Journal of the American Heart Association

ORIGINAL RESEARCH

Lower-Intensity Statins Contributing to Gaps in Care for Patients With Primary Severe Hypercholesterolemia

Wael E. Eid, MD; Emma Hatfield Sapp, PharmD; Elijah Flerlage; Joseph R. Nolan, PhD

BACKGROUND: Although severe hypercholesterolemia confers a 5-fold increased long-term risk for coronary artery disease, treatment guidelines may not be fully implemented, leading to underdiagnosis and suboptimal treatment. To further understand the clinical features and gaps in treatment approaches, we analyzed electronic medical record data from a midwestern US multidisciplinary healthcare system, between 2009 and 2020.

METHODS AND RESULTS: We retrospectively assessed the prevalence, clinical presentation, and treatment characteristics of individuals currently treated with statin therapy having a low-density lipoprotein cholesterol (LDL-C) value that is either (1) an *actual* maximum electronic medical record–documented LDL-C ≥190 mg/dL (group 1, n=7542) or (2) an *estimated* pretreatment LDL-C ≥190 mg/dL (group 2, n=7710). Comorbidities and prescribed lipid-lowering therapies were assessed. Statistical analyses identified differences among individuals within and between groups. Of records analyzed (n=266 282), 7% met the definition for primary severe hypercholesterolemia. Group 1 had more comorbidities than group 2. More individuals in both groups were treated by primary care providers (49.8%–53.0%, 32.6%–36.4%) than by specialty providers (4.1%–5.5%, 2.1%–3.3%). High-intensity lipid-lowering therapy was prescribed less frequently for group 2 than for group 1, but moderate-intensity statins were prescribed more frequently for group 2 (65%) than for group 1 (52%).

CONCLUSIONS: Two percent of patients in our study population being treated with low- or moderate-intensity statins have an *estimated* LDL-C ≥190 mg/dL (indicating severe hypercholesterolemia), but receive less aggressive treatment than patients with a maximum *measured* LDL-C ≥190 mg/dL.

Key Words: clinical inertia ■ electronic medical records ■ estimated LDL-C ■ familial hypercholesterolemia ■ gaps in care ■ lipid-lowering therapies ■ severe hypercholesterolemia ■ statin

The diagnostic criterion for severe hypercholesterolemia (SH) is low-density lipoprotein cholesterol (LDL-C) ≥190 mg/dL, regardless of underlying cause.[1–3] Individuals with SH have a 5-fold higher long-term risk for coronary heart disease and atherosclerotic cardiovascular disease (CVD), compared with individuals with average LDL-C levels.[4] Therefore, early diagnosis and aggressive therapy for SH may significantly reduce the clinical and economic burden of CVD worldwide.[2] Universal screening for both SH and familial hypercholesterolemia is the responsibility of all primary care providers (PCPs) and relevant specialty providers.[5] Managing SH includes modifying risk factors and treating with multiple lipid-lowering therapies (LLTs),[2] but recommended treatment guidelines are not universally implemented.[6,7] These guidelines recommend maximally tolerated statin therapy intensified with ezetimibe or with a PCSK9-I (proprotein convertase subtilisin/kexin type 9 inhibitor) in adults aged 20 to 75 years who have persistent LDL-C ≥100 mg/dL and other risk factors.[1] Yet there are several treatment gaps in this population,[7] including SH underdiagnosis

Correspondence to: Wael E. Eid, MD, St. Elizabeth Physicians Regional Diabetes Center, 1500 James Simpson Jr. Way, Suite 301, Covington, KY 41011. E-mail: wael.eid@usd.edu

Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.020800

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Lower-intensity statins, if used initially in patients with severe hypercholesterolemia rather than high-intensity statins, can mask the diagnosis of severe hypercholesterolemia and can contribute to clinical inertia.

What Are the Clinical Implications?

- Using electronic medical record data to estimate pretreatment low-density lipoprotein cholesterol is an easily implementable tool that potentially can facilitate severe hypercholesterolemia diagnosis in primary care and specialty practice.

Nonstandard Abbreviations and Acronyms

LLT	lipid-lowering therapy
PCSK9-I	proprotein convertase subtilisin/kexin type 9 inhibitor
SH	severe hypercholesterolemia

and consequent clinical inertia,[8] because SH can be masked in patients who are receiving a lower-intensity LLT (defined as any statin dose lower than atorvastatin [40 or 80 mg], or rosuvastatin [20 or 40 mg], or simvastatin [80 mg]).[1] To further understand the clinical features and treatment gaps for this population, we analyzed electronic medical record (EMR) data from a multidisciplinary healthcare system in the US Midwest to retrospectively assess the prevalence, clinical presentation, and treatment characteristics of 2 groups with active statin prescriptions: (1) those whose maximum EMR-recorded LDL-C was ≥190 mg/dL (group 1) and (2) those whose maximum EMR-recorded LDL-C was <190 mg/dL but ≥190 mg/dL when estimated (group 2).[1,9–14] Identifying gaps in screening and treatment between these 2 groups can reveal the factors that contribute to SH underdiagnosis and undertreatment, thus reducing atherosclerotic CVD incidence and improving care.[15]

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

We conducted a retrospective, records-based, cross-sectional study using data sets from unique EMRs of living patients presenting at a US metropolitan healthcare system. The study was approved by the St. Elizabeth Healthcare Institutional Review Board, and a waiver for informed consent was approved, allowing for retrospective data abstraction.

Using a dynamic EMR-based clinical decision-support tool, records of patients who had a clinical encounter for hypercholesterolemia in the St. Elizabeth Healthcare System between January 1, 2009, and April 30, 2020, were enrolled in a clinical query using Structured Query Language. The query identified every record of living inpatients and outpatients who had a documented LDL-C level throughout the identified date range (Figure 1). We used a validated formula (last recorded LDL-C multiplied by 1.43)[1,9–14] to calculate an estimated LDL-C for all individuals with an active statin prescription and selected all records showing a recorded or estimated maximum LDL-C ≥190 mg/dL. Records were excluded (n=981) for patients with uncontrolled secondary causes of dyslipidemia (including significant proteinuria and significantly uncontrolled hypothyroidism) at any time during the study time frame (Table 1)[16] and for those not prescribed statins (n=4443). This created 2 separate groups with an LDL-C ≥190 mg/dL: those with an EMR-documented value (group 1, n=7542) and those with an estimated value (group 2, n=7710).[17,18] The estimated LDL-C value helped identify possible SH masked by statin treatment, if the LDL-C recorded in the EMR was <190 mg/dL. A subgroup analysis (Table S1) compared groups 1 and 2 with a reference group that had a maximum LDL-C <130 mg/dL (whether EMR-documented or estimated) (Figure 1).

Comorbidities in the study population included coronary artery disease (CAD), type 1 and type 2 diabetes mellitus), essential hypertension, congestive heart failure, and obesity (Table 2). Comorbidities in the problem list of our EMR are continuously updated and reviewed by providers and by professional coders to ensure that the list always reflects the local population. We also assessed tobacco use and exposure, as well as use of different LLTs (statins, ezetimibe, and PCSK9-I). Statin intensity was classified according to the American College of Cardiology/American Heart Association cholesterol guidelines.[1]

Statistical Analysis

Data were analyzed using Minitab 18 Statistical Software.[24] Descriptive statistics for each group were computed either as count (percentage) for categorical variables or mean±standard deviation for quantitative variables (eg, Table 3). For binary categorical variables, simple group comparisons were made using *Z*-tests and confidence intervals (CIs) for proportions; for quantitative variables, *t*-tests and 95% CIs were used.

For subgroup analysis and comparison across specialties and age groups, 95% CIs arising from these

