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Drug Class Update: Non-statins for Management of Blood Cholesterol

Date of Review: May 2019

Date of Last Review: January 2018 (PCSK9 Inhibitors)
November 2016 (Non-statins)
End Date of Literature Search: March 1, 2019

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
Since the last review, new data has been published evaluating non-statin agents as add on therapy to improve cardiovascular (CV) outcomes and reduce CV mortality. Additionally, recently published guidelines for hyperlipidemia management have new recommendations for the use of non-statin therapy. These data and any additional new comparative efficacy or harms data published since the last review will be evaluated.

Research Questions:
- Is there any new evidence for non-statin lipid-lowering agents in reducing cardiovascular (CV) outcomes or mortality in adult patients being treated for the primary or secondary prevention of CV disease?
- Is there any new comparative evidence for the efficacy or harms of non-statin lipid-lowering agents in patients being treated for the primary or secondary prevention of CV disease?
- Are there subpopulations of patients based on demographics (e.g., age, sex, race, and diagnoses) for which one non-statin agent is more effective or associated with more harm than other non-statin agents?

Conclusions:
PCSK9 Inhibitors
- There is high quality evidence of a decrease in CV events with alirocumab versus placebo in patients with nonfamilial hypercholesterolemia (9.5% vs. 11.1%; hazard ratio [HR] 0.85; 95% CI 0.78 to 0.93; absolute risk reduction [ARR] 1.6%; number-needed-to-treat [NNT] 63) and moderate quality evidence of lower risk of overall mortality (3.5% vs. 4.1%; HR 0.85; 95% CI 0.73 to 0.99), but no significant difference in death due to CV causes (2.5% vs. 2.9).[1]
- There is high quality evidence of a similar decrease in CV events with evolocumab versus placebo in patients with nonfamilial hypercholesterolemia (9.8% vs. 11.3%; HR 0.85; 95% CI 0.79 to 0.92; ARR 1.5%; NNT 67) and x

Ezetimibe
- There is moderate quality evidence that ezetimibe has a modest benefit in reducing major adverse cardiovascular events (MACE) (relative risk [RR] 0.94; 95% CI 0.90 to 0.98; ARR 1.7%; NNT 59) compared to placebo. There is high-quality evidence of no difference in all-cause mortality (RR 0.98; 95% CI 0.91 to 1.05)

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and moderate quality evidence of no difference in CV mortality (RR 1.00; 95% CI 0.89 to 1.12). There was moderate quality evidence of a decrease risk of non-fatal myocardial infarction (MI; RR 0.88; 95% CI 0.81 to 0.95; ARR 1.3%; NNT 77) and non-fatal stroke (RR 0.83; 95% CI 0.71 to 0.97; ARR 0.5%; NNT 200).[2]

- There is insufficient evidence to make conclusions about the effectiveness of ezetimibe in those without atherosclerotic cardiovascular disease (ASCVD).

Niacin

- There is high quality evidence that niacin does not reduce overall mortality (RR 1.05; 95% CI 0.97 to 1.12) compared to placebo in people with or at risk of cardiovascular disease (CVD).[3] There is moderate quality evidence that niacin does not decrease the risk of fatal or non-fatal MI or CV mortality, high-quality evidence that niacin does not reduce non-cardiovascular mortality and low quality evidence that niacin does not reduce non-fatal or fatal stroke.
- There is moderate quality evidence of an increase in flushing, pruritus, rash, headache, gastrointestinal symptoms, new onset diabetes and discontinuations due to adverse events (absolute risk increase [ARI] 12%/number needed to harm [NNH] 9) with niacin compared to placebo.

Fibrates

- There is moderate quality evidence of a reduction in the primary composite CV outcome of CVD death, non-fatal with fibrates compared to placebo (RR 0.84; 95% CI 0.74 to 0.96; ARR 1%; NNT 100).[4] This difference is modest (<1%) in patients with a low baseline CV risk of 5% or lower and seems to apply to fibrates when used as monotherapy. There was no difference in CV events when including only trials that used fibrates in addition to statins (RR 1.01; 95% CI 0.78 to 1.31).
- There is low quality evidence of no difference in overall mortality (RR 1.01; 95% CI 0.81 to 1.26) and no effect on non-CVD mortality (RR 1.00; 95% CI 0.68 to 0.92) with fibrate therapy.[4]
- Low quality evidence suggests that fibrates are not associated with an increased risk for discontinuations due to adverse effects (RR 1.38; 95% CI 0.71 to 2.68).

Omega-3 Fatty Acids

- High quality evidence demonstrates no reduction in mortality with long chain omega-3 (LCn3) supplementation (RR 0.98, 95% CI 0.90 to 1.03).[5]
- There are three new randomized controlled trials (RCTs) evaluating the effects of omega-3 fatty acid supplementation on CV outcomes in both primary and secondary prevention with inconsistent findings.
- There is moderate quality evidence that omega-3 fatty acids do not decrease a composite CV outcome compared to placebo in adults with or without diabetes and without any evidence of ASCVD (HR 0.92; 95% CI 0.80 to 1.06).[6,7]Mean follow-up was almost eight years in adults with diabetes and 5.3 years in adults without diabetes
- There is low quality evidence that high dose icosapent ethyl (2 gm twice daily) may prevent a CV event (17.2% vs. 22.2%; HR 0.75; 95% CI 0.68 to 0.83; ARR 4.8%; NNT 21 over 4.9 years) in patients with hypertriglyceridemia and CV disease or with diabetes plus other CV risks on statin therapy.[8] However, this is inconsistent with prior studies and meta-analysis that have not shown a CV benefit with omega-3 fatty acids. Additionally, there are serious limitations to the study including the use of mineral oil as placebo, the disconnect between the modest triglyceride lowering seen and greater than predicted CV benefit, as well as significant funding and involvement in the study oversight and data interpretation by the manufacturer. More data is needed to confirm these findings.

Recommendations:

- Update prior authorization criteria to be consistent with the new evidence for use of non-statins to prevent ASCVD events (**Appendix 6**)
- Consider retiring the prior authorization criteria for lomitapide and mipomersen due to no utilization
- Make gemfibrozil non-preferred due to safety concerns with use in combination with statin therapy
- After review of comparative costs in executive session, make ezetimibe and evolocumab preferred.

Summary of Prior Reviews and Current Policy:

- Current PA polices for PCKS9 inhibitors, lomitapide and mipomersen, and omega-3 fatty acids are included in Appendix 6.
- There is moderate quality evidence that ezetimibe combined with a statin results in a modest (2%) improvement in CV outcomes with a long duration of follow-up (approximately 7 years). Due to the modest improvement seen and cost evaluation, ezetimibe remains non-preferred.
- Moderate quality evidence comparing statin monotherapy to a statin in combination with niacin, fibrates or omega 3 fatty acids shows no significant effect on reducing all-cause mortality, death from coronary heart disease (CHD) and inconsistent effects on other CV outcomes.
- Moderate quality evidence shows PCSK9 inhibitors are efficacious at reducing LDL-C by over 50% from baseline in high risk patients.
- There is moderate quality evidence from one large, good quality trial with a median duration of follow-up of 26 months that evolocumab added on to statin therapy reduces non-fatal CV events compared to placebo with a modest magnitude of benefit (ARR 1.5%; NNT 67) in patients with clinically evidence CVD at high risk for recurrence.
- Evolocumab and alirocumab currently require prior authorization for approval to limit use to patients with CVD or familial hypercholesterolemia at high risk for CV events who require additional LDL-C lowering despite use of other lipid-lowering agents, including statins.

Background

Hypercholesterolemia, and especially elevated low-density lipoprotein cholesterol (LDL-C), is associated with increased risk of ASCVD. Prevention of ASCVD events involves optimization of treatments that have proven benefits on reduction in ASCVD events and/or cardiovascular (CV) mortality. Until recently, only statins had strong and consistent evidence demonstrating ASCVD risk reduction. Therefore, statin therapy remains the cornerstone of treatment for both primary and secondary prevention of ASCVD. However, combination therapy to reduce ASCVD risk beyond statin use may be necessary for high-risk populations.

The utilization and place in therapy of non-statin therapy has significantly evolved over the past few decades from being routine add on therapy targeting specific LDL-C goals to having no clear indication based on a lack of data showing an improvement on CV outcomes. The recent publication of the 2018 American College of Cardiology/American Heart Association guidelines for the treatment of blood cholesterol once again re-define the role of non-statin therapy.[9] A consistent approach is to reserve non-statin add-on therapy to high risk populations on maximally tolerated statin therapy who may require additional LDL-C lowering and to use agents which have demonstrated an improvement in CV outcomes.

