Prior Authorization Requirements for Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors Across US Private and Public Payers

See Editorial by Jackevicius

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BACKGROUND: Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is) are an innovative treatment option for patients with familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who require further lowering of low-density lipoprotein cholesterol. However, the high costs of these agents have spurred payers to implement utilization management policies to ensure appropriate use. We examined prior authorization (PA) requirements for PCSK9is across private and public US payers.

METHODS AND RESULTS: We conducted an analysis of 2016 formulary coverage and PA data from a large, proprietary database with information on policies governing >95% of Americans with prescription drug coverage (275.3 million lives) within 3872 plans across the 4 major insurance segments (commercial, health insurance exchange, Medicare, and Medicaid). The key measures included administrative PA criteria (prescriber specialty, number of criteria in PA policy or number of fields on PA form, requirements for medical record submission, reauthorization requirements) and clinical/diagnostic PA criteria (approved conditions, required laboratories or other tests, required concomitant therapy, step therapy requirements, continuation criteria) for each of 2 Food and Drug Administration–approved PCSK9is. Select measures (eg, number of PA criteria/fields, medical record submission requirements) were obtained for 2 comparator cardiometabolic drugs (ezetimibe and liraglutide). Between 82% and 97% of individuals were enrolled in plans implementing PA for PCSK9is (depending on insurance segment), and one third to two thirds of these enrollees faced PAs restricting PCSK9i prescribing to a specialist. For patients with familial hypercholesterolemia, diagnostic confirmation via genetic testing or meeting minimum clinical scores/criteria was also required. PA requirements were more extensive for PCSK9is as compared with the other cardiometabolic drugs (ie, contained 3×–11× the number of PA criteria or fields on PA forms and more frequently involved the submission of medical records as supporting documentation).

CONCLUSIONS: PA requirements for PCSK9is are greater than for selected other drugs within the cardiometabolic disease area, raising concerns about whether payer policies to discourage inappropriate use may also be restricting access to these drugs in patients who need them.

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WHAT IS KNOWN

- Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are an innovative treatment option for patients with familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who require further lowering of low-density lipoprotein cholesterol; however, the high cost of these agents spurred many payers to implement prior authorization.
- Anecdotal reports have suggested that prior authorization requirements for PCSK9 inhibitors are uniquely burdensome and may pose a significant challenge for providers seeking to prescribe these medications, even in clinically appropriate patients.

WHAT THE STUDY ADDS

- This study provides the first comprehensive picture of prior authorization requirements for PCSK9 inhibitors across the 4 major US insurance segments (commercial, health insurance exchange, Medicare, and Medicaid), using data drawn from ≈4000 insurance plans covering >275 million Americans.
- More than 80% of patients in all insurance segments were enrolled in plans implementing prior authorization for PCSK9 inhibitors, and requirements were more extensive than those for the other cardiometabolic drugs examined (eg, 3×–11× as many required fields, more frequent demand for medical records).
- Burdensome prior authorization requirements for PCSK9 inhibitors may have the potential to inhibit appropriate access in patients who need them.

In the summer of 2015, the US Food and Drug Administration approved 2 cholesterol-lowering agents in a novel therapeutic class of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is). Alirocumab (Praluent) was approved for the treatment of patients with heterozygous familial hypercholesterolemia (FH) or clinical atherosclerotic cardiovascular disease (ASCVD) who require additional lowering of low-density lipoprotein cholesterol (LDL-C), and evolocumab (Repatha) received approval for an additional indication of homozygous FH. Both drugs have been shown to be capable of reducing LDL-C levels far below what can be achieved with statin therapy alone,[1] and a recent cardiovascular outcomes trial of evolocumab showed a significant relative risk reduction in major coronary events.[2]

Given the high cost of PCSK9is, their approval raised concerns that overutilization could create a budget busting effect.[3] Estimates placed the number of patients eligible for PCSK9is at 9 to 11 million,[4,5] with annualized spending projections (depending on uptake assumptions) ranging from $21.4 to $113 billion after accounting for direct medical cost offsets.[5,6] Thus, payers sought to attenuate the economic impact of potential overuse by implementing prior authorization (PA) for these drugs. Although PA is a common utilization management strategy,[7] early anecdotal reports have indicated that the PA process for PCSK9is has been particularly challenging for providers[8–11] and that rejection rates for submitted PCSK9i prescriptions have been high, including for patients with evidence of medical necessity.[12–15] Potential administrative barriers to treatment are of particular concern for patients with FH or uncontrolled ASCVD, who are at high risk of cardiovascular events. Thus, more comprehensive data on potential PA-related access barriers for PCSK9is are needed.

Using a unique data source, we conducted the first detailed analysis of PA requirements for PCSK9is across private and public US payers, examining both administrative criteria and clinical and diagnostic requirements for individuals with prescription coverage under commercial insurance, health insurance exchanges (HIX), Medicare, and Medicaid. Then, to examine the relative administrative burden for PCSK9is, we examined PA requirements for 2 comparator cardiometabolic drugs.

