

Muscle-Related Adverse Events Associated With PCSK9 Inhibitors in a Veteran Population

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Background: Statins and PCSK9 inhibitors (PCSK9i) are used to lower low-density lipoprotein cholesterol and reduce cardiovascular events, yet some patients are unable to tolerate statin therapy due to muscle-related adverse events (AEs). The effect of PCSK9i on muscle-related AEs is not well studied, and available data show inconsistent incidence rates.

Methods: The primary study outcome was to determine the percentage of patients who developed muscle-related PCSK9i AEs. A secondary outcome was to analyze data based on 4 subgroups: tolerated a full PCSK9i dose; tolerated alternative PCSK9i following initial intolerance; required a PCSK9i dose reduction, or discontinued PCSK9i. In addition, the percentage of statin- and/or ezetimibe-intolerant patients in these 4 groups was determined. Another secondary outcome was the management strategies taken for patients who were on a reduced (monthly) dose of PCSK9i who did not reach their low-density lipoprotein cholesterol goal. Statin intolerance was defined as intolerable skeletal muscle

AEs on at least 3 different statins. We conducted a single-center, retrospective review of patients prescribed a PCSK9i between December 1, 2017, and September 1, 2021, at a patient aligned care team clinic at the Wilkes-Barre Veterans Affairs Medical Center.

Results: The study included 137 veterans. Twenty-four patients (17.5%) developed a muscle-related AE while on a PCSK9i. In predefined subgroups studied, statin intolerance ranged from 68.1% to 100%, ezetimibe intolerance ranged from 41.6% to 83.3%, and both statin and ezetimibe intolerance ranged from 36.3% to 83.3%.

Conclusions: In this study, muscle-related PCSK9i AEs occurred at a similar incidence rate to that reported in previous clinical trials and exceeded the incidence rate reported in the prescribing information for alirocumab and evolocumab. It also appears that patients who have a prior muscle-related intolerance to a statin and/or ezetimibe have a higher likelihood of developing a muscle-related AE to a PCSK9i.

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Fed Pract. 2023;40(2).

Published online February 15.

doi:10.12877/fp.0357

HMG-CoA reductase inhibitors (statins) have been shown to effectively reduce low-density lipoprotein cholesterol (LDL-C) as well as morbidity and mortality in patients who have either atherosclerotic cardiovascular disease (ASCVD) or risk factors for ASCVD.¹⁻¹² However, research shows that up to 20% of patients are unable to tolerate statin therapy due to muscle-related adverse events (AEs).¹³ This presents a substantial clinical challenge, as current management strategies for patients with statin-associated muscle symptoms, such as intermittent administration of statins and ezetimibe, seldom achieve the > 50% LDL-C reduction recommended by the 2018 American Heart Association/American College of Cardiology Clinical Practice Guidelines.¹⁴ Additionally, statin-intolerant patients who have antihyperlipidemic medication lowered or discontinued are at an increased risk of future cardiovascular events.¹⁵ Observational data also show that about 70% of adult patients (primarily with genetic lipid disorders such as heterozygous familial hypercholesterolemia) do not achieve an LDL-C level < 100 mg/dL despite treatment with maximum doses of statins with or without ezetimibe.^{16,17}

PCSK9 inhibitors (PCSK9i) have robust efficacy data to support use in patients who do not meet their LDL-C goal despite maximally tolerated lipid therapy.¹⁴ However, long-term safety data for PCSK9i are not as robust as its efficacy data. Specifically, safety data relating to muscle-related AEs, which are the most widely recognized AE associated with statins, have only been reported in a few clinical trials with varying incidence rates, levels of significance, and relatively small study populations. Furthermore, the real-world prevalence of muscle-related PCSK9i AEs is unknown. Clinical guidance for management strategies for muscle-related AEs associated with PCSK9i is largely lacking. For this study, muscle-related AEs were defined as any new or unusual muscle soreness, weakness, cramping, aches, and stiffness that persists, is generally bilateral, and typically affects the large muscles. It is important to note, that muscle-related AEs associated with statins, ezetimibe, and PCSK9i can be attributed to the placebo effect.