Currently, only ezetimibe and the proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors have shown a modest benefit on clinical outcomes of interest when added to statin therapy (**Table 1**). Ezetimibe, an inhibitor of intestinal cholesterol absorption, is indicated as an adjunct to reduce elevated cholesterol and LDL-C.[10] It is generally well tolerated and can lower LDL-C by up to 25% when added to statin therapy. The IMPROVE-IT trial provides modest evidence for use of ezetimibe in combination with a statin for secondary prevention of CV events.[11] In patients with recent acute coronary syndrome (ACS), ezetimibe produced an incremental reduction in the primary composite endpoint, and specifically reduced nonfatal ischemic stroke, but did not reduce all-cause mortality or CV mortality. The manufacturer of ezetimibe applied for an additional indication for the expanded use of ezetimibe in combination with statin therapy for

reduction of CV events in patients with coronary heart disease, but an FDA advisory committee voted against the expanded indication as they felt the ezetimibe/simvastatin combination provides a weak and not particularly robust effect on CV outcomes.[10] Additionally, a moderate-intensity statin was used as the study comparator which is not consistent with current practice recommendations.

Evolocumab (Repatha®) and alirocumab (Praluent®) are subcutaneously injected human monoclonal antibodies that reduce LDL-C by inhibiting PCSK9.[12,13] PCSK9 promotes the degradation of the LDL receptor, resulting in an increase in plasma LDL-C. Both agents are effective at lowering LDL-C with reductions of up to 60% when combined with statin therapy. Both agents are approved as an adjunct with other lipid-lowering therapies (statins, ezetimibe) for primary hyperlipidemia (heterozygous familial hypercholesterolemia) and clinical ASCVD who require additional lowering of LDL-C. In 2017, evolocumab was also FDA approved for the risk reduction of MI, stroke, and coronary revascularization in adults with established CVD based on clinical outcome data from the FOURIER trial.[12,14] The ODYSSEY OUTCOMES trial, published since the last review, evaluated the effects on CV outcomes of alirocumab given in combination with statin therapy.[15]

Currently there is no evidence on CV outcomes and a limited place in therapy for other LDL-C lowering agents (fibrates, bile acid sequestrants, omega-3 fatty acids). Fibric acid derivatives should be reserved for patients with severe hypertriglyceridemia (triglycerides ≥ 500 - 1000 mg/dl). The long-term follow up of the ACCORD trial showed no benefit in fatal or non-fatal CV events with fenofibrate plus simvastatin versus simvastatin alone in patients with diabetes mellitus.[16] Gemfibrozil should not be used in combination with statin therapy due to an increased risk of muscle symptoms and rhabdomyolysis.

Omega-3 fatty acids (i.e., Lovaza®) and icosapent ethyl are two FDA-approved legend drugs for the treatment of severe hypertriglyceridemia. Icosapent ethyl is a form of eicosapentaenoic acid (EPA) while other products have both EPA and docosahexaenoic acid (DHA). There have been several new RCTs evaluating omega-3 fatty acids on CV outcomes in both primary and secondary prevention.

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted from January 1st, 2016 through March 1st, 2019. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews.

When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. The primary focus of the evidence is on high quality systematic reviews, evidence-based guidelines, and randomized controlled trials (RCTs) evaluating clinical cardiovascular (CV) outcomes. Randomized controlled trials of surrogate outcomes will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
After review, **21** systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), outcome studied (e.g., non-clinical), or included in a systematic review from a trusted source (DERP).

PSCK9 Inhibitors:

1. A systematic review and update was conducted by the Drug Effectiveness Review Project (DERP) evaluating RCTs and systematic reviews focusing on adults with familial or nonfamilial hypercholesterolemia who have not achieved recommended LDL-C serum levels despite lipid-lowering therapy.[1] Placebo controlled trials were included if the primary outcome was CV disease. Overall, there is consistent evidence that PCSK9 inhibitors are more effective than ezetimibe, standard of care and placebo at reducing LDL-C levels in various populations with both familial and nonfamilial hypercholesterolemia. In patients with heterozygous familial hypercholesterolemia (HeFH) or homozygous familial hypercholesterolemia (HoFH), there was insufficient evidence evaluating alirocumab for all outcomes. There was low quality evidence that evolocumab significantly reduced LCL-C compared to standard of care after 48 weeks of treatment (mean difference -55.7%) in patients with HeFH with insufficient evidence on CV outcomes or in HoFH. In statin-intolerant patients, there is low evidence that evolocumab resulted in no difference in CV events compared to ezetimibe based on three RCTs. The authors concluded high quality evidence based on the ODYSSEY OUTCOMES trial of a decrease in CV events with alirocumab versus placebo in patients with nonfamilial hypercholesterolemia (9.5% vs. 11.1%; HR 0.85; 95% CI 0.78 to 0.93) and moderate quality evidence of similar risks of death from CV causes (2.5% vs. 2.9%). Mortality was statistically significantly lower in the alirocumab group compared to placebo (3.5% vs. 4.1%; HR 0.85; 95% CI 0.73 to 0.99) with a similar measure of association (HR 0.85 vs. HR 0.88). Prespecified subgroup analyses concluded no difference in the primary CV composite outcome between those who were younger than 65 years and older than 65, men and women, and different ethnicities. Additionally, based on the FOURIER trial, there is high quality evidence of a statistically significant decrease in CV events with evolocumab versus placebo in patients with nonfamilial hypercholesterolemia (9.8% vs. 11.3%; HR 0.85; 95% CI 0.79 to 0.92). The absolute risk reduction is small in both trials. In regard to differences in subgroups, there is high quality evidence of similar reductions in CV events with evolocumab versus placebo in patients with and without diabetes and similar LDL-C reductions with alirocumab versus ezetimibe in men and women. There remains insufficient head to head comparative data on the effectiveness and harms of the PCSK9 inhibitors.

   The DERP review also identified a Cochrane systematic review that included 16 relevant trials on alirocumab and evolocumab. The analyses suggested a class effect of PCSK9 inhibitors. Although populations were combined (familial and nonfamilial) two additional agents were included (bococizumab and RG7652), the results showed similar magnitude of effect and direction. PCSK9 inhibitors demonstrated a significant reduction in LDL-C compared to ezetimibe (mean % change of -30.20%; 95% CI -34.18 to -26.23) and compared to ezetimibe plus statins (mean % difference of -39.20%; 95% CI -56.15 to -22.26). Additionally, there was a reduction in CV events with PCSK9 inhibitors compared to ezetimibe plus statins (OR 0.45; 95% CI 0.27 to 0.75) and an increased risk of adverse events (OR 1.18; 95% CI 1.05 to 1.34).

   There was very low evidence making it difficult to form any conclusions about treatment effects on CV outcomes in the following populations: alirocumab in statin-intolerant patients, alirocumab and evolocumab versus ezetimibe inpatients with nonfamilial hypercholesteremia, alirocumab versus other lipid-lowering regimens, and evolocumab versus ezetimibe in nonfamilial hypercholesterolemia.

2. Another high-quality systematic review evaluated the effects of PCSK9 inhibitors on major adverse cardiovascular events (MACE).[17] Forty-six RCTs were included in the meta-analysis. Pre-defined subgroup analysis was done to examine the effect based on drug type, follow-up duration, and prevention type (primary versus secondary). Twenty-two trials included alirocumab and 19 included evolocumab. The remaining trials evaluated either bococizumab, which has been discontinued from development, or drugs not yet approved. Overall, PCSK9 inhibitors were associated with a significantly reduced risk of MACE (RR 0.84; 95% CI 0.79 to 0.89; ARR 4.7% over 10 years). The quality of the evidence was rated as moderate and downgraded due to indirectness of populations which varied across trials. None of the subgroup analysis showed significant heterogeneity based on drug type, study design, population, or type of control. Therefore, the authors concluded that the effect of PCSK9 inhibitors appears to be a class effect. There was also

low-quality evidence that PCSK9 inhibitors significantly reduced non-fatal MI (RR 0.83; 95% CI 0.74 to 0.93; ARR 3.5%) and any stroke (RR 0.75; 95% CI 0.65 to 0.85; ARR 1.6%) over a 10-year time period.

