

Niacin: A Critical Component to the Management of Atherosclerosis

Contemporary Management of Dyslipidemia to Prevent, Reduce, or Reverse Atherosclerotic Cardiovascular Disease

Carol M. Mason, ARNP, CLS, FAHA, FNLA, FPCNA; Amy L. Doneen, MSN, ARNP

Niacin (nicotinic acid) is the most effective agent for raising high-density lipoprotein cholesterol levels and can improve the entire lipid panel in patients with dyslipidemia. Niacin-containing regimens are among the few treatments studied for dyslipidemia that have both elicited significant reductions in atherosclerotic progression (by angiography or imaging) and also significantly reduced (by approximately 90% vs control) the incidence of cardiovascular events in a single clinical trial. However, cutaneous flushing—an uncomfortable but typically transient adverse effect of niacin—often results in patient nonadherence with this potentially life-saving therapy. Effective counseling regarding the highly favorable benefit-risk ratio for niacin and management strategies such as careful dose escalation, follow-up monitoring, regimen adjustments, and the use of treatment adjuncts (eg, aspirin) can improve patient adherence with niacin therapy. Clinicians are uniquely positioned to provide such counseling to appropriate patients for niacin treatment and hence encourage wider use of this important and necessary cardioprotective medication.

KEY WORDS: atherosclerosis, cholesterol, drug therapy, niacin (nicotinic acid), treatment outcome

Cardiovascular disease (CVD), including coronary heart disease (CHD) and stroke, is a leading cause of premature morbidity and mortality, claiming the lives of 17 million people around the world each year.¹ In the United States, approximately 1 in 3 American adults has some form of CVD.² Population-attributable CVD risk due to type 2 diabetes mellitus (DM2) is also on the rise.³ Ap-

proximately 70% of deaths in patients with DM2 can be ascribed to CVD.⁴

Targeting elevations in low-density lipoprotein cholesterol (LDL-C), primarily with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), remains the cornerstone of treatment in consensus guidelines, whereas elevated triglyceride (TG) levels and low levels of high-density lipoprotein cholesterol (HDL-C) are secondary targets (Table 1).^{5,6} However, many patients treated optimally with statins to meet aggressive LDL-C goals harbor residual cardiovascular (CV) risk.⁷ This remaining risk is associated with low levels of HDL-C, elevations in TG levels, and a preponderance of small, dense, atherogenic LDL particles; this constellation of defects is alternatively termed the *lipid triad*, *atherogenic dyslipidemia*, *diabetic dyslipidemia*, or *mixed dyslipidemia*.^{8–11}

Diabetic or atherogenic dyslipidemia is a predominant feature of metabolic disorders associated with insulin resistance (eg, DM2, metabolic syndrome [MetSyn], and abdominal adiposity), and mixed dyslipidemia is emerging as a major clinical challenge in CVD prevention. Several clinical trials and meta-analyses have provided evidence of residual CV risk associated with the lipid triad. In a subgroup analysis of the Treating to New Targets (TNT) trial, HDL-C

Carol M. Mason, ARNP, CLS, FAHA, FNLA, FPCNA

President, Accreditation Council for Clinical Lipidology, and Certified Clinical Lipid Specialist, LifeLink Healthcare Institute, Cardiology Division, Tampa, Florida.

Amy L. Doneen, MSN, ARNP

Medical Director, Heart Attack & Stroke Prevention Center, Spokane, Washington, and Adjunct Professor, Texas Tech Health Sciences School of Nursing, Lubbock.

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Correspondence

Carol M. Mason, ARNP, CLS, FAHA, FNLA, FPCNA, 1547 Winding Willow Drive, Trinity, FL 34655 (cm_mason@msn.com).

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TABLE 1 ATP III Classification of Total, LDL, and HDL Cholesterol and Triglycerides (mg/dL)

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

Abbreviations: ATP, Adult Treatment Panel; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

levels were inversely related to risk of major CV events, even among patients treated aggressively with statins to achieve the aggressive LDL-C target of less than 70 mg/dL.¹² Data from the Framingham Heart Study demonstrated that a patient with an LDL-C level of 100 mg/dL but an HDL-C level of 25 mg/dL has an absolute CHD risk equivalent to that of a patient with an LDL-C level of 220 mg/dL and an HDL-C level of 45 mg/dL.¹³

Given the foregoing findings, it is appropriate to consider adjunctive treatments, along with alternative (non-LDL-C) treatment targets, to help reduce residual risk in patients with optimal lipid management on statin therapy or in individuals who are intolerant of statins. Indeed, a meta-analysis of 23 trials showed that reducing LDL-C and raising HDL-C levels provided an additive benefit in lowering CVD rates and that only regimens combining a statin, a bile acid resin, and/or niacin induced atherosclerotic regression and were associated with a greater than 60%

decline in CV events (Figure 1).¹⁴ Elevated TG levels may also represent a risk factor or marker for CHD. In a meta-analysis of 29 prospective studies, individuals whose TG levels were within the highest tertile had an adjusted odds ratio for CHD of 1.72 (95% confidence interval, 1.56–1.90; $P < .05$) compared with those in the lowest tertile.¹⁵

Recent analyses of landmark randomized controlled trials of niacin combination therapy—particularly the Familial Atherosclerosis Treatment Study (FATS),¹⁶ the HDL Atherosclerosis Treatment Study (HATS),¹⁷ and the Armed Forces Regression Study (AFREGS)¹⁸—revealed that patients with MetSyn experienced more rapid atherosclerotic progression and a higher frequency of CV events than did their counterparts without MetSyn (Figure 2).^{16–19} The analysis also demonstrated that niacin-containing lipid therapy effectively decreased the relative risk of major CV events in patients with or without MetSyn (Figure 3).¹⁹

Although statins effectively reduce LDL-C levels, they typically elicit modest (~5%–10%), albeit statistically significant, increases in HDL-C levels.^{6,11} Consensus guidelines by the American Diabetes Association and American College of Cardiology recommended combination therapy, including nicotinic acid (niacin), for individuals with cardiometabolic risk who have low HDL-C or elevated apolipoprotein B (Apo B) levels despite maximally tolerated statin therapy.²⁰ Niacin is unique among all available lipid-modifying agents in exerting multidimensional beneficial effects across the entire lipid/lipoprotein spectrum, including all 3 components of the lipid triad. Niacin is the most effective agent available for raising HDL-C levels.²¹

Objectives of This Review: Disease Modification Paradigm and a Case Study Approach