According to the prescribing information for alirocumab and evolocumab, myalgia, muscle spasms, and musculoskeletal pain each occurred in < 5% of the study populations.^{18,19} From these data,

TABLE Patients With Medication Intolerance Endpoints

Medication Intolerances	Tolerated full PCSK9i dose (n = 113)	Tolerated alternate PCSK9i (n = 4)	PCSK9i dose reduced (n = 16)	Discontinued PCSK9i (n = 6)
Statin, No. (%)	77 (68.1)	3 (75)	15 (93.8)	6 (100)
Ezetimibe, No. (%)	47 (41.6)	2 (50)	11 (68.8)	5 (83.3)
Statin + ezetimibe, No. (%)	41 (36.3)	2 (50)	10 (62.5)	5 (83.3)

Abbreviation: PCSK9i, PCSK9 inhibitors.

muscle-related PCSK9i AEs are thought to be relatively rare, based on the ODYSSEY-OUTCOME and FOURIER trials, which did not enroll statin-intolerant patients.^{20,21} However, currently available safety data from 3 small, randomized clinical trials specifically in statin-intolerant patients taking a PCSK9i suggest that muscle-related AEs occur at a rate of 12.2% to 32.5% and discontinuation rates varied from 0% to 15.9%.²²⁻²⁵ As the incidence rates of muscle-related AEs in the prescribing information and clinical trials varied widely, this study will provide quantitative data on the percentage of patients that developed muscle-related PCSK9i AEs in a veteran population to help shed light on a topic that is not well studied.

METHODS

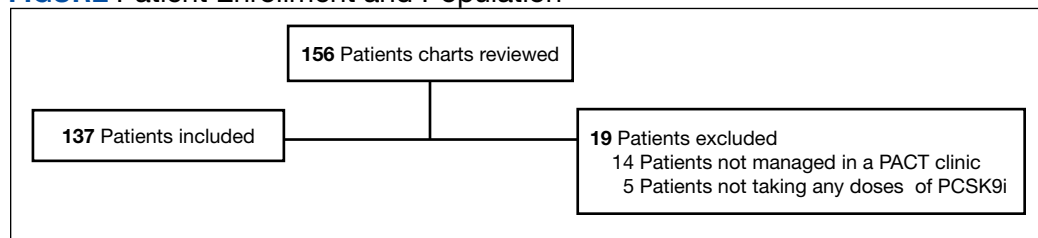
This was a single-center, retrospective chart review of patients prescribed a PCSK9i between December 1, 2017, and September 1, 2021, and were managed in a pharmacy-led patient aligned care team (PACT) clinic at the Wilkes-Barre US Department of Veterans Affairs (VA) Medical Center (WBVAMC) in Pennsylvania. This study was approved by the Coatesville VA Medical Center Institutional Review Board, which oversees research conducted at WBVAMC. Veterans aged ≥ 18 years were included in the study. Patients were excluded if they had a history of serious hypersensitivity reaction to a PCSK9i or rhabdomyolysis or did not meet the VA criteria for use.²⁶

The primary outcome was the percentage of patients who developed a muscle-related AE while on a PCSK9i in a PACT clinic. Data were further analyzed based on patients who (1) tolerated a full PCSK9i dose; (2) tolerated alternative PCSK9i following initial intolerance; (3) required a PCSK9i dose reduction, or (4) discontinued PCSK9i. A secondary outcome was the percentage of statin- and/

or ezetimibe-intolerant patients in these 4 groups. Another secondary outcome was the management strategies taken for patients who were on a reduced (monthly) dose of PCSK9i who did not reach their LDL-C goal. Management strategies that were assessed included restarting weekly statin, restarting weekly ezetimibe, increasing the dose of the same PCSK9i administered monthly, and switching to an alternative PCSK9i.

Data were collected using the VA Computerized Patient Record System (CPRS) and stored in a secure, locked spreadsheet. Baseline patient demographic characteristics collected included age (at PCSK9i start); sex; race; and PCSK9i name, dose, and frequency. We recorded when a patient switched PCSK9i, whether or not it was due to a muscle-related AE, and the name of the original PCSK9i. Also collected were lipid therapy intolerances prior to PCSK9i initiation (ie, intolerance to statin, ezetimibe, or both).