Ezetimibe:

1. A Cochrane systematic review evaluated the efficacy and safety of ezetimibe for the prevention of CVD and all-cause mortality in patients with and without established CVD.[2] Overall, 26 RCTs (n=23,499) were included in the review. Three of the studies were multi-center, two were conducted in the United States (US), and the remainder were performed outside of the US. Most studies had a follow up of one to two years. The largest study was IMPROVE-IT, which included a median follow-up of six years. Fourteen studies included patients with existing ASCVD. None of the studies included ezetimibe as monotherapy. All of the trials compared ezetimibe plus other lipid-modifying drugs (majority of them were statins; n=25) to lipid-modifying drugs alone or in combination with placebo. The majority of studies had low or unclear risk of bias. Eight studies were open-label design and had a high risk of performance bias.

   Overall, there was moderate quality evidence from 10 studies that ezetimibe had a lower risk of major adverse cardiovascular events (MACE) (RR 0.94; 95% CI 0.90 to 0.98; ARR 1.7%; NNT 59). [2] Results were largely driven by the IMPROVE-IT trial, which included differences in non-fatal MI, non-fatal stroke and urgent coronary revascularizations. There was high-quality evidence of no difference in all-cause mortality (RR 0.98; 95% CI 0.91 to 1.05) and moderate quality evidence of no difference in CV mortality (RR 1.00; 95% CI 0.89 to 1.12). [2] There was moderate quality evidence of a decrease risk of non-fatal MI (RR 0.88; 95% CI 0.81 to 0.95; ARR 1.3%; NNT 77) and non-fatal stroke (RR 0.83; 95% CI 0.71 to 0.97; ARR 0.5%; NNT 200).[2] A subgroup analysis showed no difference in primary outcomes between those with and without established ASCVD. However, fewer individuals were included without ASCVD and confidence intervals were wide. Therefore, it remains difficult to make conclusions about the effectiveness of ezetimibe in those without ASCVD.

   Pooling of adverse events was not possible due to heterogeneity in the definition of adverse events. However, the individual studies showed no difference in adverse events. There was no significant difference found in the following events: liver injury, myopathy, rhabdomyolysis, cancer, and discontinuation due to adverse events. However, the quality of evidence for liver injury and myopathy is low and very low due to imprecision and risk of bias. Results of sensitivity analyses using only studies at low risk of bias, random-effects modeling, and excluding studies with missing data did not change estimates for most outcomes. [2]

Niacin:

1. A Cochrane review assessed the effectiveness of niacin therapy versus placebo or other lipid modifying drugs, administered as monotherapy or add-on to statin based therapy in adults with or at risk of CVD.[3] Twenty-three RCTS (n=39,195) were included in the meta-analysis. The majority of trials included a mixed population, evaluating niacin in both primary and secondary prevention of CVD. The duration of treatment ranged from 6 months to 6 years, and 19 trials applied one or more methods to reduce skin flushing due to niacin. Fourteen of the trials were placebo-controlled, and the remaining 9 compared standard treatment without a placebo to niacin. The majority of studies had low or unclear risk of bias and eleven trials had a high risk of attrition bias. The majority of trials also had high risk of bias due to missing data.

There was high quality evidence from 12 studies that niacin did not reduce overall mortality (RR 1.05; 95% CI 0.97 to 1.12). [3] Sensitivity analyses did not change the primary outcome results, and meta-regression analysis did not show a significant effect modification by duration, proportion of patients with established CVD, or proportion of patients on background statin therapy. The results were robust to sensitivity analyses using different assumptions for missing data. Additionally, there was moderate quality evidence that niacin did not decrease the risk of fatal or non-fatal MI or CV mortality, high-quality evidence that niacin did not reduce non-cardiovascular mortality, and low quality of evidence that niacin did not reduce non-fatal or fatal stroke. Additionally, there was moderate quality evidence of an increase in flushing, pruritus, rash, headache, gastrointestinal symptoms, new onset diabetes and discontinuations due to adverse events (ARI 12%/ NNH 9). [3]

Fibrates:

1. A 2016 Cochrane review and meta-analysis aimed to evaluate the clinical benefits and harms of fibrate monotherapy versus placebo or usual care or fibrates in combination with other lipid-modifying drugs versus other lipid-modifying drugs alone for the primary prevention of CVD morbidity and mortality.[4] Included primary prevention RCTs were required to have fewer than 10% of participants with established CVD. The primary outcome was a composite CV outcome including CVD death, non-fatal MI or non-fatal stroke. Six eligible trials were identified including 16,135 individuals. The mean treatment duration and follow-up of participants across trials was 4.8 years. Three trials included fenofibrate and one included gemfibrozil. The other two trials included drugs not available in the U.S. The majority of trials had low risk of bias. Two trials had high attrition bias and two had a high risk of other bias due to conflicts of interest.

   There was moderate quality evidence of a reduction in the primary composite CV outcome with fibrates compared to placebo (RR 0.84; 95% CI 0.74 to 0.96; ARR 1%; NNT 100). [4] This difference is modest (<1%) in patients with a low baseline risk of 5% or lower and seems to apply to fibrates when used as monotherapy. There was low quality evidence of no difference in overall mortality (RR 1.01; 95% CI 0.81 to 1.26) and no effect on non-CVD mortality (RR 1.00; 95% CI 0.76 to 1.33). [4] Sensitivity analyses focusing only on trials that reported concealed treatment allocation showed no difference CV events (RR 1.00; 95% CI 0.77 to 1.30). [4] There was also no difference in CV events when including only trials that used fibrates in addition to statins (RR 1.01; 95% CI 0.78 to 1.31). Very low-quality evidence suggests that fibrates are not associated with an increased risk for discontinuations due to adverse effects (RR 1.38; 95% CI 0.71 to 2.68). [4]

Omega-3 fatty acids:

1. A Cochrane systematic review assessed effects of increased intake of fish- and plant-based omega-3 fatty acids on all-cause mortality, CV events, and lipids.[5] Seventy-nine RCTs (n=112,059) that lasted at least 12 months and compared supplementation and/or advice to increase omega-3 intake versus usual or lower intake were included. Trials were of 12 to 72 months' duration and included adults at varying cardiovascular risk, mainly in high-income countries. Most studies assessed long chain omega-3 (LCn3) supplementation (n=62), but some used LCn3- or alpha-linolenic acid (ALA)-rich or enriched foods or dietary advice compared to placebo or usual diet. Additionally, LCn3 was supplemented through capsules or medicinal oils. Doses of LCn3 ranged from 0.5 grams per day to greater than 5 grams per day. Twenty-five trials were deemed to be at low risk of bias. The remainder were moderate to high risk of bias.

   High quality evidence showed little or no effect on all-cause mortality (RR 0.98, 95% CI 0.90 to 1.03). Sensitivity analyses using fixed effect meta-analysis, removing studies not at low risk of bias did not change the lack of effect on all-cause mortality. The lack of effect did not differ by primary or

secondary prevention or mode of intervention (dietary advice versus supplementation). Moderate quality evidence suggests no significant effect on cardiovascular mortality (RR 0.95, 95% CI 0.87 to 1.03) and high-quality evidence shows no significant effect on cardiovascular events (RR 0.99, 95% CI 0.94 to 1.04).[5]

The funnel plots for all three of these outcomes suggest that some smaller studies with more participants experiencing the outcome in the intervention group were missing. If these studies were included, it could possibly increase the relative risk closer to null. Additionally, moderate quality evidence suggests no significant effect on CHD mortality, CHD events, stroke, or arrhythmias. There was no suggestion of a dose response or important effects from subgroup analysis or meta-regression. Studies also demonstrated that increasing ALA intake probably makes little or no difference in all-cause mortality or CV mortality. However, increased ALA probably does not reduce risk of cardiovascular events (from 4.8% to 4.7%, RR 0.95, 95% CI 0.83 to 1.07, low-quality evidence with greater effects in trials at low summary risk of bias), and probably reduces risk of arrhythmia (3.3% to 2.6%, RR 0.79, 95% CI 0.57 to 1.10). [5] Authors also determined that there was no evidence that increasing LCn3 or ALA altered serious adverse events, adiposity or lipids, except LCn3 reduced triglycerides by approximately 15% in a dose-dependent way (high-quality evidence). [5]

2. The Omega-3 Treatment Trialists' Collaboration was a meta-analysis based on aggregated study-level data from all large RCTS of omega-3 fatty acids for the prevention of CVD.[18] A total of ten trials were included in the analysis (n=77,917). Two trials did not use a placebo-treated control group. The remaining were given a low risk of bias. One trial evaluated EPA alone while the others included a combination of EPA and DHA. Overall, there was no significant effect seen in any CHD event (RR 0.96; 95% CI 0.90 to 1.01) or any individual CHD events (CHD death, nonfatal MI, stroke or revascularization) with omega-3 fatty acids compared to placebo or control. No significant effect was observed in any of the prespecified subgroups.

