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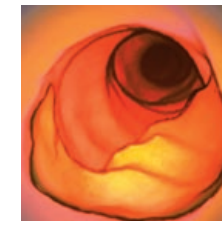

Current Recommendations for the Treatment of Dyslipidemia

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Objectives

- Describe the importance of understanding the impact of controlling dyslipidemia.
- Review the most recent Adult Treatment Panel III report recommendations for cholesterol testing and management.
- Discuss the relevant polytherapy options for dyslipidemia.

Abstract

Cardiovascular risk is independently increased by abnormalities in low-density and high-density lipoprotein-cholesterol and triglycerides. Many patients have more than one lipid abnormality. Combination therapy with lipid-modifying agents offers an important therapeutic option for improving the overall lipid profile. Combinations have demonstrated additive efficacy and significant reductions in coronary events. Health care providers who understand combination therapy can play an important role in the effective use of these treatment options for dyslipidemia.

Introduction

Coronary heart disease (CHD) affects approximately 12.9 million Americans and is the primary cause of death in both men and women. In 2000, 681,100 people (more than one in five) died as a result of CHD.[1] Dyslipidemia is one of the most important modifiable risk factors for CHD.[2] Many patients with CHD or who are at risk for CHD have more than one lipid abnormality, each of which increases cardiovascular risk. In one study of men with CHD, 87% had low-density lipoprotein-cholesterol (LDL-C) levels of 100 mg/dl or more, 64% had high-density lipoprotein cholesterol (HDL-C) below 40 mg/dl, and 33% had triglyceride levels above 200 mg/dl. Of the 58% of patients with CHD who were not definite candidates for lipid-modifying therapy (LDL-C below 130 mg/dl), 41% had HDL-C levels below 35 mg/dl.[3]

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In another survey, low HDL-C levels (below 40 mg/dl in men and below 50 mg/dl in women) were the second most common metabolic abnormality (in 35% of men and in 39% of women), after abdominal obesity, found in adults over the age of 20 living in the U.S.[4]

Clinical trial results have indicated that for every 1% reduction in LDL-C, the risk of CHD is reduced by 1%.[5–9] Although reducing LDL-C remains the primary target of therapy, the focus of treatment must turn to correcting other lipid abnormalities after patients are at or near their LDL-C goal. Both low HDL-C and elevated triglyceride levels have been shown to independently predict CHD risk.[10–12]

HDL-C itself has been correlated with CHD events regardless of total cholesterol (TC) or LDL-C levels,[10,11] and each 1% increase in HDL-C level has been associated with a 2% to 3% decrease in CHD events.[13] In fact, some data demonstrate that low HDL-C might be a better predictor of risk than elevated LDL-C.[10]

Triglyceride levels have also been shown to correlate with CHD risk, independent of other lipid parameters. One multivariate analysis found that an increase of 1 mmol/L in triglycerides increased the risk of cardiovascular disease by 14% in men and by 37% in women.[12]

In view of these findings, health care providers should take the entire lipid profile into account when managing dyslipidemia in their patients. Available treatment options allow the selection of therapy to target specific lipid abnormalities. Combining lipid-modifying drugs offers an important option for correcting multiple lipoprotein abnormalities and for treating patients who are currently not meeting lipid goals with monotherapy.

Health care providers who are aware of the efficacy and safety profiles of lipid-modifying agents and their use in combination can play a vital role in the effective management of dyslipidemia. This article reviews current treatment recommendations, the rationale behind using combination lipid-modifying therapy, and the benefits of combining available agents. It concludes with some practical advice regarding dyslipidemic therapy.

Classification of Patients: Adult Treatment Panel III

Updated recommendations for cholesterol testing and management were presented in the Third Report of the Expert

Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Adult Treatment Panel III (ATP III).[14] There have been several important changes from the previous recommendations. The updated guidelines:

1. Set new definitions for optimal LDL-C and low HDL-C concentrations and emphasize the importance of moderate triglyceride elevations (Table 1). To identify patients who might be candidates for more aggressive management, because of the presence of multiple CHD risk factors (more than two), clinicians are advised to calculate a patient's 10-year CHD risk using a modified Framingham point scale.
2. Establish a new category *(CHD risk equivalent)* that identifies conditions placing patients at the same high cardiovascular risk as those with established CHD and, consequently, warrant the same aggressive management (e.g., diabetes mellitus, other atherosclerotic disease, and a 10-year CHD risk greater than 20%.[2]
3. Consider the cardiovascular implications of the *metabolic syndrome*, an increasingly common risk factor complex characterized by abdominal obesity, atherogenic dyslipidemia (low HDL-C, elevated triglycerides, and small, dense LDL particles), hypertension, insulin resistance, and prothrombotic and proinflammatory states. This syndrome is present when three or more of the associated risk factors are present (Table 2).[2]

ATP III recognizes the increased cardiovascular risk carried by patients with the metabolic syndrome and recommends treating the individual components in such patients after the LDL-C goals have been achieved.[2] This may include treatment of the underlying cause of insulin resistance, obesity, and physical inactivity as well as management of hypertension, aspirin for prothrombotic and proinflammatory states, and perhaps drugs to lower glucose. However, evidence for the benefits of glucose-lowering drugs is currently lacking.

