Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitor Therapy

Payer Approvals and Rejections, and Patient Characteristics for Successful Prescribing

BACKGROUND: Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) are a novel class of medications for patients with familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease requiring additional lipid lowering beyond dietary measures and statin use. Because of the drugs' high cost, rates of prescription approval by payers may be low. We aimed to identify payer approval and rejection rates for PCSK9i prescriptions and the potential factors influencing these rates.

METHODS: This is a retrospective, descriptive cohort study using nationwide pharmacy claims linked to electronic medical records from a nationwide data warehouse. The data set includes >220 million patients from all 50 states and all payer types with 5140 distinct health plans. PCSK9i prescriptions were submitted for 51 466 patients in the pharmacy data set. The main outcome was approval or rejection of PCSK9i prescription claims. Factors associated with approval and rejection of these medications in the United States were assessed.

RESULTS: Among patients who were prescribed a PCSK9i, 47.0% were approved for coverage by the payer. Variables that were associated with PCSK9i approval included age >65 years ($P<0.01$), history of atherosclerotic cardiovascular disease ($P<0.01$), prescription by a cardiologist or nonprimary care provider ($P<0.01$), statin intolerance ($P=0.03$), longer statin duration ($P=0.01$), and noncommercial payers ($P<0.01$). Higher low-density lipoprotein cholesterol levels were not associated with higher approval rates. Commercial third-party payers had the lowest approval rates (24.4%) and Medicare had the highest (60.9%).

CONCLUSIONS: Rates of approval for PCSK9i therapy are low, even for patients who appear to meet labeled indications. Although a combination of clinical characteristics increases the likelihood of approval, payer type is the most significant factor.

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Key Words: insurance claim review ■ insurance coverage ■ lipid-lowering therapy ■ PCSK-9 inhibitors

Clinical Perspective

What Is New?

- This is the largest study to date of which we are aware to examine payer approvals and rejections of proprotein convertase subtilisin/kexin type 9 inhibitor therapy and patient characteristics associated with successful prescribing for patients, including approvals, rejections, medication abandonment by patients, out-of-pocket amounts, and time to approval or rejection.
- The study presents the corresponding patient clinical characteristics including low-density lipoprotein cholesterol values and stratification by primary and secondary prevention based on observed atherosclerotic cardiovascular disease.

What Are the Clinical Implications?

- In this large, national study of proprotein convertase subtilisin/kexin type 9 inhibitor prescribing, less than half of all prescribed patients received payer approval, including patients with a history of atherosclerotic cardiovascular disease and those with markedly elevated low-density lipoprotein cholesterol levels.
- Although a combination of clinical characteristics moderately influenced approval rates, the most significant factor associated with approval was payer type.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease that facilitates the degradation of receptors for low-density lipoprotein cholesterol (LDL-C) within hepatocytes.[1] Gain-of-function *PCSK9* alleles are associated with diminished clearance of LDL-C and consequently high circulating LDL-C and increased cardiovascular risk,[2,3] whereas loss-of-function *PCSK9* alleles are associated with low LDL-C and decreased cardiovascular risk.[4] Given the proven benefit of LDL-C reduction in lowering rates of major cardiovascular events,[5] PCSK9 inhibitors (PCSK9i) have been developed as a novel class of medications for use in high-risk populations.[6,7] Two monoclonal antibodies that inactivate PCSK9, alirocumab and evolocumab, have been approved by the Food and Drug Administration (FDA) for use along with diet and maximally tolerated statin therapy in patients with familial hypercholesterolemia (FH) or clinical atherosclerotic cardiovascular disease (ASCVD) who require additional LDL-C lowering.[8,9] Alirocumab and evolocumab reduce LDL-C levels by up to 60% and may decrease major adverse cardiovascular events.[10,11]

However, alirocumab and evolocumab are significantly more expensive than other lipid-lowering therapies with an average cost of $14 300 per year.[12] These costs pose a significant challenge to healthcare payers, especially in light of the uncertain long-term clinical effectiveness of these drugs.[13] Consensus among professional societies on optimal LDL-C targets among those with ASCVD and FH is still evolving. Current prescriptions of these medications therefore typically require prior authorization by health insurance companies, leading to either approval or rejection. This process may raise additional barriers in the care of patients who would most benefit from additional LDL-C lowering with new therapies. Beyond small analyses and anecdotal reports, the rates of approval and rejection for patients, and the characteristics of patients who are successfully prescribed PCSK9 inhibitors in current clinical practice, are unknown.

Our primary objective was to use nationwide pharmacy claims linked to medical claims and electronic medical records to identify the rates of payer approval and rejection for patients prescribed PCSK9i therapy. We also evaluated the demographic and clinical characteristics of patients who were approved or rejected to assess healthcare provider and payer practices in relation to current FDA-approved indications for PCSK9i. We further assessed factors associated with successful payer approval and rejection for these medications in the United States.

METHODS

Study Design and Data Sources

This retrospective, observational, descriptive cohort study used healthcare claims and electronic medical records from the Symphony Health nationwide data warehouse. This data set includes both Health Insurance Portability and Accountability Act and Health Information Technology for Economic and Clinical Health compliant patient-level data from all 50 states and all payer types, including 5140 distinct health plans. The data warehouse includes ≈220 million active, unique patients with pharmacy claims, 170 million with medical claims, and 100 million with ambulatory electronic medical records. The data are used for a range of research studies by private and public agencies including the FDA and the Scientific Registry of Transplant Recipients. These data are focused on observing patients across healthcare providers and care sites over time, include all insurance types (commercial, Medicare, Medicaid, other third-party payers), and are patient centric and health plan agnostic.