Guidelines:

ACC/AHA Guidelines on the Management of Blood Cholesterol (Grundy 2018)

Updated recommendations for reducing ASCVD risk were released following from the American College of Cardiology (ACC) / American Heart Association (AHA) in 2018.[9] Guidelines were updated based on a systematic review that identified 10 new RCTs in patients with clinical ASCVD or at high risk of ASCVD.[19] The pre-specified primary outcome was a composite of fatal CV events, nonfatal MI, or nonfatal stroke. RCTs were assessed for bias using the Cochrane Collaboration Risk of Bias Tool. A meta-analysis was not done, and direct comparisons of the included RCTs could not be performed. Results from the systematic review will be incorporated into guideline recommendations below.

Statin Therapy:

Statins remain the cornerstone of therapy and should be optimized in all patients with ASCVD and at high risk for ASCVD. Statins are recommended in the four patient management groups, which were modified slightly from the previous guidelines to allow for more personalized care and include more detailed risk assessments (**Table 1**).

Table 1: Statin Benefit Groups

Statin Benefit Group	Recommended Treatment
Clinical ASCVD	High-intensity statin (≤ 75 y/o); moderate- to high-intensity statin if > 75 y/o
Severe Hypercholesterolemia (LDL-C ≥ 190 mg/dl)	Maximally tolerated statin

Diabetes age 40-75 and LDL-C ≥ 70 mg/dl	Moderate-to high-intensity statin (based on ASCVD risk factors)
Primary Prevention (Adults 40-75 years with LDL-C ≥70)	Moderate- to high-intensity statin based on risk discussion, 10-year ASCVD risk, and ASCVD risk enhancers
Abbreviations: ASCVD: atherosclerotic cardiovascular disease; LDL-C: low density lipoprotein cholesterol; y/o: years old	

Non-statin Therapy:

A significant change in the guidelines is the addition of an LDL-C threshold of 70 mg/dl to consider adding a non-statin in clinical ASCVD. This recommendation comes from the general idea that "lower is better" for LDL-C, particularly in high-risk patients. Very high-risk ASCVD is a new category and includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions (**Table 2**).[9] The guideline recommendation is to add ezetimibe to maximally tolerated statin therapy as a first step in lowering LDL-C, followed by a PCSK9 inhibitor if LDL-C remains ≥ 70 mg/dl on both statin and ezetimibe therapy for very high risk patients only.[9]

Table 2: Very High-Risk ASCVD		
Major ASCVD events	**High-Risk Conditions**	
Recent ACS	Age ≥65	Diabetes mellitus
History of MI	HoFH	Hypertension
History of ischemic stroke	History of prior CABG or PCI	CKD Heart failure
Symptomatic PAD	Current Smoking	Persistently elevated LDL-C despite statin + ezetimibe
Abbreviations: ACS: acute coronary syndrome; ASCVD: atherosclerotic cardiovascular disease; CABG: coronary artery bypass graft; CKD: chronic kidney disease; HoFH: homozygous familial hypercholesterolemia LDL-C: low density lipoprotein cholesterol; MI: myocardial infarction; PAD: peripheral artery disease; PCI: percutaneous coronary intervention		

Ezetimibe and the PCSK9 inhibitors are recommended as add on therapy as there is new evidence for reduced morbidity. Based on the IMPROVE-IT trial (**Tables 3 and 4**), the evidence review committee concluded that ezetimibe modestly reduced ASCVD risk over 7 years (ARR 2%) when applied to a post-ACS population treated with background statins. Additionally, post hoc analysis suggested that adults with the greatest burden of risk factors experienced the largest reduction in ASCVD risk with ezetimibe. High risk individuals experienced an ARR of 6.3% over 6 years. [19]

Table 3: Characteristics of Cardiovascular Outcome trials for Non-statins[11,14,15]

	FOURIER	**ODYSSEY**	**IMPROVE-IT**
Non-Statin Study Drug	evolocumab	alirocumab	ezetimibe
Patient Population	MI, stroke or PAD	4-52 weeks post-ACS	ACS (prior 10 days)
Median LDL-C	92 mg/dl	92 mg/dl	95 mg/dl
% on High Intensity Statin	69%	89%	6%
% on Ezetimibe	5%	3%	-
Study Duration	26 months	34 months	6 years
Abbreviations: ACS: acute coronary syndrome: LDL-C: low density lipoprotein cholesterol MI: myocardial infarction; PAD: peripheral artery disease			

Four new trials evaluated the effectiveness of PCSK9 inhibitors. [19] However, two of these trials evaluated bococizumab which was discontinued in the development stage due to the formation of antidrug antibodies resulting in an attenuation of LDL-C lowering over time. The FOURIER trial demonstrated a significant LDL-C reduction (median 59%) and reduction in composite CV outcome (ARR 1.5%; NNT 67) with evolocumab plus maximally tolerated statin therapy compared to statin monotherapy in patients with clinically evident CVD. [19] There was no difference in all-cause death or death due to CVD. The ODYSSEY OUTCOMES trial evaluated alirocumab in patients with recent ACS and an LDL-C of ≥ 70 mg/dl on maximally tolerated statin. Similar to the FOURIER trial, LDL-C was significantly reduced from baseline, and there was a decrease in the composite CV outcome (ARR 1.6%; NNT 63) with a median follow-up period of 2.8 years. There was also a small decrease in all-cause mortality (3.5% vs. 4.1%; HR 0.85; 95% CI 0.73 to 0.98; ARR 0.6%; NNT 167). [19] Differences in mortality compared to evolocumab could be due to the different patient populations (recent ACS vs. chronic stable CVD). In both PCSK9 outcome trials, rates of serious adverse events, neurocognitive side effects, new onset diabetes, and discontinuations due to adverse events were not different between drug and placebo. Injection site reactions were more common than both PCSK9 inhibitors compared to placebo.

Table 4: Summary of Results from Cardiovascular Outcome Trials[11,14,15]

Outcome	Evolocumab ARR/NNT	Alirocumab ARR/NNT	Ezetimibe ARR/NNT
CV Composite Outcome	1.5% / 67	1.6% / 63	2% / 50
CV Death	NS	NS	NS
Death from any cause	NS	0.6% / 167	NS
Myocardial infarction	1.2% /84	1% / 100	1.7% / 59
Stroke	0.4% / 250	0.4% / 250	NS

The following recommendations are included in the guidelines as a result of this new data (descriptions of how recommendations and quality of evidence were graded are in Appendix 5 : [9]

Ezetimibe:

- In very-high risk ASCVD, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C remains ≥ 70 mg/dl (Class of Recommendation [COR] IIa; Level of Evidence [LOE] B-R).
- In patients with clinical ASCVD (not at very-high risk) who are receiving maximally tolerated statin therapy and whose LDL-C remains ≥ 70 mg/dl, it is reasonable to add ezetimibe (COR IIb; LOE B-R).
- In patients with severe primary hypercholesterolemia (baseline LDL ≥ 190 mg/dl), who achieve less than a 50% reduction in LDL-C and/or have an LDL-C remaining ≥ 100 mg/dl on maximally tolerated statin, it is reasonable to add ezetimibe (COR IIa; LOE B-R).
- In adults with diabetes mellitus and 10-year ASCVD risk of 20% or higher, it may be reasonable to add ezetimibe to maximally tolerated statin therapy (COR IIb; LOE C-LD).

PCSK9 Inhibitors

- In patients at very high risk whose LDL-C level remains ≥70 mg/dl on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, although the long-term safety (>3 years) is uncertain and cost effectiveness is low at mid-2018 list prices (COR IIa; LOE A).

- In patients with severe primary hypercholesterolemia and a baseline LDL-C of 220 mg/dl or higher and who achieve an on-treatment LDL-C of 130 mg/dl or higher while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered (COR IIb; LOE C-LD).
- In patients 30 to 75 years of age with HeFH and with an LDL-C level of 100 mg/dL or higher while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered (COR IIb; LOE B-R).

Although no RCT specifically tested the strategy of ezetimibe first and then a PCSK9 inhibitor, ezetimibe was allowed at entry along with statin therapy in both PCSK9 inhibitor trials but occurred in very small numbers (3% and 5% respectively). The strategy of ezetimibe before PCSK9 inhibitor is recommended because ezetimibe is widely available as a generic drug and has proven safety and tolerability.

