The associated factor *Weight incorrect or not collected* accounted for 79% (15 of 19) of all associated factors coded for this stage and was identified much more frequently in events involving alteplase (alteplase n=11; tenecteplase n=4).

Prescribing and Ordering

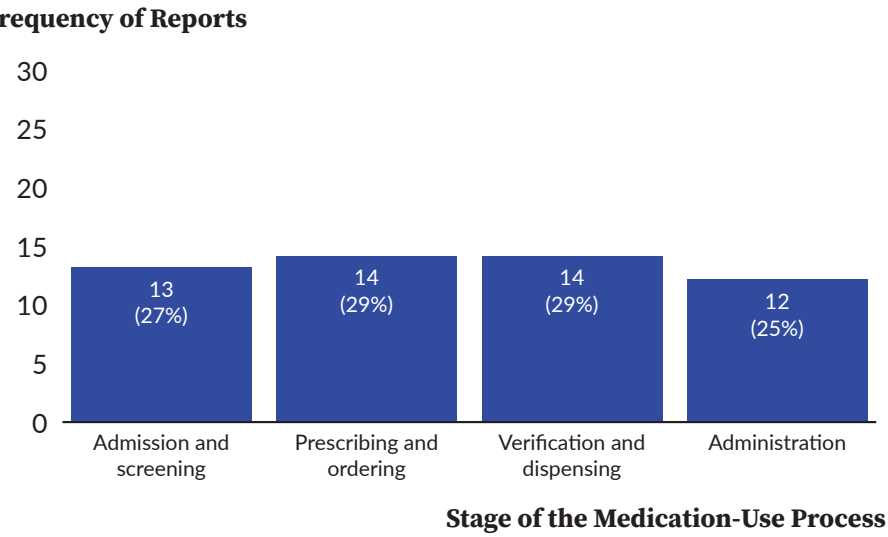
Across all associated factors, 40% (48 of 120) occurred during *Prescribing and ordering*. The two associated factors that were identified most frequently during this stage were *Order not placed in EHR* (23%, 11 of 48), which was seen more frequently with tenecteplase (alteplase n=2; tenecteplase n=9), and *Order unclear or ambiguous* (17%, 8 of 48), which also occurred more frequently with tenecteplase (alteplase n=3; tenecteplase n=5). Overall, two-thirds of all associated factors related to this stage involved tenecteplase (67%, 32 of 48).

Figure 3. Frequency of Event Reports by Intended Medication (N=92)



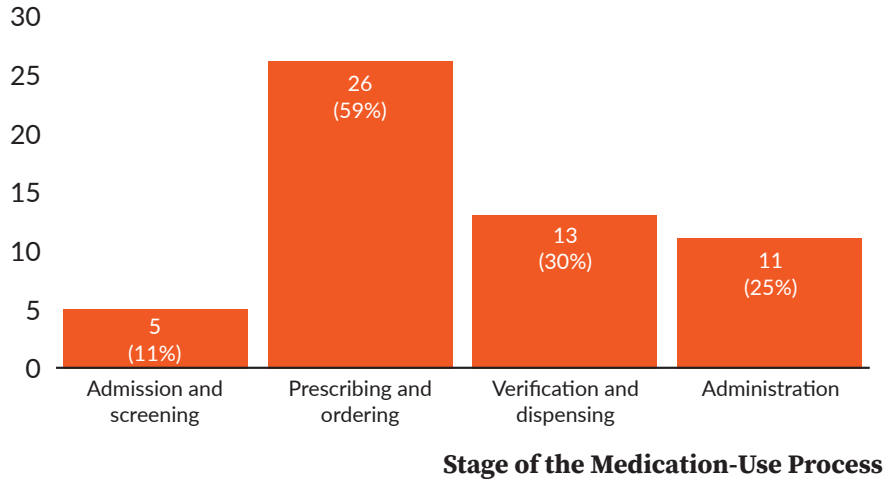
Note: Total number of event reports involving alteplase and tenecteplase included in the study was 48 and 44, respectively. Near misses are included in the total.

Figure 4. Frequency of Events Involving Alteplase by Stage of the Medication-Use Process (N=48 reports)



Note: The figure shows the frequency of events impacted by stage across 48 event reports. Each report may have had more than one stage involved in the event. Percentages shown are based on the denominator of 48.

Figure 5. Frequency of Events Involving Tenecteplase by Stage of the Medication-Use Process (N=44 reports)



Note: The figure shows the frequency of events impacted by stage across 44 event reports. Each report may have had more than one stage involved in the event. Percentages shown are based on the denominator of 44.

