Journal of the American Heart Association

ORIGINAL RESEARCH

Adoption of PCSK9 Inhibitors Among Patients With Atherosclerotic Disease

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BACKGROUND: PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors represent a promising class of lipid-lowering therapy, although their use has been limited by cost concerns.

METHODS AND RESULTS: A retrospective cohort study was conducted using a nationwide commercial claims database comprising patients with atherosclerotic cardiovascular disease (ASCVD), aged 18 to 64 years. We identified the number of patients with ASCVD started on a PCSK9 inhibitor from the dates of US Food and Drug Administration approval in quarter 3 2015 through quarter 2 2019. Secondary objectives identified the proportions of patients started on a PCSK9 inhibitor in various ASCVD risk groups based on statin use and baseline low-density lipoprotein cholesterol. We identified 126 419 patients with ASCVD on either PCSK9 inhibitor or statin therapy. Among these patients, 1168 (0.9%) filled a prescription for a PCSK9 inhibitor. The number of patients initiating a PCSK9 inhibitor increased from 2 patients in quarter 3 2015 to 119 patients in quarter 2 2019, corresponding to an increase from 0.05% to 2.5% of patients with ASCVD already on statins who started PCSK9 inhibitor therapy. Of patients with ASCVD with high adherence to a high-intensity statin, 13 643 had low-density lipoprotein cholesterol ≥70 mg/dL, and in this subgroup, 119 (0.9%) patients initiated a PCSK9 inhibitor.

CONCLUSIONS: Few patients started PCSK9 inhibitors from 2015 through mid-2019, despite increasing trial evidence of efficacy, guidelines recommending PCSK9 inhibitors in high-risk patients with ASCVD, and price reductions during this period. The magnitude of price reductions may not yet be sufficient to influence use management strategies aimed to limit PCSK9 inhibitor use.

Key Words: access to care ■ drug adoption ■ PCSK9 inhibitors ■ secondary prevention

PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors represent a novel class of lipid-lowering therapy that has been demonstrated to reduce low-density lipoprotein cholesterol (LDL-C) as well as reduce the risk of major adverse cardiovascular events (MACEs).[1,2] The PCSK9 inhibitors currently available are alirocumab and evolocumab, both approved by the US Food and Drug Administration in 2015 for use in patients with familial hypercholesterolemia or preexisting atherosclerotic cardiovascular disease (ASCVD) who require additional lowering of LDL-C despite maximally tolerated doses of statins.[3]

The enthusiasm over the clinical promise of PCSK9 inhibitors was tempered by average treatment prices of $14 000 per year, combined with studies concluding that these drugs do not meet generally acceptable cost-effectiveness thresholds.[4,5] Moreover, the high costs of PCSK9 inhibitors caused health insurers and pharmacy benefit managers to implement use management processes, such as prior authorizations and increased patient cost sharing, which have been associated with slower uptake of novel pharmaceuticals in select populations.[6,7]

In 2017, the American College of Cardiology published guidelines on the role of nonstatin therapies for

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CLINICAL PERSPECTIVE

What Is New?

- Despite increasing evidence demonstrating PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors provide improved cardiovascular outcomes, clinical guidelines recommending their use, and drug price reductions, few eligible patients with atherosclerotic disease are initiated on PCSK9 inhibitors.
- The magnitude of price reductions may not yet be sufficient to influence use management strategies aimed to limit PCSK9 inhibitor use.

What Are the Clinical Implications?

- The clinical benefits of novel therapies, such as PCSK9 inhibitors, may not be realized if barriers to access persist and adoption remains low.

Nonstandard Abbreviations and Acronyms

MACE	major adverse cardiovascular event
MPR	medication possession ratio
PCSK9	proprotein convertase subtilisin/kexin type 9

management of ASCVD, and in 2018, the American College of Cardiology/American Heart Association Multisociety Guideline on the Management of Blood Cholesterol was published. Both guidelines recommended PCSK9 inhibitors in patients with high-risk ASCVD with LDL-C ≥70 mg/dL after adoption of lifestyle modifications and treatment with standard background therapy.[8,9] In 2018, the manufacturers for both alirocumab and evolocumab announced price reductions to <$6000 per year in an attempt to meet cost-effectiveness benchmarks and improve patient access to these therapies.[10,11]

In this analysis, we identified trends in the number of patients with ASCVD initiated on PCSK9 inhibitor therapy as well as the proportion of patients with ASCVD on statin therapy who were started on a PCSK9 inhibitor from approval in 2015 through mid-2019. We also identified different patient groups with ASCVD and calculated the proportion who were initiated on a PCSK9 inhibitor.

