Niacin in the Treatment of Hyperlipidemias in Light of New Clinical Trials: Has Niacin Lost its Place?

Miroslav Zeman, Marek Vecka, František Perlík, Róbert Hromádka, Barbora Staňková, Eva Tvrzická, Aleš Žák

Corresponding Author: Miroslav Zeman, e-mail: mirozem@centrum.cz

Source of support: The study was supported by research project MPO FR-TI4/638

Niacin is considered to be a powerful drug for the treatment of lipid and lipoprotein abnormalities connected with "residual cardiovascular risk", which persist in high-risk patients even when the target goals of LDL-C are achieved with statin therapy. Recent large randomized clinical studies – AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides) and HPS2-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events) – delivered some disappointing results, leading to the conclusion that no further benefit (decreased parameters of cardiovascular risk) is achieved by adding niacin to existing statin therapy in patients with high cardiovascular risk. Moreover, in these studies, several adverse effects of the treatment were observed; therefore, niacin treatment for hypolipidemias is not recommended. In this paper, we analyze the mechanisms underlying the hypolipidemic and antiatherogenic effects of niacin as well as some limitations of the designs of the AIM HIGH and HP2-THRIVE studies. We also provide the possibilities of rational usage of niacin for specific types of dyslipidemias.

MeSH Keywords: Cardiovascular Diseases • Chemistry, Pharmaceutical • Lipids • Morbidity • Niacin • Prostaglandin Antagonists

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/893619

Authors’ Contribution: Study Design A, Data Collection B, Statistical Analysis C, Data Interpretation D, Manuscript Preparation E, Literature Search F, Funds Collection G.

1 4th Department of Medicine, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic
2 Institute of Pharmacology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic
3 Research and Development Center, C2P s.r.o., Chlumec nad Cidlinou, Czech Republic
Niacin, its Hypolipidemic Effects and Cardiovascular Risk

Despite the substantial improvement in medical care for patients suffering from cardiovascular disease (CVD), this condition contributes to about 50% of deaths in Europe [1]. Treatment of hyperlipoproteinemia, especially of elevated LDL-cholesterol (LDL-C) and treatment of arterial hypertension, which decreases the risk of thrombotic events, are among the main therapeutic targets. It has been proved that intensive hypolipidemic treatment targeting recommended goals, of which statins are the most powerful LDL-C decreasing drug, significantly decreases cardiovascular risk [2]. Moreover, statins favorably influence other parameters of lipoprotein metabolism, such as triacylglycerols (TAG) and HDL-cholesterol (HDL-C) [1,3]. Nevertheless, even if the target goals of LDL-C are achieved, the risk of cardiovascular events during the following five years remains high ranging from about 65–75% [4,5]. This risk, known as “residual cardiovascular risk”, is probably particularly high in patients with manifest coronary heart disease or diabetes mellitus. Decrease of HDL-C, elevation of serum TAG, apolipoprotein (apo) B, small dense LDL particles, lipoprotein [a] (Lp[a]) concentrations and some other factors significantly contribute to residual cardiovascular risk. In order to reduce residual risk, a combination of statins with fibrates, niacin or n-3 polyunsaturated fatty acids is usually recommended [1].

Niacin is considered to be the most powerful drug from the point of view of HDL-C increase. Furthermore, niacin significantly decreases concentrations of all apoB containing lipoproteins, i.e., VLDL, IDL, LDL, and Lp[a] [1]. The basic characteristics of controlled clinical studies with niacin are shown in Table 1. The effects on lipid parameters and cardiovascular effects reached in these studies are displayed in Table 2. The occurrence of undesirable effects, such as cephalgia, gastrointestinal discomfort, pruritus and flush, are among the major drawbacks of niacin administration, decreasing compliance with the treatment [16]. Niacin is a ligand for GPR109A receptors, which are expressed on the surface of several cell types, including adipocytes, mature neutrophils [17], the retinal pigment epithelium [18], and epidermal Langerhans cells. The latter cells consequently synthesize the prostaglandins D2 (PGD2) and PGE2. These compounds bind to the receptors DP1, EP2, and EP4 and cause flushing [19,20]. To overcome this problem, the selective antagonist of PGD2 receptors, laropiprant, has been introduced into clinical practice [21].

