Characteristics and Outcomes of Patients Treated With Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors (The Mayo Clinic Experience)

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Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors represent a novel addition to the lipid-lowering armamentarium. We attempted to characterize a real-world group of patients with a clinical indication for PCSK9 inhibitors and describe their clinical outcomes and adverse effect profile. A retrospective chart review was conducted, evaluating all patients referred to preventive cardiology at the Mayo Clinic (Minnesota) between September, 2015 and December, 2018 for management of severe dyslipidemia. A total of 222 patients were referred and a recommendation to start a PCSK9 inhibitor was given to 164 patients (73.9%). Of these, 28 patients (17.1%) declined the use of a PCSK9 inhibitor. A total of 136 previous authorizations were submitted. Of these applications, 96 (70.6%) were approved and 17 (12.5%) were rejected. The cohort's mean age was 64.1 years (range 39 to 91). High-intensity statins and ezetimibe were used in 50 (52.1%) and 80 (83.3%) of the treated patients. Mean pretreatment low-density lipoprotein cholesterol was 167.9 mg/dl. At a median follow-up of 19.0 months, the mean low-density lipoprotein reduction was 60.9% (range 0 to 90.3%). Higher low-density lipoprotein cholesterol percent reductions were seen in younger patients (p value 0.048), patients on high-intensity statins (p value 0.027), those with statin intolerance (p value 0.046), and individuals with a higher baseline triglycerides (p value 0.047). Two (2.1%) patients underwent coronary revascularization, and 1 (1.0%) patient was hospitalized for unstable angina. No cardiovascular deaths occurred. Adverse events were reported in 12 (12.5%) patients, and were all minor (injection site reactions, myalgias, and flu-like illness). In conclusion, our study shows an efficacy and safety profile that is concordant with previous investigations. The use of a standardized application form was associated with a high insurance approval rate. **(Am J Cardiol 2019;124:1669−1673)**

Statins decrease the incidence of cardiovascular events and reflect the contemporary cornerstone of dyslipidemia management.[1,2] Despite their absolute clinical efficacy, a sizable fraction of patients experience dose-limiting toxicity resulting in medication discontinuation.[3] In addition, some patients derive insufficient biochemical benefits despite maximal doses of high-intensity statins. Several randomized clinical trials, including the landmark Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial, have established PCSK-9 inhibitors as an effective lipid-lowering addition or alternative to statins and ezetimibe.[4,5] Alirocumab and evolocumab have been approved by the US Food and Drug Administration for use in patients with homozygous familial hypercholesterolemia, as an adjunct to diet and other low-density lipoprotein cholesterol (LDL-C)-lowering therapies, and in patients with severe dyslipidemia despite maximally tolerated statins and ezetimibe, also as an adjunct to diet, alone or in combination with other lipid-lowering therapies. Data about the real-world use of PCSK9 inhibitors is limited and there is a significant clinical and scientific need to expand our understanding of their clinical and public health value.

Methods

We used an institutional database consisting of all patients who were referred to a preventive cardiologist for workup and management of severe dyslipidemia. Patients were evaluated in either the prevention clinic, statin intolerance clinic, familial hypercholesterolemia clinic, or the general cardiovascular prevention clinic, all within the Mayo Clinic in Rochester, Minnesota. A total of 222 patients with severe dyslipidemia (LDL-C ≥190, or LDL-C ≥160 if on statins or younger than age 65) were referred to a preventive cardiologist between September 2015 and December 2018 (Figure 1). A recommendation to start a PCSK9 inhibit was given to 164 patients (73.9%).

