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Sanchez, Robert
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Original Research

Lipid treatment status and goal attainment among patients with atherosclerotic cardiovascular disease in the United States: A 2019 update☆☆

Jing Gu[a,*], Robert Sanchez[a], Ankita Chauhan[b], Sergio Fazio[a], Nathan Wong[c]

[a] Regeneron Pharmaceuticals, Inc., Tarrytown, NY, United States of America
[b] Axtria, Berkeley Heights, New Jersey, United States of America
[c] University of California, Irvine, California, United States of America

A B S T R A C T

Objective: To update the prevalence of atherosclerotic cardiovascular disease (ASCVD) in the United States (US) and re-evaluate lipid-lowering therapies (LLT) utilization and low-density lipoprotein cholesterol (LDL-C) goal attainment among ASCVD patients after proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have become available using data from 2019.

Methods: ASCVD patients with at least 1 valid LDL-C measurement from the 2019 Truven MarketScan Research Database were included and stratified into hierarchical cardiovascular risk groups. The number of patients in each group was extrapolated to approximate national figures based on national demographic and ASCVD prevalence numbers. Descriptive statistics on demographic and clinical characteristics, treatment status and LDL-C for each hierarchical category were reported.

Results: The overall prevalence of ASCVD in the US in 2019 was 24.0 million, approximately 10% of the total US population above 21 years old. We found heavy comorbidity burden among ASCVD patients and 31.2% were at very high risk for recurrent events. The majority of ASCVD patients were not at guideline-recommended LDL-C goal. Although there was a significant increase in the use of LLTs (especially of high-intensity statins) in 2019 compared to 2014, overall LLT utilization remained low, with only 3.8% of ASCVD patients on ezetimibe, less than 1% on PCSK9 inhibitors and over 40% on no LLTs. We also found higher utilization of LLTs among patients who were at goal of < 70 or < 55 mg/dL vs. those not at goal.

Conclusion: Despite an increase in high-intensity statins use since 2014, there was still an underutilization of LLTs in spite of evidence of their efficacy in LDL-C lowering and ability to reduce the risk of coronary heart disease. Increased awareness of guidelines by healthcare providers and urgency to treat ASCVD is needed in order to improve LLT utilization and help more patients reach the LDL-C goal.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the United States (US)[1]. The link between lower levels of low-density lipoprotein cholesterol (LDL-C) and reductions in CVD morbidity and mortality is well established[2–4]. Clinical trial data on statins in patients with or without atherosclerotic cardiovascular disease (ASCVD) suggest that every 1 mmol/L (38.67 mg/dL) decrease in LDL-C induces a 22% reduction in CVD risk[2]. Despite this evidence, medications to lower LDL-C have been underutilized and sub-optimally dosed [5].

In a previous study, we estimated the prevalence of ASCVD in the US at 18.3 million in 2014, with 74.2% of ASCVD subjects having an LDL-C $\geq$ 70 mg/dL, of whom only 9.2% were on a high-intensity statin, and more than half (54.0%) were neither on statin nor ezetimibe[6]. This analysis highlighted the underutilization of lipid-lowering therapies (LLTs).

Since 2014, other novel LLTs that provide powerful LDL-C lowering have come to market, including two proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, alirocumab and evolocumab, which lower LDL-C levels by up to 60% and reduce CV events among patients with ASCVD on statin therapy[3,4,7]. In 2018, the American Heart Association (AHA)/American College of Cardiology (ACC) Task Force on Clinical Practice Guidelines issued their recommendations on lowering the risk of CV events among patients with ASCVD. These included the use of high-intensity statin at maximally tolerated doses and the addition of ezetimibe if LDL-C is $\geq$ 70 mg/dL after statin. For the very high-risk patients, the guidelines recommended the addition of a PCSK9

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* Corresponding author at: Regeneron Pharmaceuticals, Inc., 1 Rockwood Road, Sleepy Hollow, New York, NY, 10591, USA.
E-mail address: jing.gu@regeneron.com (J. Gu).

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inhibitor when LDL-C level is ≥ 70 mg/dL after high-intensity statin and ezetimibe[8]. Similarly, the 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines for the Management of Dyslipidemias suggested a lower target LDL-C of < 55 mg/dL among patients with established ASCVD and, for patients at very high risk, recommended the addition of a PCSK9 inhibitor if not at goal on statin and ezetimibe, following the 2017 American Association of Clinical Endocrinologists (AACE) guideline which is the first guideline that recommended a treatment goal of LDL-C < 55 mg/dL for patients with extremely risk[9,10].

Despite these recommendations the use of LLTs remains low. The current analysis is a follow up to our previous paper with data from 2014 and aims at updating the prevalence of ASCVD in the US using the 2019 Truven Database, and at re-evaluating LLT utilization and LDL-C goal attainment among ASCVD patients after PCSK9 inhibitors have become available.

