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Clinical Research Study

PCSK9 Inhibitor Use and Outcomes Using Concomitant Lipid-Lowering Therapies in the Veterans Health Administration☆,☆☆,★,★★

Jessica Eloso[a], Asma Awad[b], Xinhua Zhao[c], Francesca E. Cunningham[a], Rongping Zhang[a], Diane Dong[a], Cathy Kelley[d], Peter A. Glassman[d,e,f], Sherrie L. Aspinall[a,c,g,*]

[a] VA Center for Medication Safety/Pharmacy Benefits Management Services, Hines, Ill
[b] Jesse Brown VA Medical Center, Chicago, Ill
[c] VA Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System, Pittsburgh, Pa
[d] VA Pharmacy Benefits Management Services, Washington DC
[e] VA Greater Los Angeles Healthcare System, Los Angeles, Calif
[f] David Geffen School of Medicine at UCLA, Los Angeles, Calif
[g] University of Pittsburgh School of Pharmacy, Pittsburgh, Pa

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ABSTRACT

Background: Real-world data on use of PCSK9 inhibitors (PCSK9-Is), with or without statins and/or ezetimibe, and associated outcomes, can inform more effective prescribing. The objective was to evaluate clinical effectiveness and safety of PCSK9-Is within the Veterans Health Administration (VHA).

Methods: In this retrospective cohort study, we included Veterans who had at least one outpatient prescription for alirocumab and/or evolocumab filled within VHA between August 21, 2015, and September 30, 2020. Analyses included 4 mutually exclusive subgroups: PCSK9-I alone, PCSK9-I+statin, PCSK9-I+ezetimibe, and PCSK9-I+statin+ezetimibe subgroups. Primary outcomes included medication possession ratio, persistence, and low-density lipoprotein (LDL).

Results: Among Veterans in the analytical cohort (n = 2428), 36.2% were on PCSK9-I monotherapy; 24.0% received a PCSK9-I+statin; 27.4% were on a PCSK9-I+ezetimibe; and 12.4% received triple therapy, that is, PCSK9-I+statin+ezetimibe. The mean medication possession ratio (standard deviation [SD]) for PCSK9-I monotherapy was 83.8% (13.3) compared to 84.3% (11.2) with PCSK9-I+statin therapy, 87.1% (10.1) with PCSK9-I+ezetimibe therapy, and 85.8% (11.7) with triple therapy. The percentage of patients who discontinued PCSK9-I in the monotherapy subgroup was 12.3% vs 9.5%, 6.6%, and 7.4% in the concomitant statin, ezetimibe, and triple-therapy subgroups, respectively (p = .002 among the groups). Mean LDL level was greater in the PCSK9-I monotherapy subgroup (85.6 mg/dL) compared with the concomitant statin (66.5 mg/dL), ezetimibe (65.7 mg/dL), and triple-therapy subgroups (68.1 mg/dL).

Conclusions: Veterans showed good adherence and/or persistence with PCSK9-I regimens. On average, those receiving concomitant therapy with a statin and/or ezetimibe achieved significantly lower LDL levels.

Abbreviations: LDL, low-density lipoprotein; PCSK9-I, proprotein convertase subtilisin/kexin type 9 inhibitor; VHA, Veterans Health Administration; CFU, criteria-for-use; MPR, Medication possession ratio; AIPW, augmented inverse probability weighting.

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* Corresponding author: Sherrie L. Aspinall, VA Center for Medication Safety/Pharmacy Benefits Management Services, 1st Avenue, 1 Block North of Cermak Road, Bldg 37, Rm 139, Hines, IL 60141.

E-mail address: sherrie.aspinall@va.gov (S.L. Aspinall).

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Introduction

Monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9-I) reduce the levels of low-density lipoprotein (LDL) cholesterol in primary hypercholesterolemia (eg, heterozygous familial hypercholesterolemia) and in adults with established cardiovascular (CV) disease to reduce the risk of vascular events such as myocardial infarction (MI) and stroke.[1-4] The two available agents, evolocumab and alirocumab, reduce LDL cholesterol levels in patients who are, or are not, receiving concomitant statin and/or ezetimibe therapy.[3–5]

The Veterans Health Administration (VHA) Pharmacy Benefits Management (PBM) Services developed criteria-for-use (CFU) of PCSK9-Is. Eligible patients include those with familial hypercholesterolemia or established atherosclerotic CV disease (ASCVD) at very high risk of a CV event who are receiving a maximally tolerated dose of a statin plus ezetimibe and have had one of the following: (1) new ASCVD event; (2) LDL greater than 100 mg/dL, or (3) LDL between 70 and 99 mg/dL and considered to require additional LDL lowering based upon CV risk through shared decision-making with a VHA-authorized cardiologist, lipid specialist, or endocrinologist.[6] With a lack of studies to compare the risk of CV events in patients receiving PCSK9-Is alone vs those receiving PCSK9-Is concomitantly with a statin or ezetimibe, the CFU also recommended that statins remain first-line therapy for improving CV outcomes but patients who cannot tolerate statins could be prescribed a PCSK9-I.

While several real-world studies have assessed the side effects and effectiveness (eg, LDL lowering, CV events) of PCSK9-Is,[7-10] all involved small numbers of patients. Furthermore, while there are multiple studies on the patterns of use, cost, accessibility, adherence, discontinuation, and overall place in therapy of PCSK9-Is in the treatment of hyperlipidemia,[7-23] these were conducted in populations outside of the VHA. VHA is the largest integrated health care system in the United States and provides access to needed medications with nominal, or no, copayment. Patients in VHA are, on average, older with more comorbidities—factors that could result in differences in tolerability, safety, and effectiveness of PCSK9-Is.[24] In addition, although there are CFU, prescribing patterns for PCSK9-Is in VHA have not been published. Real-world data on the use of PCSK9-Is in Veterans, with or without statins and/or ezetimibe, and associated outcomes, could help to inform more effective prescribing of PCSK9-Is.

