ORIGINAL RESEARCH

Association Between Statin Use and Cardiovascular Events After Carotid Artery Revascularization

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***Background*—**Statins are commonly used for the prevention of cardiovascular events; however, statins are underutilized in patients with noncoronary atherosclerosis. We sought to establish the rates of statin use in patients with carotid artery disease and to examine the association between statin therapy and outcomes after carotid revascularization.

***Methods and Results*—**In this population-level retrospective cohort study, we identified all individuals aged ≥66 years who underwent carotid endarterectomy or stenting in Ontario, Canada (2002–2014). The primary outcome was a composite of 1-year stroke, myocardial infarction, or death (major adverse cardiac and cerebrovascular events). Five-year risks were also examined. Adjusted hazard ratios were computed using inverse probability of treatment weighting based on propensity scores. A total of 7893 of 10 723 patients (73.6%) who underwent carotid revascularization were on preprocedural statin therapy; moderate- or high-dose therapy was utilized by 7384 patients (68.9%). The composite rate of 1-year major adverse cardiac and cerebrovascular events was lower among statin users (adjusted hazard ratio: 0.76; 95% confidence interval, 0.70–0.83). Patients who were on persistent long-term statin therapy after the carotid procedure continued to experience significantly lower risk of major adverse cardiac and cerebrovascular events at 5 years (adjusted hazard ratio: 0.75, 95% confidence interval, 0.71–0.80). The beneficial associations with statin use were observed regardless of type of carotid revascularization procedure, carotid artery symptom status, or statin dose.

***Conclusions*—**Continuous statin therapy was associated with a 25% lower risk of long-term adverse cardiovascular events in patients with significant carotid disease. Along with other supportive evidence, statins should be considered in patients undergoing carotid revascularization, and efforts are required to increase statin use in this undertreated population. **(*J Am Heart Assoc*. 2018;7:e009745. DOI: 10.1161/JAHA.118.009745.)**

Key Words: carotid artery stenting • carotid endarterectomy • carotid revascularization • carotid stenosis • statins

Statins are competitive inhibitors of 3-hydroxy 3-methylglutaryl coenzyme A reductase, an enzyme responsible for making cholesterol in the liver, resulting in a 25% to 50% reduction in circulating LDL (low-density lipoprotein) and cholesterol levels. In addition, statins have important pleiotropic cardiovascular effects including reduction of inflammation and atherosclerotic plaque stabilization.[1–3] Clinically, statins have been shown to reduce rates of stroke, myocardial infarction, and death in patients with cardiovascular disease. To that end, major

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Accompanying Tables S1 through S3 and Figures S1 through S4 are available at http://jaha.ahajournals.org/content/7/16/e009745/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Only two thirds of patients aged ≥66 years with significant carotid artery stenosis undergoing carotid revascularization were on moderate- or high-dose statin therapy at the time of the carotid procedure.
- Patients with isolated carotid artery disease were less likely to be on statin therapy compared with those who had concomitant coronary artery disease.
- Consistent use of statin therapy after carotid artery revascularization was associated with a sustained 25% reduction in the risk of stroke, myocardial infarction, or death at up to 5 years of follow-up.

What Are the Clinical Implications?

- Improving statin utilization among patients with significant carotid artery stenosis should be a key component of quality programs and may translate to better long-term outcomes.

clinical practice guidelines recommend statin therapy for secondary prevention in most patients with established cardiovascular disease and for primary prevention in high-risk patients.[4,5]

Unfortunately, despite clear guidelines, a disproportionately high gap in care exists for patients with noncoronary atherosclerosis involving the peripheral and carotid circulations. Several studies have reported underutilization of established risk-reduction therapies such as statins for peripheral artery disease relative to coronary artery disease,[6–8] which may lead to poor cardiovascular and limb outcomes.[9] Nevertheless, few data exist on the utilization of statin therapy among patients with carotid artery disease. In the multicenter randomized controlled EVA-3S (Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis) and SPACE (Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy) trials, only 49% of patients were on lipid-lowering therapy at the time of carotid revascularization.[10,11] This is particularly concerning, given data from the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial that showed carotid stenosis patients derive the greatest benefit from intense statin therapy with respect to adverse cerebro- and cardiovascular events.[12]

We set out to answer 2 specific questions in this study. First, we sought to establish the pre- and postprocedural rates of statin use in patients with established carotid artery disease (defined as those undergoing carotid artery revascularization) at a population level. Second, we sought to examine the association between statin use and long-term outcomes in patients with carotid artery disease.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results based on institutional privacy policies.

Study Design and Sources of Data

We designed a retrospective population-level cohort study using administrative healthcare databases in Ontario, Canada, between April 1, 2002, and March 31, 2015. These databases are linked using unique identifiers and capture all healthcare system interactions for 13.6 million Ontario residents with access to universal health care. The data sets we used contain information on admissions to acute care hospitals, ambulatory and emergency department visits, physician and healthcare-provider billing claims, demographic and vital statistics records, and medication prescription claims data. See Table S1 and Figure S1 for more information on the databases used in this study. These databases are routinely used for health services and pharmacoepidemiological research,[13–15] and validation studies have shown them to be of high quality.[16–19] The institutional review boards at St. Michael's Hospital and Sunnybrook Health Science Center approved this study. The need for patient consent to use these databases for research purposes was waived under the Personal Health Information Privacy Act. The first and last authors had full access to all data in the study and take responsibility for its integrity and the data analysis.

Study Population

All patients aged ≥66 years who underwent carotid artery revascularization (endarterectomy or stenting) between April 1, 2002, and March 31, 2014, were eligible for this study. We used *Canadian Classification of Health Intervention* procedure codes JE57Lx and 1JE50x to identify patients who underwent endarterectomy and stenting, respectively. A previous validation study showed that this approach accurately captures carotid revascularization patients in our databases (positive predictive value: 87–99%; sensitivity: 90–93%).[16] We excluded patients who had multiple carotid procedures during the same hospital admission and those who underwent combined coronary and carotid revascularization.

Identification of Statin Use and Intensity at Baseline and Follow-up

We used the Ontario Drug Benefit program database to establish baseline and postprocedural statin use during follow-up. This database, established in 1990 by the Ontario Ministry of Health and Health and Long Term Care, captures data on medication prescriptions filled by Ontario residents

aged ≥65 years and those on social assistance. It includes quantitative prescription information such as drug identification number, dispensed date, number of days supplied, and cost. The coding error rate in this database for dispensed prescriptions is <1%.[19]

To establish baseline statin use, we first used a 150-day look-back window from the date of the index carotid procedure to identify any prescription claims for a statin. We used a 150-day window because the maximum quantity of medications that can be dispensed at 1 time in Ontario is 100 days. In addition, we added a 50% grace period to avoid excluding patients who were admitted to the hospital or who experienced other unexpected delays in refilling their prescriptions, as conducted in previous studies.[20,21] We then checked for active statin therapy at the time of the procedure for all patients with at least 1 statin prescription claim within the 150-day window. We defined patients as baseline statin users if the date of the last statin prescription plus 1.5 times the number of prescription days supplied crossed the carotid procedure date. For example, if a patient had last filled a prescription for a 60-day supply of statin therapy, the patient must have had the carotid procedure within 90 days to be categorized as a baseline statin user. Patients who were not actively on statins at the time of the procedure were categorized as *non–statin users*. In addition, we classified statin intensity based on the 2013 American College of Cardiology/American Heart Association guidelines on the treatment of blood cholesterol (Table S2).[5]

We also used the Ontario Drug Benefit program database to capture postprocedural statin use during long-term follow-up. Among baseline statin users, we defined ongoing use as filling of the next statin prescription within the duration defined in the prescription plus a 50% grace period. We censored statin users who stopped using a statin at any time during follow-up. We defined statin discontinuation as no repeated statin prescription dispensation within the aforementioned time windows. With respect to non–statin users, we censored those who started statin therapy during follow-up at the time of prescription dispensation to allow for an "on-treatment" analysis. Finally, we also censored patients who had a repeated carotid intervention and those who reached the end of the study period (March 31, 2015). All patients received a minimum of 1-year follow-up, and we followed patients for a maximum of 5 years.