Table 4. Frequency of Associated Factor by Stage and Intended Medication (N=120)

Stage	Associated Factor	Alteplase	Tenecteplase	Total
Admission and screening	1. Weight incorrect or not collected	11	4	15
	2. Medication history inaccurate	2	0	2
	3. Vital signs or lab values not assessed	0	2	2
	Subtotal	**13**	**6**	**19**
Prescribing and ordering	4. Order not placed in EHR	2	9	11
	5. Order unclear or ambiguous	3	5	8
	6. Order placed under wrong encounter or record in EHR	3	2	5
	7. Order set available in EHR but not used	1	3	4
	8. Order misheard or misinterpreted	1	3	4
	9. Absence of warning or alert in EHR	1	2	3
	10. Knowledge and/or experience deficit	0	3	3
	11. Order for incorrect indication	1	1	2
	12. Other	4	4	8
	Subtotal	**16**	**32**	**48**
Verification and dispensing	13. Dosing information unavailable or incorrect	0	6	6
	14. Drug label wrong or missing	4	0	4
	15. Knowledge and/or experience deficit	1	3	4
	16. Medication in ADC unstocked, inaccessible, or wrong	2	2	4
	17. Wrong volume dispensed	3	1	4
	18. Medication delivery issues	2	1	3
	19. Calculation error	2	0	2
	20. Other	2	1	3
	Subtotal	**16**	**14**	**30**
Administration	21. Medication administration not documented in MAR	1	5	6
	22. Programming error with infusion pump	6	0	6
	23. Knowledge and/or experience deficit	1	4	5
	24. Other	4	2	6
	Subtotal	**12**	**11**	**23**
	Total	**57**	**63**	**120**

Note: Associated factors were not mutually exclusive; therefore, multiple associated factors could be coded for each report. Across a total of 92 event reports, 120 associated factors belonging to 24 unique categories were coded. ADC: Automated dispensing cabinet. EHR: Electronic health record. IV: Intravenous. MAR: Medication administration record.

Verification and Dispensing

Across all associated factors, 25% (30 of 120) occurred during *Verification and dispensing*. The associated factor that occurred most frequently during this stage was *Dosing information unavailable or incorrect* (20%; 6 of 30), which was relevant to only tenecteplase (alteplase n=0; tenecteplase n=6). Conversely, associated factors that were unique to only alteplase during this stage were *Drug label wrong or missing* (alteplase n=4; tenecteplase n=0) and *Calculation error* (alteplase n=2; tenecteplase n=0).

Administration

Across all associated factors, 19% (23 of 120) occurred during *Administration*. The most frequent associated factors identified for this stage were *Medication administration not documented in MAR* (26%; 6 of 23), *Programming error with infusion pump* (26%; 6 of 23), and *Other* (26%; 6 of 23). Tenecteplase was more frequently involved with the associated factors *Medication administration not documented in MAR* (alteplase n=1; tenecteplase n=5) and *Knowledge and/or experience deficit* (alteplase n=1; tenecteplase n=4), while *Programming errors with infusion pump* was relevant to only alteplase (alteplase n=6, tenecteplase n=0). The alteplase-related events coded as *Other, Administration* consisted of the inappropriate administration of infusion prior to bolus, bolus pushed too fast, suboptimal connection of lines preventing drug administration, and wrong manipulation of the infusion bag leading to drug waste.

Event Type

Figure 6 shows the distribution of event types by intended medication. Based on a total of 92 reports, the event types we identified most frequently were *Wrong dose* at 48% (44 of 92) and *Delay of therapy* at 15% (14 of 92). The event type *Wrong rate* was unique to alteplase only (alteplase n=5; tenecteplase n=0), and several event types occurred more frequently for tenecteplase, such as *Wrong drug* (alteplase n=1; tenecteplase n=4).

Figure 7 shows the subcategories of *Wrong dose* for each medication: *Overdose*, *Underdose*, and *Unable to determine*. Collectively, 75% (33 of 44) of all reports coded as *Wrong dose* resulted in an overdose. Among these, tenecteplase accounted for the majority of events leading to an overdose (alteplase n=13; tenecteplase n=20).

Event Type, Stage, And Associated Factor

Table 5 shows the frequency of stages, associated factors, and event types for each of the intended medications. The distribution of the event type *Wrong dose* and corresponding associated factors by stages are described further in the next section. The event type *Delay of therapy* had the second highest frequency of associated factors (alteplase n=9; tenecteplase n=9), and more than half of these associated factors occurred during the *Verification and dispensing* stage (56%; 10 of 18).

The event type *Wrong drug* was detected more frequently with tenecteplase and could be attributed primarily to the associated factor *Order misheard or misinterpreted* (alteplase n=1; tenecteplase n=3). In fact, all events that had the associated factor *Order misheard or misinterpreted* involved the use of the abbreviation "TPA" and led to the event type *Wrong drug*.

The event type *Wrong rate* was relevant to only alteplase, was mostly impacted by the *Programming error with infusion pump* associated factor (4 of 6), and was related with only two stages of the medication-use process: *Prescribing and ordering* and *Administration*.

The associated factor *Order not placed in EHR* was identified more frequently for tenecteplase (alteplase n=2; tenecteplase n=9) and resulted in the most diverse distribution of event types, which signifies that missing or undocumented orders can lead to many different types of events.