A *therapeutic lifestyle change* is advocated as the first step in reducing cardiovascular risk in all patients, especially those with metabolic syndrome. Unfortunately, in many patients, lifestyle changes are inadequate for reaching target lipid levels and drug therapy is required. Such changes, however, should be continued and periodically reinforced whether or not the patient has begun pharmacotherapy.[2]

Table 1 Classification of LDL-Cholesterol, HDL-Cholesterol, Total Cholesterol, and Triglyceride Levels

LDL-cholesterol (mg/dl)	
<100	Optimal
100–129	Near or above optimal
130–159	Borderline high
160–189	High
≥190	Very high
HDL-cholesterol (mg/dl)	
<40	Low
≥60	High
Total cholesterol (mg/dl)	
<200	Desirable
200–239	Borderline high
≥240	High
Triglycerides (mg/dl)	
<150	Normal
150–199	Borderline high
200–499	High
≥500	Very high

LDL = low-density lipoprotein; HDL = high-density lipoprotein.
Adapted from the Adult Treatment Panel III (ATP III). *JAMA* 2001; 285:2486–2497.[14]

Table 2 Diagnosis of the Metabolic Syndrome

Risk Factor	Defining Level
Abdominal obesity (waist circumference)	
Men	>102 cm (more than 40 inches)
Women	>88 cm (above 35 inches)
Triglycerides	≥ 150 mg/dl
High-density lipoprotein cholesterol	
Men	< 40 mg/dl
Women	< 50 mg/dl
Blood pressure	130/85 mm Hg or higher
Fasting glucose	110 mg/dl or higher

Adapted from the Adult Treatment Panel III (ATP III). *JAMA* 2001; 285:2486–2497.[14]

Lipid Metabolism

The synthesis of cholesterol by the liver is the primary source of circulating cholesterol. For cholesterol and other fatty substances (such as triglycerides) to be transported from the liver into the bloodstream, the cholesterol must first be assembled into a lipoprotein–cholesterol complex. This complex contains an inner core of cholesterol esters and triglycerides and an outer, hydrophilic coat composed of phospholipids, unesterified cholesterol, and at least one protein that allows the lipoprotein to interact at cell surfaces.

The three major lipoproteins are (1) very-low-density lipoprotein (VLDL), (2) LDL, and (3) HDL. VLDL carries approximately 20% of the total cholesterol in the systemic circulation and most of the triglycerides; LDL carries 60% to 70% of the total cholesterol. Once LDL-C is in the bloodstream, it is either removed from the systemic circulation by hepatic uptake or taken up by peripheral cells, where it may contribute to the development of atherosclerosis.

HDL particles transport cholesterol from peripheral cells back to the liver for removal or for transfer of the cholesterol to circulating LDL and VLDL particles. In each instance, cholesterol is removed from vascular tissue, decreasing the development of atherosclerosis and CHD. This process is known as *reverse cholesterol transport* and makes high concentrations of HDL-C desirable.[15]

Lipid Modification

Five classes of drugs are available for the treatment of dyslipidemia, each with different effects on the various lipid and lipoprotein parameters (Table 3):[14,16,17]

1. *Statins* are the most potent drugs available for reducing LDL-C. They bring about moderately lower triglyceride levels and modestly increase HDL-C levels. Most of the lowering effect of statins on LDL-C can be obtained with relatively low doses with less incremental benefit as doses are increased.[18]
2. *Bile acid sequestrants* mainly affect LDL-C. They have minimal effects on HDL-C and little or no effect on triglyceride concentrations. These drugs are a good option for patients who are intolerant of statins or whose condition is refractory to them.[2]
3. Of the available agents, *niacin* (vitamin B_3) has the most powerful effect on HDL-C levels; it is the only agent that improves all components of the lipid profile. It moderately lowers LDL-C and triglyceride levels and increases LDL particle size. Niacin is the only drug that decreases lipoprotein(a) levels, which the ATP III guidelines recognize as an emerging risk factor for CHD. Niacin is recommended for patients with isolated low HDL-C levels and atherogenic dyslipidemia.[2]
4. *Fibrates* exert their greatest effects on triglyceride levels, have moderate effects on HDL-C and mild effects on LDL-C,[2] and increase LDL particle size.[19] Fibrates are recommended for patients with hypertriglyceridemia and atherogenic dyslipidemia.[2]
5. *Cholesterol absorption inhibitors* are a new class of lipid-modifying agents. They lower LDL-C concentrations by almost 20%, regardless of concurrent therapy, and have a modest effect on HDL-C and triglycerides.[16,20] Ezetimibe (Zetia™, Merck/Schering–Plough Pharmaceuticals), the first agent approved in this class, might be a good option for patients who do not tolerate or respond to statin therapy. This product is contraindicated in patients with active liver disease and in patients with hypersensitivity to any component of the drug.

Combination Therapy

The available lipid-modifying agents act at different stages of lipid metabolism. Combining these agents, thereby causing interruption at several points in the pathways simultaneously, has the potential for additive efficacy (Figure 1).[15,21–23] By combining agents that affect a patient's specific lipid abnormalities, health care providers can also target therapy to improve the overall lipid profile. Combination therapy is an important option for patients with persistent abnormalities of more than one component of the lipid profile and for patients who have not achieved their lipid goals with monotherapy.

Statins and Niacin

Among the possible combinations, a statin plus niacin has a favorable effect on all components of the lipid profile. Clinical studies have shown that treatment with statin–niacin therapy can reduce LDL-C levels by 29% to 44%,[24,25] reduce triglycerides by 15% to 39%,[26,27] and increase HDL-C levels by 14% to 36%.[26,28]

In 2002, the first single-tablet combination of a statin with niacin became available for the treatment of dyslipidemia, following the patterns of antihypertensive and antidiabetic therapy. This combination of extended-release (ER) niacin and lovastatin (e.g., Mevacor®, Merck, Sharpe & Dohme) in a once-at-bedtime formulation has been shown in clinical studies to exhibit additive efficacy over the combined effects of each drug alone.[29,30]

In a long-term study of 814 men and women with dyslipidemia, ER niacin–lovastatin reduced LDL-C levels by 47%, reduced triglyceride levels by 41%, and increased HDL-C levels by 41% at one year.[29] Compared with statin monotherapy, ER niacin–lovastatin 1,000/40 mg showed similar LDL-C–lowering efficacy to atorvastatin calcium (Lipitor®, Pfizer) 10 mg (38% for both) and greater LDL-C–lowering efficacy than simvastatin (Zocor®, Merck) 20 mg (42% vs. 35%; $P \leq .05$) in the ADvicor Versus Other Cholesterol-modulating Agents Trial Evaluation (ADVOCATE). It also raised HDL-C levels by a significantly greater extent than either statin alone.[31]