Outcomes

The primary outcome was a 1-year composite risk of any stroke, myocardial infarction, or death. As secondary outcomes, we also studied individual components of this composite outcome at 1 year. With respect to long-term outcomes, we examined 5-year composite and individual risks of any stroke, myocardial infarction, or death. We used validated coding algorithms based on the *International Classification of Diseases, 10th Revision (ICD-10)* diagnosis codes to capture stroke[18] and myocardial infarction[17] as in-hospital complications of the index carotid procedure and most responsible diagnoses for readmission during follow-up.

Covariates

We measured several baseline covariates that could potentially confound the relationship between statin use and adverse cardiovascular events, including age, sex, rural residence, neighborhood income quintile (as a measure for socioeconomic status),[22] overall comorbidity burden (as indicated by the Charlson Comorbidity Index),[23] and health services utilization. We also used a 5-year look-back window to establish medical comorbidities and prior cardiovascular procedures and a 1-year look-back window to establish baseline medication use. Symptomatic carotid stenosis was defined as a previous hospital admission or emergency department visit within 6 months for ischemic stroke or transient ischemic attack. Finally, we established procedural and hospital characteristics, including year of procedure, elective versus emergent admission, and academic or specialized stroke center. See Table S3 for a complete list of the codes used to establish covariates and outcomes in this study and their accuracy.

Statistical Analysis

We compared baseline characteristics of baseline statin users versus non–statin users using standardized differences. Standardized differences, which reflect the mean difference as a percentage of the standard deviation, are more suitable for population-level studies as they are not as sensitive to sample size as traditional testing.[24] A standardized difference of >0.1 is typically felt to be significant.[24]

We conducted time-to-event analyses using Cox proportional hazards regression to compare 1- and 5-year outcomes between statin users and non–statin users. We calculated unadjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for each outcome with non–statin users as the reference group. We then used propensity score methods to adjust for potential confounding and to reduce selection bias. All variables listed in Table 1 were used to build multivariable logistic regression models to calculate propensity scores, including age, sex, rural residence, neighborhood income quintile, Charlson Comorbidity Index, health services utilization (mean outpatient physician visits in the past year and mean emergency department visits and hospital visits in the past 3 years), carotid artery symptom status, comorbid conditions (coronary artery disease, acute myocardial infarction, heart failure, peripheral artery disease, diabetes mellitus, hypertension, chronic obstructive pulmonary

Table 1. Baseline Characteristics of Patients

	No Statin (n=2830)	Statin (n=7893)	SDiff* (Unadjusted Comparison)	SDiff* (After IPTW Adjustment)
Age, y				
Mean±SD	75.6±6.2	74.7±5.6	0.15	0.00
Range, n (%)				
66–75	1462 (51.7)	4530 (57.4)	0.12	0.01
≥76	1368 (48.3)	3363 (42.6)	0.12	0.01
Female sex, n (%)	976 (34.5)	2607 (33.0)	0.03	0.00
Rural residence, n (%)†	558 (19.7)	1434 (18.2)	0.04	0.02
Neighborhood income quintile, n (%)†				
1 (lowest)	580 (20.5)	1499 (19.0)	0.04	0.00
2	606 (21.4)	1718 (21.8)	0.01	0.00
3	546 (19.3)	1605 (20.3)	0.03	0.00
4	530 (18.7)	1574 (19.9)	0.03	0.01
5 (highest)	559 (19.8)	1473 (18.7)	0.03	0.01
Charlson comorbidity index, n (%)†				
0	824 (29.1)	2123 (26.9)	0.05	0.00
1	597 (21.1)	1737 (22.0)	0.02	0.01
≥2	829 (29.3)	2720 (34.5)	0.11	0.02
Health service utilization				
Outpatient physician visits in past year, mean±SD	13.9±8.4	15.8±8.6	0.22	0.03
Emergency department visits in past 3 y, mean±SD	2.8±3.7	2.6±3.1	0.05	0.01
Hospital admissions in past 3 y, mean±SD	1.9±1.4	2.0±1.3	0.02	0.01
Comorbid conditions, n (%)				
Symptomatic carotid stenosis	1301 (46.0)	3449 (43.7)	0.05	0.00
Coronary artery disease	442 (15.6)	2018 (25.6)	0.25	0.02
Acute MI	89 (3.1)	510 (6.5)	0.16	0.01
Congestive heart failure	115 (4.1)	378 (4.8)	0.04	0.02
Peripheral arterial disease	137 (4.8)	414 (5.2)	0.02	0.02
Diabetes mellitus	787 (27.8)	3013 (38.2)	0.22	0.02
Hypertension	2305 (81.4)	6998 (88.7)	0.20	0.01
COPD	897 (31.7)	2456 (31.1)	0.01	0.02
Chronic kidney disease	90 (3.2)	325 (4.1)	0.05	0.01
Prior procedures, n (%)				
Carotid endarterectomy	101 (3.6)	319 (4.0)	0.02	0.01
Coronary revascularization	24 (0.8)	172 (2.2)	0.11	0.01
Peripheral revascularization	86 (3.0)	220 (2.8)	0.02	0.01
Procedural and hospital characteristics				
Year of procedure‡				
2002–2006	1433 (50.6)	3024 (38.3)	0.25	0.00
2007–2010	779 (27.5)	2765 (35.0)	0.16	0.00
2011–2014	618 (21.8)	2104 (26.7)	0.11	0.00

Continued

Table 1. Continued

	No Statin (n=2830)	Statin (n=7893)	SDiff* (Unadjusted Comparison)	SDiff* (After IPTW Adjustment)
Urgent admission	857 (30.3)	1437 (18.2)	0.28	0.03
Academic center	1278 (45.2)	3741 (47.4)	0.05	0.00
Stroke center	2155 (76.1)	5771 (73.1)	0.07	0.00
Medication use, n (%)				
Any antiplatelet agent§	923 (32.6)	3947 (50.0)	0.36	0.03
Acetylsalicylic acid§	501 (17.7)	1794 (22.7)	0.13	0.04
Dipyridamole	229 (8.1)	966 (12.2)	0.14	0.02
Clopidogrel	477 (16.9)	2453 (31.1)	0.34	0.04
ACEI or ARB	1260 (44.5)	5262 (66.7)	0.46	0.03
β-Blocker	715 (25.3)	3192 (40.4)	0.33	0.03
Diuretic	766 (27.1)	2706 (34.3)	0.16	0.01
Calcium channel blocker	823 (29.2)	2949 (37.4)	0.18	0.01
Oral antidiabetic	330 (11.7)	1671 (21.2)	0.26	0.02
Insulin	104 (3.7)	478 (6.1)	0.11	0.02
Warfarin	177 (6.3)	609 (7.7)	0.06	0.02
NOAC	7 (0.2)	53 (0.7)	0.06	0.00

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; IPTW, inverse probability treatment weighting; MI, myocardial infarction; NOAC, novel oral anticoagulant; SDiff, standardized difference.

