Prevalence and Characteristics of Patients With Primary Severe Hypercholesterolemia in a Multidisciplinary Healthcare System

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Severe hypercholesterolemia (SH) includes individuals with LDL-C ≥ 190 mg/dl, regardless of cause. These individuals have a fivefold increased long-term risk for coronary artery disease. Although systematic SH screening can trigger early treatment, current treatment guidelines may not be fully implemented or followed by patients. To further understand this treatment gap, we used electronic health record data to retrospectively assess SH prevalence, characteristics, and treatment in a midwest US healthcare system, between 2009 and 2020. Comorbidities, tobacco exposure, and prescribed lipid-lowering therapies were assessed. Statistical analyses were conducted to identify differences between individuals with primary SH (LDL-C ≥ 190 mg/dl, group 1) and those without primary SH (LDL-C < 190 mg/dl, group 2). Of 265,220 records analyzed, 7.4% met the definition for primary SH. These group 1 cases had more comorbidities than group 2 cases, including premature coronary artery disease (5.8% vs 2.7%). Results showed most individuals in group 1 were treated by primary care providers (43.2% to 45.7%), than by specialty providers (2.5% to 3.3%), and these primary care providers prescribed mainly moderate-intensity statins. Seventy-seven percent of group 1 individuals were treated with a statin, 27% were treated with a high-intensity statin, and 4% were treated with ezetimibe. Fewer young patients (< 40 years) were treated with statins (50% to 58.3%) than older patients (74.0% to 76.3%). Although use of general statins, high-intensity statins, and ezetimibe was higher in individuals with SH than those without SH, treatment remains below guideline recommendations, especially in younger individuals. Published by Elsevier Inc. (Am J Cardiol 2020;132:59−65)

The diagnostic criterion for severe hypercholesterolemia (SH) is LDL-C ≥ 190 mg/dl, regardless of underlying cause.[1−3] Individuals with SH have a fivefold higher long-term risk for coronary heart disease and atherosclerotic cardiovascular disease, compared with individuals with average LDL-C levels.[4] Early identification and aggressive therapy for SH may significantly reduce the clinical and economic burden of cardiovascular disease throughout the world.[2] Universal screening for SH is the responsibility of all primary care providers (PCPs) and relevant specialty providers.[5] Managing SH includes modifying risk factors and treatment with multiple lipid-lowering medications,[2] but recommended treatment guidelines are not universally implemented.[6,7] For adults aged 20 to 75 years with SH, these guidelines recommend maximum tolerated statin therapy intensified with ezetimibe and/or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor in patients with persistent LDL-C ≥ 100 mg/dl and other risk factors.[1] To further understand the clinical features and gaps in treatment approaches for this population, we used electronic health record (EHR) data from a multidisciplinary healthcare system in the midwest US to retrospectively assess the prevalence, clinical presentation, and treatment characteristics in individuals with SH (LDL-C ≥ 190 mg/dl). Identifying gaps in screening and care for this population can potentially reduce cardiovascular disease (CVD) incidence, improve patient care, and serve as baseline comparison with similar populations in other geographic areas.

Methods

We conducted a retrospective, records-based, cross-sectional study using datasets from unique EHRs of living patients presenting at a US metropolitan healthcare system. Using a dynamic EHR-based clinical decision-support tool, records of patients who had any clinical encounter within the St. Elizabeth Health Care system between January 1, 2009 and April 30, 2020, were enrolled in a clinical query using Structured Query Language. The query aimed to identify every LDL-C level documented in the EHR throughout the identified date range. The study was approved by the St.

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Characteristics of Severe Hypercholesterolemia Management
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Elizabeth Health Care Institutional Review Board and a waiver for informed consent was approved, allowing for retrospective data abstraction.

Untreated LDL-C was estimated for patients with active statin prescriptions, using their last LDL-C multiplied by 1.43.[8–11] To determine the likelihood of familial hypercholesterolemia (FH), we calculated the Dutch Lipid Clinic Network Score (DLCNS) for each record using the maximum LDL-C (whether EHR-documented or last estimated untreated) and the history of premature CVD either personally or in first-degree relatives (with LDL-C ≥ 190 mg/dl given a default DLCNS of 3) (Figure 1).[12,13] Accurate data for physical exam and genetic testing were not fully available and were not included in the study. Records were excluded (n = 1,062) for patients with DLCNS ≥ 3 and uncontrolled secondary causes of dyslipidemia (including significant, proteinuria and significantly uncontrolled hypothyroidism) at any time during the study timeframe (Table 1). Records were identified as SH (group 1) if the maximum EHR-documented LDL-C or last estimated untreated LDL-C during the timeframe was ≥ 190 mg/dl. Records of subjects not meeting these criteria were placed in group 2.

