REVIEW

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Niacin for Stroke Prevention: Evidence and Rationale

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Low levels of high-density lipoprotein (HDL) cholesterol are associated with increased atherothrombotic events, including stroke. Niacin is a safe and effective means of raising HDL, yet its role in stroke prevention is not well characterized. The purpose of the study is to determine the role of niacin in stroke prevention. A search of the PUBMED database using the keywords niacin, stroke, atherosclerosis, and/or carotid artery was undertaken to identify studies for review. National guidelines from the American Heart Asssociation and National Cholesterol Education Program were reviewed. Treatment of low serum HDL (<40 mg/dL) is an identified goal of dyslipidemic therapy. Niacin is effective in raising HDL levels and reducing cardiovascular events in individuals with high vascular risk and can be used for treatment of stroke patients with low serum HDL. Niacin can be used safely in combination with statins, the first-line dyslipidemic treatment for secondary stroke risk reduction, with increased efficacy. Studies are needed to better define the role for niacin in secondary stroke prevention. Treatment of stroke patients with extended-release (ER) of niacin, alone or in combination with statins, should be considered in stroke patients with atherosclerotic mechanisms with low serum HDL-C levels.

Introduction

Atherothrombosis is the leading cause of death worldwide through its manifestations as ischemic heart, peripheral vascular disease, and stroke. Atherothrombotic stroke is common and accounts for up to 50% of strokes via large-vessel (atherosclerosis) and small-vessel (arteriolosclerosis) disease mechanisms.

Dyslipidemia, most often manifests as elevated low-density lipoprotein (LDL) cholesterol and/or low serum high-density lipoprotein (HDL) cholesterol, is a major risk factor for atherothrombosis. Niacin (nicotinic acid, vitamin B_3) is a potent means of increasing serum HDL cholesterol and has been shown to attenuate atherosclerosis and reduce cardiovascular events. Although there is limited direct evidence for the role of niacin for secondary stroke prevention, its lipid-mediated effects, reduction of cardiovascular morbidity and desirable side-effect profile make it a promising agent for stroke patients.

National guidelines have identified LDL cholesterol as the primary target of dyslipidemic therapy and low HDL cholesterol as a secondary target [1]. There is evidence that HDL is an equally important risk factor for atherosclerosis [2]. Low serum HDL is predictive of coronary heart disease (CHD) even when LDL levels are low [3], and is more predictive than elevated LDL of premature CHD in men [4]. Low HDL is an independent risk factor for atherosclerotic stroke, and any controversy regarding HDL and stroke has to do with inclusion of nonatherosclerotic stroke subtypes [5]. In addition to lowering serum LDL, niacin is one of the most effective treatments to increase serum HDL levels.

Although low serum HDL is an important vascular risk factor, recent studies have shown that a treatment strategy aimed solely at raising serum HDL levels may not necessarily translate into reduction of clinical events [6]. Cholesteryl ester transfer protein (CETP) inhibitors which increase HDL cholesterol greatly have not been associated with clinical benefit. Niacin, however, is effective in both raising serum HDL levels and reducing cardiovascular risk. Niacin has also been shown to be safe and effective in combination with HMG CoA inhibitors (statins), the most commonly prescribed dyslipidemia agents used in stroke prevention. Thus, niacin may have an important

Table 1 Mechanisms of niacin action which may be beneficial in stroke

Niacin: mechanisms that may be beneficial in stroke
• Inhibits lypolysis in adipose tissue via recently-identified receptor [41–43]
• Decreases hepatic triglyceride synthesis, resulting in intracellular degradation of apoB [44]
• Decreases hepatic apoA-1 catabolism without affecting cholesterol removal, thus improving function of HDL [45,46]
• Increases HDL levels, mediated by CETP [47]
• Increases angiogenesis at boundary of ischemic lesion in rats, improving functional outcome [24]
• Activates PPAR-γ in macrophages, stimulating reverse cholesterol transport [48]
• Decreases fibrinogen levels [49]
• Decreases TGF-β-induced rise in plasminogen activator inhibitor type 1 (PAI-1) [49]
• Decreases TNF-α-induced rise in ICAM-1 (cell adhesion molecule) [49]
• Increases eNOS expression, resulting in improved vasorelaxation and flow-mediated dilation in patients with coronary artery disease [7]

role in atherothrombotic risk reduction in stroke patients with low serum HDL levels.