We characterized the cohort according to PCSK9 inhibitor use status and defined the group of PCSK9-inhibitor-treated patients according to age, gender, and ethnic distribution. Information regarding the profile of clinical co-morbidities, baseline cardiovascular disease status, pre- and post-treatment cholesterol levels and the development of

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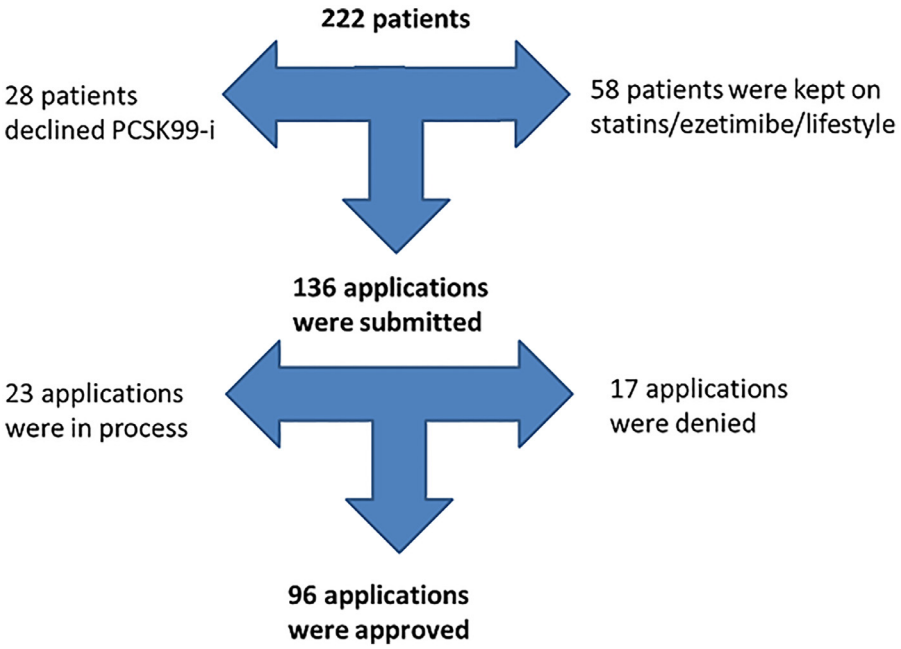

Figure 1. Cohort patients distribution by PCSK9 inhibitor status.

treatment-related side effects or cardiovascular sequela during follow-up was collected as well. The data was obtained from review of electronic medical charts and medication compliance was confirmed using a phone contact. The Institutional Review Board deemed the study exempt from informed consent procedures.

The percent reduction in LDL-C was assessed with 2 sample *t* Tests for categorical variables and linear regression for continuous variables. p Values <0.05 were considered statistically significant. A multivariable model was developed using all variables with univariate p values <0.1.

Results

Of the 164 patients who were provided a recommendation to initiate a PCSK-9 inhibitor, 28 (17.1%) declined with 8 (28.6%) stating a financial reason. Fifty eight (26.1%) patients were instructed to follow lifestyle modifications or remain on statin and/or ezetimibe with a future consideration for a PCSK9 inhibitor. A total of 136 previous authorizations were submitted to insurance companies. Of those, 96 applications were approved (70.6%), 17 were denied (12.5%), and 23 (16.9%) were still in process at the time of our analysis. During the investigated time period, the 6-month approval rate decreased from 86.7% to 100% during the first 2 years to 60% to 76.9% in the last 10 months (Table 1). A comparison of the approval rates during the 12-month period before the introduction of a new electronic medical record (May, 2018) to the subsequent 10 months revealed a statistically significant decrease (89.9% vs 68.4%, Chi-square p value 0.049).

Table 1
Medication approval rate during the study period

Time Period	Medication approval rate
09/2015-02/2016	89% (8/9)
03/2016-08/2016	90% (9/10)
09/2016-02/2017	100% (9/9)
03/2017-08/2017	87% (24/28)
09/2017-02/2018	93% (27/29)
03/2018-08/2018	77% (10/13)
09/2018-12/2018	60% (9/15)

A total of 96 patients were initiated on a PCSK9 inhibitor (Table 2). The mean age was 64.1 years old (range 39 to 91). There were 51 (53.1%) female and 45 (46.9%) male patients. Evolocumab was used in 85 (88.5%) patients and alirocumab in 11 (11.5%) patients. Hypertension, diabetes mellitus, and chronic kidney disease were documented in 55 (57.3%), 13 (13.5%), and 11 (11.5%) of the patients, respectively. A genetically-confirmed diagnosis of familial hypercholesterolemia was present in 38 (39.6%) patients. Twelve (12.5%) patients had history of any cancer. The complete baseline characteristics are outlined in Table 2.

