ORIGINAL RESEARCH

Intensity of Lipid Lowering With Statin Therapy in Patients With Cerebrovascular Disease Versus Coronary Artery Disease: Insights from the PALM Registry

Ying Xian, MD, PhD; Ann Marie Navar, MD, PhD; Shuang Li, MS; Zhuokai Li, PhD; Jennifer Robinson, MD, MPH; Salim S. Virani, MD, PhD; Michael J. Louie, MD, MPH, MSc; Andrew Koren, MD; Anne Goldberg, MD; Veronique L. Roger, MD, MPH; Peter W. F. Wilson, MD; Eric D. Peterson, MD, MPH; Tracy Y. Wang, MD, MHS, MSc

***Background*—**Current treatment guidelines strongly recommend statin therapy for secondary prevention. However, it remains unclear whether patients' perceptions of cardiovascular risk, beliefs on cholesterol, or the intensity of prescribed statin therapy differs for patients with coronary artery disease (CAD) versus cerebrovascular disease (CeVD) versus both CAD and CeVD (CAD&CeVD).

***Methods and Results*—**The PALM (Patient and Provider Assessment of Lipid Management) registry collected data on statin use, intensity, and core laboratory low-density lipoprotein cholesterol levels for 3232 secondary prevention patients treated at 133 US clinics. Among individuals with CeVD only (n=403), CAD only (n=2202), and CeVD&CAD (n=627), no significant differences were observed in patient-perceived cardiovascular disease risk, beliefs on cholesterol lowering, or perceived effectiveness and safety of statin therapy. However, patients with CeVD only were less likely to receive any statin therapy (76.2% versus 86.2%; adjusted odds ratio 0.64, 95% CI 0.45–0.91), or guideline-recommended statin intensity (34.6% versus 50.4%; adjusted odds ratio 0.60, 95% CI 0.45–0.81) than those with CAD only. Individuals with CeVD only were also less likely to achieve low-density lipoprotein cholesterol <100 mg/dL (59.2% versus 69.7%; adjusted odds ratio 0.79, 95% CI 0.64–0.99) than individuals with CAD alone. There were no significant differences in the use of any statin therapy or guideline-recommended statin intensity between individuals with CAD&CeVD and those with CAD only.

***Conclusions*—**Despite lack of significant differences in patient-perceived cardiovascular risk or statin beliefs, patients with CeVD were significantly less likely to receive higher intensity statin or achieve low-density lipoprotein cholesterol <100 mg/dL than those with CAD only. **(*J Am Heart Assoc*. 2019;8:e013229. DOI: 10.1161/JAHA.119.013229.)**

Key Words: coronary artery disease • quality of care • secondary prevention • statin • stroke

Current lipid guidelines strongly recommend statin therapy for secondary prevention in patients with atherosclerotic cardiovascular disease (ASCVD), including coronary artery disease (CAD) and cerebrovascular disease (CeVD).[1–3] Despite the overwhelming evidence that statins are highly beneficial in preventing recurrent ischemic events, secondary prevention patients are often untreated or undertreated with lower-than-recommended statin intensity in community practice.[4–10] While appropriate statin therapy is an important goal in patients with CeVD,[3] it is unclear whether CeVD patients are treated differently from those with CAD.

The PALM (Patient and Provider Assessment of Lipid Management) registry is a nationwide contemporary outpatient registry of individuals with ASCVD or at high risk for ASCVD in the United States. Using PALM registry first we examined differences in patient perceptions of cardiovascular risks, beliefs on the effectiveness and safety of statin drugs, tolerability and reported symptoms following statin use among patients with CeVD only, both CAD and CeVD (CAD&CeVD), or CAD only. Second, we compared overall statin use, and guideline-recommended statin therapy and low density lipoprotein cholesterol (LDL-C) levels, by the underlying ASCVD condition

From the Duke Clinical Research Institute, Duke University Medical Center, Durham, NC (Y.X., A.M.N., S.L., Z.L., E.D.P., T.Y.W.); University of Iowa, Iowa City, IA (J.R.); VA Medical Center and Baylor College of Medicine, Houston, TX (S.S.V.); Regeneron Pharmaceuticals, Tarrytown, NY (M.J.L.); Sanofi Pharmaceuticals, Bridgewater, NJ (A.K.); Washington University, St. Louis, MO (A.G.); Mayo Clinic, Rochester, MN (V.L.R.); Emory University, Atlanta, GA (P.W.F.W.).

An accompanying Table S1 is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013229

Correspondence to: Ying Xian, MD, PhD, Duke Clinical Research Institute, 2400 Pratt Street; Durham, NC 27705. E-mail: ying.xian@duke.edu

Received June 20, 2019; accepted August 7, 2019.

Clinical Perspective

What Is New?

- Current lipid guidelines strongly recommend statin therapy for secondary prevention in patients with atherosclerotic cardiovascular disease, including coronary artery disease and cerebrovascular disease.
- While appropriate statin therapy is an important goal, it is unclear whether patients with cerebrovascular disease are treated differently from those with coronary artery disease.

What Are the Clinical Implications?

- Despite no significant differences in patient-perceived cardiovascular disease risk, beliefs on cholesterol lowering, or perceived effectiveness and safety of statin therapy, patients with cerebrovascular disease were significantly less likely to receive higher intensity statin or achieve low-density lipoprotein cholesterol <100 mg/dL than those with coronary artery disease only.
- Greater efforts are needed to enhance clinician adoption and adherence to guidelines for patients with cerebrovascular disease.

before and after adjusting for differences in patient characteristics, perceptions, and beliefs.

Methods

The authors declare that all supporting data are available within the article and its online supplementary files.

Study Design and Data Sources

Details of the design and conduct of the PALM registry have been previously described.[11] A total of 7938 patients were enrolled from 140 cardiology, primary care, and endocrinology practices in the United States between May 2015 and November 2015. Patient sociodemographic characteristics, comorbidities, and current medications including statin use and dosage were abstracted from the medical record by study coordinators at each site. Core laboratory lipid panels were performed by LabCorp (Burlington, NC). PALM captured detailed information about patients' prior experiences with lipid-lowering therapy. The survey also assessed patients' income and education, perceived risk of cardiovascular disease, beliefs about cholesterol and lipid-lowering therapy, and self-reported intolerances to statins and prior statin adverse effects (overall survey response rate 95.3%). Patient numeracy was assessed using the Subjective Numeracy Scale, a validated self-reported instrument to quantify self-reported numeracy, to indicate how well patients can understand concepts such as cardiovascular risk and risk reduction.[12,13] All patients provided written informed consent before participation. The Duke Institutional Review Board provided approval for coordinating center activities, and individual sites obtained approval from their local institutional review board or from the central institutional review board for the study before enrolling patients in the PALM registry.

