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Original Article

Mortality After Total Anterior Circulation Stroke: A 25-Year Observational Study

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ABSTRACT: ***Background:*** Mortality remains a substantial problem after acute ischemic stroke, despite advances in acute stroke treatment over the past three decades. Mortality is particularly high among patients with Total Anterior Circulation Stroke (TACS), generally representing patients with middle cerebral artery occlusions. Notably however, these patients also stand to benefit most from new therapies including endovascular thrombectomy (EVT). In this study, we aimed to examine temporal trends in, and factors associated with, 30-day in-hospital mortality after TACS. ***Methods:*** Information on all patients with community-onset TACS from 1994 through 2019 was extracted from a prospective acute stroke registry. Multivariate analysis was performed on the primary outcome of 30-day in-hospital mortality, as well as secondary functional outcomes. ***Results:*** We studied 1106 patients hospitalized for community-onset TACS, 456 (41%) of whom experienced 30-day in-hospital mortality. Over the 25 years of observation, 30-day in-hospital mortality rose and then fell. Increased odds of mortality was associated with age and stroke severity. Decreased odds of mortality was associated with alteplase therapy and EVT, as well as presentation to hospital more than 12 hours after stroke onset. Treatment with alteplase, EVT, or both was associated with higher odds of functional independence and discharge home, and shorter lengths of stay in acute care. ***Conclusions:*** Patients receiving alteplase, EVT, or both had lower 30-day in-hospital mortality and better functional outcomes than those who were untreated. These observational data demonstrate the benefits of recanalization therapy in routine clinical practice.

RÉSUMÉ : Taux de mortalité après un AVC touchant la circulation antérieure totale : une étude observationnelle menée pendant 25 ans. ***Contexte :*** La mortalité demeure un problème important après un AVC ischémique aigu, et ce, malgré les progrès réalisés dans leur traitement au cours des trois dernières décennies. À cet égard, le taux de mortalité est particulièrement élevé chez les patients victimes d'un AVC touchant la circulation antérieure totale (CAT ou *total anterior circulation*), AVC que l'on observe généralement chez des patients atteints d'occlusions de l'artère cérébrale moyenne. Il est toutefois à noter que ces patients sont aussi ceux qui bénéficieront le plus des nouvelles thérapies, notamment la thrombectomie endovasculaire (TEV). Dans cette étude, nous avons donc voulu nous pencher sur les tendances temporelles et les facteurs associés au taux de mortalité hospitalière au bout de 30 jours à la suite d'un AVC touchant la CAT. ***Méthodes :*** Des renseignements portant sur tous les patients victimes d'un AVC à l'extérieur du système hospitalier (de 1994 à 2019) ont été extraits d'un registre prospectif d'AVC aigus. Une analyse multivariée de la mortalité hospitalière au bout de 30 jours et des résultats fonctionnels secondaires de ces patients a ensuite été effectuée. ***Résultats :*** Nous avons étudié 1106 patients hospitalisés pour un AVC touchant la CAT et survenu en dehors du système hospitalier, dont 456 d'entre eux (41 %) sont décédés à l'hôpital au bout de 30 jours. Au cours de ces 25 années d'observation, le taux de mortalité hospitalière au bout de 30 jours a augmenté puis diminué. L'augmentation du risque de mortalité a été associée à l'âge des patients mais aussi à la gravité des AVC. En revanche, la diminution du risque de mortalité a été associée à un traitement d'altéplase et au recours à la TEV de même qu'au fait de se présenter à l'hôpital plus de 12 heures après le début de l'AVC. Un traitement d'altéplase, le recours à la TEV ou les deux ont aussi été associés à des chances plus élevées d'autonomie fonctionnelle et d'obtention d'un congé ainsi qu'à des séjours plus courts au sein d'une unité de soins actifs. ***Conclusions :*** Les patients ayant bénéficié de l'altéplase, d'une TEV ou des deux ont présenté un taux de mortalité hospitalière inférieur au bout de 30 jours et de meilleurs résultats en termes d'autonomie fonctionnelle que ceux qui n'en n'avaient pas bénéficiés. Ces données observationnelles démontrent les avantages d'un traitement de recanalisation dans la pratique clinique courante.

