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Review

Long Way of Evaluating Niacin for Atherosclerosis Treatment

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Abstract: Atherosclerosis is a significant public health challenge, as it is closely associated with a wide range of cardiovascular diseases and complications. Despite its grave implications, the timely detection and treatment of atherosclerosis remain complex tasks due to the intricate pathogenesis involved, which encompasses numerous processes and mechanisms. Extensive research has been conducted to investigate various therapeutic methods and drugs aimed at targeting both the overall progression of the disease and specific pathogenic mechanisms. Recognizing the multifaceted nature of atherosclerosis, comprehensive treatment approaches have emerged as essential in effectively managing the condition. This review provides a thorough examination of the mechanisms underlying the action of niacin, a potential therapeutic agent, in the treatment of atherosclerosis. By illuminating the specific modes of action of niacin, this review contributes to our understanding of its promising role as a treatment modality for atherosclerosis and offers insights into its potential clinical applications.

Keywords: Niacin, Drug Evaluation, CVD, Atherosclerosis

Introduction

Niacin, also referred to as B3 vitamin or nicotinic acid, has a complicated medical background. It has been used as a dietary supplement available without prescription for many years, despite its side effect manifested as flushing. In the late nineties, the US Food and Drug Administration (FDA) approved a newer version of the medication which had lower side effects and was recommended as another therapy in the prevention of Cardiovascular Disease (CVD). The drug was available on prescription. Later it was also approved for lipid management, triglyceride reduction and treatment of atherosclerosis. The drug was used in combination with bile acid sequestrants and statins. Still, the later approval was withdrawn in 2016 following two large studies involving over 29K patients. The experiments demonstrated that adding niacin to the treatment had no significant impact on the prevention of the diseases and mortality rates. It was later also excluded from CVD prevention guidelines. However, prescription niacin is still widely used in the US for the treatment of other disorders, as well as the nonprescription version sold as a food supplement (D'Andrea *et al*., 2019).

The idea that niacin may reduce CVD by enhancing lipid regulation dates back to the Framingham Heart Study, which found an inverse association between HDL-C levels and the prevalence of CVD. Additionally, HDL-C concentrations were negatively correlated with the risk of recurrent cardiovascular events and mortality in CVD patients, suggesting that HDL-C can be utilized in secondary prevention therapies. This discovery heightened interest in HDL-C elevating therapies, including niacin, for CVD treatment. Consequently, the prescription of niacin tripled between 2002 and 2009. The introduction of a generic version of the drug in 2013 resulted in annual expenditures exceeding $1 billion (Casula *et al*., 2021).

The aim of the review is to provide an overview of niacin, its historical background, mechanisms of action (both lipoprotein-mediated and non-lipoprotein-related) and clinical effects, including its use in combination with other lipid-lowering drugs. The review aims to summarize the existing literature on niacin, its role in lipid regulation and cardiovascular disease prevention and its potential therapeutic benefits.

Review Objectives

- Discuss the historical background of niacin, including its use as a dietary supplement and the

development of newer versions of the medication with lower side effects
- Explore the mechanisms of niacin's action on lipoprotein metabolism and its influence on lipid profiles, including HDL cholesterol, LDL cholesterol and triglycerides
- Examine the non-lipoprotein-related effects of niacin, such as its impact on inflammation, lipoprotein-associated phospholipase A2, adiponectin levels and atherosclerosis development
- Evaluate the clinical effects of niacin, including its role in reducing the risk of non-fatal recurrent myocardial infarction, decreasing mortality and regression of atherosclerosis
- Investigate the combination use of niacin with other lipid-lowering drugs, such as colestipol, lovastatin and clofibrate and assess the additive

Basic Mechanisms of Niacin

Although niacin has been used in clinical practice for almost 50 years, there is still some uncertainty around its influence on lipoprotein metabolism and CVD (Digby *et al*., 2012a).

Being a precursor of Nicotinamide adenine dinucleotide phosphate (NADP+) and nicotinamide adenine dinucleotide (NAD), niacin is commonly used as a vitamin. NADP+ and NAD play an important role in cellular metabolism, including redox reactions and ATP production. The recommended daily amount of niacin is approximately 20 mg. However, the doses required for lipid regulation are starting at 500 mg per day (Braidy *et al*., 2019). Figure 1 for schematic representation of niacin mechanisms.

