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Statin contribution to middle cerebral artery blood flow velocity in older adults at risk for dementia

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Abstract

Purpose—It is plausible that statins could improve cerebral blood flow through pleiotropic mechanisms. The purpose of this investigation was to assess the contribution of statins to cerebrovascular variables in older adults with dyslipidemia and familial history of dementia.

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Conflict of interest The authors have no competing interests to declare that are relevant to the content of this article.

Ethics approval The protocol was reviewed and approved by the individual site's respective institutional review boards (IRB number STUDY00004510 at the KU Medical Center and STU052016-076 at the UT Southwestern Medical Center).

Consent to participate All participants provided written informed consent before study commencement.

Furthermore, we explored the interaction between statin use and sex due to prevalent bias in statin trials.

Methods—Middle cerebral artery blood flow velocity (MCAv) was measured using transcranial Doppler ultrasound. Continuous supine rest recordings lasted 8 min. Participants included in analyses were statin ($n = 100$) or non-statin users ($n = 112$).

Results—MCAv and cerebrovascular conductance were significantly higher in statin users ($p = 0.047$; $p = 0.04$), and pulsatility index (PI) was significantly lower in statin users ($p < 0.01$). An interaction effect between statin use and sex was present for PI ($p = 0.02$); female statin users had significantly lower cerebrovascular resistance than the other three groups.

Conclusion—In this cross-sectional analysis, statin use was positively associated with cerebrovascular variables in older adults at risk for dementia. Female statin users had significantly higher resting MCAv and cerebrovascular conductance than female non-statin users. The greatest contribution of statin use was the association with reduced cerebrovascular resistance. Given that cerebrovascular dysregulation is one of the earliest changes in Alzheimer's disease and related dementia pathology, targeting the cerebrovasculature with statins may be a promising prevention strategy.

Keywords

Alzheimer's disease; Cerebral blood flow velocity; Cerebrovascular; Dementia; Statin

Introduction

As the exact causes underlying Alzheimer's disease (AD) and related dementias (ADRD) are still unknown, it is vital to commit research efforts toward prevention strategies (Claassen 2015). ADRD is a disease of multifactorial origin, likely resulting from an interaction between genetic susceptibility and environmental risk factors (Kivipelto et al. 2002). While genetics are non-modifiable in relation to ADRD treatment, various environmental, thus modifiable, risk factors have been proposed (Kivipelto and Solomon 2006). One promising prevention strategy is to target the vascular system, as atherosclerosis due to hypercholesterolemia along with aging-related cerebrovascular alterations, constitute important independent factors for the development of ADRD (Iadecola 2010; Wiesmann et al. 2013; Kivipelto et al. 2001).

Statins are one of the most effective pharmacologic treatments for cardiovascular risk reduction (McConnachie et al. 2014; Mistry et al. 2012). As clinical use continues to surge, the effects of statins beyond just peripheral lipid reduction are being investigated. In a cross-sectional analysis from 3 different hospitals, the prevalence of AD in patients taking statins was 60% lower than in those taking other cardiovascular medications (Wolozin et al. 2000). However, 95% of patients from the 2 veterans affairs medical centers were men. Furthermore, in a case–control study, participants who were prescribed statins had a 70% lower odds for dementia (Odds Ratio = 0.29) than those who did not have hyperlipidemia or who were not on a lipid-lowering medication (Jick et al. 2000). With promising results like these, pleiotropic effects of statins are frequently being investigated (Liao 2005; Lahera et al. 2007; Wang et al. 2008; Kling et al. 2013). In animal models, experimental

investigations have reported an increase in cerebral blood flow independent of lowering peripheral cholesterol with statin treatment. (Endres et al. 1998; Amin-Hanjani et al. 2001; Yamada et al. 2000). In a small pilot, randomized controlled trial of individuals with an increased familial risk for AD ($n = 13$), findings suggested those prescribed statins for 4 months increased regional cerebral blood flow compared to those on placebo. (Carlsson et al. 2012). Therefore, statins may be a clinically relevant treatment for the prevention of AD onset through alterations in cerebral perfusion. In contrast, a case could also be made that more needs to be known about statins and vascular health given the consistent findings that statins cause a small but statistically significant increased risk for type 2 diabetes (Preiss et al. 2011), often worsens insulin resistance (Miller and Thyfault 2020) and markers of glycemic control (Mansi et al. 2021), which are also risk factors for AD and vascular disease.

