Statins and Intracerebral Hemorrhage

A Retrospective Cohort Study

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Background: A recent post hoc analysis of a large randomized trial in patients with cerebrovascular disease suggested that statins may increase the risk of intracerebral hemorrhage (ICH).

Objective: To examine the association between statins and ICH in patients with recent ischemic stroke in a population-based setting.

Design: Retrospective propensity-matched cohort study with accrual from July 1, 1994, to March 31, 2008.

Setting: Ontario, Canada.

Participants: A total of 17,872 patients aged 66 years and older who initiated statin therapy following acute ischemic stroke and were followed for a median of 4.2 years (interquartile range, 2.4-5.0 years). To enhance causal inference, we conducted several tests of specificity to exclude healthy user bias in this sample.

Main Outcome Measure: Hospitalization or emergency department visit for ICH defined using validated diagnosis coding.

Results: Overall, 213 episodes of ICH occurred. In the primary analysis comparing statin users with nonusers, we found no association between statins and ICH (hazard ratio=0.87; 95% confidence interval, 0.65-1.17). Subgroup and dose-response analyses yielded similar results. In tests of specificity, statin therapy was not associated with bone mineral density testing, vitamin D or B12 screening, gastrointestinal endoscopy, or elective knee arthroplasty, suggesting that results were not due to healthy user bias or differences in quality of care.

Conclusion: Statin exposure following ischemic stroke was not associated with ICH.


Patients with stroke or transient ischemic attack are at increased risk for recurrent events. On the basis of data from the Stroke Prevention by Aggressive Lowering of Cholesterol Levels (SPARCL) trial and the Heart Protection Study, clinical practice guidelines recommend 3-hydroxy-3-methylglutaryl coenzyme A inhibitors (statins) for most patients with a history of ischemic cerebrovascular events. Despite a significant reduction in total stroke of 16%, post hoc analysis of the SPARCL trial showed substantial divergence in the 2 broad categories of stroke. Whereas ischemic stroke was significantly reduced in patients receiving atorvastatin calcium, the risk of hemorrhagic stroke was increased. Similarly, the Heart Protection Study also suggested an increased risk of hemorrhagic stroke during statin therapy among patients with previous cerebrovascular disease, with no such increase evident in patients without cerebrovascular disease (interaction test for statins and cerebrovascular disease, P=.03). Together these 2 trials suggest a sizable increase in hemorrhagic stroke related to statin therapy in patients with a history of stroke or transient ischemic attack, a finding reported in 2 widely cited systematic reviews.

Several mechanisms might explain an association between statins and intracerebral hemorrhage (ICH). Statins are at least mildly antithrombotic agents that inhibit platelet aggregation, enhance fibrinolysis, and reduce thrombosis. In a recent large statin trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin;
rosuvastatin calcium reduced the risk of venous thromboembolism by 43% (hazard ratio [HR] = 0.57; 95% confidence interval [CI], 0.37-0.86), with reductions in both provoked and unprovoked thrombosis.9 A recent systematic review of statin data (both observational and randomized) supports this effect.10 In addition, cholesterol may be essential for blood vessel integrity in the brain.11 Intracerebral hemorrhage is thought to arise from small breaks in the walls of perforator arteries that branch orthogonally from major cerebral vessels; massive hemorrhage can occur when the clotting system is unable to compensate for these disruptions.12

Because the evidence linking statin therapy with ICH derives solely from exploratory analyses with relatively few events and because available data suggest that any such risk is limited to patients with cerebrovascular disease, we performed a large population-based study to examine the association between statin therapy and ICH in patients who survive an acute ischemic stroke. To test the validity of our findings, we conducted additional specificity analyses to assess for associations between statin prescribing and common screening tests and procedures that may reflect healthy user bias or quality of care (rather than pharmacological effects of statins).13