Drug prescriptions were assessed from outpatient pharmacy claims, which included National Counsel for Prescription Drug Plans–formatted records with a complete life cycle of transactions from initial submission to a definitive event of approval or rejection per patient. Private practitioner claims (CMS1500) and hospital/facility claims (UB04) were used to identify patients' demographics, clinical characteristics, and diagnoses. LDL-C levels were extracted from electronic medical records. All patient-level records were linked across settings of care and longitudinally via a Health Insurance Portability

and Accountability Act–compliant, deidentified unique patient identifier. The data were verified as meeting the deidentified standard under the Health Insurance Portability and Accountability Act privacy rule Expert Determination §164.514(b)(1) by Scheuren Ruffner Consultants with a very low statistical risk of reidentification, and the certificate is on file at Symphony Health. Therefore, the study was not considered to be human subject research, and institutional review board review was not required. The Beth Israel Deaconess Medical Center institutional review board agreed with this determination.

Study inclusion criteria were patients ≥18 years of age with ≥1 submitted claims for a PCSK9i between July 2015 and August 2016, ≥1 private practitioner or facility medical claims between January 2010 and July 2015, and at least 1 LDL-C test result (≤400 mg/dL) between July 2015 and the patient's index date (Figure 1). Less than 1% of LDL-C values were observed at >400 mg/dL and were believed to potentially represent erroneous data. In total, the study cohort was represented by 451 individual health plans and pharmaceutical benefit management companies, which themselves may manage drug formularies and policies for several hundred health plans. A total of 49 US states and the District of Columbia were represented by the included health plans and benefit management companies (Table I in the online-only Data Supplement).

Continuous healthcare data capture of the study population during the study period was required as a proxy for enrollment, with at least 1 recorded prescription before the PCSK9i claim and 1 prescription following that claim between January 1, 2010, and the end of the study period.

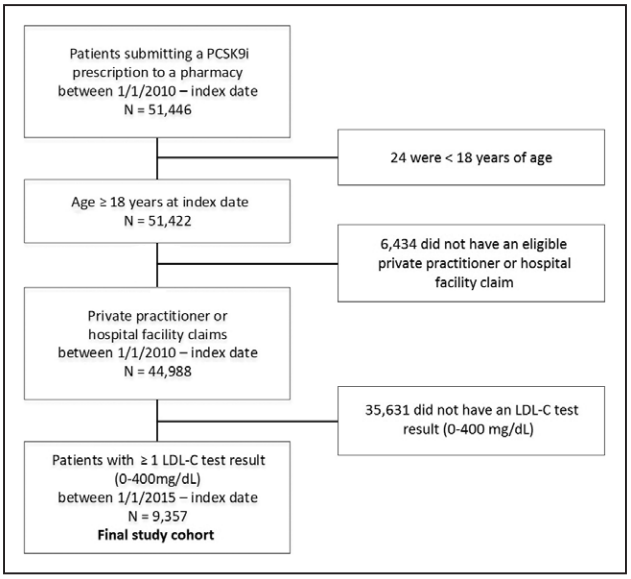

Figure 1. Selection of the study cohort.
Study inclusion criteria were patients ≥18 years of age with ≥1 submitted claims for a PCSK9i between July 2015 and August 2016, ≥1 private practitioner or facility medical claims between January 2010 and July 2015, and at least 1 LDL-C test result (≤400 mg/dL) between July 2015 and the patient's index date. LDL-C indicates low-density lipoprotein cholesterol; and PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.

End Points and Covariates

The primary end point was the percentage of patients approved or rejected for PCSK9i prescription therapy. Prescribed therapy was analyzed by using National Drug Codes. Medical histories were assessed for the identification of patient clinical characteristics using the *International Classification of Diseases, Ninth Revision* (*ICD-9*) and the *International Classification of Diseases, Tenth Revision* (*ICD-10*) and Current Procedural Terminology from private practitioner medical claims and from hospital facility claims submitted between January 2010 and July 2015. In addition, Diagnostic Related Groupings from hospital claims were converted and mapped to *ICD-9* and *ICD-10* codes. Clinical ASCVD was defined by ≥1 occurrences of any of the following: aortic and other aneurysms, cerebrovascular disease, coronary atherosclerosis/angina/old myocardial infarction, endovascular stent graft, ischemic stroke, myocardial infarction, peripheral arterial disease, transient ischemic attack, unstable angina, atherosclerosis of the arterial bed, status post–coronary artery bypass grafting/percutaneous coronary intervention, status post–carotid endarterectomy, and status post–carotid/vertebral/basilar stenting. Patients' diagnoses were then mapped to ≥1 indications for a PCSK9i. LDL-C test results were identified using Logical Observation Identifiers Names and Codes, and text queries were used as an added quality assurance step.

Statistical Analysis

The primary unit of analysis was the patient, each of whom had at least 1 PCSK9i claim submitted for approval. For the primary analysis of determining the percentage of patients approved or rejected for PCSK9i therapy, patients were assigned to 2 major, mutually exclusive groups based on their PCSK9i pharmacy submission outcome: approved and rejected (Figure I in the online-only Data Supplement). The approved cohort was defined as individuals who had at least one PCSK9i approved as a valid and compliant prescription (eg, included prior authorization) during the study period. For those approved, we additionally determined the subset percentage of those who actually purchased and took possession of the medication (approved/possessed), and those who abandoned (per processing terminology), ie, were approved but did not purchase or pick up the medication (approved/abandoned). The rejected cohort was defined as individuals whose PCSK9i claims had never been approved by the payers during the study period, and subsequently the only known claim status was rejected. For those with multiple payers, all payers must have rejected the claim for the patient to be labeled as rejected. A sensitivity analysis excluding all new patients submitting their first claim within 60 days of the end of the study period was conducted to account for prescriptions potentially under continuing review and adjudication. Patient responsibility amounts for approved/possessed and approved/abandoned were also recorded. Variability in rejection rates was calculated by payer for the highest-volume payers.

