



Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: Hyperlipidemia
-February 2017-



Background:

Statins have gained broad acceptance as first-line therapy for hyperlipidemia yet many patients either cannot tolerate statins, cannot tolerate statins at the intensity recommended for their cardiovascular disease (CVD) risk, or remain concerned about the potential harms of statins. For these patients, interest in non-statin therapy continues either as monotherapy or in combination with statins. The non-statin options for which randomized controlled trial (RCT) data on patient-oriented outcomes exists are bile acid sequestrants, niacin, fibrates, proprotein convertase subtilisin/kexin 9 (PCSK-9) inhibitors and ezetimibe. The PCSK-9 inhibitors will be evaluated separately in the near future. As a result of this review, the **National Pharmacy & Therapeutics Committee (NPTC) removed both extended-release niacin and fibric acid derivatives** from the National Core Formulary (NCF) due to lack of mortality benefit, plus either safety concerns or lack of high-quality evidence for benefit beyond narrow subgroups. **Rosuvastatin was added as a high-intensity alternative to atorvastatin.** Pravastatin and simvastatin continue on the NCF as low/moderate intensity alternatives.

Discussion:

Bile acid sequestrants available in the United States include cholestyramine, colestipol, and colesevelam. Cholestyramine decreases absolute risk of coronary heart disease (CHD) death and nonfatal myocardial infarction (MI) by 1.7% ($p < 0.05$), but only in a narrowly-defined study population with a high rate of gastrointestinal (GI) side effects(1). They require inconvenient dosing, titration, and monitoring and should be avoided in patients with triglycerides > 300 (2). Colesevelam has an improved side effect profile and lowers A1c, however patient-oriented evidence for benefit in diabetes is lacking(3).

Niacin has protean benefits for lipid profiles but patient-oriented outcomes are poor. Evidence for monotherapy comes from data from 1975, demonstrating a 3.3% decrease in absolute risk of nonfatal MI, without effect on mortality. The same data show increased arrhythmias, GI complications, gout and diabetes(4). Recent trials compare extended release niacin + simvastatin vs. simvastatin alone. The AIM-HIGH study was stopped early due to futility and a trend toward increased ischemic stroke(5). Niacin was also ineffective in the highly powered HPS2-THRIVE trial in which it also caused major GI, musculoskeletal, infectious disease, bleeding and dermatologic adverse reactions, plus increased new-onset diabetes(6). That similar adverse reactions may occur with niacin monotherapy is a concern. No niacin products are currently approved in Europe(7).

Gemfibrozil and fenofibrate are the two fibrates available in the United States. As monotherapy, gemfibrozil reduced the composite endpoint of CHD death and non-fatal MI. The absolute risk reduction was 1.4% ($p < 0.02$) in Finnish men and 4.4% ($p = 0.006$) in male veterans with low HDL, without significant change in overall mortality. Dyspepsia, moderate-severe GI symptoms and GI surgery were all significantly increased(8,9). Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis(2).

Fenofibrate has not been shown to improve primary endpoints either as monotherapy(10) or as a statin add-on(11). As monotherapy, it did reduce retinopathy and amputations but only as tertiary endpoints, with low event rates, and large numbers needed to treat(12,13). Furthermore, there was a trend toward increased mortality(10). Added on to simvastatin for diabetics, it again reduced retinopathy as a tertiary endpoint, but not vision loss(14). This was not enough to keep the Food and Drug Administration in 2016 from withdrawing its approval for co-administration with a statin(15).

Pancreatitis prevention is used as an indication for fibrates in patients with very high triglycerides. It should be noted, however, that quality evidence for this indication is lacking(16). Furthermore, in the trials cited above, fibrates increased the incidence of pancreatitis ($RR = 1.39$, $p = 0.053$)(17).

Ezetimibe has insufficient data to evaluate the efficacy and safety of monotherapy(2). Evidence for co-administration with a statin comes primarily from the IMPROVE-IT trial, in which adding ezetimibe reduced the absolute risk of nonfatal MI/stroke by 2% (p=0.016). Mortality was unchanged. Importantly, all study subjects had an acute coronary syndrome within 10 days of study entry(18). Stable CHD patients on statins were studied in the ARBITER 6-HALTS trial of ezetimibe vs. niacin. In this trial, ezetimibe increased major cardiovascular events (p=0.04). Since niacin has been shown to perform similarly to placebo, this study demonstrates harm from ezetimibe to patients with stable CHD. Of note, the ARBITER 6-HALTS study was stopped early, which can amplify results, and had only 363 patients, while IMPROVE-IT had 18,144(19).

The 2013 ACA/AHA guidelines state for statin intolerant patients that “it is reasonable to use” non-statin. For those who tolerate a statin but at inadequate potency, non-statin “may be considered” if benefits outweigh the adverse effects. Both recommendations are based on expert opinion(2).

The 2016 ESC/EAS (European) guidelines still advocate for LDL goals. They specify that ezetimibe or bile acid sequestrants “should be considered” for the statin intolerant patient. As a statin add-on for those unable to reach their LDL goal, ezetimibe “should be considered” while bile acid sequestrants “may be considered”. All recommendations are based on “C” level evidence (consensus or low quality studies)(7).

Findings: (Statins and statin selection)

Adverse reaction differences might be expected among statins due to unique pharmacology, yet no RCT evidence demonstrates that such differences exist. In RCTs, prevalence of muscle symptoms is always less than 1%, dramatically conflicting with clinical experience. On the whole, RCTs have failed to systematically define and ask about muscle symptoms, and several trials have excluded patients with adverse reactions(20). No RCTs have compared muscle adverse events in the same trial(21). No RCTs have reported significant cognitive effects from statins(22). Liver adverse reactions have been rare and unpredictable(23). Diabetes risk increases with intensity, but there are no differences among statins(24).