The purpose of this investigation was to assess if statin use contributed to resting cerebral blood flow velocity, cerebrovascular conductance, and cerebral pulsatility in older adults with dyslipidemia who were or were not undergoing statin therapy and a familial history of dementia or self-report cognitive decline. We hypothesized that statin use would positively contribute to resting cerebral blood flow velocity, cerebrovascular conductance, and cerebral pulsatility. Despite widespread statin use in both sexes, bias has been prevalent in statin trials (Bandyopadhyay et al. 2001); therefore, we also explored the statin use and sex interaction on resting cerebral blood flow velocity, cerebrovascular conductance, and cerebral pulsatility.

Materials and methods

This study utilized baseline data collected at the University of Kansas (KU) Medical Center, University of Kansas Alzheimer's Disease Research Center (KU ADRC), and the University of Texas (UT) Southwestern Medical Center as part of a multi-site clinical trial (R01 AG49749).

Study population

Whereas old age is the single most important risk factor for dementia, having a first degree relative with dementia increases risk by three to fourfold (Cupples et al. 2004). Furthermore, the co-existence of vascular risk factors with a family history of dementia further increases risk (Wang et al. 2012). The individuals included in this study, therefore, represent a high prevalence and high-risk population.

Inclusion criteria: (1) age 60–85; (2) family history of AD defined as having at least one first-degree relative (siblings or biological parents) with a clinical diagnosis of possible or probable AD with an onset age between 60 and 80 years (based on the medical records and/or the databases) or self-report of cognitive decline (Honea et al. 2012); (3) AD8 < 2 and Mini-Mental State Exam (MMSE) > 27 (based on age and education adjusted norms) to exclude dementia (Crum et al. 1993); (4) a sedentary lifestyle defined as < 90 min of moderate aerobic exercise per week over the past year; (5) hypertension defined as systolic blood pressure (sBP) ≥ 140 mmHg (James et al. 2014), subjects on anti-hypertensives were eligible; (6) dyslipidemia defined as those who have an estimate 10-year cardiovascular

disease score ≥ 7.5% (calculated using pooled cohort equations) and LDL-C ≥ 95 mg/dL (Goff et al. 2013), subjects on low-intensity statin therapy were eligible.

Exclusion criteria: (1) history of stroke or other major cerebrovascular diseases by clinical diagnosis or magnetic resonance imaging/computerized tomography scans; (2) diagnosis of AD or other type of dementia and significant neurologic diseases; (3) patients with current evidence of severe depression or other DSM-V Axis I psychopathology; (4) major and unstable heart (e.g., heart attack/cardiac arrest, severe atrial fibrillation, cardiac bypass procedures and congestive heart failure), liver, renal and other medical conditions; (5) orthostatic hypotension; (6) history of significant autoimmune disorders; (7) clinical diagnosis of type 1 or 2 diabetes (Zhang et al. 2015); (8) patients with resistant hypertension (SBP ≥ 140 or diastolic blood pressure (dBP) ≥ 90 mmHg despite 3 antihypertensive drugs at maximal doses); (9) current use of warfarin or anticoagulant therapy; (10) Regularly smoking cigarettes within the past year; (11) any conditions judged by the study investigators to be medically contraindicated, risky for the participant, or likely to have poor study adherence.

Prior to study commencement, the protocol was reviewed and approved by the individual sites respective institutional review boards (IRB number STUDY00004510 at the KU Medical Center and STU052016-076 at the UT Southwestern Medical Center). All participants provided written informed consent.

Extensive details have been previously published describing screening and fasting clinical chemistry (Szabo-Reed et al. 2019).