METHODS

Data Source

We obtained study data from Decision Resources Group's Fingertip Formulary, a proprietary database that contains formulary information along with access to PA policies and forms for public and private payers in the United States. These data were linked with enrollment information obtained from Decision Resources Group's Managed Markets Surveyor-Rx Suite, a second proprietary database containing membership information for insurers in the United States. The linked data captured the formulary coverage, tier status, step therapy, and PA requirements for PCSK9is for >95% of Americans who had insurance coverage in 2016 (see Data Supplement for additional details.) The study data cannot be made available to other researchers for purposes of reproducing the results because of terms specified in the data use agreement. The University of Pennsylvania Institutional Review Board reviewed the study protocol and deemed it exempt from institutional review board approval because no data were collected from human subjects.

Sample Selection

Information for the primary analysis was extracted for each plan so as to be representative of 100% of individuals with prescription coverage (ie, pharmacy-covered lives) across commercial insurance, HIX, Medicare, and Medicaid. For the secondary analysis comparing specific aspects of PA requirements for PCSK9is with those for other cardiometabolic drugs, we limited our analysis to a sample of the largest plans (by enrollment size), representing at least 50% of pharmacy-covered lives in a given insurance segment.

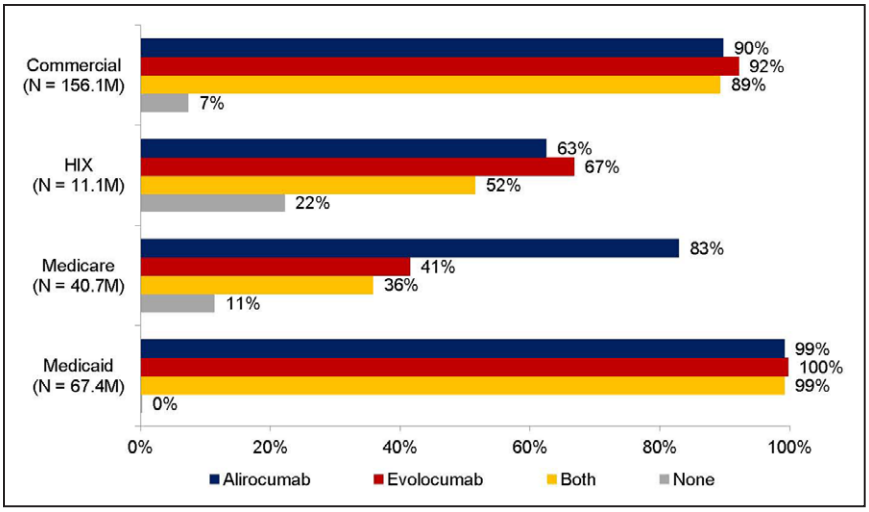

Figure. Formulary coverage for PCSK9 inhibitors in 2016, by type of insurance coverage. Reported percentages are not mutually exclusive across the alirocumab, evolocumab, and both categories. HIX indicates health insurance exchange.

To contextualize prescriber burden, we chose 2 comparator drugs from the cardiometabolic class, namely ezetimibe (Zetia) and liraglutide (Victoza). We chose these drugs as comparators because they are typically prescribed by the same types of providers (eg, cardiologists, endocrinologists) who would be prescribing PCSK9is and because they shared additional key characteristics with PCSK9is. Ezetimibe is also a nonstatin cholesterol-lowering agent, there was no generic version available during the study period, and for much of its time as a branded drug it had no cardiovascular outcomes data available. Although clearly not as expensive as the PCSK9is (wholesale acquisition cost of $228 versus ≈$1100 per 30-day supply in Q1 2017, without accounting for rebates and discounts), it was relatively expensive compared with many of the statins available as generics. Liraglutide, a novel noninsulin medication for patients with type 2 diabetes mellitus, resembles PCSK9is in that it is also approved for patients who have been unable to meet clinical goals on first-line therapy and also has a large potential target population. Although not as expensive as the PCSK9is (wholesale acquisition costs of $748 versus ≈$1100), it represents a significant absolute cost given the number of potentially eligible patients and is relatively more expensive than many of the medications approved for type 2 diabetes mellitus. It also has the same mode of administration (self-injection) as PCSK9is.

Measures

We identified whether each PCSK9i agent was covered on the plan formulary and, if covered, whether it was subject to PA, step therapy, and specialty tier cost sharing. Next, information on administrative PA criteria (prescriber specialty, number of criteria in the PA policy or number of fields on the PA form, requirements for medical record submission, and reauthorization requirements) and clinical and diagnostic PA criteria (approved conditions, required laboratory tests or other tests, mandates on concomitant therapy use, step therapy requirements, and continuation criteria) was extracted for each PCSK9i (See Data Supplement for additional details). Select outcomes (formulary coverage, whether it was subject to PA, number of PA criteria/fields, medical record submission requirements) were extracted for each comparator drug.