The overall goal of this study was to evaluate utilization patterns, clinical effectiveness, and safety of PCSK9-Is within the VHA. The primary objectives were to describe PCSK9-I treatment patterns in a Veteran population and in subgroups of patients receiving PCSK9-Is alone versus PCSK9-Is plus other lipid-lowering therapies, to evaluate adherence and persistence, and to compare baseline and achieved low-density lipoprotein levels. The secondary objectives were to assess: (1) hospitalizations and emergency department (ED) visits for CV events; (2) all-cause mortality; (3) change in glycated hemoglobin (ie, HbA1c); and (4) incidence of myalgia with PCSK9-Is alone versus with PCSK9-Is plus other lipid-lowering therapies.

Methods

Study Design and Participants

This national retrospective cohort analysis included Veterans aged ≥18 years who had at least one outpatient prescription for alirocumab and/or evolocumab filled within VHA between August 21, 2015, and September 30, 2020 (ie, study period), using data from the VA Pharmacy Benefits Management Outpatient Prescription Database v3.0. (The first prescription for alirocumab was dispensed on August 21, 2015.) We excluded patients who were not regular users of VHA (ie, <2 inpatient stays and/or outpatient visits) in the year prior to their index prescription. The index prescription date was defined as the release date (ie, date medication picked up by patient or mailed) of the first prescription for a PCSK9-I during the study period. The main analyses included patients who were assigned to 1 of 4 mutually exclusive subgroups of interest based on the presence or absence of concomitant lipid-lowering therapy (ie, PCSK9-I alone, PCSK9-I+statin, PCSK9-I+ezetimibe, or PCSK9-I+statin+ezetimibe). There were a small number of patients (n = 36) who switched subgroups during the study period and were assigned to their final category. All patients in the subgroups received the lipid-lowering regimen for at least 60 consecutive days. The study was reviewed and approved by the Institutional Review Boards at Edward Hines, Jr. VA Hospital and VA Pittsburgh Healthcare System.

Data Collection

For eligible patients, validated VA PBM databases were used to collect baseline (ie, within 12 months prior to index date) data on age, sex, race/ethnicity, LDL cholesterol, HbA1c, smoking status, and comorbidities as defined by Quan et al.'s adaptation of the Charlson Comorbidity Index.[25] Other diagnoses not included in the Charlson Comorbidity Index, namely ischemic stroke, peripheral arterial disease, hyperlipidemia, and myalgia associated with any inpatient stay or outpatient visit within 12 months prior to the index date, were identified using ICD-9/10-CM codes. Prescription data for PCSK9-Is, statins, ezetimibe, and other lipid-lowering agents during the study period were obtained from the PBM Outpatient Prescription Database.

Outcomes

Adherence and Persistence

For the measures of adherence and persistence for PCSK9-I use alone or in combination with a statin and/or ezetimibe, we included patients who received at least 2 prescriptions in the study period for a PCSK9-I and, as applicable, a statin and/or ezetimibe. Medication possession ratios were used to assess adherence to lipid-lowering therapy, defined as the number of days covered by the medication supply divided by the total number of days from the first release date of the medication until the end of the study, 1 day before death, or the last prescription release date + day's supply of the medication if it was discontinued. Patients with MPR ≥ 80% were defined as adherent.[26] Discontinuation was defined as stopping, or not refilling, the PCSK9-I, or statin and/or ezetimibe as applicable, for >60 days between the last release date + day's supply and the death date or the end of the study.

Clinical Effectiveness

Clinical outcomes included LDL levels, CV events, and all-cause mortality. LDL value(s) was obtained among the subgroups after patients received the lipid-lowering therapy for at least 30 days and continued through the end of the study period, date of death - 1 day, or the last release date + day's supply of any of the medications in the subgroups if discontinued, whichever came first. For CV outcomes, VA PBM–validated ICD-9/10-CM diagnosis codes in the primary position were pulled for hospitalizations or emergency department visits due to acute MI, ischemic stroke, unstable angina, or transient ischemic attack. Patients could have multiple events. All-cause mortality was determined using the Vital Status file. The observation periods for CV events and mortality were the same as described for LDL values, except that they began on the first day of treatment in each of the subgroups.

Safety

Adverse outcomes included an increase in HbA1c from baseline and incident myalgia. HbA1c value(s) was obtained among the subgroups after patients received the lipid-lowering therapy for at least 60 days and continued as described above for LDL levels. As a sensitivity analysis, we also evaluated HbA1c in patients receiving the regimens of interest for more than 90 days. For the outcome of incident myalgia, patients with a diagnosis of myalgia within 1 year prior to the index date were excluded. ICD-9/10-CM diagnosis codes for myalgia in any position associated with a VHA outpatient visit or hospitalization were pulled after

