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NONSTATIN DRUGS (W BORDEN, SECTION EDITOR)

Niacin: The Evidence, Clinical Use, and Future Directions

Todd C. Villines · Andrew S. Kim · Rosco S. Gore · Allen J. Taylor

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Abstract The use of FDA-approved niacin (nicotinic acid or vitamin B3) formulations at therapeutic doses, alone or in combination with statins or other lipid therapies, is safe, improves multiple lipid parameters, and reduces atherosclerosis progression. Niacin is unique as the most potent available lipid therapy to increase high-density lipoprotein (HDL) cholesterol and it significantly reduces lipoprotein (a). Through its action on the GPR109A receptor, niacin may also exert beneficial pleiotropic effects independent of changes in lipid levels, such as improving endothelial function and attenuating vascular inflammation. Studies evaluating the impact of niacin in statin-naïve patients on cardiovascular outcomes, or alone and in combination with statins or other lipid therapies on atherosclerosis progression, have been universally favorable. However, the widespread use of niacin to treat residual lipid abnormalities such as low HDL cholesterol, when used in combination with statins among patients achieving very low (<75 mg/dL) low-density lipoprotein cholesterol levels, is currently not supported by clinical outcome trials.

Keywords Niacin · Nicotinic acid · Lipids · HDL cholesterol · Lipoprotein (a) · Apolipoprotein B · Statin · Atherosclerosis · Atherosclerosis imaging · Combination lipid therapy · Laropiprant

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T. C. Villines (✉) · A. S. Kim · R. S. Gore
Cardiology Service, Department of Medicine,
Walter Reed National Military Medical Center,
8901 Rockville Pike,
Bethesda, MD 20889, USA
e-mail: todd.villines@us.army.mil

A. S. Kim
e-mail: andykim419@gmail.com

R. S. Gore
e-mail: rosco.gore@med.navy.mil

A. J. Taylor
Washington Hospital Center,
110 Irving Street Northwest,
Washington, DC 20010-3017, USA
e-mail: Allen.taylor@medstar.net

A. J. Taylor
Georgetown University School of Medicine,
110 Irving Street Northwest,
Washington, DC 20010-3017, USA

T. C. Villines
Uniformed Services University School of Medicine,
4301 Jones Bridge Road,
Bethesda, MD 20814, USA

Introduction

Statin therapy is unquestionably the cornerstone of contemporary lipid management. Numerous well-designed, large clinical outcomes trials using statin monotherapy have demonstrated a 20% to 40% relative risk reduction in major adverse cardiovascular events [1]. However, despite the widespread adoption of increasingly intensive statin therapies [2–4], which primarily reduce low-density lipoprotein cholesterol (LDL-C), residual lipid abnormalities such as low levels of high-density lipoprotein cholesterol (HDL-C), and elevated levels of various apolipoprotein B (apoB) particles are prevalent [5], confer residual cardiovascular risk, and serve as potential targets for cardiovascular risk reduction using combination lipid therapies. Current cholesterol treatment guidelines, while appropriately making targeted LDL-C reduction the primary goal of

lipid treatment, acknowledge the use of adjunctive lipid agents typically added to statin therapy, to include fibrates, bile acid resins, and niacin in specific dyslipidemic patients but remain vague in the scope of these recommendations [6].

Among non-statin agents, niacin (nicotinic acid or vitamin B3), first-described as a lipid-modifying agent in 1955 [7] and the oldest lipid-lowering drug to date, is unique in its lipid-modifying and anti-atherosclerotic effects. At standard treatment doses, niacin reduces all apoB-containing particles, such as LDL-C, very-low-density lipoprotein cholesterol (VLDL-C), triglycerides (TG), and lipoprotein (a), but is most commonly clinically utilized because it is currently the most effective available medication for raising HDL-C. Large, prospective epidemiologic studies have consistently demonstrated HDL-C levels to be strongly inversely related to cardiovascular risk, independent of LDL-C, body mass index, and other standard cardiovascular risk factors [8]. Low HDL-C is commonly encountered among high-risk patients, especially those with diabetes and/or established cardiovascular diseases despite intensive statin treatment. Among patients treated with statins, residual HDL-C levels remain a powerful independent residual risk factor for cardiovascular events independent of the degree of LDL-C reduction or statin dose [9, 10]. Niacin may also have important beneficial pleiotropic effects independent of changes in lipid levels, including improving endothelial function, attenuating vascular inflammation, enhancing plaque stability, and exerting an anti-thrombotic effect [11]. Several pivotal studies have demonstrated that niacin therapy alone or in combination with other lipid-reducing therapies, compared to placebo, significantly reduces atherosclerosis progression, cardiovascular events, and long-term mortality when used in high-risk patients [12, 13••, 14–18, 19••, 20, 21•, 22]. Among high-risk patients on appropriately intensive stable statin therapy, the addition of niacin has been shown to be safe and to consistently significantly improve measures of atherosclerosis progression compared to statin monotherapy [17, 18] or the addition of ezetimibe [21•]; however, large-scale outcomes trials supporting its widespread use in combination with statins are currently lacking. This article summarizes and highlights the relevant evidence on niacin, its clinical application and future research, and directions involving this long-standing, unique lipid therapy.