Analysis

Descriptive statistics representing the percentage of covered lives with prescription benefits were generated for formulary coverage, PA, step therapy, and specialty tier status, as well as the detailed administrative and clinical PA requirements associated with each PCSK9i. The PA burden for providers (ie, the number of PA criteria or fields on the PA forms) and medical record submission requirements for the 2 PCSK9is were compared with corresponding requirements for the 2 comparator drugs. Because enrollment size can vary dramatically across plans, all estimates were generated to be representative of the individuals (rather than plans) covered under each insurance segment.

Table 1. Utilization Management Strategies for PCSK9 Inhibitors in 2016, by Type of Insurance Coverage

	Commercial	HIX	Medicare	Medicaid
No. of covered lives with drug on formulary, in millions				
Alirocumab	140.1	6.9	33.8	66.8
Evolocumab	143.9	7.4	16.9	67.2
Both	139.5	5.7	14.6	66.8
Percentage of covered lives subject to prior authorization requirements for PCSK9is, %				
Alirocumab	83	94	96	97
Evolocumab	83	99	92	97
Both	82	96	90	97
Percentage of covered lives subject to step therapy requirements for PCSK9is, %				
Alirocumab	14	14	2	2
Evolocumab	14	14	0	2
Both	14	17	0	2
Specialty tier status for PCSK9is, %				
Alirocumab	32	44	80	0
Evolocumab	34	47	78	0
Both	42	68	93	0

HIX indicates health insurance exchange; and PCSk9is, proprotein convertase subtilisin/kexin type 9 inhibitors.

RESULTS

The Figure displays formulary coverage for PCSK9is across 275.3 million lives, with prescription drug benefits covered under 3872 plans across the 4 major insurance segments. All Medicaid enrollees (100%) had formulary coverage for at least 1 PCSK9i, whereas 22% of HIX enrollees had no coverage for either drug.

Table 1 summarizes utilization management strategies for PCSK9is among enrollees with formulary coverage for these agents. PA was the most common strategy across insurance types, with 82% to 97% of individuals facing PA for PCSK9is. Explicit step therapy requirements were minimal. Aside from Medicaid (which does not impose specialty tiers), specialty tier exposure for PCSK9is ranged from over one third of commercial enrollees to >3 quarters of the Medicare population.

Administrative PA requirements for PCSK9is are presented in Table 2. Approximately one third of Medicaid enrollees were in plans that restricted PCSK9i prescribing to a cardiologist, endocrinologist, lipid specialist, or other specialist. This requirement was also common among Medicare (42%–71%) and commercial enrollees (65%–66%).

Compared with other insurance categories, HIX plans typically required providers to complete the greatest number of individual fields or criteria to satisfy PA requirements. The mean number of fields varied across payer types, from 9 to 33. Notably, form/policy length was similar for both FH and ASCVD indications. A high proportion of individuals (40%–75%) across insurance segments were enrolled in plans that also required submission of medical records as supporting documentation to receive approval. Insurers typically did not limit the medical record requirement to a single laboratory value (eg, results from a lipid panel) but rather required physicians to justify their response to each individual PA criteria with supporting medical documentation, either through test results or extensive patient histories. Finally, a majority of individuals were in plans that required reauthorization for continued treatment beyond an initial PA approval period (typically 3 months).

Clinical and diagnostic criteria for PA varied across insurance type and by PCSK9i agent (Table 3). A large percentage of patients were covered by plans allowing use for FH and ASCVD, and a sizeable proportion of patients were in plans that considered PCSK9is to be an acceptable alternative for patients who are statin intolerant or contraindicated for statin therapy. Consistent with the Food and Drug Administration label,[16] patients receiving approval for PCSK9is were required to concomitantly take statins (unless contraindicated or statin

Table 2. Administrative Prior Authorization Requirements for PCSK9 Inhibitors in 2016, by Type of Insurance Coverage*

	Alirocumab				Evolocumab			
	Commercial	HIX	Medicare	Medicaid	Commercial	HIX	Medicare	Medicaid
No. of covered lives subject to PA requirements, in millions	116.5	6.5	32.4	65.1	119.7	7.3	15.5	65.3
Prescriber specialty %								
Medication must be prescribed by or in consultation with a specialist	66%	48	42	32	65	46	71	36
Cardiologist†	98	100	100	100	100	98	100	100
Lipid specialist†	83	56	90	88	85	59	87	92
Endocrinologist†	94	88	98	69	95	87	97	69
Specialist (not specified)†	38	35	10	6	37	35	14	6
No. of PA criteria or fields required on form								
HeFH, mean (min, max)‡	17 (6, 72)	27 (10, 44)	11 (1, 37)	19 (3, 53)	18 (6, 73)	33 (10, 39)	13 (1, 37)	16 (3, 32)
HoFH, mean (min, max)‡	N/A	N/A	N/A	N/A	19 (6, 73)	26 (7, 35)	11 (1, 47)	16 (4, 32)
ASCVD, mean (min, max)‡	21 (6, 72)	32 (10, 50)	9 (1, 39)	19 (3, 53)	20 (6, 73)	27 (9, 38)	11 (1, 39)	16 (3, 32)
Submission of medical records required for approval, %	75	58	69	40	73	55	64	43
Reauthorization required, %	64	58	98	46	61	46	100	47
Initial coverage duration specified, %§	40	33	43	35	50	40	77	36
Median duration, mo (min, max)	3 (2, 6)	3 (2, 6)	3 (2, 6)	3 (2, 6)	3 (2, 6)	3 (2, 6)	3 (2, 6)	3 (2, 6)