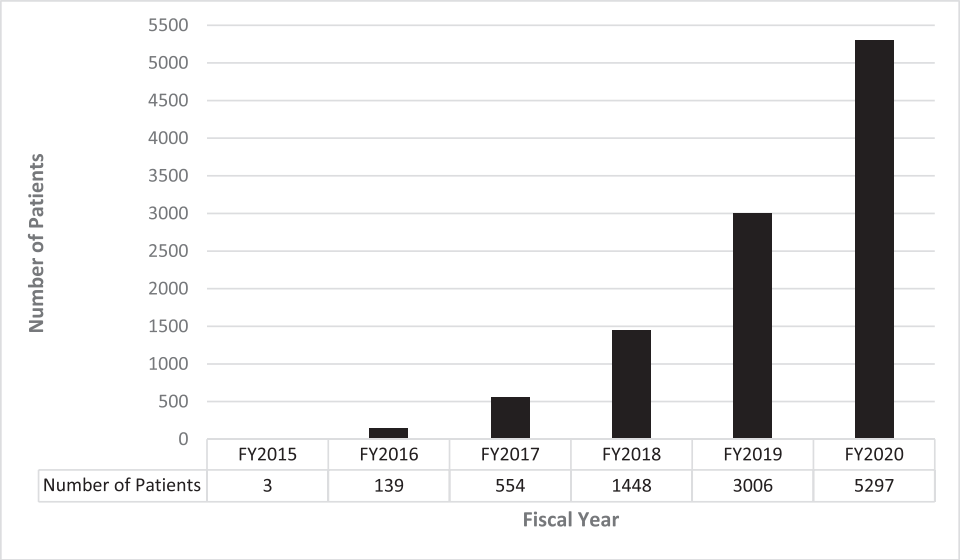

Figure 1. Number of Patients With at Least 1 Outpatient Prescription for a PCSK9-I in Each Fiscal Year of the Study.*
*Total number of patients over study period is 5846.

the index date for the PCSK9-I alone therapy, or the start of concomitant therapy, until the last release date + day's supply, first myalgia event, date of death - 1 day, or end of study.

Analysis

Over the study period, we summarized the frequency and dosing information of PCSK9-I prescriptions, and we described trends in use over time. For the subgroups of interest (ie, PCSK9-I alone, PCSK9-I+statin, PCSK9-I+ezetimibe, and PCSK9-I+statin+ezetimibe), we compared baseline patient characteristics. Tests for a difference in outcomes between the four subgroups included the nonparametric Kruskal-Wallis test for continuous variables and the Chi-square or Fisher exact test for categorical variables. For medication adherence and persistence, we calculated mean MPR and MPR over time, percentage of Veterans who had an MPR ≥ 80%, and the rate of discontinuation overall by subgroup and for each medication separately.[26]

For clinical effectiveness, we calculated the geometric means of multiple LDL measures per patient, as well as the difference between the most recent and baseline LDL values. To assess the effect of lipid-lowering therapies on the most recent LDL < 70 mg/dL and decrease in LDL of ≥40% from baseline until most recent value, we used augmented inverse probability weighting (AIPW) to address potential selection bias and confounding between groups. AIPW estimators combine both the regression adjustment and inverse probability–weighted propensity methods, which therefore makes AIPW a "doubly robust" method.[27] Standardized differences in potential confounding variables between subgroups were negligible (<0.1) after we applied the weights (Appendix A). Odds ratios with 95% CI and p-values have been reported.

We also summarized the rate of CV events and all-cause mortality per 100 person-years. Lastly, we summarized and compared the safety measures, which included change in HbA1c from baseline to more than 60 days of the lipid-lowering therapy (more than 90 days in a sensitivity analysis) and the incidence of myalgia among those patients without a history of myalgia. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

Results

PCSK9-I Prescribing

Of the 5846 patients who had at least 1 prescription for a PCSK9-I during the study period, 4970 (85.0%) received alirocumab, 388 (6.6%) received evolocumab, and 488 (8.4%) received prescriptions for each of the PCSK9-Is. Figure 1 shows the increase in the number of patients with at least 1 prescription for a PCSK9-I in each fiscal year of the study.

Concomitant Therapy and Patient Characteristics

Of the 5846 patients above, 4041 (69.1%) were regular users of VHA and received a PCSK9-I with or without other lipid-lowering therapy for at least 60 consecutive days (Figure 2). Of these 4041 patients, 878 were on PCSK9-I monotherapy. Of the remaining patients (n = 3163), those who received a statin and/or ezetimibe concomitantly for <60 consecutive days (n = 1476) or another antihyperlipidemic medication (eg, colesevelam, fenofibrate) (n = 137) with the PCSK9-I were excluded. This left 583 patients who received a PCSK9-I and statin concomitantly; 665 who were on a PCSK9-I and ezetimibe; and 302 who received triple therapy with a PCSK9-I, statin, and ezetimibe for ≥60 consecutive days (Figure 2). Among the analytical sample (N = 2428), patients in the subgroups of interest were predominantly male, and the majority were White, non-Hispanic (Table 1). The mean (SD) age of patients at baseline ranged from 61.8 (11.5) years (triple-therapy group) to 67.3 (9.1) years (PCSK9-I+ezetimibe). Except for peripheral arterial disease, the presence of comorbidities was similar among subgroups. Finally, the proportion of patients with an LDL < 70 mg/dL at baseline ranged from 5.4% (PCSK9-I alone) to 15.3% (PCSK9-I+statin), and the mean of the most recent HbA1c prior to the index date was 6.5% in all subgroups.

Adherence and Persistence

The mean (SD) MPR for PCSK9-I monotherapy was 83.8% (13.3) compared with 84.3% (11.2), 87.1% (10.1), and 85.8% (11.7) overall in the PCSK9-I+statin, PCSK9-I+ezetimibe, and triple-therapy subgroups, respectively (Table 2). The proportion of patients with an MPR ≥ 80% for the PCSK9-I medication differed among the subgroups (p = .002), with the lowest percentage observed in the monotherapy subgroup (69.7%) and the highest in the concomitant ezetimibe therapy subgroup (78.5%). Overall, the mean MPR decreased over time in all subgroups, falling to around 80% when receiving a regimen for ≥2 years. A higher percentage of patients discontinued use of the PCSK9-I in the monotherapy subgroup (12.3%) than in the concomitant statin, ezetimibe, and triple-therapy subgroups (9.5%, 6.6%, and 7.4%, respectively) (Table 2). In addition, more patients stopped the statin and/or ezetimibe than the PCSK9-I in the combination therapy subgroups (e.g., in