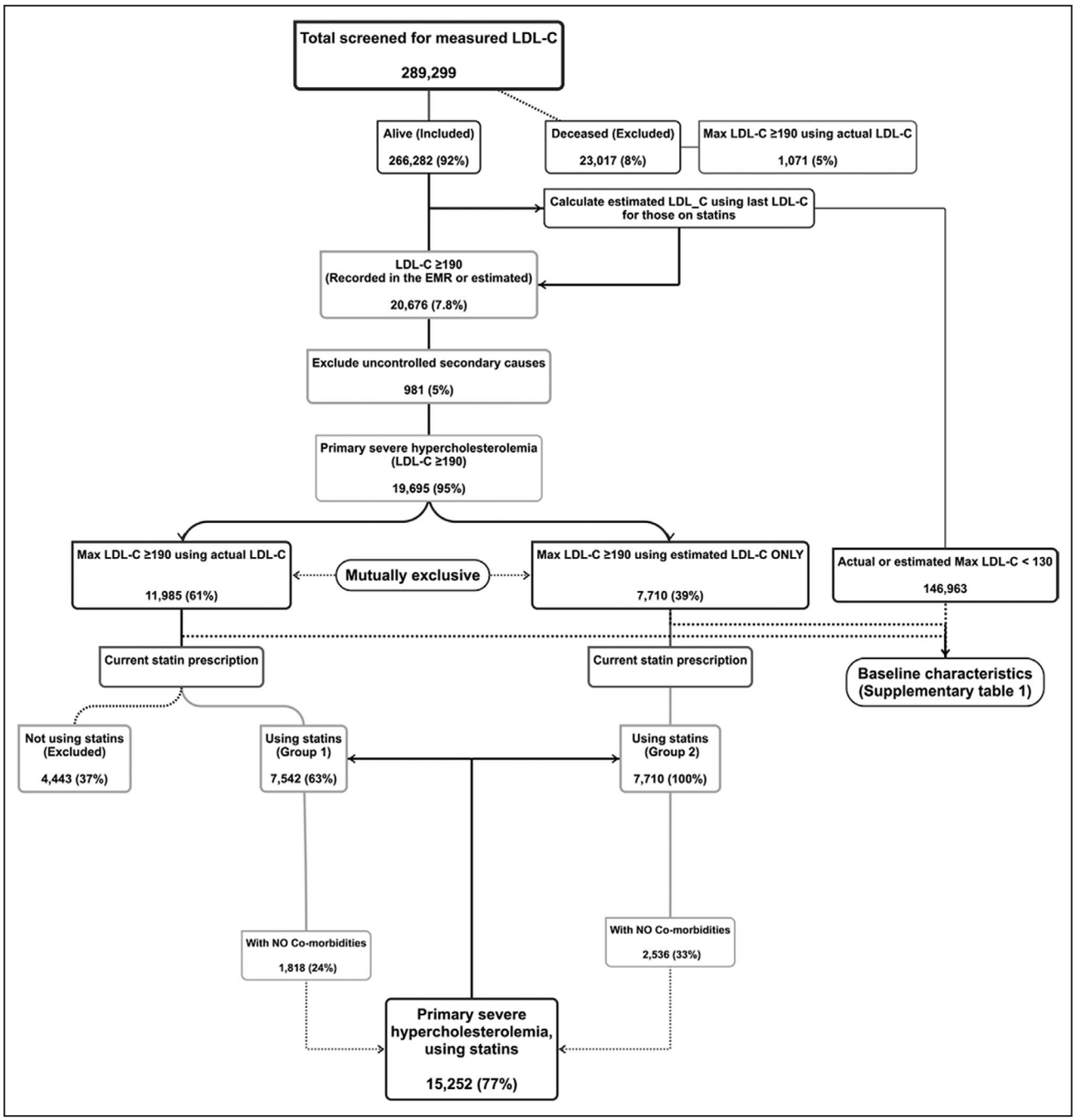


Figure 1. Distribution of screened population showing patients with an active statin prescription.
LDL-C values were estimated for every individual, using the last LDL-C value on record. Group 1 included those whose *actual* EMR-recorded LDL-C was ≥190 mg/dL. Group 2 included those whose maximum EMR-recorded LDL-C was <190 mg/dL, but whose *estimated* LDL-C was ≥190 mg/dL. EMR indicates electronic medical record; and LDL-C, low-density lipoprotein cholesterol.

models were used to estimate the prevalence of statin usage in each primary group; nonoverlapping CIs (group 1 versus group 2) for any particular specialty or age group are indicative of differences between the groups (group 1 versus group 2) for that cohort. Given the large sample sizes, the minimum distance between CIs can be reasonably interpreted as the lower bound on the amount by which the groups differ. A sensitivity analysis also was conducted to assess the impact of comorbidities (Data S1).

RESULTS

A total of 289 299 records were screened. After exclusions, 15 252 records (5.7%) of patients with active statin prescriptions and an LDL-C ≥190 mg/dL

Table 1. Distribution of Uncontrolled Secondary Causes of Dyslipidemia Among Living Patients With Severe Hypercholesterolemia*

Total Excluded=981	Uncontrolled Hypothyroidism†	Uncontrolled Proteinuria‡
Uncontrolled hypothyroidism	765	30
Uncontrolled proteinuria	30	246

*Low-density lipoprotein cholesterol ≥190 mg/dL.
†Thyrotropin >10 μU/mL more than once.
‡Urine microalbumin/creatinine ratio ≥1000 μg/mg more than once.

(EMR-documented or estimated) and no significant cause for secondary dyslipidemia were used for the analysis (Figure 1). Table 3 presents clinical and demographic characteristics for the study population.

Comparing group 1 with group 2, group 1 showed a higher prevalence of both premature and nonpremature CAD; slightly higher hierarchical condition category scores; and a higher prevalence of diabetes mellitus, congestive heart failure, hypertension, and obesity but a lower body mass index (95% CI for difference, 0.6–2.1; *P*=0.001), mean blood pressure, systolic blood pressure, and diastolic blood pressure than group 2. The most recently measured cholesterol values (total cholesterol, LDL-C, non–high-density lipoprotein, and triglycerides) were significantly lower in group 1 than group 2, and high-density lipoprotein was higher in group 1 than group 2. Although more patients in group 1 were tested for lipoprotein(a), there were no significant differences in lipoprotein(a) values between groups.

Although 95% of the total study population had persistently elevated LDL-C (≥100 mg/dL), only 42% of group 1 and 25% of group 2 were prescribed a high-intensity statin (Table 4). High-intensity statins, ezetimibe, and PCSK9-I were prescribed more frequently in group 1 than in group 2, while moderate- and low-intensity statins were prescribed more frequently in group 2 than in group 1. Despite this intensification, the data clearly show LLT was not intensified in either group using either ezetimibe or a PCSK9-I (Table 4).

Prescribing Patterns Between and Within Groups, Regardless of the Presence or Absence of the Identified Comorbidities

PCPs and endocrinologists used high-intensity statins, ezetimibe, and PCSK9-I more frequently in group 1 than in group 2 (Table 5, Figure 2, Figure S1, and Tables S2, S3).

There were some similarities where lower-intensity statins were used more often than high-intensity statins in both groups (Table 6 and Tables S1, S4, S5). High-intensity statins and ezetimibe were used more often in group 1 than in group 2, while moderate-intensity statins were used more often in group 2 than in group 1 (Table 6 and Tables S1, S4, S5).

Prescribing Patterns Between and Within Groups, in the Absence of the Identified Comorbidities

Comparing treatment between groups (Figure 2): PCPs prescribed moderate- and low-intensity statins more frequently in group 2 than in group 1. Cardiologists

Table 2. Diagnostic Criteria for Comorbidities in the Study Population

Diagnosis	Diagnostic Criteria	Reference
CAD	Active CAD diagnosis or *ICD-10:* I20, I21, I22, I23, I24, or I25 on the EMR problem list or having at least 3 instances of CAD appearing as an encounter diagnosis in the past 2 y or at least 3 CAD claim diagnoses in the last 2 y	19
Premature CAD	CAD occurring before age 55 y in males or 60 y in females	18
Ischemic cerebrovascular stroke	Active cerebrovascular stroke diagnosis or *ICD-10:* I63, I74, or I75 on the EMR problem list	19
Peripheral arterial disease	Active peripheral arterial disease diagnosis or *ICD-10:* I63, I74, or I75 on the EMR problem list	19
Diabetes mellitus	Active diabetes mellitus diagnosis on the EMR problem list or hemoglobin A_{1c} ≥6.5% more than once or random peripheral blood glucose >200 mg/dL plus hemoglobin A_{1c} ≥6.5% and no gestational diabetes mellitus	20
Obesity	Active obesity diagnosis on the EMR problem list or most recent body mass index ≥30 kg/m^2	21
Essential hypertension	Active essential hypertension diagnosis on the EMR problem list	22
Congestive heart failure	Active congestive heart failure diagnosis on the EMR problem list	23
High-intensity statin	Atorvastatin (40 or 80 mg) or rosuvastatin (20 or 40 mg) or simvastatin (80 mg)*	1
Moderate- or low-intensity statin	Any statin dose lower than the above-stated statin dose	1

CAD indicates coronary artery disease; EMR, electronic medical record; *ICD-10, International Classification of Diseases, Tenth Revision*.
*Although the use of simvastatin 80 mg is not recommended by the US Food and Drug Administration because of an increased risk for myopathy, some patient records still indicated this dose and were included in the analysis.