The ACC/AHA Systematic review identified two large RCTs that evaluated niacin in addition to statin and/or ezetimibe in the past several years.[19] The AIM-HIGH trial was conducted in patients with clinical ASCVD and was stopped early due to a lack of efficacy. The HPS2-THRIVE study also assessed niacin as add on therapy to statin and/or ezetimibe in patients with established ASCVD. Similar to AIM-HIGH, participants on niacin saw no reduction in CVD events. The combination of niacin and laropiprant (a prostaglandin antagonist used to reduce flushing) was associated with an increased risk of serious adverse effects, including worsening diabetic control, gastrointestinal, muscle and skin abnormalities, as well as increased risk of infection and bleeding. The guidelines do not include niacin as a recommended add-on therapy.

New FDA Safety Alerts:
None identified

New formulations or Indications:
In December, 2017 FDA approved evolocumab to reduce the risk of MI, stroke and coronary revascularization in adults with established CVD based on the results of the FOURIER trial.[12]

In April 2019, a new chewable bar formulation of colesevelam (Welchol) was FDA approved.[20] Each bar (chocolate, strawberry or caramel flavors) contains approximately 80 calories per bar and should be taken with a meal. It is approved as adjunct to diet and exercise to reduce LDL-C in adults with primary hyperlipidemia and to improve glycemic control in patients with type 2 diabetes mellitus. The approval was based on studies conducted with colesevelam tablets. The effect on colesevelam on cardiovascular morbidity or mortality has not been demonstrated.

Randomized Controlled Trials:
A total of 339 citations were manually reviewed from the initial literature search. After further review, 335 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 4 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 5. Summary of Clinical Trials Evaluating Clinical CV Outcomes

Study	Comparison	Population	Primary Outcome	Results	
REDUCE-IT[8] DB, PC, MC, RCT	Icosapent ethyl 2gm BID vs. placebo Median duration: 4.9 years	Adults ≥ 45 y/o with CVD or ≥ 50 y/o with DM and at least one additional risk factor, on background statin therapy with TG 150-499 mg/dl and LDL 41-100 mg/dl (n=8,179)	Composite of CV death and nonfatal MI or stroke, coronary revascularization or unstable angina	<u>Composite CV Outcome:</u> Icosapent: 705 (17.2%) Placebo: 901 (22%) HR 0.75; 95% CI 0.68 to 0.83 ARR 4.8% / NNT 21 <u>Death from any cause:</u> Icosapent: 274 (6.7%) Placebo: 310 (7.6%) HR 0.87; 95% CI 0.74 to 1.02	<u>CV death:</u> Icosapent: 174 (4.3%) Placebo: 213 (5.2%) HR 0.80; 95% CI 0.66 to 0.98 ARR 0.9% / NNT 112 <u>Atrial fibrillation:</u> Icosapent: 215 (5.3%) Placebo: 159 (3.9%) ARI 1.4% / NNH 72 <u>Peripheral edema:</u> Icosapent: 267 (6.5%) Placebo: 203 (5.0%) ARI 1.5% / NNH 67
ASCEND[6] RCT	Omega-3 fatty acids 1gm daily versus placebo Mean follow up of 7.4 years	Adults ≥ 40 y/o with diabetes but no evidence of ASCVD (n=15,480)	First serious vascular event (nonfatal MI or stroke, TIA or vascular death)	<u>Serious vascular event:</u> Omega-3: 689 (8.9%) Placebo: 712 (9.2%) RR 0.97; 95% CI 0.87 to 1.08 There were no significant differences in serious adverse events	
ODYSSEY OUTCOMES[15] RCT, DB, PC, MC	Alirocumab 75 mg or 150 mg SQ Q2W vs. placebo Median duration: 2.8 years	Adults with LDL ≥ 70 mg/dl, non-HDL ≥ 100 mg/dl or apolipoprotein B ≥ 80 mg/dl, hospitalized 1-12 months prior for ACS on maximally tolerated statin (n=18,924)	Composite of CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, and unstable angina requiring hospitalization	<u>CV composite outcome:</u> Alirocumab: 903 (9.5%) Placebo: 1052 (11.1%) HR 0.85; 95% CI 0.78 to 0.93 ARR 1.6% / NNT 63	<u>Death from CV causes:</u> Alirocumab: 240 (2.5%) Placebo: 271 (2.9%) HR 0.88; 95% CI 0.74 to 1.05 <u>Death from any cause:</u> Alirocumab: 334 (3.5%) Placebo: 392 (4.1%) HR 0.85; 95% CI 0.73 to 0.98 ARR 0.6% / NNT 167
VITAL[7] RCT, PC, DB	Omega-3 fatty acids (1 gm per day) vs. placebo Median duration: 5.3 years	Men ≥ 50 y/o and women ≥ 55 y/o (primary prevention) (n=25,871)	Composite of MI, stroke and death from CV cause	<u>CV composite outcome:</u> Omega-3 fatty acids: 386 (3.0%) Placebo: 419 (3.2%) HR 0.92; 95% CI 0.80 to 1.06	

Abbreviations: ACS = acute coronary syndrome; ARI = absolute risk increase; ARR = absolute risk reduction; ASCVD = atherosclerotic cardiovascular disease; CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; DB = double blind; DM = diabetes mellitus; HDL = high density lipoprotein cholesterol; HR = hazard ratio; LDL-C = low density lipoprotein cholesterol; MC = multi-centered; mg = milligram; MI = myocardial infarction; NNH = number needed to harm; NNT = number needed to treat; PC = placebo controlled; Q2W = every 2 weeks; QMO = every month; RCT = randomized controlled trial; RR = relative risk; SQ = subcutaneously; TIA = transient ischemic attack; TG = triglycerides; y/o = years old

References:

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7. Manson JE, Cook NR, Lee IM, et al. Marine n-3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer. *The New England journal of medicine.* 2019;380(1):23-32.
8. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *The New England journal of medicine.* 2019;380(1):11-22.
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10. Ezetimibe (Zetia) Prescribing Information.Whitehouse Station NJ: Merck & Co., INC; 2013.
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13. Alirocumab (Praluent) injection, solution [package insert].Bridgewater, NJ: Sanofi-Aventis U.S. LLC; 2018.
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20. Colesevelam (Welchol) Prescribing Information. Basking Ridge, New Jersey. Daiichi Sankyo, Inc. 2019.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
cholestyramine (with sugar)	CHOLESTYRAMINE	POWD PACK	Y
cholestyramine (with sugar)	QUESTRAN	POWD PACK	Y
cholestyramine (with sugar)	CHOLESTYRAMINE	POWDER	Y
cholestyramine (with sugar)	QUESTRAN	POWDER	Y
cholestyramine/aspartame	CHOLESTYRAMINE LIGHT	POWD PACK	Y
cholestyramine/aspartame	PREVALITE	POWD PACK	Y
cholestyramine/aspartame	CHOLESTYRAMINE LIGHT	POWDER	Y
cholestyramine/aspartame	PREVALITE	POWDER	Y
cholestyramine/aspartame	QUESTRAN LIGHT	POWDER	Y
fenofibrate	FENOFIBRATE	TABLET	Y
gemfibrozil	GEMFIBROZIL	TABLET	Y
gemfibrozil	LOPID	TABLET	Y
alirocumab	PRALUENT PEN	PEN INJCTR	N
alirocumab	PRALUENT SYRINGE	SYRINGE	N
colesevelam HCl	COLESEVELAM HCL	POWD PACK	N
colesevelam HCl	WELCHOL	POWD PACK	N
colesevelam HCl	COLESEVELAM HCL	TABLET	N
colesevelam HCl	WELCHOL	TABLET	N
colestipol HCl	COLESTID	GRANULES	N
colestipol HCl	COLESTIPOL HCL	GRANULES	N
colestipol HCl	COLESTID	PACKET	N
colestipol HCl	COLESTIPOL HCL	PACKET	N
colestipol HCl	COLESTID	TABLET	N
colestipol HCl	COLESTIPOL HCL	TABLET	N
evolocumab	REPATHA SURECLICK	PEN INJCTR	N
evolocumab	REPATHA SYRINGE	SYRINGE	N
evolocumab	REPATHA PUSHTRONEX	WEAR INJCT	N
ezetimibe	EZETIMIBE	TABLET	N
ezetimibe	ZETIA	TABLET	N
fenofibrate	FENOFIBRATE	CAPSULE	N
fenofibrate	LIPOFEN	CAPSULE	N
fenofibrate	FENOFIBRATE	TABLET	N
fenofibrate	FENOGLIDE	TABLET	N
fenofibrate nanocrystallized	FENOFIBRATE	TABLET	N
fenofibrate nanocrystallized	TRICOR	TABLET	N
fenofibrate nanocrystallized	TRIGLIDE	TABLET	N
fenofibrate,micronized	ANTARA	CAPSULE	N

