THE OREGON STATE DRUG REVIEW©

AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug-policy/newsletter

March, 2019 Volume 9, Issue 3

Non-statin Low-Density Lipoprotein Cholesterol (LDL-C) Lowering Therapy and Cardiovascular Outcomes

Megan Herink, Pharm.D, BCPS, Drug Use Research & Management, Oregon State University College of Pharmacy

Hypercholesterolemia, and especially elevated low-density lipoprotein cholesterol (LDL-C), is associated with increased risk of atherosclerotic cardiovascular disease (ASCVD). Prevention of ASCVD events involves optimization of treatment that have proven benefits on reduction in ASCVD events and/or cardiovascular (CV) mortality. Until recently, only statins had strong and consistent evidence demonstrating an ASCVD risk reduction. Therefore, statin therapy remains the cornerstone of treatment after therapeutic lifestyle changes (TLC). However, combination therapy to reduce ASCVD risk beyond statin use may be necessary for high-risk populations. The purpose of this newsletter is to review recent data and discuss the place in therapy of non-statin medications. Key recommendations from the recently updated 2018 American College of Cardiology (ACC)/American Heart Association (AHA) Blood Cholesterol guideline will also be discussed.[1,2]

Management of Hypercholesterolemia

After TLC, the 2018 ACC/AHA Blood Cholesterol guideline recommends moderate- or high-intensity statins to patients in which there is evidence of ASCVD risk reduction (Table 1).[1]

Table 1: Statin Benefit Groups

Statin Benefit Group	Recommended Treatment
Clinical ASCVD	High-intensity statin
Severe Hypercholesterolemia (LDL-C ≥ 190 mg/dl)	High-intensity statin
Diabetes age 40-75 and LDL-C ≥ 70 mg/dl	Moderate-to high-intensity statin (based on ASCVD risk factors)
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

A significant change in the guidelines is the re-implementation of a 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 1 major ASCVD event and multiple high-risk conditions (Table 2).[1] The guideline recommendation is to add ezetimibe to maximally tolerated statin therapy as a first step in lowering LDL-C, followed by a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor if LDL-C remains ≥ 70 mg/dl on both statin and ezetimibe therapy for very high risk only.[1] Ezetimibe is recommended as first-line add on therapy because it is widely available as a generic and is well tolerated. Additionally, ezetimibe was allowed at baseline along with a statin in both PCSK9 inhibitor outcome trials.[3,4]

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
Symptomatic PAD	Current Smoking	Heart failure
	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

Ezetimibe is an inhibitor of intestinal cholesterol absorption indicated as an adjunct to reduce elevated cholesterol and LDL-C. Ezetimibe 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.[2] In this trial, simvastatin 40mg/ezetimibe 10mg was compared to simvastatin 40mg in patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days (Table 3).[2] The primary endpoint was a composite of CV death, nonfatal myocardial infarction (MI), unstable angina requiring re-hospitalization, coronary revascularization, or nonfatal stroke. 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 (Table 4). Additionally, the median LDL-C was reduced to 53.7 mg/dl in the ezetimibe group, as compared with 69.5 mg/dl in the simvastatin monotherapy group would still be considered at goal in this population. 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 effect on CV outcomes with ezetimibe/simvastatin combination was not particularly robust.[5] Additionally, a moderate-intensity statin was used as the study comparator which is not consistent with current practice recommendations.

Table 3: Characteristics of Cardiovascular Outcome trials for Non-statins[2-4]

	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 at baseline	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

PCSK9 Inhibitors

Evolocumab (Repatha®) and alirocumab (Praluent®) are subcutaneously injected human monoclonal antibodies that reduce LDL-C by inhibiting PCSK9.[6,7] PCSK9 promotes the degradation of the LDL receptor, resulting in an increase in plasma LDL-C. Both agents are effective at lowering LDL-C and can lower LDL-C by an average of 50% 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.[6,7] 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.[6]

FOURIER Trial (evolocumab)

The FOURIER trial is the first published PCSK9 inhibitor trial that evaluated CV clinical outcomes as the primary outcome (Table 3).[3] It is a parallel group, double-blind, large, good quality randomized controlled trial (RCT) (n=27,654) that included adults with history of clinically evident CVD with LDL-C greater than or equal to 70 mg/dl with at least one major risk factor (diabetes, smoker, age ≥65 years, recent acute coronary syndrome [ACS]) or two minor risk factors (coronary revascularization, residual coronary artery disease [CAD], metabolic syndrome, LDL-C ≥130 mg/dl).

