

Reduction in Stroke After Transient Ischemic Attack in a Province-Wide Cohort Between 2003 and 2015

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ABSTRACT: Background: Improvements in management of transient ischemic attack (TIA) have decreased stroke and mortality post-TIA. Studies examining trends over time on a provincial level are limited. We analyzed whether efforts to improve management have decreased the rate of stroke and mortality after TIA from 2003 to 2015 across an entire province. **Methods:** Using administrative data from the Canadian Institute for Health Information's (CIHI) databases from 2003 to 2015, we identified a cohort of patients with a diagnosis of TIA upon discharge from the emergency department (ED). We examined stroke rates at Day 1, 2, 7, 30, 90, 180, and 365 post-TIA and 1-year mortality rates and compared trends over time between 2003 and 2015. **Results:** From 2003 to 2015 in Ontario, there were 61,710 patients with an ED diagnosis of TIA. Linear regressions of stroke after the index TIA showed a significant decline between 2003 and 2015, decreasing by 25% at Day 180 and 32% at 1 year ($p < 0.01$). The 1-year stroke rate decreased from 6.0% in 2003 to 3.4% in 2015. Early (within 48 h) stroke after TIA continued to represent approximately half of the 1-year event rates. The 1-year mortality rate after ED discharge following a TIA decreased from 1.3% in 2003 to 0.3% in 2015 ($p < 0.001$). **Interpretation:** At a province-wide level, 1-year rates of stroke and mortality after TIA have declined significantly between 2003 and 2015, suggesting that efforts to improve management may have contributed toward the decline in long-term risk of stroke and mortality. Continued efforts are needed to further reduce the immediate risk of stroke following a TIA.

RÉSUMÉ : Réduction du nombre d'AVC consécutifs à des accidents ischémiques transitoires au sein d'une cohorte de patients d'une même province canadienne. Contexte : Les améliorations dans la prise en charge des accidents ischémiques transitoires (AIT) ont eu pour effet de réduire le nombre d'AVC et le taux de mortalité post AIT. Chose certaine, les études examinant ces tendances au niveau des provinces et dans le temps sont rares. Nous avons ainsi analysé dans quelle mesure les efforts pour améliorer la prise en charge des patients ont permis de diminuer leur taux d'AVC et leur taux de mortalité à la suite d'un AIT, et ce, de 2003 à 2015 en Ontario. **Méthodes :** C'est au moyen de données administratives de l'Institut canadien d'information sur la santé (ICIS) que nous avons identifié une cohorte de patients chez qui l'on avait diagnostiqué un AIT avant qu'ils n'obtiennent leur congé d'un service d'urgence. Nous avons alors examiné leurs taux d'AVC pour les jours 1, 2, 7, 30, 90, 180 et 365 consécutifs à un AIT ainsi que leurs taux de mortalité au bout de 12 mois pour ensuite analyser l'évolution des tendances entre 2003 et 2015. **Résultats :** En Ontario, de 2003 à 2015, on a recensé 61 710 patients chez qui l'on avait diagnostiqué un AIT après une admission dans un service d'urgence. Des régressions linéaires des AVC après un AIT initial ont montré une réduction notable de leur nombre entre 2003 et 2015, à savoir 25 % au jour 180 et 32 % au bout de 12 mois ($p < 0,01$). Le taux d'AVC au bout de 12 mois est également passé de 6,0 % en 2003 à 3,4 % en 2015. Des AVC apparus rapidement à la suite d'un AIT, c'est-à-dire dans les 48 heures, ont continué à représenter environ la moitié des incidents survenus pendant 12 mois. Enfin, le taux de mortalité de ces patients 12 mois après leur congé d'un service d'urgence est passé de 1,3 % en 2003 à 0,3 % en 2015 ($p < 0,001$). **Interprétation :** À l'échelle de l'Ontario, on observe donc que les taux d'AVC ainsi que les taux de mortalité pendant une période de 12 mois ont été réduits de manière notable entre 2003 et 2015, ce qui suggère que les efforts pour améliorer la prise en charge des patients pourraient avoir contribué à la réduction des risques à long terme d'être victime d'un AVC et d'en décéder. Il s'ensuit que des efforts continus sont nécessaires pour réduire encore davantage les risques immédiats d'AVC à la suite d'un AIT.

Keywords: Stroke, TIA, Mortality

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INTRODUCTION

Transient ischemic attack (TIA) is a significant risk factor for stroke, with approximately one in eight acute strokes being preceded by a TIA.¹ The risk of stroke is highest within the first 48 h after a TIA^{2–5}; meta-analyses suggest a pooled

stroke risk of 3.5% within this time frame.⁶ The risk of stroke accumulates over time,^{6,7} from day 1 to day 90 and beyond, with a 1-year risk between 5.1%⁸ and 6.1%.⁹

However, over the past 15 years, the management of TIA has changed significantly, with improved recognition and

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diagnostic strategies, better implementation of secondary prevention strategies, and greater efforts at knowledge translation.¹⁰ Public health initiatives have aimed to increase awareness of stroke symptoms,^{11,12} and early assessment of the intracranial and extracranial vasculature¹³ as well as improved scoring systems that utilize clinical and imaging information¹⁴ have improved prediction of stroke. The role of primary care in the rapid treatment of TIA has been recognized.^{15,16} Rapid assessment and treatment in specialized clinics have reduced the risk of stroke following TIA (FASTER,⁵ EXPRESS trials¹⁷). Patients managed in outpatient TIA clinics have lower rates of stroke at 90 d compared to those managed in regular clinical practices or compared to patients' predicted risk scores.^{6,8,17–20} In Ontario, the Ontario Stroke System – launched in 2000 and fully implemented in 2005 – has led to significant improvements in TIA/stroke care and outcomes.^{21–25}

While results are improved for people seen in specialized clinics, studies examining the impact of these improvements, and changes over time in outcomes at a province-wide level are limited. Many patients are not treated in specialized TIA clinics and the extent of improved care for those treated in the hospital or in general practitioner care has not been evaluated. We sought to examine temporal trends of stroke and mortality following a TIA in Ontario in a province-wide hospital-based cohort between 2003 and 2015.

METHODS

Setting

Ontario is the most populous province in Canada with a population of 14 million.²⁶ All Ontarians have access to a publicly-funded, universal healthcare system. Stroke care in the province is distributed over 11 regional networks with each region being covered by a regional stroke center and a number of district stroke centers.²⁷ Regional stroke centers provide the full range of stroke care through an on-call stroke team and the capability to deliver tissue plasminogen activator (tPA), endovascular thrombectomy (EVT), and provide other essential services like an acute stroke unit and stroke prevention clinic.

Data Source

We utilized administrative data from 2003 to 2015 from the Canadian Institute of Health Information's (CIHI) National Ambulatory Care Reporting System (NACRS) database and the Discharge Analysis Database (DAD). NACRS receives ambulatory and emergency department (ED) data from select reporting institutions while the DAD receives inpatient information from all institutions (except Quebec) across Canada. All hospitals in Ontario report information to both NACRS and DAD. Data is coded based on the most responsible diagnosis using the International Classification of Diseases, 10th revision. We identified visits for TIA or ischemic stroke using the ICD-10 codes G45, I63, and I64; all of which are validated in the Canadian administrative data.²⁸

Study Population

All patients who had their first ED visit with a TIA in the NACRS database prior to a hospital admission for ischemic

stroke and who had complete records (with readmission data for stroke and/or death) were identified. Patients who had incomplete records or who died before discharge from the ED were excluded. If a patient had an emergency room visit for their first TIA (as recorded in NACRS) but was admitted to the hospital within 12 h (reflected by a transfer from NACRS to DAD), they were excluded.

CIHI provides coders with the option to utilize a “Q” or “query” prefix for an ICD-10 diagnosis when there is uncertainty documented by a physician.²⁹ To minimize any effect of identification bias, this analysis excluded patients coded with a “query” prefix.

Data Analysis

Our outcomes were readmission to hospital with an ischemic stroke (ICD-10 code I63, I64), death (R99), and all-cause readmission at 24 h, 48 h, and 7, 30, 90, 180, 365 d after the initial TIA.

We used descriptive statistics to characterize patient demographics. Using linear regression analyses, we explored trends over time of stroke occurrence at multiple time points after stroke (24 h, 48 h, 7, 30, 90, 180, and 365 d) and calculated percent change. We also examined the rates of 1-year mortality over time. We were unable to adjust for age and sex because there was insufficient power to account for additional variables. All analyses were conducted using SAS and IBM SPSS Statistics 22. Statistical significance was set at $p < 0.05$.