2. Methods

This study used de-identified healthcare claims and laboratory data from the Truven MarketScan Research Database. Truven MarketScan is a large and representative database consisting of US administrative health records from commercial and Medicare supplemental health plans. Enrollees were included in the analysis if all of the following criteria were met: at least 1 valid LDL-C measurement in 2019 with values between 2 and 1000 mg/dL (date of last LDL-C measurement defined as index date), age ≥ 21 years at index date, continuous enrollment in the database for at least 5 years prior to the index date (baseline period defined as the five years prior to index), a diagnosis of ASCVD based on International Classification of Diseases, Tenth Revision (ICD-10) codes during the baseline period (**Appendix Table 1**). Patients with likely heterozygous familial hypercholesterolemia were excluded (based on claims-assessable Dutch Lipid Clinic Criteria). We stratified patients into four mutually exclusive cardiovascular risk groups, defined using the following hierarchy: 1) recent acute coronary syndrome (ACS) within 1 year; 2) ischemic stroke; 3) peripheral arterial disease (PAD); 4) other coronary heart disease (CHD), which included coronary revascularization (coronary artery bypass graft and percutaneous coronary intervention), stable angina, or non-specific CHD diagnoses. Patients were assigned to the highest category. For example, patients with recent ACS could also have evidence of PAD and other CHD, whereas patients assigned to other CHD group did not have evidence of hierarchically superior diagnoses. We also identified patients at very high risk, defined as those with a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions based on the 2018 AHA/ACC guideline (**Appendix Table 2**)[8].

The number of patients in each disease group based on the database was extrapolated to approximate national figures based on national demographic and ASCVD prevalence numbers. The extrapolation method has been described previously[6]. Briefly, we used an optimization algorithm to ensure that the number of observations in the extrapolated dataset was in line with the adult US population and the national prevalence of CHD, ischemic stroke, diabetes and PAD. These data were anchored to the 2019 US census data and AHA Heart Disease and Stroke Statistics report in 2021[11,12].

Treatment status was assessed according to evidence of a filled prescription for statins, ezetimibe, and/or PCSK9 inhibitors. A patient was considered to be on a medication if the medication supply was within 30 days of the index date. Otherwise, they were considered not on treatment. For those not on treatment, we further stratified them as "not on current treatment" or "never on treatment" based on whether evidence for an LLT was present in the 5-year baseline period. LDL-C values were assessed on the index date and were examined according to the following cut points: < 55 mg/dL, < 70 mg/dL, ≥ 70 mg/dL, and ≥ 100 mg/dL. Several comorbidities and risk factors of interest were assessed for each disease group, including hypertension, diabetes (both determined based on ICD-10 diagnosis codes, **Appendix Table 1**), polyvascular disease and recurrent events. Polyvascular disease was defined as disease in 2 or more vascular beds (coronary, cerebrovascular, peripheral); recurrent events were defined as 2 or more events (including the same type of event twice) of unstable angina with hospitalization, nonfatal ischemic stroke, nonfatal MI, or elective revascularization. We used descriptive statistics to describe the demographic, clinical characteristics, assessment of treatment status and LDL-C for each hierarchical category.

3. Results

Table 1 shows the patient counts in 2019 database as well as the extrapolated US population number for each hierarchical disease group. There were 25,339 ASCVD patients in the MarketScan database, representing a total of 24.0 million (9.9% of total) adults in the US. Of these, 823,490 had an ACS within 1 year, 6276,933 had an ischemic stroke, 5769,364 had PAD, and 11,136,171 had other CHD. This represents a large increase compared to the 2014 data, when there were 18.3 million ASCVD patients, accounting for 8.0% of adult Americans. In the 2019 database, we also identified 4526 ASCVD patients who were at very high risk, representing 7488,308 patients in the US, which accounted for 31.2% of overall ASCVD patients and 3.1% of total US adults. Among those with very high risk, 42.7% had multiple major CV events and the remaining had 1 major CV event and multiple high-risk conditions.

