

CLINICAL INQUIRIES

What are effective medication combinations for dyslipidemia?

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EVIDENCE-BASED ANSWER

Many combination drug therapies are effective in treating dyslipidemia. Compared with statin monotherapy, combinations that include ezetimibe (Zetia), a bile acid sequestrant, or niacin further lower low-density lipoprotein (LDL) cholesterol (strength of recommendation [SOR]: **A**), and increase the likelihood of attaining National Cholesterol Education Program (NCEP) LDL cholesterol goals (SOR: **B**). Adding ezetimibe to a bile acid sequestrant reduces LDL cholesterol (SOR: **B**). Fibrate or niacin added to statin monotherapy provide mixed lipid-modifying

effects for combined dyslipidemia (SOR: **A**).

Most combination therapies increase the risk of intolerance or side effects, including myopathy. The statin/gemfibrozil combination has the highest risk of myopathy, whereas statin/ezetimibe or statin/bile acid sequestrant have the least increased risk (SOR: **B**). Studies evaluating patient-oriented outcomes (morbidity, mortality) with combination therapy vs monotherapy have not yet been conducted; however, combination therapies have demonstrated reduced atherosclerotic lesion progression.

CLINICAL COMMENTARY

When statins alone don't work, think before writing a second prescription

When patients are unable to reach their lipid goal on a single medication, they should first be evaluated for dietary noncompliance before adding another medication that can be difficult to manage. Unfortunately, the older bile acid sequestrants have multiple drug interactions (ie, warfarin, digitalis, phenobarbital), and patients dislike them, since they must remember to take other medications >1 hour before or >4 hours later (these problems are not seen with colesevelam, a newer drug). Some physicians are reluctant to prescribe

statin/fibrate combinations due to the interaction of gemfibrozil with statins; plus, patients must forego grapefruit juice with fibrates to avoid toxicity. Niacin has a low risk of toxicity, but fears of flushing may give patients pause (premedication with aspirin can reduce flushing). Ezetimibe/statins are effective, have relatively low toxicity and are convenient due to availability of commercial combinations. When choosing medications, think carefully about the patient before prescribing another lipid-lowering medication.

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■ Evidence summary

Hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitors, better known as statins (atorvastatin, fluvastatin, lovastatin, rosuvastatin, pravastatin, simvastatin), have been shown to lower LDL cholesterol in the primary and secondary prevention of cardiovascular disease. Although often effective as monotherapy, combination regimens

may be needed to reach LDL cholesterol goals.¹⁻⁴ Ezetimibe, niacin, and bile acid sequestrants (cholestyramine [Questran], colesevelam [WelChol], colestipol [Colestid]) have complementary effects that suggest they may be appropriate for use in combination with a statin.

Adding a bile acid sequestrant to statin monotherapy does not appear to increase the risk of systemic toxicity.⁵

A systematic review found that adding colestipol or cholestyramine to a statin provides an additional 7% to 20% absolute LDL cholesterol reduction.¹ A randomized placebo-controlled trial demonstrated that combination therapy with colesvelam has similar effects. The absolute LDL cholesterol reduction of with atorvastatin (Lipitor) alone (10 mg daily) increased from 38% to 48% after adding colesvelam 3.8 g daily (10% absolute LDL cholesterol reduction).⁶

Statin/ezetimibe combination therapy is FDA-approved, and provides an additional 12% to 21% absolute LDL cholesterol reduction.² Although considered safe, adding ezetimibe increases the incidence of elevated hepatic transaminases from 0.4% to 1.3%.⁷ A double-blind trial randomized 769 patients on statin monotherapy who were above their NCEP LDL goal to either placebo or ezetimibe 10 mg daily.³ Absolute LDL cholesterol reductions were 25.1% with ezetimibe vs 3.7% with placebo, and LDL goal attainment was 71.5% with ezetimibe vs 18.9% with placebo (secondary endpoint). In one retrospective analysis, ezetimibe provided a 19% absolute LDL cholesterol reduction when added to a bile acid sequestrant.⁸

Combinations of statins with fibrates (fenofibrate [Tricor], gemfibrozil [Lopid]) can treat combined dyslipidemia by decreasing LDL cholesterol more than 40%, decreasing triglycerides over 50%, and raising high-density lipoprotein (HDL) cholesterol more than 20%.⁹ Prospective controlled trials have shown regression of atherosclerotic lesions with this combination, but have also shown increased risks of myopathy.^{6,10} In an analysis of 36 controlled clinical trials (1674 patients) that evaluated statin-fibrate combinations, 0.12% of patients developed myopathy, but none developed rhabdomyolysis or kidney failure.¹⁰ Experts believe myopathy risk is greater with gemfibrozil than fenofibrate, based on gemfibrozil's inhibition of statin glucuronidation, and case reports in the lit-

