Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: *2018 ACC/AHA Cholesterol Guideline*

-November 2019-

Background:

The IHS National Pharmacy & Therapeutics Committee (NPTC) reviewed the 2018 AHA/ACC cholesterol treatment guideline at the November 2019 meeting. Cardiovascular disease (CVD) is the leading cause of death in the U.S. as well as in American Indians/Alaska Natives (AI/AN) despite improvements in both prevention and treatment. Statin therapy remains the first line treatment for dyslipidemia and both the primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD). Presently, two high-intensity statins (rosuvastatin, atorvastatin) and two low/moderate-intensity statins (simvastatin, pravastatin) are listed on the IHS National Core Formulary (NCF). As a result of this review, the NPTC **added the non-statin medication, ezetimibe, to the NCF.**

Discussion:

The 2018 ACC/AHA cholesterol guidelines continue to support fixed-dose statin therapy for the four statin benefit groups (clinical ASCVD, LDL-C ≥190 mg/dL, 40-75 year olds with diabetes and a LDL ≥70mg/dL, and 40-75 year olds with a LDL ≥70mg/dL and ASCVD risk >7.5%) and monitoring the percentage decrease in LDL-C. One of the biggest changes from the 2013 guidelines is now targeting an LDL-C level to less than 70 mg/dL. In those patients unable to achieve a LDL-C level of <70 mg/dL on maximally tolerated statin therapy, the addition of a non-statin therapy is suggested. Ezetimibe is recommended as the first-line add-on therapy due to favorable tolerability, lower cost, modest LDL-C lowering ability and cardiovascular benefits, followed by the proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors.

=Non-Statin Therapy=

Ezetimibe demonstrated modest improvement in LDL-C reduction and primary cardiovascular outcomes when added to a moderate-intensity statin. The IMPROVE-IT trial was a large RCT comparing simvastatin 40mg/ezetimibe 10mg to simvastatin 40mg/placebo in patients hospitalized with recent acute coronary syndrome. The primary composite outcome of death from CVD, major cardiovascular events (MACE) or nonfatal stroke was significantly reduced in the simvastatin/ezetimibe group (HR: 0.93; 95% CI: 0.89-0.99; p=0.016). The mean starting LDL-C level was 93.6 mg/dL; after one year the simvastatin/ezetimibe group reported LDL-C levels of 53.2 mg/dL versus 69.5 mg/dL in the monotherapy groups (p<0.001), a 24% reduction with ezetimibe. No significant differences in safety endpoints were reported. Additionally, a 2018 Cochrane review concluded that ezetimibe had modest beneficial effects on CVD endpoints, which was driven primarily by non-fatal myocardial infarction (MI) and non-fatal strokes for secondary prevention but had little evidence to support use in primary prevention or as monotherapy.

The PCSK9 inhibitors, alirocumab and evolocumab, were evaluated in a 2017 Cochrane review which concluded that PCSK9 inhibitors showed benefit in reducing CVD risk (OR 0.86; 95% CI: 0.80-0.92), however there was no benefit to all-cause mortality (OR 1.02; 95% CI: 0.91-1.14) and reported an increase in adverse events (OR 1.08; 95% CI: 1.04-1.12). Both agents are approved for the treatment of hyperlipidemia (primary prevention) and for secondary prevention of CV events. Two trials, the FOURIER and ODYSSEY, were specifically designed to evaluate the impact of PCSK9 inhibitors on a composite of CV outcomes. The FOURIER trial compared evolocumab to placebo in groups who also received moderate to high-intensity statins. Evolocumab significantly reduced adverse CV outcomes compared with placebo (HR 0.85, 95% CI: 0.79-0.92; p<0.001), however rates of CV death and overall mortality did not differ between groups. The ODYSSEY trial examined similar CV outcomes in patients receiving alirocumab and also reported a 15% risk reduction (HR 0.85, 95% CI: 0.78-0.93; p<0.001) favoring alirocumab over placebo. As a secondary endpoint, the ODYSSEY trial demonstrated reduction in death from any cause (HR 0.85, 95% CI: 0.73-0.98). Both PCSK9 inhibitors lowered LDL-C by an average of 50% when used with statin therapy for secondary prevention.

=Secondary ASCVD Prevention=

Patients with clinical ASCVD should emphasize heart-healthy lifestyles. Patients not at “very-high” risk and ≤75 years of age should be started on a high-intensity statin, with the goal of reducing LDL-C by 50%. If a high-intensity statin is not tolerated, a moderate-intensity statin should be used. If a LDL-C goal of <70mg/dL is not achieved on a maximally tolerated statin dose, a non-statin therapy should be added, with ezetimibe recommended as first-line. If the patient is >75 years of age with clinical ASCVD, a moderate or high-intensity statin is reasonable.