At baseline, 50 (52.1%) patients were on high-intensity statins and 80 (83.3%) were on ezetimibe. A diagnosis of statin intolerance was documented in 84 (87.5%) of the patients. The most common reason for statin intolerance was musculoskeletal pain (70, 73%). Aspirin, β-blockers, and angiotensin converting enzyme inhibitors or angiotensin receptor blockers were used in 81 (84.4%), 53 (55.2%), and 46 (47.9%) of the patients, respectively.

The mean baseline total cholesterol level was 255.5 mg/dl and the mean baseline triglycerides, high-density lipoprotein, cholesterol and Lipoprotein(a) were 240.3 mg/dl, 54.1 mg/dl, and 60.7, respectively. The mean pretreatment LDL-C was 167.9 mg/dl. The characteristics of the 17 patients whose applications were rejected are presented in Table 3.

The mean value of the first on-treatment LDL-C, obtained 2 to 6 months following initiation of therapy, was 72.2 mg/dl. Mean duration of follow up was 19 months (interquartile range 9,26) with an average of 2.8 (range 0

Table 2
Characteristics of PCSK9-i-treated patients (n = 96)

Age (mean, range)	64.1 (39-91)
Evolocumab	85, (89%)
Women	51, (53%)
Body mass index >30 kg/m^2	49, (51%)
Body mass index (mean)	31
Hypertension	55, (57%)
Smoker	36, (38%)
Impaired fasting glucose among nondiabetics (n = 83)	36, (43%)
Low high-density lipoprotein cholesterol (men: <40 mg/dl, women: <50 mg/dl)	35, (36%)
Diabetes mellitus	13, (14%)
Chronic kidney disease	11, (12%)
Prior myocardial infarction	19, (20%)
Stroke	3, (3%)
Peripheral arterial disease	6, (6%)
Active smoker	3, (3%)
Familial hypercholesterolemia	38, (40%)
History of cancer	12, (13%)
High-intensity statin use	50, (52%)
Ezetimibe use	80, (83%)
Statin intolerance	84, (88%)
Aspirin use	81, (84%)
Beta-blocker use	53, (55%)
Angiotensin convertin enzyme inhibitor/angiotensin receptor blocker use	46, (48%)
Baseline total cholesterol, mean (mg/dl)	255
Baseline triglycerides (mg/dl)	240
Baseline high-density lipoprotein cholesterol (mg/dl)	54
Baseline lipoprotein a (n = 53)	61
Baseline Apolipoprotein B-100 (n = 62)	136
Baseline ceramide score (n = 54)	7.4
Baseline hemoglobin, mean (mg/dl)	12.9
Baseline platelet count, mean (10^9/L)	231
Pre-treatment low-density lipoprotein cholesterol, mean (mg/dl)	168
On-treatment low-density lipoprotein cholesterol, mean (mg/dl) (3-6 months)	72
Lowest on-treatment low-density lipoprotein cholesterol, mean (mg/dl)	64
% Low-density lipoprotein cholesterol reduction, mean	61%, (range 0-90%)
Time to lowest low-density lipoprotein cholesterol, mean (months)	8.1
Duration of follow up, mean (months)	16.6

Table 3
Characteristics of patients whose applications were denied (n = 17)