The primary aims of the present review were to (1) review the efficacy and safety/tolerability profiles of

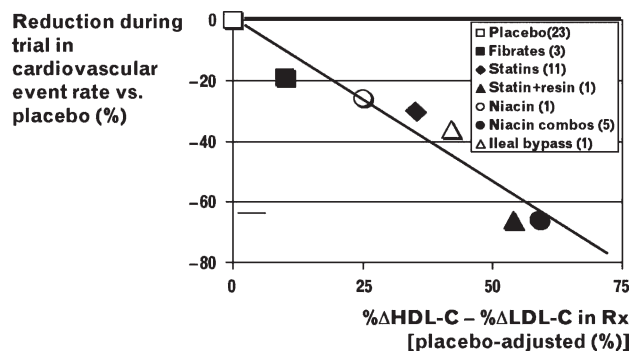
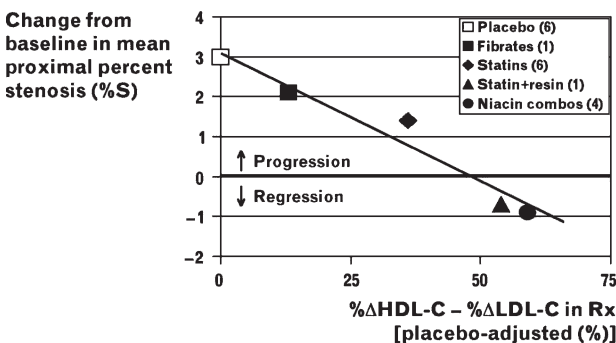


FIGURE 1. Effects of various drug classes on coronary stenosis progression or regression and effects of various drug classes on primary clinical event rates. HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Rx, therapy. Reproduced with permission from Brown et al.¹⁴

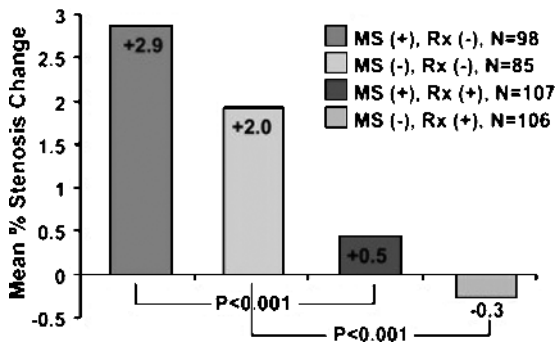


FIGURE 2. Change in mean proximal diameter coronary stenosis ($\Delta\%S_{prox}$) in patients with and without metabolic syndrome (MS) after intensive lipid therapy (Rx). Patients with MS had more rapid coronary stenosis progression than did those without (2.9% vs 2.0% stenosis for those not receiving Rx and 0.5% vs -0.3% stenosis for those receiving Rx; overall $P = .02$ after adjustment for treatment). Lipid therapy significantly decreased stenosis progression in patients with MS (0.5% vs 2.9% stenosis; $P < .001$) and induced regression in those without (-0.3% vs 2.0% stenosis; $P < .001$). Reprinted from Zhao et al.¹⁹ © 2009 with permission from Elsevier.

niacin-containing treatments, (2) identify potential candidates for such therapies, (3) delineate patient considerations concerning adherence to niacin therapy and patient-counseling themes to promote such adherence (ie, explaining the benefit-risk ratio of continuing to take niacin), and (4) provide strategies to minimize niacin flushing and other adverse effects. To illustrate these and other points, case studies largely drawn from the authors' practices are included, with an eye toward better acquainting clinicians with an emerging atherosclerotic disease-modification paradigm.

Background/Clinical Efficacy

A water-soluble vitamin (B_3), niacin has been in use as a lipid-lowering agent (at higher gram doses compared with milligram doses for vitamin supplementation) for more than 5 decades. As mentioned previously, niacin-containing regimens are among the few treatments that have demonstrated reduction in atherosclerotic progression (or induced regression) and/or prevented the majority of clinical events in randomized controlled trials.^{17,18,22-28} Despite its long clinical track record and multidimensional benefits across the lipid/lipoprotein panel, niacin use may be suboptimal in actual clinic practice, in part because many patients find it difficult to tolerate. In fact, niacin has a very favorable benefit-risk ratio, and clinicians managing patients at risk for CVD are ideally poised to counsel appropriate candidates for therapy about dyslipidemia and its attendant clinical risks, the potential beneficial effects of niacin on these risks, and sound strategies to enhance niacin tolerability.

Table 2 summarizes key studies^{16-18,22-24,26,28,29} that demonstrate the significant clinical benefits of niacin in reducing CV events and/or decreasing atherosclerotic progression (or inducing regression). Results of the HATS trial in patients with CHD, low HDL-C levels, and normal LDL-C levels showed an approximately 90% reduction in the incidence of CV events in patients receiving simvastatin/niacin compared with those receiving placebo ($P = .03$) and a 0.4% regression in average stenosis compared with a 3.9% progression among those receiving placebo ($P < .001$).¹⁷ More recently, in patients with CVD or CHD risk equivalents, the addition of niacin extended-release (NER) to statin therapy resulted in a significantly greater reduction in carotid intima-media thickness (CIMT) and significantly fewer clinical events compared with the addition of ezetimibe to statins.²⁶ Figure 4 illustrates the dose-dependent improvements in key lipid levels associated with treatment including an extended-release formulation of niacin (NER).^{11,30-33}

Niacin exerts its lipid-modifying effects through a complex mechanism of action that ultimately results in decreased mobilization of free fatty acids from adipose tissue to the liver and subsequent reductions in hepatic synthesis of TG and very low density lipoprotein (VLDL) particles.³⁴ Niacin also inhibits synthesis of Apo B, increases VLDL catabolism mediated via the activity of lipoprotein lipase, and seems to shift LDL