**SETTING AND DATA SOURCES**

We conducted our study in Ontario, Canada, using linked health care databases in accordance with a prespecified research protocol. Throughout the study, Ontario was Canada’s most populous and ethnically diverse province with a total population of more than 12 million, of whom 1.8 million were older than 65 years. Elderly patients in Ontario had universal access to health care services, including outpatient medical visits, hospital care, home care, and prescription drugs. The large databases that record this care have been used extensively in previous research, contain little missing information, and have been validated for a range of cardiovascular and cerebrovascular events.14-16

We used 6 health care databases: the Canadian Institute for Health Information Discharge Abstract Database, which recorded all hospital admissions in the province including detailed diagnostic and procedural information; the Ontario Health Insurance Plan Database, which recorded information on outpatient medical visits and testing; the National Ambulatory Care Reporting System Database, which recorded emergency department visits, dialysis, oncologic care, and cardiac catheterization; the Canadian Institute for Health Information Same Day Surgery Database, which recorded information on same-day interventions and procedures; the Ontario Drug Benefit Database, which recorded all prescription medications dispensed to outpatients aged 65 years and older; and the Registered Persons Database, which collected vital statistics on all Ontario residents. The study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre.

**SAMPLE AND SELECTION**

We included patients aged 66 years and older who were admitted to any Ontario hospital with a primary diagnosis of acute ischemic stroke (International Classification of Diseases, ninth revision, clinical modification [ICD-9-CM] codes 434 and 436; International Statistical Classification of Diseases, 10th revision [ICD-10] codes H34.1, I63 [but not I63.6], and I64) between July 1, 1994, and March 31, 2008.17 Validation studies in Canada document excellent accuracy for these codes. We focused on patients aged 66 years and older because outpatient medication use can be reliably ascertained in this group and because ICH is particularly common in older patients.18

The index date for each patient was defined as 120 days following discharge from the index hospitalization. We excluded patients who died prior to the index date because short-term decedents are less likely to have received statins.19 We also excluded patients who used statins during the year preceding hospitalization, thereby creating an inception cohort of patients commencing therapy with statins after an acute ischemic stroke; this is known as a new user design.20 We defined statin exposure on the basis of at least 1 pharmacy statin dispensation in the 120-day interval immediately following discharge from the stroke hospitalization. Controls received no statin within this interval.

**PROPENSITY-BASED MATCHING**

Because statin users may differ in important ways from nonusers, we used a multistep algorithm to match statin users with nonusers based on their likelihood of receiving statin therapy following stroke.21 First, we conducted logistic regression analysis to derive propensity scores by modeling statin exposure as the dependent variable and all baseline characteristics as independent variables. Using greedy matching, we then matched statin users with untreated controls in a 1:1 fashion based on the logit of the propensity score with a caliper of 0.2 SD. We assessed intergroup standardized differences of the mean to determine whether there were important differences between matched pairs on baseline characteristics, and we found none.22,23

**OUTCOMES**

The primary study outcome was time to ICH (defined as a hospitalization or emergency department visit with a primary diagnosis coded by ICD-9-CM code 431 or ICD-10 code I61).24 Validation data demonstrate excellent accuracy for this condition. Patients were followed from the index date until ICH, death, or March 31, 2010 (whichever occurred first). Using an intention-to-treat type of framework, all analyses were conducted according to the initial statin exposure categorization at the start of follow-up.25

**SENSITIVITY ANALYSES**

We further explored the association of statins with ICH by stratifying the sample by age (66-75, 76-85, and >85 years); sex; socioeconomic status (above or below the sample median); history of diabetes mellitus, hypertension, or chronic kidney disease; and treatment with warfarin sodium or antiplatelet agents other than aspirin (specifically clopidogrel bisulfate, ticlopidine hydrochloride, or combination acetylsalicylic acid-dipyridamole). For these analyses, we matched patients by propensity score (±0.2 SD) and the subgroup characteristic.

