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ABSTRACT

BACKGROUND AND PURPOSE: Acute statin therapy improves neurologic outcome and diminishes infarct growth in animal models of stroke. Clinical studies suggest that premorbid and early statin use is associated with improved outcome after major stroke. We studied the association between statin therapy and radiographic and clinical outcomes in patients with high-risk TIA and minor stroke.

MATERIALS AND METHODS: Patients with high-risk TIA and minor stroke (NIHSS ≤3) were prospectively enrolled within 24 hours of symptom onset. Patients were followed clinically for 3 months, and a subset had a repeat MR imaging at 90 days.

RESULTS: Of 418 patients, 23% were prescribed statins before their stroke. Statins were continued in 20% and initiated in 42%. Patients on prior statin therapy were older and more hypertensive, treated with aspirin, and more likely to have symptomatic carotid disease compared with those not on statin. Adjusting for these differences, prior statin treatment was not associated with DWI positivity (adjusted OR = 1.3; 95% CI, 0.77–2.1; P = .32) or smaller median baseline infarct volume, 1.1 mL (interquartile range = 4) versus 1 mL (interquartile range = 2.5; P = .56). Early or continued treatment with statins did not improve the risk of clinical deterioration (adjusted OR = 0.66; 95% CI, 0.27–1.6; P = .35) or poor functional outcome at 3 months (adjusted OR = 0.66; 95% CI, 0.35–1.24; P = .19).

CONCLUSIONS: Prestroke or early-stroke statin therapy was not associated with a reduction in the number of DWI lesions, infarct volume, or improved clinical or functional outcome at 3 months. The effect of acute statin treatment in patients with ischemic stroke/TIA remains unclear and needs further investigation.

ABBREVIATIONS: CATCH = CT and MR Imaging in the Triage of TIA and Minor Cerebrovascular Events to Identify High Risk Patients; IQR = interquartile range

The benefit from 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors (statins) to prevent fatal and nonfatal stroke in patients with transient ischemic attack and all severity of strokes has been established in a randomized controlled trial.[1] Beyond their lipid-lowering property, these drugs have been shown to have a neuroprotective effect, with smaller infarct sizes and better functional outcome on pretreatment with statins in animal models of stroke.[2-4] Nevertheless, the results of clinical studies on the effects of early initiation, continuation, or withdrawal of statin therapy on clinical outcomes have been conflicting.[5,6] In one study, acute discontinuation of statins after the ischemic event conferred a higher risk of early neurologic deterioration and increased death and dependency at 90 days.[5] In contrast, the functional outcome of patients randomized to early statin treatment versus placebo was no different in a pilot randomized controlled trial.[6] Observational studies have also shown conflicting reports, with some reporting a reduction in mortality[7] and improvement in functional outcomes[8-10] in patients with stroke pretreated or acutely treated with statins. Other studies have shown worse outcomes in patients on statins at stroke onset.[11] A recent meta-analysis found improved functional outcome in patients on statins at the time of stroke onset.[10]

Patients with TIA and minor stroke have an early unstable clinical course, with most recurrent ischemic events occurring in the first 48 hours after symptom onset.[12-14] If statins have a neuroprotective effect, it would be important to see an effect in this population. However, the results of the Fast Assessment of Stroke and TIA to Prevent Early Recurrence trial did not support the

hypothesis that acute statin therapy prevents early stroke recurrence.[15] In fact, there was a nonsignificant trend toward higher 90-day ischemic events in the statin arm. A recent multicenter analysis of patients with TIA showed a decrease in the rate of stroke recurrence in patients with carotid stenosis with urgent treatment or pretreatment with statin therapy.[16] However, the authors did not find a reduction in the recurrent stroke rate in patients without carotid stenosis. To date, a clinical study assessing the effects of statin therapy on acute MR imaging findings of patients with TIA and minor stroke has not been undertaken.

We therefore aimed to determine the effects of premorbid or early-initiated statin therapy on radiographic and clinical outcomes in a prospective cohort of patients with TIA and minor stroke.

