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Original Article

Safety and Real-World Effectiveness in the Transition from Alteplase to Tenecteplase for Stroke Treatment

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ABSTRACT: ***Background:*** Tenecteplase has been shown to be non-inferior to alteplase for the treatment of acute ischemic stroke within 4.5 hours of stroke onset. While not formally approved by regulatory authorities, many jurisdictions have transitioned to using tenecteplase for routine stroke treatment because it is simpler to use and has cost advantages. ***Methods:*** We report a three-phase time-series analysis over 2.5 years and the process for transition from use of alteplase to tenecteplase for the routine treatment of acute ischemic stroke from a system-wide perspective involving an entire province. The transition was planned and implemented centrally. Data were collected in clinical routine, arising from both administrative sources and a prospective stroke registry, and represent real-world outcome data. Data are reported using standard descriptive statistics. ***Results:*** A total of 1211 patients were treated with intravenous thrombolysis (477 pre-transition using alteplase, 180 transition period using both drugs, 554 post-transition using tenecteplase). Baseline characteristics, adverse events and outcomes were similar between epochs. There were four dosing errors with tenecteplase, including providing the cardiac dose to two patients. There were no instances of major hemorrhage associated with dosing errors. ***Discussion:*** The transition to using intravenous tenecteplase for stroke treatment was seamless and resulted in identical outcomes to intravenous alteplase.

RÉSUMÉ : Sécurité et efficacité réelle en cas de transition de l'altéplase au ténectéplase pour le traitement des AVC. ***Contexte :*** Le ténectéplase s'est avéré non inférieur à l'altéplase pour le traitement de l'AVC ischémique aigu dans les 4,5 heures suivant l'apparition de l'AVC. Bien qu'il n'ait pas été formellement approuvé par les autorités réglementaires, de nombreuses juridictions sont passées à l'utilisation du ténectéplase pour le traitement de routine de l'AVC en raison de sa simplicité d'utilisation et de ses avantages en termes de coûts. ***Méthodes :*** Dans une perspective systémique impliquant une province entière, nous voulons nous pencher ici sur une analyse de séries chronologiques en trois phases s'échelonnant sur 2,5 ans ainsi que sur le processus de transition de l'altéplase au ténectéplase pour le traitement de routine de l'AVC ischémique aigu. La transition a été planifiée et mise en œuvre au niveau central. Les données ont été ensuite collectées dans un contexte de routine clinique et proviennent de sources administratives et d'un registre prospectif des AVC. Elles représentent des résultats obtenus dans un contexte réel et sont présentées à l'aide d'outils statistiques descriptifs standards. ***Résultats :*** Au total, 1211 patients ont été traités par thrombolyse intraveineuse (477 avant la transition en utilisant l'altéplase ; 180 pendant la période de transition en utilisant les deux médicaments ; 554 après la transition en utilisant le seul ténectéplase). Les caractéristiques à l'amorce d'un traitement, les événements indésirables et les résultats obtenus ont été similaires d'une phase à l'autre. On a recensé 4 erreurs de dosage avec le ténectéplase, y compris l'administration d'une dose cardiaque à 2 patients. Précisons aussi qu'il n'y a pas eu d'hémorragie majeure associée à des erreurs de dosage. ***Discussion :*** La transition vers le ténectéplase intraveineux pour le traitement de l'AVC s'est faite en douceur et a donné des résultats identiques à ceux de l'altéplase intraveineux.

Keywords: acute ischemic stroke; alteplase; intravenous thrombolytic treatment; real-world evidence; tenecteplase

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Highlights

- Transition to treatment of acute ischemic stroke from intravenous alteplase to tenecteplase occurred on a province-wide, managed process in Alberta after completion of the ACT trial.
- Although there were a priori concerns about dosing, only 4 (0.3%) dosing errors occurred; none had adverse sequelae.
- Clinical outcomes were nearly identical for alteplase-treated versus tenecteplase-treated patients.

