Expert Opinion

informa
healthcare

Present-day uses of niacin: effects on lipid and non-lipid parameters

Sanjukta Sanyal, Richard H Karas & Jeffrey T Kuvin†
Tufts-New England Medical Center, Department of Medicine, Division of Cardiology, 750 Washington Street, Box 315, Boston, Massachusetts 02111, USA

Existing guidelines for the prevention and treatment of coronary artery disease focus on lowering low-density lipoprotein cholesterol (LDL-C) as the primary lipid target. However, there has been increasing interest in raising high-density lipoprotein cholesterol (HDL-C) due to strong evidence linking low HDL-C levels with an increased risk of atherosclerosis. Raising HDL-C levels with lifestyle changes and pharmacologic interventions appear to reduce the risk of coronary artery disease beyond that of lowering LDL-C alone. Niacin has a substantial HDL-C raising effect, and also may beneficially alter total cholesterol, LDL-C and triglyceride levels. Niacin also exhibits antioxidant, anti-inflammatory and other beneficial effects on atherosclerosis. Niacin is safe and effective to use in women, in patients with diabetes mellitus and/or metabolic syndrome, and when used in combination with statins. Niacin has the promise of being a powerful pharmacologic agent in the fight against atherosclerotic disease, although additional clinical studies are required to examine this further.

Keywords: HDL-cholesterol, lipids, niacin

Expert Opin. Pharmacother. (2007) 8(11):1711-1717

1. Introduction

Rudolph Altschul discovered that nicotinic acid lowered plasma levels of cholesterol ~ 50 years ago [1]. Over the years, numerous studies have shown cardiovascular benefit from the addition of niacin, primarily due to its ability to augment high-density lipoprotein cholesterol (HDL-C) levels. Recently, there has been increased awareness and interest in the effects of niacin beyond raising HDL-C, such as alteration of lipoprotein subfractions and markers of inflammation, which may act as independent risk factors for atherogenesis. Growing evidence supports that niacin is effective in favorably altering lipid and non-lipid markers when taken alone, and when used in combination with statins. Niacin continues to be a valuable asset to the pharmacologic armamentarium against vascular disease. The purpose of this review is to discuss the safety and effectiveness of niacin for treatment of atherosclerosis.

2. Importance of HDL-C in atherosclerosis

Existing guidelines for the prevention of coronary artery disease focus on lowering low-density lipoprotein cholesterol (LDL-C) as the primary target of lipid-modifying therapy [2]. However, there has been growing interest in HDL-C as a secondary target of therapy, based on strong epidemiologic data suggesting that HDL-C levels are inversely related to the development of atherosclerosis. In the Framingham Heart Study, investigators noted that in patients aged 49 – 82 who were initially free of clinically-apparent cardiovascular disease, those with the highest HDL-C levels had the lowest risk of developing coronary artery disease during the ensuing 35 years [3].

In fact, each 1% increase in HDL-C was linked to a 2% reduction in the development of coronary artery disease. Later, the PROCAM (Prospective Cardiovascular Munster) study showed that the risk for coronary artery disease increased with lower levels of HDL-C, regardless of LDL-C levels [4]. In addition to epidemiologic data, there is also a direct relationship between HDL-C levels and coronary and peripheral arterial vasomotor tone, a prognostic marker of vascular function [5].

The primary mechanism by which HDL-C exerts its atheroprotective effects is reverse cholesterol transport (RCT). During this process, cholesterol is extracted from macrophages, foam cells and atherosclerotic plaque, and is delivered to the liver [6]. The ATP binding cassette transporter 1 (ABCA1) binds to apolipoprotein (apo) A-I and allows transmembrane transport of free cholesterol and phospholipids from peripheral tissue to preβ-HDL [6,7]. As apoA-I binds to more cholesterol, it undergoes a speciation reaction in which HDL is converted to progressively larger and more spherical HDL complexes, including HDL2 and HDL3. Cholesterol ester transfer protein (CETP) facilitates exchange of cholesterol esters in HDL for triglycerides in apo-B containing particles, a major pathway by which HDL-C is returned to the liver [8]. Recent findings support the role of HDL in RCT by showing that intravenous injection of apoA-I phosphatidylcholine discs increase plasma preβ-HDL levels, increasing reverse cholesterol transport in humans [9]. Moreover, Nissen *et al.* demonstrated that weekly intravenous infusions of apoA-I Milano/phospholipid complexes, an HDL analog, were associated with a 4.2% reduction in atheroma in a 5 week period [10]. These data suggest that HDL can induce rapid plaque regression, potentially reversing atherosclerotic disease. In addition to RCT, HDL has also shown to be atheroprotective by exerting anti-inflammatory and antioxidant effects on the vascular endothelium [11].

