Journal of the American Heart Association

ORIGINAL RESEARCH

Factors Associated With PCSK9 Inhibitor Initiation Among US Veterans

Catherine G. Derington ⓘD, PharmD, MS; Lisandro D. Colantonio ⓘD, MD, PhD; Jennifer S. Herrick ⓘD, MS; James Cook ⓘD, MS; Jordan B. King ⓘD, PharmD, MS; Robert S. Rosenson ⓘD, MD; Bharat Poudel ⓘD, MSPH; Keri L. Monda, PhD; Ann Marie Navar ⓘD, MD, PhD; Katherine E. Mues, PhD, MPH; Vanessa W. Stevens, PhD; Richard E. Nelson, PhD; Megan E. Vanneman ⓘD, PhD, MPH; Paul Muntner ⓘD, PhD; Adam P. Bress ⓘD, PharmD, MS

BACKGROUND: Few adults at high risk for atherosclerotic cardiovascular disease events use a PCSK9i (proprotein convertase subtilisin/kexin type 9 inhibitor).

METHODS AND RESULTS: Using data from the US Veterans Health Administration, we identified veterans who initiated a PCSK9i between January 2018 and December 2019, matched 1:4 to veterans who did not initiate this medication over this time period (case-cohort study). Two cohorts of veterans were analyzed: (1) atherosclerotic cardiovascular disease, with a most recent low-density lipoprotein cholesterol (LDL-C) ≥70 mg/dL; and (2) severe hypercholesterolemia (ie, familial hypercholesterolemia or any prior LDL-C ≥190 mg/dL, with most recent LDL-C ≥100 mg/dL). Conditional logistic regression was used to analyze factors associated with PCSK9i initiation, adjusting for all factors, simultaneously. There were 2394 initiators and 9576 noninitiators in the atherosclerotic cardiovascular disease cohort (median LDL-C, 141 and 96 mg/dL, respectively; $P<0.001$). Factors associated with a higher likelihood of PCSK9i initiation included age 65 to <75 versus <65 years, highest versus lowest quartile of median area-level income, familial hypercholesterolemia, former statin use, and current ezetimibe use. PCSK9i initiation was lower among veterans of a race/ethnicity other than non-Hispanic White. There were 245 initiators and 980 noninitiators in the severe hypercholesterolemia cohort (median LDL-C, 183 and 151 mg/dL, respectively; $P<0.001$). Age ≥75 versus <65 years, history of chronic kidney disease, former statin use, and current ezetimibe use were associated with a higher likelihood of PCSK9i initiation.

CONCLUSIONS: Several patient-level factors, including age, sex, and race/ethnicity, were significantly associated with PCSK9i initiation, suggesting an unmet treatment need in several patient groups.

Key Words: antihypercholesteremic agents ■ cardiovascular disease ■ coronary disease ■ dyslipidemias ■ lipid-lowering therapy ■ PCSK9 ■ veterans

The PCSK9i (proprotein convertase subtilisin/kexin type 9 inhibitors) alirocumab and evolocumab lower low-density lipoprotein cholesterol (LDL-C) levels by up to 60% and reduce cardiovascular events among patients with atherosclerotic cardiovascular disease (ASCVD) taking statins.[1–3] The 2018 American Heart Association/American College of Cardiology multisociety blood cholesterol guideline recommends ezetimibe or PCSK9i for adults with ASCVD who have a treated LDL-C above the threshold of 70 mg/dL and are at high risk for recurrent events or those with familial hypercholesterolemia (FH) who are above the LDL-C threshold of 100 mg/dL despite maximally tolerated statin therapy.[4]

Prior studies using electronic health record and commercial insurance claims data found low proportions of patients initiating PCSK9i.[5–10] These reports of low PCSK9i initiation represent data from multiple

CLINICAL PERSPECTIVE

What Is New?

- In the current study of veterans receiving care at the Veterans Health Administration in 2018 and 2019, among veterans with atherosclerotic cardiovascular disease, female sex and those of Black race, Hispanic ethnicity, and Asian race were significantly less likely than White veterans to initiate a PCSK9i (proprotein convertase subtilisin/kexin type 9 inhibitor).
- Among veterans without atherosclerotic cardiovascular disease but with primary severe hypercholesterolemia, female sex, chronic kidney disease, current ezetimibe use, and former statin use were associated with a higher likelihood of PCSK9i initiation.

What Are the Clinical Implications?

- The current study identified that there is an unmet treatment need in several patient groups.
- Interventions to optimize lipid-lowering therapy among high-risk and very-high-risk patients are needed overall and in several populations, including age, sex, and race subgroups.

Nonstandard Abbreviations and Acronyms

FH	familial hypercholesterolemia
PCSK9i	proprotein convertase subtilisin/kexin type 9 inhibitor
VHA	Veterans Health Administration

nonintegrated healthcare delivery systems with a range of care delivery models, cost of PCSK9i therapy, and access to care. The Veterans Health Administration (VHA) is the largest integrated healthcare delivery system in the United States and mediates medication cost and access barriers by structuring copays according to an 8-group priority system based on military service history and level of disability and income, among other factors. Veterans in priority group 1 have a $0 copay for all medications, and veterans in groups 2 through 8 have a flat $33 tier 3 monthly copay for PCSK9i therapy.[11] The current appropriate use criteria at the VHA guide the initiation of PCSK9i among patients with high ASCVD risk or with FH who are taking a maximally tolerated statin and ezetimibe therapy.[12] Evaluating PCSK9i initiation within an integrated healthcare delivery system, such as the VHA, may allow for the identification of patient factors associated with PCSK9i initiation independently of cost,

which would provide opportunities to improve LDL-C control and reduce ASCVD events.

The goals of the current study were to (1) characterize LDL-C levels among veterans who did and did not initiate a PCSK9i and (2) determine characteristics associated with PCSK9i initiation in 2018 and 2019 among 2 high-risk cohorts: veterans with ASCVD and LDL-C ≥70 mg/dL, the ASCVD cohort; and veterans without ASCVD but with primary severe hypercholesterolemia and LDL-C ≥100 mg/dL, the severe hypercholesterolemia cohort.

METHODS

Design, Setting, and Data Sources

This retrospective matched case-control study used clinical, pharmacy, and administrative data from >140 VHA hospitals and 1200 VHA outpatient clinics. We obtained demographic, clinical, healthcare use, and pharmacy data from the Corporate Data Warehouse. The University of Utah Institutional Review Board and the Salt Lake City Veterans Affairs Health Care System Research and Development Office approved this study with a waiver of informed consent. Data used in this study are available from the VHA on request through VHA data access procedures.

Study Population

We identified all veterans whose first ever fill for a PCSK9i was between January 1, 2018, and December 31, 2019 (ie, veterans with a fill for a PCSK9i before January 1, 2018, were not included). For each veteran who initiated a PCSK9i between January 1, 2018, and December 31, 2019, the date of his/her earliest PCSK9i fill defined the index date. We then selected PCSK9i initiators who meet all of the following eligibility criteria: (1) had continuous enrollment, defined by having at least 1 outpatient or inpatient encounter in the first and last 6 months of the 1-year period before their index date (the "preindex period"); and (2) were alive on their index date and without multiple death dates recorded in the database. Among PCSK9i initiators who met the eligibility criteria above, we selected 2 mutually exclusive cohorts based on the following criteria:

1. Veterans with ASCVD whose most recent preindex LDL-C before their index date was ≥70 mg/dL (the ASCVD cohort).
2. Veterans without ASCVD who had primary severe hypercholesterolemia, defined by either a diagnosis of FH or an LDL-C ≥190 mg/dL at any point in the past, and whose most recent preindex LDL-C before their index date was ≥100 mg/dL (the severe hypercholesterolemia cohort).

Table 1. Characteristics of Initiators and Noninitiators of a PCSK9i in the VHA With ASCVD and a Preindex LDL-C ≥70 mg/dL

Characteristic	Initiators (n=2394)	Noninitiators (n=9576)	P Value
Index date calendar year 2019	1544 (64.5)	6176 (64.5)	1.000
Age, mean (SD), y	68.1 (8.6)	70.5 (11.8)	<0.001
Age category, y			
<65	631 (26.4)	2454 (25.6)	<0.001
65–<75	1321 (55.2)	4034 (42.1)	
≥75	442 (18.5)	3088 (32.2)	
Women	115 (4.8)	480 (5.0)	0.67
Race/ethnicity			
Non-Hispanic, White	1975 (84.8)	6782 (73.9)	<0.001
Non-Hispanic, Black	248 (10.7)	1631 (17.8)	
Asian	3 (0.1)	51 (0.6)	
Hispanic	73 (3.1)	533 (5.8)	
Other*	29 (1.2)	176 (1.9)	
Median area-level income			
Quartile 1 ($0–$41 757)	531 (22.2)	2461 (25.7)	<0.001
Quartile 2 ($41 758–$51 357)	563 (23.5)	2430 (25.4)	
Quartile 3 ($51 363–$64 870)	645 (26.9)	2348 (24.5)	
Quartile 4 ($64 878–$212 394)	655 (27.4)	2337 (24.4)	
Supplemental health insurance	2001 (83.7)	7921 (83.0)	0.44
Priority group			
1	1159 (48.5)	3643 (38.2)	<0.001
2–8	1229 (51.5)	5902 (61.8)	
VISN region			
Northeast	692 (28.9)	2607 (27.2)	<0.001
Southeast	1010 (42.2)	3691 (38.5)	
Continental	462 (19.3)	1845 (19.3)	
Pacific	230 (9.6)	1433 (15.0)	
Current smoking	429 (17.9)	1552 (16.2)	0.04
Comorbidities			
Diabetes mellitus	1220 (51.0)	4019 (42.0)	<0.001
Hypertension	2179 (91.0)	8080 (84.4)	<0.001
Chronic kidney disease	1050 (43.9)	3833 (40.0)	<0.001
Heart failure	535 (22.3)	1377 (14.4)	<0.001
Familial hypercholesterolemia	181 (7.6)	27 (0.3)	<0.001
History of CHD	2314 (96.7)	8204 (85.7)	<0.001
Prior coronary revascularization	835 (34.9)	2054 (21.4)	<0.001
Cerebrovascular disease	344 (14.4)	1430 (14.9)	0.49
Peripheral artery disease	441 (18.4)	1676 (17.5)	0.29
Statin use			
Never	131 (5.5)	1720 (18.0)	<0.001
Former	1436 (60.0)	3509 (36.6)	
Current: low intensity	94 (3.9)	325 (3.4)	
Current: moderate to high intensity	733 (30.6)	4022 (42.0)	
Ezetimibe use			
Never or former	1380 (57.6)	9472 (98.9)	<0.001
Current	1014 (42.4)	104 (1.1)	
LDL-C, median (IQR), mg/dL	141.0 (116.0–169.0)	96.0 (82.0–119.0)	<0.001

(Continued)

Table 1. Continued

Characteristic	Initiators (n=2394)	Noninitiators (n=9576)	P Value
LDL-C category, mg/dL			
70–<100	301 (12.6)	5240 (54.7)	<0.001
100–<130	611 (25.5)	2698 (28.2)	
130–<190	1168 (48.8)	1519 (15.9)	
≥190	314 (13.1)	119 (1.2)	

Numbers are expressed as number (percentage) unless otherwise indicated. The were 469 (3.9%) veterans with missing race. ASCVD indicates atherosclerotic cardiovascular disease; CHD, coronary heart disease; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; VHA, Veterans Health Administration; and VISN, Veterans Integrated Service Network.

*Other indicates American Indian or Alaska Native, Mixed, Native Hawaiian or other Pacific Islander, or missing ethnicity.

ASCVD was defined as a history of coronary heart disease, cerebrovascular disease, or peripheral artery disease before each veteran's index date (Table S1).[13–15] PCSK9i initiators who did not meet the criteria for the ASCVD or severe hypercholesterolemia cohorts were excluded from the analysis.

We identified all veterans who did not fill a PCSK9i at any point on or before December 31, 2019 (ie, noninitiators) to serve as controls. For each PCSK9i initiator included in the analysis, we randomly selected without replacement 4 noninitiators who meet the same eligibility criteria and cohort criteria using as the noninitiator's index date a random date in the same calendar quarter of his/her matched initiator's index date. In other words, initiators and noninitiators were matched on the calendar quarter of their index date and on their cohort criteria (ie, ASCVD or severe hypercholesterolemia cohort).

Veteran Characteristics and Comorbidities

Veteran characteristics were identified using data from the 1-year preindex period. Comorbidities and medication use were identified using all available data before the index date. Codes and algorithms

Figure 1. Distribution of the most recent low-density lipoprotein cholesterol (LDL-C) levels in the 1-year preindex period among PCSK9i (proprotein convertase subtilisin/kexin type 9 inhibitor) initiators and noninitiators among veterans in the atherosclerotic cardiovascular disease cohort, overall.

We used LDL-C measurements within 365 days before each veteran's index date, inclusive. For veterans with multiple LDL-C measurements during this time period, we used the one closest to their index date (ie, the most recent).

used to identify patient characteristics, comorbidities, medication use, ASCVD events, and laboratory values are provided in Tables S1 and S2. As the use of PCSK9i may vary by region, Veterans Integrated Service Networks were categorized into 4 regions: Northeast, Southeast, Continental, and Pacific (Data S1). We also identified veterans with supplemental insurance coverage beyond their VHA benefits (eg, Medicare supplemental or Medicaid insurance). These patient- and facility-level factors were selected a priori on the basis of prior studies.[16–18] We used all prescription fills at VHA pharmacies before the index date to identify veterans who never used a statin, were former statin users, or were current users of a low-intensity or moderate- to high-intensity statin. We used all prescription fills at VHA pharmacies before the index date to identify veterans who were never or former ezetimibe users or current ezetimibe users. The most recent preindex LDL-C in the 1 year before the index date was identified for each veteran and categorized as 70 to <100, 100 to <130, 130 to <190, and ≥190 mg/dL. Veterans with a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions were categorized as having high risk for future ASCVD events, as outlined in the 2018 American Heart Association/American College of Cardiology multisociety blood cholesterol guideline (Data S1).[4]

Statistical Analysis

All analyses were conducted for the ASCVD cohort and severe hypercholesterolemia cohort, separately. Veterans' characteristics and the distribution of LDL-C levels were calculated among PCSK9i initiators and noninitiators, separately. We used conditional logistic regression to calculate odds ratios and 95% CIs for initiating a PCSK9i associated with each characteristic, comorbidity, statin and ezetimibe use, and preindex LDL-C category. We conducted 3 nested models. Model 1 was unadjusted. Model 2 was adjusted for age, sex, and race-ethnicity. Model 3 included the variables in model 2 with additional adjustment for median area-level income,
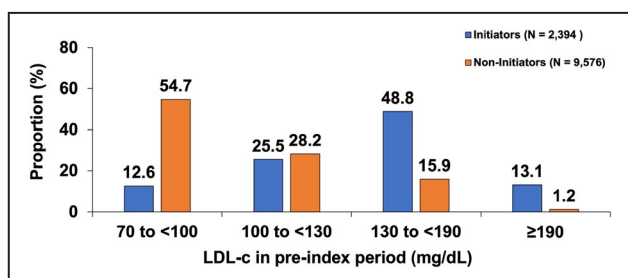
Table 2. Odds Ratios for Initiating a PCSK9i Associated With Patient Characteristics Among Veterans in the ASCVD Cohort