Table 1. Basic characteristics of controlled clinical studies with niacin (adapted from [6]).

| Study*          | Study Population                                      | Duration | Treatment                                                                 |
|-----------------|-------------------------------------------------------|----------|---------------------------------------------------------------------------|
| CDP [7]         | 8 341 M after MI                                      | 6 years  | Niacin or clofibrate vs. placebo                                         |
| Stockholm trial [8] | 558 patients after MI, aged <70                   | 4 years  | Clofibrate 2+1 g + niacin 3×1 g vs. placebo                               |
| CDP follow-up [9]          | 162 M after CABG                                      | 15 years | Niacin 3–12 g/day + colestipol 30 g/day vs. placebo                       |
| HATS [11]       | 160 patients with CAD and low HDL-C**                | 3.0 years| Group A: simvastatin 10–20 mg/d plus niacin 2–4 g/d                      |
| ARBITER-2 [2]   | 167 patients with CAD and HDL-C <1.17 mmol/l         | 1.0 years| ER-niacin 1 g/day vs. placebo + stable statin therapy                     |
| ARBITER-6 [12]  | 208 patients (≥30 years) with CAD or equivalent of CAD risk | 1.2 years| ER-niacin vs. ezetimibe + pre-existing statin therapy                     |
| AFREGS [13]     | 143 patients (≥76 years) with low HDL-C and coronary disease | 30 months| Niacin 0.25–3 g gemfibrozil 1.2 g cholestyramine 2 g vs. placebo          |
| AIM-HIGH [14]   | 3 414 patients (≥ 45 years) with CVD                  | 3.0 years| ER-niacin (1.5–2.0 g /day) vs. placebo (+ pre-existing statin therapy with/without ezetimibe) |
| HPS2-THRIVE [15]| 25 673 patients (aged 50–80) with history of MI/stroke/PAD, or DM with CAD | 3.9 years| Baseline therapy: simvastatin 40 mg with/without ezetimibe ER-niacin/laropiprant (2 g/40 mg) or placebo |

* Citation follows the study acronym; abbreviations: CAD – coronary artery disease; apo B – apolipoprotein B; ER – extended release; MI – myocardial infarction; PAD – peripheral arterial disease; CVD – cardiovascular diseases; DM – diabetes mellitus; CABG – coronary artery bypass grafting; ** for men <0.9 mmol/l, for women <1.04 mmol/l.
Table 2. Niacin influence on plasma lipids and selected cardiovascular effects.

| Study* | Changes in lipids | Cardiovascular effects |
|--------|-------------------|------------------------|
| CDP [7] | TC ↓ by 9.9%, TAG ↓ by 26.1% | ↓ nonfatal MI by 27%, ↓ cerebrovascular events by 24% |
| CDP follow up [9] | | ↓ mortality by 11% |
| Stockholm trial [8] | TC ↓ by 26%, TAG ↓ by 30% | ↓ nonfatal MI by 50% |
| CLAS [10] | TC ↓ 15–20%, LDL-C ↓ by 43%, HDL-C ↑ by 31% | In 16.2% of patients net atherosclerotic regression at 2 years and 17.9% at 4 years, compared with 2.4% and 6.4%, respectively, in the placebo group (p=0.002 and p=0.04) |
| HATS [11] | ↓ LDL-C by 42%, ↑ HDL-C by 26% (group A) | group A: regression of the most severe stenosis in proximal coronary segments by 0.4% vs. placebo (P<0.0001); ↓ the composite clinical endpoint* by 88% (P=0.03) |
| ARBITER-2 [2] | ↑ HDL-C by 21% | ↓ progression of cIMT in niacin group without insulin resistance (P=0.026) |
| ARBITER-6 [12] | ↓LDL-C more pronounced in EZE (20% vs. 12%, P=0.01) ↑ HDL-C more pronounced in ERN (+18% vs. –7% in EZE, P=0.001) | ↓ incidence of cardiovascular events by 5% in ERN vs. 1% in EZE (P=0.04) |
| AFREGS [13] | 26% decrease in LDL-C and 36% increase in HDL-C | 13.7% decrease of combined cardiovascular events (MI, hospitalization for angina, TIA, stroke, death and cardiovascular procedures (P=0.04) |
| AIM-HIGH [14] | Higher decrease in LDL-C and TAG (14% vs. 8% and 31% vs. 10%) and higher increase in HDL-C (25% vs. 12%) in ERN | No significant difference in the incidence of cardiovascular events |
| HPS2-THRIVE [15] | ERN/LPT: decrease in LDL-C by 10%, TAG by 33%, increase in HDL-C by 6% | No evidence for benefit in addition of ERN/LPT to effective LDL lowering statin therapy on primary cardiovascular end points*** |