We also analyzed patients according to statin dosing on the prescription immediately preceding the index date. Dosing was defined on the basis of unique drug information numbers for each medication and dose prescribed; doses were deemed high when the index statin prescription contained the maximum allowable dose in the product monograph (eg, atorvastatin calcium, 80 mg/d, or rosuvastatin calcium, 40 mg/d), with all other doses classified as low.26 We then analyzed the effects of dose by restricting the propensity-based cohort to the matched pairs...
containing the relevant comparison (high dose vs unexposed or low dose vs unexposed, respectively).

To assess the effects of adherence on the association between statins and subsequent ICH, we replicated the primary analysis after first excluding 2 groups of patients who crossed over during follow-up: (1) statin-treated patients who subsequently failed to fill further statin prescriptions after the index prescription; and (2) unexposed control patients who filled statins late during follow-up. For this analysis, we repeated the propensity-matching schema with these 2 groups of patients removed.

To put the potential harms of statins into perspective, we also analyzed incident ischemic stroke risk in our cohort as defined by the following codes in the most responsible diagnosis field of the hospitalization database: ICD-9-CM codes 434 and 436 or ICD-10 codes H34.1, I63 (but not I63.6), and I64. These are the same codes used to define this cohort of patients with acute ischemic stroke. We also examined fatal hemorrhagic stroke in relation to statins, defined as the occurrence of death within 30 days of admission to the emergency department or hospital with a most responsible diagnosis of ICH (as defined in our primary analysis).

SPECIFICITY ANALYSES

We examined the association of statins with 5 additional outcomes in the propensity-matched cohort: subsequent serum vitamin B12 screening, vitamin D screening, gastrointestinal endoscopy, bone mineral density screening, and elective knee arthroplasty. The purpose of these analyses was to enhance causal inference by testing for the absence of an association where none was expected based on the biological effects of statins. In increased rates of screening events in statin users might suggest access bias or hidden asymmetry in patient characteristics.

STATISTICAL ANALYSIS

We used Cox proportional hazards analysis to test the association of statins with ICH after stratifying on the matched pairs. We computed HRs with 95% CIs. Finally, given its much larger sample size, we analyzed independent predictors of ICH in the prematched parent cohort (n=66 201) by running a traditional multivariable Cox proportional hazards regression model with all baseline characteristics entered as covariates (including statin exposure). We deemed a 2-tailed P < .05 as statistically significant. We conducted analyses using SAS version 9.2 statistical software (SAS Institute, Inc, Cary, North Carolina).

RESULTS

COHORT CREATION

We identified 145 351 patients hospitalized for acute ischemic stroke between July 1, 1994, and March 31, 2008, in Ontario (Figure 1). We excluded 10 981 patients for administrative reasons (eg, missing demographic data, nonresidence in Ontario), 25 686 patients who died during hospitalization or within 120 days of discharge, 26 507 patients who were younger than 66 years and therefore could not be linked to the prescription drug database, and 15 976 patients who had received statins in the year prior to stroke admission. This produced a prematched sample of 66 201 patients, of whom 11 933 initiated statin therapy within 120 days following hospital discharge. After matching these patients on propensity score and excluding unmatched subjects, the final cohort contained 17 872 patients (8936 statin users and 8936 controls). Overall, 75% of statin users were successfully matched following stroke.

DESCRIPTION OF PATIENTS

Patients were well matched on measured characteristics (Table 1). The mean (SD) age of the sample was 78 (7.1) years; slightly more than half (54%) were women. In addition to a history of ischemic stroke (100%), established risk factors for ICH were common, including hypertension (80%), diabetes mellitus (26%), chronic kidney disease (26%), and dementia (21%). Many patients received medications previously associated with ICH, including oral anticoagulants (23%), antiplatelet agents (53%), nonsteroidal anti-inflammatory drugs (29%), and selective serotonin reuptake inhibitors (18%).

PRIMARY OUTCOME

The propensity-matched cohort provided a total of 64 273 patient-years of follow-up (median, 4.2 years; interquartile range, 2.4-5.0 years). Altogether, we identified 213 episodes of ICH, with a slightly lower rate in statin-treated patients than in matched controls (2.94 vs 3.71 episodes per 1000 patient-years, respectively). The HR for statin exposure was 0.87 (95% CI, 0.65-1.17), indicating no association between statins and ICH.