ASCVD indicates atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia; HIX, health insurance exchange; HoFH, homozygous familial hypercholesterolemia; N/A, not applicable; PA, prior authorization; and PCSK9, proprotein convertase subtilisin/kexin type 9.

*Percentages may not add to 100 because of rounding.

†Denominator for these estimates is the percentage of enrollees subject to the prescriber specialty requirement.

‡All mean estimates are weighted by the number of enrollees in each plan.

§Denominator for this estimate is the percentage of enrollees subject to reauthorization.

Table 3. Clinical and Diagnostic Prior Authorization Requirements for PCSK9 Inhibitors in 2016, by Type of Insurance Coverage*

	Alirocumab				Evolocumab			
	Commercial	HIX	Medicare	Medicaid	Commercial	HIX	Medicare	Medicaid
No. of covered lives subject to PA requirements, in millions	116.5	6.5	32.4	65.1	119.7	7.3	15.5	65.3
Approved diagnoses, %								
Any FDA-approved indication	25	16	98	86	12	9	100	91
HeFH	95	88	90	56	89	68	79	57
HoFH	N/A	N/A	N/A	N/A	82	67	79	54
ASCVD	92	85	90	52	88	66	79	54
Patient contraindicated for statins	59	48	61	24	54	44	57	24
Statin intolerance	74	65	90	33	70	55	70	35
Payer requires confirmation that statin intolerance cannot be attributed to other conditions†	20	15	0	52	50	35	0	48
Payer requires concomitant therapy use to approve drug, %	81	73	83	48	81	64	64	50
With statins‡	100	100	100	100	100	100	100	100
With ezetimibe‡	56	73	0	55	67	89	34	58
With other lipid-lowering therapy‡	6	11	0	13	7	9	48	13
Adjunctive use to diet‡	41	64	29	66	39	50	4	69
Required laboratory tests/tests/documentation, %								
Genetic testing for FH§	65	70	84	21	60	51	64	20
Dutch Lipid Network Clinical Criteria (score >8) for FH§	43	36	60	27	38	34	62	27
Simon-Broome Criteria for FH§	19	7	28	19	16	7	24	19
LDL-C levels (mg/dL), %								
HeFH	84	85	87	53	84	64	74	56
LDL-C value specified‖	76	73	82	85	78	76	81	66
HoFH	N/A	N/A	N/A	N/A	76	62	79	49
LDL-C value specified‖	N/A	N/A	N/A	N/A	72	78	83	71
ASCVD	81	82	85	52	82	61	73	52
LDL-C value specified‖	81	75	77	67	79	71	82	65
Payer uses step therapy as part of prior authorization requirements, %	90	80	85	70	90	68	81	64
Single#	20	39	94	21	35	35	91	34
Double#	57	39	4	50	36	28	9	51
Triple#	17	16	0	12	28	33	0	13
Quadruple#	6	1	0	2	0	0	0	2
Unspecified step therapy#	0	4	2	15	2	4	0	1
Continuation criteria								
Plan requires reduction in LDL-C with PCSK9 inhibitor, %								
HeFH	63	65	39	46	57	55	39	47
HoFH	N/A	N/A	N/A	N/A	49	51	38	46
ASCVD	59	53	39	44	54	45	39	45
Plan requires adherence to PCSK9 inhibitor and concomitant lipid-lowering treatment, %	42	39	0	36	40	38	0	32

ASCVD indicates atherosclerotic cardiovascular disease; FDA, Food and Drug Administration; HeFH, heterozygous familial hypercholesterolemia; HIX, health insurance exchange; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; N/A, not applicable; PA, prior authorization; and PCSK9, proprotein convertase subtilisin/kexin type 9.

*Percentages may not add to 100 because of rounding.

†Denominator for these estimates is the percentage of enrollees in plans approving PCSK9 inhibitors for statin intolerance.

‡Denominator for these estimates is the percentage of enrollees with concomitant therapy requirements.

§These are not necessarily mutually exclusive requirements; some forms allowed providers to choose which type of diagnostic confirmation to provide. The percentages of patients in plans that only listed genetic testing for diagnostic confirmation of FH on their PA form for alirocumab were 38% commercial, 63% HIX, 29% Medicare, and 20% Medicaid and for evolocumab were 40% commercial, 50% HIX, 4% Medicare, and 19% Medicaid.

