

# New Perspectives on the Use of Niacin in the Treatment of Lipid Disorders

James McKenney, PharmD

**T**herapy with niacin (nicotinic acid) is unique in that it improves all lipoprotein abnormalities. It significantly reduces low-density lipoprotein cholesterol, triglyceride, and lipoprotein(a) levels, while increasing high-density lipoprotein cholesterol levels. This makes niacin ideal for treating a wide variety of lipid disorders, including the metabolic syndrome, diabetes mellitus, isolated low high-density lipoprotein cholesterol, and hypertriglyceridemia. Niacin-induced changes in serum lipid levels produce significant improvements in both coronary artery disease and clinical outcomes. Niacin is currently available in 3 formulations (immediate release, extended release, and long acting), which differ significantly with respect to their safety and efficacy profiles. Immediate-release niacin is generally taken 3 times a day and is associated with adverse flushing, gastrointestinal symptoms, and elevations in blood glucose levels. Long-acting niacin can be taken once daily and is associated with significantly reduced flushing, but its metabolism increases the risk of hepatotoxic effects. Extended-release niacin, also given once daily, has an absorption rate intermediate between the other formulations and is associated with fewer flushing and gastrointestinal symptoms without increasing hepatotoxic risk. *Arch Intern Med.* 2004;164:697-705

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are the most effective pharmacologic means of lowering low-density lipoprotein cholesterol (LDL-C) levels (**Table 1**).<sup>1</sup> They have been extensively studied in large, randomized clinical trials involving more than 50 000 men and women and shown to decrease atherosclerotic progression, cardiovascular events, and total mortality.<sup>2-7</sup> Despite their efficacy, statins alone are not suitable for every patient and lipid abnormality. An estimated 25% to 50% of high-risk patients will not achieve their LDL-C goal, even at the highest statin doses. Additionally, some patients cannot tolerate statin therapy; in major trials, between 2.2% and 13.6% of subjects discontinued statin therapy because of adverse events.<sup>2-4</sup>

Finally, statins may be relatively ineffective in patients with mixed hyperlipidemia. They raise high-density lipoprotein cholesterol (HDL-C) levels a modest 3% to 10% and lower triglyceride levels 15% to 35% depending on baseline triglyceride levels.<sup>1,8</sup>

Bile acid sequestrants lower LDL-C levels 15% to 30%; however, they have minimal, if any, effect on HDL-C and may increase triglyceride levels, especially in patients with borderline or high triglyceride levels.<sup>1</sup> Ezetimibe, a cholesterol absorption inhibitor, was recently approved by the Food and Drug Administration (FDA) and like bile acid sequestrants, reduces LDL-C levels about 18% to 24% with very little effect on HDL-C or triglyceride levels.<sup>9,10</sup> Fibrates generally raise HDL-C levels 5% to 15% and reduce triglyceride levels 20% to 50%, making them useful in patients with mixed dyslipidemia; however, their effect on LDL-C is variable and in patients with moderate to high triglyceride levels, they may raise LDL-C.<sup>1,11</sup>

*From National Clinical Research and Virginia Commonwealth University, Richmond. Dr McKenney has served as a consultant for AstraZeneca and Pfizer; received speaking honoraria from AstraZeneca, Kos Pharmaceuticals, Merck, and Pfizer; and received research grants from AstraZeneca, BMS, GSK, Kos Pharmaceuticals, Merck, Pfizer, Sanyo, and Schering Plough.*

**Table 1. Drugs for the Treatment of Adult Dyslipidemias**

Drug Class	Effect, %		
	LDL-C	HDL-C	TG
HMG-CoA reductase inhibitors (statins)	-18 to -55	+5 to +15	-7 to -30
Bile acid sequestrants	-15 to -30	+3 to +5	No change or increase
Niacin	-5 to -25	+15 to +35	-20 to -50
Fibric acids	-5 to -20	+10 to +20	-20 to -50

Abbreviations: HDL-C, high-density lipoprotein cholesterol; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Niacin (nicotinic acid) favorably affects all lipids and lipoproteins, making it an alternative to fibrates for treating patients with mixed hyperlipidemia, and may be used either alone or in combination with other agents.<sup>1</sup> This article reviews the scientific rationale and use of niacin in a variety of dyslipidemias. It discusses the different niacin formulations and the principal adverse events associated with each and provides guidance for minimizing these events and improving patient tolerance.

### NIACIN FORMULATIONS

Three different niacin formulations are currently available: immediate release (IR, crystalline), extended release (ER), and long acting (LA).