Statin–niacin therapy also improves clinical outcomes. Simvastatin plus niacin was studied in patients with CHD who

Table 3 Drugs That Affect Lipoprotein Metabolism

Drug Class or Agent	Lipid and Lipoprotein Effects		
	LDL-Cholesterol	*HDL-Cholesterol*	*Triglycerides*
Statins	↓ 18%–55%	↑ 5%–15%	↓ 7%–30%
Bile acid sequestrants	↓ 15%–30%	↑ 3%–5%	No change or increase
Niacin	↓ 5%–25%	↑ 15%–35%	↓ 20%–50%
Fibric acid	↓ 5%–20% (may be increased in patients with high triglyceride levels)	↑ 10%–20%	↓ 20%–50%
Cholesterol absorption inhibitors[16,17]	↓ 17%–19%	↑ 1%–4%	↓ 0–6%

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Data from the Adult Treatment Panel III (ATP III). *JAMA* 2001;285:2486–2497;[14] Bays HE, Moore PB, Drehobl MA, et al. *Clin Ther* 2001;23:1209–1230;[16] and Dujovne CA, Ettinger MP, McNeer JF, et al. *Am J Cardiol* 2002;90:1092–1097.[17]

had low HDL-C levels and normal LDL-C levels in the HDL–Atherosclerosis Treatment Study (HATS).[32] In patients receiving combination therapy, proximal coronary stenosis regressed slightly (0.4%); in patients receiving placebo, there was a 3.9% progression. The rate of clinical events, including death, myocardial infarction (MI), stroke, and revascularization, was reduced by 90% ($P = 0.03$) (Figure 2).[32]

Statins have proved to be very safe in most patients, but myopathy remains a concern (Table 4),[33] especially when statins are used in combination with other drugs. Statin–niacin combinations are well tolerated in clinical studies, and myopathy has rarely been reported.[33,34] In clinical trials with ER niacin–lovastatin, no cases of myopathy have been reported.[29–31] Furthermore, of 871 reports to the U.S. Food and Drug Administration (FDA) of statin-associated rhabdomyolysis, only four cases (0.46%) were associated with concomitant niacin use.[35]

Adverse hepatic effects have also been a concern with statin therapy, although the risk does not seem to be increased with the combination of agents. In clinical studies, including 263 patients treated with niacin–statin combination therapy, elevation in liver enzymes was not the reason for withdrawal in any patient;[25–28,34,36–40] liver enzyme elevations above three times the upper limit of normal (ULN) have occurred in fewer than 1% of patients receiving ER niacin–lovastatin.[29–31]

Table 4 Muscle-Related Adverse Effects Associated with Statin Therapy

Condition	Definition
Myopathy	Any disease of the muscles
Myalgia	Muscle aches or weakness without elevations in CK
Myositis	Muscle aches or weakness with elevations in CK
Rhabdomyolysis	Muscle symptoms with marked elevations in CK (usually greater than 10 times the ULN)

CK = creatine kinase; ULN = upper limit of normal.

Data from Pasternak RC, Smith SC Jr, Bairey-Merz CN, et al. *Circulation* 2002; 106:1024–1028; and *J Am Coll Cardiol* 2002;40:567–572.[33]

Statins and Fibrates

The efficacy of statin–fibrate therapy has been documented in numerous clinical studies. Treatment with this combination has been shown to reduce LDL-C levels by 23% to 46%,[41,42] to lower triglyceride levels by 36% to 57%,[41,43] and to raise HDL-C levels by 12% to 22%.[43,44]