‖Denominator for these estimates is the percentage of enrollees in a plan that reports an LDL-C requirement.

#Denominator for these estimates is the percentage of enrollees in a plan that contains step therapy as an implicit part of the PA process.

intolerant); although not in the Food and Drug Administration label, a substantial proportion of individuals in commercial, HIX, and Medicaid plans were permitted to have concomitant therapy with ezetimibe rather than statins.

A majority of individuals were enrolled in plans wherein insurers (with the exception of Medicaid) required patients with FH to have documentation confirming their diagnosis. Genetic testing was frequently required. In other cases, clinical diagnostic criteria, such as the Dutch Lipid Network Clinical Criteria or Simon-Broome Criteria, were acceptable alternatives although meeting the minimum score/criteria under both is easier with genetic test results. Finally, LDL-C levels were the clinical criteria most frequently required by payers across all insurance types (regardless of FH or ASCVD indication). Some plans did not specify the LDL-C levels required to meet PA criteria. When plans did specify required on-treatment LDL-C levels, requirements ranged widely: from 100 to 190 for heterozygous FH, from 100 to 500 for homozygous FH, and from 70 to 130 for ASCVD (data not shown). Some plans also required providers to document the patient's untreated LDL-C level (data not shown). Despite minimal explicit step therapy requirements, most patients (outside of Medicare) were required to try multiple lipid-lowering drugs before receiving approval for PCSK9is (ie, implicit step therapy). In addition, there was little consistency regarding which combinations of lipid-lowering medications or dosages payers deemed necessary to fulfill these requirements (data not shown).

Continuation criteria tended to be less exhaustive than the initial PA process. Across all insurance types,

Table 4. Comparison of Prior Authorization Burden Across Similar Drug Classes by Type of Insurance Coverage, Across Plans Representing >50% of US Insured Population in 2016

	Commercial	HIX	Medicare	Medicaid
No. of covered lives in largest plans, in millions	81.1	6.4	25.3	34.2
Alirocumab				
Percentage of covered lives with the drug on formulary*	87%	65%	100%	99%
Percentage of covered lives subject to prior authorization	100%	91%	97%	96%
No. of PA criteria or fields required on form				
HeFH, mean (min, max)†	16 (5, 31)	29 (3, 45)	8 (1, 12)	19 (4, 53)
HoFH, mean (min, max)†	N/A	N/A	N/A	N/A
ASCVD, mean (min, max)†	21 (6, 53)	31 (4, 50)	8 (2, 13)	19 (4,53)
Plan requires submission of medical records	89%	63%	58%	46%
Evolocumab				
Percentage of covered lives with the drug on formulary*	89%	61%	64%	99%
Percentage of covered lives subject to prior authorization	100%	92%	93%	98%
No. of PA criteria or fields required on form				
HeFH, mean (min, max)†	19 (5, 33)	33 (7, 39)	8 (6, 9)	17 (4, 32)
HoFH, mean (min, max)†	20 (5, 33)	27 (6, 35)	7 (6, 9)	15 (4, 32)
ASCVD, mean (min, max)†	21 (5, 33)	30 (6, 38)	7 (5, 8)	17 (4, 32)
Plan requires submission of medical records	89%	62%	69%	48%
Ezetimibe				
Percentage of covered lives with the drug on formulary*	95%	98%	100%	100%
Percentage of covered lives subject to prior authorization	20%	20%	0%	23%
No. of PA criteria or fields required on form, mean (min, max)†	6 (4, 7)	5 (2, 7)	N/A	3 (1, 11)
Plan requires submission of medical records	9%	11%	N/A	35%
Liraglutide				
Percentage of covered lives with the drug on formulary*	81%	100%	95%	99%
Percentage of covered lives subject to prior authorization	60%	62%	0%	44%
No. of PA criteria or fields required on form, mean (min, max)†	2 (1, 9)	3 (1, 12)	N/A	4 (1, 12)
Plan requires submission of medical records	11%	34%	N/A	21%

ASCVD indicates atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia; HIX, health insurance exchange; HoFH, homozygous familial hypercholesterolemia; N/A, not applicable; and PA, prior authorization.

*These values are used as denominators for each successive row.

†All mean estimates are weighted by the number of enrollees in each plan.

a substantial proportion of patients were in plans that required reduction in LDL-C levels in order for a patient to continue treatment. In addition, over one third of patients were in commercial, HIX, and Medicaid plans that required providers to document adherence (eg, >80% proportion of days covered) to the PCSK9i and concomitant lipid-lowering drugs for continuation of therapy requests.

PA burden across PCSK9is and our 2 comparator drugs is shown in Table 4. Commercial and HIX plans were more likely to subject comparator drugs to PA as compared with Medicare or Medicaid plans. With the exception of Medicare, the mean number of criteria or fields on the PA forms for PCSK9is was 3× to 11× greater than what was required for comparator drugs across payer segments. Individuals in all insurance types were more likely to be in plans that required the submission of medical records for PCSK9i approval as compared with the other drugs.