3. Lipid-altering mechanisms of niacin

The exact mechanism of action of niacin on lipoprotein physiology is only now starting to be explained. It is believed that activation of the nicotinic acid receptor HM74 by nicotinic acid in adipocytes results in a decrease in cyclic AMP (cAMP) causing diminished lipolysis of triglycerides by downregulation of hormone-sensitive lipase [12]. This diminished lipolysis causes an acute decrease in serum free fatty acids (FFAs). In addition, it has also been demonstrated that niacin inhibits the secretion of triglycerides carried in very low density lipoprotein (VLDL) particles [13]. As a result, pharmacologic doses of niacin beneficially affect many classes of lipoproteins. Niacin lowers total cholesterol, low-density lipoprotein cholesterol and triglycerides. At present, it is the most effective agent available for raising HDL-C, specifically the large HDL2 subclass, which transports esterified cholesterol from the periphery to the liver via RCT [14]. Niacin is also effective in selectively decreasing lipoprotein(a), an independent risk factor for cardiovascular disease. Evidence indicates that the subfraction of HDL-C containing apolipoprotein A-I only (without apolipoprotein A-II) is more anti-atherogenic than HDL-C particles containing both subfractions. In a randomized, placebo-controlled trial by Sakai *et al.*, the mechanism of action of increased Apo A-I concentration was found to be mediated by decreased hepatic removal of Apo A-I particles, which are felt to be more efficient in RCT [15].

4. Non-lipid effects of niacin

Emerging data indicate that niacin has beneficial effects in atherosclerosis, in addition to its lipid effects. Niacin has been shown to have powerful antioxidant properties, including alterations in glutathione and catalase activity [16]. Furthermore, it has been shown that niacin decreases lipoprotein associated phospholipase A2 and C-reactive protein, both of which are markers of inflammation [17]. Niacin also lowers the risk of atherothrombotic events by lowering prothombotic factors, such as fibrinogen and cell adhesion molecules (CAM). Intercellular adhesion molecule (ICAM)-I is a significant predictor of future coronary events, and in a study by Tavintharan *et al.*, niacin reduced TNF-α-induced increases in ICAM-I levels by 66% to 89% [18]. Finally adiponectin, an atheroprotective substance that has independent associations with atherosclerosis and is generally reduced in individuals with obesity, diabetes and metabolic syndrome, has also been shown to be increased substantially (by > 50%) following the use of niacin [19].

5. Clinical pharmacology and side effects of niacin

Niacin undergoes first-pass metabolism in the liver, processed by the conjugative pathway and the amidation pathway. The conjugative pathway results in the formation of glycine conjugates of niacin such as nicoturinic acid (NUA) that has been associated with vasodilation and flushing. It is a low-affinity, high-capacity pathway that is only used when the amidation pathway is saturated. The amidation pathway is a high-affinity and low capacity system that results in the formation of nicotinamide and pyrimidine metabolites associated with hepatoxicity.

In the US, there are presently three formulations of niacin available. Each preparation differs with respect to dissolution rates, which in turn influence how it is metabolized. Immediate release (IR) niacin was first introduced in the mid-1950s and is now available by prescription and has been approved by the FDA for the treatment of dyslipidemia (Niacor, Upsher-Smith Laboratories) [20]. Although IR niacin is highly effective, its use is associated with a relatively high incidence of adverse effects, mainly prostaglandin-mediated cutaneous facial and truncal flushing characterized by warmth, redness and itching [21]. Due to the rapidity of its action, IR niacin is typically administered two to three times per day. Administration of COX inhibitors, such as aspirin and indometacin (before

ingestion of niacin) can attenuate the niacin-induced cutaneous reactions in most patients [22,23].

In the mid-1960s, sustained-release (SR) niacin was developed with the aim of reducing the incidence of flushing. SR niacin releases the drug slowly over time causing the majority of drug to be metabolized by the amidation pathway, thereby generating a greater amount of metabolites associated with hepatotoxicity [24]. SR niacin is not FDA approved for dyslipidemia.