RESULTS

Demographics (Figures 1, 2 and Table 1)

A total of 61,710 patients were discharged from EDs in Ontario from 2003 to 2015 with a diagnosis of TIA. An additional 34,614 patients were coded with a “query” prefix and were excluded from the current analysis (Figure 1 and Table 1). The number of patients with TIA remained relatively stable from 2003 to 2015 (Figure 2; $M = 4746.9$, $SD = 324.6$).

Ischemic Stroke Following TIA (Figures 3 and 4)

Readmission dates and values were available for 61,666 patients. Between 2003 and 2015, linear regression analyses showed that there were significant reductions in cumulative stroke occurrence at day 180 ($p = 0.026$) and 1 year ($p = 0.008$) following a TIA from 2003 to 2015 (Figure 3). The reduction in cumulative stroke occurrence at 90 days nearly achieved statistical significance ($p = 0.052$), and was not significant at the 1-, 2-, 7, or 30-day time points.

Over the 13-year period, stroke at Day 180 and 1-year post-TIA decreased by 25% and 32%, respectively. The slopes of the linear regressions for each time point became increasingly more negative, suggesting that there is a cumulative reduction in stroke occurrence between days 1 and 365 after a TIA (Figure 3). Figure 4 illustrates the rates of stroke at each time point for every fiscal year from 2003 to 2015. The overall rate of stroke 1 year after a TIA decreased from 6.0% in 2003 to 3.4% in 2015 (Figures 3 and 4). The risk of early stroke following a TIA remains high, with approximately 50% of all strokes after TIA occurring during the first year in 2015 still occurring within the first 48 h (Figure 3 and Table 2).

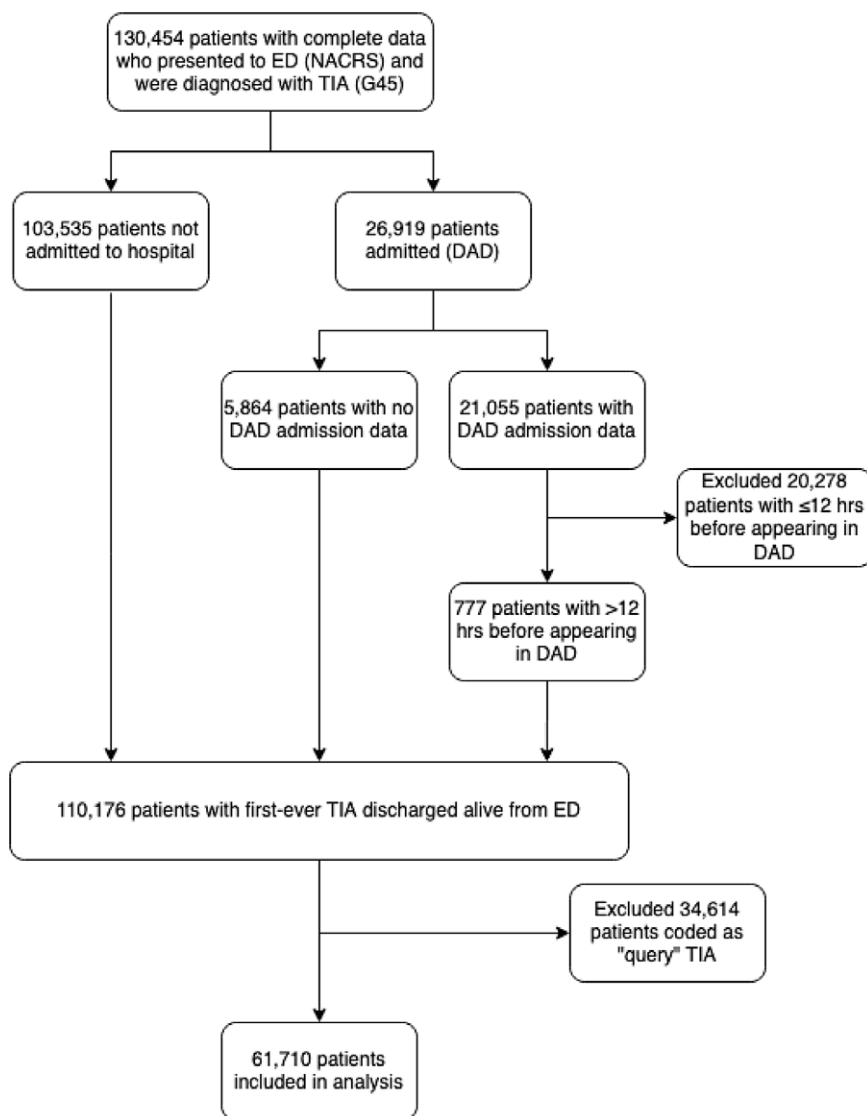


Figure 1: Patient selection flowchart. ED = emergency department; TIA = transient ischemic attack; NACRS = National Ambulatory Care Reporting System database; DAD = Discharge Analysis Database.