Although the effects of statin–fibrate therapy on clinical out-

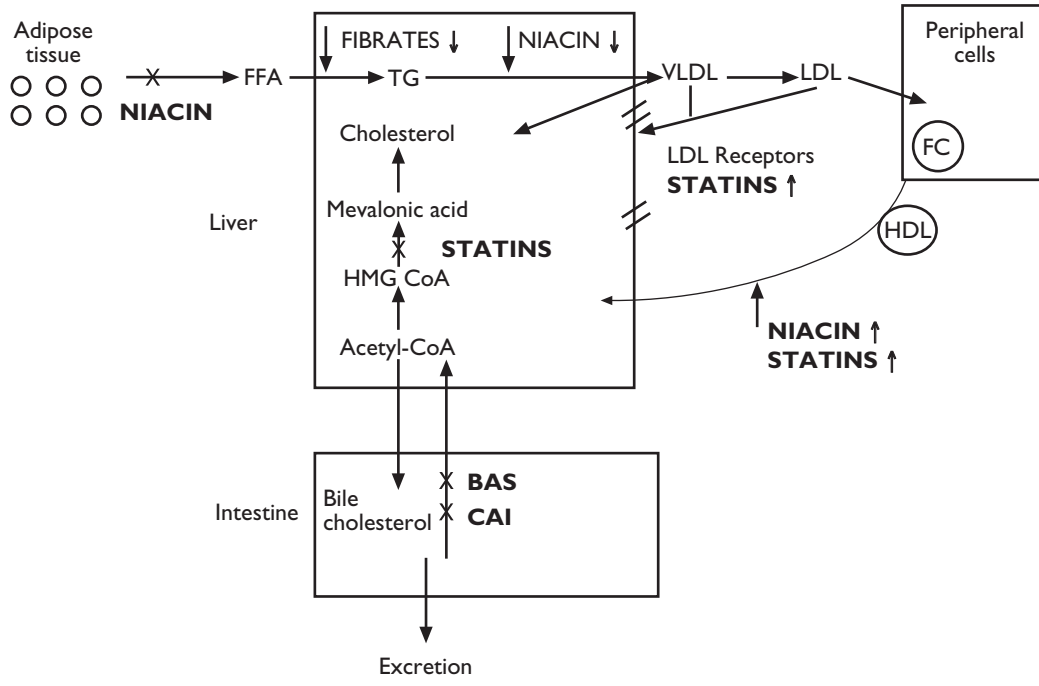

Figure 1 Lipid metabolism and site of action of lipid-modifying drugs. BAS = bile acid sequestrant; CAI = cholesterol absorption inhibitor; FC = free cholesterol; FFA = free fatty acid; HDL = high-density lipoprotein; HMG–CoA = 3-hydroxy-3-methylglutaryl coenzyme A; LDL = low-density lipoprotein; TG = triglycerides; VLDL = very-low-density lipoprotein. (Adapted from Knopp RH, Ginsberg J, Albers JJ, et al. *Metabolism* 1985;34:642–650, with permission from Elsevier Science.[21] Additional data from McKenney JM. *In: Applied Therapeutics: The Clinical Use of Drugs*, 6th ed. Vancouver, WA: Applied Therapeutics, Inc.; 1995;[15] Knopp RH. *Am J Cardiol* 1998;82:24U–28U; [22] and Dailey JH, Gray DR, Bradberry JC, Talbert RL. *In: Handbook on the Management of Lipid Disorders*, 2nd ed. St. Louis: National Pharmacy Cardiovascular Council, Health Tech Solutions, 2001:124–166.[23])

comes have not been studied, atorvastatin plus fenofibrate (Tricor®, Abbott) significantly reduced the 10-year probability of MI from 21.6% to 4.2%, as shown by a previously published risk calculator ($P < .05$ vs. both monotherapies and $P < .0001$ vs. baseline values).[42]

Concern about the safety of statins in combination emerged when cerivastatin (Baycol®, Bayer) was withdrawn from the market in August 2001 because of its association with as many as 100 fatalities, including deaths from rhabdomyolysis (see Table 4). The rate of rhabdomyolysis was 16 to 80 times higher with cerivastatin than with any other statin, and adverse effects were reported most frequently when this drug was used at higher doses, particularly in combination with gemfibrozil (Lopid®, Pfizer, formerly Parke–Davis). At the time of the withdrawal of cerivastatin, the FDA had received reports of 31 deaths in the U.S. caused by severe rhabdomyolysis associated with the use of this drug; 12 of the deaths involved the concomitant use of gemfibrozil.[33]

The risk of myopathy in patients taking statin–fibrate therapy appears to be higher than that with statin–niacin therapy. In the 871 cases of statin-associated rhabdomyolysis, the concomitant use of fibrates was reported in 80 cases (9.2%).[35] In clinical studies of statin–fibrate therapy, 1% of the patients experienced creatine kinase elevations more than three times the ULN without symptoms of myalgia, and 1% withdrew from the studies because of muscle symptoms.[33] An analysis of 36 clinical trials and 29 case reports documented the incidence of myopathy at 0.12%.[45]

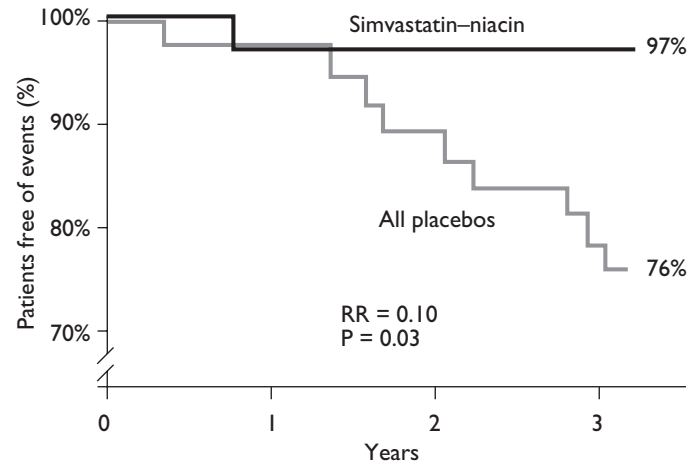

Figure 2 Kaplan–Meier curve for time to the first primary clinical endpoint (coronary death, nonfatal myocardial infarction, confirmed stroke, or revascularization for worsening ischemia) for 76 patients taking simvastatin–niacin or placebo. The relative risk (RR) of an event was 0.10 (95% confidence interval, 0.01–0.81). (Reprinted with permission from Brown BG, Zhao XQ, Chait A, et al. *N Engl J Med* 2001;345:1583–1592. Copyright 2001, Massachusetts Medical Society. All rights reserved.[32])

Statins and Bile Acid Sequestrants

Combining a statin and bile acid sequestrant is an option for patients who are not reaching their LDL-C goals with statin monotherapy, but this combination has only minimal effects on the rest of the lipid profile. Studies evaluating cholestyramine (Questran®, Par) plus pravastatin sodium (Pravachol®, Bristol-Myers Squibb) or lovastatin noted LDL-C reductions of 36% and 46%, HDL-C elevations of 3% and 15%, and triglyceride reductions of 0.5% and 8%, respectively.[46,47] Therapy with colesevelam (Welchol®), Sankyo Pharma), a newer bile acid sequestrant, and either atorvastatin or lovastatin, reduced LDL-C levels by 48% and 34%, raised HDL-C levels by 11% and 3%, and reduced triglyceride levels by 1.0% and 9%, respectively.[48,49]

Because bile acid sequestrants are not absorbed from the gut, the incidence of systemic adverse effects and drug–drug interactions is low; however, treatment with cholestyramine is limited by gastrointestinal (GI) side effects. In one study, 56% of patients receiving cholestyramine alone and 45% receiving pravastatin plus cholestyramine reported GI symptoms, compared with only 12% who received pravastatin alone.[46]

Another major concern with bile acid sequestrants such as cholestyramine and colestipol (e.g., Colestid®, Pharmacia & Upjohn) is their potential to interact with numerous drugs, consequently producing decreased absorption and pharmacokinetic alterations. Colesevelam does not seem to bind with other drugs and thus might be a better option than other bile acid sequestrants, especially when it is given concomitantly with other drugs.[50]

The Familial Atherosclerosis Treatment Study (FATS) evaluated the clinical benefit of combined lovastatin–colestipol therapy. After 2.5 years of treatment, patients receiving combination therapy showed less frequent progression of coronary lesions than did patients receiving conventional therapy (21% vs. 46% of patients), more frequent regression (32% vs. 11%; $P < 0.005$), and a reduced incidence of coronary events (death, MIs, or revascularization for worsening symptoms) (6.5% vs. 19.2%).[47]

Statins and Ezetimibe

Combination statin–ezetimibe therapy yields substantial reductions in LDL-C levels. When ezetimibe was added to ongoing statin therapy, further reductions of 25% in LDL-C levels, decreases of 14% in triglyceride levels, and increases of 2.7% in HDL-C levels were observed.[51] The combination therapy appeared to be as safe and tolerable as statin monotherapy.[51] A combination statin–ezetimibe product is currently under development and might become an important option for patients with extreme or refractory elevations in LDL-C.