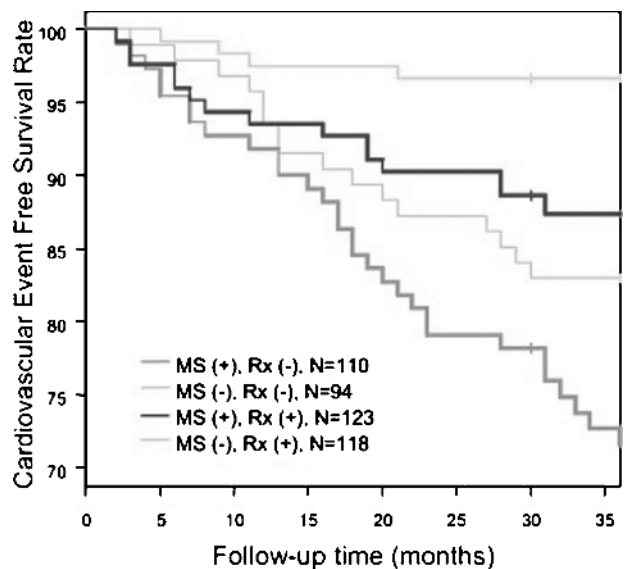


FIGURE 3. Kaplan-Meier curves of cardiovascular (CV) event-free survival by metabolic syndrome (MS) and therapy (Rx) status. Patients with MS had a higher rate of composite major CV events than did those without (28% vs 17% for those not receiving Rx and 13% vs 3% for those receiving Rx; overall $P = .01$). Lipid Rx significantly decreased the event rate in patients with (13% vs 28%; $P = .03$) and without (3% vs 17%; $P = .002$) MS. Reprinted from Zhao et al.¹⁹ © 2009 with permission from Elsevier.

TABLE 2 Efficacy and Tolerability Findings From Major Randomized Controlled Trials of Niacin-Containing Therapies

Study ^a	Population	Follow-up, y	Treatment, g (n) ^b	Changes From BL in BL in Lipids (Active Treatment), %	Changes From BL in Clinical/Angiographic/ Imaging Endpoints, % (Niacin vs Placebo or Other Comparator)	Frequency of Flushing (ever), % Adherence (Niacin vs Pbo or Other Comparator)
CDP ^{22,23}	Men 30–64 y post-MI	5–15	NIR 3.0 (1119) Pbo (2789)	TC, -10 TG, -19	-27 nonfatal MI (5 y) ($P < .05$) -11 total mortality (15 y) ($P = .0004$) Atherosclerotic regression: 16 NIR vs 2 pbo ($P = .002$)	Flushing: 92 vs 4 ($P < .05$) Mean adherence: 66 vs 78 Flushing: 91 vs 6 ($P < .01$)
CLAS ^{24,29}	Men 40–59 y post-CABG	2–4	NIR 3.0–12.0 (mean, 4.3) + BAR (80) Pbo (82)	TG, -22 LDL-C, -43 HDL-C, +37	Atherosclerotic regression: 16 NIR vs 2 pbo ($P = .002$)	Adherence: 86 NIR-BAR vs 89 pbo-BAR
FATS ¹⁶	Men ≤ 62 y with high Apo B + CHD	2.5	NIR 0.25–6.0 g + BAR 15–30 (36) Pbo-BAR (46)	TG, -29 HDL-C, +43 LDL-C, -32	Atherosclerotic regression: 39 NIR-BAR vs 11 pbo ($P < .005$) Clinical events ^c : 4 NIR-BAR vs 19 pbo-BAR ($P < .01$)	Adherence: 86 NIR-BAR vs 89 pbo-BAR
HATS ¹⁷	Adults <70 y with CHD + low HDL-C + ≥ 3 coronary arteries with $\geq 30\%$ stenosis	3	NSR 0.5–2.0 → NIR 3–4 g if inadequate \uparrow HDL (mean, 2.4) + SA (+0.1 g niacin) (33) Pbo (34)	TG, -36 LDL-C, -42 HDL-C, +26	Atherosclerotic regression: by 0.4 on niacin vs progression by 3.9 on pbo ($P < .001$) Clinical events ^d : 3 vs 24 (-90% ; $P = .03$)	Flushing: 30 vs 23 ($P = .35$) Adherence: 80 NSR-SA vs 80 pbo
ARBITER 2 ²⁸	Adults >30 y with CHD + low HDL-C on statin	1	NER 0.5–1.0 + statin (87) Pbo + statin (80)	TG, -13 LDL-C, -2 HDL-C, +21	CIMT progression: -0.004 vs +0.044 mm in euglycemics ($P = .026$)	Flushing: 69 vs 13 ($P < .001$) Adherence: 90–95 ($P > .05$ vs pbo) Flushing: 92 vs 25 ($P < .001$)
AFREGS ¹⁸	Adults <76 y with CHD + low HDL-C	2.5	GF 1.2 NIR 0.25–3 BAR 16 (71) Pbo + TLC (72)	TG, -46 LDL-C, -22 HDL-C, +38	Clinical events ^e : 13 vs 26 ($P = .04$)	Adherence: 87–90 vs 88–92
ARBITER 6-HALTS ²⁶	Adults with atherosclerotic CHD or vascular disease, CHD risk equivalent or 10-y Framingham absolute CHD risk $\geq 20\%$, and LDL-C <100 mg/dL and HDL-C <50 mg/dL (men) or <55 mg/dL (women)	1.2	NER 2.0 (target, or MDT) (97) or EZ 10 mg (111) + ongoing statin at stable dose	NER/statin: LDL-C, -12.4 HDL-C, +17.6 EZ/statin: LDL-C, -21.0 HDL-C, -6.5 ($P \leq .01$ for each between-group comparison)	CIMT progression: NER/statin: -0.0142 mm EZ/statin: -0.0007 mm ($P = .01$) Clinical events ^e : NER/statin: 1% incidence EZ/statin: 5% incidence ($P = .04$)	Flushing: 36 vs NA Adherence: 88 vs 95 ($P < .001$)

AFREGS, Armed Forces Regression Study; Apo B, apolipoprotein B; ARBITER, Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol; ARBITER-6-HALTS, Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol; BAR, bile acid resin (sequestrant); BL, baseline; CABG, coronary artery bypass graft; CDP, Coronary Drug Project; CHD, coronary heart disease; CIMT, carotid intima-media thickness; CLAS, Cholesterol-Lowering Atherosclerosis Study; EZ, ezetimibe; FATS, Familial Atherosclerosis Treatment Study; GF, gemfibrozil; HATS, HDL Atherosclerosis Treatment Study; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDT, maximum dose tolerated; MI, myocardial infarction; NIR, niacin extended-release; NIR, niacin immediate-release (ie, crystalline niacin); NSR, niacin sustained-release; pbo, placebo; SA, simvastatin; TC, total cholesterol; TG, triglyceride; TLC, therapeutic lifestyle counseling.

^aStudy reports presented in ascending order of date published for major clinical trials reporting data on both efficacy and tolerability/adherence.

^bNumber randomized.