The 2013 ACA/AHA guidelines categorize statin regimens into high, moderate, and low intensity based on their LDL-lowering capacity. In general, high-intensity statins result in decreased CVD events (though not better mortality) than low-intensity for those with established CVD. Equivalent intensity statins have not been compared in RCTs(26). Based on this evidence, all guidelines recommend either high-intensity statins or very low LDL goals (generally only achievable with high-intensity statins) for patients at high atherosclerotic CVD risk(2,7,27).

Discontinuation of statins due to adverse events is common, occurring in 10-20% of patients. However, 90% of those re-challenged with a statin remain on a statin for at least a year(28). Even among patients intolerant to 2 statins, 73% can tolerate a different statin if re-challenged properly(29). These data highlight the importance of other statins as alternatives for those who do not tolerate their initial statin. Rosuvastatin is the only high-intensity statin alternative for high-risk CVD patients who do not tolerate atorvastatin(2).

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:

1. The Lipid Research Clinics Coronary Primary Prevention Trial Results: I. Reduction in Incidence of Coronary Heart Disease. JAMA. 1984;20;251(3):351–64.
2. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;1;63(25, Part B):2889–934.
3. Ooi CP, Loke SC. Colesevelam for type 2 diabetes mellitus. In: Cochrane Database of Systematic Reviews [Internet]. John Wiley & Sons, Ltd; 2012 [cited 2017 Feb 18]. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009361.pub2/abstract>
4. Clofibrate and Niacin in Coronary Heart Disease. JAMA. 1975;231(4):360–81.
5. Investigators TA-H. Niacin in Patients with Low HDL Levels Receiving Intensive Statin Therapy. N Engl J Med. 2011;365(24):2255–67.
6. Group TH-TC. Effects of Extended-Release Niacin with Laropiprant in High-Risk Patients. N Engl J Med. 2014;371(3):203–12.
7. Catapano A, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for Management of Dyslipidaemias. Eur Heart J. 2016;37(39):2999–3058.
8. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: Primary-Prevention Trial with Gemfibrozil in Middle-Aged Men with Dyslipidemia. N Engl J Med. 1987;317(20):1237–45.

9. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the Secondary Prevention of Coronary Heart Disease in Men with Low Levels of High-Density Lipoprotein Cholesterol. *N Engl J Med.* 1999;341(6):410–8.
10. Investigators TF study. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *The Lancet.* 2005;366(9500):1849–61.
11. Group TAS. Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus. *N Engl J Med.* 2010;362(17):1563–74.
12. Keech A, Mitchell P, Summanen P, et al. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *The Lancet.* 2007;370(9600):1687–97.
13. Rajamani K, Colman PG, Li LP, et al. Effect of fenofibrate on amputation events in people with type 2 diabetes mellitus (FIELD study): a prespecified analysis of a randomised controlled trial. *The Lancet.* 2009;373(9677):1780–8.
14. Group TAS, Group AES. Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes. *N Engl J Med.* 2010;363(3):233–44.
15. AbbVie Inc. et al; Withdrawal of Approval of Indications Related to the Coadministration With Statins in Applications for Niacin Extended-Release Tablets and Fenofibric Acid Delayed-Release Capsules. *Fed Regist.* 81(74):22612–3.
16. Rosenson RS. Approach to the patient with hypertriglyceridemia. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA (Accessed on January 24, 2017).
17. Preiss D, Tikkanen MJ, Welsh P, et al. Lipid-Modifying Therapies and Risk of Pancreatitis: A Meta-analysis. *JAMA.* 2012;308(8):804–11.
18. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med.* 2015; 18;372(25):2387–97.
19. Taylor AJ, Villines TC, Stanek EJ, et al. Extended-Release Niacin or Ezetimibe and Carotid Intima Media Thickness. *N Engl J Med.* 2009; 26;361(22):2113–22.
20. Ganga HV, Slim HB, Thompson PD. A systematic review of statin-induced muscle problems in clinical trials. *Am Heart J.* 2014; 168(1):6–15.
21. Rosenson RS, Baker SK, Jacobson TA, et al. An assessment by the Statin Muscle Safety Task Force: 2014 update. *J Clin Lipidol.* 2014; 8 (3, Supplement):S58–71.
22. Rojas-Fernandez CH, Goldstein LB, Levey AI, et al. An assessment by the Statin Cognitive Safety Task Force: 2014 update. *J Clin Lipidol.* 2014: 8(3, Supplement):S5–16.
23. Bays H, Cohen DE, Chalasani N, et al. An assessment by the Statin Liver Safety Task Force: 2014 update. *J Clin Lipidol.* 2014;8(3, Supplement):S47–57.
24. Maki KC, Ridker PM, Brown WV, et al. An assessment by the Statin Diabetes Safety Task Force: 2014 update. *J Clin Lipidol.* 2014; 8(3, Supplement):S17–29.
25. Kellick KA, Bottorff M, Toth PP. A clinician’s guide to statin drug-drug interactions. *J Clin Lipidol.* 2014; 8(3, Supplement):S30–46.
26. Rosenson RS. Clinical trials of cholesterol lowering in patients with cardiovascular disease or diabetes. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA (Accessed on January 24, 2017).
27. Jellinger PS. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis - Executive Summary © 2017 [Internet]. 2017. Available from: <https://www.aace.com/files/lipid-guidelines.pdf>
28. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings: A cohort study. *Ann Int Med.* 2013;158(7):526–34.
29. Mampuya WM, Frid D, Rocco M, et al. Treatment strategies in patients with statin intolerance: The Cleveland Clinic experience. *Am Heart J.* 2013; 166(3):597–603.