* Citation follows study acronym; * coronary death, MI or stroke, or revascularization; ** non-fatal MI or coronary death, stroke or revascularization. apoB – apolipoprotein B; cIMT – carotid intima-media thickness; ERN – ER-Niacin; LPT – laropiprant; EZE – ezetimibe; MI – myocardial infarction; ↓ – decrease; ↑ – increase.

New formulations of niacin with extended release (ER) as well as combinations with laropiprant have been the subjects of large randomized clinical studies: AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides) [14] and HPS2-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events) [15].

These studies delivered disappointing results leading to the conclusion that no further benefit (decreased parameters of cardiovascular risk) is achieved by adding niacin to existing statin therapy in patients with high cardiovascular risk. Moreover, in these studies, several adverse effects of the treatment were observed; therefore, niacin treatment for hyperlipidemias is not recommended. However, some authors still believe that niacin monotherapy has beneficial effects on lipid profile in specific groups of patients, such as in individuals with atherogenic dyslipidemia [6]. These positive effects of niacin can be caused not only by its effects on lipid/lipoprotein metabolism, but also by pleiotropic extra-hypolipidemic effects, of which the most important are anti-oxidative and anti-inflammatory actions and increasing serum adiponectin [22,23]. The aim of this paper is to provide a critical perspective on the exclusion of niacin from hypolipidemic treatment as a response to the results of the abovementioned AIM-HIGH and HPS2-THRIVE studies.

The recent meta-analysis by Lavigne and Karas [24] dealing with studies using niacin in monotherapy as well as in combination with other hypolipidemics, which does not include the results of HPS2 THRIVE, demonstrated the favorable effects of niacin treatment on cardiovascular events. These include increase of HDL-C in addition to other effects of niacin, such as possible anti-inflammatory effects, inhibition of free oxygen radical generation, increase of serum adiponectin levels and positive influence on pro-coagulation states [6,22]. Due to the great number of patients included in the abovementioned AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides) and HPS2-THRIVE...
Table 3. Limitations of the AIM HIGH and HPS2 THRIVE studies.

| Study limitations                                                                 |
|----------------------------------------------------------------------------------|
| **AIM-HIGH**                                                                     |
| Small doses of niacin were administered to patients in the placebo-group         |
| The placebo group received a higher mean statin dose                             |
| More patients in the placebo group received ezetimibe                            |
| The study may have stopped prematurely                                           |
| Baseline lipid values were too low to substantiate the addition of another lipid-lowering drug |
| Laropiprant could have altered the frequency of ADRs in the niacin group          |
| Laropiprant seems to attenuate reverse cholesterol transport                      |
| **HPS2 THRIVE**                                                                  |
| Positive results in some specific subgroups may indicate inappropriate inclusion criteria |

ADRs – adverse drug reactions; AIM-HIGH – atherothrombosis intervention in metabolic syndrome with low HDL/high triglycerides: impact on global health outcomes; HPS2-THRIVE – heart protection study 2-treatment of HDL to reduce the incidence of vascular events. Adapted partly according to [25,26,32].

studies, which produced the inconsistent results, these studies deserve more detailed analysis. In our opinion, these 2 studies are characterized by some methodological flaws, which reduce the value of the published conclusions. See also Table 3 – Limitations of Studies.