METHODS

Study Data

Data were obtained from Optum's deidentified Clinformatics Data Mart Database. The database consists of comprehensive inpatient, outpatient, laboratory, and pharmacy claims for >17 million patients annually throughout the United States and includes each patient's dates of insurance coverage. Demographic data were also available through ZIP code linked enrollment data from the US Census Bureau. The study protocol was deemed exempt by the University of Pennsylvania Institutional Review Board. The proprietary data that support the findings of this study are available from the corresponding author on reasonable request, although they will be subject to data privacy rules and licensing requirements of Optum.

Study Cohort

Using administrative claims from January 1, 2015, through June 30, 2019, we included patients with ASCVD, aged 18 to 64 years, who filled a prescription for either a PCSK9 inhibitor or a statin. Pharmacy claims, including National Drug Codes, fill dates, and days supplied, were used to identify PCSK9 inhibitor and/or statin use. Drug classes were identified using National Drug Codes.[12] To identify ASCVD, we examined all inpatient and outpatient claims occurring 12 months before the index prescription, and included patients with a history of coronary artery disease, stroke or transient ischemic attack, and peripheral arterial disease. ASCVD diagnoses were identified using *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*), codes and *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*), codes from summaries of the Medicare Chronic Conditions Warehouse.[13] We excluded patients who had <12 months of continuous insurance enrollment before the index prescription for either a PCSK9 inhibitor or a statin during the study period to accurately capture patient comorbidities as well as assess for medication adherence. We also excluded patients with no serum lipid measurement in the 12 months before the index prescription for a PCSK9 inhibitor or a statin so we could describe baseline LDL-C levels for patients initiated or not initiated on a PCSK9 inhibitor.

Outcomes

The primary outcome was the number of patients with ASCVD who filled a first prescription for a PCSK9 inhibitor during the study period of January 1, 2015, through June 30, 2019. We also compared the proportion of patients with ASCVD who filled a first prescription for a PCSK9 inhibitor with patients with ASCVD who were filling statin prescriptions over the same time period.

Among patients with ASCVD, we also identified 3 subgroups of patients based on statin use and LDL-C

levels: (1) patients with concurrent high-intensity statin use, (2) patients highly adherent to a high-intensity statin, and (3) patients highly adherent to a high-intensity statin with measured serum LDL-C ≥70 mg/dL. We identified these subgroups because those with high cardiovascular risk who were adherent to maximal statin therapy were potentially the patients who would benefit the most from PCSK9 inhibitor initiation, and thus we expected the proportion of these patients who were treated with a PCSK9 inhibitor to be higher than the general group of patients with ASCVD.

High-intensity statin use was defined as filling prescriptions for either atorvastatin, 40 to 80 mg, or rosuvastatin, 20 to 40 mg.[9] High adherence to a statin was indicated by a medication possession ratio (MPR) ≥0.80 in the past 12 months. MPR is defined by the sum of the days supplied of all prescriptions filled for a drug in a given time period, divided by the number of days in the time period, and MPR ≥0.80 is commonly used as a marker for high adherence.[14,15] Last, we identified serum LDL-C. If serum LDL-C was measured more than once in the prior year, we included the most recent LDL-C measurement (ie, the laboratory result closest in date to the index PCSK9 inhibitor or high-intensity statin prescription).

Among patients with ASCVD, demographic characteristics, including age, sex, race, and US geographic region, were compared by the following groups: patients adherent to a high-intensity statin with LDL-C ≥70 mg/dL who were not started on a PCSK9 inhibitor, patients adherent to a high-intensity statin with LDL-C ≥70 mg/dL who were started on a PCSK9 inhibitor, and patients without consistent use of a high-intensity statin (ie, MPR <0.8) and/or with an LDL-C <70 mg/dL who were started on a PCSK9 inhibitor. Using *ICD-9-CM* and *ICD-10-CM* diagnosis codes from data summaries of the Medicare Chronic Conditions Warehouse, history of hypertension, diabetes mellitus, and premature ASCVD (aged <55 years in men and aged <60 years in women) was also compared. MACEs in the past year, defined as an inpatient hospitalization with a diagnosis code for acute myocardial infarction or transient ischemic attack/stroke, were compared by group.

Using National Drug Codes from pharmacy claims, we identified other lipid-lowering therapies (ie, ezetimibe, bile acid sequestrants, and fibrates) that patients filled in the prior 12 months, given guidelines also recommend using ezetimibe in patients with ASCVD with high cardiovascular risk and LDL-C ≥70 mg/dL.[8,9] We also determined the proportion of patients who had an outpatient cardiologist visit as well as the number of outpatient cardiologist visits in the past year to assess for an association between intensity of specialist care and PCSK9 inhibitor initiation. Specialty of provider was identified on the outpatient claim by Medicare taxonomy codes.[16] Last, we compared serum LDL-C.