Lipoprotein-Mediated Actions

The mechanisms of niacin action in regulating the lipoprotein profile are not yet well described. Recent identification of Hydroxycarboxylic Acid receptor 2 (HCA2), also known as niacin receptor 1 has shed some light on the exact pathways of niacin involvement in lipid metabolism. This receptor can be found in various cell types, including fat cells and immune cells (Gasperi *et al*., 2019). When the receptor is activated in fat cells, it reduces adenylate cyclase via G-protein activity and decreases 3′,5′-Cyclic adenosine monophosphate accumulation. This results in lower protein kinase A activity and lower phosphorylation of hormone-sensitive lipase, leading to a decrease in the hydrolysis of triglycerides and expression of fatty acids with their subsequent transport to the liver. Lower hepatic content of fatty acids suppresses synthesis of triglycerides and VLDL-C (Li *et al*., 2022). Furthermore, this process is presumably accompanied by a reduction in the interchange of triglycerides for cholesteryl esters between VLDL and HDL, resulting in an increase in HDL-C. Experiments involving APOE*3-Leiden mouse models expressing human CETP confirm this theory. In these models, niacin administration resulted in higher HDL-C levels and a reduction in triglycerides and total cholesterol. Still, HDL-C increase required CETP availability, otherwise no such effect was observed. These findings indicate CETP involvement in niacin-related HDL-C elevation (Bijland *et al*., 2010).

In addition, niacin can influence hepatic apolipoprotein B (apoB) metabolism and this effect is not receptor-dependent. *In vitro* trials in human liver cells (Hep G2 cells) have shown that niacin can enhance apoB degradation within the cells and reduce apoB expression into the growth media. Furthermore, niacin has been demonstrated to suppress the expression of ATP synthase β-chains on the cell surface which are endocytosed during HDL-c uptake by the cells (Zhang *et al*., 2012). Microsomal diacylglycerol acyltransferase activity can also be suppressed by niacin in vitro. The enzyme mediates final reactions in the production of triglycerides. However, this effect was only observed at high niacin levels, so the significance of this effect under physiological conditions is doubtful (Alves-Bezerra and Cohen, 2017).

In humans, cholesterol is predominantly accumulated in body fat. The tissue also releases ATP binding cassette transporter A1 (ABCA1), responsible for cholesterol transportation in HDL biogenesis. The role of ABCA1 in the production of HDL has recently been demonstrated (Lee *et al*., 2012). Earlier studies suggested that niacin accelerates cholesterol transportation from fat cells to apoA1 through the PPARγ–LXRα–ABCA1 cascade. These findings indicate another pathway through which niacin may influence HDL-c production (Vyletelová *et al*., 2022).

