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

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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.
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 either 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 χ² 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/m², % | 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        |

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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 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.

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

| Perception                                                                 | CeVD Only n=383 | CAD&CeVD n=601 | CAD Only n=2106 | P Value |
|----------------------------------------------------------------------------|-----------------|----------------|-----------------|---------|
| **Patient perceptions, %**                                                 |                 |                |                 |         |
| How often do you think or worry that you 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)       |         |
| Statins 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 | Agree | Neither agree nor disagree | Disagree | Strongly disagree | Do not know/not sure | Missing |
|---|---|---|---|---|---|---|---|
| Strongly agree | 22 (5.7) | 89 (23.2) | 54 (14.1) | 33 (8.6) | 4 (1.0) | 138 (36.0) | 43 (11.2) |
| Agree | 27 (4.5) | 133 (22.1) | 85 (14.1) | 39 (6.5) | 10 (1.7) | 242 (40.3) | 65 (10.8) |
| Neither agree nor disagree | 85 (4.0) | 547 (26.0) | 284 (13.5) | 144 (6.8) | 21 (1.0) | 812 (38.6) | 213 (10.1) |
| Disagree | 662 (31.4) | 190 (9.0) | 383 (21.2) | 190 (9.0) | 49 (2.3) | 556 (26.4) | 201 (9.5) |

I think statins can cause memory loss

| | Strongly agree | Agree | Neither agree nor disagree | Disagree | Strongly disagree | Do not know/not sure | Missing |
|---|---|---|---|---|---|---|---|
| Strongly agree | 4 (1.0) | 39 (10.2) | 58 (15.1) | 61 (15.9) | 17 (4.4) | 160 (41.8) | 44 (11.5) |
| Agree | 11 (1.8) | 74 (12.3) | 77 (12.8) | 79 (13.1) | 19 (3.2) | 277 (46.1) | 64 (10.7) |
| Neither agree nor disagree | 41 (2.0) | 230 (10.9) | 324 (15.4) | 277 (13.2) | 75 (3.6) | 947 (45.0) | 212 (10.1) |
| Disagree | 241 (62.9) | 396 (65.9) | 1412 (67.1) | 138 (37.1) | 70 (3.6) | 1612 (76.6) | 708 (33.6) |

How much would you say you trust your doctors’ decision about your medical care

| | Completely trust | Generally trust | Neither trust nor distrust | Generally distrust | Completely distrust | Missing |
|---|---|---|---|---|---|---|
| Completely trust | 241 (62.9) | 111 (29.0) | 5 (1.3) | 8 (2.1) | 15 (3.9) | 3 (0.8) |
| Generally trust | 396 (65.9) | 165 (27.5) | 6 (1.0) | 4 (0.7) | 23 (3.8) | 7 (1.2) |
| Neither trust nor distrust | 1412 (67.1) | 556 (26.4) | 24 (1.1) | 22 (1.0) | 69 (3.3) | 23 (1.1) |
| Generally distrust | 138 (37.1) | 70 (3.6) | 708 (33.6) | 1612 (76.6) |  |  |
| Completely distrust | 70 (3.6) | 22 (1.0) | 1612 (76.6) |  |  |  |
| Missing | 708 (33.6) | 23 (1.1) |  |  |  |  |

Report symptoms, %

| | If currently taking a statin N=292 | Not taking a statin N=1774 |
|---|---|---|
| Muscle aches, cramps | 85 (29.1) | 545 (30.7) |
| Missing | 20 (6.9) | 123 (6.9) |
| Memory loss, forgetfulness, or confusion | 34 (11.6) | 188 (10.6) |
| Missing | 21 (7.2) | 123 (6.9) |
| Weakness | 43 (14.7) | 197 (11.1) |
| Missing | 21 (7.2) | 125 (7.1) |
| Nausea, vomiting, stomach upset | 18 (6.2) | 74 (4.2) |
| Missing | 21 (7.2) | 125 (7.1) |
| Constipation | 28 (9.6) | 144 (8.1) |
| Missing | 21 (7.2) | 125 (7.1) |
| Fatigue | 46 (15.8) | 277 (15.6) |

Continued
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-C \(\geq 100\) 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.