Immediate-release niacin is sold over the counter as a dietary supplement for niacin deficiency; one IR product, Niacor (Upsher-Smith, Minneapolis, Minn), has been FDA approved for lipid-altering therapy by prescription. The IR formulation is quickly absorbed and quickly excreted. Peak serum levels are obtained within 30 to 60 minutes of oral dosing and the metabolic half-life is approximately 1 hour. It is most often prescribed in multiple daily doses.<sup>12</sup>

Long-acting niacin, also referred to as timed-release, controlled-release, or sustained-release niacin, is created through a variety of absorption-delaying techniques<sup>13</sup> that lead to dissolution times that typically exceed 12 hours but are variable even within lots of the same product.<sup>12-14</sup> All LA niacin products are sold over the counter for treating niacin deficiencies and none have been FDA approved for the treatment of lipid disorders.<sup>12</sup>

Extended-release niacin is absorbed over 8 to 12 hours, intermediate between IR and LA niacin. This

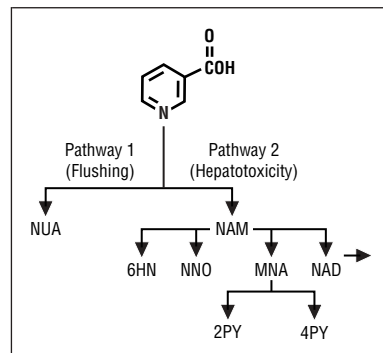
makes it suitable for once-daily bedtime dosing.<sup>14</sup> One ER niacin product is currently FDA approved for lipid lowering and is available by prescription as Niaspan from Kos Pharmaceuticals (Miami, Fla).

The differences in release characteristics among various niacin products are important because they determine how the drug is metabolized, in turn influencing the side effect profile of the product. Niacin is metabolized through 2 separate metabolic pathways (**Figure 1**).<sup>12,15</sup> The flushing effect with some niacin products results from prostaglandin-mediated vasodilation associated with the formation of nicotinic acid by the conjugation pathway, while hepatotoxicity is associated with the metabolites of the nicotinamide pathway.<sup>12</sup>

The nicotinamide pathway is a high-affinity, low-capacity pathway. The IR niacin formulation quickly saturates this pathway and is predominantly metabolized through the high-capacity conjugation pathway. It is therefore associated more with flushing but not hepatotoxicity. In contrast, LA niacin is very slowly absorbed and preferentially metabolized via the nicotinamide pathway. Because of this, LA niacin rarely causes flushing but significantly increases the risk of serious, dose-related hepatotoxic effects. The ER niacin formulation, with its intermediate absorption rate, has a more balanced metabolism between the 2 pathways. The result is less flushing and less risk of hepatotoxic effects, at least with daily doses of 2 g or less.

### LDL-C AND TRIGLYCERIDE EFFECTS OF NIACIN

Niacin indirectly affects LDL-C by reducing synthesis of the LDL pre-



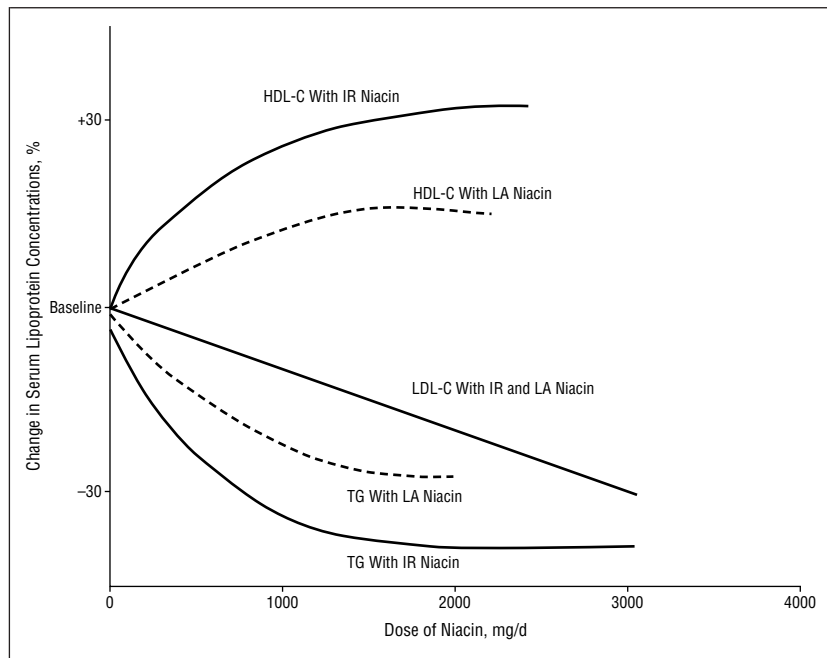
**Figure 1.** Niacin metabolism. Niacin is metabolized via 2 pathways. In the first pathway, it is conjugated with glycine to form nicotinic acid (NUA). The second pathway involves a number of oxidation-reduction reactions that produce nicotinamide (NAM) and ultimately pyrimidine metabolites. 6HN indicates 6-hydroxy-nicotinamide; MNA, *N*-methylnicotinamide; NAD, nicotinamide adenine dinucleotide; NNO, nicotinamide-*N*-oxide; 2PY, *N*-methyl-2-pyridone-5-carboxamide; 4PY, *N*-methyl-4-pyridone-5-carboxamide. Reprinted with permission from Piepho,<sup>12</sup> with permission from Excerpta Medica Inc.