Cerebrovascular and hemodynamic measurements

Once in the supine position, participants completed a rest period of at least 10 min in a quiet, temperature-controlled room (22–24 °C) before data collection. During the rest period, participants were instrumented for the hemodynamic and cerebrovascular measurements. Heart rate was measured via a 5-lead electrocardiogram at KU Medical Center (Cardiocard, Nasiff Associates, Central Square, NY, USA) or a 3-lead electrocardiogram at UT Southwestern Medical Center (Hewlett-Packard, Palo Alto, CA, USA). Mean arterial pressure (MAP) was measured using a brachial sphygmomanometer (Tango M2 Stress Test Monitor, Sun-Tech Medical, Inc., Morrisville, NC, USA; Finapres Medical Systems, Amsterdam, The Netherlands). End-tidal CO_2 was measured via a nasal cannula attached to a gas analyzer (BCI Capnocheck 9004, Smiths Medical, Columbia, SC, USA; Carpnograd, Novamatrix, Wallingford, CT, USA). Transcranial Doppler ultrasound (TCD; RobotoC2MD System, Multigon Industries, Yonkers, NY, USA; Multi-Dop X2, Compumedics/DWL, Singen, Germany) was used to measure mean middle cerebral artery blood flow velocity (MCAv) with a 2 Hz probe placed on the right or left trans-temporal window using a signal depth between 40 and 65 mm. The TCD probe was secured with headgear to maintain the optimal position and angle.

Heart rate, end-tidal CO_2, and TCD rest recordings lasted for eight minutes. At KU Medical Center, data were collected with a sampling frequency of 500 Hz (National Instruments, Austin, TX) with data acquisition and analysis completed with a custom MATLAB script

(The Math Works, Inc., Version 2019a, Natick, MA, USA). At UTSW, data were collected with a sampling frequency of 1000 Hz and stored in a computer for off-line analysis using a data acquisition and analysis software (Acknowledge, BIOPAC systems, Goleta, CA, USA). Three brachial blood pressure measurements were taken before recordings started. MCAv was calculated by averaging the MCAv within each cardiac cycle. Heart rate, end-tidal CO_2 and MCAv were averaged over the recorded duration for each participant. Cerebrovascular conductance index (CVCi) was calculated by dividing mean MCAv by MAP. Pulsatility index (PI) was calculated as the difference between systolic and diastolic MCAv divided by the mean MCAv ($[MCAv_{systolic} - MCAv_{diastolic}]$/mean MCAv) (Gosling and King 1974).

Statistical analysis

All statistical analyses were performed using R language for statistical computing (R Core Team, version 4.0.3, 2020). Continuous variables are reported as mean ± standard deviation and all categorical variables as count (%) unless otherwise stated. Differences were considered significant at $p < 0.05$.

Statin vs. no statin groups were assessed using a one-way analysis of variance (ANOVA) or a Kruskal–Wallis test depending on whether the assumption of normality was violated. Normality was assessed using the Shapiro–Wilk test and Q-Q plot visualization. Group differences for categorical variables was assessed using χ^2 test. The statin use by sex groups were assessed using a one-way ANOVA with Bonferroni correction for multiple comparisons.

A forward and backward stepwise model selection based on Akaike Information Criterion (AIC) was used for the linear regression to determine if statin use contributed to the cerebrovascular outcomes. Within the initial model, the independent variables included statin use, age, sex, beta-blocker use, LDL-C levels, HDL-C levels, heart rate, mean arterial pressure and end-tidal CO_2. Variance inflation factor was checked for all initial models and final models. To assess statin and sex interaction effects, linear regression models without forward and backward stepwise AIC selections were completed. The independent variables that remained in the model after the AIC model selections were included in the models for the statin and sex interaction analyses.

Results

Analyses were conducted in 212 participants with 100 in the statin group and 112 in the non-statin group (Tables 1 and 2). As expected, those undergoing statin therapy had lower cholesterol values (LDL-C, HDL-C, and total cholesterol) compared to those not undergoing statin therapy. Additionally, significantly fewer participants were taking beta-blockers in the statin group compared to the non-statin group. When controlling for other potentially confounding variables (stepwise AIC selection models), statin use significantly contributed to the cerebrovascular variables (Table 3). Statin use was positively and significantly associated with MCAv ($p = 0.047$) and CVCi ($p = 0.04$), indicating that within statin users cerebral blood flow velocity and conductance tended to be higher than non-statin users. Furthermore, statin use was negatively and significantly associated with PI ($p < 0.01$),

indicating that within the statin users cerebrovascular resistance tended to be lower than non-statin users.

For MCAv and CVCi, the female statin group was significantly higher than the male statin group ($p < 0.001$; $p < 0.001$; Table 4). For PI, the female statin group trended towards but was not significantly lower than the male statin group ($p = 0.07$). Additionally, the female statin group was significantly lower than female non-statin group ($p = 0.046$).