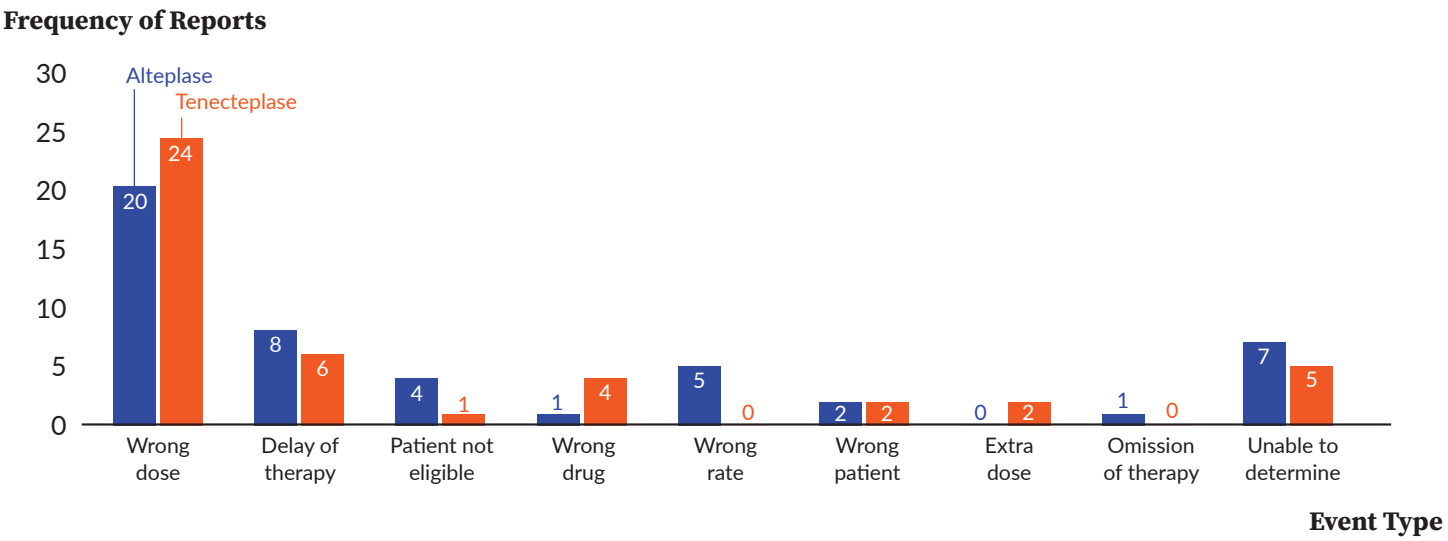
Wrong Dose and Associated Factor

The complete table of associated factors for the event type *Wrong dose*, as detailed by *Overdose*, *Underdose*, and *Unable to determine*, can be found in **Table 6**. An overdose involving alteplase was most frequently associated with *Weight incorrect or not collected* (n=6), *Wrong volume dispensed* (n=3), and *Calculation error* (n=2). Two of these categories of associated factors, *Wrong volume dispensed* and *Calculation error*, both involved the wrong dose preparation during the *Verification and dispensing* stage as a result of the failure to remove the correct amount of overfill and/or incorrect calculation of bolus and/or infusion doses.

For tenecteplase, overdoses were most frequently related with the associated factors *Knowledge and/or experience deficit* (n=7), *Dosing information unavailable or incorrect* (n=4), and *Order unclear or ambiguous* (n=4). The associated factor *Knowledge and/or experience deficit* spanned across three different stages, *Prescribing and ordering*, *Verification and dispensing*, and *Administration*, which highlights the prevalence and implication throughout the medication-use process. All four reports coded with the associated factor *Dosing information unavailable or incorrect* involved confusion with the wrong indication for AMI, which led to exceeding the maximum dose of 25 milligrams recommended for the treatment of AIS.

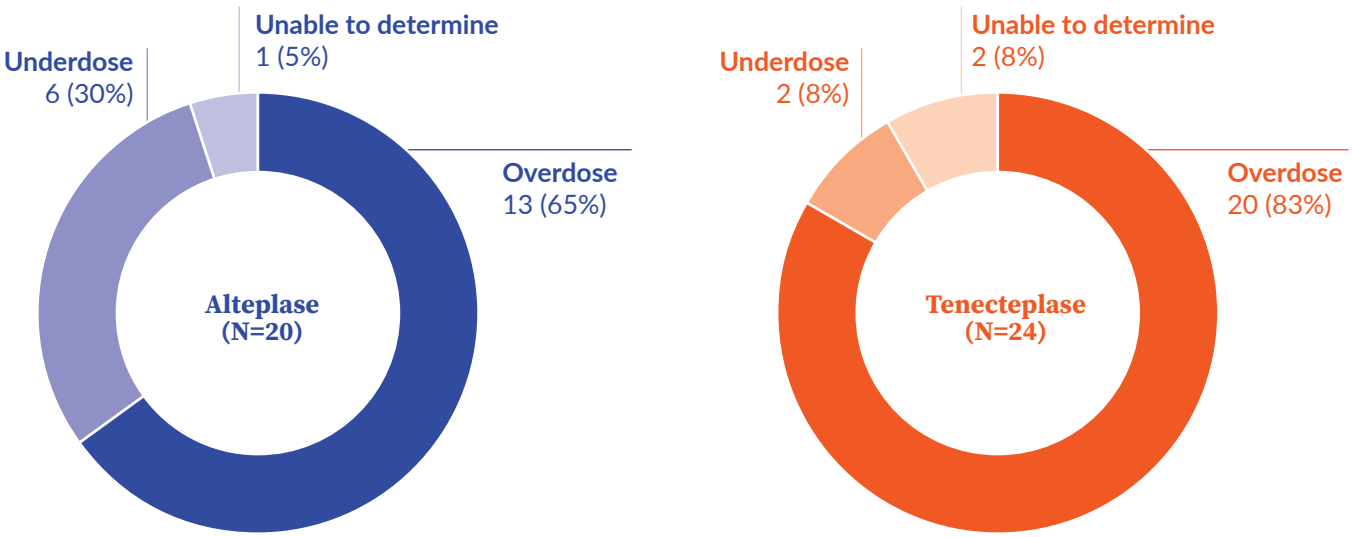
A quarter of all tenecteplase-related overdose events (25%; 5 of 20) involved a wrong indication in which a staff member either chose a wrong order set intended for AMI in the EHR or followed the wrong dosing instructions intended for AMI provided in the medication kit.