Study Population and Variables of Interest

The current analyses included 3232 patients with CeVD only, CAD&CeVD, or CAD only from 133 sites in the PALM registry. CeVD was defined as a medical history of prior stroke, transient ischemic attack, or carotid artery stenosis with or without revascularization. CAD was defined as a medical history of coronary artery disease, prior myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention. The primary outcomes were statin use and dosage, use of guideline-recommended statin intensity, and LDL-C levels <100 mg/dL.[1] Statin intensity was assessed based on whether the patient was on at least the guideline-recommended statin dose according to the 2013 American Heart Association/American College of Cardiology Guideline, which was the guideline in place at the time of the survey. If patients were recommended for high-intensity statin and were on high-intensity statin, or recommended for moderate-intensity statin and were on either a moderate- or high-intensity statin, they were considered to be on guideline-recommended statin dose. High-intensity statin use was defined as atorvastatin ≥40 mg or rosuvastatin ≥20 mg daily; and moderate-intensity statin use was defined as 10 mg ≤atorvastatin <40 mg, 5 mg ≤rosuvastatin <20 mg, simvastatin ≥20 mg, pravastatin ≥40 mg, lovastatin ≥40 mg, fluvastatin ≥80 mg, or pitavastatin ≥2 mg daily.

Statistical Analysis

Medians (25th–75th percentile [p25–p75]) and frequencies (percentages) were used to describe the distribution of continuous and categorical variables, respectively. Baseline characteristics, patient perceptions of cardiovascular risk, beliefs about statins, and patient-reported statin-associated symptoms were compared across 3 groups (CeVD only, CAD&CeVD, and CAD only) using Pearson χ^2 test or Fisher exact test for categorical variables and Kruskal-Wallis test for continuous variables.

Multivariable logistic regression models were performed to investigate the association between underlying ASCVD (CeVD only, CAD&CeVD, or CAD only) and outcomes (statin use, guideline-recommended statin therapy, and LDL-C <100 mg/dL). Adjusted odds ratio (aOR) and 95% CI were

Table 1. Characteristics of Patients

	CeVD Only n=403	CAD&CeVD n=627	CAD Only n=2202	*P* Value
Age, median (p25 to p75), y	70 (63–76)	72 (66–78)	70 (63–77)	<0.001
Range	32 to 97	39 to 94	25 to 99	
Women, %	222 (55.1)	213 (34.0)	735 (33.4)	<0.001
Race, %				
White	331 (82.1)	552 (88.0)	1940 (88.1)	<0.001
Black	58 (14.4)	63 (10.1)	213 (9.7)	
Asian	12 (3.0)	11 (1.8)	46 (2.1)	
Other	2 (0.5)	1 (0.2)	3 (0.1)	
Ethnicity/Hispanic, %	41 (10.2)	39 (6.2)	140 (6.4)	0.02
Insurance, %				
Private	212 (52.6)	349 (55.7)	1264 (57.5)	0.14
Government	187 (46.4)	274 (43.7)	902 (41.1)	
Other	4 (1.0)	4 (0.6)	31 (1.4)	
Education, %				
Middle school	30 (7.9)	44 (7.4)	149 (7.2)	0.69
High school	112 (29.4)	184 (31.1)	588 (28.4)	
Some college	100 (26.3)	174 (29.4)	573 (27.6)	
College graduate	84 (22.1)	119 (20.1)	483 (23.3)	
Postgraduate degree	55 (14.4)	71 (12.0)	281 (13.6)	
Income, %				
<$35 000	101 (27.6)	144 (24.6)	480 (23.5)	0.004
$35 000 to $74 999	78 (21.3)	128 (21.8)	419 (20.5)	
$75 000 to $99 999	17 (4.6)	41 (7.0)	157 (7.7)	
$100 000	33 (9.0)	54 (9.2)	292 (14.3)	
Do not know or refused	137 (37.4)	219 (37.4)	695 (34.0)	
Numeracy score, median (p25 to p75)	16 (11–20)	16 (12–21)	16 (12–21)	0.19
Body mass index ≥30 kg/m^2, %	169 (42.4)	282 (45.2)	1051 (47.9)	0.09
Medical history, %				
Prior myocardial infarction	0	209 (33.3)	799 (36.3)	. . .
Prior coronary artery bypass graft	0	206 (32.9)	592 (26.9)	. . .
Prior percutaneous coronary intervention	0	307 (49.0)	1107 (50.3)	. . .
Prior stroke	158 (39.2)	183 (29.2)	0	. . .
Prior transient ischemic attack	106 (26.3)	145 (23.1)	0	. . .
Carotid stenosis	199 (49.4)	426 (67.9)	0	. . .
Peripheral artery disease	47 (11.7)	152 (24.2)	189 (8.6)	<0.001
Hypertension	323 (80.2)	561 (89.5)	1869 (84.9)	<0.001
Diabetes mellitus	154 (38.2)	277 (44.2)	857 (38.9)	0.05
Chronic kidney disease	59 (14.6)	107 (17.1)	251 (11.4)	<0.001
Dialysis	5 (1.2)	6 (1.0)	16 (0.7)	0.54
Elevated liver function	16 (4.0)	23 (3.7)	75 (3.4)	0.83
Myopathy	15 (3.7)	43 (6.9)	131 (6.0)	0.10

Continued

Table 1. Continued

	CeVD Only n=403	CAD&CeVD n=627	CAD Only n=2202	*P* Value
Tobacco use				
Current	48 (11.9)	76 (12.1)	234 (10.6)	0.002
Quit within past year	3 (0.8)	7 (1.1)	45 (2.0)	
Quit >1 y ago	157 (39.1)	311 (49.6)	961 (43.6)	
Never	194 (48.3)	233 (37.2)	962 (43.7)	
Site characteristics, %				
Rural	41 (10.2)	43 (6.9)	213 (9.7)	0.08
Provider type				
Cardiologist	212 (52.6)	441 (70.3)	1518 (68.9)	<0.001
Primary care/family medicine	163 (40.5)	167 (26.6)	612 (27.8)	
Endocrinology	16 (4.0)	6 (1.0)	27 (1.2)	
Other	12 (3.0)	13 (2.1)	45 (2.0)	

CAD indicates coronary artery disease; CeVD, cerebrovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

presented with CAD only as the reference group for comparison. Generalized estimating equations with a compound symmetry working correlation matrix and empirical (sandwich) standard error estimates were used to account for clustering of patients within sites. The statin therapy model adjusted for clinically relevant variables possibly associated with statin therapy or used in previous PALM studies.[4,14,15]

Covariates included age, sex, race, ethnicity, insurance, education, annual household income, numeracy score, medical history of peripheral artery disease, hypertension, diabetes mellitus, chronic kidney disease/dialysis, elevated liver function, history of myopathy, tobacco use, patient's perceptions of heart attack or stroke, beliefs about high cholesterol, beliefs about statin safety and effectiveness, patient-reported trust in clinician in Likert scales, clinic location, and provider type. Missing data for most of the covariates were rare (<1%), except for the patient survey questions (4.4%–14.5%). Multiple imputation was used and the results from the multivariable models were combined across 20 imputed data sets. Similar covariates were included in the LDL-C model, except for patient's perceptions, beliefs, trust in clinician because these variables are not expected to affect LDL-C levels directly except through statin treatment. In addition to the overall population, subgroup analyses were performed by age (≤75 and >75 years) for all outcomes and by LDL-C levels (<100 and ≥100 mg/dL) for statin therapy, by fitting separate models for each subgroup.

All statistical analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc, Cary NC). All *P* values are 2-sided, with $P<0.05$ considered statistically significant.