MATERIALS AND METHODS
Patients
We included patients who underwent MR imaging in the study entitled CT and MR Imaging in the Triage of TIA and Minor Cerebrovascular Events to Identify High Risk Patients (CATCH).[17] The methods of the CATCH study have previously been published. Briefly, patients with high-risk TIA (focal weakness or speech disturbance lasting ≥5 minutes) or minor ischemic stroke (with an initial National Institute of Health Stroke Scale score of ≤3) were prospectively enrolled. All patients presented to the Foothills Medical Centre, Calgary, Alberta, Canada. Informed consent was obtained before enrollment. All patients underwent MR imaging, standard clinical and demographic information was recorded, and secondary stroke-prevention measures were implemented in accordance with current practice guidelines.[18]

Baseline CT and MR Imaging Protocol
All patients underwent a noncontrast CT of the head, followed immediately by CT angiography of the circle of Willis and neck from the aortic arch to skull vertex. CT scans were performed on a 64-section scanner (Somotom Sensation 64; Siemens, Erlangen, Germany). Patients underwent MR imaging brain scans as soon as possible. Patients were imaged using either a 3T scanner ($n = 349$) (Discovery 750; GE Healthcare, Milwaukee, Wisconsin) or a 1.5T MR imaging scanner ($n = 69$) (Avanto; Siemens). Sequences included sagittal T1, axial T2, and axial fluid-attenuated inversion recovery. Acute ischemic lesions were identified on diffusion-weighted imaging. Follow-up MR imaging was performed in a subpopulation of patients who had their original MR imaging on the 3T scanner at day 90.

Image Analysis
Details of this assessment have been previously reported.[19] Briefly, MR imaging sequences (DWI/ADC, FLAIR, and T2) were reviewed for the presence of ischemic lesions at each time point. DWI hyperintense lesion borders were defined by using a semiautomated threshold-intensity technique. We referenced these lesions to the corresponding areas on the apparent diffusion coefficient maps to avoid selecting regions of T2 shinethrough. The $b=1000$ image was used as the primary template because quantitative ADC thresholds tend to vary depending on the time after stroke onset and concurrent perfusion status. Planimetric DWI and FLAIR lesion volume measurement was performed by using

Quantomo software.[20] CTAs were assessed for the presence of any intra- or extracranial vessel occlusion or stenosis of ≥50% ipsilateral to the clinically relevant ischemic brain tissue (positive CTA finding). Symptomatic carotid disease was defined as a TIA or minor stroke referable to an extracranial carotid artery with ≥50% stenosis. All images were assessed by a neuroradiologist who remained blinded to the results of the other imaging modalities and was given information regarding the clinical symptoms only.

Radiographic and Clinical Outcomes
Radiographic worsening was defined as evidence of either infarct growth (a priori defined as contiguous growth of the initial infarct by ≥2 mL)[19] or infarct recurrence (development of a new ischemic lesion) on follow-up FLAIR imaging at day 90 with or without any clinical manifestations.

Poor functional outcome was defined as mRS ≥2 at day 90.[21] Recurrent clinical events (stroke progression or a distinct recurrent stroke) were a priori defined[22] as a functional deterioration in neurologic status of vascular origin lasting 24 hours or a new sudden focal neurologic deficit of vascular origin lasting at least 24 hours that was not thought to be secondary to other nonvascular factors such as drugs, fever, or infection.

Statistical Analysis
Statistical analyses were performed by using Statistical Package for Social Sciences, Version 20.0 (IBM, Armonk, New York). The primary outcome was the rate of DWI positivity and the median acute infarct volume in those with positive lesions on DWI. Secondary outcomes were the rate of recurrent stroke (imaging and clinical) and poor functional outcome. Outcomes were stratified by whether the patient was known to be on a statin at the time of the presenting event. Clinical outcomes (clinical deterioration, either progression of previous symptoms or a new recurrent stroke, and poor functional outcome) and radiographic outcomes (DWI positivity on baseline MR imaging, radiographic infarct progression, and radiographic recurrence) were reported by using multivariate regression analysis, adjusting for baseline differences in age, hypertension, diabetes, prior aspirin use, and symptomatic internal carotid artery disease. For the secondary outcomes, both statin use at the time of the presenting event and early initiation of a statin were assessed. Clinical and radiographic outcomes were reported by using multilevel regression analysis, adjusting for differences in age, sex, hypertension, and baseline positive CTA and DWI findings. Data are reported by using standard descriptive statistics. DWI volumes were log-transformed before analysis because the volumes were not normally distributed.