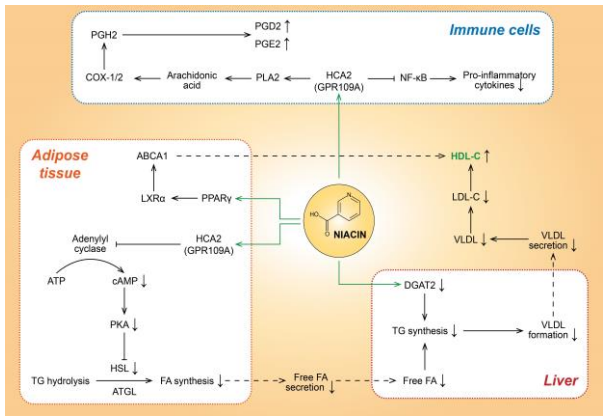

Fig. 1: Overview of niacin action mechanisms

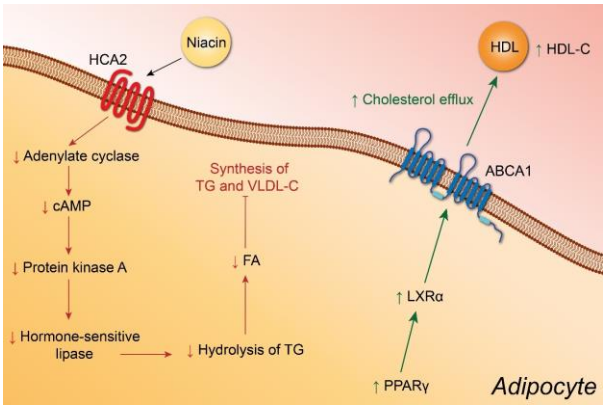

Fig. 2: The mechanisms of lipoprotein-mediated niacin action

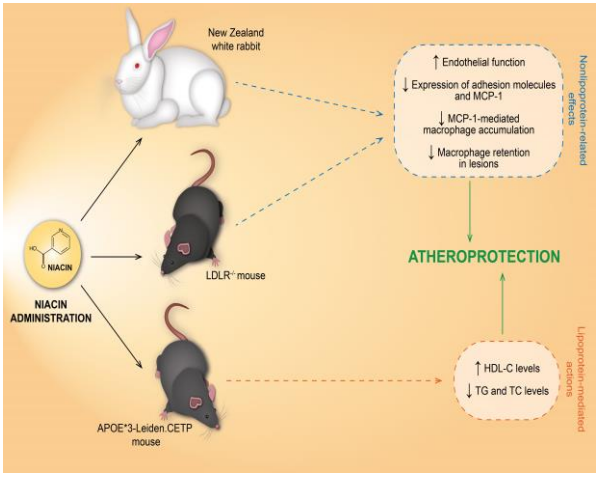

Fig. 3: Effect of niacin in animal models

Thus, niacin can potentially regulate the lipoprotein profile through a variety of mechanisms. Still, more research is required in order to understand the respective role of each pathway (Vosper, 2009). Figure 2, we summarized lipoprotein-mediated niacin action mechanisms.

Non-lipoprotein-Related Effects of Niacin

More and more studies report non-lipoprotein-related mechanisms by which nicotinic acid influences some physiological processes and which potentially may be clinically beneficial. In CVD subjects, the drug has been shown to decrease inflammation and lower lipoprotein-associated Phospholipase A2 (PLA2) and C-Reactive Protein (CRP) levels (Guyton *et al*., 2013). Moreover, niacin has been shown to increase adiponectin content presumably through interaction with GPR109A. Adiponectin is negatively correlated with risk for MI and CHD in men. The protein is abundantly expressed in various cell types, including adipocytes. Furthermore, in fat cells, niacin suppresses TNF-α-induced release of proinflammatory cytokines and chemokines which may promote accumulation of macrophages and T-cells in atherosclerotic plaques. Thus, niacin may have an impact on atherosclerosis-associated inflammatory processes through its effect on the adipose tissue (Graff *et al*., 2020).

A study carried out by Lukasova *et al*. on LDLR-/- mice demonstrated that niacin slowed down the development of atherosclerosis (Lukasova *et al*., 2011). Noteworthy, this effect was nonlipoprotein-related, since no changes were observed in the lipoprotein profile of the animals. However, no such effect was observed in Ldlr−/− and GPR109A−/−double knockout models. Transplantation of bone marrow showed that GPR109A played a key role in the atheroprotective action of niacin, followed by the suppression of Monocyte Chemotactic Protein-1 (MCP-1)-mediated accumulation of macrophages and their retention in the lesions. Other observed effects included a decrease in adhesion molecule expression in the arteries of Ldlr knockout mice treated with niacin. These findings indicate a GPR109A receptor-dependent atheroprotective action of niacin which is not associated with the lipoprotein profile (Chai *et al*., 2013). Figure 3, we summarized the effects of niacin in various model animals.

Non GPR109A-related antiinflammatory action of nicotinic acid has also been observed in vitro in endothelial cells. In vivo, administration of 0.6% and 1.2% niacin in the New Zealand White rabbits for 14 days resulted in enhanced endothelial function. This effect was not associated with changes in lipoproteins. 24 h after periarterial collar placement there was observed lower expression of adhesion molecules and MCP-1 compared to the control group (Digby *et al*., 2012b).

A usual adverse effect of niacin is flushing which often prevents the patients from completing the treatment. Niacin-related flushing is primarily due to prostaglandin D2 (PGD2) and E2 expression by Langerhans cells followed by prostaglandin E2 expression by keratinocytes. In order to avoid this adverse action, niacin has been often used with laropiprant, an antagonist of the PGD2 receptor (Kamanna *et al*., 2009). However, this method only allowed to suppress one of the pathways causing the side effect, which made it impossible to eliminate it completely. Some researchers were concerned that suppression of PGD2 could potentially impact the anti-inflammatory action of nicotinic acid, such as PGD2-induced inhibition of antigen-presenting Dendritic Cells (DC) activation in inflammation (VanHorn *et al*., 2012). A study involving mouse models has demonstrated that short-term administration of niacin can suppress the retention of DC in lymph nodes and that this effect is not abolished by naproxen-induced suppression of prostaglandin generation (Krmeska *et al*., 2022). Furthermore, another in vitro experiment in human monocytes has clearly shown that the anti-inflammatory action of niacin was not affected by PGD2 inhibition, as evidenced by the measurements of

TNF-α, MCP1 and interleukin 6 (Giri *et al*., 2019). Figure 4, we provided the schematic representation of non-lipoprotein-related niacin effects.