Patients were considered statin intolerant due to a muscle-related AE in accordance with the VA PCSK9i Criteria for Use, which requires trial of at least 3 statins, one of which was trialed at the lowest dosage approved by the US Food and Drug Administration (FDA) and resulted in intolerable skeletal muscle AEs that worsened during treatment and resolved when the statin was stopped. For our study purposes, patients taking alternative day dosing of statins due to muscle-related AEs (ie, 2- or 3-times weekly dosing) were not considered statin intolerant; however, patients taking once-weekly statin dosing were considered statin intolerant. Patients were considered ezetimibe intolerant due to a muscle-related AE if the intolerance was due to skeletal muscle concerns that worsened during treatment and resolved when ezetimibe was stopped. Patients were considered PCSK9i intolerant due to a

FIGURE Patient Enrollment and Population

Abbreviations: PACT, patient aligned care team; PCSK9i, PCSK9 inhibitors.

muscle-related AE if the intolerance was due to skeletal muscle concerns that worsened during treatment and resolved when the PCSK9i was stopped. Patients with non-muscle-related intolerances to statins, ezetimibe, and PCSK9i were not considered statin, ezetimibe, and PCSK9i intolerant.

Alirocumab was initiated at 75 mg subcutaneous (SQ) once every 2 weeks or evolocumab 140 mg SQ once every 2 weeks in our study. The protocol allowed for a dose reduction of alirocumab 75 mg SQ once monthly if a patient experienced AEs, but this dose reduction strategy was not used for any patients on evolocumab in this study. Of note, alirocumab 75 mg SQ once monthly is not an FDA-approved dosing strategy. However, it is similar in concept to the alternative statin dosing (ie, alternate day dosing, once-weekly dosing) and may avoid the need to discontinue PCSK9i therapy altogether.

A review of the CPRS also documented whether a muscle-related AE occurred while the patient was on a PCSK9i (if yes, the specific AE was recorded), the result of PCSK9i therapy (tolerated full dose, required a dose reduction, switched medication, or discontinued), and management strategies taken for patients who did not meet their LDL-C goal while on a reduced (monthly) PCSK9i dose. Prior lipid therapy intolerances, PCSK9i-related AEs, results of PCSK9i therapy, and management strategies for patients who did not meet LDL-C goal while on a reduced PCSK9i dose were obtained by reviewing the PACT pharmacist's clinic notes and assessment, along with clinic notes and medication history listed within the CPRS.

Statistical Analysis

Descriptive statistics were used for the demographic characteristics of study patients. The primary outcome was calculated as a binary measure (yes/no) of whether the pa-

tient developed a muscle-related AE while on a PCSK9i. The secondary outcome of statin, ezetimibe, or statin and ezetimibe intolerances in subgroups also was calculated as a binary measure.

RESULTS

For the study, 156 charts were reviewed and 137 patients were included (Figure). Nineteen patients were excluded; 14 were not managed in a PACT clinic and 5 were not taking any doses of the PCSK9i during the time of the review. The mean (SD) patient age at PCSK9i initiation was 68 (8) years. Most patients were male ($n = 131$, 95.6%), 129 (94.2%) were White veterans, and 132 (96.4%) were prescribed alirocumab at baseline. We found that 24 patients (17.5%) developed a muscle-related AE while on a PCSK9i.

For the secondary results, 4 patients (2.9%) tolerated an alternate PCSK9i (evolocumab 140 mg SQ every 2 weeks) after initial intolerance to PCSK9i, 16 (11.7%) required a dose reduction, and 6 (4.4%) discontinued PCSK9i due to a muscle-related AE. Two patients had their PCSK9i reduced to monthly dosing and then later switched and tolerated an alternate PCSK9i due to not meeting their LDL-C goal. These patients were accounted for twice in the categories above (Table).

Statin intolerance was most common in all groups, followed by ezetimibe intolerance, and intolerance to statins + ezetimibe. Of the 113 patients who tolerated a full dose of PCSK9i, 77 (68.1%) had intolerance to statin, 47 (41.6%) to ezetimibe, and 41 (36.3%) to both statins and ezetimibe. Of the 6 patients who discontinued PCSK9i, all had intolerance to statins, 5 (83.3%) to ezetimibe, and 5 (83.3%) to statins and ezetimibe.

