Practice-level variation in statin use and low-density lipoprotein cholesterol control in the United States: Results from the Patient and Provider Assessment of Lipid Management (PALM) registry

Michael G. Nanna, MD,[a] Ann Marie Navar, MD, PhD,[a] Tracy Y. Wang, MD, MHS, MSc,[a] Shuang Li, MS,[a] Salim S. Virani, MD, PhD,[b] Zhuokai Li, PhD,[a] Jennifer G. Robinson, MD, MPH,[c] Veronique L. Roger, MD, MPH,[d] Peter W. F. Wilson, MD,[e] Anne C. Goldberg, MD,[f] Andrew Koren, MD,[g] Michael J. Louie, MD, MPH, MSc,[h] and Eric D. Peterson, MD, MPH[a] *Durham, NC; Houston, TX; Iowa City, IA; Rochester, MN; Atlanta, Georgia; St. Louis, MO; Bridgewater, NJ; and Tarrytown, NY*

Background Adherence to guideline-recommended statin recommendations in the United States is suboptimal. Patients' likelihood to be treated according to guidelines may vary by the practice in which they are treated.

Methods Variation in the use of statin therapy in 5445 patients, with known or at high risk for atherosclerotic cardiovascular disease (ASCVD) and meeting a statin treatment indication, was examined across 74 US Patient and Provider Assessment of Lipid Management (PALM) Registry clinics. Multivariable generalized linear mixed modeling was used to determine the median odds ratio (MOR) for statin use and 2013 American College of Cardiology/American Heart Association guideline-recommended statin intensity by practice. MOR quantifies between-practice variation by comparing the odds of receiving guideline-recommended statin treatment in a patient from a randomly selected practice with a similar patient from another random practice. Risk-adjusted low-density lipoprotein cholesterol (LDL-C) control (<100 and <70 mg/dL) was compared among practice tertiles based on percentage of eligible patients receiving recommended statin intensity.

Results Among 74 practices (43.2% cardiology) comprised of 300 healthcare providers enrolling 5445 patients (56.2% with ASCVD), statin use at the guideline-recommended intensity at practices varied widely (12.7–71.4%; adjusted MOR 1.45, 95% confidence interval [CI] 1.35–1.64). Results were consistent when evaluated for any statin use overall (adjusted MOR 1.75, 95% CI 1.48–1.99) and when stratified by primary versus secondary prevention patients. Relative to practices with lowest or mid-tertile statin use of statins, highest tertile clinics were more frequently cardiology practices (68.0% vs 48.0% vs 12.5%, $P < .001$). Compared with lowest tertile clinics, patients at highest tertile clinics were more likely to achieve LDL-C <70 mg/dL (adjusted odds ratio [OR] 1.49, 95% CI 1.08–2.04) and <100 mg/dL (adjusted OR 1.78, 95% CI 1.41–2.25).

Conclusions US clinics varied widely in their adherence to guideline recommendations for statin therapy, which contributed to significant differences in LDL-C levels. (Am Heart J 2019;214:113-24.)

From the [a]Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, [b]Baylor College of Medicine, Houston, TX, [c]The University of Iowa College of Public Health, Iowa City, IA, [d]Mayo Clinic, Rochester, MN, [e]Atlanta Veterans Affairs Medical Center and Emory Clinical Cardiovascular Research Institute, Atlanta, Georgia, [f]Washington University, St. Louis, MO, [g]Sanofi, Bridgewater, NJ, and [h]Regeneron Pharmaceuticals, Inc., Tarrytown, NY.

Melvyn Rubenfire, MD served as guest editor for this article.
Submitted February 15, 2019; accepted May 14, 2019.

Reprint requests: Michael G. Nanna, MD, Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC 27710.
E-mail: michael.nanna@duke.edu

0002-8703

https://doi.org/10.1016/j.ahj.2019.05.009

Prior work has demonstrated that the use of statins in community practice is suboptimal overall and varies widely among sites.[1-3] A nationwide study of facility-level variation among primary care patients seen in the Veterans Affairs Health Care System from 2012–2013 demonstrated significant facility-level variation in any statin use, as well as moderate- to high-intensity statin use.[2] A subsequent investigation of US cardiology practices in the Practice INNovation And Clinical Excellence (PINNACLE) Registry also demonstrated practice-level variation in statin prescription rates for primary prevention in patients with diabetes,[3] as did an

investigation of patients with low-density lipoprotein cholesterol (LDL-C) ≥190 mg/dL.[4] Whether practice-level variation has persisted following the release of the 2013 American College of Cardiology/American Heart Association Cholesterol Guideline in the broader population of patients eligible for statin therapy is unknown. Furthermore, the factors driving this heterogeneity in observed treatment remain unclear.

The Patient and Provider Assessment of Lipid Management (PALM) Registry is a US registry of patients with or at high risk for atherosclerotic cardiovascular disease (ASCVD; n = 7938) conducted at 140 outpatient practices in 2015. Among 74 practices that enrolled ≥20 eligible patients, we aimed to: 1) examine the extent to which practices varied in their use of statins among eligible patients; 2) evaluate what patient and practice characteristics were associated with more versus less intensive statin prescribing practices; and 3) assess whether patients seen in more intensive statin prescribing practices were more likely to have LDL-C control (<100 mg/dL or <70 mg/dL).

Methods

Data description: the PALM registry

The design and rationale of the PALM Registry have been outlined previously.[5] Briefly, we evaluated patient and practice characteristics, beliefs, and information regarding statin use using patient and provider surveys completed on an iPAD® at 140 US community cardiology, primary care, and endocrinology practices in patients with or at high risk for ASCVD in 2015, after more than a year of exposure to the 2013 ACC/AHA Cholesterol Guideline.[6] Clinical data and current statin dosing intensity were subsequently abstracted by study coordinators from the medical record, and lipid levels were measured using a core laboratory. Clinical practice site files included data regarding practice type and results from the site feasibility survey which included the number of healthcare providers at the site. Healthcare providers from participating practices completed surveys, which collected healthcare provider-reported guideline use, knowledge, attitudes, and beliefs about statin therapy, as well as healthcare provider characteristics (provider type, time in practice, specialty, and board certification). Healthcare provider beliefs were from provider survey questions with responses on a five-point Likert scale.

Data definitions

Guideline-recommended statin intensity was based on the 2013 ACC/AHA Cholesterol Guideline.[6] Patients qualified for high-intensity statin therapy if they met any of the following criteria: 1) ≤75 years old with any history of ASCVD; 2) LDL-C ≥190 mg/dL; or 3) diabetics (40–75 years old) with 10-year ASCVD risk ≥7.5% based on the pooled cohort equation with LDL-C ≥70 mg/dL (if not on a statin) or with any LDL-C if already on a statin. Moderate-intensity statin treatment was indicated if the patient did not meet the above criteria, but met any of the following: 1) older adults (>75 years old) with ASCVD; 2) non-diabetic adults (aged 40–75 years) with ASCVD risk ≥7.5% and LDL-C >70 mg/dL or on a statin; or 3) diabetic individuals (40–75 years old) with 10-year ASCVD risk <7.5% with LDL-C ≥70 mg/dL or on a statin. Individuals were classified as having ASCVD if they had a history of any of the following: (1) coronary artery disease (CAD; including prior myocardial infarction, CAD, coronary artery bypass grafting, and/or percutaneous coronary intervention); (2) cerebrovascular disease (including prior stroke and/or transient ischemic attack); and 3) peripheral artery disease (including prior abdominal aortic aneurysm, peripheral artery disease, carotid artery stenosis, and/or non-coronary arterial revascularization).