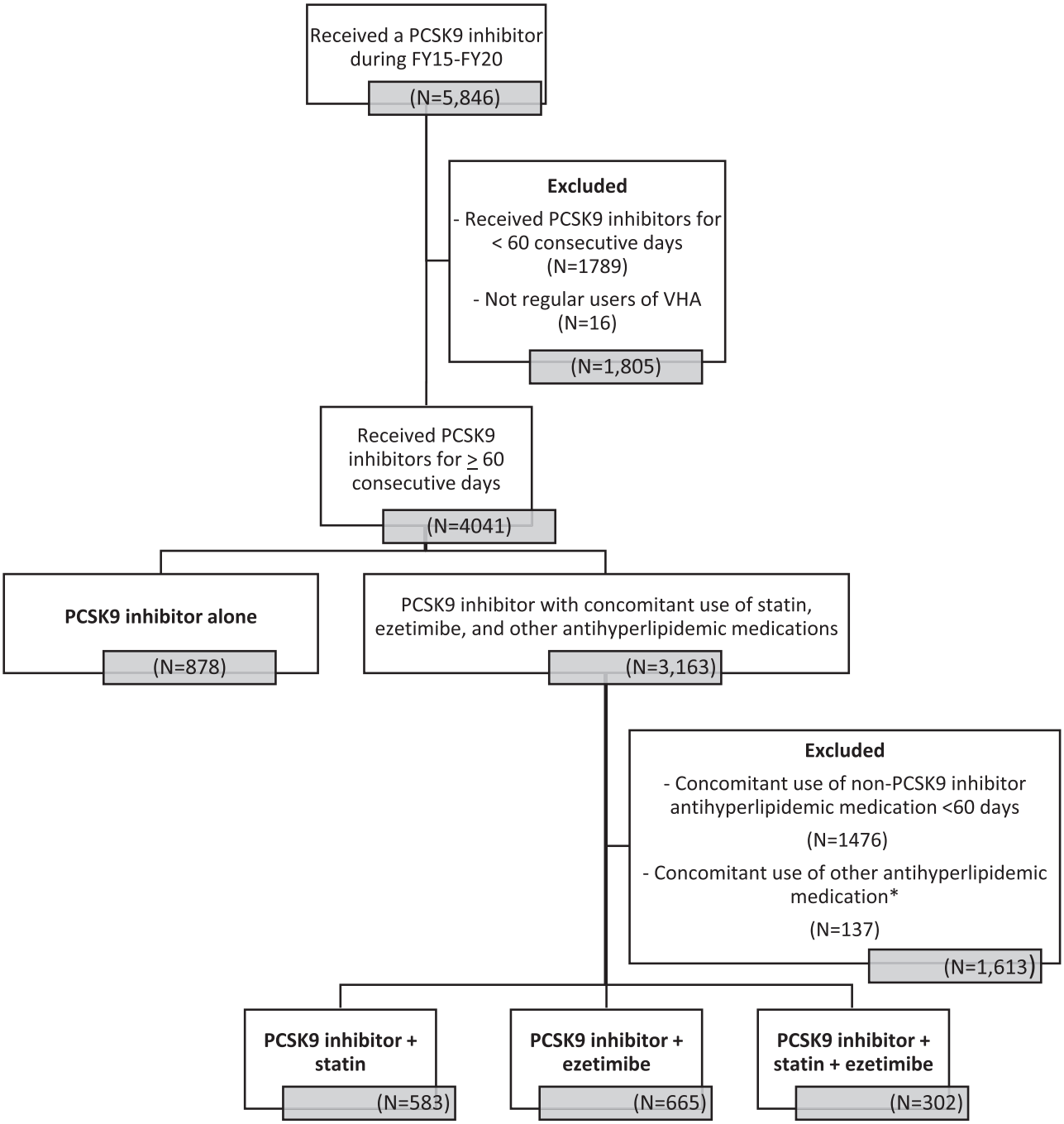

Figure 2. Flowchart of Included and Excluded Patients to Establish Subgroups.

the PCSK9-I + statin subgroup, 25.1% discontinued the statin and 9.5% stopped the PCSK9-I).

Clinical Effectiveness

Among patients with at least one LDL value beyond 30 days of therapy, the mean (arithmetic) LDL differed among the subgroups ($p < .0001$), with the highest value observed with PCSK9-I monotherapy (85.6 mg/dL) and the lowest with concomitant ezetimibe (65.7 mg/dL). The average decrease in LDL from baseline to most recent value was 64.3 mg/dL, 67.6 mg/dL, 76.5 mg/dL, and 72.7 mg/dL in the PCSK9-I monotherapy, concomitant statin, concomitant ezetimibe, and triple-therapy subgroups, respectively ($p < .0001$ among subgroups). The mean baseline LDL levels were 146.4 mg/dL, 131.3 mg/dL, 139.4 mg/dL, and 135.9 mg/dL in these subgroups, respectively. The triple-therapy subgroup had the highest proportion of patients with an LDL ≤ 70 mg/dL (80.9%), followed by the concomitant statin subgroup (79.9%), concomitant ezetimibe subgroup (73.3%), and PCSK9-I monotherapy subgroup (61.0%) (Table 3). In the AIPW logistic regression model, the subgroups with concomitant statin and/or ezetimibe therapy had significantly increased odds of achieving an LDL < 70 mg/dL and a ≥40% decrease from baseline to the most recent LDL value vs a PCSK9-I alone (Table 4).