Mechanisms of Action

Niacin has both lipid and nonlipid mediated effects which may be beneficial in the setting of stroke (Table 1). Niacin has been employed as a treatment for dyslipidemia since the 1950s when it was first noted to lower plasma cholesterol levels [1]. It is known to decrease plasma levels of atherogenic lipoproteins such as very low density lipoprotein (VLDL), LDL, and lipoprotein(a) and greatly increase plasma levels of HDL. In 2003, a nicotinic acid receptor, GPR109A, (2–4) was identified in human adipocytes and immune cells, and it has been suggested that its endogenous ligand may be beta-hydroxybutyrate [1,5].

In adipose tissue, binding of niacin to its receptor results in inhibition of adenylyl cyclase activity causing a decrease in intracellular cAMP, which is responsible for activating protein kinase A (PKA). Without active PKA, intracellular lipases cannot be activated and so there is a reduction in the hydrolysis of triacylglycerol (TAG) to free fatty acids (FFAs) [1,6]. By inhibiting lipolysis, niacin decreases the mobilization of FFAs to the liver, and therefore deprives the liver of substrate needed for VLDL and LDL production. Niacin may also facilitate the intracellular degradation of apoB, the main protein constituent of LDL, IDL, and VLDLD, by inhibiting proteins necessary for its synthesis in the liver [7,8]. It is the availability of both triglycerides and apoB which determine the production of these atherogenic lipoproteins and niacin has mechanisms to reduce the availability of both substrates. In normolipidemic patients treated for 1 month with niacin, VLDL production remained diminished during fasting in the face of increasing plasma FFAs. The same study also showed that after acute administration of niacin, decreased VLDL synthesis persisted long after the antilipolytic effects have terminated suggesting other complementary actions [9].

The effect of niacin on HDL likely involves more than simply increasing serum concentration. Much of HDL's functional antiatherogenic properties depend on its balance of protein; for example, ApoA-I-containing HDL particles are more antiatherogenic than particles containing both apoA-I and apoA-II. Clinical studies have shown that niacin selectively elevates the apoA-I fraction of HDL [10], possibly by decreasing the hepatic removal of HDL apoA-I particles. Importantly, niacin did not decrease the hepatic removal of cholesterol esters. By inhibiting the catabolism of apoA-I-containing particles without disrupting cholesterol removal, niacin may increase the levels of functional HDL [11,12]. This may differentiate niacin from other treatments, which may increase serum HDL, such as CETP inhibitors, but leads to more dysfunctional particles and thus no net benefit. Increasing HDL with Niacin therapy significantly improved endothelium-dependent vasodilation in CHD patients with low initial HDL [7].

Low Serum HDL Cholesterol Should Be Treated

In the United States, the prevalence of low HDL (<40mg/dL) is 35% in men and 15% in women and is expected to rise because of increasing rates of obesity, diabetes, and the metabolic syndrome. Increasing HDL is an effective means of risk reduction; each 1-mg/dL increase in HDL-C was associated with a significant 2% decrease in CHD risk in men and a 3% decrease in women [3]. In relation to stroke, some initial epidemiological studies did not find an independent inverse relationship between serum HDL and stroke risk, but were limited by the heterogeneity of the populations studied and the inclusion

Table 2 Summary of trials evaluating the role of high density lipoprotein in stroke