Last, we assessed patient factors associated with being initiated on a PCSK9 inhibitor. Using a multivariable logistic regression model with PCSK9 inhibitor initiation as the dependent variable, the independent variables measured were age in years, sex, race, US region, annual household income, history of hypertension, history of diabetes mellitus, MACE in the past year, baseline LDL-C in mg/dL, and having a cardiology outpatient encounter in the past year. To assess the patients likely to have the most benefit from PCSK9 inhibitor initiation, we included patients with ASCVD who were highly adherent to a high-intensity statin and with LDL-C ≥70 mg/dL and compared them with the patients with ASCVD initiated on a PCSK9 inhibitor with LDL-C ≥70 mg/dL in the logistic regression model.

Statistical Analysis

Differences in characteristics and outcomes between groups were compared using χ^2 tests for categorical variables and ANOVA for continuous variables. All statistical tests were 2 sided, with $P<0.05$ indicating statistical significance. In the multivariable logistic regression model, estimated adjusted odds ratios (ORs) are reported with 95% CIs, and each OR reported is adjusted for all other covariables in the model. Analyses were performed using Stata, version 15.1 (StataCorp).

RESULTS

Among patients with at least 1 year of continuous insurance eligibility, we identified 1 696 007 patients on statin therapy and 3463 patients initiated on a PCSK9 inhibitor. After excluding patients without serum lipid measurement data in the 12 months before the index prescription for a PCSK9 inhibitor or statin, we identified 569 572 patients on a statin and 1520 patients on PCSK9 inhibitor therapy.

After restricting the cohort to patients with a history of ASCVD, we identified 126 419 patients with ASCVD on either PCSK9 inhibitor or statin therapy from January 1, 2015, to June 30, 2019. Among these patients, we identified a total of 1168 (0.9%) who filled a prescription for a PCSK9 inhibitor. The number of patients filling a first prescription for a PCSK9 inhibitor increased from 2 patients in the third quarter of 2015 to 119 patients in the second quarter of 2019, corresponding to an increase from 0.05% to 2.5% of patients with ASCVD already on statins who started PCSK9 inhibitor therapy (Figure 1).

In our subgroup analysis, we identified 54 815 patients with ASCVD on a high-intensity statin; of these patients, 478 (0.9%) were initiated on a PCSK9 inhibitor (Figure 2). Among the 27 122 patients who were highly adherent to a high-intensity statin, 143 (0.5%) were started on a PCSK9 inhibitor. Of these patients with

