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CLINICAL INVESTIGATIVE STUDY

Statin treatment intensity and cerebral vasomotor reactivity response in patients with ischemic stroke

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Abstract

Background and Purpose: Cerebral vasomotor reactivity (VMR) is vital for regulating brain blood flow and maintaining neurological function. Impaired cerebral VMR is linked to a higher risk of stroke and poor post-stroke outcomes. This study explores the relationship between statin treatment intensity and VMR in patients with ischemic stroke.

Methods: Seventy-four consecutive patients (mean age 69.3 years, 59.4% male) with recent ischemic stroke were included. VMR levels were assessed 4 weeks after the index stroke using transcranial Doppler, measuring the breath-holding index (BHI) as an indicator of the percentage increase in middle cerebral artery blood flow (higher BHI signifies higher VMR). Multistep multivariable regression models, adjusted for demographic and cerebrovascular risk factors, were employed to examine the association between statin intensity treatment and BHI levels.

Results: Forty-one patients (55%) received high-intensity statins. Patients receiving high-intensity statins exhibited a mean BHI of 0.85, whereas those on low-intensity statins had a mean BHI of 0.67 (mean difference 0.18, 95% confidence interval: 0.13-0.22, *p*-value<.001). This significant difference persisted in the fully adjusted model (adjusted mean values: 0.84 vs. 0.68, *p*-value: .008). No significant differences were observed in BHI values within patient groups on high-intensity or low-intensity statin therapy (all *p*-values>.05). Furthermore, no significant association was found between baseline low-density lipoprotein (LDL) levels and BHI.

Conclusions: High-intensity statin treatment post-ischemic stroke is linked to elevated VMR independent of demographic and clinical characteristics, including baseline LDL level. Further research is needed to explore statin therapy's impact on preserving brain vascular function beyond lipid-lowering effects.

KEYWORDS
breath-holding index, statin, stroke, transcranial Doppler, vasomotor reactivity

INTRODUCTION

Ischemic stroke is a leading cause for mortality and disability worldwide.[1] Despite the acute nature of stroke at the time of presentation, the underlying vascular damage is a consequence of prolonged accumulations of diverse pathologies, including inflammation, atherosclerosis, and endothelial damage.[2] Thus, assessing the extent of cerebrovascular dysfunction can offer valuable insights into the likelihood of future stroke occurrences and post-stroke outcomes.

Cerebral vasomotor reactivity (VMR) serves as an established indicator of the cerebral vasculature's ability to increase blood flow in response to hypercapnia.[3] Clinically, compromised VMR is linked to a diminished cerebrovascular reserve and an elevated risk of stroke.[4] Furthermore, impaired VMR is associated with a higher risk of subcortical infarcts and small vessel vasculopathy in individuals with a history of transient ischemic attack and stroke.[5] Various methodologies can be employed to assess VMR, and the breath-hold test emerges as a convenient and noninvasive approach, utilizing transcranial Doppler (TCD) ultrasound to measure the "breath-holding index" (BHI). During this procedure, patients can induce hypercapnia by briefly pausing respiration while recording simultaneous changes in cerebrovascular hemodynamics.[6] This measure is widely utilized to evaluate the functional integrity of brain vessels, with higher BHI values indicating higher VMR.[7]

Previous studies have demonstrated that statins, in addition to their lipid-lowering properties, confer beneficial effects on endothelial cell functions and reduce inflammation through a direct impact on endothelial cells.[8–10] Theoretically, and in accordance with previous literature, statins may positively influence VMR, potentially benefiting patients by reducing the occurrence of strokes and improving clinical outcomes.[11] In this study, we assessed VMR using BHI during the fourth-week follow-up period in patients recovering from ischemic stroke. Comparisons were drawn between BHI values and the prescribed statin intensity, aiming to explore the association between statin therapy intensity and VMR response.