Results

Baseline characteristics of the study population are shown in Table 1. Of 3232 secondary prevention patients evaluated in PALM, 403 had CeVD only, 627 CAD&CeVD, and 2202 CAD only. The median ages were 70, 72, and 70 years for the 3 cohorts, respectively ($P<0.001$). More than half of patients with CeVD only were women, whereas only one third were women in the CAD&CeVD or CAD only groups. Patients with CeVD also had lower incomes and a higher proportion of race/ethnicity minorities. Besides their underlying conditions, 11.7% of patients with CeVD had peripheral artery disease, 80.2% hypertension, 38.2% diabetes mellitus, and 14.6% chronic kidney disease. There were no significant differences in insurance, education, numeracy score, medical history of elevated liver function, or myopathy across the 3 groups.

Patient Perceptions of Cardiovascular Risk, Beliefs on Statin Drugs, and Reported Symptoms

Despite differences in their underlying conditions, there were no significant differences in patients' perceptions of cardiovascular disease risk, beliefs about cholesterol, the effectiveness and safety of statin therapy, and trust in physicians' decision about their medical care, although patients with CeVD were less likely to believe statins can cause muscle aches or pain (Table 2). Among those who were currently or previously taking statin therapy, patients with CeVD were less likely to report hives/itching. In addition, nausea, vomiting, stomach upset, or constipation were less likely to be reported by CeVD patients among those previously taking statins.

Table 2. Patient Perceptions of Cardiovascular Risks, Beliefs on Statin Drugs, and Reported Symptoms

	CeVD Only n=383	CAD&CeVD n=601	CAD Only n=2106	*P* Value
Patient perceptions, %				
How often do think or worry that may have a heart attack or stroke?				
Often	54 (14.1)	59 (9.8)	246 (11.7)	0.45
Occasionally	104 (27.2)	158 (26.3)	574 (27.3)	
Rarely	106 (27.7)	164 (27.3)	591 (28.1)	
Never	97 (25.3)	179 (29.8)	576 (27.4)	
Missing	22 (5.7)	41 (6.8)	119 (5.7)	
Patient beliefs, %				
People with high cholesterol are more likely to have a heart attack or stroke than people with low cholesterol				
Strongly agree	82 (21.4)	108 (18.0)	456 (21.7)	0.34
Agree	205 (53.5)	341 (56.7)	1118 (53.1)	
Neither agree nor disagree	16 (4.2)	25 (4.2)	116 (5.5)	
Disagree	14 (3.7)	24 (4.0)	81 (3.9)	
Strongly disagree	20 (5.2)	18 (3.0)	72 (3.4)	
Do not know/not sure	24 (6.3)	47 (7.8)	147 (7.0)	
Missing	22 (5.7)	38 (6.3)	116 (5.5)	
Statins are effective in reducing the risk of heart disease and stroke				
Strongly agree	50 (13.1)	93 (15.5)	308 (14.6)	0.15
Agree	193 (50.4)	323 (53.7)	1149 (54.6)	
Neither agree nor disagree	27 (7.1)	47 (7.8)	190 (9.0)	
Disagree	9 (2.4)	8 (1.3)	35 (1.7)	
Strongly disagree	7 (1.8)	9 (1.5)	32 (1.5)	
Do not know/not sure	62 (16.2)	70 (11.7)	223 (10.6)	
Missing	35 (9.1)	51 (8.5)	169 (8.0)	
Stains are safe medications				
Strongly agree	25 (6.5)	39 (6.5)	137 (6.5)	0.09
Agree	149 (38.9)	247 (41.1)	932 (44.3)	
Neither agree nor disagree	67 (17.5)	96 (16.0)	357 (17.0)	
Disagree	18 (4.7)	32 (5.3)	133 (6.3)	
Strongly disagree	8 (2.1)	15 (2.5)	25 (1.2)	
Do not know/not sure	76 (19.8)	107 (17.8)	319 (15.2)	
Missing	40 (10.4)	65 (10.8)	203 (9.6)	
I think statins can cause diabetes mellitus				
Strongly agree	3 (0.8)	7 (1.2)	11 (0.5)	0.23
Agree	20 (5.2)	40 (6.7)	134 (6.4)	
Neither agree nor disagree	47 (12.3)	59 (9.8)	276 (13.1)	
Disagree	70 (18.3)	108 (18.0)	390 (18.5)	
Strongly disagree	36 (9.4)	37 (6.2)	137 (6.5)	
Do not know/not sure	166 (43.3)	280 (46.6)	942 (44.7)	
Missing	41 (10.7)	70 (11.7)	216 (10.3)	
I think statins can cause muscle aches or pain				
Strongly agree	42 (11.0)	84 (14.0)	229 (10.9)	0.04

Continued

Table 2. Continued

	CeVD Only n=383	CAD&CeVD n=601	CAD Only n=2106	*P* Value
Agree	96 (25.1)	146 (24.3)	662 (31.4)	
Neither agree nor disagree	41 (10.7)	64 (10.7)	219 (10.4)	
Disagree	47 (12.3)	62 (10.3)	190 (9.0)	
Strongly disagree	9 (2.4)	14 (2.3)	49 (2.3)	
Do not know/not sure	108 (28.2)	166 (27.6)	556 (26.4)	
Missing	40 (10.4)	65 (10.8)	201 (9.5)	
I think statins can cause liver damage				
Strongly agree	22 (5.7)	27 (4.5)	85 (4.0)	0.41
Agree	89 (23.2)	133 (22.1)	547 (26.0)	
Neither agree nor disagree	54 (14.1)	85 (14.1)	284 (13.5)	
Disagree	33 (8.6)	39 (6.5)	144 (6.8)	
Strongly disagree	4 (1.0)	10 (1.7)	21 (1.0)	
Do not know/not sure	138 (36.0)	242 (40.3)	812 (38.6)	
Missing	43 (11.2)	65 (10.8)	213 (10.1)	
I think statins can cause memory loss				
Strongly agree	4 (1.0)	11 (1.8)	41 (2.0)	0.56
Agree	39 (10.2)	74 (12.3)	230 (10.9)	
Neither agree nor disagree	58 (15.1)	77 (12.8)	324 (15.4)	
Disagree	61 (15.9)	79 (13.1)	277 (13.2)	
Strongly disagree	17 (4.4)	19 (3.2)	75 (3.6)	
Do not know/not sure	160 (41.8)	277 (46.1)	947 (45.0)	
Missing	44 (11.5)	64 (10.7)	212 (10.1)	
How much would you say you trust your doctors' decision about your medical care				
Completely trust	241 (62.9)	396 (65.9)	1412 (67.1)	0.53
Generally trust	111 (29.0)	165 (27.5)	556 (26.4)	
Neither trust nor distrust	5 (1.3)	6 (1.0)	24 (1.1)	
Generally distrust	8 (2.1)	4 (0.7)	22 (1.0)	
Completely distrust	15 (3.9)	23 (3.8)	69 (3.3)	
Missing	3 (0.8)	7 (1.2)	23 (1.1)	
Report symptoms, %				
If currently taking a statin	N=292	N=489	N=1774	
Muscle aches, cramps	85 (29.1)	159 (32.5)	545 (30.7)	0.72
Missing	20 (6.9)	24 (4.9)	123 (6.9)	
Memory loss, forgetfulness, or confusion	34 (11.6)	68 (13.9)	188 (10.6)	0.16
Missing	21 (7.2)	24 (4.9)	123 (6.9)	
Weakness	43 (14.7)	68 (13.9)	197 (11.1)	0.10
Missing	21 (7.2)	24 (4.9)	125 (7.1)	
Nausea, vomiting, stomach upset	18 (6.2)	22 (4.5)	74 (4.2)	0.30
Missing	21 (7.2)	24 (4.9)	125 (7.1)	
Constipation	28 (9.6)	54 (11.0)	144 (8.1)	0.15
Missing	21 (7.2)	24 (4.9)	125 (7.1)	
Fatigue	46 (15.8)	90 (18.4)	277 (15.6)	0.43