Niacin and Bile Acid Sequestrants

Combining niacin with a bile acid sequestrant is an option for patients who cannot tolerate statin therapy, who need further reductions in LDL-C levels than those achieved with

monotherapy, or who have multiple lipid abnormalities. In clinical trials, this combination reduced LDL-C levels by up to 43%, lowered triglyceride levels by up to 29%, and increased HDL-C levels by up to 43%.[47,52,53]

In the FATS trial, patients receiving niacin–colestipol therapy experienced less frequent progression of coronary lesions than did patients receiving conventional therapy (25% vs. 46% of patients), more frequent regression (39% vs. 11%; $P < 0.005$), and reductions in the incidence of coronary events (4.2% vs. 19.2%).[47] In the Cholesterol-Lowering Atherosclerosis Study (CLAS), a greater percentage of patients treated with niacin–colestipol than placebo showed either no progression or regression of coronary artery lesions.[52,53]

Practical Advice for Health Care Providers

The Need for Patient Monitoring

A Clinical Advisory on the Use and Safety of Statins, published jointly by the American College of Cardiology, the American Heart Association, and the National Heart, Lung and Blood Institute,[33] summarizes the current understanding of statin use, with a focus on myopathy, and provides recommendations for the safe and appropriate use of statins as monotherapy and in combination with other agents. According to the advisory, (1) statins can be used safely in combination and (2) statin–niacin therapy might carry a lower risk for myopathy than statin–fibrate therapy. Because of the possibility of myopathy, however, health care providers should monitor all patients taking statin monotherapy or combination therapy by:

1. evaluating muscle symptoms before therapy is initiated.
2. assessing baseline creatine kinase (CK) levels with follow-up testing at six to 12 weeks after therapy begins and at each follow-up visit. Patients with CK levels that exceed 10 times the ULN (below 150 IU/ml for women and below 200 IU/ml for men), along with muscle symptoms, should stop therapy. If CK levels are three to 10 times the ULN, they should be checked weekly until symptoms resolve and enzyme elevation ceases. Patients with symptom progression and an increase in enzyme release should discontinue therapy.
3. counseling patients to report muscle symptoms not associated with muscle damage or higher than normal levels of activity that last for more than three days.
4. performing liver-function tests at the baseline evaluation, at 12 weeks after the initiation of therapy, and then annually.

Health care providers can be instrumental in helping patients become aware of and identifying symptoms of myopathy (e.g., headache; dyspepsia; and sore, tender, or painful muscles).[33]

Niacin Formulations

Health care providers should become familiar with the various formulations of niacin and the differences in their efficacy and safety. Three formulations are available: immediate-release (IR), sustained-release (SR), and extended-release (ER). These formulations differ mainly in their dissolution characteristics and absorption rates, which thus dictate their metabolism and, in turn, their efficacy, safety, and tolerability profiles (Figure 3).[54]

During the initial days of treatment with *IR niacin*, most patients experience prostaglandin-mediated facial and truncal flushing, characterized by warmth, redness, and itching on the upper body.[55]

Although *SR niacin* successfully reduces the incidence and severity of flushing, it is associated with an increased rate of GI side effects, and, unfortunately, with hepatotoxic effects in some cases.[56] This effect has been most commonly observed when patients switch from IR niacin to equal doses of SR niacin.[57–59] There may be differences in efficacy as well. In a study by McKenney et al., SR niacin was more effective in lowering LDL-C levels at doses of 1,500 mg/day or greater; IR niacin was more successful in raising HDL-C levels at all doses

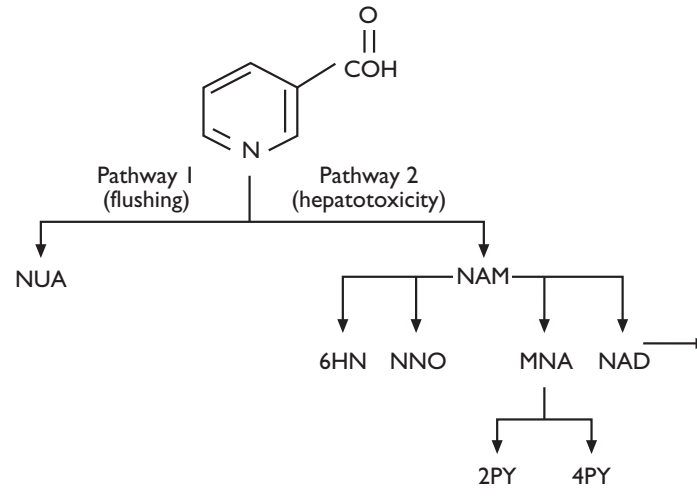

Figure 3 Niacin metabolism. Niacin is metabolized by two pathways: in Pathway 1, niacin is conjugated with glycine, resulting in the formation of nicotinuric acid, and in Pathway 2, several oxidation-reduction reactions produce nicotinamide and, finally, pyrimidine metabolites. Pathway 1 is a low-affinity, high-capacity pathway that operates when the high-affinity, low-capacity Pathway 2 becomes saturated. Immediate-release formulations quickly saturate Pathway 2, forcing much of the niacin dose to be metabolized via the conjugative Pathway 1, resulting in flushing. In contrast, the slowly absorbed, sustained-release formulations are mostly metabolized via Pathway 2, which produces many potentially hepatotoxic metabolites. COH = carboxy; 6HN = 6-hydroxy nicotinamide; MNA = *N*-methyl nicotinamide; NAD = nicotinamide adenine dinucleotide; NAM = nicotinamide; NNO = nicotinamide-*N*-oxide; NUA = nicotinuric acid; 2PY = *N*-methyl-2-pyridone-5-carboxamide; 4PY = *N*-methyl-4-pyridone-5-carboxamide. (From Piepho RW. *Am J Cardiol* 2000;86[Suppl 12A]:35L–40L. Reprinted with permission from Excerpta Medica, Inc.[54])