The interaction between statin-use and sex for MCAv and CVCi trended towards but was not significant ($p = 0.08$; $p = 0.06$; Table 5; Fig. 1). For PI, however, a significant interaction was present across sex ($p = 0.02$), suggesting female statin users had lower cerebrovascular resistance than men statin or non-statin users.

Discussion

Our primary findings are that statin use was a significant contributing factor for resting cerebrovascular variables in older adults with dyslipidemia and a familial history of dementia. Statin users tended to have higher cerebral blood flow velocity and cerebrovascular conductance as well as lower cerebrovascular resistance than non-statin users. Furthermore, there was a statin and sex interaction effect, such that female statin users had lower cerebrovascular resistance than female non-statin users as well as male statin and non-statin users.

In relation to statin effects on cerebral blood flow, many of the investigations have been completed using magnetic resonance imaging. In a pilot clinical trial of asymptomatic middle-aged adults at risk for AD ($n = 16$), participants were randomized to four months of atorvastatin or placebo (Carlsson et al. 2012). At baseline and month 4, regional cerebral blood flow was measured using arterial spin-labeling magnetic resonance imaging. They reported greater increases in regional cerebral blood flow in bilateral hippocampi, fusiform gyrus, putamen, and insular cortices compared to placebo. Other studies have demonstrated relative hypoperfusion in the posterior cingulate, and the parietal and medial temporal lobes in adults with mild cognitive impairment (Johnson et al. 2005), cognitively healthy apolipoprotein E4 allele carriers (Scarmeas et al. 2003), and non-demented persons with memory complaints who later develop AD (El Fakhri et al. 2003). These previous studies provide support for our findings of increased cerebral blood flow velocity and cerebral conductance within the middle cerebral artery within statin users.

Sex differences in vascular risk factors associated with ADRD have not been studied systematically, with the majority of studies adjusting for sex; preventing the assessment of sex related effects on outcomes (Ferretti et al. 2018). Differences in aging related brain structure (Ruigrok et al. 2014) and function (Laws et al. 2016) between sexes are emerging, as are sex effects on the manifestation and progression of neurological conditions (Cordonnier et al. 2017). Previous research indicates that sex can modulate not only the prevalence of risk factors for AD but also the susceptibility to AD conferred by a given risk factor. For example, the first manifestation of cardiovascular disease differs between sexes, which could differentially influence the risk of AD (Ruitenberg et al. 2005). Given

the evidence that vascular factors contribute to AD risk and our evidence suggesting statin contribution significantly supports cerebrovascular health in females, sex differences in prevention and treatment strategies for ADRD deserve further examination.

The brain is one of the most cholesterol enriched organs in the body and contains about 25% of total body cholesterol. As cholesterol is essential for cell membranes and plays a crucial role in the development and maintenance of neuronal plasticity and function, cholesterol homeostasis within the brain is strictly regulated (Pfrieger 2003). The exchange rate between peripheral and brain cholesterol is predominantly, but not fully, independent of blood cholesterol levels (Dietschy and Turley 2004). When blood cholesterol levels are not regulated and hypercholesterolemia occurs, individuals increase their risk for the development of ADRD related pathologies. This conclusion has been supported by previous investigations. Arvanitakis et al. (2016) reported that large and small cerebral vessel pathology (i.e., atherosclerosis) were associated with lower cognitive performance and increased risk for AD. Beach et al. (2007) demonstrated that individuals with AD exhibit substantial atherosclerosis in the arteries of the circle of Willis, with lesions being more severe and more stenotic than in age-matched controls. Importantly, these finding have been validated within a large cohort, reporting that common pathophysiological mechanisms promote both vascular pathology and amyloid plaque as well as tau tangle pathology (Yarchoan et al. 2012).