Characteristics	Odds Ratio (95% CI)		
	Model 1	Model 2	Model 3
Age category, y			
<65	1 (Reference)	1 (Reference)	1 (Reference)
65–<75	1.28 (1.15–1.43)	1.15 (1.03–1.28)	1.37 (1.10–1.70)
≥75	0.56 (0.49–0.64)	0.48 (0.42–0.55)	0.63 (0.49–0.81)
Women	0.96 (0.78–1.18)	0.97 (0.78–1.21)	0.69 (0.48–0.99)
Race/ethnicity			
Non-Hispanic, White	1 (Reference)	1 (Reference)	1 (Reference)
Non-Hispanic, Black	0.52 (0.45–0.60)	0.48 (0.41–0.55)	0.32 (0.25–0.41)
Asian	0.21 (0.06–0.66)	0.22 (0.07–0.71)	0.04 (0.01–0.25)
Hispanic	0.47 (0.36–0.60)	0.45 (0.35–0.57)	0.43 (0.28–0.65)
Other*	0.57 (0.38–0.85)	0.51 (0.35–0.77)	0.24 (0.12–0.49)
Median area-level income			
Quartile 1 ($0–$41 757)	1 (Reference)	1 (Reference)	1 (Reference)
Quartile 2 ($41 758–$51 357)	1.07 (0.94–1.22)	0.97 (0.85–1.11)	1.00 (0.80–1.24)
Quartile 3 ($51 363–$64 870)	1.27 (1.12–1.44)	1.15 (1.01–1.31)	1.11 (0.89–1.39)
Quartile 4 ($64 878–$212 394)	1.30 (1.14–1.47)	1.20 (1.06–1.37)	1.28 (1.02–1.61)
Supplemental health insurance			
No	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.05 (0.93–1.18)	1.17 (1.01–1.34)	1.07 (0.84–1.35)
Priority group			
1	1 (Reference)	1 (Reference)	1 (Reference)
2–8	0.65 (0.59–0.71)	0.71 (0.64–0.78)	0.84 (0.71–0.98)
VISN region			
Northeast	1 (Reference)	1 (Reference)	1 (Reference)
Southeast	1.03 (0.93–1.15)	1.11 (0.99–1.24)	0.99 (0.82–1.20)
Continental	0.94 (0.82–1.07)	0.93 (0.81–1.07)	0.81 (0.65–1.02)
Pacific	0.60 (0.51–0.71)	0.63 (0.54–0.75)	0.55 (0.42–0.73)
Smoking status			
Never/former	1 (Reference)	1 (Reference)	1 (Reference)
Current	1.13 (1.00–1.27)	1.01 (0.90–1.14)	0.83 (0.66–1.02)
Comorbidities			
Diabetes mellitus	1.43 (1.31–1.57)	1.47 (1.34–1.61)	1.49 (1.27–1.74)
Hypertension	1.89 (1.62–2.20)	2.10 (1.80–2.46)	1.72 (1.34–2.21)
Chronic kidney disease	1.17 (1.07–1.28)	1.33 (1.21–1.47)	1.08 (0.92–1.27)
Heart failure	1.72 (1.53–1.92)	1.83 (1.63–2.06)	1.57 (1.27–1.93)
Familial hypercholesterolemia	27.75 (18.40–41.87)	29.35 (19.25–44.73)	38.74 (20.16–74.45)
History of CHD	4.78 (3.80–6.01)	4.71 (3.74–5.94)	5.08 (3.49–7.39)
Prior coronary revascularization	1.97 (1.78–2.17)	1.89 (1.71–2.09)	1.29 (1.09–1.54)
Cerebrovascular disease	0.96 (0.84–1.09)	0.97 (0.86–1.11)	1.35 (1.06–1.71)
Peripheral artery disease	1.06 (0.95–1.19)	1.11 (0.99–1.25)	1.18 (0.95–1.46)
Statin use			
Never	1 (Reference)	1 (Reference)	1 (Reference)
Former	5.35 (4.42–6.46)	5.55 (4.57–6.73)	2.34 (1.78–3.07)
Current: low intensity	3.86 (2.88–5.18)	3.99 (2.95–5.39)	2.63 (1.64–4.22)
Current: moderate to high intensity	2.39 (1.97–2.91)	2.31 (1.90–2.83)	1.18 (0.89–1.58)

(*Continued*)

Table 2. Continued

	Odds Ratio (95% CI)		
Characteristics	Model 1	Model 2	Model 3
Use of ezetimibe			
Never or former	1 (Reference)	1 (Reference)	1 (Reference)
Current	76.98 (58.10–102.00)	80.75 (60.50–107.77)	70.85 (50.70–98.99)
LDL-C category, mg/dL			
70–<100	1 (Reference)	1 (Reference)	1 (Reference)
100–<130	3.97 (3.41–4.61)	3.99 (3.42–4.64)	3.44 (2.79–4.24)
130–<190	13.25 (11.43–15.35)	13.57 (11.66–15.79)	13.98 (11.28–17.31)
≥190	46.67 (35.98–60.55)	49.68 (37.90–65.11)	54.38 (37.44–78.98)

Model 1: unadjusted. Model 2: adjusted for age, sex, and race/ethnicity. Model 3: adjusted for all the variables listed in the left-hand column of the table. There were 469 (3.9%) veterans in the ASCVD cohort with missing data on race. ASCVD indicates atherosclerotic cardiovascular disease; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; and VISN, Veterans Integrated Service Network.

*Other indicates American Indian or Alaska Native, Mixed, Native Hawaiian or other Pacific Islander, or missing ethnicity.

supplemental health insurance status, priority group status, Veterans Integrated Service Network region, smoking status, comorbid conditions, statin use, ezetimibe use, and preindex LDL-C levels.

Among veterans in the ASCVD cohort, characteristics, LDL-C levels, and odds ratios for PCSK9i initiation were calculated in subgroups with (1) history of coronary heart disease, (2) history of cerebrovascular disease, (3) history of peripheral artery disease, (4) high risk for future ASCVD events, (5) current moderate- to high-intensity statin use, and (6) current ezetimibe use. Among veterans in the severe hypercholesterolemia cohort, characteristics, LDL-C levels, and odds ratios associated with PCSK9i initiation were calculated in subgroups with (1) any prior LDL-C ≥190 mg/dL and (2) any prior LDL-C ≥220 mg/dL. Analyses were performed using SAS v9.2 (SAS Institute, Cary, NC).

RESULTS
ASCVD Cohort
Characteristics and Preindex LDL-C Levels

There were 2394 PCSK9i initiators and 9576 matched noninitiators included in the ASCVD cohort (Figure S1). Those who initiated a PCSK9i were younger than noninitiators (mean age, 68.1 versus 70.5 years; P<0.001), and 4.8% of initiators and 5.0% of noninitiators were women (Table 1). The median most recent preindex LDL-C was higher in initiators versus noninitiators (141.0 versus 96.0 mg/dL; Figure 1). The proportion currently taking a moderate- to high-intensity statin was 30.6% and 42.0% among initiators and noninitiators, respectively.

Characteristics Associated With Initiation

In fully adjusted models, veterans aged ≥75 versus <65 years, women, and non-Hispanic Black, Asian,

and Hispanic versus non-Hispanic White veterans were less likely to initiate PCSK9i (Table 2). Veterans in priority groups 2 through 8 were less likely to initiate PCSK9i compared with veterans in priority group 1. Veterans receiving care in the Pacific Veterans Integrated Service Network region were less likely to initiate PCSK9i compared with veterans in the Northeast region. Veterans in the highest compared with lowest quartile of median area-level income were more likely to initiate a PCSK9i. Veterans with diabetes mellitus, hypertension, heart failure, FH, history of coronary heart disease, prior coronary revascularization, and cerebrovascular disease were more likely to initiate a PCSK9i compared with their counterparts without these conditions. Compared with veterans who had never taken a statin, former and current low-intensity statin use was associated with a higher likelihood of PCSK9i initiation. Current ezetimibe users were more likely to initiate a PCSK9i compared with never/former users. The likelihood of PCKS9i initiation increased at progressively higher LDL-C levels. Veteran's characteristics, preindex LDL-C levels, and factors associated with PCSK9i initiation in subgroup analyses in the ASCVD cohort are shown in Tables S3 and S4 and Figure S2.

Severe Hypercholesterolemia Cohort
Characteristics and Preindex LDL-C Levels

There were 245 PCSK9i initiators and 980 matched noninitiators in the severe hypercholesterolemia cohort (Figure S1). PCSK9i initiators were older than noninitiators (mean age, 60.7 versus 58.4 years), and 20.0% of initiators and 13.9% of noninitiators were women (Table 3). The median most recent preindex LDL-C was higher in initiators versus noninitiators (183.3 versus 150.9 mg/dL; Figure 2). The proportion currently taking a moderate- to high-intensity statin

Table 3. Characteristics of Initiators and Noninitiators of a PCSK9i in the VHA With Severe Hypercholesterolemia and a Preindex LDL-C ≥100 mg/dL

Characteristic	Initiators (n=245)	Noninitiators (n=980)	P Value
Index date calendar year 2019	155 (63.3)	620 (63.3)	1.000
Age, mean (SD), y	60.7 (12.3)	58.4 (13.0)	0.010
Age category, y			
<65	128 (52.2)	625 (63.8)	0.004
65–<75	92 (37.6)	279 (28.5)	
≥75	25 (10.2)	76 (7.8)	
Women	49 (20.0)	136 (13.9)	0.017
Race/ethnicity			
Non-Hispanic, White	156 (67.5)	629 (67.6)	0.06
Non-Hispanic, Black	58 (25.1)	189 (20.3)	
Asian	1 (0.4)	14 (1.5)	
Hispanic	11 (4.8)	87 (9.4)	
Other*	5 (2.2)	11 (1.2)	
Median area-level income			
Quartile 1 ($0–$43 173)	62 (25.3)	244 (24.9)	0.112
Quartile 2 ($43 264–$51 738)	47 (19.2)	259 (26.4)	
Quartile 3 ($51 740–$66 333)	69 (28.2)	238 (24.3)	
Quartile 4 ($66 359–$174 205)	67 (27.3)	239 (24.4)	
Supplemental health insurance	156 (63.9)	562 (57.5)	0.07
Priority group			
1	125 (51.2)	445 (45.5)	0.11
2–8	119 (48.8)	534 (54.5)	
VISN region			
Northeast	63 (25.7)	209 (21.3)	0.001
Southeast	120 (49.0)	394 (40.2)	
Continental	38 (15.5)	206 (21.0)	
Pacific	24 (9.8)	171 (17.4)	
Current smoking	31 (12.7)	139 (14.2)	0.54
Comorbidities			
Diabetes mellitus	96 (39.2)	219 (22.3)	<0.001
Hypertension	164 (66.9)	553 (56.4)	0.003
Chronic kidney disease	72 (29.4)	199 (20.3)	0.002
Heart failure	5 (2.0)	8 (0.8)	0.09
Familial hypercholesterolemia	65 (26.5)	11 (1.1)	<0.001
Statin use			
Never	18 (7.3)	194 (19.8)	<0.001
Former	156 (63.7)	457 (46.6)	
Current: low intensity	11 (4.5)	18 (1.8)	
Current: moderate to high intensity	60 (24.5)	311 (31.7)	
Ezetimibe use			
Never or former	153 (62.4)	972 (99.2)	<0.001
Current	92 (37.6)	8 (0.8)	
LDL-C, median (IQR), mg/dL	183.3 (159.0–205.0)	150.9 (124.4–178.6)	<0.001
LDL-C category, mg/dL			
100–<130	18 (7.3)	299 (30.5)	<0.001
130–<190	119 (48.6)	513 (52.3)	
≥190	108 (44.1)	168 (17.1)	

Numbers are expressed as number (percentage) unless otherwise indicated. The were 64 (5.2%) veterans with missing race. Primary severe hypercholesterolemia is defined as (1) familial hypercholesterolemia or (2) ever LDL-C ≥190 mg/dL. No veterans in the severe hypercholesterolemia cohort had a most recent LDL-C <100 mg/dL, as having an LDL-C ≥100 mg/dL was an inclusion criterion for this cohort. IQR indicates interquartile range; LDL-C, low-density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; VHA, Veterans Health Administration; and VISN, Veterans Integrated Service Network.

*Other indicates American Indian or Alaska Native, Mixed, Native Hawaiian or other Pacific Islander, or missing ethnicity.
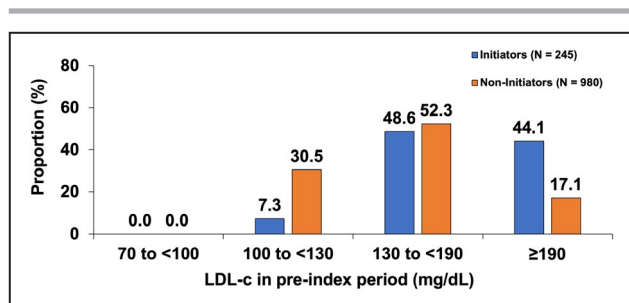
Figure 2. Distribution of the most recent low-density lipoprotein cholesterol (LDL-C) levels in the 1-year preindex period among PCSK9i (proprotein convertase subtilisin/kexin type 9 inhibitor) initiators and noninitiators among veterans in the severe hypercholesterolemia cohort, overall. We used LDL-C measurements within 365 days before each veteran's index date, inclusive. For veterans with multiple LDL-C measurements during this time period, we used the one closest to their index date (ie, the most recent).

was 24.5% and 31.7% among initiators and noninitiators, respectively.

Characteristics Associated With Initiation

In fully adjusted models, veterans aged ≥75 versus <65 years and those of female sex were more likely to initiate PCSK9i (Table 4). Veterans with chronic kidney disease and FH were associated with a higher likelihood of PCSK9i initiation. Former statin use was associated with an increased likelihood of PCSK9i initiation compared with never statin use. Current ezetimibe use was associated with an increased likelihood of PCSK9i initiation compared with never/former ezetimibe use. The likelihood of PCKS9i initiation increased among veterans with progressively higher LDL-C. Veteran's characteristics, preindex LDL-C levels, and factors associated with PCSK9i initiation in subgroup analyses in the severe hypercholesterolemia cohort are shown in Tables S5 and S6 and Figure S3, respectively.

DISCUSSION

In the current study of veterans with ASCVD or severe hypercholesterolemia receiving care at the VHA in 2018 and 2019, several factors were associated with PCSK9i initiation, including age, sex, race/ethnicity, median area-level income, statin and ezetimibe use, comorbidities, and region. Among veterans with ASCVD, female sex and those of Black race, Hispanic ethnicity, and Asian race were significantly less likely than White veterans to initiate a PCSK9i. Preindex LDL-C levels were substantially higher among those who initiated versus did not initiate a PCSK9i in both cohorts. Only 31% of veterans with ASCVD who initiated a PCSK9i were currently taking a moderate- or

high-intensity statin. Among veterans without ASCVD but with primary severe hypercholesterolemia, female sex, chronic kidney disease, current ezetimibe use, and former statin use were associated with a higher likelihood of PCSK9i initiation in the fully adjusted model. The current study supports the implementation of interventions to optimize lipid-lowering therapy among high-risk and very-high-risk patients overall and in several populations, including age, sex, and race subgroups.

In the current analysis, there were differences in PCSK9i initiation by race among veterans with ASCVD. Black, Asian, and Hispanic veterans were each significantly less likely to initiate a PCSK9i compared with White veterans. This finding is consistent with prior studies reporting differences in the use of statin, antihypertensive, antiplatelet, and anticoagulant medication classes by race-ethnicity.[19–23] One study of commercial and government prescription claims data found that paid PCSK9i prescription claims versus rejected claims were more common among White patients compared with patients of non-White races-ethnicities.[5] Other studies show that Black veterans were less likely to receive lipid-lowering medications and achieve target LDL-C measures compared with White veterans.[24,25] Interventions to increase the appropriate use of lipid-lowering therapy among minorities are needed.