We identified comorbidities in the study population (Table 2), including coronary artery disease (CAD), diabetes mellitus (type 1 DM or type 2 DM), essential hypertension (HTN), congestive heart failure (CHF), and obesity (OB). We also assessed tobacco use and exposure, as well as use of different lipid-lowering therapies, primarily statins, ezetimibe, and PCSK9 inhibitors. Statin intensity was classified according to the American College of Cardiology (ACC)/ American Heart Association (AHA) cholesterol guidelines.[1]

Data were analyzed using Minitab 18 Statistical Software.[17] Logistic regression models were used to produce

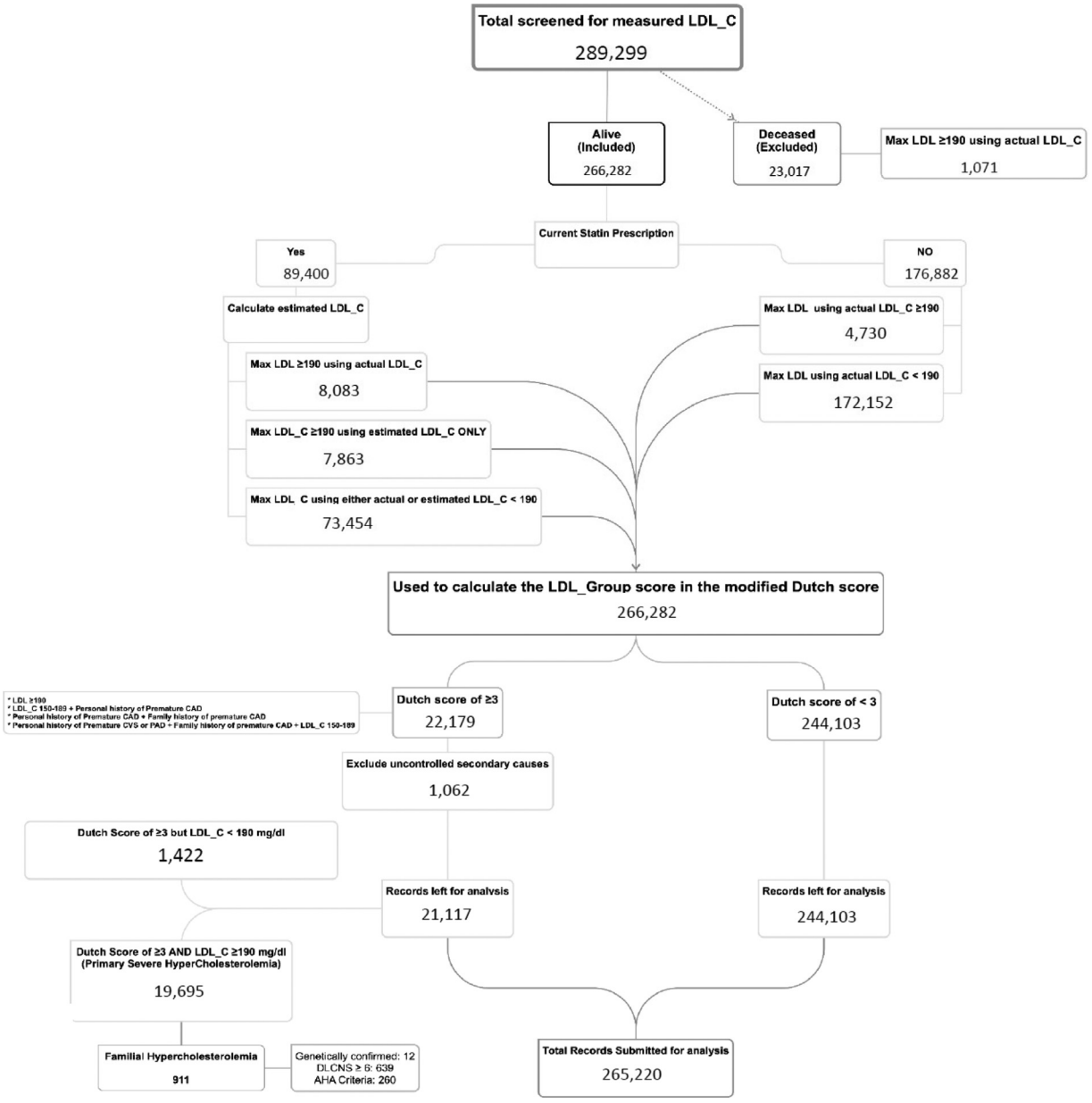

Figure 1. Distribution of screened population.