Keywords: Neurovascular; Stroke; Therapeutics; Thrombolysis; Outcomes research

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Introduction

Acute ischemic stroke is a common problem, with close to 8 million incident cases worldwide each year.[1] Globally, stroke is the second-leading cause of death and the third leading cause of death and disability.[1] Mortality after stroke has been related, directly or indirectly, to age, female sex, premorbid functional status, comorbidity, and stroke severity.[2–5] Due to the variation of mortality and morbidity by cause and severity, classification systems have arisen to describe stroke phenotypes. The Oxfordshire Community Stroke Project (OCSP) classification of ischemic stroke subtypes[6] has found widespread application because it requires only the findings from the clinical examination and a non-contrast CT scan to exclude hemorrhage and stroke mimics, and provides useful information regarding likely cause and outcome. The Total Anterior Circulation Stroke (TACS) subtype correlates well with severe stroke (median National Institutes of Health Stroke Scale score 18),[7] caused by middle cerebral artery (MCA) infarction.[8–12] In population-based studies conducted in the 1980s and 1990s, TACS was associated with a mortality rate of 35-48% at one-month post-stroke.[6,13,14]

Over the past three decades, there have been significant advances in the treatment of acute ischemic stroke. Intravenous alteplase was first reported to improve outcome after stroke in 1995[15] and is now routinely offered to all eligible ischemic stroke patients.[16] Despite its established benefit on functional outcome, the randomized trials of alteplase treatment did not demonstrate a mortality benefit at three or six months.[17] Endovascular thrombectomy (EVT) for anterior circulation ischemic stroke caused by intracranial large-artery occlusion (mainly MCA stroke) also clearly improves functional outcome,[18–20] though only two individual trials[21,22] and one[20] of three metanalyses[18,19] showed a mortality benefit. A case-control analysis from our center reported a reduction in both death and disability.[23]

Despite the advances in acute stroke care, mortality and morbidity remain a major consequence of stroke. Patients with TACS are most at risk of death and also most likely to be eligible for EVT. TACS patients therefore represent an ideal population in which to assess the association between mortality and recanalization therapy, particularly EVT.

Aims and Hypothesis

The intention of this project was to examine temporal trends in, and factors influencing, 30-day in-hospital mortality of patients experiencing TACS from 1994 to 2019. Our hypotheses were that in-hospital mortality after TACS would be substantial and would be influenced by age, sex, pre-stroke functional and cognitive status, history of prior stroke, and stroke severity. We additionally hypothesized that EVT, but not alteplase treatment, would be associated with lower 30-day in-hospital mortality.

Methods

Setting

The Queen Elizabeth II (QEII) Health Sciences Centre is a comprehensive stroke center in Nova Scotia, Canada, providing primary and secondary care for approximately 300,000 individuals and tertiary care for close to one million. The QEII has managed acute stroke patients in an organized stroke unit since 1997,[24] mainly under the direction of two neurologists (GG and SP), and in accordance with Canadian Stroke Best Practice Recommendations,[16] available at strokebestpractices.ca. Intravenous thrombolysis has been used since 1996 and EVT since 2011.

Registry

All patients admitted to the QEII acute stroke unit (ASU) are entered prospectively into a registry, which records baseline information, details of stroke presentation, stroke subtype, and outcome data at the time of discharge from the ASU. Cause of in-hospital death is not captured. The registry exists independently of this study for the purpose of quality improvement. The Nova Scotia Health Research Ethics Board granted approval for accession and analysis of data for the purposes of this study.

Subjects and Data Capture

For all patients coded as experiencing community-onset TACS, the following information was extracted from the registry: age, sex, history of stroke or transient ischemic attack (TIA), pre-admission functional and cognitive status, time to presentation in the emergency department, stroke severity, hemispheric localization, symptoms first noted on waking or not, use of thrombolysis and EVT, length of stay (LOS) on the ASU, and discharge destination. Functional dependence was defined as a score of 3–5 on the Oxford Handicap Score,[25] a commonly used variant of the modified Rankin Score.[26] Stroke severity was measured on a scale from previous international trials[27,28] that has been validated at our center,[29] categorized as mild (0–4), moderate (5–7), or severe (8–10).

The primary outcome was 30-day in-hospital mortality. Secondary outcomes for survivors were functional status at discharge from the ASU, LOS, and discharge destination. Secondary outcomes for the deceased were receipt of – and time to initiation of – palliative care.