*SDiff >0.1 indicates significant difference.

†Missing values: ≤5 rural residence; 33 neighborhood income quintile (0.3%); 1893 Charlson comorbidity (17.7%).

‡For 2002, only procedures performed after March 31, 2002, are included. For 2014, procedures performed after March 31, 2014 are not included.

§Acetylsalicylic acid use is underreported because over-the-counter purchases of this drug were not captured.

disease, chronic kidney disease), prior procedures (carotid endarterectomy, coronary revascularization, and peripheral revascularization), year of procedure (2002–2006, 2007–2010, or 2011–2014), urgent admission, academic center, stroke center, and baseline medication use (acetylsalicylic acid, dipyridamole, clopidogrel, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, β-blocker, diuretic, calcium channel blocker, oral antidiabetic drug, insulin, warfarin, and novel oral anticoagulant). The variable *any antiplatelet agent* was removed from the model due to collinearity (defined as a variance inflation factor >5).

Inverse probability of treatment weighting (IPTW) analysis was then used to adjust for differences between the 2 groups based on the propensity scores.[25,26] We used the methods described by Austin and Stuart[27] to calculate standardized differences post-IPTW adjustment to ensure all baseline covariates were equally distributed in the adjusted cohorts. We then built IPTW-adjusted Cox proportional hazards regression models to calculate adjusted HRs for the risk of each outcome and estimated IPTW-adjusted survival curves using the approach of Cole and Hernán.[28] Finally, we conducted subgroup analyses for the primary composite outcome at 1 and 5 years by type of carotid procedure (endarterectomy or stenting), carotid artery symptom status (symptomatic or asymptomatic), and statin dose (high or moderate/low). We combined moderate- and low-dose statin groups because of the relatively small sample size of the low-dose statin group. We also used interaction terms to test for heterogeneity between subgroups.

We visually inspected log–log survival curves and examined the statistical significance of time-dependent covariates to test the proportional hazards assumption of all our models. All analyses were robust with the proportional hazards assumptions. All *P* values are 2-sided, and $P<0.05$ was considered statistically significant. All statistical analyses were conducted using SAS Enterprise Guide v7.1 (SAS Institute).

Results

Patient Cohort

We identified a total of 10 723 patients, of which 7893 (73.6%) were on statin therapy and 2830 (26.4%) were not at baseline. Statin use was highest among those with concomitant coronary artery disease (82.0% versus 71.1%; $P<0.0001$; Figure 1). With respect to the intensity of statins, 4843 patients (45.2%) were on moderate-dose therapy, 2541 (23.7%) were on high-dose therapy, and 509 (4.8%) were on low-dose therapy (Figure 1). The most commonly prescribed statin was atorvastatin (54.9%), followed by rosuvastatin (24.3%) and simvastatin (13.8%) (Figure S2).

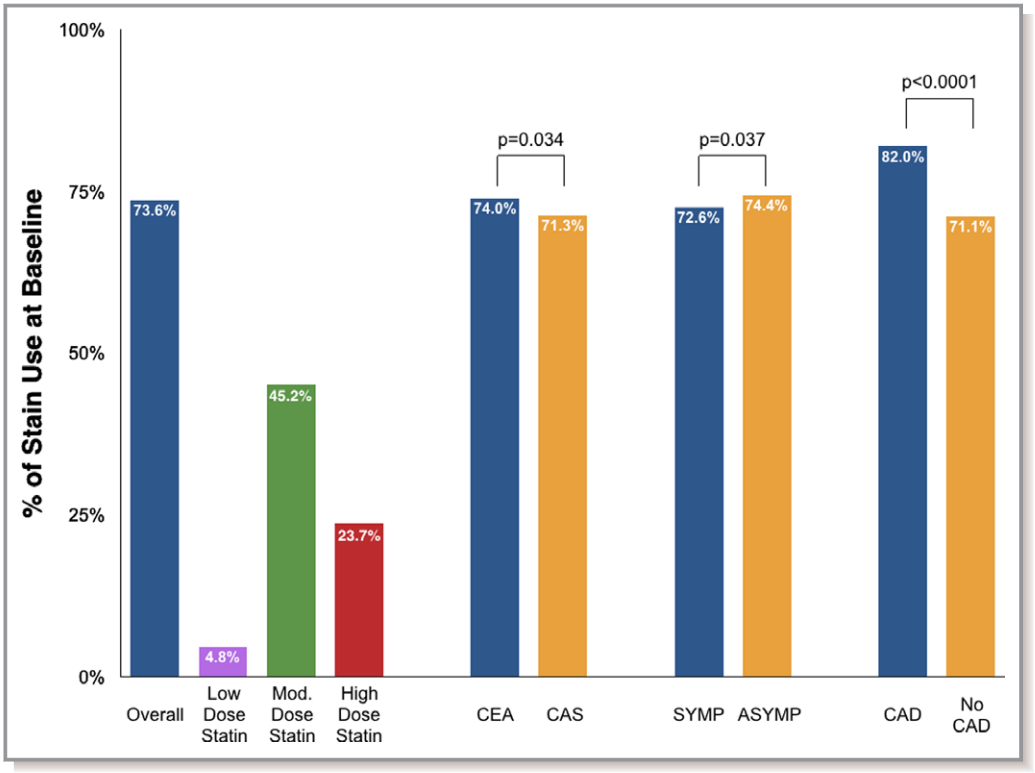

Figure 1. Proportion of patients on preprocedural statin therapy. ASYMP indicates asymptomatic carotid stenosis; CAD, coronary artery disease; CAS, carotid artery stenting; CEA, carotid endarterectomy; Mod., moderate; SYMP, symptomatic carotid stenosis.

Statin users were slightly younger than non–statin users (mean age: 74.7 versus 75.4 years). Overall, about a third were female, and 44% to 46% had symptomatic carotid stenosis. Statin users were more likely to have greater overall comorbidity burden (including a history of coronary disease, myocardial infarction, diabetes mellitus, hypertension, and prior coronary revascularization); tended to utilize more health services; and were more likely to be on antiplatelet, antihypertensive, or antidiabetic medications at baseline. Non–statin users were more likely to have urgent admission and undergo the carotid procedure earlier in the study period. After IPTW adjustment, all baseline variables were equally distributed between the statin and non–statin user groups (Table 1).