**AIM-HIGH Study**

The AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides) study tested whether extended-release niacin combined with intensive statin therapy, compared with statin therapy alone, would reduce the risk of cardiovascular events in patients with established atherosclerotic cardiovascular disease and atherogenic dyslipidemia [14]. Baseline lipid values were quite low: LDL-C, 72 mg/dl, i.e., 1.86 mmol/l; HDL-C, 35 mg/dl, i.e., 0.90 mmol/l; triacylglycerols, 163 mg/dl, i.e., 1.84 mmol/l. Participants in this study included 3 424 subjects with established cardiovascular disease and low HDL-C levels. The treatment group was given ER 1500–2000 mg of niacin + simvastatin; the placebo group was treated with simvastatin + placebo (+50 mg of niacin IR). Both groups were supplemented with 10 mg/d of ezetimibe in cases where the target LDL-C needed to be reached. LDL-C concentrations during treatment with statins (in some cases combined with ezetimibe) varied between 40–80 mg/dl (1.04–2.08 mmol/l) [14]. After 2 years, the HDL cholesterol level had increased by 25.0% (to 1.09 mmol/l) in the niacin group, whereas it had increased by 9.8% in the placebo group (P<0.001). Triglyceride levels had decreased by 28.6% in the niacin group and by 8.1% in the placebo group. The LDL cholesterol level had further decreased by 12.0% in the niacin group and by 5.5% in the placebo group. These changes persisted over 3 years of follow-up [14]. Insignificant differences in cardiovascular events after a duration of three years led to cessation of the clinical observation.

According to some researchers, the AIM-HIGH study was prematurely terminated [25]. Moreover, in this study, administration of niacin in combination with simvastatin or ezetimibe, respectively, was not well balanced in both study arms. In the niacin group, the average daily dose of simvastatin was 43 mg, while in the control group it was 49 mg. Furthermore, ezetimibe was administered to 10% of patients in the niacin group, but to up to 22% of those in the control group [14,26]. This seems to show significant bias in light of the recently published results of the IMPROVE-IT trial [27], where it was proved that, in patients with post high-risk acute coronary syndrome, adding 10 mg of ezetimibe to 40 mg of simvastatin daily significantly reduces cardiovascular events in comparison with 40 mg of simvastatin alone. Moreover, in post-hoc analysis of the AIM-HIGH study, the possible benefits of niacin administration were discovered in the subgroup of patients with LDL-C<32 mg/dl (0.83 mmol/l) and TAG>200 mg/dl (2.26 mmol/l), in which the primary endpoint decreased by 37% (HR 0.63, p=0.017) [28].

**HPS2-THRIVE Study**

There are even more controversial areas in the design of the HPS2-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events) study. This study was carried out on a high-risk group of patients suffering from clinical manifestations of atherosclerosis (enrolled patients with...
coronary atherosclerosis, cerebrovascular disease and peripheral vascular disease [15]. In this study, probands were randomized to ER-Niacin and laropiprant (an anti-flushing agent) versus a placebo. Before randomization, both arms received 40 mg of simvastatin daily, with or without ezetimibe, to maintain a total cholesterol target of <135 mg/dl (3.50 mmol/l). Baseline lipid values, calculated as mean ±SD were as follows: Total plasma cholesterol, 128±22 mg/dl, i.e., 3.31±0.57 mmol/l; LDL 63±17 mg/dl, i.e., 1.63±0.44 mmol/l; HDL, 44±11 mg/dl, i.e., 1.13±0.28 mmol/l; and triglycerides, 125±74 mg/dl, i.e., 1.41±0.83 mmol/l. The Merck Company stated in its report that adding ER-Niacin/laropiprant in combination with statin treatment did not reduce the risk of combined endpoints (coronary death, non-fatal myocardial infarction, stroke or revascularization) in comparison with treatment with statins alone. Moreover, in the ER-Niacin/laropiprant group, a significant increase of non-fatal adverse effects was recorded [15]. In the ER-Niacin/laropiprant arm, the risk of diabetic complications was increased by 3.7% (P<0.05) and the risk of new diabetes manifestation was also increased (by 1.8%). Furthermore, in the ER-Niacin/laropiprant arm, the risk of infections was increased by 1.4% and the risk of bleeding by 0.7%. Adding ER-Niacin/laropiprant to statins increased the risk of myopathy [75 cases (0.16%/year) vs. 17 cases (0.04%/year)]. The number of patients, treated with a combination of extended release formulation of niacin and laropiprant, enrolled in the HPS2-THRIVE study, was three times higher than the number of niacin-treated patients participating in the other studies. Therefore, meta-analysis including probands from the HPS2-THRIVE study revealed substantially different results from other recently published meta-analysis [24].