Participants were randomized to evolocumab or placebo. Patients in both groups were on moderate- or high-intensity statin therapy, with or without ezetimibe as background therapy. Only around 5% of those in each group were on ezetimibe, and almost 70% were on high intensity statin.[3] The study population had a relatively well-controlled lipid profile with a median LDL-C of 92 mg/dl and triglycerides of 133 mg/dl. The median duration of follow-up was 26 months.[3] The primary outcome was a CV composite outcome including CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization.

The primary CV composite outcome was modestly reduced with evolocumab compared to placebo (9.8% vs. 11.3%; HR 0.85; 95% [confidence interval] CI 0.79 to 0.92; absolute risk reduction [ARR] 1.5%; number needed to treat [NNT] 67) (Table 4).[3] There was no significant reduction in individual outcomes including CV death or overall mortality. There was numerically a higher rate of overall mortality (3.2% vs. 3.1%) and CV death (1.8% vs. 1.7%) in the evolocumab group compared to placebo. The small reduction of 1.5% in the primary composite outcome was largely driven by a difference in non-fatal events (MI, stroke, or coronary revascularization). Although the follow-up duration was shorter than planned due to a higher than expected event rate (26 of 48 months planned), it was still surprising that there was no trend toward a reduction in death from CV disease.

Consistent with previous studies, LDL-C was significantly reduced with evolocumab compared to placebo, with a least-squares mean reduction of 59% compared to placebo (95% CI, 55 to 57).[3] At 48 weeks, LDL-C was reduced to less than or equal to 70 mg/dl in 87% of evolocumab-treated patients compared to 18% in the placebo group (ARR 69%; NNT 2).

Table 4: Summary of Results from Cardiovascular Outcome Trials[2,3,9]

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

Abbreviations: ARR: absolute risk reduction; CV: cardiovascular; NNT: number needed to treat; NS: non-significant

ODYSSEY OUTCOMES Trial (alirocumab)

The ODYSSEY OUTCOMES trial is a double-blind, placebo-controlled RCT comparing alirocumab to placebo in patients who had been hospitalized with ACS one to 12 months before randomization and had an LDL-C of at least 70 mg/dl on a high-intensity statin (n=18,924).[4] The primary outcome was a CV composite outcome including CV death, MI, stroke, or hospitalization for unstable angina.

The majority of patients qualified with a MI (83%) and the median time from ACS to randomization was 2.6 months. Most patients were stable on a high-intensity statin (89%) and median LDL-C was 92 mg/dl. Unlike the FOURIER trial, dose adjustments were made to avoid sustained LDL-C levels below 15 mg/dl.

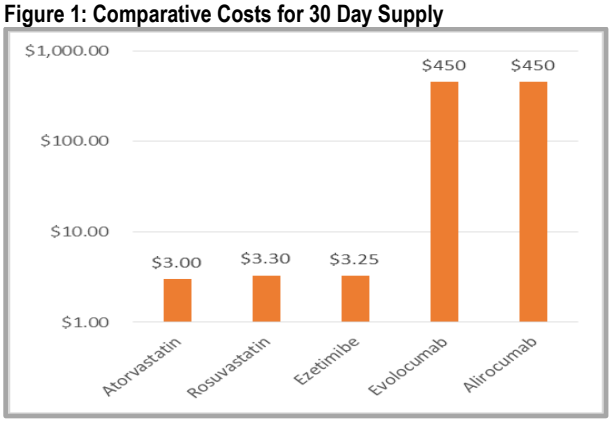
The primary CV composite outcome was reduced with alirocumab compared to placebo (9.5% vs. 11.1%; ARR 1.6%; NNT 63).[4] There was no significant death due to CV causes but unlike the evolocumab trial, there was a significant reduction in overall mortality (Table 4). This difference could be in part due to the longer study duration in the ODYSSEY OUTCOMES.