Medication cost, both to the health system and patient, can be a factor in the decision to initiate PCSK9i in indicated patients. For example, in a recent qualitative study of community-dwelling patients prescribed a PCSK9i, patient out-of-pocket cost was the leading reported reason for PCSK9i discontinuation.[26] In the ASCVD cohort in the current analysis, those in priority groups 2 to 8, where the copay is $33 for a PCSK9i, were less likely to initiate a PCSK9i compared with those in priority group 1, who have no copay for prescription medications. In addition, in the ASCVD cohort, higher median area-level income was associated with an increased likelihood of initiating a PCSK9i. The current analysis suggests that a patient's area-level income and a relatively small increase in copay may be associated with the likelihood of PCSK9i initiation.

Current national guidelines recommend using statins at maximally tolerated doses, then adding PCSK9i therapy with or without ezetimibe.[4] In the current analysis, only 31% and 25% of veterans in the ASCVD and severe hypercholesterolemia cohorts, respectively, who initiated a PCSK9i were taking a moderate- to high-intensity statin. These data are similar to prior reports showing that 30% to 40% of patients with an insurance-approved PCSK9i prescription claim were taking a statin,[5,7,27,28] suggesting that PCSK9i use may be prioritized among patients unable or unwilling to use moderate- or high-intensity statins. Furthermore, in the

Table 4. Odds Ratios for Initiating a PCSK9i Associated With Patient Characteristics Among Veterans in the Severe Hypercholesterolemia Cohort

Characteristics	Odds Ratio (95% CI)		
	Model 1	Model 2	Model 3
Age category, y			
<65	1 (Reference)	1 (Reference)	1 (Reference)
65–<75	1.62 (1.19–2.20)	1.70 (1.24–2.33)	1.50 (0.81–2.77)
≥75	1.63 (1.00–2.68)	1.80 (1.09–2.98)	2.76 (1.03–7.43)
Women	1.59 (1.10–2.31)	1.66 (1.13–2.45)	1.99 (1.03–3.87)
Race/ethnicity			
Non-Hispanic, White	1 (Reference)	1 (Reference)	1 (Reference)
Non-Hispanic, Black	1.22 (0.86–1.72)	1.28 (0.91–1.82)	0.84 (0.45–1.57)
Asian	0.28 (0.04–2.17)	0.35 (0.04–2.72)	0.26 (0.01–6.13)
Hispanic	0.50 (0.26–0.97)	0.59 (0.30–1.15)	0.44 (0.14–1.39)
Other*	1.86 (0.63–5.52)	1.89 (0.63–5.67)	0.86 (0.09–8.01)
Median area-level income			
Quartile 1 ($0–$43 173)	1 (Reference)	1 (Reference)	1 (Reference)
Quartile 2 ($43 264–$51 738)	0.72 (0.47–1.09)	0.69 (0.45–1.06)	0.45 (0.20–1.00)
Quartile 3 ($51 740–$66 333)	1.14 (0.78–1.69)	1.15 (0.77–1.71)	1.14 (0.55–2.35)
Quartile 4 ($66 359–$174 205)	1.10 (0.74–1.63)	1.13 (0.75–1.70)	0.89 (0.42–1.89)
Supplemental health insurance			
No	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.32 (0.98–1.77)	1.05 (0.75–1.46)	0.90 (0.52–1.58)
Priority group			
1	1 (Reference)	1 (Reference)	1 (Reference)
2–8	0.79 (0.60–1.05)	0.68 (0.51–0.92)	0.88 (0.51–1.52)
VISN region			
Northeast	1 (Reference)	1 (Reference)	1 (Reference)
Southeast	1.01 (0.71–1.44)	1.03 (0.71–1.48)	0.81 (0.42–1.58)
Continental	0.62 (0.40–0.97)	0.65 (0.41–1.01)	0.59 (0.27–1.30)
Pacific	0.46 (0.27–0.77)	0.45 (0.27–0.77)	0.51 (0.22–1.15)
Smoking status			
Never/former	1 (Reference)	1 (Reference)	1 (Reference)
Current	0.87 (0.57–1.33)	0.95 (0.61–1.46)	0.94 (0.44–2.02)
Comorbidities			
Diabetes mellitus	2.18 (1.62–2.92)	2.06 (1.52–2.80)	1.55 (0.89–2.71)
Hypertension	1.57 (1.17–2.12)	1.41 (1.03–1.92)	1.19 (0.68–2.08)
Chronic kidney disease	1.61 (1.18–2.19)	1.45 (1.05–2.00)	1.97 (1.09–3.58)
Heart failure	2.79 (0.83–9.34)	2.35 (0.70–7.89)	1.84 (0.23–14.81)
Familial hypercholesterolemia	35.77 (16.39–78.08)	41.97 (18.74–93.98)	143.50 (36.65–561.83)
Statin use			
Never	1 (Reference)	1 (Reference)	1 (Reference)
Former	3.75 (2.23–6.30)	3.64 (2.14–6.19)	3.72 (1.72–8.04)
Current: low intensity	6.37 (2.63–15.42)	6.22 (2.50–15.47)	4.02 (0.54–29.97)
Current: moderate to high intensity	2.11 (1.20–3.71)	2.08 (1.18–3.69)	1.79 (0.72–4.42)
Use of ezetimibe			
Never or former	1 (Reference)	1 (Reference)	1 (Reference)
Current	52.22 (24.22–112.63)	55.38 (25.23–121.54)	98.10 (31.67–303.87)
LDL-C category, mg/dL			
100–<130	1 (Reference)	1 (Reference)	1 (Reference)
130–<190	3.78 (2.25–6.35)	3.76 (2.23–6.34)	3.30 (1.45–7.53)
≥190	10.48 (6.12–17.96)	11.56 (6.64–20.12)	18.89 (7.66–46.56)

Model 1: unadjusted. Model 2: adjusted for age, sex, and race/ethnicity. Model 3: adjusted for all the variables listed in the left-hand column of the table. There were 64 (5.2%) veterans in the severe hypercholesterolemia cohort with missing data on race. LDL-C indicates low-density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; and VISN, Veterans Integrated Service Network.

*Other indicates American Indian or Alaska Native, Mixed, Native Hawaiian or other Pacific Islander, or missing ethnicity.

ASCVD cohort, veterans taking low-intensity statins were 2.6 times as likely to initiate PCSK9i compared with never users. The greater likelihood of PCSK9i initiation among low-intensity statin users may be indicative of patients exhibiting some level of statin intolerance to higher doses, although this remains an area of future research. In addition, current use of ezetimibe among PCSK9i initiators was substantially higher than prior reports (42.4% versus 1.1%–19.7% in prior studies).[6–8,28] The greater likelihood of PCSK9i initiation among veterans currently taking a statin of any intensity or currently taking ezetimibe could be attributed to the VHA appropriate use criteria for PCSK9i use, which encourage the addition of ezetimibe to statin therapy before PCSK9i initiation.[12]

In the current analysis, we did not find a linear association between age and PCSK9i initiation. Among veterans with a history of ASCVD, those aged 65 to <75 years were more likely, whereas those aged ≥75 years were less likely, to initiate a PCSK9i versus their counterparts aged <65 years. A shorter life expectancy and therapeutic nihilism (ie, perception of low benefit) may contribute to explain the lower use of a PCSK9i among the old veterans with a history of ASCVD. Among veterans with primary severe hypercholesterolemia, those aged ≥75 years were more likely to initiate a PCSK9i versus those aged <65 years. It is possible that older adults with severe hypercholesterolemia who have not developed ASCVD may be perceived by clinicians as more likely to benefit from additional lipid-lowering therapy with a PCSK9i versus their counterparts of younger age. The association between age and PCSK9i initiation warrants further investigation.

This study has several strengths. We used a large, national, well-characterized data source that contains a breadth of clinical and administrative variables for research purposes. The use of dispensing data identifies veterans who fulfilled a prescription for a PCSK9i, statin, or ezetimibe, which allowed more valid estimates of medication use compared with medication lists in the electronic medical record or provider order data. However, the current study should be interpreted within the context of known limitations. We defined primary severe hypercholesterolemia using any prior LDL-C ≥190 mg/dL, which may capture some patients without true FH.[29] However, in a subgroup analysis changing the threshold to any prior LDL-C ≥220 mg/dL, results were consistent with the main analysis using the LDL-C ≥190 mg/dL threshold. We were not able to identify veterans with statin intolerance, which may indicate the degree to which PCSK9i are used to substitute statin therapy. Validated algorithms to identify statin-intolerant patients in claims data remain an area of research.[30–32] The use of dispensing data from VHA pharmacies in the current analysis did not capture

veterans who received PCSK9i directly from the clinic, manufacturer, or a non-VHA pharmacy. Although we found a reduced likelihood of PCSK9i initiation among women in the ASCVD cohort, few women were included in the analyses, and the population in this study may not be generalizable to the larger US population. Data on duration of ASCVD and severe hypercholesterolemia before each veteran's index date were unavailable. Results from subgroup analyses should be interpreted with caution as the large number of comparisons may increase the likelihood of a spurious association.

In conclusion, among veterans with ASCVD or severe hypercholesterolemia in 2018 and 2019, several patient-level factors, including age, sex, and race/ethnicity, were significantly associated with PCSK9i initiation, suggesting an unmet treatment need in several patient groups. Preindex LDL-C levels were substantially higher among patients who initiated versus did not initiate a PCSK9i. Among those with ASCVD, women compared with men and non-Hispanic Black, Asian, and Hispanic veterans were less likely to initiate a PCSK9i than non-Hispanic White veterans. The factors associated with PCSK9i initiation among patients with high and very-high ASCVD risk in this study suggest opportunities to optimize lipid-lowering therapies.

Supplementary Material

Data S1
Tables S1–S6
Figures S1–S3

REFERENCES

1. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713–1722. DOI: 10.1056/NEJMoa1615664.

2. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018;379:2097–2107. DOI: 10.1056/NEJMoa1801174.

3. Navarese EP, Kolodziejczak M, Schulze V, Gurbel PA, Tantry U, Lin Y, Brockmeyer M, Kandzari DE, Kubica JM, D'Agostino RB, et al. Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia: a systematic review and meta-analysis. *Ann Intern Med*. 2015;163:40–51. DOI: 10.7326/M14-2957.

4. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e1082–e1143. DOI: 10.1161/CIR.0000000000000625.

5. Myers KD, Farboodi N, Mwamburi M, Howard W, Staszak D, Gidding S, Baum SJ, Wilemon K, Rader DJ. Effect of access to prescribed PCSK9 inhibitors on cardiovascular outcomes. *Circ Cardiovasc Qual Outcomes*. 2019;12:e005404. DOI: 10.1161/CIRCOUTCOMES.118.005404.

6. Chamberlain AM, Gong Y, Shaw KM, Bian J, Song W-L, Linton MF, Fonseca V, Price-Haywood E, Guhl E, King JB, et al. PCSK9 inhibitor use in the real world: data from the National Patient-Centered Research Network. *J Am Heart Assoc*. 2019;8:e011246. DOI: 10.1161/JAHA.118.011246.

7. Hess GP, Natarajan P, Faridi KF, Fievitz A, Valsdottir L, Yeh RW. PCSK9 inhibitor therapy: payer approvals and rejections, and patient characteristics for successful prescribing. *Circulation*. 2017;136:2210–2219. DOI: 10.1161/CIRCULATIONAHA.117.028430.

8. Navar AM, Taylor B, Mulder H, Fievitz E, Monda KL, Fievitz A, Monda KL, Fievitz A, Maya JF, López J, et al. Association of prior authorization and out-of-pocket costs with patient access to PCSK9 inhibitor therapy. *JAMA Cardiol*. 2017;2:1217–1225. DOI: 10.1001/jamacardio.2017.3451.

9. Knowles JW, Howard WB, Karayan L, Baum SJ, Wilemon KA, Ballantyne CM, Myers KD. Access to nonstatin lipid-lowering therapies in patients at high risk of atherosclerotic cardiovascular disease. *Circulation*. 2017;135:2204–2206. DOI: 10.1161/CIRCULATIONAHA.117.027705.

10. Glueck CJ, Shah P, Goldenberg N, Prince M, Lee K, Jetty V, Kumar A, Goldenberg M, Wang P. Eligibility for PCSK9 treatment in 734 hypercholesterolemic patients referred to a regional cholesterol treatment center with LDL cholesterol ≥70 mg/dl despite maximal tolerated cholesterol lowering therapy. *Lipids Health Dis*. 2016;15:55. DOI: 10.1186/s12944-016-0227-2.

11. US Department of Veterans Affairs. VA priority groups 2019. https://www.va.gov/health-care/eligibility/priority-groups/. Accessed February 25, 2020.

12. US Department of Veterans Affairs. Pharmacy benefits management services: VA formulary 2020. https://www.pbm.va.gov/apps/VANationalFormulary/. Accessed February 25, 2020.

13. Kent ST, Safford MM, Zhao H, Levitan EB, Curtis JR, Kilpatrick RD, Kilgore ML, Muntner P. Optimal use of available claims to identify a Medicare population free of coronary heart disease. *Am J Epidemiol*. 2015;182:808–819. DOI: 10.1093/aje/kwv116.

14. Kumamaru H, Judd SE, Curtis JR, Ramachandran R, Hardy NC, Rhodes JD, Safford MM, Kissela BM, Howard G, Jalbert JJ, et al. Validity of claims-based stroke algorithms in contemporary Medicare data: REGARDS study linked with Medicare claims. *Circ Cardiovasc Qual Outcomes*. 2014;7:611–619. DOI: 10.1161/CIRCOUTCOMES.113.000743.

15. Hirsch AT, Hartman L, Town RJ, Virnig BA. National health care costs of peripheral arterial disease in the Medicare population. *Vasc Med*. 2008;13:209–215. DOI: 10.1177/1358863X08089277.

16. Colantonio LD, Rosenson RS, Deng L, Monda KL, Dai Y, Farkouh ME, Safford MM, Philip K, Mues KE, Muntner P. Adherence to statin therapy among US adults between 2007 and 2014. *J Am Heart Assoc*. 2019;8:e010376. DOI: 10.1161/JAHA.118.010376.

17. Colantonio LD, Hubbard D, Monda KL, Mues KE, Huang L, Dai Y, Jackson EA, Brown TM, Rosenson RS, Woodward M, et al. Atherosclerotic risk and statin use among patients with peripheral artery disease. *J Am Coll Cardiol*. 2020;76:251–264. DOI: 10.1016/j.jacc.2020.05.048.

18. Bittner V, Colantonio LD, Dai Y, Woodward M, Mefford MT, Rosenson RS, Muntner P, Monda KL, Kilgore ML, Jaeger BC, et al. Association of region and hospital and patient characteristics with use of high-intensity statins after myocardial infarction among Medicare beneficiaries. *JAMA Cardiol*. 2019;4:865–872. DOI: 10.1001/jamacardio.2019.2481.

19. Riestenberg RA, Furman A, Cowen A, Pawlowksi A, Schneider D, Lewis AA, Kelly S, Taiwo B, Achenbach C, Palella F, et al. Differences in statin utilization and lipid lowering by race, ethnicity, and HIV status in a real-world cohort of persons with human immunodeficiency virus and uninfected persons. *Am Heart J*. 2019;209:79–87. DOI: 10.1016/j.ahj.2018.11.012.