Figure 6. Event Type by Intended Medication (N=92 reports)



Note: Each of the 92 event reports was coded with one event type.

Figure 7. Subcategories of Wrong Dose by Intended Medication (N=44 reports)



Note: Each of the 44 reports that were coded as event type *Wrong dose* was further identified as *Overdose*, *Underdose*, or *Unable to determine*.

Table 5. Frequency of Relationships Between Event Types (N=92), Stages, and Associated Factors (N=120)

		Event type																			
		Wrong dose		Delay of therapy		Patient not eligible		Wrong drug		Wrong rate		Wrong patient		Extra dose		Omission of therapy		Unable to determine		Total	
	Total (1 per report)	44 (48%)		14 (15%)		5 (5%)		5 (5%)		5 (5%)		4 (4%)		2 (2%)		1 (1%)		12 (13%)		92 (100%)	
Stage	Associated Factor	AI	Te	AI	Te	AI	Te	AI	Te	AI	Te	AI	Te	AI	Te	AI	Te	AI	Te	AI	Te
Admission and screening	1. Weight incorrect or not collected	11	2	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	11	4
	2. Medication history inaccurate	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-
	3. Vital signs or lab values not assessed	-	-	-	1	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	2
	Subtotal	**11**	**2**	**-**	**3**	**2**	**1**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**13**	**6**
Prescribing and ordering	4. Order not placed in EHR	-	4	-	-	-	1	-	-	1	-	-	-	-	1	-	-	1	3	2	9
	5. Order unclear or ambiguous	1	5	-	-	1	-	1	-	-	-	-	-	-	-	-	-	-	-	3	5
	6. Order placed under wrong encounter or record in EHR	-	-	-	-	-	-	-	-	-	-	2	2	-	-	-	-	1	-	3	2
	7. Order set available in EHR but not used	-	3	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	3
	8. Order misheard or misinterpreted	-	-	-	-	-	-	1	3	-	-	-	-	-	-	-	-	-	-	1	3
	9. Absence of warning or alert in EHR	-	1	-	-	1	-	-	-	-	-	-	-	-	1	-	-	-	-	1	2
	10. Knowledge and/or experience deficit	-	2	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	3
	11. Order for incorrect indication	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1
	12. Other	2	3	-	1	2	-	-	-	-	-	-	-	-	-	-	-	-	-	4	4
	Subtotal	**4**	**19**	**1**	**1**	**4**	**1**	**2**	**3**	**1**	**-**	**2**	**2**	**-**	**3**	**-**	**-**	**2**	**3**	**16**	**32**
Verification and dispensing	13. Dosing information unavailable or incorrect	-	4	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	6
	14. Drug label wrong or missing	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	3	-	4	-
	15. Knowledge and/or experience deficit	1	2	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	3
	16. Medication in ADC unstocked, inaccessible, or wrong	-	-	1	1	-	-	-	1	-	-	-	-	-	-	-	-	1	-	2	2
	17. Wrong volume dispensed	3	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	1
	18. Medication delivery issues	-	-	2	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	1
	19. Calculation error	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-
	20. Other	1	-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	1
	Subtotal	**7**	**7**	**5**	**5**	**-**	**-**	**-**	**1**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**4**	**1**	**16**	**14**
Administration	21. Medication administration not documented in MAR	-	1	-	-	-	-	-	-	-	-	-	-	-	1	-	-	1	3	1	5
	22. Programming error with infusion pump	1	-	1	-	-	-	-	-	4	-	-	-	-	-	-	-	-	-	6	-
	23. Knowledge and/or experience deficit	1	4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	4
	24. Other	-	2	2	-	-	-	-	-	1	-	-	-	-	-	1	-	-	-	4	2
	Subtotal	**2**	**7**	**3**	**-**	**-**	**-**	**-**	**-**	**5**	**-**	**-**	**-**	**-**	**-**	**1**	**-**	**1**	**3**	**12**	**11**
	Total	**24**	**35**	**9**	**9**	**6**	**2**	**2**	**4**	**6**	**-**	**2**	**2**	**-**	**4**	**1**	**-**	**7**	**7**	**57**	**63**

