














Statin Use in Cervical Artery Dissection and Subsequent Ischemic Stroke

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ABSTRACT: Background and purpose: The role of statins in preventing recurrent ischemic strokes in the setting of non-traumatic cervical artery dissection remains unclear. This study, a secondary analysis of Antithrombotic Treatment for Stroke Prevention in Cervical Artery Dissection (STOP-CAD) study, investigates the impact of statin therapy on subsequent ischemic stroke. Methods: STOP-CAD, a multicenter retrospective observational study, included 4023 patients with non-major trauma-related CAD. For this sub study, we included 2610 patients with ischemic stroke, excluding those with non-ischemic presentations and missing statin information. Patients were stratified based on statin use at hospital discharge and a sensitivity analysis was conducted based on intensity: high-intensity, moderate-intensity, low-intensity, or no statin. Primary outcome was the incidence of subsequent ischemic stroke after hospital discharge. Secondary outcomes included major hemorrhage, mortality and 90-day functional outcomes. Statistical analyses included univariate analyses, Cox regression models to evaluate odds and hazard ratios. Results: There was no significant difference in subsequent ischemic strokes after hospital discharge between the statin group (3.1%) and no statin group (3.3%) (aHR 0.73 95% CI, 0.43-1.24, p=0.25). Similarly, the incidence of major hemorrhage, mortality and 90-day functional outcomes showed no significant differences between the groups. Conclusion: Statin therapy did not significantly reduce the risk of subsequent ischemic stroke, major hemorrhage, functional outcome, or mortality. While statins are beneficial in reducing vascular events and improving outcomes in ischemic stroke, its benefits in CAD-related ischemic strokes are less clear. These findings highlight the need for individualized treatment strategies and further research to optimize secondary prevention in CAD-related stroke.

KEYWORDS: Cervical artery dissection, acute stroke; statin.

Introduction

Cervical artery dissection (CAD) represents about 2% of ischemic strokes, occurring at an incidence rate of 2.97 per 100,000 population annually [1].

Notably, CAD is the etiology in up to 25% of cases of ischemic stroke in individuals under the age of 50 [2,3].

The primary treatment approach for CAD is Antithrombotic therapy [4-6].

However, the benefits of other prevention measures commonly implemented after ischemic stroke are unknown in CAD.

In general, statins have lowered the risk of stroke recurrence [7,8] but their effect in CAD related stroke is unclear, as such patients were not necessarily included in trials [8,9,10,11].

Omitting statins after an ischemic stroke is associated with adverse outcomes.

Instances of cardiovascular death, recurrent ischemic stroke, and myocardial infarction were found to be more prevalent in cases where early statin use was absent [12].

However, lack of statin therapy after CAD had not been well studied.

Processes such as endothelial injury, clot formation, inflammation, oxidative stress, abnormal angiogenesis, are noteworthy processes in the systemic and local pathways leading to cerebral ischemic pathogenesis.

By inhibiting HMG-CoA reductase, statins induce a comprehensive reduction not only in cholesterol but also in various intermediate metabolites[13].

The predominant hypothesis concerning the pathogenesis of CAD is underlying weakness in the vessel wall that may be genetically determined.

Additionally, environmental factors and certain risk factors are believed to potentially serve as triggers in the manifestation of CAD. Hence, the benefits of statin therapy should not be generalized to the stroke mechanism for CAD [14,15].

In CAD, statins might influence angiogenesis by increasing vascular endothelial growth factor at injury sites, potentially stimulating endothelial progenitor cells to aid repair. A retrospective observational study found no link between statin use and vascular healing before or after statin use in CAD [16].

A small preliminary prospective cohort study had statistically significant results for high potency statins, correlating with the best functional outcome.

Moreover, the discontinuation of statin therapy may have a poor functional outcome. However, statin therapy was ineffective in preventing stroke recurrence [17].

Hence, further research with larger sample size is warranted.