Table 1
Distribution of uncontrolled secondary causes of dyslipidemia in patients with Dutch Lipid Clinic Network Score (DLCNS) ≥ 3[13]

Total excluded = 1062	Severe Hypercholesterolemia*	Uncontrolled Hypothyroidism†	Uncontrolled Proteinuria‡
Severe hypercholesterolemia	981	765	246
Uncontrolled hypothyroidism	765	807	31
Uncontrolled proteinuria	246	31	286

* LDL_C ≥ 190 mg/dl.
† TSH > 10 μU/ml more than once.
‡ Urine microalbumin/Cr ratio ≥ 1000 mcg/mg more than once.

Table 2
Diagnostic criteria for study population comorbidities identified through the electronic health record

Diagnosis	Diagnostic criteria	Reference
Coronary artery disease (CAD)	Active CAD diagnosis or ICD-10: I20, I21, I22, I23, I24, or I25 on the EHR problem list or having at least 3 instances of CAD appearing as an encounter diagnosis in last 2 years or at least 3 CAD claim diagnoses in the last 2 years	14
Premature CAD	CAD occurring before age 55 years in men or 60 years in women	13
Ischemic cerebrovascular stroke (CVS)	Active CVS diagnosis or ICD0-10: ICD-10: I63, I74, or I75 on the EHR problem list	14
Peripheral arterial disease (PAD)	Active PAD diagnosis or ICD0-10: I63, I74, or I75 on the EHR problem list	14
Diabetes mellitus (DM)	Active DM diagnosis on the EHR problem list or HbA1c ≥ 6.5% more than once or random peripheral blood glucose higher 200 mg/dl, along with HbA1c ≥ 6.5% and not gestational diabetes	15
Obesity	Active obesity diagnosis on the EHR problem list or most recent BMI ≥ 30 kg/m^2	16
Essential hypertension (HTN)	Active essential HTN diagnosis on the EHR problem list	
Congestive heart failure (CHF)	Active CHF diagnosis on the EHR problem list	
High-intensity statin	atorvastatin (40 mg or 80 mg) or rosuvastatin (20 mg or 40 mg)	1

95% confidence intervals estimating the prevalence of statin usage in group 1 versus group 2.[18] Additional factors (e.g., comorbidities) were incorporated into these models to obtain subgroup analyses. Since this was a retrospective study, non-overlapping confidence intervals (group 1 vs group 2) for any particular subgroup were assessed as indicative of group differences . The minimum distance between confidence intervals can be reasonably interpreted as the lower bound on the amount by which the groups differ.

Results

A total of 289,299 records were screened. After excluding records for deceased individuals (n = 23,017) or those with secondary dyslipidemia (n = 1,062), 265,220 records were used for the analysis, with 19,695 having LDL-C ≥ 190 mg/dl. Nine hundred eleven patients (4.6%) with LDL-C ≥ 190 mg/dl met one of the criteria for FH (12 genetically confirmed, 639 with DLCNS ≥ 6, and 260 meeting AHA criteria for FH).[13,19]

Table 3 presents clinical and demographic characteristics for the screened population. Group 1 individuals generally were 3 to 4 years older than those in group 2 and had a slightly higher prevalence of CAD due mainly to a higher prevalence of premature CAD. Group 1 individuals also had a minimal, but significant increased prevalence of non-premature CAD and slightly higher Hierarchical Condition Category scores. Group 1 had a slightly higher prevalence of OB, but a lower body mass index than group 2 (p = 0.000, CI = 0.5 to 1.2) and a higher prevalence of DM. More individuals in group 1 were exposed to smoking (active or passive) than in group 2. Prevalence of CHF did not differ between the groups, but group 1 had a higher prevalence of HTN and a higher mean BP, systolic BP, and diastolic BP than group 2. As expected, the most recently measured cholesterol values [total cholesterol, LDL-C, non-HDL, TG, and Lp (a)] were significantly higher for group 1 than for group 2, but lower for HDL.

Cholesterol-lowering therapy used in group 1 included general statins (77%) and high-intensity statins (27%). Eighty-three percent of these individuals had persistently elevated LDL-C ≥ 100 mg/dl and 22% of these were prescribed a high-intensity statin (Table 4). Even if these individuals had been taking a maximum tolerated statin, the data clearly show therapy was not intensified using either ezetimibe or a PCSK9 inhibitor (Table 4).