Mortality (Figure 5)

A linear regression analysis showed that mortality at 1 year decreased from 1.3% (70 deaths) in 2003 to 0.3% (16 deaths) in 2015 (Figure 5). In addition, 1-year mortality after TIA decreased by 61% on average over the 13-year study period.

DISCUSSION

In the current study, we were able to analyze rates of stroke and mortality up to 1 year after a TIA and observed that long-term stroke occurrence and mortality after TIA significantly declined from 2003 to 2015 in an Ontario-wide hospital-based cohort, with a 32% reduction in stroke and 61% reduction in mortality at 1 year. The high risk of early stroke remains, with the majority of strokes occurring in the first 7 d (Figure 4). This is further illustrated by the fact that the slopes of each line from 2003 to 2015 for the first 30 d following a TIA have not changed significantly (Figure 4). However, the risk of stroke decreased

from 1.9% in 2003 to 1.7% in 2015 for 48-hour risk, and from 6.0% to 3.4% for 1-year risk.

Over the past 15 years, public health initiatives, knowledge translation efforts, diagnostic strategies, primary and emergency care, and organized secondary prevention after TIA have significantly improved. Few previous studies have evaluated the impact of improved TIA management at a provincial level over time; most assess risk in specialized stroke centers.^{6,7} In 2014, Sundararajan et al. conducted a population-based study in Australia and reported an overall 90-day stroke risk of 2.9%.³⁰ In addition, after adjusting for age and sex, the risk of stroke at 90 d after a TIA decreased by 3% per year over a 10-year period. However, it remains unclear whether treatment is merely delaying stroke, or truly reducing occurrence in the longer term.

Ontario's universal healthcare system provides public funding for doctor and hospital visits and has had an organized stroke care system, which began in 2000 and was fully implemented in 2005. Using data from the Ontario Stroke Registry from 2000,

Table 1: Demographics

	All N = 61,710	2003 N = 5201	2015 N = 4927
Age, median (IQR)	73 (19)	74 (17)	72 (20)
Age, n (%)			
00–19	105 (0.2%)	9 (0.2%)	7 (0.1%)
20–29	323 (0.5%)	19 (0.4%)	34 (0.7%)
30–39	880 (1.4%)	62 (1.2%)	68 (1.4%)
40–49	3429 (5.6%)	246 (4.7%)	255 (5.2%)
50–59	8181 (13.3%)	588 (11.3%)	691 (14.0%)
60–69	12,691 (20.6%)	933 (17.9)	1091 (22.1%)
70–79	17,225 (27.9%)	1677 (32.2%)	1263 (25.6%)
80–89	15,529 (25.2%)	1427 (27.4%)	1171 (23.8%)
90+	3346 (5.4%)	240 (4.6%)	347 (7.0%)
Male, n (%)	29,743 (48.20%)	2505 (48.16%)	2494 (50.62%)
Discharged with antiplatelet therapy, n (%) Data available for n = 12,366	7712 (62.36%)		
Discharged with SPC ^a referral, n (%) Data available for n = 14,337	9558 (66.67%)		

^aSPC = stroke prevention clinic.