DISCUSSION

The diverse insurance market in the United States—and the fact that payer policies and administrative requirements are not necessarily publicly available—make it difficult to capture comprehensive and objective data on PA-related provider burden. Our findings provide a rare picture of PA policies and requirements governing the prescription of PCSK9is across the US insurance market. Our analysis found that PA requirements for PCSK9is are widespread and pose administrative burden on providers, both in regard to volume (eg, high number of form fields) and type (eg, frequent medical record submission requirements). At the same, specific PA policies and requirements for PCSK9is vary considerably both within and between insurance segments, likely leading to additional provider burden for clinicians seeing patients covered by a variety of payers and plans. This burden may be exacerbated for physicians in smaller practices without dedicated staff or resources to assist with PA submissions.[17] Our findings raise the question of whether PA-related challenges are limiting access to PCSK9is for the most appropriate patients, particularly because individuals with FH—who are likely to have more clear-cut eligibility for PCSK9is—were subject to the same extensive PA requirements as were patients with ASCVD. They also highlight the relevance of recent efforts to streamline and standardize PA requirements.[8,18]

Our study identified 5 notable features of the PA requirements for PCSK9is. First, many payers required submission of medical records along with PA forms for PCSK9is but not for comparator drugs, with providers being asked to justify their response to individual PA criteria with medical record submissions. Second, some PA documentation requirements involved data that may be challenging for providers to access (eg, adherence measures that are typically calculated from pharmacy claims, off-treatment LDL-C levels that may not be available for patients who have been on statins for years and changed providers during that time). Third, payers frequently restricted PCSK9i approval to specialty prescribers. It is not uncommon for FH and ASCVD to be managed in a primary care setting,[19,20] and thus specialist consultation may represent a significant hurdle for some individuals, particularly rural, low-income, and minority patients who are at risk for health disparities.[21,22] Fourth, in addition to the high out-of-pocket costs typically associated with specialty drugs, some PA requirements introduce additional costs that may compound financial burden. Genetic testing for FH is not standard practice in the United States, and many insurers will not cover the cost of testing even when they require the results as part of PA. Most insurers also require higher copayments for specialist visits. Fifth, although clinical guidelines endorse use of PCSK9is after treatment with high intensity statins, patients were often required to try multiple lipid-lowering regimens before receiving approval for PCSK9is.[16] Collectively, these hurdles may increase the risk that clinically appropriate patients will not receive treatment.

The complexity of PA requirements we observed may also increase the risk of confusion and oversights when completing forms or submitting medical documentation, which may help to explain previous reports about rejection rates and approval turnaround times for submitted PCSK9i prescriptions.[12–15] Claims-based analyses have reported that only ≈20% of PCSK9i prescriptions were initially approved, with ultimate approval rates of 43% to 47% after additional attempts.[13,14] A recent study reported that only 37% to 42% of submitted PCSK9i prescriptions were ultimately approved for FH and ASCVD patients with LDL-C >190 and 100 mg/dL, respectively, despite evidence of use of appropriate lipid-lowering therapy—and approval took >2 months for 40% of these prescriptions.[15] That is, even in patients who should have met medical necessity criteria, rejection rates were high and approvals were often slow.

It remains to be seen how payers will respond to accumulating evidence on PCSK9is from cardiovascular outcomes trials[2,23] and cost-effectiveness studies.[24,25] In addition, some states have passed legislation requiring standardized PA forms across drug classes, which may also influence PA policies for PCSK9is in the future. Further research is needed to understand how PA requirements impact prescribing and initiation of PCSK9is and how this affects cardiovascular outcomes in this patient population.

Limitations

We were able to undertake a broad analysis of PA requirements, but our data were restricted to available

PA forms and written PA policies. We were unable to capture informal criteria that may be used during coverage determinations. Furthermore, we did not have visibility into the approval process and were, therefore, unable to obtain information on how strictly these policies are enforced or to document burden related to appeals. Although we chose comparator drugs in the cardiometabolic drug class to contextualize PCSK9i policies in relation to other PA requirements faced by similar prescribers, we were not able to find a comparator drug in the cardiometabolic class that was identical on all key points. For example, both comparator drugs were less expensive than PCSK9is (ie, wholesale acquisition costs ranging from $228 to $748 versus ≈$1100, without accounting for rebates and discounts). Because of limitations in our ability to extract data across multiple therapeutic classes, comparison data were also limited to the largest plans in the United States covering at least 50% of the general population and a subset of PA criteria. Because sociodemographic information was not available in this policy database, we cannot determine the degree to which this subsample is representative of the insured population as a whole. Nonetheless, even a 50% sample results in a far more comprehensive picture of the policy landscape than has been available in any published study to date.