fenofibrate,micronized	FENOFIBRATE	CAPSULE	N
fenofibric acid	FENOFIBRIC ACID	TABLET	N
fenofibric acid	FIBRICOR	TABLET	N
fenofibric acid (choline)	FENOFIBRIC ACID	CAPSULE DR	N
fenofibric acid (choline)	TRILIPIX	CAPSULE DR	N
icosapent ethyl	VASCEPA	CAPSULE	N
inositol	INOSITOL	TABLET	N
lomitapide mesylate	JUXTAPID	CAPSULE	N
niacin	NIACIN	CAPSULE ER	N
niacin	NIACIN ER	TAB ER 24H	N
niacin	NIASPAN	TAB ER 24H	N
niacin	NIACIN	TABLET	N
niacin	NIACOR	TABLET	N
niacin	NIACIN	TABLET ER	N
niacin	SLO-NIACIN	TABLET ER	N
omega-3 acid ethyl esters	LOVAZA	CAPSULE	N
omega-3 acid ethyl esters	OMEGA-3 ACID ETHYL ESTERS	CAPSULE	N

Appendix 2: Abstracts of Clinical Trials

Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT Jr, Juliano RA, Jiao L, Granowitz C, Tardif JC, Ballantyne CM; REDUCE-IT Investigators. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. N Engl J Med. 2019 Jan 3;380(1):11-22. doi: 10.1056/NEJMoa1812792. Epub 2018 Nov 10.

Abstract

BACKGROUND:

Patients with elevated triglyceride levels are at increased risk for ischemic events. Icosapent ethyl, a highly purified eicosapentaenoic acid ethyl ester, lowers triglyceride levels, but data are needed to determine its effects on ischemic events.

METHODS:

We performed a multicenter, randomized, double-blind, placebo-controlled trial involving patients with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting triglyceride level of 135 to 499 mg per deciliter (1.52 to 5.63 mmol per liter) and a low-density lipoprotein cholesterol level of 41 to 100 mg per deciliter (1.06 to 2.59 mmol per liter). The patients were randomly assigned to receive 2 g of icosapent ethyl twice daily (total daily dose, 4 g) or placebo. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. The key secondary end point was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

RESULTS:

A total of 8179 patients were enrolled (70.7% for secondary prevention of cardiovascular events) and were followed for a median of 4.9 years. A primary end-point event occurred in 17.2% of the patients in the icosapent ethyl group, as compared with 22.0% of the patients in the placebo group (hazard ratio, 0.75; 95% confidence interval [CI], 0.68 to 0.83; P<0.001); the corresponding rates of the key secondary end point were 11.2% and 14.8% (hazard ratio, 0.74; 95% CI, 0.65 to 0.83; P<0.001). The rates of additional ischemic end points, as assessed according to a prespecified hierarchical schema, were significantly lower in the icosapent ethyl group than in the placebo group, including the rate of cardiovascular death (4.3% vs. 5.2%; hazard ratio, 0.80; 95% CI, 0.66 to 0.98; P=0.03). A larger percentage of patients in the icosapent ethyl group than in the placebo group were hospitalized for atrial fibrillation or flutter (3.1% vs. 2.1%, P=0.004). Serious bleeding events occurred in 2.7% of the patients in the icosapent ethyl group and in 2.1% in the placebo group (P=0.06).

CONCLUSIONS:

Among patients with elevated triglyceride levels despite the use of statins, the risk of ischemic events, including cardiovascular death, was significantly lower among those who received 2 g of icosapent ethyl twice daily than among those who received placebo. (Funded by Amarin Pharma; REDUCE-IT ClinicalTrials.gov number, NCT01492361).

Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, Barton J, Murphy K, Aung T, Haynes R, Cox J, Murawska A, Young A, Lay M, Chen F, Sammons E, Waters E, Adler A, Bodansky J, Farmer A, McPherson R, Neil A, Simpson D, Peto R, Baigent C, Collins R, Parish S, Armitage J. Collaborators ASCEND Study Collaborative Group, Effects of n-3 Fatty Acid Supplements in Diabetes Mellitus. N Engl J Med. 2018 Oct 18;379(16):1540-1550. doi: 10.1056/NEJMoa1804989. Epub 2018 Aug 26.

Abstract
BACKGROUND:
Increased intake of n-3 fatty acids has been associated with a reduced risk of cardiovascular disease in observational studies, but this finding has not been confirmed in randomized trials. It remains unclear whether n-3 (also called omega-3) fatty acid supplementation has cardiovascular benefit in patients with diabetes mellitus.

METHODS:
We randomly assigned 15,480 patients with diabetes but without evidence of atherosclerotic cardiovascular disease to receive 1-g capsules containing either n-3 fatty acids (fatty acid group) or matching placebo (olive oil) daily. The primary outcome was a first serious vascular event (i.e., nonfatal myocardial infarction or stroke, transient ischemic attack, or vascular death, excluding confirmed intracranial hemorrhage). The secondary outcome was a first serious vascular event or any arterial revascularization.

RESULTS:
During a mean follow-up of 7.4 years (adherence rate, 76%), a serious vascular event occurred in 689 patients (8.9%) in the fatty acid group and in 712 (9.2%) in the placebo group (rate ratio, 0.97; 95% confidence interval [CI], 0.87 to 1.08; P=0.55). The composite outcome of a serious vascular event or revascularization occurred in 882 patients (11.4%) and 887 patients (11.5%), respectively (rate ratio, 1.00; 95% CI, 0.91 to 1.09). Death from any cause occurred in 752 patients (9.7%) in the fatty acid group and in 788 (10.2%) in the placebo group (rate ratio, 0.95; 95% CI, 0.86 to 1.05). There were no significant between-group differences in the rates of nonfatal serious adverse events.

CONCLUSIONS:
Among patients with diabetes without evidence of cardiovascular disease, there was no significant difference in the risk of serious vascular events between those who were assigned to receive n-3 fatty acid supplementation and those who were assigned to receive placebo. (Funded by the British Heart Foundation and others; Current Controlled Trials number, ISRCTN60635500 ; ClinicalTrials.gov number, NCT00135226).

Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby JF, Tricoci P, White HD, Zeiher AM; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med. 2018 Nov 29;379(22):2097-2107.

Abstract
BACKGROUND:

Patients who have had an acute coronary syndrome are at high risk for recurrent ischemic cardiovascular events. We sought to determine whether alirocumab, a human monoclonal antibody to proprotein convertase subtilisin-kexin type 9 (PCSK9), would improve cardiovascular outcomes after an acute coronary syndrome in patients receiving high-intensity statin therapy.

METHODS:
We conducted a multicenter, randomized, double-blind, placebo-controlled trial involving 18,924 patients who had an acute coronary syndrome 1 to 12 months earlier, had a low-density lipoprotein (LDL) cholesterol level of at least 70 mg per deciliter (1.8 mmol per liter), a non-high-density lipoprotein cholesterol level of at least 100 mg per deciliter (2.6 mmol per liter), or an apolipoprotein B level of at least 80 mg per deciliter, and were receiving statin therapy at a high-intensity dose or at the maximum tolerated dose. Patients were randomly assigned to receive alirocumab subcutaneously at a dose of 75 mg (9462 patients) or matching placebo (9462 patients) every 2 weeks. The dose of alirocumab was adjusted under blinded conditions to target an LDL cholesterol level of 25 to 50 mg per deciliter (0.6 to 1.3 mmol per liter). The primary end point was a composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization.

RESULTS:
The median duration of follow-up was 2.8 years. A composite primary end-point event occurred in 903 patients (9.5%) in the alirocumab group and in 1052 patients (11.1%) in the placebo group (hazard ratio, 0.85; 95% confidence interval [CI], 0.78 to 0.93; P<0.001). A total of 334 patients (3.5%) in the alirocumab group and 392 patients (4.1%) in the placebo group died (hazard ratio, 0.85; 95% CI, 0.73 to 0.98). The absolute benefit of alirocumab with respect to the composite primary end point was greater among patients who had a baseline LDL cholesterol level of 100 mg or more per deciliter than among patients who had a lower baseline level. The incidence of adverse events was similar in the two groups, with the exception of local injection-site reactions (3.8% in the alirocumab group vs. 2.1% in the placebo group).