METHODS

Study population

Reactivity Evaluation in Stroke Patients On the correlation of Statin Intensity and Vasomotor Effect study is a cross-sectional observational study that included adults aged 18 years or older who had experienced an ischemic stroke within the previous 4 weeks without any evidence of large vessel occlusion in intra or extracranial vascular imaging. Exclusion criteria included individuals unable to undergo TCD ultrasound due to a poor temporal window, severely ill patients unable to perform the breath-holding test (BHT) as well as a history of brain cancer and brain radiation. In addition, to ensure that significant cervical carotid occlusive disease or intracranial stenosis does not impact cerebral VMR measures, we excluded patients with large vessel occlusion or with significant stenosis in intra or extracranial vascular imaging (>50%). Alongside reviewing all radiology reports, a vascular neurologist (R.B.S) meticulously reviewed cervical and cerebral vascular imaging data for each patient. This comprehensive review aimed to confirm the absence of significant intracranial or extracranial stenosis within the anterior or posterior circulations. Among the patients assessed, 44 individuals exhibited mild degrees of atherosclerosis, which did not significantly affect cerebrovascular hemodynamics. Stroke diagnosis was based on clinical symptoms and confirmed using relevant neuroimaging. The stroke mechanism was determined using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. The TOAST classification signifies five subtypes of ischemic stroke: (1) large-artery atherosclerosis; (2) cardioembolism; (3) small-vessel occlusion; (4) stroke of other determined etiology; and (5) stroke of undetermined etiology.[12] None of these patients were mechanical thrombectomy candidates; however, those who received intravenous thrombolytic therapy were not excluded from the study. At the time of post-stroke follow-up assessment, all patients were receiving either a high- or low-intensity statin according to their last low-density lipoprotein (LDL) level and based on the American Heart Association/American Stroke Association guidelines.[13] High-intensity statin therapy dosing was defined as 40 or 80 mg of Atorvastatin (or an equivalent), whereas moderate- to low-intensity statin therapy was defined as 10-20 mg of Atorvastatin (or an equivalent of other types of statins, including Pravastatin, Rosuvastatin, and Simvastatin).[14] For each patient, treating vascular neurologists determined the intensity of statin treatment based on several factors. These factors included the presence of cardiovascular risk factors, such as diabetes, smoking, and hyperlipidemia, as well as atherosclerotic vascular diseases, like coronary artery disease, peripheral vascular disease, or carotid artery disease. Additionally, prior intolerance to high-dose statins, evidenced by symptoms such as muscle aches, pains, weakness, or cramps, was considered in determining the appropriate statin treatment intensity. All demographic data and past medical history, including recent admissions and recent lab results, were collected through the patient chart review. This study was approved by the Ethics Committee of the University of California, San Diego Institutional Review Board (UCSD, IRB# 809200). The Ethics Committee at our institution waived the need for written patient consent given that TCD is a part of standard care in the management of patients with ischemic stroke in our department with no safety issues.

VMR assessment

TCD was performed by a well-experienced vascular neurologist with a fellowship in neurosonology (R.B.S.) and 10 years of experience in TCD. We used a DWL TCD machine (Multi-Dop T digital) and performed the procedure at the Neurovascular lab at the University of California, San Diego. First (M1) segment of both middle cerebral arteries was identified clearly in all patients. A head frame was used to secure the transducer to measure time-averaged maximum mean velocities (MMVs) based on the highest flow velocity within the segment. The assessment was conducted in a calm environment, with participants

lying supine while maintaining continuous arterial blood pressure measurement throughout the session using a standard blood pressure cuff. Patients received instructions regarding the BHT before the TCD examination. The BHT comprised a 5-minute resting period followed by three 30-second periods of transient apnea. Throughout the test, verbal coaching was provided by the vascular technician. Participants were advised to avoid hyperventilation and to perform a moderate inspiratory breath hold to prevent a Valsalva episode. Additionally, a quick exhalation of residual air was performed after the breath hold to measure increased end-tidal carbon dioxide resulting from the apnea period. Time-averaged MMV was recorded before and after each apnea period. The BHI was calculated using the formula (CBF: Cerebral blood flow, V: Velocity, max: maximum, min: minimum): (CBF-Vmax − CBF-Vmin)/time of breath hold) × 100. Per previously established criteria, absolute impaired BHI is identified as values <0.21, while an impaired BHI is defined as values between 0.21 and 0.60.[3]

Statistical analysis

Normally distributed continuous data were summarized using means and standard deviations, while non-normally distributed data were represented by medians and interquartile ranges. Comparisons of means and medians were done using appropriate parametric tests, such as the *t*-test and the Mann-Whitney U test (for nonparametric comparisons). Analysis of covariance was used to calculate the adjusted means and standard errors for BHI in various groups of statin treatment and evaluation of the differences between groups. We performed the analyses in three steps using incremental statistical adjusted models. Model 1 was unadjusted. Model 2 was adjusted for age, sex, smoking, and diabetes history given the significant differences between high- and low-intensity statin treatment groups. Model 3 was additionally adjusted for baseline LDL level to evaluate the effect of LDL status on the results. All of the continuous variables were added to the statistical models in their original format without categorization. We evaluated the association between BHI and LDL levels using multivariable linear regression analyses in both unadjusted and adjusted models. All statistical analyses were performed using IBM SPSS Statistics (v26, SPSS Inc., Chicago IL, USA, https://www.ibm.com/products/spss-statistics) with the significance level set at *p*-value<.05.