For patients who were on a reduced (monthly) dose of a PCSK9i who did not

reach their LDL-C goal, we found that 16 patients (11.7%) required a PCSK9i dose reduction following muscle-related AEs. Of the patients who had their dose of PCSK9i reduced to monthly dosing, 5 (31%) met their LDL-C goal. For the 11 patients who did not meet their LDL-C goal, different management strategies were taken. Lifestyle modifications were made in 6 patients (54%), the monthly PCSK9i dose was increased to alirocumab 150 mg SQ monthly in 4 patients (36%), and 1 patient (9.1%) was switched to an alternative PCSK9i. There were no identified muscle-related AEs recorded in patients whose dose was increased to alirocumab 150 mg SQ monthly.

DISCUSSION

This retrospective study found 17.5% of patients experienced muscle-related PCSK9i AEs. These occurred at a higher rate than reported in the prescribing information (< 5%) and were similar to the incidence rates reported in the GAUSS-2, GAUSS-3, and ODYSSEY-ALTERNATIVE clinical trials (12.0%-32.5%), which is what we hypothesized.^{18,19,22-25} It is important to note that the incidence rates of muscle-related AEs reported in the prescribing information for alirocumab and evolocumab were based on trials that did not include statin- and/or ezetimibe-intolerant patients; whereas many patients in our study and patients in the clinical trials were statin and/or ezetimibe intolerant.

Additionally, a new study by Donald and colleagues found an incidence rate of 32% to 36% for muscle-related PCSK9i AEs.²⁷ Collectively, the data from clinical trials and our study indicate that patients with prior intolerances to statin and/or ezetimibe appear to have a higher likelihood of developing a muscle-related PCSK9i intolerance. In our study, 23 of 24 patients who developed a muscle-related PCSK9i AE had a prior history of statin and/or ezetimibe intolerances. This should alert clinicians prescribing PCSK9i in patients with a history of statin and/or ezetimibe intolerance to counsel their patients on the possibility of muscle-related PCSK9i AEs and management strategies. However, it is important to note that there was a substantial number of patients in our study who were statin and/

or ezetimibe intolerant due to a prior muscle-related AE who tolerated the full dose of PCSK9i.

To our knowledge, this was the first trial to evaluate muscle-related PCSK9i AEs in a veteran population. Additionally, our study appears to be the first to use 2 PCSK9i dosing strategies that are not FDA approved: Dose reduction for patients who experienced a muscle-related AE on alirocumab 75 mg SQ every 2 weeks and dose escalation for patients who did not meet their LDL-C goal on alirocumab 75 mg SQ monthly following an initial intolerance to 2-week dosing. The dose-reduction strategy allowed patients who experienced a muscle-related AE to alirocumab 75 mg to reduce administration from every 2 weeks to monthly.

This strategy was only performed with alirocumab, the preferred PCSK9i at WBVAMC, but the same dose-reduction strategy can theoretically be used with evolocumab as well. Reduced monthly dosing of alirocumab allowed patients with a prior intolerance to remain on a lower dosage without discontinuation. This is important because as noted by Myers and colleagues, individuals without access to PCSK9i were found to have a significantly higher incidence ratio of cardiovascular events compared with those taking PCSK9i.¹⁵ Also of note, > 30% of patients on the reduced monthly dose of alirocumab still met their LDL-C goal. Therefore, using this dose-reduction strategy (instead of patients discontinuing therapy altogether due to a muscle-related intolerance) can lessen the risk of major adverse cardiovascular events (MACE) as well as mitigate muscle-related AEs that occurred while on 2-week PCSK9i dosing regimens. While we acknowledge that this reduced monthly dose of either alirocumab or evolocumab is not FDA approved, it is similar to alternative statin dosing that also is not FDA approved but may minimize the need to discontinue PCSK9i therapy. It would be beneficial if these dosing strategies were investigated by future research.

