© Copyright 2012 Oregon State University. All Rights Reserved

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

A Class Update: Non-statins for Hyperlipidemia

Date of Review: November 2016

Date of Last Review: September 2014
PSCK9 inhibitors in November 2015
Mipomersen and lomitapide in May 2016

Current Status of PDL Class: Non-statins
See **Appendix 1**.

Research Questions:

1. Is there any new comparative 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?
2. Is there any new comparative evidence for harms of non-statin lipid-lowering agents in patients being treated for the primary or secondary prevention of CV disease?
3. 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:

- Four systematic reviews evaluated comparative evidence for ezetimibe, niacin, fibrates, or omega 3 fatty acids on all-cause mortality, cardiovascular mortality, stroke, and myocardial infarction (MI) with or without concurrent statin therapy. [1–4]
    - There is moderate quality evidence that ezetimibe combined with a statin results in a modest improvement in cardiovascular outcomes. In the IMPROVE-IT trial, the primary endpoint was a composite of death from cardiovascular disease, a major coronary event (non-fatal MI, unstable angina requiring hospitalization, coronary revascularization), or non-fatal stroke in patients that had been recently hospitalized for acute coronary syndrome.[5] At 7 years, the Kaplan-Meier event rate for the composite endpoint was 32.7% in the ezetimibe/statin group compared to 34.7% in the statin monotherapy group (absolute risk difference, 2.0 %, hazard ratio (HR), 0.936, 95% confidence interval (CI), 0.89 to 0.99, p = 0.016). [5] There were no differences noted in all- cause mortality (HR, 0.95, 95% CI, 0.91 to 1.07, p = 0.78) or cardiovascular death (HR, 1.00, 95% CI, 0.89-1.13, p=1.00) between the two groups.[5]
    - Moderate quality evidence from systematic reviews compared statin monotherapy to a statin in combination with ezetimibe, niacin, fibrates or omega 3 fatty acids and revealed inconsistent effects on CV outcomes and no significant differences in reducing all- cause mortality, death from CHD (coronary heart disease) or stroke.[1–4]
- There is insufficient data to support any role for omega 3 fatty acids to reduce all-cause mortality and CV outcomes.[4]

Author: Deanna Moretz, PharmD, BCPS

Date: November 2016

DRAFT

- Moderate quality evidence shows proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are efficacious at reducing low-density lipoprotein cholesterol (LDL-C) levels by over 50% from baseline. However, evidence is insufficient at this time to support the use of PCSK9 inhibitors to reduce adverse CV outcomes including all-cause mortality.[6–8]
- There is moderate quality evidence from short term trials that the incidence of adverse events is similar between ezetimibe combined with a statin and statin monotherapy.[9]
- Moderate quality evidence from short term trials suggests PCSK9 inhibitors are associated with increased neurocognitive adverse events compared to placebo.[8] The FDA has directed developers of PCSK9 inhibitors to monitor for neurocognitive adverse effects in ongoing clinical trials. A higher frequency of neurocognitive adverse events was observed with both evolocumab (0.9% versus 0.3% for placebo) and alirocumab (1.2% versus 0.5% for placebo).[10]
- Current guidance do not recommend combining statin therapy with fibrates, niacin, bile acid sequestrants, or omega 3 fatty acids for primary or secondary prevention of adverse CV events due to insufficient evidence that demonstrates CV risk reduction. [11–14] Ezetimibe may be used as an alternative for patients intolerant to statins or high risk patients unable to attain effective LDL-C lowering with statin monotherapy. The PCSK9 inhibitors are currently recommended for patients at high risk for cardiovascular disease (CVD) and persistently elevated LDL levels despite use of other lipid-lowering agents, including high intensity statin therapy. These recommendations are based on short term, multicenter, manufacturer-sponsored Phase 3 RCTs. [15–17] The PCSK9 inhibitors can be used as an adjunct to maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH) who require additional lowering of LDL-C.

Recommendations:

- Ezetimibe is currently a non-preferred medication on the Oregon Health Plan (OHP) Preferred Drug List (PDL). Based on a review of recent evidence, there is no need to modify the status of ezetimibe on the PDL.
- Revise prior authorization criteria to remove failure or contraindication of niacin therapy as condition for approval of omega 3 fatty acids.
- No other changes to the PDL or clinical prior authorization (PA) criteria are needed.

Previous Conclusions:

- There remains insufficient evidence for improved CV outcomes for non-statin lipid lowering agents.
- For high risk patients, it may be reasonable to add a non-statin lipid-lowering agent in high-risk patients who have a less than anticipated response to statins, who are unable to tolerate a less than recommended intensity of a statin or who are completely statin intolerant.
- There is moderate quality evidence that gemfibrozil as monotherapy may reduce the risk for stroke and CV mortality.
- There is no clinical evidence of superiority of one fenofibrate agent over another.
- There is insufficient evidence comparing iscopaent ethyl (ICP) to any of the current therapies. When compared to the efficacy of current treatments such as fibrates or niacin, ICP has similar TG lowering ability but there is insufficient data to compare CV risk lowering or pancreatitis risk lowering in any of these therapies. ICP is at least as safe as fibrates or niacin and has significantly fewer treatment-associated adverse effects.
- In patients with familial hypercholesterolemia, there is insufficient evidence that directly compares efficacy and harms between PCSK9 inhibitors.
    - In patients with heterozygous familial hypercholesterolemia already on a statin and ezetimibe, there is low quality evidence from short-term data that alirocumab can improve LDL-C by a difference of -57% compared to placebo; however, there is high quality evidence from short-term data that evolocumab can improve LDL-C by a difference of -61% compared to placebo.
    - In patients with homozygous familial hypercholesterolemia already on a statin and ezetimibe, there is insufficient evidence to use alirocumab; however, there is low quality evidence from short-term data that evolocumab can improve LDL-C by a difference of -32% compared to placebo.

DRAFT

- In patients with non-familial hypercholesterolemia intolerant to statins, there is insufficient evidence that directly compares efficacy and harms between PCSK9 inhibitors.
    - In addition, there is insufficient evidence for use of alirocumab in this population; however, there is low quality evidence from short-term data that evolocumab can improve LDL-C by a difference of -47% compared to ezetimibe alone.
- In patients with non-familial hypercholesterolemia who cannot achieve adequate LDL-C reduction with their current lipid-lowering regimen, there is insufficient evidence that directly compares efficacy and harms between PCSK9 inhibitors.
    - However, there is high quality evidence from short-term data that use of alirocumab can result in a significantly higher proportion of patients at high risk for (CV) events to achieve an LDL-C of less than 70 mg/dL versus placebo, with as much as a -62% greater reduction in LDL-C.
    - However, there is low quality evidence of no difference in CV events between alirocumab and placebo at 52- and 78-week follow-up when alirocumab and placebo were continued long-term with concomitant statin therapy. In addition, there is moderate quality evidence of no difference in CV events between alirocumab and ezetimibe at 52-week follow-up when both treatments were continued long-term with concomitant statin therapy.
    - There is high quality evidence from short-term data that use of evolocumab can result in a significantly higher proportion of patients at high risk for CV events to achieve an LDL-C of less than 70 mg/dL versus placebo. When compared to the addition of ezetimibe, there is low quality evidence that the addition of evolocumab can also result in higher achievement rates of target LDL-C of less than 70 mg/dL.
- In a mix of all populations studied above, there is insufficient evidence to draw conclusions on the effect of evolocumab on CV outcomes.
- There is insufficient evidence to differentiate between differences in harms between PCSK9 inhibitors. It is unknown if significantly lowering LDL-C will adversely affect gastrointestinal, metabolic and neurocognitive functions.

Previous Recommendations

- Designate alirocumab and evolocumab as non-preferred. Preferred status cannot be made at this time due to limited evidence of long-term CV benefit and harms.
- Restrict use of PCSK9 Inhibitors to populations with clinical atherosclerotic disease and 1) non-familial hypercholesterolemia unable to achieve at least 50% LCL-C reduction despite high-intensity statin therapy and ezetimibe; 2) familial hypercholesterolemia; or 3) history of rhabdomyolysis or creatinine kinase levels greater than 10-times the upper limit of normal with muscle symptoms.
- Make iscopaent ethyl a non-preferred lipotropic agent and use the non-PDL prior authorization criteria due to its use as an alternative to a fibric acid derivative and niacin for hypertriglyceridemia.
- Make ezetimibe a non-preferred agent due to insufficient outcome data, and implement the non-PDL prior authorization criteria for use.
- Niacin drug products are not preferred due to questionable evidence for reduction in CV outcomes.

Background:

The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Practice Guidelines advocate for a substantial shift in strategies to assess and manage elevated cholesterol to reduce CV disease (CVD).[11] Recommendations were derived from randomized trials, meta-analyses, and observational studies that were considered high quality using National Heart, Lung and Blood Institute (NHLBI) criteria.[11] The previous Adult Treatment Panel (ATP) III guidelines focused on reducing LDL-C and non-high density lipoprotein cholesterol (non-HDL-C) to specific target levels. The updated ACC/AHA guidelines recommend adjusting the intensity of statin therapy to reduce CVD risk in patients most likely to benefit from therapy using a risk estimator.[11] According to the ACC/AHA, non-statin therapies do not provide acceptable CVD risk reduction benefits.[11] For high risk patients including those with

DRAFT

atherosclerotic CVD, LDL ≥ 190 mg/dl and diabetics who are statin intolerant or unable to achieve sufficient response to statins, non-statin options such as niacin, fibric acid derivatives, ezetimibe, or omega-3 fatty acids can be considered to further lower LDL-C.[11] However, the benefit of CVD risk reduction with non-statin therapy should be evaluated against the risks of adverse effects and drug-drug interactions.[11] The PCSK9 inhibitors were not part of the ACC/AHA practice guidelines since they were not yet approved in 2013.