RESULTS

We enrolled 74 consecutive eligible patients who experienced a recent ischemic stroke from June 2023 to December 2023. Forty-one patients (55.4%) were prescribed high-intensity statins, with 29 patients receiving Atorvastatin, 5 receiving Pravastatin, 5 receiving Rosuvastatin, and 2 taking Simvastatin. Total 7 patients received thrombolysis: 2 patients received tenecteplase, and 5 patients were treated with alteplase within the first 4.5 hours from the last known well. Thirty-three patients (44.6%) were treated with low-intensity statins with 20 patients receiving Atorvastatin, 5 receiving Pravastatin, 5 receiving Rosuvastatin, and 3 taking Simvastatin. Table 1 presents the characteristics of the study participants. Average age of participants was 69.3 years and 59.4% were male. Patients in the high-intensity statin treatment group were younger and a larger proportion of patients in this group were female, smoker, or had diabetes mellitus (*p* both <.05). The most common mechanism for stroke in our population was cerebral small vessel disease (56%). The prevalence of cerebral small vessel disease was significantly higher in patients who received high-intensity statin treatment. There was no difference in stroke severity between high- and low-intensity statin treatment groups (*p*-value = .618). There was no significant association between LDL levels and BHI in unadjusted and adjusted models for sociodemographic and vascular risk factors (*p*>.05).

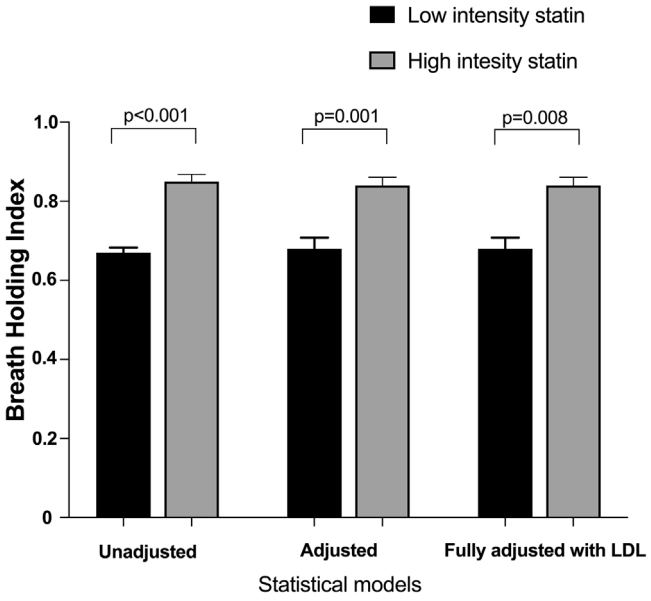

FIGURE 1 Breath-holding index values in relation to low- and high-intensity statin treatment in various statistical models including unadjusted, adjusted (age, sex, diabetes, smoking), and fully adjusted with low-density lipoprotein (LDL) (age, sex, diabetes, smoking, LDL level).

Mean BHI in patients who received high-intensity statins was 0.85 versus 0.67 in patients who received low-intensity statins (mean difference [MD] 0.18 with 95% confidence interval: 0.13-0.22, *p*-value<.001). After adjustment for age, sex, and vascular risk factors, VMR was consistently higher in the high-intensity statin treatment group. After introducing baseline serum LDL levels into the model, the observed difference in BHI between the two groups remained statistically significant. Figure 1 demonstrates differences in high- versus low-intensity statin treatment groups in different statistical models. To assess a dose-response association, we compared BHI values in four groups of participants on different statin doses (10, 20, 40, and 80 mg atorvastatin or equivalent). There was no significant difference between BHI values within patient groups on high-intensity (40 vs. 80 mg) or low-intensity statin therapy (10 vs. 20 mg) (all *p*-values>.05). However, patients who received 40 and 80 mg of atorvastatin had significantly higher BHI values when compared to each group of

TABLE 1 Baseline characteristics of participants in two groups of high- and low-intensity statin treatment.