Statistical analysis

We identified 74 practices that enrolled ≥20 patients who were eligible for statin therapy based on the 2013 ACC/AHA Cholesterol Guideline and whose statin status and intensity at the visit were available (total patients n = 5445).[1] In order to describe the distribution of practice-level variation in guideline-recommended statin treatment and determine whether treatment varied among practices, the percentage and the 95% exact binomial confidence interval (CI) of eligible patients receiving guideline-recommended statin treatment use and dosing intensity for every practice was calculated. Practices were divided into tertiles based on the percentage of eligible patients receiving guideline-recommended statin treatment use and dosing intensity: 1) highest tertile; 2) mid-tertile; and 3) lowest tertile. We also assessed the distribution of cardiology versus non-cardiology practices among three tertiles and conducted sensitivity analysis to determine whether practices changed tertiles when considering practice-level guideline-recommended statin treatment of only patients with primary or secondary prevention statin indications (based on a minimum of 10 patients per site in each indication category). We then evaluated whether practice traits, healthcare provider characteristics, healthcare provider beliefs, patient characteristics, and average lipid levels differed among practice tertiles. Categorical variables are presented as frequencies (percentages) and compared using the Cochran-Armitage test for trend of one category versus other categories if the categorical variable was a nominal categorical variable, or using Spearman correlation for ordinal categorical variables. Continuous variables are presented as the median (first and third quartile) and were compared using the Spearman correlation.

To further assess the extent of practice-level variation in guideline-recommended statin intensity and overall statin treatment in patients with an indication for therapy (regardless of intensity), practices were included as a random effect in generalized linear mixed models for guideline-recommended statin use and any statin use. In

both unadjusted and adjusted analyses adjusting for other relevant covariates, the median odds ratio (MOR) with 95% confidence intervals (CIs) was calculated and presented. The MOR quantifies the median difference in the likelihood that a patient would receive statin treatment or guideline-recommended statin intensity at one practice compared with a similar patient at any other randomly selected practice. The adjusted MOR describes how practice variation changes after adjusting for other relevant covariates. In order to assess differences in patient-specific LDL-C levels <70 mg/dL, as well as LDL-C levels <100 mg/dL and guideline-recommended statin treatment among patients treated in three pre-specified believer groups, we used logistic regression modeling to estimate unadjusted and adjusted odds ratios (OR) using the lowest tertile practice group as the reference. Clustering of patients within the same site was accounted for using the generalized estimating equation (GEE) method. For both generalized linear mixed modeling and logistic regression, covariates for risk adjustment consisted of patient age, sex, race, prior CAD (including myocardial infarction, history of CAD, prior coronary artery bypass grafting, or prior percutaneous coronary intervention), prior cerebrovascular disease (including prior transient ischemic attack or stroke), prior peripheral artery disease (including abdominal aortic aneurysm, peripheral artery disease, carotid artery stenosis, and non-coronary arterial revascularization), diabetes, obesity, smoking, hypertension, heart failure, annual household income, insurance status, education level (college vs none), cardiologist versus non-cardiologist, site level urban versus rural setting, clinician reporting use of the 2013 ACC/AHA guideline, and the clinician's number of years in practice. The missing rate for most of covariates was low, except for a few variables such as income (missing in 7.8%, refused, or didn't know in 29.8%), healthcare provider responses to their use of the 2013 ACC/AHA guideline (10.5% missing), and the number of years a clinician had been in practice (missing in 10.5% of patients). Multiple imputation was used for all missing values of all covariates in the multivariable models for the risk adjustment. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC). All $P < .05$ were considered statistically significant.

Results

Statin treatment patterns at sites

This analysis was conducted among 5445 patients eligible for 2013 ACC/AHA cholesterol guideline-recommended statin treatment (56.2% with ASCVD) treated at 74 US practices (43.2% cardiology, 56.8% non-cardiology). The median guideline-recommended treatment rate was 42.5% (interquartile range [IQR] 34.1–53.2% in these practices. Nevertheless, use of guideline-recommended statin treatment varied widely among practices ($P < .001$; Figure 1). When stratified by tertiles, the median rate of guideline-recommended treatment was 58.5% in the highest tertile, 42.0% in the mid-tertile, and 29.8% in the lowest tertile. We identified 58 qualifying practices with ≥10 primary prevention patients; 10 out of the 13 qualifying highest tertile practices remained in the highest tertile when considering guideline-recommended treatment among primary prevention patients only (Figure 2). We identified 63 qualifying practices with ≥10 secondary prevention patients; 18 out of the 24 qualifying highest tertile practices remained in the highest tertile when considering guideline-recommended treatment among secondary prevention patients only (Figure 3).

We observed significant differences in characteristics of patients seen across the practice tertiles (Table I). When comparing highest tertile practices with mid-tertile and lowest tertile practices, patients were older (median age 70 years old), more frequently white (90.5% vs 79.2% vs 80.8%), wealthier in terms of annual household income (26.7% vs 18.6% vs 14.7%, with ≥$100,000 annually), more frequently had private health insurance (63.8% vs 54.5% vs 51.8%), and a history of ASCVD (70.5% vs 56.0% vs 42.6%) ($P < .001$).

