For years, niacin and fibrates have been recommended as add-on therapy to statin treatment in patients not meeting their lipid goals. The evidence to support this practice has been murky, with insufficient data to support a benefit in clinically meaningful outcomes. Based on the evolving body of knowledge, the manufacturers of extended-release niacin and delayed-release fenofibric acid voluntarily ceased marketing these products for use with statins last year. However, widespread prescribing of such combinations has continued.

In late April, the US Food and Drug Administration (FDA) took regulatory action to formally withdraw the indication for co-administration of niacin or fenofibric acid with statin drugs, and to remove two niacin-statin combinations from the market. The article that follows will summarize the FDA’s decision and the trial data upon which it was based. In addition, clinical practice guidance that addresses the benefit of LDL-lowering therapy in the elderly will be briefly reviewed.

Recent FDA Action
In taking action against niacin and fibrates, the FDA published two separate documents in the Federal Register. The first, Docket No. FDA-2016-N-1127, withdraws approval of the indications related to co-administration with a statin for extended-release niacin tablets and delayed-release fenofibric acid capsules. Affected products appear in Box 1 below.

Prior to issuing this notice, the FDA reviewed the results of large scale clinical trials of cardiovascular outcomes. Although niacin and fibrates improved lipid biomarkers, no incremental benefit in cardiovascular morbidity or mortality was seen when compared to statin monotherapy. Therefore, the FDA concluded that “the totality of the scientific evidence no longer supports that a drug-induced reduction in triglyceride levels and/or increase in HDL-cholesterol levels in statin-treated patients results in a reduction in the risk of cardiovascular events.” As such, the benefits of adding niacin or fenofibric acid to the profile of a statin-treated patient no longer outweighs the risks, and these combinations should be avoided.

In accordance with this decision, the FDA also published Docket No. FDA-2016-N-1097, which withdraws approval of the New Drug Applications for the branded products Advicor (a fixed-dose niacin extended-release and lovastatin combination) and Simcor (a fixed-dose niacin extended-release and simvastatin combination), both marketed by AbbVie (see Box 1). Because these products were withdrawn due to reasons of safety and effectiveness, the FDA will no longer accept New Drug Applications which reference Advicor and Simcor.
This action by the FDA does not impact other approved indications of niacin and fibrate products. Extended-release niacin remains approved for several indications, presented in Box 2 below.\textsuperscript{5} Delayed-release fenofibric acid remains approved for the treatment of severe hypertriglyceridemia, primary hypercholesterolemia, or mixed dyslipidemia as adjunctive therapy to diet.\textsuperscript{6}

<table>
<thead>
<tr>
<th>Name</th>
<th>Manufacturer(s)</th>
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<tbody>
<tr>
<td>Niaspan\textsuperscript{®}</td>
<td>AbbVie</td>
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<td>Trilipix\textsuperscript{®}</td>
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<tr>
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<td>Simcor\textsuperscript{®}</td>
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Supporting Trial Data

The FDA cited three clinical trials in their decision to withdraw the indication for co-administration of niacin or fenofibric acid with statin drugs: ACCORD, AIM-HIGH, and HPS2-THRIVE.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group aimed to compare statin monotherapy to combination therapy with a statin plus a fibrate in patients with type 2 diabetes.\textsuperscript{7} Over 5500 patients, with a mean age of 62 years, were randomized to receive either fenofibrate or placebo in addition to open-label simvastatin. The primary outcome of the ACCORD study was a composite of nonfatal myocardial infarction (MI), nonfatal stroke, and death from cardiovascular causes.
Although fenofibrate significantly improved HDL cholesterol and triglyceride levels compared to placebo, there was no difference in the rates of clinical cardiovascular outcomes. The annual rate of the primary outcome was 2.2% in the fenofibrate group, compared to 2.4% in the placebo group (hazard ratio = 0.92, 95% CI 0.79-1.08, p=0.32). In type 2 diabetics at high risk of cardiovascular disease, the addition of fenofibrate to simvastatin therapy did not reduce the rate of fatal or nonfatal cardiovascular events.

AIM-HIGH represents the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes trial. In AIM-HIGH, more than 3400 patients with established cardiovascular disease were randomized to receive extended-release niacin 1500-2000mg/day or placebo. All patients also received high-intensity simvastatin therapy, with or without ezetimibe, targeting a goal LDL cholesterol level of 40-80mg/dL. Mean age of the AIM-HIGH trial participants was 64 years. The primary outcome was a composite of death from coronary heart disease, nonfatal MI, ischemic stroke, hospitalization for an acute coronary syndrome, and coronary or cerebral revascularization. After 3 years, the AIM-HIGH trial was stopped early due to a lack of efficacy in the niacin group. While niacin significantly improved HDL, triglyceride, and LDL levels, no improvement was seen in cardiovascular outcomes. The primary outcome occurred in 16.4% of patients in the niacin group, compared to 16.2% in the placebo group (hazard ratio = 1.02, 95% CI 0.87-1.21, p=0.79). Therefore, niacin offered no additional clinical benefit in patients with cardiovascular disease receiving high-intensity statin therapy.