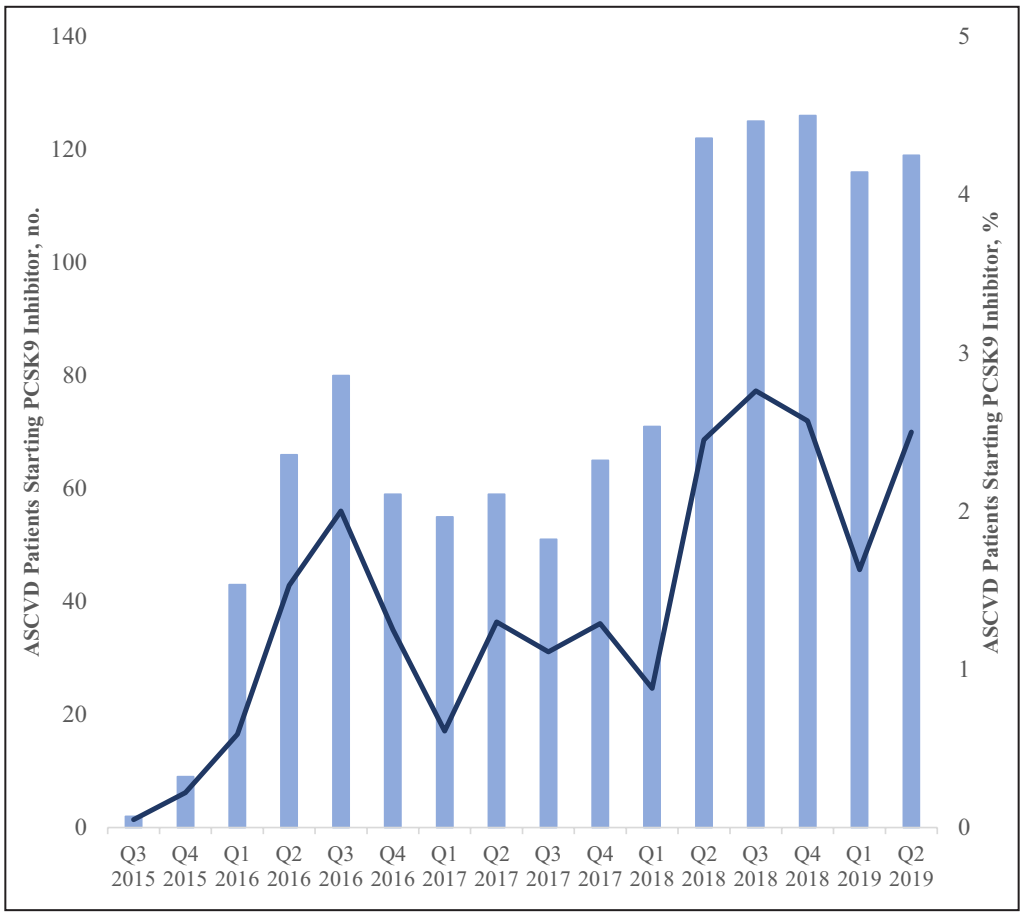

Figure 1. Trends in patients with atherosclerotic cardiovascular disease (ASCVD) initiated on PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor therapy, 2015 to 2019.
The bars represent the number of patients with ASCVD initiated on a PCSK9 inhibitor from US drug approval in second quarter (Q) 2015 to the second quarter of 2019. The line represents the proportion of patients with ASCVD started on a PCSK9 inhibitor among patients with incident ASCVD on statin therapy.

ASCVD with high adherence to a high-intensity statin, 13 643 had LDL-C ≥70 mg/dL; and in this subgroup, 119 (0.9%) patients were started on a PCSK9 inhibitor.

Clinical Characteristics of PCSK9 Inhibitor Initiation

Patients with ASCVD who were adherent to high-intensity statins, with LDL-C ≥70 mg/dL and not started on a PCSK9 inhibitor (ie, high-intensity statin only), were more likely to be women compared with patients with ASCVD who were adherent to a high-intensity statin, with LDL ≥70 mg/dL and started on a PCSK9 inhibitor (ie, PCSK9 inhibitor and high-intensity statin). Both of these groups were less likely to be women when compared with patients with ASCVD started on a PCSK9 inhibitor without consistent prior high-intensity statin use and/or LDL-C <70 mg/dL (ie, PCSK9 inhibitor only) (29.7% versus 26.9% versus 38.2%; *P*<0.001) (Table 1). There were no significant differences in age or US geographical region among the 3 groups. Patients in the high-intensity statin-only group were less likely to be White patients compared with the PCSK9 inhibitor and high-intensity statin group and the PCSK9 inhibitor only group (63.3% versus 77.3% versus 66.7%; *P*<0.001). Compared with the 2 groups started on a PCSK9 inhibitor, the high-intensity statin only group was more likely to have experienced MACEs in the past year (28.2% versus 19.3% versus 18.7%; *P*<0.001), more likely to have a history of stroke (17.7% versus 5.9% versus 9.0%; *P*<0.001), more likely to have diabetes mellitus (43.8% versus 32.8% versus 39.2%; *P*=0.001), and more likely to have hypertension (86.2% versus 81.5% versus 83.9%; *P*=0.04). There were no significant differences in prevalence of premature ASCVD or peripheral arterial disease among the 3 groups.

For use of nonstatin lipid-lowering therapies in the preceding 12 months, the high-intensity statin only group was less likely to have filled prescriptions for ezetimibe (6.7% versus 55.5% versus 31.6%; *P*<0.001) and bile acid sequestrants (1.1% versus 8.4% versus 5.1%;