Table 3. Prevalence, Clinical Features, and Demographics of the Study Population*

	Group 1	Group 2	*P* Value* (for Difference)	95% CI for Differences
Prevalence, n (%)	7542 (49.45)	7710 (50.55)		
Age, y, mean±SD	60.3±12.2	58.1±12.2	<0.001	1.7 to 2.5
Men, n (%)	3070 (40.7)	3872 (50.2)	<0.001	7.9 to 11.1
Women, n (%)	4472 (59.3)	3838 (49.8)		
Comorbidities				
Total CAD and CVS, n (%)	1507 (20.0)	1204 (15.6)	<0.001	3.2 to 5.6
Premature CAD, n (%)	488 (6.5)	415 (5.4)	0.004	−0.3 to 1.8
Nonpremature CAD, n (%)	876 (11.6)	614 (8.0)	<0.001	2.7 to 4.6
Hierarchical condition category score	0.48	0.44	<0.001	0.03 to 0.05
Obesity,† n (%)	3300 (43.8)	2943 (38.2)	<0.001	4.0 to 7.1
Diabetes mellitus,‡ type 1 or type 2, n (%)	2046 (27.1)	1770 (23.0)	<0.001	2.8 to 5.5
Smoker—current, former, or passive, n (%)	3897 (51.7)	4086 (53.3)	0.055	0.0 to 3.1
Congestive heart failure,§ n (%)	369 (4.9)	240 (3.1)	<0.001	1.2 to 2.4
Hypertension,§ n (%)	4264 (56.5)	3448 (44.7)	<0.001	10.2 ton 13.4
Mean arterial blood pressure, mm Hg	94.8	95.8	<0.001	0.8 to 1.2
Systolic blood pressure, mm Hg	127.9	128.9	<0.001	0.6 to 1.3
Diastolic blood pressure, mm Hg	78.8	79.8	<0.001	0.8 to 1.2
Most recent cholesterol results (mean), mg/dL				
Total cholesterol	206	234	<0.001	26.8 to 29.7
Low-density lipoprotein	125	153	<0.001	26.9 to 29.4
Serum triglyceride	164	168	0.015	0.8 to 7.7
High-density lipoprotein	48.7	48.0	0.005	0.2 to 1.1
Non–high-density lipoprotein	157	186	<0.001	27.5 to 30.4
Patients tested for lipoprotein(a), n (%)	130 (1.7)	54 (0.7)	<0.001	0.1 to 1.4
Maximum lipoprotein(a)	57	44	0.096	−2.5 to 29.6
Current treatment, n (%)				
High-intensity statin‖ (%)	3322 (44.0)	1920 (24.9)	<0.001	17.7 to 20.6
Moderate-intensity statin (%)	3881 (51.5)	5045 (65.4)	<0.001	12.4 to 15.5
Low-intensity statin (%)	320 (4.2)	683 (8.9)	<0.001	3.8 to 5.4
Ezetimibe prescription (%)	409 (5.4)	132 (1.7)	<0.001	3.1 to 4.3
PCSK9-I prescription (%)	93 (1.2)	23 (0.3)	<0.001	0.7 to 1.2

CAD indicates coronary artery disease; CVS, ischemic cerebrovascular stroke; and PCSK9-I, proprotein convertase subtilisin/kexin type 9 inhibitor.

*Descriptive statistics are expressed as averages or counts (percentages), as appropriate: proportions tests for binary categorical data and *t*-tests for quantitative data.

†Obesity is defined as those with last body mass index ≥30.

‡Diabetes mellitus is defined by having active type 1 or type 2 diabetes mellitus on the EMR problem list, hemoglobin A_{1c} ≥6.5% more than once, or random blood glucose >200 mg/dL and hemoglobin A_{1c} ≥6.5%.

§Hypertension and congestive heart failure are indicated as active on the electronic medical record problem list.

‖High-intensity statin is defined as atorvastatin (40 or 80 mg) or rosuvastatin (20 or 40 mg) or simvastatin (80 mg).[1]

showed no difference in the use of statins, ezetimibe, or PCSK9-I in either group.

In comparing treatment within groups, there was no difference among PCPs, endocrinologists, and cardiologists in the use of high-, moderate-, or low-intensity statins (Table 5); however, PCPs and endocrinologists showed greater use of moderate- compared with high-intensity statins. There was no difference among PCPs, endocrinologists, and cardiologists in the use of ezetimibe or PCSK9-I, although endocrinologists prescribed ezetimibe and PCSK9-I slightly more than PCPs for group 1.

There was no difference in prescribing patterns for high-, moderate-, or low-intensity statins by age in group 1. However, in group 2, individuals aged <40 years were treated less frequently with high-intensity statins and more frequently with moderate-intensity statins, compared with individuals aged >40 years (Table 6).

We assessed the prevalence of patient visits to PCPs, endocrinologists, or cardiologists in the absence of any of the 5 identified comorbidities (Table 6). Although a large percentage of patients with SH in both groups did not have established care with a PCP, more patients in

Table 4. Lipid Treatment Status in Individuals With SH, an Active Statin Prescription, and Persistent LDL-C ≥100 mg/dL

SH Prevalence (LDL-C ≥100 mg/dL), n (%) n=14 490 (95%)	Active Prescription, n (%)				
	Low-Intensity Statin	Moderate-Intensity Statin	High-Intensity Statin	Ezetimibe	PCSK9-I
Group 1: 6781 (47)	326 (5)	3626 (53)	2829 (42)	334 (5)	64 (1)
Group 2: 7710 (53)	745 (10)	5045 (65)	1920 (25)	132 (2)	23 (0.3)
P value	<0.001	<0.001	<0.001	<0.001	<0.001
95% CI for difference* (%)	4–6	10–14	15–18	3–4	0.3–0.9

LDL-C indicates low-density lipoprotein cholesterol; PCSK9-I, proprotein convertase subtilisin/kexin type 9 inhibitor; and SH, severe hypercholesterolemia.
*Two-sample proportions tests/CIs.

group 1 had established PCP or endocrinology care than patients in group 2. The incidence of cardiology visits did not differ significantly between groups 1 and 2. Use of MyChart (electronic health record patient portal) was slightly higher in group 1, compared with group 2.

Comparing the Study Groups With the Reference Group

Analysis of the study groups compared with the reference group (Table S1) showed a subtle increased prevalence of CVD (CAD and ischemic cerebrovascular stroke) in group 1 compared with group 2, but a higher prevalence of CVD in both groups, compared with the referent population. Although there was minimal difference between groups 1 and 2 in the prevalence of premature CAD, both groups had a much higher prevalence of CAD than the reference group.

Prescribing Patterns Between and Within Groups, With Comorbidities

Two additional sensitivity analyses were performed. Table S2 and Figure S1 summarize the sensitivity analysis of prescribing patterns by clinical specialty for the study population (regardless of comorbidities). Tables S3 through S5 summarize an additional sensitivity analysis of the study population (clinical features, demographics, and treatment characteristics), including individuals with other comorbidities, but excluding those with CVD.

DISCUSSION

Management of SH has been reported previously for our study population[8] and for the general population.[1,7,8] Using direct laboratory reports (actual LDL-C values from EMR data) to identify individuals with SH

Table 5. Prescribing Patterns by Specialty for Patients Without Comorbidities

	Group 1 95% CI (%)	Group 2 95% CI (%)	*P* Value* (for Difference)	95% CI* for Differences (%)
Primary care				
High-intensity statin	28.9–34.6	13.1–18.0	<0.001	12.5 to 20.0
Moderate-intensity statin	59.9–65.8	71.8–77.7	<0.001	7.8 to 16.1
Low-intensity statin	4.1–7.0	7.6–11.6	0.001	1.7 to 6.5
Ezetimibe	2.2–4.5	0.3–1.5	<0.001	1.3 to 3.7
PCSK9-I	0.3–1.4	0.0–0.3	0.008	0.2 to 1.2
Endocrinology				
High-intensity statin	22.4–43.2	7.5–26.1	0.012	3.8 to 30.2
Moderate-intensity statin	50.7–72.3	52.4–76.5	0.681	–12.2 to 18.7
Low-intensity statin	2.0–13.3	9.8–29.6	0.024	1.6 to 22.8
Ezetimibe	5.9–20.8	0.4–10.5	0.031	0.8 to 16.9
PCSK9-I	2.0–13.3	0.0–4.4	0.021	0.9 to 11.0
Cardiology				
High-intensity statin	13.3–45.5	14.9–41.1	0.941	–18.8 to 20.3
Moderate-intensity statin	45.1–79.6	44.2–73.0	0.684	–17.0 to 25.9
Low-intensity statin	1.9–24.3	2.4–22.2	0.866	–11.8 to 14.1
Ezetimibe	0.1–15.8	0.0–5.9	0.310	–2.8 to 8.9
PCSK9-I	0.0–8.7	0.0–5.9	1.000	N/A

N/A indicates not applicable; and PCSK9-I, proprotein convertase subtilisin/kexin type 9 inhibitor.
*Two-sample proportions tests/CIs.