Demographic and clinical characteristics of each hierarchical disease group show heavy comorbidity burden among ASCVD patients (Table 2). Overall, 39.1% of ASCVD patients had comorbid diabetes, 71.0% had hypertension and 48.8% had polyvascular disease. Among patients with recent ACS, 36.3% had recurrent CV events, 36.3% had ischemic stroke, 15.7% had PAD, and 89.6% had other CHD. Subjects in the hierarchical ischemic stroke group included 21.0% who also had PAD and 92.9% who had other CHD. Thirty-six percent of patients from the hierarchical PAD group also had other CHD. Based on the definition of the 2018 AHA/ACC guideline, 31.2% of the overall ASCVD patients (91.8% of recent ACS, 59.0% of ischemic stroke, 39.7% of PAD and 6.6% of other CHD) are considered to have very high risk for recurrent events. The majority of ASCVD patients in any group did not achieve the guideline-recommended LDL-C goal of <70 mg/dL (56.2% of patients with a recent ACS, 69.2% of patients with ischemic stroke, 80.8% of patients with PAD, and 71.5% of patients with other CHD). Only 11.6% of ASCVD patients had LDL-C < 55 mg/dL. Moreover, 37.5% of ASCVD patients had LDL-C ≥ 100 mg/dL.

The treatment status of each disease group comparing 2014 to 2019 is shown in Table 3. The proportion of ASCVD patients without any LLT claims in the last five years decreased from 54% in 2014 to 41% in 2019. This was driven by a significant 27% increase in the use of statins from 2014 to 2019 (44.1% and 56.1%, respectively). Of note, there was a significant increase in the use of high-intensity statins across each disease group comparing 2014 and 2019 data (20.1% vs. 52.4% for ACS, 9.2% vs. 29.4% for ischemic stroke, 7.9% vs. 16.4% for PAD, and 13.0% vs. 22.9% for other CHD). Meanwhile, utilization of moderate to low-intensity statins stayed relatively flat, from 32.9% to 32.1% for total ASCVD patients. We also observed an increase in the use of ezetimibe from 2.4% in 2014 to 3.8% in 2019. Utilization of high-intensity statin and ezetimibe combination also increased significantly, though the overall use remained low (0.8%). Less than 1% of ASCVD patients were treated by PCSK9 inhibitors in 2019. It was most commonly used by patients with a recent ACS, followed by patients with ischemic stroke, PAD and other CHD.

Treatment status of each disease group stratified by LDL-C levels is shown in Table 4. In general, within each disease group, patients with LDL-C < 70 mg/dL had higher utilization of high-intensity statins and PCSK9 inhibitors compared to patients with LDL-C ≥ 70 mg/dL. Absence of any LLTs at baseline was less common for those with LDL-C < 70 mg/dL than for those with LDL-C ≥ 70 mg/dL (15.1% vs. 50.3%). Among

Table 1
Hierarchical ASCVD disease group count in the Truven Database and extrapolated population.

	Database, count	Database, %	Extrapolated US population size, count	Extrapolated US population size,%
ASCVD				
	Recent ACS < 1 year	887	0.4%	823,490 0.3%
	Ischemic stroke without ACS	1173	0.5%	6276,933 2.6%
	PAD without ACS or ischemic stroke	4452	2.0%	5769,364 2.4%
	Other CHD	18,827	8.3%	11,136,171 4.6%
Very high risk ASCVD	*4526*	*2.0%*	*7488,308*	*3.1%*
Multiple major events	*2379*	*1.0%*	*3196,856*	*1.3%*
1 major event + multiple high-risk conditions	*2147*	*0.9%*	*4291,452*	*1.8%*
No ASCVD	201,778	88.8%	218,443,829	90.1%
Total population aged >= 21 (ASCVD + no ASCVD)	227,117	100.0%	242,449,787	100.0%

Abbreviations: ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; PAD, peripheral arterial disease.

Table 2
Demographic and clinical characteristics for hierarchical ASCVD disease groups.

Baseline Characteristics (Extrapolated Population)	Recent ACS < 1 Year	Ischemic Stroke	PAD	Other CHD	Total ASCVD
Number	823,490	6276,933	5769,364	11,136,171	24,005,959
Demographics					
Age (mean)	63.5	58.3	60.0	65.7	62.3
Male (%)	55.8%	54.3%	52.7%	47.3%	50.7%
Baseline Comorbidities (%)					
Recent ACS	100.0%	0.0%	0.0%	0.0%	3.4%
Ischemic Stroke	36.3%	100.0%	0.0%	0.0%	27.4%
PAD	15.7%	21.0%	100.0%	0.0%	30.1%
Other CHD	89.6%	92.9%	36.0%	100.0%	82.4%
Other Comorbidities (%)					
CKD Stage III	18.4%	11.3%	9.1%	13.2%	11.9%
CKD Stage IV-V	6.3%	4.7%	3.4%	3.5%	3.9%
Hypertension	73.9%	72.3%	68.3%	71.4%	71.0%
Diabetes Mellitus	47.5%	33.8%	31.6%	45.3%	39.1%
Polyvascular Disease	59.1%	95.3%	62.7%	14.6%	48.8%
Recurrent Events	36.3%	4.8%	1.4%	2.8%	4.1%
Index LDL-C (mean, mg/dL)	81.3	90.6	98.9	91.6	92.8
LDL-C < 55 mg/dL (%)	25.2%	13.0%	7.9%	11.7%	11.6%
LDL-C < 70 mg/dL (%)	43.8%	30.8%	19.2%	28.5%	27.4%
LDL-C ≥ 70 mg/dL (%)	56.2%	69.2%	80.8%	71.5%	72.6%
LDL-C ≥ 100 mg/dL (%)	27.8%	34.9%	44.6%	36.0%	37.5%
Very High Risk (%)	91.8%	59.0%	39.7%	6.6%	31.2%
Multiple major events	63.6%	27.5%	3.7%	6.6%	13.3%
1 major event + multiple high-risk conditions	28.2%	31.5%	36.0%	0.0%	17.9%