This class update will focus on recent evidence regarding the safety and efficacy of non-statin therapy including niacin, fibric acid derivatives, bile acid sequestrants, ezetimibe, omega 3 fatty acids and PCSK9 inhibitors in management of hyperlipidemia to reduce adverse CV outcomes and mortality. **Table 1** in **Appendix 4** outlines the effects of each of these agents on specific lipoproteins and their Food and Drug Administration (FDA)-approved indications. Mipomersen and lomitapide, two agents approved for management of homozygous familial hypercholesterolemia (HoFH), were reviewed by this committee at the May 2016 meeting so they are not included in this review.

The effectiveness of niacin extended release (ER) when added to statin therapy is questionable after 2 recent RCTs did not demonstrate significant reductions in CV events in patients with established coronary artery disease and low HDL-C.[2, 3] The AIM-HIGH trial was stopped after a mean follow-up of 3 years due to lack of efficacy in reducing CV events and an increased rate of ischemic stroke in the niacin group.[20] The HPS2-THRIVE trial was designed to assess the effect of adding niacin ER in combination with laropiprant to simvastatin 40 mg with or without ezetimibe in patients with CV disease.[19] Laropiprant is a prostaglandin antagonist was used to reduce the adverse effect of flushing commonly associated with niacin therapy. After a mean 3.9 years of follow-up, niacin–laropiprant was not associated with a statistically significant reduction in the incidence of major CV events but was associated with more fatal and nonfatal serious adverse events, including worsening glucose control in patients with diabetes, gastrointestinal adverse effects, excessive rates of infection and bleeding.[19] Prescribing information for niacin was updated in April 2015 to state that the addition of niacin ER does not reduce CV morbidity or mortality in patients treated already on statin therapy.[21] In April 2016, the FDA withdrew approval for Advicor®(niacin ER and lovastatin) and Simcor® (niacin ER and simvastatin) as results from these trials showed that the risks of combination therapy outweighs the benefits.[22]

Fibric acid derivatives include gemfibrozil, fenofibric acid, and fenofibrate. In the ACCORD trial, fenofibrate was studied in combination with simvastatin in patients with diabetes mellitus to assess the impact on CV disease. After a mean follow-up of 4.7 years, no significant benefit in fatal or non-fatal CV events was noted with fenofibrate and simvastatin versus simvastatin alone.[23] According to the ACC/AHA guidelines, fenofibrate may only be considered to be used concomitantly with a low- or moderate-intensity statin if the benefits from CVD risk reduction or triglyceride-lowering (when triglycerides are >500 mg/dL) are judged to outweigh the potential risk for adverse effects.[11] The prescribing information for fenofibrate was revised to remove the indication about co-administration with a statin due to the fact that the risks outweigh the benefits of combination therapy.[24] Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis.[11]

The efficacy of ezetimibe as monotherapy has not been evaluated in comparison with statin therapy and there are no published trials that have evaluated ezetimibe in primary prevention of CVD. Although ezetimibe effectively lowers LDL-C, the long-term effects on CV morbidity and mortality are unclear. Two RCTs (ENHANCE and SEAS) failed to show a statistically significant reduction in the progression of atherosclerosis among patients with heterozygous familial hypercholesterolemia who were treated with ezetimibe/simvastatin versus simvastatin alone.[6, 7] The SEAS trial investigators reported cancer in 105/1873 (11.1%) patients in the ezetimibe/simvastatin cohort compared to 70/1873 (7.5%) of the patients in the placebo group.[27] The FDA subsequently reviewed cancer prevalence data from the SEAS, SHARP and IMPROVE-IT trials. Based on an assessment of cancer risk in a larger number of patients (n=20,167) the FDA did not find a significant correlation between cancer and ezetimibe therapy.[28] The IMPROVE-IT trial provides modest evidence for use of ezetimibe in combination with a statin for secondary prevention of CVD. In this trial, simvastatin was compared to the combination of simvastatin/ezetimibe in patients who had been

hospitalized for an acute coronary syndrome within the preceding 10 days. The primary endpoint was a composite of multiple different endpoints: CV death, nonfatal myocardial infarction, unstable angina requiring re-hospitalization, coronary revascularization, or nonfatal stroke.[5] 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.[5] 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.[29]

Bile-acid sequestrants (BAS) include cholestyramine, colestipol, and colesevelam. No RCTs have evaluated combination therapy of BAS with statins and their impact on CV outcomes. When used as monotherapy, there is evidence BAS can lower LDL-C levels. The ACC/AHA guidelines recommend against the use of BAS in individuals with baseline fasting triglyceride levels ≥300 mg/dL or type III hyperlipoproteinemia due to elevated risk for severe hypertriglyceridemia.[11] It is reasonable to use BAS with caution if baseline triglyceride levels are 250 to 299 mg/dL; however, BAS therapy should be discontinued if triglycerides exceed 400 mg/dL.[11]

Omega-3 fatty acids (i.e., Lovaza®) and icosapent are two FDA-approved legend drugs for the treatment of severe hypertriglyceridemia.[30,31] However, the effect of omega-3 fatty acids on reducing CV risk in patients with hypertriglyceridemia has not been proven.[22, 23] The ongoing REDUCE-IT trial plans to evaluate the effect of icosapent ethyl in reducing long-term CV events in hypertriglyceridemic patients maintained on statin therapy.[32]

The first PCSK9 two inhibitors evolocumab and alirocumab were approved in 2015. Bococizumab is a third agent in this class currently being studied in Phase 3 trials but has not yet been approved by the FDA.[33] The PCSK9 inhibitors can lower LDL-C by more than 50% but their capacity to reduce adverse CV events is not clear and these agents are currently being evaluated in long-term clinical trials.[34]

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. 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), Cochrane Collection, 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. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

DRAFT

New Systematic Reviews:

Ezetimibe, Niacin, Fibrates, or Omega 3 Fatty Acids on Mortality and Cardiovascular Outcomes with or without Statin Therapy:

A systematic review published in 2015 assessed the safety and efficacy of ezetimibe.[1] A total of 9 RCTs (n=2,212) published through December 2013 were evaluated. Two trials compared ezetimibe in combination with simvastatin to placebo. Seven trials compared ezetimibe and another lipid-lowering drug to the respective lipid-lowering drug alone at the same dosage: 5 compared ezetimibe to simvastatin 20 to 80 mg daily, 2 compared ezetimibe to atorvastatin 10 mg daily, and one trial compared ezetimibe to fenofibrate 160 mg daily. All trials followed participants for at least 24 weeks. The following outcomes were evaluated: all-cause mortality, CV mortality, stroke, MI, cancer, and serious adverse events (SAEs). The trials were of low to medium quality with uncertain risk of bias due to poor reporting of study parameters or selective reporting of outcomes. When results were pooled for meta-analysis, ezetimibe/simvastatin did not demonstrate significant differences in outcomes compared to placebo: MI (Relative Risk (RR) 0.81; 95% CI 0.66-to 1.00); all-cause mortality (RR 1.02; 95% CI 0.95 to 1.09); CV death (RR 0.91; 95% CI 0.80 to 1.04); non-CV mortality (RR 1.08; 95% CI 0.99 to 1.1); stroke (RR 0.86; 95% CI 0.72 to1.04;); cancer (RR 1.18; 95% CI 0.8 to 1.74; and SAEs (RR 1.01; 95% CI 0.96 to 1.06).[1] When the fixed-dose combination ezetimibe/simvastatin was compared to simvastatin alone, there were non-significant effects for all-cause mortality (RR 2.52; 95% CI 0.65 to 9.74), CV mortality (RR 3.04; 95% CI 0.48 to 19.21), non-CV mortality (RR 3.03; 95% CI 0.12 to 73.50), MI (RR 1.91; 95% CI 0.42 to 8.70), stroke (RR 2.38; 95% CI 0.46 to 12.35), cancer (RR 11.11; 95% CI 0.62 to 198.29), and SAEs (RR 1.45; 95% CI 0.95 to 2.23).[1] The increased risk of cancer with ezetimibe may be due to the inclusion of one trial that found an increased risk of cancer with ezetimibe by post-hoc analysis.[26] The primary limitation of this meta-analysis was that the data did not yield precise results due to the small number of reported events.[17] The authors concluded ezetimibe in combination with simvastatin compared to a statin alone or placebo had inconsistent effects on CV outcomes and no firm conclusions could be drawn in regards to the efficacy of combination ezetimibe/statin therapy at reducing the risk of adverse CV outcomes.[1]

A 2015 systematic review evaluated the impact on adverse CV outcomes and mortality when a lipid-lowering drug was added to statin therapy.[2] Major adverse CV events (MACE), defined as a composite of death from coronary heart disease (CHD), non-fatal MI or stroke, were evaluated.[2] No trials with bile acid sequestrants or PCSK9 inhibitors met the inclusion criteria. Eight RCTs (n=77,118) randomized patients to either: statin/niacin or statin (n=29,254); statin/omega 3 fatty acid or statin (n=23,482); statin/fenofibrate or statin (n=5,518 patients); or statin/ezetimibe or statin (n=18,864 patients). One RCT that evaluated omega 3 fatty acids was open-label but the other 7 trials were double-blinded. The follow-up period ranged from 1.5 to 6 years. The authors rated the evidence as high quality with low risk of bias. The IMPROVE-IT, HPS2-THRIVE, ACCORD and AIM-HIGH trials were all included in the meta-analysis. In the overall analysis, the incidence of MACE with statin combination therapies was 0.22% lower than statin monotherapy (9.70% vs. 9.92%, respectively; RR 0.99; 95% CI 0.93 to 1.05, p=0.76).[2] In subgroup analyses, no significant findings were noted for statins combined with niacin (RR 1.03; 95% CI 0.85 to 1.25, p=0.79), omega 3 fatty acids (RR 0.98; 95% CI 0.88 to 1.09, p=0.70), or fenofibrate (RR 0.93; 95% CI 0.80 to 1.09, p=0.38) compared to a statin alone.[2] However, results with ezetimibe combined with a statin found a small statistically significant reduction in MACE (RR 0.92; 95% CI 0.87 to 0.97, p=0.004) compared to a statin alone.[2] The overall meta-analysis of individual CV events did not find statistically significant differences between statin combinations and statin monotherapy for death from CHD or stroke (RR 0.97; 95% CI 0.90 to 1.05, p=0.47 and RR 1.04; 95% CI 0.89 to 1.22, p=0.63, respectively).[2] Subgroup analyses for each statin combination also did not show a statistically significant reduction in death from CHD or stroke. The overall meta-analysis of risk for non-fatal MI was also not statistically significant (RR 0.96; 95% CI 0.89 to 1.04, p=0.28) between statin combinations and statins alone; however, subgroup analysis showed a statistically significant reduction in non-fatal MI (RR 0.89; 95% CI 0.82 to 0.95, p=0.001) for ezetimibe combined with a statin versus a statin alone.[2] Adding lipid-lowering therapy to statins increased the risk of liver injury (675/34,943 versus 435/34,959; p=0.031).[2] No statistically significant increase in creatine kinase levels between the 2 comparisons were found (194/22,015 versus 189/22,106, p=0.778).[2] The authors concluded that the addition of niacin, omega 3 fatty acids or fibrates to statin therapy do not

result in improved long-term CV outcomes but the addition of ezetimibe to statin therapy may provide a very modest clinical benefit for patients at high risk of CVD.[2]