cursor, very low-density lipoprotein (VLDL). It decreases the mobilization of free fatty acids from adipose tissue and the resultant decrease in triglyceride levels reduces hepatic synthesis and triglyceride content of VLDL.<sup>16,17</sup> Niacin also inhibits synthesis of apolipoprotein B-100, essential for the assembly of VLDL particles,<sup>18</sup> and enhances VLDL catabolism by inducing lipoprotein lipase.<sup>17,19</sup>

Niacin decreases LDL-C levels by 5% to 25% and triglyceride levels by 20% to 50% (Table 1).<sup>1,20</sup> In addition, niacin favorably alters LDL composition, shifting distribution from small, dense LDL particles to larger, more buoyant particles.<sup>21-25</sup> This may be important to niacin's ability to reduce coronary heart disease (CHD) risk.<sup>26-28</sup> In the Familial Atherosclerosis Treatment Study (FATS), change in the size and buoyancy of LDL particles was the single most important factor associated with regression of coronary stenosis.<sup>23</sup>

### HDL-C EFFECTS OF NIACIN

Niacin reduces the amount of apolipoprotein A-I extracted and catabolized from HDL during the hepatic uptake of cholesterol, thus preserving the structural and functional integrity of HDL particles.<sup>25,29,30</sup> As a result, cholesterol-deficient apolipoprotein A-I-containing HDL par-



**Figure 2.** Effects of immediate-release (IR) and long-acting (LA) niacin on serum lipoprotein concentrations. Low-density lipoprotein cholesterol (LDL-C) reduction follows a linear relationship with dose. Titration of the daily dose to 2 g is required to lowering LDL-C 25%. Increases in high-density lipoprotein cholesterol (HDL-C) and reductions in triglycerides (TG) follow a curvilinear relationship with dose. Reprinted with permission from Knopp.<sup>32</sup> Copyright 1999 Massachusetts Medical Society.

ticles are recirculated from the liver to peripheral cells, maintaining HDL levels and enhancing reverse cholesterol transport.<sup>12,31</sup>

Niacin is the most effective pharmacologic agent currently on the market for raising HDL-C levels, with increases of 15% to 35%.<sup>1</sup> It follows a relatively flat dose-response curve<sup>32</sup> so most of the rise in HDL-C with niacin occurs at daily doses of 1 to 1.5 g (**Figure 2**).<sup>14,18,20,32</sup>

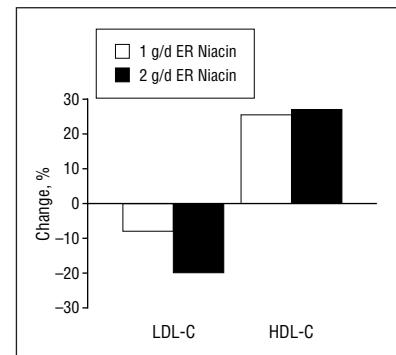
#### NIACIN COMBINATION THERAPY

Niacin's effects on lipid levels have been shown to be additive when combined with other lipid-altering therapies. In the Cholesterol Lowering Atherosclerosis Study (CLAS), niacin plus the bile acid sequestrant colestipol reduced LDL-C level by 43% and raised HDL-C level by 37% after 2 years and by 40% and 37%, respectively, after 4 years of treatment.<sup>33,34</sup> Similarly, in FATS, 2½ years of niacin-colestipol therapy reduced LDL-C levels by 32% and raised HDL-C levels by 43%.<sup>35</sup>

Given the superior efficacies of niacin and statins on HDL-C and LDL-C, respectively, combining them provides a regimen with greater over-

all lipid-altering efficacy than either drug can provide alone.<sup>1</sup> In one study, patients assigned to niacin plus fluvastatin had significantly greater reductions in both LDL-C (40% vs 25%) and the LDL-C/HDL-C ratio (52% vs 43%) than patients receiving niacin plus placebo.<sup>36</sup>

Similar results are seen with ER niacin. In one study, the addition of 1 g/d of ER niacin to a stable dose of statin monotherapy lowered LDL-C levels an additional 8% and raised HDL-C levels an additional 24%, whereas the addition of 2 g/d of ER niacin lowered LDL-C levels an additional 20% and raised HDL-C levels an additional 27% (**Figure 3**).<sup>37</sup> Note the similar increase in HDL-C levels with the 2 doses but the substantially greater lowering of LDL-C with the higher dose as would be expected from the dose-dependent pattern illustrated in Figure 2. Recently, a once-daily single tablet combination of ER niacin and lovastatin became available (Advicor, Kos Pharmaceuticals). In an open-label, 52-week, multicenter study evaluating 814 dyslipidemic patients receiving 2 g of ER niacin and 40 mg of lovastatin in the fixed-dose combination tablet, LDL-C and triglyceride levels were reduced 45%