Niaspan is an extended-release form of niacin specifically designed to minimize flushing, a common side effect of niacin.

Niaspan is considered a brand name of extended-release niacin. It is essentially a form of niacin that releases into the body over an extended period, providing a steady release of the vitamin and minimizing the intensity of flushing compared to immediate-release niacin.

The duration of niacin treatment can vary depending on various factors such as individual patient characteristics, underlying conditions and treatment goals. Typically, niacin treatment for managing cholesterol levels is considered long-term, often involving continuous usage. However, the specific duration should be determined by a healthcare professional based on individual needs and response to treatment.

Niacin is not specifically known to "clean" arteries. However, it can help improve cholesterol profiles and reduce the buildup of plaque in the arteries over time. The exact time frame for noticeable improvements can vary among individuals and it is generally a gradual process. Niacin's effects on plaque reduction depend on various factors like dosage, adherence to treatment, individual response and overall cardiovascular health. The best time to take niacin, including Niaspan, largely depends on an individual's specific needs and the recommended dosing schedule provided by a healthcare professional. However, to minimize flushing, it is often recommended to take niacin with food. It's important to follow the prescribing healthcare professional's instructions regarding dosage and timing for optimal effectiveness and to minimize potential side effects.

Thus, the therapeutic potential of niacin in atherosclerosis could presumably be based on its lipoprotein-independent beneficial action on various inflammatory mediators.

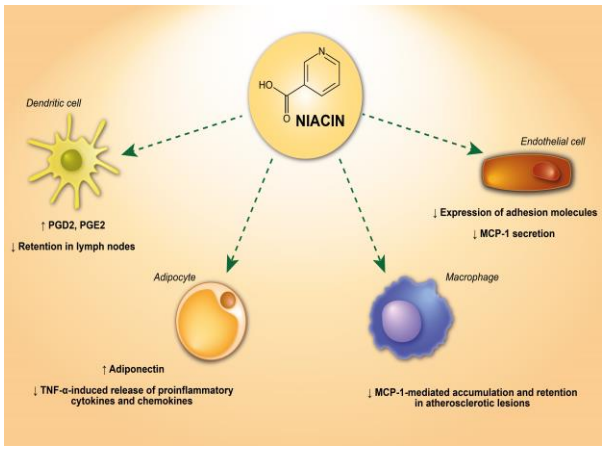

Fig. 4: Non-lipoprotein-related mechanisms of niacin action

Clinical Effects of Niacin

The first major study assessing the effect of nicotinic acid in subjects who have suffered MI, was the coronary drug project (Berge *et al*., 1991). Niacin was shown to decrease the risk of non-fatal recurrent infarction by 27% during the first 5 years of follow up and reduced mortality by 9% within the 15 years follow up period.

Further studies have assessed the efficacy of nicotinic acid used together with other available lipid-lowering drugs. The FATS, a double-blind study evaluating the effects of nicotinic acid administered in combination with colestipol (Zhao *et al*., 2016). The relative efficacy of the method was compared to treatment with lovastatin or conventional treatment (either colestipol in subjects with higher baseline LDL-C or placebo). The study involved 146 men below 62 with confirmed CAD and a familial record of CAD. There was observed a 43% increase in HDL-C with subsequent regression of atherosclerosis and 73% decrease in associated cardiovascular events in 39% of the group administered nicotinic acid during a 30 months' follow up period.

The CLAS study again proved the efficacy of nicotinic acid used in combination with colestipol in subjects who have undergone coronary artery bypass surgery (Hemphill, 2015). There was reported an elevation in HDL-C levels as well as angiographic decrease in atherosclerosis at 2 and 4 years of follow up.