A 2014 meta-analysis completed in 2014 investigated the effects of non-statin therapies that increase HDL levels on CV outcomes.[3] The benefit of niacin (n=11 studies) and fibrates (n=20 studies) on all-cause mortality, CHD mortality, non-fatal MI and stroke was evaluated in 81,410 patients randomized to 31 trials conducted from 1966 through 2013.[3] The authors noted that maintenance of blinding in the niacin studies would have been difficult due to the high risk of flushing associated with niacin therapy. Otherwise, the authors assessed the niacin trials as having low risk of bias. The methodology of older fibrate trials had limited trial quality but later trials provided adequate study design. No statistically significant effects were seen for niacin or fibrates on all-cause mortality (odds ratio (OR) 1.03, 95% CI 0.92 to 1.15, p=0.59 for niacin and OR 0.98, 95% CI 0.89 to 1.08, p=0.66 for fibrates), on CHD mortality (OR 0.93, 95% CI 0.76 to 1.12, p=0.44 for niacin and OR 0.92, 95% CI 0.81 to 1.04, p=0.19 for fibrates); [3] Niacin monotherapy was associated with a statistically significant reduction in non-fatal MI (OR 0.69, 95% CI 0.56 to 0.85, p=0.0004) but addition of niacin to a statin did not reduce non-fatal MI (OR 0.96, 95% CI 0.85 to 1.09, p=0.52).[3] A similar trend was found with fibrates: fibrate monotherapy reduced non-fatal MI (OR 0.78, 95% CI 0.71 to 0.86, p<0.001) but no difference was found with addition of fibrate therapy in patients on a statin (OR 0.83, 95% CI 0.69 to 1.01, p=0.07).[3] The authors concluded neither niacin nor fibrate in combination with a statin reduce all-cause mortality, coronary CHD mortality, MI, or stroke.[3]

In 2016, the Agency for Healthcare Research and Quality (AHRQ) published an updated systematic review that evaluated the evidence from 2002 through June 2015 for omega 3 fatty acids and their impact on CV outcomes and risk factors for CV outcomes.[4] Outcomes evaluated in the search included all-cause death, CV events, cerebrovascular events, and peripheral vascular events, major CVD risk factors (blood pressure and key plasma lipids), and adverse events. One hundred forty-seven articles met the inclusion criteria; 61 RCTs (in 82 articles) and 37 longitudinal observational studies (in 65 articles). The studies were evaluated as having a low risk of bias. The most common risks of bias were lack of intention-to-treat, unclear blinding, and attrition bias.[4] The observational studies were primarily conducted in generally healthy populations while the RCTs were conducted in populations at increased risk for CVD, largely related to dyslipidemia. Overall, there was insufficient evidence regarding the effect of omega 3 fatty acids on clinical CV outcomes or CVD risk factors. No significant association was noted between omega 3 fatty acid intake and all-cause death (RR 0.97; 95% CI 0.92 to 1.03) or MACE (RR 0.96; 95% CI 0.91 to 1.02).[4] In addition, there was insufficient evidence for preventing cardiac death, heart failure death, ischemic stroke death, hemorrhagic stroke death, revascularization, acute coronary syndrome, angina pectoris, ventricular arrhythmia, and hypertension with the use of omega 3 fatty acids.[4] There was high quality evidence for the effect of omega 3 fatty acids on lowering triglycerides (TG) [net change in TG = -24 mg/dL; 95% CI -31 to -18 mg/dL].[4] The authors concluded that evidence regarding the impact of omega 3 fatty acids on reducing CV outcomes is insufficient.[4]

The focus of a 2015 systematic review was to evaluate the safety of co-administration of ezetimibe with statins.[9] A total of 20 RCTs published between 2002 through 2014 met inclusion criteria (n=14,856). The included trials lasted from 6 to 12 weeks. The authors noted a low risk of bias in most of the studies.[9] However, some studies had a high risk of bias due to incomplete outcome data or selective reporting. Total adverse events were reported in 16 studies, with 1165 events occurring in 3856 patients (30%) treated with ezetimibe and statins, compared with 1198 events in 4171 patients (29%) treated with statins alone.[9] There was no significant difference in total adverse events between the 2 groups (95% CI 0.85 to 1.06; p=0.34).[9] Co-administration of ezetimibe and statins did not result in significant increases in serious adverse events (2% vs. 1.6% with statin alone; 95% CI 0.75 to 1.45 , p=0.81) or allergic reactions (0.9% vs. 1.3% with statin alone; 95% CI 0.41 to 1.35, p=0.33).[9] This analysis provides moderate evidence that the incidence of adverse events is similar between ezetimibe and statin combination therapy and statin monotherapy.

Safety and Efficacy of PCSK9 Inhibitors

A 2015 systematic review evaluated the safety and efficacy of PCSK9 inhibitors in 25 RCTs (n=12,200).[6] The trials were published or unpublished and presented at major conferences between 2012 and 2014. Most trials had low to unclear risk of bias due to inadequate descriptions of study parameters, unclear role of sponsorship, or inadequate description of data management.[6] Primary efficacy endpoints were reductions in LDL-C. Safety outcomes were evaluated by assessment of rates of adverse events. Twelve trials compared evolocumab to placebo or ezetimibe and 13 trials compared alirocumab to placebo or ezetimibe. The rates of common adverse events were not statistically significantly different between PCSK9 inhibitors and placebo (or ezetimibe), except that alirocumab was associated with an increased rate of injection-site reactions (RR 1.48; 95% CI 1.05 to 2.09, p=0.02).[6] By week 12, monthly evolocumab treatment significantly reduced LDL-C compared to placebo (mean reduction: -54.6 %; 95% CI -58.7 to -50.5%) and when compared to ezetimibe (mean reduction: -36.3%; 95% CI -38.8 to -33.9%). All evolocumab doses except for the monthly 280 mg dose increased HDL when compared to placebo by 7.6 % (95% CI 5.7 to 9.5%) and by 6.9% versus ezetimibe (95% CI 5.4 to 8.4%).[6] Biweekly alirocumab therapy lowered LDL by a mean reduction of -52.6% (95% CI -58.2 to -47.0%) versus placebo, by a mean reduction of -29.9% (95% CI -32.9 to -26.9%) versus ezetimibe, and increased HDL by 8.0% (95% CI 4.2-11.7%) versus placebo.[6] In the short term evolocumab and alirocumab appear to be safe and effective, however long term safety data and clinically relevant outcomes are still being evaluated.

Another 2015 systematic review assessed the efficacy and safety of PCSK9 inhibitors in adults with hypercholesterolemia.[7] Phase 2 and 3 RCTs that compared PCSK9 inhibitors to placebo or ezetimibe were included. The authors rated the quality of evidence as moderate to high with minimal bias. Most of the patients in the trials were also maintained on statin therapy. Trials lasted from 8 to 48 weeks. Twenty-four trials (n=10,159 patients) met inclusion criteria for the analysis. Primary clinical endpoints were all-cause mortality and CV mortality. Secondary clinical endpoints included MI, unstable angina, and SAEs. Primary efficacy endpoints were percent change from baseline in LDL-C and HDL-C levels. Overall, the meta-analysis revealed a statistically significant 0.22% reduction in all-cause mortality with use of PCSK9 inhibitors compared to placebo or ezetimibe (0.31% vs. 0.53%, respectively; OR 0.45; 95% CI 0.23 to 0.86, p=0.015).[7] Reduction in CV mortality with use of PCSK9 inhibitors was not statistically significantly different from placebo or ezetimibe (0.19% vs. 0.33%, respectively; OR 0.50, 95% CI 0.23 to 1.10, p=0.084).[7] Compared with placebo or ezetimibe, treatment with PCSK9 inhibitors markedly reduced LCL-C (mean difference (MD) -47.49%; 95% CI -69.64% to -25.35%, p<0.001).[7] Serious adverse events did not significantly increase with administration of PCSK9 inhibitors. There was no significant difference in the overall incidence of adverse effects among patients treated with PCSK9 inhibitors (9.26%) and patients who received placebo or ezetimibe (7.73%) [OR 1.01; 95% CI 0.87 to 1.18, p=0.879].[7] This meta-analysis provides moderate evidence that PCSK9 inhibitors are safe and effective in lowering LDL. The effect on cardiovascular events and mortality are currently being investigated in long term trials.