The dose-escalation strategy for patients who did not meet their LDL-C goal while on the reduced, monthly dose of alirocumab also was unique. Alirocumab was increased from 75 mg SQ once monthly to 150 mg SQ once monthly. Interestingly, we found that through the end of the chart review period,

all patients tolerated the increase well, despite having an initial muscle-related AE to alirocumab 75 mg every 2 weeks, which is the same total monthly dosage. This approach is similar to that of once-weekly statin dosing or a drug holiday and may be explained by the long half-life of PCSK9i. Regardless of the mechanism, this finding suggests that an increased monthly dose of PCSK9i is a potential alternative for patients who cannot tolerate the FDA-approved dose. However, the ability for patients to achieve goal LDL-C on the monthly dosage requires future study.

In our study, only 6 patients (4.4%) discontinued PCSK9i therapy. This low discontinuation rate is largely attributable to our unique study design, which allowed for a dose reduction in patients who experienced muscle-related AEs. The earlier ODYSSEY-ALTERNATIVE trial evaluated the safety and efficacy of alirocumab compared with ezetimibe in confirmed statin-intolerant subjects after 24 weeks. This trial did not use a dose-reduction strategy and found 15.9% of patients discontinued alirocumab due to a muscle-related AE.²⁴ This is notably higher than our discontinuation rate of 4.4%. If patients with a muscle-related AE discontinued PCSK9i instead of reducing the dose, they would likely return to their baseline LDL-C, which would increase the risk of MACE.

In general, myalgias due to antihyperlipidemic medications are not completely understood. One possible mechanism for statin-induced myalgias is the depletion of ubiquinone. However, this theory cannot explain muscle-related AEs associated with PCSK9i or ezetimibe, which have not been shown to deplete ubiquinone. We also found that the onset of muscle-related AEs associated with PCSK9i tends to appear later in therapy than what we know about statin therapy. Our study showed that the onset of a muscle-related PCSK9i AE occurred a mean (SD) 8 (5.3) months after initiation (range, 1-19). Statin muscle-related AEs typically occur within the initial 4 to 8 weeks of treatment, although they can occur at any time.²⁸

Limitations

The results of this study should be considered with the following limitations. First, this was a retrospective chart review per-

formed over a prespecified period. Any muscle-related AEs or LDL-C lowering effects from PCSK9i that occurred outside the review period were not captured. Our study was small and only included 137 patients, though it was similar in size to the GAUSS-2, GAUSS-3, and ODYSSEY-ALTERNATIVE trials.²²⁻²⁴ Additionally, the study was primarily composed of White men and may not be representative of other populations. Some muscle-related PCSK9i AEs may be attributed to the placebo. Last, our study did not capture patients on a PCSK9i who were not followed in the PACT clinic.

CONCLUSIONS

We found that muscle-related PCSK9i AEs occurred at a similar rate as those reported in previous clinical trials and exceeded the incidence rate reported in the prescribing information for alirocumab and evolocumab. It appears that patients who have a prior muscle-related intolerance to a statin and/or ezetimibe had a higher likelihood of developing a muscle-related PCSK9i AE. In our study, only 1 patient developed a muscle-related PCSK9i AE who did not have a prior history of muscle-related intolerance to either a statin or ezetimibe. However, in our study, a substantial percentage of patients with statin and/or ezetimibe intolerances tolerated the full PCSK9i dose well, proving that PCSK9i are still a reasonable alternative for patients with prior intolerances to statins and/or ezetimibe.

Acknowledgments

This material is the result of work supported with resources and the use of facilities at the US Department of Veterans Affairs Medical Center, Wilkes-Barre, Pennsylvania.

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Author contributions

Conception and design, final approval, and accountable for all aspects of the work (all); data analysis and interpretation (JC, CA); manuscript writing (JC, CA).

Author disclosures

The authors report no actual or potential conflicts of interest or outside sources of funding with regard to this article.

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indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.

Ethics and consent

All authors completed education requirements through the Collaborative Institutional Training Initiative program. This study was approved by the Coatesville Veterans Affairs Institutional Review Board (VISN 4 M/S), Coatesville Veterans Affairs Medical Center.

References

1. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344(8934):1383-1389.
2. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med*. 1996;335(14):1001-1009. doi:10.1056/NEJM199610033351401
3. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339(19):1349-1357. doi:10.1056/NEJM199811053391902.
4. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360(9326):7-22. doi:10.1016/S0140-6736(02)09327-3
5. Koren MJ, Hunninghake DB; ALLIANCE Investigators. Clinical outcomes in managed-care patients with coronary heart disease treated aggressively in lipid-lowering disease management clinics: the alliance study. *J Am Coll Cardiol*. 2004;44(9):1772-1779. doi:10.1016/j.jacc.2004.07.053
6. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998;279(20):1615-1622. doi:10.1001/jama.279.20.1615
7. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA*. 2002;288(23):2998-3007. doi:10.1001/jama.288.23.2998
8. Sever PS, Dahlöf B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003;361(9364):1149-1158. doi:10.1016/S0140-6736(03)12948-0
9. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359(21):2195-2207. doi:10.1056/NEJMoa0807646
10. Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. *Lancet*. 2006;368(9542):1155-1163. doi:10.1016/S0140-6736(06)69472-5
11. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet*. 2002;360(9346):1623-1630. doi:10.1016/S0140-6736(02)11600-x
12. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 1995;333(20):1301-1307. doi:10.1056/NEJM199511163332001
13. Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *Eur Heart J*. 2015;36(17):1012-1022. doi:10.1093/eurheartj/ehv043
14. Grundy SM, Stone NJ, Bailey AL, et al. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73(24):e285-350. doi:10.1016/j.jacc.2018.11.003
15. Myers KD, Farboodi N, Mwamburi M, et al. Effect of access to prescribed PCSK9 inhibitors on cardiovascular outcomes. *Circ Cardiovasc Qual Outcomes*. 2019;12(8):e005404. doi:10.1161/CIRCOUTCOMES.118.005404
16. Wong ND, Chuang J, Zhao Y, Rosenblit PD. Residual dyslipidemia according to low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B among statin-treated US adults: National Health and Nutrition Examination Survey 2009-2010. *J Clin Lipidol*. 2015;9(4):525-532. doi:10.1016/j.jacl.2015.05.003
17. Della Badia LA, Elshourbagy NA, Mousa SA. Targeting PCSK9 as a promising new mechanism for lowering low-density lipoprotein cholesterol. *Pharmacol Ther*. 2016;164:183-194. doi:10.1016/j.pharmthera.2016.04.011
18. Praluent (alirocumab) injection. Prescribing information. Regeneron Pharmaceuticals; 2021.
19. Repatha (evolocumab) injection. Prescribing information. Amgen; 2021.
20. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018;379(22):2097-2107. doi:10.1056/NEJMoa1801174
21. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376(18):1713-1722. doi:10.1056/NEJMoa1615664
22. Stroes E, Colquhoun D, Sullivan D, et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. *J Am Coll Cardiol*. 2014;63(23):2541-2548. doi:10.1016/j.jacc.2014.03.019
23. Nissen SE, Stroes E, Dent-Acosta RE, et al. Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance: the GAUSS-3 randomized clinical trial. *JAMA*. 2016;315(15):1580-1590. doi:10.1001/jama.2016.3608
24. Moriarty PM, Thompson PD, Cannon CP, et al. Efficacy and safety of alicumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: the ODYSSEY ALTERNATIVE randomized trial. *J Clin Lipidol*. 2015;9(6):758-769. doi:10.1016/j.jacl.2015.08.006
25. Mesi O, Lin C, Ahmed H, Cho LS. Statin intolerance and new lipid-lowering treatments. *Cleve Clin J Med*. 2021;88(7):381-387. Published 2021 Jul 1. doi:10.3949/ccjm.88a.20165
26. US Department of Veterans Affairs. Clinical Guidance - Criteria For Use. September 2016. Accessed January 23, 2023. <https://www.pbm.va.gov/clinicalguidance/criteriaforuse.asp>
27. Donald DR, Reynolds VW, Hall N, DeClercq J, Choi L. Exploring rates of PCSK9 inhibitor persistence and reasons for treatment non-persistence in an integrated specialty pharmacy model. *J Clin Lipidol*. 2022;16(3):315-324. doi:10.1016/j.jacl.2022.03.004
28. Warden BA, Guyton JR, Kovacs AC, et al. Assessment and management of statin-associated muscle symptoms: A clinical perspective from the National Lipid Association. *J Clin Lipidol*. Published online September 10, 2022. doi:10.1016/j.jacl.2022.09.001