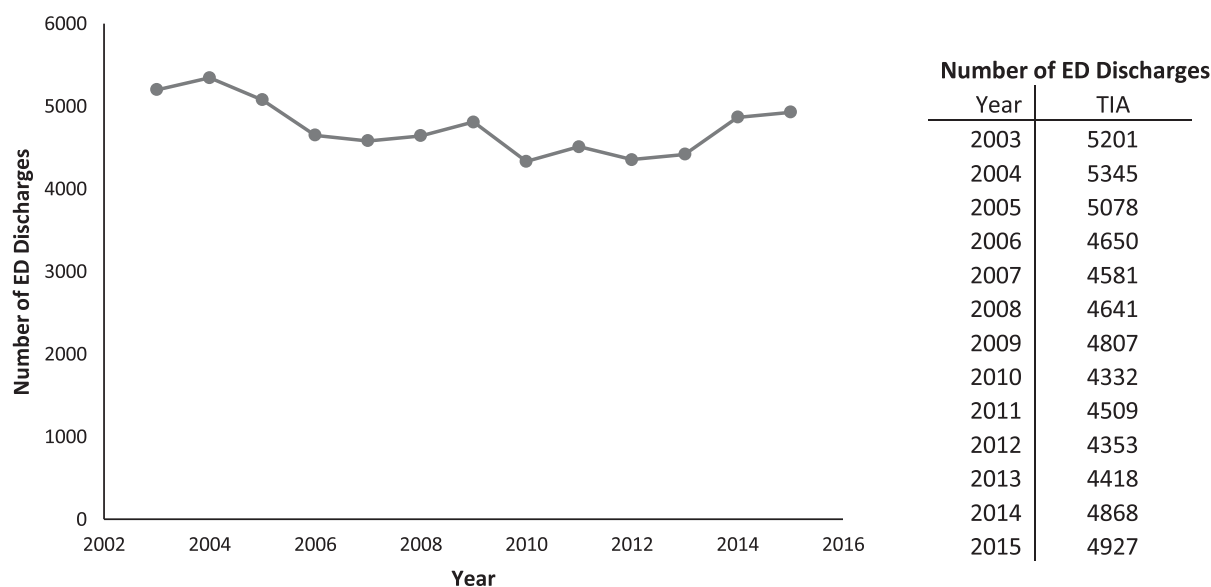


Figure 2: Number of emergency department discharges following TIA. ED = emergency department.

Gladstone et al.² reported a 30-day risk of stroke at 5%. In our larger population-based sample, we found a lower rate of stroke at day 30 in 2003 (3.8%) and decline over the next decade to 2.7% in 2015. It is likely that rates were already decreasing between 2000 and 2003. In addition, two previous registry-based studies have evaluated stroke risk at 1 year after TIA and reported risk at 6.1%⁹ and 5.1%.⁸

Comparisons of the earlier hospital-, registry- and community-based studies to more recent studies illustrate similar trends. Two meta-analyses of previous studies between 1973 and 2007 reported pooled risk of stroke at 2 d of 3.1⁷–3.5%,⁶ and 5.2%,⁷ 8.0%,⁶ and 9.2%⁶ at 7, 30, and 90 days, respectively. A more

recent meta-analysis including interventional studies (with an urgent assessment and management strategy) from 2007 to 2015 suggests that the risk of stroke has reduced by almost half³¹; with pooled stroke risks of 1.4%, 2.1%, 2.8%, and 3.4% at 2, 7, 30, and 90 days, respectively. This 50% reduction seen in the registry- and hospital-based cohorts directly mirrors the population-based results reported here.

Compared to these studies, that included patients from specialized centers, we observed a lower risk of stroke (3.4%) among TIA patients in Ontario. It is possible that administrative codes may have less specificity than registry-based/clinic-based studies which could increase the number of lower risk TIA