RESULTS
A total of 418 patients were included in this substudy during 29 months, of whom 98% completed the clinical follow-up at day 90. The median time from index event to CT/CTA was 5.2 hours (IQR = 6), and to MR imaging, it was 17.5 hours (12.3). At the time of the index event, 23% (96/418) of patients were on statin therapy, and this was continued in 89% (85/96). Patients on prior statin therapy were older and more hypertensive, had more diabetes mellitus, and were more likely to be on aspirin and have symptomatic extracranial carotid disease (Table 1).

Baseline MR Imaging Findings of Patients Based on Premorbid Statin Therapy

Fifty-seven percent (238/418) of patients had an acute ischemic lesion on a baseline DWI study, of whom 26% (61/238) were on statin therapy. Prior statin treatment was not associated with lower rates of DWI positivity (Adjusted OR = 1.3; 95% CI, 0.77–2.1; P = .32). The median DWI volume was 1.045 mL (interquartile range [IQR] = 3.55) in those with an acute infarct. Premorbid statin therapy was not associated with a smaller DWI lesion (median = 1 mL [IQR = 2.5], geometric mean = 1.1 mL versus median = 1.1 mL [IQR = 4], geometric mean = 1.3 mL, P = .56).

Clinical and Radiographic Outcome Based on Premorbid Statin Therapy

Ninety-eight percent (410/418) of patients had 90-day clinical follow-up. Clinical deterioration (progression of symptoms or a distinct recurrent stroke) occurred in 7% (29/410) by day 90. There was no difference in the rate of clinical deterioration in those on prior statin treatment (7.3%) versus those not on it (7%; adjusted OR = 1.13; 95% CI, 0.43–3.01; P = .92). A distinct recurrent stroke occurred in 3.2% (13/410), and symptom progression, in 4.1% (17/410). There was no difference in the rate of

symptom progression (adjusted OR = 0.44; 95% CI, 0.09–2.2; P = .32) or clinical stroke recurrence (adjusted OR = 2.06; 95% CI, 0.57–7.4; P = .26) in patients previously on versus those not on statins.

Poor functional outcome at 90 days was seen in 15% (62/410) of patients. Pretreatment with statins did not affect the rate of poor functional outcome (adjusted OR = 1.43; 95% CI, 0.77–2.67; P = .25).

Fifty-two percent (217/418) of patients had follow-up MR imaging at day 90 in this study. Radiographic deterioration (a new ischemic infarct or infarct growth) was seen in 13.4% (29/217) of patients. There was no difference in the rate of radiographic deterioration in those on premorbid statin (adjusted OR = 2.32; 95% CI, 0.88–6.13; P = .89).

The Effects of Continued or Early Initiation of Statin Therapy on Clinical and Radiographic Outcomes

Sixty percent (251/418) of patients in the study had acute statin treatment either initiated (n = 166) or continued (n = 85). The median time from symptom onset to statin initiation was 12 hours (IQR = 0–24 hours). Fifty percent of patients had statins initiated in the emergency department. The patients in the statin group were older, were a high percentage male, were more likely hypertensive, had more atherosclerotic disease (symptomatic relevant intra- or extracranial occlusion or stenosis ≥50%), and had a higher rate of DWI positivity at baseline (Table 2).

Poor functional outcome at 90 days was seen in 15.7% (39/249) of those on statin treatment versus 14.3% (23/161) in those without statin therapy (adjusted OR = 0.66; 95% CI, 0.35–1.24; P = .19). There was no difference in the rate of any clinical deterioration in the statin-treated group versus those not on statin treatment (adjusted OR = 0.66; 95% CI, 0.27–1.6; P = .35). The results did not change when the analysis was restricted to distinct recurrent stroke alone (adjusted OR = 0.47; 95% CI, 0.14–1.6; P = .23). Similarly, in patients who had follow-up MR imaging at 90 days, the rate of radiographic worsening (either new ischemic recurrence or infarct growth) was not different in patients who were treated with statin versus those who were not after the index event (adjusted OR = 1.59; 95% CI, 0.6–4.15; P = .34).