Study	N	Years followed	Stroke type	HDL categories	Adjusted risk	CI	Ref.
Copenhagen	19,698	6	Ischemic	1 mmol/L increase	0.53	0.34–0.83	[50]
Israeli ischemic heart disease	8586	21	Ischemic	High vs. low tertile	0.75	0.54–1.05	[51]
British regional heart	7735	16.8	All	High vs. low quintile	0.68	0.46–0.99	[52]
Dubbo	2805	8.2	Ischemic	1 mmol/L increase	0.64	0.44–0.94	[53]
Honolulu Heart Program	2444	6	Ischemic	≥60 vs. <40 mg/dL	0.37	0.17–0.83	[54]
Atherosclerosis risk in communities	14,175	10	Ischemic	High vs. low quartile	0.81	0.54–1.20	[55]
Oyabe	4989	10	Ischemic	≥60 vs. <30 mg/dL	0.34	0.14–0.85	[56]

of multiple stroke subtypes. Recent studies identifying ischemic stroke subtypes have confirmed this inverse association, which is even more robust when considering atherosclerotic stroke (Table 2).

The National Cholesterol Education Panel (NCEP), Adult Treatment Panel (ATP), and American Diabetes Association guidelines recommend raising serum HDL-C levels when below 40mg/dL as a secondary target [1,8]. The Expert Group on HDL, a working group reporting on low HDL-C levels, advised additional treatment with a fibrate or niacin in persons with diabetes, the metabolic syndrome, or HDL levels <40 mg/dL [9]. The importance of raising HDL-C in reducing cardiovascular and stroke risk has also been highlighted in recent reviews [10,11].

There are various pharmacological and nonpharmacological means to increase serum HDL-C [12]. Lifestyle-associated improvement in HDL-C appears to be greatest in persons with the highest baseline HDL cholesterol levels (≥60 mg/dL) [13]. Many of these lifestyle modifications have been shown to reduce overall stroke risk, but it is unclear what effect they will have in patients with low-HDL at the highest risk of cardiovascular disease. Fibrates are effective at raising HDL-C levels [14], but there is a risk of increased muscle toxicity in combination with statins [15]. Niacin is a means of treating low HDL which is well-tolerated in monotherapy [16] and in combination with statins [17]. In a head-to-head comparison study, niacin 2000 mg/day increased HDL-C more than gemfibrozil 1200 mg/day, and decreased the total cholesterol-to-HDL-C ratio, lipoprotein (a), and fibrinogen levels more significantly [18].

The effects of statin therapy on HDL-C are modest and vary based on the particular agent and dose used [19]. For example, high-dose rosuvastatin (40mg) increases HDL-C by 14%[20], whereas high-dose atorvastatin (80mg) increases HDL-C by less than 3% [19]. A study of in-hospital initiation of statin in stroke patients found no significant effect on HDL-C at 3 months from statin initiation [21]. Although not very effective in raising HDL levels, statins treatment is beneficial in risk reduction for patients with low HDL-C and elevated triglycerides [22], possibly by an improvement in HDL function [23].

Niacin in Preclinical Models of Stroke

Niacin has multiple mechanisms that are desirable in the setting of stroke; it can improve endothelial function, reduce inflammation, increase plaque stability, and diminish thrombosis. Niacin has also been shown to increase vascular endothelial growth factor (VEGF) and angiopoietin-1 (Ang1), important regulators of cerebral blood flow and angiogenesis. Preclinical models of stroke have tested niacin, or its long-acting extended-release (ER) formulation (niaspan).

The effects of niaspan treatment of stroke on neurological functional outcome and angiogenesis in a rat model of middle cerebral artery occlusion were recently reported [24] niaspan, administered 24 hours after stroke, increased HDL and significantly improved functional recovery. Perhaps the most interesting finding was an increase in angiogenesis within the boundary zone of ischemia associated with upregulation of angiogenic factors. It was unclear if the effects of niaspan treatment in this model were mediated by the increase in HDL or by independent mechanisms.