LDL was significantly reduced from baseline with alirocumab compared to placebo by 62.7% at 4 months.[4] However, the mean LDL-C in the alirocumab increased over the duration of the study from 40 mg/dl at four months to 66 mg/dl at 48 months. This could be due to the blinded dose reduction or crossover to placebo (7.7%) for LDL-C less than 25 mg/dl and 15 mg/dl, respectively.

Safety of PCSK9 inhibitors

There was no difference in serious adverse events or discontinuations due to adverse events in the CV outcome trials with PSCK9 inhibitors. There was also no significant difference in incident of new-onset diabetes between either PCSK9 inhibitor and placebo. Potential risks of adverse neurological effects from sustained, extremely low LDL-C levels have been hypothesized. In a 2-year subgroup analysis of the FOURIER trial designed to detect cognitive changes, no significant difference in cognitive function was observed.[8] However, long-term safety beyond 2-4 years remains unknown and more long-term data is needed.

Figure 1: Comparative Costs for 30 Day Supply



Clinical Use of Non-statin Lipid Lowering Agents

Current standard of care is to optimize TLC and statin therapy for patients with CV disease and for those with a high CV risk. Statins have been shown to reduce all-cause mortality in patients with CV disease (NNT 25), as well as vascular events.[1] Additionally, high intensity statins have shown a greater reduction in events compared to low intensity statins driven by a greater LDL-C lowering ability, highlighting the importance of dose optimization. More recent clinical trials have demonstrated a modest absolute benefit (<2%) on non-fatal CV events with ezetimibe and PCSK9 inhibitors as adjuncts to moderate- to high-intensity statin therapy with no proven CV mortality benefit. The cost versus benefit of PCSK9 inhibitors prevents widespread use (Figure 1), and the ACC/AHA guideline gives them a low-cost value for patients at very high risk of ASCVD.[1] Additionally, the long-term safety of PCSK9 inhibitors remains to be seen.

Non-statin therapy should be reserved for high risk patients with clinical ASCVD who have LDL-C of at least 70 mg/dl on high intensity statin therapy, or those with severe hypercholesterolemia (initial LDL-C ≥ 190 mg/dl), especially familial hypercholesterolemia (FH), with a LDL of at least 100 mg/dl on maximally tolerated statin. Ezetimibe has shown similar benefits as add on therapy over a longer duration (7 years), but at a much lower cost than the PCSK9 inhibitors (Figure 1) and is extremely well tolerated. Ezetimibe is a reasonable first-line add on therapy for patients with CVD with the ability to incrementally lower LDL-C up to 25% on top of statin therapy. There is limited evidence on CV outcomes and a limited place in therapy for other LDL-C lowering agents (fibrates, bile acid sequestrants, niacin, and omega-3 fatty acids), but may still be useful to achieve additional LDL-C lowering in patients with FH.

Oregon Health Plan (OHP) Fee-For-Service (FFS) Policy

- PCSK9 inhibitors are non-preferred and are subject to prior authorization criteria requiring:
  - Clinical ASCVD on high-intensity statin and ezetimibe requiring additional LDL-C lowering
  - Heterozygous or homozygous familial hypercholesterolemia on a maximally tolerated statin

Peer Reviewed By: Bart Duell, M.D., Professor of Medicine, Division of Cardiovascular Medicine School of Medicine at Oregon Health and Science University

References:

1. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018.
2. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. The New England journal of medicine. 2015;372(25):2387-2397.
3. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. The New England journal of medicine. 2017;376(18):1713-1722.
4. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. The New England journal of medicine. 2018;379(22):2097-2107.
5. FDA Briefing Document: Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) - UCM476505.pdf. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM476505.pdf. .
6. Evolocumab (Repatha) for injection [package insert]. Thousand Oaks, CA: Amgen Inc.; 2019.
7. Alirocumab (Praluent) injection, solution [package insert].Bridgewater, NJ: Sanofi-Aventis U.S. LLC; 2018.
8. Giugliano RP, Mach F, Zavitz K, et al. Cognitive Function in a Randomized Trial of Evolocumab. The New England journal of medicine. 2017;377(7):633-643.
9. Schwartz GG, Bessac L, Berdan LG, et al. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY outcomes trial. Am Heart J. 2014;168(5):682-689.