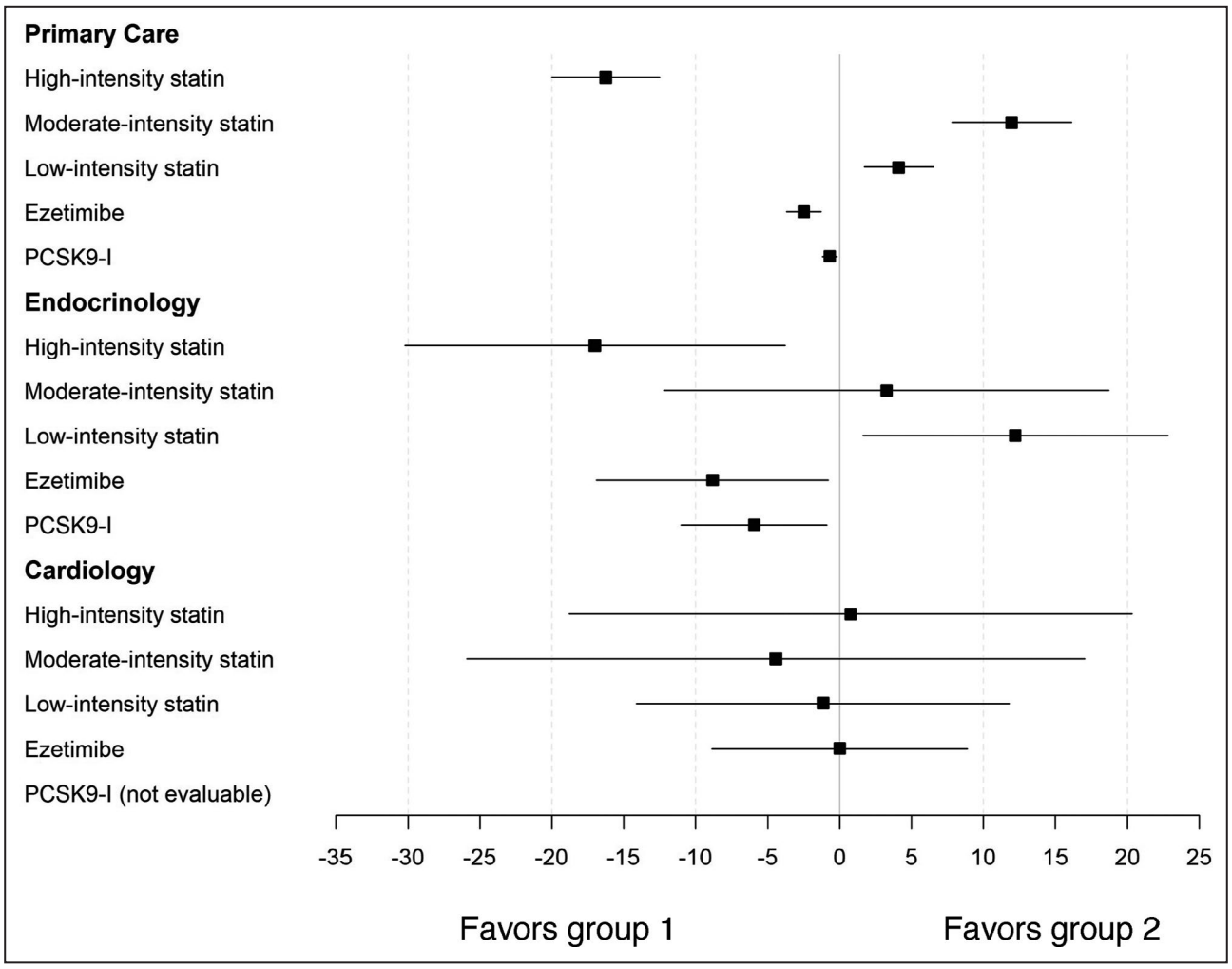


Figure 2. CIs (95%) estimating the mean difference in prescribing patterns by clinical specialty (group 2 minus group 1) for patients without comorbidities.
Solid black horizontal lines represent the CI for the difference between the groups. The solid black boxes are point estimate for the CI. PCSK9-I indicates proprotein convertase subtilisin/kexin type 9 inhibitor.

or with familial hypercholesterolemia also has been suggested previously,[25] and database methods[26] have been used to assess the prevalence of SH.[7,17,25–28] None of these studies reported adjusting for a treatment effect on LDL-C for individuals who have an active statin prescription. Our study reveals an additional gap in SH management: lack of identification of high-risk individuals attributable to the masking effects of suboptimal LLT, representing a lost opportunity to initiate appropriate and timely treatment in high-risk patients. When this treatment effect was included, SH prevalence increased to nearly 7%, similar to prevalence figures reported for familial hypercholesterolemia by Khera et al[3] and by the Analysis of the National Health and Nutrition Examination Survey.[10] To our knowledge, this is the first study to compare the clinical characteristics and treatment patterns of individuals diagnosed with SH based on an *estimated* LDL-C and individuals diagnosed based on an *actual* EMR-documented LDL-C.

SH Prevalence and Treatment Characteristics

Although both groups in our study population are at high-risk for CVD,[3,10] they had different clinical characteristics and were managed differently. In comparison with the reference group (maximum LDL-C <130 mg/dL), both groups 1 and 2 showed a substantial risk for atherosclerotic CVD and premature CAD. Group 1 had more comorbidities than group 2. Comorbidities in both groups are similar to those documented by studies[4,8,10] in which patients with SH have a higher burden of CVD and exhibited other CVD risk factors. Virani et al[29] showed that patients with more comorbidities are more likely to receive LLT intensification.

Table 6. Health System Usage and Active LLT Prescriptions for Groups 1 and 2 Without Comorbidities

	Group 1 (n=1818)	Group 2 (n=2536)
	95% CIs (%)	
Previous PCP appointment	49.8–53.0	32.6–36.4
PCP appointment scheduled	5.5–7.1	2.9–4.4
Established care with endocrinologist (has seen or will see)	4.1–5.5	2.1–3.3
Established care with cardiologist (has seen or will see)	2.5–3.7	2.1–3.4
MyChart enrollment	56.3–59.5	43.8–47.7
Active LLT prescriptions*		
High-intensity statin†	29.5–33.8	14.7–17.6
High-intensity by age group		
<40	16.4–31.7	4.4–13.5
40–75	30.5–35.2	15.2–18.4
>75	18.5–34.3	10.5–20.4
Moderate-intensity statin	58.8–63.4	70.0–73.6
Moderate-intensity by age group		
<40	60.0–76.6	75.0–87.5
40–75	58.0–62.9	69.7–73.6
>75	51.9–69.4	58.6–71.8
Low-intensity statin	5.6–8.0	9.7–12.2
Low-intensity by age group		
<40	2.7–11.9	5.8–15.7
40–75	5.2–7.7	9.2–11.9
>75	6.7–18.6	11.3–21.5
Ezetimibe	3.1–4.3	0.8–1.7

LLT indicates lipid-lowering therapies; PCP, primary care provider; and PCSK9-I, proprotein convertase subtilisin/kexin type 9 inhibitor.

*PCSK9-I prescriptions were too few, and therefore, not statistically significant.

†High-intensity statin intensity is defined as atorvastatin (40 or 80 mg) or rosuvastatin (20 or 40 mg) or simvastatin (80 mg).[1]

This might explain some of the treatment differences observed between our groups. Although the rate of treatment with statins in our study population (77%) is higher than that reported by the National Health and Nutrition Examination Survey (47.7%) and reflects other studies[6,10] showing that statin use in adults with SH may be increasing, actual statin use in individuals with SH from our study (63%) and others (52%–69%)[6,7,25] is not yet optimal.[1]

Decreased screening and diagnostic awareness of SH have been reported.[10] In previous surveys, 49% of providers in training and 53% of those in practice were unable to correctly identify the 4 statin benefit groups, including patients with SH,[30] and only 29% of providers in practice knew the definition of low-, moderate-, and high-intensity statin therapy.[30] Although the 30% to 40% use of high-intensity statins in group 1 (in the absence or presence of comorbidities) is similar to that reported nationally,[7,10] there may be a failure to identify *all* high-risk patients during routine clinical care whose current lower-intensity statin treatment masks an existing LDL-C ≥190 mg/dL. Not calculating an estimated LDL-C value to identify patients with SH may lead to decreased awareness of this high-risk population and to delayed implementation of guideline-based therapies.[1,27,30,31] This may partially explain the observed treatment gap and decreased lipid control for patients in group 2. Consequently, evidence of clinical inertia[32] is reflected in groups 1 and 2 but is more evident in group 2 because medication was not intensified as recommended by published clinical guidelines.[1,33] This is consistent with previous studies showing that the most frequent treatment intensification response is LLT *initiation*, rather than *intensification,* of already existing therapy.[29]

Health System Usage

In the absence of comorbidities, the number of patients who consulted a cardiologist was small and comparable for both groups 1 and 2, which might explain the lower prevalence of SH in cardiology practice registries and the smaller sample of patients in our study seen by cardiologists. This pattern (a majority of patients with SH having established PCP care versus specialty care) is similar to community care provided elsewhere and might be attributable to reduced awareness among clinicians of the significance of high LDL-C levels in SH patients or to infrequent use of coronary heart disease risk assessment tools.[6,15,30,31]

Prescribing Patterns

Previous studies have shown an age effect on statin prescribing.[6,10,25] Similarly, our data showed that patients' age correlated with the use of high- or low-intensity statins in group 2, but not in group 1. High-intensity statins were used less frequently in patients aged <40 years compared with older age groups, and moderate-intensity statins were used more frequently in middle-age groups, which is similar to other studies.[13]

Providers' prescribing patterns in this study are consistent with studies showing higher insurance approval rates for PCSK9-I prescriptions when prescribed by endocrinologists (odds ratio, 1.36; 95% CI, 1.15–1.93) or through a specialty pharmacy (odds ratio, 1.36; 95% CI, 1.06–1.73).[34] It also is consistent with reports revealing a knowledge gap in guideline recommendations between internal/family medicine providers (39%) and cardiology/endocrinology providers (67%).[7] Our results showed less aggressive LLT use by all providers for patients in group 2 compared with group 1, indicating reduced awareness regarding the significance of estimated LDL-C values.