Data Analysis

Descriptive statistics are reported as counts and percentages for categorical variables, means and standard deviations for normally distributed continuous variables, and medians and interquartile ranges (IQR) for non-normally distributed continuous variables. Univariate logistic regression was performed to compare baseline patient characteristics for the primary outcome. Multivariate logistic regression analysis was performed on variables significant at $p < 0.1$ in univariate analysis. A generalized additive model was also fit to 30-day mortality to explore non-linear spline relationships with baseline covariates. Secondary outcomes of discharge destination, discharge functional status, and LOS were modeled using ordinal logistic regression, logistic regression, and generalized linear models with a gamma distribution, respectively. The Kendall Tau test for trend was used to investigate change in rates of variables over time. All statistical analyses were performed with SAS STAT software 14.3 version 9.4 (SAS Institute, Cary, N.C.), with a significance level of alpha = 0.05

Results

From January 1, 1994, to December 31, 2019, there were 1106 patients with community-onset TACS admitted to the ASU (Table 1). The median age was 78 (IQR 68–85), and 57% were women. Most were previously functionally independent with no history of stroke or cognitive impairment; 33% received thrombolysis, and 9% received EVT. Due to the severity of these strokes, 45% of patients died in hospital, and 87% of survivors were functionally dependent at discharge. The median LOS for all patients was 12 (IQR 5–29) days and 24 (IQR 12–43) days for survivors.

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Table 1: Demographics and outcomes for patients with Total Anterior Circulation Stroke (TACS)

Stroke Unit Admissions		9476	
Ischemic Strokes		6985	74%
Community-onset TACS		1106	16%
Age, Median (IQR)		78	(68–85)
Age Category	<60	148	13%
	60–80	480	44%
	>80	478	43%
Sex	Female	630	57%
	Male	476	43%
Stroke History*	Prior Stroke or TIA	278	27%
	First Ever Stroke	740	73%
Pre-stroke Cognition*	Prior Cognitive Impairment	131	23%
	No Cognitive Impairment	437	77%
Pre-stroke Functional Status	Dependent	244	22%
	Independent	862	78%
Wakeup Stroke	Yes	178	17%
	No	870	83%
Stroke Localization	Left Hemisphere	583	53%
	Right Hemisphere	523	47%
Initial Stroke Severity	Moderate	253	23%
	Severe	852	77%
Time to Assessment	<3 hours	775	70%
	3 hours to <6 hours	145	13%
	6 hours to <12 hours	55	5%
	>12 hours	131	12%
Recanalization Treatment	No	714	65%
	Yes	392	35%
tPA	No	746	67%
	Yes	360	33%
EVT	No	1001	91%
	Yes	105	9%
tPA and EVT		73	7%
In-Hospital Mortality	No	612	55%
	Yes	494	45%
30-day In-Hospital Mortality	No	650	59%
	Yes	456	41%
Length of Admission (days), Median (IQR)		12	(5–29)
Discharge destination	Home	136	12%
	Rehab	264	24%
	Long-term Care	112	10%
	Other	100	9%
Discharge Functional Status	Deceased	494	45%
	Dependent	534	49%
	Independent	72	7%

*Denotes variables that were introduced after the initial registry creation.

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Table 2: Univariate analysis of variables associated with 30-day in-hospital mortality after Total Anterior Circulation Stroke (TACS)

Variable	Odds Ratio	95% CI	p-value
Age (per 10-year increment)	**1.70**	1.52–1.90	**<0.0001**
Sex (Female vs Male)	**1.59**	1.25–2.04	**0.0002**
History of Stroke or TIA	**1.82**	1.38–2.41	**<0.0001**
Pre-stroke Cognitive Impairment	**1.92**	1.29–2.86	**0.0013**
Pre-stroke Functional Dependence	**2.40**	1.79–3.21	**<0.0001**
Onset on Waking	1.17	0.85–1.62	0.3348
Localization (Right vs Left)	0.83	0.65–1.05	0.1219
Stroke Severity (Severe vs Moderate)	**2.87**	2.08–3.96	**<0.0001**
Time to Assessment			
3 to < 6 hrs (vs < 3)	0.88	0.61–1.26	0.4768
6 to < 12 hrs (vs < 3)	0.79	0.91–1.06	0.4125
> 12 hrs (vs < 3)	**0.52**	0.35–0.78	**0.0017**
Use of tPA Alone	**0.67**	0.51–0.89	**0.0063**
Use of EVT Alone	**0.30**	0.12–0.75	**0.0102**
Use of tPA and EVT Together	**0.14**	0.07–0.30	**<0.001**
Calendar Year (per 5-year increment)	1.00	0.93–1.08	0.9453

The primary outcome of 30-day in-hospital mortality occurred in 456 patients (41%), with variation over time represented in Figure 1. Due to a rise and fall during the observation period, this was significant for a spline interaction ($p < 0.001$) but not for a linear one ($p = 0.9981$).