Nevertheless, there were several underlying drawbacks to the HPS2-THRIVE study. Looking at the entry lipid values (see above), one could question whether there was a need for any additional treatment of these patients. Moreover, the design used in the study “could lead to more drug interactions and, therefore, more side-effects in the group receiving multiple drugs” [29].

It was not possible to evaluate the effects of ER-niacin in monotherapy, so one cannot assess whether the results obtained (including the adverse effects) were caused by ER-Niacin, or by laropiprant, which can cause a number of yet unknown vascular or immune-modifying effects [30]. The principal product of PGD₂ metabolism, the 15-deoxy prostaglandin J₂, acts as an agonist of PPAR (peroxisome proliferator-activated receptor)-γ, the activation of which can cause some favorable effects of niacin. Administration of laropiprant can impede these effects [31]. Recently, it was found that administration of laropiprant could block the contributory effects of macrophage-released prostanoids on the cAMP-mediated modulation of reverse cholesterol transport, thus negating the macrophage-mediated anti-atherosclerotic activity of niacin [32]. Moreover, it should be noted that DP1 receptors occur not only in muscle cells of the dermis vasculature, but are also expressed on dendritic and other cells of the immune system. Their activation modulates crosstalk between the individual components of the immune system and influences adaptive immune reactions [33,34]. Moreover, the HPS2 THRIVE study included more than 11 000 Chinese probands, and these particular patients have a higher risk of side-effects than other patient subgroups. Recently, it was discovered that the Chinese population may have some genetic predisposition to unpredictable adverse events after ER-niacin/laropiprant medication [35]. Later analysis of the data presented in the HPS2 THRIVE study revealed that there was a significant interaction between baseline lipids and the impact of ER-niacin/laropiprant on outcomes with those with an LDL-C level of >77 mg/dl (2.0 mmol/l) or a TAG level of >151 mg/dl (1.70 mmol/l), which suggests there is some benefit. Moreover, post hoc analysis showed potential benefits of niacin in men and European populations with significant decreases in rates of coronary revascularizations [28].

Therefore, we believe that it would be appropriate to selectively evaluate the functioning of ER-Niacin alone in the subgroup of patients suffering from low HDL-C and high TAG. These patients could serve as a target group, in which case, adding ER-niacin to statin treatment could be of benefit in lowering residual cardiovascular risk.

Niacin and Other B Vitamins in Cardiovascular Risk

Niacin (vitamin B3) is used in a variety of multivitamin supplements together with other vitamins of class B, such as thiamine (vitamin B1), riboflavin (vitamin B2), and pyridoxine (vitamin B6). According to the National Institutes of Health (NIH), the U.S. Recommended Daily Allowance (RDA) for adults ranges from 16 to 18 mg daily [36]. Daily intake of niacin via multivitamin supplements maximally reaches tens of milligrams, which is far below the pharmacologically active hypo-lipidemic dosage (1–3 g/day). The main sources of dietary niacin are meat, fish, and nuts [37]. Both experimental and clinical data provide evidence for the importance of B vitamins in the pathophysiology of metabolic syndrome and in the prevention of cardiovascular diseases. Recent studies have shown that low levels of thiamine, niacin, and pyridoxine are associated with increased insulin resistance, metabolic syndrome, diabetes, and cardiovascular disease [38,39].