Mechanisms of Effect

Niacin (nicotinic acid or vitamin B3) acts via the G protein–coupled receptor (GPR109A), which inhibits the formation of intracellular cyclic adenosine monophosphate and down-regulates lipolysis and the production of free fatty acids [23–25]. This leads to a decrease in the amount of free fatty acids available to the liver for the production of TG and VLDL-C. Decreased levels of VLDL-C lead to diminished hepatic and peripheral production of IDL-C and LDL-C. In addition, niacin also directly inhibits hepatocyte diacylglycerol acyltransferase-2, a key enzyme for TG synthesis. Although the precise mechanism by which niacin induces HDL-C levels to rise is unclear, it is thought to be a multi-faceted process. Niacin increases apolipoprotein A1 (apoA1) levels primarily through lowering of its catabolic rate, resulting in increased apoA1 HDL subfractions that augment reverse cholesterol transport. In addition, niacin inhibits hormone-sensitive TG lipase, down-regulates the production of cholesterol ester transfer protein (CETP) gene expression and CETP activity, and inhibits hepatic uptake of HLD-C [23]. Finally, niacin may also improve reverse cholesterol transport efficiency through increasing expression of peroxisome proliferator-activated receptor γ and stimulated ABCA1 transporter in monocytes and macrophages [26].

Niacin may also have pleiotropic effects that are due in part to the presence of GPR109A receptors on monocytes, macrophages, and dendritic cells. Lukasova et al. [27] recently demonstrated that niacin reduces atherosclerosis progression independently of changes in lipids through the activation of GPR109A on immune cells in mice. Specifically, macrophages localized to atherosclerotic lesions express GPR109A and that niacin activation resulted in expression of the cholesterol transporter ABCG1 and cholesterol efflux to HDL-C. In an in vitro study of human aortic cells, niacin at pharmacologic doses was found to significantly reduce the formation of angiotensin II-induced reactive oxygen species, LDL oxidation, tumor necrosis factor-α, vascular cell adhesion molecule-1, and monocyte chemotactic protein-1 [28•]. Down-regulation of inflammatory proteins may contribute to the atherosclerotic stabilization and anti-thrombotic effects of niacin. Niacin has been shown in several studies to significantly improve abnormal vascular endothelial function, as measured using flow-mediated dilation, in numerous patient subsets [29–31].

Clinical Evidence

The fully-reported clinical studies investigating the use of niacin are summarized in Table 1. The Coronary Drug Project (CDP) [32] was one of the first studies to demonstrate the potential clinical impact of niacin and, despite being performed in the late 1960s to early 1970s, maintains relevance as one of a few niacin trials that has assessed long-term clinical endpoints. The CDP was a randomized, double-blinded, multi-center, placebo-controlled trial involving 8341 male survivors of a prior myocardial infarction (MI) between the ages of 30 and

Table 1 Selected clinical trials involving niacin and its effect on lipid parameters and clinical and/or surrogate endpoints