Patient demographics and clinical characteristics (eg, ASCVD status, statin intolerance as defined previously,[14] and prescriber specialty) between patients with approved and rejected claims were assessed for significant differences using χ^2 or *t* tests as appropriate, using a significance level of

α=0.05. Comparisons were also stratified by ASCVD diagnosis (primary or secondary prevention). A secondary analysis population consisted of patients who met all criteria, with the exception of the requirement for at least 1 test for LDL-C. Multivariable mixed-effects logistic regression was performed to identify patient characteristics and clinical criteria independently associated with final approval or rejection of PCSK9i therapy, with health plan or benefit management companies modeled as a random effect. The model included age, sex, physician specialty, history of ASCVD, LDL-C level, ezetimibe and statin use, payer type, and an interaction term between LDL level and statin use, as well.

RESULTS

Within the final study population of 9357 patients, 39.6% had no ASCVD diagnosis (primary preventative measures), and 60.4% had an ASCVD diagnosis (secondary preventative measures). Demographic and clinical history for all patients and for patients stratified by ASCVD diagnosis are shown in Table 1. In the total study population, 4397 (47.0%) were approved for PCSK9i therapy and 4960 (53.0%) were rejected (Table 2). The results of a sensitivity analysis excluding patients who submitted their first claim within 60 days of the end of the study period showed similar results (Table II in the online-only Data Supplement). Of those approved, 2844 (64.7%) took possession of the medication (approved/possessed) and 1553 (35.3%) did not purchase or receive the medication (approved/abandoned). For the highest volume of payers comprising ≈80% of the patients, rejection rates ranged from 2.4% to 92.7% (Figure II in the online-only Data Supplement). On average, the time from first submission to approval was 29 days, whereas time to rejection was 24 days. For the 451 health plans and pharmaceutical benefit management companies observed, the mean patient responsibility was $202.87±12.92 for approved/possessed patients in comparison with $478.83±27.32 for approved/abandoned patients.

Table 2 shows the demographics and clinical history for all patients either approved or rejected for PCSK9i therapy. Approved patients were more often older than 65 years of age, more often had a history of ASCVD, and more often were given a prescription by their cardiologist. Commercial payers and Medicaid had the lowest approval rates (24.4% and 31.2%, respectively), and Medicare had the highest (60.9%, $P<0.01$). As anticipated, nearly all patients (98.4%) who paid cash were approved. Approval rates were no different based on use of maximal statin therapy or use of statin/ezetimibe combination therapy.

The distribution of patients with approvals and rejections for PSCK9i therapy by LDL-C value proximal to the final disposition is shown in Figure 2 for patients with an ASCVD diagnosis (Figure 2A) or no ASCVD

Table 1. Demographic and Clinical Characteristics for All Patients (Study Population) and Stratified by ASCVD Diagnosis (Primary or Secondary Prevention)

Demographic and Clinical Characteristics	Patients Prescribed PCSK9i					
	All Patients		Diagnosis			
			Primary Prevention (No ASCVD Diagnosis)		Secondary Prevention (ASCVD Diagnosis)	
	n	%	n	%	n	%
9357	**100**	**3708**	**39.6**	**5649**	**60.4**	
65+ y of age	5609	59.9	2027	54.7	3582	63.4
Female	4714	50.4	2129	57.4	2585	45.8
Prescriber specialty						
Cardiologist	5564	59.5	1911	51.5	3653	64.7
Primary care (family medicine, internal medicine)	2514	26.9	1218	32.8	1296	22.9
Endocrinologist	378	4.0	208	5.6	170	3.0
Other	901	9.6	371	10.0	530	9.4
Mean LDL-C (mean of values over time)						
<70 mg/dL	546	5.8	171	4.6	375	6.6
71–100 mg/dL	1509	16.1	484	13.1	1025	18.1
100–129 mg/dL	2408	25.7	814	22.0	1594	28.2
130–159 mg/dL	2276	24.3	969	26.1	1307	23.1
160–189 mg/dL	1418	15.2	651	17.6	767	13.6
190–249 mg/dL	967	10.3	512	13.8	455	8.1
250–329 mg/dL	201	2.1	97	2.6	104	1.8
≥ 330 mg/dL	32	0.3	10	0.3	22	0.4
LDL-C value proximal to approval or last rejection						
<70 mg/dL	993	10.6	322	8.7	671	11.9
71–100 mg/dL	1430	15.3	458	12.4	972	17.2
100–129 mg/dL	1828	19.5	619	16.7	1209	21.4
130–159 mg/dL	2096	22.4	847	22.8	1249	22.1
160–189 mg/dL	1535	16.4	707	19.1	828	14.7
190–249 mg/dL	1177	12.6	618	16.7	559	9.9
250–329 mg/dL	256	2.7	122	3.3	134	2.4
≥330 mg/dL	42	0.4	15	0.4	27	0.5
Ezetimibe use (monotherapy or combination therapy within 12 mo of the index date)	1847	19.7	680	18.3	1167	20.7
Statin intensity (within 12 mo of the index date)						
High intensity	1430	15.3	706	19.0	1230	21.8
Medium/low intensity	1936	20.7	885	23.9	1317	23.3
Not on statin within 12 mo of index date	2202	23.5	2117	57.1	3102	54.9
No. of statins used (within 12 mo of index date)						
0	5219	55.8	2117	57.1	3102	54.9
1	3350	35.8	1272	34.3	2078	36.8
2	699	7.5	289	7.8	410	7.3
3	80	0.9	28	0.8	52	0.9
>3	9	0.1	2	0.1	7	0.1

(*Continued*)

