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Nonstatin Therapies for Management of Dyslipidemia: A Review

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ABSTRACT

Purpose: Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the United States. Recently published cholesterol treatment guidelines emphasize the use of statins as the preferred treatment strategy for both primary and secondary prevention of CVD. However, the optimal treatment strategy for patients who cannot tolerate statin therapy or those who need additional lipid-lowering therapy is unclear in light of recent evidence that demonstrates a lack of improved cardiovascular outcomes with combination therapy. The purpose of this review is to summarize and interpret evidence that evaluates nonstatin drug classes in reducing cardiovascular outcomes, to provide recommendations for use of nonstatin therapies in clinical practice, and to review emerging nonstatin therapies for management of dyslipidemia.

Methods: Relevant articles were identified through searches of PubMed, International Pharmaceutical Abstracts, and the Cochrane Database of Systematic Reviews by using the terms niacin, omega-3 fatty acids (FAs), clofibrate, fibrate, fenofibrate, fenofibric acid, gemfibrozil, cholestyramine, colestipol, colesevelam, ezetimibe, proprotein convertase subtilisin/kexin 9 (PCSK9), cholesteryl ester transfer protein (CETP), and cardiovascular outcomes. Only English language, human clinical trials, meta-analyses, and systematic reviews were included. Additional references were identified from citations of published articles.

Findings: Niacin may reduce cardiovascular events as monotherapy; however, recent trials in combination with statins have failed to show a benefit. Trials with omega-3 FAs have failed to demonstrate significant reductions in cardiovascular outcomes. Fibrates may improve cardiovascular outcomes as monotherapy; however, trials in combination with statins have failed to show a benefit, except in those with elevated triglycerides (>200 mg/dL) or low HDL-C (<40 mg/dL). There is a lack of data that evaluates bile acid sequestrant in combination with statin therapy on reducing cardiovascular events. Ezetimibe–statin combination therapy can reduce cardiovascular outcomes in those with chronic kidney disease and following vascular surgery or acute coronary syndrome. Long-term effects of emerging nonstatin therapies (CETP and PCSK9 inhibitors) are currently being evaluated in ongoing Phase III trials.

Implications: Nonstatin therapies have a limited role in reducing cardiovascular events in those maintained on guideline-directed statin therapy. In certain clinical situations, such as patients who are unable to tolerate statin therapy or recommended intensities of statin therapy, those with persistent severe elevations in triglycerides, or patients with high cardiovascular risk, some nonstatin therapies may be useful in reducing cardiovascular events. Future research is needed to evaluate the role of nonstatin therapies in those who are unable to tolerate guideline-directed statin doses. (*Clin Ther*. 2015;▮:▮▮▮–▮▮▮)

Key words: non-statin therapy, niacin, omega-3 fatty acid, ezetimibe, fenofibrate, bile acid sequestrant.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the United States, accounting for more than one-third (33.6%) of all deaths.[1] Death rates from CVD have declined in the United States because of the greater recognition of CVD risk factors and use of effective lipid-lowering therapies. However, questions remain regarding the optimal approach for further reducing morbidity and mortality

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associated with CVD. Recently published cholesterol treatment guidelines emphasize the use of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) as the preferred treatment strategy for both primary and secondary prevention of atherosclerotic cardiovascular disease.[2,3] Nonstatin therapies (e.g., nicotinic acid, fibrates, omega-3 fatty acids [FAs], bile acid sequestrants [BAS], cholesterol absorption inhibitors) have previously been recommended for use in combination with statins to achieve LDL-C goals, raise non–HDL-C levels, treat severe triglyceride (TG) elevations, and raise HDL-C levels.[4] However, there is a lack of evidence to support the combination of nonstatin drugs with statin therapy to further reduce atherosclerotic CVD events.[2] Furthermore, recent clinical trials have cast doubt on the effectiveness of nonstatin therapies in reducing cardiovascular morbidity and mortality in high-risk individuals.[5–7] Despite the lack of evidence supporting a continued role for nonstatin medications in those maintained on appropriate intensity of statin therapy, certain patients may have an insufficient responses, contraindications to, or intolerance of preferred statin therapy. The use of nonstatin therapies may be considered in these clinical scenarios. The purpose of this review is to summarize and interpret the evidence that evaluates nonstatin drug classes in reducing cardiovascular events, to provide recommendations for use of nonstatin therapies in clinical practice, and to review emerging nonstatin therapies for management of dyslipidemia.

MATERIALS AND METHODS

PubMed, International Pharmaceutical Abstracts, and the Cochrane Database of Systematic Reviews were searched using the following terms: niacin, omega-3 FAs, clofibrate, fibrate, fenofibric acid, fenofibrate, gemfibrozil, cholestyramine, colestipol, colesevelam, ezetimibe, proprotein convertase subtilisin/kexin 9 (PCSK9), cholesteryl ester transfer protein (CETP), and cardiovascular outcomes. Only English language human clinical trials, meta-analyses, and systematic reviews, published between 1970 and June 30, 2015, were included. Additional trials and reviews were identified from citations of published articles.

RESULTS

Nicotinic Acid (Niacin)

Nicotinic acid, or "niacin," strongly inhibits diacylglycerol acyltransferase-2, which reduces TG synthesis and lowers circulating LDL-C levels. Niacin also reduces hepatic catabolism of HDL-C.[8] Niacin can reduce LDL-C by 5% to 25%, TG by 20% to 50%, and is the most effective agent for increasing HDL-C.[4] Common adverse effects with niacin include cutaneous flushing, increases in glucose, uric acid, and hepatic transaminases, and gastrointestinal symptoms.[4] In clinical practice, niacin is often used in combination with statin therapy in those with suboptimal HDL-C levels (although evidence is lacking to support this practice), inadequate reductions in LDL-C, or in those unable to tolerate statin therapy.

A total of 14 relevant randomized controlled trials (RCTs), meta-analyses, and systematic reviews were identified that evaluated the effects of niacin alone or in combination with other lipid-lowering therapies on cardiovascular outcomes (**Table I**). The first study to evaluate the effect of niacin on all-cause mortality and mortality from cardiovascular causes was the Coronary Drug Project (CDP).[9] Immediate-release niacin (up to 3 g/day) did not significantly reduce all-cause mortality; however, patients in the niacin group had a significantly lower incidence of nonfatal myocardial infarction (MI) (niacin 8.9%, placebo 12.2%; $P < 0.005$). A 15-year follow-up of patients from the CDP found significantly fewer deaths in those randomized to niacin ($P = 0.0004$).[10] Median survival time was increased for those randomized to niacin, which was largely driven by a reduction in coronary heart disease (CHD). The survival benefit with niacin was evident despite the nearly 30% of the niacin-treated patients who adhered poorly to the treatment regimen (defined as taking <60% of the protocol amount of drug). The only other study designed to evaluate effects of niacin on cardiovascular outcomes was the Stockholm Ischemic Heart Disease study.[11] After 5 years of follow-up, the niacin–clofibrate group demonstrated a 26% reduction in total mortality versus placebo ($P < 0.05$). However, the incremental effects of niacin on these outcomes could not be determined because it was studied in combination with clofibrate.

From 1987 to 2009, several RCTs demonstrated the beneficial effects of immediate or extended-release niacin (up to 4 g/day) in combination with other lipid-lowering agents on surrogate outcomes (changes in angiographically confirmed stenosis or carotid intima-media thickness) in populations with established coronary artery disease (CAD).[12–18] The reduced risk of composite cardiovascular endpoints or individual cardiovascular events in these RCTs is difficult to