Extended-release (ER) niacin (Niaspan, Abbott Laboratories) has a dissolution rate between IR and SR niacin, and is approved by the FDA for treatment of dyslipidemia. ER niacin has comparable efficacy to IR and SR niacin for altering lipids, but has improved tolerability. ER niacin produces a lower amount of amidation products than SR niacin, thereby resulting in less hepatotoxicity. It also produces a lower proportion of glycine conjugates than IR niacin, causing a lower incidence of flushing. In addition, an optimized (reformulated) version of ER niacin has recently been shown to have significantly reduced flushing intensity compared with the prior version [25]. Vogt *et al.* reported that flushing was experienced at a higher incidence in women as compared with men [26], and women had a longer duration of flushing than men. Knopp *et al.* reported that the lipid-modifying effects were similar for IR and ER niacin. However, the incidence of flushing was significantly higher in patients treated with IR versus ER niacin [27]. When comparing the various preparations of niacin, a 9% reduction in total cholesterol has been observed with both ER and IR niacin at 1.5 g/day and 18% reduction with 3 g/day [28]. A total of an 18% increase in HDL-C was appreciated with ER-niacin compared with a 20% increase with IR-niacin (versus placebo). However, HDL-C increased more with IR niacin than SR niacin (43 versus 30%) and plasma triglyceride reductions were greater in IR niacin (32%) than SR niacin (6%) [28]. Furthermore, LDL-C was reduced by 20% with IR niacin and only 12% with SR niacin.

In addition to flushing, other less common side effects limiting the use of niacin include hyperuricemia, gout, gastrointestinal upset including activation of peptic ulcer disease, cardiac arrhythmias, tachycardia, palpitations, migraines, insomnia and ancanthosis nigricans [29]. Niacin, in combination with statins, may cause myopathy and rhabdomyolysis; however, the incidence of these adverse effects are low and indistinguishable from those seen with statins alone. However, the adverse event report rates of combination statin and niacin compared with statins alone showed no significant difference in side effects [30]. Hyperglycemia was previously viewed as a potentially important side effect of niacin therapy. However, this issue has been attenuated by recent large-scale studies using ER niacin. The changes in blood glucose with ER niacin are typically modest and transient and more prevalent in patients with diabetes [31,32]. On average, the rise in HbA1c levels is small and can be managed by titrating hypoglycemic therapy, but blood sugar levels should be closely monitored in patients with difficult-to-treat diabetes mellitus.

6. Niacin and diabetes mellitus

Diabetes mellitus is considered a coronary heart disease risk equivalent by the National Cholesterol Education Programme Adult Treatment Panel III [2]. Thus, diabetics represent a high cardiovascular risk group. Diabetic dyslipidemia is characterized by elevated plasma triglyceride levels and triglyceride-rich remnants, such as VLDL, low HDL-C levels and small, dense LDL particles that contribute to atherogenesis [33]. The lipid-altering properties of niacin make it an ideal choice for the treatment of diabetic dyslipidemia. However, the use of niacin in patients with diabetes has been somewhat discouraged because high doses (> 4 g/day) have been reported to worsen glycemic control [34]. However, these reports have been based mainly on uncontrolled case reports with a small number of subjects. Recent randomized, controlled studies have not supported this concern about niacin in patients with diabetes. The ADMIT (Arterial Disease Multiple Intervention Trial), a large, placebo-controlled, randomized study, investigated the effect of niacin on glucose and glycosylated hemoglobin (HbA1c) levels, and reported that niacin modestly elevated glucose levels in patients with and without diabetes [31]. This effect of niacin on glucose was greater in participants with diabetes than in those without the disease. Furthermore, the levels of HbA1c were unchanged from baseline to follow-up in diabetic participants treated with niacin. The ADVENT report (Assessment of Diabetes Control and Evaluation of the Efficacy Niaspan Trial) also showed that, after 16 weeks of treatment with 1000 mg of ER niacin, HbA1c decreased by 0.02% in the placebo group and increased 0.07% in the Niaspan® group. HbA1c increased by 0.07% in the placebo and 0.3% in Niaspan group for participants treated with 1500 mg of Niaspan [32].

7. Niacin outcome studies

In clinical trials, niacin, alone and in combination with other lipid lowering agents, has been shown to slow progression of coronary atherosclerosis and decrease cardiovascular morbidity and mortality. The Coronary Drug Project was conducted between 1966 and 1975 to assess the long-term efficacy and safety of five lipid-influencing drugs, including two estrogen regimens, dextrothyroxine, clofibrate and niacin [35]. Initially, niacin treatment showed modest benefit in decreasing non-fatal recurrent myocardial infarction, but did not decrease overall total mortality. However, Canner *et al.* reported that with a mean follow-up of 15 years following the termination of the Coronary Drug Project, the mortality from all causes in the niacin group was 11% lower than in the placebo group [36]. The Cholesterol-Lowering Atherosclerosis Study and the Familial Atherosclerosis Treatment Study both demonstrated that niacin in combination with colestipol decreased atherosclerotic progression and increased regression of plaques in coronary arteries [37,38].