1-Year Outcomes

The risk-adjusted rate of the primary composite outcome of 1-year stroke, myocardial infarction, or death was 26% lower among statin users (9.6% versus 11.2% for non–statin users; adjusted HR: 0.76; 95% CI, 0.70–0.83). Statin use was also associated with lower rates of 1-year stroke or death (7.4% versus 9.1% for non–statin users; adjusted HR: 0.75; 95% CI, 0.68–0.82), stroke (4.4% versus 5.6% for non–statin users; adjusted HR: 0.76; 95% CI, 0.67–0.86), death (4.2% versus 4.7% for non–statin users; adjusted HR: 0.76; 95% CI, 0.67–0.87), and myocardial infarction (2.7% versus 2.9% for non–statin users; adjusted HR: 0.81; 95% CI, 0.69–0.95; Table 2).

5-Year Outcomes

The median follow-up for the 5-year outcome analysis was 3.0 years (interquartile range: 0.48–5.0 years). We found that continuous statin use was associated with a 25% lower composite risk of stroke, myocardial infraction, or death at 5 years (adjusted HR: 0.75; 95% CI, 0.71–0.80). Individual rates of 5-year stroke (adjusted HR: 0.80; 95% CI, 0.72–0.89), death (adjusted HR: 0.73; 95% CI, 0.68–0.79), and myocardial infarction (adjusted HR: 0.83; 95% CI, 0.73–0.93) were consistently lower among statin users. See Table 2 for 5-year outcomes and Figure 2 for IPTW-adjusted survival curves for the 5-year composite outcome.

Statin Use at Follow-up

We examined postprocedural statin adherence among those patients alive at 1 and 5 years. More than half (53.6%, 1445/2696) of non–statin users at baseline were initiated on statin therapy by 1-year follow-up, and more than three quarters (76.2%, 1892/2483) were taking a statin by 5 years. With respect to baseline statin users, 13.1% (993/7559) were no

Table 2. One and 5-Year Outcomes After Carotid Revascularization by Statin Therapy

	1-Year Period		5-Year Period	
Outcome	Unadjusted HR (95% CI)	IPTW-Adjusted HR (95% CI)	Unadjusted HR (95% CI)	IPTW-Adjusted HR (95% CI)
Stroke, MI, or death	0.69 (0.60–0.79)	0.76 (0.70–0.83)	0.71 (0.65–0.78)	0.75 (0.71–0.80)
Stroke or death	0.65 (0.56–0.75)	0.75 (0.68–0.82)	0.69 (0.62–0.76)	0.75 (0.71–0.80)
Stroke	0.69 (0.57–0.83)	0.76 (0.67–0.86)	0.72 (0.61–0.86)	0.80 (0.72–0.89)
Death	0.62 (0.51–0.76)	0.76 (0.67–0.87)	0.68 (0.61–0.77)	0.73 (0.68–0.79)
MI	0.92 (0.76–1.13)	0.81 (0.69–0.95)	0.84 (0.69–1.02)	0.83 (0.73–0.93)

Values are presented as n (%). CI indicates confidence interval; HR, hazard ratio; IPTW, inverse probability treatment weighting; MI, myocardial infarction.

longer adherent to a statin at 1 year—this number increased slightly to 16.0% (1047/6553) at 5 years. Overall, statin adherence increased from 73.6% at baseline to 78.1% at 1-year follow-up and 81.9% at 5-year follow-up.

Subgroup Analyses

For the composite risk of stroke, myocardial infarction, or death by carotid procedure, we conducted subgroup analyses for symptom status, and statin intensity (Figure 3). The 5-year composite risk was lower among statin users who underwent carotid endarterectomy (adjusted HR: 0.73; 95% CI, 0.69–0.78) and carotid artery stenting (adjusted HR: 0.86, 95% CI, 0.75–0.98)—this benefit of statin therapy appeared to be greater in the endarterectomy group (P=0.002 for interaction). See Figure S3 for adjusted survival curves by type of carotid procedure. Of note, our previous work has shown that patients who receive carotid stenting in Ontario are more likely to have symptomatic carotid stenosis and a higher comorbidity burden compared with those who receive

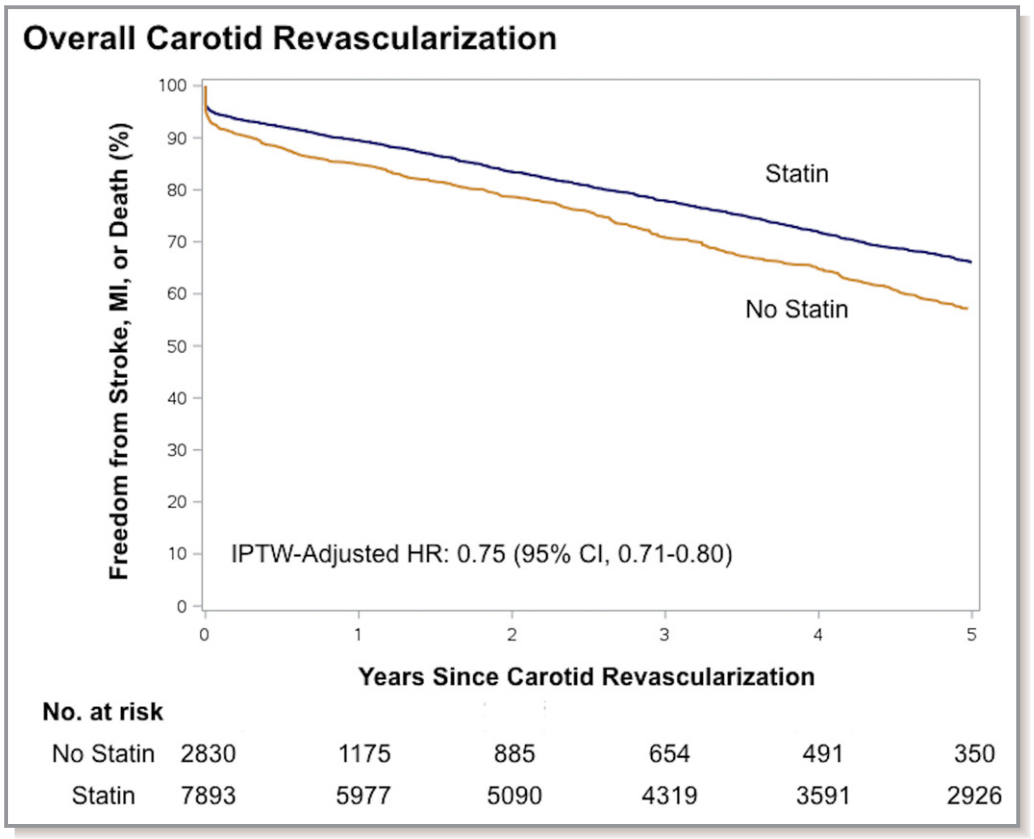

Figure 2. Adjusted Kaplan–Meier curves of 5-year outcomes after carotid revascularization by statin therapy. Shown are the 5-year adjusted Kaplan–Meier curves for freedom from any stroke, myocardial infarction, or death after carotid revascularization. CI indicates confidence interval; HR hazard ratio; IPTW, inverse probability of treatment weighting; MI, myocardial infarction.

