

HIGHLIGHTS

N E W S L E T T E R

Solving Drug Therapy Issues in Patients Using Niacin

Cardiovascular disease (CVD) is the leading cause of death in the United States. According to data from the Centers for Disease Control and Prevention and the National Center for Health Statistics, more than 930,000 people died from CVD in 2001, and more than 13 million suffered from coronary heart disease (CHD).¹

A number of approaches can help prevent CHD, including lifestyle modification (for example, a low-fat diet and exercise), revascularization procedures, and pharmacologic strategies. Pharmacologic strategies include the use of aspirin, beta-blockers, ACE inhibitors, and lipid-modifying therapies. The

These proceedings are based on the educational program Dimensions in Cholesterol Care. Solving Drug Therapy Issues in Patients Using Niacin conducted during APhA2005, the American Pharmacists Association Annual Meeting & Exposition. The speakers for this program were James M. McKenney, PharmD; President and Chief Executive Officer, National Clinical Research, Richmond, Virginia; and Richard H. Karas, MD, PhD; Associate Professor of Medicine, Tufts University School of Medicine; Co-director, Molecular Cardiology Research Center; Director, Preventive Cardiology Center; and Director, Women's Heart Center, Tufts-New England Medical Center, Boston, Massachusetts.

patients' levels of various lipid parameters guide the selection of the appropriate lipid modifying therapies.

Lipid Modifying Therapies

Lipoproteins, including low-density lipoprotein (LDL) and high-density lipoprotein (HDL), are made up of triglycerides (TG), cholesterol, phospholipids, and other proteins—and function to transport lipids in plasma. LDL-C has atherogenic effects, promoting the development of atherosclerosis; HDL-C has an antiatherogenic effect. High TG has been identified as an independent risk factor for CHD. The classification of various lipid levels is shown in Table 1.^{2,3} Dyslipidemias include elevated total cholesterol (TC), LDL-C, and TG levels and decreased HDL-C levels. Elevated TG levels signal the presence of atherogenic lipoproteins including very low density lipoprotein (VLDL)-C and LDL-C and are usually accompanied by low HDL-C—patients who have this lipid profile are considered to have “atherogenic dyslipidemia.” Estimated prevalences of selected dyslipidemias are shown in Table 2.

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) report, released in 2001, represents expert opinion on the management of dyslipidemia.³ This report reaffirmed the importance of LDL-C as the primary target of therapy. It points out, however, that although the emphasis is on LDL-C, low HDL-C and high TG also are important risk factors, and it identifies non-HDL-C as the secondary target of therapy. Non-HDL-C, which includes both LDL-C and VLDL-C, is calculated by subtracting HDL-C from TC. An NCEP clinical update released in 2004 further

Niacin is an effective treatment for dyslipidemia, but different formulations result in great variations in clinical outcomes.

Proceedings of an educational session presented at APhA2005, the American Pharmacists Association Annual Meeting & Exposition, April 3, 2005, Orlando, Florida.



American Pharmacists Association™
Improving medication use. Advancing patient care.

Supported by an educational grant from Kos Pharmaceuticals, Inc.

KOS
Pioneering Medicines
for a Better Life®

defined therapeutic targets for high-risk patients.⁴ This update recommends that when LDL-lowering drug therapy is used in high-risk or moderately high-risk patients, the intensity of therapy should be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.

The 2004 update also reaffirmed TG and non-HDL-C as important therapeutic targets. For the first time, this report recommended pharmacologic interventions specifically for patients with high TG and low HDL-C. Although ATP III does not set targets for TG and HDL-C, further emerging evidence suggests that low HDL-C should be aggressively treated to prevent CHD. New, evidence-based guidelines for CVD prevention in women recommend that HDL-C should be raised above 50 mg/dL in women.² These guidelines indicate that high-risk women should be treated with niacin or a fibrate if HDL-C is <50 mg/dL or if non-HDL-C or TG is high.

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are very effective agents for reducing LDL-C and are widely used for the treatment of dyslipidemia. They have undergone extensive evaluation in large, randomized clinical trials and have been shown to reduce atherosclerotic progression, cardiovascular events, CHD, stroke, peripheral vascular disease, and

Niacin improves blood lipids, slows the progression of atherosclerosis, and may improve coronary outcomes.

total mortality. Statin therapy generally is very well tolerated. Elevated hepatic transaminases occur in 0.5% to 2% of patients and are dose dependent; however, hepatotoxicity manifested as liver failure is exceedingly rare.