The 2018 ACC/AHA guidelines define “very high-risk” as having 2 or more major ASCVD events or a major ASCVD event plus a high-risk condition (i.e., prior revascularization, diabetes mellitus (DM), hypertension, current smoker, eGFR 15-59 ml/min/1.73m^2, a LDL-C≥100 mg/dL, age >65 years of age, heterozygous familial hypercholesterolemia, or congestive heart failure). For patients at “very high-risk” with a LDL-C ≥70mg/dL or non-HDL ≥100mg/dL despite receiving both a maximally tolerated statin and ezetimibe, a PCSK9 inhibitor is recommended.

=Primary ASCVD Prevention=
For patients 40-75 years old with a LDL-C of ≥70-189 mg/dL without DM, statin therapy should be initiated based on the 10-year ASCVD risk. The 2018 guidelines did not change the recommendations for low (<5%) or borderline risk (5%-7.5%) categories. However, two new categories were added, namely intermediate risk (7.5%-20%) and high risk (>20%). For patients categorized as intermediate risk, moderate-intensity statin therapy should be initiated. For high risk category patients, a high-intensity statin should be started. If risk is uncertain, coronary artery calcium (CAC) can be considered to guide therapy. A CAC score of zero is considered low risk and statin therapy can be delayed unless the patient has other ASCVD risk enhancers. A CAC score of 1-99 favors starting a statin whereas a CAC score >100 indicates initiation of statin therapy is necessary.

For patients with severe hypercholesterolemia aged 20-75 years with a baseline LDL-C ≥190mg, a high-intensity statin or maximally tolerated statin should be started. Following statin initiation, if the LDL-C reduction is <50% from baseline and/or the LDL-C remains ≥100 mg/dL, ezetimibe should be started. If LDL-C reduction of 50% is still not achieved, a bile acid sequestrant can be added if triglycerides are ≤300 mg/dL. For patients aged 30-75 years with heterozygous familial hypercholesterolemia or aged 40-75 years with a baseline LDL-C ≥220 mg/dL and on a maximally tolerated statin and ezetimibe, PCSK9 inhibitors should be added.

In patients with diabetes mellitus between 40-75 years of age with a LDL-C level of 70-189 mg/dL, a moderate-intensity statin is recommended. If these patients have multiple ASCVD risk factors or are 50-75 years old, a high-intensity statin is recommended. Additionally, if the 10-year ASCVD risk is >20%, ezetimibe should be added to maximally tolerated statin therapy. Patients between 20-39 years of age with diabetes-specific risk enhancers should also be started on a moderate-intensity statin.

=Hypertriglyceridemia=
The 2018 guidelines recommend in adults aged ≥20 years with moderate hypertriglyceridemia (fasting or non-fasting triglycerides levels of 175-499 mg/dL) that clinicians review and address lifestyle factors, secondary factors, and medications that may increase triglycerides. In adults 40-75 years of age with moderate hypertriglyceridemia and ASCVD risk of ≥7.5%, the recommendations are the same as above, however consideration should also be given to initiating or intensifying statin therapy. If severe hypertriglyceridemia is present (fasting triglycerides ≥500 mg/dL and ASCVD risk of ≥7.5%), guidelines suggest addressing reversible causes and starting a statin. In addition to these recommendations, if triglycerides remain persistently high, clinicians may also consider targeted dietary recommendations and fibrate therapy initiation.

Findings:
Statin therapy should be optimized for both patients with ASCVD and those with ASCVD risk. Statins continue to be supported as first-line agents in managing hyperlipidemia and high-intensity statins show greater reduction in cardiovascular events compared to low-intensity statins. Ezetimibe and PCSK9 inhibitors are the preferred non-statins as adjuncts to maximally tolerated statins. The 2018 ACC/AHA cholesterol guidelines recommend ezetimibe as first-line, add-on therapy over PCSK9 inhibitors.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

References:

- U.S. Centers for Disease Control and Prevention. Heart disease facts. Updated 28 November 2017.
- 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. *Circulation.* 2019; 139:e1082–1143.
- Cannon CP, Blazing MA, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *NEJM.* 2015; 372: 2387-97.
- Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *NEJM.* 2017; 376:1713-22.
- Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *NEJM.* 2018; 379:2097-2107.