Study (year)	Design, follow-up subjects, *n*	Measured primary endpoint	Treatment	Lipid effect of niacin (reported % change from baseline)							Clinical or surrogate outcome findings
CDP (1975)	R, DB, PCT 74 months *n*=8341, Men post-MI, 30–64 yo	Total mortality	Placebo (*n*=2789)	TG +7 TC −6							27% decrease in nonfatal MI vs placebo (8.9% v 12.2%) ($P<0.005$), however no overall mortality difference in either clofibrate or niacin arm vs placebo; also decrease in known/suspected CVA ($P<0.05$) and need for cardiac surgery ($P<0.005$)
			Clofibrate 1.8 g/d (*n*=1103)								
			Niacin 3 g/d (*n*=1119)	TG −26 TC −10							
FATS (1990)	R, DB, PCT 2.5 years *n*=120, Men with high ApoB, CAD, +FHx	Mean change in % coronary artery stenosis and MLD (worst segment) in 9 proximal segments	Placebo + colestipol if LDL-C elevated (*n*=46)	TG	TC	LDL	HDL	Lp(a)	ApoB	ApoA1	Decreased CA stenosis and improved MLD in niacin > lovastatin >> placebo ($P=0.005$)
			Lovastatin up to 80 mg/d + colestipol 30 g/d (*n*=38)	+15	−4	−7	+6	−11	−5	+1	Fewer clinical events in lovastatin and niacin groups compared with placebo (3/46, 2/48, 10/52 respectively)
			Niacin up to 6 g/d + colestipol 30 g/d (*n*=36)	−9	−34	−45	+16	−10	−35	+7	
				−29	−23	−32	+41	−26	−28	+14	
HATS (2001)	R, DB, PCT 3 years *n*=160, CHD with low HDL and normal LDL	Mean change in % coronary artery stenosis (worst segment) in 9 proximal segments and first CV event	Placebo + simvastatin 10 mg/d if LDL elevated	TG	TC	LDL	HDL	Lp(a)	ApoB	ApoA1	Decreased plaque progression in nacin vs placebo (+3.9% vs −0.4%, $P<0.001$)
			Simvastatin up to 30 mg/d + Niacin up to 4 g/d	−3	−6	−9	+6	−3	−12	+4	~90% RRR with niacin vs placebo for CV events (3% vs 24% placebo, $P=0.03$)
				−38	−31	−43	+29	−15	−38	+14	
ARBITER-2 (2004)	R, DB, PCT 1 year, *n*=167, CHD and low HDL on statins	CIMT Mean change after 1 yr	Placebo	TG	TC	LDL	HDL				Net regression of CIMT in Niaspan group vs slight increase in placebo; increased in patients followed for 2 years
			Niaspan 1 g/d	−5	−3	−5	+0				
				−13	+1	−2	+21				
ARBITER-3 (2006)	PC, OL, *n*=130	CIMT between 1 yr–2 yr	Post-placebo niacin 1 year	TG	TC	LDL	HDL				HDL found to be independently associated with CIMT regression
			Niaspan 1 g/d for 2 years	−33		−12	+24				
				−22		−9	+23				
AFREGS (2005)	R, DB, PCT 2.5 years *n*=143, CHD and low HDL	Mean % change in global coronary artery stenosis	Placebo + diet + cholestyramine 16 g/d (if LDL elevated)	TG	TC	LDL	HDL				Mean change global and focal CA stenosis favoring niacin (−2.1,−.8%) vs (+1.4%) ($P=0.04$)
			Niacin(up to 3 g/d) + gemfibrozil 1.2 g/d + cholestyramine 16 g/d	+4	+3	+5	−2				Composite CV outcomes favored niacin group (13% v 26%, $P=0.04$)
				−46	−17	−22	+38				
ARBITER-6 HALTS (2009)	R, OL, PCT 14 months* *n*=208, CHD or risk equivalent with LDL <100, HDL <50 men or <55 women on statin	Between group change in mean CIMT from baseline to 14 months	Ezetimibe 10 mg/d (+ statin)	TG	TC	LDL	HDL				Niaspan produced greater change and plaque regression over 14 months ($P=0.003$)
			Niaspan 2 g/d (+statin)	−7	−13	−21	−6				Decreased CV events between niacin vs ezetimibe group ($P=0.04$)
				−29	−5	−12	+17				

ApoA1 apolipoprotein A1; *ApoB* apolipoprotein B; *CHD* coronary heart disease; *CIMT* carotid intima-media thickness; *DB* double-blind; *HDL* high-density lipoprotein; *LDL* low-density lipoprotein; *Lp(a)* lipoprotein(a); *MLD* minimal luminal diameter; *OL* open label; *PCT* placebo-controlled trial; *R* randomized; *TC* total cholesterol; *TG* triglycerides

64 years. Patients received one of six treatment strategies, including niacin (3 g/d, immediate release), clofibrate (1.8 g/d), and placebo and were followed over an average of 6 years. Niacin (n=1119) and clofibrate (n=1103) failed to show a reduction in overall mortality, the primary outcome during the initial analysis. However, a statistically significant 14% relative risk reduction in non-fatal MI was noted in the niacin arm versus placebo. A similar reduction in definite/suspected cerebral vascular attacks was also noted in the niacin (8.5%) vs placebo arms (11.2%; P< 0.05). Interestingly, a follow-up analysis performed 15 years after the completion of the trial demonstrated a significant absolute overall 11% reduction in mortality in niacin-treated compared to placebo-treated subjects [33], suggesting that the impact of niacin may not be fully realized until after longer-term follow-up horizons, the so-called "legacy effect".