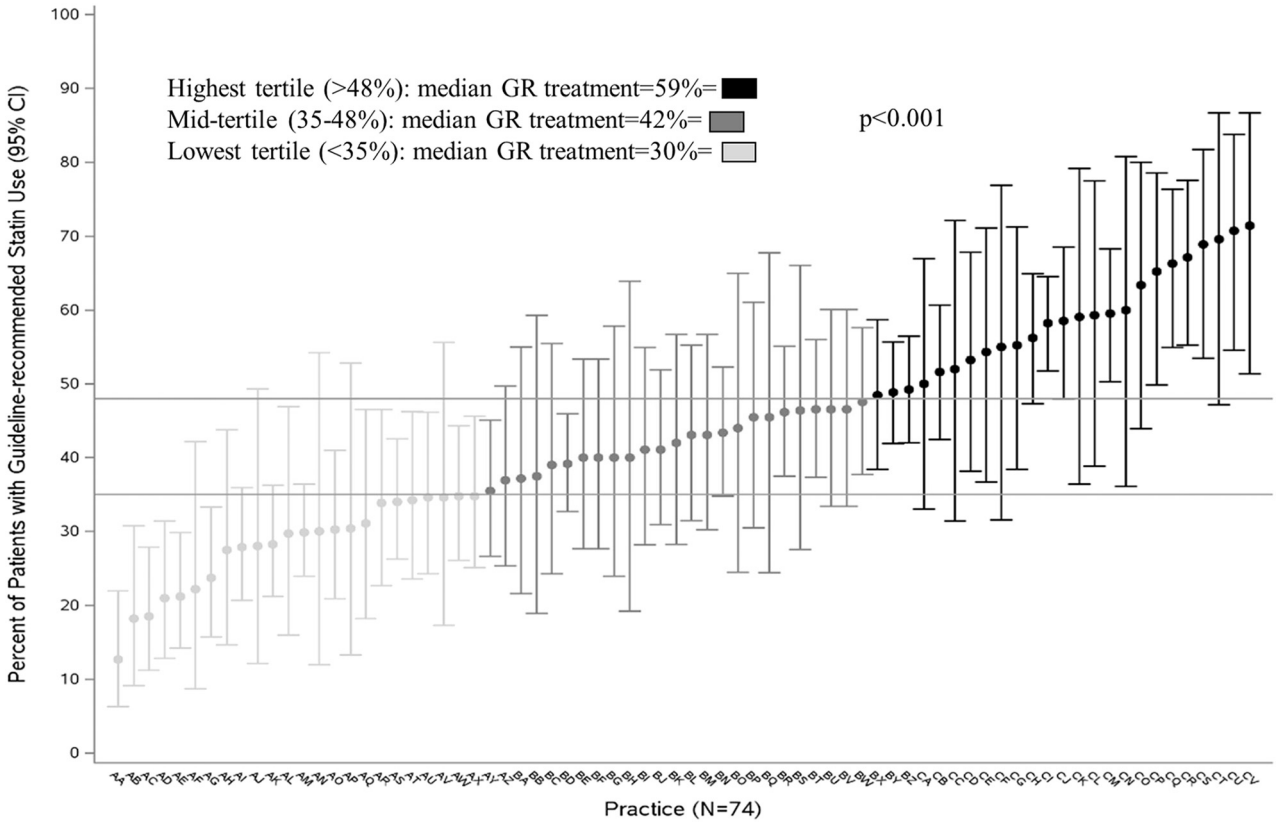
Inter-practice variation in statin use

The median difference in the likelihood of a patient receiving a guideline-recommended statin at one randomly selected practice was up to twofold compared with another randomly selected site (unadjusted MOR = 1.99, 95% CI 1.87–2.16). These results indicate a median increase of 99% in the odds of guideline-concordant statin use if a patient receives care in a more intensive statin prescribing practice compared with a less intensive one. This variation, although reduced, was still substantial after adjustment for various patient- and practice-level variables (adjusted MOR = 1.45, 95% CI 1.35–1.64). The variation in guideline-recommended statin treatment across practices remained consistent in both primary and secondary prevention patient populations (primary prevention: adjusted MOR = 1.56, 95% CI 1.28–1.78; secondary prevention: adjusted MOR = 1.52, 95% CI 1.31–1.69).

After adjusting for demographics, clinical characteristics, socioeconomic status, insurance status, education, and provider characteristics, patients seen at the highest tertile clinics had almost triple the odds of receiving guideline-recommended statin treatment (adjusted OR 2.86, 95% CI 2.45–3.34, $P < .001$), while mid-tertile clinic patients had close to double the odds of receiving guideline-recommended therapy (adjusted OR 1.81, 95% CI 1.52–2.17, $P < .001$) compared with patients treated in the lowest tertile clinics.

Practice variation was also observed when evaluating overall statin use (regardless of whether used at the guideline-recommended intensity) in patients with an

Figure 1



Practice-level variation in statin treatment. This figure displays practice-level variation in guideline-recommended statin treatment according to three tertiles of statin treatment: highest tertile, mid-tertile, and lowest tertile. Points represent the point estimates of the percentage of patients receiving guideline-recommended statin treatment for each practice with a 95% confidence interval.

indication for therapy (unadjusted MOR = 2.27, 95% CI 2.09–2.51; adjusted MOR = 1.75, 95% CI 1.48–1.99). Variation in statin treatment similarly remained consistent even when stratified into primary and secondary prevention patient populations (primary prevention: adjusted MOR = 1.53, 95% CI 1.25–1.74; secondary prevention: adjusted MOR = 1.87, 95% CI 1.50–2.20).