20. Tran HV, Waring ME, McManus DD, Erskine N, Do VTH, Kiefe CI, Goldberg RJ. Underuse of effective cardiac medications among women, middle-aged adults, and racial/ethnic minorities with coronary artery disease (from the National Health and Nutrition Examination Survey 2005 to 2014). *Am J Cardiol*. 2017;120:1223–1229. DOI: 10.1016/j.amjcard.2017.07.004.

21. Choudhry NK, Bykov K, Shrank WH, Toscano M, Rawlins WS, Reisman L, Brennan TA, Franklin JM. Eliminating medication copayments reduces disparities in cardiovascular care. *Health Aff (Millwood)*. 2014;34:863–870. DOI: 10.1377/hlthaff.2013.0654.

22. Mochari-Greenberger H, Liao M, Mosca L. Racial and ethnic differences in statin prescription and clinical outcomes among hospitalized patients with coronary heart disease. *Am J Cardiol*. 2014;113:413–417. DOI: 10.1016/j.amjcard.2013.10.010.

23. Qato DM, Lindau ST, Conti RM, Schumm LP, Alexander GC. Racial and ethnic disparities in cardiovascular medication use among older adults in the United States. *Pharmacoepidemiol Drug Saf*. 2010;19:834–842. DOI: 10.1002/pds.1974.

24. Woodard LCD, Kressin NR, Petersen LA. Is lipid-lowering therapy underused by African Americans at high risk of coronary heart disease within the VA health care system? *Am J Public Health*. 2004;94:2112–2117. DOI: 10.2105/AJPH.94.12.2112.

25. Williams ML, Morris MT, Ahmad U, Yousseff M, Li W, Ertel N. Racial differences in compliance with NCEP-II recommendations for secondary prevention at a Veterans Affairs medical center. *Ethn Dis*. 2002;12:S1–S58.

26. Bradley CK, Shrader P, Sanchez RJ, Peterson ED, Navar AM. The patient journey with proprotein convertase subtilisin/kexin type 9 inhibitors in community practice. *J Clin Lipidol*. 2019;13:725–734. DOI: 10.1016/j.jacl.2019.06.008.

27. Rymer JA, Mues KE, Monda KL, Bratton EW, Wirtz HS, Okerson T, Overman RA, Brookhart MA, Muntner P, Wang TY. Use of low-density lipoprotein-lowering therapies before and after PCSK9 inhibitor initiation. *J Am Heart Assoc*. 2020;9:e014347. DOI: 10.1161/JAHA.119.014347.

28. Hines DM, Rane P, Patel J, Harrison DJ, Wade RL. Treatment patterns and patient characteristics among early initiators of PCSK9 inhibitors. *Vasc Health Risk Manag*. 2018;14:409–418. DOI: 10.2147/VHRM.S180496.

29. Khera AV, Won H-H, Peloso GM, Lawson KS, Bartz TM, Deng X, van Leeuwen EM, Natarajan P, Emdin CA, Bick AG, et al. Diagnostic yield of sequencing familial hypercholesterolemia genes in severe hypercholesterolemia. *J Am Coll Cardiol*. 2016;67:2578–2589. DOI: 10.1016/j.jacc.2016.03.520.

30. Bellows BK, Sainski-Nguyen AM, Olsen CJ, Boklage SH, Charland S, Mitchell MP, Brixner DI. Identification of patients with statin intolerance in a managed care plan: a comparison of 2 claims-based algorithms. *J Manag Care Spec Pharm*. 2017;23:926–934. DOI: 10.18553/jmcp.2017.23.9.926.

31. Schulman KL, Lamerato LE, Dalal MR, Sung J, Jhaveri M, Koren A, Mallya UG, Foody JM. Development and validation of algorithms to identify statin intolerance in a US administrative database. *Value Health*. 2016;19:852–860. DOI: 10.1016/j.jval.2016.03.1858.

32. Colantonio LD, Kent ST, Huang L, Chen L, Monda KL, Serban MC, Manthripragada A, Kilgore ML, Rosenson RS, Muntner P. Algorithms to identify statin intolerance in Medicare administrative claim data. *Cardiovasc Drugs Ther*. 2016;30:525–533. DOI: 10.1007/s10557-016-6680-3.

Supplemental Material

Data S1.

Supplemental Methods

Categorization of variables for analyses
- Age was categorized into <65, 65 to <75, and ≥75 years.
- Race-ethnicity was categorized into non-Hispanic white, non-Hispanic black, Asian, Hispanic, and other/missing.
- Median income was categorized into quartiles in the ASCVD cohort and the severe hypercholesterolemia cohort, separately.
- Veterans Integrated Service Network (VISN): Categorized VISN into one of four regions: Northeast, Southeast, Continental, and Pacific according to the VA regional offices map
- The Northeast region was comprised of VISNs 1, 2, 4, 5, 10, and 12. The Southeast region was comprised of VISNs 5, 6, 7, 8, 9, and 16. The Continental region consisted of VISNs 15, 17, 18, 19, and 23. Finally, the Pacific region was comprised of VISNs 20, 21, and 22.

Very high-risk criteria
As defined in the AHA/ACC Blood Cholesterol guideline, individuals were classified as very high-risk for future ASCVD if they had a history of multiple major ASCVD events or 1 major ASCVD event and multiple high risk conditions:
- Age ≥65 years
- Heterozygous FH
- History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
- Diabetes
- Hypertension
- Chronic Kidney Disease (estimated glomerular filtration rate 15-59 mL/min/1.73m^2)
- Current smoking
- LDL-C ≥100 mg/dL despite statin therapy and ezetimibe
- Congestive heart failure

Priority Group Status
The VHA prescription copay structure is based on a Veteran's priority group, categorized as a number between 1 (highest need) and 8 (lowest need) according to military service history, disability rating, income level, and participation in other benefits.

VHA Appropriate Use Criteria for PCSK9 inhibitors
During the study period, the VHA employed appropriate use criteria for PCSK9 inhibitor for both primary and secondary prevention populations. Under the appropriate use criteria, Veterans with homozygous FH alone or heterozygous FH with LDL-C reduction <50% from baseline despite maximally-tolerated statin and ezetimibe therapy are eligible for PCSK9 inhibitor. Additionally, Veterans with ASCVD with confirmed adherence to maximally-tolerated statin and ezetimibe therapy may be eligible if they also have: 1) a history of at least two ASCVD events; 2) very-high risk conditions (recurrent ASCVD events, multiple uncontrolled risk factors) and LDL-C ≥100 mg/dL; or 3) very high risk conditions (as above), LDL-C remains 70-99 mg/dL, and receiving care from a VA-authorized cardiologist, lipid specialist, endocrinologist, or expert.

Table S1. Definitions and codes used to define history of atherosclerotic cardiovascular disease.

History of ASCVD	Defined by a history of CHD, cerebrovascular disease, or peripheral artery disease, as defined below.

History of CHD[13]	Algorithm based on ICD-9 codes: Any of the following using all available claims before the index date:
	    (a) An inpatient claim diagnosis codes of 410.xx-414.xx, V45.81 or V45.82.
	    (b) An outpatient or carrier file claim, linked to E&M code, with diagnosis codes of codes 410.xx-414.xx, V45.81 or V45.82.
	
	Algorithm based on ICD-10 codes: Any of the following using all available claims before the index date:
	    (a) An inpatient claim diagnosis codes of I20.0, I21.xx, I22.xx, I24.0, I24.8, I24.9, I25.10, I25.110, I25.700, I25.710, I25.720, I25.730, I25.750, I25.760, I25.790, I25.810, I25.811, I25.812, I25.3, I25.41, I25.42, Z95.1 or Z9861.
	    (b) An outpatient or carrier file claim, linked to E&M code, with diagnosis codes of codes I20.0, I21.xx, I22.xx, I24.0, I24.8, I24.9, I25.10, I25.110, I25.700, I25.710, I25.720, I25.730, I25.750, I25.760, I25.790, I25.810, I25.811, I25.812, I25.3, I25.41, I25.42, Z95.1 or Z9861.
	
	Veterans who met the definition of a prior coronary revascularization, as defined below, will be also considered to have a history of CHD.

Prior coronary revascularization	Defined by ≥ 1 inpatient or outpatient procedure with a current procedure terminology (CPT) code for coronary revascularization (33510-33519, 33521-33523, 33530, 33533-33536, 92920, 92921, 92924, 92925, 92928, 92929, 92933, 92934, 92937, 92938, 92941, 92943, and 92944), an ICD-9 procedure code of 00.66, 36.0, 36.01-36.19, 36.2, or an ICD-10 procedure code starting with any of the following 4 digits: 0210, 0211, 0212, 0213, 0270, 0271, 0272, 0273, 02C0, 02C1, 02C2, 02C3, 3E07 using all available claims prior to each Veteran's index date. In addition to having 1 inpatient or outpatient procedure, Veterans are required to meet at least 1 of the following criteria: • Have no inpatient claims with a diagnosis code for acute myocardial infarction (410.x0 or 410.x1 or ICD10 codes I21.xx or I22.xx) within 60 days prior to the procedure. • Have primary discharge diagnosis code for non-elective CHD-related hospitalization prior to the index date (arrhythmia [ICD-9 diagnosis code of 427.xx, except 427.5 or ICD-10 diagnosis code of I47.1, I47.2, I47.9, I48.91, I48.92, I49.01, I49.02, I49.1, I49.3, I49.40, I49.49, I49.5, I49.8, I49.9, R00.1], cardiac arrest [ICD-9 diagnosis code of 427.5 or ICD-10 diagnosis code of I46.9], heart failure [ICD-9 diagnosis code of 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.x or ICD-10 diagnosis code of I11.0, I13.0, I13.2, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43, I50.9], and unstable angina [ICD-9 diagnosis code of 411.xx or ICD-10 diagnosis code of I20.0, I24.0, I24.1, I24.8]).
Cerebrovascular disease[14]	Algorithm based on ICD-9 codes: Any of the following using all available claims before the index date: • At least 1 inpatient ICD-9 diagnosis (primary or secondary position) of 433.x1 or 434.x1 • At least 1 outpatient or carrier claim with ICD-9 diagnoses (any position) of 433.x1 or 434.x1, linked by CLAIM_ID to an ambulatory physician evaluation and management claim. • At least 1 claim with ICD-9 diagnoses (any position) of 433.x1 or 434.x1 in other file types (Home Health Agency [HHA], durable medical equipment [DME], Hospice, SNF).

	Algorithm based on ICD-10 codes: Any of the following using all available claims before the index date: • At least 1 inpatient ICD-10 diagnosis (primary or secondary position) I63.xx • At least 1 outpatient or carrier claim with ICD-10 diagnoses (any position) of I63.xx linked by CLAIM_ID to an ambulatory physician evaluation and management claim • At least 1 claim with ICD-10 diagnoses (any position) of I63.xx in other file types (Home Health Agency [HHA], durable medical equipment [DME], Hospice, SNF). • At least one inpatient ICD-10 procedure code in ('03CH0ZZ', '03CH4ZZ', '03CJ0ZZ', '03CJ4ZZ', '03CK0ZZ', '03CK4ZZ', '03CL0ZZ', '03CL4ZZ', '03CM0ZZ', '03CM4ZZ', '03CN0ZZ', '03CN4ZZ', '03RH07Z', '03RH0JZ', '03RH0KZ', '03RH47Z', '03RH4JZ', '03RH4KZ', '03RJ07Z', '03RJ0JZ', '03RJ0KZ', '03RJ47Z', '03RJ4JZ', '03RJ4KZ', '03RK07Z', '03RK0JZ', '03RK0KZ', '03RK47Z', '03RK4JZ', '03RK4KZ', '03RL07Z', '03RL0JZ', '03RL0KZ', '03RL47Z', '03RL4JZ', '03RL4KZ', '03RM07Z', '03RM0JZ', '03RM0KZ', '03RM47Z', '03RM4JZ', '03RM4KZ', '03RN07Z', '03RN0JZ', '03RN0KZ', '03RN47Z', '03RN4JZ', '03RN4KZ') Veterans with ≥1 inpatient or outpatient claim with a CPT code for carotid revascularization (35301, 35390, 37215, 37216, 0005T, 0075T, or 0076) will be also considered to have a history of cerebrovascular disease.

History of PAD[15]	Algorithm based on ICD-9 codes: Any of the following using all available claims prior to the index date:
	    (a) ≥1 inpatient claim with a discharge diagnosis code of peripheral vascular disease (ICD-9-CM diagnosis codes 440.20-440.24, 440.31, 444.2, 443.9, or 444.81) in any position, or
	    (b) ≥2 physician evaluation and management outpatient or carrier claims with an ICD-9-CM diagnosis code of peripheral vascular disease on separate days, or
	    (c) ≥1 inpatient, outpatient or carrier claim with a CPT code 37205 or 75962.
	
	Algorithm based on ICD-10 codes: Any of the following using all available claims before the index date:
	    (a) ≥1 inpatient claim with a discharge diagnosis code of peripheral vascular disease (ICD-10-CM diagnosis codes 'I70.209', 'I70.219, 'I70.229', 'I70.25', 'I70.269', 'I70.499', 'I73.9') or
	    (b) ≥2 physician evaluation and management outpatient or carrier claims with an ICD-10-CM diagnosis code of peripheral vascular disease on separate days, or
	    (c) ≥1 inpatient, outpatient or carrier claim with a CPT code 37205 or 75962.

Table S2. Definitions and codes used to define study variables.

Variable	Definition
Patient Characteristics	
Age	Age of Veterans calculated on the index date based on the date of birth available in the Veteran summary file.
Sex	Male or female
Race	Black, White, Hispanic, Asian, and Other
Area level income	Using ZIP and FIPS codes based on data obtained from the American Community Survey. The variable ZCTA was matched to ZIP code in the American Community Survey. If ZCTA and ZIP did not match, then FIPS code (county level) from the American Community Survey was used.
Supplemental health insurance	Dichotomous variable (yes/no) describes whether the Veteran has additional health insurance coverage beyond VHA insurance coverage.
VISN region	The Veteran's Integrated Service Network (VISN) in which the Veteran receives most of his or her care. VISN was further categorized into Northeast, Southeast, Continental, and Pacific regions according to the VA regional offices map (see Supplemental Methods).
Priority group status	categorized as a number between 1 (highest need) and 8 (lowest need) according to military service history, disability rating, income level, and participation in other benefits (see Supplemental Methods).
Current Smoking	Algorithm based on ICD-9 diagnosis codes: Any of the following within 365 days prior to the index date. (a) ≥1 hospitalization with a discharge diagnosis code of tobacco use (ICD-9 CM diagnosis code of 305.1, 649.0x, 989.84, or V15.82) in any discharge position (b) ≥1 physician evaluation and management visit with a diagnosis code of tobacco use (ICD-9-CM diagnosis code of 305.1, 649.0x, 989.84, or V15.82) in any discharge position (c) ≥1 hospitalization with a discharge diagnosis code or physician evaluation and management visit of tobacco use with a CPT code of 99406, 99407, G0436, G0437, G9016, S9453, S4995, G9276, G9458, 1034F, 4004F, 4001F (d) ≥1 pharmacy fill for nicotine or varenicline. Algorithm based on ICD-10 diagnosis codes: Any of the following within 365 days prior to the index date. (a) ≥1 hospitalization with a discharge diagnosis code of tobacco use (ICD-10 CM diagnosis code of F17.200, F17.201, F17.210, F17.211, F17.220, F17.221, F17.290, F17.291, or Z87.891) in any discharge position (b) ≥1 outpatient visit with a diagnosis code of tobacco use (ICD-10 CM diagnosis code of F17.200, F17.201, F17.210, F17.211, F17.220, F17.221, F17.290, F17.291, or Z87.891) in any discharge position (c) ≥1 hospitalization with a discharge diagnosis code or physician evaluation and management visit of tobacco use with a CPT code of 99406, 99407, G0436, G0437, G9016, S9453, S4995, G9276, G9458, 1034F, 4004F, 4001F (d) ≥1 pharmacy fill for nicotine or varenicline.
Comorbid conditions	
Diabetes	Algorithm for diabetes based on ICD-9 codes: Any of the following using all available claims before the index date: (a) At least 1 inpatient claim with a discharge ICD-9 diagnosis (any position) of 250.xx, 357.2, 362.0x, or 366.41. (b) At least 2 carrier claims, carrier line or outpatient claims with ICD-9 diagnoses (any position) of 250.xx, 357.2, 362.0x, or 366.41, linked by CLAIM_ID to an ambulatory physician evaluation and management claim, with the 2 claims occurring at least 7 days apart. (c) At least 1 pharmacy claim for an oral antidiabetic drug fill or insulin.