Table 5 Recommendations to Increase Patient Adherence

Focus on the Patient
- Keep the regimen as simple as possible.
- Give patients clear instructions.
- Discuss adherence, at least briefly, at each visit.
- Concentrate on those patients who don't reach treatment goals.
- Always call patients who miss appointments.
- Use two or more strategies for patients who do not meet treatment goals.
- Encourage the support of family and friends.
- Reinforce and reward adherence.
- Increase visits for patients who are unable to achieve treatment goals.
- Increase the convenience and access to care.

Focus on the Physician and Medical Office
- Teach physicians to implement lipid treatment guidelines.
- Use reminders to prompt physicians to address lipid management.
- Identify a patient advocate in the office to help deliver or prompt care.
- Encourage patients to prompt preventive care.
- Develop a standardized treatment plan to structure care.
- Use feedback from past performance to foster change in future care.
- Remind patients of appointments, and follow up on missed appointments.

Adapted from the Adult Treatment Panel III (ATP III). *JAMA* 2001; 285:2486–2497;[14] Piepho RW. *Am J Cardiol* 2000;86(Suppl 12A): 35L–40L;[54] Pieper JA. *Am J Manag Care* 2002;8(12 Suppl):S308– S314;[55] and American Society of Health-System Pharmacists. *Am J Health Syst Pharm* 1997;54:2815–2819.[61]

(500 to 3,000 mg/day).[56]

The absorption rate of *ER niacin* is intermediate, between that of IR and SR niacin. The result is a reduced incidence of flushing compared with IR niacin and without the increased hepatic risk seen with some of the SR niacin products.[56] After eight weeks of treatment, IR and ER niacin, given at a dose of 1,500 mg/day, had similar efficacy; LDL-C levels were lowered by 12% and 12%; triglycerides, by 18% and 16%; and lipoprotein(a), by 11% and 15%, respectively. HDL-C levels were increased by 17% and 20% in the IR and ER niacin groups, respectively.[60]

IR niacin is available by prescription (e.g., Niacor®, Upsher-Smith) and over the counter (OTC) under various brand names. SR niacin (also called timed-release, delayed-release, and long-acting niacin) is approved as a dietary supplement, not for the treatment of dyslipidemia, and it is available OTC as a vitamin. ER niacin is available by prescription only (e.g., Niaspan®, Kos).

Several societies have released position statements regarding the use of niacin in the treatment of dyslipidemia that emphasize the need for ongoing supervision by health care providers.[2,23,61] The Center for Drug Evaluation and Research (CDER) also cautions against the use of OTC products to treat dyslipidemia.[62]

Table 6 Counseling Patients During Niacin Therapy

- Take aspirin 325 mg or a nonsteroidal anti-inflammatory drug 30 minutes before you take the first niacin dose.
- Take niacin with food, preferably a low-fat snack.
- Avoid hot beverages, spicy foods, and hot showers soon after you take your medication.
- Avoid interruptions in therapy to maintain any tolerance to flushing that develops.
- It is best to use once-daily, extended-release niacin; the incidence and severity of flushing are lower, and bedtime dosing allows flushing to occur while you are sleeping.

Data from the Adult Treatment Panel III (ATP III). *JAMA* 2001;285: 2486–2497;[14] Piepho RW. *Am J Cardiol* 2000;86(Suppl 12A): 35L–40L;[54] Pieper JA. *Am J Manag Care* 2002;8(12 Suppl)S308–S314;[55] and American Society of Health-System Pharmacists. *Am J Health Syst Pharm* 1997;54:2815–2819.[61]

Because many of the OTC niacin formulations can cause serious toxic side effects, health care providers can play a crucial role by advising patients about the selection of niacin products, by discouraging self-treatment of dyslipidemia, and by working with patients and their physicians to ensure adequate monitoring of the efficacy, tolerability, and safety of niacin therapy.[23,61] Clinicians need to be especially careful not to substitute nonprescription SR niacin products for prescriptions written for ER niacin or Niaspan®, because there is no A/B equivalent.

Promoting Patient Adherence

Although lipid-modifying therapy can significantly reduce the risk of CHD, patient adherence remains a significant barrier to the optimal management of dyslipidemia. According to one survey, only 40% of patients who had been prescribed lipid-modifying therapy were still taking it one year after the initiation of therapy, and 25% of these discontinuations occurred during the first month of therapy.[63]

The ATP III guidelines outline interventions to improve adherence that focus specifically on patients, on physicians and the medical office, and on the health-delivery system (Table 5).[2] For adherence to increase, a combination of all three approaches will probably be required. Niacin, because of its common association with flushing and its OTC availability, has its own unique adherence problems. Health care providers should counsel patients on how to increase their tolerability of niacin and on ways to reduce the incidence and severity of flushing (Table 6).[2,54,55,61]

Summary

Cardiovascular risk is significantly increased by abnormalities in lipids and lipoproteins, including LDL-C, HDL-C, and triglycerides, and many patients have abnormalities in more than one lipid parameter. After LDL-C goals have been

achieved, the focus of management must turn to the improvement of other lipid risk factors, including those associated with atherogenic dyslipidemia.