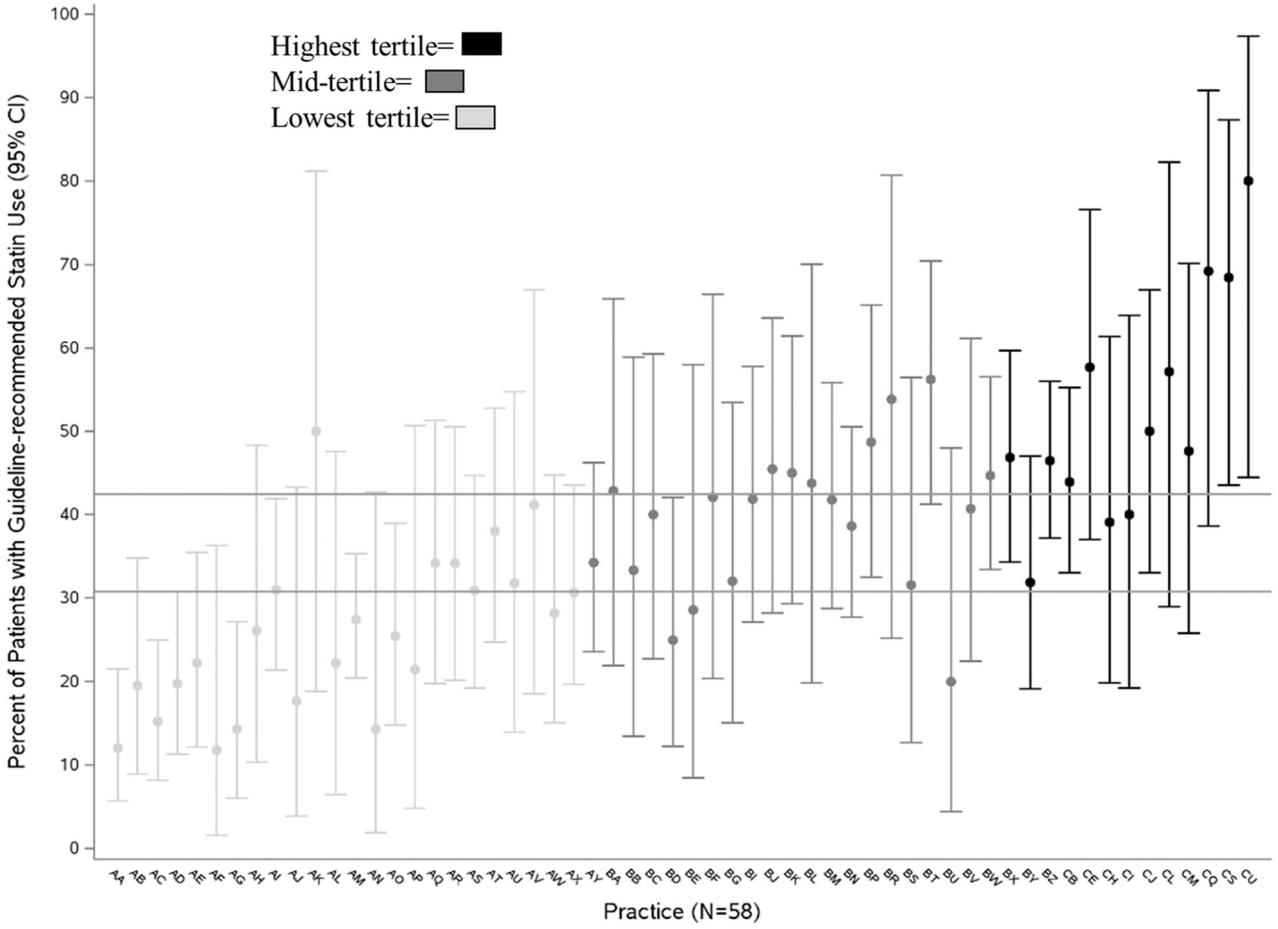
Practice and clinician characteristics

Patients treated at the highest tertile practices were more frequently cared for by physicians (90.5%) versus mid-tertile (83.9%) versus lowest tertile (74.1%) (P = .005); Table II. Patients in the lowest tertile practices were the most likely to be seen by an advanced practice provider (51.3% in lowest tertile vs 31.5% in mid-tertile vs 29.2% in highest tertile, P = .02). Clinics in the highest tertile for recommended statin use were more often cardiology practices (68.0% vs 48.0% vs 12.5%, P < .001) and board certification in cardiology was more frequent among clinicians in the highest tertile (82.1%) versus mid-tertile (48.7%) versus lowest tertile (11.6%) (P < .001). Lowest tertile practices were frequently primary care/family practice/internal medicine practices (70.8% vs 44.0% of mid-tertile vs 28.0% of the highest tertile, P < .001). Clinicians in the highest tertile practices more frequently reported adopting the 2013 ACC/AHA Cholesterol Guideline (80.2%) compared with mid- (67.8%) or lowest tertile practices (59.3%) (P = .003). The majority of non-cardiology practices that met the pre-specified minimum enrollment criteria of ≥20 patients meeting a guideline-indication for statin therapy were primary care/family practice/internal medicine, although three endocrinology practices were also included. Of the three endocrinology practices included in the analysis, one was classified in the highest tertile and two were classified as mid-tertile.

Clinician beliefs

Clinician beliefs about statins and cholesterol varied across practice tertiles (Table III), with highest tertile healthcare providers most likely to agree or strongly agree with the statements that statins are safe (72.8% vs

Figure 2



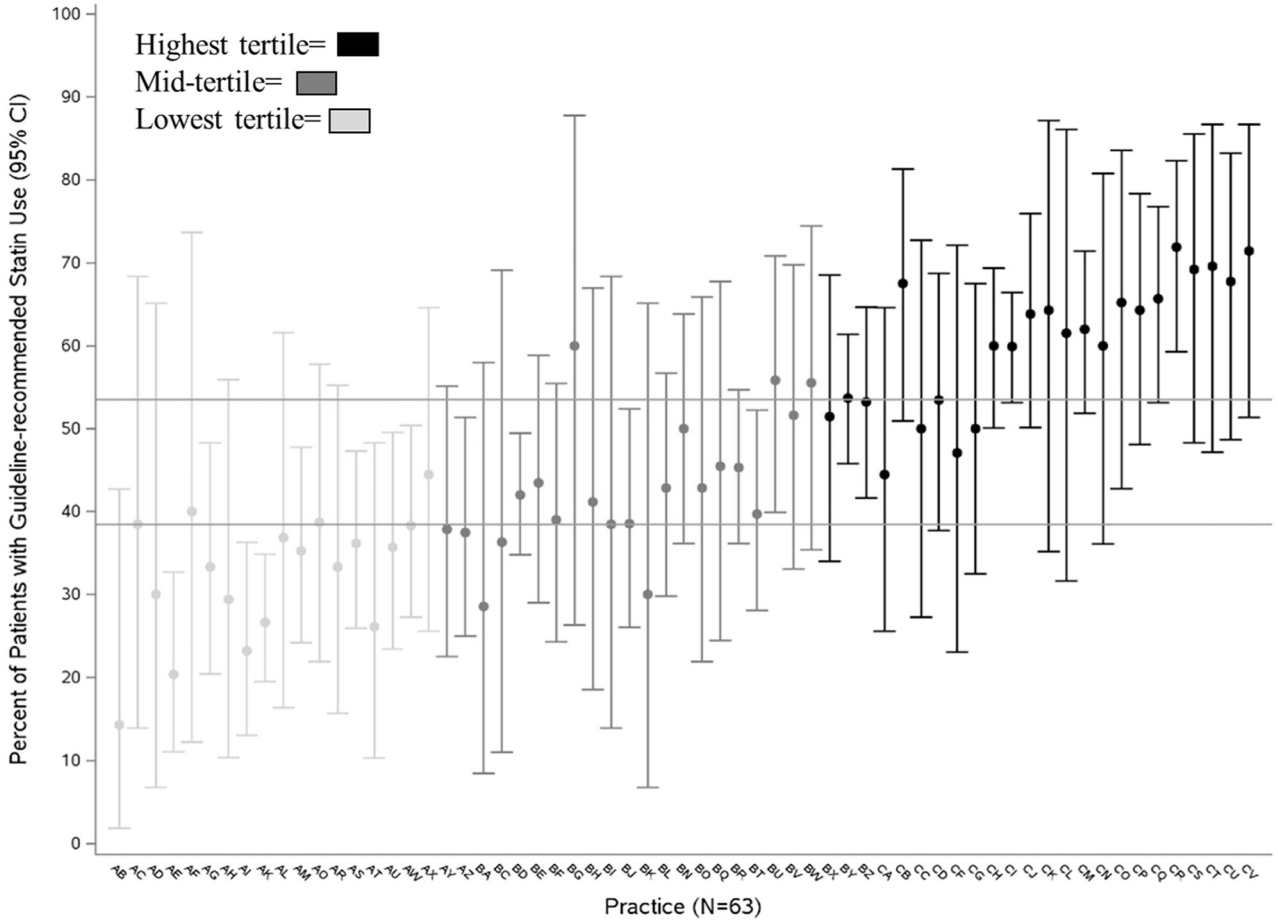
Practice performance when evaluating guideline-recommended statin treatment among patients with a primary prevention indication. This figure displays practice-level variation in guideline-recommended statin treatment among patients with a primary prevention indication for statin therapy, with practices presented in the same order as in Figure 1; this is meant to demonstrate whether practices perform as well in primary prevention patients as they did overall. Points represent the point estimates of the percentage of patients receiving guideline-recommended statin treatment for each practice with a 95% confidence interval. The threshold lines for the three tertiles of statin treatment for the 58 hospitals evaluated for the primary prevention indication (highest tertile, mid-tertile, and lowest tertile) are provided for reference. Colors (black, gray and light gray) were derived from the overall patient population.

69.8% vs 56.6%, $P < .05$) and prolong life (79.0%, vs 72.1% vs 53.7%, $P < .001$), but less frequently reported checking lipids more than once a year in patients with known cardiovascular disease (30.2% vs 59.8% vs 64.8%, $P < .001$). Highest tertile practice providers appeared to be willing to try additional statins before switching off of statin therapy compared with mid- or lowest tertile providers ($P = .05$), while being less likely to recommend switching to a non-statin therapy ($P < .001$).

