The Role of Nonstatin Therapy in Managing Hyperlipidemia
JONATHAN R. MURROW, MD, Medical College of Georgia—University of Georgia Medical Partnership, Athens, Georgia

Hyperlipidemia is a potent biomarker for predicting the development of cardiovascular disease.\(^1,2\) Reducing low-density lipoprotein (LDL) cholesterol levels with statin use improves morbidity and mortality.\(^3,4\) Although statins are generally safe, up to 10 percent of patients who are prescribed statin therapy experience toxicity that leads to the discontinuation of therapy.\(^5\) In other patients, optimal statin dosing fails to achieve lipid-lowering goals.\(^6\) Accordingly, when treating hyperlipidemia, physicians often face the question of the clinical value of nonstatin drugs, including bile acid sequestrants, fibrates (fibrin acid derivatives), niacin, and cholesterol-absorption inhibitors. This editorial highlights the most prominent trial data and examines the merit of these drugs in the primary and secondary prevention of heart disease.

Cholestyramine (Questran) is a bile acid sequestrant that inhibits cholesterol absorption. In the Lipid Research Clinics Coronary Primary Prevention Trial, cholestyramine reduced LDL cholesterol levels by 12.6 percent compared with placebo.\(^6\) In 3,806 men with hyperlipidemia, cholestyramine therapy led to a 19 percent relative reduction in the combined end point (i.e., definite coronary heart disease death, nonfatal myocardial infarction [MI], or both) compared with the control group over a 7.4-year follow-up period.

Fibrates lower LDL cholesterol levels by perturbing triglyceride metabolism. Studies of gemfibrozil (Lopid) and fenofibrate (Tricor) suggest a potential benefit of fibrates on cardiovascular risk. The Helsinki Heart Study compared gemfibrozil with placebo in 4,081 men with hyperlipidemia, and found a 34 percent reduction in the incidence of definite coronary heart disease death, nonfatal MI, or both in the fibrate group at the five-year follow-up.\(^7\) In a secondary prevention trial of 2,531 men with coronary heart disease followed for 5.1 years, participants treated with gemfibrozil showed a 22 percent relative reduction in MI or cardiac death compared with the control group.\(^8\) A secondary prevention study of 9,795 high-risk patients treated with fenofibrate versus placebo found a 24 percent reduction in nonfatal MI in the fenofibrate group.\(^9\) Notably, a 2009 systematic review of 20 clinical trials found that fibrate therapy for hyperlipidemia offers a reduction in nonfatal MI, although overall mortality is not affected.\(^10\)

Niacin lowers LDL cholesterol levels by influencing very-low–density lipoprotein metabolism. In the Coronary Drug Project, patients with coronary heart disease receiving niacin were followed over 15 years, and were found to have a lower all-cause mortality rate compared with those receiving placebo (52 versus 58 percent; \(P < .001; \text{number needed to treat} = 16\)).\(^11\) When combined with simvastatin (Zocor), extended-release niacin has been shown to attenuate progression of subclinical atherosclerosis (measured by carotid intima-media thickness) in persons with dyslipidemia.\(^12\) The clinical impact of niacin therapy, however, remains unresolved. An ongoing study seeks to compare the combination of simvastatin and extended-release niacin with simvastatin alone.\(^13\)

Ezetimibe (Zetia) selectively blocks gut uptake of cholesterol. Although it is safe and effective, the ability of ezetimibe to reduce cardiovascular risk remains unproven.\(^14\) In a study measuring subclinical atherosclerosis, ezetimibe did not attenuate progression of carotid intima-media thickness as an adjunct to simvastatin.\(^15\) Such intermediate end points, however, are of modest predictive value and should not necessarily be interpreted to dismiss the potential value of a drug. A multicenter study is underway to examine the effect of ezetimibe on reducing death, MI, or stroke.\(^16\)

Recent studies of statin therapy in patients with coronary heart disease have demonstrated a reduction in clinical events disproportionate to the degree of LDL–cholesterol lowering, which implies multiple mechanisms of action.\(^17\) Although intriguing, these observations do not necessarily overshadow the direct impact of LDL–cholesterol lowering on attenuating cardiovascular risk. Likewise, they do not invalidate the role of nonstatin drugs in the management of hyperlipidemia. Even in the absence of robust clinical trial...
data, rational management of risk involves weighing the cholesterol−lowering effects of statin and nonstatin drugs against the potential for adverse effects. Uncontrolled cholesterol levels, like uncontrolled blood pressure, signify elevated cardiovascular risk and deserve an appropriate response.

Address correspondence to Jonathan R. Murrow, MD, at jmurrow@mcg.edu. Reprints are not available from the author.

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REFERENCES


