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

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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. 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. Therefore, early diagnosis and aggressive therapy for SH may significantly reduce the clinical and economic burden of CVD worldwide. Universal screening for both SH and familial hypercholesterolemia is the responsibility of all primary care providers (PCPs) and relevant specialty providers. Managing SH includes modifying risk factors and treating with multiple lipid-lowering therapies (LLTs), but recommended treatment guidelines are not universally implemented. 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. Yet there are several treatment gaps in this population, including SH underdiagnosis.
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

| Abbreviation | Definition                           |
|--------------|-------------------------------------|
| 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 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
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

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.
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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 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.

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

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 \( A_\text{s} \geq 6.5\% \) more than once or random peripheral blood glucose >200 mg/dL plus hemoglobin \( A_\text{s} \geq 6.5\% \) and no gestational diabetes mellitus | 20 |
| Obesity | Active obesity diagnosis on the EMR problem list or most recent body mass index ≥30 kg/m² | 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.
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 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)    | <0.001          | 1.7 to 2.5      |
| Age, y, mean±SD                              | 60.3±12.2       | 58.1±12.2       | 0.004           | −0.3 to 1.8     |
| 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 to 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             | 188             | <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 29.8    |
| 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 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 or 80 mg) or rosuvastatin (20 or 40 mg) or simvastatin (80 mg).
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.

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 (%) | 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.

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 and for the general population. 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

| Specialty                  | 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  | 45.1–70.6          | 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           | 0.0–6.9            | 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.
or with familial hypercholesterolemia also has been suggested previously; 25 and database methods 26 have been used to assess the prevalence of SH. 7,17,22–28 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.


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 showing that the most frequent treatment intensification 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.5,10,25 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

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**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             | 58.3–59.5       | 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                            | 8.7–18.6        | 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).
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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.

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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
Data S1

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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.”

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. However, in a study by Bucholz et al, 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. 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. 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
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SUPPLEMENTAL MATERIAL
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

Data S1.
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              | Group 2              | Reference Group     | 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%**                               |
| Condition                          | Current | Former | Passive | Current, Former, or Passive | Congestive heart failure§ | Hypertension§ | Mean arterial blood pressure (mm Hg) | Systolic blood pressure (mm Hg) | Diastolic blood pressure (mm Hg) | Most recent cholesterol results (mean) (mg/dL) | Current treatment (n, %) |
|-----------------------------------|---------|--------|---------|-----------------------------|---------------------------|---------------|-------------------------------------|-------------------------------|-------------------------------|-----------------------------------------------|--------------------------|
| 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%** |
| 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, %)           | 3322 (27.7%) | 1920 (24.9%) | 10136 (6.9%) | 1.6-4.1%**  | 20.0-21.6%** | 17.0-19.0%** |
| Moderate-intensity statin         | 3881 (32.4%) | 5045 (65.4%) | 18851 (12.8%) | 31.7-34.4%** | 18.7-20.4%** | 51.5-54.5%** |
| Statin Type      | Count (Percentage) | LDL-C Range | Lp(a) Range | Hypertension Range | Congestive Heart Failure Range |
|------------------|--------------------|-------------|-------------|-------------------|-------------------------------|
| Low-intensity statin | 320 (2.7%)        | 683 (8.9%)  | 2383 (1.6%) | 5.5-6.9%**        | 0.7-1.3%**                   |
|                   | 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%**                   |
|                   | 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%**                   |
|                   | 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 once.
§ 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).
* 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.

| 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

| Specialty       | High-intensity statin | Moderate-intensity statin | Low-intensity statin | Ezetimibe | PCSK9-I |
|-----------------|------------------------|---------------------------|----------------------|----------|---------|
| **Primary care**| 38.3-41.2%             | 19.9-22.5%                | 3.5-4.6%             | 3.4-4.5% | 0.4-0.8%|
| 95% CI          | 19.9-22.5%             | 68.7-71.6%                | 7.6-9.4%             | 0.9-1.6% | 0.0-0.3%|
| **Endocrinology**| 47.5-54.9%             | 25.8-33.7%                | 3.0-6.1%             | 5.0-8.8% | 1.5-3.9%|
| 95% CI          | 25.8-33.7%             | 55.9-64.3%                | 7.2-12.3%            | 1.2-3.9% | 0.0-1.0%|
| **Cardiology**  | 37.8-48.2%             | 21.0-32.0%                | 2.3-6.7%             | 3.6-8.7% | 0.6-3.6%|
| 95% CI          | 21.0-32.0%             | 57.8-69.7%                | 5.3-12.4%            | 0.6-4.4% | 0.1-2.7%|

* 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**

|                          | Group 1                      | Group 2                      | \(P\) value * of differences | 95% CI * of differences |
|--------------------------|------------------------------|------------------------------|------------------------------|-------------------------|
| 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)**

|                          | Group 1                      | Group 2                      | \(P\) value * of differences | 95% CI * of differences |
|--------------------------|------------------------------|------------------------------|------------------------------|-------------------------|
| 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**

|                          | Group 1                      | Group 2                      | \(P\) value * of differences | 95% CI * of differences |
|--------------------------|------------------------------|------------------------------|------------------------------|-------------------------|
| 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).

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=6066 |
|--------------------------------------|----------------|----------------|
|                                      | 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‡                |                |                |
| 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             |                |                |
| 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                  |                |                |
| 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 by specialty (group 2 minus group 1).

Primary Care
- High-intensity statin
- Moderate-intensity statin
- Low-intensity statin
- Ezetimibe
- PCSK9-I

Endocrinology
- High-intensity statin
- Moderate-intensity statin
- Low-intensity statin
- Ezetimibe
- PCSK9-I

Cardiology
- High-intensity statin
- Moderate-intensity statin
- Low-intensity statin
- Ezetimibe
- PCSK9-I

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