Table 1: Baseline clinical and radiographic characteristics of patients based on prior statin treatment

Baseline Characteristics	Prior Statin (n = 96)	No Prior Statin (n = 322)	P Value
Age (yr) (median) (IQR)	73 (14)	66 (24)	<.001
Sex (% male)	68% (65/96)	58% (187/322)	.09
Smoking	15% (14/96)	15% (49/322)	.87
Hypertension (%)	73% (70/96)	50% (159/322)	<.001
Diabetes mellitus (%)	19% (18/96)	12% (39/322)	.044
Prior ASA treatment (%)	65% (62/96)	22% (71/322)	<.001
Symptomatic carotid disease[a]	19% (18/96)	7% (21/322)	.001
Symptomatic intracranial disease[b]	12% (11/96)	21% (67/322)	.174
Positive CTA finding[c]	31% (30/96)	27% (88/322)	.45
DWI-positive	64% (61/96)	55% (177/322)	.08
DWI infarct volume (mL) (median) (IQR)	1.0 (2.5)	1.1 (4)	.56

Note:—ASA indicates aspirin.
[a] Symptomatic carotid disease: extracranial carotid stenosis of ≥50%.
[b] Symptomatic intracranial disease: symptomatic intracranial vascular occlusion or stenosis of ≥50%.
[c] Positive CTA finding: relevant intra- or extracranial occlusion or stenosis of ≥50%.

Table 2: Baseline clinical and radiographic characteristics stratified by statin treatment (statin therapy either continued or acutely started) or not

Baseline Characteristics	On Statin Treatment[a] (n = 251)	No Statin Treatment (n = 167)	P Value
Age (yr) (median) (IQR)	70 (18)	62 (25)	<.001
Hypertension (%)	63% (159/251)	42% (70/167)	<.001
Sex (% male)	65% (163/251)	53% (89/167)	.01
Smoking	17% (42/251)	13% (21/167)	.24
Diabetes mellitus (%)	15% (38/251)	11% (19/167)	.38
Symptomatic extracranial carotid disease ≥50% (%)	13% (33/251)	4% (6/167)	.001
Symptomatic intracranial vascular occlusion/ stenosis ≥50% (%)	25% (63/251)	15% (25/167)	.013
Positive CTA finding[b]	36% (89/251)	17% (29/167)	<.001
DWI-positive on baseline MRI	69% (172/251)	40% (66/167)	<.001
DWI infarct volume (mL) (median) (IQR)	1.1 (3.8)	1.0 (2.9)	.48

[a] Statin treatment either acutely started or continued.
[b] Positive CTA finding: relevant intra- or extracranial occlusion or stenosis of ≥50%.

Effects of Statin Therapy on Ischemic Outcome Based on the Mechanism of Strokes

Patients were more likely to be treated with statins (either started or continued) if the mechanism of their event was large-artery atherosclerosis (adjusted OR = 5.24; 95% CI, 1.9–13.9; P < .001). A total of 48.5% (203/418) had some degree of carotid disease, and 9.3% (39/418) had a significant symptomatic extracranial carotid stenosis (stenosis of ≥50%) on CTA, 85% (33/39) of whom were treated with statins. Carotid revascularization was performed in 19/39 (8 endarterectomies and 11 stent placements). Treatment with statins did not affect the rate of clinical (relative risk = 0.3; 95% CI, 0.08–1.05; P = .06) or ra-

diographic (adjusted OR = 0.42; 95% CI, 0.06–2.69; P = .36) deterioration in this subgroup with symptomatic carotid disease. Similarly, the rate of poor functional outcome at day 90 was not different in this subgroup with or without statin therapy (adjusted OR = 0.67; 95% CI, 0.22–2.03; P = .48).