There is emerging evidence that HDL is neuroprotective in preclinical stroke models. HDL has been shown to reduce neuronal damage after onset of ischemic stroke, possibly by antioxidative/antiinflammatory mechanisms, in both excitotoxic and middle cerebral artery (MCA) occlusion models of stroke [25]. Additionally, treatment with apo A-1 reduces brain lesion size by 64% in the MCA occlusion model [26]. The mechanism of HDL neuroprotection may be via apo A-1. Infusing HDL or apo A-1 into humans decreases inflammation, stabilizes plaque, and has the potential to improve outcomes. Niacin's mechanisms of action may potentiate both apo A-1 and HDL mediated neuroprotective mechanisms, further strengthening the case for use in a stroke patient.

Preparations of Niacin

Niacin has been used for many years to treat hypercholesterolemia. Despite having many ideal characteristics, general usage and widespread acceptance have been hindered by the need to take it four times a day and by the high incidence of flushing. Niaspan (ER-niacin) is easier to take and has fewer side effects [27]. This more-tolerable formulation in combination with the more stringent goals set by the NCEP has brought about a new interest in niacin, especially in combination with statins. Niacin currently comes in an immediate-release, sustained-release, and ER preparations.

In addition to being better tolerated, with fewer flushing episodes; ER niacin has none of the liver toxicity of other preparations, in particular the sustained-release preparation. It can be taken once a day, and has not demonstrated significant liver toxicity in doses up to 2000 mg/day. Generally, ER niacin has to be gradually titrated, giving 500 mg first, increasing to 1000 mg, and 2000 mg as needed.

Apart from flushing, other side effects reported in studies of niacin include glucose intolerance, increased uric acid levels, cystoid macular edema and liver-function abnormalities. Although caution is generally recommended with regard to use of high-dose niacin in diabetic patients (because it can increase glucose levels) [8], the Arterial Disease Multiple Intervention Trial (ADMIT) showed that niacin can be safely used in patients with diabetes [28].

Clinical Trials of Niacin in Cardiovascualr Disease

Niacin has usually been studied in the setting of cardiovascular disease, usually in combination with other agents (Table 3). The first large study to evaluate niacin monotherapy was the Coronary Drug Project (CDP), performed from 1966 to 1971, in which men with previous myocardial infarction (MI) on electrocardiogram (EKG) were randomized to niacin versus placebo. Over the 5 years of the study, niacin was associated with a 27% reduction in MI at 6 years [29], but no effect was initially seen on mortality. Fifteen years after the study, the niacin group had an 11% decrease in overall mortality [30]. Limitations included applicability, given the exclusion of women, and the lack of stroke as an outcome measure.

Niacin has been best-studied in the setting of combination therapy, most often with statins or fibrates. In the Stockholm Ischemic Heart Disease Secondary Prevention Study, patients with prior MI were randomized to combination of clofibrate and niacin versus placebo. While HDL cholesterol levels were not independently reported, the treatment group did experience a 13% reduction in serum cholesterol and a 19% reduction in serum triglyceride levels. CHD mortality was reduced by 36% and total mortality by 26% in the treatment [31].

In the HDL-Atherosclerosis Treatment Study (HATS), men and women with confirmed CHD and low HDL cholesterol levels were randomized to four groups: simvastatin plus niacin, antioxidant vitamins, simvastatin-niacin plus antioxidants, and all placebos. The clinical end points were a change in coronary artery stenosis by angiogram, and the occurrence of a first cardiovascular event, including stroke. In the simvastatin-niacin group, LDL levels decreased by 42% and HDL levels increased by 26%. When antioxidant vitamins were added to the regimen, they appeared to blunt the beneficial effects on HDL. There was a significant (90%) reduction in clinical events among the simvastatin-niacin group compared to the placebo group. It is also important to note that on angiography, the effects of simvastatin plus niacin were greater than those from statins alone—rather than slowed progression, regression of stenosis was actually observed in the treatment group [32].