Furthermore, more recent studies have explored the idea of combining statins with niacin. The HATS (HDL Atherosclerosis Treatment Study), a 3-year, double-blind, placebo-controlled study quantitatively evaluated coronary angiographic data in patients with low HDL-C [39]. Patients were randomized to one of four groups: simvastatin plus niacin, antioxidants, simvastatin-niacin plus antioxidants and placebo. The use of simvastatin and niacin significantly reduced LDL-C and triglycerides by an average of 42 and 36%, respectively, while increasing HDL-C by 26%. Quantitative angiography showed significant differences in favor of the combination of niacin and simvastatin compared with placebo. However, the protective increase in HDL and HDL2 with simvastatin plus niacin was somewhat attenuated with concurrent antioxidant therapy. Since then, other studies have also evaluated the combined lipid lowering effect of niacin and statins. The ADVOCATE (Advicor Versus Other Cholesterol-Modulating Agents Trial Evaluation) study compared the relative efficacy of once/day ER niacin/lovastatin fixed-dose combination with standard doses of atorvastatin or simvastatin in subjects with elevated LDL-C and decreased HDL-C. This study showed that niacin/lovastatin increased HDL-C (especially the HDL2 subfraction) significantly more than atorvastatin or simvastatin at all compared doses [40]. By week 12, niacin/lovastatin (at a 2000/40 mg dose) increased HDL2 subfraction by 189% in addition to significant improvements in triglyceride, lipoprotein(a), apoplipoprotein A-1 and apolipoprotein B levels.

The COMPELL (Comparative Effects on Lipid Levels of Combination Therapy with a Statin and Extended-release Niacin and Ezetimibe versus a Statin Alone) study also compared lipid levels of combination therapy at low-to-moderate doses of a statin plus niacin ER, a statin plus ezetimibe and a statin alone. LDL-C was lowered equally (by ~ 50%) among all groups; however, the statin/niacin ER combination regimens increased HDL-C and large HDL (HDL2) and lowered triglycerides and lipoprotein(a) significantly more than the other regimens [41]. It has been shown that the addition of ER niacin to stable statin therapy in patients with coronary artery disease improves brachial artery vasomotion during reactive hyperemia, which is a marker of peripheral vascular endothelial function [42]. Finally, ARBITER 2 and 3 (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol) examined the incremental effect of niacin added to statin therapy on cardiovascular outcomes by measuring carotid intima-media thickness (CIMT) at 1 and 2 years, respectively [43,44]. After 12 months, the mean CIMT increased significantly in the placebo group and was unchanged in the niacin group. There was a net regression of CIMT of -0.027 mm in participants treated with ER niacin for 12 months and an additional regression of CIMT of -0.041 mm in participants treated for 24 months, thereby indicating that ER niacin significantly induces atherosclerosis regression, in addition to increasing HDL-C levels.

8. Safety and tolerability of niacin

The safety, tolerability and patient compliance of niacin, alone and in combination with statins, have also been examined in several studies. Patients studied from the HATS trial had similar rates of side effects, such as muscle toxicity, hepatic toxicity, gastrointestinal upset and hyperuricemia in both the simvastatin/niacin group and in the placebo group [45]. Furthermore, glycemic control among diabetics declined mildly in the simvastatin-niacin group, but returned to their pretreatment levels at 8 months and remained stable for the rest of the study. The rates of adverse event reports documented by the FDA, associated with the combination of lovastatin/ER niacin, have been compared with commonly used statins alone, keeping in mind that FDA reports may reflect actual adverse event reports [30]. The rate of serious adverse events reports associated with the combination lovastatin/niacin-ER was similar to that of lovastatin or niacin-ER alone and significantly less than that of atorvastatin or simvastatin. Finally, a 77% patient compliance rate for niacin was found in the recent IMPACT (Initial Therapy in the Impact of Medical Subspecialty on Patient Compliance to Treatment) study [46].