A 2015 systematic review of RCTs in patients with primary hypercholesterolemia compared the impact of PCSK9 inhibitors with placebo and ezetimibe on lipoproteins, all-cause mortality, and CV events.[8] Seventeen trials randomized 13,083 patients to PCKS9 inhibitors (n=8250), placebo (n=3957), ezetimibe (n=846) or a combination of ezetimibe with PCSK9 inhibitors (n=30). In almost all of the studies the patients were on statins as baseline therapy. The duration for most of the trials was 12 weeks, although 4 trials lasted 24 weeks and one trial was conducted over 52 weeks. [8] The 17 trials were assessed as having low risk of bias using the Cochrane Collaboration tool and were deemed high quality using the GRADE system.[8] The PCSK9 inhibitors reduced LDL by a mean difference of -59.56 (95% CI -60.54 to -58.58).[8] Odd ratios were generated with random-effects models to compare outcomes.[8] In comparison to placebo, PCSK9 inhibitors reduced the incidence of all-cause mortality (OR 0.43, 95% CI 0.22 to 0.82, p=0.01).[8] However, the impact of PCSK9 inhibitors on CV mortality and major cardiac events was not different from placebo (OR 0.50 95% CI 0.22 to 1.13, p=0.10 and OR 0.67, 95% CI 0.43 to 1.04, p = 0.07 respectively).[8] The authors did not specify which major cardiac events were included in the meta-analysis. When PCSK9 inhibitors were compared to ezetimibe, there were no significant differences in all-cause mortality or CV events. An increased incidence of neurocognitive adverse events with PCSK9 inhibitors was found compared with placebo (OR 2.34, 95% CI 1.11

to 4.93, p=0.02).[8] This meta-analysis reveals there is a risk of adverse neurocognitive effects in conjunction with PCSK9 therapy. In addition, more RCTs adequately powered to assess long term clinical outcomes are needed to determine the role of PCSK9 inhibitors in managing hyperlipidemia.

New Guidelines:

National Lipid Association (NLA)

In 2014, the NLA published recommendations in an attempt to synthesize evidence from both the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III and the 2013 ACC/AHA guidelines.[13,35] The committee adapted a hybrid of NHLBI evidence rating which was used in the AHA/ACC 2013 guidelines in addition to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system of evidence rating in guideline development.[36] Due to the volume of information the panel had compiled for dissemination, the report was published in two parts. The expert panel was guided by the primary principle that reducing elevated levels of non-HDL cholesterol reduces the risk for CVD.[13] The NLA authors agreed with the ACC/AHA approach of statin based-intensity therapy, but noted it was imperative to target specific numeric lipoprotein goals to assess risk reduction. The NLA recommendations advocate for an LDL-C goal less than 100 mg/dL for everyone except the highest risk patients.[13] In patients with CVD or diabetes mellitus (DM), the goal LDL-C is less than 70 mg/dL.[13] In contrast to the 2013 ACC/AHA guidelines, the NLA supports additional or alternative lipid-lowering therapies for at-risk patients not at non-HDL-C or LDL-C goals or who cannot tolerate statins.[35]

The NLA recommends that the following statin combination therapies be considered in the indicated order:

1. Ezetimibe 10 mg daily is recommended as a first-line statin combination therapy since it has been shown to reduce CVD events when added to a statin in a controlled clinical trial.[35]
2. Colesevelam 625 mg 3 tablets twice a day (or 3.75 g powder form every day or in divided doses) is recommended as a second-line statin combination therapy because the drug class has been shown to reduce CVD events when used alone and it is better tolerated than the other resins.[35]
3. Extended release niacin titrated to a maximum of 2000 mg daily is recommended as a third-line statin combination therapy because it has demonstrated lower CVD events when used alone, and may have benefit when given with a statin to patients with LDL-C or non-HDL-C levels not at goal. However, it provides only modest LDL-C lowering efficacy, and use of niacin in combination with a statin is not recommended for patients whose LDL-C is less than 70 mg/dL based on evidence for no benefit and possible harm in this group.[35]
4. Patients with dyslipidemia (elevated TG and VLDL-C plus low HDL-C) may need targeted therapy with fibrates and/or omega-3 fatty acids to achieve lipid goals.[35]

The NLA acknowledged that PCSK9 inhibitors have a role in managing patients with CVD risk despite statin and lifestyle therapy. Until CV outcomes trials are completed the PCSK9 inhibitors should be considered for the following situations:

1. Patients with CVD who have LDL-C ≥100 mg/dL (non-HDL-C ≥130 mg/dL) while on maximally-tolerated statin (±ezetimibe) therapy[35]
2. HeFH patients without CVD who have LDL-C ≥130 mg/dL (non-HDL-C ≥160 mg/dL) while on maximally-tolerated statin (±ezetimibe) therapy[35]

There is low quality evidence to employ PCSK9 inhibitors for secondary prevention in patients that have not met treatment goals (i.e. LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL) or in selected high-risk patients who meet the definition of statin intolerance and require substantial cholesterol reduction. Such uses should be based on clinical judgment after the potential but unknown benefits are weighed against the risks and extreme high cost of therapy.[35]

National Institute for Health and Care Excellence (NICE)

The United Kingdom's NICE guidance for utilizing lipid-lowering therapy for CVD risk reduction was updated as of July 2016.[14] Similar to ACC/AHA, the statins are considered first-line drug therapy to prevent CVD in addition to lifestyle modification. Fibrates, niacin, BAS and omega 3 fatty acids are not recommended in combination with statins for primary or secondary prevention of CV disease including patients with CKD or diabetes.[14] The NICE committee evaluated the relevance of the IMPROVE-IT trial (ezetimibe/simvastatin vs. simvastatin) and concluded that the population studied in IMPROVE-IT was not representative of the population receiving ezetimibe in the current British National Health Service.[37] In IMPROVE-IT, patients had acute coronary syndrome and were being treated for secondary prevention and not primary prevention of CV disease.[38]

The specific NICE guidance for ezetimibe therapy is as follows:

1. Ezetimibe monotherapy is recommended as an option for treating primary hypercholesterolemia in adults in whom initial statin therapy is contraindicated or in patients who cannot tolerate statin therapy.[38]
2. Addition of ezetimibe to current statin therapy is recommended as an option for treating primary hypercholesterolemia in adults who have:
    a. total cholesterol or LDL-C is not controlled after appropriate dose titration of initial statin or because dose titration is limited by intolerance to the initial statin therapy; and
    b. a change from initial statin therapy to an alternative statin is being considered.[38]

NICE guidance regarding PCSK9 inhibitors was published in June 2016. Alirocumab and evolocumab are recommended as options for treatment of primary hypercholesterolemia or mixed dyslipidemia only if LDL-C concentrations are persistently above the thresholds specified for high or very high risk of CVD despite maximal tolerated lipid-lowering therapy.[15] In other words, either the maximum statin dose has been reached or further titration is limited by intolerance. NICE created a separate guidance document for each PCSK9 medication. The recommendations for evolocumab have specific dosing parameters in addition to guidance for which patients warrant therapy. Without evidence for the monthly dosage, the committee was unable to recommend evolocumab 420 mg monthly for primary hypercholesterolemia (heterozygous-familial and non-familial) or mixed dyslipidemia.[37] Evolocumab and alirocumab are recommended as options in combination with a statin or as monotherapy for treatment of primary hypercholesterolemia or mixed dyslipidemia as outlined Table 1.

Table 1: Low density lipoprotein cholesterol concentrations above which alirocumab and evolocumab are recommended per NICE guidance[15,37]

Diagnosis	**Without CVD**	**With CVD**	
		High Risk of CVD*	**Very High Risk of CVD****
Primary non-familial hypercholesterolemia or mixed dyslipidemia	Not recommended at any LDL-C concentration	Recommended only if LDL-C‑C concentration is persistently above 155 mg/dL	Recommended only if LDL-C‑C concentration is persistently above 135 mg/dL
Primary heterozygous- familial hypercholesterolemia	Recommended only if LDL-C concentration is persistently above 190 mg/dL	Recommended only if LDL-C‑C concentration is persistently above 135 mg/dL	

*High risk of CVD is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalization), coronary or other arterial revascularization procedures, chronic heart disease, ischemic stroke, or peripheral arterial disease.
**Very high risk of CVD is defined as recurrent CV events or CV events in more than 1 vascular bed.

International Atherosclerosis Society (IAS)

IAS updated their recommendations for the management of dyslipidemia in 2014. The international panel reached consensus after reviewing epidemiologic studies, genetic studies and clinical trials. The recommendations were further determined by a review of pathologic studies, pharmacology, metabolic studies, clinical trials, meta-analyses of clinical trials, and animal studies.[12] The committee identified non HDL-C as the major atherogenic lipoprotein and defined atherogenic cholesterol as either LDL-C or non-HDL-C cholesterol and recommended optimal target levels for each lipoprotein level.[12] For primary prevention in high risk adults, an optimal LDL-C is less than 100 mg/dL and the optimal non-HDL-C level is less than 130 mg/dL.[12] Consistent with other guidelines, statins are recommended as first-line drug therapy for primary and secondary prevention after lifestyle interventions have been implemented. For high risk patients intolerant to statins, alternative agents such as ezetimibe, BAS and niacin are recommended for lowering LDL-C in primary prevention. For secondary prevention, IAS recommends adding ezetimibe or BAS to statin therapy. For patients with high triglycerides, niacin or fibric acid derivatives are reasonable alternatives.[12]

Canadian Agency for Drugs and Technologies in Health (CADTH)

CADTH recommends alirocumab or evolocumab be used as an adjunct to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH) who require additional lowering of LDL-C if the following clinical criteria and conditions are met:[16,17]

1. Patient has a confirmed diagnosis of HeFH; and
2. Patient is unable to reach the target LDL-C level specified in current guidelines (i.e. LDL-C <135 mg/dL); and
3. Patient is currently receiving maximally tolerated statin therapy with or without ezetimibe

Alirocumab is also recommended as an adjunct to diet and maximally tolerated statin therapy in adult patients at high risk for CV events who require additional lowering of LDL-C if the following clinical criteria and conditions are met:[16]

1. Patient is at high risk for CV events
2. Patient is unable to reach the target LDL-C level (< 155 mg/dl); and
3. Patient is currently receiving maximally tolerated statin therapy with or without ezetimibe

CADTH guidance does not recommend evolocumab as adjunctive therapy for clinical atherosclerotic CV disease due to insufficient evidence to evaluate the risks of therapy compared to benefits for this indication.[17]

Safety Updates:

Gemfibrozil (March 2016): The combination therapy of gemfibrozil with dasabuvir is contraindicated.[39] Gemfibrozil is a CYP2C8 inhibitor, which may increase exposure of CYP2C8 substrates when administered concomitantly. Co-administration of gemfibrozil with dasabuvir increased dasabuvir AUC and maximum drug concentrations (ratios: 11.3 and 2.01, respectively) due to CYP2C8 inhibition. Increased dasabuvir exposure may increase the risk of QT prolongation.[40]