^cDeath, MI, revascularization, or worsening ischemia.

^dCoronary death, MI, stroke, revascularization for worsening ischemia.

^eDeath from CHD, hospitalization for acute coronary syndrome, revascularization, MI.

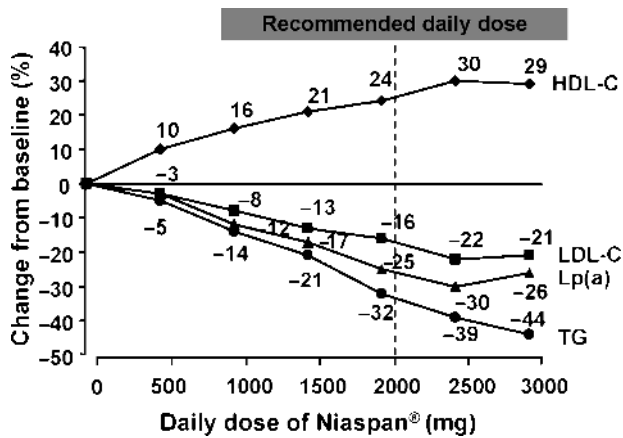


FIGURE 4. Dose-response curves for the efficacy of niacin extended-release in reducing plasma levels of triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), and lipoprotein(a) [Lp(a)] and in raising high-density lipoprotein cholesterol (HDL-C) level in patients with dyslipidemia. Reprinted from McGovern,³⁰ by permission of the European Society of Cardiology.

particle size distribution from predominantly small, dense LDL particles to larger, more buoyant, less atherogenic ones.³⁴ Small, dense LDL particles have been shown to be more atherogenic than larger, more buoyant particles. In vitro data suggest that niacin also has a beneficial effect on scavenger receptor class B type I-mediated cholesterol efflux and on adenosine triphosphate-binding cassette transporter A1-mediated cholesterol efflux from macrophages, an effect that can contribute to reverse cholesterol transport via niacin-mediated increases in HDL-C.³⁵ Emerging evidence also suggests that the beneficial effects of niacin may be mediated in part by its effects on acute atherosclerotic inflammation.^{36–38}

Indications for Niacin Use

Because niacin exerts beneficial effects on each of the key components of the lipid profile, it finds clinical application in the management of various atherogenic lipid phenotypes. In patients with primary hyperlipidemia and mixed dyslipidemia, niacin increases HDL-C and lowers total cholesterol (TC), LDL-C, Apo B, and TG levels.³⁹ Niacin also has been shown to lower TG levels in adults with severe endogenous hypertriglyceridemia (Fredrickson type IV hyperlipidemia).⁴⁰ Niacin is contraindicated in patients with active liver disease or unexplained persistent elevations in hepatic transaminases, active peptic ulcer disease, or arterial bleeding.⁴¹

Niacin has been associated with potentially adverse effects on glycemic regulation, including reduced peripheral insulin sensitivity. However, the effects of niacin (at ≤ 2.0 g/d), alone or in combination with

statins, on fasting glucose and glycosylated hemoglobin (hemoglobin A_{1c}) levels have been shown to be modest, transient, reversible, and typically amenable to adjustments in oral hypoglycemic regimens without discontinuing niacin.⁴² On a population basis, the significant reductions in the incidences of CV events and atherosclerotic progression clearly outweighed the typically mild, manageable and reversible effects of niacin on glycemic regulation.⁴²

Patient Considerations in Adherence to Niacin Therapy

Until a CV event occurs, atherosclerotic CHD is an essentially asymptomatic condition. Because atherosclerosis can be diagnosed before a clinical event occurs, and because approximately 50% of men and 64% of women who die suddenly of CHD have no previous symptoms of the disease,⁴³ the goal of treatment is to identify subclinical atherosclerosis and stabilize or reverse atherosclerotic plaque.

According to the Health Belief Model,^{44–47} patients are more likely to adhere to a medication regimen if they perceive themselves to be susceptible to a disease and believe that the medication can reduce this susceptibility (without causing offsetting untoward effects). Hence, to promote niacin adherence, even in the face of ostensibly silent benefits yet distressing, palpable adverse effects, clinicians need to facilitate an informative dialogue to enhance patients' understanding of treatment benefits. Initially, this may be a somewhat "tough sell" because patients at risk for, or living with, a chronic, progressive disease such as CHD are being asked to take a medication that may cause unpleasant adverse effects although they "feel healthy" and have no overt symptoms of atherosclerosis. In many patients' minds, the treatment (ie, niacin) creates more symptoms than the disease itself. The "symptom" usually seen is cutaneous vasodilation with flushing, a receptor-mediated, prostaglandin (PGD₂ and PGE₂)–driven response.^{48–51}

Table 3 offers some key "talking points" to foster the needed dialogue and potentially strengthen the clinician-patient alliance.⁵¹ It is important for patients to understand that, although the statin therapy that they may already be taking reduces the risk of CHD events or death by as much as 30% to 40%,^{52–54} introduction of niacin to the medication regimen can further help to reduce most CV events.^{17,18,22–28} It should also be emphasized that the benefits of niacin are ongoing or "continuous" when the medication is taken as directed. This point is amply illustrated by the 15-year follow-up study of the Coronary Drug Project (CDP), in which the initial niacin treatment group experienced a significant 11% reduction in all-cause mortality.²² By contrast, the adverse effects of