Continued

Table 2. Continued

	CeVD Only n=383	CAD&CeVD n=601	CAD Only n=2106	*P* Value
Missing	21 (7.2)	24 (4.9)	124 (7.0)	
Hives and/or itching	4 (1.4)	26 (5.3)	53 (3.0)	0.008
Missing	21 (7.2)	24 (4.9)	125 (7.1)	
Other	0	4 (0.8)	19 (1.1)	0.01
Missing	21 (7.2)	24 (4.9)	125 (7.1)	
If previously taking a statin	N=26	N=59	N=152	
Muscle aches, cramps	12 (46.2)	36 (61.0)	81 (53.3)	0.51
Missing	2 (7.7)	2 (3.4)	9 (5.9)	
Memory loss, forgetfulness, or confusion	2 (7.7)	8 (13.6)	12 (7.9)	0.47
Missing	2 (7.7)	2 (3.4)	9 (5.9)	
Weakness	2 (7.7)	16 (27.1)	41 (27.0)	0.11
Missing	2 (7.7)	2 (3.4)	9 (5.9)	
Nausea, vomiting, stomach upset	0	5 (8.5)	9 (5.9)	0.04
Missing	2 (7.7)	2 (3.4)	9 (5.9)	
Constipation	1 (3.9)	7 (11.9)	11 (7.2)	0.03
Missing	2 (7.7)	2 (3.4)	9 (5.9)	
Fatigue	2 (7.7)	16 (27.1)	40 (26.3)	0.12
Missing	2 (7.7)	2 (3.4)	9 (5.9)	
Hives and/or itching	1 (3.9)	6 (10.2)	8 (5.3)	0.04
Missing	2 (7.7)	2 (3.4)	9 (5.9)	
Other	0	0	5 (3.5)	0.10
Missing	2 (7.7)	2 (3.4)	9 (5.9)	

Meanwhile, there were no statistically significant differences in reported symptoms such as muscle aches, memory loss, weakness, or fatigue across 3 cohorts. The reported symptoms were similar across 3 cohorts in the subgroup analyses by guideline-recommended statin therapy and LDL-C levels (Table S1).

Statin Use and LDL-C Levels

Overall, 84.3% of patients received statin therapy and 48.3% were on guideline-recommended statin intensity. Fewer patients with CeVD only were received statin therapy (76.2% versus 82.6% versus 86.2%, $P<0.001$) or treated at the guideline-recommended intensity (34.6%, versus 49.8% versus 50.4%, $P<0.001$) than individuals with CAD&CeVD or those with CAD only. Only 6.8% of patients with CeVD had previously taken a statin and then discontinued it as compared with 9.8% of those with CAD&CeVD or 7.2% of those with CAD only. In contrast, more patients with CeVD had never taken a statin at all (17.0% versus 8.8% versus 8.6%, $P<0.001$). After risk adjustment, patients with CeVD only were less likely to be treated with any statin (aOR 0.64, 95% CI 0.45–0.91) or at the guideline-recommended intensity (aOR 0.60, 95% CI 0.45–0.81) compared with CAD only patients. Similar trends of lower statin use and statin intensity were observed in subgroup analyses by age and LDL-C levels, although the differences were not statistically significant in older patients and those with LDL≥100 mg/dL (Figures 1 and 2). Meanwhile, there were no statistically significant differences in any statin use and statin intensity between patients with CAD&CeVD versus CAD only.

The median (p25–p75) LDL-C levels were 90 (73–114), 88 (69–111), and 83 (66–107) mg/dL for patients with CeVD only, CAD&CeVD, or CAD only, respectively ($P<0.001$). In addition, 59.2% of patients with CeVD only had LDL-C levels <100 mg/dL (Figure 3). In contrast, 63.7% of patients with CAD&CeVD and 69.7% with CAD only had LDL-C <100 mg/dL. After risk adjustment, patients with CeVD only (aOR 0.79, 95% CI 0.64–0.99) or CAD&CeVD (aOR 0.73, 95% CI 0.61–0.87) were less likely to have an LDL-C <100 mg/dL as compared with CAD only patients. Similar results were seen in the subgroup analysis by age ≤75 or >75 years, although the difference was not statistically significant in patients aged >75 years.

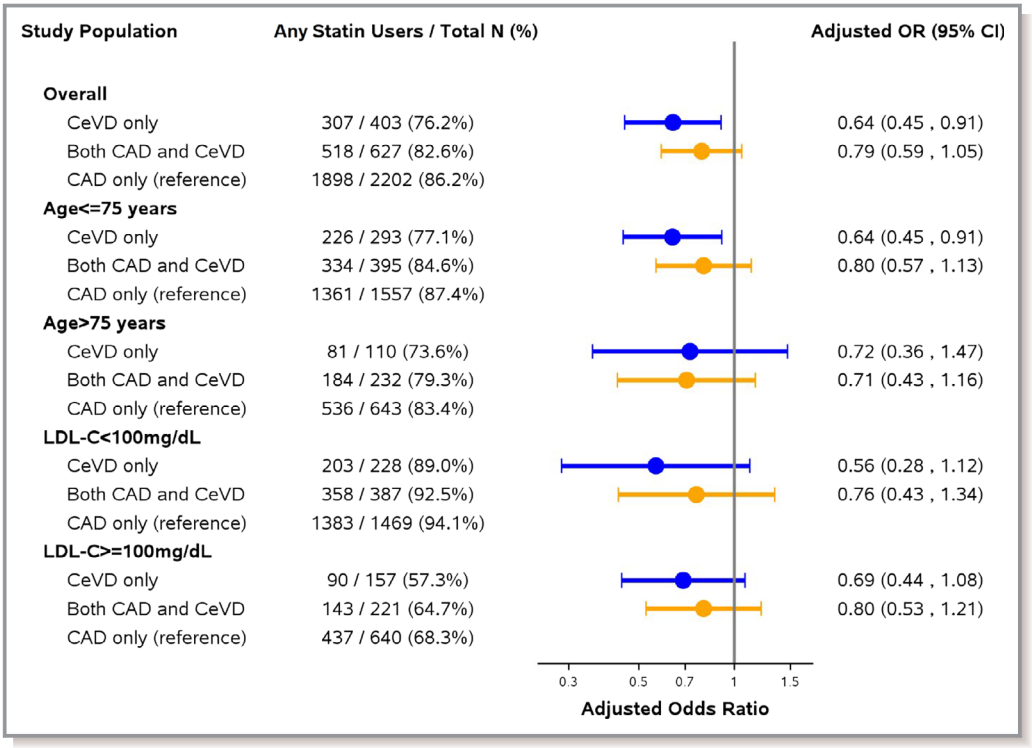

Figure 1. Any statin use by underlining atherosclerotic cardiovascular disease. Adjust for age, sex, race, ethnicity, insurance, education, annual household income, numeracy score, medical history of peripheral artery disease, hypertension, diabetes mellitus, chronic kidney disease/dialysis, elevated liver function, myopathy, tobacco use status, patient's perceptions of heart attack or stroke, beliefs about high cholesterol, beliefs about statin safety and effectiveness, trust in clinician, clinic location (rural/urban), provider type, and clinic-level clustering effect. CAD indicates coronary artery disease; CeVD, cerebrovascular disease; LDL-C, low density lipoprotein cholesterol; OR, odds ratio.

