ORIGINAL RESEARCH

# Young Stroke Survivors With No Early Recurrence at High Long-Term Risk of Adverse Outcomes

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***Background—***Approximately 8% to 21% of strokes affect adults aged <45 years. Although early stroke recurrence conveys the largest risk, long-term risks for young survivors with no early complications are unclear.

***Methods and Results—***Longitudinal matched case-control study (2003–2013). Consecutive patients with ischemic stroke or transient ischemic attack (young, ≤44 years) discharged from emergency or regional stroke centers in Ontario, Canada, with no death, recurrent stroke/transient ischemic attack, myocardial infarction, all-cause hospitalization, or admission to a long-term or continuing care facility (≤90 days) were matched 10:1 to general population controls on age (±1 year), sex, income, geography, and case date (±50 days). The primary outcome was a composite of death, stroke, myocardial infarction, and long-term or continuing care facility admission at 1, 3, and 5 years. Absolute event rates for young stroke/transient ischemic attack patients were lower than for older patients at 1 (2.2% versus 9.9%), 3 (4.7% versus 24.6%), and 5 (7.1% versus 37.2%) years. However, piecewise constant hazard modeling revealed that, even after adjustment for vascular comorbidities, young patients showed a 7-fold increased hazard of the composite outcome compared with young controls at 1 year (hazard ratio, 7.3; 95% CI, 4.0–13.6). Adjusted 5-year piecewise hazard also remained >5× that of young controls (hazard ratio, 5.2; 95% CI, 2.8–9.4), compared with a 30% increase at 5 years for older patients (hazard ratio, 1.3; 95% CI, 1.3–1.4).

***Conclusions—***Young stable stroke/transient ischemic attack survivors show a higher long-term hazard of adverse outcomes compared with matched controls than older patients. Findings support the need for long-term follow-up and aggressive risk reduction in young survivors and suggest secondary prevention guidelines for these patients are required. **(*J Am Heart Assoc.* 2019;8:e010370. DOI: 10.1161/JAHA.118.010370.)**

**Key Words:** case-control study • secondary prevention • young, stroke in

Unlike the decline in ischemic stroke rates observed for the general population,[1] the incidence of stroke among young adults is increasing,[2] with ≈8% to 21% affecting adults aged <45 years.[3] These strokes are associated with high early mortality[4] and disability[5] and, for working-age adults, have a particularly significant economic impact.[6] Although, for young patients, early recurrence after stroke or transient ischemic attack (TIA) conveys the largest risk,[7] less is known about long-term morbidity and mortality among *stable* young stroke/TIA patients who show no complications during the early high-risk period after stroke or TIA and, specifically, whether long-term risk returns to baseline in these patients. The purpose of this study was to quantify long-term risks of death, major cardiovascular outcomes, and institutionalization among young stroke/TIA patients with no early complications versus young matched control adults, compared with risks for older stroke/TIA patients with no early complications compared with older matched control adults.

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An earlier version of this study was presented as an oral presentation at the Canadian Stroke Congress, September 17 to 19, 2015, in Toronto, Ontario, Canada.

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Received July 19, 2018; accepted November 30, 2018.



## Methods

### Study Design and Data Sources

For this longitudinal retrospective matched case-control registry study, data were obtained from the Ontario Stroke

## Clinical Perspective

### What Is New?

- This study provides new evidence that long-term risks of major vascular events and adverse complications are elevated for young stroke survivors, even if they are clinically stable in the early high-risk period after stroke/transient ischemic attack.

### What Are the Clinical Implications?

- This work has implications for the management of young stroke/transient ischemic attack patients, supporting aggressive long-term risk reduction, and suggests that guidelines for secondary prevention in these young high-risk patients are required.