TABLE 3 Patient Education About Niacin and Flushing

1. Why has your clinician prescribed treatment with niacin (or a niacin-containing treatment)?
 - You have had a heart attack (myocardial infarction), stroke, or other disease of your blood vessels (arteries); and/or
 - You have a pattern of blood lipids (“dyslipidemia”) that can cause a serious disease of your arteries (“atherosclerosis”) and increase your risk of having a heart attack or stroke. This includes low levels of “good” (HDL) cholesterol.
 - You may feel fine. However, you are still at higher risk and need to take your niacin to prevent a myocardial infarction or stroke.
2. What is niacin flushing?
 - It is a feeling of warmth/“prickly heat” with redness, usually in your face or torso; itching; and/or tingling. It is not an allergy.
 - Scientists believe that it is caused when niacin dilates small blood vessels (capillaries) in your skin.
 - Many people who use niacin for the first time experience flushing within about 2 h, and it usually lasts from several minutes to 1–3 h.
 - Niacin flushing may be uncomfortable or even disrupt your sleep but usually does not reduce quality of life.
 - Many niacin users flush less often and/or less severely over time (especially after the first week or two) while on the drug.
3. Why is it important to try your best to keep taking your niacin despite flushing?
 - Unlike flushing, which usually passes in 1–3 h, the benefits of niacin are continuous (if you keep taking it!).
 - Within weeks of taking your niacin, the health of your arteries should improve.
 - Within months, your atherosclerosis may slow or stop progressing (or even reverse), and you can prevent a heart attack or stroke.
 - Within years, you can prevent a heart attack, stroke, or other causes of death.
 - Every time you increase your niacin dose by 500 mg (0.5 g) up to about 2000 mg (2.0 g), you can raise your HDL (good) cholesterol level by 8% and lower your LDL (bad) cholesterol level by 4%.
4. What can you do to prevent or reduce niacin flushing (besides discussing it with your clinician)?
 - Take an aspirin or NSAID 30 minutes before, with, or shortly after taking your niacin.
 - Take your niacin with a low-fat snack (eg, applesauce, piece of fruit, low-fat yogurt) to avoid having a stomachache or other digestive symptoms. This may also help to increase the amount of niacin your body absorbs.
 - Be aware that eating spicy foods, drinking hot beverages or alcohol, and taking hot showers or baths after taking your niacin can potentiate flushing.
 - Try not to miss doses of your niacin. If you do, your clinician may advise you to restart your medicine at a lower dose (eg, the dose you originally started with) and take an aspirin or NSAID as you did when initially using the medication.

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; NSAID, nonsteroidal anti-inflammatory drug.

Data from Jacobson (reproduced with permission of Dowden Health Media, Inc, conveyed through Copyright Clearance Center, Inc).⁵¹

niacin are typically transient. In a recent study, 53% of niacin users did not reach recommended daily maintenance doses of greater than 1.0 g (and 92% did not reach 2 g), with the severity of flushing significantly predicting niacin treatment discontinuation.^{55,56} Patients need to understand that, although flushing is nearly uniform when initiating or restarting niacin dosing, this cutaneous vasoactive manifestation typically resolves within a matter of days or weeks with continued dosing.

Overview of Niacin Formulations, With a Focus on Safety/Tolerability Profiles

Niacin immediate-release (NIR; also termed *plain* or *crystalline* niacin) was the earliest formulation available, with some being available as dietary supplements and others with US Food and Drug Administration (FDA)–approved labeling as lipid-modifying therapies (NIACOR [Upsher-Smith, Maple Grove, Minnesota]). Niacin sustained-release (NSR) formulations combined crystalline niacin with an inert (resinous) base to limit flushing via a slower release of drug (SLO-NIACIN [Upsher-Smith] and Nicobid [sanofi-aventis]).²⁵ Endurance Products Company (Tigard, Oregon) manufactured niacin formulated in a wax matrix (ENDUR-ACIN). Inositol hexanicotinate (Niacinol [Integrative Therapeutics, Green

Bay, Wisconsin]) is a synthetic prodrug comprising 6 niacin molecules chemically attached to 1 molecule of inositol. Promoted as “flush-free,” it is likely also to be “effect-free” because of the limited bioavailability of this formulation of niacin and the absence of substantive data indicating beneficial lipid effects.^{57,58}

Three FDA–approved prescription formulations containing NER are available in the United States: Niaspan,⁴¹ NER/lovastatin (Advicor),⁵⁹ and NER/simvastatin (Simcor⁶⁰; all from Abbott, Abbott Park, Illinois).

According to the American Heart Association, nonprescription, dietary supplement formulations of niacin should not be considered equivalent to prescription formulations. “Nonprescription immediate-release forms of niacin usually have the most side effects. Dietary supplement niacin is not regulated by the FDA the same way that prescription niacin is. It may contain widely variable amounts of niacin: from none to much more than the label states. The amount of niacin may even vary from lot to lot of the same brand.”⁶¹ Given these considerations, the American Heart Association⁶¹ concluded that “dietary supplement niacin must *not* be used as a substitute for prescription niacin.” Use of nonprescription formulations is of particular concern with sustained-release niacin dietary supplements, which have been associated with

severe liver toxicity at very high doses.⁶² Furthermore, a meta-analysis of randomized controlled trials demonstrated more pronounced HDL-C-raising effects of NIR (average of 23% increase) and NER (22% increase) compared with NSR (13% increase).⁶³

Brief Overview of Niacin Flushing Pathophysiology

Niacin-stimulated GPR109A receptors located on epidermal Langerhans cells allow increases in cytosolic calcium, which trigger the mobilization of arachidonic acid and its conversion to the vasodilator prostaglandins PGD₂ and PGE₂, which in turn drive the characteristic flushing response.^{48,64} Flushing can be blunted or prevented by blocking PGD₂ synthesis via inhibition of cyclooxygenase (COX; chiefly COX-1) using aspirin (acetylsalicylic acid) or nonsteroidal anti-inflammatory drugs (NSAIDs). These agents help to prevent or minimize flushing by attenuating the rise in PGD₂.⁶⁵ (For a comprehensive review of niacin flushing, see Jacobson⁵¹ or Kamanna.⁶⁶) The choice of medication used to blunt the niacin flushing response should be made on an individual patient basis.

Niacin is metabolized via 2 saturable pathways that mediate all pharmacodynamic effects—a low-affinity, high-capacity conjugative pathway and a high-affinity, low-capacity amidative pathway.^{67,68} Niacin immediate-release rapidly saturates the low-capacity amidative pathway because it is completely absorbed from the gastrointestinal (GI) tract in 1 to 2 hours and is thus primarily metabolized by the high-capacity conjugative pathway (associated with flushing).^{25,69–71} Niacin sustained-release is not completely dissolved and absorbed from the GI tract for more than 12 hours. This slower absorption profile results in metabolism primarily via the amidative pathway and is more frequently associated with hepatic or GI adverse effects.^{69–71} Niacin extended-release has an intermediate dissolution and absorption profile (8–12 hours).^{67,71}

Typical Clinical Presentation of Niacin Flushing

Flushing is experienced initially by nearly all niacin users, typically starting 15 to 30 minutes after NIR administration, 30 to 120 minutes after NER administration, or at more variable times after NSR administration.⁷¹ Patients typically describe flushing as a perception of “prickly heat” or other sensation of warmth in the face, neck, ears, trunk, and, less frequently, the extremities. Flushing is often associated with erythema, itching, and tingling, and symptoms typically last for less than 1 hour up to 2.5 hours.^{72,73} It typically subsides in intensity and frequency over time, as long as there are no major lapses in dosing of the medication.⁵¹