In the absence of the 5 identified comorbidities (Table 5), general statins, high-intensity statins and ezetimibe were used more often in group 1 than in group 2. There was no evidence of differences in statin therapy use in patients with SH in primary care (confidence interval (CI) = 79.7% to 81.3%), endocrinology (CI = 78.5% to 85.1%), or cardiology (CI = 80.5% to 97.6%) providers. Cardiologists initiated high-intensity statin therapy more frequently (CI = 36.2% to 45.7%) than PCPs (CI = 24.1% to 25.8%), but not much more than endocrinologists (CI = 30.4% to 38.6%). Ezetimibe was prescribed more in patients treated by PCP − endocrinologist teams (CI = 6.5% to 9.6%); PCP − cardiologist teams (CI = 7.4% to 10.5%); or PCP − endocrinologist − cardiologist teams (CI = 12.2% to 20.6%),

Table 3
Comparative prevalence, clinical features, and demographics of patients with severe hypercholesterolemia (LDL≥190 mg/dl)* versus those with LDL<190 mg/dl

	LDL≥190 (Group 1)	LDL<190(Group 2)	p	95% CIof differences
Prevalence (No/%)	19,695 (7.4%)	245,525 (92.6%)		
Age (mean)	59.2	54.5	0.000	4.4−4.8
SD	13.0	17.5		
Men	8,535 (43.3%)	114,783 (46.8%)	0.000	2.7−4.1%
Women	11,160 (56.7%)	128,764 (53.2%)		
Most recent cholesterol results (mean) (mg/dl)				
Total cholesterol	228	173	0.000	53.5−55.0
Low-density lipoprotein	146	97	0.000	48.0−49.3
Serum triglyceride	167	128	0.000	37−41
High-density lipoprotein	48.8	50.8	0.000	1.8−2.2
Non-high-density lipoprotein	179	123	0.000	55.6−57.0
Patients tested for LP(a)	208 (1%)	1,348 (0.5%)	0.000	0.4−0.7%
Max LP(a)	54	40	0.002	5−22
Comorbidities				
Total CAD and CVS	3,202 (16.3%)	30,932 (12.6%)	0.000	3.1−4.2%
Premature CAD	1,133 (5.8%)	6,679 (2.7%)	0.000	2.7−3.4%
Non-premature CAD	2,076 (10.5%)	24,140 (9.8%)	0.002	0.3−1.2%
Hierarchical Condition Category (HCC) score	0.47	0.43	0.000	2.86−3.97
Obesity†	7,744 (39%)	89,047 (36%)	0.000	2.34−3.76%
Diabetes‡ (type 1 DM or type 2 DM)	4,509 (23%)	4,4131 (18%)	0.000	4.3−5.5%
Smoker (Current, former or passive)	10,052 (51%)	107,905 (44%)	0.000	6.4−7.8%
Congestive heart failure§	758 (4%)	9,109 (4%)	0.318	-0.1−0.4%
Hypertension§	9,487 (48%)	93,483 (38%)	0.000	9.37−10.81%
Mean arterial blood pressure (mm Hg)	95.09	92.94	0.000	2.0−2.3
Systolic blood pressure (mm Hg)	128.1	125.3	0.000	2.7−3.0
Diastolic blood pressure (mm Hg)	79.1	77.3	0.000	1.7−1.9
Current treatment				
High-intensity statin¶	5,242 (27%)	22,490 (9%)	0.000	16.8−18.1%
Moderate-intensity statin	8,926 (45%)	44,490 (18%)	0.000	26.5−27.9%
Low-intensity statin	1,003 (5%)	6,021 (2%)	0.000	2.3−3.0%
Total taking statin	15,171 (77%)	73,001 (30%)	0.000	46.7−47.9%
ezetimibe prescription	864 (4%)	3,422 (1%)	0.000	2.7−3.3%
PCSK9 inhibitor prescription	273 (1%)	334 (0.1%)	0.000	1.1−1.4%