In a recently published study [40], high dietary content of B vitamins (thiamine, riboflavin, and niacin) was the only nutritional factor to correlate negatively with the incidence of metabolic syndrome. Pyridoxine (vitamin B6) considerably influences
the metabolism of lipids. The active form of pyridoxine, pyrdoxal-5-phosphate, is an important cofactor of many enzymes. In the Boston Puerto Rican Health Study, the authors found a positive correlation between PLP and HDL-C [39]. Riboflavin adequacy is essential for the metabolism of other B vitamins. This is connected with flavin coenzyme activity, e.g., studies in humans and animals have shown impaired synthesis of PLP in riboflavin deficiency [41]. Thiamine was described to influence lipid levels. It was found that HDL levels were reduced and triacylglycerol and total cholesterol (TC) levels were increased in thiamine-deficient diabetic rats as well, while high-dose thiamine administration (70 mg/kg) normalized TAG and TC levels, but no effect was found on HDL [42]. This effect can be partly explained by the influence of thiamine on the activities of enzymes of lipid metabolism, such as the lowering of liver fatty acid synthase activity [42].

Furthermore, pyridoxine influences the metabolism of fatty acids. The study on volunteers with marginal nutritional deficiency of vitamin B6 showed decreased plasma concentrations of polyunsaturated fatty acids (PUFA) of the n-6 and n-3 families, whereas the levels of TC, LDL-C, HDL-C, and TAG did not change [43]. Altered synthesis of unsaturated, particularly n-6 and n-3 PUFA, was proved in cultured human hepatoma (HepG2) cells under the condition of vitamin B-6 restriction [44]. These changes could participate in mechanisms by which vitamin B-6 inadequacy influences cardiovascular risk [44].

Recently, it was found that, in the isolated gonadal white adipose tissue of hyperlipidemic mice, niacin causes the upregulation of the biosynthesis of PUFA accompanied by high secretion of DHA and a consequent increase of DHA content in serum, a higher DHA/AA ratio, as well as a higher concentration of a DHA metabolite – 19,20-dihydroxydocosapentaenoic acid (19,20-diHDPA) [45]. This influence on the profiles of PUFA that were synthesized by adipose tissue could be a part of the mechanism by which niacin favorably influences cardiovascular risk.

Conclusions

In conclusion, niacin, in addition to its hypolipidemic effects, is characterized by complex metabolic functioning, exhibiting a plethora of pleiotropic effects, of which the most important are anti-oxidative and anti-inflammatory actions and increasing serum adiponectin. By combining these effects with the anti-hipoletic action of niacin and the amplification of reverse cholesterol transport, niacin treatment could serve as a treatment which specifically targets atherogenic dyslipidemia influencing metabolic syndrome, notwithstanding the fact that treatment with niacin in the HPS2-THRIVE study led to slightly increased levels of blood glucose and a mild increase of new diabetes incidence. We believe that the observed slight dysregulation of glucose homeostasis caused by niacin is comparable to a similar problem observed in patients treated with statins [46,47]. It has been reported that although treatment with statins slightly increases the risk of the new-onset of type 2 diabetes, the benefits of statins in reducing cardiovascular events clearly compensate for this risk [48].

Therefore, the clinical evaluation of niacin, especially with regard to its extended release formulations, is worthy of further attention. Niacin could find a place among the group of hypolipidemic drugs used for patients with concomitant hypercholesterolemia and statin intolerance, high non-HDL cholesterol, and metabolic syndrome, or for patients who are unresponsive to hypolipidemic therapy of targeted LDL cholesterol values.