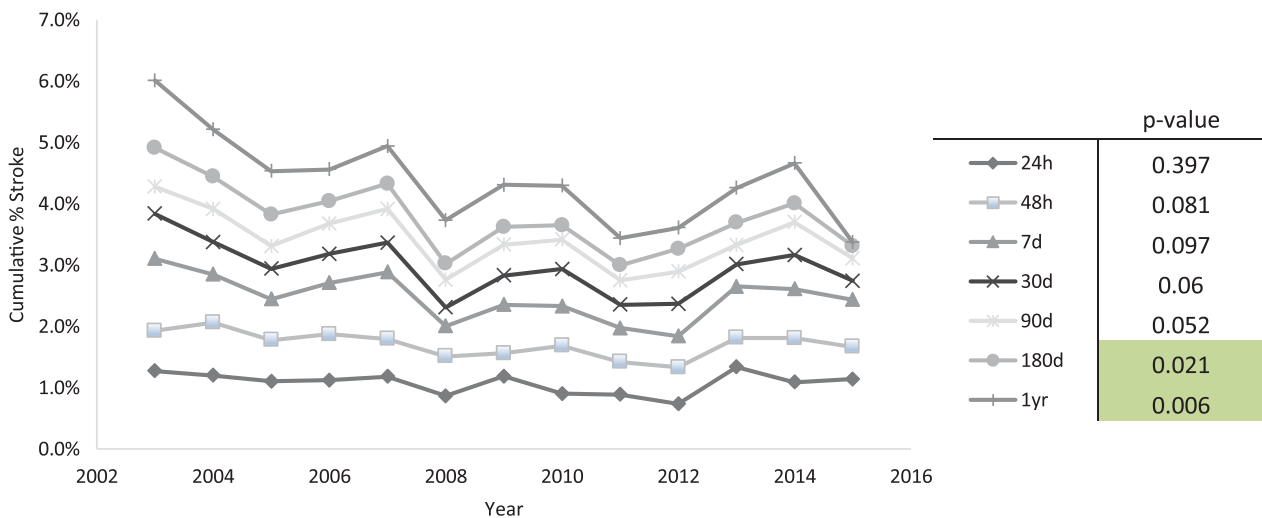


Figure 3: Temporal trends of cumulative ischemic stroke after emergency department discharge following TIA.

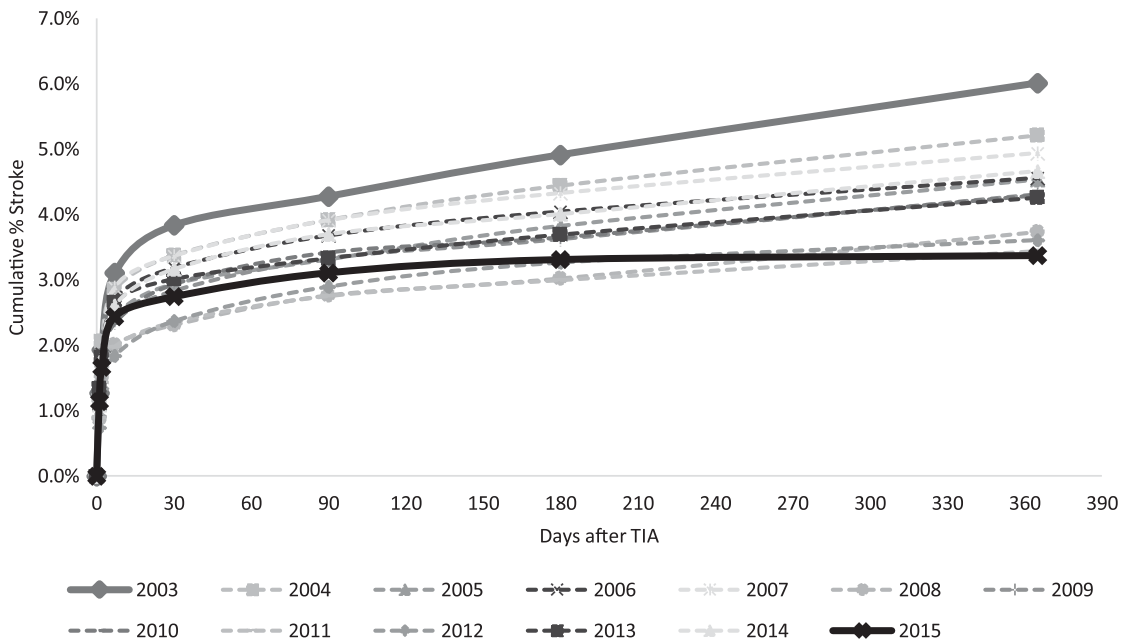


Figure 4: Ischemic stroke after emergency department discharge following a TIA.

patients and may underestimate the risk of stroke;^{20–22} however, the time-curves of stroke rates were nearly identical to those seen in the analysis by Gladstone et al.,² Johnston et al.³² (ABCD2) and others.³³ In addition, if more low-risk patients were being diagnosed with TIA, we would expect to see the rates of early stroke decrease and the slopes of the initial part of the curves in Figure 4 flatten over time, however, this was not observed. While our study limits sampling biases, studies based on administrative databases may have lower specificity for TIA diagnoses.^{34–36} However, data by Yu et al., suggest that administrative codes for TIA have good specificity (92.5%) and positive predictive value (PPV) of 76.0%,³⁷ and that coding accuracy is associated with physician documentation.³⁸ ICD-10 codes for ischemic stroke and TIA are also well-validated in the Canadian administrative databases.²⁸ Furthermore, we were able to use the same methodology over a 13-year period, in a publicly funded system,

without changes to hospital or physician remuneration based on identifying TIA/stroke. This helps to increase confidence that the findings reported here are attributable to changes in care, rather than greater identification and labeling of low-risk patients. This is, especially, important when considering that 1-year mortality is now a fraction of what it was in 2003 (70 deaths, 1.3%), with only 16 deaths in 2015.