In this sub-study of the Antithrombotic Treatment for Stroke Prevention in Cervical Artery Dissection: The STOP-CAD study, we aim to compare the risks of subsequent ischemic stroke, major hemorrhage, and functional outcome in individuals with CAD with and without statin therapy.

Methods

Institutional review board approval

This analysis adhered to the ethical guidelines of the original STOP-CAD study, which received Institutional Review Board approval at Lifespan (1894800-5) [6].

Because this study was a secondary analysis of anonymized data without any identifiable personal information, the requirement for informed consent was waived by IRB. Summary data are available from the STOP-CAD principal investigator upon reasonable request.

Study design and patient population

Patients were classified into two groups for univariate analyses: those prescribed statins and those not on statins upon discharge.

Categorical variables were compared using Chi-square or Fisher's exact tests, and continuous variables using Wilcoxon rank-sum or Student's t-tests, as appropriate.

Cox regression models evaluated the association between statin use and outcomes, and models were adjusted for age, admission National Institute of Health Stroke Scale score (NIHSS), history of ischemic stroke, infarct on CT or MRI, presentation within one week of symptoms and occlusive dissection (full occlusion).

For major hemorrhage, 90 day functional outcome and mortality we adjusted for age and NIHSS on admission.

The day of discharge was considered as day zero of follow-up, and patients were followed until recurrent ischemic stroke, death, or last follow-up, up to a maximum of 180 days, whichever occurred first.

Sensitivity analysis compared outcomes between high-intensity statin therapy and low-to-moderate intensity statin therapy. Kaplan-Meier curves illustrated event rates by statin group (Figures 1A-C).

All statistical analyses were performed using Stata SE 18 software, with statistical significance set at $p < 0.05$. Missing data were addressed through pairwise deletion without imputation.

Primary exposure

Exposures were defined based on treatment onset within 180 days. The primary exposure was the statin regimen categorized into High-Intensity, Moderate-Intensity, Low-Intensity dosing Table 1.0 [18] or no statin.

Table 1. Classification of Statin Therapies [18].

Statin	High-Intensity	Moderate-Intensity	Low-Intensity
Atorvastatin	40mg-80mg	10mg-20mg	
Rosuvastatin	20mg-40mg	5mg-10mg	
Lovastatin		40mg	20mg
Simvastatin		20mg-40mg	10mg
Pravastatin		40mg-80mg	10mg-20mg
Fluvastatin (XL)		80mg	
Fluvastatin		40mg (twice daily)	20mg-40mg
Pitavastatin		2mg-4mg	1mg

Study Outcomes

The primary outcome was recurrent ischemic stroke after hospital discharge, defined as new or worsening neurological symptoms lasting ≥ 24 hours, or symptoms lasting < 24 hours with imaging evidence of new or enlarging acute infarction in the vascular territory of the dissected artery

The safety outcome was major hemorrhage after hospital discharge. Major hemorrhage included both major extracranial hemorrhage and symptomatic intracranial hemorrhage.

Major extracranial hemorrhage was defined as a non-cerebral hemorrhage requiring blood transfusion or leading to a drop in hemoglobin level of $\geq 2\text{g/dL}$.

Symptomatic intracranial hemorrhage was defined as a new or worsening intracranial hemorrhage, causing new or worsening neurologic symptoms. 90-day functional outcome defined as functional independence with Modified Rankin scale (mRS) of less than or equal to 2 and mortality after hospital discharge were secondary outcomes.

As described in the STOP-CAD study, outcomes were abstracted and reviewed from medical records, with stroke outcomes confirmed by imaging and neurologists when available, and site principal investigators re-adjudicated events to align with study-specific definitions before finalizing the dataset [6].

Study Variables

We collected the following covariates:

Baseline demographics: sex, age, race (Black, White, Asian, Other), and ethnicity (Hispanic, non-Hispanic).

Comorbidities: hypertension, diabetes, hyperlipidemia, smoking, coronary artery

disease, connective tissue disease, pregnancy at time of dissection symptoms, antiphospholipid antibody syndrome.