Discussion

Statins are the mainstay of secondary prevention for both CAD and CeVD patient populations.[1–3] Our study of real-world clinical practice found significant gaps in the usage and dosing of statins in patients with different types of ASCVD. Treatment patterns were less optimal for patients with CeVD only versus CAD only. Nearly 25% of individuals with CeVD only who met the guideline indication for secondary prevention failed to receive any statin therapy. Even among those taking statins, under-dosing was common. Only one third of patients with CeVD only were on the statin intensity recommended by the guidelines. Except for less concerns about muscle symptoms or reported symptoms from statin use in individuals with CeVD only, no significant differences were observed in patient perceptions and beliefs about cholesterol lowering. Collectively, these findings suggest room for improvement in clinical management of lipids in patients with CeVD.

The reasons for statin underuse are complex.[16–28] Although some cite statin intolerance and concerns of adverse effects as potential causes,[7] we found similar patient beliefs in safety of statins among those with CAD and/or CeVD. Importantly, more patients with CeVD only never took a statin and or had discontinued statin therapy than those with CAD only. Among those currently or previously taking a statin, similar rates of symptoms were reported in patients with CeVD only, CAD only, or both, including muscle pain, cognitive decline, weakness, nausea, vomiting, or constipation. While uncommon, patients with CeVD experienced less hives or itching. Similar results were found in the analyses by statin intensity and LDL-C level.

Patients with CeVD only reported similarly high perceived risk of ASCVD, and shared similar beliefs in the role of high cholesterol on heart attack or stroke, as well as the effectiveness and safety of statin therapy as those with CAD only. There were no differences in perceived long-term side effects such as developing diabetes mellitus, causing liver damage, and cognitive decline. Additionally, >92% of patients trust their physicians. While previous studies suggested that lower-income individuals and minorities are less likely to receive statins and more likely to discontinue statins, the differences in statin use between CeVD and CAD persisted after risk

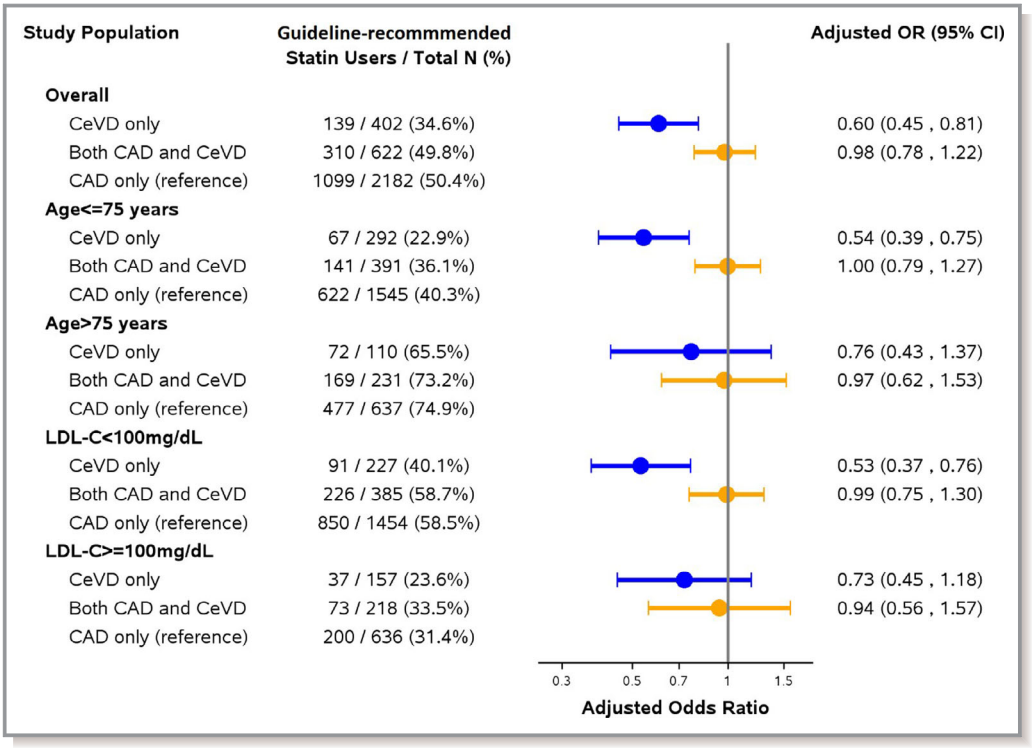

Figure 2. Guideline-recommended statin therapy by underlining atherosclerotic cardiovascular disease. Guideline-recommended statin therapy is defined as patient who meets the recommendation for high-intensity statin therapy is on high-intensity statin or patient who meets the recommendation for moderate-intensity statin is on either high- or moderate-intensity statin. High intensity: atorvastatin ≥40 mg or rosuvastatin ≥20 mg. Moderate intensity: 10≤atorvastatin<40 mg, 5≤rosuvastatin<20, simvastatin≥20 mg, pravastatin ≥40 mg, lovastatin ≥40 mg, fluvastatin ≥80 mg, or pitavastatin ≥2 mg. Adjust for age, sex, race, ethnicity, insurance, education, annual household income, numeracy score, medical history of peripheral artery disease, hypertension, diabetes mellitus, chronic kidney disease/dialysis, elevated liver function, myopathy, tobacco use status, patient's perceptions of heart attack or stroke, beliefs about high cholesterol, beliefs about statin safety and effectiveness, trust in clinician, clinic location (rural/urban), provider type, and clinic-level clustering effect. CAD indicates coronary artery disease; CeVD, cerebrovascular disease; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio.

adjustment.[5,29] Therefore, the decision for not prescribing statin therapy is unlikely to be attributable to patient characteristics and concerns alone.