Although statins are very effective at reducing the risk for cardiovascular events, many patients who are treated with these medications do experience adverse cardiovascular events. A number of factors may explain this, including the multifactorial nature of CHD risk, the

possibility that LDL-C lowering therapy has not been aggressive enough, and the possibility that non-LDL-C parameters are playing an important role in modifying risk.

Niacin for Dyslipidemias

Data from the Framingham Heart Study clearly demonstrate that low levels of HDL-C are synergistic with high LDL-C in raising the risk for CHD events.⁵ Medications that raise HDL-C include statins, bile acid sequestrants, fibric acid derivatives, and niacin. Among these classes of medications, niacin is the most effective for raising HDL-C, raising it by as much as 35% in some studies. Niacin also lowers LDL-C (although generally not as much as the statins), and has a potent effect on lowering TG levels. Therefore, niacin is particularly useful for patients who require modification of HDL-C and TG in addition to LDL-C. It can be used as single-agent therapy in patients with atherogenic dyslipidemia who do not have substantially increased LDL-C and as combination therapy in those who do have higher LDL-C levels.

Niacin has been shown to reduce mortality and nonfatal myocardial infarction (MI) in large clinical trials. For example, in the Coronary Drug Project, patients with a history of MI were randomized to receive niacin (n = 1,119) or placebo (n = 2,789) for 5 years.⁶ The risk of MI was significantly reduced in patients receiving niacin at 5 years, but niacin had no significant effect on mortality at this time point. However, in a 10-year follow-up of patients in this study (15 years after the study was initiated), mortality was significantly lower in patients who had been treated with niacin than in those who had received placebo.⁷

Combination therapy with niacin and a statin has additive benefits for blood lipids and also improves coronary outcomes. The HDL-Atherosclerosis Treatment Study (HATS) was a double-blind, placebo-controlled trial in 160 patients with CHD, low HDL levels, and LDL <145 mg/dL. This study investigated the effects of 3 years of treatment with one of four regimens: an antioxidant and vitamin cocktail, niacin-simvastatin, niacin-simvastatin-antioxidant, or placebo.⁸ The

rates of coronary events during the study were as follows: 21% in the antioxidant group, 3% in the niacin-simvastatin group, 14% in the niacin-simvastatin-antioxidant group, and 24% in the placebo group. Thus, the niacin-simvastatin combination reduced the rate of coronary events by 60% to 90%, indicating a clinical benefit in patients with CHD who have low HDL-C and normal LDL-C levels.

Treatment with niacin has also been shown to slow the progression of atherosclerosis in patients with CHD. The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 2 (ARBITER-2) trial was a placebo-controlled, double-blind study of 167 patients with established CHD and HDL-C levels <45 mg/dL.⁹ Prior to enrolling in the study, patients were receiving a statin and had a mean LDL-C of 89 mg/L. Patients were randomized to treatment with the addition of extended release niacin 1,000 mg/day or placebo for 1 year. The primary end point was the change in common carotid intima-media thickness (CIMT). (CIMT is strongly correlated with CHD event rates). After 1 year of therapy, the mean CIMT was significantly increased in patients receiving placebo plus statin but was not significantly changed in patients receiving niacin plus statin. HDL-C was significantly increased (21%) and TG was significantly decreased (13%) in patients receiving niacin. CVD events occurred in 9.6% of patients receiving placebo and 3.8% of patients receiving niacin representing a 50% decrease in cardiovascular events; however, this difference was not significant because of the small sample size.

Niacin in Patients with Diabetes

The use of niacin in patients with diabetes has been debated in recent years. Patients with diabetes are at increased risk for CHD and often have atherogenic dyslipidemia. Niacin therapy may cause hyperglycemia, producing modest changes in fasting blood glucose levels in about one third of patients. In addition, patients with impaired fasting glucose may progress to diabetes when niacin therapy is initiated. These findings have

Table 1. Classification of Selected Lipid Parameters

Cholesterol Concentration (mg/dL)	Classification
LDL cholesterol	
<100	Optimal
100–129	Near optimal/above optimal
130–159	Borderline high
160–189	High
≥190	Very high
Total cholesterol	
<200	Desirable
200–239	Borderline high
≥240	High
HDL cholesterol	
<40 in men, <50 in women	Low
≥60	High
Triglycerides	
<150	Normal
150–199	Borderline high
200–499	High
≥500	Very high

HDL = high-density lipoprotein; LDL = low-density lipoprotein.
Source: References 2 and 3.

led some to consider diabetes a relative contraindication to treatment with niacin. More recent trials show that the effect of niacin on glycemic control is minimal in most patients and is tempered by the cardiovascular benefits that niacin treatment provides.