SENSITIVITY ANALYSES

We found no interaction between statin therapy and prespecified subgroup characteristics, including age, sex, socioeconomic status, major comorbidities, or therapy with antiplatelets or anticoagulants (Figure 2). Patients
taking high or low doses of statins had ICH risks similar to those of unexposed patients (HR=1.33; 95% CI, 0.30-5.96; and HR=0.86; 95% CI, 0.64-1.16, respectively). We found no association between statins and fatal hemorrhagic stroke (HR=0.96; 95% CI, 0.63-1.45). After excluding nonadherent patients and unexposed controls who started therapy with statins during follow-up, analysis of the remaining patients who did not cross over between groups revealed a statistically lower risk of ICH (HR=0.65; 95% CI, 0.47-0.91). Analysis of ischemic stroke showed a significantly lower end point rate in statin-treated patients, in keeping with recent randomized trials (HR=0.83; 95% CI, 0.75-0.92). The breakdown by stroke type (ischemic vs hemorrhagic) did not differ between groups. In the statin group, 10.09% of all strokes were hemorrhagic. In the control group, 10.23% of all strokes were hemorrhagic.

### SPECIFICITY ANALYSES

During follow-up, there were 8606 vitamin B12 tests, 727 vitamin D tests, 2636 bone density tests, 2557 endoscopies, and 222 knee replacements (with patients counted only once per procedure). As anticipated, we found no association between statin exposure and any of these events (Table 2). These findings argue against major healthy user bias or screening bias in our cohort.

### PREDICTORS OF ICH

Finally, we examined the magnitude of association of various baseline characteristics with the primary outcome in the larger prematched parent cohort of 66 201

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**Table 1. Baseline Characteristics of 17,872 Participants in the Propensity-Matched Cohort**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Statin Group (n=8936)</th>
<th>Control Group (n=8936)</th>
<th>Standardized Difference of the Mean</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>77.9 (7.0)</td>
<td>77.9 (7.1)</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>4767 (53)</td>
<td>4828 (54)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>High socioeconomic status, No. (%)</td>
<td>5058 (57)</td>
<td>4977 (56)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Rural location, No. (%)</td>
<td>1314 (15)</td>
<td>1316 (15)</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>ICH risk factors, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>7150 (80)</td>
<td>7177 (80)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2273 (25)</td>
<td>2286 (26)</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>2303 (26)</td>
<td>2312 (26)</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>212 (2)</td>
<td>228 (3)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>1876 (21)</td>
<td>1930 (22)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Previous ICH</td>
<td>83 (1)</td>
<td>90 (1)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>316 (4)</td>
<td>331 (4)</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ACE, angiotensin-converting enzyme; ICH, intracerebral hemorrhage;

- Standardized differences are less sensitive to large sample sizes than traditional hypothesis testing with P values. They express the difference between the means of 2 populations as a proportion of the pooled SD. Standardized differences greater than 10% are deemed significant.
- Quintiles 3 through 5.

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**Figure 2.** Subgroup analyses. Risk for intracerebral hemorrhage (ICH) in relation to statin exposure in predefined subgroups. Squares indicate hazard ratios (HRs); whiskers, 95% confidence intervals; and SES, socioeconomic status.
patients (which incurred 733 episodes of ICH during follow-up). As expected, hypertension, previous ICH, chronic liver disease, and exposure to oral anticoagulants or antiplatelet agents were associated with ICH (Table 3). Conversely, statins had a borderline protective association with the primary outcome (multivariable HR=0.79; 95% CI, 0.63-0.99; P=.04). Female sex and use of potassium-sparing diuretics were additional protective factors.