LDL-C levels

Patient's LDL-C levels distributed differently across practice tertiles (highest tertile median LDL-C = 86 mg/dL vs mid = 98 mg/dL vs lowest tertile = 100 mg/dL, $P < .001$). Patients treated in the highest tertile practices consistently achieved LDL-C levels <70 mg/dL and< 100 mg/dL more frequently than those seen at the lowest tertile practices, including patients with either primary or secondary prevention indications for statin therapy (Figure 4). When compared with the lowest tertile clinics using multivariable modeling, patients at the highest tertile clinics were more likely to achieve LDL-C < 70 mg/dL (adjusted OR 1.49, 95% CI 1.08–2.04, $P = .01$) and <100 mg/dL (adjusted OR 1.78, 95% CI 1.41–2.25, $P < .001$). Similar lipid patterns were seen when stratified by primary and secondary prevention treatment indications (Figure 4). When compared with the lowest tertile clinics, patients seen at mid-tertile clinics did not have

Figure 3



Practice performance when evaluating guideline-recommended statin treatment among patients with a secondary prevention indication. This figure displays practice-level variation in guideline-recommended statin treatment among patients with a secondary prevention indication for statin therapy, with practices presented in the same order as in Figure 1. This is meant to demonstrate whether practices perform as well in secondary prevention patients as they did overall. Points represent the point estimates of the percentage of patients receiving guideline-recommended statin treatment for each practice with a 95% confidence interval. The threshold lines for the three tertiles of statin treatment for the 63 hospitals evaluated for the secondary prevention indication (highest tertile, mid-tertile, and lowest tertile) are provided for reference. Colors (black, gray, and light gray) were derived from the overall patient population.

significantly better lipid control after adjustment (LDL-C < 70 mg/dL adjusted OR 1.08, 95% CI 0.77–1.52, P = .65; LDL-C < 100 mg/dL adjusted OR 1.13, 95% CI 0.88–1.45, P = .34).

Discussion

Significant practice-level variation in statin treatment in contemporary practice exists with corresponding effects on lipid control. Patients seen at the highest tertile practices had a nearly three-fold increased odds of receiving guideline-recommended statin treatment compared with patients seen at the lowest tertile practices. We identified several potential influences on this variation including differences in baseline patient characteristics, provider type, and provider beliefs. Top performing sites were frequently cardiology practices, with providers who believe in the safety and efficacy of statins and who were more likely to try additional statins prior to switching to a non-statin lipid-lowering therapy.

Our analyses demonstrated significant practice-level variation in statin use, which is consistent with prior work. Prior studies preceding the 2013 ACC/AHA Cholesterol guideline have demonstrated facility-level variation in statin use in the Veterans Affairs Health Care System,[2] as well as across US cardiology practices treating diabetic patients for primary prevention.[3] A subsequent study of patients with LDL-C ≥ 190 mg/dL demonstrated similar practice variability in primary prevention use of lipid-lowering therapies.[4] Our study confirms the

Table I. Patient characteristics at 74 US practices (n = 5445 patients) according to cholesterol guideline-recommended treatment tertile*

	Highest tertile (n = 1839)	Mid-tertile (n = 1706)	Lowest tertile (n = 1900)	P†
Age (median)	70.0 (64.0, 75.0)	67.0 (60.0, 73.0)	67.0 (60.0, 73.0)	<0.001
Race				
White	1664 (90.5%)	1351 (79.2%)	1535 (80.8%)	
Black	133 (7.2%)	325 (19.1%)	314 (16.5%)	<0.001‡
Other/unknown	42 (2.3%)	30 (1.8%)	51 (2.7%)	
Hispanic ethnicity	72 (3.9%)	343 (20.1%)	181 (9.5%)	<0.001
Body mass index	29.5 (26.1, 34.1)	30.0 (26.4, 34.6)	30.1 (26.5, 35.1)	0.01
10-year risk (among those w/out ASCVD)	15.0% (10.5%, 21.6%)	14.3% (9.6%, 21.5%)	14.9% (9.3%, 22.9%)	0.79
ASCVD	1297 (70.5%)	955 (56.0%)	809 (42.6%)	<0.001
History of MI	467 (25.4%)	254 (14.9%)	159 (8.4%)	<0.001
History of stroke	98 (5.3%)	95 (5.6%)	112 (5.9%)	0.45
History of diabetes	671 (36.5%)	763 (44.7%)	1008 (53.1%)	<0.001
Hypertension	1472 (80.0%)	1420 (83.2%)	1544 (81.3%)	0.35
Heart failure	262 (14.4%)	181 (10.7%)	107 (5.7%)	<0.001
History of myopathy	117 (6.4%)	62 (3.6%)	50 (2.7%)	<0.001
Chronic kidney disease	232 (12.6%)	141 (8.3%)	202 (10.6%)	0.05
Current smoker	174 (9.5%)	260 (15.2%)	263 (13.8%)	<0.001
College or above	709 (40.8%)	571 (35.0%)	553 (32.1%)	<0.001
Insurance				
Private	1172 (63.8%)	930 (54.5%)	983 (51.8%)	<0.001‡
Government	641 (34.9%)	729 (42.7%)	874 (46.1%)	
Other (non-US)	0 (0.0%)	1 (0.1%)	1 (0.1%)	
No insurance	24 (1.3%)	46 (2.7%)	40 (2.1%)	
Income				
<35,000	247 (24.9%)	505 (43.7%)	488 (38.9%)	<0.001‡
35,000-74,999	351 (35.5%)	321 (27.8%)	439 (35.0%)	
75,000-99,999	128 (12.9%)	114 (9.9%)	143 (11.4%)	
≥100,000	264 (26.7%)	215 (18.6%)	185 (14.7%)	
Lipid-lowering treatment				
Not on a statin	293 (15.9%)	413 (24.2%)	710 (37.4%)	<0.001
On a guideline-recommended statin	1040 (56.6%)	720 (42.2%)	533 (28.1%)	<0.001
On ezetimibe	95 (5.2%)	58 (3.4%)	113 (6.0%)	0.26
Lipid levels				
Total cholesterol mg/dL (overall)	158.0 (136.0, 188.0)	173.5 (146.0, 206,0)	175.0 (149.0, 208.0)	<0.001
LDL-C mg/dL (on treatment)	81.0 (65.0, 98.0)	90.0 (71.0, 112.0)	89.0 (71.0, 113.0)	<0.001
LDL-C mg/dL (overall)	86.0 (68.0, 110.0)	98.0 (76.0, 124.0)	100.0 (79.0, 128.0)	<0.001
Triglycerides (overall)	128.0 (91.0, 182.0)	140.0 (97.0, 205.0)	141.1 (100.0, 199.0)	<0.001
HDL-C mg/dL (overall)	51.0 (42.0, 62.0)	51.0 (42.0, 62.0)	51.0 (42.0, 62.0)	0.85

ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction.
* Data are presented as median (interquartile range) for continuous variables and n (%) for categorical variables
† *P* values were calculated by comparing only non-missing row values.
‡ *P* value for trend calculated as binary categorical variable using this row versus all others in this category.

persistence of this practice-level variation in a broader population of US outpatients, with both primary and secondary prevention indications and across a variety of practice types that frequently prescribe statin therapy.