Table 1. Continued

Demographic and Clinical Characteristics	Patients Prescribed PCSK9i					
	All Patients		Diagnosis			
			Primary Prevention (No ASCVD Diagnosis)		Secondary Prevention (ASCVD Diagnosis)	
Duration of statin use (mean within 12 mo of index date)						
0 mo	5219	55.8	2117	57.1	3102	54.9
>0–3 mo (up to 90 days)	2128	22.7	840	22.7	1288	22.8
3–6 mo (91–180 days)	549	5.9	215	5.8	334	5.9
>6 mo (181+ days)	1461	15.6	536	14.5	925	16.4
LDL-C level on statin therapy						
LDL-C >70 on max tolerated statin	2611	27.9	1043	28.1	3102	54.9
LDL-C >100 on max tolerated statin	2051	21.9	870	23.5	1288	22.8
LDL-C >130 on max tolerated statin	1463	15.6	199	5.4	334	5.9
LDL-C >70 on statin + ezetimibe	963	10.3	348	9.4	925	16.4
LDL-C >100 on statin + ezetimibe	767	8.2	292	7.9	3102	54.9
LDL-C >130 on statin + ezetimibe	527	5.6	86	2.3	1288	22.8
Not on statin therapy or patients with mean LDL-C ≤70	5219	55.8	2117	57.1	334	5.9
Statin-intolerant	3184	34.0	1230	33.2	1954	34.6
Payer type						
Medicare	4913	52.5	1713	46.2	3200	56.6
Commercial	3713	39.7	1679	45.3	2034	36.0
Medicaid	279	3.0	108	2.9	171	3.0
All other	326	3.5	141	3.8	185	3.3
Cash	126	1.3	67	1.8	59	1.0

ASCVD indicates atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; max, maximum; and PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.

diagnosis (Figure 2B). No clear relationship was observed between LDL-C and approval, with more than half of claims being rejected at every level of LDL-C. Even in cases (n=32) in which LDL-C levels were ≥330 mg/dL, 59.4% of patients were not approved for PCSK9i therapy.

After multivariable adjustment, the strongest factor associated with PCSK9i approval was payer type, with noncommercial (odds ratio [OR], 12.32; 95% confidence interval [CI], 7.09–21.39), cash payment (OR, 245.34; 95% CI, 63.16–952.97), and Medicare (OR, 5.37; 95% CI, 4.23–6.80) all having a higher likelihood of approval than commercial insurance (P<0.01). The approval rate for Medicaid was also higher than that of commercial insurance (OR, 1.31; 95% CI, 0.85–2.00), but this relationship was

Table 2. Differences Between PCSK9i Therapy Rejection or Approval for All Patients (n=9357)

Demographic and Clinical Characteristics	n	PCSK9i Approved	PCSK9i Rejected	P Value
		n=4397	n=4960	
Age, n (%)				<0.01
<65 y	3748	1261 (28.70)	2487 (50.10)	
65+ y	5609	3136 (71.30)	2473 (49.90)	
Sex, n (%)				0.18
Female	4714	2246 (51.10)	2466 (49.70)	
Male	4643	2149 (48.90)	2494 (50.30)	
Prescriber specialty, n (%)				
Cardiologist	5564	2770 (63.00)	2794 (56.30)	<0.01
Endocrinologist	378	156 (3.50)	222 (4.50)	0.03
PCP (FM, IM)	2514	1029 (23.40)	1485 (29.90)	<0.01
Other	901	442 (10.10)	459 (9.30)	0.20
Diagnoses, n (%)				
Primary prevention (no ASCVD diagnoses)	3708	1573 (35.80)	2135 (43.00)	<0.01
Secondary prevention (ASCVD diagnoses)	5649	2824 (64.20)	2825 (57.00)	<0.01
Mean LDL-C, n (%)				
<70 mg/dL	546	257 (5.80)	289 (5.80)	1.00
71–100 mg/dL	1509	702 (16.00)	807 (16.30)	0.71
100–129 mg/dL	2408	1197 (27.20)	1211 (24.40)	<0.01
130–159 mg/dL	2276	1079 (24.50)	1197 (24.10)	0.66
160–189 mg/dL	1418	648 (14.70)	770 (15.50)	0.30
190–249 mg/dL	967	409 (9.30)	558 (11.30)	0.11
250–329 mg/dL	201	92 (2.10)	109 (2.20)	0.78
≥ 330 mg/dL	32	13 (0.30)	19 (0.40)	0.59
LDL-C value proximal to approval or last rejection, n (%)				
<70 mg/dL	993	488 (11.10)	505 (10.20)	0.16
71–100 mg/dL	1430	677 (15.40)	753 (15.20)	0.79
100–129 mg/dL	1828	905 (20.60)	923 (18.60)	0.02
130–159 mg/dL	2096	998 (22.70)	1098 (22.10)	0.53
160–189 mg/dL	1535	681 (15.50)	854 (17.20)	0.03
190–249 mg/dL	1177	512 (11.60)	665 (13.40)	0.01
250–329 mg/dL	256	118 (2.70)	138 (2.80)	0.82
≥ 330 mg/dL	42	18 (0.40)	24 (0.50)	0.70
Ezetimibe use (within 12 mo of index date), n (%)				
Monotherapy or combination therapy	1847	900 (20.50)	947 (19.10)	0.10
Statin intensity (within 12 mo of index date), n (%)				
High intensity	1936	866 (19.70)	1070 (21.60)	0.03
Medium/low intensity	2202	1055 (24.00)	1147 (23.10)	0.34
Not on statin within 12 mo of index date	5219	2476 (56.30)	2743 (55.30)	0.34
No. of statins used (within 12 mo of index date), n (%)				
0 Statin use	5219	2476 (56.30)	2743 (55.30)	0.34

(*Continued*)