Clinical & laboratory variables: clinical presentation as ischemic stroke, stroke severity, NIHSS on admission, & LDL.

Imaging variables: Occlusive dissection.

Statistical Analysis

Standard univariate analyses compared the patients in two groups: the statin and no-statin group. Categorical data were analyzed using Chi-square or Fisher's exact tests, and continuous data using Wilcoxon rank-sum or Student's t-tests.

Patients were censored at recurrent ischemic stroke, death, or last follow-up within 180 days.

Cox regression models were used for adjusting variables associated with subsequent ischemic stroke, age, NIHSS, major hemorrhage, 90-day functional outcome and mortality.

Sensitivity analysis compared outcomes between high-intensity statin therapy and low-to-moderate intensity statin therapy.

Cox regression analysis was used to construct Kaplan-Meier curve to show event rates across statin arms (Figures 1A-C).

Analyses were performed using Stata SE 18, with a p-value < 0.05 considered statistically significant. Missing data were not imputed.

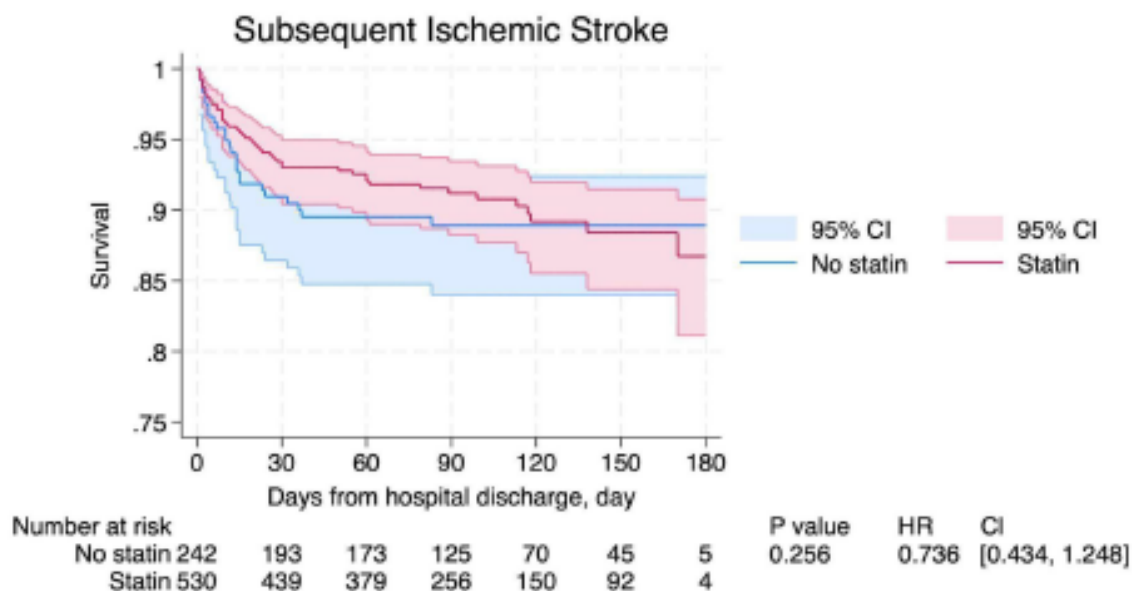


Figure 1A. Kaplan-Meier Estimates comparing subsequent ischemic stroke, with statins and no statins.