Conclusions

Given the cost of PCSK9is and the number of patients potentially eligible for treatment, payer concerns over the budget impact of these therapies are justified. However, it is possible that current PA policies for PCSK9is may be restricting access for high-risk patients.[2] Our findings underscore the importance of efforts to reduce administrative burden on providers while ensuring clinically appropriate use of PCSK9is.

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DISCLOSURES

Dr Rader reported serving on the scientific advisory board of Alnylam Pharmaceuticals and as a consultant to Pfizer. Dr Doshi reported serving as a consultant for Sanofi and receiving research funding from Biogen, Janssen, PhRMA, Pfizer, and Sanofi, all unrelated to the current study. Her spouse holds stock in Merck and Pfizer. The other authors report no conflicts.

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FOOTNOTES

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REFERENCES

1. Everett BM, Smith RJ, Hiatt WR. Reducing LDL with PCSK9 inhibitors: the clinical benefit of lipid drugs. *N Engl J Med*. 2015;373:1588–1591. doi: 10.1056/NEJMp1508120.
2. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713–1722. doi:10.1056/NEJMoa1615664.
3. Silverman ED. How much?! Those new cholesterol drugs could cost $23 billion a year. *The Wall Street Journal*. June 9, 2015. Available at: http://blogs.wsj.com/pharmalot/2015/06/09/how-much-those-new-cholesterol-drugs-could-cost-23-billion-a-year/. Accessed April 5, 2017.
4. Wong ND, Young D, Zhao Y, Nguyen H, Caballes J, Khan I, Sanchez RJ. Prevalence of the American College of Cardiology/American Heart Association statin eligibility groups, statin use, and low-density lipoprotein cholesterol control in US adults using the National Health and Nutrition Examination Survey 2011-2012. *J Clin Lipidol*. 2016;10:1109–1118. doi: 10.1016/j.jacl.2016.06.011.
5. Tice JA, Ollendorf DA, Cunningham C, Pearson SD, Kazi DS, Coxson PG. PCSK9 inhibitors for treatment of high cholesterol: effectiveness, value, and value-based price benchmarks. Institute for Clinical and Economic Review. Available at: https://icer-review.org/wp-content/uploads/2016/01/Final-Report-for-Posting-11-24-15-1.pdf. Accessed April 5, 2017.
6. Kazi DS, Moran AE, Coxson PG, Penko J, Ollendorf DA, Pearson SD, Tice JA, Guzman D, Bibbins-Domingo K. Cost-effectiveness of PCSK9 inhibitor therapy in patients with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease. *JAMA*. 2016;316:743–753. doi: 10.1001/jama.2016.11004.
7. MacKinnon NJ, Kumar R. Prior authorization programs: a critical review of the literature. *J Manag Care Spec Pharm*. 2001;7:297–303.
8. Baum SJ, Toth PP, Underberg JA, Jellinger P, Ross J, Wilemon K. PCSK9 inhibitor access barriers-issues and recommendations: improving the access process for patients, clinicians and payers. *Clin Cardiol*. 2017;40:243–254. doi: 10.1002/clc.22713.
9. Kolata G. Study shows promise for expensive cholesterol drugs, but they are still hard to obtain. *The New York Times*. November 15, 2016. Available at: https://www.nytimes.com/2016/11/16/health/cholesterol-drugs-pcsk9-inhibitors.html? _r=0. Accessed April 21, 2017.
10. Berkrot B. Amgen cholesterol drug reduces artery-clogging plaque in study. *Reuters*. November 15, 2016. Available at: http://www.reuters.com/article/us-heartamgen-cholesterol-idUSKBN13A27Q. Accessed April 21, 2017.
11. Chen C, Cortez M. Amgen's Repatha unclogs arteries in good sign for future sales. *Bloomberg Markets*. November 15, 2016. Available at: https://www.bloomberg.com/news/articles/2016-11-15/amgen-s-repatha-unclogs-arteries-in-good-sign-for-future-sales. Accessed April 21, 2017.