Table 2. Continued

Demographic and Clinical Characteristics	n	PCSK9i Approved n=4397	PCSK9i Rejected n=4960	*P* Value
1 Statin	3350	1577 (35.90)	1773 (35.70)	0.92
2 Statins	699	311 (7.10)	388 (7.80)	0.18
3 Statins	80	29 (0.70)	51 (1.00)	0.07
>3 Statins	9	4 (0.10)	5 (0.10)	1.00
Average duration of statin use (within 12 mo of index date), n (%)				
0 mo	5219	2476 (56.30)	2743 (55.30)	0.34
>0–3 mo (up to 90 days)	2128	936 (21.30)	1192 (24.00)	<0.01
3–6 mo (91–180 days)	549	254 (5.80)	295 (5.90)	0.76
>6 mo (181+ days)	1461	731 (16.60)	730 (14.70)	0.01
LDL-C level on statin therapy, n (%)				
LDL-C >70 on max tolerated statin	2611	1168 (26.60)	1443 (29.10)	0.01
LDL-C >100 on max tolerated statin	2051	911 (20.70)	1140 (23.00)	0.01
LDL-C >130 on max tolerated statin	1463	635 (14.40)	828 (16.70)	<0.01
LDL-C >70 on statin+ezetimibe	963	475 (10.80)	488 (9.80)	0.13
LDL-C >100 on statin+ezetimibe	767	378 (8.60)	389 (7.80)	0.20
LDL-C >130 on statin+ezetimibe	527	263 (6.00)	264 (5.30)	0.18
Not on statin therapy or patients with mean LDL-C ≤70	5783	2754 (62.60)	3029 (61.10)	0.13
Statin intolerant, n (%)				
Statin intolerant	3184	1445 (32.90)	1739 (35.10)	0.03
Payer type, n (%)				
Commercial	3713	907 (20.60)	2806 (56.60)	<0.01
Medicare	4913	2992 (68.00)	1921 (38.70)	<0.01
Medicaid	279	87 (2.00)	192 (3.90)	<0.01
All other	326	287 (6.50)	39 (0.80)	<0.01
Cash	126	124 (2.80)	2 (0.00)	<0.01

ASCVD indicates atherosclerotic cardiovascular disease;
FM, family medicine;
IM, internal medicine;
LDL-C, low-density lipoprotein cholesterol; max, maximum; PCP, primary care physician; and
PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.

not statistically significant (*P*=0.20). In addition, age >65 years (OR, 1.20; 95% CI, 1.05–1.38; *P*=0.01), prior ASVCD (OR, 1.22; 95% CI, 1.10–1.36; *P*<0.01), prescription by a cardiologist (OR, 1.61; 95% CI, 1.42–1.81; *P*<0.01) or nonprimary care provider, and longer statin duration (OR, 1.20; 95% CI, 1.01–1.42 for 181+ day duration; *P*=0.03) were associated with approval (Figure 3). Statin intolerance was associated with lower likelihood of claim approval. The adjusted model also showed that the most recent LDL-C value

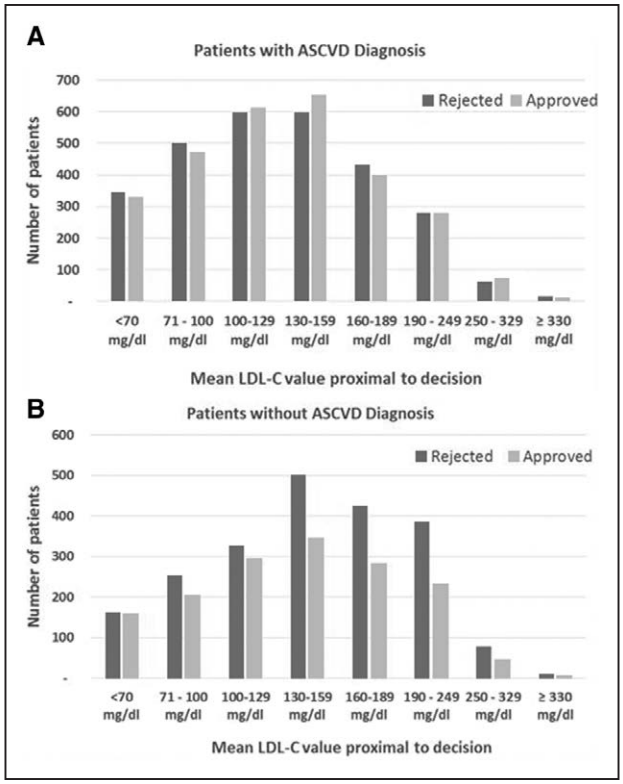

Figure 2. Distribution of approvals or rejections for PCSK9i therapy by mean LDL-C level proximal to the decision for patients with an ASCVD diagnosis (A) or no ASCVD diagnosis (B).
No clear relationship was observed between LDL-C and approval, with more than half of claims being rejected at every level of LDL-C. ASCVD indicates atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; and PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.

was not associated with any difference in approval, and this was true independent of whether or not patients were on high-intensity statins.

DISCUSSION

During the study period of July 2015 through August 2016, representing the first 12 months after FDA approval of the PCSK9 inhibitors alirocumab and evolocumab commercial availability, less than half (47.0%) of patients who were prescribed PCSK9i therapy were approved by healthcare payers. Our analysis included both approvals and rejections in conjunction with patients' medical and clinical characteristics, and included data from 49 states across all payer types. Rates of rejection were high for all clinical groups studied including those with ASCVD, with high LDL-C, and on statin therapy. Coverage by a noncommercial payer was the factor most strongly associated with approval, with 61.8% of these patients being approved, and only 24.4% of patients covered by commercial payers being