### 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)         |             |

Table 2. Continued

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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, 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.

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.

| Study Population | Any Statin Users / Total N (%) | Adjusted OR (95% CI) |
|------------------|-----------------------------|----------------------|
| Overall          |                             |                      |
| CeVD only        | 307 / 403 (76.2%)           | 0.64 (0.45 , 0.91)   |
| Both CAD and CeVD| 518 / 627 (82.6%)           | 0.79 (0.59 , 1.05)   |
| CAD only (reference) | 1869 / 2202 (86.2%)    |                      |
| Age<75 years     |                             |                      |
| CeVD only        | 226 / 293 (77.1%)           | 0.64 (0.45 , 0.91)   |
| Both CAD and CeVD| 334 / 395 (84.6%)           | 0.80 (0.57 , 1.13)   |
| CAD only (reference) | 1361 / 1557 (87.4%)    |                      |
| Age>75 years     |                             |                      |
| CeVD only        | 81 / 110 (73.6%)            | 0.72 (0.36 , 1.47)   |
| Both CAD and CeVD| 184 / 232 (79.3%)           | 0.71 (0.43 , 1.16)   |
| CAD only (reference) | 536 / 643 (83.4%)          |                      |
| LDL-C<100mg/dL   |                             |                      |
| CeVD only        | 203 / 228 (89.0%)           | 0.56 (0.28 , 1.12)   |
| Both CAD and CeVD| 358 / 387 (92.5%)           | 0.76 (0.43 , 1.34)   |
| CAD only (reference) | 1383 / 1469 (94.1%)   |                      |
| LDL-C>100mg/dL   |                             |                      |
| CeVD only        | 90 / 157 (57.3%)            | 0.69 (0.44 , 1.08)   |
| Both CAD and CeVD| 143 / 221 (64.7%)           | 0.80 (0.53 , 1.21)   |
| CAD only (reference) | 437 / 640 (68.3%)          |                      |
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
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.

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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       | 10 (8.6)  | 38 (14.6) | 97 (10.5)| 0.12    |
| confusion                            |           |           |          |         |
| 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       | 0         | 0         | 2 (8.7)  | 0.54    |
| confusion                            |           |           |          |         |
| 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       | 24 (15.7) | 29 (14.5) | 89 (12.6)| 0.52    |
| confusion                            |           |           |          |         |
| 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       | 2 (9.1)   | 8 (15.7)  | 10 (8.3) | 0.35    |
| confusion                            |           |           |          |         |
| 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    |
|                     | LDL-C <100mg/dL, % | LDL-C ≥100mg/dL, % |
|---------------------|-------------------|-------------------|
|                     | N=195             | N=339             | N=1300            |
| If currently taking a statin |
| Muscle aches, cramps | 54 (29.7)         | 109 (34.0)        | 355 (29.7)        | 0.33 |
| Memory loss, forgetfulness, or confusion |
| 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 |
| Muscle aches, cramps | 1 (20.0)         | 2 (22.2)          | 14 (43.8)         | 0.05 |
| Memory loss, forgetfulness, or confusion |
| 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 |
|                     | N=86              | N=137             | N=406             |
| If currently taking a statin |
| Muscle aches, cramps | 28 (35.4)         | 47 (35.6)         | 169 (43.3)        | 0.18 |
| Memory loss, forgetfulness, or confusion |
| 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 |
| Muscle aches, cramps | 11 (61.1)         | 32 (69.6)         | 65 (63.1)         | 0.71 |
| Memory loss, forgetfulness, or confusion |
| Weakness            | 2 (11.1)          | 8 (17.4)          | 7 (6.8)           | 0.01 |
| Nausea, vomiting, stomach upset | 1 (5.6) | 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 |