Frequencies of Flushing and Related Discontinuations With Niacin-Containing Regimens

In several landmark trials of niacin (primarily NIR) with or without bile acid resins, discontinuation of treatment was observed in only a fraction of patients who reported flushing (2.5%–10% discontinuing treatment vs 92% experiencing flushing) (Table 2).^{17,18,22–26} A number of other studies examining lipid outcome measures in response to NER-containing regimens have shown that (1) 29% to 74% of patients experienced at least 1 flush, (2) 75% to 92% of flushing episodes were rated as mild or moderate, (3) the incidence of flushing decreased with continued treatment, and (4) approximately 4% to 12% of patients discontinued niacin treatment because of flushing.^{74–79}

“How to Beat a Flush”: Strategies to Prevent or Manage Niacin Flushing

Pharmacotherapeutic Strategies

Aspirin represents 1 possible option to prevent or limit niacin flushing. The number of flushing-related discontinuations and the proportion of patients experiencing moderate or greater flushing have also been reduced with the associated use of aspirin.^{80,81} Attenuation of flushing and itching observed with aspirin 325 mg was significantly greater than that observed with ibuprofen 200 mg.^{82–84} Because flushing is typically a time-limited phenomenon, aspirin or NSAIDs may be viewed as temporary “bridges” over flushing during the first few weeks of treatment, when niacin doses are being titrated, or when restarting treatment after a lapse in dosing.⁵¹ In light of the documented association of COX-2 inhibition with adverse CV effects, and the ability of aspirin at higher doses to inhibit COX-2 (when it loses the COX-1 selectivity of lower doses), all clinicians should discuss these issues with patients to whom they recommend aspirin or NSAIDs to minimize flushing.^{85,86}

Titration of niacin dosing should be individualized for each patient. This individualization process can be fostered during a scheduled follow-up visit approximately 4 to 8 weeks after treatment initiation, when patient concerns about flushing are likely to be identified and both lipid and other biochemical parameters (eg, liver enzymes) are assessed. Some patients will benefit from a “start-low-and-go-slow” approach to niacin dosing, whereas others will tolerate bolder dose advances. Manufacturers’ labeling for NER does not recommend an increment of more than 0.5 g in niacin daily dosing every 4 weeks.⁴¹ One approach is to administer NER 0.5 g over weeks 1 to 4, 1.0 g over weeks 5 to 8, and then titrate to the maximum dose

(2.0 g) according to patients' responses and tolerance in the following weeks. Follow-up laboratory testing enables the clinician to assess the safety and tolerability of niacin and make appropriate adjustments in dosage and, importantly, review key counseling messages. At subsequent follow-up visits, the CVD and lipid benefits of niacin should be reinforced and patients focused on achievable intermediate objectives (eg, cholesterol goal attainment) to promote adherence; making and keeping laboratory follow-up appointments have been associated with enhanced lipid-altering medication adherence.⁸⁷

Counseling Strategies and Messages to Prevent or Manage Niacin Flushing

As discussed previously, patients with dyslipidemia, who are largely asymptomatic, may be reluctant to take a medication that initially causes distressing adverse effects. It is therefore essential to contrast the stable, long-lasting benefits of continuing niacin therapy in preventing CVD against the transient nature of niacin flushing (Table 3).^{51,88} Patients need to know that, for many individuals who have CVD or are at otherwise elevated risk, niacin treatment is often needed throughout adulthood. Flushing and GI tolerability can be improved by taking niacin before bedtime with a low-fat, high-fiber, high-pectin snack with a low glycemic index (eg, apple sauce) or by taking it with the evening meal, which may also increase niacin's bioavailability.⁸⁹ Ideally, niacin should be taken at nighttime so that flushing has a better chance of passing unnoticed during sleep and nocturnal release of free fatty acids is blunted. To counter the perception of heat associated with flushing, patients may wish to take niacin with a cold (nonalcoholic) beverage, and they should be counseled to avoid alcohol, spicy foods, hot beverages, and/or hot showers or baths around the time of dosing, which can potentiate flushing effects. Patients should also be advised to avoid missing doses and note lapses in dosing to their clinicians. Ongoing patient counseling by clinicians and reminders may assist in promoting niacin adherence.⁹⁰

Case Studies*

Case Study 1: A Patient With Metabolic Syndrome

Exposition

A 58-year-old Hispanic American man with no history of CVD visited his primary care provider for

a physical examination, as required for a new job. Five years earlier, he had been informed that he had "prediabetes" but had not seen a clinician since then. He was referred to the CVD prevention clinic for his dyslipidemia. The patient's family history was significant for diabetes and stroke in both parents, but he had no significant medical history of CVD or hospitalizations. He enjoyed rich food and strayed from his diet frequently, admitted to drinking 1 or 2 beers daily, but did not smoke cigarettes. Baseline lipid panel values were as follows: TC, 215 mg/dL; TG, 312 mg/dL; HDL-C, 32 mg/dL; LDL-C, 121 mg/dL; and direct LDL-C, 140 mg/dL. The patient was 5 ft 10 in tall and weighed 222 lb (for a body mass index of 31.8 kg/m²). His blood pressure was 140/90 mm Hg. Other relevant baseline risk factors for CVD are summarized in Table 4.

Based on the initial presentation, this patient's estimated 10-year risk of developing CHD using Framingham risk assessment equations was 14%. The patient was started on NER/simvastatin 0.5 g/20 mg and counseled to take the medication at bedtime with a low-fat, high-fiber snack, such as apple sauce or whole-wheat crackers, to help improve the GI tolerability and increase the likelihood that any flushing might go unnoticed during sleep. He met with a registered dietitian to review his eating habits, learn measures to prevent diabetes, and develop a plan to lose weight and increase his level of activity.

At 4 weeks, the patient was congratulated for losing weight and achieving lower TG levels (220 mg/dL) (Table 4). His daily dose of NER/simvastatin was increased to 1 g/40 mg. He reported occasional mild flushing and was reminded to take the medicine nightly, because missing doses might result in a return of, or an increase in, flushing. The patient was encouraged to visit the registered dietitian again and increase his level of exercise (to walking up to 45 minutes daily).