Several randomized trials have subsequently evaluated niacin or niacin combination therapy for the assessment of anti-atherosclerosis outcomes (coronary artery stenosis assessment, carotid intima-media thickness [CIMT]) in addition to short-term clinical outcomes. The Familial Atherosclerosis Treatment Study (FATS) trial [34] assessed 120 men with CAD, apoB levels≥125 mg/dL, and a family history of vascular disease over a 2.5-year period. Patients were given dietary counseling and were randomly assigned to one of three treatments: lovastatin (20 mg twice daily) + colestipol (30 g/d); immediate-release niacin (1 g four times daily) + colestipol (30 g/d); or placebo + colestipol. Coronary artery disease angiographic progression was smallest in the niacin + colestipol group, as were rates of combined cardiac events (death, MI, symptom-driven revascularization) when compared to both lovastatin and conventional therapy.

The HDL Atherosclerosis Treatment Study (HATS) [35] evaluated the use of antioxidants in addition to simvastatin (mean 13 mg/d) plus niacin (mean 2.4 g/d) combination therapy in patients with known CAD and low HDL-C (≤ 35 mg/dL in men; ≤ 45 mg/dL in women). The endpoints were the change in coronary artery disease lesions from baseline using invasive quantitative coronary angiography and combined cardiovascular events (coronary death, myocardial infarction, stroke, or revascularization). This trial is most notable for an impressive 90% relative risk reduction of the combined clinical endpoint in the simvastatin + niacin arm versus placebo (P=0.03), an effect beyond that expected from statin therapy alone.

The Armed Forces Regression Study (AFREGS) [36] evaluated 143 military retirees with low HDL-C (<40 mg/dL) and angiographically proven CAD (30%–80% stenosis) and randomized them to intensive combination therapy (gemfibrizol 1.2 g/d, niacin up to 3 g/d, cholestyramine 16 g/d) or placebo for 2.5 years. Focal coronary percent stenosis increased by 1.4% in the placebo group but decreased by 0.8% in the drug group (difference=−2.16%; P=0.04). Furthermore, patients in the intensive-treatment arm experienced a decrease in adverse cardiovascular events (9% vs 19%) compared to placebo (P=0.04).

The Arterial Biology for the Investigation of Treatment Effects of Reducing Cholesterol (ARBITER 2) [17] and ARBITER 3 [18] studies assessed 1 g/d of niacin extended-release (NER) in addition to baseline statin therapy (>90% of patients were on baseline simvastatin therapy >20 mg/d; mean LDL-C 89 mg/dL) in patients with low HDL (<45 mg/dL) and known CHD on the primary endpoint of change in common carotid IMT over 12 months. HDL-C increased in the niacin group from 39±7 mg/dL to 47±16 mg/dL (P=0.002) and was unchanged in the placebo arm. TGs also decreased significantly in the niacin group (164±83 mg/dL to 134±87 mg/dL). Over 12 months, CIMT increased significantly in the placebo group and was unchanged in the niacin group. After 24 months, ARBITER 3 patients continued on niacin therapy demonstrated CIMT regression, again suggesting that the effects of niacin on atherosclerosis may continue to accrue over longer treatment durations. These studies were the first to demonstrate an incremental effect of niacin added to background, adequate statin therapy among high-risk patients, on atherosclerosis progression as measured using CIMT, a surrogate endpoint demonstrated to correlate with future adverse cardiovascular events [16].

In 2009, Taylor et al. [19••] reported the results of the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6- HDL and LDL Treatment Strategies in Atherosclerosis (ARBITER-6 HALTS) trial. This was the first clinical trial to directly compare the effects of two combination therapies, niacin extended-release (HDL-increasing strategy) or ezetimibe (further LDL-reduction strategy), added to stable statin monotherapy, on CIMT progression over 14 months. Patients with CHD (or CHD equivalent) with LDL-C <100 mg/dL and HDL-C <50 mg/dL for men or <55 mg/dL for women (mean HDL-C, 42.4±8.5 mg/dL) already on baseline statin therapy (mean duration 6 years) were randomized to either open-label ezetimibe (10 mg/d) or niacin extended-release (goal dose 2 g/d). As expected, patients treated with niacin had significantly increased HDL-C (+18.4% to a mean of 50 mg/dL) and significant decreases in LDL-C (−12.4%; 80.5 to 70.5 mg/dL) and TGs (−28.6%; 126 to 90 mg/dL) as compared to ezetimibe patients who experienced primarily significant decreases in LDL-C (−21%; 83.7 to 66.1 mg/dL) and HDL-C (−6.9%; 43.3 to 40.5 mg/dL). The trial was stopped early following a pre-specified, blinded interim analysis showing superior efficacy in the niacin arm based on the change in mean CIMT between groups and a reduction in cardiovascular events in niacin (n=97) patients versus ezetimibe (n=

111) (1% vs 5%; P=0.04) among patients who had completed the entire 14 months of treatment at the time of the interim analysis. The final results of the trial, which included patients in whom treatment was stopped early due to trial termination, including the full trial population (n=315) confirmed the initial findings [21•]. Interestingly, increased cumulative drug exposure to niacin was related to regression of CIMT, whereas patients with increased exposure to ezetimibe experienced paradoxical CIMT progression (Fig. 1).