In univariate analysis, the odds of experiencing 30-day in-hospital mortality were increased with age (OR 1.70, 95% confidence interval [CI] 1.52–1.90, per 10-year increment), female sex (OR 1.59, 95% CI 1.25–2.04), history of prior stroke or TIA (OR 1.82, 95% CI 1.38–2.41), pre-existing cognitive impairment (OR 1.92, 95% CI 1.29–2.86), pre-stroke functional dependence (OR 2.40, 95% CI 1.80–3.21), and severe stroke (OR 2.87, 95% CI 2.08–9.96, Table 2). Patients presenting after 12 hours (OR 0.52, 95% CI 0.35–0.78) and those receiving alteplase or EVT (OR 0.379, 95% CI 0.29–0.51) were less likely to die within 30 days of hospitalization.

Variables significant in univariate analysis were included in a multivariate analysis (Figure 2), with the exception of pre-stroke cognition which was excluded because of a large number of missing values. When controlling for other variables, only age and stroke severity were shown to be associated with increased odds of mortality, while presentation after 12 hours and recanalization treatment were associated with reduced mortality. Notably, a significant reduction in odds of mortality was present for those treated with alteplase alone (OR 0.49, 95% CI 0.35–0.67), EVT alone (OR 0.20, 95% CI 0.08–0.52), or both (OR 0.15, 95% CI 0.07–0.33). An exploratory multivariate analysis including available data on pre-stroke cognition within the model yielded similar results (data not shown).

No single factor accounted for the shape of the mortality curve (see Supplemental Figures 1–7). Of the variables associated with mortality, the proportion of patients receiving recanalization treatment changed most during the observation period (Figure 3).

Analyses of secondary outcomes showed that recanalization treatment was associated with reduced LOS and improved odds of functional independence at discharge (Supplemental Table 1). An ordinal logistic regression analysis of discharge destination showed that recanalization treatment was associated with reduced odds of discharge to a less favorable destination, where discharge to long-term care was defined as the least favorable outcome, discharge to a rehabilitation unit was better, and discharge home was best (discharge to other locations [$n = 100$] was excluded from this analysis).

The majority of deaths (456/494, or 92.3%) were anticipated, occurring in patients who were receiving comfort measures only. Time to initiation of palliative care did not vary substantially over the 25-year observation period (data not shown).

Additional sensitivity analyses showed no important differences between patients who died within 30 days of hospitalization and those who died later, and no difference in the primary outcome when patients who were discharged to another acute care hospital were excluded (data not shown).

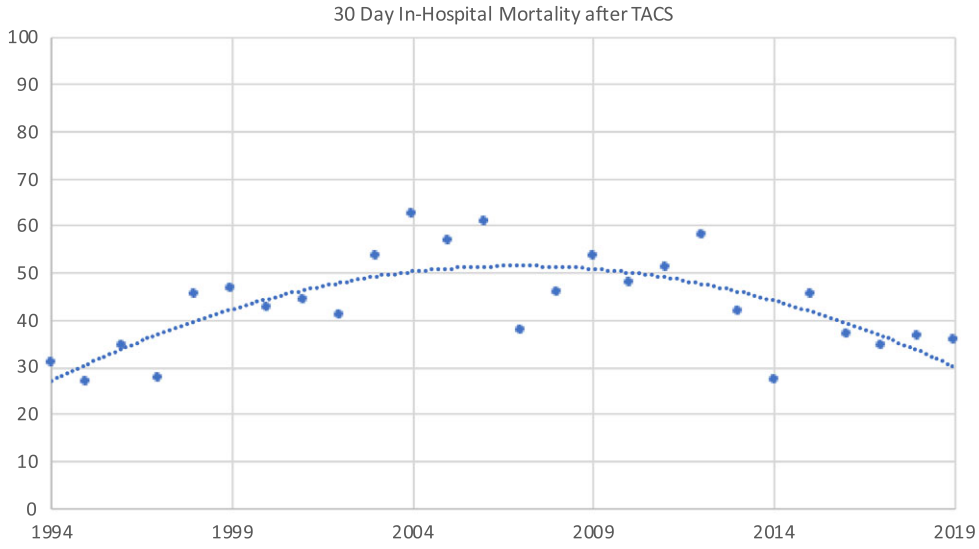


Figure 1: Unadjusted 30-day in-hospital mortality after Total Anterior Circulation Stroke (TACS), 1994–2019