Addressing this practice-level variation requires an understanding of the factors driving the heterogeneity in observed treatment. While prior analyses from the PALM Registry have focused on patient-level characteristics associated with statin intensity,[7-9] reasons for statin under-utilization,[8-11] and patient versus provider perception of risk,[2] our study is one of the first to identify specific attributes of high-performing practices which may inform future practice-level interventions. We found that top performing statin treatment practices were often cardiology practices while the lowest tertile statin treatment practices were more frequently primary care/family practice/internal medicine. The highest tertile practices more frequently reported adopting the 2013 ACC/AHA Cholesterol Guideline (80.2%) versus lowest tertile practices (59.3%), which emphasizes the importance of improving adoption of cholesterol guideline recommendations into primary care clinics. Physicians represented >90% of providers in the highest tertile practices while making up <75% of providers in the lowest tertile practices; correspondingly, patients in the lowest tertile practices were seen by advanced practice providers 51.3% of the time, compared with 29.2% of the time in the highest tertile practices. A prior study by Virani et al. demonstrated a small difference in statin use among patients receiving care from physicians versus

Table II. Practice and clinician characteristics by guideline-recommended statin treatment tertile (n = 74)

Practice characteristics	Highest tertile (n = 25)	Mid-tertile (n = 25)	Lowest tertile (n = 24)	P*
Total number of providers at site†	11.0 (5.0, 19.0)	4.0 (3.0, 10.0)	2.0 (2.0, 4.0)	<.001
Practice location‡				
Rural	1 (4.0%)	2 (8.0%)	2 (8.7%)	.52
Urban	24 (96.0%)	23 (92.0%)	21 (91.3%)	
Principal investigator specialty§				
Cardiology	17 (68.0%)	12 (48.0%)	3 (12.5%)	<.001‖
Primary care/family practice/internal medicine	7 (28.0%)	11 (44.0%)	17 (70.8%)	
Endocrinology	0 (0.0%)	2 (8.0%)	1 (4.2%)	
Other	1 (4.0%)	0 (0.0%)	3(12.5%)	

Provider characteristics¶	Highest tertile (n = 143)	Mid-tertile (n = 97)	Lowest tertile (n = 60)	P*
Provider types				
Physician (MD, DO, MBBS/MBBCh)	114 (90.5%)	73 (83.9%)	40 (74.1%)	.005‖
APP	12 (9.5%)	13 (14.9%)	14 (25.9%)	
Clinician in training	0 (0.0%)	1 (1.2%)	0 (0.0%)	
If physician, sees patients alone (%Yes)	52 (46.0%)	38 (52.1%)	18 (46.2%)	.79
Patients seen by APP (if provider is a physician)	33 (29.2%)	23 (31.5%)	20 (51.3%)	.02
Patients seen with APP (%Yes)	34 (30.1)	14 (19.2%)	13 (33.3%)	.85
Sees patients with a trainee (if provider is a physician)	10 (8.9%)	3 (4.1%)	5 (12.8%)	.76
Primary guideline for cholesterol management				
2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Disease	101 (80.2%)	59 (67.8%)	32 (59.3%)	.003‖
Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults	20 (15.9%)	18 (20.7%)	12 (22.2%)	
American Association of Clinical Endocrinologists' Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis	0 (0.0%)	5 (5.8%)	5 (9.3%)	
European Society of Cardiology/European Atherosclerosis Society Guidelines for the Management of Dyslipidemias	0 (0.0%)	1 (1.2%)	0 (0.0%)	
Other	2 (1.6%)	2 (2.3%)	0 (0.0%)	
None, I don't use any of these routinely to guide my practice	3 (2.4%)	2 (2.3%)	5 (9.3%)	
Years in practice				
0–5 years	19 (15.1%)	16 (18.4%)	9 (16.7%)	.69‖
6–10 years	12 (9.5%)	12 (13.8%)	4 (7.4%)	
10–20 years	42 (33.3%)	20 (23.0%)	21 (38.9%)	
20+ years	53 (42.1%)	39 (44.8%)	20 (37.0%)	
Board-certified (Yes)	113 (89.7%)	80 (92.0%)	45 (83.3%)	.33
Board-certified in internal medicine (Yes)	56 (50.0%)	32 (41.0%)	16 (37.2%)	.11
Board-certified in family practice (Yes)	9 (8.0%)	23 (29.5%)	26 (60.5%)	<.001
Board-certified in cardiology (Yes)	92 (82.1%)	38 (48.7%)	5 (11.6%)	<.001
Board-certified in endocrinology (Yes)	1 (0.9%)	9 (11.5%)	0 (0.0%)	.40
Board-certified in "other" (Yes)	25 (22.3%)	9 (11.5%)	3 (7.0%)	.009

ACC/AHA = American College of Cardiology/American Heart Association; APP = advanced practice provider
Data are presented as median (interquartile range) for continuous variables and n (%) for categorical variables
* *P* values were calculated by comparing only non-missing row values.
† "Total number of providers" was obtained from the site feasibility survey but had significant missingness (29 of 74 missing). All missing values were imputed with the results from the provider survey.
‡ Rural vs. urban classified using US census data by practice zip code.
§ Based on practice specialty obtained from the original site file.
‖ *P* for trend calculated as binary categorical variable using this row vs. all others in this category
¶ Based on results of the provider survey.

advanced practice providers (adjusted OR = 0.94, 0.93-0.95), though this difference was not felt to be clinically meaningful.[12] Given the critical role of mid-level clinicians in the primary care and cardiology settings, further study is necessary in order to close this treatment gap.

In addition to differences in practice, clinician beliefs also varied among practices in different statin treatment tiers in the PALM Registry. Highest tertile practice clinicians were more willing to try additional statins before switching off statin therapy and reluctant to

Table III. Clinician beliefs*

	Highest tertile (n = 143)	Mid-tertile (n = 97)	Lowest tertile (n = 60)	P*
The provider "often" or "always" calculates CVD risk	64 (50.8%)	39 (44.8%)	27 (50%)	.76
How frequently does the provider report checking lipids in patients with cardiovascular disease?				
More than once a year	38 (30.2%)	52 (59.8%)	35 (64.8%)	<.001†
Once a year	75 (59.5%)	29 (33.3%)	17 (31.5%)	
Some other frequency	13 (10.3)	6 (6.9%)	2 (3.7%)	
What percentage of providers responded "agree" or "strongly agree" when asked to rate their agreement with the following statements?‡				
I worry that risks of statins may be underreported or underappreciated	25 (20.0%)	14 (16.3%)	13 (24.1%)	.70
Statins are extremely safe	91 (72.8%)	60 (69.8%)	30 (56.6%)	<.05
Statins are unnecessary in adults with low LDL levels (<70 mg/dL)	26 (20.8%)	24 (27.9%)	17 (31.5%)	.10
Statins are very effective in reducing risk of heart attack or stroke	116 (92.8%)	82 (95.4%)	47 (87.0%)	.31
Statins prolong life	98 (79.0%)	62 (72.1%)	29 (53.7%)	<.001
How often does the provider report seeing the following side effects from statins?§				
Myalgias	33 (26.6%)	30 (34.9%)	16 (29.6%)	.49
Memory loss	1 (0.8%)	1 (1.2%)	0 (0.0%)	.67
Diabetes	3 (2.4%)	1 (1.2%)	1 (1.9%)	.70
In general, for patients who experience myalgias/muscle aches on statin therapy, how many statins do the provider recommend a patient try before considering the patient "intolerant" of any statin?				.05‖
1 statin (i.e. I don't try any other statin)	0 (0.0%)	2 (2.4%)	0 (0.0%)	
2 statins	29 (23.0%)	28 (32.9%)	19 (35.2%)	
3 statins	63 (50.0%)	41 (48.2%)	31 (57.4%)	
4 or more statins	34 (27.0%)	14 (16.5%)	4 (7.4%)	
How often does the provider recommend switching to a non-statin lipid lowering medication for patients who report muscle aches while on statin therapy?				
Almost never	55 (43.7%)	17 (19.8%)	11 (20.8%)	<.001†
Sometimes	70 (55.6%)	59 (68.6%)	37 (69.8%)	
Often	1 (0.8%)	10 (11.6%)	5 (9.4%)	