* Descriptive statistics are expressed as averages or counts (percentages), as appropriate.
† Obesity is defined as those with last BMI of >=30.
‡ Diabetes is defined by having active DM on the EHR problem list, or having HbA1c ≥ 6.5% more than once, or having random blood glucose > 200 mg/dl and HbA1c ≥ 6.5%.
§ Hypertension and congestive heart failure are indicated as active on the EHR problem list.
¶ High-intensity statin intensity is defined as atorvastatin (40 mg or 80 mg) or rosuvastatin (20 mg or 40 mg).1

compared with patients treated only by PCPs (CI = 3.3% to 4.0%). Both general statins and high-intensity statins were used less frequently in patients younger than 40 years or older than 75 years, than in other age groups. Given the small number of patients in group 2, we could not assess for the effect of age on ezetimibe use. Insurance carrier and smoking status did not affect initiation of general statins, high-intensity statins, or ezetimibe. The presence of comorbidities (HTN alone or combined with any of the other studied comorbidities for statin use; DM or HTN, alone or combined; CAD combined with HTN, DM, or OB; or OB alone or combined with DM, CAD, HTN for ezetimibe use) was associated with more frequent use of these medications in both groups, regardless of whether or not the patient had SH.

We assessed the prevalence of patient visits in PCPs, endocrinologists, or cardiologists in the absence of any of the 5 comorbidities (CAD, CHF, DM, HTN, OB) (Table 5). We found no significant difference between groups for having established care with a PCP; however, a slightly larger proportion of group 1 patients were scheduled for future PCP appointments. The incidence of cardiology consultation was slightly higher in group 1 than in group 2, regardless of comorbidities, but the incidence of endocrinology consultation did not differ significantly. Use of MyChart (EHR) was slightly lower in group 1 compared with group 2.

Discussion

This study demonstrates the use of a systematic, cost-effective, reproducible method to screen an entire healthcare system in Kentucky for patients with primary severe hypercholesteremia (SH) and to identify those who might benefit from intensified lipid lowering therapy. The overall prevalence of primary SH was 7.4%, which is similar to that reported by other studies[17,3] including the Analysis of the National Health and Nutrition Examination Survey (NHANES) (6.6% prevalence).[10] Compared with group 2, individuals in group 1 generally were older, predominantly

Table 4
Lipid treatment status in individuals with severe hypercholesterolemia (SH) and persistent LDL-C ≥ 100 mg/dl*

SH prevalence (LDL-C≥100 mg/dl)% (n)	Active Prescription % (n)					No statin prescription
	Low-intensity statin	Moderate-intensity statin	High-intensity statin	ezetimibe	PCSK9	
83% (16,409)	6% (952)	46% (7,588)	22% (3,674)	4% (637)	1% (159)	25% (4,119)

* LDL-C ranges in individuals with SH: 100−189 mg/dl, 69% (13,528); 190−300 mg/dl, 14% (2,822); > 300 mg/dl, 0.3% (59); persistent LDL-C ≥ 190 mg/dl, 5% (994)

Table 5
Health system usage and active prescriptions for lipid-lowering therapies in patients with severe hypercholesterolemia (LDL≥190 mg/dl) compared with those with LDL<190 mg/dl in the absence of identified comorbidities

		LDL ≥190(Group 1)n = 6166	LDL <190(Group 2)n = 10 1170
		95% Confidence Intervals (%)	
Previous PCP appointment		43.2−45.7%	44.1−44.7%
PCP appointment scheduled		4.6−5.8%	3.5−3.7%
Established care with endocrinologist (has seen or will see)		3.4−4.4%	3.6−3.8%
Established care with cardiologist (has seen or will see)		2.5−3.3%	2.1−2.3%
MyChart use		51.7−54.2%	55.3−55.9%
Statin use			
Any intensity		71.7−74.0%	12.0−12.4%
Any intensity by age group	<40	50.0−58.3%	0.7−0.9%
	40−75	74.0−76.3%	14.7−15.3%
	>75	65.6−73.6%	38.8−41.1%
High-intensity*	15.0−16.9%	2.2−2.4%	
High-intensity by age group	<40	5.9−10.4%	0.1−0.2%
	40−75	16.1−18.2%	2.8−3.1%
	>75	10.1−15.9%	6.7−7.9%
ezetimibe		2.2−3.1%	0.4−0.6%