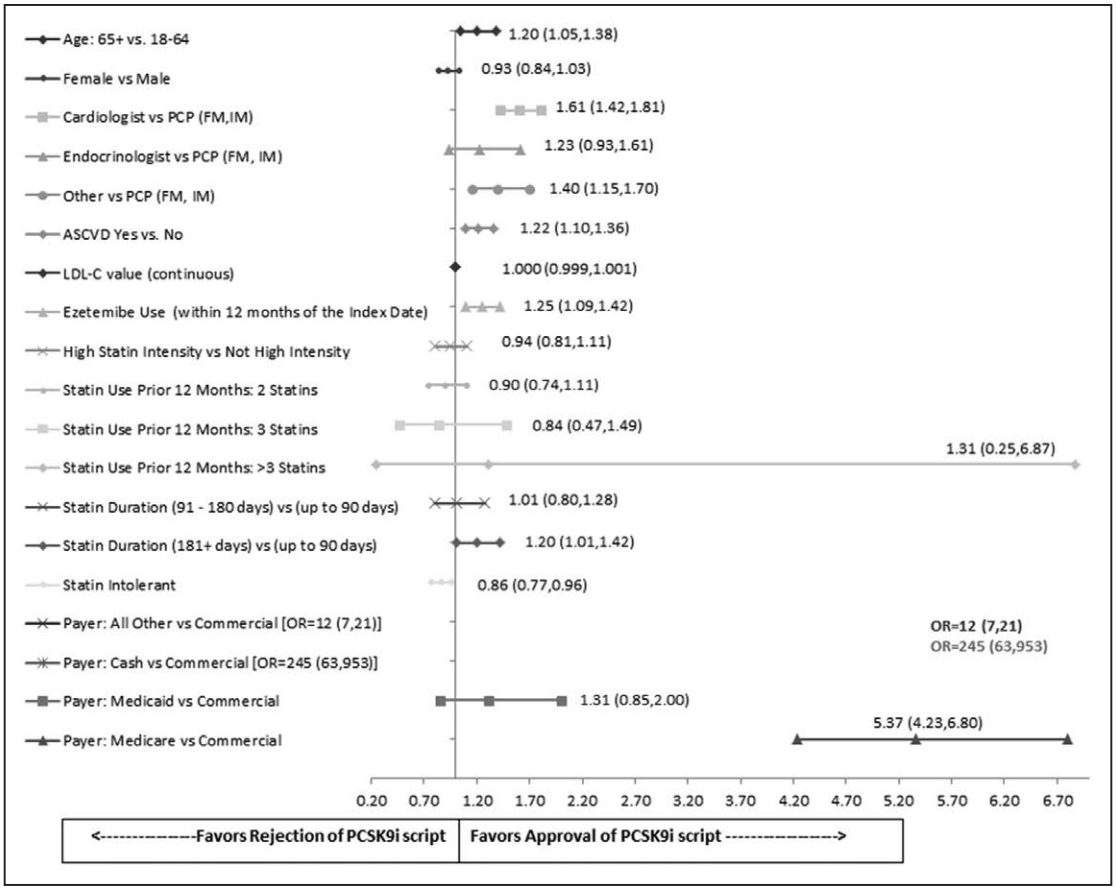

Figure 3. Forest plot of multivariable logistic regression analysis of factors associated with PCSK9i approval. The strongest factor associated with PCSK9i approval was payer type, with noncommercial, cash payment, and Medicare all having higher likelihood of approval in comparison with commercial insurance. Age >65 years, prior ASVCD, prescription by a cardiologist or nonprimary care provider, and longer statin duration were associated with approval. Statin intolerance was associated with lower likelihood of claim approval, and the most recent LDL-C value was not associated with any difference in approval. ASCVD indicates atherosclerotic cardiovascular disease; FM, family medicine; IM, internal medicine; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; PCP, primary care physician; PCSK9, proprotein convertase subtilisin/kexin type 9; and PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.

approved. Older age, presence of ASCVD, and prescription by a cardiologist or nonprimary care provider were also associated with higher rates of PCSK9i therapy approval.

Published clinical trial data have demonstrated that alirocumab and evolocumab significantly reduce LDL-C levels.[10,11] Meta-analyses suggest that treatment with PCSK9 inhibitors may be associated with a reduced risk of death from all causes and a reduction in cardiovascular deaths.[15] The recently published results of the FOURIER trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) showed that cholesterol lowering with PCSK9i on a background of statin therapy led to reductions in major cardiovascular events.[16] However, at current prices, the cost-effectiveness of these drugs has been called into question.[17] It remains to be seen how the results of recent and ongoing clinical outcomes trials may affect future payer approvals. As scientific and outcomes data accumulate, approval processes and criteria become clearer, and other market forces potentially reduce direct and indirect costs, payer approval of PCSK9i therapy may increase.

Current rates of PCSK9i therapy rejection are high. Given that 40% of patients prescribed these medications do not have ASCVD and over half are not currently on statin therapy, the high rates of rejection could be driven in part by prescriptions for patients who may not meet currently accepted indications. However, rates of rejection were high even for groups with very high LDL-C values who might be expected to benefit from PCSK9i. In stratifying the study population for those with a history of ASCVD events (secondary prevention), a key labeled indication, there was only a 3% increase in approval in comparison with the total study population. In the same group of ASCVD patients, almost 50% of patients had an LDL-C test result ≥130 mg/dL proximal to their rejection. Because of the limitations of *ICD-9*

and *ICD-10* diagnosis data, we were unable to accurately identify patients with FH. We found that statin intolerance was associated with a lower approval rate for PCSK9i. Because more than half of individual patients reporting statin intolerance can be successfully rechallenged with statins before considering PCSK9i, we suspect that payers may require recent rechallenge before approving such prescriptions, resulting in lower approval rates than prescriptions based on other indications.

Although certain patient clinical variables including age >65 years, cardiology and specialty prescribing, statin intolerance, longer duration of statin use, and LDL-C >130 on statin+ezetimibe had statistically significant associations with approval, payer type was much more strongly associated with approval. Commercial third-party payers had the lowest approval rates. Medicare was the dominant payer type for the total study population (52.5%) and had a much higher rate of approval (60.9%) than commercial payers, and Medicaid (31.2%), as well. These findings are consistent with prior investigations suggesting high rates of coverage for drugs and biologics for FDA-approved indications.[18] Future investigations into whether other health plan characteristics or geographic factors were associated with different rates of approval could add insight into understanding the variation observed between plans.