At 8 weeks, there were further decreases in TG level (to 190 mg/dL), LDL-C level (to 108 mg/dL), and body weight (to 205 lb) and an increase in HDL-C level (to

TABLE 4 Laboratory Results for Case Study 1: Baseline and Lipid Clinic Visits at 4-Week Intervals

	Baseline	4 wk	8 wk	12 wk
Cholesterol, mg/dL	215	210	188	160
Triglycerides, mg/dL	312	220	190	155
High-density lipoprotein cholesterol, mg/dL	32	35	42	43
Low-density lipoprotein cholesterol, mg/dL	121	133	108	86
Fasting blood glucose, mg/dL	118	120	110	105
Hemoglobin A _{1c} , %	6.8	6.8	6.8	6.7
Body mass index, kg/m ²	31.8	30.4	29.4	28.4
Weight, lb	222	212	205	198

*Authors' note: The following case studies are largely based on the authors' practices but also contain supplemental information to enhance educational messages. These cases and the information they convey should not be substituted for clinician judgment and decision making in individual patients.

42 mg/dL) (Table 4). The patient was encouraged to continue to lose weight and to exercise; his NER/simvastatin dose was increased again, to 1.5 g/40 mg, and ezetimibe 10 mg (Zetia, Merck and Co, Inc, Whitehouse Station, New Jersey) was introduced into the regimen. At 12 weeks, the patient had achieved further reductions in TG and LDL-C levels.

Author Commentary

Multiple risk factors, including the presence of MetSyn, low HDL-C level, elevated TG level, and elevated LDL-C level, were identified in this patient's initial presentation, which placed him at high risk for a CV event. The choice of a statin-niacin combination regimen for this patient was supported by subgroup analyses of 2 landmark trials (CDP and HATS) that focused specifically on the benefits of niacin in patients with (vs without) MetSyn and CHD in eliciting reductions in atherosclerotic progression and preventing clinical events.^{91,92} In a post hoc analysis of the HATS trial, a significant 47% reduction in the incidence of CV events was observed in the subgroup of patients with MetSyn that was comparable to the decline observed in the overall patient population treated with niacin/simvastatin (60% reduction).⁹¹ In a post hoc analysis of the CDP, niacin treatment decreased the 6-year recurrence of myocardial infarction and 15-year all-cause mortality to a similar degree among patients with or without MetSyn.⁹²

Case Study 2: A "Healthy," Asymptomatic Patient

Exposition

A 45-year-old man with no CV symptoms visited a CVD prevention clinic for an annual physical examination.

His most recent examination was during his senior year in high school. His current daily medications included a multivitamin, aspirin 81 mg, and vitamin C. The 10-year Framingham Risk Score was 3%. The patient's family history was significant for hypertension (mother) and acute coronary syndrome (father, at age 52 years).

The patient's baseline lipid panel values were as follows: TC, 232 mg/dL; TG, 221 mg/dL; HDL-C, 35 mg/dL; and LDL-C, 153 mg/dL. Other relevant baseline laboratory values, structural test results, and risk factors for CVD are summarized in Table 5.

The workup resulted in the following diagnoses: hypertension; hyperlipidemia; atherosclerotic CVD (ASCVD) identified with a mean CIMT of 0.736 mm; insulin resistance with impaired fasting glucose; and MetSyn.

Medical management, which was titrated over a course of 6 to 9 months, included pravastatin 40 mg, NER 1.0 g, ramipril 10 mg, and aspirin 81 mg. The patient was advised to take niacin at bedtime with a low-fat, high-fiber snack and to avoid alcohol, spicy foods, or hot beverages for several hours before or after niacin dosing.

After 1 year of treatment, the patient experienced marked improvements in most biochemical CV risk markers (TC, 159 mg/dL; TG, 98 mg/dL; LDL-C, 107 mg/dL), blood pressure, and atherosclerotic plaque regression as evidenced by reduced CIMT (0.638 mm) and no identified plaque (all <1.2 mm). Over the second year of treatment, lifestyle modifications (weight loss and exercise) and medication regimen changes (addition of prescription ω -3 fatty acid ethyl esters [P-OM3s] 2.0 g and replacement of pravastatin and NER with NER/simvastatin 1 g/40 mg) resulted

TABLE 5 Case Study 2: Laboratory and Structural Test Results at Baseline and After 1 and 2 Years of Treatment

	Baseline	1 y of Treatment	2 y of Treatment
Blood pressure, mm Hg	132/98	126/84	NA
Weight/waist circumference, lb/in	205/42	206/41	178/34
Total cholesterol, mg/dL	232	159	118
TG, mg/dL	221	98	74
HDL cholesterol, mg/dL	35	32	43
LDL cholesterol, mg/dL	153	107	60
TG/HDL	6.3	3.1	1.7
Fasting blood glucose, mg/dL	118	93	92
Hemoglobin A _{1c} , %	5.4	5.3	5.4
Advanced cardiovascular risk markers			
Apolipoprotein B, mg/dL	126	82	NA
HDL, 2b fraction, %	11	NA	NA
LDL 3a + 3b, %	37	NA	NA
Fibrinogen, mg/dL	382	NA	NA
High-sensitivity C-reactive protein, mg/L	2.0	1.7	NA
Initial structural tests			
Common carotid artery intima-media thickness	Mean, 0.736 mm; maximum focal plaque, 1.5 mm; 1.2-mm soft plaque at left bifurcation; 1.5-mm primary and 1.1-mm secondary soft plaque at right bifurcation	Mean, 0.638 mm; no plaque identified; all <1.2 mm	NA

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not applicable or not available; TG, triglyceride.

in further lipid panel improvements (TC, 118 mg/dL; TG, 74 mg/dL; HDL-C, 43 mg/dL; LDL-C, 60 mg/dL) (Table 5).

Author Commentary

The multifactorial risk factor assessment and aggressive management exemplified in this case represent an emerging disease-modification paradigm approach to treating atherosclerosis. Several reliable, noninvasive measures are available to detect subclinical atherosclerosis in asymptomatic patients, including carotid artery ultrasonography to detect plaque and determine CIMT; computed tomography (CT) to assess calcification of the coronary arteries and determine a coronary artery calcium score; and stress echocardiography to evaluate obstructive CHD.^{93,94} Selective use of such methods may refine traditional risk factor assessment to better guide the initiation or intensification of appropriate treatment to slow the progression (or induce regression) of underlying atherosclerotic disease.^{95,96} Consensus has yet to be reached regarding the population to be targeted for these imaging tests, with opinions ranging from aggressive screening of all asymptomatic middle-aged and older men and women⁹⁷ to a recommendation by the US Preventive Services Task Force against screening adults at low risk for CHD⁹⁸ to recommendations for screening only individuals at intermediate or higher CV risk.^{99,100}

Treatments with NER plus a statin along with P-OM3s in this case were initiated to manage the patient's hyperlipidemia and ASCVD. As discussed previously, a number of clinical trials and several meta-analyses have demonstrated that niacin-containing regimens are among the few treatments that have elicited both reductions in atherosclerotic progression (or induced regression) and also prevented most clinical events in randomized controlled trials.