References:

1. Chapman MJ, Ginsberg HN, Amarenco P et al: Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. Eur Heart J, 2011; 32: 1345–61
2. Taylor AJ, Sullenberger LE, Lee HJ, 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: 3512–17
3. Gotto AM, Pownall H: Manual of Lipid Disorders. 3rd ed. Philadelphia, USA: Lippincott Williams & Wilkins, 2003
4. Baigent C, Keech A, Kearney PM et al: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet, 2005; 366: 1267–78
5. Creider J C, Hegele RA, Joy TR: Niacin: another look at an underutilized lipid-lowering medication. Nat Rev Endocrinol, 2012; 8: 517–28
6. Gotto AM, Pownall H: Manual of Lipid Disorders. 3rd ed. Philadelphia, USA: Lippincott Williams & Wilkins, 2003
7. [No authors listed] Clofibrate and niacin in coronary heart disease. JAMA, 1975; 231: 360–81
8. Carlson LA, Danielson M, Ekberg I et al: Atherosclerosis. Reduction of myocardial reinfarction by the combined treatment with clofibrate and nicotinic acid. Atherosclerosis, 1977; 28: 61–86
9. Banegas JR, Zethraeus N, Vessby B, et al: Ethnic differences in the influence of atherosclerotic cardiovascular disease risk factors on the risk of coronary heart disease: the MONICA Study. Atherosclerosis, 1996; 121: 185–201
10. Blankenhorn DH, Nessim SA, Johnson RL et al: Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. JAMA, 1987; 257: 3233–40
11. Brown BG, Zhao XQ, Chait A et al: Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med, 2001; 345: 1583–89
12. Taylor AJ, Villines TC, Stanek EJ et al: Extended-release niacin or ezetimibe and carotid intima-media thickness. N Engl J Med, 2009; 361: 2113–22
13. Whitney EJ, Krasuski RA, Personsio BE et al: A randomized trial of a strategy for increasing high-density lipoprotein cholesterol levels: effects on progression of coronary heart disease and clinical events. Ann Intern Med, 2005; 142: 95–104
30. Kones R: Molecular sources of residual cardiovascular risk, clinical signals, and innovative solutions: relationship with subclinical disease, undertreatment, and poor adherence: implications of new evidence upon optimizing cardiovascular patient outcomes. Vasc Health Risk Manag, 2013; 9: 617–70

29. van den Oever IA, Nurmohamed MT, Lems WF: Niacin for reduction of cardiovascular risk. N Engl J Med, 2014; 371: 1942

28. Al-Hijji M, Martin SS, Joshi PH, Jones SR. Effect of equivalent on-treatment lipid lowering drugs on circulating adipokines. World J Diabetes, 2010; 1: 116–28

27. Cannon CP, on behalf of the IMPROVE-IT Investigators. IMPROVE-IT Trial: A randomized trial of cardio-protective and anti-thrombotic intervention for lower cardiovascular events in patients with acute coronary syndromes. N Engl J Med, 2014; 371: 1942–55

26. Blomgarden Z, Handelsman Y: Did AIM-HIGH aim too low? J Diabetes, 2012; 4: 134–42

25. Nicholls SJ: Is niacin ineffective? Or did AIM-HIGH miss its target? Cleve Clin J Med, 2012; 79: 38–43

24. Paolini JF, Mitchel YB, Reyes R et al: Effects of laropiprant on nicotinic acid-induced flushing in patients with dyslipidemia. Am J Cardiol, 2008; 101: 625–30

23. Florentin M, Liberopoulos EN, Kei A et al: Pleiotropic effects of nicotinic acid: beyond high density lipoprotein cholesterol elevation. Curr Vasc Pharmacol, 2011; 9: 385–400

22. Walkers D, Plaisance EP, Judd RL: Pharmacological effects of lipid-lowering drugs on circulating adipokines. World J Diabetes, 2010; 1: 116–28

21. Digby JE, Ruparelia N, Choudhury RP: Niacin in cardiovascular disease: recent preclinical and clinical developments. Arterioscler Thromb Vasc Biol, 2012; 32: S82–S88