Undertreatment of patients with SH has been reported previously.[1,7,8] This study illustrates a

double-treatment paradox in which 2 groups at high-risk for CVD were undertreated, with undertreatment occurring more frequently in one group than the other, reflecting a general assumption of, "You cannot manage what you don't measure. You manage what you know and measure."[35,36]

Study Limitations

We did not assess patients' LLT adherence and have described treatments recorded in the EMR as "active prescriptions" but could not determine if suboptimal management was attributable to patient preference, including statin intolerance. This approach might imperfectly estimate adjusted LDL-C values, given the heterogeneity in drug selection, dosing, response, familial hypercholesterolemia mutation status, and variability across baseline LDL-C levels.[3] However, in a study by Bucholz et al,[10] varying the LDL-C multiplier for statin therapy based on whether a lower- or higher-intensity LLT was used did not significantly affect the sensitivity analysis. In addition, some LDL samples might have been from nonfasting patients, which would increase the estimated LDL-C value and lead to an overestimated prevalence. At least one study suggests that routine nonfasting lipid measurements might facilitate atherosclerotic CVD risk screening and treatment, including consideration of when to initiate statin therapy.[37] We used only one LDL-C ≥190 mg/dL measurement (either *actual* maximum EMR-documented or *estimated* pretreatment) in our analysis. Although there may be some concerns about spurious laboratory results with a single value measurement, we excluded obvious common secondary causes of dyslipidemia and the total prevalence of those with SH-matched nationally reported data.[3,9] Lack of evidence of a difference in the use of LLT by cardiologists or endocrinologists in group 1 or 2 (in the absence of comorbidities) likely reflects the limited power to do such analysis, since a difference in LLT use was present when tested for the entire study population (Table S1). We did not include family history of premature CAD in our analysis which, if present, might indicate familial hypercholesterolemia and consequently affect treatment characteristics.

In conclusion, calculating an estimated LDL-C value revealed an additional 3% of the study population at our midwestern US regional health system to have undiagnosed primary SH. This demonstrates that SH can be masked in patients receiving statin treatment and underdiagnosed if an estimated LDL-C value is not calculated. Although this population has a higher CVD risk than the general population, treatment is not adequately optimized compared with guideline-approved treatment for individuals who have an actual EMR-documented LDL-C measurement. Further studies can assess the validity of considering incorporating estimated LDL-C values in the EMR of patients using statins to properly diagnose SH and to treat this high-risk population.

ARTICLE INFORMATION

Received March 18, 2021; accepted June 21, 2021.

Affiliations

St. Elizabeth Physicians Regional Diabetes Center, Covington, KY (W.E.E.); University of Kentucky College of Medicine, Lexington, KY (W.E.E.); University of South Dakota Sanford School of Medicine, Sioux Falls, SD (W.E.E.); Faculty of Medicine, University of Alexandria, Alexandria, Egypt (W.E.E.); St. Elizabeth Healthcare, Edgewood, KY (E.H.S.); and Department of Mathematics and Statistics, Northern Kentucky University, Highland Heights, KY (E.F., J.R.N.).

Acknowledgments

We thank Amy Neil McBride, MS, MAP, for editing assistance, and Krista Doerman and Jeff Gunderson for IT support. We also thank St. Elizabeth Physicians for financial support of the statistical analysis and the Burkardt Consulting Center at Northern Kentucky University for conducting the statistical analysis.

Sources of Funding

This research received funding from St. Elizabeth Physicians, a not-for-profit organization, to support statistical analysis of the data.

Disclosures

Dr Eid is on the speaker bureau of Amgen and Esperion Pharmaceuticals. The remaining authors have no disclosures to report.

Supplementary Material

Data S1
Tables S1–S5
Figure S1

REFERENCES

1. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary. *Circulation*. 2018;73:CIR0000000000000624. DOI: 10.1016/j.jacc.2018.11.002.
2. Sniderman AD, Tsimikas S, Fazio S. The severe hypercholesterolemia phenotype: clinical diagnosis, management, and emerging therapies. *J Am Coll Cardiol*. 2014;63:1935–1947. DOI: 10.1016/j.jacc.2014.01.060.
3. Khera AV, Won H-H, Peloso GM, Lawson KS, Bartz TM, Deng X, van Leeuwen EM, Natarajan P, Emdin CA, Bick AG, et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. *J Am Coll Cardiol*. 2016;67:2578–2589. DOI: 10.1016/j.jacc.2016.03.520.
4. Perak AM, Ning H, de Ferranti SD, Gooding HC, Wilkins JT, Lloyd-Jones DM. Long-term risk of atherosclerotic cardiovascular disease in us adults with the familial hypercholesterolemia phenotype. *Circulation*. 2016;134:9–19. DOI: 10.1161/CIRCULATIONAHA.116.022335.
5. Hopkins PN, Toth PP, Ballantyne CM, Rader DJ; National Lipid Association Expert Panel on Familial H. Familial hypercholesterolemias: prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011;5:S9–S17. DOI: 10.1016/j.jacl.2011.03.452.
6. Rodriguez F, Knowles JW, Maron DJ, Virani SS, Heidenreich PA. Frequency of statin use in patients with low-density lipoprotein cholesterol >/=190 mg/dl from the Veterans Affairs Health System. *Am J Cardiol*. 2018;122:756–761. DOI: 10.1016/j.amjcard.2018.05.008.
7. Virani SS, Kennedy KF, Akeroyd JM, Morris PB, Bittner VA, Masoudi FA, Stone NJ, Petersen LA, Ballantyne CM. 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. DOI: 10.1161/CIRCOUTCOMES.118.00465.
8. Eid WE, Sapp EH, McCreless T, Nolan JR, Flerlage E. Prevalence and characteristics of patients with primary severe hypercholesterolemia in a multidisciplinary healthcare system. *Am J Cardiol*. 2020;132:59–65. DOI: 10.1016/j.amjcard.2020.07.008.
9. de Ferranti SD, Rodday AM, Mendelson MM, Wong JB, Leslie LK, Sheldrick RC. Prevalence of familial hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES). *Circulation*. 2016;133:1067–1072. DOI: 10.1161/CIRCULATIONAHA.115.018791.
10. Bucholz EM, Rodday AM, Kolor K, Khoury MJ, de Ferranti SD. Prevalence and predictors of cholesterol screening, awareness, and statin treatment among US adults with familial hypercholesterolemia or other forms of severe dyslipidemia (1999–2014). *Circulation*. 2018;137:2218–2230. DOI: 10.1161/CIRCULATIONAHA.117.032321.
11. Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Familial hypercholesterolemia in the Danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. *J Clin Endocrinol Metab*. 2012;97:3956–3964. DOI: 10.1210/jc.2012-1563.
12. Edwards JE, Moore RA. Statins in hypercholesterolaemia: a dose-specific meta-analysis of lipid changes in randomised, double blind trials. *BMC Fam Pract*. 2003;4:18. DOI: 10.1186/1471-2296-4-18.
13. Myocardial Infarction Genetics Consortium I, Stitziel NO, Won HH, Morrison AC, Peloso GM, Do R, Lange LA, Fontanillas P, Gupta N, Duga S, Goel A, et al. Inactivating mutations in NPC1L1 and protection from coronary heart disease. *N Engl J Med*. 2014;371:2072–2082.
14. Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Mutations causative of familial hypercholesterolaemia: screening of 98 098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217. *Eur Heart J*. 2016;37:1384–1394. DOI: 10.1093/eurheartj/ehw028.
15. Representatives of the Global Familial Hypercholesterolemia C, Wilemon KA, Patel J, Aguilar-Salinas C, Ahmed CD, Alkhnifsawi M, Almahmeed W, Alonso R, Al-Rasadi K, Badimon L, Bernal LM, et al. Reducing the clinical and public health burden of familial hypercholesterolemia: a global call to action. *JAMA Cardiol*. 2020;5:217–229. DOI: 10.1001/jamacardio.2019.5173.
16. Yanai H, Yoshida H. Secondary dyslipidemia: its treatments and association with atherosclerosis. *Glob Health Med*. 2021;3:15–23. DOI: 10.35772/ghm.2020.01078.
17. Abul-Husn NS, Manickam K, Jones LK, Wright EA, Hartzel DN, Gonzaga-Jauregui C, O'Dushlaine C, Leader JB, Lester Kirchner H, Lindbuchler DM, et al. Genetic identification of familial hypercholesterolemia within a single U.S. health care system. *Science*. 2016;354:aaf7000. DOI: 10.1126/science.aaf7000.
18. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, Wiklund O, Hegele RA, Raal FJ, Defesche JC, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J*. 2013;34:3478–3490. DOI: 10.1093/eurheartj/eht273.
19. National Center for Health Statistics. Center for Disease Control and Prevention. Available at: https://icd10cmtool.cdc.gov/?fy=FY2021. Accessed May 29, 2021.
20. American Diabetes A. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2020. *Diabetes Care*. 2020;43(Suppl 1):S14–S31. DOI: 10.2337/dc20-S002.
21. Defining adult overweight and obesity. Center for Disease Control and Prevention. Available at: https://www.cdc.gov/obesity/adult/defining.html. Accessed May 29, 2021.
22. Boisvenue JJ, Oliva CU, Manca DP, Johnson JA, Yeung RO. Feasibility of identifying and describing the burden of early-onset metabolic syndrome in primary care electronic medical record data: a cross-sectional analysis. *CMAJ Open*. 2020;8:E779–E787. DOI: 10.9778/cmajo.20200007.
23. Xu Y, Lee S, Martin E, D'souza AG, Doktorchik CTA, Jiang J, Lee S, Eastwood CA, Fine N, Hemmelgarn B, et al. Enhancing ICD-code-based case definition for heart failure using electronic medical record data. *J Card Fail*. 2020;26:610–617. DOI: 10.1016/j.cardfail.2020.04.003.
24. *Minitab 18 Statistical Software*. [computer program]. Version Minitab 18. State College, PA: Minitab, Inc.; 2010.
25. Al-Kindi SG, DeCicco A, Longenecker CT, Dalton J, Simon DI, Zidar DA. Rate of statin prescription in younger patients with severe dyslipidemia. *JAMA Cardiol*. 2017;2:451–452. DOI: 10.1001/jamacardio.2016.5162.
26. Gold ME, Nanna MG, Doerfler SM, Schibler T, Wojdyla D, Peterson ED, Navar AM. Prevalence, treatment, and control of severe hyperlipidemia. *Am J Prev Cardiol*. 2020;3:100079. DOI: 10.1016/j.ajpc.2020.100079.
27. Rodriguez F, Knowles JW. Enough evidence, time to act! *Circulation*. 2016;134:20–23. DOI: 10.1161/CIRCULATIONAHA.116.023010.
28. Elshazly MB, Martin SS, Blaha MJ, Joshi PH, Toth PP, McEvoy JW, Al-Hijji MA, Kulkarni KR, Kwiterovich PO, Blumenthal RS, et al. Non-high-density lipoprotein cholesterol, guideline targets, and population percentiles for secondary prevention in 1.3 million adults: the VLDL-2 study (very large database of lipids). *J Am Coll Cardiol*. 2013;62:1960–1965. DOI: 10.1016/j.jacc.2013.07.045.
29. Virani SS, Woodard LD, Chitwood SS, Landrum CR, Urech TH, Wang D, Murawsky J, Ballantyne CM, Petersen LA. Frequency and correlates of treatment intensification for elevated cholesterol levels in patients with cardiovascular disease. *Am Heart J*. 2011;162:725–732.e1. DOI: 10.1016/j.ahj.2011.07.013.
30. Virani SS, Pokharel Y, Steinberg L, Chan W, Akeroyd JM, Gowani SA, Kalra A, Polsani V, Miedema MD, Jones PH, et al. Provider understanding of the 2013 ACC/AHA cholesterol guideline. *J Clin Lipidol*. 2016;10:497–504.e4. DOI: 10.1016/j.jacl.2015.11.002.
31. Shillinglaw B, Viera AJ, Edwards T, Simpson R, Sheridan SL. Use of global coronary heart disease risk assessment in practice: a cross-sectional survey of a sample of U.S. physicians. *BMC Health Serv Res*. 2012;12:20. DOI: 10.1186/1472-6963-12-20.
32. O'Connor PJ, Sperl-Hillen JAM, Johnson PE, Rush WA, Biltz G. Clinical inertia and outpatient medical errors. In: Henriksen K, Battles JB, Marks ES, Lewin DI, eds. *Advances in Patient Safety: From Research to Implementation (Volume 2: Concepts and Methodology)*. Rockville, MD: Agency for Healthcare Research and Quality (US); 2005:293–308.
33. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, 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. *J Am Coll Cardiol*. 2014;63:2889–2934. DOI: 10.1016/j.jacc.2013.11.002.
34. Doshi JA, Li P, Puckett JT, Pettit AR, Raman S, Parmacek MS, Rader DJ. Trends and factors associated with insurer approval of proprotein convertase subtilisin/kexin type 9 inhibitor prescriptions. *Value Health*. 2020;23:209–216. DOI: 10.1016/j.jval.2019.08.011.
35. Aita A, Sciacovelli L, Plebani M. Laboratory-related errors: you cannot manage what you don't measure. You manage what you know and measure. *Diagnosis (Berl)*. 2017;4:193–195. DOI: 10.1515/dx-2017-0038.
36. Soriano BD, Rudberg K, Stevenson JG. Going beyond right and wrong: building the framework for quality improvement in congenital echocardiography–you can't manage what you don't measure. *J Am Soc Echocardiogr*. 2014;27:624–626. DOI: 10.1016/j.echo.2014.04.007.
37. Mora S, Chang CL, Moorthy MV, Sever PS. Association of nonfasting vs fasting lipid levels with risk of major coronary events in the Anglo-Scandinavian Cardiac Outcomes Trial-lipid lowering arm. *JAMA Intern Med*. 2019;179:898–905. DOI: 10.1001/jamainternmed.2019.0392.