	Algorithm for diabetes based on ICD-10 codes: Any of the following all available claims before the index date: (a) At least 1 inpatient claim with a discharge ICD-10 diagnosis (any position) of 'E0836', 'E0842', 'E0936', 'E0942', 'E1010', 'E1011', 'E1029', 'E10311', 'E10319', 'E1036', 'E1039', 'E1040', 'E1042', 'E1051', 'E10618', 'E10620', 'E10621', 'E10622', 'E10628', 'E10630', 'E10638', 'E10641', 'E10649', 'E1065', 'E1069', 'E108', 'E109', 'E1100', 'E1101', 'E1129', 'E11311', 'E11319', 'E11329', 'E11339', 'E11349', 'E11359', 'E1136', 'E1139', 'E1140', 'E1142', 'E1151', 'E11618', 'E11620', 'E11621', 'E11622', 'E11628', 'E11630', 'E11638', 'E11641', 'E11649', 'E1165', 'E1169', 'E118', 'E119', 'E1310', 'E1336', 'E1342'. (b) At least 2 carrier claims, carrier line or outpatient claims with ICD-10 diagnoses (any position) of 'E0836', 'E0842', 'E0936', 'E0942', 'E1010', 'E1011', 'E1029', 'E10311', 'E10319', 'E1036', 'E1039', 'E1040', 'E1042', 'E1051', 'E10618', 'E10620', 'E10621', 'E10622', 'E10628', 'E10630', 'E10638', 'E10641', 'E10649', 'E1065', 'E1069', 'E108', 'E109', 'E1100', 'E1101', 'E1129', 'E11311', 'E11319', 'E11329', 'E11339', 'E11349', 'E11359', 'E1136', 'E1139', 'E1140', 'E1142', 'E1151', 'E11618', 'E11620', 'E11621', 'E11622', 'E11628', 'E11630', 'E11638', 'E11641', 'E11649', 'E1165', 'E1169', 'E118', 'E119', 'E1310', 'E1336', 'E1342', linked by CLAIM_ID to an ambulatory physician evaluation and management claim, with the 2 claims occurring at least 7 days apart. (c) At least 1 pharmacy claim for an oral antidiabetic drug fill or insulin.
Hypertension	Algorithm based on ICD-9 codes: Any of the following using all available claims before the index date: • ≥1 inpatient claim with an ICD-9 discharge diagnosis code of 401.x, 403.0x, 403.1x, 403.9x in any discharge diagnosis position • ≥2 outpatient claims with an ICD-9 diagnosis code of 401.x, 403.0x, 403.1x, 403.9x in any position at least 30 days apart Algorithm based on ICD-10 codes: Any of the following using all available claims before the index date: • 1 inpatient claim with an ICD-10 discharge diagnosis code of I10, I12.0, I12.9 in any discharge diagnosis position • ≥2 outpatient claims with an ICD-10 diagnosis code of I10, I12.0, I12.9 in any position at least 30 days apart Algorithm based on pharmacy fills: A pharmacy fill for an antihypertensive medication within 365 days prior to the index date.
Chronic kidney disease	Algorithm based on ICD-9 codes: Any of the following using all available claims before the index date (this definition is from the United States Renal Data System [USRDS] annual report): (a) ≥1 inpatient claim with a discharge diagnosis code of chronic kidney disease (ICD-9 diagnosis code of 016.0, 095.4, 189.0, 189.9, 223.0, 236.91, 250.4, 271.4, 274.1, 283.11, 403.x1, 403.x0, 404.x2, 404.x3, 404.x0, 404.x1, 440.1, 442.1, 447.3, 572.4, 580–588, 591, 642.1, 646.2, 753.12–753.17, 753.19, 753.2, 794.4) in any discharge diagnosis position. (b) ≥1 physician evaluation and management visit with a diagnosis code of chronic kidney disease (ICD-9-CM diagnosis code of 016.0, 095.4, 189.0, 189.9, 223.0, 236.91, 250.4, 271.4, 274.1, 283.11, 403.x1, 403.x0, 404.x2, 404.x3, 404.x0, 404.x1, 440.1, 442.1, 447.3, 572.4, 580.xx–588.xx, 591, 642.1, 646.2, 753.12–753.17, 753.19, 753.2, or 794.4) in any position. (c) Additionally, if the flag ESRD_IND in the Master Veteran summary file is checked then the participant will be categorized as having a history of CKD. (d) Estimated glomerular filtration (eGFR) rate of 15-59 mL/min/1.73m^2

	Algorithm based on ICD-10 codes: Any of the following using all available claims prior to the index date:
	(a) ≥1 inpatient claim with a discharge diagnosis code of chronic kidney disease (ICD-10 diagnosis code of 'A1811', 'A5275', 'C649', 'C689', 'D3000', 'D4100', 'D4120', 'D593', 'E1021', 'E1029', 'E1121', 'E1129', 'E748', 'I120', 'I129', 'I130', 'I1310', 'I1311', 'I132', I701', 'I722', 'K767', 'M1030', 'N003', 'N008', 'N009', 'N013', 'N022', 'N032', 'N033', 'N035', 'N038', 'N039', 'N040', 'N043', 'N044', 'N048', 'N049', 'N052', 'N055', 'N058', 'N059', 'N08', 'N1330', 'N170', 'N171', 'N172', 'N178', 'N179', 'N181', 'N182', 'N183', 'N184', 'N185', 'N186', 'N189', 'N19', 'N250', 'N251', 'N2581', 'N2589', 'N259', 'N269','Q6102', 'Q6119', 'Q612', 'Q613', 'Q614', 'Q615', 'Q618', 'Q6210', 'Q6211', 'Q6212', 'Q6231', 'Q6239', 'R944') in any discharge diagnosis position.
	(b) ≥1 physician evaluation and management visit with a diagnosis code of chronic kidney disease (ICD-10-CM diagnosis code of 'A1811', 'A5275', 'C649', 'C689', 'D3000', 'D4100', 'D4120', 'D593', 'E1021', 'E1029', 'E1121', 'E1129', 'E748', 'I120', 'I129', 'I130', 'I1310', 'I1311', 'I132', I701', 'I722', 'K767', 'M1030', 'N003', 'N008', 'N009', 'N013', 'N022', 'N032', 'N033', 'N035', 'N038', 'N039', 'N040', 'N043', 'N044', 'N048', 'N049', 'N052', 'N055', 'N058', 'N059', 'N08', 'N1330', 'N170', 'N171', 'N172', 'N178', 'N179', 'N181', 'N182', 'N183', 'N184', 'N185', 'N186', 'N189', 'N19', 'N250', 'N251', 'N2581', 'N2589', 'N259', 'N269','Q6102', 'Q6119', 'Q612', 'Q613', 'Q614', 'Q615', 'Q618', 'Q6210', 'Q6211', 'Q6212', 'Q6231', 'Q6239', 'R944') in any position.
	(c) Additionally, if the flag ESRD_IND in the Master Veteran summary file is checked then the participant will be categorized as having a history of CKD.
	(d) Estimated glomerular filtration rate of 15-59 mL/min/1.73m^2. The eGFR reading used is the most recent within the one-year pre-index period. To account for data/reading errors, only eGFR values between 0 and 250 were considered.
Heart failure	Algorithm based on ICD-9 codes: Any of the following using all available claims before the index date: (a) ≥ 1 inpatient claim with ICD-9 diagnoses (any position) of 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.x, or (b) ≥ 2 outpatient or carrier claims on separate calendar days with ICD-9 diagnoses (any position) of 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.x. Algorithm based on ICD-10 codes: Any of the following using all available claims before the index date: (a) ≥ 1 inpatient claim with ICD-10 diagnoses (any position) of 'I110', 'I130', 'I132', 'I501', 'I5020', 'I5021', 'I5022', 'I5023', 'I5030', 'I5031', 'I5032', 'I5033', 'I5040', 'I5041', 'I5042', 'I5043', 'I509', or (b) ≥ 2 outpatient or carrier claims on separate calendar days with ICD-10 diagnoses (any position) of 'I110', 'I130', 'I132', 'I501', 'I5020', 'I5021', 'I5022', 'I5023', 'I5030', 'I5031', 'I5032', 'I5033', 'I5040', 'I5041', 'I5042', 'I5043', 'I509'.
Familial hypercholesterolemia	≥1 physician evaluation and management outpatient visit or ≥1 inpatient claim with a diagnosis code of familial hypercholesterolemia (ICD-10-CM diagnosis code of E78.00 and E78.01) in any position using all available claims before the index date.
Medication use	
Statin use	Defined using all available pharmacy fills for a statin prior to each Veteran's index date and categorized as: Never: have no pharmacy fills for a statin.

	Former: have ≥1 pharmacy fill for a statin ≥90 days before each Veteran's index date, with no pharmacy fills for a statin within 90 days prior to the index date. Current low intensity: have ≥1 pharmacy fill for a low-intensity statin within 90 days prior to each Veteran's index date. Current moderate- or high-intensity: have ≥1 pharmacy fill for a moderate- or high-intensity statin within 90 days prior to each Veteran's index date.
Use of ezetimibe	Defined using all available pharmacy fills for ezetimibe prior to each Veteran's index date and categorized as: Never: have no pharmacy fills for ezetimibe. Former: have ≥1 pharmacy fill for ezetimibe ≥90 days before each Veteran's index date, with no pharmacy fills for ezetimibe within 90 days prior to the index date. Current: have ≥1 pharmacy fill for ezetimibe within 90 days prior to each Veteran's index date.
ASCVD events	
Recent acute coronary syndrome[13]	Overnight hospitalization with a discharge diagnosis code for myocardial infarction (ICD9 codes 410.x0 or 410.x1 or ICD10 codes I21.xx or I22.xx) or unstable angina (ICD9 codes 411.1, 411.81, 411.89 or ICD10 codes I20.0, I24.0, I24.8, I24.9, I25.110, I25.700, I25.710, I25.720, I25.730, I25.750, I25.760, I25.790) in any position within 365 days prior to each Veteran's index date.
Prior acute myocardial infarction[13]	Overnight hospitalization with a discharge diagnosis code for myocardial infarction (ICD9 codes 410.x0 or 410.x1 or ICD10 codes I21.xx or I22.xx) in any position before 365 days prior to each Veteran's index date (acute myocardial infarctions within 365 days prior to each Veteran's index date are defined as acute coronary syndromes).
History of myocardial infarction[13]	Inpatient or outpatient claim with a code for 'old MI' (ICD9 code 412.xx or ICD10 code I25.2) in any position prior to the earliest recent acute coronary syndrome or prior acute myocardial infarction (as defined above).
Prior acute ischemic stroke[14]	Overnight hospitalization with a discharge diagnosis code for ischemic stroke (ICD9 codes 433.x1 or 434.x1, or ICD10 code I63.xx) in the primary position prior to each Veteran's index date.
History of ischemic stroke[14]	Outpatient claim with a code for ischemic stroke (ICD9 codes 433.x1 or 434.x1, or ICD10 code I63.xx) in any position or an inpatient claim with a code for ischemic stroke (ICD9 codes 433.x1 or 434.x1, or ICD10 code I63.xx) in any position other than the primary position prior to the earliest prior acute ischemic stroke (as defined above), or prior to the Veteran's index date (for Veterans without a prior acute ischemic stroke).
Had a repeat ASCVD event while taking a statin and ezetimibe	In the one-year pre index period, had 2 ASCVD events and had ≥1 pharmacy fill for a statin and ezetimibe within 90 days prior to the 2nd ASCVD event.
Laboratory values	
LDL-C Level	The LDL-C value closest to the index date in the pre-index period. Defined using OMOP's mapping where LOINC_Mapped in ('13457-7','18262-6','2089-1','2574-2','9346-8') and Topography in ('SERUM', 'PLASMA', 'BLOOD', 'SER/PLA', 'BLOOD*', 'SER/PLAS', 'BLOOD.', 'WS-PLASMA', 'CC SERUM','HIBBING SERUM', 'MOFH SERUM', 'OPCC-SERUM','BLOOD VENOUS', 'LC-SER', 'SERUM (QUEST)').
Estimated glomerular filtration rate (eGFR)	Used to define chronic kidney disease. Calculated using the Modified Diet in Renal Disease equation using the serum creatinine value closest to the index date in the pre-index period. Defined using OMOP's mapping where LOINC_mapped in '33914-3' and

	Topography in ('PLASMA', 'SERUM',' BLOOD',' SER/PLA', 'BLOOD*', 'BLOOD.', 'VENOUS BLOOD', 'BLOOD, VENOUS', 'ARTERIAL BLOOD', 'PLAS', 'SER/PLAS').

Table S3. Characteristics of initiators and non-initiators of a PCSK9 inhibitor in the Veterans Health Administration among Veterans in the ASCVD cohort, overall and among subgroups.