**Figure 3.** Mean percent change in low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) following 1 g/d or 2 g/d of extended-release (ER) niacin when added to a stable dose of statin monotherapy. The HDL-C effect is near maximal with low-dose niacin, whereas a greater LDL-C effect requires high-dose niacin. Adapted with permission from Wolfe et al,<sup>37</sup> with permission from Excerpta Medica Inc.

and 42%, respectively, and HDL-C level was increased 41%.<sup>38</sup>

#### IMPACT OF NIACIN ON OUTCOMES

In clinical trials, niacin, alone and in combination, has been shown to slow progression and promote regression of coronary atherosclerosis and to decrease cardiovascular morbidity and mortality. The Coronary Drug Project (CDP) evaluated niacin monotherapy in men with prior myocardial infarction.<sup>39</sup> Niacin was found to reduce the 5-year incidence of nonfatal reinfarction by 27%. Moreover, after a mean follow-up of 15 years, nearly 9 years after the trial was completed, all-cause mortality was 11% lower in niacin-treated patients compared with placebo-treated patients ( $P < .001$ ).<sup>40</sup>

In both CLAS and FATS, angiographic assessments demonstrated that niacin plus colestipol produced significant reductions in the progression of atherosclerosis; moreover, regression of atherosclerosis occurred in 16% and 18% of CLAS patients at 2 years and 4 years, respectively, and in 39% of FATS patients at 2½ years.<sup>33-35</sup> FATS also demonstrated a significant 73% reduction in the incidence of cardiovascular events in patients receiving intensive therapy with colestipol plus either niacin or lovastatin.<sup>35</sup> In a 10-year follow-up, triple therapy with niacin, lovastatin, and colesti-

pol, compared with usual care, resulted in significantly less all-cause mortality (1.3% vs 19.8%;  $P < .001$ ) and cardiovascular events (5.3% vs 18.8%;  $P < .001$ ).<sup>41</sup>

Combination therapy with niacin and a fibrate has also been shown efficacious. The Stockholm Ischaemic Heart Disease Secondary Prevention Study evaluated niacin plus fibrate therapy in consecutive survivors of myocardial infarction.<sup>42</sup> Compared with the control group, which did not receive drug therapy, niacin-fibrate therapy reduced CHD mortality by 36%.

The HDL-Atherosclerosis Treatment Study (HATS) evaluated niacin plus simvastatin combination therapy in patients with low HDL-C and normal LDL-C levels.<sup>43</sup> Compared with a mean 3.9% progression in coronary stenosis with placebo, niacin-simvastatin therapy caused a mean regression of 0.4% ( $P < .001$ ) and reduced the composite primary end point of death from coronary causes, confirmed myocardial infarction or stroke, or revascularization for worsening ischemia by 60% vs placebo ( $P = .02$ ).

#### NIACIN THERAPY IN SELECTED PATIENT TYPES

A variety of patients with difficult-to-treat dyslipidemias are frequently seen in clinical practice. Niacin is often a valuable treatment option for these patients, because of its ability to modify all components of the lipid profile.

#### Atherogenic Dyslipidemia and the Metabolic Syndrome

In the United States, mixed lipid disorders are relatively common, especially in high-risk patients. In a study of more than 8500 men with CHD who were not receiving lipid-altering drug therapy, fasting lipid testing revealed 87% had LDL-C levels greater than 100 mg/dL (2.59 mmol/L), 63% had HDL-C levels less than 40 mg/dL (1.04 mmol/L), and 33% had triglyceride levels greater than 200 mg/dL (2.26 mmol/L).<sup>44</sup> Isolated lipid abnormalities were rare; only 8% of patients had isolated low HDL-C and only 1% had isolated hypertriglyceridemia. Furthermore,

only 7% of patients had LDL-C levels less than 100 mg/dL (2.59 mmol/L) and HDL-C levels at or above 35 mg/dL (0.91 mmol/L).

Atherogenic dyslipidemia is the combined presence of elevated triglycerides, increased remnant lipoproteins (ie, remnant VLDL), reduced HDL-C, increased small LDL particles, and increased number of lipoprotein particles. It frequently occurs in association with other cardiovascular risk factors, metabolic syndrome, and diabetes mellitus, and is associated with premature atherosclerosis.<sup>1</sup>

Adequate treatment of patients with atherogenic dyslipidemia first requires lowering LDL-C to goal and then non-HDL-C to goal. Non-HDL-C includes all apolipoprotein B-containing lipoproteins, VLDL, intermediate-density lipoproteins, and LDL. If LDL-C (which in most laboratories also includes intermediate-density lipoprotein cholesterol) has been reduced to goal and triglyceride levels are greater than 200 mg/dL (2.26 mmol/L), the non-HDL-C level will often be elevated because of an elevated VLDL-C. The non-HDL-C goal is set 30 mg/dL (0.78 mmol/L) above the LDL-C goal by the latest Adult Treatment Panel (ATP III).<sup>1</sup>