CONCLUSIONS:
Among patients who had a previous acute coronary syndrome and who were receiving high-intensity statin therapy, the risk of recurrent ischemic cardiovascular events was lower among those who received alirocumab than among those who received placebo. (Funded by Sanofi and Regeneron Pharmaceuticals; ODYSSEY OUTCOMES ClinicalTrials.gov number, NCT01663402).

Manson JE, Cook NR, Lee IM, Christen W, et al. Marine n-3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer. N Engl J Med. 2019 Jan 3;380(1):23-32. doi: 10.1056/NEJMoa1811403. Epub 2018 Nov 10.

BACKGROUND:
Higher intake of marine n-3 (also called omega-3) fatty acids has been associated with reduced risks of cardiovascular disease and cancer in several observational studies. Whether supplementation with n-3 fatty acids has such effects in general populations at usual risk for these end points is unclear.

METHODS:
We conducted a randomized, placebo-controlled trial, with a two-by-two factorial design, of vitamin D3 (at a dose of 2000 IU per day) and marine n-3 fatty acids (at a dose of 1 g per day) in the primary prevention of cardiovascular disease and cancer among men 50 years of age or older and women 55 years of age or older in the United States. Primary end points were major cardiovascular events (a composite of myocardial infarction, stroke, or death from cardiovascular causes) and invasive cancer of any type. Secondary end points included individual components of the composite cardiovascular end point, the composite end

point plus coronary revascularization (expanded composite of cardiovascular events), site-specific cancers, and death from cancer. Safety was also assessed. This article reports the results of the comparison of n-3 fatty acids with placebo.

RESULTS:
A total of 25,871 participants, including 5106 black participants, underwent randomization. During a median follow-up of 5.3 years, a major cardiovascular event occurred in 386 participants in the n-3 group and in 419 in the placebo group (hazard ratio, 0.92; 95% confidence interval [CI], 0.80 to 1.06; P=0.24). Invasive cancer was diagnosed in 820 participants in the n-3 group and in 797 in the placebo group (hazard ratio, 1.03; 95% CI, 0.93 to 1.13; P=0.56). In the analyses of key secondary end points, the hazard ratios were as follows: for the expanded composite end point of cardiovascular events, 0.93 (95% CI, 0.82 to 1.04); for total myocardial infarction, 0.72 (95% CI, 0.59 to 0.90); for total stroke, 1.04 (95% CI, 0.83 to 1.31); for death from cardiovascular causes, 0.96 (95% CI, 0.76 to 1.21); and for death from cancer (341 deaths from cancer), 0.97 (95% CI, 0.79 to 1.20). In the analysis of death from any cause (978 deaths overall), the hazard ratio was 1.02 (95% CI, 0.90 to 1.15). No excess risks of bleeding or other serious adverse events were observed.

CONCLUSIONS:
Supplementation with n-3 fatty acids did not result in a lower incidence of major cardiovascular events or cancer than placebo. (Funded by the National Institutes of Health and others; VITAL ClinicalTrials.gov number, NCT01169259 .).

Appendix 3: Medline Search Strategy
Database: Ovid MEDLINE(R) <2016 to February Week 4 2019>
Search Strategy:
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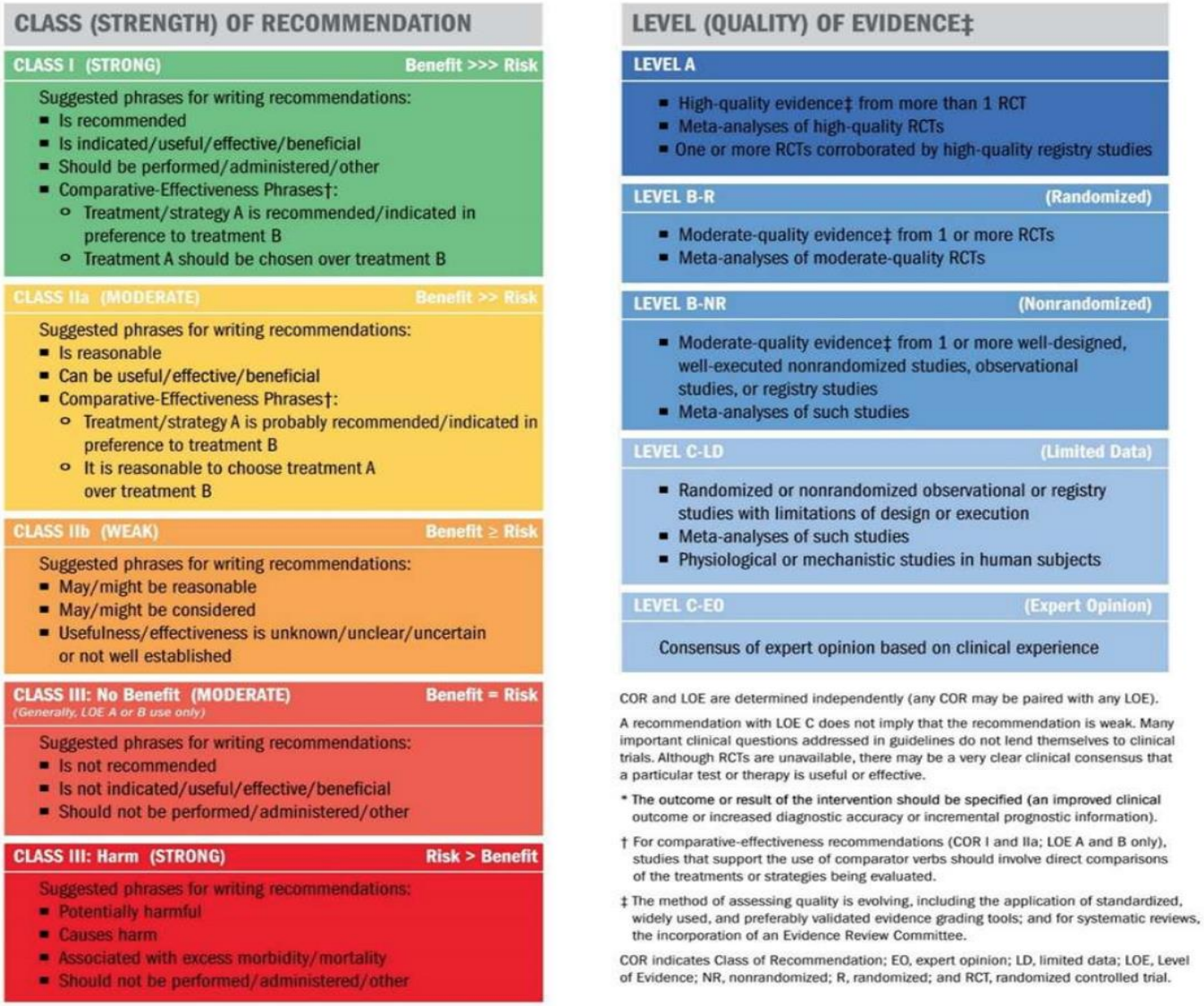
1 (Cholestyramine Resin or Colesevelam Hydrochloride or Colestipol or Docosahexaenoic Acids or Eicosapentaenoic acid or ezetimibe or ezetimibe, simvastatin drug combination or Fatty acids, Omega-3 or Fenofibrate or Fenofibrate micronized or Gemfibrozil or Inositol or Icosapent ethyl or Fenofibric acid or Niacin or Nicotinamide or Nicotinic acid or Lovaza or Bile acid sequestrants or Statin, high-intensity or Lomitapide or Mipomersen or alirocumab or evolocumab or psck9 inhibitors).af. (106523)
2 (Coronary Artery Disease or Coronary Disease or Dyslipidemia or Dyslipidemias or Hypertriglyceridemias or Myocardial Infarction or Stroke or Cardiovascular Disease or Cardiovascular Diseases).af. (844491)
3 ((Cholestyramine Resin or Colesevelam Hydrochloride or Colestipol or Docosahexaenoic Acids or Eicosapentaenoic acid or ezetimibe or ezetimibe, simvastatin drug combination or Fatty acids, Omega-3 or Fenofibrate or Fenofibrate micronized or Gemfibrozil or Inositol or Icosapent ethyl or Fenofibric acid or Niacin or Nicotinamide or Nicotinic acid or Lovaza or Bile acid sequestrants or Statin, high-intensity or Lomitapide or Mipomersen or alirocumab or evolocumab or psck9 inhibitors) and (Coronary Artery Disease or Coronary Disease or Dyslipidemia or Dyslipidemias or Hypertriglyceridemias or Myocardial Infarction or Stroke or Cardiovascular Disease or Cardiovascular Diseases)).af. (8963)
4 limit 3 to (english language and humans) (6967)
5 limit 4 to (english language and humans and yr="2016 -Current" and (clinical trial, all or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review" or systematic reviews as topic) and (in process or medline)) (339)