Characteristic	Overall		History of CHD		History of cerebrovascular disease		History of PAD		Very high risk for future ASCVD		Current moderate- or high-intensity statin user	
	Initiator (n = 2,394)	Non-initiator (n = 9,576)	Initiator (n = 2,314)	Non-initiator (n = 8,204)	Initiator (n = 344)	Non-initiator (n = 1,430)	Initiator (n = 441)	Non-initiator (n = 1,676)	Initiator (n = 1,238)	Non-initiator (n = 3,693)	Initiator (n = 733)	Non-initiator (n = 4,022)
Index date calendar year 2019	1,544 (64.5)	6,176 (64.5)	1,487 (64.3)	5,288 (64.5)	241 (70.1)	942 (65.9)	297 (67.3)	1,070 (63.8)	785 (63.4)	2,402 (65.0)	487 (66.4)	2,611 (64.9)
Age, years mean (SD)	68.1 (8.6) ‡	70.5 (11.8) ‡	68.1 (8.7) ‡	70.5 (11.8) ‡	69.1 (7.6) ‡	71.2 (11.2) ‡	70.1 (6.4) ‡	73.2 (9.9) ‡	68.0 (8.6) ‡	72.1 (10.3) ‡	65.2 (9.6) ‡	70.6 (9.7) ‡
Age category, years												
<65	631 (26.4) ‡	2,454 (25.6) ‡	606 (26.2) ‡	2,088 (25.5) ‡	73 (21.2) ‡	342 (23.9) ‡	72 (16.3) ‡	287 (17.1) ‡	326 (26.3) ‡	764 (20.7) ‡	285 (38.9) ‡	922 (22.9) ‡
65 to <75	1,321 (55.2) ‡	4,034 (42.1) ‡	1,273 (55.0) ‡	3,432 (41.8) ‡	207 (60.2) ‡	617 (43.1) ‡	272 (61.7) ‡	747 (44.6) ‡	691 (55.8) ‡	1,631 (44.2) ‡	369 (50.3) ‡	1,952 (48.5) ‡
≥75	442 (18.5) ‡	3,088 (32.2) ‡	435 (18.8) ‡	2,684 (32.7) ‡	64 (18.6) ‡	471 (32.9) ‡	97 (22.0) ‡	642 (38.3) ‡	221 (17.9) ‡	1,298 (35.1) ‡	79 (10.8) ‡	1,148 (28.5) ‡
Female	115 (4.8)	480 (5.0)	105 (4.5)	393 (4.8)	22 (6.4)	75 (5.2)	20 (4.5)	61 (3.6)	59 (4.8)	152 (4.1)	34 (4.6)	147 (3.7)
Race-Ethnicity												
Non-Hispanic, White	1,975 (82.5) ‡	6,782 (70.8) ‡	1,918 (82.9) ‡	5,893 (71.8) ‡	284 (82.6) ‡	972 (68.0) ‡	365 (82.8) ‡	1,172 (69.9) ‡	1,015 (82.0) ‡	2,604 (70.5) ‡	559 (76.3)	2,916 (72.5)
Non-Hispanic, Black	248 (10.4) ‡	1,631 (17.0) ‡	230 (9.9) ‡	1,322 (16.1) ‡	38 (11.0) ‡	300 (21.0) ‡	50 (11.3) ‡	334 (19.9) ‡	132 (10.7) ‡	693 (18.8) ‡	100 (13.6)	656 (16.3)
Asian	3 (0.1) ‡	51 (0.5) ‡	3 (0.1) ‡	44 (0.5) ‡	2 (0.6) ‡	6 (0.4) ‡	0 (0.0) ‡	2 (0.1) ‡	3 (0.2) ‡	11 (0.3) ‡	3 (0.4)	20 (0.5)
Hispanic	73 (3.0) ‡	533 (5.6) ‡	69 (3.0) ‡	453 (5.5) ‡	11 (3.2) ‡	66 (4.6) ‡	10 (2.3) ‡	93 (5.5) ‡	44 (3.6) ‡	190 (5.1) ‡	31 (4.2)	222 (5.5)
Other	29 (1.2) ‡	176 (1.8) ‡	28 (1.2) ‡	143 (1.7) ‡	4 (1.2) ‡	35 (2.4) ‡	6 (1.4) ‡	27 (1.6) ‡	19 (1.5) ‡	69 (1.9) ‡	11 (1.5)	66 (1.6)
Missing	66 (2.8) ‡	403 (4.2) ‡	66 (2.9) ‡	349 (4.3) ‡	5 (1.5) ‡	51 (3.6) ‡	10 (2.3) ‡	48 (2.9) ‡	25 (2.0) ‡	126 (3.4) ‡	29 (4.0)	142 (3.5)
Median area-level income												
Q1 ($0 - $41,757)	531 (22.2) ‡	2,461 (25.7) ‡	511 (22.1) ‡	2,080 (25.4) ‡	90 (26.2)	392 (27.4)	98 (22.2) ‡	481 (28.7) ‡	287 (23.2) ‡	1,019 (27.6) ‡	159 (21.7) ‡	1,073 (26.7) ‡
Q2 ($41,758 - $51,357)	563 (23.5) ‡	2,430 (25.4) ‡	543 (23.5) ‡	2,085 (25.4) ‡	85 (24.7)	358 (25.0)	113 (25.6) ‡	443 (26.4) ‡	294 (23.7) ‡	981 (26.6) ‡	199 (27.1) ‡	1,023 (25.4) ‡
Q3 ($51,363 - $64,870)	645 (26.9) ‡	2,348 (24.5) ‡	627 (27.1) ‡	2,028 (24.7) ‡	79 (23.0)	347 (24.3)	116 (26.3) ‡	409 (24.4) ‡	321 (25.9) ‡	889 (24.1) ‡	187 (25.5) ‡	995 (24.7) ‡
Q4 ($64,878 - $212,394)	655 (27.4) ‡	2,337 (24.4) ‡	633 (27.4) ‡	2,011 (24.5) ‡	90 (26.2)	333 (23.3)	114 (25.9) ‡	343 (20.5) ‡	336 (27.1) ‡	804 (21.8) ‡	188 (25.6) ‡	931 (23.1) ‡
Health insurance	2,001 (83.7)	7,921 (83.0)	1,941 (84.0)	6,833 (83.5)	292 (85.1)	1,168 (82.0)	398 (90.7) ‡	1,451 (86.8) ‡	1,038 (84.0)	3,107 (84.4)	570 (77.8) ‡	3,350 (83.5) ‡
Priority group												
1	1,159 (48.5) ‡	3,643 (38.2) ‡	1,117 (48.4)	3,180 (38.9)	175 (51.2) ‡	540 (37.9) ‡	235 (53.4) ‡	607 (36.3) ‡	600 (48.5) ‡	1,355 (36.8) ‡	391 (53.4) ‡	1,694 (42.2) ‡
2 to 8	1,229 (51.5) ‡	5,902 (61.8) ‡	1,191 (51.6)	5,002 (61.1)	167 (48.8) ‡	883 (62.1) ‡	205 (46.6) ‡	1,066 (63.7) ‡	636 (51.5) ‡	2,326 (63.2) ‡	341 (46.6) ‡	2,320 (57.8) ‡
VISN Region												
Northeast	692 (28.9) ‡	2,607 (27.2) ‡	668 (28.9) ‡	2,239 (27.3) ‡	92 (26.7)	360 (25.2)	151 (34.2) ‡	527 (31.4) ‡	370 (29.9) ‡	1,052 (28.5) ‡	193 (26.3) ‡	1,133 (28.2) ‡

Southeast	1,010 (42.2) ‡	3,691 (38.5) ‡	972 (42.0) ‡	3,183 (38.8) ‡	155 (45.1)	578 (40.4)	179 (40.6) ‡	631 (37.6) ‡	525 (42.4) ‡	1,420 (38.5) ‡	341 (46.5) ‡	1,563 (38.9) ‡
Continental	462 (19.3) ‡	1,845 (19.3) ‡	450 (19.4) ‡	1,584 (19.3) ‡	62 (18.0)	270 (18.9)	77 (17.5) ‡	292 (17.4) ‡	228 (18.4) ‡	695 (18.8) ‡	131 (17.9) ‡	785 (19.5) ‡
Pacific	230 (9.6) ‡	1,433 (15.0) ‡	224 (9.7) ‡	1,198 (14.6) ‡	35 (10.2)	222 (15.5)	34 (7.7) ‡	226 (13.5) ‡	115 (9.3) ‡	526 (14.2) ‡	68 (9.3) ‡	541 (13.5) ‡
Current smoking	429 (17.9) ‡	1,552 (16.2) ‡	417 (18.0) ‡	1,293 (15.8) ‡	81 (23.5)	254 (17.8) ‡	124 (28.1) ‡	383 (22.9) ‡	278 (22.5)	780 (21.1)	167 (22.8) ‡	736 (18.3) ‡
Comorbidities												
Diabetes	1,220 (51.0) ‡	4,019 (42.0) ‡	1,175 (50.8) ‡	3,469 (42.3) ‡	209 (60.8) ‡	630 (44.1) ‡	273 (61.9) ‡	854 (51.0) ‡	690 (55.7) ‡	1,786 (48.4) ‡	359 (49.0)	1,991 (49.5)
Hypertension	2,179 (91.0) ‡	8,080 (84.4) ‡	2,109 (91.1) ‡	6,947 (84.7) ‡	325 (94.5) ‡	1,263 (88.3) ‡	419 (95.0) ‡	1,518 (90.6) ‡	1,188 (96.0) ‡	3,482 (94.3) ‡	666 (90.9)	3,656 (90.9)
Chronic kidney disease	1,050 (43.9) ‡	3,833 (40.0) ‡	1,016 (43.9) ‡	3,298 (40.2) ‡	186 (54.1) ‡	685 (47.9) ‡	248 (56.2) ‡	829 (49.5) ‡	617 (49.8)	1,829 (49.5)	298 (40.7)	1,738 (43.2)
Heart failure	535 (22.3) ‡	1,377 (14.4) ‡	531 (22.9) ‡	1,300 (15.8) ‡	96 (27.9)	222 (15.5) ‡	140 (31.7) ‡	337 (20.1) ‡	391 (31.6) ‡	746 (20.2) ‡	172 (23.5) ‡	724 (18.0) ‡
Familial hypercholesterolemia	181 (7.6) ‡	27 (0.3) ‡	177 (7.6) ‡	26 (0.3) ‡	16 (4.7) ‡	3 (0.2) ‡	21 (4.8) ‡	2 (0.1) ‡	87 (7.0) ‡	11 (0.3) ‡	90 (12.3) ‡	15 (0.4) ‡
Very high-risk for ASCVD events	1,238 (51.7) ‡	3,693 (38.6) ‡	1,166 (50.4) ‡	2,479 (30.2) ‡	324 (94.2)	1,302 (91.0)	438 (99.3) ‡	1,601 (95.5) ‡	1,283 (100)	3,693 (100)	413 (56.3) ‡	1,735 (43.1) ‡
Statin use												
Never	131 (5.5) ‡	1,720 (18.0) ‡	125 (5.4) ‡	1,459 (17.8) ‡	7 (2.0) ‡	168 (11.7) ‡	11 (2.5) ‡	191 (11.4) ‡	37 (3.0) ‡	365 (9.9) ‡	0	0
Former	1,436 (60.0) ‡	3,509 (36.6) ‡	1,383 (59.8) ‡	2,984 (36.4) ‡	227 (66.0) ‡	561 (39.2) ‡	278 (63.0) ‡	663 (39.6) ‡	743 (60.0) ‡	1,448 (39.2) ‡	0	0
Current - Low intensity	94 (3.9) ‡	325 (3.4) ‡	93 (4.0) ‡	259 (3.2) ‡	9 (2.6) ‡	59 (4.1) ‡	19 (4.3) ‡	73 (4.4) ‡	45 (3.6) ‡	145 (3.9) ‡	0	0
Current - Moderate-high intensity	733 (30.6) ‡	4,022 (42.0) ‡	713 (30.8) ‡	3,502 (42.7) ‡	101 (29.4) ‡	642 (44.9) ‡	133 (30.2) ‡	749 (44.7) ‡	413 (33.4) ‡	1,735 (47.0) ‡	733 (100)	4,022 (100)
Use of ezetimibe												
Never or Former	1,380 (57.6) ‡	9,472 (98.9) ‡	1,327 (57.3) ‡	8,103 (98.8) ‡	201 (58.4) ‡	1,411 (98.7) ‡	235 (53.3) ‡	1,654 (98.7) ‡	677 (54.7) ‡	3,649 (98.8) ‡	360 (49.1) ‡	3,974 (98.8) ‡
Current	1,014 (42.4) ‡	104 (1.1) ‡	987 (42.7) ‡	101 (1.2) ‡	143 (41.6) ‡	19 (1.3) ‡	206 (46.7) ‡	22 (1.3) ‡	561 (45.3) ‡	44 (1.2) ‡	373 (50.9) ‡	48 (1.2) ‡
LDL-C (mg/dL), median (IQR)	141.0 (116.0, 169.0) ‡	96.0 (82.0, 119.0) ‡	140.0 (116.0, 168.0) ‡	96.0 (82.0, 118.7) ‡	144.0 (118.0, 170.0) ‡	97.0 (82.0, 120.0) ‡	140.0 (115.0, 165.0) ‡	94.0 (82.0, 113.0) ‡	139.0 (115.0, 166.0) ‡	95.0 (81.0, 116.2) ‡	135.0 (112.4, 164.0) ‡	90.0 (78.0, 108.0) ‡
LDL-C category, mg/dL												
70 to <100	301 (12.6) ‡	5,240 (54.7) ‡	297 (12.8) ‡	4,519 (55.1) ‡	39 (11.3) ‡	764 (53.4) ‡	50 (11.3) ‡	989 (59.0) ‡	162 (13.1) ‡	2,127 (57.6) ‡	121 (16.5) ‡	2,629 (65.4) ‡
100 to <130	611 (25.5) ‡	2,698 (28.2) ‡	599 (25.9) ‡	2,289 (27.9) ‡	88 (25.6) ‡	413 (28.9) ‡	126 (28.6) ‡	450 (26.8) ‡	331 (26.7) ‡	979 (26.5) ‡	207 (28.2) ‡	943 (23.4) ‡
130 to <190	1,168 (48.8) ‡	1,519 (15.9) ‡	1,126 (48.7) ‡	1,295 (15.8) ‡	169 (49.1) ‡	234 (16.4) ‡	213 (48.3) ‡	216 (12.9) ‡	592 (47.8) ‡	543 (14.7) ‡	302 (41.2) ‡	416 (10.3) ‡
≥190	314 (13.1) ‡	119 (1.2) ‡	292 (12.6) ‡	101 (1.2) ‡	48 (14.0) ‡	19 (1.3) ‡	52 (11.8) ‡	21 (1.3) ‡	153 (12.4) ‡	44 (1.2) ‡	103 (14.1) ‡	34 (0.8) ‡

Numbers are expressed as number (percentage) unless otherwise indicated.

ASCVD: atherosclerotic cardiovascular disease; CHD: coronary heart disease; IQR: interquartile range; LDL-C: low density lipoprotein cholesterol; PAD: peripheral artery disease; PCSK9: Proprotein convertase subtilisin/kexin type 9; SD: standard deviation; VISN: Veterans Integrated Service Network. *Defined as a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions based on the presence of at least one of the following: age ≥ 65 years, heterozygous familial hypercholesterolemia, history of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s), diabetes, hypertension, chronic kidney disease (eGFR 15-59 mL/min/1.73m2), current smoking, LDL-C ≥ 100 mg/dL despite maximally tolerated statin therapy and ezetimibe, or congestive heart failure. ‡ P value <0.05 for comparison between initiators and non-initiators.

Table S4. Odds ratios for initiating a PCSK9 inhibitor associated with patient characteristics among Veterans in the ASCVD cohort in select subgroups.