New Formulations or Indications:

The FDA approved a device that can deliver a single monthly injection of evolocumab, the PCSK9 inhibitor manufactured by Amgen in July 2016.[41] Evolocumab is currently administered by subcutaneous injection in a 140-mg dose every 2 weeks or as a 420 mg monthly dose. The monthly dose had been given as 3 separate 140 mg/mL injections administered consecutively within 30 minutes. The Pushtronex™ system is an on-body infusor with a prefilled cartridge of evolocumab that delivers 420 mg in 3.5 mL over 9 minutes subcutaneously. The device adheres to the body and is hands-free. While receiving the injection, patients are able to perform moderate physical activities such as walking, bending or reaching.[42]

Randomized Controlled Trials:

A total of 158 citations were manually reviewed from the literature search. After manual review, 154 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). The remaining 3 trials are briefly described in the table below. Full abstracts are included in **Appendix 2**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Cannon, et al.[5] DB, RCT, MC N=18,144 39 countries Median follow-up: 6 years	Simvastatin 40 mg + Ezetimibe 10 mg vs Simvastatin 40 mg + Placebo	Adults age ≥50 years hospitalized for ACS with LDL-C 50-125 mg/dL if not on lipid-lowering therapy or LDL-C 50-100 mg/dL if already on lipid-lowering therapy Exclusion: CABG, CrCl <30 mL/min, active liver disease, >40 mg simvastatin dose or equivalent	Composite endpoint: CV death, non- fatal MI, unstable angina requiring re-hospitalization, coronary revascularization (≥ 30 days after randomization), or nonfatal stroke	Simvastatin + ezetimibe: 32.7% Simvastatin + placebo: 34.7% ARR 2.0% (HR 0.936; 95% CI 0.89-0.99; p=0.016) Secondary Endpoint: Median time weighted average LDL-C: Simvastatin + ezetimibe: 53.7 mg/dL Simvastatin + placebo: 69.5 mg/dL p<0.001
Maki, et al.[43] DB, PG, RCT, PC, MC n=647 96 sites in US Duration: 6 weeks (after 6 week run-in)	Statin + OM3-FFA 2 gm vs Statin + OM3-FFA 4 gm vs Statin + OO (placebo)	Adults age ≥18 years at high risk for CV disease with fasting TG 200-500 mg/dL treated with maximally tolerated statin or statin with ezetimibe Exclusion: non-HDL-C < 90 mg/dL, h/o pancreatitis, T1DM, HbA1C >10%, BP ≥160/100 mmHg, hypothyroidism, elevated LFTs	Primary endpoint: Percent change from baseline in non-HDL-C	**Percent change in non-HDL-C from baseline*** Statin + OM3-FFA 2 gm: -3.9% (p<0.05 vs. OO) Statin + OM3-FFA 3 gm: -6.9% (p<0.001 vs. OO) Statin + OO: -0.9% Secondary Endpoints: Percent change in TG from baseline* Statin + OM3-FFA 2 gm: -14.6% (p<0.001 vs. OO) Statin + OM3-FFA 3 gm: -20.6% (p<0.001 vs. OO) Statin + OO: -5.9% Percent change in HDL-C from baseline* Statin + OM3-FFA 2 gm: +2.6% (p=? vs. OO) Statin + OM3-FFA 3 gm: +3.3% (p=? vs. OO) Statin + Olive Oil: +2.2% *95% CIs not reported

DRAFT

Kastelein, et al.[44] DB, RCT, MC, PG n=399 74 sites in US, Europe, and India Duration: 12 weeks (after 6 week run-in)	OM3-FFA 2 gm vs OM3-FFA 3 gm vs OM3-FFA 4 gm vs OO 4 gm	Adults age ≥18 years with TG 500-2000 mg/dL treated on stable dose of statin and/or CAI or untreated Exclusion: pancreatitis, HbA1C ≥9%, recent CV event, hypothyroidism, BP ≥ 160/100 mmHg, elevated LFTs, CrCl <30 mL/min, platelets <60 x$10^{9/}$L or Hgb <10 g/dL	Primary endpoint: Percent change in TG from baseline	**Percent change in TG from baseline:** OM3-FFA 2 gm: -25.9% (95% CI -32.8 to -18.3%; p <0.01 vs. OO) OM3-FFA 3 gm: -25.5% (95% CI -32.4 to -17.8%; p <0.01 vs. OO) OM3-FFA 4 gm: -30.9% (95% CI -37.3 to -23.7%; p<0.001 vs. OO) OO: -4.3% (95% CI -13.1-5.4%) Secondary Endpoints: Percent change in non-HDL-C from baseline: OM3-FFA 2 gm: -7.6% (95% CI -12.0 to -3.0%; p<0.05 vs. OO) OM3-FFA 3 gm: -6.9% (95% CI -11.4 to -2.2%; p<0.05 vs. OO) OM3-FFA 4 gm: -9.6% (95% CI -14.o to -5.1%; p<0.01 vs. OO) OO: 2.5% (95% CI -2.3 to 7.6%) Percent change in HDL-C from baseline: OM3-FFA 2 gm: 7.4% (95% CI 3.2 to 11.7%; p=? vs. OO) OM3-FFA 3 gm: 3.8% (95% CI -0.3 to 8.0%; p=? vs. OO) OM3-FFA 4 gm: 5.8% (95% CI 1.7 to 10.1%; p=? vs. OO) OO: 1.9% (95% CI -2.0 to 6.0%)
Nissen, et al.[45] DB, PC, CO, RCT n=511s 48 weeks (initial 4 week washout, 24 weeks of therapy then 2 week washout before second 24	Phase A: atorvastatin 20 mg vs. placebo Phase B: randomized 2:1 to evolocumab 420 mg SC once a month vs. ezetimibe 10 mg PO daily	Adults age 18-80 years with uncontrolled LDL-C* and h/o intolerance to ≥2 statins *Defined as: pts with CHD and LDL ≥100 mg/dL; pts w/o CHD and LDL ≥ 130 mg/dL plus ≥2 risk factors; LDL-C >160 mg/dL with 1 risk factor; or LDL >190 mg/dL with no risk factors	Co-Primary Endpoints 1. Mean % change in LDL-C from baseline to the mean at weeks 22 and 24 2. Mean % change in LDL-C from baseline to week 24	**Mean % change in LDL-C from baseline to the mean for week 22 and 24** Ezetimibe: -16.7%; 95% CI -20.5 to -12.9%, p<0.001 (week 22) vs. -16.7 (95% CI -20.8 to -12.5 p < 0.001 (week 24) Evolocumab: -54.5% ;95% CI -57.2 to -51.8%, p<0.001 (week 22) vs -52.8 ;95% CI -55.8 to -49.8 p < 0.001 (week24) **Mean % change in LDL-C from baseline LDL-C to week 24** Ezetimibe: -16.7% (95% CI -20.8 to -12.5%, p<0.001) Evolocumab: -54.5% (95% CI -55.8 to -49.8%, p<0.001)

week phase)		Exclusion: h/o MI, unstable angina, coronary revascularization, or stroke 3 months before study enrollment		

Abbreviations: ACS = acute coronary syndrome; ARR = absolute risk reduction; BP = blood pressure; CABG = coronary artery bypass graft; CHD = coronary heart disease; CrCl = creatinine clearance; DB = double blind; CAI =cholesterol absorption inhibitor; CI = confidence interval; CO = crossover; CV = cardiovascular; dL = deciliter; HbA1c = glycosylated hemoglobin; HDL-C = high density lipoprotein cholesterol; h/o = history of; HR = hazard ratio; LDL-C = low density lipoprotein cholesterol; LFT = liver function tests; MC = multi-centered; mg = milligram; MI = myocardial infarction; OM3-FFA = omega-3 fatty acid; PC = placebo controlled; PG = parallel group; RCT = randomized controlled trial; T1DM = type 1 diabetes mellitus; TLC = therapeutic lifestyle changes; TG = triglycerides; OO = olive oil; PO = oral; SC = subcutaneous

References:

1. Battaggia A, Donzelli A, Font M, Molteni D, Galvano A. Clinical efficacy and safety of Ezetimibe on major cardiovascular endpoints: systematic review and meta-analysis of randomized controlled trials. [Review]. *PLoS ONE [Electronic Resource]*. 2015;10(4). doi:10.1371/journal.pone.0124587.

2. Ip C, Jin D, Gao J, et al. Effects of add-on lipid-modifying therapy on top of background statin treatment on major cardiovascular events: A meta-analysis of randomized controlled trials. *Int J Cardiol*. 2015;191:138-148. doi:10.1016/j.ijcard.2015.04.228.

3. Keene D, Price C, Shun-Shin MJ, Francis DP. Effect on cardiovascular risk of high density lipoprotein targeted drug treatments niacin, fibrates, and CETP inhibitors: meta-analysis of randomised controlled trials including 117,411 patients. *BMJ*. 2014;349:g4379.

4. Omega-3 Fatty Acids and Cardiovascular Disease: An Updated Systematic Review. Agency for Healthcare Research and Quality. 8/2016. https://www.effectivehealthcare.ahrq.gov/ehc/products/609/2262/fatty-acids-cardiovascular-disease-report-160812.pdf. Accessed September 8, 2016.

5. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *New England Journal of Medicine*. 2015;372(25):2387-2397. doi:10.1056/NEJMoa1410489.

6. Zhang X-L, Zhu Q-Q, Zhu L, et al. Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials. *BMC Medicine*. 2015. doi:10.1186/s12916-015-0358-8.

7. Navarese EP, Kolodziejczak M, Schulze V, et al. Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia: A Systematic Review and Meta-analysis. *Ann Intern Med*. 2015;163(1):40-51. doi:10.7326/M14-2957.

8. Lipinski MJ, Benedetto U, Escarcega RO, et al. The impact of proprotein convertase subtilisin-kexin type 9 serine protease inhibitors on lipid levels and outcomes in patients with primary hypercholesterolaemia: a network meta-analysis. *Eur Heart J*. 2016;37(6):536-545. doi:10.1093/eurheartj/ehv563.