There was no difference in the rate of ED visits and hospitalizations for all CV events combined (ie, acute MI, ischemic stroke, unstable angina, transient ischemic attack) in a comparison of PCSK9-Is

Table 1
Baseline Characteristics of Patients Taking PCSK9 Inhibitors for ≥60 Days,* by Subgroup

Characteristic *N* = 2428	PCSK9-I Alone *N* = 878 (36.2%) *n* (%)	PCSK9-I+Statin *N* = 583 (24.0%) *n* (%)	PCSK9-I+Ezetimibe *N* = 665 (27.4%) *n* (%)	PCSK9-I+Statin+Ezetimibe *N* = 302 (12.4%) *n* (%)	*P*-Value
Age (in Years), Mean (SD)	66.8 (9.5)	64.5 (10.3)	67.3 (9.1)	61.8 (11.5)	<.0001
Male Sex	819 (93.3)	547 (93.8)	629 (94.6)	284 (94.0)	.77
Race/Ethnicity†					.02
White, non-Hispanic	704 (80.5)	447 (76.9)	538 (81.3)	212 (70.9)	
Black, non-Hispanic	112 (12.8)	91 (15.7)	91 (13.7)	60 (20.1)	
Other	17 (1.9)	14 (2.4)	11 (1.7)	11 (3.7)	
Hispanic	41 (4.7)	29 (5.0)	22 (3.3)	16 (5.4)	
Charlson Comorbidity Index‡	2.0 (2.0)	2.1 (2.1)	2.2 (2.1)	1.9 (2.0)	.18
Acute MI	97 (11.1)	68 (11.7)	76 (11.5)	49 (16.3)	.10
Diabetes	388 (44.2)	244 (41.9)	305 (45.9)	123 (40.7)	.36
Other Comorbidities‡					
Hyperlipidemia	757 (86.2)	484 (83.0)	576 (86.6)	247 (81.8)	.08
Ischemic Stroke	68 (7.7)	51 (8.7)	56 (8.4)	28 (9.3)	.83
Peripheral Arterial Disease	82 (9.3)	78 (13.4)	74 (11.1)	45 (14.9)	.02
Myalgia	274 (31.2)	159 (27.3)	212 (31.9)	74 (24.5)	.046
HbA1c§ (%)					
Baseline Value Present, # patients (%)	708 (80.6)	471 (80.8)	548 (82.4)	249 (82.5)	.77
Mean (SD)	6.5 (1.2)	6.5 (1.4)	6.5 (1.2)	6.5 (1.4)	.33
<7	519 (73.3)	353 (74.9)	395 (72.1)	193 (77.5)	.39
LDL Cholesterol§ (mg/dL)					
Baseline LDL Value Present, # Patients (%)	848 (96.6)	554 (95.0)	637 (95.8)	289 (95.7)	.53
Mean (SD)	146.4 (51.5)	131.3 (60.1)	139.4 (48.1)	135.9 (56.9)	<.0001
<70	46 (5.4)	85 (15.3)	36 (5.7)	25 (8.7)	<.0001
Ezetimibe Use Within 6 Months Prior to Index Date‖	486 (55.4)	218 (37.4)	595 (89.5)	272 (90.1)	<.0001
Statin Use Within 6 Months Prior to Index Date‖	385 (43.8)	255 (43.7)	297 (44.7)	135 (44.7)	.98
Statin Dose Intensity Within 6 Months Prior to Index Date Among Those Above Who Received a Statin#					.58
Low	135 (35.1)	76 (29.8)	105 (35.4)	41 (30.4)	
Moderate	59 (15.3)	44 (17.3)	45 (15.2)	17 (12.6)	
High	191 (49.6)	135 (52.9)	147 (49.5)	77 (57.0)	
Statin and Ezetimibe Use Within 6 Months Prior to Index Date‖	203 (23.1)	91 (15.6)	269 (40.5)	123 (40.7)	<.0001

LDL = low-density lipoprotein; PCSK9-I = proprotein convertase subtilisin/kexin type 9 inhibitor.

* Patients received a PCSK9-I alone or concomitantly with a statin and/or ezetimibe for a minimum of 60 days.

† There were a total of 12 (0.5%) patients missing race, with 2-4 patients missing race across groups.

‡ Any inpatient stay or outpatient visit within 12 months prior to the index date, using ICD-9/10-CM codes in any position.

§ Most recent value within 1 year prior to index date.

‖ Patients received at least 1 dose of the medications.

Statin dosage was categorized as follows. If a patient received multiple statins over the study time period, then the highest dosing classification among the drugs was used. Atorvastatin: High Dose—40-80 mg; Mod. Dose—10-39 (<40) mg; Low Dose—<10 mg; Fluvastatin: High Dose—>80 mg; Mod. Dose—40-80 mg; Low Dose—<40 mg; Lovastatin: High Dose—>80 mg; Mod. Dose—80 mg; Low Dose—<80 mg; Pitavastatin: High Dose—>4 mg; Mod. Dose—2-4 mg; Low Dose—<2 mg; Pravastatin: High Dose—>80 mg; Mod. Dose—40-80 mg; Low Dose—<40 mg; Rosuvastatin: High Dose—20-40 mg; Mod. Dose—>5-19 (<20) mg; Low Dose—≤5 mg; Simvastatin: High Dose—>40 mg; Mod. Dose—20-40 mg; Low Dose—<20 mg.

alone vs the other three subgroups together (2.8 vs 3.1 events per 100 person-years, respectively; $p = .68$). (Data are not shown for individual events and all-cause mortality because the numbers were in the single digits.)

Safety

Regarding potential adverse events, the geometric mean (SD) HbA1c after at least 60 days of therapy was 6.6% (1.2) in the PCSK9-I+ezetimibe subgroup and 6.5% (1.2) in the other subgroups. Given the mean baseline HbA1c of 6.5%, a change in HbA1c after initiating a PCSK9-I was not calculated. In the sensitivity analysis, the geometric mean (SD) HbA1c after at least 90 days of therapy ranged from 6.4% (1.2) in the PCSK9-I+statin subgroup to 6.7% (1.2) in the PCSK9-I+ezetimibe subgroup. Finally, the incidence of myalgia associated with an outpatient visit or hospitalization was similar between the PCSK9-I monotherapy subgroup (15.5%) and the concomitant statin, ezetimibe, and triple-therapy subgroups (15.3%, 16%, and 14.9%, respectively).

