Background:
The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a drug review of agents for treatment of hyperlipidemia. Cardiovascular disease (CVD) is a leading cause of morbidity and mortality among American Indian/Alaska Native (AI/AN) people. AI/AN people have a life expectancy that is 5 years shorter than the general population and are more likely to die of heart disease or stroke. Reduction of blood cholesterol, specifically low-density lipoprotein (LDL), is proportionately linked to better cardiovascular outcomes.¹

National and international clinical guidelines for treatment of hyperlipidemia were reviewed. Statins are unanimously recommended as first-line pharmacotherapy for primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD). In most cases, ezetimibe is recommended as adjunct therapy when treatment goals are not achieved with statin therapy alone. The IHS National Core Formulary (NCF) currently includes four statin drugs (atorvastatin, pravastatin, rosuvastatin, simvastatin) and one non-statin drug (ezetimibe) for the treatment of hyperlipidemia. No changes were made to the NCF.

Discussion:
This review builds on recent NPTC guidance for cholesterol management. A 2014 detailed review of statin drugs led to the addition of a high-intensity statin (atorvastatin) to the NCF.² This was supported by further review of safety and efficacy in 2017, which led to addition of a second high-intensity statin option (rosuvastatin). This review also highlighted evidence that fibrates do not improve cardiovascular outcomes, and could be harmful in combination with statins. Fibric acid derivatives were removed from the NCF following this review.³ The 2019 review of American College of Cardiology and American Heart Association (ACC/AHA) guidelines highlighted the role for ezetimibe as an adjunct to statin therapy in certain high-risk patients – citing a significant reduction in cardiovascular death, major acute cardiovascular events (MACE) or non-fatal stroke. As a result, ezetimibe was added to the NCF.⁴

The 2019 ACC/AHA guidelines for primary prevention of CVD focus largely on therapy other than lipid-lowering medications and refer to the 2018 guidelines for management of blood cholesterol. Both documents urge the use of a cardiovascular risk calculator for risk stratification, then the choice of moderate or high-intensity statin therapy for primary prevention of CVD when indicated.⁵ This approach is affirmed by the United States Preventive Services Task Force statement (updated 2020) on statin use in primary prevention of CVD.⁶ The 2021 American Diabetes Association (ADA) guidelines for standard of care in diabetes agree with this approach to primary prevention, recommending the choice of moderate or high-intensity statin therapy based on risk factors and without specific numerical LDL treatment targets⁷. Both the ACC/AHA and the ADA guidelines make exceptions for patients with certain risk factors, suggesting treatment to a goal LDL reduction of >50% - using maximally tolerated statin therapy, then ezetimibe. The ACC/AHA guidelines go on to suggest triple therapy with either a bile acid sequestrant (BAS) or proprotein convertase subtilisin/kinin type 9 (PCSK-9) inhibitor in certain circumstances.⁸ The 2020 American Academy of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) guidelines recommend the use of numerical LDL goals in all patients, with stepwise therapy of lifestyle interventions, maximal statin, ezetimibe, and PCSK-9 inhibitors. They add that a PCSK-9 inhibitor may be recommended before ezetimibe in cases where a >25% reduction in LDL is needed to reach goals for treatment.⁹

The 2019 European Society of Cardiology and European Atherosclerosis Society (ESC/EAS) guidelines for the management of dyslipidemias also advise the use of maximally-tolerated statin therapy, then ezetimibe, and in some cases triple therapy (adding BAS or PCSK-9). These guidelines differ from the ACC/AHA guidelines in that they advise consideration of triple therapy with PCSK-9 inhibitors more broadly in patients at very high risk.⁸ The 2021 ESC guidelines for CVD prevention recommend numerical LDL treatment goals for primary prevention in healthy patients at high risk of CVD. A 2021 ESC/EAS statement on PCSK-9 inhibitors supports their use in accordance with the ESC guidelines and goes on to provide a cost/benefit analysis based on risk groups. The price reduction for PSCK-9 inhibitors over the last 5 years may allow for more liberal use. It is noted that statin therapy will only meet target-based LDL treatment goals for about 40% of patients with hyperlipidemia.⁹