All data are percentages unless otherwise stated.
Abbreviations: ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CKD, chronic kidney disease; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral arterial disease; UA, unstable angina.

patients who had met the LDL-C goal of < 70 mg/dL, the proportions of patients using PCSK9 inhibitors were 3.3%, 1.4%, 2.8%, and 1.5% for patients with recent ACS, ischemic stroke, PAD and other CHD, respectively. In contrast, the utilization of PCSK9 inhibitors was much lower among those with LDL-C ≥ 70 mg/dL (1.6% for recent ACS patients and less than 1% for the other categories). Utilization of high-intensity statin and ezetimibe combination was also much lower among patients with LDL-C ≥ 70 mg/dL than those with LDL-C < 70 mg/dL (0.4% vs. 1.9% among ASCVD patients). We also examined treatment status for patients who reached LDL-C < 55 mg/dL vs. those who did not, and observed the same treatment pattern (**Appendix table 3**). In addition, we noticed that older patients had higher utilization of LLTs, and the utilization of statins (especially high-intensity statins) and ezetimibe were slightly higher among male patients than female patients, however, the average LDL-C values were similar (data not shown).

Table 5 shows the treatment status by LDL-C levels for patients with very high risk. Overall, 34.8% of patients with very high risk achieved the LDL-C goal of < 70 mg/dL and 16.7% of patients achieved the goal of < 55 mg/dL, both higher than the numbers for overall ASCVD patients (27.4% and 11.6%, respectively). The utilization of both ezetimibe and PCSK9 inhibitors was higher among patients with very high risk vs. those without (4.1% vs. 3.8% for ezetimibe and 1.3% vs. 0.9% for PCSK9 inhibitors). Among very-high risk patients, those with LDL-C < 70 mg/dL had higher utilization of high-intensity statins, ezetimibe and PCSK9 inhibitors than those with LDL-C ≥ 70 mg/dL (51.4% vs. 24.7% for high-intensity statins, 5.7% vs. 3.2% for ezetimibe, 1.9% vs. 1.0% for PCSK9 inhibitors). This pattern was seen both in patients who had at least 2 major CV events and patients with 1 CV event and multiple high-risk conditions. The proportion of patients without any LLTs was much lower for patients with LDL-C < 70 mg/dL compared to patients with LDL-C ≥ 70 mg/dL (14.9% vs. 42.4%). We also observed that whereas utilization of high-intensity statins and ezetimibe was similar comparing patients with LDL-C <70 mg/dL and patients with LDL-C < 55 mg/dL, PCSK9 inhibitors utilization was higher for those who achieved the lower LDL-C goal (3.1% for LDL-C < 55 vs. 1.9% for LDL-C < 70) among patients with very high risk.

Table 3
Treatment status for hierarchical ASCVD disease groups in 2014 vs. 2019.