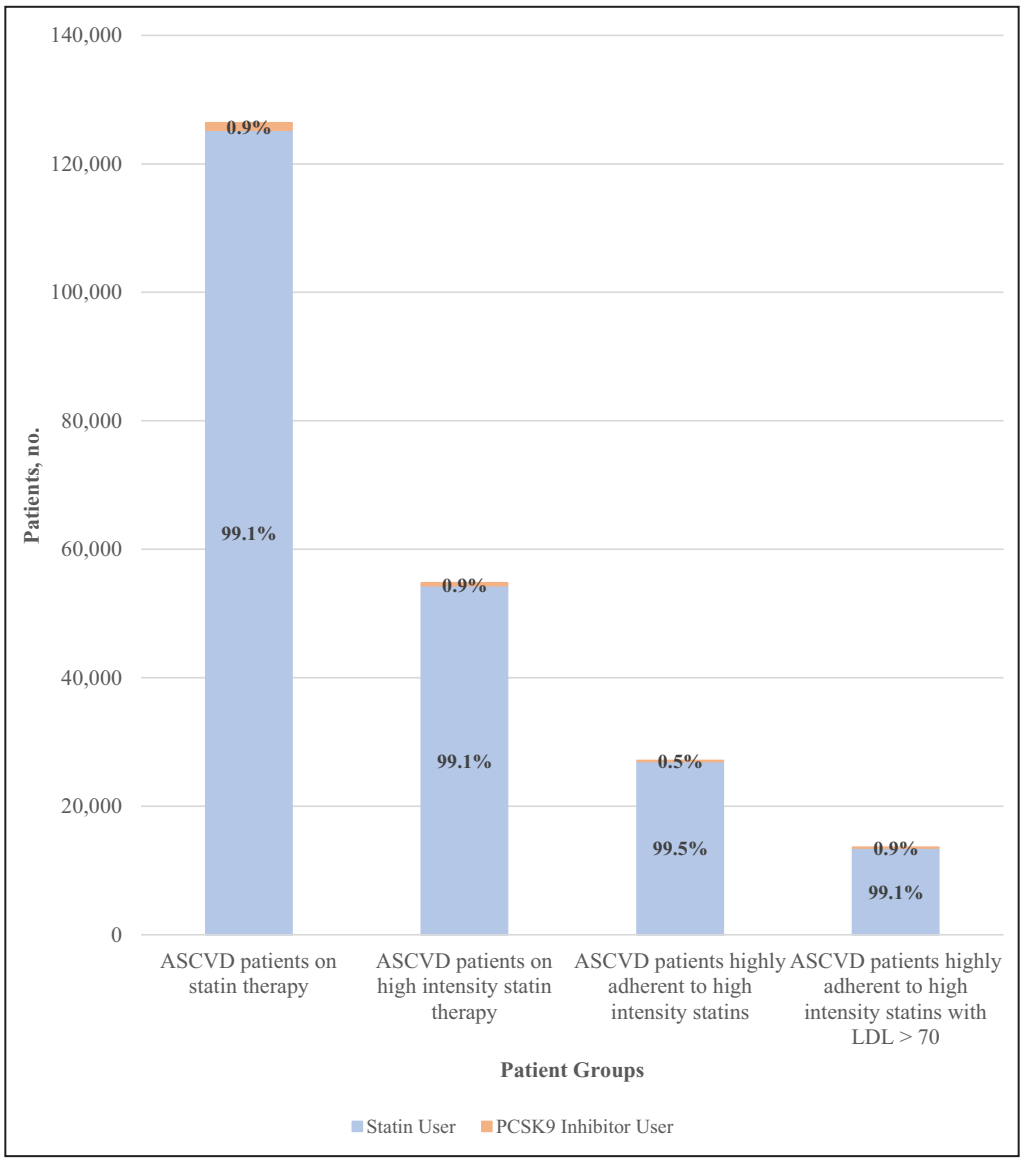

Figure 2. Number of patients initiated on a PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor among different patient groups with atherosclerotic cardiovascular disease (ASCVD). The orange bars represent the number of patients started on a PCSK9 inhibitor, and the blue bars represent the number of patients not started on PCSK9 inhibitor therapy, among different patient groups with ASCVD. LDL indicates low-density lipoprotein.

P<0.001) compared with the 2 groups started on a PCSK9 inhibitor.

The high-intensity statin only group had a lower median number of outpatient cardiology visits in the preceding 12 months (2; interquartile range, 0–4), compared with the PCSK9 inhibitor and high-intensity statin group (3; interquartile range, 1–5) and the PCSK9 inhibitor only group (3; interquartile range, 2–6) (*P*<0.001).

Factors Associated With PCSK9 Inhibitor Initiation

In multivariable analysis (Table 2), female patients were more likely to be started on a PCSK9 inhibitor than male patients (OR, 1.44; 95% CI, 1.22–1.68; *P*<0.001). Patients with annual household income between $50 000 and $99 999 were more likely to be started on PCSK9 inhibitors than patients with annual household income <$50 000 (OR, 1.31; 95% CI, 1.05–1.65; *P*=0.02); patients with household income >$100 000 were also more likely to be started on PCSK9 inhibitors than patients with annual household income <$50 000 (OR, 2.06; 95% CI, 1.66–2.55; *P*<0.001). Patients with MACEs in the past year were less likely to be initiated on a PCSK9 inhibitor (OR, 0.59; 95% CI, 0.49–0.71; *P*<0.001), and patients with a cardiology outpatient visit in the past year

Table 1. Demographic and Clinical Characteristics of Patients With ASCVD by Adherence to a High-Intensity Statin, Baseline LDL-C, and PCSK9 Inhibitor Initiation