Kaplan-Meier survival curve for subsequent ischemic stroke (1A) comparing statin vs no statin and censoring at the time of subsequent ischemic stroke, death, or last follow-up up to day

180. Unadjusted hazard ratios (HRs) were calculated with survival regression with no statin as the reference group.

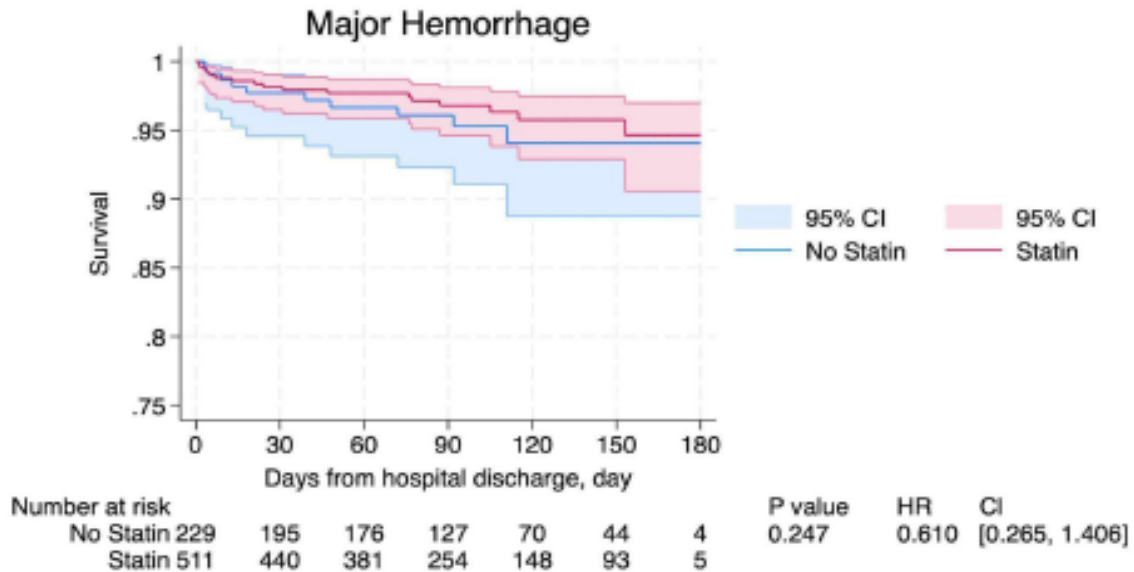


Figure 1B. Kaplan-Meier Estimates comparing major hemorrhage, with statins and no statins.

Kaplan- Meier survival curve for major hemorrhage (1B) comparing statin vs no statin and censoring at the time of subsequent ischemic stroke, death, or last follow-up up to day 180.

Unadjusted hazard ratios (HRs) were calculated with survival regression with no statin as the reference group.

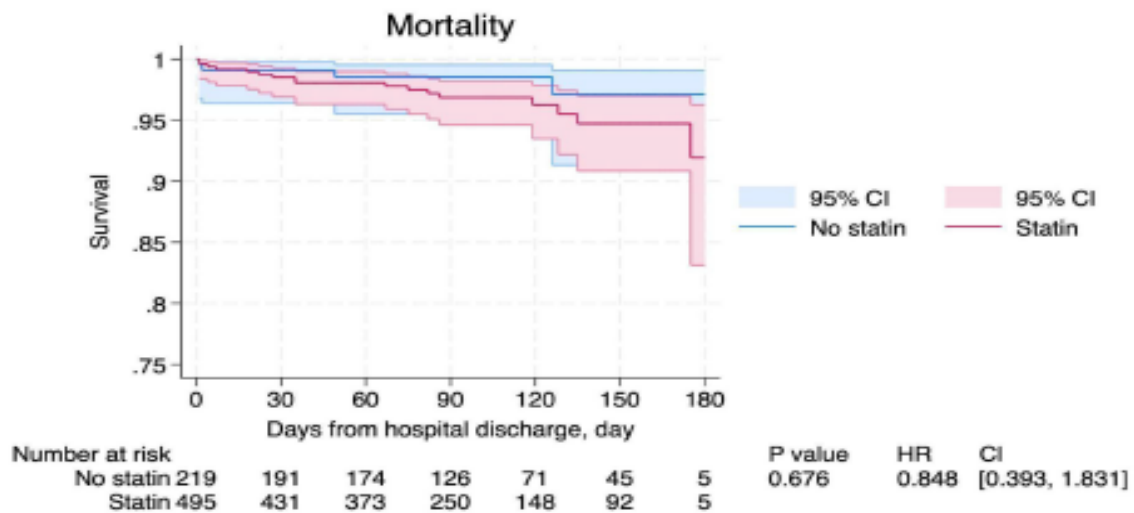


Figure 1C. Kaplan-Meier Estimates comparing mortality, with statins and no statins.