	Recent ACS < 1 year		Ischemic stroke without ACS		PAD without ACS or ischemic stroke		Other CHD		Total ASCVD	
	2014	2019	2014	2019	2014	2019	2014	2019	2014	2019
Number	690,524	823,490	4912,555	6276,933	3588,654	5769,364	9121,504	11,136,171	18,313,236	24,005,959
High-intensity statin,%*	**20.1%**	**52.4%**	**9.2%**	**29.4%**	**7.9%**	**16.4%**	**13.0%**	**22.9%**	**11.2%**	**24.0%**
Monotherapy	*98.9%*	*97.9%*	*98.1%*	*98.6%*	*98.3%*	*94.7%*	*98.5%*	*93.8%*	*98.4%*	*95.8%*
Plus ezetimibe	*1.1%*	*0.9%*	*1.9%*	*0.8%*	*1.7%*	*4.2%*	*1.5%*	*5.5%*	*1.6%*	*3.5%*
Plus PCSK9i (with or without ezetimibe)	—	*1.2%*	—	*0.6%*	—	*1.0%*	—	*0.7%*	—	*0.7%*
Moderate to low-intensity statin,%*	**32.9%**	**22.1%**	**35.0%**	**28.9%**	**30.7%**	**30.9%**	**32.7%**	**35.1%**	**32.9%**	**32.1%**
Monotherapy	*99.0%*	*94.1%*	*99.2%*	*99.1%*	*98.9%*	*98.4%*	*99.0%*	*99.0%*	*99.0%*	*98.8%*
Plus ezetimibe	*1.0%*	*5.2%*	*0.8%*	*0.9%*	*1.1%*	*1.3%*	*1.0%*	*0.9%*	*1.0%*	*1.1%*
Plus PCSK9i (with or without ezetimibe)	—	*0.7%*	—	*0.0%*	—	*0.3%*	—	*0.0%*	—	*0.1%*
Ezetimibe,%*	**1.3%**	**3.5%**	**1.4%**	**2.4%**	**1.9%**	**1.9%**	**2.1%**	**3.1%**	**1.9%**	**2.6%**
Ezetimibe only	*100.0%*	*97.4%*	*100.0%*	*96.5%*	*100.0%*	*93.5%*	*100.0%*	*97.3%*	*100.0%*	*96.5%*
Plus PCSK9i	—	*2.6%*	—	*3.5%*	—	*6.5%*	—	*2.7%*	—	*3.5%*
PCSK9i only,%*	—	**1.5%**	—	**0.7%**	—	**0.5%**	—	**0.5%**	—	**0.6%**
No LLT,%*	**45.7%**	**20.5%**	**54.4%**	**38.6%**	**59.5%**	**50.3%**	**52.3%**	**38.4%**	**54.0%**	**40.7%**

* Numbers in these rows denote absolute percentages and add up to 100% vertically. All other numbers are relative percentages of the absolute percentages
Abbreviations: ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; LLT, lipid-lowering therapy; PAD, peripheral arterial disease; PCSK9i, PCSK9 inhibitor.

Table 4
Treatment status for hierarchical ASCVD disease groups stratified by LDL-C (<70 vs. >=70 mg/dL).

	Recent ACS < 1 year		Ischemic stroke without ACS		PAD without ACS or ischemic stroke		Other CHD		Total ASCVD	
	LDL-C<70	LDL-C>=70	LDL-C<70	LDL-C>=70	LDL-C<70	LDL-C>=70	LDL-C<70	LDL-C>=70	LDL-C<70	LDL-C>=70
Number	360,401	463,089	1934,425	4342,508	1107,201	4662,163	3168,446	7967,725	6570,474	17,435,485
High-intensity statin,%*	**66.0%**	**41.8%**	**49.4%**	**20.5%**	**33.4%**	**12.3%**	**40.0%**	**16.1%**	**43.1%**	**16.9%**
Monotherapy	*96.6%*	*99.6%*	*98.4%*	*98.8%*	*91.7%*	*96.6%*	*91.4%*	*96.2%*	*94.3%*	*97.3%*
Plus ezetimibe,%	*1.3%*	*0.4%*	*0.5%*	*1.2%*	*6.3%*	*2.9%*	*7.6%*	*3.5%*	*4.5%*	*2.5%*
Plus PCSK9i (with or without ezetimibe)	*2.1%*	*0.0%*	*1.1%*	*0.0%*	*2.0%*	*0.4%*	*1.0%*	*0.3%*	*1.2%*	*0.2%*
Moderate to low-intensity statin,%*	**23.5%**	**21.0%**	**30.1%**	**28.4%**	**40.2%**	**28.7%**	**41.1%**	**32.7%**	**36.8%**	**30.3%**
Monotherapy	*91.9%*	*95.9%*	*99.1%*	*99.2%*	*98.6%*	*98.3%*	*98.8%*	*99.1%*	*98.6%*	*98.9%*
Plus ezetimibe	*6.6%*	*4.1%*	*0.9%*	*0.8%*	*0.9%*	*1.5%*	*1.1%*	*0.9%*	*1.2%*	*1.1%*
Plus PCSK9i (with or without ezetimibe)	*1.5%*	*0.0%*	*0.0%*	*0.0%*	*0.6%*	*0.2%*	*0.1%*	*0.0%*	*0.2%*	*0.1%*
Ezetimibe,%*	**5.7%**	**1.8%**	**3.5%**	**1.8%**	**2.5%**	**1.8%**	**4.9%**	**2.3%**	**4.2%**	**2.1%**
Ezetimibe only	*96.4%*	*100.0%*	*92.3%*	*100.0%*	*82.7%*	*97.1%*	*94.9%*	*99.4%*	*93.1%*	*99.0%*
Plus PCSK9i	*3.6%*	*0.0%*	*7.7%*	*0.0%*	*17.3%*	*2.9%*	*5.1%*	*0.6%*	*6.9%*	*1.0%*
PCSK9i only,%*	**1.4%**	**1.6%**	**0.6%**	**0.7%**	**1.5%**	**0.3%**	**0.8%**	**0.4%**	**0.9%**	**0.5%**
No LLT,%*	**3.5%**	**33.8%**	**16.3%**	**48.5%**	**22.3%**	**56.9%**	**13.1%**	**48.4%**	**15.1%**	**50.3%**
No LLT within 30 days	*49.4%*	*65.5%*	*54.1%*	*51.3%*	*48.5%*	*34.9%*	*65.7%*	*43.2%*	*57.5%*	*43.0%*
Never LLT (no LLT within 5 years)	*50.6%*	*34.5%*	*45.9%*	*48.7%*	*51.5%*	*65.1%*	*34.3%*	*56.8%*	*42.5%*	*57.0%*