SUPPLEMENTAL MATERIAL

Data S1.

Sensitivity analyses of prescribing patterns by clinical specialty for each group were performed for the study population, regardless of comorbidities (Table S2 and Figure S1):

Comparing prescribing patterns between groups 1 and 2

- PCPs and endocrinologists prescribed high-intensity statins, ezetimibe, and PCSK9-I more frequently in group 1 than in group 2, and moderate- and low-intensity statins more frequently in group 2 than in group 1 (similar to those with no comorbidities).
- Cardiologists showed the same prescribing patterns for high-intensity statins and ezetimibe, but not for PCSK9-I, largely due to the small sample size for this group (Table S2).

Comparing prescribing patterns within groups 1 and 2

- Both groups:
    - Endocrinologists prescribed more high-intensity statins than PCPs.
    - PCPs prescribed more moderate-intensity statins than endocrinologists.
    - PCPs showed greater use of moderate- compared with high-intensity statins.
    - This is the same pattern as that identified for the total population after exclusion of those with CVD comorbidity.
- Group 1
    - PCPs showed greater use of moderate-intensity statins and endocrinologists showed greater use of high-intensity statins.
    - Endocrinologists prescribed ezetimibe and PCSK9-I more than PCPs.
- Group 2

- PCPs, cardiologists, and endocrinologists showed greater use of moderate- compared with high-intensity statins. This is the same pattern as that identified for the total population after exclusion of those with CVD comorbidity.

A sensitivity analysis of clinical features, demographics, and treatment characteristics also was conducted for the study population in the presence of the other identified comorbidities, but excluding those with CVD (tables S3, S4, S5).

Comparing prescribing patterns between groups 1 and 2

- PCPs and endocrinologists prescribed high-intensity statins, ezetimibe, and PCSK9-I more frequently in group 1 than in group 2 (similar to those with no comorbidities).
- PCPs and endocrinologists prescribed moderate- and low-intensity statins more frequently in group 2 than in group 1.
- Cardiologists showed the same prescribing pattern for high-intensity statins and ezetimibe, but not for PCSK9-I (largely due to the small sample size for this group) (Table S5).

Comparing prescribing patterns within groups 1 and 2

- Both groups
  - Endocrinologists prescribed more high-intensity statins than PCPs.
  - PCPs prescribed more moderate-intensity statins than endocrinologists.
  - PCPs showed greater use of moderate- compared with high-intensity statins
  - This is the same pattern as that identified for the total population with all identified comorbidities.
- Group 1

    - Endocrinologists prescribed ezetimibe and PCSK9-I slightly more than PCPs for group 1.
- Group 2
    - PCPs, cardiologists, and endocrinologists showed greater use of moderate- compared with high-intensity statins in group 2. This is the same pattern as that identified for the total population with all identified comorbidities.

There was no difference in prescribing patterns for high-, moderate-, or low-intensity statins by age in group 2. However, in group 1, individuals younger than 40 years or older than 75 years were treated less frequently with high-intensity statins, compared with the middle age group (Table S4).

Although more patients were seen by PCPs in general (Table S4) than in the absence of all identified comorbidities (Table 5), we observed the same health system usage: more patients in group 1 had established PCP or endocrinology care, and to some extent cardiology care, than patients in group 2. This might be due to the higher rate of comorbidities in group 1 than in group 2 (Table S3).