Discussion

To our knowledge, our study is the first to assess real-world effectiveness and safety of PCSK9-Is in a national cohort of Veterans. Other studies of LDL lowering and side effects involve relatively small numbers of patients (eg, <300).[7-10,16,20,28] Furthermore, we compared PCSK9-I monotherapy versus PCSK9-I combination therapy with a statin and/or ezetimibe, and we found good adherence among all treatment groups and greater LDL lowering with PCSK9-I combination therapy. These findings have implications for the optimal use of PCSK9-Is in VHA and other health care systems.

The PBM PCSK9-I CFU[6] allow eligible patients who cannot tolerate statins because of myalgia to be prescribed a PCSK9-I. While we do not know which criteria individual patients met, most received a PCSK9-I alone (21.7%) or a PCSK9-I+ezetimibe (16.5%). This seems to suggest that a relatively higher proportion of patients were unable to tolerate a statin.

In addition, when assessing persistence with lipid-lowering therapy, the mean duration of treatment in all four subgroups was approximately

Table 2
Adherence and Persistence by Antihyperlipidemic Regimen Among Patients Receiving >1 PCSK9 Inhibitor Prescription

Measures of Adherence and Persistence	PCSK9-I Alone *N* = 862* *n* (%)	PCSK9-I+Statin *N* = 526* *n* (%)	PCSK9-I+Ezetimibe *N* = 594* *n* (%)	PCSK9-I+Statin+Ezetimibe *N* = 269* *n* (%)	*P*-Value
MPR, Mean (SD)					
PCSK9-I	83.8 (13.3)	85.1 (12.7)	86.5 (12.2)	85.0 (13.0)	.0003
Statin		83.6 (16.8)		87.0 (14.8)	.004
Ezetimibe			87.7 (14.9)	86.2 (17.3)	.54
Overall Mean (All Medications in Column)	83.8 (13.3)	84.3 (11.2)	87.1 (10.1)	85.8 (11.7)	<.0001
MPR ≥ 80%, *n* (%)					
PCSK9-I	601 (69.7%)	395 (75.1%)	467 (78.5%)	198 (73.6%)	.002
Statin		371 (70.5%)		205 (76.2%)	.09
Ezetimibe			474 (79.8%)	207 (77.0%)	.34
MPR of PCSK9-I Over Time,† Mean (SD)					<.001
6 Months	*n* = 92	*n* = 59	*n* = 97	*n* = 46	
	95.6 (5.9)	94.4 (6.3)	93.7 (6.3)	92.1 (9.8)	
6 to <12 Months	*n* = 225	*n* = 148	*n* = 204	*n* = 86	
	86.6 (10.3)	86.0 (10.3)	88.7 (8.7)	89.5 (8.9)	
12 to <24 Months	*n* = 310	*n* = 170	*n* = 189	*n* = 82	
	81.7 (14.0)	83.2 (10.3)	85.5 (9.8)	83.0 (12.3)	
24+ Months	*n* = 235	*n* = 149	*n* = 104	*n* = 55	
	79.2 (13.8)	79.9 (11.8)	80.7 (11.5)	78.8 (11.7)	
Discontinued Medication, *n* (%)					
PCSK9-I	106 (12.3%)	50 (9.5%)	39 (6.6%)	20 (7.4%)	.002
Statin		132 (25.1%)		51 (19.0%)	.052
Ezetimibe			146 (24.6%)	70 (26.0%)	.65
Duration of Therapy (Days),‡ Mean (SD)	555 (353)	559 (364)	458 (322)	495 (354)	<.0001

MPR = medication possession ratio; PCSK9-I = proprotein convertase subtilisin/kexin type 9 inhibitor.

* Patients received >1 prescription for PCSK9-I in the observation period and >1 prescription for a statin and/or ezetimibe, as applicable, to calculate adherence and persistence. Therefore the 'N' in each group is lower than the total 'N' from Table 1.

† Duration of therapy is categorized. Therefore the number of patients in each cell varies.

‡ Duration of therapy is calculated as the number of days from the PCSK9-I index date to the last PCSK9-I release date + day's supply. In patients receiving a PCSK9-I and a statin (or ezetimibe), the start date for the statin (or ezetimibe) is the first release date of the statin (or ezetimibe) within the PCSK9-I observation period, and the end date is the last statin (or ezetimibe) release date + day's supply. For the group with concomitant use of a PCSK9-I, statin, and ezetimibe, the start date was the first date of triple therapy, and the end date was the last date of triple therapy.

Table 3
LDL Cholesterol by Antihyperlipidemic Regimen*

	PCSK9-I Alone† *N* = 777	PCSK9-I+Statin† *N* = 477	PCSK9-I+Ezetimibe† *N* = 535	PCSK9-I+Statin+Ezetimibe† *N* = 251	*P*-Value‡
Number of LDL Values, Mean (SD)	3.5 (2.7)	3.5 (2.9)	2.9 (2.5)	3.2 (2.9)	<.0001
Most Recent LDL (mg/dL), Mean (SD)	85.0 (45.0)	64.3 (42.4)	64.4 (38.1)	67.5 (51.8)	<.0001
Mean LDL (mg/dL), Arithmetic Mean (SD)	85.6 (42.0)	66.5 (38.6)	65.7 (34.3)	68.1 (47.2)	<.0001
Mean LDL (mg/dL), Geometric Mean (SD)	83.3 (41.3)	63.5 (37.5)	63.8 (33.7)	64.2 (44.9)	<.0001
LDL < 70 mg/dL (Any LDL), *n* (%)	474 (61.0)	381 (79.9)	392 (73.3)	203 (80.9)	<.0001
LDL < 70 mg/dL (Most Recent LDL), *n* (%)	339 (43.6)	320 (67.1)	339 (63.4)	161 (64.1)	<.0001
Decrease in LDL From Baseline to Most Recent Value,§ Mean (SD)	64.3 (40.2)	67.6 (55.4)	76.5 (46.1)	72.7 (55.2)	<.0001
≥40% Decrease From Baseline LDL to Most Recent Value, *n* (%)	468 (61.5)	317 (69.2)	395 (76.1)	187 (76.3)	<.0001

LDL = low-density lipoprotein; PCSK9-I = proprotein convertase subtilisin/kexin type 9 inhibitor.