Characteristic	High-intensity statin therapy ($n = 41$)	Low-intensity statin therapy ($n = 33$)	*p*-value
Age in years, mean ± SD	67.6 ± 8.0	71.45 ± 7.8	.043
Sex, *n* (%)			
Male	20 (48.8)	24 (72.7)	.037
History of vascular risk factors, *n* (%)			
Hypertension	41 (100)	33 (100)	N/A[a]
Hyperlipidemia	11 (26.8)	12 (36.4)	.378
Diabetes mellitus	29 (70.7)	8 (24.2)	<.001
Smoking	36 (87.8)	5 (15.1)	<.001
LDL level (median mg/dL, IQR)	66.0 (60.0-72.0)	66.0 (44.0-83.5)	.220
Peripheral vascular disease, *n* (%)	7 (17.1)	12 (36.4)	.059
Cerebral small vessel disease as stroke mechanism	32 (78.0)	10 (30)	<.001
NIHSS (median, IQR)	4 (3-4.5)	4 (3-5)	.618
Antiplatelet therapy, *n* (%)			
Mono-antiplatelet therapy[b]	20 (48.8)	13 (39.4)	.419
Dual-antiplatelet therapy[c]	21 (51.2)	20 (60.6)	

Abbreviations: dL, deciliter; IQR, interquartile range; LDL, low-density lipoprotein; mg, milligram; N/A, not applicable; NIHSS, National Institute of Health Stroke Scale; *n*, number; SD, standard deviation.
[a]All participants had hypertension.
[b]Aspirin only.
[c]Aspirin + Clopidogrel or Ticagrelor.

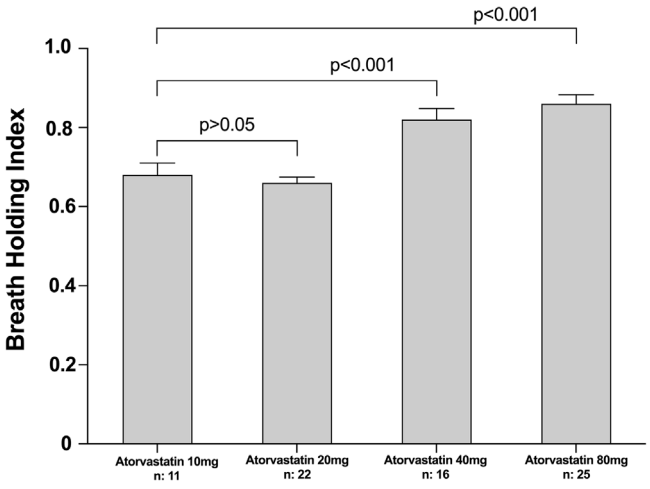

FIGURE 2 Breath-holding index adjusted mean values in relation to atorvastatin (or equivalent statins) doses. Analyses were adjusted for age, sex, diabetes, smoking, and low-density lipoprotein level. Abbreviations: mg, milligram; *n*, number.

participants on 10 and 20 mg of atorvastatin (40 vs. 10 mg: MD = 0.13, *p*-value = .001; 40 vs. 20 mg: MD = 0.15, *p*-value<.001; 80 vs. 10 mg: MD = 0.18, *p*-value<.001; 80 vs. 20 mg: MD = 0.20, *p*-value<.001). Further adjustments of the analyses for sociodemographic and vascular risk factors did not change the results. A graphic representation of BHI values across different statin doses in fully adjusted model including LDL levels is provided in Figure 2. In a separate analysis, we added cerebral small vessel disease as a covariate in multivariate model. The addition of cerebral small vessel disease did not materially change the results.

DISCUSSION

In this study, our primary objective was to explore the association between statin therapy intensity and cerebral VMR, a critical factor influencing outcomes in ischemic stroke, as assessed by the BHI. Our findings reveal that individuals receiving high-intensity statin therapy exhibited higher BHI values compared to those on lower-intensity statin regimens. Our analyses demonstrated that the link between statin therapy intensity and VMR is independent of vascular risk factors, including age, sex, diabetes, smoking, and LDL levels.