Table S1. Prevalence, Clinical Features, and Demographics of Groups 1 and 2 Compared with the Reference Group[*]

	Group 1 (Actual LDL-C ≥ 190 mg/dL)	**Group 2 (Estimated LDL-C ≥190 mg/dL)**	**Reference Group Actual or Estimated LDL-C < 130**	**95% CI of differences (Group 1 – Group 2)**	**95% CI of differences (Group 1 – Group 3)**	**95% CI of differences (Group 2 – Group 3)**
Prevalence (n,%)	11985 (7.2%)	7710 (4.6%)	146963 (88.2%)			
Age (mean, yrs.)	59.8	58.1	51.9	1.3-2.0[**]	7.6-8.2[**]	5.9-6.5[**]
SD	13.4	12.3	18.7			
Males (n, %)	4663 (38.9%)	3872 (50.2%)	68051 (46.3%)	10.0-12.7%[**]	6.5-8.3%[**]	2.8-5.1%[**]
Females (n, %)	7322 (61.1%)	3838 (49.8%)	78903 (53.7%)			
Comorbidities (n, %)						
Total CAD and CVS	1998 (16.7%)	1204 (15.6%)	16440 (11.2%)	0.0-2.1%[#]	4.8-6.2%[**]	3.6-5.3%[**]
Premature CAD	590 (4.9%)	415 (5.4%)	2481 (1.7%)	-0.1-1.1%	2.8-3.6%[**]	3.2-4.2%[**]
Non-premature CAD	1230 (10.3%)	614 (8.0%)	12518 (8.5%)	1.5-3.1%[**]	1.2-2.3%[**]	-0.1-1.2%
Hierarchical Condition Category (HCC) score	0.48	0.44	0.42	0.03-0.05[**]	0.05-0.06[**]	0.01-0.03[**]
Obesity[†]	4801 (40.1%)	2943 (38.2%)	49719 (33.8%)	0.5-3.3%[#]	5.3-7.1%[**]	3.2-5.5%[**]
Diabetes[‡] (T1 or T2)	2739 (22.9%)	1770 (23.0%)	24422 (16.6%)	-1.1-1.3%	5.5-7.0%[**]	5.4-7.3%[**]

Smoker (current, former or passive)	5966 (50.4%)	4086 (53.3%)	63174 (44.2%)	1.5-4.4%**	5.2-7.1%**	7.9-10.2%**
Congestive heart failure§	518 (4.3%)	240 (3.1%)	5203 (3.5%)	0.7-1.7%**	0.4-1.2%**	0.0-0.8%*
Hypertension§	6039 (50.4%)	3448 (44.7%)	47670 (32.4%)	4.2-7.1%**	17.0-18.9%**	11.1-13.4%**
Mean arterial blood pressure (mm Hg)	94.6	95.8	92.1	1.0-1.4**	2.4-2.7**	3.6-3.9**
Systolic blood pressure (mm Hg)	127.7	128.9	124.1	0.9-1.5**	3.4-3.8**	4.5-5.0**
Diastolic blood pressure (mm Hg)	78.7	79.8	76.6	1.0-1.4**	2.0-2.2**	3.1-3.4**
Most recent cholesterol results (mean) (mg/dL)						
Total cholesterol	223	234	161	9.7-12.2**	61.2-63.4**	72.7-73.9**
Low-density lipoprotein	141	153	86	11.0-13.0**	54.5-56.4**	67.1-67.8**
Serum triglyceride	166	168	120	-0.9-5.2	44.1-48.3**	46.1-50.7**
High-density lipoprotein	49	48	51	0.9-1.7**	1.8-2.3**	3.1-3.7**
Non-high-density lipoprotein	174	186	110	11.1-13.5**	63.3-65.5**	76.1-77.3**
Patients tested for LP(a) (n,%)	182 (1.5%)	54 (0.7%)	829 (0.6%)	0.5-1.1%**	0.7-1.2**	-0.1-0.3%
Max LP(a) (mg/dL)	57	44	37	-1.6-27.7	9.3-29.8**	-5.1-18.0
Current treatment (n, %)						
High-intensity statin‖	3322 (27.7%)	1920 (24.9%)	10136 (6.9%)	1.6-4.1%**	17.0-20.0-21.6%**	19.0%**
Moderate-intensity statin	3881 (32.4%)	5045 (65.4%)	18851 (12.8%)	31.7-34.4%**	18.7-20.4%**	51.5-

						53.7%**
Low-intensity statin	320 (2.7%)	683 (8.9%)	2383 (1.6%)	5.5-6.9%**	0.7-1.3%**	6.6-7.9%**
ezetimibe	732 (6.1%)	132 (1.7%)	1415 (1.0%)	3.9-4.9%**	4.7-5.6%**	0.5-1.0%**
PCSK9-I	250 (2.1%)	23 (0.3%)	84 (0.1%)	1.5-2.1%**	1.8-2.3%**	0.1-0.4%**

* Descriptive statistics are expressed as averages or counts (percentages), as appropriate: T-tests for quantitative data; proportions tests for binary categorical data.

† Obesity is defined as those with last body mass index ≥ 30.

‡ Diabetes is defined by having active type 1 or type 2 diabetes mellitus on the electronic medical record problem list, or having a hemoglobin A1c ≥ 6.5% more than onc

random blood glucose > 200 mg/dL and a hemoglobin A1c ≥ 6.5%.

§ Hypertension and congestive heart failure are indicated as active on the electronic medical record problem list.

‖ High-intensity statin is defined as atorvastatin (40 mg or 80 mg) or rosuvastatin (20 mg or 40 mg).[1]

$0.001 < P < 0.05$

** $P < 0.001$

Abbreviations: LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein a; PCSK9-I, proprotein convertase subtilisin/kexin type 9 inhibitor.

Table S2. Prescribing Patterns by Specialty.

	Group 1	Group 2	*P* value * of differences	95% CI * of differences
Primary care				
High-intensity statin	43.3-45.9%	23.7-26.3%	<0.001	17.8-21.4%
Moderate-intensity statin	50.3-52.9%	65.6-68.4%	<0.001	13.4-17.3%
Low-intensity statin	3.2-4.2%	7.1-8.7%	<0.001	3.2-5.1%
ezetimibe	4.7-5.9%	1.2-2.0%	<0.001	3.0-4.4%
PCSK9-I	1.1-1.7%	0.2-0.6%	<0.001	0.6-1.3%
Endocrinology				
High-intensity statin	52.8-59.1%	27.8-35.3%	<0.001	19.7-29.3%
Moderate-intensity statin	37.5-43.8%	54.8-62.7%	<0.001	13.2-23.1%
Low-intensity statin	2.3-4.6%	7.0-11.6%	<0.001	3.2-8.3%
ezetimibe	8.0-11.9%	1.7-4.5%	<0.001	4.7-9.2%
PCSK9-I	3.9-6.8%	0.3-1.9%	<0.001	2.8-5.9%
Cardiology				
High-intensity statin	47.6-57.6%	29.8-43.1%	<0.001	8.3-24.5%
Moderate-intensity statin	38.9-48.9%	48.0-61.7%	0.009	2.8-19.3%
Low-intensity statin	1.9-5.8%	4.0-11.2%	0.080	-0.4-7.3%
ezetimibe	7.1-13.2%	1.0-6.0%	<0.001	3.4-10.7%
PCSK9-I	1.6-5.2%	0.3-4.0%	0.166	-0.7-3.9%

* Two-sample proportions tests / confidence intervals.

Abbreviation: PCSK9-I, proprotein convertase subtilisin/kexin type 9 inhibitor.

Table S3. Prescribing Patterns by Specialty for Patients without Cardiovascular Disease

	Group 1 95% CI	Group 2 95% CI	*P* value* of differences	95% CI* of differences
Primary care				
High-intensity statin	38.3-41.2%	19.9-22.5%	<0.001	16.7-20.5%
Moderate-intensity statin	54.7-57.6%	68.7-71.6%	<0.001	11.9-16.1%
Low-intensity statin	3.5-4.6%	7.6-9.4%	<0.001	3.4-5.5%
ezetimibe	3.4-4.5%	0.9-1.6%	<0.001	2.1-3.4%
PCSK9-I	0.4-0.8%	0.0-0.3%	0.001	0.2-0.7%
Endocrinology				
High-intensity statin	47.5-54.9%	25.8-33.7%	<0.001	16.3-26.9%
Moderate-intensity statin	40.6-47.9%	55.9-64.3%	<0.001	10.4-21.4%
Low-intensity statin	3.0-6.1%	7.2-12.3%	0.001	2.2-8.0%
ezetimibe	5.0-8.8%	1.2-3.9%	<0.001	2.3-6.7%
PCSK9-I	1.5-3.9%	0.0-1.0%	<0.001	1.1-3.5%
Cardiology				
High-intensity statin	37.8-48.2%	21.0-32.0%	<0.001	9.3-24.1%
Moderate-intensity statin	47.6-58.1%	57.8-69.7%	0.007	3.2-18.7%
Low-intensity statin	2.3-6.7%	5.3-12.4%	0.034	0.3-8.2%
ezetimibe	3.6-8.7%	0.6-4.4%	0.009	1.0-6.8%
PCSK9-I	0.6-3.6%	0.1-2.7%	0.298	-0.8%-2.6%

* Two-sample proportions tests / confidence intervals.
Abbreviation: PCSK9-I, proprotein convertase subtilisin/kexin type 9 inhibitor.