Appendix 4: Key Inclusion Criteria

Population	Patients with cardiovascular disease or at high risk for cardiovascular disease
Intervention	Pharmacotherapy listed in Appendix 1
Comparator	Pharmacotherapy listed in Appendix 1 or placebo
Outcomes	Quality of life Morbidity Mortality Major CV events (CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization) Serious Adverse Events Discontinuation from Serious Adverse Events
Timing	Any study duration; literature search from January 2016 through March 1st 2019
Setting	Outpatient

Appendix 5: 2018 Cholesterol Guidelines Class of Recommendation and Level of Evidence Descriptions



CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — **Benefit >>> Risk**

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) — **Benefit >> Risk**

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK) — **Benefit ≥ Risk**

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

CLASS III: No Benefit (MODERATE) — **Benefit = Risk**

(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

CLASS III: Harm (STRONG) — **Risk > Benefit**

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R (Randomized)
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL B-NR (Nonrandomized)
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C-LD (Limited Data)
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

LEVEL C-EO (Expert Opinion)

Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

PCSK9 Inhibitors

Goal(s):

- Promote use of PCSK9 inhibitors that is consistent with medical evidence
- Promote use of high value products

Length of Authorization:

- Up to 12 months

Requires PA:

- All PCSK9 inhibitors

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code; go to #3	

Approval Criteria		
3. Does the patient have very high-risk clinical atherosclerotic cardiovascular disease (ASCVD), defined as documented history of multiple major ASCVD events **OR** one major ASCVD event and multiple high-risk conditions (See below) <u>Major ASCVD events</u> • Recent ACS (within past 12 months) • History of MI (other than recent ACS from above) • History of ischemic stroke • Symptomatic peripheral artery disease <u>High-Risk Conditions:</u> • Age ≥ 65 • Heterozygous familial hypercholesterolemia • History of prior CABG or PCI • Diabetes Mellitus • Hypertension • Chronic Kidney Disease • Current smoking • Persistently elevated LDL-C ≥ 100 despite maximally tolerated statin therapy and ezetimibe • History of congestive heart failure	**Yes:** Go to #4	**No:** Go to #7

Approval Criteria		
4. Has the patient taken a daily high-intensity statin (see table below) and ezetimibe 10 mg daily for at least 3 months with a LDL-C still ≥ 70 mg/dl or non-HDL ≥ 100 mg/dl? Prescriber to submit chart documentation of: 1) Doses and dates initiated of statin and ezetimibe; 2) Baseline LDL-C (untreated); 3) Recent LDL-C	**Yes:** Confirm documentation; go to #5 1. Statin: Dose: Date Initiated: 2. Ezetimibe 10 mg daily Date Initiated: Baseline LDL-C _____ mg/dL Date:_____ Recent LDL-C _____ mg/dL Date:_____	**No:** Go to #6
5. Is the patient adherent with a high-intensity statin and ezetimibe?	**Yes:** Approve for up to 12 months Note: pharmacy profile may be reviewed to verify >80% adherence (both lipid-lowering prescriptions refilled 5 months' supply in last 6 months)	**No:** Pass to RPh; deny for medical appropriateness
6. Does the patient have a history of rhabdomyolysis caused by a statin; or alternatively, a history of creatinine kinase (CK) levels >10-times upper limit of normal with muscle symptoms determined to be caused by a statin? Note: Prescriber must provide chart documentation of diagnosis or CK levels. A recent LDL-C level (within last 12 weeks) must also be submitted.	**Yes:** Confirm chart documentation of diagnosis or labs and approve for up to 12 months Recent LDL-C _____ mg/dL Date:_____	**No:** Pass to RPh; deny for medical appropriateness

Approval Criteria		
7. Does the patient have a diagnosis of homozygous or heterozygous familial hypercholesterolemia? Note: Prescriber must provide chart documentation of diagnosis and recent LDL-C (within last 12 weeks).	**Yes:** Go to #8	**No:** Pass to RPh; deny for medical appropriateness.
8. Does the patient still have a LDL-C of ≥ 100 mg/dl while taking a maximally tolerated statin and ezetimibe?	**Yes:** Approve for up to 12 months Recent LDL-C _____ mg/dL Date:_____	**No:** Pass to RPh; deny for medical appropriateness.

Renewal Criteria		
1. What is the most recent LDL-C (within last 12 weeks)?	Recent LDL-C _____ mg/dL Date:_____ ; go to #2	
2. Is the patient adherent with PCSK9 inhibitor therapy?	**Yes:** Approve for up to 12 months Note: pharmacy profile may be reviewed to verify >80% adherence (PCSK9 inhibitor prescription refilled 10 months' supply in last 12 months)	**No:** Pass to RPh; deny for medical appropriateness

High- and Moderate-intensity Statins.

High-intensity Statins (≥50% LDL-C Reduction)	**Moderate-intensity Statins** (30 to <50% LDL-C Reduction)	
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Fluvastatin 80 mg Lovastatin 40-80 mg	Pitavastatin 1-4 mg Pravastatin 40-80 mg Simvastatin 20-40 mg Rosuvastatin 5-10 mg

P&T / DUR Review: *5/19 (MH); 1/18; 11/16; 11/15*
Implementation: *7/1/2019; 3/1/18; 1/1/1*

Mipomersen and Lomitapide

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which mipomersen or lomitapide has been shown to be effective and safe.

Length of Authorization:

- Up to 6 months

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the drug prescribed by or in consultation with a specialist in lipid disorders?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis homozygous familial hypercholesterolemia?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient tried and failed or does the patient have a medical contraindication to maximum lipid lowering therapy with a combination of traditional drugs (high-intensity statin with ezetimibe (see Table 1)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has the patient failed or are they not appropriate for LDL-C apheresis; **OR** is LDL-C apheresis not available?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Table 1. High-intensity Statins.

High-intensity Statins (≥50% LDL-C Reduction)

Atorvastatin 40-80 mg	Rosuvastatin 20-40 mg

Ref. Stone NJ, et al. 2013 ACC/AHA Blood Cholesterol Guideline.

P&T/DUR Review: *5/19 (MH); 11/16 (DM); 5/16; 9/13; 7/13; 5/13*
Implementation: *1/1/17; 1/1/14; 11/21/2013*

Omega-3 Fatty Acids

Goal(s):

- Restrict use of omega-3 fatty acids to patients at increased risk for pancreatitis.

Length of Authorization:

- Up to 12 months

Requires PA:

Omega-3-Acid Ethyl Esters (Lovaza®)
Icosapent Ethyl (Vascepa®)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis an OHP funded diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP

Approval Criteria		
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #4
4. Does the patient have clinically diagnosed hypertriglyceridemia with triglyceride levels ≥ 500 mg/dL?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Has the patient failed or have a contraindication to an adequate trial (at least 8 weeks) of a fibric acid derivative (fenofibrate or gemfibrozil) at a maximum tolerable dose (as seen in dosing table below); **OR** Is the patient taking a statin and unable to take a fibric acid derivative due to an increased risk of myopathy?	**Yes:** Approve up to 1 year.	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of other agent(s).

Table 1: Dosing of Fenofibrate and Derivatives for Hypertriglyceridemia.

Trade Name (generic)	Recommended dose	Maximum dose
Antara (fenofibrate capsules)	43-130 mg once daily	130 mg once daily
Fenoglide (fenofibrate tablet)	40-120 once daily	120 mg once daily
Fibricor (fenofibrate tablet)	25-105 mg once daily	105 mg once daily
Lipofen (fenofibrate capsule)	50-150 mg once daily	150 mg once daily
Lofibra (fenofibrate capsule)	67-200 mg once daily	200 mg once daily
Lofibra (fenofibrate tablet)	54-160 mg once daily	160 mg once daily
Lopid (gemfibrozil tablet)	600 mg twice daily	600 mg twice daily
Tricor (fenofibrate tablet)	48-145 mg once daily	145 mg once daily
Triglide (fenofibrate tablet)	50-160 mg once daily	160 mg once daily
Trilipix (fenofibrate DR capsule)	45-135 mg once daily	135 mg once daily