Two recent meta-analyses that included most of the above-mentioned clinical trials each concluded that among primarily secondary prevention patients, the use of niacin at therapeutic doses, as either monotherapy or in combination with other lipid-lowering agents including statins, was associated with significant reductions in cardiovascular events (coronary revascularization, nonfatal MI, and stroke/transient ischemic attack) and measures of atherosclerosis progression [13••, 15].

The AIM-HIGH Trial: A Contemporary Clinical Outcomes Trial of Combination Niacin Therapy

The clinical trials discussed above, although individually small in size and/or utilizing surrogate endpoints mainly involving atherosclerosis progression, taken in aggregate and combined with the mechanism of action of niacin discussed above strongly suggested that niacin therapy would be beneficial for the reduction of clinical cardiovascular outcomes when added to contemporary statin therapy among high-risk patients with residually low levels of HDL-C. However, the full determination of benefit of clinical therapeutics requires the performance of adequately powered clinical outcomes trials. Recently, the Atherosclerosis Intervention in Metabolic syndrome with low HDL/high triglycerides: impact on Global Health outcomes (AIM-HIGH) trial [37•], a study designed to evaluate the potential impact of niacin extended-release (Niaspan; Abbott, Abbott Park, IL) when added to background statin therapy among patients with cardiovascular disease, high TGs, and low HDL-C (≤ 40 mg/dL in men, ≤50 mg/dL in women), was stopped 18 months prematurely due to lack of clinical effect of niacin (stopped due to futility) [38]. As of the time of enrollment completion in April 2010, the trial had randomized 3414 subjects (92% had CAD, 34% diabetes, 71% hypertension, and 20% were actively smoking) to 1500 to 2000 mg/d (as tolerated) or placebo, and actively treated patients in both groups to aggressively lower LDL-C using simvastatin 40 to 80 mg/d±ezetimibe 10 mg/d, as needed, to achieve an LDL-C target of 40 to 80 mg/dL (final achieved LDL-C of 71 mg/dL) over an average follow-up of 32 months. The primary outcome was the composite of CHD death, non-fatal MI, ischemic stroke, and hospitalization for non-ST segment acute coronary syndrome (ACS) or symptom-driven coronary or cerebral revascularization.

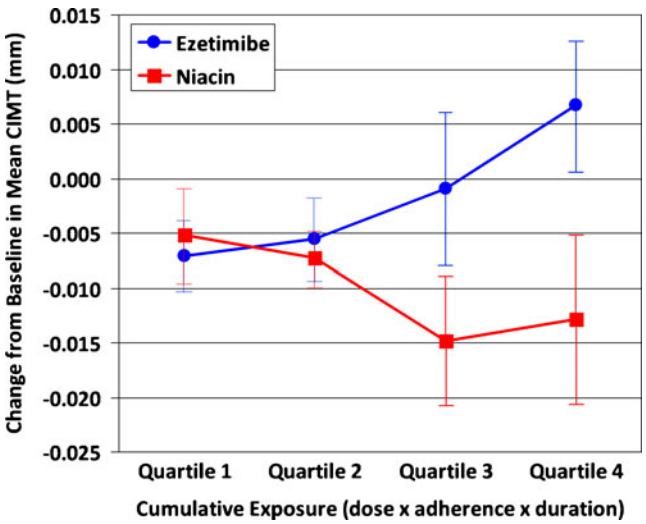

Fig. 1 Relationship between quartiles of cumulative drug exposure to ezetimibe and niacin and change in carotid intima-media thickness (CIMT). Cumulative drug exposure was calculated as the product of mean study drug adherence, dose, and time in the study. The relationship between quartiles of drug exposure (lowest [quartile 1] to highest [quartile 4]) and change in mean CIMT for all subjects using the method of last observation carried forward is shown. The relationship between quartiles of cumulative drug exposure and change in CIMT is shown separately for ezetimibe (*blue line*) (analysis of variance [ANOVA] P=0.05) and niacin (*red line*) (ANOVA P=0.23). (*From* Villines et al. [21•]; with permission)

The final results of this important National Heart, Lung, and Blood Institute (NHLBI) co-sponsored trial have not been fully reported. It will be of interest to assess, given the inclusion of relatively "soft" clinical endpoints (coronary revascularization, stroke, and hospitalization for ACS) and the active use of ezetimibe, a drug lacking clinical outcomes data, if there were patient subsets (eg, those with particular clinical profiles and/or lipid particle abnormalities) that may benefit from the use of niacin, or if the use of niacin in similar patients with very low achieved LDL-C should be discouraged due to lack of efficacy. Of note, this trial did not assess the use of niacin as an adjunctive therapy among patients with residually elevated LDL-C or non–HDL-C despite statin therapy, those with low–HDL-C who cannot achieve very low LDL-C levels despite aggressive LDL-lowering therapies, or patients who cannot tolerate high statin doses.