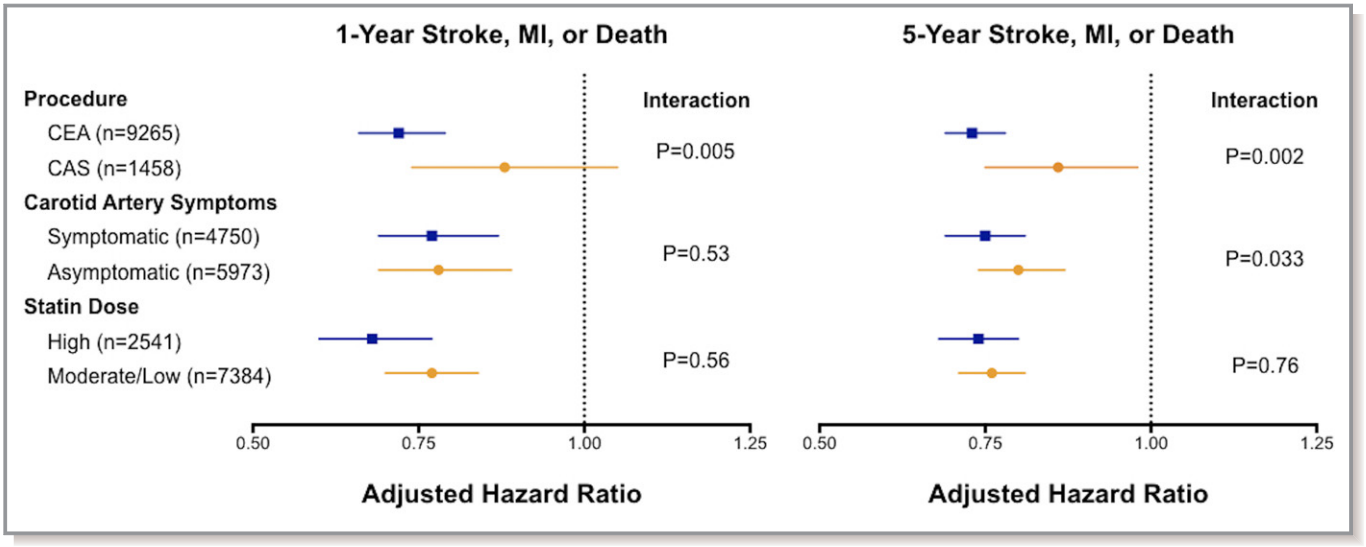

Figure 3. Risk of stroke, myocardial infarction, or death after carotid revascularization among subgroups by statin therapy. CAS indicates carotid artery stenting; CEA, carotid endarterectomy; MI, myocardial infarction.

endarterectomy.[29] With respect to carotid artery symptom status, patients on statin therapy, whether symptomatic (adjusted HR: 0.75; 95% CI, 0.69–0.81) or asymptomatic (adjusted HR: 0.80; 95% CI, 0.74–0.87), had lower 5-year event rates, with the symptomatic group receiving a slightly greater benefit (*P*=0.033 for interaction). We did not observe a dose-dependent effect of statins, as both high-dose statins (adjusted HR: 0.74; 95% CI, 0.68–0.80) and moderate/low-dose statins (adjusted HR: 0.76; 95% CI, 0.71–0.81) were associated with similar reductions in 5-year events (*P*=0.76 for interaction). We also observed similar associations between statin use and the individual rates of stroke in these subgroups (Figure S4).

Discussion

In the current analysis, we found that only three quarters of older adult patients undergoing carotid artery revascularization were on statin therapy at the time of the carotid procedure—postprocedural statin use increased modestly to 82% at 5-year follow-up. Patients with isolated carotid artery disease were less likely to be on statin therapy (71%) compared with those who had concomitant coronary artery disease (82%). Consistent use of statin therapy after carotid artery revascularization was associated with a sustained 25% reduction in the risk of stroke, myocardial infarction, or death at up to 5 years of follow-up. Events rates were lower after both carotid endarterectomy and stenting with statin use, and the protective association with statin use was observed regardless of carotid artery symptom status and statin intensity. Given the significant morbidity and disability associated with stroke,[30] our results may have important public health implications.

To the best of our knowledge, this study is the first to examine the association between statin use and long-term outcomes after carotid artery revascularization while considering postprocedural statin use based on actual medication prescription claims. The few previous studies in this area have been limited by lack of data on statin use after the carotid procedure and/or lack of data on statin intensity. AbuRhama and colleagues conducted a retrospective analysis of 500 patients who underwent carotid endarterectomy over a 3-year period and found that those on baseline statin therapy had a 50% reduction in the risk of death after a mean follow-up of 2.3 years.[31] Their study, however, was limited by a single-center design and lacked information about the use of statin therapy after endarterectomy. In a retrospective analysis of 2127 carotid endarterectomies performed between 1989 and 1999, LaMuraglia and colleagues observed improved anatomic durability and survival among patients on lipid-lowering drugs after mean follow-up of 6.2 years.[32] Despite longer follow-up, their study also lacked detailed information about postprocedural statin use and intensity. A study of 1083 patients who underwent carotid stenting in Italy showed that statin use was associated with half the risk of mortality and borderline reduced risk of ischemic stroke at 5 years compared with non–statin use.[33] The investigators, however, could not accurately capture details of postprocedural statin use and intensity in their cohort. Baseline statin use at the time of the carotid procedure ranged from 43% to 60% in these studies, which was lower than what we observed in the current study (74%)—this might be because our cohort was limited to older patients who are more likely to be treated with lipid-lowering therapy.

SPARCL was a randomized controlled trial that compared high-dose statin therapy (atorvastatin 80 mg once daily) with

placebo in 4731 patients with a history of stroke or transient ischemic attack.[34] The 5-year risk of adverse cardiovascular events was 20% lower with atorvastatin in the overall trial (17.2% versus 14.1% for atorvastatin; HR: 0.80; 95% CI, 0.69–0.92). Furthermore, a subsequent subanalysis of SPARCL showed that patients with carotid stenosis in the trial had a higher rate of cardiovascular events and also benefited more from high-dose statin therapy (21.0% versus 14.2% for atorvastatin; HR: 0.64; 95% CI, 0.47–0.86).[12] In the current analysis, the vast majority (94%) of statin users were on moderate- or high-dose therapy at the time of the carotid procedure. Interestingly, we did not find a dose-dependent relationship between statin therapy and long-term outcomes, as both high- and moderate/low-dose statins were associated with ≈25% reductions in cardiovascular events. In contrast, a recent retrospective registry-based analysis of 397 patients undergoing carotid stenting showed a trend toward lower risk of 30-day events among patients treated with high-dose statins, suggesting a potential dose-dependent benefit of statins in this population.[35] Furthermore, clinical trials of patients with stable coronary artery disease, such as TNT (Treating to New Targets), suggest an incremental clinical benefit of high-dose statin therapy over moderate-dose therapy.[36] Although it is unclear why we did not observe a similar dose response in the carotid stenosis population in this study, variations in study cohort and LDL levels may help explain this discrepancy.