TABLE
Commonly used combination therapies with estimated changes in lipid values

COMBINATION	CHANGE IN LDL-C	CHANGE IN HDL-C	CHANGE IN TGD
Statin/bile acid sequestrant	↓↓↓	↑	↓
Statin/ezetimibe	↓↓↓	↑	↓
Statin/fibrate	↓↓	↑↑	↓↓↓
Statin/niacin	↓↓↓	↑↑↑	↓↓↓
Ezetimibe/bile acid sequestrant	↓↓	↑	↓

Key: One arrow, small change; 2 arrows, moderate change; 3 arrows, large change. LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TGD, triglycerides

erature.⁵ Accordingly, the maximum approved daily doses of lovastatin (Mevacor), simvastatin (Zocor), and rosuvastatin (Crestor) are lowered (20, 10, and 10 mg, respectively) when used with gemfibrozil.

Adding niacin to statin monotherapy can modify combined dyslipidemia as does a statin/fibrate combination, by lowering LDL cholesterol and triglycerides, and raising HDL cholesterol to an even greater extent. Patients are more intolerant to a statin/niacin combination (eg, flushing) than to a statin/fibrate combination, but have a lower risk of myopathy with the former.⁵ The combination of statin/niacin may be more desirable than statin/fibrate for patients with more severe mixed dyslipidemia, especially those with very low HDL cholesterol values, when monotherapy regimens are not completely effective. A fixed combination of lovastatin with extended-release niacin (Advicor) is commercially available.^{4,11}

Recommendations from others

The NCEP Adult Treatment Panel III recommends adding a bile acid sequestrant, niacin, or ezetimibe to a statin when additional LDL cholesterol-lowering is needed to reach NCEP-III goals, and adding niacin or a fibrate to a statin to lower non-HDL cholesterol for patients with

FAST TRACK

Ezetimibe, niacin, and bile acid sequestrants have complementary effects in combination with a statin

persistently high triglycerides or low HDL cholesterol.^{12,13}

The American Association of Clinical Endocrinologists also recommends using these combinations for the following circumstances: severe dyslipidemia, inadequate response to monotherapy, dose-dependent adverse effects, and certain mixed dyslipidemias.¹⁴ However, the clinical advisory on statins by American Heart Association/American College of Cardiology/National Heart, Lung and Blood Institute warns that statin/fibrate combinations (especially with gemfibrozil) or statin/niacin (although rare) are risk factors for statin-associated myopathy.⁵

REFERENCES

- Schechtman G, Hiatt J. Dose-response characteristics of cholesterol-lowering drug therapies: implications for treatment. *Ann Intern Med* 1996; 125:990-1000.
- Jeu L, Cheng JW. Pharmacology and therapeutics of ezetimibe (SCH 58235), a cholesterol-absorption inhibitor. *Clin Ther* 2003; 25:2352-2387.
- Gagne C, Bays HE, Weiss SR, et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. *Am J Cardiol* 2002; 90:1084-1091.
- Hunninghake DB, McGovern ME, Koren M, et al. A dose-ranging study of a new, once-daily, dual-component drug product containing niacin extended-release and lovastatin. *Clin Cardiol* 2003; 26:112-118.
- Pasternak RC, Smith SC Jr, Bairey-Merz CN, Grundy SM, Cleeman JI, Lefant C. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002; 40:567-572.
- Hunninghake D, Insull W Jr, Toth P, Davidson D, Donovan JM, Burke SK. Coadministration of colesevelam hydrochloride with atorvastatin lowers LDL cholesterol additively. *Atherosclerosis* 2001; 158:407-416.
- Zetia [package insert]. North Wales, Pa: Merck-Schering-Plough Pharmaceuticals; March 2005.
- Xydakis AM, Guyton JR, Chiou P, Stein JL, Jones PH, Ballantyne CM. Effectiveness and tolerability of ezetimibe add-on therapy to a bile acid resin-based regimen for hypercholesterolemia. *Am J Cardiol* 2004; 94:795-797.
- Xydakis AM, Ballantyne CM. Combination therapy for combined dyslipidemia. *Am J Cardiol* 2002; 90(10B):21K-9K.
- Shek A, Ferrill MJ. Statin-fibrate combination therapy. *Ann Pharmacother* 2001; 35:908-917.
- Insull W, Jr., McGovern ME, Schrott H, et al. Efficacy of extended-release niacin with lovastatin for hypercholesterolemia: assessing all reasonable doses with innovative surface graph analysis. *Arch Intern Med* 2004; 164:1121-1127.
- Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; 285:2486-2497.
- Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004; 110:227-239.
- AACE medical guidelines for clinical practice for the diagnosis and treatment of dyslipidemia and prevention of atherogenesis. *Endocr Pract* 2000; 6:162-213.

FAST TRACK

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