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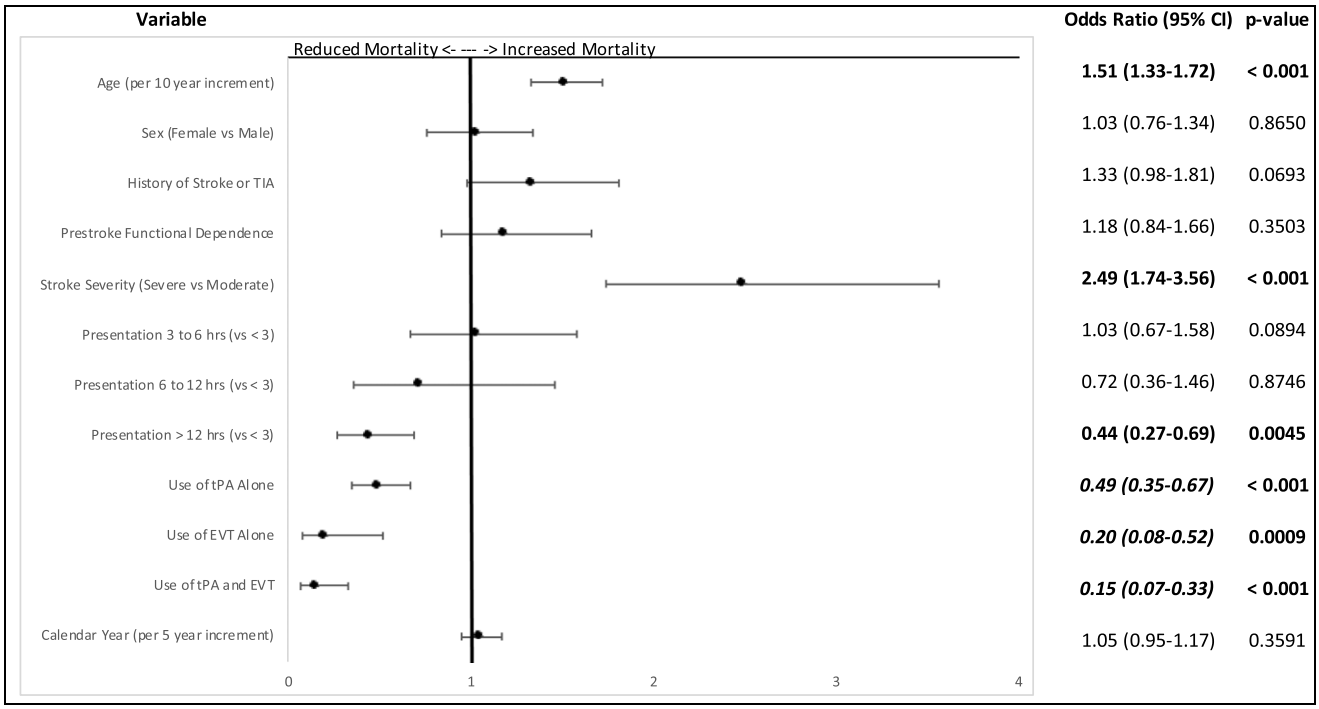


Figure 2: Forest plot of variables associated with 30-day in-hospital mortality after Total Anterior Circulation Stroke (TACS) in multivariate analysis.