DISCUSSION

In this prospective study of patients with high-risk TIA and minor stroke, we did not find that pretreatment with statins reduced the rate of DWI positivity or the volume of acute ischemic lesions. Similarly, neither pretreatment nor acute statin initiation conferred a beneficial effect on functional, clinical, or radiographic outcome. In keeping with data from previous studies,[16] patients on premorbid statin therapy were older and generally had more vascular risk factors than their statin-naïve counterparts. If one adjusted for these differences, premorbid or early statin initiation did not improve clinical or radiographic outcome in this population.

Early initiation of preventive measures is associated with a reduction of further vascular events and better clinical outcome in patients with TIA.[23,24] Although statins were part of the treatment regimen in these studies, their specific effect was not studied in isolation. The effects of pretreatment with statins on recurrent vascular events were studied in a recent multicenter analysis of patients with TIA.[16] In this study, statin pretreatment was associated with reduced stroke risk in the subtype of patients with TIA with symptomatic carotid stenosis. We did not find similar results in our study. However, this outcome may be due to the small number of patients with symptomatic carotid disease and the associated high rate of statin use in our population.

In rat models of stroke, pretreatment or acute treatment with statins has been shown to reduce the infarct size and improve neurologic outcome.[25-27] It is postulated that in the acute ischemic phase, the pleiotropic effects of statins have a bigger role in prevention of recurrent vascular events rather than their effects on low-density lipoprotein reduction.[28] Some pleiotropic properties of statins include inhibition of the inflammatory response, plaque stabilization, improved cerebral vasoreactivity, improved endothelial function, and increased nitric oxide bioavailability.[29] The acute anti-inflammatory effects of statins resulting in plaque stabilization are thought to be the basis for prevention of recurrent vascular events in coronary artery disease.[30,31]

The effects of statin therapy on infarct size have been previously reported in retrospective studies.[32,33] In one study, a smaller infarct volume was associated with the interaction between statin pretreatment and the presence of diabetes in patients with stroke.[32] A different study identified statin therapy, age, and a recent history of TIA as independent factors associated with smaller DWI volume.[33] In both studies, patients with TIA were excluded. In our study, pretreatment with statins did not improve the acute radiologic profile of patients with high-risk TIA/minor stroke either by reducing the rate of DWI positivity or the infarct volume. One possible explanation is that the infarct size in this population is so small to begin with that detecting a meaningful difference with statin pretreatment would be difficult.

Multiple groups have evaluated the association between statin pretreatment and the severity of stroke.[7,34,35] Similar to ours, findings in most studies do not suggest a beneficial role for statins in reducing the severity of clinical symptoms at presentation.[7,35] Previous observations have shown a trend toward better functional outcomes[34-36] and a reduction in ischemic progression/ recurrent events[7] or in-hospital mortality in patients pretreated with statins.[7] Furthermore, a recent meta-analysis of observational and randomized studies looking only at patients receiving statins at the time of ischemic stroke versus those who were not, showed an improvement in the functional independence rate and survival in the statin-treated subgroup.[10] In our study, however, statin therapy did not confer an improvement in functional outcome in patients with TIA and minor stroke. The previously reported results might have been confounded because in the meta-analysis,[10] the observed benefit from acute statin therapy disappeared after adjusting for differences in age, severity of stroke, and vascular risk factors.

Our study is limited due to the lack of knowledge regarding the details of statin treatment at the time of presentation (duration of treatment and type and doses of medication). Pretreatment with statins was adjudicated on the basis of the patient having an active prescription at the time of their index event. In addition, our study is limited by inclusion of subjects in whom we were able to obtain an MR imaging, making our cohorts nonsequential. In addition, in our study, patients were assessed early and secondary preventive measures were implemented in a timely fashion, which may explain the low outcome rates in our population and this may have reduced our study power. However, these low outcome rates have also been reported in previous studies with similar rigorous and early treatment initiation in a TIA/minor stroke population and are not unique to our study.[23,24]

CONCLUSIONS

In this prospective imaging study of high-risk TIA and minor stroke, we did not find a reduction in the rate or the size of acute infarct with pretreatment with statins. We also found no difference in recurrent stroke rates in patients either previously on statins or acutely started on statins at the time of their event. The effect of acute statin therapy in patients with TIA and minor stroke requires further study.

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