Reducing non-HDL-C to goal is accomplished by uptitrating the statin dose or selecting therapies that lower triglyceride levels (Table 1). In patients with significant LDL-C elevations, a statin is generally required. Thereafter, statin therapy may be advanced if the triglyceride level is only modestly elevated (ie, 200-350 mg/dL [2.26-3.95 mmol/L]), or niacin or a fibrate may be added to the statin to lower triglyceride levels and achieve the non-HDL-C goal when triglyceride levels are significantly elevated (ie, >350 mg/dL [3.95 mmol/L]). Niacin's effect on triglycerides is among the best of the agents available.<sup>1</sup> In patients with hypertriglyceridemia and modest LDL-C elevations, niacin lowers triglyceride levels 20% to 50% and LDL-C about 20% at a 2-g/d dose (Figure 2).<sup>32</sup>

#### Diabetes

Approximately 70% of patients with diabetes will die of some form of cardiovascular disease.<sup>45</sup> Patients with diabetes typically have lipid abnor-

malities associated with atherogenic dyslipidemia.<sup>1</sup> Niacin's effects on the lipid profile (raising HDL-C level, lowering triglyceride and LDL-C levels, and increasing LDL particle size) make it a good option for this type of mixed dyslipidemia. Significant improvements in lipid parameters in patients with diabetes similar to those without diabetes have been shown with niacin therapy.<sup>46-50</sup> However, niacin can adversely affect glucose levels and may necessitate initiation or intensification of hyperglycemic therapy in patients with impaired fasting glucose levels or diabetes.<sup>51</sup> Some small studies, generally using relatively high IR niacin doses (ie, 3-4.5 g/d), found significant rises in blood glucose levels in both diabetic and nondiabetic subjects. Other studies, using smaller daily doses (ie,  $\leq 1.5$  g/d), have detected few or no such alterations.<sup>47-50</sup>

Several recent studies have added to our understanding of the use of niacin in a diabetic population. The Arterial Disease Multiple Intervention Trial (ADMIT) included subjects with and without diabetes randomized to IR niacin or placebo for 48 weeks.<sup>48</sup> Small but significant increases in glycosylated hemoglobin ( $A_{1c}$ ) levels were seen in niacin-treated patients with diabetes, but not in those without diabetes. Glucose levels rose as niacin was titrated from 1 to 3 g/d, but subsequently returned to baseline 6 weeks after achieving a stable niacin dose. Presumably, adjustments in the insulin dose, made in 13% of the diabetic patients, partially accounted for the return of glucose to baseline levels. However, niacin therapy did not significantly affect the use of oral hypoglycemic agents and, for patients using insulin at both their first and final visits, did not significantly affect insulin dose. Moreover, withdrawal due to glucose intolerance was not significantly different between the niacin (4 of 64 subjects) and placebo (2 of 61 subjects) groups.

In the Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial (ADVENT), patients with type 2 diabetes were randomized to treatment with ER niacin or placebo. Fasting blood glu-

cholesterol levels initially rose at visits 4 and 8 weeks but returned to baseline by week 16 of ER niacin therapy. As in ADMIT, alterations in hypoglycemic therapy may partially account for this return to baseline, with a trend for worsening glycemic control requiring the addition or intensification of drug therapy with increasing doses; however, this trend was not statistically significant.

Recently, CDP investigators reported that fasting and 1-hour postprandial blood glucose levels were increased in patients assigned to the IR niacin group in their study (the magnitude of the increase was not specified).<sup>52</sup> However, they also reported that nonfatal myocardial infarction or all-cause death after 6 years of therapy was reduced 29% and 12%, respectively, among patients with a 1-hour postprandial glucose level of less than 140 mg/dL (7.77 mmol/L) compared with a reduction of 42% and 20%, respectively, among patients with a 1-hour postprandial glucose level of 220 mg/dL (12.2 mmol/L) or higher. This suggests that the CHD risk reduction associated with niacin use in the overall study was preserved in diabetic patients despite an increase in blood glucose levels.

The risks vs benefits of treating diabetic patients with niacin must be weighed by health care providers. Niacin therapy is often appropriate for the lipid abnormalities encountered in these patients. Moreover, it is not contraindicated and can be successfully tolerated by most diabetic patients without deterioration in their glucose control. When statins are not adequate to achieve lipid targets, niacin can be considered, with appropriate adjustment of hypoglycemic therapy to maintain glucose under good control.

### Isolated Low HDL-C

Niacin is an ideal choice to treat isolated low HDL-C levels because of its superior HDL-C-raising effect at low, very tolerable doses. In an early study of patients with fasting HDL-C levels less than 35 mg/dL (0.91 mmol/L) and triglyceride levels less than 250 mg/dL (2.82 mmol/L), IR niacin resulted in a significant 30% increase in HDL-C level.<sup>53</sup> In an-

other study, patients with HDL-C levels less than 40 mg/dL (1.04 mmol/L), LDL-C levels less than 160 mg/dL (4.14 mmol/L), and triglyceride levels less than 200 mg/dL (2.26 mmol/L) experienced a greater increase in HDL-C with IR niacin than with gemfibrozil (35% vs 15%;  $P < .005$ ); combining the 2 drugs was not statistically different from niacin monotherapy.<sup>54</sup>

Evidence of clinical benefit from raising HDL-C levels in patients with isolated low HDL-C is mostly theoretical. A few trials have included patients with normal total cholesterol and low HDL-C levels.<sup>43,55-57</sup> Although outcomes improved with treatment, the inclusion of patients with hypertriglyceridemia in these trials makes it difficult to determine the relative contribution of raising HDL-C vs lowering triglycerides.