Note: Across a total of 92 event reports, 120 associated factors belonging to 24 unique categories were coded. Only one event type was identified in each of the 92 reports; however, based on the context of the individual report, more than one associated factor may have been identified in each report. Multiple associated factors per event type indicate that more than one factor was present and may have influenced the event type as described in the report. The area at the top of the table shaded in green identifies the nine categories of event types and the frequency per type. The **tan** shaded areas to the far left represent the stages of the medication-use process and the **grey** shaded areas to the right of the stages show the associated factors. Twenty-four different associated factors were organized into four stages of the medication-use process, which were then tabulated into columns corresponding with each of the nine event types. The last row in each stage of the medication-use process contains the subtotal of the associated factors identified in that particular stage. The far-right column shows the sum of the associated factors across all 9 categories of event type. Cells with a - represent a zero frequency. AI: Alteplase. Te: Tenecteplase

Table 6. Frequency of Associated Factors (N=59) by Subcategories of *Wrong dose* (N=44) and Intended Medications

		Wrong Dose							
		Overdose		Underdose		Unable to determine		Total	
Stage	Associated Factor	Alteplase	Tenecteplase	Alteplase	Tenecteplase	Alteplase	Tenecteplase	Alteplase	Tenecteplase
Admission and screening	1. Weight incorrect or not collected	6	1	4	1	1	-	11	2
	2. Medication history inaccurate	-	-	-	-	-	-	-	-
	3. Vital signs or lab values not assessed	-	-	-	-	-	-	-	-
	Subtotal	**6**	**1**	**4**	**1**	**1**	**-**	**11**	**2**
Prescribing and ordering	4. Order not placed in EHR	-	3	-	1	-	-	-	4
	5. Order unclear or ambiguous	-	4	1	-	-	1	1	5
	6. Order placed under wrong encounter or record in EHR	-	-	-	-	-	-	-	-
	7. Order set available in EHR but not used	-	3	-	-	-	-	-	3
	8. Order misheard or misinterpreted	-	-	-	-	-	-	-	-
	9. Absence of warning or alert in EHR	-	1	-	-	-	-	-	1
	10. Knowledge and/or experience deficit	-	2	-	-	-	-	-	2
	11. Order for incorrect indication	1	1	-	-	-	-	1	1
	12. Other	2	2	-	-	-	1	2	3
	Subtotal	**3**	**16**	**1**	**1**	**-**	**2**	**4**	**19**
Verification and dispensing	13. Dosing information unavailable or incorrect	-	4	-	-	-	-	-	4
	14. Drug label wrong or missing	-	-	-	-	-	-	-	-
	15. Knowledge and/or experience deficit	1	1	-	-	-	1	1	2
	16. Medication in ADC unstocked, inaccessible, or wrong	-	-	-	-	-	-	-	-
	17. Wrong volume dispensed	3	1	-	-	-	-	3	1
	18. Medication delivery issues	-	-	-	-	-	-	-	-
	19. Calculation error	2	-	-	-	-	-	2	-
	20. Other	-	-	1	-	-	-	1	-
	Subtotal	**6**	**6**	**1**	**-**	**-**	**1**	**7**	**7**
Administration	21. Medication administration not documented in MAR	-	-	-	1	-	-	-	1
	22. Programming error with infusion pump	1	-	-	-	-	-	1	-
	23. Knowledge and/or experience deficit	-	4	1	-	-	-	1	4
	24. Other	-	2	-	-	-	-	-	2
	Subtotal	**1**	**6**	**1**	**1**	**-**	**-**	**2**	**7**
	Total	**16**	**29**	**7**	**3**	**1**	**3**	**24**	**35**

Note: Across a total of 44 event reports that were identified with the event type *Wrong dose*, 59 associated factors belonging to 24 total possible unique categories were coded. Multiple associated factors could be coded for each report, while only one event type was coded per report. The area at the top of the table shaded in green identifies the subcategories of *Wrong dose: Overdose, Underdose,* and *Unable to determine*. The **tan** shaded areas to the far left represent the stages of the medication-use process and the **grey** shaded areas to the right of the stages show the associated factors. The 24 associated factors were organized into four stages of the medication-use process which are represented in tan. The last row in each stage of the medication-use process contains the subtotal of the associated factors identified in that particular stage. The far-right column shows the sum of the associated factors across all subcategories of *Wrong dose* event type. Cells with a - represent a zero frequency.

Discussion

In Part I of our study, we measured the frequency of reports submitted to PA-PSRS in which either alteplase or tenecteplase was the medication prescribed, regardless of indication, and this revealed a notable increase in reported events involving tenecteplase. In Part II of our study, we analyzed numerous variables to better understand the nature of medication errors involving the use of either alteplase or tenecteplase to treat AIS. To our knowledge, this is the first study of medication events involving alteplase and tenecteplase to treat AIS that delineated event types and associated factors with the stage of the medication-use process.