9. Dyslipidemia and the metabolic syndrome

Metabolic syndrome is highly prevalent, affecting ~ 25% of American adults [47]. Individuals with metabolic syndrome are often overweight or obese and have a high risk for development of cardiovascular disease and stroke, in both men and women [48,49]. The VA-HIT (Veterans Affairs HDL Intervention Trial) was designed to examine the role of therapy directed at raising low levels of HDL-C and its impact on long-term clinical events in individuals with low or normal LDL-C levels [50]. The participants in VA-HIT had a high prevalence of subjects with the metabolic syndrome, including insulin resistance, obesity and hypertriglyceridemia. The lowest 5-year coronary artery disease event rates were observed in patients whose HDL-C levels were > 35 mg/dl, suggesting that HDL-C is an independent risk factor for coronary artery disease in individuals with metabolic syndrome [50]. Niacin represents an ideal choice in treating the triad of lipid abnormalities seen in metabolic syndrome because it raises HDL-C, lowers triglycerides and increases LDL-C particle size. In fact, a post hoc analysis from the Coronary Drug Project that evaluated the effects of niacin monotherapy on nonfatal definite myocardial infarction in patients with and without metabolic syndrome reflected a niacin effect that was more favorable in patients with metabolic syndrome [51].

10. Niacin and cardiovascular disease in women

In the US alone, more than 500,000 women die of cardiovascular disease each year, exceeding the number of deaths in men and the next seven causes of death in women

combined [52]. Nearly two thirds of women who die suddenly, secondary to coronary heart disease, have no previously recognized symptoms. Based on many observational and clinical studies, LDL-C is a strong predictor for cardiovascular disease risk in women and is the primary target for intervention. Triglyceride levels appear to have a stronger correlation with heart disease in women compared to men [53]. HDL-C levels are also higher in women than in men for each decade of life. Although studies that address raising HDL-C have not been performed exclusively in women, many studies, such as the Framingham Heart Study, HATS and the COMPELL study, have included a significant percentage of women so that certain recommendations can be generalized to women. Optimal levels of lipids and lipoproteins in women are LDL-C < 100 mg/dl, HDL-C > 50 mg/dl, triglycerides < 150 mg/dl and non-HDL-C < 130 mg/dl [52]. In the updated American Heart Association guidelines, niacin is recommended for the treatment of low HDL-C and elevated non-HDL cholesterol in women at high cardiovascular risk. Treatment of these abnormalities may be started along with LDL-C lowering therapy; however, in women with lower risk levels, niacin therapy should be considered once the LDL-C goal has been reached [52]. More targeted studies are indicated to further explore the effects of niacin in women for an individualized treatment strategy aimed at reducing cardiovascular morbidity and mortality.

11. Conclusions

Niacin has many lipid and non-lipid effects that appear to be favorable for primary and secondary prevention of atherosclerosis. In addition to its HDL-raising abilities, niacin has effects on other plasma lipoproteins, such as decreasing triglycerides, VLDL, small, dense LDL and lipoprotein(a). Niacin also has anti-inflammatory, antithrombogenic and antioxidant properties. Given its broad array of atheroprotective effects, niacin should be aggressively used alone and in combination with other lipid lowering agents in patients at high risk for coronary heart disease. Niacin has been well-studied and is safe and effective in patients with diabetes and metabolic syndrome. Although more research regarding women and heart disease is warranted, it is now recommended that niacin be used in the treatment of low HDL-C levels in women and for others at high risk of developing coronary heart disease.

12. Expert opinion

While the present mainstay of lipid modifying therapy primarily targets lowering LDL-C levels, some studies indicate that raising HDL-C offers additional atheroprotective effects beyond lowering LDL-C alone. At present, niacin is the single lipid-altering agent that is most effective at raising HDL-C levels. Furthermore, niacin has also been shown to confer atheroprotective effects in addition to lipid lowering. Studies now indicate that niacin has anti-inflammatory and antioxidant properties, and can aid in plaque regression when used in combination with statins. Niacin has been under used due to side effects such as flushing and hepatotoxicity, but newer formulations of niacin are now available that are more tolerable with less side effects. Recent research also demonstrates that niacin is safe to use in patients with diabetes and metabolic syndrome. The newer American Heart Association guidelines recognize the importance of using pharmacologic agents such as niacin to raise HDL-C in men and women who are at high risk for developing atherosclerotic disease. When used in combination with other pharmacologic agents such as statins, niacin can potentially provide additional benefits in the prevention of cardiovascular disease. A large, randomized placebo-controlled trial called AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with low HDL/high Triglycerides and Impact on Global Health Outcomes) is underway to evaluate whether a statin/niacin combination is superior in preventing cardiovascular events to statins alone. For now, existing data indicate that niacin can be used safely in a wide population in the prevention of cardiovascular disease.