### Hypertriglyceridemia

The National Cholesterol Education Program has recently affirmed an important association between hypertriglyceridemia and CHD risk.<sup>1</sup> Which drug to use often depends on the degree of hypertriglyceridemia and the patient's LDL-C level. In patients with very high triglyceride levels ( $\geq 500$  mg/dL [5.65 mmol/L]), niacin or fibrates are usually required. The triglyceride lowering with statins (eg, 25%-40%) is greatest in patients with very high triglyceride levels, but this lowering would generally not be sufficient to bring triglyceride levels to the normal range of less than 150 mg/dL (1.70 mmol/L). In patients with less severe hypertriglyceridemia (ie, 200-350 mg/dL [2.26-3.95 mmol/L]), statin monotherapy may be useful. When LDL-C is only modestly elevated in the presence of hypertriglyceridemia, niacin or a fibrate alone may be used.<sup>1,58,59</sup> However, because fibrates typically raise LDL-C levels 5% to 30% in these patients, they must usually be coadministered with a statin.<sup>1,60</sup>

### NIACIN OR FIBRATES

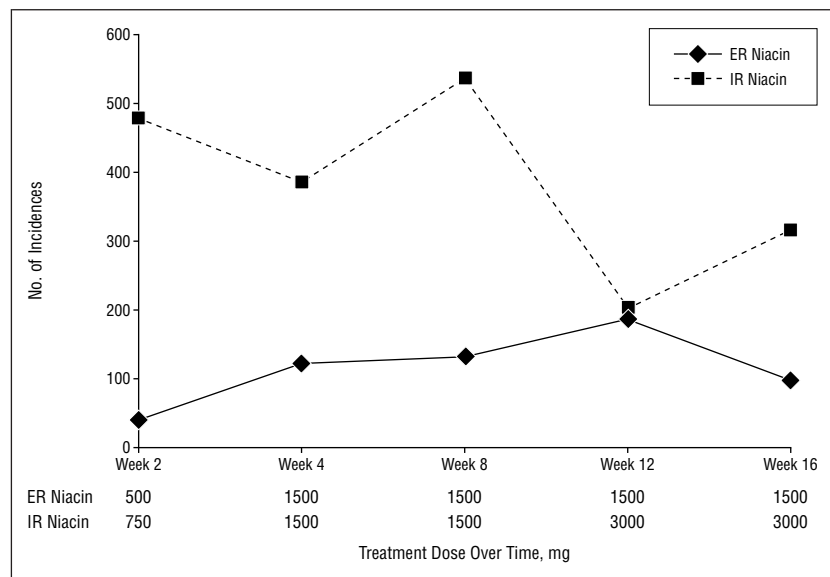
Both niacin and fibrates can be effective choices for lowering LDL-C and triglyceride levels and raising HDL-C levels, and both have been

shown to reduce cardiovascular events. Thus, choosing between them often depends on specific patient factors. As previously discussed, one factor is the presence of hypertriglyceridemia. In patients with hypertriglyceridemia, fibrates usually increase rather than reduce LDL-C levels.<sup>1,60</sup>

The degree of dyslipidemia may be another factor. In an early trial, subjects received first gemfibrozil (0.6 g twice daily) then IR niacin (1.5 g 3 times per day) for 8 weeks separated by an 8-week control period.<sup>61</sup> Gemfibrozil produced a 25% fall in fasting triglyceride levels but no change in LDL-C or HDL-C level. Niacin similarly did not affect LDL-C, but increased HDL-C levels by 30% and decreased triglyceride levels by 35%. In a subsequent randomized, double-blind trial, ER niacin (2 g/d) produced a 2-fold greater increase in HDL-C level (26% vs 13%;  $P < .001$ ) than gemfibrozil (0.6 g twice daily); gemfibrozil produced a greater fall in triglyceride levels (40% vs 29%;  $P = .02$ ) but also a significant rise in LDL-C level (9% vs 0%;  $P = .004$ ).<sup>11</sup> The presence of elevated lipoprotein(a) levels may also influence therapy selection. Lipoprotein(a) is an emerging cardiovascular risk factor with a strong association with CHD risk<sup>62,63</sup> and has been reported to have synergy with accompanying LDL-C elevation in increasing CHD risk.<sup>1</sup> Niacin is the only lipid-modifying agent that significantly affects lipoprotein(a), with reductions of 20% to 38%.<sup>64</sup> Therefore, in patients with dyslipidemia that includes elevated lipoprotein(a) levels, niacin would be the preferred agent.