The Stockholm Ischaemic Heart Disease Secondary Prevention Study estimated the efficiency of a combined treatment with niacin and clofibrate compared to controls who received placebo (Carlson and Rosenhamer, 1988). The niacin-treated group demonstrated a 26 and 36% decrease in overall mortality and CHD mortality correspondingly in subjects who had survived MI at five years.

In the HATS study, subjects receiving extended-release niacin combined with simvastatin were compared to those on dual placebo (Vittone *et al*., 2007). Coronary atheroma regressed in the niacin-treated group. There was also observed a 90% decrease in angiographically estimated endpoints such as prevalence of cardiovascular events or alterations in the arterial stenosis. However, it was not possible to evaluate relative contribution of niacin and statin, thus the results of the study are somewhat limited.

The most discussed issue is whether nicotinic acid really contributes to the beneficial effect of statins on cholesterol levels. Some non-invasive imaging methods have been used to examine the additional contribution of nicotinic acid when combined with other drugs (Schandelmaier *et al*., 2017). One of such trials was the ARBITER 2 trial which estimated the additional benefit from nicotinic acid in subjects treated with statin therapy (Taylor *et al*, 2007). Initially, no changes in the Carotid Intima-Media Thickness (CIMT) were observed. By contrast, the statin-only treated controls showed positive changes. A decrease in CIMT was observed following 1 year

open-label treatment. A recent study involving magnetic resonance imaging was the first one to report an additive effect of niacin added in high doses (2 mg/day) to statin treatment. The trial reported a decrease in CIMT over a 1 year follow up period (Lee *et al*., 2009).

The ARBITER 6 trial evaluated the additional effect of nicotinic acid compared to ezetimibe when added to statin therapy (Devine *et al*., 2007). The trial compared the efficacy of further LDL-C lowering and HDL-C elevation. The study was not completed, although the interim result showed a clear decrease in CIMT at 8 and 14 months of follow up.

In addition to the imaging trials, larger outcome trials have also been carried out. One of them is the AIM-HIGH, a randomized, placebo-controlled clinical study that involved 3414 subjects over 45 years of age (Guyton *et al*., 2013). All the patients had documented CVD and dyslipidaemia (low HDL-C and elevated TG levels). The trial was aimed at assessing the additory effect of nicotinic acid in simvastatin-treated patients as per the measured LDL-C levels at 4 years of follow up. The aim was also to assess the benefit of HDL-C elevation and TG regulation compared to conventional LDL-C lowering strategy in treating proatherogenic dyslipidaemia. Baseline end-points included acute coronary syndrome hospitalization, CVD-related death, ischemic stroke, non-fatal MI and coronary or cerebral revascularization.

Another major clinical trial was HPS2-THRIVE, a large international, placebo-controlled, randomized trial aimed at assessing the additional effect of regulating HDL-C and TG in subjects with high cardiovascular risk who already received statins (Haynes *et al*., 2019). The trial involved 25 673 patients who had MI, atherosclerosis or diabetes-induced-peripheral arterial disease. LDL-C levels were normalized with statins (and, if necessary, ezetimibe) prior to a randomized division into two groups that were to receive niacin and laropiprant or placebo. The patients were followed up over 4 years. The end-points of the study comprised MI, need for revascularization, cardiovascular death or stroke.

Statin Therapy Alone is Not Sufficient to Defeat Coronary Atherosclerosis

Despite multiple studies confirming the beneficial role of statins in reducing CV events, statins alone are insufficient to fully counteract atherosclerosis due to significant residual risk. Statistical data does not always align with the actual clinical situation for every individual (Tarkin *et al*., 2019). While statin therapy provides a 25 percent relative risk reduction, it only translates to a 3 percent absolute risk reduction. This means that solely reducing LDL-C levels is not enough to prevent CV events. An analysis of several statin clinical studies involving over 30 thousand subjects demonstrated a 31 percent relative risk reduction in CHD events (Vavlukis and Vavlukis, 2018). However, the absolute risk reduction over a follow-up period of 5-6 years was only 3.6%, reflecting the difference between 13.3% in the placebo group and 9.7% in the statin therapy group. This reduction rate indicates that around thirty individuals needed to be treated to prevent the first event (Vaccarino *et al*., 2009). In contrast, clinical studies combining niacin with LDL-C reducing drugs showed that around ten individuals needed to receive treatment to prevent the first event. One such trial, JUPITER, evaluated approximately 18000 individuals with normal blood lipid profiles and elevated hs-CRP who were given either rosuvastatin or a placebo (Ridker *et al*., 2012). The trial reported a 50% reduction in LDL-C levels and a significant decrease in the baseline cardiovascular endpoint. However, a CV event occurred in 2.8% of subjects in the placebo group compared to 1.6% in the statin group. Therefore, statin therapy alone is insufficient in preventing cardiovascular events. The JUPITER trial also demonstrated that residual small dense LDLs can be a sole predictor of cardiovascular events and niacin has been shown to effectively lower small dense LDL levels (Collins and Sattar, 2016).