In the Arterial Disease Multiple Intervention Trial (ADMIT), 468 patients with peripheral arterial disease (125 of whom had diabetes) were randomized to treatment with immediate-release niacin (titrated up to an average dose of 2,553 mg/day), antioxidant vitamins, and warfarin, or matching placebos for 48 weeks.¹⁰ HDL-C, TG, and LDL-C all significantly improved. Glucose concentrations increased 8.1 mg/dL in patients receiving niacin and decreased 8.7 mg/dL in those receiving placebo. A1c was unchanged in patients receiving niacin and decreased 0.3% in placebo-treated patients.

In the Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan

Trial (ADVENT), 148 patients with type 2 diabetes were treated with extended-release niacin 1,000 or 1,500 mg once daily or placebo for 16 weeks.¹¹ HDL-C and TG significantly improved in both niacin groups compared with placebo. Treatment did not produce significant differences in mean fasting glucose. The group treated with 1,500 mg/day experienced a small increase in A1c that was significant compared with placebo. In addition, 29% of patients in this group required an increase in oral hypoglycemic medication, but this change was not significantly different from placebo. This study did not assess doses greater than 1,500 mg of niacin per day.

A subanalysis of patients with diabetes in the Coronary Drug Project found that, although niacin marginally increased the mean glucose levels in these patients, the coronary event rates were reduced at least as much as they were in patients without diabetes.¹² Thus, although the use of niacin may require some modification of

diabetes therapy, its overall effect results in an improvement of coronary outcomes.

In summary, niacin therapy in patients with diabetes appears to have a small impact on glucose control. However, niacin does reduce the risk of cardiac events in patients with elevated fasting glucose, diabetes, or metabolic syndrome. (Metabolic syndrome is defined as the presence of a waist circumference greater than 40 inches [102 cm] in men or greater than 35 inches [88 cm] in women, serum triglycerides ≥150 mg/dL, HDL-C ≤40 mg/dL in men or ≤50 mg/dL in women, blood pressure ≥130/85 mm Hg, and fasting blood glucose level ≥110 mg/dL).

Because cardiac events are an important cause of morbidity and mortality in patients with CHD, niacin may be an appropriate treatment option in patients with diabetes, particularly those who do not tolerate statins, or fibrates or those who require further treatment of HDL-C, TG, or both.

Clinical Issues in the Use of Niacin

Several different forms of niacin are currently available and product selection has an important impact on clinical outcomes. Vitamin B₃ includes niacin (nicotinic acid) and niacinamide (nicotinamide). The term *niacin* refers specifically to nicotinic acid but is also sometimes used to refer to niacinamide. When ingested in physiologic levels sufficient to prevent pellagra (niacin deficiency), niacin is metabolized to niacinamide. (The U.S. Recommended Daily Allowance of niacin for adults is 16 mg/day for men and 14 mg/day for women.) Only nicotinic acid affects blood lipids; niacinamide does not. Dietary supplements containing niacinamide have no pharmacologic effects on lipid profiles and should not be used for this purpose. The treatment of dyslipidemia with niacin requires pharmacologic dosages that are approximately two orders of magnitude greater than those required to prevent niacin deficiency.

Formulations of Niacin

Niacin is available in immediate-release (IR), long-acting (LA), extended-

release (ER), and inositol hexaniacinate formulations. These products are described by various classification schemes in the medical literature.

IR niacin is available as both a prescription (Niacor®, Upsher-Smith) and as a dietary supplement, LA niacin is only available as a dietary supplement, and ER niacin is available only as a prescription (Niaspan®, Kos Pharmaceuticals). Although dietary supplements are sometimes referred to as over-the-counter (OTC) products because they can be purchased without a prescription, dietary supplements and OTC drugs are subject to very different levels of regulatory review. OTCs are subject to the same level of Food and Drug Administration (FDA) scrutiny as prescription products and require FDA approval prior to marketing. In contrast, the FDA's jurisdiction over dietary supplements is limited to labeling claims and obvious safety issues that emerge after a product is marketed.¹³

According to the American Heart Association (AHA) and the American Society of Health-System Pharmacists, dietary-supplement niacin should not be used to treat dyslipidemias, or as a replacement for prescription niacin.^{14,15} AHA has issued a statement that “Dietary supplement niacin must **not** be used as a substitute for prescription niacin. [Patients] should **not** use it for cholesterol lowering because of potential very serious side effects.”¹⁴

The most common adverse events associated with IR niacin therapy include

flushing, pruritus, rashes, nausea, dyspepsia, abdominal pain, and diarrhea. Hepatotoxicity is a serious concern for patients who use LA niacin but is much less likely to occur in patients who use other forms. Other adverse events listed in the product labeling for niacin include hyperuricemia and gout, cardiac arrhythmias, tachycardia, palpitations, hypotension, dizziness, chills, edema, migraine, insomnia, acanthosis nigricans, and peptic ulcer disease.