20. Paolini JF, Mitchel YB, Reyes R et al: Effects of laropiprant on nicotinic acid-induced flushing in patients with dyslipidemia. Am J Cardiol, 2008; 101: 625–30

19. Viljoen A, Wierzbicki AS: Safety and efficacy of laropiprant and extended-release niacin combination in the management of mixed dyslipidemias and primary hypercholesterolemia. Drug Health Patient Saf, 2010; 2: 61–71

18. Martin PM, Ananth S, Cresci G et al: Expression and localization of GPR109A (PUMA-G/HM74A) mRNA and protein in mammalian retinal pigment epithelium. Mol Vis, 2009; 15: 362–72

17. Kostylina G, Simon D, Fey MF, Yousefi S, Simon HU. Neutrophil apoptosis mediated by nicotinic acid receptors (GPR109A). Cell Death Differ, 2008; 15: 134–42

16. Guyton JR, Bays HE: Safety considerations with niacin therapy. Am J Cardiol, 2007; 99(6 Suppl.1): S22–S31

15. HPS2-THRIVE Collaborative Group, Landray MJ, Haynes R, Hopewell JC et al: Comparison of Ezetimibe/Simvastatin versus Simvastatin Monotherapy on athero-protective and innovative solutions: relationship with subclinical disease, undertreatment, and poor adherence: implications of new evidence upon optimizing cardiovascular patient outcomes. Vasc Health Risk Manag, 2013; 9: 617–70

14. Boden WE, Probstfield JL, Anderson T et al: Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med, 2011; 365: 2255–67

13. Yang YL, Hu M, Chang M, Tomlinson B: A high incidence of exanthematous eruption associated with niacin/laropiprant combination in Hong Kong Chinese patients. J Clin Pharm Ther, 2013; 38: 528–32

12. Food and Nutrition Board, Institute of Medicine. Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin and choline. Washington, D.C.: National Academy Press, 1998; 123–49

11. Shils ME, Shike M (eds.), Modern nutrition in health and disease. 10th ed. Lippincott Williams & Wilkins, 2006

10. Ford ES, Mokdad AH, Giles WH, Brown DW: The metabolic syndrome and antioxidant concentrations: findings from the third national health and nutrition examination survey. Diabetes, 2003; 52: 2346–52

9. Shen I, Lai CQ, Mattei J et al: Association of vitamin B-6 status with inflammation, oxidative stress, and chronic inflammatory conditions: The Boston Puerto Rican Health Study. Am J Clin Nutr, 2010; 91: 337–42

8. Bhat S, Gao Y, Zhang M et al: Dietary nutrient intake and metabolic syndrome risk in Chinese adults: a case-control study. Nutr J, 2013; 12: 106

7. Powers HL: Riboflavin (vitamin B-2) and health. Am J Clin Nutr, 2003; 77: 1352–60

6. Babaei-Jadidi R, Karachalias N, Kupich C et al: High-dose thiamine therapy counters dyslipidemia in streptozotocin-induced diabetic rats. Diabetologia, 2004; 47: 2235–46

5. Zhao M, Lamers Y, Ralat MA et al: Marginal vitamin B-6 deficiency decreases plasma (n-3) and (n-6) PUFA concentrations in healthy men and women. J Nutr, 2012; 142: 1791–97

4. Zhao M, Ralat MA, da Silva V et al: Vitamin B-6 restriction impairs fatty acid synthesis in cultured human hepatoma (HepG2) cells. Am J Physiol Endocrinol Metab, 2013; 304(4): E342–51

3. Heemskerk MM, Dhariaur HK, van den Berg SA et al: Prolonged niacin treatment leads to increased adipose tissue PUFAsynthesis and anti-inflammatory lipid and oxylipin plasma profile. J Lipid Res, 2014; 55: 2532–40

2. Ridker PM, Danielson E, Fonseca F et al: Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med, 2008; 359: 2195–207

1. Sattar N, Preiss DJ, Murray HM et al: Statins and the risk of diabetes: evidence from a large population-based cohort study. Diabetes Care, 2014; 37: 2225–32