Kaplan- Meier survival curve for mortality (1C) comparing statin vs no statin and censoring at the time of subsequent ischemic stroke, death, or last follow-up up to day 180.

Unadjusted hazard ratios (HRs) were calculated with survival regression with no statin as the reference group.

Results

Of the 4,023 patients enrolled in STOP-CAD, 1,407 were excluded due to non-ischemic presentations, as statins are not indicated in patients without ischemic stroke. Six patients were excluded because statin treatment data were unavailable.

This left 2,610 patients with CAD for analysis, of whom 1,750 received statins and 860 did not, as depicted in Figure 2.

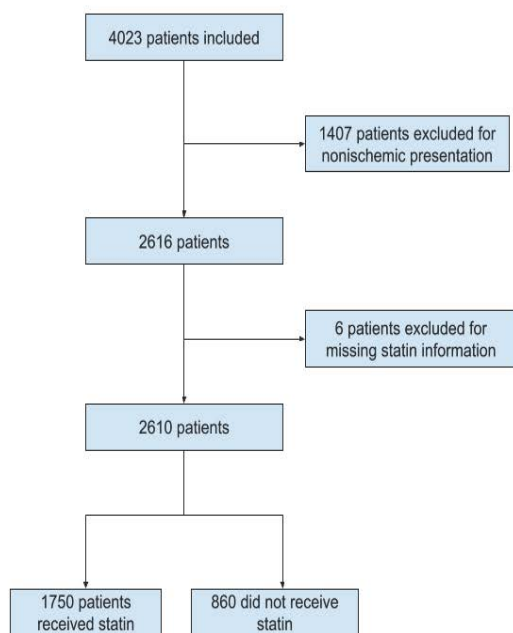


Figure 2. Study flow chart.

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Baseline Demographics and Clinical Variables

As shown in Table 2, the median age at diagnosis was greater in the statin group than in the no-statin group (49 years [IQR 41-58] vs. 42 years [IQR 34-51], $p < 0.001$). A higher proportion of females was observed in the no-statin group (46.5%) compared with the statin group (34.3%, $p < 0.001$).

Patients receiving statins had a greater prevalence of cardiovascular risk factors, including hypertension (43.3% vs. 23.6%, $p < 0.001$), diabetes mellitus (12.9% vs. 3.4%, $p < 0.001$), hyperlipidemia (30.9% vs. 11.5%, $p < 0.001$), coronary artery disease (4.3% vs. 1.4%, $p < 0.001$), and active tobacco use (24.6% vs. 18.1%, $p < 0.001$).

NIHSS at admission were similar in median value between groups (1 [IQR 0-4] vs. 1 [IQR 0-3]) although the p -value was < 0.001 due to distribution differences.

Baseline LDL levels were higher in the statin group than in the no-statin group (median 107mg/dL [IQR 82-131] vs. 95mg/dL [IQR 75-114], $p < 0.001$).

Table 2. Clinical & laboratory characteristics.