Although the focus of the current analysis was on long-term outcomes in patients with carotid artery disease, several studies have also observed an association between statin use and better periprocedural outcomes after carotid revascularization. Kennedy and colleagues reported a protective association with statins in 2031 symptomatic patients who underwent carotid endarterectomy in western Canada with respect to in-hospital mortality (75% odds reduction) and in-hospital ischemic stroke or death (45% odds reduction).[37] Similarly, another single-center retrospective study showed that statin use was associated with a 3-fold lower risk of 30-day stroke (1.2% versus 4.5%) and 5-fold lower risk of 30-day mortality (0.3% versus 2.1%) after carotid endarterectomy.[38] More recent studies of carotid stenting have also reported similar results. In an analysis of 344 carotid stenting patients in Germany, the authors reported a lower composite risk of periprocedural ischemic stroke, myocardial infarction, or death (odds ratio: 0.31) with statin use.[39] Data from smaller prospective studies of carotid artery stenting patients also suggest a protective effect of statin therapy on periprocedural ischemic complications.[40,41] Furthermore, Tadros and colleagues showed that preprocedural statin use is associated with less embolic debris during the carotid stenting procedure.[42] In addition, accumulating observational evidence suggests that statin use is associated with reduced rates of periprocedural complications and mortality after other types of major noncardiac surgery procedures.[43]

Studies of populations with other manifestations of atherosclerosis have also demonstrated protective effects of statins. Kumbhani and colleagues used the Reduction of Atherothrombosis of Continued Health (REACH) registry to demonstrate a 17% lower rate of the 4-year composite rate of cardiovascular death, myocardial infarction, or stroke among statin users with symptomatic peripheral arterial disease.[44] In a study of patients undergoing percutaneous coronary interventions, Chan and colleagues reported 45% and 33% lower rates of all-cause mortality with statin therapy during the periprocedural and 6-month periods, respectively.[45] Systematic reviews and meta-analyses of patients undergoing cardiac surgery[46] and abdominal aortic aneurysm repair[47] have also reported similar associations with lower rates of periprocedural events in statin users. Finally, high-quality multicenter randomized controlled trials of general populations at risk for cardiovascular events indicate that statin therapy is associated with a 20% to 30% reduction in long-term cardiovascular event rates.[48,49] We observed similar reductions in rates of 5-year events after carotid revascularization among statin users. Given these data, it is not surprising that major societal clinical practice guidelines recommend statin therapy in most patients undergoing carotid artery revascularization despite no specific randomized clinical trial data in this population.[50,51]

Our study has some limitations. First, as with all nonrandomized studies, potential imbalances in unmeasured confounders, such as race, ethnicity, smoking history, and body mass index, may have biased our results; however, we used propensity score methods to ameliorate this potential bias. Second, although we used validated coding to capture patients, covariates, and outcomes as possible, inaccurate coding in our databases may have biased our results. Third, we could not differentiate between new versus long-term statin users before cohort entry, and this may bias our findings.[52] Fourth, our databases lacked laboratory information on lipid levels at baseline and follow-up and medication data on those aged <65 years; the care gap of statin underuse may be larger among younger patients with carotid artery disease. Furthermore, we did not capture data on temporal changes in the types of preferred statins over the study period, and this could confound our results. Fifth, the proportion of patients receiving aspirin therapy is underestimated in our study, as aspirin is generally purchased as an over-the-counter drug in Ontario. Finally, the subanalysis of outcomes by carotid artery symptoms should be interpreted with caution because we were not able to capture minor neurological events for which patients did not seek hospital treatment; therefore, the proportion of symptomatic patients may have been underestimated. Despite the aforementioned

limitations, our study is the largest evaluating the role of statins in the incident risk of cardiovascular disease among patients undergoing carotid revascularization with long-term follow-up.

Conclusions

In summary, this study showed that continuous statin use is associated with a 25% lower rate of adverse cardiovascular events after carotid artery revascularization with up to 5 years of follow-up. Along with other supportive evidence, clinicians should consider statins for patients undergoing carotid artery revascularization. In addition, we found that statin therapy is underused before and after carotid artery revascularization. Improving statin utilization by these patients should be a key component of quality programs and may translate to better long-term outcomes. Future research in this area should focus on exploring the influence of different lipid levels on carotid plaques and clinical outcomes.

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Author Contributions

All authors made substantial contributions to conception and design of the study, interpretation of data, critical revision of the article, and approval of the final article. Hussain did the statistical analysis and wrote the first draft of the article. Hussain and Al-Omran take overall responsibility for the analyses and the article.

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SUPPLEMENTAL MATERIAL

Supplemental Tables

Table S1. Sources of data for the current population-level study.

Database	Description
Canadian Institute for Health Information Discharge Abstract Database	Records all hospitalizations in Ontario acute care hospitals
Ontario Health Insurance Plan Claims Database	Records data on physician and healthcare provider billing claims
Registered Persons Database	Records demographic and vital statistics data
National Ambulatory Care Reporting System	Records data on ambulatory and emergency department visits
Ontario Drug Benefit Claims	Records medication prescription claims data for Ontario residents aged 65 years or older
Ontario Diabetes Database	Disease-specific Institute for Clinical Evaluative Sciences-derived cohort
Ontario Hypertension Database	Disease-specific Institute for Clinical Evaluative Sciences-derived cohort

Table S2. Classification of statin intensity based on the 2013 American College of Cardiology/ American Heart Association Guidelines on the Treatment of Blood Cholesterol (1).

High Intensity Statin	**Moderate Intensity Statin***	**Lose Intensity Statin**
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg	Pravastatin 10-20 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg	Lovastatin 20 mg
	Simvastatin 20-40 mg	
	Pravastatin 40-80 mg	
	Lovastatin 40-80 mg	
	Fluvastatin 40 mg BID	

* All patients on moderate dose statin therapy were first identified based on this list. Patients on doses higher than moderate intensity were classified has high dose statin. Patients on doses lower than moderate intensity were classified as low dose statin.

Table S3. Coding definitions for identifying patients, comorbid conditions and outcomes.

	Database	Codes	Validity
Carotid Revascularization Procedure			
Carotid endarterectomy	CIHI-DAD	**CCI** 1JE57Lx	99% PPV, 90% sensitivity (2)
Carotid-artery stenting	CIHI-DAD	**CCI** 1JE50x	87% PPV, 93% sensitivity (2)
Outcomes			
Any stroke	CIHI-DAD	**ICD-10** I60.x I61.x I62.x I63.x, I64.x, H34.1 (excluding I63.6)	92% accurate (3)
Myocardial infarction	CIHI-DAD	**ICD-10** I21.x, I22.x	87% PPV, 89% sensitivity (4) 89% PPV, 89% sensitivity, 93% specificity (5)
Comorbid Conditions			
Symptomatic carotid stenosis*	CIHI-DAD	**ICD-10** I63, I64, G45, H34.1 (excluding I63.6 and G45.4) **ICD-9** 362.3, 433.x1, 434.x1, 436, 435.x	85% PPV (ischemic stroke diagnosis) (3) 97% PPV (TIA diagnosis) (3) 85% PPV (ischemic stroke diagnosis) (3) 70% PPV (TIA diagnosis) (3)
Coronary artery disease	CIHI-DAD	**ICD-10** I21.x, I22.x, I23.x, I24.x, I25.x, Z95.5, Z95.8, Z95.9, R93.1, T82.2 **ICD-9** 410.x, 412.x, 414.x, 429.2, 429.5, 429.6, 429.7 **CCI** 1IJ26x, 1IJ27x, 1IJ54x, 1IJ57x, 1IJ50x, 1IJ76x **CCP** 48.01, 48.02, 48.03, 48.04, 48.05, 48.1, 48.2, 48.3	Codes based on previous study (6)
	OHIP	R741, R742, R743, G298, E646, E651, E652, E654, E655, G262, Z434, Z448	
Myocardial infarction	CIHI-DAD	**ICD-10** I21.x, I22.x **ICD-9** 410.x	87% PPV, 89% sensitivity (4) 89% PPV, 89% sensitivity, 93% specificity (5)
Congestive heart failure	CIHI-DAD	**ICD-10** I50.x **ICD-9** 428.x	85% PPV, 79% sensitivity (4)
Peripheral arterial	CIHI-DAD	**ICD-10** I70.2, I73.9, I74.3, I74.4	Codes suggested by Cardiovascular