Similar to the 2013 and 2018 American College of Cardiology/American Heart Association cholesterol guidelines, the stroke prevention guidelines in patients with stroke or transient ischemic attack also recommend statin therapy with intensive lipid-lowering effects to reduce the risk of recurrent stroke and cardiovascular events.[1–3] As of today, the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) study remains the only clinical trial examining high-intensity statin for secondary prevention in patients with stroke or transient ischemic attack.[16] Atorvastatin 80 mg reduced stroke by 16% and major cardiovascular events by 20% as compared with placebo. Yet, high-intensity statin was associated with a small but significant increase in the incidence of hemorrhagic stroke (hazard ratio 1.68, 95% CI 1.09–2.59), which was associated with a baseline history of hemorrhagic stroke or poorly controlled hypertension, but no differences in the incidence of fatal hemorrhagic stroke between the groups.[22] Meta-analyses of clinical trials data including the SPARCL found a slight increase in intracerebral hemorrhage, which was outweighed 50-fold by the number of stroke major vascular events prevented.[30] While we were unable to determine the reasons behind treatment decisions, providers' preferences and concern over hemorrhage risk, whether unfounded or not, may have contributed to the statin underutilization or under-dosing in patients with CeVD. It may also be that cardiologists are involved in the care of many CAD patients, whereas neurologists or surgeons may be the primary specialists caring for CeVD. The risk aversion of hemorrhagic stroke may also explain the treatment-risk paradox in patients with CAD&CeVD, who were less likely to receive statin and achieve LDL-C <100 mg/dL despite their higher risk profiles. Further

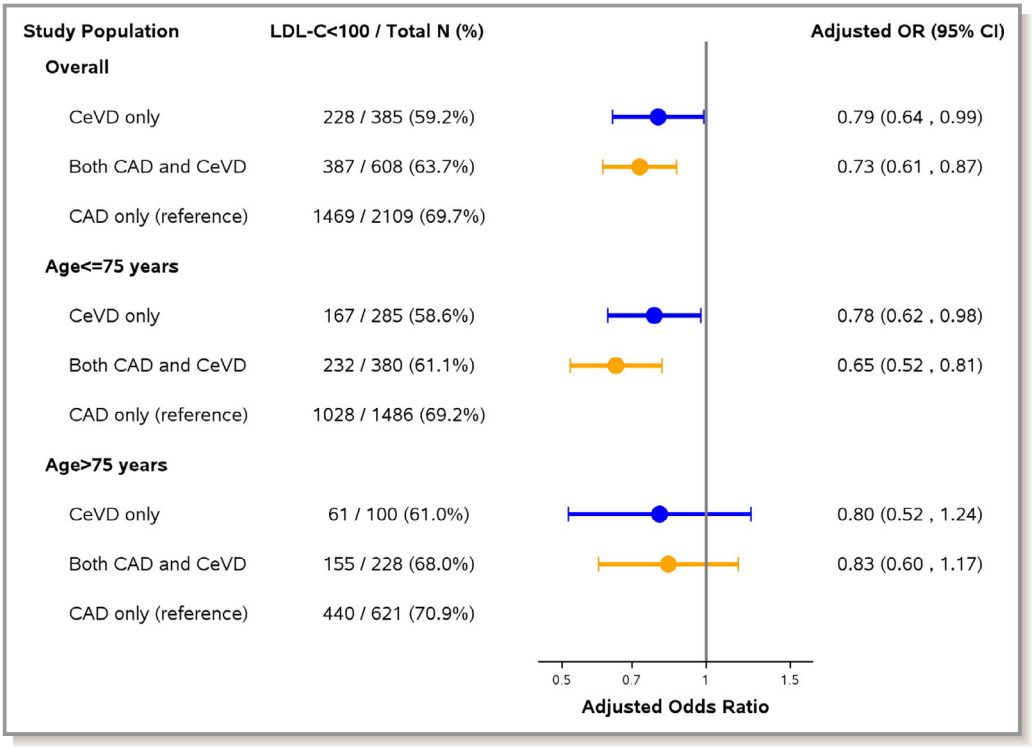

Figure 3. LDL-C <100 mg/dL by underlining atherosclerotic cardiovascular disease. Adjust for age, sex, race, ethnicity, insurance, education, annual household income, medical history of peripheral artery disease, hypertension, diabetes mellitus, chronic kidney disease/dialysis, elevated liver function, myopathy, tobacco use status, clinic location (rural/urban), provider type, and clinic-level clustering effect. CAD indicates coronary artery disease; CeVD, cerebrovascular disease; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio.

research is needed to evaluate provider preferences and beliefs and how these factors may have influenced treatment decision making.

This study has several limitations. First, while we used an objective measure of statin use abstracted from the medical record, we did not have access to data on documented reasons for not prescribing statins. Second, we were unable to determine the type and timing of the prior stroke event. Although there are no firm recommendations on the use of statins in intracerebral hemorrhage, a medical history of hemorrhagic stroke may have influenced some clinicians. Some strokes may not have an atherosclerotic origin. However, all stroke patients should be considered for cholesterol lowering therapy unless contraindicated. A related issue is the inclusion of carotid stenosis in CeVD, where the degree of stenosis and cannot be determined in the registry. Third, the PALM registry is targeted at outpatient practice with primary care, cardiology, and endocrinology providers. Therefore, the practice patterns may be different for patients seen by neurologists, especially for those with CeVD only or CAD&CeVD. Our results therefore cannot be extrapolated to patients treated by neurologists or vascular neurologists. In addition, individuals with CeVD are in general older than those with CAD in community practice, yet the age differences are relatively small in our cohort, possibly reflecting patient section in the registry. Finally, the PALM is a voluntary outpatient registry. Participating providers may have been more likely to focus on lipid management. While these study results might not be extrapolated to non-participating providers, it could be argued that statin therapy could be even worse in community clinics, thus further highlighting the challenge in implementation of evidence-based statin therapy in real-world practice.

Conclusion

In conclusion, patients with CeVD only were less likely to receive statin therapy at the guideline-recommended dose, or to achieve LDL-C <100 mg/dL than patients with CAD only despite similar patient-perceived risk of future ASCVD events, beliefs in the safety, and reported side effects of statins. Future efforts are needed to promote optimal use of statin therapy in patients with cerebrovascular disease and stroke.

Sources of Funding

This study was supported by Sanofi Pharmaceuticals and Regeneron Pharmaceuticals.

Disclosures

Dr Navar receives research grants from Amgen, Sanofi, Regeneron, Janssen, Amarin and NHLBI (K01HL133416), and acts as a consultant and advisory board member for Amgen, Amarin, Sanofi, Regeneron, Astra Zeneca, and Novo Nordisk. Dr Robinson receives research grants to Institution from Acasti, Amarin, Amgen, Astra-Zeneca, Esai, Esperion, Merck, Regeneron, Sanofi, Takeda and acts as a consultant for Amgen, Medicines Company, Merck, Novartis, Novo-Nordisk, Pfizer, Regeneron, Sanofi. Dr Virani receives research grants from the American Heart Association, American Diabetes Association, and Veterans Affairs; honoraria from American College of Cardiology and National Lipid Association. Dr Goldberg receives research grants to institution: Amarin, Amgen, IONIS, Pfizer, Regeneron, Sanofi. Consultant: Sanofi/Regeneron, AKCEA, Novartis, Esperion, 23andMe. Editorial: Merck Manual. Dr Koren is an employee of Sanofi. Dr Louie is an employee of Regeneron Pharmaceuticals Inc. Dr Peterson receives research grants from Amgen, Sanofi, AstraZeneca, and Merck and fees as a consultant and advisory board member to Amgen, AstraZeneca, Merck, and Sanofi Aventis. Dr Wang receives research grants from Amgen, AstraZeneca, Bristol Myers Squibb, Cryolife, Novartis, Pfizer, Portola, and Regeneron Pharmaceuticals and honoraria from Gilead, and Grifols. The remaining authors have no disclosures to report.