9. Luo L, Yuan X, Huang W, et al. Safety of coadministration of ezetimibe and statins in patients with hypercholesterolaemia: a meta-analysis. *Internal Medicine Journal*. 2015;45(5):546-557. doi:10.1111/imj.12706.

10. PCSK9 Inhibitor Monoclonal Antibodies for the Treatment of Hypercholesterolemia | CADTH.ca. https://www.cadth.ca/dv/pcsk9-inhibitor-monoclonal-antibodies-treatment-hypercholesterolemia. Accessed July 18, 2016.

11. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. *Circulation*. January 2013:01.cir.0000437738.63853.7a. doi:10.1161/01.cir.0000437738.63853.7a.

12. Expert Dyslipidemia Panel of the International Atherosclerosis Society Panel members. An International Atherosclerosis Society Position Paper: global recommendations for the management of dyslipidemia--full report. *J Clin Lipidol*. 2014;8(1):29-60. doi:10.1016/j.jacl.2013.12.005.

13. Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1--full report. *J Clin Lipidol*. 2015;9(2):129-169. doi:10.1016/j.jacl.2015.02.003.

14. Cardiovascular disease: risk assessment and reduction, including lipid modification. Guidance and guidelines .National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/cg181. Accessed August 2, 2016.

15. Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. Guidance and guidelines . National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/ta393. Accessed July 18, 2016.

16. Canadian Agency for Drugs and Technologies Final Recommendation for Praluent - SR0469_complete_Praluent_Jul-20-16.pdf. https://www.cadth.ca/sites/default/files/cdr/complete/SR0469_complete_Praluent_Jul-20-16.pdf. Accessed August 4, 2016.

17. Canadian Agency for Drugs and Technologies in Health. Common Drug Review: Evolocumab (Repatha). https://www.cadth.ca/sites/default/files/cdr/complete/SR0441_complete_Rapatha-Feb-23_16_e.pdf. Accessed August 4, 2016.

18. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *Journal of the American College of Cardiology*. 2016;68(1):92-125. doi:10.1016/j.jacc.2016.03.519.

DRAFT

19. HPS2-THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. *Eur Heart J*. 2013;34(17):1279-1291. doi:10.1093/eurheartj/eht055.

20. Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *New England Journal of Medicine*. 2011;365(24):2255-2267. doi:10.1056/NEJMoa1107579.

21. Niacin extended release (Niaspan) Prescribing Information. North Chicago, IL: Abbvie, Inc.; April 2015.

22. AbbVie, FDA Withdraw Two Cholesterol Drugs from US Market as Benefits No Longer Outweigh Risks | RAPS. http://www.raps.org/Regulatory-Focus/News/2016/04/15/24777/AbbVieFDA-Withdraw-Two-Cholesterol-Drugs-from-US-Market-as-Benefits-No-Longer-Outweigh-Risks/.aspx. Accessed August 23, 2016.

23. ACCORD Study Group, Ginsberg HN, Elam MB, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med*. 2010;362(17):1563-1574. doi:10.1056/NEJMoa1001282.

24. Fenofibrate (Fenoglide) Prescribing Information. San Diego, CA: Santarus, Inc.: October 2012.

25. Kastelein JJP, Akdim F, Stroes ESG, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med*. 2008;358(14):1431-1443. doi:10.1056/NEJMoa0800742.

26. Farmer JA. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis (the SEAS trial). *Curr Atheroscler Rep*. 2009;11(2):82-83.

27. Rossebø AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med*. 2008;359(13):1343-1356. doi:10.1056/NEJMoa0804602.

28. Research C for DE and. Drug Safety Information for Heathcare Professionals - Follow-Up to the August 2008 Early Communication About an Ongoing Safety Review of Ezetimibe/Simvastatin (marketed as Vytorin), Simvastatin (marketed as Zocor) and Ezetimibe (marketed as Zetia) - FDA Investigates a Report from the SEAS Trial. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm194964.htm. Accessed August 19, 2016.

29. FDA Briefing Document: Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) - UCM476505.pdf. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM476505.pdf. Accessed July 27, 2016.

30. Icosapent ethyl (Vascepa) Prescribing Information. Dublin, Ireland: Amarin, Pharma, Inc. June 2016.

DRAFT

31. Omega-3-acid ethyl esters (Lovaza) Prescribing Information. Research Triangle Park, NC: GlaxoSmithKline. September 2015.

32. A Study of AMR101 to Evaluate Its Ability to Reduce Cardiovascular Events in High Risk Patients With Hypertriglyceridemia and on Statin. The Primary Objective is to Evaluate the Effect of 4 g/Day AMR101 for Preventing the Occurrence of a First Major Cardiovascular Event. - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01492361?term=icosapent&rank=15. Accessed July 26, 2016.

33. Rosei EA, Salvetti M. Management of Hypercholesterolemia, Appropriateness of Therapeutic Approaches and New Drugs in Patients with High Cardiovascular Risk. *High Blood Press Cardiovasc Prev*. 2016;23(3):217-230. doi:10.1007/s40292-016-0155-2.

34. Hassan M. OSLER and ODYSSEY LONG TERM: PCSK9 inhibitors on the right track of reducing cardiovascular events. *Glob Cardiol Sci Pract*. 2015;2015(2):20. doi:10.5339/gcsp.2015.20.

35. Jacobson TA, Maki KC, Orringer CE, et al. National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2. *J Clin Lipidol*. 2015;9(6 Suppl):S1-122.e1. doi:10.1016/j.jacl.2015.09.002.

36. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.AD.

37. Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. Guidance and guidelines. National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/ta394. Accessed July 18, 2016.

38. Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia .Guidance and guidelines . National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/ta385?unlid=979832004201631511465 1,97563078920166304611. Accessed July 18, 2016.

39. U.S. Food and Drug Administration. Safety Information - Lopid (gemfibrozil) tablets. http://www.fda.gov/safety/medwatch/safetyinformation/ucm175927.htm. Accessed September 8, 2016.

40. Lopid (gemfibrozil) Prescribing Information. New York, NY, Pfizer, Inc., March 2016.

41. CardioBrief: PCSK9 Drug Approved for Single Monthly Injection. http://www.medpagetoday.com/Cardiology/CardioBrief/59008. Published July 11, 2016. Accessed July 13, 2016.

42. Repatha (evolocumab) Prescribing Information. Thousand Oaks, CA; Amgen, Inc. , July 2016.

43. Maki KC, Orloff DG, Nicholls SJ, et al. A highly bioavailable omega-3 free fatty acid formulation improves the cardiovascular risk profile in high-risk, statin-treated patients with residual hypertriglyceridemia (the ESPRIT trial). *Clin Ther*. 2013;35(9):1400-1411-3. doi:10.1016/j.clinthera.2013.07.420.

44. Kastelein JJP, Maki KC, Susekov A, et al. Omega-3 free fatty acids for the treatment of severe hypertriglyceridemia: the EpanoVa fOr Lowering Very high triglyceridEs (EVOLVE) trial. *J Clin Lipidol*. 2014;8(1):94-106. doi:10.1016/j.jacl.2013.10.003.

45. Nissen SE, Stroes E, Dent-Acosta RE, et al. Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance: The GAUSS-3 Randomized Clinical Trial. *JAMA*. 2016;315(15):1580-1590. doi:10.1001/jama.2016.3608.

46. Micromedex Solutions (Internet Database). Truven Health Analytics. 2016.

47. Lexicomp Online. (Internet Database). Hudson, OH: Wolters Kluwer, Inc. Updated June 2016.

DRAFT

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	POWD PACK	CHOLESTYRAMINE	CHOLESTYRAMINE (WITH SUGAR)	Y
ORAL	POWD PACK	CHOLESTYRAMINE LIGHT	CHOLESTYRAMINE/ASPARTAME	Y
ORAL	POWD PACK	PREVALITE	CHOLESTYRAMINE/ASPARTAME	Y
ORAL	POWD PACK	QUESTRAN	CHOLESTYRAMINE (WITH SUGAR)	Y
ORAL	POWDER	CHOLESTYRAMINE	CHOLESTYRAMINE (WITH SUGAR)	Y
ORAL	POWDER	CHOLESTYRAMINE LIGHT	CHOLESTYRAMINE/ASPARTAME	Y
ORAL	POWDER	PREVALITE	CHOLESTYRAMINE/ASPARTAME	Y
ORAL	POWDER	QUESTRAN	CHOLESTYRAMINE (WITH SUGAR)	Y
ORAL	POWDER	QUESTRAN LIGHT	CHOLESTYRAMINE/ASPARTAME	Y
ORAL	TABLET	FENOFIBRATE	FENOFIBRATE	Y
ORAL	TABLET	GEMFIBROZIL	GEMFIBROZIL	Y
ORAL	TABLET	LOFIBRA	FENOFIBRATE	Y
ORAL	TABLET	LOPID	GEMFIBROZIL	Y
ORAL	CAPSULE	JUXTAPID	LOMITAPIDE MESYLATE	N
ORAL	GRANULES	COLESTID	COLESTIPOL HCL	N
ORAL	GRANULES	COLESTIPOL HCL	COLESTIPOL HCL	N
ORAL	PACKET	COLESTID	COLESTIPOL HCL	N
ORAL	PACKET	COLESTIPOL HCL	COLESTIPOL HCL	N
ORAL	POWD PACK	WELCHOL	COLESEVELAM HCL	N
ORAL	TABLET	COLESTID	COLESTIPOL HCL	N
ORAL	TABLET	COLESTIPOL HCL	COLESTIPOL HCL	N
ORAL	TABLET	WELCHOL	COLESEVELAM HCL	N
SUB-Q	PEN INJCTR	PRALUENT PEN	ALIROCUMAB	N
SUB-Q	PEN INJCTR	REPATHA SURECLICK	EVOLOCUMAB	N
SUB-Q	SYRINGE	KYNAMRO	MIPOMERSEN SODIUM	N
SUB-Q	SYRINGE	PRALUENT SYRINGE	ALIROCUMAB	N
SUB-Q	SYRINGE	REPATHA SYRINGE	EVOLOCUMAB	N
ORAL	CAPSULE	ANTARA	FENOFIBRATE,MICRONIZED	N
ORAL	CAPSULE	FENOFIBRATE	FENOFIBRATE	N
ORAL	CAPSULE	FENOFIBRATE	FENOFIBRATE,MICRONIZED	N
ORAL	CAPSULE	LIPOFEN	FENOFIBRATE	N
ORAL	CAPSULE	LOFIBRA	FENOFIBRATE,MICRONIZED	N
ORAL	CAPSULE	OMEGA-3 ACID ETHYL ESTERS	OMEGA-3 ACID ETHYL ESTERS	N
ORAL	CAPSULE	VASCEPA	ICOSAPENT ETHYL	N