Various explanations can be proposed for the observed association between high-intensity statin use and cerebrovascular VMR. First, there is a possibility that confounding factors play a role on this link. Patients with higher cerebrovascular risk factors, on the one hand, are more likely to receive high-intensity statins and, on the other hand, are more likely to have lower VMR due to long-term cerebrovascular damage and endothelial dysfunction.[15] However, we observed that adjustments for sociodemographic and vascular factors did not change the association and also patients who took high-intensity statins had higher cerebral VMR and not lower levels. Another possible confounder could be the baseline LDL levels which determined the

indication for initiation of high- or low-intensity statin treatment. In our study, we found no significant association between LDL levels and BHI, challenging the notion that lower LDL levels result in higher cerebrovascular VMR.[8,16] In the same line, previous studies have shown that traditional nonstatin lipid-lowering agents do not reduce stroke risk despite significant decreases in serum cholesterol levels.[17,18]

Previous studies have shown favorable cerebrovascular effects of statins on CBF and VMR.[19–21] In a randomized, double-blinded study, regional VMR, measured by blood oxygen level-dependent functional MRI, was improved in patients who were given 40 mg of atorvastatin.[20] In another study, a 2-week course of oral pravastatin significantly improved VMR measured by TCD, especially in patients with initial low VMR values. The effect of statins on VMR in the mentioned study was more pronounced on the seventh day of statin therapy.[21] Likewise, in an interventional study by Forteza et al. involving 36 patients, high-intensity atorvastatin enhanced VMR, and this improvement persisted for up to 6 weeks after discontinuation of statin therapy. However, statin therapy did not enhance VMR among the subset of patients with preserved baseline VMR indices.[15] Improvement in the bioavailability of endothelium-derived nitric oxide (eNO) has been proposed as a possible mechanism for these favorable hemodynamic outcomes.[22] eNO triggers arterial vasodilation and supports regular vascular vasomotor function. This vasodilatory effect induced by NO depends on an undamaged endothelial integrity, which can be compromised in patients with constant elevated LDL levels, attributable to its direct toxic impact on the endothelium and its promotion of atherosclerosis.[23–25] In addition to their LDL-lowering properties, statins have been found to possess anti-inflammatory properties on endothelial cells via reduction of inflammatory cytokines and oxidative stress.[26,27] Previous reports have indicated that impaired VMR is linked to subcortical and multifocal silent infarcts and associated white matter lesions.[5,28] Various studies indeed showed that cerebral small vessel disease is associated with increased pulsatility index and lower cerebrovascular reserve.[29–31] Another clear example is reduced cerebrovascular reactivity in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, suggesting an early role of impaired cerebral vasoreactivity in the evolution of this syndrome.[32,33] In our study, we show that high-intensity statin treatment is associated with more favorable VMR despite a higher burden of previously established cerebral small vessel disease in the high-intensity statin treatment group. Experimental animal studies have shown a dose-dependent increase in NO after treatment with statins, supporting the notion that statin treatment intensity can provide additional cerebrovascular benefit.[34,35] Further long-term clinical and translational studies are needed to confirm the dose and duration-dependent benefits of statin in regards to cerebrovascular function and to unravel the exact mechanisms underlying this association. Such efforts have an implication in developing personalized treatments based on individuals' brain vascular endothelial functional and biological integrity.

This study comprises a relatively large sample size of patients with recent ischemic stroke with detailed TCD and clinical data. To the best of our knowledge, it is the first study to compare post-stroke VMR in patients receiving high- and low-intensity statin therapy. Previous studies have focused on the effects of either high- or low-intensity statins on breath-holding indices. Despite the cross-sectional design of this study, the current data can trigger further studies on the impact of statin therapy on post-stroke cerebrovascular recovery. Several limitations of this study need to be acknowledged. First, we measured VMR once, and future studies are warranted to evaluate changes in VMR over time. Second, we excluded patients with critical intracranial or extracranial stenosis which introduces a potential selection bias and limits the generalizability of our findings to a specific subset of patients without significant cerebrovascular stenosis. Third, given the observational nature of this study, at best our results are suggestive of the favorable effect of high-dose statins on VMR, and randomized clinical trials are needed to better assess the role of statin treatment intensity in improving VMR in patients with ischemic stroke.

In summary, our study highlights a significant association between high-intensity statin treatment post-ischemic stroke and elevated VMR, irrespective of demographic and clinical factors, including baseline LDL levels. Subsequent research endeavors should expand upon these findings, addressing identified limitations and delving into the long-term impact of statin therapy on VMR.

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