Combination therapy with agents that target various components of the lipid profile can provide overall improvement of the lipid values and help patients meet their aggregate target lipid levels. Because of its effect on cholesterol metabolism at multiple steps, combination therapy may produce additive efficacy. Combination therapy is thus an important therapeutic option to consider for patients with more than one lipid abnormality and for those who cannot achieve lipid target levels with monotherapy. Combination products (e.g., ER niacin–lovastatin) and future products currently in development may be helpful in providing broad-spectrum lipid modification in a single tablet.

References

1. American Heart Association. Heart Disease and Stroke Statistics: 2003 Update. Last update 2002. Available at: http://www.americanheart.org/downloadable/heart/1040391091015HDS_Stats_03.pdf. Accessed July 24, 2003.
2. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). 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) final report. *Circulation* 2002;106:3143–3421.
3. Rubins HB, Robins SJ, Collins D, et al. Department of Veterans Affairs HDL Intervention Trial Study Group. Distribution of lipids in 8,500 men with coronary artery disease. *Am J Cardiol* 1995;75:1196–1201.
4. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among U.S. adults: Findings from the Third National Health and Nutrition Examination Survey. *JAMA* 2002;287:356–359.
5. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4,444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–1389.
6. Shepherd J, Cobbe SM, Ford I, et al. West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301–1307.
7. Sacks FM, Pfeffer MA, Moye LA, et al. Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001–1009.
8. Downs JR, Clearfield M, Weis S, et al. Air Force/Texas Coronary Atherosclerosis Prevention Study. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. *JAMA* 1998;279:1615–1622.
9. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349–1357.
10. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. *Am J Med* 1977;62:707–714.
11. Miller GJ, Miller NE. Plasma-high-density-lipoprotein concentration and development of ischaemic heart disease. *Lancet* 1975;1:16–19.
12. Austin MA. Plasma triglyceride as a risk factor for cardiovascular disease. *Can J Cardiol* 1998;14(Suppl B):14B–17B.
13. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease: Four prospective American studies. *Circulation* 1989;79:8–15.
14. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. 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.
15. McKenney JM. Dyslipidemias. *In:* Young LY, Koda-Kimble M, eds. *Applied Therapeutics. The Clinical Use of Drugs,* 6th ed. Vancouver, WA: Applied Therapeutics, Inc.; 1995:9-1–9-26.
16. Bays HE, Moore PB, Drehobl MA, et al. The Ezetimibe Study Group. Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: Pooled analysis of two phase II studies. *Clin Ther* 2001;23:1209–1230.
17. Dujovne CA, Ettinger MP, McNeer JF, et al. The Ezetimibe Study Group. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, *ezetimibe*, in patients with primary hypercholesterolemia. *Am J Cardiol* 2002;90:1092–1097.
18. Schectman G, Hiatt J. Dose–response characteristics of cholesterol-lowering drug therapies: Implications for treatment. *Ann Intern Med* 1996;125:990–1000.
19. Kontopoulos AG, Athyros VG, Papageorgiou AA, et al. Effects of simvastatin and ciprofibrate alone and in combination on lipid profile, plasma fibrinogen, and low density lipoprotein particle structure and distribution in patients with familial combined hyperlipidaemia and coronary artery disease. *Coron Artery Dis* 1996;7:843–850.
20. Gupta EK, Ito MK. Ezetimibe: The first in a novel class of selective cholesterol-absorption inhibitors. *Heart Dis* 2002;4:399–409.
21. Knopp RH, Ginsberg J, Albers JJ, et al. Contrasting effects of unmodified and time-release forms of niacin on lipoproteins in hyperlipidemic subjects: Clues to mechanism of action of niacin. *Metabolism* 1985;34:642–650.
22. Knopp RH. Clinical profiles of plain versus sustained-release niacin (Niaspan) and the physiologic rationale for nighttime dosing. *Am J Cardiol* 1998;82:24U–28U.
23. Dailey JH, Gray DR, Bradberry JC, Talbert RL, Crawford KM. Lipid-modifying drugs. *In:* McKenney JM, Hawkins D, eds. *Handbook on the Management of Lipid Disorders,* 2nd ed. St. Louis: National Pharmacy Cardiovascular Council, Health Tech Solutions; 2001:124–166.
24. Stein EA, Davidson MH, Dujovne CA, et al. Efficacy and tolerability of low-dose simvastatin and niacin, alone and in combination, in patients with combined hyperlipidemia: A prospective trial. *J Cardiovasc Pharmacol Ther* 1996;1:107–116.
25. Pasternak RC, Brown LE, Stone PH, et al. Effect of combination therapy with lipid-reducing drugs in patients with coronary heart disease and "normal" cholesterol levels: A randomized, placebo-controlled trial. *Ann Intern Med* 1996;125:529–540.
26. Tsalamandris C, Panagiotopoulos S, Sinha A, et al. Complementary effects of pravastatin and nicotinic acid in the treatment of combined hyperlipidaemia in diabetic and non-diabetic patients. *J Cardiovasc Risk* 1994;1:231–239.
27. O'Keefe JH Jr, Harris WS, Nelson J, Windsor SL. Effects of pravastatin with niacin or magnesium on lipid levels and postprandial lipemia. *Am J Cardiol* 1995;76:480–484.
28. Gardner SF, Marx MA, White LM, et al. Combination of low-dose niacin and pravastatin improves the lipid profile in diabetic patients without compromising glycemic control. *Ann Pharmacother* 1997;31:677–682.
29. Kashyap ML, McGovern ME, Berra K, et al. Long-term safety and efficacy of a once-daily niacin/lovastatin formulation in patients with dyslipidemia. *Am J Cardiol* 2002;89:672–678.
30. 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.
31. Bays HE, Dujovne CA, McGovern ME, et al. Comparison of once-daily, *niacin extended-release/lovastatin* with standard doses of *atorvastatin* and *simvastatin* (the ADvicor Versus Other Cholesterol-modulating Agents Trial Evaluation [ADVOCATE]). *Am J Cardiol* 2003;91:667–672.

32. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001;345:1583–1592.
33. Pasternak RC, Smith SC Jr, Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *Circulation* 2002;106:1024–1028; and *J Am Coll Cardiol* 2002;40:567–572.
34. Guyton JR, Capuzzi DM. Treatment of hyperlipidemia with combined niacin–statin regimens. *Am J Cardiol* 1998;82:82U–84U.
35. Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. *Ann Pharmacother* 2002;36:288–295.
36. Davignon J, Roederer G, Montigny M, et al. Comparative efficacy and safety of *pravastatin, nicotinic acid,* and the two combined in patients with hypercholesterolemia. *Am J Cardiol* 1994;73:339–345.
37. Jacobson TA, Chin MM, Fromell GJ, et al. Fluvastatin with and without niacin for hypercholesterolemia. *Am J Cardiol* 1994;74:149–154.
38. Vacek JL, Dittmeier G, Chiarelli T, et al. Comparison of lovastatin (20 mg) and nicotinic acid (1.2 g) with either drug alone for type II hyperlipoproteinemia. *Am J Cardiol* 1995;76:182–184.
39. Gardner SF, Schneider EF, Granberry MC, Carter IR. Combination therapy with low-dose lovastatin and niacin is as effective as higher-dose lovastatin. *Pharmacotherapy* 1996;16:419–423.
40. Brown BG, Bardsley J, Poulin D, et al. Moderate dose, three-drug therapy with niacin, lovastatin, and colestipol to reduce low-density lipoprotein cholesterol < 100 mg/dl in patients with hyperlipidemia and coronary artery disease. *Am J Cardiol* 1997;80:111–115.
41. Papadakis JA, Ganotakis ES, Jagroop IA, et al. Statin + fibrate combination therapy: Fluvastatin with bezafibrate or ciprofibrate in high-risk patients with vascular disease. *Int J Cardiol* 1999;71:237–244.
42. Athyros VG, Papageorgiou AA, Athyrou VV, et al. Atorvastatin and micronized fenofibrate alone and in combination in type 2 diabetes with combined hyperlipidemia. *Diabetes Care* 2002;25:1198–1202.
43. Athyros VG, Papageorgiou AA, Hatzikonstandinou HA, et al. Safety and efficacy of long-term statin–fibrate combinations in patients with refractory familial combined hyperlipidemia. *Am J Cardiol* 1997;80:608–613.
44. Ellen RL, McPherson R. Long-term efficacy and safety of fenofibrate and a statin in the treatment of combined hyperlipidemia. *Am J Cardiol* 1998;81:60B–65B.
45. Shek A, Ferrill MJ. Statin–fibrate combination therapy. *Ann Pharmacother* 2001;35:908–917.
46. Eriksson M, Hadell K, Holme I, Walldius G, Kjellström T. Compliance with and efficacy of treatment with pravastatin and cholestyramine: A randomized study on lipid-lowering in primary care. *J Intern Med* 1998;243:373–380.
47. Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med* 1990;323:1289–1298.
48. Hunninghake D, Insull W Jr, Toth P, et al. Coadministration of colesevelam hydrochloride with atorvastatin lowers LDL cholesterol additively. *Atherosclerosis* 2001;158:407–416.
49. Davidson MH, Toth P, Weiss S, et al. Low-dose combination therapy with colesevelam hydrochloride and lovastatin effectively decreases low-density lipoprotein cholesterol in patients with primary hypercholesterolemia. *Clin Cardiol* 2001;24:467–474.
50. Donovan JM, Stypinski D, Stiles MR, et al. Drug interactions with colesevelam hydrochloride, a novel, potent lipid-lowering agent. *Cardiovasc Drugs Ther* 2000;14:681–690.
51. Gagne C, Bays HE, Weiss SR, et al. The Ezetimibe Study Group. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. *Am J Cardiol* 2002;90:1084–1091.
52. Blankenhorn DH, Nessim SA, Johnson RL, et al. Beneficial effects of combined colestipol–niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA* 1987;257:3233–3240.
53. Cashin-Hemphill L, Mack WJ, Pogoda JM, et al. Beneficial effects of colestipol–niacin on coronary atherosclerosis: A 4-year follow-up. *JAMA* 1990;264:3013–3017.
54. Piepho RW. The pharmacokinetics and pharmacodynamics of agents proven to raise high-density lipoprotein cholesterol. *Am J Cardiol* 2000;86(Suppl 12A):35L–40L.
55. Pieper JA. Understanding niacin formulations. *Am J Manag Care* 2002;8(12 Suppl):S308–S314.
56. McKenney JM, Proctor JD, Harris S, Chinchili VM. A comparison of the efficacy and toxic effects of sustained- vs immediate-release niacin in hypercholesterolemic patients. *JAMA* 1994;271: 672–677.
57. Dalton TA, Berry RS. Hepatotoxicity associated with sustained-release niacin. *Am J Med* 1992;93:102–104.
58. Mullin GE, Greenson JK, Mitchell MC. Fulminant hepatic failure after ingestion of sustained-release nicotinic acid. *Ann Intern Med* 1989;111:253–255.
59. Rader JI, Calvert RJ, Hathcock JN. Hepatic toxicity of unmodified and time-release preparations of niacin. *Am J Med* 1992;92:77–81.
60. Knopp RH, Alagona P, Davidson M, et al. Equivalent efficacy of a time-release form of niacin (Niaspan) given once-a-night versus plain niacin in the management of hyperlipidemia. *Metabolism* 1998;47:1097–1104.
61. American Society of Health-System Pharmacists. ASHP therapeutic position statement on the safe use of niacin in the management of dyslipidemias. *Am J Health Syst Pharm* 1997;54:2815–2819.
62. Center for Drug Evaluation and Research. Guidance for industry. Over-the-counter treatment for hypercholesterolemia. Rockville, MD: U.S. Food and Drug Administration; 1997.
63. Simons LA, Levis G, Simons J. Apparent discontinuation rates in patients prescribed lipid-lowering drugs. *Med J Aust* 1996;164:208–211.

Disclosure

Dr. Talbert has disclosed that he has served on the KOS Speakers Bureau and Advisory Board.