Case Study 3: Secondary Prevention

Exposition

A 58-year-old woman presented to a CVD prevention clinic without CV symptoms; however, her diagnoses included CHD, hypertension, hyperlipidemia, and DM2. She had had revascularization of the left anterior descending artery with placement of drug-eluting stents in 2001 and twice in 2003. Her family history was significant for CHD (sister and father [died]), stroke (mother [died]), and DM2 (father). The patient was 5 ft 4 in tall and weighed 166 pounds, with a waist circumference of 39.5 in (100.3 cm). Her blood pressure was 128/76 mm Hg, and her pulse was 72 beats per minute. Medications on presentation were metformin 500 mg twice a day, a high-dose high-potency statin, lisinopril 10 mg daily, aspirin 81 mg (clopidogrel discontinued in 2005 per cardiologist),

and dietary supplements including ω -3 fatty acid supplement and flaxseed.

The patient's baseline lipid levels were as follows: TC, 145 mg/dL; TG, 165 mg/dL; HDL-C, 55 mg/dL; and LDL-C, 57 mg/dL. The ankle-brachial index indicated borderline peripheral artery disease (right, 0.94; left, 0.92). Results of single photon emission CT (SPECT) from 2003 indicated anterior and apical ischemia. Other relevant baseline laboratory values and risk factors for CVD are summarized in Table 6.

On the basis of the foregoing workup and findings, optimization of the treatment plan included switching from monotherapy with a high-dose, high-potency statin to a combination of NER titrated up to 1.5 g daily plus a lower-potency statin while continuing with ω -3 fatty acid supplementation, aspirin 81 mg, and lisinopril. After 1 year of treatment, the patient experienced marked improvements in TG and HDL-C levels (TG, 38 mg/dL; HDL-C, 73 mg/dL) without erosion in glycemic control (Table 6). In addition, atherosclerotic plaque regression was evidenced by reduced heterogeneous plaque on ultrasonographic imaging at year 1 (2.0 mm) and at year 2 (1.7 mm). Results of a repeat SPECT 5 years after the first one did not reveal any trace of the previously noted anterior and apical ischemia.

Author Commentary

The "recidivistic" pattern of events (multiple revascularization events) in this patient while receiving statin monotherapy constitutes a relevant example of residual CV risk. The decision to add NER to the statin regimen to help manage this patient's ASCVD was

TABLE 6 Case Study 3: Laboratory Test Results at Baseline and After 1 and 2 Years of Treatment

	Baseline	1 y of Treatment	2 y of Treatment
Total cholesterol, mg/dL	145	167	157
Triglycerides, mg/dL	165	38	37
High-density lipoprotein cholesterol, mg/dL	55	73	77
Low-density lipoprotein cholesterol, mg/dL	57	86	73
Apolipoprotein B, mg/dL	68	68	56
Fibrinogen, mg/dL	406	NA	342
Urinary microalbumin/creatinine ratio, mg/g	10.2	7.0	4.4
High-sensitivity C-reactive protein, mg/L	0.6	0.6	0.7
Lp-PLA ₂ , ng/mL	190	174	165
Fasting blood glucose, mg/dL	168	101	106
Hemoglobin A _{1c} , %	6.6	6.2	6.4
Blood pressure, mm Hg	128/76	100/78	102/72
Waist circumference, in	39.5	38.0	38.5

Abbreviations: Lp-PLA₂, lipoprotein-associated phospholipase A2; NA, not applicable or not available.

Clinical Pearls

- Type 2 diabetes mellitus, MetSyn, and other insulin-resistance syndromes are increasingly frequent reasons for visits to clinicians.
- Although reducing LDL-C levels remains the chief objective of coronary-prevention strategies, many patients with the foregoing conditions do not have profoundly elevated LDL-C levels and hence harbor residual CV risk even after optimal treatment with LDL-C-lowering medications (principally statins).
- To raise HDL-C levels and confer other, multidimensional benefits across the lipid and lipoprotein panel, niacin (nicotinic acid) is the single most effective available medication.
- Despite decades of clinical experience with niacin at lipid-altering doses, many patients eligible for such therapy either do not receive a prescription or do not continue to adhere to their regimens.
- By contrasting the significant, lasting benefits of long-term niacin treatment on both clinical and angiographic/imaging endpoints against the transient, largely reversible nature of flushing, the clinician can help patients to realize the full cardioprotective benefits of niacin.

supported by findings from the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: HDL and LDL Treatment Strategies (ARBITER-6-HALTS) study, which reported significant benefits of NER/statin on both mean and maximal CIMT in patients with known ASCVD or a CHD risk equivalent.²⁶ This benefit of NER/statin was superior to that conferred by ezetimibe/statin despite similar reductions in non-HDL-C and Apo B levels, suggesting that some of the clinical benefits of the niacin-containing regimen may be ascribed to other salutary lipid (or nonlipid) effects.

Conclusions

Niacin has been in use as a lipid-lowering agent for more than 50 years. Treatment with this water-soluble vitamin improves the entire lipid panel in patients with dyslipidemia and is the most effective available agent for raising HDL-C levels. Niacin-containing regimens are among the few lipid therapies that have both elicited reductions in atherosclerotic progression (or elicited regression) and prevented most clinical events in randomized controlled trials. However, niacin continues to be perceived as difficult and time-consuming to administer. Obstacles to more widespread use include tolerability and safety issues, particularly niacin's association with cutaneous flushing. Effective counseling concerning the highly favorable benefit-risk ratio for niacin, along with careful dose escalation; follow-up monitoring; regimen adjustments and optimization via strong, 2-way communications between clinicians and

patients; and the use of behavioral modifications and treatment adjuncts (eg, aspirin) can improve patient adherence with niacin therapy and optimize overall treatment outcomes. Clinicians managing patients at risk for or living with CVD are ideally poised to enunciate these key benefit-risk counseling messages and hence encourage wider use of this cardioprotective medication by appropriate candidates with CVD or elevated CVD risk.

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