Characteristic	Patient Group With ASCVD			
	Adherent to High-Intensity Statin With LDL-C ≥70 mg/dL and Not Started on PCSK9 Inhibitor (n=13 524)	Adherent to High-Intensity Statin With LDL-C ≥70 mg/dL and Started on PCSK9 Inhibitor (n=119)	Started on PCSK9 Inhibitor Without Adherence to High-Intensity Statin and/or With LDL-C <70 mg/dL (n=1049)	*P* Value
Age, mean (SD), y	57.0 (5.9)	56.0 (6.5)	57.0 (6.3)	0.053
Women	4015 (29.7)	32 (26.9)	401 (38.2)	<0.001
Region				0.63
Northeast	1368 (10.1)	13 (10.9)	108 (10.3)	
Midwest	1767 (13.1)	13 (10.9)	118 (11.3)	
South	7858 (58.1)	68 (57.1)	615 (58.6)	
West	2503 (18.5)	24 (20.2)	205 (19.5)	
Unknown	28 (0.2)	1 (0.8)	3 (0.3)	
Race/ethnicity				<0.001
White	8566 (63.3)	92 (77.3)	700 (66.7)	
Black	1384 (10.2)	10 (8.4)	91 (8.7)	
Hispanic	1258 (9.3)	9 (7.6)	116 (11.1)	
Asian	321 (2.4)	1 (0.8)	30 (2.9)	
Unknown	1995 (14.8)	7 (5.9)	112 (10.7)	
Cardiovascular risk factors				
Premature ASCVD	5053 (37.4)	51 (42.9)	405 (38.6)	0.35
MACE in past year	3811 (28.2)	22 (19.3)	196 (18.7)	<0.001
Coronary artery disease	11 251 (83.2)	114 (95.8)	975 (93.0)	<0.001
Stroke/TIA	2395 (17.7)	7 (5.9)	94 (9.0)	<0.001
Peripheral arterial disease	3006 (22.2)	24 (20.2)	219 (20.9)	0.52
Diabetes mellitus	5923 (43.8)	39 (32.8)	411 (39.2)	0.001
Hypertension	11 661 (86.2)	97 (81.5)	880 (83.9)	0.04
Baseline medications				
Ezetimibe	911 (6.7)	66 (55.5)	331 (31.6)	<0.001
Bile acid sequestrants	148 (1.1)	10 (8.4)	53 (5.1)	<.001
Fibrates	1478 (10.9)	17 (14.3)	123 (11.7)	0.38
Use				
Outpatient cardiology visit	10 137 (75.0)	95 (79.8)	930 (88.7)	<0.001
No. of cardiology visits, median (IQR)	2 (0–4)	3 (1–5)	3 (2–6)	<0.001
Baseline LDL-C, mg/dL				<0.001
<70	N/A	N/A	154 (14.7)	
70–99	9920 (73.4)	33 (27.7)	146 (13.9)	
100–129	2610 (19.3)	38 (31.9)	220 (21.0)	
≥130	994 (7.4)	48 (40.3)	529 (50.4)	

Data are given as number (percentage) of each group, unless otherwise indicated. ASCVD indicates atherosclerotic cardiovascular disease; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; N/A, not applicable; PCSK9, proprotein convertase subtilisin/kexin type 9; and TIA, transient ischemic attack.

were more likely to be started on a PCSK9 inhibitor (OR, 2.89; 95% CI, 2.32–3.60; *P*<0.001). Relative to patients with a baseline LDL-C of 70 to 99 mg/dL, patients with baseline LDL-C of 100 to 129 mg/dL (OR, 5.79; 95% CI, 4.75–7.06; *P*<0.001) and baseline LDL-C ≥130 mg/dL (OR, 36.29; 95% CI, 30.09–43.77; *P*<0.001) were more likely to be initiated on a PCSK9 inhibitor. There was no significant association

Table 2. Multivariable Logistic Regression on Factors Associated With PCSK9 Inhibitor Initiation

Patient Characteristic	PCSK9 Inhibitor Initiation	
	OR (95% CI)	*P* Value
Age, y	1.00 (0.99–1.02)	0.58
Women	1.44 (1.22–1.68)	<0.001
Race/ethnicity		
White	1 (Reference)	
Black	0.79 (0.61–1.03)	0.08
Hispanic	1.03 (0.80–1.31)	0.83
Asian	0.64 (0.39–1.07)	0.09
Unknown	0.76 (0.58–1.01)	0.06
US region		
Northeast	1 (Reference)	
South	0.92 (0.72–1.17)	0.50
Midwest	0.73 (0.53–0.99)	0.04
West	1.09 (0.83–1.44)	0.53
Unknown	2.12 (0.58–7.71)	0.25
Annual household income, $		
<50 000	1 (Reference)	
50 000–99 999	1.31 (1.05–1.65)	0.02
>$100 000	2.06 (1.66–2.55)	<0.001
Unknown	1.00 (0.78–1.28)	0.98
Hypertension	0.85 (0.69–1.04)	0.11
Diabetes mellitus	0.85 (0.73–1.00)	0.05
MACE in past year	0.60 (0.50–0.72)	<0.001
Baseline LDL-C, mg/dL		
70–99	1 (Reference)	
100–129	5.79 (4.75–7.06)	<0.001
≥ 130	36.29 (30.09–43.77)	<0.001
Cardiology outpatient visit in past year	2.80 (2.27–3.45)	<0.001

LDL-C indicates low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; OR, odds ratio; and PCSK9, proprotein convertase subtilisin/kexin type 9.

Patients included in the model were patients with ASCVD with high adherence to a high-intensity statin and LDL-C ≥70 mg/dL who were not started on a PCSK9 inhibitor as well as patients with ASCVD with LDL-C ≥70 mg/dL who were initiated on a PCSK9 inhibitor.

between PCSK9 inhibitor initiation and age in years, race, and history of hypertension.