Introduction

Multiple studies have now explored intravenous tenecteplase for the treatment of acute ischemic stroke.[1–10] Key advantages of tenecteplase include the single bolus dosing as compared to a 60-minute infusion with alteplase, greater fibrin specificity and a longer serum half-life. From the perspective of a stroke system of care, interfacility transport is expedited as paramedics do not need to manage an infusion en route to a tertiary stroke center for potential endovascular thrombectomy (EVT). Large pivotal studies have now confirmed that intravenous tenecteplase treatment at 0.25 mg/kg dosing is non-inferior to intravenous alteplase at 0.9 mg/kg dosing.[11–13] Major stroke guidelines around the world now recommend the use of tenecteplase.[14,15] In the Canadian province of Alberta, a defined structure of 17 stroke centers that deliver intravenous thrombolytic treatment has been in place for more than two decades, and routine quality improvement data are collected on all patients who are treated with intravenous thrombolysis for stroke.

Because the Alteplase Compared to Tenecteplase (AcT) trial[11] was conducted in Canada with trial leadership based in Calgary, we had knowledge of results after the study was completed but prior to the formal publication and began a formal transition process from routine alteplase to routine tenecteplase treatment, prior to changes in national guidelines. Key concerns in the transition process included drug distribution, dosing errors and clinical outcomes. We report the safety and real-world effectiveness of the transition.

Methods

The province of Alberta, Canada, has a population of approximately 4.5 million. Like all provinces in Canada, the provincial government serves as the single insurer for acute hospital care, such that all residents of Alberta have insured access to acute stroke care. A small proportion of Albertans who are members of the military, the Royal Canadian Mounted Police and First Nations access the same system of care but are funded by the federal government. In Alberta, there were approximately 4000 ischemic stroke admissions annually during the study period.[16] Public healthcare delivery, including delivery of acute stroke services andemergency medical services (EMS), is managed by a single health authority, Alberta Health Services.

There are 17 hospitals designated as stroke centers in Alberta; two are comprehensive tertiary care centers that provide EVT. The remaining 15 include 1 urban primary stroke center and 14 rural primary stroke centers that provide intravenous thrombolysis and are distributed to provide geographic coverage for the population. The EMS ambulance system includes both ground and air transport, and paramedics are trained to use a standardized stroke screen (Alberta Health Services stroke screen) and to assess stroke severity using the Los Angeles Motor Score (LAMS). In general, EMS will transport suspected stroke patients to the most appropriate nearest stroke center. For patients with severe deficits (LAMS 4 or 5), a primary stroke center may be bypassed where transport times to a comprehensive stroke center are short.

Tenecteplase (TNKase™) is supplied in Canada by Hoffmann-La Roche Canada Ltd but manufactured in San Francisco, USA, by Genentech Ltd. The drug is supplied in 50 mg vials only and marketed for the treatment of acute myocardial infarction. Health Canada has not approved tenecteplase for "on-label" treatment of ischemic stroke. However, tenecteplase was used in the setting of active clinical trials including the TNK-tPA Evaluation for Minor ischemic stroke with Proven Occlusion (TEMPO-2) and AcT trials, which were both active in all or part of the reporting periods. We sought and received formal medical approval from the executive leadership team at Alberta Health Services. In addition, we worked with the Provincial Pharmacy Service to orchestrate the transition. Because alteplase in standard dosing vials of 50 and 100 mg was largely used for ischemic stroke with a small number of treatments of pulmonary thromboembolism, we designed a plan to use up the existing stock of alteplase during the transition. Rural sites would be the first to utilize tenecteplase while transferring their existing alteplase stock to urban sites (transition phase, November 1, 2022). After the switch to tenecteplase was made, the supply of alteplase was curtailed and generally available for use only for the treatment of pulmonary embolus. Once provincial alteplase stock was depleted, urban sites would then transition to using tenecteplase (post-transition, March 1, 2023). As compared to the possibility of wasting vials of alteplase, this resulted in a direct drug cost-savings of approximately $0.44M.

Working closely with the zone stroke programs, we developed the support resources needed for the transition, including order sets, information sheets and an education program surrounding dosing. Because the available ("off the shelf") tenecteplase is a 50 mg vial with package insert and documentation describing the cardiac dosing regimen at 0.5 mg/kg, educational material and education on dosing for ischemic stroke (0.25 mg/kg) were widely distributed. Through a collaborative effort with the zone stroke programs, EMS and involving leaders from the Medicine, Acute, and Critical Care Strategic Clinical Networks (SCN™), the transition plan (including relevant support documents and resources) was broadly communicated creating general awareness of this practice change within and beyond the 17 stroke centers. Support documents and resources included (a) an e-learning module titled "*Acute Ischemic Stroke Treatment with Thrombolysis*" (Available from the corresponding author upon request); (b) podcasts providing a review of the AcT trial, the transition plan and drug reconstitution, dosing and implications; (c) a poster highlighting the difference between alteplase and tenecteplase; and (d) updated stroke order sets and protocols (both on the electronic and paper-based charting and order-entry platforms).

We collected data in clinical routine through the Quality Improvement and Clinical Research (QuICR) stroke registry[17] and administrative data. The decision to use 1 year before and 1 year after was a convenience sample and not based on a defined sample size calculation. Case finding including active surveillance at each site and a post hoc quarterly reconciliation with pharmacy records to identify any missed cases. We collected and compared dosing errors through the Reporting and Learning System for Patient Safety (RLS) system, a routinely used system for error and safety reporting of any type throughout Alberta Health Services, and actively sought reports of dosing errors related to the use of

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Table 1. Baseline characteristics

	Pre-transition epoch (alteplase) Nov 1, 2021–Oct 31, 2022	Transition Nov 1, 2022–Feb 28, 2023	Post-transition (tenecteplase) Mar 1, 2023–Feb 29, 2024
N	477	180	554
DEMOGRAPHICS			
Age (y) at admission	70 (61–80)	72 (62–82)	72 (62–81)
Sex			
Female	208 (43.6%)	80 (44.4%)	257 (46.4%)
Male	269 (56.4%)	99 (55.0%)	293 (52.9%)
UTD/Other	0 (0.0%)	1 (0.6%)	4 (0.7%)
MEDICAL HISTORY			
Hypertension	303 (63.5%)	120 (66.7%)	372 (67.1%)
Diabetes mellitus	130 (27.3%)	45 (25.0%)	135 (24.4%)
Atrial fibrillation	72 (15.1%)	30 (16.7%)	65 (11.7%)
Coronary artery disease	7 (1.5%)	3 (1.7%)	9 (1.6%)
Congestive heart failure	17 (3.6%)	10 (5.6%)	14 (2.5%)
Chronic renal disease	10 (2.1%)	5 (2.8%)	14 (2.5%)
UTD medical history	30 (6.3%)	9 (5.0%)	33 (6.0%)
CLINICAL			
NIHSS baseline	10 (6–17)	9 (6–16)	10 (5–16)
Onset to door time (min)	84 (57–130)	88 (60–157)	82 (54–136)
Door to NCCT time (min)	14 (10–19)	15 (11–22)	15 (11–21)
Onset to IV thrombolysis time (min)	134 (103–189)	144 (105–222)	138 (99–203)
Door to IV thrombolysis time (min)	42 (32–58)	48 (36–64)	44 (32–65)
NCCT to IV thrombolysis time (min)	25 (17–42)	30 (18–44)	27 (16–46)

UTD = unable to determine; NIHSS = National Institutes of Health Stroke Scale score; NCCT = non-contrast computed tomographic scan; IV = intravenous.
All values are presented as *N* (%) or median(interquartile range).
Note that the medical history variables were determined from the discharge abstract diagnosis coding of the medical record. Apart from hypertension and diabetes mellitus, which are known to be well-coded in Canadian administrative data, the medical history coding appears to under-represent the known prevalence of comorbid conditions in acute ischemic stroke patients. Clinical variables were collected prospectively by stroke coordinators at each site.
During the pre-transition epoch (alteplase), there were 84 additional patients who received tenecteplase for the treatment of stroke in the context of ongoing clinical trials. Similarly, in the post-transition epoch (tenecteplase), there were four patients who received alteplase. These 88 patients baseline characteristics are not included in Table 1.

Table 2. Adverse events

	Pre-transition epoch (alteplase) Nov 1, 2021–Oct 31, 2022	Transition Nov 1, 2022–Feb 28, 2023	Post-transition (tenecteplase) Mar 1, 2023–Feb 29, 2024
N	477	180	554
Urinary tract infection	34 (7.1%)	16 (8.9%)	28 (5.1%)
Pneumonia	16 (3.4%)	9 (5.0%)	25 (4.5%)
Respiratory failure	7 (1.5%)	0 (0.0%)	10 (1.8%)
COVID-19	10 (2.1%)	3 (1.7%)	7 (1.3%)
Electrolyte disturbance	14 (2.9%)	5 (2.8%)	18 (3.2%)
Intracranial hemorrhage	9 (1.9%)	3 (1.7%)	9 (1.6%)
Acute kidney injury	6 (1.3%)	5 (2.8%)	12 (2.2%)
Atrial fibrillation or flutter	9 (1.9%)	5 (2.8%)	6 (1.1%)
Delirium	7 (1.5%)	3 (1.7%)	9 (1.6%)
Arterial access complication	12 (2.5%)	1 (0.6%)	6 (1.1%)
Sepsis	3 (0.6%)	0 (0.0%)	5 (0.9%)
Epistaxis	3 (0.6%)	0 (0.0%)	2 (0.4%)
Pulmonary embolus or DVT	3 (0.6%)	0 (0.0%)	2 (0.4%)
Seizure or convulsion	2 (0.4%)	1 (0.6%)	1 (0.2%)
Ischemic stroke recurrence	2 (0.4%)	3 (1.7%)	1 (0.2%)

DVT = deep venous thrombosis. Electrolyte disturbance includes hypokalemia and hyperkalemia and hyponatremia and hypernatremia. Intracranial hemorrhage includes intracerebral hemorrhage, subarachnoid hemorrhage and intraventricular hemorrhage.
All values are presented as *N* (%) or median(interquartile range).
Note that adverse events (top 15 by frequency) were derived from type 2 diagnoses from the discharge abstract diagnosis coding of the medical record.
During the pre-transition epoch (alteplase), there were 84 additional patients who received tenecteplase for the treatment of stroke in the context of ongoing clinical trials. Similarly, in the post-transition epoch (tenecteplase), there were four patients who received alteplase. These 88 patients are not included in Table 2.

tenecteplase. Broad criteria were used to capture as many cases as possible, and then each case was reviewed to confirm the diagnosis and treatment for stroke. Clinical outcomes are reported using home time, which is derived from administrative data. Home time is defined as the number of nights spent outside of healthcare institutions within 90 days of the index admission to an acute care hospital, and this outcome is associated with global disability after stroke. Patients who died in hospital after the index stroke have a home time of zero days.[18–20] Data are reported comparing three serial time epochs: (1) pre-transition, treatment with alteplase from November 1, 2021, to October 21, 2022; (2) transition where rural sites switched to tenecteplase and urban sites continued with alteplase from November 1, 2022, to February 28, 2023; and (3) post-transition where all sites used tenecteplase from March 1, 2023, to February 29, 2024. Data are reported with standard descriptive statistics.

Results

During the study period, 9332 patients were discharged with a final diagnosis of ischemic stroke (3973 during the pre-transition (alteplase) period, 1341 during the transition period and 4018 during the post-transition (tenecteplase) period). A total of 1211 patients were treated with intravenous thrombolysis (477 pre-transition, 180 transition, 554 post-transition). Of these 1211 patients, 84 (6.9%) were stroke mimics defined as having a final non-ischemic stroke syndrome discharge diagnosis. Thus, the proportion of ischemic stroke patients treated with thrombolysis was 1127/9332 (12.1%). Among these patients, the proportion that

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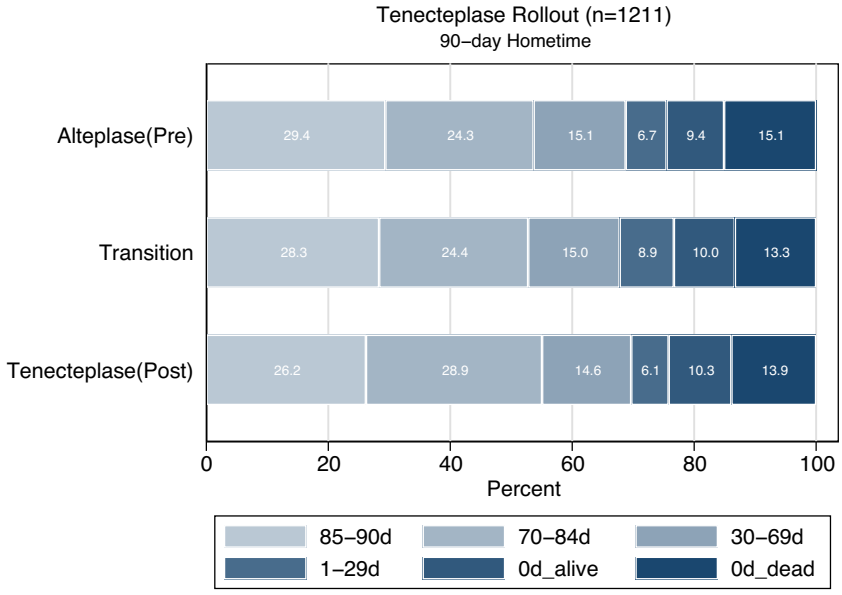

Figure 1. Clinical outcomes at 90 days.

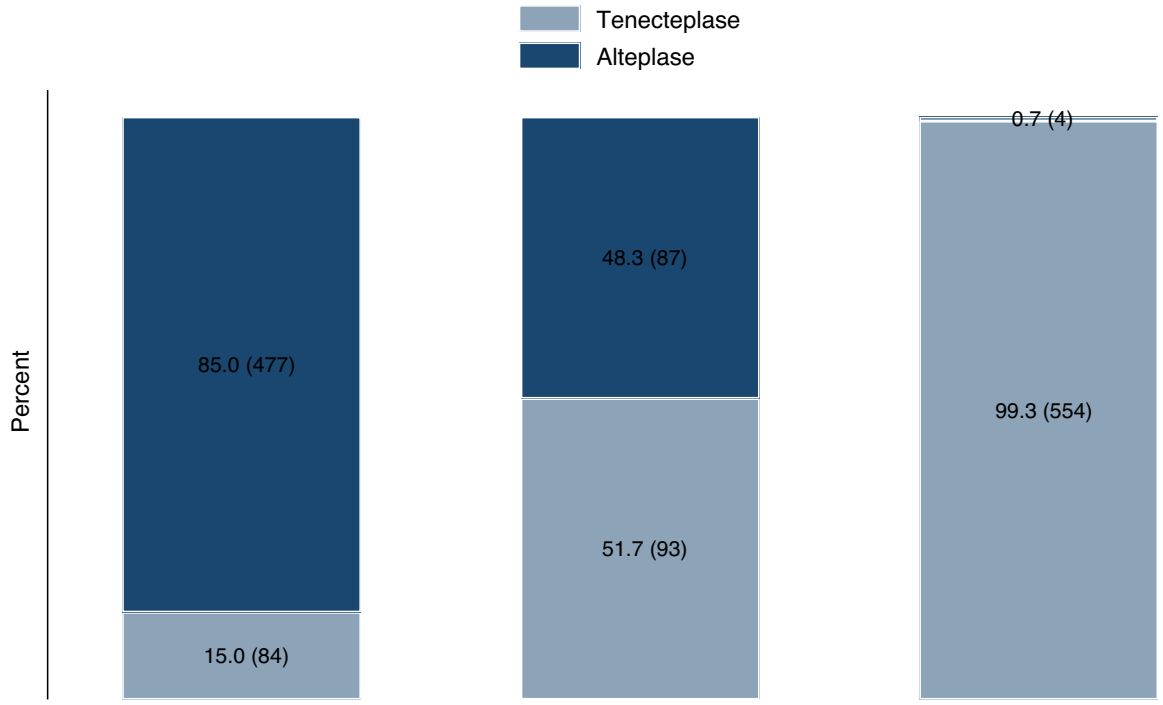

Figure 2. During the pre-transition epoch (alteplase), there were 84 additional patients who received tenecteplase for the treatment of stroke in the context of ongoing clinical trials. Similarly, in the post-transition epoch (tenecteplase), there were four patients who received alteplase. These 88 patients are included and represented in this figure.

underwent EVT was 26.2% (125/477), 22.8% (41/180) and 28.5% (158/554) in each phase, respectively. An additional 84 patients were treated with tenecteplase as part of a randomized clinical trial during the pre-transition epoch, and 4 patients were treated with alteplase during the post-transition epoch; these 88 patients were not included in the comparative analysis.

Baseline characteristics (Table 1) and adverse events were typical of stroke patients (Table 2). There were no significant differences in baseline characteristics or adverse events by epoch. Home-time outcomes are shown in Figure 1, and similarly, there were no differences in outcomes by epoch. The evolution of the transition is shown in Figure 2.

In the post-transition phase, there were 22 flagged potential safety concerns for tenecteplase in the RLS system, of which 12 were identified as treatment for myocardial infarction. Of 10 potential dosing safety concerns in stroke patients, 6 were clerical

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errors and 4 were determined to have had a dosing error. Of these errors, two occurred at rural sites, and eight occurred at urban sites. The six clerical errors including delays in obtaining drug from pharmacy or improper documentation. The four tenecteplase dosing errors included two patients given the full 50 mg vial unadjusted for weight, one patient given cardiac dosing of tenecteplase and 1 instance of the incorrect patient, who did not have a stroke, receiving the appropriate stroke dosing due to a communication error between the medical team and Emergency Department (ED) nursing team. Using a similar review of the RLS system, in the pre-transition phase, four dosing errors with alteplase were identified including two patients underdosed due to incorrect programming of the infusion pump, one patient underdosed due to the use of two 50 mg alteplase vials reconstituted in a syringe for a syringe pump and failure of the syringe pump to reactivate when the appropriate change was made to the second syringe and one patient overdosed due a 2 kg difference in weight used to calculate the dose. There were no instances of intracranial or extracranial hemorrhage associated with these four dosing errors.

Discussion

In Alberta, the transition in stroke treatment from intravenous alteplase to tenecteplase proceeded in a planned fashion without adverse consequence. Very few dosing errors were observed, and in retrospect, these were avoidable. Outcomes, as predicted from the randomized trial evidence, were identical. Savings in drug costs were achieved by pragmatically exhausting the existing stock of intravenous alteplase.

A similarly favorable experience has been reported from New Zealand.[21] A relevant consideration is that tenecteplase is not yet approved for acute ischemic stroke treatment by Health Canada. Tenecteplase has recently been approved with a formal ischemic stroke indication in the USA, and a similar regulatory review is currently underway in Canada. This meant using "off-the-shelf" tenecteplase in 50 mg vials with pre-existing default cardiac indication and dosing package inserts. While there are well-educated healthcare personnel responsible for drug administration, we were very concerned about the possibility of dosing errors, and dosing errors did occur. Overdosing stroke patients has the potential to be associated with fatal intracranial hemorrhage. Approval by Alberta Health Services medical leadership and the subsequent demonstrated safety of the transition were reassuring. It is impossible to know if our education campaign and teaching resources were essential to this result.

We note that treatment times were not substantially different between epochs. Practically, this result makes sense because the process of reconstituting lyophilized drug with sterile water and giving a bolus injection is the same for tenecteplase as it is for the initial bolus of alteplase. We did not measure the benefits of reduction in nursing time, hospital resource utilization or improvements in EMS transport times from simplified dosing protocols and elimination of infusion pump requirements during inter-facility transfers.

Our report is observational and presents empirical data on a real-world stroke treatment transition. We did not calculate a sample size, and a limitation is that we are underpowered to show small differences. Data are retrospective from health system administrative sources, and this may introduce slight inaccuracies as compared to a fully prospective data collection process. We caution that there is likely to have been underreporting of adverse events using administrative data.[22,23]

Overall, we found that tenecteplase treatment was identical to alteplase treatment for acute ischemic stroke in real-world clinical practice, and the transition was seamless.

Author contributions. The primary paper was written by MDH, MLH and JS. Data analytics were provided by JS. MDH performed statistical analysis. All authors both contributed to patient care, data collected and provided critical review and revision of the manuscript.

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