The pleiotropic effect of statins on cerebral blood flow are not well understood but may be attributed to several processes resulting from the inhibition of 3-hydroxy-3-methyl-glutarylo-coenzyme A (HMG-CoA) reductase. Statins main effect is the inhibition of cholesterol and isoprenoid synthesis, which may result in lower circulating endothelial nitric oxide synthase, an enzyme responsible for vascular endothelial function, and thus improved pathophysiologic response (Liao and Laufs 2005). In addition to this main effect, statins may also induce antioxidant effects via the decreased production of NADPH oxidase and resulting reactive oxidant species in circulation (Endres et al. 1998). Inflammatory markers such as C-reactive protein have also been shown to be reduced by statins, leading to the hypothesis that statins have anti-inflammatory properties (Li et al. 2010). By impairing production of β-amyloid proteins and apolipoprotein E and exerting anti-inflammatory effects, statins are proposed to decrease the amount of tau fibrillization in the pathophysiologic process of Alzheimer’s disease. Studies are underway to clarify the impact of statins on these ADRD-related processes and whether modifying these potential mechanisms of disease leads to long-term improved cognition and reduced risk for AD. In contrast, statins have been implicated in worsening glycemic control which itself is a risk factor for vascular complications and AD. However, this study excluded those with type 2 diabetes or elevated glycemia. Thus, a possible negative effect of statins on vascular effects through glycemia was likely avoided in this study. A future study examining the impact of statins on cerebrovascular blood flow control in those with pre-diabetes or type 2 diabetes is warranted.

There are several limitations to the investigation that should be considered. First, using transcranial Doppler ultrasound to quantify cerebral blood flow requires the assumption that vessel length, vessel radius and blood viscosity remain constant for velocity to be a

surrogate for cerebral blood flow (Serrador et al. 2000). Evidence suggests changes in MAP and end-tidal CO_2 are associated with changes in the diameter of the MCA (Verbree et al. 2017). However, transcranial Doppler ultrasound measurements for the study were collected in a resting state and MCA diameter most likely was not affected. Additionally, only unilateral MCAv was assessed, therefore, results may not reflect the trajectory of age-related change in posterior cerebral circulation and/or global cerebral circulation. Secondly, the statin and beta-blocker medication doses as well as duration of medication use were not recorded. It is unknown, therefore, within our results if medication doses play a role in the cerebrovascular outcomes, especially within the statin and sex interaction assessment. Third, intracranial atherosclerosis was not analyzed, thus, we could not account for varying degrees of stenosis in the common and internal carotid arteries. Lastly, this investigation was a cross-sectional analysis and the effects of statin use on cerebrovascular outcomes cannot be directly surmised, however, we will explore this further once the clinical trial is complete (NCT02913664). Moreover, we cannot directly tell if the statin drug itself or the statin induced change in circulating cholesterol is the primary driver of the differences observed between groups. However, the significant effects from the current study along with the previous investigations discussed, further investigation into the longitudinal effects with a focus on statin therapy dose and duration, and the impact of sex on cerebrovascular function should be completed.

Conclusions

In this cross-sectional analysis, statin use positively contributed to cerebrovascular outcomes in older adults at risk for dementia. Specifically, females showed the greatest contribution to cerebrovascular outcomes from statin use. Given that cerebrovascular dysregulation is one of the earliest changes in ADRD pathology, (Iadecola 2004) targeting cerebral perfusion with statins may be a promising prevention strategy to delay or prevent ADRD. Intervention studies are currently underway that may highlight the effects of, as well as mechanisms behind, statin use on cerebrovascular function in individuals at a high-risk for ADRD.

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Data availability

Data related to this manuscript will be available upon reasonable request to the corresponding author.

Abbreviations

AIC	Akaike information criterion
ANOVA	Analysis of variance

AD	Alzheimer's disease
AD8	Eight-item informant interview to differentiate aging and dementia
ADRD	Alzheimer's disease and related dementias
CVCi	Cerebrovascular conductance index
dBP	Diastolic blood pressure
DSM-V	Diagnostic and statistical manual of mental disorders fifth edition
HDL-C	High-density lipoprotein
LDL- C	Low-density lipoprotein
MAP	Mean arterial pressure
MCAv	Middle cerebral artery blood flow velocity
MMSE	Mini-mental state exam
PI	Pulsatility index
sBP	Systolic blood pressure
TCD	Transcranial Doppler ultrasound

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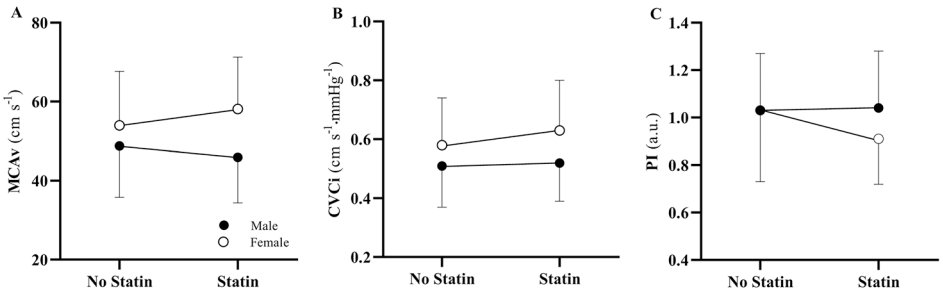

Fig. 1.