disease		**ICD-9** 440.2, 443.9, 444.2	Health in Ambulatory Care Research Team (CANHEART) investigators (7)
Diabetes mellitus	Ontario Diabetes Database	Diagnosis date in Ontario Diabetes Database that precedes the index date	80% PPV, 86% sensitivity, 97% specificity (8)
Hypertension	Ontario Hypertension Database	Diagnosis date in Ontario Hypertension Database that precedes the index date	87% PPV, 73% sensitivity, 95% specificity, 88% NPV (9)
Chronic obstructive pulmonary disease	Ontario COPD Database	Diagnosis date in Ontario COPD Database that precedes the index date	85% sensitivity, 78% specificity, 94% NPV (10)
Chronic kidney disease	CIHI-DAD	**ICD-10:** N032-N037, N052-N057, N18, N19, N250, Z490-Z492, Z940, Z992 **ICD-9:** 4030, 4031, 4039, 4040, 4041, 4049, 582, 5830-5837, 585, 586, 5880, V420, V451, V56	As defined in the calculation of Charlson Comorbidity Index by the Institute of Clinical Evaluative Sciences
Coronary revascularization	CIHI-DAD	**CCI** 1IJ50x, 1IJ54x, 1IJ57GQ, 1IJ76x **CCP** 48.02, 48.03, 48.1x	94-96% PPV (11)
Peripheral revascularization	CIHI-DAD	**CCI** 1KG76 **CCP** 51.29	88% PPV, 87% sensitivity (4) 91% PPV (12)
	OHIP	J025 (excluding records with the following associated OHIP diagnosis codes: 435 436 437 584 585 403)	

* Symptomatic carotid stenosis defined as a prior admission or emergency department visit within the last 6 months with ischemic stroke or transient ischemic attack.

CIHI-DAD, Canadian Institute for Health Information Discharge Abstract Database; CCI, Canadian Classification of Health Interventions; PPV, positive predicative value; ICD, International Statistical Classification of Diseases*;* CCP, Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures; OHIP, Ontario Health Insurance Plan; NPV, negative predictive value; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease.

Figure S1. Overview of Ontario healthcare administrative databases.

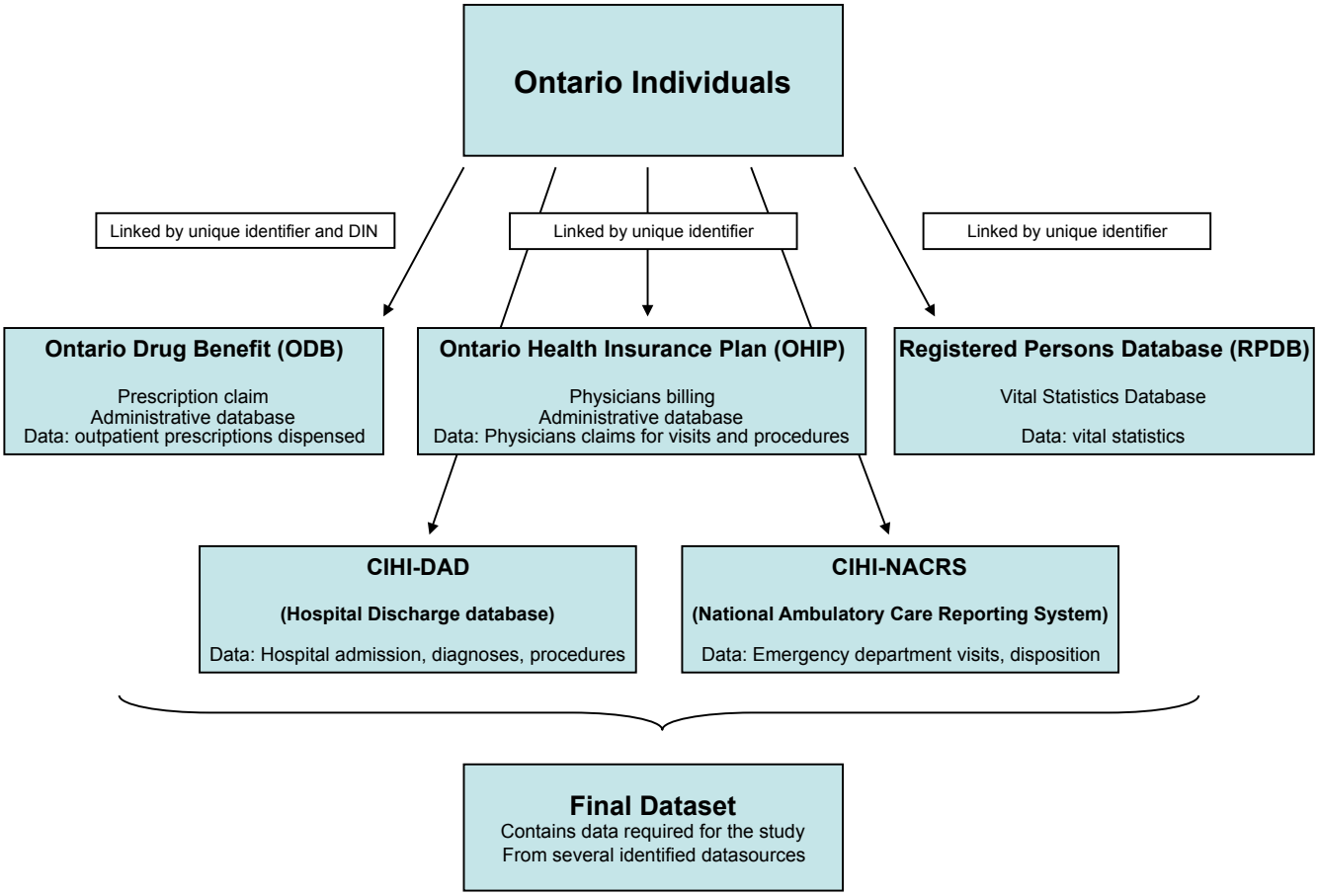


Figure S2. Types of statins prescribed to patients at baseline who underwent carotid artery revascularization (n=7893).