Clinical Use

Although niacin is best known for its ability to raise HDL-C, it has been repeatedly shown to also reduce

serum LDL-C, lipoprotein (a), and TG levels. At a daily dose of 1500 mg, immediate-release niacin typically results in a 13% reduction in LDL-C, 20% reduction in Lp(a), 10% reduction in TG, and a 19% increase in HDL-C when compared to placebo [39]. Similar effects have been demonstrated in the extended-release niacin formulation (Niaspan) as well as the extended-release formulation combined with the anti-flushing agent laropiprant [40–44]. The effect of niacin on lipid parameters within the published clinical trials is listed in Table 1. The lipid-modifying properties of niacin become significant at a daily dose of 1 g and plateau at 2 g, the therapeutic target dose. Importantly, niacin's effect on cholesterol is additive to those patients who are already on statin therapy.

The current iteration of the Nation Cholesterol Education Program (NCEP) guidelines [6] on the treatment of high blood cholesterol, Adult Treatment Panel III (ATP III), recommends that niacin be considered for use as a single agent for patients with high cardiovascular risk, atherogenic dyslipidemia, and only mildly elevated or normal LDL-C levels or as adjunctive therapy for lowering of non–HDL-C (total cholesterol minus HDL-C) among high-risk patients who have achieved LDL-C goal using statins but have residually elevated TGs (≥ 200 mg/dL). Additionally, for those needing a greater reduction in LDL-C, niacin is considered as an adjunctive agent. Lastly, niacin may be used as in patients with severely elevated levels of TGs (≥ 500 mg/dL) in order to prevent triglyceride-induced pancreatitis. ATP III defines a HDL-C <40 mg/dL as an independent cardiovascular risk and encourages the use of nondrug and drug therapies to raise HDL cholesterol, but stops short of an HDL-C treatment goal.

A meta-analysis of 18 prospective studies has shown that subjects with elevated levels of Lp(a) significantly increased risk of CHD, independent of other lipid levels, including LDL-C [45], and that patients with elevated Lp(a) are common [46•]. Although niacin is the most potent therapy to reduce Lp(a) (often ≥30% reduction) [47], current lipid treatment guidelines and recent prevention guidelines [48] do not recommend the routine measurement of Lp(a) or other advanced lipid particle levels affected by niacin therapy, such as apoB, apoA-1,LDL-C, and HDL-C particle sizes, based on a lack of outcomes studies demonstrating the added utility of this approach beyond the measurement and treatment of current commonly measured lipid parameters. However, among patients with clinically advanced CHD and a lack of established cardiovascular risk factors except family history, we often will measure Lp(a) given its genetic basis and if elevated, add niacin to statin-based lipid therapies in this unique patient subset.

Niacin Formulations

Existing niacin products can be broadly classified into prescription niacin and dietary supplement niacin (Tables 2 and 3). Only two US Food and Drug Administration (FDA)-approved prescription niacin products are available in the United States for the treatment of dyslipidemia; an IR niacin product (Niacor; Upsher-Smith, Maple Grove, MN) and NER (Niaspan; Abbott, Abbott Park, IL). Niacin ER has comparable efficacy and safety to equivalent doses of IR niacin, with improved tolerability and once-daily dosing [39, 49–51]. A third prescription product involves the addition of laropiprant, a prostaglandin receptor antagonist, to a moderate-release formulation of niacin (Tredaptive; Merck, Whitehouse Station, NJ) and has recently been released in Europe but failed to garner FDA approval. Studies to date using this medication have been encouraging and suggest this new formulation retains the therapeutic effects of intermediate release niacin with reduced flushing [40–44, 52].

Niacin (nicotinic acid or vitamin B3) products that are available as over-the-counter dietary supplements include IR, SR, and "no-flush" formulations (Table 3). These products lack the regulatory oversight provided by the FDA in regards to safety, manufacturing oversight, and efficacy. In addition, limited studies to date examining their use suggest that dietary forms of niacin do not increase HDL-C or reduce TGs to the same extent as prescription IR niacin [49, 53–55]. It is important to note that "no flush" niacin preparations contain several niacin compounds (eg, inositol hexanicotinate); however, these products contain, nor are converted to, little if any clinically active niacin (nicotinic acid) [56, 57]. Additionally, certain over-the-counter slow-release niacin preparations also increase the risk for hepatotoxicity due to amidation pathway buildup of nicotinamide adenine dinucleotide (NAD) described below. Hence, the use of non-prescriptions forms of niacin is currently not recommended. The American Heart Association and the American Pharmacists Association both specifically recommend against their use as a substitute for prescription niacin. For these reasons, patients and practitioners should discuss the differences between dietary supplement niacin and prescription niacin and the limited evidence and potential harm related to non-prescription niacin.