* Numbers in these rows denote absolute percentages and add up to 100% vertically. All other numbers are relative percentages of the absolute percentages
Abbreviations: ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; LLT, lipid-lowering therapy; PAD, peripheral arterial disease; PCSK9i, PCSK9 inhibitor.

4. Discussion

In this study, we estimated that the overall prevalence of ASCVD in the US in 2019 to be 24.0 million, approximately 10% of the total US population above 21 years old. We found heavy comorbidity burden among ASCVD patients, and 31.2% were at very high risk for recurrent events. Furthermore, the majority of ASCVD patients were not at guideline-recommended LDL-C goal. Although there was a significant increase in the use of LLTs (especially of high-intensity statins) in 2019 compared to 2014, overall LLT utilization remained low, with only 3.8% of ASCVD patients on ezetimibe, less than 1% on PCSK9 inhibitors and over 40% on no LLTs. We also found higher utilization of LLTs among patients who were at goal of <70 or <55 mg/dL vs. those not at goal.

Compared to our previous analysis using 2014 data, we observed an increased prevalence in ASCVD in 2019. Although such increase is greater than the overall increase in US population over 21 years old (from 72.7% to 73.7%), it is consistent with the statistic reports by AHA, which showed an increasing trend in the prevalence of all major categories of cardiovascular disease in the 2014–2019 period, including stroke, PAD, and CHD[13,14]. Such increase highlights the magnitude and continuing progression of the cardiovascular disease burden in the US, though it may also be partly driven by the extended survival of CHD patients due to more effective LLTs becoming available. The proportion of patients with very high risk remained stable compared to 2014.

Despite the significant increase in utilization of LLTs, such as high-intensity statins and ezetimibe among ASCVD patients in 2019 compared to 5 years ago, overall utilization of LLTs remains low. This is especially true for PCSK9 inhibitors and high-intensity statin and ezetimibe combination, both of which were used by less than 1% of ASCVD patients in spite of guideline recommendation. Such low utilization of PCSK9 inhibitors was also reported by Chamberlain et al., who found <1% of patients with dyslipidemia or coronary heart disease were prescribed PCSK9 inhibitors[15]. One important barrier for physicians to prescribe PCSK9 inhibitors is the complex and time-consuming pre--authorization process[16]. Clinical inertia may also explain in part the failure to timely treatment of PCSK9 inhibitors[17]. In addition, only

Table 5
Treatment status for ASCVD patients with very high risk stratified by LDL-C.

	Multiple major events			1 major event + multiple high-risk conditions			Overall very high risk		
	LDL-C < 55	LDL-C < 70	LDL-C >=70	LDL-C < 55	LDL-C < 70	LDL-C >=70	LDL-C < 55	LDL-C < 70	LDL-C >=70
N	603,974	1266,081	1930,775	650,104	1342,538	2948,914	1254,078	2608,619	4879,689
High-intensity statin,%*	**58.6%**	**58.4%**	**29.4%**	**43.8%**	**44.7%**	**21.7%**	**50.9%**	**51.4%**	**24.7%**
Monotherapy	94.3%	96.0%	97.4%	94.7%	96.6%	96.7%	94.4%	96.3%	97.0%
Plus ezetimibe	2.5%	2.5%	1.6%	2.7%	1.9%	3.3%	2.6%	2.2%	2.5%
Plus PCSK9i (with or without ezetimibe)	3.2%	1.5%	0.9%	2.6%	1.5%	0.0%	3.0%	1.5%	0.4%
Moderate to low-intensity statin, %*	**24.4%**	**23.9%**	**27.1%**	**36.0%**	**33.9%**	**31.4%**	**30.4%**	**29.1%**	**29.7%**
Monotherapy	99.1%	96.2%	98.1%	98.3%	98.0%	98.9%	98.6%	97.3%	98.6%
Plus ezetimibe	0.0%	3.4%	1.9%	1.7%	2.0%	1.0%	1.0%	2.6%	1.3%
Plus PCSK9i (with or without ezetimibe)	0.9%	0.4%	0.0%	0.0%	0.0%	0.1%	0.3%	0.2%	0.1%
Ezetimibe,%*	**4.6%**	**5.3%**	**2.2%**	**1.7%**	**2.4%**	**2.2%**	**3.1%**	**3.8%**	**2.2%**
Ezetimibe only	97.0%	98.8%	98.9%	51.9%	84.0%	100.0%	84.2%	93.9%	99.6%
Ezetimibe plus PCSK9i	3.0%	1.2%	1.1%	48.1%	16.0%	0.0%	15.8%	6.1%	0.4%
PCSK9i only,%*	**0.4%**	**0.8%**	**1.4%**	**1.6%**	**0.9%**	**0.6%**	**1.0%**	**0.8%**	**0.9%**
No LLT,%*	**12.1%**	**11.6%**	**39.9%**	**16.9%**	**18.1%**	**44.1%**	**14.6%**	**14.9%**	**42.4%**
No LLT within 30 days	*59.3%*	*61.3%*	*68.6%*	*72.7%*	*55.4%*	*53.2%*	*67.3%*	*57.6%*	*58.9%*
Never LLT (no LLT within 5 years)	*40.7%*	*38.7%*	*31.4%*	*27.3%*	*44.6%*	*46.8%*	*32.7%*	*42.4%*	*41.1%*