Registry and linked via unique personal identifiers with administrative databases housed at the Institute for Clinical Evaluative Sciences (ICES), using methods previously described.[8] The data set from this study is held securely in coded form at ICES. Although data sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at http://www.ices.on.ca/DAS. The full data set creation plan and underlying analytic code are available from the authors on request, understanding that the programs may rely on coding templates or macros that are unique to ICES. This study was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre. Because the Ontario Stroke Registry is a prescribed registry within ICES and ICES is a prescribed entity under Ontario's Personal Health Information Protection Act, data collection for the Ontario Stroke Registry is permitted without patient consent.

## Case-Control Selection

All consecutive patients with ischemic stroke or TIA discharged from emergency departments or regional stroke centers in Ontario, Canada, between July 2003 and March 2013 were identified. Cases were restricted to patients who did not experience any adverse event (death, hospitalization for stroke, TIA, myocardial infarction [MI], admission for any other cause, or admission to a long-term or complex continuing care facility) within 90 days and then categorized by age (≤44 versus ≥45 years).

Controls were identified from the general Ontario population from 2003 to 2013 and were required to have ≥1 medical contact during the study period. Controls were matched to cases using a 10:1 ratio on age (±1 year), sex, income quintile, and area of residence. To ensure a similar length and period of follow-up, controls were also matched to cases on the case index event date, where possible (±50 days), and followed up for up to 5 years from the case discharge date. Those with a death date before the case index event date or any adverse complication within 90 days of the case's index event date were excluded from the present analysis.

## Outcome and Statistical Analyses

The primary outcome was a composite measure of mortality and morbidity, including: death, hospitalization for recurrent stroke or MI, or admission to a long-term or complex continuing care facility.

Descriptive statistics were used to characterize demographic and clinical variables. Standardized difference in means or proportions were used to compare young and older patients with young and older matched controls, with significant differences defined as an absolute value >0.20 (small effect size).

We used stratified log-rank tests to compare proportions of young stroke/TIA patients with the composite outcome with young matched controls and older stroke/TIA patients with no early complications with older matched controls at 1, 3, and 5 years after stroke/TIA. We then generated age-, sex-, and geography-standardized Cox proportional hazards models with robust SE methods to account for clustering in matched pairs to estimate the 1-, 3-, and 5-year piecewise constant hazard of the composite outcome, both unadjusted (model 1) and with adjustment for vascular comorbidities (model 2). All statistical analyses were conducted using SAS, Version 14.2.

## Results

A total of 26 560 patients were discharged with ischemic stroke or TIA from hospital or emergency departments at regional stroke centers within the study period and had no adverse complications within 90 days of stroke/TIA. Successful matching was achieved for 26 366 (99.2%), yielding a total of 1352 young and 25 308 older patients matched to controls on age, sex, income, and geography (Table 1). Among both young and older groups, comparisons revealed significant differences between patients and controls for the history of hypertension and diabetes mellitus (Table 1).

Both younger and older stroke/TIA patients experienced significantly higher proportions of the primary composite outcome of death, admission for stroke or MI, or admission to a long-term or complex continuing care facility than their matched controls at 1, 3, and 5 years (Table 2). However, piecewise constant hazards modeling revealed that, although older stroke/TIA patients showed almost 2 times the hazard of older matched controls for events in the primary composite outcome at 1 year (hazard ratio [HR], 1.8; 95% CI, 1.7–1.9),

**Table 1.** Demographic and Clinical Characteristics for Young (≤44 Years; N=1341) Versus Older (≥45 Years; N=25 025) Stroke and TIA Patients and Young (≤44 Years; N=13 410) Versus Older (≥45 Years; N=250 250) Matched Controls