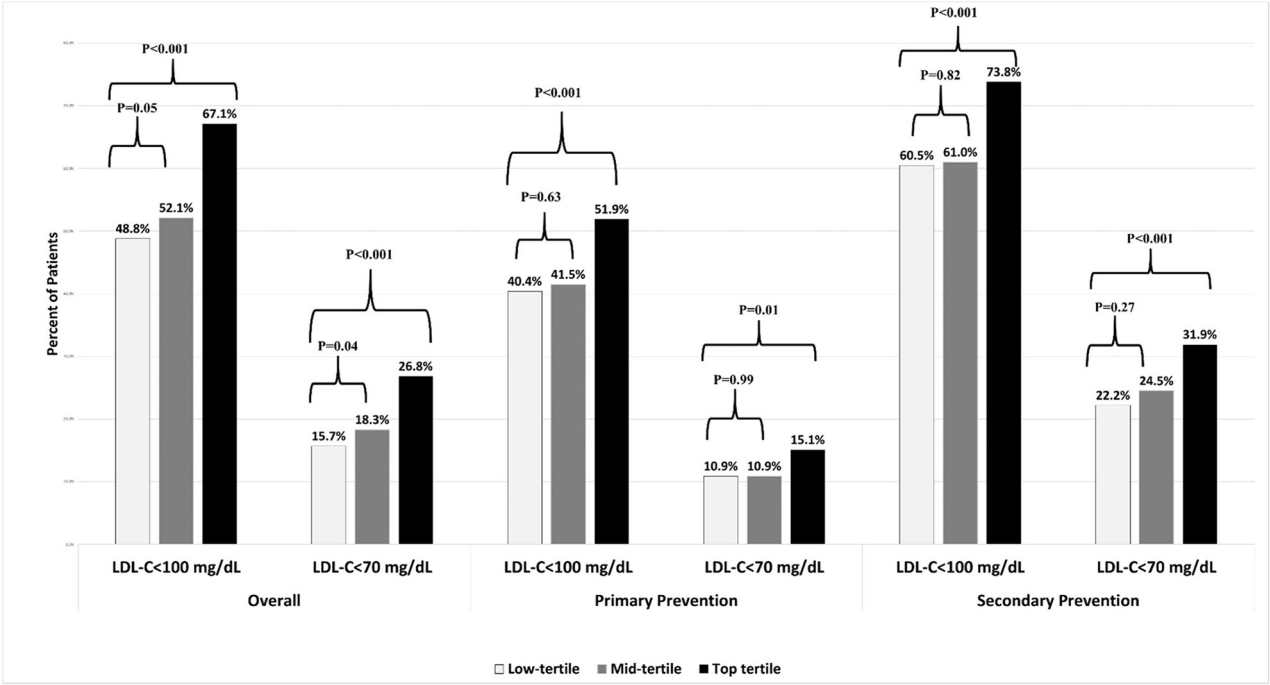
CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol
Data are presented as n (%)
* *P* values were calculated by comparing only non-missing row values.
† *P* value for trend calculated as binary categorical variable using this row vs. all others in this category
‡ Data represent the percentage of subjects who responded "agree" or "strongly agree" on a five-point Likert scale to the patient survey question
§ Data represent the percentage of subjects who responded "Often" or "Frequently" on a five-point Likert scale to the patient survey question
‖ *P* value for trend calculated as binary variable of 3 or more statins vs 1 or 2 statins.

recommend switching to non-statin therapies. In conjunction with the emerging evidence supporting the use of non-statin lipid-lowering therapies,[13-17] we hypothesize that the beliefs of healthcare providers at the highest tertile practices regarding non-statin therapies may shift in the future so it will be important to emphasize the need for using maximally-tolerated statin therapy before adding non-statin therapy, and to avoid switching if possible. Notably, recent proprotein convertase subtilisin/kexin type 9 inhibitor cardiovascular outcomes trials have been performed in patients receiving primarily high-intensity statins.[13,14,16,17] Despite the wealth of evidence demonstrating the efficacy of statin therapy for the primary and secondary prevention of cardiovascular disease, more work must be done to convince all providers that stains are the most effective treatment.[6,18,19]

We observed a number of differences in patient characteristics between different practice tiers. Patients seen at the highest tertile practices tended to be wealthier, white, and have private insurance, compared with patients seen at mid- and lowest tertile practices; these findings are similar to one large study of English primary care practices that demonstrated evidence of social inequalities in statin prescribing for primary prevention in 2006 to 2007 at lower prescribing practices.[1] Patients seen at the highest tertile practices had much higher rates of ASCVD, though we observed practice-level treatment variation even after adjustment for this variable. Furthermore, when we stratified into primary and secondary prevention subgroups, the majority of practices remained in their original treatment tier and practice-level variation by MOR remained similar or even more pronounced. We hypothesize that practices caring for higher-risk patients who more frequently need high-intensity statin therapy may have an increased comfort with prescribing guideline-recommended statin therapy; consequently, this increases the likelihood of treating all eligible patients with optimal statin doses.

Differences in statin prescribing patterns corresponded with practice-level differences in lipid control. Patients

Figure 4



LDL-C levels by practice tertile of guideline adherence. This figure displays differences in LDL-C control (<70 and <100 mg/dL) across three tertiles of statin treatment: Highest tertile, mid-tertile and lowest tertile. *P* values represent the results of comparison between the indicated practice tier (mid- or highest) and the lowest tertile as the reference group. LDL-C = low-density lipoprotein cholesterol.

seen at the highest tertile practices had lower LDL-C levels, even when adjusting for potential confounders. Compared with a patient seen at a lowest tertile practice, a patient seen at a highest tertile practice had nearly double the odds of having an LDL-C < 100 mg/dL; this finding is in line with findings from PINNACLE that demonstrated significant variation in LDL-C control to <100 mg/dL among primary prevention patients with diabetes seen at US cardiology practices.[3] With the reintroduction of LDL-C treatment triggers for the initiation of non-statin lipid-lowering therapies in the most recent cholesterol guideline,[20] our results indicate there is significant room for improvement to reduce the risk of ASCVD among US outpatients. Close to 80% of patients with known ASCVD in our lowest tertile practices had LDL ≥70 mg/dL and would likely qualify for intensified lipid-lowering therapy under the 2018 guideline recommendations. We did not formally compare the frequencies of achieved LDL-C levels for the primary and secondary prevention groups, but we observed that providers were generally prescribing statins that achieved lower LDL-C on therapy for secondary prevention than for primary prevention. Even in top-tertile practices, nearly 70% of secondary prevention patients met the intensified treatment trigger of LDL >70 mg/dL. Given the strong association between LDL-C reduction and reduction in major vascular events,[21-23] addressing practice-level variation in statin treatment and its likely impact on LDL-C control is a critical area for future interventions.