Our study has some limitations. We did not have access to patient-level data such as past medical history, vascular risk factors, medications, carotid surgery, or treatment adherence. In addition, due to large time span that we analyzed, we could not account for the effect of improved access to stroke imaging modalities such as MRI and the effect of the endorsement of the “tissue-based definition” of TIA in 2009.^{39,40} Imaging studies of TIA patients have found that around one-third of patients presenting with transient symptoms were found to

Table 2: Outcomes 2003 versus 2015

Number (and %) of patients							
Outcome	Within 1 d	Within 2 d	Within 7 d	Within 30 d	Within 90 d	Within 180 d	Within 365 d
2003							
Ischemic stroke	66 (1.3)	100 (1.9)	161 (3.1)	199 (3.8)	222 (4.3)	255 (4.9)	312 (6.0)
Ischemic stroke or death	66 (1.3)	101 (1.9)	162 (3.1)	203 (3.9)	234 (4.5)	274 (5.3)	342 (6.6)
All-cause readmission	102 (2.0)	159 (3.1)	254 (4.9)	332 (6.4)	393 (7.6)	473 (9.1)	599 (11.5)
2015							
Ischemic stroke	56 (1.1)	82 (1.7)	120 (2.4)	135 (2.7)	153 (3.1)	163 (3.3)	166 (3.4)
Ischemic stroke or death	56 (1.1)	83 (1.7)	123 (2.5)	138 (2.8)	160 (3.2)	171 (3.5)	174 (3.5)
All-cause readmission	76 (1.5)	114 (2.3)	188 (3.8)	225 (4.6)	261 (5.3)	280 (5.7)	299 (6.1)

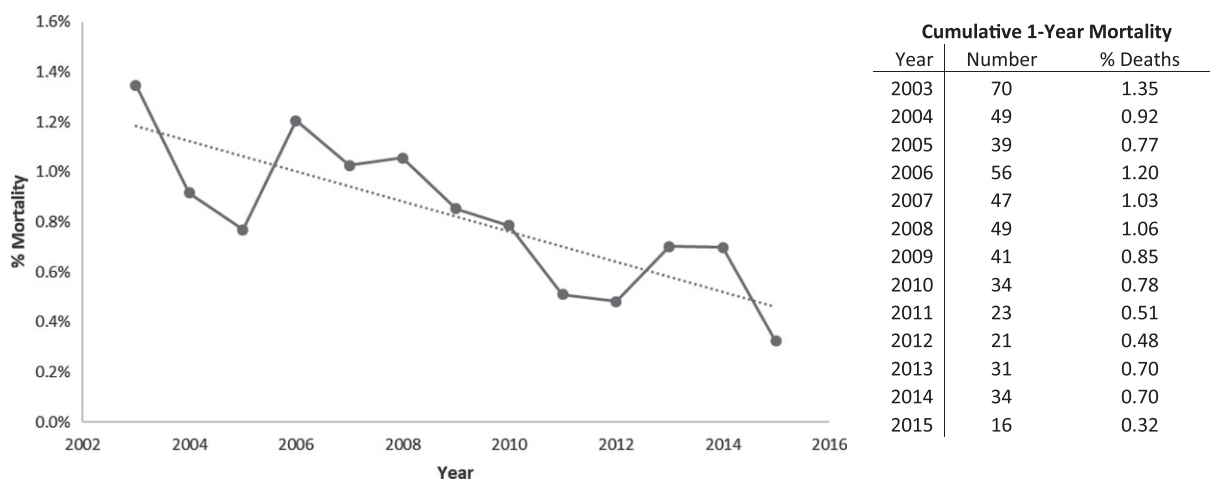


Figure 5: One-year mortality after discharge from the emergency department following TIA.

have an abnormality in diffusion-weighted imaging (DWI).^{39,41,42} Ovbiagele et al.⁴³ estimated that adopting a tissue-based definition of TIA could result in a 33% reduction in the incidence of TIAs and a 7% increase in ischemic stroke annually. In our data, we did not observe significant changes in the number of TIA diagnoses per year. It is unknown how much this would influence our data given that MRI is more costly and time-consuming in the acute setting compared to CT imaging and is not widely available across the province.⁴⁴ The effect of the tissue-based definition on TIA diagnoses will therefore depend on both the timing of clinical evaluation and access to DWI.⁴⁵ There was a significant amount of missing data on MRI utilization in our study, which hindered our ability to examine the potential impact of MRI on TIA diagnoses. In addition, our study was underpowered to examine trends over time for rates of stroke and mortality in patients coded with a “query” prefix, given that data was only available starting 2008. We were also unable to control for age and sex in our regression models examining trends over time; given that data was available only for 13 time points, there was insufficient power to account for the effect of additional variables.

The observed reduction in stroke and mortality could be attributed to numerous potential factors. One factor could be improved management of TIA facilitated by the Ontario Stroke Strategy.²¹ Improved early diagnostic strategies, such as

assessment of the intracranial vasculature using CTA,¹³ and greater awareness of stroke symptoms resulting in faster hospital arrival has improved acute treatment. From 2008 to 2013, the proportion of TIA patients referred to secondary stroke prevention services after ED discharge increased from 62.3% to 79.6%, highlighting increased awareness of the importance of timely specialized follow-up.⁴⁶ Moreover, management guidelines for hypertension,⁴⁷ atrial fibrillation⁴⁸ diabetes⁴⁹ and dyslipidemia⁵⁰ as well as changes to secondary prevention treatment guidelines resulting from pivotal clinical trials (CHANCE,⁵¹ SPARCL,⁵² ESPRIT⁵³) may have led to improvements in treatment strategies. Moreover, awareness initiatives such as the Cardiovascular Health Awareness Program (CHAP)⁵⁴ and early management of TIA by primary and emergency care physicians¹⁵ may also be contributing to this trend.

These reductions could also be a result of the changing demographic of patients in 2015 compared to 2003. Stroke is becoming increasingly common among young adults,⁵⁵ likely due to increasing prevalence of classic vascular risk factors and emerging risk factors, and lifestyle changes, among younger adults. Younger patients may be at a lower risk of stroke compared to older,⁵⁶ and represent a greater proportion of our sample in 2015 compared to 2003; however, the proportion of young adults (<50 years) increased only from 6.5% to 7.4%, and

thus is unlikely, in isolation, to account for a 50% drop in stroke incidence. Our results could also partly be explained by changing the incidence of stroke etiologies, such as the decreasing rate of large artery atherosclerosis, given improvements in controlling hypertension and hyperlipidemia,⁵⁷ and management of atrial fibrillation.^{8,58–64} Many of these factors may have synergistically contributed to the reduction in stroke incidence and mortality observed in this study.

The economic benefit of this reduction in stroke could be substantial. Previous studies have estimated that comprehensive and optimal stroke care in Canada could be associated with a cost avoidance of up to \$682 million annually.⁶⁵ In 2004, the average 1-year direct costs of managing TIA and ischemic stroke in Canada were \$17,769 and \$53,576, respectively.⁶⁶ The number of strokes within 1 year has reduced from 312 in 2003 to 166 in 2015 and this is estimated to have saved at least \$7.8 million (based on the 1-year cost of stroke determined in 2004). Actual savings would be greater, given increases in cost; investment in organized stroke care strategies could reduce both the personal and economic burden of stroke and TIA in the long term.

Despite organized stroke care, many patients are not treated in specialized TIA clinics and the extent of improved care for those treated in the hospital or in general practitioner care requires further evaluation. Additionally, geographic differences and regional differences remain, even in publicly-funded systems.⁶⁷ Further work examining inequities in care, and ways to improve the implementation of best practices in community and primary care settings, are needed. Ongoing advances in secondary prevention after TIA^{51,68} may contribute to further reductions in stroke. However, future clinical trials must be sufficiently powered to account for the reduced event rates seen with modern, aggressive secondary prevention strategies. Efforts to further improve the short- and long-term risk of stroke following a TIA, and advances in the implementation of best practices across populations are needed to reduce the global burden of stroke.

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STATEMENT OF AUTHORSHIP

RW, AK, and RHS contributed to the literature search. RW, AK, PL, CG, AYXY, and RHS created the data analysis plan, and analyzed and interpreted the data. RW, AK, PL, AYXY, DJG, and RHS contributed to writing and editing the manuscript.

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