| | Young | | | Older | | |
|---|---|---|---|---|---|---|
| Variable | Case N (%) | Control N (%) | Standardized Difference* | Case N (%) | Control N (%) | Standardized Difference* |
| Age, median (IQR), y | 39 (34–42) | 39 (34–42) | 0.001 | 73 (62–81) | 73 (62–81) | 0.003 |
| Female sex | 612 (45.6) | 6120 (45.6) | 0 | 11 748 (46.9) | 117 480 (46.9) | 0 |
| Rural residence | 186 (13.9) | 1860 (13.9) | 0 | 2348 (9.4) | 23 480 (9.4) | 0 |
| Income quintile | | | | | | |
| 1 | 327 (24.4) | 3270 (24.4) | 0 | 5612 (22.4) | 56 120 (22.4) | 0 |
| 2 | 258 (19.2) | 2580 (19.2) | 0 | 5048 (20.2) | 50 480 (20.2) | 0 |
| 3 | 259 (19.3) | 2590 (19.3) | 0 | 4501 (18.0) | 45 010 (18.0) | 0 |
| 4 | 252 (18.8) | 2520 (18.8) | 0 | 4608 (18.4) | 46 080 (18.4) | 0 |
| 5 | 245 (18.3) | 2450 (18.3) | 0 | 5256 (21.0) | 52 560 (21.0) | 0 |
| Medical history | | | | | | |
| Congestive heart failure | 17 (1.3) | 10 (0.1) | 0.15 | 3546 (14.2) | 20 238 (8.1) | 0.19 |
| Hypertension | 386 (28.8) | 834 (6.2) | 0.62 | 19 135 (76.5) | 139 896 (55.9) | 0.45 |
| Diabetes mellitus | 139 (10.4) | 392 (2.9) | 0.30 | 7602 (30.4) | 51 513 (20.6) | 0.23 |
| Hyperlipidemia | 89 (6.6) | 572 (4.3) | 0.10 | 5143 (20.6) | 44 579 (17.8) | 0.07 |

IQR indicates interquartile range; TIA, transient ischemic attack.
*Standardized differences are used for comparisons. Difference in means or proportions divided by SE; imbalance defined as absolute value >0.20 (small effect size).

young stroke/TIA patients showed a 13-fold increased hazard at 1 year (HR, 13.3; 95% CI, 7.6–23.3) compared with young matched controls, remaining at a 9-fold risk compared with controls at 5 years (HR, 9.1; 95% CI, 5.3–15.6) (Table 3). Notably, even after adjustment for a history of vascular comorbidities, including hypertension, prior MI, and congestive heart failure, the hazard of mortality and morbidity among young patients did not return to baseline, but remained at 7 times that of young matched controls at 1 year (HR, 7.3; 95% CI, 4.0–13.9) and 5 times higher at 5 years (HR, 5.2; 95% CI, 2.8–9.4) (Table 3).

## Discussion

The present study determined that young stroke/TIA patients who are clinically stable with no adverse complications in the early high-risk period after stroke/TIA have an increased hazard of long-term adverse outcomes compared with young matched controls, with risks substantially exceeding those observed for older stroke/TIA patients versus older controls. Although, in the present study, long-term absolute risk of death, stroke, or MI, or admission to a long-term or complex continuing care facility for young stable patients was low compared with older patients, piecewise hazard modeling revealed that long-term hazard among stable young stroke/TIA patients was particularly high and did not return to baseline (ie, that of matched controls), but remained elevated for at least 5 years. These findings indicate that survival after stroke and TIA is a marker of major long-term risk and support the need for aggressive long-term risk reduction strategies in young stroke/TIA patients, even if they have no early adverse complications.

Population- and hospital-based registry studies have shown that key modifiable risks associated with stroke in younger adults include hypertension, diabetes mellitus, smoking, and dyslipidemia.[9,10] Consistent with these studies, significant differences were observed between young patients and young matched controls for the presence of comorbid hypertension and diabetes mellitus in the present study (Table 1). Adjustment for these and other vascular comorbidities significantly reduced the hazard of adverse clinical outcomes at 1, 3, and 5 years (model 2), indicating that these conditions may be important potential treatment targets for the mitigation of long-term hazard in young stroke/TIA patients. However, despite population-based data demonstrating high rates of diabetes mellitus incidence among young stroke survivors and an increased likelihood of recurrence among those with diabetes mellitus and impaired fasting glucose,[10] a recent analysis of national health survey data reported that only 50%