These findings suggest that, although practitioners are prescribing PCSK9i therapy based on FDA approval and available efficacy data to date, healthcare payers are rejecting approval for the therapy perhaps over concerns of high costs and other considerations. When we examine the adoption in US health care of other novel, highly effective, costly therapies, similar patterns of low approval are often seen. As a recent example in a different therapeutic area, ledipasvir-sofosbuvir therapy for patients with hepatitis C was more effective than other treatment regimens with sustained virological responses of ≥95%,[19] but was more costly.[20]

In patients who were approved, but ultimately abandoned the therapy, ie, did not take possession of the approved medication, payment responsibility was likely a factor. The mean patient responsibility for patients who ultimately abandoned the therapy was more than twice that of patients who took possession of the medication. Other factors such as the injectable formulation may also have contributed to this patient cohort (≈35% of approved patients).

Although a complete and systematic analysis of specific reasons for rejection are beyond the scope of the current article, the high rejection rates observed indicate a major administrative burden to physicians prescribing these medications for their patients. Prior authorization forms consisting of multiple pages are typically required for approval by the majority of health plans. With <10 000 health plans in the United States, there is great variability in payer-required prior authorization forms with many cases of differing requirements and definition of terms. The increasing rates of approval over time may in part be a reflection of prescribers moving up the learning curve for satisfactory completion of the forms. The forms require substantial time and create a direct cost for healthcare providers, and an indirect cost for patients repeatedly attempting to receive the prescribed medication, as well. Studies on administrative costs consistently report that 20% to 30% of US healthcare expenditures are spent on administration, including claims submissions and providers' time and efforts to be reimbursed.[21]

From the pharmacist perspective, each attempt for payer approval of a PCSK9i is typically made up of many transmissions and ≥1 submissions, also known as claims. Transmissions are a series of electronic entries and queries between a pharmacy and the payer. A variety of transmissions are often required by pharmacists to achieve medication approval by adjusting script prescription parameters on a specific date including the quantity of medication to be dispensed, the primary payer, etc. For each patient prescribed a PCSK9i during the study period, an average of 4 distinct claims submissions were observed with 6 associated electronic transmissions from pharmacies. Analyzing the cost of multiple submissions, transmissions, prior authorizations, and related activities in a future study will help to better understand the negative direct and indirect economic impact to our society.

There are limitations inherent to retrospective analyses, which can only provide associations and not causality, and the use of claims data, which are collected primarily for reimbursement purposes rather than research. First, although the current indication for primary preventive PCSK9i therapy is restricted to FH, we were unable to assess diagnostic accuracy given the absence of clinical genetic testing or available clinical history such as family history. Furthermore, more specific *ICD-10* codes for FH were not yet operational during the study period. Second, based on the necessity of a cutoff date to define the end of the study period, it is also possible that some rejected patients would eventually be approved in the future. Our analyses may therefore overreport rejected patients to some degree. In addition, our analysis may underreport statin duration for some patients, because patients with mail orders or who are otherwise not represented in the database may be missed. In addition, because our data sets do not include enrollment information for patients, we used the presence of claims as proxies for continuous enrollment, which may further underestimate statin duration for some patients. Our exclusion of LDL-C test results >400 mg/dL may omit some patients with homozygous FH, but this is rare and would represent a small fraction of our study population, and it would have little impact on the overall findings of the study. Finally, we were unable to determine how many cash-paying patients were

uninsured versus paying cash as a deductible or copay, but we were able to compare the patient responsibility amounts between the approved and rejected cohorts.

Conclusions

In this large, national study of PCSK9i prescribing, less than half of all prescribed patients received payer approval. These results were observed among patients with a history of ASCVD and among those with markedly elevated LDL-C levels, as well. Although a combination of clinical characteristics moderately influenced approval rates, the most significant factor associated with approval was payer type.

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DISCLOSURES

Dr Natarajan reports receiving consulting fees from Amarin Corp. The other authors have no disclosures to report. All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. No funding was provided by Amgen or Sanofi, manufacturers of PCSK9 inhibitors, for this study. Neither company played a role in the data analysis, interpretation of results, or preparation of the manuscript. The data reported here have been supplied by Symphony Health, under the direction of Drs Hess and Yeh. The interpretation and reporting of these data are the responsibility of the authors.

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FOOTNOTES

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Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitor Therapy: Payer Approvals and Rejections, and Patient Characteristics for Successful Prescribing

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Final study cohort stratified by state based on ZIP-2 code.

State Abbreviation	State Name*	Number of Patients
AA, FL	*Armed Forces: The Americas, Florida*	2
AK	Alaska	18
AK, WA	*Alaska, Washington*	3
AL	Alabama	280
AP, AS, CA, FM, GU, HI, MH, MP, PW	*American Samoa, Armed Forces: Area Pacific, California, Federated States Of Micronesia, Guam, Hawaii, Marshall Islands, Northern Mariana Islands, Palau*	1
AR	Arkansas	155
AR, LA	*Arkansas, Louisiana*	4
AR, TX	*Arkansas, Texas*	2
AZ	Arizona	395
CA	California	734
CO	Colorado	149
CT	Connecticut	49
DC	District Of Columbia	3
DE	Delaware	38
DE, PA	*Delaware, Pennsylvania*	2
FL	Florida	1224
GA	Georgia	288
HI	Hawaii	3
IA	Iowa	171
ID	Idaho	29
ID, WY	*Idaho, Wyoming*	3
IL	Illinois	453
IN	Indiana	111
KS	Kansas	186
KY	Kentucky	163
LA	Louisiana	181
MA	Massachusetts	24
MD	Maryland	82
ME	Maine	50
MI	Michigan	277
MN	Minnesota	8
MO	Missouri	480
MS	Mississippi	145
MS, TN	*Mississippi, Tennessee*	2
MT	Montana	15