The Heart Protection Study 2 – Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) was published in 2014. HPS2-THRIVE enrolled over 25000 patients with atherosclerotic vascular disease and a mean age of 65 years. In addition to simvastatin therapy with or without ezetimibe, patients were randomized to receive either extended release niacin 2000mg/day plus 40mg laropiprant, or placebo. Laropiprant is a prostaglandin antagonist designed to reduce flushing from niacin, but has never been approved for use in the United States. The primary outcome of AIM-HIGH was the first occurrence of a major vascular event, defined as nonfatal MI, death from coronary causes, stroke, or arterial revascularization. After four years, niacin plus laropiprant significantly improved LDL and HDL levels compared to placebo. However, no effect was seen with regard to the primary outcome; major vascular events occurred in 13.2% of patients in the niacin group, compared to 13.7% in the placebo group (rate ratio = 0.96, 95% CI 0.90-1.03, p=0.29). Treatment with niacin plus laropiprant was associated with a significant increase in the risk of serious adverse events, including gastrointestinal disorders, musculoskeletal problems (including myopathy), infections, bleeding, and a loss of diabetes control.

In patients receiving simvastatin, the ACCORD, AIM-HIGH, and HPS2-THRIVE studies found that improvements in HDL and triglycerides from fenofibrate or niacin were not associated with an incremental benefits in clinical cardiovascular outcomes. This consistent evidence from large scale, high-quality clinical trials formed the basis for the FDA’s recent actions. Like most clinical trials of lipid-modifying therapy, ACCORD and HPS2-THRIVE excluded patients aged greater than 80 years. Thus, important questions remain about the benefit of LDL-lowering treatments in many elderly patients.
Clinical Practice Guidance

Clinical practice guidance on the management of hyperlipidemia is issued by the American College of Cardiology and American Heart Association (ACC/AHA). The ACC/AHA guidelines, released in 2013, were designed to update and replace the guidance previously published by the National Cholesterol Education Program (known as NCEP-ATP III). ACC/AHA focuses on cardiovascular risk reduction in four specific groups of patients who have been shown to benefit from statin therapy. According to the guidelines, nonstatin therapies do not provide acceptable cardiovascular risk reduction relative to their safety profile, and should be reserved as adjuncts to maximally tolerated statin doses when additional LDL-lowering is needed.

The “statin benefit groups” identified by ACC/AHA include: 1) patients with clinical atherosclerotic cardiovascular disease (ASCVD), defined as acute coronary syndromes, history of myocardial infarction, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin; 2) patients with primary elevations of LDL cholesterol ≥190mg/dL; 3) patients aged 40-75 years with diabetes who do not have clinical ASCVD but with LDL cholesterol 70-189mg/dL; and 4) patients aged 40-75 years without diabetes or clinical ASCVD with LDL cholesterol 70-189mg/dL and an estimated 10-year ASCVD risk of ≥7.5%. Most individuals within these groups should receive high-intensity statin therapy. Of note, ACC/AHA found insufficient evidence to support the use of specific LDL or non-HDL cholesterol targets. Therefore, they consider intensity of statin therapy the goal of treatment rather than target ranges of any biomarker. This is in contrast to the previous NCEP-ATP III guidelines, which set LDL goals of <100mg/dL for high risk patients and <70mg/dL for very high risk patients.

ACC/AHA also provides guidance on lipid lowering in patients ≥75 years of age. For secondary prevention in elderly patients with clinical ASCVD, expert opinion suggests that it is reasonable to weigh the benefits and risks of treatment before initiating a moderate- or high-intensity statin. If patients are already tolerating statin therapy, it should be continued. Because age >75 years is a predisposing factor for statin adverse effects, caution should be used when initiating statin therapy for any indication in these patients.

Because this guidance is somewhat broad, there remains confusion about when institutionalized elderly patients should be screened and treated for hyperlipidemia. In 2012, the American Medical Directors Association (AMDA) issued clinical practice guidelines for health maintenance in the long-term care setting. These guidelines recommend initial screening for dyslipidemia in elderly patients who have not previously been screened. Repeat screening is less important in patients older than 65 years, as lipid levels are unlikely to change after this time. Total cholesterol levels are less predictive of coronary heart disease risk in older adults than in younger patients. In addition, secondary causes of hypercholesterolemia should be considered. In elderly patients, these often include liver or kidney disease, hypothyroidism, and use of atypical antipsychotics.
AMDA guidelines recommend treatment of identified hyperlipidemia in older adults for secondary prevention of cardiovascular events, including patients aged greater than 75 years. Although randomized controlled trials of antihyperlipidemics have excluded patients older than 80 years, cohort trial data suggests that these individuals may experience more benefit from LDL-lowering therapy than those younger than 80 years. While AMDA generally supports the use of LDL-lowering therapy in long-term care patients, the guidelines conclude that evidence for this population is limited and treatment recommendations should therefore be individualized.

In order to individualize therapy in elderly patients, the patient’s overall condition and treatment goals must be considered. Statin therapy is not appropriate in patients with palliative goals of care, or for whom therapy is focused on symptomatic management. Estimates of the time to benefit from statin treatment have ranged from 1-3 years; therefore, life expectancy must also be taken into account. Degree of frailty may be more useful than chronological age, as it can offer a better representation of the patient’s clinical condition.

Because older adults are likely to have multiple comorbid conditions, the potential for morbidity and drug-drug or drug-disease interactions may lower the benefit-risk ratio of LDL-lowering therapy. Non-statin therapies may aggravate comorbid conditions in elderly patients. For example, niacin can cause facial flushing that aggravates rosacea or increase uric acid levels, leading to exacerbations of gout.

There is conflicting evidence regarding the safety of statin drugs in elderly patients, but data suggests that age greater than 80 years increases the risk of statin-induced myopathy. Therefore, greater caution is warranted when initiating or titrating drug therapy in this group. Gemfibrozil exhibits multiple pharmacokinetic interactions with statin drugs, increasing the risk of myopathy. Lipid-lowering therapy should be discontinued in elderly patients when there are adverse effects which impair quality of life and cannot be managed by dose reduction or switching agents.

References
References, Continued