References

1. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr. Tomaselli GF and American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *Circulation*. 2014;129:S1–S45.
2. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr, Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary. *Circulation*. 2019;139:e1046–e1081.
3. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:2160–2236.
4. Navar AM, Wang TY, Li S, Robinson JG, Goldberg AC, Virani S, Roger VL, Wilson PWF, Elassal J, Lee LV, Peterson ED. Lipid management in contemporary community practice: results from the provider assessment of lipid management (PALM) registry. *Am Heart J*. 2017;193:84–92.
5. Nanna MG, Navar AM, Zakroysky P, Xiang Q, Goldberg AC, Robinson J, Roger VL, Virani SS, Wilson PWF, Elassal J, Lee LV, Wang TY, Peterson ED. Association of patient perceptions of cardiovascular risk and beliefs on statin drugs with racial differences in statin use: insights from the patient and provider assessment of lipid management registry. *JAMA Cardiol*. 2018;3:739–748.
6. Hulley SB, Grady D, Browner WS. Statins: underused by those who would benefit. *BMJ*. 2000;321:971–972.
7. Hirsh BJ, Smilowitz NR, Rosenson RS, Fuster V, Sperling LS. Utilization of and adherence to guideline-recommended lipid-lowering therapy after acute coronary syndrome. *J Am Coll Cardiol*. 2015;66:184.
8. Arnold SV, Spertus JA, Masoudi FA, Daugherty SL, Maddox TM, Li Y, Dodson JA, Chan PS. Beyond medication prescription as performance measures. *J Am Coll Cardiol*. 2013;62:1791.
9. McBride CL, Akeroyd JM, Ramsey DJ, Nambi V, Nasir K, Michos ED, Bush RL, Jneid H, Morris PB, Bittner VA, Ballantyne CM, Petersen LA, Virani SS. Statin prescription rates and their facility-level variation in patients with peripheral artery disease and ischemic cerebrovascular disease: insights from the department of veterans affairs. *Vasc Med*. 2018;23:232–240.
10. Hira RS, Cowart JB, Akeroyd JM, Ramsey DJ, Pokharel Y, Nambi V, Jneid H, Deswal A, Denktas A, Taylor A, Nasir K, Ballantyne CM, Petersen LA, Virani SS. Risk factor optimization and guideline-directed medical therapy in us veterans with peripheral arterial and ischemic cerebrovascular disease compared to veterans with coronary heart disease. *Am J Cardiol*. 2016;118:1144–1149.
11. Navar AM, Wang TY, Goldberg AC, Robinson JG, Roger VL, Wilson PF, Virani SS, Elassal J, Lee LV, Webb LE, Peterson ED. Design and rationale for the patient and provider assessment of lipid management (PALM) registry. *Am Heart J*. 2015;170:865–871.
12. Fagerlin A, Zikmund-Fisher BJ, Ubel PA, Jankovic A, Derry HA, Smith DM. Measuring numeracy without a math test: development of the subjective numeracy scale. *Med Decis Making*. 2007;27:672–680.
13. Zikmund-Fisher BJ, Smith DM, Ubel PA, Fagerlin A. Validation of the subjective numeracy scale: effects of low numeracy on comprehension of risk communications and utility elicitations. *Med Decis Making*. 2007;27:663–671.
14. Nanna MG, Navar AM, Wang TY, Mi X, Virani SS, Louie MJ, Lee LV, Goldberg AC, Roger VL, Robinson J, Peterson ED. Statin use and adverse effects among adults >75 years of age: insights from the patient and provider assessment of lipid management (PALM) registry. *J Am Heart Assoc*. 2018;7:e008546. DOI: 10.1161/JAHA.118.008546.
15. Navar AM, Peterson ED, Li S, Robinson JG, Roger VL, Goldberg AC, Virani S, Wilson PWF, Nanna MG, Lee LV, Elassal J, Wang TY. Prevalence and management of symptoms associated with statin therapy in community practice. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004249.
16. Amarenco P, Bogousslavsky J, Callahan A III, Goldstein LB, Hennerici M, Rudolph AE, Sillesen H, Simunovic L, Szarek M, Welch KM, Zivin JA; Stroke Prevention by Aggressive Reduction in Cholesterol Levels I. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355:549–559.
17. Hackam DG, Woodward M, Newby LK, Bhatt DL, Shao M, Smith EE, Donner A, Mamdani M, Douketis JD, Arima H, Chalmers J, MacMahon S, Tirschwell DL, Psaty BM, Bushnell CD, Aguilar MI, Capampangan DJ, Werring DJ, De Rango P, Viswanathan A, Danchin N, Cheng CL, Yang YH, Verdel BM, Lai MS, Kennedy J, Uchiyama S, Yamaguchi T, Ikeda Y, Mrkobrada M. Statins and intracerebral hemorrhage: collaborative systematic review and meta-analysis. *Circulation*. 2011;124:2233–2242.
18. McKinney JS, Kostis WJ. Statin therapy and the risk of intracerebral hemorrhage: a meta-analysis of 31 randomized controlled trials. *Stroke*. 2012;43:2149–2156.
19. Heart Protection Study Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20 536 people with cerebrovascular disease or other high-risk conditions. *Lancet*. 2004;363:757–767.
20. Iso H, Jacobs DR, Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. *N Engl J Med*. 1989;320:904–910.
21. Leppala JM, Virtamo J, Fogelholm R, Albanes D, Heinonen OP. Different risk factors for different stroke subtypes: association of blood pressure, cholesterol, and antioxidants. *Stroke*. 1999;30:2535–2540.
22. Goldstein LB, Amarenco P, Szarek M, Callahan A III, Hennerici M, Sillesen H, Zivin JA, Welch KM. Hemorrhagic stroke in the stroke prevention by aggressive reduction in cholesterol levels study. *Neurology*. 2008;70:2364–2370.
23. Evans MA, Golomb BA. Statin-associated adverse cognitive effects: survey results from 171 patients. *Pharmacotherapy*. 2009;29:800–811.
24. Beydoun MA, Beason-Held LL, Kitner-Triolo MH, Beydoun HA, Ferrucci L, Resnick SM, Zonderman AB. Statins and serum cholesterol's associations with incident dementia and mild cognitive impairment. *J Epidemiol Community Health*. 2011;65:949–957.
25. Bettermann K, Arnold AM, Williamson J, Rapp S, Sink K, Toole JF, Carlson MC, Yasar S, DeKosky S, Burke GL. Statins, risk of dementia, and cognitive function: secondary analysis of the ginkgo evaluation of memory study. *J Stroke Cerebrovasc Dis*. 2012;21:436–444.
26. Muldoon MF, Ryan CM, Sereika SM, Flory JD, Manuck SB. Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults. *Am J Med*. 2004;117:823–829.