DISCUSSION

In a sample of 126 419 privately insured patients with a history of ASCVD and on statin therapy, <1% of patients were started on a PCSK9 inhibitor in the 4 years after the introduction of the first US Food and Drug Administration–approved agents in this therapeutic class. Over this time period, the proportion of potentially eligible patients with ASCVD on statin therapy who were initiated on a PCSK9 inhibitor modestly increased. Before 2018, the proportion of these patients started on a PCSK9 inhibitor was approximately 1%, and in 2018 through mid-2019, the proportion of patients started on PCSK9 inhibitor therapy was approximately 2%. This was despite clinical trials showing improvement in cardiovascular outcomes, guidelines recommending PCSK9 inhibitors in patients with ASCVD with high cardiovascular risk, and price reductions in these drugs over this time period. The low use of PCSK9 inhibitors among patients with ASCVD was not substantially different among the different patient groups with ASCVD identified over the study period; the most inclusive group (ie, patients with ASCVD on a statin) and the most stringent group (ie, patients with ASCVD who were highly adherent to a high-intensity statin for a year with suboptimal LDL-C levels) both had <1% PCSK9 inhibitor initiation. In addition, we found that after factoring for demographic, socioeconomic, and clinical characteristics, patients with MACEs in the past year were less likely to be initiated on a PCSK9 inhibitor, suggesting the highest-risk patients may not be receiving PCSK9 inhibitor therapy.

Our findings highlight the fact that patients who could potentially benefit from PCSK9 inhibitors far outnumber the patients currently receiving PCSK9 inhibitor therapy, even after drug price reductions and society guidelines recommended their use. A national estimate using American College of Cardiology registry data found 700 000 to 10 million patients would be eligible for PCSK9 inhibitor therapy, depending on LDL-C threshold.[17] Another study using American College of Cardiology registry data found <2% of patients with an LDL-C ≥190 mg/dL were receiving PCSK9 inhibitors.[18] Even among the highest-risk patients with ASCVD who were highly adherent to high-intensity statins and had suboptimal LDL-C levels, the number of patients aged 18 to 64 years who were eligible for PCSK9 inhibitors far outnumbered the number of patients receiving a PCSK9 inhibitor.

Investigation into the barriers to PCSK9 inhibitor use has largely been focused on prior authorization requirements and patient cost sharing implemented by payers, which are themselves a result of high drug prices.[6,7] Less than half of patients prescribed a PCSK9 inhibitor receive prior authorization approval from their insurer; of the patients who receive approval, more than a third never fill a prescription, with high copayments appearing to play a substantial role in primary nonadherence.[6] It had been anticipated that insurer requirements and high out-of-pocket costs would become lower barriers after the manufacturers of alirocumab and evolocumab announced plans to reduce the price of both drugs in 2018.[16] However, our analysis found only a modest increase in patients initiated on a

PCSK9 inhibitor in the year after these announcements were made. Moreover, our multivariable analysis found that annual household income was one of the strongest factors associated with PCSK9 inhibitor initiation, with a graded association for the low-, middle-, and high-income groups. Thus, relative to higher-income patients, the costs of PCSK9 inhibitors for the lower- and middle-income insured patients in our study may be a barrier to their use.

PCSK9 inhibitors are representative of the growing number of biologic drug classes that comprise a greater share of new drug approvals by the US Food and Drug Administration each year.[19] Biologics are used by only 2% of Americans but have nonetheless been a large factor in increased drug spending in recent years.[20] In 2015, biologics accounted for nearly 40% of US prescription drug spending and for 70% of prescription drug spending growth from 2010 to 2015.[21] Inherently, complex manufacturing processes compared with small-molecule drug production as well as patent protections and patent disputes have limited generic drug manufacturers from producing and marketing biosimilars, which would increase market competition and potentially reduce prices for biologics.[20,22] Thus, the likelihood of increased competition reducing PCSK9 inhibitor prices in the near future appears low.

However, the phenomenon of drug prices limiting the adoption of novel therapies is not limited to biologics. Within cardiovascular medicine, sacubitril/valsartan and sodium-glucose cotransporter-2 inhibitors are examples of small-molecule drugs that, despite having substantial clinical benefit and being guideline-recommended therapies, have had slow adoption because of insurance coverage restrictions linked to high-priced novel therapies.[23,24] Payers are likely to impose coverage restrictions and strict use management strategies for high-priced novel therapies for common conditions, such as ASCVD, diabetes mellitus, or heart failure, given the potential large budgetary impact inherent in providing these new therapies to millions of eligible patients. Ultimately, the potential clinical benefits these novel therapies might provide to patients may not be realized if significant underuse remains.