Adverse Effects and Safety

Common side effects of niacin include gastrointestinal complaints and flushing. Less common adverse effects include increased plasma concentration of uric acid and glucose as well as hepatotoxicity. Cutaneous flushing is by

Table 2 Prescription niacin

Type	Name	Goal dosage	Year of FDA approval	Absorption	Clinical trials
Immediate release	Niacor (Upsher Smith)	2 g, 2 or 3× daily	2000	<1 h	CDP, AFREGS, HATS, FATS
Extended release	Niaspan (Abbott)	2 g, once daily	1997	4–5 h	ARBITER2/3, ARBITER 6-HALTS; AIM-HIGH
Modified release + laropiprant	Tredaptive (Merck)	2 g /40 mg once daily	2008 (only in Europe)	4–5 h for niacin component	HPS2-THRIVE

far the biggest obstacle to widespread use of and adherence to niacin. Symptoms can include erythema, itching, tingling and warmth of the face and upper body and typically last between 30 and 60 min. Flushing is thought to be induced in by cutaneous vasodilatory prostanoids, prostacyclin I2, prostaglandin E2, and prostaglandin D2 via activation of GPR109A on epidermal Langerhan cells [58, 59]. A recent telephone survey of patients taking immediate-release niacin showed that as many as 84% suffered some flushing and that the severity of symptom as associated with discontinuation of niacin as high as 27% [60]. However, we and others have noted that subjects treated with niacin extended-release generally develop some degree of drug tolerance, experiencing significantly reduced flushing frequency and intensity over time [17, 18, 19••, 61, 62].

There has been significant concern about the potential adverse effects of niacin on mean plasma glucose concentration. Early data using high-dose (>3 g/day) immediate-release niacin showed a 16% increase in mean plasma glucose concentrations [63]. However, clinical trial data have demonstrated that niacin is particularly beneficial in reducing atherosclerosis progression in patients with diabetes and impaired fasting glucose [22, 64, 65]. In addition, recent investigations have suggested that the use of niacin extended-release may have beneficial pleiotropic effects on vascular and adipose tissues in patients with impaired fasting glucose, such as improved insulin sensitivity and reduced mean adipocyte size [30, 66•]. Finally, a systematic review of all trials involving niacin from 1990 to 2007 reported that niacin alone or in combination with statins had a minimal, transient impact on fasting glucose (increase 4%–5%) and hemoglobin A1C (increase of ≤0.3%) and was infrequently associated with incident diabetes or the need for new insulin prescriptions [67].

A rare but clinically more significant side effect of niacin is hepatotoxicity. Niacin is metabolized in the liver by two independent, saturable pathways. One is a low-affinity, high-capacity conjugation pathway resulting in the production of nicotinuric acid, which is associated with prostaglandin induced flushing. The other pathway is a high-affinity, low-capacity amidation pathway resulting in the production of NAD, which is associated with hepatotoxicity [24]. Immediate-release (IR) formulations provide a short-lived bolus of niacin, overwhelming the high-affinity, low-capacity pathway, resulting in more nicotinuric acid production and, subsequently, intense flushing. Sustained-release (SR) niacin formulations employ a variety of controlled dissolution mechanisms that lengthen niacin dissolution times, slow absorption rates, and limit flushing. However, a dose-dependent incidence of hepatic effects has been observed in some patients using non-prescription forms of sustained-release niacin [68]. The use of niacin extended-release rarely is associated (<1%) with elevations of liver-associated enzymes, either as monotherapy or in combination with statins [49, 61, 69–71].

Patient Use and Education

The impact of patient education on compliance with niacin cannot be overstated. Strategies should focus on realistic patient expectations, proper administration to mitigate symptoms, and titration of medications to goal doses. We generally have patients begin niacin extended-release at a

Table 3 Dietary niacin

Type	Other name	FDA approval	Absorption	Effect	Clinical profile
Immediate release	Crystalline, plain	None	<1 h	Limited studies	Highest rates of flushing
Extended release	Endur-acin, wax-matrix niacin	None	6–8 h	Reported efficacy in small, non-randomized US and Russian trials	
Sustained	Controlled-release, long-acting, timed-release	None	>12 h	Decrease impact on high-density lipoprotein	Highest rates of hepatotoxicity
"No flush" or "flush free"	Zero-Flush	None	Unknown	Limited studies indicate no effect	Contains no free/active niacin

starting dose of 500 mg at bedtime, increasing the dose by 500 mg/d every 2 to 4 weeks, as tolerated, to a goal of 2000 mg/d, similar to the titration schedule utilized in ARBITER-6 HALTS [19••]. Patients should be informed that extended-release tablets should never be cut in half or taken with or temporally close to the intake of alcohol or warm liquids (eg, coffee) as this intensifies flushing.