### COMMENT

In this large observational cohort of older patients surviving acute ischemic stroke, we found no harmful association between statins and subsequent ICH. This lack of harmful association was consistent regardless of analytic technique (propensity-based matching or multivariable adjustment in the parent cohort), maintained across subgroup analyses, and irrespective of statin dosing. Predefined tracer analyses found no evidence that statin users were healthier or received more health care than nonusers. Results from this study are in accord with the recently updated meta-analysis of statin trials from the Cholesterol Treatment Trialists’ Collaboration.27

In the SPARCL study, the absolute increase in risk of hemorrhagic stroke related to treatment was small (<1%).28 Moreover, this analysis was exploratory with a wide 95% CI reflecting the fact that only 1 in 8 strokes in the trial were deemed hemorrhagic. Further uncertainty is introduced by the pooling of subarachnoid hemorrhage and ICH under the more general rubric of hemorrhagic stroke.29 Even if this finding was not due to chance, its magnitude was more than 7 times smaller than the absolute risk reduction in all cardiovascular events in the SPARCL trial.4 It is difficult to determine whether the analysis was a chance finding; the main trial article presented 49 distinct statistical analyses, with no adjustment for multiple hypothesis testing.

Secondary analyses of the SPARCL data suggest that risk for hemorrhagic stroke was magnified by older age (HR=1.37 per decade), male sex (HR=1.77), previous hemorrhagic stroke (HR=5.81), and stage 2 hypertension (HR=6.19).28 However, none of these characteristics interacted significantly with statin exposure in the SPARCL study. Similarly, we found no significant interaction between statin exposure and age, sex, or major comorbidities that tend to increase the risk of ICH. Conversely, a recent Markov decision analysis strongly suggested that patients with previous hemorrhagic stroke, in particular those with lobar hemorrhage, should not receive statins.30 Because fewer than 1% of patients in our study had a history of ICH, we could not test this important subset. Given the findings of the decision analysis and the high risk of recurrence of ICH, caution must be applied when considering statins in such patients.31

In addition to advantages conferred by our large sample size, relatively long follow-up, and population-based setting, we used a number of techniques to reduce potential bias in our study. Through cohort restriction, we selected a relatively homogeneous population of patients, all of whom survived an acute ischemic stroke, were aged 66 years or older, and had no recent history of statin exposure, the latter enabling a new user design.20 We further homogenized the cohort by matching on propensity to receive a statin, derived from 75 measured characteristics. We used validated codes for defining acute ischemic stroke, ICH, and statin exposure. Finally, we tested for major selection biases related to statin exposure and found none.

Conversely, a number of study limitations merit comment. We had no access to other characteristics related to risk of hemorrhagic stroke such as blood pressure profile, serum lipids, leukoaraiosis on neuroimaging, and lifestyle habits (smoking, body habitus, and exercise).32 Because this was an observational study, we cannot infer causality for the association (or lack thereof) of statins and ICH. Indeed, because selection for therapy was not randomized, subtle biases in terms of patient allocation might still be present, despite the multiple adjustments. Our findings are based on a cohort of older patients; hence, applicability to younger individuals is unknown. Furthermore, owing to privacy concerns, events could not be adjudicated in this retrospective cohort study. We had no access to brain imaging data and could not discern whether small vessel disease is a predictor of ICH in relation to statins. Associations were conservatively based on the initial categorization of exposure, which may have introduced an element of misclassification bias due to non-

### Table 2. Specificity Analyses

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Statin Group</th>
<th>Control Group</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B12 testing</td>
<td>4356 (189)</td>
<td>4250 (198)</td>
<td>0.98 (0.93-1.04)</td>
</tr>
<tr>
<td>Vitamin D testing</td>
<td>354 (11)</td>
<td>373 (12)</td>
<td>0.90 (0.76-1.07)</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>1340 (44)</td>
<td>1217 (43)</td>
<td>1.05 (0.96-1.15)</td>
</tr>
<tr>
<td>Knee arthroplasty</td>
<td>120 (4)</td>
<td>102 (3)</td>
<td>1.22 (0.90-1.64)</td>
</tr>
<tr>
<td>Bone density testing</td>
<td>1397 (47)</td>
<td>1239 (44)</td>
<td>1.04 (0.96-1.14)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