12. Pierson R. New cholesterol drugs won't be budget busters: Express Scripts. *Reuters*. September 30, 2015. Available at: http://www.reuters.com/article/us-express-scr-cholesterol-idUSKCN0RU2PL20150930. Accessed April 5, 2017.
13. Baum SJ, Chen CC, Rane PB. Characteristics of patients approved and denied access in PCSK9i therapy by payers. Paper presented at: 66th Scientific Session of the American College of Cardiology; March 17–19, 2017; Washington, DC.
14. Navar AM, Taylor BT, Mulder H, Fievitz E, Monda KL, Fievitz A, Maya JF, Lopez JAG, Peterson ED. 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.
15. 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.
16. Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly DD, DePalma SM, Minissian MB, Orringer CE, Smith SC. 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 2016;68:92–125.
17. American Medical Association. 2016 AMA Prior Authorization Physician Survey. 2017. Available at: https://www.ama-assn.org/sites/default/files/media-browser/public/government/advocacy/2016-pa-survey-results.pdf. Accessed April 26, 2017.
18. American Medical Association. Prior authorization and utilization management reform principles. Available at: https://www.ama-assn.org/sites/default/files/media-browser/principles-with-signatory-page-for-slsc.pdf. Accessed April 26, 2017.
19. Watts GF, Gidding S, Wierzbicki AS, Toth PP, Alonso R, Brown WV, Bruckert E, Defesche J, Lin KK, Livingston M, Mata P, Parhofer KG, Raal FJ, Santos RD, Sijbrands EJ, Simpson WG, Sullivan DR, Susekov AV, Tomlinson B, Wiegman A, Yamashita S, Kastelein JJ; International FH Foundation. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation: executive summary. *J Atheroscler Thromb*. 2014;21:368–374.
20. Zupec JF, Marrs JC, Saseen JJ. Evaluation of statin prescribing for secondary prevention in primary care following new guideline recommendations. *Ann Pharmacother*. 2016;50:17–21. doi: 10.1177/1060028015608199.
21. Crowley R; American College of Physicians. Racial and ethnic disparities in health care, updated. 2010. Available at: https://www.acponline.org/system/files/documents/advocacy/current_policy_papers/assets/racial_disparities.pdf. Accessed April 26, 2017.
22. Reschovsky JD, Staiti AB. Access and quality: does rural America lag behind? *Health Aff (Millwood)*. 2005;24:1128–1139. doi: 10.1377/hlthaff.24.4.1128.
23. Schwartz GG, Bessac L, Berdan LG, Bhatt DL, Bittner V, Diaz R, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Mahaffey KW, Moryusef A, Pordy R, Roe MT, Rorick T, Sasiela WJ, Shirodaria C, Szarek M, Tamby JF, Tricoci P, White H, Zeiher A, Steg PG. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY outcomes trial. *Am Heart J*. 2014;168:682–689. doi: 10.1016/j.ahj.2014.07.028.
24. Kazi DS, Penko J, Coxson PG, Moran AE, Ollendorf DA, Tice JA, Bibbins-Domingo K. Updated cost-effectiveness analysis of PCSK9 inhibitors based on the results of the FOURIER trial. *JAMA*. 2017;318:748–750. doi: 10.1001/jama.2017.9924.
25. Fonarow GC, Keech AC, Pedersen TR, Giugliano RP, Sever PS, Lindgren P, van Hout B, Villa G, Qian Y, Somaratne R, Sabatine MS. Cost-effectiveness of evolocumab therapy for reducing cardiovascular events in patients with atherosclerotic cardiovascular disease. *JAMA Cardiol*. 2017;2:1069–1078. doi: 10.1001/jamacardio.2017.2762.

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Prior Authorization Requirements for Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors Across US Private and Public Payers

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SUPPLEMENTAL MATERIAL

Additional Methodological Details

Description of Insurance Segments

Commercial plans in the Decision Resources Group (DRG) database included a wide range of private payers, including BlueCross/BlueShield groups, employer-sponsored plans (including plans offered by federal, state, and local governments), and pharmacy benefit managers. Health exchange plans were those available on state- and federally-facilitated marketplaces, including those that were contracted by private companies. Medicare plans included all stand-alone Part D plans and Medicare Advantage prescription drug (MA-PD) plans as well as special needs plans (SNPs), employer group waiver plans (EGWPs), and Programs of All-Inclusive Care for the Elderly (PACE). Medicaid plans included both fee-for-service State Medicaid and Managed Medicaid plans.

Additional Information on Data Source

Study data were obtained from Decision Resource Group (DRG)'s Fingertip Formulary (PA policy/form database) and Managed Markets Surveyor-Rx Suite (medical and pharmacy benefit enrollment data). DRG sources its PA criteria data directly from payers, supplemented by additional data from providers and pharmacists. This ensures that DRG captures both the most recent utilization management restrictions as well as the PA policies/forms actually encountered by providers. All criteria are reviewed for accuracy and updated on a quarterly basis; however, DRG updates restriction data for the largest U.S. payers more frequently. The data is expected to be reflective of the policy landscape for >95% of insured Americans. Additional information can be found on each proprietary database by following the links provided below:

- Fingertip Formulary: https://decisionresourcesgroup.com/solutions/us-managed-markets-solutions/drg-knows-formulary/
- Managed Market Surveyor-Rx Suite: https://decisionresourcesgroup.com/solutions/us-managed-markets-solutions/managed-market-surveyor/

List of Prior Authorization Criteria

Prior authorization forms from the largest U.S. commercial insurers were analyzed to create a master list of all key themes and criteria across payer policies governing PCSK9 inhibitors. Additionally, high-volume prescribers of these medications at the University of Pennsylvania Health System were asked to review these criteria and identify any additional prior authorization requirements they had faced in clinical practice. From this initial review and consultation, we generated a comprehensive list of elements to be systematically extracted from payer forms/policies available via Decision Resource Group's formulary database. Prior authorization forms for alirocumab and evolocumab can be readily accessed on payer websites.