Niacin-induced flushing, occurring in as much as 70% to 80% of patients, should be expected by patients and providers. It is important to convey to patients that this is not an allergic reaction, is not harmful, and although particularly intense during the first 1 to 2 weeks of dosing, typically subsides over a few weeks of consistent therapy, often despite medication dose escalation [19••, 61, 72]. Research performed at our institution actually showed more consistent HDL-C effects in those patients who experienced increased cutaneous flushing [62], a fact that may be discussed as added motivation for patients to maintain compliance during the initiation and up-titration periods. Strategies to decrease flushing symptoms include taking niacin at bedtime (which allows for symptom occurrence while the patient sleeps), and with a light non-fat snack, which decreases flushing and improves gastrointestinal tolerance. It has also been proposed that avoiding hot or spicy foods and hot showers around the time of niacin ingestion can reduce the incidence of flushing. Finally, taking aspirin 30 min prior to niacin has also been shown to reduce the incidence and severity of flushing by inhibiting prostaglandin synthesis [73–75].

Future Directions

The Treatment of HDL to reduce the incidence of Vascular Events (HPS2-THRIVE) study is an international, multicenter, randomized, placebo-controlled trial sponsored by the University of Oxford and Merck (Whitehouse Station, NJ) investigating the effects of extended-release niacin/laropiprant added to a background of simvastatin±ezetimibe [76]. Eligibility criteria for this trial are age 50 to 80 years, history of MI, peripheral/cerebrovascular disease, or diabetes plus symptomatic CHD. Patients will receive extended-release niacin/laropiprant (goal dose 2 g/d) versus placebo, with both groups actively treated with background of simvastatin 40 mg/d±ezetimibe based on LDL levels. Patients will be followed for 4 to 5 years for the primary outcome of time to first nonfatal MI, cardiac death, stroke, or revascularization. At the time of this review, enrollment is complete with over 25,000 patients enrolled. A report of baseline characteristics is pending and study completion is expected in early 2013.

In addition to awaiting the full outcomes of the AIM-HIGH and HPS2-THRIVE studies, additional studies are needed to assess the impact of niacin among patients in whom aggressive LDL-C reduction is unable to be obtained or with elevated residual non–HDL-C, those recently post-ACS (patients that were excluded from AIM-HIGH and HPS2-THRIVE), and in patients not actively treated with ezetimibe, a therapy with unproven clinical efficacy. In addition, there are numerous GPR109A agonists or partial agonists in development or being studied in clinical trials in an attempt to design novel therapies similar to niacin but perhaps with improved tolerability and/or efficacy. Specifically, recently more than 35 patent publications on GPR109A agonists have been reported [77] with many progressing to clinical trial phase.

Conclusions

Statins significantly reduce rates of cardiovascular events, forming the foundation of lipid management in most patients. Despite the increasingly widespread use of statins, many patients continue to experience initial or recurrent cardiovascular events. It is important to note that the treatment of residual lipid abnormalities are but one of several areas in which residual risk among statin-treated patients may be impacted. Indeed, the application of evidence-based medical and lifestyle therapeutics regarding blood pressure, body weight, physical activity level, diet, cigarette smoking, and the use of anti-platelet drugs, if not adhered to, will surely diminish the impact of lipid-modifying therapies.

The use of prescription forms of niacin, alone or in combination with statins or other lipid therapies, has been proven over several decades to be a safe and effective method that favorably impacts lipids, atherosclerosis evolution, and adverse cardiovascular event rates in high-risk patients. Niacin is unique from among other lipid agents as it reduces all apoB-containing particles and is currently the most potent pharmacotherapy for raising HDL-C and reducing Lp(a), each independent risk factors for cardiovascular outcomes that often remain suboptimal despite statin therapy. However, long-term clinical outcome trials supporting the widespread use of niacin in combination with adequate statin therapy are lacking. We anxiously await the results of the AIM-HIGH and HPS2-THRIVE studies, which will significantly improve our understanding of niacin and its role in contemporary lipid management. In the interim, niacin remains the most proven non-statin lipid therapy available to providers to assist in achieving current NCEP-ATP III lipid goals.

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