Age (mean, range)	60.5, 33-88
Women	7, (41%)
Hypertension	10, (59%)
Diabetes mellitus	3, (18%)
Chronic kidney disease	1, (6%)
History of myocardial infarction	4, (24%)
Stroke	1, (6%)
Peripheral arterial disease	0
Active smoker	2, (12%)
Familial hypercholesterolemia	7, (41%)
History of cancer	3, (18%)
High-intensity statin use	7, (41%)
Ezetimibe use	13, (77%)
Statin intolerance	13, (77%)
Aspirin use	16, (94%)
Beta-blocker use	7, (41%)
Angiotensin convertin enzyme inhibitor/ angiotensin Receptor blocker use	10, (59%)
Baseline total cholesterol, mean (mg/dl)	245
Baseline low-density lipoprotein cholesterol, mean (mg/dl)	168
Baseline triglycerides (mg/dl)	156
Baseline high-density lipoprotein cholesterol (mg/dl)	50
Baseline lipoprotein a (n = 12)	33
Baseline apolipoprotein B-100, (mg/dl) (n = 10)	129
Baseline ceramide score (n = 8)	8.7

Table 4
Clinical events at follow up and adverse effects of PCSK9−i-treated patients (n = 96)

Hospitalization for unstable angina pectoris	1, (1%)
Stroke	0
Coronary revascularization	2, (2%)
Cardiovascular death	0
Any adverse event	12, (13%)
Injection-site reaction	3, (3%)
Muscle-related event	3, (3%)
Cataract	0
New diabetes mellitus	0
Neurocognitive event	0

to 15) LDL-C measurements after therapy initiation. The mean of the lowest on-treatment LDL-C was 64.5 mg/dl and the mean percent reduction was 60.9% (range 0% to 90.3%). The mean time to the lowest measured LDL-C was 8.1 months. To evaluate the trend of LDL-C over time, we fit a model to predict the last LDL-C value. The time since first treatment was adjusted for the LDL-C value at baseline by including both as independent variables in the model. No significant association between time and final LDL-C was found (p value 0.36), indicating that there was no trend of attenuation in the LDL-C reduction.

During follow up, there were no reported cardiovascular deaths (Table 3). One patient (1.0%) was hospitalized for unstable angina and 2 patients (2.1%) underwent coronary revascularization. Adverse effects were reported in 12 (12.5%) patients and were all minor, as described in Table 4. No cataracts, confirmed neurocognitive events or new diagnosis of diabetes mellitus were encountered.

Statistically significant greater LDL-C percent reductions were seen in younger patients (p value 0.048; 4.4% lower LDL-C reduction for every 10 year increase in age), patients on high-intensity statins (p value 0.027), those with statin intolerance (p value 0.046), and individuals with a higher baseline Tg (p value 0.047; 0.6% higher LDL-C reduction with every 10 mg/dl increase in Tg). There were no differences in the LDL-C reduction between genders, patients with and without hypertension, diabetes mellitus, chronic kidney disease, history of myocardial infarction, stroke, cancer, active nicotine use, and peripheral arterial disease. There was no difference between the magnitude of LDL-C percent reduction in patients with or without genetically-determined familial hypercholesterolemia (62.5%,

59.9%, p value 0.61, CI 53.5 to 66.3). The use of antiplatelet drugs, β-blockers or angiotensin convertin enzyme inhibitor/angiotensin receptor blocker was also not associated with a statistically different LDL-C drop. Baseline total cholesterol, LDL-C, HDL, Lpa, Apo B, ceramide, hemoglobin, and platelet levels had no association with greater LDL-C reduction as well. In a multivariable analysis, only young age (p value 0.039) and high-intensity statin use (p value 0.012) were associated with greater LDL-C reductions.

Discussion

In a single-center retrospective analysis, we show that PCSK9 inhibitors are associated with a magnitude of LDL-C reduction and incidence of adverse effects that are equivalent to those demonstrated in the seminal randomized controlled trials. Data regarding real-world utilization and efficacy of PCSK9 inhibitors has been recently reported by various groups using distinct methodological approaches. An investigation of 18 US health care systems within the National Patient-Centered Clinical Research Network has determined that in patients with coronary heart disease, 0.2% of patients were prescribed a PCSK9 inhibitor, with a trend toward an increase in its use over time.[6] PCSK9 inhibitors were used by only 0.02% of patients with dyslipidemia (but not coronary heart disease) with stable prescribing patterns over time. A European physician-based study of 3,073 patients receiving lipid lowering therapies showed overall PCSK9 prescription rates of 12.6%, higher in Germany (20.2%) and lower in the UK (6.9%). PCSK9 inhibitor users were younger, had higher baseline LDL-C levels, and were more likely to have had myocardial infarction or acute coronary syndrome compared with those on non-PCSK9 inhibitor-based therapies.[7] Another real-world data regarding PCSK9 inhibitors is derived from the experience of a regional lipid clinic in Israel.[8] In that study, 101 patients were treated with PCSK9 inhibitors, approximately 1/2 of which had probable/definite familial hypercholesterolemia. Mean LDL-C reduction was reported as 59% and the side effect profile predominantly consisted of musculoskeletal complaints, leading 15% of the patients to discontinue treatment.

In our analysis, over a period of 40 months, 222 patients with severe dyslipidemia were referred for further evaluation by a preventive cardiologist. A relatively high proportion of patients refused a PCSK9 inhibitor, with approximately 1/3 of whom stating an economical reason. Approximately 1/8 of the prior authorizations were declined by the patient's insurance company, which is a significantly lower figure than the rejection rate commonly reported in the literature, which is in the 70% to 80% range.[9,10] Our high insurance approval rates could be attributed to the use of a standardized "Guidelines for Requesting a PCSK9 Inhibitor" form which ensures that patients meet clinical and biochemical criteria (i.e., atherosclerotic cardiovascular disease, lipid levels, use of high-intensity statins/statin intolerance, genetically-confirmed familial hypercholesterolemia, etc) before submission of the application. The form also includes a notation regarding the consumption of low-fat diet and participation in routine physical activity program, which we have found as essential for third-party payers to cover the medication's expenses. In addition, our cohort had a relatively high proportion of patients with genetically-confirmed familial hypercholesterolemia which has been associated with higher approval likelihood. In addition, the PCSK9 inhibitor was prescribed by cardiologists, a factor that also correlates with higher approval rate.

Patients whose applications were denied had a mildly more favorable baseline cardiovascular risk profile (lower rates of chronic kidney disease, peripheral arterial disease) and were less likely to have been on high-intensity statins or ezetimibe or to have experienced statin-related adverse effects. Indeed, our standardized submission process included those parameters and has facilitated the prescription of PCSK9 inhibitors in cases with a clear medical indication, after maximization of lifestyle and pharmacologic therapies has been achieved.

Our cohort of 96 treated patients reveals similar biochemical efficacy to that described by the seminal PCSK9 inhibitor clinical trials. Our mean group LDL-C reduction of 60.9% compares very well with FOURIER's median LDL-C reduction of 59% and ODYSSEY LONG TERM's mean LDL-C drop of 62.0%. As to the cardiovascular event rate, ours was significantly lower compared with landmark trials, which could be explained by our cohort's smaller size, its relatively low baseline cardiovascular risk and the lack of a centralized monitoring process to collect and review all events. A minority of the patients experienced side effects and these were predominantly minor and tolerable. The incidence of any side effect was significantly lower in our patients compared with that described by the large-scale clinical trials, but injection-site reactions and myalgias occurred in a similar rate.

Limitations of our study include its retrospective and single-institution nature. It is possible that hospitalizations or cardiovascular events occurred in an outside medical facility and were not captured by our electronic medical records although at the time of PCSK9 inhibitor prescription initiation, all patients were requested to notify the clinic if any cardiovascular events occurred. Of note, the number of clinical events was low and there was no control arm with which to compare it.

In summary, a sizable cohort of patients referred to preventive cardiology for workup and management of dyslipidemia revealed a high PCSK9 inhibitor refusal rate by patients but a relatively high approval rate by insurance. Biochemical efficacy was congruent with that previously reported in the literature, with excellent safety profile. Further investigations will help shed light on the real-world performance of PCSK9 inhibitors as well as the relevant obstacles to its effective dissemination.

Disclosures

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Clinic Support Services, Texas – Board Member, Mayo Clinic CV P&T Task Force – Member.

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