Aside from drug pricing, patient access to specialists and clinician variation in prescribing practices may be important barriers to PCSK9 inhibitor prescribing. Two thirds of commercial insurers restrict PCSK9 inhibitor approval to specialty prescribers,[7] and in our sample, patients prescribed PCSK9 inhibitors had a higher intensity of cardiology outpatient visits. Specialist access may be a significant barrier for some patients, particularly rural, low-income, and minority patients.[25,26] Furthermore, PCSK9 inhibitor prescribing varies among lipid specialists, with 17% reporting never having prescribed a PCSK9 inhibitor when ASCVD is the indication, and more than half reporting they rarely prescribe PCSK9 inhibitors for ASCVD (and more commonly prescribe to patients with familial hypercholesterolemia).[27] In our sample, we found 1 in 8 patients started on a PCSK9 inhibitor had an LDL-C <70 mg/dL before initiation, whereas more than half of the cohort highly adherent to a high-intensity statin had suboptimal LDL-C control, which may partly be reflective of differences in clinician practice, such as treating to a specific LDL-C target versus treating to a specific statin dose.

We also found that, after factoring for multiple demographic, socioeconomic, and clinical characteristics, patients with MACEs in the past year were less likely to be initiated on PCSK9 inhibitors, suggesting that many of the highest-risk patients are not being initiated on PCSK9 inhibitor therapy. In addition, even though patients with an LDL-C ≥70 mg/dL are potential candidates for PCSK9 inhibitors, patients with LDL-C ≥100 mg/dL were much more likely to be initiated on PCSK9 inhibitors compared with patients with baseline LDL-C between 70 and 99 mg/dL. This difference may be explained by clinician prescribing practices and/or by insurer coverage.

The rate of suboptimal statin use (ie, low- or moderate-intensity statin use in patients with ASCVD) in our overall patient sample is consistent with rates found in various populations.[28–30] Although most patients using PCSK9 inhibitors had filled a statin prescription in the previous year, notably only 41% had filled a high-intensity statin prescription and <15% demonstrated high adherence rates to a high-intensity statin in the prior year. The nature of administrative claims precludes determination of the causes for relatively low statin use, whether it be adverse effects/intolerance, patient preferences for nonstatin medications, other reasons for patient-level nonadherence, or variation in clinician prescribing practices. Moreover, there was low use of ezetimibe in our sample of patients with ASCVD with suboptimal LDL-C, despite guidelines recommending its use. Given ezetimibe was available as a generic medication for most of the study period, its underuse may be attributable to nonfinancial factors, such as low physician prescribing.

Limitations

This study has limitations inherent to retrospective studies using administrative claims. Our study data lacked detailed clinical information, which would have more accurately confirmed ASCVD and other baseline comorbidities. Although we identified high-risk patients given they had ASCVD with prevalent comorbidities and suboptimal LDL-C despite adherence to high-intensity statins, we did not implement the guideline definition of “very-high-risk ASCVD” given the administrative claims database used did not allow

us to observe all the criteria included in the guideline definition. However, we used well-validated administrative codes to optimally identify patients with the data available. Notably, specific *ICD-10-CM* codes for familial hypercholesterolemia became effective in late 2016 and were not widely used in our data set during the period studied, which precluded us from identifying the prevalence of these patients within our sample. However, familial hypercholesterolemia is estimated to only represent 5% of the target population for PCSK9 inhibitors, and studies suggest barriers to access are similar to patients with ASCVD.[31,32] In addition, although we used National Drug Codes to identify prescription claims, past analyses have noted that statin use is underestimated in administrative claims, often attributed to patients filling their prescription through generic drug discount programs offered at major retail pharmacies rather than through their insurer[33,34]; thus, this analysis may have underestimated statin use and adherence in our study population.

Our demographic measures were derived from ZIP code–linked US Census data rather than direct patient measurement, and therefore these measures may not accurately reflect individual patients' demographic information; nevertheless, similar measures have been used extensively in the literature as a reasonable proxy for group-level analysis. Our measure of adherence (MPR) is a commonly used, although indirect, measure of adherence. It does not indicate how many days a patient actually took a medication; hence, MPR tends to overestimate medication adherence.[35,36] Finally, although the study sample came from a large, nationally representative commercially insured population, our results may not be representative for patients with public health insurance.

CONCLUSIONS

We observed small numbers of potentially eligible patients starting PCSK9 inhibitors from US Food and Drug Administration approval in 2015 through mid-2019, a period during which increasing clinical evidence demonstrated PCSK9 inhibitors improved cardiovascular outcomes, guidelines recommended PCSK9 inhibitors in patients with ASCVD with high cardiovascular risk, and manufacturers reduced prices of the drugs. Among various patient subgroups identified as potentially greatly benefiting from PCSK9 inhibitors, we still found <1% were started on PCSK9 inhibitor therapy. Thus, the magnitude of price reductions may not yet be sufficient to influence use management strategies aimed to limit PCSK9 inhibitor use, despite increased guideline recommendations for their use. The potential clinical benefits of novel therapies, such as PCSK9 inhibitors, may not be realized if barriers to access remain.

ARTICLE INFORMATION

Received September 10, 2020; accepted February 3, 2021.

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Sources of Funding

None.

Disclosures

None.

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