DRAFT

ORAL	CAPSULE DR	FENOFIBRIC ACID	FENOFIBRIC ACID (CHOLINE)	N
ORAL	CAPSULE ER	NIACIN	NIACIN	N
ORAL	TAB ER 24H	NIACIN ER	NIACIN	N
ORAL	TAB ER 24H	NIASPAN	NIACIN	N
ORAL	TABLET	FENOFIBRATE	FENOFIBRATE	N
ORAL	TABLET	FENOFIBRATE	FENOFIBRATE NANOCRYSTALLIZED	N
ORAL	TABLET	FENOFIBRIC ACID	FENOFIBRIC ACID	N
ORAL	TABLET	FENOGLIDE	FENOFIBRATE	N
ORAL	TABLET	FIBRICOR	FENOFIBRIC ACID	N
ORAL	TABLET	NIACOR	NIACIN	N
ORAL	TABLET	ZETIA	EZETIMIBE	N
ORAL	CAPSULE DR	TRILIPIX	FENOFIBRIC ACID (CHOLINE)	
ORAL	TABLET	TRICOR	FENOFIBRATE NANOCRYSTALLIZED	
ORAL	TABLET	TRIGLIDE	FENOFIBRATE NANOCRYSTALLIZED	

DRAFT

Appendix 2: Abstracts of Clinical Trials

Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. New England Journal of Medicine. 2015; 372(25):2387-2397. Doi :10.1056/NEJMoa1410489.

BACKGROUND: Statin therapy reduces low-density lipoprotein (LDL-C) cholesterol levels and the risk of CV events, but whether the addition of ezetimibe, a non-statin drug that reduces intestinal cholesterol absorption, can reduce the rate of CV events further is not known.

METHODS: We conducted a double-blind, randomized trial involving 18,144 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days and had LDL-C cholesterol levels of 50 to 100 mg per deciliter (1.3 to 2.6 mmol per liter) if they were receiving lipid-lowering therapy or 50 to 125 mg per deciliter (1.3 to 3.2 mmol per liter) if they were not receiving lipid-lowering therapy. The combination of simvastatin (40 mg) and ezetimibe (10 mg) (simvastatin-ezetimibe) was compared with simvastatin (40 mg) and placebo (simvastatin monotherapy). The primary end point was a composite of CV death, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization (≥30 days after randomization), or nonfatal stroke. The median follow-up was 6 years.

RESULTS: The median time-weighted average LDL-C cholesterol level during the study was 53.7 mg per deciliter (1.4 mmol per liter) in the simvastatin-ezetimibe group, as compared with 69.5 mg per deciliter (1.8 mmol per liter) in the simvastatin-monotherapy group (P<0.001). The Kaplan-Meier event rate for the primary end point at 7 years was 32.7% in the simvastatin-ezetimibe group, as compared with 34.7% in the simvastatin-monotherapy group (absolute risk difference, 2.0 percentage points; hazard ratio, 0.936; 95% confidence interval, 0.89 to 0.99; P=0.016). Rates of prespecified muscle, gallbladder, and hepatic adverse effects and cancer were similar in the two groups.

CONCLUSIONS: When added to statin therapy, ezetimibe resulted in incremental lowering of LDL-C cholesterol levels and improved CV outcomes. Moreover, lowering LDL-C cholesterol to levels below previous targets provided additional benefit. (Funded by Merck; IMPROVE-IT ClinicalTrials.gov number, NCT00202878.)

Maki KC, Orloff DG, Nicholls SJ, et al. A highly bioavailable omega-3 free fatty acid formulation improves the CV risk profile in high-risk, statin-treated patients with residual hypertriglyceridemia (the ESPRIT trial). Clin Ther. 2013;35(9):1400-1411-3. doi:10.1016/j.clinthera.2013.07.420.

BACKGROUND: A novel omega-3 formulation in free fatty acid form (OM3-FFA) has as much as 4-fold greater bioavailability than ethyl ester forms and reduces triglyceride (TG) levels in patients with severe hypertriglyceridemia.

OBJECTIVE: This study was designed to evaluate the efficacy of adding OM3-FFA (2 or 4 g/d) to statin therapy for lowering non-HDL-C and TG levels in subjects with persistent hypertriglyceridemia and at high risk for CV disease.

METHODS: In this double-blind, parallel-group study, 647 diet-stable patients with fasting TG levels ≥ 200 mg/dL and <500 mg/dL (treated with a maximally tolerated dose of statin or statin with ezetimibe) and at high risk for CV disease were randomized to 6 weeks of treatment with capsules of control (olive oil [OO]) 4 g/d, OM3-FFA 2 g/d (plus 2 g/d OO), or OM3-FFA 4 g/d. Assessments included fasting serum levels of lipids and apolipoproteins (apo); plasma concentrations of eicosapentaenoic acid, docosahexaenoic acid, docosapentaenoic acid, and arachidonic acid; and laboratory safety values and adverse events.

RESULTS: In the 627 subjects in the intention to treat sample, non-HDL-C levels were reduced with OM3-FFA 2 g/d and OM3-FFA 4 g/d (-3.9% and -6.9%, respectively) compared with OO (-0.9%) (both, P < 0.05), as were TG levels (-14.6% and -20.6%, respectively, vs -5.9%; both, P < 0.001). LDL-C levels increased with OM3-FFA 2 g/d (4.6%) compared with OO (1.1%) (P = 0.025) but not with OM3-FFA 4 g/d (1.3%). Total cholesterol and VLDL-C concentrations were reduced compared with OO with both OM3-FFA dosages, and the total cholesterol/HDL-C ratio and apo AI and apo B levels were significantly lowered with OM3-FFA 4 g/d only (all at least P < 0.05). Percent changes from baseline in HDL-C did not differ between OO and either OM3-FFA group. Plasma concentrations of docosahexaenoic acid, eicosapentaenoic acid, and docosapentaenoic acid were significantly increased and arachidonic acid was significantly reduced in both OM3-FFA treatment groups compared with the OO responses (all, P < 0.001). Withdrawals related to treatment-emergent adverse events ranged from 0.9% with OO to 3.2% with OM3-FFA 4 g/d.

CONCLUSIONS: OM3-FFA was well tolerated and lowered non-HDL-C and TG levels at both 2- and 4-g/d dosages in patients with persistent hypertriglyceridemia taking a statin, with the 4-g/d dosage providing incremental improvements compared with 2 g/d.

Kastelein JJP, Maki KC, Susekov A, et al. Omega-3 free fatty acids for the treatment of severe hypertriglyceridemia: the EpanoVa fOr Lowering Very high triglyceridEs (EVOLVE) trial. J Clin Lipidol. 2014;8(1):94-106. doi:10.1016/j.jacl.2013.10.003.

BACKGROUND: Omega-3 fatty acids in free fatty acid form have enhanced bioavailability, and plasma levels are less influenced by food than for ethyl ester forms.

OBJECTIVE: The aim was to evaluate the safety and lipid-altering efficacy in subjects with severe hypertriglyceridemia of an investigational pharmaceutical omega-3 free fatty acid (OM3-FFA) containing eicosapentaenoic acid and docosahexaenoic acid.
METHODS: This was a multinational, double-blind, randomized, out-patient study. Men and women with triglycerides (TGs) ≥ 500 mg/dL, but <2000 mg/dL, took control (olive oil [OO] 4 g/d; n = 99), OM3-FFA 2 g/d (plus OO 2 g/d; n = 100), OM3-FFA 3 g/d (plus OO 1 g/d; n = 101), or OM3-FFA 4 g/d (n = 99) capsules for 12 weeks in combination with the National Cholesterol Education Program Therapeutic Lifestyle Changes diet.

RESULTS: Fasting serum TGs changed from baseline by -25.9% (P < .01 vs OO), -25.5% (P < .01 vs OO), and -30.9% (P < .001 vs OO) with 2, 3, and 4 g/d OM3-FFA, respectively, compared with -4.3% with OO. Non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol-to-HDL-C ratio, very low-density lipoprotein cholesterol, remnant-like particle cholesterol, apolipoprotein CIII, lipoprotein-associated phospholipase A2, and arachidonic acid were significantly lowered (P < .05 at each OM3-FFA dosage vs OO); and plasma eicosapentaenoic acid and docosahexaenoic acid were significantly elevated (P < .001 at each OM3-FFA dosage vs OO). With OM3-FFA 2 and 4 g/d (but not 3 g/d), low-density lipoprotein cholesterol was significantly increased compared with OO (P < .05 vs OO). High-sensitivity C-reactive protein responses with OM3-FFA did not differ significantly from the OO response at any dosage. Fewer subjects reported any adverse event with OO vs OM3-FFA, but frequencies across dosage groups were similar. Discontinuation due to adverse event, primarily gastrointestinal, ranged from 5% to 7% across OM3-FFA dosage groups vs 0% for OO.

CONCLUSIONS: OM3-FFA achieved the primary end point for TG lowering and secondary end point of non-HDL-C lowering at 2, 3, and 4 g/d in persons with severe hypertriglyceridemia.

Nissen SE, Stroes E, Dent-Acosta RE, et al. Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance: The GAUSS-3 Randomized Clinical Trial. JAMA. 2016;315(15):1580-1590. doi:10.1001/jama.2016.3608.

OBJECTIVE: To identify patients with muscle symptoms confirmed by statin rechallenge and compare lipid-lowering efficacy for 2 non-statin therapies, ezetimibe and evolocumab.