	Statin	No statin	P value
Baseline demographics			
Age at time of diagnosis	49 (41-58)	42 (34-51)	<0.001
Female	601/1750 (34.3%)	400/860 (46.5%)	<0.001
Ethnicity	158/1603 (9.9%)	82/750 (10.9%)	0.421
Race			
White	1227/1750 (70.1%)	620/860 (72.1%)	0.296
Black	144/1750 (8.2%)	37/860 (4.3%)	0.001
Asian	79/1750 (4.5%)	35/860 (4.1%)	0.601
Other	300/1750 (17.1%)	168/860 (19.5%)	0.134
Comorbidities			
Hypertension	757/1750 (43.3%)	203/860 (23.6%)	<0.001
Diabetes Mellitus	225/1750 (12.9%)	29/860 (3.4%)	<0.001
Hyperlipidemia	541/1750 (30.9%)	99/860 (11.5%)	<0.001
Coronary Artery Disease	76/1750 (4.3%)	12/860 (1.4%)	<0.001
Active tobacco smoker	430/1750 (24.6%)	156/860 (18.1%)	<0.001
Known connective tissue disease (including FMD)	19/1750 (1.1%)	19/860 (2.2%)	0.024
Pregnant at the first time of dissection symptoms	2/1750 (0.1%)	2/860 (0.2%)	0.602
Within 12 weeks postpartum at the first time of dissection symptoms	10/1750 (0.6%)	11/860 (1.3%)	0.057
History of antiphospholipid antibody syndrome	4/1750 (0.2%)	2/860 (0.2%)	1
NIHSS on admission	1 (0-4)	1 (0-3)	<0.001
LDL (mg/dL)	107 (82-131)	95 (75-114)	<0.001

Outcomes

Subsequent ischemic stroke

As summarized in Table 3, the incidence of recurrent ischemic stroke after hospital discharge

did not differ significantly between the statin (3.1%) and no-statin (3.3%) groups (p=0.815).

The unadjusted hazard ratio (HR) was 0.89 (95% CI, 0.55-1.45; p=0.658), and the adjusted HR was 0.73 (95% CI, 0.43-1.24; p=0.256).

Table 3. Adjusted and Unadjusted Analysis of Preselected Variables Across Patients With or Without Statin use and Cox Regression Showing Hazard Ratios for Significant Variables.

	Outcomes (after hospital discharge)			Unadjusted Hazard Ratios for Significant Variables	Adjusted Hazard Ratios for Significant Variables
	Statin	No statin	P Value	HR or OR, 95% CI, P value	Adjusted HR or OR, 95% CI, P value
Subsequent ischemic stroke	54/1750 (3.1%)	28/860 (3.3%)	0.815	HR 0.896, [0.552, 1.455], 0.658	HR 0.736, [0.434, 1.248], 0.256
Major Hemorrhage	22/1750 (1.3%)	10/860 (1.2%)	0.837	HR 0.929, [0.426, 2.029], 0.854	HR 0.610, [0.265, 1.406], 0.247
90 day functional outcome	1082/1379 (78.5%)	569/707 (80.5%)	0.283	OR 0.884, [0.705, 1.108], 0.283	OR 0.983, [0.740, 1.307], 0.907
Mortality	34/1731 (2.0%)	10/854 (1.2%)	0.143	HR 1.462, [0.703, 3.039], 0.309	HR 0.848, [0.393, 1.831], 0.676

For subsequent ischemic stroke we adjusted for age, NIHSS on admission, history of ischemic stroke, infarct on imaging, presentation within one week of symptoms and occlusive dissection.

For major hemorrhage, 90-day functional outcome and mortality we adjusted for age and NIHSS on admission

HR=Hazard ratio; OR=Odds ratio; CI=confidence interval

Major Hemorrhage

The post-discharge incidence of major hemorrhage after hospital discharge was 1.3% in the statin group and 1.2% in the no-statin group (p=0.837) and was not significant.

Unadjusted HR and adjusted HR were also non-significant: 0.92 (95% CI, 0.42-2.02; p=0.854) and 0.61 (95% CI, 0.26-1.40; p=0.247), respectively.

90-Day Functional Outcome

At 90 days, functional independence (mRS ≤2) was achieved in 78.5% of the statin group and 80.5% of the no-statin group (p=0.283) showed no significant difference.