The Armed Forces Regression Study (AFREGS) used a combination of gemfibrozil, niacin, and cholestyramine in the treatment group in order to evaluate HDL levels as an independent risk factor for cardiovascular events. The mean dose of niacin achieved was 2.5g. The treatment group experienced a 20% decrease in total cholesterol, a 36% increase in HDL, a 26% decrease in LDL, and a 50% decrease in triglyceride levels compared with the placebo group. Patients were evaluated using coronary angiography, and the treatment group was found to have a decrease in coronary artery stenosis. In addition, the treatment group had a 13.7% decrease in clinical events [33]. The population studied and the small size make it difficult to draw conclusions regarding the effects of triple therapy on stroke, but this study highlights an intervention aimed at increasing HDL levels in patients with vascular risk factors.

Niacin in Carotid Atherosclerosis

Large-vessel atherothrombosis of the cervical and cerebral arteries is a common etiology for ischemic stroke. Several studies have evaluated niacin's effects on carotid athereosclerosis, most often using carotid intima-media thickness (CIMT), as a surrogate marker of atherosclerosis [34]. Increasing CIMT and CIMT progression are risk factors for stroke and in the Second Manifestations of Arterial disease (SMART) study, CIMT was higher among patients with stroke or TIA caused by a large vessel atherothrombosis mechanism [35].

Table 3 Summary of clinical trials evaluating niacin, alone and in combination with other agents

Clinical trial	Agent	Compared to	Study population	Clinical outcomes	Reference
CDP	Niacin	Placebo	Men with EKG-documented prior MI	27% ↓ in nonfatal reinfarction at 6 years (3) 11% ↓ in overall mortality at 15 years (4)	[29,30]
Stockholm	Clofibrate + niacin	Placebo	Patients with prior MI	13% ↓ in serum cholesterol 19% ↓ in serum triglyceride levels 36% ↓ in ischemic heart disease mortality 26% ↓ in total mortality	[31]
HATS	Simvastatin + niacin	Placebo	Men and women with CAD and low HDL levels	↓ LDL 42% ↑ HDL 26% 90% ↓ in cardiovascular events, including stroke Regression of coronary artery stenosis by angiogram	[32]
AFREGS	Gemfibrozil, cholestyramine, and niacin (mean dose: 2.5 g)	Placebo	Military retirees <76 years old with CAD and low HDL levels	20% ↓ in total cholesterol 36% ↑ in HDL 26% ↓ in LDL 50% ↓ in triglyceride levels ↓ in coronary artery stenosis by angiography 13.7% ↓ in clinical events, and a 2.8% ↓ in CVA or TIA specifically (*P*-value >0.2)	[33]
CLAS	Colestipol + niacin	Placebo	Nonsmoking men ages 40–59 with previous coronary bypass surgery	Atherosclerosis regression measured by carotid IMT, which correlated with ↑ HDL levels	[57]
ARBITER 2	Simvastatin + ER-niacin	Simvastatin + placebo	Patients with CAD and low HDL levels	Slowed atherosclerosis progression by 68%, measured by carotid IMT ↑ HDL 21%	[17]
ARBITER 3	Simvastatin + ER-niacin	Simvastatin + placebo	Same subjects as above	↑ HDL 23% Significant atherosclerosis regression	[38]

CDP = Coronary Drug Project; HATS = HDL-Atherosclerosis Treatment Study; AFREGS = Armed Forces Regression Study; CLAS = Cholesterol Lowering Atherosclerosis Study; ARBITER = Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol.

In the Cholesterol Lowering Atherosclerosis Study (CLAS), patients were randomized to colestipol and niacin or placebo. At 2 and 4 years, CIMT showed a significant regression in the treatment group compared with placebo, which correlated with an increase in HDL cholesterol levels [36]. These results indicate that treatment aimed at raising HDL-C may play a key role in atherosclerosis stabilization and regression.