Niacin should be used with caution in patients who consume substantial quantities of alcohol, have a past history of liver disease, or both. Active liver diseases or unexplained transaminase elevations are contraindications to the use of niacin. Additional contraindications include active or recent peptic ulcer disease, arterial bleeding, or a known hypersensitivity to niacin.

Immediate-Release Niacin. IR niacin is quickly absorbed, achieving peak plasma concentrations within 30 to 60 minutes. It is usually administered in multiple daily doses. IR niacin, available both by prescription and as a dietary supplement, is sometimes called *plain niacin* or *crystalline niacin*.

Flushing (an uncomfortable sensation

of warmth, reddening, itching, or tingling) is one of the most common adverse events associated with IR niacin. It affects almost all patients at the beginning of therapy, and 10% to 50% of patients in IR niacin studies discontinue therapy as a result of this adverse event.¹³

Long-Acting Niacin. LA niacin products delay niacin absorption by the use of various formulation techniques. Dissolution of these products may be extended to 12 hours or more. LA niacin products differ considerably from one another, and patients should be advised not to switch among these products or use them interchangeably with other niacin products. In addition, because these products are not required to be manufactured following good manufacturing processes, niacin content may vary substantially even within lots of the same products. LA niacin products are only available as dietary supplements, and are also sometimes called *controlled-release*, *timed-release*, *extended-release*, or *sustained-release niacin*.

LA formulations of niacin were developed to minimize the effect of flushing. Although LA niacin products are associated with a greatly decreased incidence of flushing, they increase the risk of hepatotoxicity. In a randomized, double-blind, parallel comparison of IR and LA niacin administered sequentially at 500, 1,000, 1,500, 2,000, and 3,000 mg per day, each for 6 weeks, 39% of the patients receiving the IR dosage form withdrew before completing the study; the most common reason for withdrawal was flushing.¹⁶ In comparison, 78% of the patients assigned to the LA dosage form withdrew before completing the study; the most common reasons for withdrawal were gastrointestinal tract symptoms, fatigue, and increases in levels of liver aminotransferases, often with symptoms of hepatic dysfunction. None of the patients taking IR niacin developed hepatotoxic effects, whereas 52% of the patients taking LA niacin did.

Inositol Hexaniacinate. Some products that are labeled as no-flush niacin contain inositol hexaniacinate (also called *inositol nicotinate*). This compound consists of

Niacin has been shown to improve coronary outcomes in patients with diabetes.

Table 2. Prevalence of Abnormal Blood Cholesterol Levels in 2001

Value	Affected Individuals (in millions)	Percentage of U.S. Population
TC ≥ 200 mg/dL	104.7	50.7
TC ≥ 240 mg/dL	37.0	18.3
LDL-C ≥ 130 mg/dL	93.0	45.8
HDL-C < 40 mg/dL	53.6	26.4

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol.
Source: Reference 1.

six nicotinic acid molecules bound to an inositol molecule. Inositol hexaniacinate is partially absorbed and slowly metabolized to release free niacin. Although few data on the pharmacokinetics of this compound exist, one study found that the plasma concentration of free nicotinic acid after an oral dose of 1,600 mg of inositol hexaniacinate was 0.6 $\mu\text{mol/L}$. In comparison, plasma concentrations of IR niacin after an oral 1,000-mg dose peak at 244 $\mu\text{mol/L}$; after an oral 2,000-mg dose of SR niacin, plasma concentrations of niacin peak between 22 and 40 $\mu\text{mol/L}$.¹⁷ Thus, available data indicate that inositol hexaniacinate products are incapable of achieving plasma concentrations that produce lipid effects. The inability to achieve sufficient plasma concentrations probably also explains why these products do not produce flushing.

Clinical data supporting the use of inositol hexaniacinate in humans are scant; however, existing studies suggest that these products have no effects on lipid concentrations. Metabolism in humans is much slower than that in rats or dogs, which may explain why some animal studies have shown lipid effects but human studies have not.