### Table 3. Multivariable Predictors of Intracerebral Hemorrhage

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>0.84 (0.71-0.98)</td>
</tr>
<tr>
<td>Urban residence</td>
<td>1.91 (1.48-2.45)</td>
</tr>
<tr>
<td>Accrual date per 5 y</td>
<td>1.14 (1.01-1.29)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.29 (1.04-1.60)</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>1.60 (1.09-2.35)</td>
</tr>
<tr>
<td>Previous ICH</td>
<td>3.64 (2.58-5.13)</td>
</tr>
<tr>
<td>Hospitalizations in past 3 y, No.</td>
<td>0.92 (0.86-0.99)</td>
</tr>
<tr>
<td>CADG of acute minor</td>
<td>1.35 (1.02-1.80)</td>
</tr>
<tr>
<td>Statins</td>
<td>0.79 (0.63-0.99)</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>2.01 (1.67-2.43)</td>
</tr>
<tr>
<td>Oral antiplatelets</td>
<td>1.18 (1.00-1.39)</td>
</tr>
<tr>
<td>Potassium-sparing diuretics</td>
<td>0.67 (0.50-0.90)</td>
</tr>
</tbody>
</table>

Abbreviations: CADG, collapsed ambulatory diagnosis grouping; CI, confidence interval; HR, hazard ratio; ICH, intracerebral hemorrhage.

*Data are presented as number of patients with event (rate per 1000 patient-years of follow-up).
adherence; however, relatively few patients crossed over between groups during follow-up.

At present, more than 80% of patients discharged from the hospital with a diagnosis of ischemic stroke are prescribed statin therapy. In a large North American jurisdiction, we found no evidence that such patients are at higher risk for cerebral bleeding than individuals who do not receive statins. Physicians should continue to adhere to current treatment guidelines recommending statin therapy for most patients with a history of ischemic stroke.

Accepted for Publication: June 27, 2011.
Published Online: September 12, 2011. doi:10.1001/archneur.2011.228

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Author Contributions: Dr Hackam had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Hackam, Juurlink, Mamdani, Paterson, and Kapral. Acquisition of data: Hackam, Huang, and Kapral. Analysis and interpretation of data: Hackam, Austin, Huang, Mamdani, Paterson, Hachinski, Li, and Kapral. Drafting of the manuscript: Hackam and Kapral. Critical revision of the manuscript for important intellectual content: Hackam, Juurlink, Mamdani, Paterson, and Kapral. Statistical analysis: Austin, Huang, Juurlink, Mamdani, and Li. Obtained funding: Hackam and Kapral. Study supervision: Hackam, Hachinski, and Kapral.

Financial Disclosure: Dr Mamdani has received honoraria for serving on advisory boards for Pfizer, Eli Lilly and Co, Novartis, GlaxoSmithKline, and Boehringer Ingelheim.

Funding Support: This study was supported by a peer-reviewed grant-in-aid from the Physicians’ Services Incorporate Foundation (a nonprofit medical research charity). Dr Hackam was supported by a Canadian Institutes for Health Research New Investigator Award. Dr Austin was supported by a Career Investigator Award from the Heart and Stroke Foundation of Ontario. Dr Kapral was supported by a Canadian Institutes for Health Research New Investigator Award and also receives support from the Canadian Stroke Network. This project was conducted at the Institute for Clinical Evaluative Sciences, which is supported by an annual grant from the Ontario Ministry of Health and Long-Term Care.

Role of the Sponsor: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

Disclaimer: Opinions, results, and conclusions in this article are those of the authors and are independent from the funding sources. No endorsement by the Institute for Clinical Evaluative Sciences or the Ontario Ministry of Health and Long-Term Care is intended or should be inferred.

Additional Contributions: Nick Daneman, MD, MSc, Amit Garg, MD, PhD, Marko Mrkobrada, MD, Donald Redelmeier, MD, MSHSR, and Matthew Weir, MD, provided helpful comments on the manuscript; these individuals were not compensated for their assistance.

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