* Numbers in these rows denote absolute percentages and add up to 100% vertically. All other numbers are relative percentages of the absolute percentages

Abbreviations: ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; LLT, lipid-lowering therapy; PAD, peripheral arterial disease; PCSK9i, PCSK9 inhibitor.

about 4% of ASCVD patients were on ezetimibe despite the fact that ezetimibe has been generic for several years and recommended by guidelines for all ASCVD patients not at goal with statins. Previous studies on LLT utilization in the real-world using recent data also underscored LLT underutilization among ASCVD patients, reporting 51% - 57% of ASCVD patients not on any LLTs[18–20]. This is consistent with our 2014 analysis reporting 54% not on any LLTs[6]. However, these results are lower compared to registry-based studies, which generally have more stringent inclusion and exclusion criteria, and are not generalizable to the entire US[21,22]. The increases we observed in LLT utilization in 2019 comparing to 2014 indicate improved awareness on the urgency to treat ASCVD and more compliance to guideline recommendations among healthcare providers. Additionally, patients who reached the goal suggested by guideline had significantly higher utilization in high-intensity statin/ezetimibe combination and PCSK9 inhibitors compared to those who did not. Such treatment pattern was also found among patients with very high risk. We observed an even higher PCSK9 inhibitor utilization among those who achieved the lower LDL-C goal (55 vs. 70 mg/dL). Such findings indicate the value of adding PCSK9 inhibitors for reaching LDL-C target levels.

This study provides the most up-to-date estimate on the prevalence of ASCVD in the US, as well as a description on the treatment pattern and LDL-C goal attainment in this population. It is also one of very few studies that reported the real-world utilization of PCSK9 inhibitors in the United States[15]. However, this analysis has several limitations. First, we used Truven MarketScan data, which represents a subset of US insured population, including those commercially insured in part by employers and those with Medicare supplement plans. Therefore, the results may not be generalizable to uninsured, Medicaid patients, or those using some other commercial plans not included in Truven. Second, due to data limitations, we were not able to report any disparities in LLT utilization by race/ethnicity. The lack of information on race/-ethnicity and other social determinants of health may limit the generalizability of this study to the entire US population. We were also not able to evaluate the treatment status and LDL-C goal attainment for a subgroup of very-high risk patients who had multiple CV events within the last 2 years, for whom the EAS/ESC guideline recommended an even lower treatment goal of LDL-C < 40 mg/dL[9]. These are important directions for future study. In addition, we considered patients currently on LLT if the runout date of an LLT prescription was within 30 days of index date. There is a chance of misclassification if a prescription was written following the index LDL-C measurement but took over 30 days to get approved. This is possible for new initiators on PCSK9 inhibitors due to the access barriers put in place by payors.

In conclusion, we estimate that approximately 24 million patients in the US had ASCVD in 2019 and highlight an overall underutilization of LLTs despite an increase in high-intensity statins use since 2014. Yet High-intensity statins were used in only 24.0% of ASCVD patients, and among those with LDL-C $\geq$ 70 mg/dL, ezetimibe was prescribed in only 2.8% and PCSK9 inhibitors in less than 1% of ASCVD patients in spite of evidence of their efficacy in LDL-C lowering and ability to reduce CHD risk, as well as the generic status of statins and ezetimibe. Increased awareness of guidelines by healthcare providers and urgency to treat ASCVD is needed in order to improve LLT utilization and help more patients reach the LDL-C goal.