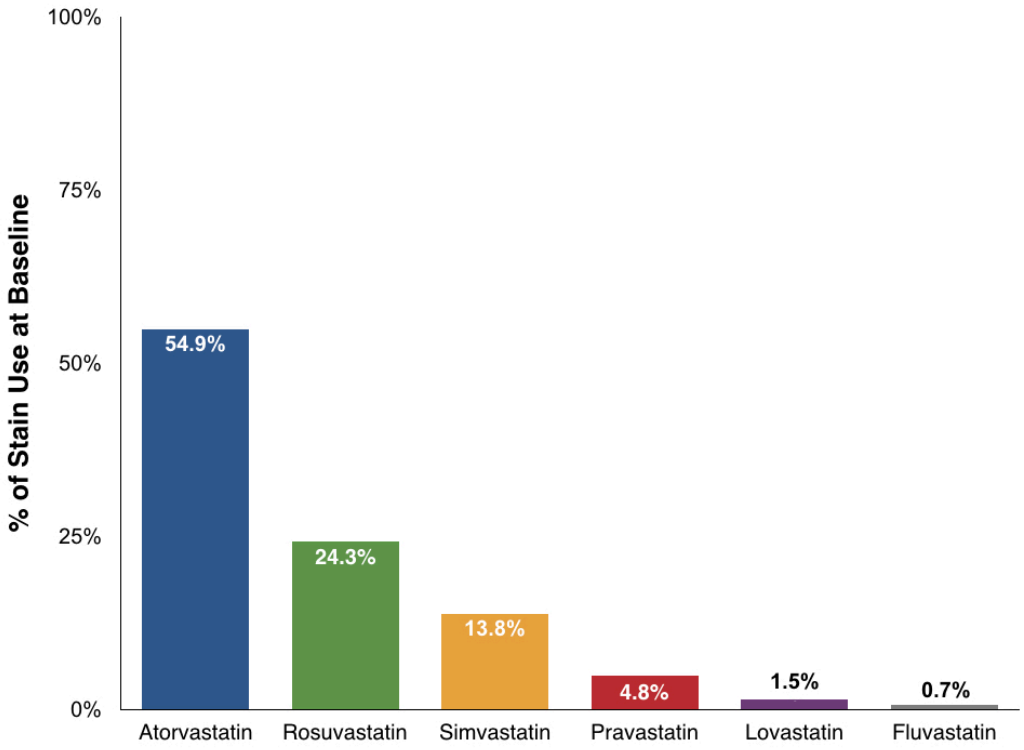
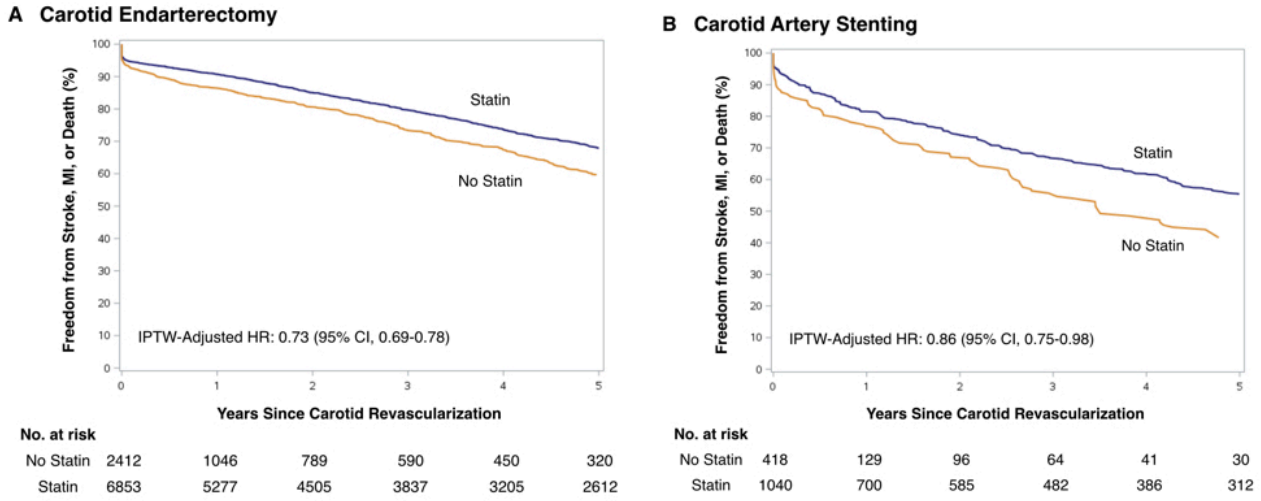


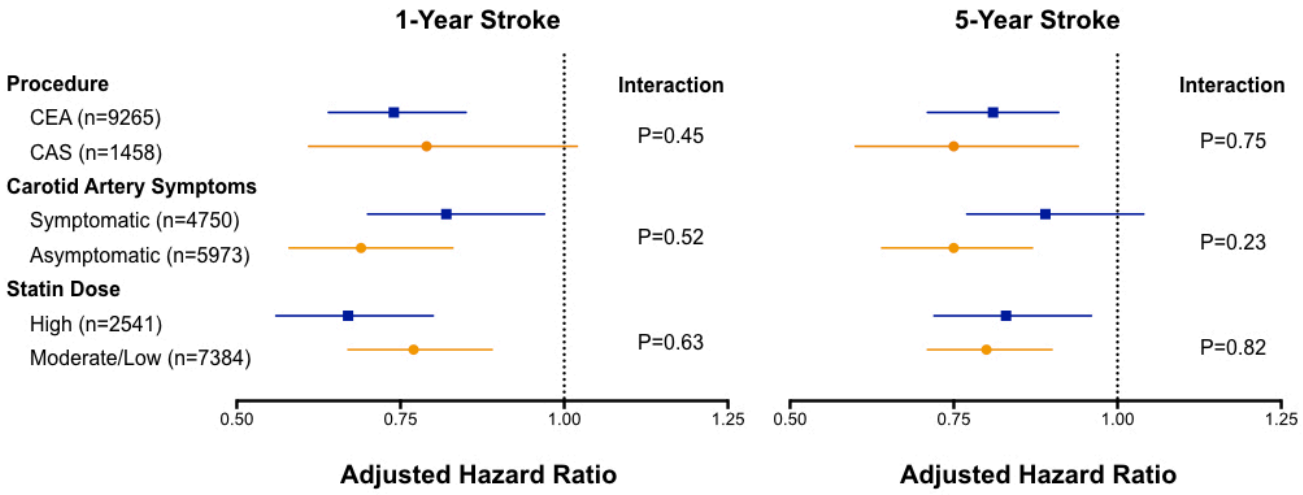
Figure S3. Adjusted Kaplan-Meier curves of 5-year outcomes after carotid endarterectomy (A) and stenting (B) by statin therapy.



Shown are the 5-year adjusted Kaplan-Meier curves for freedom from any stroke, myocardial infarction, or death after (A) carotid endarterectomy, and (B) carotid artery stenting.

MI, myocardial infarction; IPTW, inverse probability of treatment weighting; HR, hazard ratio; CI, confidence interval.

Figure S4. Risk of stroke after carotid revascularization among subgroups by statin therapy.



CEA, carotid endarterectomy; CAS, carotid artery stenting.

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