For both medications, we found *Wrong dose* to be the event type with the highest frequency, which was identified in almost half of all reports included in the study. For alteplase, *Weight incorrect or not collected* was the factor most frequently associated with *Wrong dose*. When an inaccurate weight is used to calculate the dose, the patient could receive a dose that is considerably different from what is appropriate, safe, and effective.[39] For example, two separate studies of reports found that 44% and 42% of all wrong weight events led to an overdose.[39,40] In our study, the associated factor *Weight incorrect or not collected* was identified in 55% of all events that were coded overdoses with alteplase.

Additionally, we found that the *Verification and dispensing* stage and *Administration* stage of the medication-use process were associated with several safety gaps unique to alteplase. Our findings revealed safety challenges associated with the multistep preparation of the bolus and infusion doses of alteplase, use of the infusion pump, and different rates of administration for bolus and infusion. For example, we identified the associated factor *Programming error with infusion pump* and the event type *Wrong rate* only in reports involving alteplase.

Unlike alteplase, the bolus administration of tenecteplase eliminates problems associated with use of an infusion pump, such as setup issues, air in tubing, and staff required during interfacility patient transfers.[10,11] It has also been shown to be associated with a shorter door-to-needle time.[8,32]

Despite these advantages, our study showed that tenecteplase has several distinct safety gaps. Many were related to the use of a medication kit and confusion with a wrong indication (AMI) leading to an overdose. Because tenecteplase is currently approved for the treatment of AMI only, the medication is supplied from the manufacturer inside a kit that contains dosing, preparation, and administration instructions intended for AMI, not AIS.[4,41] The maximum recommended dose of tenecteplase for treatment of AMI as provided in the kit is 50 mg, which is double the maximum recommended dose of tenecteplase for the off-label treatment of AIS.[4,18,41] Accordingly, in our study, all tenecteplase-related events coded as *Dosing information unavailable or incorrect* led to the event type *Wrong dose* and were in fact, overdoses.

Furthermore, more than half of the reports involving tenecteplase involved the *Prescribing and ordering* stage of the medication-use process. In particular, several associated factors involving the use of the EHR were identified more frequently with tenecteplase than with alteplase, such as *Order not placed in EHR*, *Order set available in EHR but not used*, and *Absence of warning or alert in EHR*. During the *Administration* stage, the associated factor *Medication administration not documented in MAR* was also identified more frequently with tenecteplase. These findings suggest that providers are not using the EHR to place or document an order, orders are placed without using the correct order set, and the EHR is not optimized to detect and mitigate errant orders.

Lastly, the associated factor *Knowledge and/or experience deficit* was identified across multiple stages, occurring throughout *Prescribing and ordering*, *Verification and dispensing*, and *Administration* stages. When combined altogether across the stages, it represented the second most frequently coded associated factor in the study, and 83% of these were observed with tenecteplase. This indicates that the lack of knowledge and/or experience with tenecteplase was a factor in many events.

Potential Strategies

Table 7 shows a list of potential strategies that can be adopted at the provider and system levels. Because every facility has its own unique workflow, processes, and resources, it is important to identify those that are both applicable and meaningful to each facility. The potential strategies should be reviewed with the interdisciplinary members of the stroke team and the relevant hospital committees, as well as the patient safety officer and the medication safety officer of the institution, with the overall goal of assessing current practices and continuously monitoring for improvement.

Limitations

One limitation of our study is the inherent nature of event reporting; a report does not necessarily represent the results of a thorough investigation and therefore may not provide insight into root causes. We do not recommend using our results for benchmarking or direct comparison because differences in culture, patient populations, resources, and error detection methods and systems may exist across facilities.[57] In addition, the definitions used in our study may differ from definitions used in other studies. For example, one study involving alteplase defined "delay" as a contributing factor,[37] while our study described it as an event type. Other studies may also categorize the medication-use process into stages different from those in our study.[60] Readers are encouraged to carefully compare results from other similar studies and refer to Methods II for definitions used in our study.

Given that this study presents aggregate data, facilities may gain important insight from performing site-specific investigations, such as a root cause analysis to retrospectively examine an event, a medication-use evaluation (MUE)[58,59] to answer a particular safety question, or a failure mode and effects analysis (FMEA)[49,50] to prospectively identify and mitigate high risk processes.

Table 7. Potential Strategies for Prevention of Medication Errors Involving Alteplase and Tenecteplase Throughout the Medication-Use Process

Stage of the Medication-Use Process	Potential Strategies
Admission and screening	Obtain an accurate weight of the patient
	• Establish a routine procedure for weighing patients upon admission and routinely reweighing patients in anticipation of fluctuating weight.[39,40,42,43] • Obtain weight in metric units, e.g., kilograms. [39,40,42,43] • Standardize weight measurement in metric units on medication orders, medical records, guidelines, protocols, infusion pumps, and other medication devices.[39,40,42,43] • Require the entry of weight prior to processing orders.[39,40,43] • Avoid the use of an estimated, stated, or historical weight.[39,40,42,43] • Document the date of the weight measurement.[39,40] • Build a "hard stop" or automated clinical decision support into computerized provider order entry (CPOE) systems to ensure the documentation of the most recent weight.[39,40]
	Screen for indication and patient eligibility for treatment