Unadjusted Odds Ratio (OR) and Adjusted OR were also non-significant, 0.88 (95% CI, 0.70-1.10; p=0.283) and 0.98 (95% CI, 0.70-1.30; p=0.907), respectively.

Mortality

Post-discharge mortality was 2.0% in the statin group and 1.2% in the no-statin group (p=0.143) showed significant difference.

Unadjusted HR and Adjusted HR were also non-significant, 1.46 (95% CI, 0.70-3.03; p=0.309) and 0.84 (95% CI, 0.39-1.83; p=0.676), respectively.

Sensitivity Analysis

The sensitivity analysis comparing high intensity versus low-to-moderate intensity statin therapy was conducted to further validate the outcomes as shown in Table 4.

No significant difference was observed in recurrent ischemic stroke based on statin intensity with 3.1% (41 out of 1304) on high intensity statins, 2.9% (13 out of 441) in the non-high intensity statin group, and 3.3% (28 out of 860) in the no statin group, (p=0.956).

For major hemorrhage, rates were 1.4% for high-intensity, 0.9% for low-to-moderate-intensity, and 1.2% for no statin (p=0.721) that was without significant difference.

Similarly, the 90-day functional outcome did not show a significant difference based on statin intensity (p=0.364).

A favorable 90-day functional outcome was observed in 79.2% (786 out of 993) of patients on high intensity statins, 76.8% (295 out of 384) of those on non-high intensity statins, and 80.5% (569 out of 707) of patients not on statins.

However, the sensitivity analysis comparing mortality rate differed significantly between the groups (p=0.009).

Mortality was 1.5% (19 out of 1287) in the high intensity statin group, 3.4% (15 out of 439) in the low-to-moderate intensity statin group, and 1.2% (10 out of 854) in the no statin group

Table 4 Sensitivity Analysis.

	Outcomes (after hospital discharge)		
	High intensity statin	Non-high intensity statin	No statin
Subsequent ischemic stroke	41/1304 (3.1%)	13/441 (2.9%)	28/860 (3.3%)
Major Hemorrhage	18/1304 (1.4%)	4/441 (0.9%)	10/860 (1.2%)
90 day functional outcome	786/993 (79.2%)	295/384 (76.8%)	569/707 (80.5%)
Mortality	19/1287 (1.5%)	15/439 (3.4%)	10/854 (1.2%)

Discussion

In this sub-study of STOP-CAD examining statin outcomes after non-traumatic CAD with ischemic stroke, no significant differences were observed for recurrent ischemic stroke, major hemorrhage, 90-day functional outcome with mRS equal to or less than 2, and mortality, between patients prescribed statin or no statin.

Unadjusted and adjusted analysis also revealed no significant outcome differences between statin and non-statin groups for subsequent ischemic stroke, major hemorrhage, 90-day functional outcome except significantly lower mortality seen in high intensity statin group, no statin group as compared to low-to-moderate intensity group.

Statins are strongly recommended in guidelines with Class A evidence for reducing recurrent stroke recurrence and cardiovascular events [19].

Statins have been studied for their impact on ischemic stroke in randomized controlled trials, indicating that statin therapy could potentially reduce the risk by 50%.

However, these trials did not explicitly include patients with CAD. The atherosclerotic stroke subtype reveals the greatest benefit in reducing risk of subsequent ischemic stroke.

There is potentially increased risk of ICH with statin use, without a clear benefit for reducing subsequent ischemic stroke in CAD, suggesting that treatment for all subtypes should not be generalized to CAD.

There are no randomized controlled trials assessing the role of statins in secondary prevention of stroke after CAD. Similar to our study, a small prospective cohort study assessing the role of statin in CAD suggested no difference in subsequent ischemic stroke [8,9,10,11,17,20].

Subsequent ischemic stroke events were lower in our study than STOP-CAD because we excluded in-hospital events [6].

Given in STOP-CAD there were 1750 patients on statin therapy and 860 patients without statin is likely due to lack of consensus on statin therapy amongst physicians and practice variability.