**Table 2.** Proportions of Young Cases (N=1341) and Matched Controls (N=13 410) and Older Cases (N=25 025) and Matched Controls (N=250 250) With the Composite and Individual Outcomes at 1, 3, and 5 Years After Stroke/TIA*

| | Young | | | Older | | |
|---|---|---|---|---|---|---|
| Variable | Case N (%) | Control N (%) | *P* Value† | Case N (%) | Control N (%) | *P* Value† |
| Primary composite | | | | | | |
| Death, admission for stroke or MI, or admission to CCC/LTC facility | | | | | | |
| 1 y | 29 (2.2) | 22 (0.2) | <0.0001 | 2467 (9.9) | 14 190 (5.7) | <0.0001 |
| 3 y | 51 (4.7) | 59 (0.5) | <0.0001 | 5035 (24.6) | 29 170 (14.3) | <0.0001 |
| 5 y | 56 (7.1) | 72 (0.9) | <0.0001 | 5498 (37.2) | 32 725 (22.1) | <0.0001 |
| Individual outcomes | | | | | | |
| Death | | | | | | |
| 1 y | 9 (0.7) | 14 (0.1) | <0.0001 | 1324 (5.3) | 10 795 (4.3) | <0.0001 |
| 3 y | 23 (2.1) | 35 (0.3) | <0.0001 | 3349 (16.4) | 22 738 (16.4) | <0.0001 |
| 5 y | 29 (3.7) | 39 (0.5) | <0.0001 | 4026 (27.2) | 26 248 (17.8) | <0.0001 |
| Admission for stroke | | | | | | |
| 1 y | 9 (0.7) | ≤5 | <0.0001 | 661 (2.6) | 999 (0.4) | <0.0001 |
| 3 y | 18 (1.7) | 9 (0.1) | <0.0001 | 1155 (5.6) | 2179 (5.6) | <0.0001 |
| 5 y | 24 (3.0) | 8 (0.1) | <0.0001 | 1197 (8.1) | 2549 (1.7) | <0.0001 |
| Admission for MI | | | | | | |
| 1 y | 6 (0.4) | ≤5 | <0.0001 | 256 (1.0) | 1571 (0.6) | <0.0001 |
| 3 y | 9 (0.8) | 10 (0.1) | <0.0001 | 552 (2.7) | 3395 (1.7) | <0.0001 |
| 5 y | 10 (1.3) | 17 (0.2) | <0.0001 | 591 (4.0) | 3922 (2.7) | <0.0001 |
| Admission to LTC/CCC facility | | | | | | |
| 1 y | 9 (0.7) | ≤5 | <0.0001 | 673 (2.7) | 2622 (1.0) | <0.0001 |
| 3 y | 10 (0.9) | ≤5 | <0.0001 | 1310 (6.4) | 6151 (3.0) | <0.0001 |
| 5 y | 7 (0.9) | 10 (0.1) | <0.0001 | 1386 (9.4) | 7302 (9.4) | <0.0001 |

CCC indicates complex continuing care; LTC, long-term care; MI, myocardial infarction; TIA, transient ischemic attack.
*Small cell sizes (≤5) suppressed.
†*P* values are for stratified log-rank comparisons.

of young stroke survivors (<50 years) had fasting glucose testing within the previous 12 months, suggesting that young stroke survivors may not be optimally managed for long-term risk reduction.[11] Furthermore, a recent analysis of trends in the prevalence of cardiovascular risk factors, including hypertension, diabetes mellitus, and smoking, and associated cardiovascular diseases (carotid stenosis and coronary artery disease) among hospitalized stroke patients showed significant increases in prevalence for both risk factors and outcomes over a recent 10-year period (2004–2014), with a