* LDL values after receiving medication(s) for at least 30 days. For the subgroup of PCSK9-Is alone, LDL values were drawn from the observation period for the PCSK9-I. For the subgroups of concomitant therapy, LDL values were drawn from the concomitant therapy period.

† Patients with at least 1 LDL value beyond 30 days of therapy. Therefore, the 'N' in each group is lower than the total 'N' from Table 1.

‡ For the comparison between PCSK9-I monotherapy and the other three subgroups of PCSK9-I+statin, PCSK9-I+ezetimibe, and PCSK9-I+statin+ezetimibe, $P < .05$ for all comparisons, except PCSK9-I+statin and decrease in LDL from baseline to most recent value.

§ Sample sizes of *n* = 761, 458, 519, and 245 for each of the four subgroups, respectively. A small number of patients did not have baseline LDL values.

15-18 months (456-561 days). However, a higher percentage of prescriptions for a statin and/or ezetimibe (19-26%) than a PCSK9-I (7%-12%) were not refilled, meaning the prescription was discontinued, not renewed, or stopped by the patient. This could indicate that patients had an adverse reaction to the statin or ezetimibe but were tolerating the PCSK9-I. Another possibility is that their LDL dropped "too low" in the opinion of the practitioner or patient, and the practitioner continued the PCSK9-I but stopped the statin and/or ezetimibe. This may be particularly applicable with ezetimibe, which only has evidence of improved CV outcomes in combination with statins.[29,30] Retrospective studies on real-world use of PCSK9-Is outside of VHA found shorter durations of therapy.[15,21] Using IQVIA's pharmacy claims database, Hines et al. reported a mean persistence of 202 days for PCSK9-Is.[15] In another study by Rymer et al. that utilized prescription claims from the MarketScan database, interruptions in PCSK9-I treatment occurred at a mean of 155 days after initiation.[21] The longer duration of therapy in our study could be related to increased accessibility of PCSK9-Is due to a lower copayment (at most, $11 for a 30-day supply) in VHA. Also, atorvastatin, simvastatin, pravastatin, and lovastatin were Tier 1 formulary medications starting in 2017, meaning Veterans pay $5 for a 30-day supply. (Rosuvastatin and ezetimibe were made Tier 1 medications in fiscal year 2022.) Given the CFU, it is also possible that Veterans in our

Table 4
Association Between Subgroup of Lipid-Lowering Therapy and Most Recent LDL< 70 mg/dL and ≥40% Decrease in LDL

Unadjusted Model	Most Recent LDL< 70 mg/dL		≥40% Decrease From Baseline to Most Recent LDL Value	
	OR (95% CI)	*P*-Value	OR (95% CI)	*P*-Value
PCSK9-I Alone	1.00		1.00	
PCSK9-I+Statin	2.89 (2.19, 3.80)	<.0001	2.15 (1.64, 2.83)	<.0001
PCSK9-I+Ezetimibe	2.30 (1.79, 2.96)	<.0001	2.34 (1.80, 3.06)	<.0001
PCSK9-I+Statin+Ezetimibe	3.09 (2.18, 4.37)	<.0001	3.08 (2.15, 4.41)	<.0001
Adjusted Model*				
PCSK9-I Alone	1.00		1.00	
PCSK9-I+Statin	2.45 (1.88, 3.01)	<.0001	2.02 (1.52, 2.51)	<.0001
PCSK9-I+Ezetimibe	1.93 (1.52, 2.34)	<.0001	2.07 (1.58, 2.56)	<.0001
PCSK9-I+Statin+Ezetimibe	2.33 (1.63, 3.03)	<.0001	2.69 (1.74, 3.65)	<.0001

LDL = low-density lipoprotein; PCSK9-I = proprotein convertase subtilisin/kexin type 9 inhibitor.

* Augmented inverse probability weighting was used to address potential selection bias and potential confounding between groups. The confounding variables included the patient characteristics of age, sex, race and ethnicity, comorbidities, adherence, duration of therapy prior to most recent LDL, and baseline LDL value.

study were at higher risk for another atherosclerotic CV disease event and more motivated to continue lipid-lowering therapy.

In addition to good persistence with therapy, the mean MPR was >80% for all medications in each of the subgroups, suggesting that patients in our study were adherent, on average. Although the MPR declined over time, Veterans generally remained adherent to LDL-lowering therapies throughout the entire treatment period. Other real-world studies of PCSK9-Is have also found high adherence.[10,23,28] A retrospective cohort study in 2018 found that among 350 providers who prescribed PCSK9-Is in Europe, anecdotal reports showed that an average of 77% of their patients took PCSK9-Is greater than 80% of the time; however, no pharmacy fill data were used to confirm the reports.[23] A study by Gayoso-Rey et al. reported an MPR of 98.1% at 6 months of treatment, and 91% at 6-24 months, in a cohort of 154 patients who received a PCSK9-I.[9] This MPR is higher than what we found; although, it may be explained by adherence monitoring that was done with each prescription fill in their study.[10] Overall, Veterans in our study were persistent and adherent with their PCSK9-containing antihyperlipidemic regimens. These reassuring findings are important because they address a potential concern whenever medication outcomes are discussed or presented.