Declaration of interest

R Karas has served as a speaker for Abbott. J Kuvin and R Karas have received research support from Kos Pharmaceuticals. This article was independently commissioned and no fee was received for preparation of the manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. ALTSCHUL R, HOFFER A, STEPHEN JD: Influence of nicotinic acid on serum cholesterol in man. *Arch. Biochem.* (1955) **54**:558-559.
2. Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults, executive summary of the third report of the national cholesterol education program (NCEP) expert panel on the detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* (2001) **285**:2486-2497.

•• **Present guidelines and recommendations in lipid lowering strategy in the prevention of cardiovascular disease.**

3. TOTH PP: High-density lipoprotein as a therapeutic target: clinical evidence and treatment strategies. *Am. J. Cardiol.* (2005) **96**(Suppl.):k50-k58.

• **A nice review of the emerging clinical evidence of the importance of raising HDL.**

4. ASSMANN G, SCHULTE H, VON ECKARDSTEIN A, HUANG Y: High-density lipoprotein cholesterol as a predictor of coronary heart disease risk. The PROCAM experience and pathophysiological implications for reverse cholesterol transport. *Atherosclerosis* (1996) **124**(Suppl. 1):S11-S20.
5. KUVIN JT, PATEL AR, SIDHU M *et al.*: Relation between high-density lipoprotein cholesterol and peripheral vasomotor function. *Am. J. Cardiol.* (2003) **92**(3):275-279.
6. BARTER PJ, RYE K: Molecular mechanisms of reverse cholesterol transport. *Curr. Opin. Lipidol.* (1996) 7:82-87.
7. FREDENRICH A, BAYER P: Reverse cholesterol transport, high density lipoproteins and HDL cholesterol: recent data. *Diabetes Metab.* (2003) **29**:201-205.
8. TALL AR: Plasma high density lipoproteins; metabolism and relationship to atherogenesis. *J. Clin. Invest.* (1990) **86**:379-384.
9. KUJIRAOKA T, NANJEE MN, OKA T *et al.*: Effects of intravenous apolipoprotein A-I/phosphatidylcholine discs on LCAT, PLTP, and CETP in plasma and peripheral lymph in humans. *Arterioscler. Thromb. Vasc. Biol.* (2003) **23**:1653-1659.
10. NISSEN SE, TSUNODA T, TUZCU EM *et al.*: Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. *JAMA* (2003) **290**:2292-2300.
11. NEGRE-SALVAYRE A, DOUSSET N, FERRETTI G, BACCHETTI T, CURATOLA G, SALVAYRE R: Antioxidant and cytoprotective properties of high-density lipoproteins in vascular cells. *Free Radic. Biol. Med.* (2006) **41**(7):1031-1040.
12. SOUDIJU W, WIJNGAARDEN IV, IJZERMAN AP: Nicotinic acid receptor subtypes and their ligands. *Med. Res. Rev.* (2007).
13. GRUNDY SM, MOK HY, ZECH L, BERMAN M: Influence of nicotinic acid on metabolism of cholesterol and triglycerides in man. *J. Lipid Res.* (1981) **22**:24-36.
14. MORGAN JM, CAREY CM, LINCOFF A, CAPUZZI DM: The effects of niacin on lipoprotein subclass distribution. *Prev. Cardiol.* (2004) 7(4):182-187.
15. SAKAI T, KAMANNA VS, KASHYAP ML: Niacin, but not gemfibrozil, selectively increases LP-AI, a cardioprotective subfraction of HDL, in patients with low HDL cholesterol. *Arterioscler. Thromb. Vasc. Biol.* (2001) **21**:1783-1789.
16. ATAC IA, PEKSEL A, YANARDAG R, SOKMEN BB, DOGER MM, BILEN ZG: The effect of combined treatment with niacin and chromium (III) chloride on different tissues of hyperlipemic rats. *Drug Chem. Toxicol.* (2006) **29**(4):363-377.
17. KUVIN JT, DAVE DM, SLINEY KA *et al.*: Effects of extended-release niacin on lipoprotein particle size, distribution, and inflammatory markers in patients with coronary artery disease. *Am. J. Cardiol.* (2006) **98**(6):743-745.
18. TAVINTHARAN S, SIVAKUMAR M, LIM SC, SUM CF: Niacin affects cell adhesion molecules and plasminogen activator inhibitor-1 in HepG2cells. *Clinica Chimica Acta* (2007) **376**:41-44.
19. WESTPHAL S, BORUCKI K, TANEVA E, MAKAROVA R, LULEY C: Extended-release niacin raises adiponectin and leptin. *Atherosclerosis* (2006).
20. PIEPER JA: Overview of niacin formulations: difference in pharmacokinetics, efficacy and safety. *Am. J. Health-Syst. Pharm.* (2003) **60**(Suppl. 2):S9-S14.