**Table 3.** The 1-, 3-, and 5-Year Piecewise Constant HRs for the Composite Outcome in Stroke/TIA Patients Versus Matched Controls, Estimated Using Cox Proportional Hazards Regression With Robust SEs for Matched Pair Data

| | Model 1, Unadjusted HR (95% CI) | | Model 2, Adjusted HR (95% CI)* | |
|---|---|---|---|---|
| Variable | Young Patients vs Young Controls | Older Patients vs Older Controls | Young Patients vs Young Controls | Older Patients vs Older Controls |
| Primary composite | | | | |
| Death, admission for stroke or MI, or admission to CCC/LTC facility | | | | |
| 1 y | 13.3 (7.6–23.3) | 1.8 (1.7–1.9) | 7.3 (4.0–13.6) | 1.3 (1.2–1.3) |
| 3 y | 7.8 (4.9–12.4) | 1.9 (1.8–2.0) | 4.3 (2.6–7.3) | 1.4 (1.3–1.4) |
| 5 y | 9.1 (5.3–15.6) | 1.8 (1.7–1.9) | 5.2 (2.8–9.4) | 1.3 (1.3–1.4) |

CCC indicates complex continuing care; HR, hazard ratio; LTC, long-term care; MI, myocardial infarction; TIA, transient ischemic attack.
*Adjusted for history of stroke, MI, congestive heart failure, hypertension, hyperlipidemia, and diabetes mellitus.

high prevalence of risk factors among both younger (aged 18–39 years) and older (aged 60–79 years) patients.[12] Although hypertension and diabetes mellitus control, smoking cessation, and physical activity are essential to address high long-term risks of recurrence,[13] specific guidelines for long-term preventive management in this population are lacking.

Important strengths of the present study were the global population approach used to identify young clinically stable patients with stroke and TIA, the adjustment for vascular comorbidities to enable risk comparisons between young and older stroke/TIA patients and their matched controls, and the length of follow-up to evaluate whether long-term risks returned to baseline (ie, that of population controls) over time. However, this study also had limitations. Because information on stroke etiology is not available from the Ontario Stroke Registry, we were unable to identify potential differences in long-term risk associated with different potential etiologic mechanisms of the entry event. Emergency department diagnoses of TIA show only low-to-moderate sensitivity[14] and, as a result, emergency department–diagnosed TIA cases included in the study cohort may be subject to misclassification. In addition, because absolute event rates for young stroke and TIA patients in the present study were low, we were unable to obtain adjusted estimates of cause-specific hazard for individual outcomes included in the composite measure or evaluate differences among potentially clinically relevant subgroups, including sex, presenting event type (stroke versus TIA), and diabetes mellitus status. Further research with larger cohorts of young patients is required to elucidate these differences.

## Conclusion

Young stroke/TIA survivors with no early recurrence show high long-term risk of adverse outcomes versus matched controls, with markedly higher hazard than that observed for older stroke/TIA patients versus older controls. Findings support long-term follow-up and aggressive risk reduction in young stable stroke/TIA patients and suggest that evidence-based recommendations for the optimal management of these patients are required.

## Sources of Funding

This study was supported by an operating Grant-in-Aid from the Heart and Stroke Foundation of Ontario grant 000392, 2012-2014; the Canadian Institute of Health Research grant 1012404, 2014-2018; the New Investigator Award and the Henry J. Barnett Award from the Heart and Stroke Foundation of Canada; the Heart and Stroke Foundation Canadian Partnership for Stroke Recovery; and the Departments of Medicine at Sunnybrook Health Sciences Centre and at the University of Toronto to Swartz. This study was also supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results, and conclusions reported in this article are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred. At the time of this study, Edwards held a Post-Doctoral Fellowship Award from the Heart and Stroke Foundation of Canada and Kapral held a Heart and Stroke Foundation of Canada Career Investigator Award.

## Disclosures

None.

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