While real-world studies have shown superior LDL reductions when a PCSK9-I is combined with a statin and/or ezetimibe versus a PCSK9-I alone,[7,9,28] our study design adds to the evidence by directly comparing several treatment groups. Regardless of how LDL was assessed (eg, mean LDL, LDL < 70 mg/dL, decrease in LDL from baseline), patients who received a PCSK9-I with a statin or ezetimibe or both had significantly better LDL-lowering compared with those taking a PCSK9-I alone. Although patients on PCSK9-I monotherapy achieved very good LDL lowering (mean baseline LDL = 146 mg/dL; geometric mean LDL = 84 mg/dL after treatment), providers should attempt to utilize concomitant therapy with a PCSK9-I for improved LDL results.

Although patients who received a statin and/or ezetimibe with a PCSK9-I had better LDL outcomes in our descriptive analyses, we realize there is a potential selection bias as patients with a greater risk of CV events may be more likely to receive combination therapy. Therefore, we used AIPW to adjust for selection bias, and in the balanced subgroups, we continued to find that PCSK9-I combination therapy was significantly associated with both increased odds of the most recent LDL being <70 mg/dL and a ≥40% decrease from baseline to the most recent LDL value versus PCSK9-I monotherapy.

In a secondary analysis, there was no difference in the rates of CV outcomes (ie, acute MI, ischemic stroke, unstable angina, or transient ischemic attack and all-cause mortality) among the subgroups, and the number of events was still relatively small even when we combined the three subgroups with concomitant therapy and the CV events. We expect that incremental benefits (above that seen with PCSK9-Is or statins alone) with combination therapy may occur over longer periods of time (eg, >2 years) and with greater numbers of patients. In the FOURIER and ODYSSEY OUTCOMES clinical trials, the addition of a PCSK9-I to a statin, versus using statins alone, resulted in fewer CV events at approximately 2 years with large numbers of high-risk patients.[3,4] There are no clinical trials of PCSK9-Is as a single agent versus dual or triple therapy, and based on our limited data, we do not believe a conclusion can be made regarding the effectiveness of PCSK9-Is alone versus combination therapy in reducing CV events. Data on CV events and mortality with PCSK9-I monotherapy versus combination therapy remain areas for future study. Finally, we did not see a change in HbA1c over the study period in any of the subgroups, and the rates of myalgia were similar across treatment regimens. While hyperglycemia[31] and musculoskeletal symptoms[32] have been well described with statins, and we did not expect to find a difference among the subgroups, these adverse events have been reported with PCSK9-Is.[33-35]

Our study has several limitations beyond those expected with an observational study (eg, generalizability, residual confounding). We do not know if patients took the medications, nor do we know the reasons for discontinuing them. Review of the electronic medical record would be required to answer the second question. We also could not capture prescriptions, LDL levels, and hospitalizations from outside of VHA. However, we did have data on all medications prescribed by community care providers who have a contract with VHA. Also, the proportion of patients who had bloodwork or hospitalizations outside VHA is unlikely to vary by medication subgroup. Finally, our analysis did not include other agents besides statins and ezetimibe.

Conclusions

In conclusion, we found that Veterans had good adherence and persistence with PCSK9-I regimens, even when taking dual or triple therapy. Those receiving concomitant therapy with a statin and/or ezetimibe had significantly greater LDL lowering than when a PCSK9-I was used alone.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

Appendix A

Table A1

Table A1
Standardized* Differences Between Patient Characteristics for Subgroups of Lipid-Lowering Therapy, Before (Raw) and After (Weighted) Propensity Score Weighting

Characteristics	PCSK9-I+Statin vs PCSK9-I Alone†		PCSK9-I+Ezetimibe vs PCSK9-I Alone†		PCSK9-I+Statin+Ezetimibe vs PCSK9-I Alone†	
	Raw	Weighted	Raw	Weighted	Raw	Weighted
	(n = 456)	(n = 501)	(n = 516)	(n = 498)	(n = 243)	(n = 475)
Age (in Years), Mean (SD)	−0.259	0.007	0.007	−0.005	−0.518	−0.063
Male Sex	0.008	−0.016	0.048	−0.010	0.000	−0.003
Race/Ethnicity						
White	ref	ref	ref	ref	ref	ref
Black	0.105	0.000	0.052	−0.014	0.195	0.002
Other	0.003	−0.025	−0.029	0.012	0.143	0.032
Hispanic	−0.001	−0.005	−0.077	0.010	0.021	0.025
Charlson Comorbidity Index	0.029	0.011	0.099	0.012	−0.047	0.017
Other Comorbidities						
Ischemic Stroke	0.042	−0.013	0.030	−0.001	0.076	0.033
Peripheral Arterial Disease	0.125	−0.007	0.042	0.009	0.188	0.023
Myalgia	−0.115	−0.006	0.016	−0.008	−0.168	−0.040
Baseline LDL Cholesterol (mg/dL)	−0.317	0.075	−0.165	−0.015	−0.175	−0.069
MPR ≥ 80%	−0.253	0.005	−0.059	0.010	−0.340	−0.019
Duration of Therapy Prior to Most Recent LDL Cholesterol	0.046	0.011	−0.176	0.021	−0.061	−0.041

LDL = low-density lipoprotein; PCSK9-I = proprotein convertase subtilisin/kexin type 9 inhibitor.

* A standardized difference of <0.1 is considered to be negligible.

† The raw and weighted sample sizes for the PCSK9-I group alone were n = 757 and n = 494, respectively. The raw and weighted sample sizes for a PCSK9-I+statin, PCSK9-I+ezetimibe, and PCSK9-I+statin+ezetimibe were 456 and 501; 516 and 498; and 243 and 475, respectively. The sample sizes are smaller because of missing covariates.

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