Interaction plots for statin use by sex for each cerebrovascular outcome. **A** MCAv, middle cerebral artery blood flow velocity. **B** CVCi, cerebrovascular conductance index. **C** PI, pulsatility index

Table 1

Participant characteristics

	Statin *n* = 100	**No statin *n* = 112**	***p***
Age	69 ± 6	69 ± 6	0.68
Female, *n* (%)	51 (51%)	74 (66%)	**0.03**
Height, cm	170 ± 9	168 ± 10	0.13
Weight, kg	88 ± 18	84 ± 19	0.12
Body mass index, kg m^{-2}	30 ± 5	30 ± 6	0.32
Heart rate, bpm	58 ± 7	57 ± 8	0.27
End-tidal CO_2, mmHg	35 ± 3	35 ± 4	0.93
sBP, mmHg	130 ± 15	132 ± 15	0.19
dBP, mmHg	73 ± 9	76 ± 9	0.08
MAP, mmHg	92 ± 10	95 ± 10	0.08
LDL-C, mg dL^{-1}	93 ± 29	119 ± 31	< **0.0001**
HDL-C, mg dL^{-1}	53 ± 16	62 ± 20	< **0.001**
Total cholesterol, mg dL^{-1}	170 ± 36	203 ± 37	< **0.0001**
Beta-blocker, *n* (%)	75 (75%)	100 (89%)	< **0.01**

Bold font indicates significance at $p < 0.05$

Continuous variables are mean ± standard deviation. Categorical variables are count (%)

dBP diastolic blood pressure, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, MAP, mean arterial pressure, *sBP* systolic blood pressure

Table 2

Cerebrovascular outcomes

	No statin *n* = 112	**Statin *n* = 100**	***p***
MCAv, cm s^{-1}	52.22 ± 13.63	52.50 ± 13.20	0.88
CVCi, cm s^{-1}·$mmHg^{-1}$	0.56 ± 0.15	0.58 ± 0.16	0.42
PI, a.u	1.03 ± 0.28	0.97 ± 0.23	0.09

Variables are mean ± standard deviation. *p* values are unadjusted and a comparison between groups

CVCi cerebrovascular conductance index, *MCAv* middle cerebral artery blood flow velocity, *PI* pulsatility index

Table 3

Regression results for cerebrovascular outcomes

	MCAv	CVCi	PI
Statin	3.88 [0.04–7.71] **(0.047)**	0.04 [0.002–0.09] **(0.04)**	− 0.09 [− 0.16 to − 0.03] **(< 0.01)**
Age	–	–	0.02 [0.01–0.02] **(< 0.0001)**
Female	6.83 [2.79–10.86] **(< 0.01)**	0.08 [0.03–0.12] **(< 0.001)**	–
Beta-blockers	− 4.69 [− 9.44 to 0.06] (0.05)	− 0.05 [− 0.10 to 0.005] (0.07)	–
LDL-C	0.05 [− 0.01 to 0.11] (0.10)	0.0005 [− 0.0001 to 0.011] (0.13)	− 0.001 [− 0.002 to − 0.000002] **(0.049)**
HDL-C	0.10 [− 0.0004 to 0.21] (0.05)	0.001 [− 0.00002 to 0.002] (0.05)	–
Heart rate	0.24 [0.03–0.46] **(0.03)**	0.003 [0.0004–0.01] **(0.02)**	0.004 [0.0002–0.007] **(0.04)**
Mean arterial pressure	–	− 0.006 [− 0.008 to − 0.004] **(< 0.001)**	–
End-tidal CO_2	0.39 [− 0.05 to 0.84] (0.08)	0.004 [− 0.008 to 0.009] (0.10)	–
Intercept	8.60 [− 12.89 to 30.09] (0.43)	0.63 [0.32–0.94] **(< 0.001)**	− 0.37 [− 0.77 to 0.02] (0.06)
R-squared	0.17	0.29	0.29
Adjusted R-squared	0.14	0.27	0.28
Residual Std. error	12.34	0.13	0.21
F statistic	5.90 df = 7; 200 **(< 0.001)**	10.33 df = 8; 199 **(< 0.001)**	20.74 df = 4; 203 **(< 0.001)**

Bold indicates significance at $p < 0.05$

For each variable the primary number is β-weight. A dash (−) indicates the variable dropped during the AIC model selection. 95% confidence intervals are reported in brackets. *p*-values are reported in parentheses

CVCi cerebrovascular conductance index, *HDL-C* high-density lipoprotein, *LDL-C* low-density lipoprotein, *MCAv*, middle cerebral blood flow velocity, *PI* pulsatility index

Table 4

Cerebrovascular characteristics by statin use and sex

	Males			Females			M vs. F No statin	M vs. F statin	Main effect
	No statin *n* = 38	**Statin *n* = 49**	***p***	**No statin *n* = 74**	**Statin *n* = 51**	***p***	***p***	***p***	***p***
MCAv, cm s^{-1}	48.78 ± 13.00	46.62 ± 10.53	0.99	53.99 ± 13.69	58.14 ± 13.11	0.45	0.25	< **0.001**	< **0.001**
CVCi, cm s^{-1}·$mmHg^{-1}$	0.51 ± 0.14	0.52 ± 0.13	0.99	0.58 ± 0.16	0.63 ± 0.17	0.43	0.10	< **0.001**	< **0.001**
PI, a.u	1.03 ± 0.24	1.04 ± 0.24	0.99	1.03 ± 0.30	0.91 ± 0.19	**0.047**	0.99	0.07	**0.03**

Bold indicates significance at $p < 0.05$

Variables are mean ± standard deviation

CVCi cerebrovascular conductance index, *F* females, *M* males, *MCAv* middle cerebral artery blood flow velocity, *PI* pulsatility index

Table 5

Regression results for statin use and sex interaction effect for cerebrovascular outcomes

	MCAv	CVCi	PI
Statin*female	6.32 [− 0.64 to 13.29] (0.08)	0.07 [− 0.004 to 0.15] (0.06)	− 0.14 [− 0.26 to − 0.02] **(0.02)**
Statin	0.26 [− 5.26 to 5.78] (0.93)	0.002 [− 0.06 to 0.06] (0.96)	− 0.01 [− 0.10 to 0.09] (0.87)
Female	3.50 [− 1.93 to 8.94] (0.20)	0.04 [− 0.02 to 0.10] (0.19)	0.07 [− 0.01 to 0.16] (0.10)
Age	–	–	0.02 [0.01–0.02] **(< 0.001)**
Beta-blockers	− 4.81 [− 9.53 to − 0.09] **(0.046)**	− 0.05 [− 0.10 to 0.003] (0.06)	–
LDL-C	0.05 [− 0.01 to 0.19] (0.09)	0.001 [− 0.0001 to 0.001] (0.12)	− 0.001 [− 0.002 to 0.00002] (0.05)
HDL-C	0.11 [0.01–0.22] **(0.04)**	0.001 [0.00007–0.002] **(0.04)**	–
Heart Rate	0.23 [0.02–0.45] **(0.03)**	0.003 [0.0002–0.005] **(0.03)**	0.004 [0.0004–0.008] **(0.03)**
Mean Arterial Pressure	–	− 0.01 [− 0.008 to − 0.004] **(< 0.001)**	
End-tidal CO_2	0.41 [− 0.03 to 0.85] (0.07)	0.004 [− 0.0006 to 0.009] (0.09)	–
Constant	10.18 [− 11.26 to 31.63] (0.35)	0.67 [0.36–0.98] **(< 0.001)**	− 0.45 [− 0.85 to − 0.05] **(0.03)**
R-squared	0.18	0.31	0.31
Adjusted R-squared	0.15	0.27	0.29
Residual Std. error	12.28	0.13	0.21
F statistic	5.62 df = 8; 199 **(< 0.001)**	9.69 df = 9; 198 **(< 0.001)**	15.02 df = 6; 201 **(< 0.001)**

Bold indicates significance at $p < 0.05$

For each variable the primary number is β-weight. A dash (−) indicates the variable dropped during the AIC model selection. 95% confidence intervals are reported in brackets. *p* values are reported in parentheses

CVCi cerebrovascular conductance index, *HDL-C* high-density lipoprotein, *LDL-C* low-density lipoprotein, *MCAv* middle cerebral blood flow velocity, *PI* pulsatility index

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