27. Trompet S, van Vliet P, de Craen AJ, Jolles J, Buckley BM, Murphy MB, Ford I, Macfarlane PW, Sattar N, Packard CJ, Stott DJ, Shepherd J, Bollen EL, Blauw GJ, Jukema JW, Westendorp RG. Pravastatin and cognitive function in the elderly. Results of the PROSPER study. *J Neurol*. 2010;257:85–90.

28. Richardson K, Schoen M, French B, Umscheid CA, Mitchell MD, Arnold SE, Heidenreich PA, Rader DJ, deGoma EM. Statins and cognitive function: a systematic review. *Ann Intern Med*. 2013;159:688–697.

29. Wei MY, Ito MK, Cohen JD, Brinton EA, Jacobson TA. Predictors of statin adherence, switching, and discontinuation in the usage survey: understanding the use of statins in America and gaps in patient education. *J Clin Lipidol*. 2013;7:472–483.

30. Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–1681.

SUPPLEMENTAL MATERIAL

Table S1. Reported symptoms across 3 cohorts in the subgroup analyses by guideline-recommended statin therapy and LDL-C levels.

	CeVD only	CAD&CeVD	CAD only	P value
On guideline-recommended statin therapy, %				
If currently taking a statin	N=127	N=278	N=997	
Muscle aches, cramps	34 (28.8)	86 (33.0)	267 (28.9)	0.44
Memory loss, forgetfulness, or confusion	10 (8.6)	38 (14.6)	97 (10.5)	0.12
Weakness	13 (11.1)	39 (14.9)	104 (11.3)	0.26
Nausea, vomiting, stomach upset	6 (5.1)	13 (5.0)	36 (3.9)	0.66
Constipation	12 (10.3)	35 (13.4)	82 (8.9)	0.10
Fatigue	15 (12.8)	49 (18.8)	147 (15.9)	0.32
Hives and/or itching	1 (0.9)	19 (7.3)	27 (2.9)	0.001
Other	0	3 (1.2)	12 (1.3)	0.06
If previously taking a statin	N=2	N=7	N=26	
Muscle aches, cramps	0	2 (33.3)	9 (39.1)	0.15
Memory loss, forgetfulness, or confusion	0	0	2 (8.7)	0.54
Weakness	0	1 (16.7)	6 (26.1)	0.23
Nausea, vomiting, stomach upset	0	1 (16.7)	2 (8.7)	0.34
Constipation	1 (50.0)	0	3 (13.0)	0.11
Fatigue	0	1 (16.7)	5 (21.7)	0.27
Hives and/or itching	0	0	0	-
Other	0	0	0	-
Not on any statin therapy or not on guideline-recommended statin therapy, %				
If currently taking a statin	N=164	N=207	N=759	
Muscle aches, cramps	51 (33.3)	71 (35.5)	271 (38.2)	0.48
Memory loss, forgetfulness, or confusion	24 (15.7)	29 (14.5)	89 (12.6)	0.52
Weakness	30 (19.6)	28 (14.0)	89 (12.5)	0.07
Nausea, vomiting, stomach upset	12 (7.8)	9 (4.5)	38 (5.4)	0.37
Constipation	16 (10.5)	18 (9.0)	61 (8.6)	0.77
Fatigue	30 (19.6)	40 (20.0)	128 (18.1)	0.78
Hives and/or itching	3 (2.0)	7 (3.5)	24 (3.4)	0.64
Other	0	1 (0.5)	7 (1.0)	0.09
If previously taking a statin	N=24	N=52	N=126	
Muscle aches, cramps	12 (54.6)	34 (66.7)	72 (60.0)	0.57
Memory loss, forgetfulness, or confusion	2 (9.1)	8 (15.7)	10 (8.3)	0.35
Weakness	2 (9.1)	15 (29.4)	35 (29.2)	0.14
Nausea, vomiting, stomach upset	0	4 (7.8)	7 (5.8)	0.06
Constipation	0	7 (13.7)	8 (6.7)	0.01

Fatigue	2 (9.1)	15 (29.4)	35 (29.2)	0.14
Hives and/or itching	1 (4.6)	6 (11.8)	8 (6.7)	0.04
Other	0	0	5 (4.2)	0.09
LDL-C <100mg/dL, %				
If currently taking a statin	N=195	N=339	N=1300	
Muscle aches, cramps	54 (29.7)	109 (34.0)	355 (29.7)	0.33
Memory loss, forgetfulness, or confusion	22 (12.1)	46 (14.3)	124 (10.4)	0.13
Weakness	28 (15.4)	46 (14.3)	133 (11.1)	0.11
Nausea, vomiting, stomach upset	10 (5.56)	17 (5.3)	53 (4.4)	0.71
Constipation	20 (11.0)	37 (11.5)	100 (8.4)	0.15
Fatigue	31 (17.0)	62 (19.3)	194 (16.2)	0.42
Hives and/or itching	2 (1.1)	19 (5.9)	36 (3.0)	0.08
Other	0	3 (0.9)	13 (1.1)	0.04
If previously taking a statin	N=5	N=10	N=34	
Muscle aches, cramps	1 (20.0)	2 (22.2)	14 (43.8)	0.05
Memory loss, forgetfulness, or confusion	0	0	5 (15.6)	0.15
Weakness	1 (20.0)	1 (11.1)	6 (18.8)	0.16
Nausea, vomiting, stomach upset	0	0	1 (3.1)	0.70
Constipation	1 (20.0)	1 (11.1)	2 (6.3)	0.14
Fatigue	1 (20.0)	0	7 (21.9)	0.06
Hives and/or itching	0	1 (11.1)	0	0.20
Other	0	0	2 (6.3)	0. 48
LDL-C ≥100mg/dL %				
If currently taking a statin	N=86	N=137	N=406	
Muscle aches, cramps	28 (35.4)	47 (35.6)	169 (43.3)	0.18
Memory loss, forgetfulness, or confusion	10 (12.8)	21 (15.9)	58 (14.9)	0.83
Weakness	13 (16.7)	22 (16.7)	54 (13.9)	0.65
Nausea, vomiting, stomach upset	8 (10.3)	5 (3.8)	18 (4.6)	0.09
Constipation	8 (10.3)	17 (12.9)	38 (9.7)	0.60
Fatigue	15 (19.2)	27 (20.5)	72 (18.5)	0.88
Hives and/or itching	2 (2.6)	7 (5.3)	16 (4.1)	0.63
Other	0	1 (0.8)	6 (1.5)	0.12
If previously taking a statin	N=20	N=47	N=110	
Muscle aches, cramps	11 (61.1)	32 (69.6)	65 (63.1)	0.71
Memory loss, forgetfulness, or confusion	2 (11.1)	8 (17.4)	7 (6.8)	0.01
Weakness	1 (5.6)	14 (30.4)	34 (33.0)	0.06
Nausea, vomiting, stomach upset	0	5 (10.9)	6 (5.8)	0.04
Constipation	0	5 (10.9)	9 (8.7)	0.04
Fatigue	1 (5.6)	15 (32.6)	32 (31.1)	0.07
Hives and/or itching	1 (5.6)	5 (10.9)	7 (6.8)	0.06
Other	0	0	2 (1.9)	0.38