Design, Setting, and Participants Two-stage randomized clinical trial including 511 adult patients with uncontrolled low-density lipoprotein cholesterol (LDL-C) levels and history of intolerance to 2 or more statins enrolled in 2013 and 2014 globally. Phase A used a 24-week crossover procedure with atorvastatin or placebo to identify patients having symptoms only with atorvastatin but not placebo. In phase B, after a 2-week washout, patients were randomized to ezetimibe or evolocumab for 24 weeks.

INTERVENTIONS: Phase A: atorvastatin (20 mg) vs placebo. Phase B: randomization 2:1 to subcutaneous evolocumab (420 mg monthly) or oral ezetimibe (10 mg daily).

MAIN OUTCOME AND MEASURES: Co-primary end points were the mean percent change in LDL-C level from baseline to the mean of weeks 22 and 24 levels and from baseline to week 24 levels.

RESULTS: Of the 491 patients who entered phase A (mean age, 60.7 [SD, 10.2] years; 246 women [50.1%]; 170 with coronary heart disease [34.6%]; entry mean LDL-C level, 212.3 [SD, 67.9] mg/dL), muscle symptoms occurred in 209 of 491 (42.6%) while taking atorvastatin but not while taking placebo. Of these, 199 entered phase B, along with 19 who proceeded directly to phase B for elevated creatine kinase (N = 218, with 73 randomized to ezetimibe and 145 to evolocumab; entry mean LDL-C level, 219.9 [SD, 72] mg/dL). For the mean of weeks 22 and 24, LDL-C level with ezetimibe was 183.0 mg/dL; mean percent LDL-C change, −16.7% (95% CI, −20.5% to −12.9%), absolute change, −31.0 mg/dL and with evolocumab was 103.6 mg/dL; mean percent change, −54.5% (95% CI, −57.2% to −51.8%); absolute change, −106.8 mg/dL (P < .001). LDL-C level at week 24 with ezetimibe was 181.5 mg/dL; mean percent change, −16.7% (95% CI, −20.8% to −12.5%); absolute change, −31.2 mg/dL and with evolocumab was 104.1 mg/dL; mean percent change, −52.8% (95% CI, −55.8% to −49.8%); absolute change, −102.9 mg/dL (P < .001). For the mean of weeks 22 and 24, between-group difference in LDL-C was −37.8%; absolute difference, −75.8 mg/dL. For week 24, between-group difference in LDL-C was −36.1%; absolute difference, –71.7 mg/dL. Muscle symptoms were reported in 28.8% of ezetimibe-treated patients and 20.7% of evolocumab-treated patients (log-rank P = .17). Active study drug was stopped for muscle symptoms in 5 of 73 ezetimibe-treated patients (6.8%) and 1 of 145 evolocumab-treated patients (0.7%).

CONCLUSIONS: Among patients with statin intolerance related to muscle-related adverse effects, the use of evolocumab compared with ezetimibe resulted in a significantly greater reduction in LDL-C levels after 24 weeks. Further studies are needed to assess long-term efficacy and safety.

DRAFT

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to June 5 Week 1 2016, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 7, 2016

1 HYPERLIPIDEMIA.mp. or exp Hyperlipidemias/ 40720
2 exp Cholestyramine Resin/ 501
3 exp Fenofibrate/ 1927
4 exp Gemfibrozil/ 838
5 LOMITAPIDE.mp. 77
6 exp Colestipol/ 64
7 ALIROCUMAB.mp. 88
8 EVOLOCUMAB.mp. 55
9 FENOFIBRATE MICRONIZED.mp. 3
10 Hypertriglyceridemia/ or Fatty Acids, Omega-3/ or Docosahexaenoic Acids/ or OMEGA-3 ACID ETHYL ESTERS.mp. or Eicosapentaenoic Acid/ 18738
11 Eicosapentaenoic Acid/ 3658
12 exp Niacin/ 2411
13 Ezetimibe, Simvastatin Drug Combination/ or Ezetimibe/ 1567
14 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 25451
15 limit 14 to (humans and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) and last 3 years) 1286
16 limit 15 to last 2 years 835
17 16 and 1 158

DRAFT

Appendix 4: Effect on Lipoproteins for non-Statin Medications

Table 1: Effect on Lipoproteins for non-Statin Medications.[43, 44]

Drug	LDL-C	HDL-C	TG	Approved Indications
Bile Acid Sequestrants				
Cholestyramine	↓15-30%	Minimal Effects	May ↑	Adjunct in the treatment of hypercholesterolemia
Colesevelam	↓ 15-20%	Minimal Effects	May ↑	-Management of elevated LDL-C in adults with primary HL -Type 2 Diabetes -Management of HeFH
Colestipol	↓ 15-30%	Minimal Effects	May ↑	Adjunct in the treatment of hypercholesterolemia
Fibric Acid Derivatives				
Fenofibrate	↓ 20-30%	↑ 10-15%	↓ 30-50%	- Adjunct to diet in the treatment of hypercholesterolemia -Adjunct to diet for treatment of hypertriglyceridemia
Gemfibrozil	↓ 5-10%	↑ 10-20%	↓ 40-60%	-Adjunct to diet in the treatment of hypercholesterolemia -Adjunct to diet for treatment of hypertriglyceridemia
Omega 3 Fatty Acids				
Lovaza	↑ up to 49%	↑ 10%	↓ 25-45%	Reduce TG in patients with TG > 500 mg/dl
Icosapent (Vascepa)	No effect	↑ 10%	↓ 25-45%	Reduce TG in patients with TG > 500 mg/dl
PCSK9 Inhibitors				
Alirocumab	↓ 43-58%	↑ 8%	Unknown	Adjunct to diet and maximally tolerated statin therapy in the treatment of hypercholesterolemia
Evolocumab	↓ 55-75%	↑ 4-9%	↓ 2-23%	-Adjunct to diet and maximally tolerated statin therapy in the treatment of hypercholesterolemia -Adjunct to diet and other LDL-C lowering therapies for treatment of HoFH
Other Agents				
Ezetimibe	↓ 15-20%	Minimal Effects	Minimal Effects	-Combination therapy with statins or fenofibrate to treat primary HL -As adjunct therapy to diet to treat primary HL -Combination therapy with statins to treat HoFH
Niacin	↓ 10-25%	↑ 15-35%	↓ 20-50%	-Treatment of dyslipidemia as mono or adjunctive therapy -Reduce the risk of MI in patients with a history of MI and HL -Adjunctive therapy for the treatment of TG

Abbreviations: LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; TG = triglycerides; HeFH = Heterozygous Familial Hypercholesterolemia; HL = hyperlipidemia, HoFH = Homozygous Familial Hypercholesterolemia

DRAFT

Omega-3 Fatty Acids

Goal(s):

- Promote safe and effective therapies for lipid lowering agent.

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
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products have received evidence-based reviews for comparative effectiveness and safety by the Pharmacy & Therapeutics Committee	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #4

Approval Criteria		
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)**.** ~~**AND**~~ ~~**niacin 1-2 mg/day**~~ **OR** Is patient taking a statin and is 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

Drug	Recommended dose	Maximum dose
Antara (micronized)	43-130 mg once daily	130 mg once daily
Fenoglide	40-120 once daily	120 mg once daily
Fibricor	25-105 mg once daily	105 mg once daily
Lipofen	50-150 mg once daily	150 mg once daily
Lofibra (micronized)	67-200 mg once daily	200 mg once daily
Lofibra (tablets_	54-160 mg once daily	160 mg once daily
TriCor	48-145 mg once daily	145 mg once daily
Triglide	50-160 mg once daily	160 mg once daily
Trilipix	45-135 mg once daily	135 mg once daily
Gemfibrozil	600 mg twice daily	600 mg twice daily

P&T/DUR Review: *11/16 (DM); 3/14*
Implementation: *5/1/14*

DRAFT

PCSK9 Inhibitors

Goal:

- Restrict use of PCSK9 inhibitors to populations in which the drugs have demonstrated efficacy.

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	
3. Does the patient have clinical atherosclerotic CV disease, defined as documented history of ≥1 of the following: • Myocardial infarction • Unstable angina • Coronary revascularization procedure (PCI or CABG) • Diagnosis of clinically significant coronary heart disease by coronary angiography, stress test using treadmill, stress echocardiography or nuclear imaging	**Yes:** Go to #4	**No:** Go to #6

Approval Criteria		
4. Has the patient taken a daily high-intensity statin (see table below) and ezetimibe 10 mg daily for at least 12 months with <50% LDL-C reduction? Prescriber to submit chart documentation of: 1) Doses and dates initiated of statin and ezetimibe; 2) Baseline LDL-C (untreated); 3) Recent LDL-C (within last 12 weeks).	**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; 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:** Go to #7

Approval Criteria		
7. Does the patient have a diagnosis of homozygous or heterozygous familial hypercholesterolemia and already takes a maximally tolerated statin and/or ezetimibe? Note: Prescriber must provide chart documentation of diagnosis and recent LDL-C (within last 12 weeks).	**Yes:** Document diagnosis and approve for up to 12 months Recent LDL-C _____ mg/dL Date:_____	**No:** Pass to RPh. Deny; 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; medical appropriateness

High- and Moderate-intensity Statins. Stone NJ, et al. 2013 ACC/AHA Blood Cholesterol Guideline.

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 mg	Pitavastatin 2-4 mg Pravastatin 40-80 mg Simvastatin 20-40 mg Rosuvastatin 5-10 mg

References:
1. NICE Clinical Guideline 181. Lipid modification: CV risk assessment and the modification of blood lipids for the primary and secondary prevention of CV disease. Available at: guidance.nice.org.uk/cg181. Accessed 18 September 2015.

2. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic CV Risk in Adults. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;129(25 Suppl 2):S1-45. doi: 10.1161/01.cir.0000437738.63853.7a.

P&T Review: *11/16 (DM); 11/15*
Implementation: *1/1/16*

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 to them?	**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 Review: *11/16 (DM); 5/16; 9/13; 7/13; 5/13*
Implementation: *1/1/14; 11/21/2013*

DRAFT