	• Obtain the best possible medication history (BPMH) using multiple sources such as patient interview, medical records, pharmacy records, and interview with a family member or caregiver.[44]
	• Assess for any contraindications by obtaining and reviewing:[45]
	  ◦ Medication history
	  ◦ Laboratory results
	  ◦ Past medical history
	  ◦ Allergies and associated reactions

Prescribing and ordering	Ensure the correct indication of the order

	• Require the placement of an order using the appropriate order set.
	• Establish a separate order set for each indication.[20,21,24,31]
	• Confirm the accuracy of the medication order by reviewing:[45]
	  ◦ Medication administration record (MAR)
	  ◦ Current medical condition
	  ◦ Past medical history

	Minimize the risk of confusion between alteplase and tenecteplase
	• Do not use the abbreviation "TPA" to refer to the entire class of tissue plasminogen activators.[20,21,24,25,28,46] Do not use "TPA" to refer to alteplase or "TNK" for tenecteplase.[6,20,21,24-26,28,30,47] • Remove the abbreviation "TPA" or "TNK" from standardized order sets, CPOE screens, and treatment protocols.[6,28,30,31,46] • Use the full generic names of the medications in verbal orders, order sets, and treatment protocols.[6,20,21,24-26,28,30,46] • Repeat back the verbal orders to ensure that they are heard correctly.[48] • Limit fibrinolytic agents on the hospital formulary.[20,21,25] If not possible, consider limiting one fibrinolytic to an indication. • When discussing the addition of a thrombolytic to the formulary, include a section on safety assessment and recommendations after reviewing the literature[49] and/or the results of a failure mode and effects analysis (FMEA).[50]
	Establish clinical decision support within the EHR

	• Create a hard stop for:
	  ◦ A dose exceeding 25 mg for the treatment of AIS. **(Tenecteplase only)**
	  ◦ Absent documentation of the most recent weight.[39,40]
	  ◦ Duplicate therapy.
	  ◦ Any present or past use of anticoagulants when thrombolytics are ordered.
	  ◦ Absolute contraindications per the manufacturer, such as active internal bleeding and severe uncontrolled hypertension.[4]
	  ◦ Relative contraindications per institutional guidelines, such as low platelet levels.
	• Automate the stat status with the thrombolytics order to expedite its preparation and delivery during the stroke alert.
	• Continuously monitor for effectiveness of the alerts and combat alert fatigue (e.g., compare the number of times an alert has triggered against the number of times a change has been made based on the alert).

	Other recommendations to optimize the use of the EHR
	• Review the "hold" functionality within the EHR and implement strategies as necessary, such as implementing pharmacist reverification upon release of held orders, evaluating parameters for orders on hold, and ensuring continuity of therapy when orders are held during transfer.[51]
	Provide education and competency training for staff
	• Establish protocols and guidelines for stroke alert and/or the use of thrombolytics. The document should be available and easily accessible to all members of the healthcare team. Include instructions pertaining to the use of thrombolytics throughout all stages of the medication-use process. • Provide competency assessment at orientation and prior to any changes to the stroke protocol. • Provide routine education to providers regarding updates to the formulary.[24,25] • Identify the personnel who are trained and qualified to routinely handle the fibrinolytic agents.[20,21]

Table 7. (continued)

Verification and dispensing	Confirm the accuracy of the medication
	• Do not prepare or dispense the medication until the order has been placed and, as much as possible, verified independently by a second healthcare provider such as a pharmacist. If the independent double check is not possible due to the emergent nature of the situation, confirm the details of the order verbally out loud for the members of the healthcare team to verify.[20,21,24,45] • Do not autoverify thrombolytics, given that they are considered high-alert, require weight-based dosing, interact with other medications, and require multistep dose calculation and preparation.[52] • Include a pharmacist in the interdisciplinary team who can ensure correct eligibility, dosing, and admixture administration of the fibrinolytics.[37]
	Minimize compounding errors
	• Prepare the medication using the IV workflow management system, if available. • Dedicate specialized personnel to prepare the medication,[20,21] especially during dose calculation and preparation of alteplase. • Adhere to best practices such as avoiding the syringe pull-back method.[49] Whenever possible, have the pharmacist prepare and/or physically inspect the final product with the accompanying supplies.
	Minimize errors involving the ADC
	• Dedicate a separate medication kit for individual medication based on indication.[20,21] Ensure that the kit contains supplies and dosing instructions appropriate for the indication. • Affix dosing and warning stickers on medication kits to identify the indication and medication name. • Require a medication order before the medication can be dispensed from the ADC.[53] • Provide profiled ADCs by directing providers to patient-specific medications that have been reviewed and verified by pharmacy.[53] • Establish a protocol if overrides are allowed at the institution.[49,53] Require the provider to indicate the rationale for override, and assess the frequency and reason for overrides to continuously monitor and create strategies for improvement. • Display medication names using full generic names.[54] See above category "Minimize the risk of confusion between alteplase and tenecteplase" for additional recommendations. • Require scanning of the individual medication prior to stocking the ADC.[20,21,53] • Establish a clean, quiet, distraction-free work environment for preparing and dispensing the medication[45,48,53]
Administration	Minimize programming errors involving the infusion pump **(Alteplase only)**