5. Disclosures

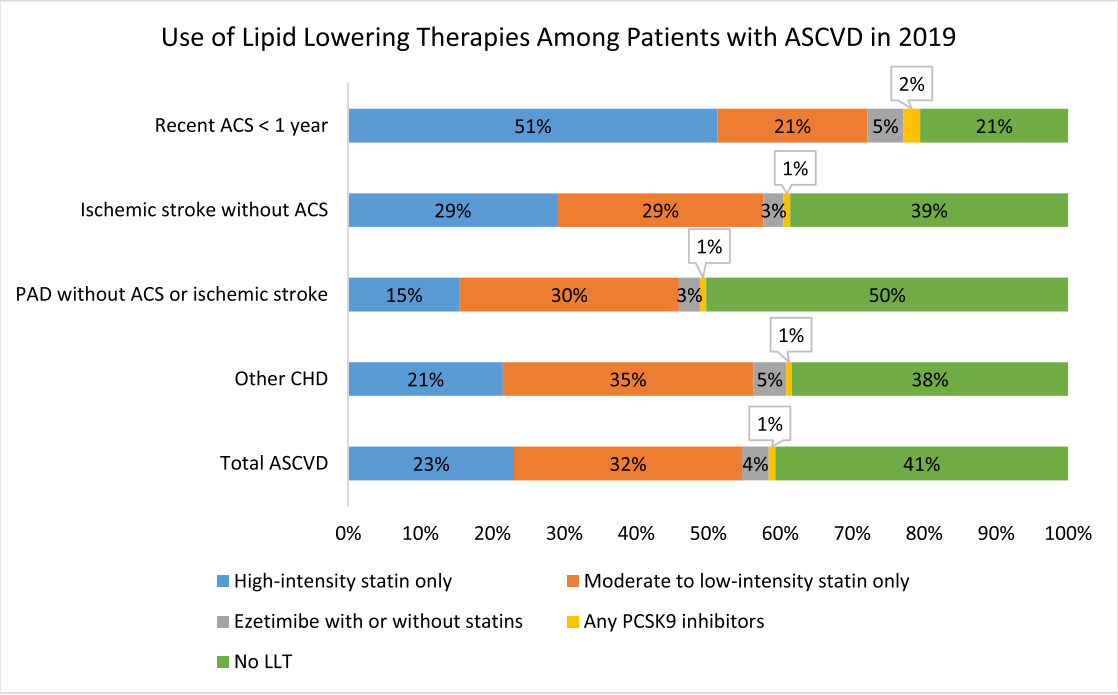
Jing Gu, Robert Sanchez and Sergio Fazio are employees of and stockholders in Regeneron Pharmaceuticals, Inc. Ankita Chauhan is an employee of Axtria. Nathan Wong reports research support through his institution from Novartis and Gilead, is a consultant for Novartis, and reports advisory board participation with Amgen during the last 12 months. The sponsors were involved in the study design, and collection, analysis and interpretation of data, as well as data checking of information provided in the manuscript. All authors had unrestricted access to study data, were responsible for all content and editorial decisions, and received no honoraria related to the development of this publication.

Statement of authorship

Jing Gu, Robert Sanchez and Sergio Fazio designed the study. Ankita Chauhan conducted the analysis. All authors contributed to writing and editing, and provided final review and approval of the manuscript.

Declaration of interests

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



ACS: acute coronary syndrome; ASCVD: atherosclerotic cardiovascular disease; CHD: coronary heart disease; PAD: peripheral arterial disease; LLT: lipid lowering therapies

Central illustration
ACS: acute coronary syndrome; ASCVD: atherosclerotic cardiovascular disease; CHD: coronary heart disease; PAD: peripheral arterial disease; LLT: lipid lowering therapies

Jing Gu reports a relationship with Regeneron Pharmaceuticals Inc that includes: employment and equity or stocks. Robert Sanchez reports a relationship with Regeneron Pharmaceuticals Inc that includes: employment and equity or stocks. Sergio Fazio reports a relationship with Regeneron Pharmaceuticals Inc that includes: employment and equity or stocks. Ankita Chauhan reports a relationship with Axtria that includes: employment. Nathan Wong reports a relationship with Novartis that includes: consulting or advisory and funding grants. Nathan Wong reports a relationship with Gilead that includes: funding grants. Nathan Wong reports a relationship with Amgen Inc that includes: board membership. The sponsors were involved in the study design, and collection, analysis and interpretation of data, as well as data checking of information provided in the manuscript. All authors had unrestricted access to study data, were responsible for all content and editorial decisions, and received no honoraria related to the development of this publication.

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Supplementary materials

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