Concomitant disorders and the need for additional medications are also determining factors in whether to use niacin or fibrate therapy. Because of strong protein binding, fibrates have the potential for significant drug-drug interactions.<sup>1</sup> In addition, combining gemfibrozil with a statin increases the risk of myopathy.<sup>1,65,66</sup> Although myopathy may also occur when niacin is added to a statin, the incidence is much lower than combination statin-fibrate therapy.<sup>66</sup>

The principal limitation of niacin is the potential for sustained-release niacin to cause adverse hepatotoxic ef-



**Figure 4.** Incidence of all flushing episodes between office visits during 16 weeks of therapy with escalating doses of extended-release (ER) niacin (n=74 patients) and immediate-release (IR) niacin (n=76 patients). Reprinted from Knopp et al.<sup>25</sup> with permission from Elsevier Science.

fects and for IR niacin and, to a lesser extent, for ER niacin to cause bothersome side effects such as flushing. These side effects, discussed below, often lead to hesitancy in prescribing niacin. However, they can be significantly reduced to the point that niacin can be tolerated during long-term therapy by 70% or more of patients.

#### ADVERSE EFFECTS OF NIACIN THERAPY

Niacin's use has been limited mainly by dose-dependent adverse effects including flushing, pruritus, rashes, nausea, dyspepsia, abdominal pain, and diarrhea; 10% to 50% of patients in IR niacin trials discontinued therapy as a result of cutaneous flushing. This uncomfortable sensation of warmth, reddening, itching, and/or tingling occurs initially in almost all individuals at the start of therapy.<sup>67,68</sup> The LA niacin formulation was developed to circumvent this problem,<sup>69</sup> which it did, but as previously discussed, its metabolism increases the risk of hepatotoxic effects.<sup>14,70</sup> In a randomized, double-blind, force-titration study comparing IR and LA niacin, approximately 50% of the IR-treated and none of the LA-treated patients experienced flushing. However, approximately 75% of the LA-treated patients had to discontinue therapy, mostly because of transaminase elevations more than 3 times the upper limit of

normal, and many with symptoms of hepatic dysfunction. In contrast, none of the IR-treated subjects experienced significant changes in liver function test results.<sup>67</sup>

Consistent with its intermediate absorption profile, ER niacin produces less flushing than IR niacin and fewer hepatotoxic effects than LA niacin. This has been demonstrated in one randomized trial that directly compared ER and IR niacin. The ER niacin regimen produced significantly less flushing than IR niacin (**Figure 4**) without increasing the risk of elevated liver enzymes or hepatotoxic effects.<sup>25</sup> In another study with ER niacin, flushing occurred in approximately 50% of the patients during the initial 4 weeks of therapy but resolved in most by week 24.<sup>71</sup> Only 5% of study patients discontinued ER niacin therapy as a result of flushing (less than the 10% to 50% reported with IR niacin). Elevations in liver enzyme levels greater than 2 times the upper limit of normal occurred in 2.6% of patients, mostly in those receiving combination therapy with either a statin or bile acid sequestrants, and most resolved without a dose reduction.

As previously discussed, hyperglycemia is another important side effect associated with niacin therapy. In most well-controlled clinical trials, mean changes in fasting blood glucose levels are gener-

ally modest and transient.<sup>48-50,68,71</sup> Niacin-induced hyperglycemia does not occur in all patients; it is more prevalent in patients with diabetes, 10% to 35% of whom it is estimated will require a change in hypoglycemic therapy.<sup>48,50</sup> In addition, a few patients with impaired fasting glucose levels (and not diabetes) may develop diabetes, requiring initiation of hypoglycemic therapy. The prevalence of these effects appears to be similar with IR and ER niacin, although percent increases tend to be higher with IR niacin; less is known about the effect of LA niacin on these parameters.

Other potential adverse effects of niacin include hyperuricemia and gout, cardiac arrhythmias, tachycardia, palpitations, hypotension, dizziness, chills, edema, migraine, insomnia, acanthosis nigricans, and activation of peptic ulcer disease and are seen to varying extents with all niacin formulations.<sup>18,72,73</sup>

It is widely believed that combining niacin with a statin increases the risk of muscle toxic effects. Myopathy (generally defined as creatine kinase level >10 times the upper limit of normal plus muscle symptoms including weakness, soreness, or pain) has been reported in a small number of cases with niacin monotherapy,<sup>74,75</sup> and myopathy and rhabdomyolysis have been reported with both IR and LA niacin in combination with a statin.<sup>76-78</sup> The true incidence of muscle side effects, however, cannot be determined from these isolated case reports. It is probably very low and indistinguishable from that seen with statins alone, ie, approximately 2 to 4 cases of myopathy per 1000 treated patients. Of 601 FDA-reported statin-induced cases of rhabdomyolysis, 4 (0.7%) were associated with niacin-statin combination therapy.<sup>65</sup>