The second Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER-2) clinical trial provides perhaps the most convincing evidence for the role of niacin in stroke prevention. The first ARBITER trial had shown that a high-dose, high-potency statin, atorvastatin 80 mg, was superior to a standard-dose statin, pravastatin 40 mg in progression of CIMT. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial demonstrated treatment with atorvastatin 80 mg significantly reduced the risk of recurrent stroke [37]. Given the findings of SPARCL, many stroke patients are being treated with statins.

As many stroke patients will be on statins, the results of ARBITER-2 are especially interesting. Patients who were taking statin at baseline were randomized to ER niacin or placebo. It was found that niacin slowed atherosclerosis progression by 68% and increased HDL-C levels by

21% at the end of 12 months in addition to background statin therapy [17]. In ARBITER-3, these patients were followed for an additional 12 months. After a total of 2 years, patients taking ER niacin in addition to a statin had a 23% increase in HDL-C and significant atherosclerosis regression on CIMT [38]. ARBITER-6 is currently underway, comparing further LDL-C reduction therapy with ezetimibe to HDL-C raising therapy with ER niacin and their effects on atherosclerosis progression [39].

Ongoing Studies

The National Institutes of Health (NIH) is sponsoring the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) trial, which will evaluate the merits of simultaneously lowering LDL and raising HDL cholesterol levels, in patients randomized to ER niacin plus simvastatin or to simvastatin alone. AIM-HIGH trial will exclude patients who cannot tolerate ER niacin (after a 4-week open-label period) before randomization, so that most patients should be able to remain on the drug throughout the trial. Another study, the ACCORD trial, is testing fenofibrate plus a statin versus a statin alone in patients with type2 diabetes.

Heart Protection Study 2- Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) will assess whether a combination tablet containing ER niacin and a specific blocker of prostaglandin D2 to prevent flushing prevents MI, stroke, or revascularization procedures in patients with existing vascular disease. Investigators plan to enroll approximately 20,000 patients. LDL-cholesterol levels will be optimized with statin therapy before randomization to either placebo or the combination HDL-raising drug. Patients will be followed for a minimum of 4 years.

Current Guidelines

Current guidelines for secondary prevention of stroke address the role of niacin in secondary stroke prevention [40]: "Ischemic stroke or TIA patients with low HDL cholesterol may be considered for treatment with niacin or gemfibrozil." Based on the lack of direct clinical trial data regarding niacin in ischemic stroke, the recommendation is class IIb, level B.

The NCEP ATP III guidelines endorse the use of niacin in individuals with high cardiovascular risk, but do not make recommendations as to its use in stroke. In high-risk persons with dyslipidemia and low or normal LDL-C levels, niacin can be used as a single agent. In most cases with low HDL and elevated LDL, the recommendation is for its use in combination with other cholesterol-lowering drugs such as statins.

Summary and Opinions

The American Stroke Association recommends that a statin should be initiated during hospitalization for first ischemic stroke of atherosclerotic origin [37]. This applies to ischemic strokes caused by small-vessel disease or large-vessel atherosclerosis or for strokes of other mechanisms in the setting of documented atherosclerosis. The primary goal of treatment is LDL-C <100 mg/dL in most, and an LDL-C goal of <70 mg/dL in the very high-risk—a figure that is based on updated recommendations from the National Cholesterol Education Program [38]. When atherosclerotic stroke occurs in the setting of low HDL-C levels, strong consideration should be given to treatment with ER-niacin. Treatment goal is HDL-C $\geq$40 mg/dL, and ER-niacin can be used safely in combination with statins.

All dyslipidemic treatments should form part of a multimodal approach to vascular risk reduction after stroke, which should also include antithrombotics, normoglycemics where indicated, and antihypertensives. Ongoing studies of niacin in large populations will provide greater evidence of its benefit for a range of cardiovascular outcomes, including stroke. As evidence continues to emerge in favor of aggressive risk factor reduction, niacin may have an increasing role either alone or in combination with statins in attenuating the cardiovascular risk of low serum HDL.

Conflict of Interest

The authors declare no conflict of interest.

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