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

female, and had more comorbidities (premature CAD, OB, DM; smoking exposure; and HTN), which was reflected by the higher Hierarchical Condition Category score. These comorbidities are similar to those documented by other studies[10,4] in which patients with SH had a higher burden of CVD and exhibited other CVD risk factors. Although our study population was high-risk, all the lipid parameters for patients in group 1 were still uncontrolled. This may be due to sociodemographic and treatment characteristics, such as a lack of pretreatment identification of LDL-C ≥ 190 mg/dl during routine care or SH masked by the use of moderate-intensity statins.[1,20,21] Thirty-nine percent (7,710) of patients in group 1, were included in this study based on a last estimated untreated LDL-C ≥ 190 who would have been misclassified if actual LDL-C ≥ 190 mg/dl alone was used. Undertreatment in this high-risk group is reflected by the number of patients with statin use (77%) and high-intensity statin use (27%) with persistently elevated LDL-C ≥100 mg/dl observed in 83% of patients (Table 4). Five percent (994 patients) had persistent LDL-C ≥ 190 mg/dl due either to a lack of treatment with lipid-lowering therapy or to no treatment intensification. This illustrates a clinical inertia[22] with insufficient implementation of both previous and currently recommended guidelines.[1,23]

The use of statins and high-intensity statins in patients with SH is slightly higher than that reported by previous studies (52% to 66% and 10%, respectively).[1,6,7,23−25] This might be explained by the trend toward increased use of statins and high-intensity statins between 1999 and 2014, shown by NHANES data[10] and by Veterans Affairs (VA) Health System[6] data. The use of high-intensity statins also is more prevalent (42%) at specialized lipid clinics[26] and our results are similar to those reported at such clinics (75%) for general intensity statins[24] and those reported at national cardiology practices (30%) for high-intensity statins.[7,26] Ezetimibe use in our study is similar to that for the general population (4%) and to that reported for cardiology practices (5.8%),[1] but lower (2.2% to 3.1%) for patients without comorbidities. Intensified treatment was implemented more frequently by specialists and high-intensity statins were used more often by cardiologists than by PCPs.[7,26]

Our data also showed statins were less prescribed for patients younger than 40 years or older than 75 years (Table 5), a pattern similar to the inverted U-shaped association between statin use and age shown by the VA Health System data.[6] This reflects a treatment-risk paradox in which patients at highest risk for CVD should be treated most aggressively, but often are not.[6,10,27−29] The ultimate outcome of such suboptimal care for this high-risk group is evidenced by the rate of hospitalizations for myocardial infarction (MI) in individuals aged 30 to 54 years that has not decreased for the last decade.[28]

Patients with regular access to care, as in our study, tend to have statin therapy compared with individuals without regular access to care.[10] Most patients with primary SH but no comorbidities were treated primarily by PCPs (CI = 43.2% to 45.7%), rather than by specialty providers (cardiologists or endocrinologists), and the majority of

statins prescribed by PCPs were moderate or low-intensity, rather than high-intensity. This pattern is similar to community care provided elsewhere and might be due to reduced awareness in clinicians of the significance of high LDL-C levels in SH patients or to infrequent use of coronary heart disease risk assessment tools.[6,20,21,30]

We did not assess patients' adherence to lipid-lowering therapies and have described treatments recorded in the EHR as 'active prescriptions,' but could not determine if a lack of treatment was due to patient preference, including statin intolerance. We also did not have adequate data to analyze PCSK9 inhibitor prescription patterns.

This study will serve as a startup project to optimize lipid treatment for high-risk individuals in primary care settings. This dataset also offers a platform to identify patients with FH through ongoing efforts to optimize family histories of CAD in patients with SH.

In conclusion, there is a 7.4% prevalence of primary SH in the patient population at our midwestern US regional health system and these patients have more comorbidities than patients without SH. Most of these patients are treated by PCPs than by endocrinologists or cardiologists, and PCPs tend to prescribe more moderate-intensity statins than high-intensity statins for this high-risk group. Use of moderate-intensity statins in patients with LDL-C $\geq$ 190 mg/dl pretreatment might mask their need for high-intensity statin therapy. In this study, the use of statins and high-intensity statins was higher in patients with SH, but still far below that recommended by current guidelines, especially for younger patients.[1] There remains a significant opportunity to improve the use of lipid-lowering therapies for this high-risk population.

Author contributions

Wael Eid: Conceptualization, Methodology, Software, Validation, Investigation, Resources, Data Curation, Writing - Original Draft, Visualization, Supervision, Funding acquisition. Emma Hatfield Sapp: Methodology, Investigation, Writing - Original Draft. Tamuchin McCreless: Software. Joseph R. Nolan: Methodology, Validation, Formal analysis, Investigation, Writing - Original Draft. Elijah Flerlage: Software, Validation, Formal analysis, Investigation, Writing - Original Draft.

Disclosures

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

- Dr. Eid is on the Speaker Bureau of Amgen and Esperion Pharmaceuticals.
- Other authors have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this study.

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