	• Do not assume units when programming parameters into the infusion pump. Confirm that all units are correct (e.g., min vs hr, mg vs mL)
	• Perform and document an independent double check of high-alert medications to verify:[20,55]
	  ◦ Patient
	  ◦ Patient weight
	  ◦ Drug name
	  ◦ Drug concentration
	  ◦ Rate of infusion
	  ◦ Channel selection
	  ◦ Line attachment

	Build an optimal drug library and build support for the infusion pumps **(Alteplase only)**
	• Include the indication in the drug library.[20,21] • Remove the abbreviation "TPA" from the drug library and infusion pumps.[31,46] See above category "Minimize the risk of confusion between alteplase and tenecteplase" for additional recommendations. • Implement dose error-reduction systems (DERS) such as hard stops on maximum dose and infusion rate.[55,56] • Build a clinical advisory into the infusion pump to require a second nurse to independently verify and document the correct programming of the pump.[55] • Monitor error frequencies and use data (i.e., compliance rate with DERS) on infusion pumps.[42,48,55]
	Document medication administration correctly in EHR
	• Use barcoded medication administration (BCMA).[49] • Require a dual sign-off on the MAR at medication administration. • Avoid backcharting the order or administration in the EHR. Document the placement of the order or the administration of the medication in a timely manner. • Avoid documenting the administration solely into the patient's progress notes of the EHR. The medication administration should be scanned into the patient's MAR.

Note: ADC: Automated dispensing cabinet. BCMA: Barcoded medication administration. BPMH: Best possible medication history. CPOE: Computerized provider order entry. DERS: Dose error-reduction systems. EHR: Electronic health record. FMEA: Failure mode and effects analysis. IV: Intravenous. MAR: Medication administration record.

Conclusions

Both alteplase and tenecteplase have been used in clinical practice for decades; however, the increasing off-label use of tenecteplase for the treatment of AIS[5,7,8,11,61,62] created new safety challenges. By analyzing the stages of the medication-use process, associated factors, and event types, we identified aspects to medication safety that occurred with both alteplase and tenecteplase, as well as those that were unique to each individual medication. The event type *Wrong dose* was the most prevalent event type for both medications; however, the related stages and associated factors for the individual medication were variable. Our study underscores the need for increased awareness surrounding these medication errors and the provision of necessary support and training for providers. We encourage readers to review the potential strategies that fit the needs of their institutions and to supplement the analyses of their own institution-specific data and investigations with our findings to improve safety of patients receiving thrombolytics for treatment of AIS.

Note

This analysis was exempted from review by the Advarra Institutional Review Board.

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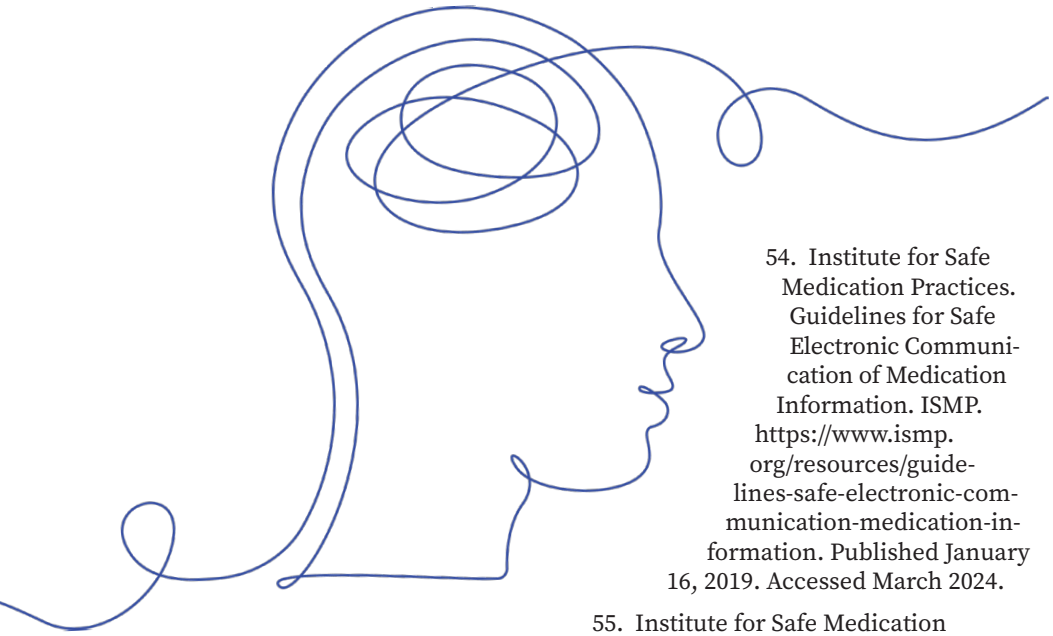

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