NC	North Carolina	183
ND	North Dakota	5
NE	Nebraska	165
NH	New Hampshire	17
NJ	New Jersey	173
NM	New Mexico	28
NV	Nevada	265
NY	New York	267
OH	Ohio	270
OK	Oklahoma	147
OR	Oregon	88
PA	Pennsylvania	363
RI	Rhode Island	1
SC	South Carolina	226
SD	South Dakota	5
TN	Tennessee	379
TX	Texas	669
UT	Utah	26
VA	Virginia	164
VA, WV	*Virginia, West Virginia*	1
WA	Washington	55
WI	Wisconsin	66
WV	West Virginia	62
WY	Wyoming	2
	TOTAL	**9,357**

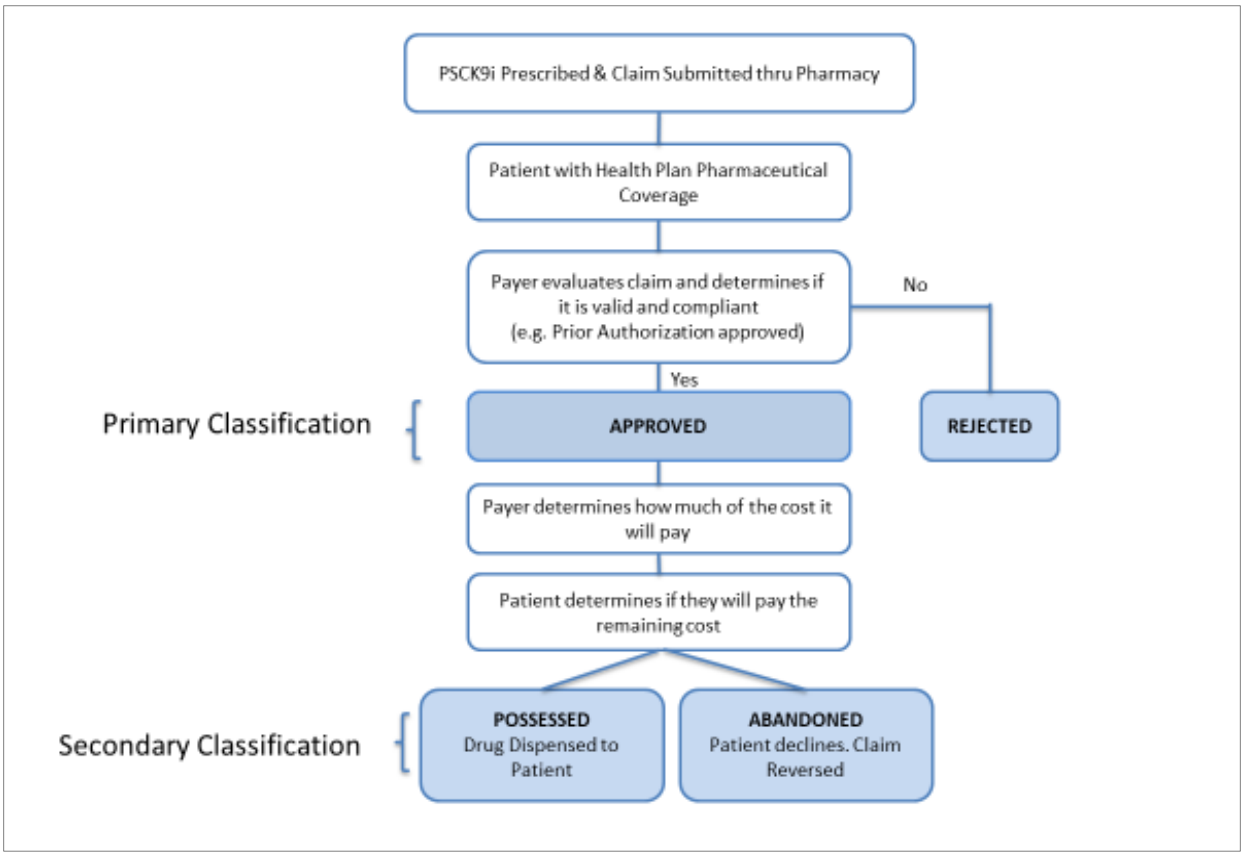
*This table is based on ZIP-2 codes, which roughly align with state boundaries but some cross more than a single state. 1,390 patients in the study cohort are associated with a ZIP-2 code that crosses state boundaries. For these patients, the state of a local pharmacy with the highest volume of total prescriptions for that patient was used to determine their state. The remaining 17 patients in the table with more than one state listed would require additional analysis to place into one state.

Supplemental Table 2. Sensitivity analysis showing approvals and rejections for the entire study cohort compared with patients submitting their first PCSK9i claim before the last 60 days of the study period.

Patient's 1st PCSK9i Claim Submitted During the Entire Study Period: July 1, 2015 - August 31, 2016								
Rejected		**Approved**						**Total**
		Possessed		**Abandoned**		**Total**		
4,960	53.0%	2,844	64.7%	1,553	35.3%	4,397	47.0%	9,357

Patient's 1st PCSK9i Claim Submitted Before the Last 60 Days of the Study: July 1, 2015 - June 30, 2016								
Rejected		**Approved**						**Total**
		Possessed		**Abandoned**		**Total**		
3,512	49.3%	2,425	67.2%	1,181	32.8%	3,606	50.7%	7,118

Supplemental Figure 1. Health plan pharmacy claims processing.



Supplemental Figure 2. Patient rejection rates by payer for the highest volume payers, representing about 80% of the study sample.