• **This is an excellent review of the different formulations of niacin and their differences in pharmacodynamics and side effect profile.**

21. MORROW JD, AWAD JA, OATES JA, ROBERTS LJ II: Identification of skin as a major site of prostaglandin D2 release following oral administration of niacin in humans. *J. Invest. Dermatol.* (1992) **98**:812-815.
22. KAIJSER L, EKLUND B, OLSSON AG *et al.*: Dissociation of the effects of nicotinic acid on vasodilation and lipolysis by a prostaglandin synthesis inhibitor, indomethacin, in man. *Med. Biol.* (1979) **57**:114-117.
23. WILKIN JK, WILKING O, KAPP R, DONACHIE R, CHERNOSKY ME, BUCKNER J: Aspirin blocks nicotinic acid induced flushing. *Clin. Pharmacol. Ther.* (1982) **31**:478-482.
24. PEIPHO RW: The pharmacokinetics and pharmacodynamics of agents proven to raise high-density lipoprotein cholesterol. *Am. J. Cardiol.* (2000) **86**(Suppl.):L35-L40.
25. CEFALI EA, SIMMONS PD, STANEK EJ, MCGOVERN ME, KISSLING CJ: Aspirin reduces cutaneous flushing after administration of an optimized extended-release niacin formulation. *Int. J. Clin. Pharmacol. Ther.* (2007) **45**:78-88.
26. VOGT A, KASSNER U, HOSTALEK U, STEINHAGEN-THIESSEN E: Evaluation of the safety and tolerability of prolonged-release nicotinic acid in a usual care setting: the NAUTILUS study. *Curr. Med. Res. Opin.* (2006) **22**(2):417-425.
27. KNOPP RH, ALAGONA P, DAVIDSON M *et al.*: Equivalent efficacy of a time-release form of niacin (Niaspan) given once-a-night versus plain niacin in the management of hyperlipidemia. *Metabolism* (1992) **41**:879-881.
28. KNOPP RH: Evaluating niacin in its various forms. *Am. J. Cardiol.* (2000) **86**(12A):L51-L56.
29. MCKENNEY J: New perspectives on the use of niacin in the treatment of lipid disorders. *Arch. Intern. Med.* (2004) **164**:697-705.

30. ALSHEIKH-ALI AA, KARAS RH: Safety of lovastatin/extended release niacin compared with lovastatin alone, atorvastatin alone, pravastatin alone, and simvastatin alone (from the United States Food and Drug Administration Adverse Event Reporting System). *Am. J. Cardiol.* (2007) **99**:379-381.

31. ELAM MB, HUNNINGHAKE DB, DAVIS KB *et al.*: Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral artery disease: the ADMIT study: a randomized trial. *JAMA* (2000) **284**(10):1263-1270.

32. GRUNDY SM, VEGA GL, MCGOVERN ME *et al.*: Efficacy, safety and tolerability of once-daily niacin for the treatment of dyslipidemia associated with Type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of niaspan trial. *Arch. Intern. Med.* (2002) **162**:1568-1576.

33. UK PROSPECTIVE DIABETES STUDY GROUP, PROSPECTIVE DIABETES STUDY 27: Plasma lipids and lipoproteins at diagnosis of NIDDM by age and sex. *Diabetes Care* (1997) **20**:1683-1687.

34. GARG A, GRUNDY SM: Nicotinic acid as therapy for dyslipidemia in non-insulin-dependent diabetes mellitus. *JAMA* (1990) **264**(6):723-726.

35. Clofibrate and niacin in coronary heart disease. *JAMA* (1975) **231**(4):360-381.

36. CANNER PL, BERGE KG, WENGER NK *et al.*: Fifteen year mortality in coronary drug project patients: long-term benefit with niacin. *J. Am. Coll. Cardiol.* (1986) **8**(6):1245-1255.