#### IMPROVING ADHERENCE WITH NIACIN THERAPY

Poor adherence is one of the greatest challenges facing clinicians in the management of dyslipidemia. Although it takes 6 to 12 months of treatment before benefits become apparent, fewer than 50% of patients adhere to any lipid-altering therapy for this long.<sup>1,79</sup> Niacin, because of

**Table 2. Steps to Prevent and Reduce Niacin-Induced Symptoms and Improve Adherence**

Initiate therapy using small, divided doses (0.1 g 3 times per day) taken with meals and then slowly titrate upward over several weeks to achieve treatment goals.<sup>18</sup>

Take an adult aspirin or other nonsteroidal prostaglandin inhibitor 30 min prior to the morning dose to reduce prostaglandin-mediated vasodilation.<sup>80-82</sup>

Avoid taking niacin concurrently with alcohol, spicy foods, or hot beverages.<sup>18</sup>

Avoid interrupting niacin therapy whenever possible; continuous therapy promotes tolerance, and flushing symptoms are likely to recur every time niacin is begun.

Use extended-release (ER) instead of immediate-release (IR) niacin. Since ER niacin is only taken once a day at bedtime, most flushing symptoms will occur while the patient is sleeping. As with IR niacin, slowly titrating the dose of ER niacin (0.5 g once nightly for 1 month, 1 g once nightly for 1 month, and then 1.5 g once nightly) is likely to minimize side effects. If needed, the dose can be increased to 2 g nightly.<sup>14</sup>

its associated adverse effects, has its own unique adherence issues.<sup>68</sup>

With IR niacin, the biggest hurdle to overcome is the flushing effect. Tolerance develops such that within several weeks of initiating niacin therapy approximately 60% of patients will have only mild flushing and only about 3% will continue to have severe flushing.<sup>68</sup> Unfortunately, many patients discontinue niacin therapy before developing this tolerance or initiating other approaches to lessen symptoms.<sup>80</sup> In addition, approximately 20% of patients receiving IR niacin experience symptoms of gastrointestinal irritation. Usually, these symptoms are transitory and can be minimized by taking IR niacin with food.<sup>68</sup> Alternatively, ER niacin can be used since, relative to placebo, it does not increase the frequency of gastrointestinal symptoms<sup>20</sup> and may, by itself, promote better patient adherence than IR niacin by allowing once-daily dosing. **Table 2** lists these and several other practical steps for limiting symptoms and improving adherence with niacin therapy.<sup>14,18,80-82</sup> Importantly, LA niacin should not be used to avoid flushing and should not

be substituted for IR niacin at doses of 2 g/d or more because of the associated risk of hepatotoxic effects.<sup>67,83</sup> If used at all, the dose should be kept to 2 g/d or less and the patient should be monitored for liver toxicity.<sup>67</sup>

As with all therapies, long-term adherence depends on good patient education. This includes frank discussion about benefits expected from lipid-modifying therapy and potential adverse drug effects, including how long they might last and how to lessen their consequences. Following this discussion, it is important to obtain the patient's acceptance of the therapy being advocated. Aspirin administration 30 minutes before the morning dose should be recommended, if not contraindicated. Finally, the overriding message needs to be the importance of continuing therapy in order to achieve long-term CHD risk reduction.

## CONCLUSIONS

Appropriate management of dyslipidemia can significantly reduce cardiovascular morbidity and mortality. Statins are the most effective pharmacologic agents for lowering LDL-C levels, and their benefits in reducing cardiovascular risk have been documented in numerous clinical trials. However, they are not tolerated by all patients and are less effective in managing other lipoprotein abnormalities. Niacin has the ability to improve all lipoprotein abnormalities and decrease cardiovascular events. However, tolerability issues have limited its wider use. Niacin is available in 3 formulations (IR, ER, and LA), and adverse effects are directly related to the specific formulation being used; IR niacin may cause flushing and related symptoms, sustained-release niacin may cause hepatotoxic effects, and ER niacin may cause less flushing and fewer hepatotoxic effects. Only IR and ER niacin are FDA approved for the treatment of dyslipidemia.

Given the superior efficacies of niacin and statins with regard to HDL-C and LDL-C, respectively, their combination is an ideal choice for patients with abnormalities of more than 1 lipid parameter or when

monotherapy is insufficient for achieving lipoprotein goals. Several studies have confirmed the safety and efficacy of this combination. Although it is widely believed that combining niacin with a statin increases the risk of muscle toxicity, this risk appears to be extremely low and may not be significantly different from that of statin monotherapy. The greatest potential advantage of this combination, confirmed in several small studies, is the additional reduction in cardiovascular risk that may be achieved when HDL-C-raising effects of niacin are added to the well-documented beneficial LDL-C-lowering effects of statins. A large clinical trial with niacin vs placebo randomly added to a statin background is needed to fully establish this benefit.

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Corresponding author and reprints: James McKenney, PharmD, National Clinical Research, 2809 Emerywood Pkwy, Suite 140, Richmond, VA 23294 (e-mail: jmkkenney@ncrinc.net).

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