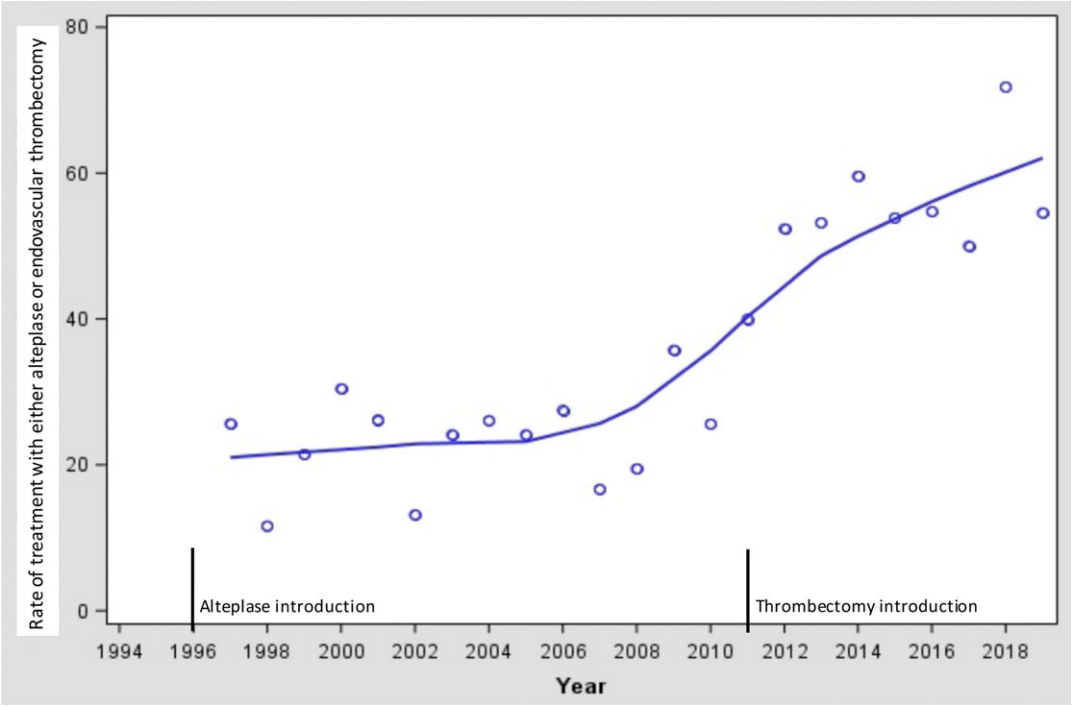


Figure 3: Rate of treatment with recanalization therapy after Total Anterior Circulation Stroke (TACS), 1994–2019. Annotations are provided to indicate the introduction of alteplase (1996) and endovascular thrombectomy (late 2011).

Discussion

Over 25 years of observation at a Canadian comprehensive stroke center, 30-day in-hospital mortality after TACS rose and then fell. In multivariate analysis, age and stroke severity were shown to be associated with increased odds of mortality, while recanalization treatment and presentation after 12 hours were associated with reduced mortality. Patients receiving recanalization therapy also had shorter hospital stays and were more likely to be functionally independent at the time of discharge from the ASU. Mortality was also lower among patients who presented to medical attention

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more than 12 hours after stroke onset, possibly because they had already survived a critical phase of their illness or possibly due to a milder phenotype below the resolution of the severity scale. However, these patients had worse functional outcomes than those who were treated.

The observation of a mortality benefit from alteplase treatment was somewhat unexpected because in the randomized controlled trials treatment was associated with an early increase in mortality (due to treatment-related intracranial hemorrhage),[17] with neutral mortality seen at one and three months, and with improved survival only apparent among a subset of patients who were followed for three years after enrollment in the IST-3 trial.[30] Furthermore, a case-control study of alteplase treatment (including all ischemic stroke subtypes) previously published from our center did not identify a mortality benefit at the time of discharge from acute care.[31] However, mortality at three months following alteplase treatment in the European Safe Implementation of Thrombolysis in Stroke-Monitoring (registry) Study was lower than that reported in the randomized trials,[32] and a mortality benefit has been reported elsewhere in the literature. Improved survival after alteplase treatment has been reported in propensity-matched observational studies in both intermediate[33] and 10-year long-term follow-up data, where the effect was most noted among older patients with severe strokes (NIHSS $\geq$ 16).[34]

The explanation for the mortality benefit from alteplase that we observed is unclear. We acknowledge that our multivariate analysis could not control for all possible confounders. Symptomatic intracranial hemorrhage was not collected over the entire duration of the study, and pre-stroke cognitive status was missing for about half of the cohort (Table 1). Treatment was not randomly allocated, and exploratory analyses showed that treated patients were younger, and pre-stroke were more likely to have been functionally independent and cognitively intact than untreated patients (data not shown), which may have biased our findings. However, there were more severe strokes among treated patients than untreated patients, suggesting that baseline differences do not explain the results. Locally, the process and structure of stroke care have improved over time,[35] and similar work in other jurisdictions has been associated with reduced in-hospital mortality following alteplase treatment,[36] possibly through improved patient selection and increased emphasis on rapid treatment.[37]

The observed mortality benefit from EVT was hypothesized, having been shown previously.[21–23] Most recently, a study from a comprehensive stroke center in the United States that used methods similar to our own showed that EVT was independently associated with significantly reduced odds of mortality (OR 0.61, 95% CI 0.35–1.00, $p = 0.048$) at 90 days post-stroke.[38] EVT may be more likely than alteplase to improve survival after large vessel anterior circulation strokes because of faster and more efficacious recanalization. At six hours after administration, alteplase opens proximal MCA occlusions only about 30% of the time,[39] whereas the EVT recanalization rate at our center is 79%.[40] The introduction of EVT in our hospital roughly coincides with the observed downturn in mortality, indicating the powerful effect of this treatment at the population level, particularly when combined with thrombolysis.

Limitations of this study include its observational nature and thus the inability to conclude causation from the data. Our multivariate analysis is constrained by variables not captured in our registry, but these are not thought to alter its interpretation. The acute stroke registry captures data concerning major risk factors for stroke unit mortality (age, stroke severity, atrial fibrillation, prior stroke or TIA, and pre-stroke functional status) but does not include information regarding hypertension, diabetes, dyslipidemia, or other medical comorbidities. Race and socioeconomic status are not recorded in the registry. Decompressive hemicraniectomy is life-saving after malignant MCA territory infarction,[16] but this procedure is not captured in the registry. The intervention is performed rarely at our center (we identified 11 cases from 2009 to 2019, with no data available prior to 2009), and thus, it is unlikely to have influenced our results.

Strengths of this study include the number of subjects, the duration of observation, and the consistency of medical leadership provided by SP and GG over time. The data set included patients for three years prior to the introduction of thrombolysis, during the period of thrombolysis alone, and during the current era of thrombolysis and EVT. The primary outcome is objective, as well as key secondary outcomes such as discharge destination and LOS. Our study included more than ten times as many TACS patients as there were in the original OCSP and describes a quarter-century of practice. Although our population is an urban North-American one, we believe that the results of this study are generalizable to other tertiary care centers with established systems of stroke care, including pre-hospital management and emergency department pathways. The simplicity of the OCSP, requiring only a clinical examination and unenhanced CT scan, allows generalizability of certain results to resource-limited settings.

In conclusion, mortality remains substantial after TACS. Risk of mortality increases with age and other demographic factors, and thus represents a significant public health challenge in an aging population. In this observational study, patients treated with alteplase, EVT, or both had lower odds of 30-day in-hospital mortality and improved functional outcomes. Clinicians should remain confident in the effectiveness of acute stroke treatments and support the allocation of resources to maximize their utilization.

Supplementary Material. To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2022.262.

Data Availability. Data for this study were extracted from the QEII Acute Stroke Registry. Interested parties may contact the authors to discuss the results and data. Any request for access to the data would be subject to review by the Nova Scotia Health Research Ethics Board.

Conflict of Interest. SH will receive an honorarium for authorship of an upcoming book chapter for the Canadian Pharmacist's Association. GG serves on the advisory committee for Heart and Strokes' Canadian Stroke Best Practice guidelines. The current research and submitted manuscript are unfunded and received no specific support from funding organizations or industry. The authors declare no conflicts with respect to the contents of this project.

Statement of Authorship. JON co-conceived and led the study, and was responsible for drafting and revising the article. SH critiqued the manuscript bringing insights from her case-control study of EVT at our center. JR critiqued the manuscript bringing insights from his case-control study of alteplase therapy at our center. KM guided and performed all the statistical analyses and provided drafting and revision of article content. GG provided staff physician leadership. WS is the stroke program coordinator and collects data for the acute stroke registry. CC is the stroke program data manager. SP co-conceived the study, provided staff physician leadership for registry collection, and was responsible for drafting and revising the article. All authors reviewed the manuscript to provide comments and revisions.

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