Extended-Release Niacin. Compared with other forms of niacin, ER niacin (only available by prescription) has an intermediate-release pharmacokinetic profile and is released over 8 to 12 hours. This intermediate release minimizes both flushing and hepatotoxicity.

In placebo-controlled clinical trials of ER niacin in 245 patients, with dosages ranging from 500 to 3,000 mg daily, no patient with normal serum transaminase levels at baseline experienced elevations to more than three times the upper limit of normal (indicating a hepatic adverse event) during treatment. Fewer than 1% discontinued treatment as a result of transaminase elevations greater than twice the upper limit of normal.¹³ In patients receiving ER niacin, elevations in transaminases do not appear to be related to treatment duration, but they are more common at higher doses. Elevated transaminase levels were reversible with discontinuation of ER niacin. Flushing does occur in patients receiving ER niacin, but the incidence and severity are generally less than those observed with IR niacin. In placebo-controlled trials, fewer than 6% of patients discontinued therapy as a result of flushing.¹³

Metabolism of Niacin

The rate of release of the various niacin formulations determines the metabolic pathway that is predominantly used and as a result, the likelihood of certain adverse events associated with niacin. Niacin is metabolized by either the conjugative pathway, in which it is conjugated with glycine to form nicotinuric acid, or the amidation pathway, in which it goes through a series of oxidation-reduction reactions that produce nicotinamide and ultimately pyrimidine metabolites (Figure 1).¹⁸ The amidation pathway is a high-affinity, low-capacity pathway whereas the conjugation pathway is a low-affinity, high-capacity pathway.

The rapid absorption time of IR niacin results in quick saturation of the low-capacity amidation pathway, and the conjugation pathway, which is associated with flushing, dominates its metabolism. Conversely, the slow absorption of LA niacin results in most of the product being metabolized by the high-affinity amidation pathway, which increases the risk of hepatotoxicity. Because ER niacin has an intermediate absorption rate, its metabolism is balanced between the two pathways, resulting in a reduced risk for flushing and hepatotoxicity.

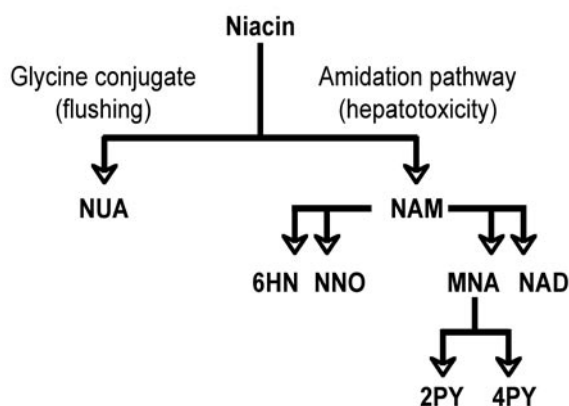
Counseling Strategies for Patients Using Niacin

For patients who are prescribed lipid-modifying therapies, pharmacists can play an important role in promoting adherence to therapy. Pharmacists should ensure that patients understand the long-term health benefits associated with niacin and should prepare them for adverse events that they might experience with therapy.

Pharmacists should advise patients who use niacin of the likelihood of flushing (the most common adverse event) and of steps that they can take to reduce the incidence of flushing. Patient counseling tips that may help manage flushing include:

- Take niacin at bedtime.
- Take niacin with a low-fat snack.
- Take aspirin or ibuprofen about 30 minutes before taking niacin (with

Figure 1. Metabolic Pathways for Pharmacologic Doses of Niacin



MNA = *N*-methylnicotinamide; NAD = nicotinamide adenine dinucleotide; NAM = nicotinamide; NNO = nicotinamide-*N*-oxide; NUA = nicotinuric acid; 6HN = 6-hydroxy-nicotinamide; 2PY and 4PY = pyridine metabolites.

Source: Reference 18. Reprinted with permission from Excerpta Medica Inc.

approval of the health care team).

- Avoid alcoholic beverages, hot beverages, and spicy foods near the time of taking niacin. (This strategy remains unproven but may be helpful for some patients.)

Pharmacists should advise patients that if they awaken while experiencing flushing, they should use caution if they decide to get out of bed. Patients should rise slowly, particularly if they start to feel faint or dizzy. This is particularly important in patients who take antihypertensive medications.

If patients using IR niacin continue to be bothered by flushing, they may benefit from switching to ER niacin. Patients who switch forms of niacin, however, should not be switched to an equivalent dosage. If the form of niacin is changed, treatment with the new form should be initiated with low doses and titrated to the desired therapeutic response.