The ACC/AHA guidelines also recommend statin therapy for first-line treatment of moderate or severe hypertriglyceridemia and increased cardiovascular risk. Fibrates are mentioned as an option to prevent pancreatitis in refractory cases. In contrast, the ESC/EAS guidelines recommend the use of high dose prescription omega-3-fatty acids before the use of fibrates.⁸

Patients with a history of clinical ASCVD and risk of additional heart disease require treatment for secondary prevention. Each of the above cited guidelines agree on the use of maximally-tolerated statin therapy to a target LDL reduction. When
statin therapy is not adequate to meet the goal, guidelines agree that ezetimibe should be used as second-line, and PCSK-9 inhibitors should be considered for triple therapy. The 2019 ESC/EAS guidelines affirm PCSK-9 inhibitor use in this setting with their highest recommendation (class 1 recommendation, level of evidence – A) while the 2018 ACC/AHA guidelines give it a lower recommendation (class IIa – moderate)\(^8\).

Recommendations for use of PCSK-9 inhibitors are primarily based on the ODESSEY trial (alirocumab) and the FOURIER trial (evolocumab) which have been previously reviewed by the NPTC.\(^4\) Further support for this class comes from a 2020 Cochrane review of PCSK-9 inhibitors for the primary and secondary prevention of CVD. This systematic review of randomized controlled trials (RCT) included 24 studies with >60,000 patients. For alirocumab vs. placebo, the primary end points of MACE (OR 0.87, 95% CI 0.80 to 0.94), all-cause mortality (OR 0.83, 95% CI 0.72 to 0.96), myocardial infarction (OR 0.86, 95% CI 0.79 to 0.94), and stroke (OR 0.73, 95% CI 0.58 to 0.91) were all reduced. For evolocumab vs. placebo, the primary end points of MACE (OR 0.84, 95% CI 0.78 to 0.91), myocardial infarction (OR 0.72, 95% CI 0.64 to 0.82), and stroke (OR 0.79, 95% CI 0.65 to 0.94) were also all reduced. There was insufficient evidence for reduction of all-cause mortality (OR 1.04, 95% CI 0.91 to 1.19). There were no safety signals identified for secondary outcomes including incidence of hypertension, type 2 diabetes, cancer, or influenza.\(^10\)

There is a renewed interest in the use of omega-3-fatty acids for treatment of hyperlipidemia and prevention of ASCVD. REDUCE-IT, a multicenter, double-blind, RCT compared high dose (2 gm bid) icosapent ethyl vs. placebo in >8,000 patients with established ASCVD or diabetes with one additional ASCVD risk factor. The study showed a reduction in MACE (HR, 0.75; 95% CI 0.68 to 0.83; P<0.001) and cardiovascular death (4.3% vs. 5.2%; HR, 0.80; 95% CI 0.66 to 0.98; P=0.03). The intervention group experienced higher rates of hospitalization for atrial fibrillation or atrial flutter (3.1% vs. 2.1%, P=0.004) and were more likely to experience serious bleeding events (2.7% vs. 2.1% P=0.06).\(^11\)

**Findings:**
Guidelines agree that statin therapy should be first line for treatment of hyperlipidemia in primary and secondary prevention of CVD. There is a trend toward treatment to goal LDL rather than fixed dose therapy, especially in high risk patients and among specialty organizations.

Ezetimibe should be used as second-line therapy in cases where treatment goals cannot be achieved using statin therapy alone. PCSK-9 inhibitors are now recommended as second or third-line therapy, and have strong evidence for improved cardiovascular outcomes. Although recommendations for PCSK-9 inhibitor use are strengthening over time, there remains debate over cost/value balance and the ideal patient selection for this class of medication.

The REDUCE-IT trial suggests that prescription strength omega-3-fatty acids may provide cardiovascular benefits for patients with hypertriglyceridemia. Other recent trials have not confirmed this benefit, and there is some criticism regarding the choice of placebo in this trial. Further study may be needed before more clinical guidelines feature its use.

Current usage trends suggest that many AI/AN patients would benefit from optimized statin therapy and/or addition of ezetimibe before consideration of a PCSK-9 inhibitor or other non-statin therapies. Fibrates should be reserved for cases of extreme hypertriglyceridemia and should generally be avoided in combination with statin therapy.

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:**