Niacin Treatment of Atherogenic Dyslipidemia

FDA has recently raised a question of whether statin therapy without niacin is enough to regulate blood cholesterol and, consequently, CV events (Guthrie, 2010). It is known that atherogenic dyslipidemia patients with insulin resistance syndrome have an excess of small, dense low-density lipoprotein in blood (Manjunath *et al*., 2013). While statins cannot significantly change the particle size, niacin was demonstrated to more effectively reduce small dense LDLs compared to other drugs (Toth *et al*., 2012). In individuals with abnormal levels of lipids in blood, a decrease in small LDL due to niacin therapy improved the arteriogram and was clinically beneficial irrespective of the standard lipid profile (Linton *et al*., 2019). Besides, niacin has pleiotropic effects related to its key role in energy metabolism, including anti-inflammatory and anti-oxidative action, which may also be beneficial for CV patients (Zeman *et al*., 2016).

One important pathway involves the modification of HDL cholesterol levels. Niacin has been shown to increase levels of high-density lipoprotein, commonly known as "good" cholesterol. HDL plays a crucial role in removing excess cholesterol from arterial walls and transporting it back to the liver for elimination. By enhancing HDL levels, niacin helps promote the removal of cholesterol from arteries, slowing down the progression of atherosclerosis.

Another pathway is the reduction of Lipoprotein (a) (Lp (a)). Elevated levels of Lp (a) have been associated with an increased risk of atherosclerosis and

cardiovascular events. Studies have shown that niacin can lower Lp (a) levels, providing an additional benefit in managing atherosclerosis.

Improvement of endothelial function is another pathway affected by niacin treatment. Endothelial function refers to the ability of blood vessels to properly dilate and constrict. Endothelial dysfunction is a common precursor of atherosclerosis and cardiovascular disease. Niacin has been reported to improve endothelial function, promoting a healthier vascular environment and reducing the risk of atherosclerosis progression.

Niacin also plays a role in reducing triglyceride levels. Elevated triglyceride levels are associated with atherogenic dyslipidemia and an increased risk of cardiovascular events. By decreasing triglyceride levels, niacin contributes to improving overall lipid profiles and reducing the development of atherosclerosis.

These pathways collectively emphasize the multifaceted effects of niacin on lipid metabolism, vascular health and the management of atherosclerosis. By addressing HDL modification, Lp (a) reduction, endothelial function improvement and triglyceride level reduction, niacin offers a comprehensive approach to mitigating the risk and progression of atherosclerosis.

Conclusion

Recent knowledge of atherosclerosis pathophysiology has determined new therapeutic strategies. Now it is clear that only lipid control is not enough and that high dose statins together with LDL-C- lowering therapy help avert only a few CV events (Kim and Park, 2023). With new facts about the ability of HDL-C to oppose atherosclerosis, there appeared scientific interest in niacin as the drug that can effectively raise HDL-C levels and at the same time possesses cholesterol-lowering functions (Mani and Rohatgi, 2015).

Recent trials, HPS2-THRIVE and AIM-HIGH, together with long-term follow-ups, studied the efficacy of niacin in CV patients and provided somewhat controversial results (Hassan, 2014). To lower niacin's adverse effects and mediate its potency, laropiprant, a prostaglandin D2 receptor antagonist, was added to extended-release niacin in HPS2-THRIVE study (Viljoen and Wierzbicki, 2010). Better understanding of niacin mechanism of action became possible due to the establishment of the GPR109A receptor (Geisler *et al*., 2021).

However, future research is necessary to improve knowledge in niacin. New medications may appear that will specifically improve its beneficial properties and also inhibit the associated adverse effects (Villines *et al*., 2012).

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Author's Contributions

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Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

Conflicts of Interest

The authors declare no conflict of interest.

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