Our data also suggests that the differences are likely individualized given differences observed in table 2 with those having cardiovascular comorbidities and higher LDL were possibly prescribed a statin.

Therefore, statins could be considered when there is underlying cardiovascular or atherosclerotic cerebrovascular disease and may not be beneficial in all patients with CAD.

There is also concern regarding a potential increase in intracerebral hemorrhage risk with statin therapy in secondary prevention as suggested by meta-analysis, Heart Protection Study and The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial [8].

The increased risk of hemorrhagic stroke appeared largely attributable to data from the SPARCL trial and was not seen in other trials when looked at separately [9,10].

Our study was non-significant for major hemorrhage with or without statin use in patients with CAD.

Some studies in ischemic stroke populations have reported improved functional outcomes with statin therapy, although this effect has not been consistent across all trials [21-23].

The INSPIRES trial suggested a modest benefit at 90 days with immediate statin initiation in patients with high-risk intracranial or extracranial atherosclerosis, but our CAD cohort did not show such an association.

Cardiovascular death was found to be higher without statin use in a population-based study [12].

All-cause mortality was non-significant between statin and non-statin groups in meta-analysis for all ischemic strokes, hemorrhagic strokes and TIA, and there was no significant difference in mortality between statin and placebo in SPARCL [21].

While mortality was non-significant for statin and no statin groups, only the sensitivity analysis comparing mortality was significant and was lower for high intensity statin group and no statin group as compared to low-moderate intensity group.

This could be explained by practice variability with higher use of statins in patients with vascular or atherosclerotic cerebrovascular disease and patients with no statins having less cardiovascular risk factors.

Several limitations warrant consideration. The retrospective, observational design introduces the potential for indication bias, with statin prescribing decisions likely influenced by patient comorbidities and physician judgment.

Contraindications to specific therapies, variability in treatment protocols across participating sites, and the predominance of tertiary academic centers may also limit generalizability.

Furthermore, data on the exact timing of statin initiation and adherence during follow-up were unavailable, restricting the ability to assess time-dependent effects.

Larger prospective studies or an individual patient data meta-analysis will be required to clarify the role of statins in secondary prevention after CAD-related stroke.

Conclusion

In this large multicenter study of patients with CAD, statin therapy was not associated with a statistically significant reduction in the risk of subsequent ischemic stroke, major hemorrhage, 90-day functional outcome, or mortality after hospital discharge.

These findings suggest that while statin therapy may have beneficial effects in the general ischemic stroke population, its specific benefits in CAD-related stroke require further investigation studies.

Acknowledgements

We would like to thank all the participating STOP-CAD sites

Author Contributions

Conceptualization: O.L, S.Y, L.S, N.C, C.G, J.K, S.E, C.T, W.K, A.Z, A.A, J.M and M.A; Methodology: O.L, S.Y, L.S, N.C, C.G, J.K, S.E, C.T, W.K, A.Z, A.A, J.M, M.A; Data analysis: O.L, S.Y, L.S, N.C, C.G, J.K, S.E, C.T, and M.A; Manuscript writing and initial draft: O.L, S.Y, L.S, N.C, C.G, J.K, S.E, C.T, and M.A; Manuscript Review and editing: O.L, S.Y, L.S, N.C, C.G, J.K, S.E, C.T, W.K, A.Z, A.A, J.M and M.A; Final Approval: O.L, S.Y, L.S, N.C, C.G, J.K, S.E, C.T, W.K, A.Z, A.A, J.M, M.A; Supervision: O.L, S.Y and M.A

All authors read and approved the final manuscript

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

Institutional Review Board

This analysis adhered to the ethical guidelines of the original STOP-CAD study, which received Institutional Review Board approval at Lifespan (1894800-5) [6].

Consent Statement

This study was a secondary analysis of anonymized data without any identifiable personal information, the requirement for informed consent was waived by IRB.

Data Availability

Summary data are available from the STOP-CAD principal investigator upon reasonable request

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