Our study had several limitations. First, the cross-sectional nature of the PALM Registry prevented us from determining temporal trends in statin treatment following the release of the 2013 ACC/AHA Cholesterol Guideline. For example, primary care practices may have had a delayed uptake of the 2013 guideline due to its initial dissemination by major cardiology societies (ACC/AHA), but potentially increased guideline-recommended treatment over time. Second, our consideration of non-statin therapies was limited and preceded the publication of several studies supporting the use of these therapies in high-risk patients, as well as the most recent ACC/AHA cholesterol guideline published in late 2018,[20] which may influence future practice patterns. Third, while our missing rate was low, we did need to use multiple imputation for a few variables such as income (missing in 7.8%, refused or didn't know in 29.8%), healthcare provider responses to their use of the 2013 ACC/AHA guideline (10.5% missing), and the number of years a clinician had been in practice (missing in 10.5% of patients). Fourth, the PALM Registry did not capture certain practice-level variables (e.g., whether a practice

was a part of a larger healthcare system or an academic medical center). Finally, we did not capture specific factors influencing provider decisions regarding statin treatment at the individual patient level, which may have affected ultimate treatment choices. While contraindications may have appropriately prevented statin treatment in certain cases, we would not expect to observe significant heterogeneity of this unmeasured confounder across different practices.

Conclusion

Significant practice-level variation in statin treatment has persisted following the release of the 2013 ACC/AHA Cholesterol Guideline with corresponding effects on lipid control. Potential reasons underlying this variation include differences in provider beliefs and provider type, with significant differences in treatment patterns seen between cardiologists and primary care providers. Ultimately, the practice location a patient chooses should not significantly impact whether they receive optimal cardiovascular risk reduction; the responsibility lies with healthcare providers to close this treatment gap.

Acknowledgements

We thank Erin Campbell, MS, for her editorial contributions to this manuscript. Ms. Campbell did not receive compensation for her contributions, apart from her employment at the institution where this study was conducted.

Sources of funding

This study was supported by Sanofi Pharmaceuticals and Regeneron Pharmaceuticals. Dr. Navar is also funded by NIH K01HL133416–01. Dr. Nanna is supported by NIH training grant T-32-HL069749–15.

Conflict of interest disclosures

MG Nanna: No relationship(s) to disclose.

AM Navar: Research Grant: Significant; Amarin, Janssen, Amgen, Sanofi, and Regeneron Pharmaceuticals. Consultant/Advisory Board: Significant; Amarin, Novonordisk, AstraZeneca, Sanofi and Regeneron.

TY Wang: Research Grant: Modest; Amgen, Bristol Myers Squibb, Cryolife, Novartis, Pfizer, Portola. Research Grant: Significant; AstraZeneca, Regeneron Pharmaceuticals. Honoraria: Modest; Grifols, Gilead.

S Li: No relationship(s) to disclose.

SS Virani: Research Grant: Significant; AHA, ADA, VA. Honoraria: Significant; AMERICAN COLLEGE OF CARDIOLOGY (Associate Editor for Innovations, acc.org).

Z Li: No relationship(s) to disclose.

JG Robinson: Research Grant: Significant; Acasti, Amarin, Amgen, Astra-Zeneca, Esai, Esperion, Merck, Regeneron, Sanofi, Takeda. Consultant/Advisory Board: Modest; Amgen, Merck, Novartis, Novo-Nordisk, Pfizer. Consultant/Advisory Board: Significant; Sanofi, Regeneron.

VL Roger: No relationship(s) to disclose.

PWF Wilson: No relationship(s) to disclose.

AC Goldberg: Research Grant: Modest; Amarin, Pfizer. Research Grant: Significant; Amgen, Regeneron, Sanofi, IONIS. Honoraria: Modest; Merck Manual. Consultant/Advisory Board: Modest; Regeneron/Sanofi, Esperion, Novartis, AKCEA.

A Koren: Employment: Significant; Sanofi.

MJ Louie: Employment: Significant; Regeneron. Ownership Interest: Modest; Regeneron.

ED Peterson: Research Grant: Significant; Amgen, Sanofi, Astrazeneca, Merck. Consultant/Advisory Board; Modest; Amgen. Consultant/Advisory Board: Significant; AstraZeneca, Merck, and Sanofi Aventis.

References

1. Fleetcroft R, Schofield P, Ashworth M. Variations in statin prescribing for primary cardiovascular disease prevention: cross-sectional analysis. BMC Health Serv Res 2014;14:414.
2. Pokharel Y, Akeroyd JM, Ramsey DJ, et al. Statin use and its facility-level variation in patients with diabetes: insight from the Veterans Affairs National Database. Clin Cardiol 2016;39:185-91.
3. Pokharel Y, Gosch K, Nambi V, et al. Practice-level variation in statin use among patients with diabetes. insights from the PINNACLE Registry J Am Coll Cardiol 2016;68:1368-9.
4. Virani SS, Kennedy KF, Akeroyd JM, et al. Variation in lipid-lowering therapy use in patients with low-density lipoprotein cholesterol >/=190 mg/dL: insights from the National Cardiovascular Data Registry-Practice Innovation and Clinical Excellence Registry. Circ Cardiovasc Qual Outcomes 2018;11, e004652.
5. Navar AM, Wang TY, Goldberg AC, et al. Design and rationale for the Patient and Provider Assessment of Lipid Management (PALM) Registry. Am Heart J 2015;170:865-71.
6. Stone NJ, Robinson JG, Lichtenstein AH, et al. 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.
7. Navar AM, Wang TY, Li S, et al. Lipid management in contemporary community practice: results from the Provider Assessment of Lipid Management (PALM) Registry. Am Heart J 2017;193:84-92.
8. Nanna MG, Navar AM, Zakroysky P, et al. 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;3:739-48.
9. Nanna MG, Navar AM, Wang TY, et al. 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.
10. Lowenstern A, Li S, Navar AM, et al. Does clinician-reported lipid guideline adoption translate to guideline-adherent care? An

evaluation of the Patient and Provider Assessment of Lipid Management (PALM) Registry. Am Heart J 2018;200:118-24.
11. Navar AM, Peterson ED, Li S, et al. Prevalence and management of symptoms associated with statin therapy in community practice: insights from the PALM (Patient and Provider Assessment of Lipid Management) Registry. Circ Cardiovasc Qual Outcomes 2018;11, e004249.
12. Virani SS, Akeroyd JM, Ramsey DJ, et al. Comparative effectiveness of outpatient cardiovascular disease and diabetes care delivery between advanced practice providers and physician providers in primary care: implications for care under the Affordable Care Act. Am Heart J 2016;181: 74-82.
13. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713-22.
14. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372:2387-97.
15. Karatasakis A, Danek BA, Karacsonyi J, et al. Effect of PCSK9 inhibitors on clinical outcomes in patients with hypercholesterolemia: a meta-analysis of 35 randomized controlled trials. J Am Heart Assoc 2017;6.
16. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med 2015;372:1489-99.
17. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379:2097-107.
18. Taylor F, Ward K, Moore TH, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2011(1), CD004816.
19. Chou R, Dana T, Blazina I, et al. Statins for Prevention of Cardiovascular Disease in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 2016;316:2008-24.
20. Grundy SM, Stone NJ, Bailey AL, et al. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary. Circulation 2018:CIR0000000000000624; 2018.
21. Cholesterol Treatment Trialists' (CTT) Collaboration. Baigent C, Blackwell L, et al. 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;376:1670-81.
22. Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. JAMA 2016;316:1289-97.
23. Mihaylova B, Emberson J, Blackwell L, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012;380:581-90.