Characteristics	Sub-group (N for initiators / non-initiators)				
	History of CHD	History of cerebrovascular disease	History of PAD	Very high risk for future ASCVD	Taking moderate/high intensity statin
	N, initiators / non-initiators 2,314/8,204	N, initiators / non-initiators 344/1,430	N, initiators / non-initiators 441/1,674	N, initiators / non-initiators 1,238/3,693	N, initiators / non-initiators 733/4,022
Age category, years					
<65	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
65 to <75	1.38 (1.10, 1.73)	0.72 (0.04, 12.24)	4.34 (0.81, 23.30)	1.32 (0.81, 2.16)	0.80 (0.44, 1.44)
>=75	0.65 (0.49, 0.85)	0.11 (0.00, 3.80)	1.06 (0.16, 6.85)	0.37 (0.21, 0.64)	0.28 (0.12, 0.62)
Female	0.62 (0.42, 0.91)	7.89 (0.30, 208.72)	0.35 (0.04, 3.26)	1.18 (0.53, 2.64)	0.77 (0.23, 2.59)
Race-Ethnicity					
Non-Hispanic, White	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Non-Hispanic, Black	0.31 (0.24, 0.40)	0.08 (0.00, 2.93)	0.41 (0.08, 2.23)	0.32 (0.19, 0.53)	0.34 (0.17, 0.68)
Asian	0.05 (0.01, 0.26)	3.21 (0.00, I)	*	0.06 (0.00, 1.21)	0.01 (0.00, 0.10)
Hispanic	0.42 (0.27, 0.64)	0.01 (0.00, 4.96)	0.17 (0.01, 2.27)	0.53 (0.22, 1.30)	0.24 (0.08, 0.70)
Other	0.22 (0.11, 0.46)	0.08 (0.00, 4.14)	0.01 (0.00, 2.66)	0.51 (0.14, 1.88)	0.43 (0.08, 2.32)
Missing	0.78 (0.51, 1.18)	0.00 (0.00, 0.52)	28.12 (0.14, 5725.11)	0.99 (0.35, 2.79)	0.58 (0.21, 1.60)
Median area-level income					
Q1 ($0 - $41,757)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Q2 ($41,758 - $51,357)	1.03 (0.82, 1.29)	5.11 (0.55, 47.77)	0.41 (0.08, 2.16)	1.11 (0.69, 1.78)	1.64 (0.92, 2.92)
Q3 ($51,363 - $64,870)	1.19 (0.95, 1.50)	1.22 (0.25, 5.95)	0.37 (0.08, 1.71)	1.05 (0.64, 1.70)	1.64 (0.89, 3.02)
Q4 ($64,878 - $212,394)	1.29 (1.02, 1.62)	3.30 (0.38, 28.90)	0.62 (0.15, 2.58)	1.22 (0.75, 1.97)	1.65 (0.87, 3.14)
Health insurance					
No	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Yes	1.13 (0.88, 1.45)	0.19 (0.01, 3.97)	0.30 (0.05, 1.74)	1.10 (0.65, 1.85)	1.10 (0.60, 2.03)
Priority group					
1	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
2 to 8	0.88 (0.75, 1.04)	0.21 (0.02, 2.00)	0.40 (0.15, 1.08)	0.87 (0.61, 1.23)	0.81 (0.52, 1.28)
VISN region					
Northeast	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Southeast	1.00 (0.82, 1.21)	1.75 (0.28, 10.96)	2.83 (0.76, 10.58)	0.92 (0.61, 1.40)	1.18 (0.72, 1.94)
Continental	0.80 (0.63, 1.01)	0.27 (0.03, 2.54)	0.22 (0.04, 1.24)	0.67 (0.40, 1.10)	0.83 (0.45, 1.54)
Pacific	0.58 (0.43, 0.77)	0.16 (0.01, 4.24)	0.18 (0.04, 0.94)	0.43 (0.23, 0.79)	0.39 (0.17, 0.91)
Smoking status					
Never/former	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Current	0.84 (0.67, 1.05)	0.09 (0.00, 1.56)	2.78 (0.78, 9.90)	0.82 (0.55, 1.21)	0.85 (0.49, 1.48)
Comorbidities					
Diabetes	1.47 (1.25, 1.74)	3.11 (0.49, 19.86)	1.92 (0.63, 5.83)	1.39 (1.01, 1.93)	0.95 (0.60, 1.50)
Hypertension	1.80 (1.38, 2.34)	1.20 (0.02, 63.61)	3.22 (0.56, 18.52)	1.08 (0.54, 2.16)	1.28 (0.64, 2.56)
Chronic kidney disease	1.08 (0.91, 1.28)	3.72 (0.47, 29.40)	0.71 (0.24, 2.13)	1.20 (0.85, 1.67)	1.58 (1.01, 2.48)
Heart failure	1.62 (1.31, 2.00)	0.47 (0.06, 3.80)	1.93 (0.52, 7.24)	1.50 (1.01, 2.23)	1.63 (0.96, 2.78)

Familial hypercholesterolemia	40.65 (20.69, 79.87)	725.49 (0.55, 953666.2)	3453849 (0.00, I)	12.26 (3.43, 43.84)	10.13 (2.15, 47.70)
History of CHD	*	16.76 (1.11, 253.01)	11.30 (1.98, 64.39)	4.76 (2.74, 8.26)	5.35 (1.72, 16.68)
Prior coronary revascularization	1.31 (1.10, 1.56)	10.35 (0.70, 152.75)	2.24 (0.65, 7.68)	2.15 (1.47, 3.16)	1.33 (0.86, 2.06)
Cerebrovascular disease	1.25 (0.96, 1.63)	*	1.82 (0.62, 5.35)	0.95 (0.65, 1.40)	1.03 (0.57, 1.84)
Peripheral artery disease	1.25 (0.98, 1.58)	3.44 (0.60, 19.61)	*	0.89 (0.63, 1.25)	1.14 (0.62, 2.11)
Statin use					
Never	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	*
Former	2.42 (1.82, 3.22)	41.73 (0.76, 2296.31)	1.29 (0.18, 9.20)	1.33 (0.64, 2.73)	*
Current - Low intensity	2.60 (1.59, 4.27)	14.23 (0.09, 2276.91)	1.91 (0.06, 63.39)	0.94 (0.31, 2.84)	*
Current - Moderate-high intensity	1.24 (0.91, 1.67)	3.27 (0.10, 111.17)	0.17 (0.02, 1.71)	0.73 (0.35, 1.53)	*
Use of ezetimibe					
Never or Former	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Current	70.12 (49.49, 99.34)	78.43 (3.28, 1876.54)	59.08 (8.63, 404.27)	42.77 (22.79, 80.28)	174.86 (60.00, 509.61)
LDL-c category, mg/dL					
70 to <100	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
100 to <130	3.43 (2.76, 4.25)	22.30 (1.33, 372.40)	13.17 (2.97, 58.33)	4.01 (2.60, 6.20)	6.17 (3.60, 10.56)
130 to <190	14.38 (11.49, 17.98)	62.30 (5.16, 752.63)	22.75 (5.59, 92.53)	16.01 (10.13, 25.32)	17.18 (9.78, 30.17)
LDL-c category, mg/dL					

All models adjusted for all variables in left-hand side of table.

ASCVD: atherosclerotic cardiovascular disease; CHD: coronary heart disease; LDL-C: low density lipoprotein cholesterol; PAD: peripheral artery disease; PCSK9: proprotein convertase subtilisin/kexin type 9; VISN: Veterans Integrated Service Network

* Not calculated due to low frequency or inclusion of variable in definition of subgroup.

Table S5. Characteristics of initiators and non-initiators of a PCSK9 inhibitor in the Veterans Health Administration among Veterans in the severe hypercholesterolemia cohort, overall and in subgroups.

Characteristic	Overall		Prior LDL-C ≥190 mg/dL		Prior LDL-C ≥220 mg/dL	
	Initiator (n = 245)	Non-initiator (n = 980)	Initiator (n = 240)	Non-initiator (n = 971)	Initiator (n = 157)	Non-initiator (n = 277)
Index date calendar year 2019	155 (63.3)	620 (63.3)	151 (62.9)	615 (63.3)	91 (58.0)	176 (63.5)
Age, years mean (SD)	60.7 (12.3) ‡	58.4 (13.0) ‡	60.5 (12.3) ‡	58.5 (13.0) ‡	59.0 (12.9)	59.1 (12.7)
Age category, years						
<65	128 (52.2) ‡	625 (63.8) ‡	127 (52.9) ‡	618 (63.6) ‡	90 (57.3)	173 (62.5)
65 to <75	92 (37.6) ‡	279 (28.5) ‡	89 (37.1) ‡	277 (28.5) ‡	53 (33.8)	80 (28.9)
≥75	25 (10.2) ‡	76 (7.8) ‡	24 (10.0) ‡	76 (7.8) ‡	14 (8.9)	24 (8.7)
Female	49 (20.0) ‡	136 (13.9) ‡	49 (20.4) ‡	136 (14.0) ‡	38 (24.2) ‡	39 (14.1) ‡
Race-Ethnicity						
Non-Hispanic, White	156 (63.7)	629 (64.2)	152 (63.3)	622 (64.1)	94 (59.9)	175 (63.2)
Non-Hispanic, Black	58 (23.7)	189 (19.3)	58 (24.2)	187 (19.3)	40 (25.5)	52 (18.8)
Asian	1 (0.4)	14 (1.4)	1 (0.4)	14 (1.4)	0 (0.0)	2 (0.7)
Hispanic	11 (4.5)	87 (8.9)	11 (4.6)	87 (9.0)	9 (5.7)	30 (10.8)
Other	5 (2.0)	11 (1.1)	5 (2.1)	11 (1.1)	4 (2.5)	4 (1.4)
Missing	14 (5.7)	50 (5.1)	13 (5.4)	50 (5.1)	10 (6.4)	14 (5.1)
Median area-level income						
Q1 ($0 - $43,173)	62 (25.3)	244 (24.9)	61 (25.4)	242 (24.9)	40 (25.5)	77 (27.8)
Q2 ($43,264 - $51,738)	47 (19.2)	259 (26.4)	46 (19.2)	258 (26.6)	33 (21.0)	61 (22.0)
Q3 ($51,740 - $66,333)	69 (28.2)	238 (24.3)	66 (27.5)	234 (24.1)	41 (26.1)	69 (24.9)
Q4 ($66,359 - $174,205)	67 (27.3)	239 (24.4)	67 (27.9)	237 (24.4)	43 (27.4)	70 (25.3)
Health insurance	156 (63.9)	562 (57.5)	152 (63.6)	557 (57.5)	95 (60.9)	151 (54.5)
Priority group						
1	125 (51.2)	445 (45.5)	122 (51.0)	440 (45.4)	81 (51.9)	130 (46.9)
2 to 8	119 (48.8)	534 (54.5)	117 (49.0)	530 (54.6)	75 (48.1)	147 (53.1)
VISN Region						
Northeast	63 (25.7) ‡	209 (21.3) ‡	62 (25.8) ‡	208 (21.4) ‡	37 (23.6) ‡	66 (23.8) ‡
Southeast	120 (49.0) ‡	394 (40.2) ‡	117 (48.8) ‡	389 (40.1) ‡	83 (52.9) ‡	105 (37.9) ‡
Continental	38 (15.5) ‡	206 (21.0) ‡	37 (15.4) ‡	203 (20.9) ‡	23 (14.6) ‡	65 (23.5) ‡
Pacific	24 (9.8) ‡	171 (17.4) ‡	24 (10.0) ‡	171 (17.6) ‡	14 (8.9) ‡	41 (14.8) ‡
Current smoking	31 (12.7)	139 (14.2)	31 (12.9)	137 (14.1)	19 (12.1)	46 (16.6)
Comorbidities						
Diabetes	96 (39.2) ‡	219 (22.3) ‡	93 (38.8) ‡	218 (22.5) ‡	57 (36.3)	83 (30.0)
Hypertension	164 (66.9) ‡	553 (56.4) ‡	161 (67.1) ‡	548 (56.4) ‡	104 (66.2)	176 (63.5)
Chronic kidney disease	72 (29.4) ‡	199 (20.3) ‡	70 (29.2) ‡	197 (20.3) ‡	48 (30.6)	71 (25.6)

Heart failure	5 (2.0)	8 (0.8)	5 (2.1)	8 (0.8)	3 (1.9)	3 (1.1)
Familial hypercholesterolemia	65 (26.5) ‡	11 (1.1) ‡	60 (25.0) ‡	2 (0.2) ‡	45 (28.7) ‡	0 (0.0) ‡
Very high-risk for ASCVD events*	2 (0.8) ‡	1 (0.1) ‡	2 (0.8) ‡	1 (0.1) ‡	2 (1.3)	0 (0.0)
Statin use						
Never	18 (7.3) ‡	194 (19.8) ‡	18 (7.5) ‡	188 (19.4) ‡	9 (5.7) ‡	33 (11.9) ‡
Former	156 (63.7) ‡	457 (46.6) ‡	152 (63.3) ‡	456 (47.0) ‡	94 (59.9) ‡	141 (50.9) ‡
Current - Low intensity	11 (4.5) ‡	18 (1.8) ‡	11 (4.6) ‡	18 (1.9) ‡	9 (5.7) ‡	6 (2.2) ‡
Current - Moderate-high intensity	60 (24.5) ‡	311 (31.7) ‡	59 (24.6) ‡	309 (31.8) ‡	45 (28.7) ‡	97 (35.0) ‡
Use of ezetimibe						
Never or Former	153 (62.4) ‡	972 (99.2) ‡	148 (61.7) ‡	963 (99.2) ‡	92 (58.6) ‡	273 (98.6) ‡
Current	92 (37.6) ‡	8 (0.8) ‡	92 (38.3) ‡	8 (0.8) ‡	65 (41.4) ‡	4 (1.4) ‡
LDL-C (mg/dL), median (IQR)	183.3 (159.0, 205.0) ‡	150.9 (124.4, 178.6) ‡	184.0 (159.0, 205.0) ‡	151.0 (124.6, 179.0) ‡	192.2 (163.0, 211.2) ‡	154.0 (126.0, 183.0) ‡
LDL-C category, mg/dL						
100 to <130	18 (7.3) ‡	299 (30.5) ‡	17 (7.1) ‡	296 (30.5) ‡	9 (5.7) ‡	79 (28.5) ‡
130 to <190	119 (48.6) ‡	513 (52.3) ‡	115 (47.9) ‡	507 (52.2) ‡	64 (40.8) ‡	149 (53.8) ‡
≥190	108 (44.1) ‡	168 (17.1) ‡	108 (45.0) ‡	168 (17.3) ‡	84 (53.5) ‡	49 (17.7) ‡

Numbers are expressed as number (percentage) unless otherwise indicated.

ASCVD: atherosclerotic cardiovascular disease; CHD: coronary heart disease; IQR: interquartile range; LDL-C: low density lipoprotein cholesterol; PAD: peripheral artery disease; PCSK9: Proprotein convertase subtilisin/kexin type 9; SD: standard deviation; VISN: Veterans Integrated Service Network

* Defined as a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions based on the presence of at least one of the following: age ≥ 65 years, heterozygous familial hypercholesterolemia, history of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s), diabetes, hypertension, chronic kidney disease (eGFR 15-59 mL/min/1.73m2), current smoking, LDL-C ≥ 100 mg/dL despite maximally tolerated statin therapy and ezetimibe, or congestive heart failure.

† Not calculated due to low frequency or inclusion of variable in definition of subgroup.

‡ P value <0.05 for comparison between initiators and non-initiators.