Because hepatotoxicity also is a concern, liver function testing is advised when pharmacologic doses of niacin are used. Pharmacists should work with both the patient and other members of the health care team to ensure that the patient's hepatic function is appropriately monitored. Hepatotoxicity is much less common with ER and IR niacin than with LA niacin. LA forms of niacin should be avoided to reduce the likelihood of this adverse event. According to the American Heart Association, "All patients taking niacin to lower blood cholesterol should have their doctor closely monitor them to get the best effect and to avoid complications from this medication. Self-medication with niacin should definitely be avoided...because not all preparations of niacin are safe to take on a regular basis."¹⁴ If pharmacists identify patients who are purchasing dietary-supplement forms of niacin, they should counsel these patients to ensure that they are receiving appropriate monitoring for adverse events and outcomes.

Pharmacists should never recommend dietary-supplement forms of niacin as a substitute for prescription forms of niacin because they are not therapeutically equivalent. Some forms of dietary-supplement niacin (for example, inositol

hexaniacinate) contain little or no actual niacin, placing the patient at risk for undertreatment of dyslipidemia. Some others that do contain niacin are associated with serious safety concerns, placing patients at much greater risk than prescription products. Cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in patients who have substituted LA niacin products for IR niacin at equivalent doses.

References

1. American Heart Association. *Heart Disease and Stroke Statistics—2004 Update*. Dallas, Tex: American Heart Association; 2003. Available at: <http://www.americanheart.org/downloadable/heart/1079736729696HDSStats2004UpdateREV3-19-04.pdf>. Accessed July 20, 2004.
2. Mosca L, Appel LJ, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women. *Circulation*. 2004;109:672–93.
3. 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;106:3143–421.
4. 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;110:227–39.
5. Gordon T, Castelli WP, Hjortland MC, et al. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. *Am J Med*. 1977;62:707–14.
6. Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *JAMA*. 1975;231:360–81.
7. Canner PL, Furberg CD, Terrin ML, McGovern ME. Benefits of niacin by glycemic status in patients with healed myocardial infarction (from the Coronary Drug Project). *Am J Cardiol*. 2005;95:254–7.
8. 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;345:1583–92.
9. Taylor AJ, Sullenberger LE, Lee HJ, et al. Arterial biology for the investigation of the treatment effects of reducing cholesterol (ARBITER) 2. *Circulation*. 2004;110:3512–7.
10. Elam MB, Hunninghake DB, Davis KB, et al. Effect of niacin on lipid and lipoprotein levels and glycaemic control in patients with diabetes and peripheral arterial disease. The ADMIT Study: a randomized trial. *JAMA*. 2000;284:1263–70.
11. Grundy SM, Vega GL, McGovern ME, et al. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of Niaspan trial. *Arch Intern Med*. 2002;162:1568–76.
12. Canner PL, Furberg CD, McGovern ME. Niacin decreases myocardial infarction and total mortality in patients with impaired fasting glucose or glucose intolerance: results from the Coronary Drug Project. Presented at: Annual Meeting of the American Heart Association; November 20, 2002; Chicago, Illinois.
13. McKenney J. Niacin for dyslipidemia: Considerations in product selection. *Am J Health-Syst Pharm*. 2003;60:995-1005.
14. American Heart Association. *Cholesterol-Lowering Drugs*. Available at: <http://www.americanheart.org/presenter.jhtml?identifier=163>. Accessed March 1, 2004.
15. 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;54:2815–9.
16. McKenney JM, Proctor JD, Harris S, Chinchilli VM. A comparison of the efficacy and toxic effects of sustained- vs immediate-release niacin in hypercholesterolemic patients. *JAMA*. 1994;271:672–7.
17. Meyers DC, Carr MC, Park S, Brunzell JD. Varying cost and free nicotinic acid content in over-the-counter niacin preparations for dyslipidemia. *Ann Intern Med*. 2003;139:996-1002.
18. Piepho RW. The pharmacokinetics and pharmacodynamics of agents proven to raise high-density lipoprotein cholesterol. *Am Cardiol*. 2000;86(suppl):35L–40L.

Selected Resources

American Heart Association

<http://www.americanheart.org>

Food and Drug Administration, Center for Food Safety and Applied Nutrition

Dietary Supplements page

<http://www.cfsan.fda.gov/~dms/supplmnt.html>

National Heart, Lung, and Blood Institute, National Institutes of Health

National Cholesterol Education Program Adult Treatment Panel III

<http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm>