

2023

Social determinants may limit the success of PCSK9 inhibitors, an effective treatment for hyperlipidemia in statin-intolerant patients

Abigail C. Kuplicki

Wayne State University, ga7242@wayne.edu

Follow this and additional works at: <https://digitalcommons.wayne.edu/crp>



Part of the [Cardiovascular Diseases Commons](#), [Medical Education Commons](#), [Medical Humanities Commons](#), [Therapeutics Commons](#), and the [Translational Medical Research Commons](#)

Recommended Citation

KUPLICKI AC. Social determinants may limit the success of PCSK9 inhibitors, an effective treatment for hyperlipidemia in statin-intolerant patients. *Clin Res Prac*. Nov 1 2023;9(1):eP3264. <https://doi.org/10.22237/crp/1698019740>

This Clinical Decision Report is brought to you for free and open access by the Open Access Journals at DigitalCommons@WayneState. It has been accepted for inclusion in *Clinical Research in Practice: The Journal of Team Hippocrates* by an authorized editor of DigitalCommons@WayneState.

Social determinants may limit the success of PCSK9 inhibitors, an effective treatment for hyperlipidemia in statin-intolerant patients

ABIGAIL C. KUPLICKI, Wayne State University School of Medicine, ga7242@wayne.edu

ABSTRACT A clinical decision report using:

Moriarty PM, Thompson PD, Cannon CP, et al. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial. *J. Clin. Lipidol.* 2015;9(6):758-769.
<https://doi.org/10.1016/j.jacl.2015.08.006>

for a statin-intolerant patient with hyperlipidemia.

Keywords: *statin-intolerance, PCSK9 inhibitors, alirocumab, ezetimibe, statin, patient trust, statin alternatives, veteran, female veteran, red yeast rice*

Clinical-Social Context

Ms. Brenda Howard [pseudonym], a single black woman and veteran in her mid-60s, was seen in clinic to discuss management of hyperlipidemia. Ms. Howard has been retired for a few years and receives a modest income through social security. She has less than 100% insurance coverage through the Veterans Administration (VA). Though retired, Ms. Howard continues to stay active by growing a vegetable garden and learning how to can and preserve her harvests for winter. Her BMI is overweight, and she lamented the discontinuation of a water aerobics program formerly sponsored by the VA before the Covid-19 pandemic. Because she has osteoarthritis of her knees, she is not interested in a non-water-based exercise program at this time, and she does not have the financial resources to join a fitness center with a pool herself. Despite efforts to improve her cholesterol through lifestyle, Ms. Howard has significant hyperlipidemia (LDL 196) but has previously refused medical management.

Through further interview, Ms. Howard admitted that she tried multiple statin medications for her hyperlipidemia with her former primary care physician several years ago. She described significant myalgia and severe fatigue while taking them. She was then prescribed niacin, which led to flushing and hot flashes. Since then, she has tried to manage her hyperlipidemia with diet and exercise, without much improvement. Because she already suffers osteoarthritis pain, she is unwilling to take another statin drug and hesitant to try alternative cholesterol-lowering pharmacotherapy. However, she is willing to learn about her options and wants to know how much of a benefit she could expect as well as potential side effects of alternative therapies.

ABIGAIL C. KUPLICKI is a medical student at Wayne State University School of Medicine.



ISSN: 2379-4550

<http://digitalcommons.wayne.edu/crp>, © 2023 The Author(s)

Licensed under [Creative Commons Attribution 4.0 International \(CC-BY-4.0\)](https://creativecommons.org/licenses/by/4.0/)

Clinical Question

What are the best alternatives for managing hyperlipidemia in statin-intolerant patients?

Research Article

Moriarty PM, Thompson PD, Cannon CP, et al. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial. *J. Clin. Lipidol*. 2015;9(6):758-769.
<https://doi.org/10.1016/j.jacl.2015.08.006>¹

Description of Related Literature

Randomized controlled trials were identified by using advanced search in PubMed with the following search algorithm: ((statin intolerance) AND (alternative)) AND (randomized controlled trial OR randomized clinical trial), which yielded 30 results. Titles and abstracts were reviewed to identify the most relevant studies. Several studies identified by this search were meta-analyses of randomized controlled trials, n-of-1 trials evaluating statin intolerance itself, or studies that combined alternative lipid-lowering therapies with statins to quantify additional benefits. These studies were eliminated as the primary aim of this search was to find primary evidence for the use of non-statin lipid-lowering therapies alone in statin-intolerant patients. Reports of ongoing clinical trials without completed data analysis were also eliminated.

After this screening, 10 relevant studies were identified (Table 1) and reviewed in detail. Studies were prioritized that (1) used therapeutic regimens commercially available in the United States, (2) had a control group, (3) minimized additional variables, (4) enrolled statin-intolerant participants, and (5) measured LDL-C concentration as a primary outcome.

Seven studies evaluated nutraceutical regimens as statin alternatives. Studies by Marazzi et al. (2011), Mitchell et al. (2012), Marazzi et al. (2015), Pisciotta et al. (2012), Kopecky et al. (2022), and Verhoeven et al. (2013) used combination preparations of bioactive nutrients in the form of capsules, drinks, or fortified snacks.²⁻⁷ While these studies had compelling evidence for use as statin alternatives, most of these regimens are not commercially available in the U.S., and all included too many variables to assess which particular components produced observed results, making it poorly applicable to the patient, Ms. Howard. Halbert et al. (2010) studied specifically red yeast rice versus moderate-dose pravastatin but was excluded because the primary outcomes were myalgia and therapy discontinuation rates, and the measured efficacy was likely impacted by the weekly 3.5-hour weekly lifestyle training concurrently given to participants.⁸

Three studies evaluated widely available statin pharmacotherapies. Moriarty et al. (2020) was eliminated because it was an open-label trial of only subcutaneous alirocumab without a control group.⁹ Kumar et al. (2009) evaluated an ezetimibe and fenofibrate combination versus 10 mg atorvastatin, and, at 6 weeks, the changes in average LDL-C among the groups were down -34.6% and -36.7%, respectively.¹⁰ The difference between these groups was not significant. Sample size was relatively small (n=41), and participants were not strictly screened for prior statin intolerance.

Of the studies reviewed, Moriarty et al. (2015) had the most robust evaluation of statin alternatives.¹ This study had the largest sample size of the randomized studies (n=250), measured change in LDL-C concentration as a primary outcome, and had the strictest criteria for selecting statin-intolerant patients. The trial also evaluated 2 different statin alternatives, alirocumab and ezetimibe, as independent monotherapies, making possible a direct comparison. Furthermore, the control group included moderate-dose atorvastatin in addition to a subcutaneous placebo, allowing researchers to consider the true presence of statin intolerance among participants. For these reasons, the study by Moriarty et al. (2015) was selected for critical appraisal. The strength of evidence for PCSK9 inhibitors, such as alirocumab, as a lipid-lowering therapy by the Strength of Recommendation Taxonomy (SORT) criteria is Grade of Recommendation A and Level of Evidence I.¹¹ This is based on two randomized controlled trials, the ODYSSEY trial discussed by Moriarty et al. (2015) and the FOURIER trial by Sabatine et al. (2017).^{1,12} Studies on the FOURIER trial were not included in this review because participants were concurrently taking statins. Thus, the Grade of Recommendation for alirocumab use in specifically statin-intolerant patients is B with Level of Evidence I since the study by Moriarty et al. (2015) is the only good-quality randomized controlled trial in this patient population.¹¹



Critical Appraisal

Study Methodology:

The report by Moriarty et al. (2015) used data from the ODYSSEY ALTERNATIVE study, a randomized, double-blind, double-dummy, active-controlled, and parallel-group trial.¹ This study had two alternative pharmacologic treatment arms, ezetimibe versus alirocumab, and one moderate-dose atorvastatin control group. The primary outcome was change in LDL-C concentration over the 24-week double-blind treatment period. Reported side effects, namely skeletal muscle complaints, were a secondary outcome.

Strict inclusion criteria for statin intolerance were utilized in this trial. Participants age ≥ 18 with primary hyperlipidemia were selected with prior inability to tolerate ≥ 2 different statins due to otherwise unexplained muscle symptoms (e.g., not due to strain or trauma). At least one of the statins previously used had to have been discontinued at or below the lowest approved daily starting dose. LDL-C ≥ 100 mg/dL was also required at screening. Patients taking medications with the potential to influence metabolism of the drugs being studied were excluded.

The study included 5 periods, a 1-week screening, a 2-week washout, 4 weeks of placebo run-in to exclude patients with other causes of muscle symptoms, a 24-week double-blind treatment, and 8 weeks of off-treatment follow-up. There were 3 treatment arms: (1) 75 mg subcutaneous alirocumab plus oral placebo, (2) subcutaneous placebo plus 10 mg oral ezetimibe, and (3) subcutaneous placebo plus 20 mg oral atorvastatin. Oral medications were taken daily, while subcutaneous injections were received biweekly. After the treatment phase, eligible patients were offered an open-label treatment phase with alirocumab 75 mg for 3 years. This phase of the trial is described by Moriarty, et al. (2020).⁹

All efficacy comparisons by Moriarty et al. (2015) were assessed between ezetimibe and alirocumab during the double-blind treatment phase, and ezetimibe was considered the active control.¹ The atorvastatin group was not assessed in this manner because this arm was only included to define the statin-intolerant patient population.

While LDL-C concentration from baseline to 24 weeks was the primary outcome, secondary measures included apolipoprotein B, non-HDL-C, total cholesterol, lipoprotein(a), HDL-C, apolipoprotein A1, and fasting triglyceride concentrations. Self-reported adverse events, especially skeletal muscle symptoms, were also described.

The outcomes were evaluated using an intent-to-treat approach; for the primary outcome of change in mean LDL-C concentration from baseline to week 24, all LDL-C values, regardless of adherence, were included. A mixed-effect model with repeated measures approach was used to account for missing data. Study sample size of 250 (100 each to alirocumab and ezetimibe, 50 to statin) during the double-blind treatment period was planned to both provide enough power to detect a 20% difference between ezetimibe and alirocumab groups and account for withdrawal. Efficacy was analyzed for binary endpoints with the multiple imputation approach and logistic regression, while continuous efficacy end points were analyzed with robust regression following the multiple imputation approach. Statistical significance was considered P value $\geq .05$.

Results:

Patient characteristics: 519 patients were originally screened, and 361 met eligibility criteria. 314 completed the placebo-run in, and those who failed were mostly excluded due to reports of skeletal muscle symptoms. The remaining patients were randomized to treatment arms: 125 to ezetimibe, 126 to alirocumab, and 63 to atorvastatin. Mean age of participants was 63.4 years with 54.8% men. Participants were also 93.9% white. Baseline average LDL-C was 191.4 mg/dL, with a range of 81.0-577.0 mg/dL. Lipid parameters were evenly distributed across the groups. About half of patients receiving alirocumab in the double-blind phase had lipid levels requiring a dose increase from 75 to 150 mg per protocol.

Efficacy: For the primary outcome, change in LDL-C concentration from baseline to 24 weeks was -45.0% (2.2%) in the alirocumab group and -14.6% (2.2%) for ezetimibe. The difference between the group was -30.4% (3.1%; P < .0001). This meant that, at week 24, 41.9% of patients on alirocumab met the treatment goal of LDL-C < 70 mg/dL in very high-risk patients or < 100 mg/dL in moderate-to-high risk patients, whereas only 4.4% on ezetimibe reached goal.



For secondary outcomes apolipoprotein B, non-HDL-C, total cholesterol, and lipoprotein(a), reductions were greater with alirocumab than ezetimibe ($P < .0001$). Changes in triglycerides, HDL-C, and apolipoprotein A1 were not statistically significant between the two groups.

In term of tolerability, myalgia was the most common self-reported adverse event. The difference in skeletal muscle-related adverse events was significantly lower with alirocumab than atorvastatin ($P = .042$), but this difference between alirocumab and ezetimibe was not statistically significant. The rate of treatment discontinuation due to these adverse events was not significantly different between the three groups. Other reported adverse events in $\geq 5\%$ of patients were nasopharyngitis, upper respiratory tract infection, and arthralgia on alirocumab and nasopharyngitis, upper respiratory tract infection, arthralgia, and back pain on ezetimibe. In the statin arm, fatigue, headache, muscular weakness, paresthesia, and vomiting were also reported.

Conclusions: In this study, alirocumab outperformed ezetimibe as a statin-alternative monotherapy. Consistent with previous reports, ezetimibe did result in an appreciable decrease in LDL-C concentration among patients, but this trial demonstrated that alirocumab has an overall larger impact on cholesterol levels with a comparable and perhaps superior short-term safety profile.

This study had several major strengths. First, the inclusion criteria for statin intolerant patients were very strict and specific, especially when compared to several other studies which often included patients who refused statins without evidence of prior intolerance. This study required patients to have at least two documented trials of different statins. This aspect of the study is directly applicable to Ms. Howard, who had tried more than one statin drug in the past with significant muscle symptoms. Another strength was the inclusion of a statin arm to assess the true rate of statin intolerance among participants. Finally, the option for patients to continue an open-label trial of alirocumab for up to 3 years at the end of this study was essential to evaluating the long-term safety of this relatively new therapeutic option.

The weakness in application of this study to our patient was most evident in terms of social determinants. Study participants were 93.9% white and majority male. As a black female, we cannot assume the tolerability and effect size will be the same for Ms. Howard. Furthermore, alirocumab, while commercially available, is much more expensive than ezetimibe and requires relatively complicated administration with biweekly injections. Researchers did not discuss cost, transportation issues, or other difficulties making biweekly appointments which can be anticipated in our patient population. Socioeconomic status was not considered in the randomization or analysis.

Clinical Application

Based on this trial, alirocumab is superior to ezetimibe in terms of its effect on lipid profile and short-term safety. Long-term safety, based on the open-label treatment portion of the trial published by Moriarty, et al., 2020, is promising.⁹ Thus, in statin-intolerant patients with significant hyperlipidemia, alirocumab may be the best monotherapy alternative.

Despite its shortcomings with regards to participant characteristics, the inclusion criteria of the study by Moriarty et al. (2015) did match our patient, Ms. Howard.¹ Because statins are still the superior and first-line lipid-lowering medication,¹³ Ms. Howard was first offered another trial of statin but refused. Initially, Ms. Howard refused any lipid lowering medications, but after discussing her options, the risks of untreated hyperlipidemia, and the expected decrease in LDL-C concentration with treatment, she agreed to a trial of ezetimibe. In this patient with barriers to treatment, including decreased mobility, financial limitations, and substantial drug hesitancy, ezetimibe is, for now, the most realistic option. The potential benefit of ezetimibe monotherapy in this patient is relatively small, compared to alirocumab, but so is the risk of harm. Although this may seem like a failure to apply research to patient care, building trust with a patient-centered approach, one where Ms. Howard was given options and chose the medication with which she felt most comfortable and would have the greatest success, is a favorable outcome of the clinic visit compared to her initial position that she would not take a lipid-lowering drug at all. Perhaps through trust-building and continued respect for her autonomy, in addition to seeing ezetimibe decrease in her LDL-C, a number that is very important to Ms. Howard, she may become more amenable to additional therapies in the future.

New Knowledge Related to Clinical Decision Science

Statin intolerance is an important topic in research with promising leads in both nutraceuticals and conventional pharmacy. The study by Moriarty, et al. offers the most thorough comparison of commercially available ezetimibe and alirocumab in specifically statin-intolerant patients.¹ Although this was an important trial for determining efficacy and safety of alirocumab, perhaps the most effective statin alternative available, there is a significant gap in the research its and the applicability to more challenging social contexts.

Patient trust has been identified as a significant variable in clinical decision reports. For example, in O'Dell (2022), patient mistrust of the medical system was identified as a major barrier to care.¹⁴ While providers should be hesitant to recommend less effective therapies as first-line treatments, it is reasonable to consider these options for patients who are resistant to the standard of care, assuming no significant potential for harm. This maintains patient autonomy and may foster trust between the individual and provider. Notably, it is also important to inform the patient of the potential need to escalate treatment if the selected therapy fails.

Financial barriers are also consistently identified as an obstacle to patients' access to medical therapies in the United States, including the female veteran population.¹⁵ Many veterans, like Ms. Howard, still have significant copayments for their prescriptions.¹⁶ While mistrust in the medical system was the primary focus of this case, patients' financial status should always be taken into consideration when discussing treatment options.

Conflict Of Interest Statement

The authors declare no conflicts of interest.

References

1. Moriarty PM, Thompson PD, Cannon CP, et al. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial. *J. Clin. Lipidol*. 2015;9(6):758-769. <https://doi.org/10.1016/j.jacl.2015.08.006>
2. Marazzi G, Cacciotti L, Pelliccia F, et al. Long-term effects of nutraceuticals (berberine, red yeast rice, policosanol) in elderly hypercholesterolemia patients. *Adv. Ther*. 2011;28(12):1105-1113. <https://doi.org/10.1007/s12325-011-0082-5>
3. Mitchell K, Rubenstein M, Rudnick C, Brejda J. A multicenter study of nutraceutical drinks for cholesterol (evaluating effectiveness and tolerability). *J. Clin. Lipidol*. 2012;6(2):150-158. <https://doi.org/10.1016/j.jacl.2011.09.004>
4. Marazzi G, Pelliccia F, Campolongo G, et al. Usefulness of nutraceuticals (Armolidip Plus) versus ezetimibe and combination in statin-intolerant patients with dyslipidemia with coronary heart disease. *Am. J. Cardiol*. 2015;116:1798-1801. <https://doi.org/10.1016/j.amicard.2015.09.023>
5. Pisciotta L, Bellocchio A, Bertolini S. Nutraceutical pill containing berberine versus ezetimibe on plasma lipid pattern in hypercholesterolemic subjects and its additive effect in patients with familial hypercholesterolemia on stable cholesterol-lowering treatment. *Lipids Health Dis*. 2012;11:123. <https://doi.org/10.1186/1476-511x-11-123>
6. Kopecky SL, Alias S, Klodas E, Jones PJH. Reduction in serum LDL cholesterol using a nutrient compendium in hyperlipidemic adults unable or unwilling to use statin therapy: A double-blind randomized crossover clinical trial. *J. Nutr*. 2022;152(2):458-465. <https://doi.org/10.1093/jn/nxab375>
7. Verhoeven V, Hartmann ML, Remmen R, Wens J, Apers S, Royen PV. Red yeast rice lowers cholesterol in physicians - a double blind, placebo controlled randomized trial. *BMC Complement. Altern. Med*. 2013;13(1):178. <https://doi.org/10.1186/1472-6882-13-178>
8. Halbert SC, French B, Gordon RY, et al. Tolerability of red yeast rice (2,400 mg twice daily) versus pravastatin (20 mg twice daily) in patients with previous statin intolerance. *Am. J. Cardiol*. 2010;105(2):198-204. <https://doi.org/10.1016/j.amicard.2009.08.672>
9. Moriarty PM, Thompson PD, Cannon CP, et al. Efficacy and safety of alirocumab in statin-intolerant patients over 3 years: Open-label treatment period of the ODYSSEY ALTERNATIVE trial. *J. Clin. Lipidol*. 2020;14(1):88-97. <https://doi.org/10.1016/j.jacl.2020.01.001>

10. Kumar SS, Lahey KA, Day A, LaHaye SA. Comparison of the efficacy of administering a combination of ezetimibe plus fenofibrate versus atorvastatin monotherapy in the treatment of dyslipidemia. *Lipids Health Dis.* 2009;8(1):56. <https://doi.org/10.1186/1476-511x-8-56>
11. Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): A Patient-Centered Approach to Grading Evidence in the Medical Literature. *J Am Board Fam Pract.* 2004;17(1):59-67. <https://doi.org/10.3122/jabfm.17.1.59>
12. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N. Eng. J. Med.* 2017;376(18):1713-1722. <https://doi.org/10.1056/nejmoa1615664>
13. Hariri EH, Al Hammoud MM, Nissen SE, Hammer DF. Primary and secondary prevention of atherosclerotic cardiovascular disease: A case-based approach. *Cleveland Clin. J. Med.* 2022;89(9):513-522. <https://doi.org/10.3949/ccjm.89a.21103>
14. O'Dell RA. Exploring alternative treatment options for a patient with heavy menstrual bleeding and mistrust of the healthcare system. *Clin. Res. Pract.* 2022;8(2):eP2810. <https://doi.org/10.22237/crp/1667260920>
15. Delcher C, Wang Y, Maldonado-Molina M. Trends in Financial Barriers to Medical Care for Women Veterans, 2003-2004 and 2009-2010. *Prev. Chronic Dis.* 2013;10:130071. <https://doi.org/10.5888/pcd10.130071>
16. Health Benefits. U.S. Department of Veterans Affairs. Updated April 2, 2018. Accessed August 15, 2023. [https://www.va.gov/healthbenefits/resources/publications/hbco/hbco_copayments.asp#:~:text=If%20found%20to%20be%20catastrophically,\(long-term%20care\).](https://www.va.gov/healthbenefits/resources/publications/hbco/hbco_copayments.asp#:~:text=If%20found%20to%20be%20catastrophically,(long-term%20care).)

Appendix: Description of the 10 most relevant trials identified by PubMed search

Table 1. Description of the 10 most relevant trials identified by PubMed search

| Citation | N | Groups | Control | Treatment duration | Outcome | Other considerations |
|-----------------------|--------|---|---|--------------------|--|---|
| Halbert, et al., 2010 | N = 43 | Red yeast rice versus moderate-dose pravastatin | Moderate-dose pravastatin | 12 weeks | Insignificant difference in reported myalgia and discontinuation rates between intervention and control groups; decrease in LDL-C was significant and comparable in both groups (-30% with red yeast rice and -27% with pravastatin) | Patients also attended 3.5 hours of lifestyle training per week throughout study period |
| Kopecky, et al., 2022 | N = 54 | Ready-to-eat snacks fortified with functional bioactive nutrients versus calorie-matched grocery snacks | Standard calorie-matched grocery snacks | 4 weeks | Statistically significant decrease in LDL-C in intervention group (-8.80 ± 1.69 mg/dL) with no change in control group | Decrease in LDL-C in intervention group was small and unlikely to be clinically significant |
| Kumar, et al., 2009 | N = 41 | Combination ezetimibe and fenofibrate versus low-dose atorvastatin | Low-dose atorvastatin | 6 weeks | Both intervention and control resulted in significantly decreased LDL-C (-34.6% and -36.7%, respectively), with no significant difference between the two groups | Participants did not necessarily have prior statin intolerance |
| Marazzi, et al., 2011 | N = 80 | Combined nutraceutical-based pill versus placebo pill | Placebo pill | 12 months | LDL-C decreased by -31% on combined nutraceutical with no change in placebo group | Elderly only (≥ 75 years) |



KUPLICKI AC. Social determinants may limit the success of PCSK9 inhibitors, an effective treatment for hyperlipidemia in statin-intolerant patients. *Clin Res Prac.* Nov 1 2023;9(1):eP3264.
<https://doi.org/10.22237/crp/1698019740>

| | | | | | | |
|-------------------------|---------|--|---|---|--|---|
| Marazzi, et al., 2015 | N = 100 | Ezetimibe versus combined nutraceutical; if patients failed to reach target, then ezetimibe and nutraceutical combined treatment versus nutraceutical alone | N/A | 12 weeks; then 1 year with treatment arm versus nutraceutical | None on ezetimibe alone reached target LDL-C > 100 mg/dL at 12 weeks, compared to 28% on nutraceutical alone; at 1 year, 73% on combined treatment reached target at 1 year and 100% who remained on nutraceutical alone maintained target | All participants had coronary heart disease with prior percutaneous coronary intervention in addition to statin intolerance |
| Mitchell, et al., 2012 | N = 59 | 3 groups: placebo fruit drink, nutraceutical combination drink, and red yeast rice plus nutraceutical drink | Placebo drink | 8 weeks | LDL-C in red yeast rice group had -17.8% decrease with no change observed in nutraceutical or placebo drink groups | |
| Moriarty, et al., 2015 | N = 250 | 3 groups: subcutaneous alirocumab plus oral placebo, oral ezetimibe plus subcutaneous placebo, and moderate-dose oral atorvastatin plus subcutaneous placebo | Oral moderate-dose atorvastatin plus subcutaneous placebo | 24 weeks | Alirocumab group LDL-C decreased -45% while ezetimibe group decreased -14.6% | Statin arm included to assess statin intolerance among participants, not included in analysis |
| Moriarty, et al., 2020 | N = 281 | Open label subcutaneous alirocumab following 24 week double-blinded treatment with alirocumab, statin, or ezetimibe | N/A | Up to 3 years | Skeletal muscle events reported in 38.4% on alirocumab, with 3.2% discontinuing; LDL-C reduction of -55.1% and -53.7% at 100 and 148 weeks | Not blinded |
| Pisciotta, et al., 2012 | N = 228 | Combined nutraceutical-based pill versus placebo pill, followed by combination in patients for whom change in LDL-C was less than median change | N/A | 6 months; then 3 months for combination therapy | Nutraceutical significantly more effective than ezetimibe in decreasing LDL-C (-31.7% and -25.4%, respectively); combination treatment saw -13.6% decrease in LDL-C | Participants had primary polygenic hypercholesterolemia without evidence of cardiovascular disease |
| Verhoeven, et al., 2013 | N = 52 | Combined nutraceutical-based pill versus placebo pill | Placebo pill | 8 weeks | LDL-C decreased in intervention group by -22% compared to no change in control group | Participants were physicians and their spouses |