Table S6. Odds ratios for initiating a PCSK9 inhibitor associated with patient characteristics among Veterans in the severe hypercholesterolemia cohort in subgroups.

| Characteristics	Any LDL-C ≥190 mg/dL N, initiators / non-initiators 240/971	Any LDL-C ≥220 mg/dL N, initiators / non-initiators 157/275
Age category, years		
<65	1 (Ref)	1 (Ref)
65 to <75	1.52 (0.81, 2.86)	0.07 (0.00, 1.42)
>=75	2.98 (1.08, 8.22)	0.19 (0.00, 13.12)
Female	1.84 (0.94, 3.62)	4.41 (0.31, 62.10)
Race-Ethnicity		
Non-Hispanic, White	1 (Ref)	1 (Ref)
Non-Hispanic, Black	0.80 (0.42, 1.52)	0.15 (0.01, 1.58)
Asian	0.15 (0.00, 8.35)	Undefined
Hispanic	0.30 (0.09, 1.06)	0.07 (0.00, 3.99)
Other	0.88 (0.10, 8.09)	5.45 (0.00, 1.9057E8)
Median area-level income		
Q1 ($0 - $43,173)	1 (Ref)	1 (Ref)
Q2 ($43,264 - $51,738)	0.44 (0.19, 1.03)	0.05 (0.00, 1.45)
Q3 ($51,740 - $66,333)	1.16 (0.54, 2.49)	0.38 (0.03, 4.45)
Q4 ($66,359 - $174,205)	0.88 (0.40, 1.92)	0.10 (0.01, 1.76)
Health insurance		
No	1 (Ref)	1 (Ref)
Yes	0.89 (0.50, 1.57)	2.72 (0.30, 24.28)
Priority group		
1	1 (Ref)	1 (Ref)
2 to 8	0.91 (0.52, 1.60)	8.12 (0.70, 93.60)
VISN region		
Northeast	1 (Ref)	1 (Ref)
Southeast	0.92 (0.46, 1.87)	1.44 (0.12, 16.82)
Continental	0.59 (0.26, 1.34)	0.31 (0.02, 4.05)
Pacific	0.53 (0.23, 1.22)	11.91 (0.39, 366.31)
Smoking status		
Never/former	1 (Ref)	1 (Ref)
Current	0.82 (0.37, 1.82)	2.08 (0.18, 23.66)
Comorbidities		
Diabetes	1.65 (0.93, 2.91)	3.50 (0.51, 23.90)
Hypertension	1.21 (0.68, 2.16)	2.84 (0.33, 24.85)
Chronic kidney disease	2.11 (1.14, 3.91)	0.72 (0.09, 5.58)
Heart failure	1.70 (0.22, 13.09)	375.01 (0.19, 723852.2)
Familial hypercholesterolemia	848.27 (68.12, 10562.53)	Undefined
Statin use		
Never	1 (Ref)	1 (Ref)
Former	3.31 (1.50, 7.32)	2.18 (0.07, 72.29)
Current - Low intensity	4.90 (0.60, 40.43)	8.10 (0.03, 1934.27)

Current - Moderate-high intensity	1.65 (0.65, 4.19)	5.87 (0.17, 205.35)
Use of ezetimibe		
Never or Former	1 (Ref)	1 (Ref)
Current	79.95 (26.53, 240.92)	485.23 (16.21, 14521.98)
LDL-c category, mg/dL		
100 to <130	1 (Ref)	1 (Ref)
130 to <190	3.66 (1.54, 8.66)	14.34 (1.02, 202.09)
>=190	21.70 (8.34, 56.44)	1456.56 (8.77, 241873.7)

All models adjusted for all variables in left-hand side of table.

ASCVD: atherosclerotic cardiovascular disease; CHD: coronary heart disease; LDL-C: low density lipoprotein cholesterol; PAD: peripheral artery disease; PCSK9: proprotein convertase subtilisin/kexin type 9; VISN: Veterans Integrated Service Network

* Not calculated due to low frequency or inclusion of variable in definition of subgroup.

Figure S1. Flow-chart showing the application of inclusion and exclusion criteria for initiators of a PCSK9 inhibitor in the Veterans Health Administration.
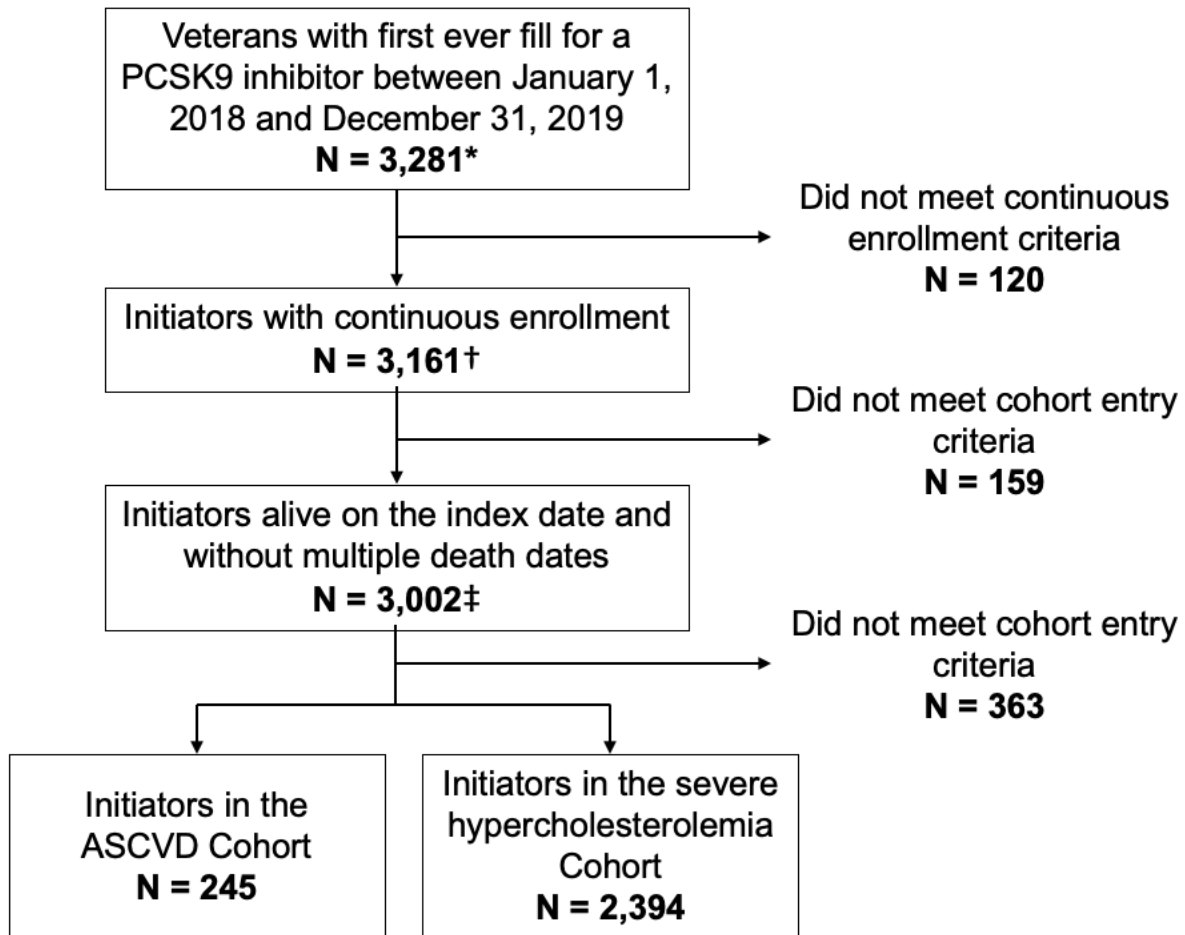
*Veterans with a fill for a PCSK9i before January 1, 2018 were excluded.

† Continuous enrollment is defined as at least one outpatient or inpatient encounter in both the first and last 6 months of the one-year pre-index period.

‡ For each Veteran who initiated a PCSK9i between January 1, 2018, and December 31, 2019, the index date was defined as the date of their earliest PCSK9i fill between January 1, 2018, and December 31, 2019.

ASCVD: Atherosclerotic cardiovascular disease, PCKS9i: Proprotein convertase subtilisin/kexin type 9 inhibitors.

Veterans who initiated a PCSK9i between January 1, 2018 and December 31, 2019 were matched 1:4 to Veterans who did not have a fill for a PCSK9i on or before December 31, 2019 (i.e., non-initiators). For each non-initiator, an index date was randomly selected within the calendar quarter corresponding to their matched initiator's index date.

Figure S2. Distribution of most recent LDL-C levels in the one-year pre-index period among PCSK9 inhibitor initiators and non-initiators among Veterans in the ASCVD cohort, by subgroup.
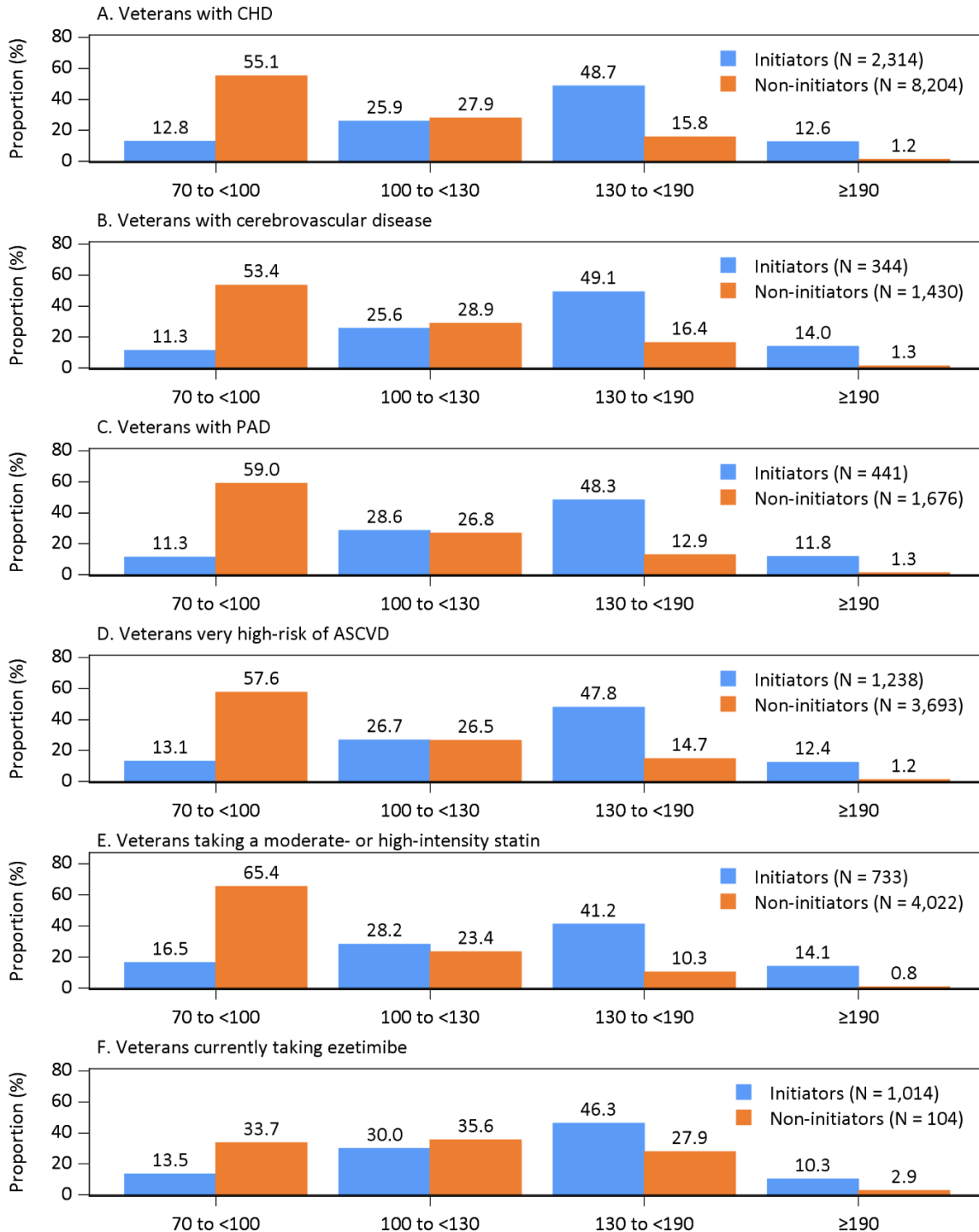
We used LDL-C measurements within 365 days before each Veteran's index date, inclusive. For Veterans with multiple LDL-C measurements during this time period, we used the one closest to their index date (i.e., the most recent). With CHD (Panel A), with cerebrovascular disease (Panel B), with PAD (Panel C), with very high-risk for ASCVD (Panel D), taking moderate or high intensity statin (Panel E), or taking ezetimibe (Panel F). ASCVD: atherosclerotic cardiovascular disease; CHD: coronary heart disease; LDL-C: low density lipoprotein cholesterol; PAD: peripheral artery disease; PCSK9: proprotein convertase subtilisin/kexin type 9.

Figure S3. Distribution of most recent LDL-C levels in the one-year pre-index period among PCSK9 inhibitor initiators and non-initiators among Veterans in the severe hypercholesterolemia cohort, by subgroup.
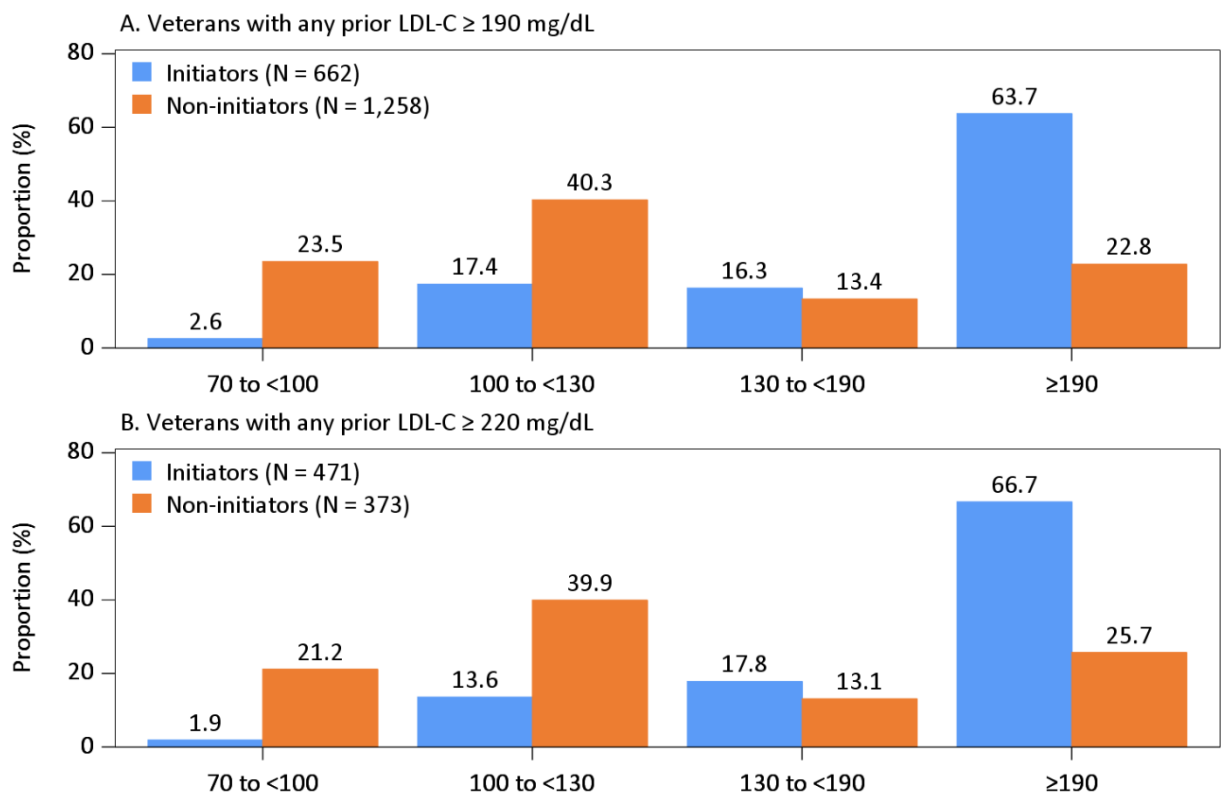
We used LDL-C measurements within 365 days before each Veteran's index date, inclusive. For Veterans with multiple LDL-C measurements during this time period, we used the one closest to their index date (i.e., the most recent). Caption: With any prior LDL-C ≥190 mg/dL (Panel A), or with any prior LDL-C ≥220 mg/dL (Panel B). Legend: ASCVD: atherosclerotic cardiovascular disease; LDL-C: low density lipoprotein cholesterol; PCSK9: proprotein convertase subtilisin/kexin type 9.