Table S4. Prevalence, Clinical Features, and Demographics of the Study Population Excluding those with Cardiovascular Disease

	Group 1	Group 2	*P* value * of differences	95% CI * of differences
Prevalence (%)	6035 (48.12%)	6506 (51.88%)		
Age (Mean ± SD)	58.8 ± 12.0	57.1 ± 12.0	<0.001	1.2-2.1
Males (%)	2398 (39.7%)	3174 (48.8%)	<0.001	7.3-10.8%
Females (%)	3637 (60.3%)	3332 (51.2%)		
Comorbidities				
Total CAD and CVS (%)	0	0	NA	NA
Premature CAD (%)	0	0	NA	NA
Non-premature CAD (%)	0	0	NA	NA
Hierarchical Condition Category (HCC)	0.43	0.40	<0.001	0.02-0.04
Obesity† (%)	2621 (43.4%)	2514 (38.6%)	<0.001	3.1-6.5%
Diabetes‡ type 1 or type 2 (%)	1399 (23.2%)	1404 (21.6%)	<0.001	0.1-3.1%
Smoker- current, former or passive (%)	2909 (48.3%)	3250 (50.2%)	0.029	0.2-3.7%
Congestive heart failure§ (%)	119 (2.0%)	93 (1.4%)	0.019	0.1-1.0%
Hypertension§ (%)	3093 (51.3%)	2724 (41.9%)	<0.001	7.6-11.1%
Mean arterial blood pressure (mmHg)	94.9	95.9	<0.001	0.7-1.2
Systolic blood pressure (mmHg)	127.6	128.7	<0.001	0.8-1.5
Diastolic blood pressure (mmHg)	79.1	80.0	<0.001	0.7-1.1
Most recent cholesterol results (mean) (mg/dL)				
Total cholesterol	210	235	<0.001	23.4-26.6
Low-density lipoprotein	129	154	<0.001	23.4-26.1
Serum triglyceride	162	167	0.005	1.6-9.2
High-density lipoprotein	49.4	48.7	0.006	0.2-1.2
Non-high-density lipoprotein	161	186	<0.001	24.2-27.3
Patients tested for lipoprotein(a)	81 (1.3%)	42 (0.6%)	<0.001	0.3-1.0%
Maximum lipoprotein(a)	49	44	0.643	-14.0-22.6
Current treatment				
High-intensity statin ‖ (%)	2352 (39.0%)	1336 (20.5%)	<0.001	16.8-20.0%
Moderate-intensity statin (%)	3385 (56.1%)	4490 (69.0%)	<0.001	11.2-14.6%
Low-intensity statin (%)	281 (4.7%)	626 (9.6%)	<0.001	4.1-5.9%
Ezetimibe prescription (%)	245 (4.1%)	82 (1.3%)	<0.001	2.2-3.4%
PCSK9-I prescription (%)	30 (0.5%)	8 (0.1%)	<0.001	0.2-0.6%

* Descriptive statistics are expressed as averages or counts (percentages), as appropriate: T-tests for quantitative data; proportions tests for binary categorical data.

† Obesity is defined as those with last body mass index ≥30.

‡ Diabetes is defined by having active diabetes mellitus on the electronic medical record problem list, hemoglobin A1c ≥ 6.5% more than once, or random blood glucose > 200 mg/dl and hemoglobin A1c ≥ 6.5%.

§ Hypertension and congestive heart failure are indicated as active on the electronic medical record problem list.

‖ High-intensity statin is defined as atorvastatin (40 mg or 80 mg) or rosuvastatin (20 mg or 40 mg) or simvastatin (80 mg).[1]

Abbreviations: CAD, coronary artery disease; CVS, ischemic cerebrovascular stroke; PCSK9-I, proprotein convertase subtilisin/kexin type 9 inhibitor.

Table S5. Health System Usage and Active LLT[*] Prescriptions for Groups 1 and 2 without Cardiovascular Disease

		Group 1 n=6035	Group 2 n=6506
		95% Confidence Intervals (%)	
Previous PCP appointment		74.8-77.0%	56.3-58.8%
PCP appointment scheduled		15.3-17.2%	8.0-9.3%
Established care with endocrinologist (has seen or will see)		11.3-12.9%	7.6-8.9%
Established care with cardiologist (has seen or will see)		5.4-6.6%	3.6-4.5%
MyChart enrollment		68.2-70.6%	56.2-58.6%
Active LLT prescriptions[*, †]			
High-intensity statin[‡]		37.7-40.2%	19.6-21.5%
High-intensity by age group	<40	27.8-37.4%	13.3-20.0%
	40-75	38.8-41.5%	19.9-22.0%
	>75	27.7-36.2%	16.4-24.0%
Moderate-intensity statin		54.8-57.3%	67.9-70.1%
Moderate-intensity by age group	<40	57.6-67.5%	70.5-78.3%
	40-75	53.8-56.6%	67.7-70.1%
	>75	55.7-64.4%	59.6-68.8%
Low-intensity statin		4.1-5.2%	8.9-10.4%
Low-intensity by age group	<40	2.6-6.9%	6.7-11.9%
	40-75	3.9-5.0%	8.6-10.1%
	>75	4.9-9.6%	10.9-17.7%
ezetimibe		3.6-4.6%	1.0-1.6%

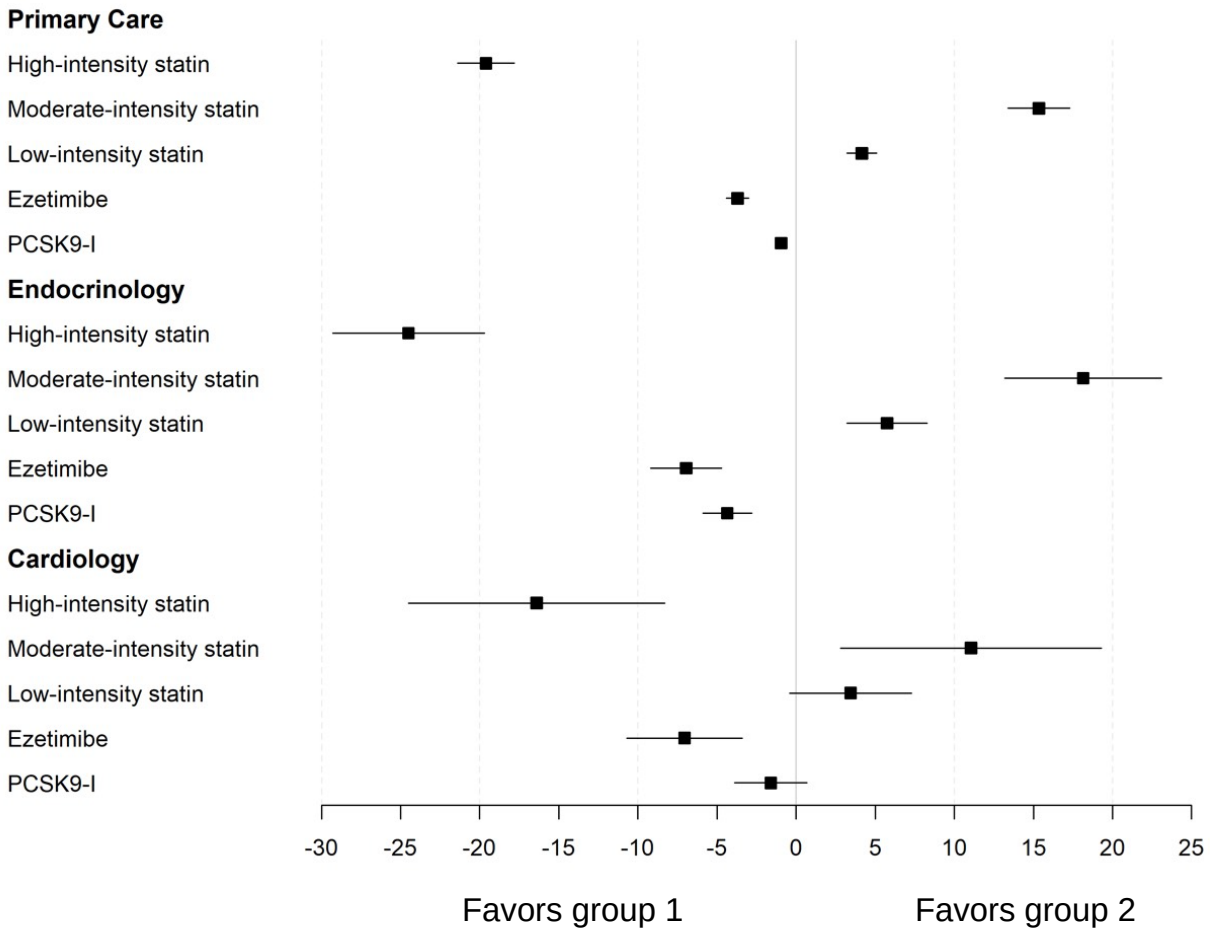
[*] LLT: lipid-lowering therapies.

[†] PCSK9-I (proprotein convertase subtilisin/kexin type 9 inhibitor) prescriptions were too few; therefore, not statistically significant.

[‡] High-intensity statin intensity is defined as atorvastatin (40 mg or 80 mg) or rosuvastatin (20 mg or 40 mg) or simvastatin (80 mg).[1]

Abbreviations: CVD, cerebrovascular disease; PCP, primary care provider; LLT, lipid-lowering therapy.

Figure S1. Confidence intervals (95%) estimating the mean difference in prescribing patterns b specialty (group 2 minus group 1).



PCSK9-I indicates proprotein convertase subtilisin/kexin type 9 inhibitor.