37. BLANKENHORN DH, NESSIM SA, JOHNSON RL, SANMARCO ME, AZEN SP, CASHIN-HEMPHILL L: Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA* (1987) **257**(23):3233-3240.

38. BROWN G, ALBERS JJ, FISHER LD *et al.*: Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N. Engl. J. Med.* (1990) **323**:1289-1298.

39. BROWN BG, ZHAO XQ, CHAIT A *et al.*: Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary artery disease. *N. Engl. J. Med.* (2001) **345**(22):1583-1592.

40. BAYS HE, DUJOVNE CA, MCGOVERN ME *et al.*: Comparison of once-daily, niaicin extended-release/ lovastatin with standard doses of atorvastatin and simvastatin (The Advicor Versus Other Cholesterol-Modulating Agents Trial Evaluation [ADVOCATE]). *Am. J. Cardiol.* (2003) **91**:667-672.

41. MCKENNEY JM, JONES PH, BAYS HE *et al.*: Comparative effects on lipid levels of combination therapy with a statin and extended-release niacin or ezetimibe versus a statin alone (COMPELL study). *Atherosclerosis* (2007).

42. KUVIN JT, RAMET ME, PATEL AR, PANDIAN NG, MENDELSOHN ME, KARAS RH: A novel mechanism for beneficial vascular effects of high-density lipoprotein cholesterol: enhanced vasorelaxtion and increased endothelial nitric oxide synthase expression. *Am. Heart J.* (2002) **144**(1):165-172.

43. TAYLOR AJ, SULLENBERGER LE, LEE HJ, LEE JK, GRACE KA: Arterial biology for the investigation of the treatment effects of reducing cholesterol (ARBITER) 2, a double-blind placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. *Circulation* (2004) **110**:3512-3517.

44. TAYLOR AJ, LEE HJ, SULLENBERGER LE: The effect of 24 months of combination statin and extended-release niacin on carotid intima-media thickness: ARBITER 3. *Curr. Med. Res. Opin.* (2006) **22**(11):2243-2250.

45. ZHAO XQ, MORSE JS, DOWDY AA *et al.*: Safety and tolerability of simvastatin plus niacin in patients with coronary artery disease and low high-density lipoprotein cholesterol (the HDL atherosclerosis treatment study). *Am. J. Cardiol.* (2004) **93**:307-312.

46. RUBENFIRE M: Safety and compliance with once-daily niacin extended-release/ lovastatin as initial therapy in the impact of medical subspecialty on patient compliance to treatment (IMPACT) study. *Am. J. Cardiol.* (2004) **94**:306-311

47. ITO MK: The metabolic syndrome: pathophysiology, clinical relevance, and use of niacin. *Ann. Pharmacother.* (2004) **38**(2):277-285.

48. ISOMAA B, ALMGREN P, TUOMI T *et al.*: Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* (2001) **24**:683-689.

49. KAWAMOTO R, TOMITA H, INOUE A, OHTSUKA N, KAMITANI A: Metabolic syndrome may be a risk factor for early carotid atherosclerosis in women but not in men. *J. Atheroscler. Thromb.* (2007) **14**(1):36-43.

50. BODEN WE: High-density lipoprotein cholesterol as an independent risk factor in cardiovascular disease: assessing the data form framingham to the veterans affairs high-density lipoprotein intervention trial. *Am. J. Cardiol.* (2000) **86**(Suppl.):L19-L22.

51. CANNER PL, FURBERG CD, MCGOVERN ME: Benefits of niacin in patients with versus without the metabolic syndrome and healed myocardial infarction (from the coronary drug project). *Am. J. Cardiol.* (2006) **97**:477-479.

52. MOSCA L, APPEL LJ, BENJAMIN EJ *et al.*: Evidence-based guidelines for cardiovascular disease prevention in women. *Circulation* (2004) **109**:672-693.

• **A nice guideline of the AHA recommendations presently available that are generalizable to women.**

53. MOSCA L: Management of dyslipidemia in women in the post-hormone therapy era. *J. Gen. Intern. Med.* (2005) **20**:297-305.

Affiliation

Sanjukta Sanyal MD,
Richard H Karas MD PhD &
Jeffrey T Kuvin MD†
†Author for correspondence
Tufts-New England Medical Center,
Department of Medicine,
Division of Cardiology,
750 Washington Street, Box 315,
Boston, Massachusetts 02111, USA
Tel: +1 617 636 5846; Fax: +1 617 636 4769;
E-mail: jkuvin@tufts-nemc.org