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REVIEW

Increasing HDL cholesterol with extended-release nicotinic acid: from promise to practice

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ABSTRACT

Background: The inverse relation between high-density lipoprotein cholesterol (HDL-C) and cardiovascular (CV) disease underscores the need for clinical evaluation of the effect of HDL-C increasing drugs on the prevalence of CV disease.

Methods: We review the efficacy of Niaspan on serum lipids and the occurrence of side effects either alone or in combination with statins, in randomised controlled trials (RCT) and comparative cohort trials (CCT).

Results: In four RCTs, low-density lipoprotein cholesterol (LDL-C), triglycerides (TG) and lipoprotein(a) (Lp(a)) were decreased by 13, 26, and 17%, respectively, whereas HDL-C increased by 18%. In four CCTs a combination of Niaspan and statins showed an additional 22% reduction in LDL-C, 8% in TG and 6% in Lp(a) levels, compared with Niaspan monotherapy. Statin therapy had a minor additional effect of 1% on a total of 25% HDL-C increase during Niaspan treatment. Flushes occurred in 69% of the patients without any additional toxicity during combination therapy.

Conclusion: Niaspan effectively raises HDL-C with concomitant beneficial effects on TG and LDL-C. Niaspan can be combined safely with statins and is also effective in patients with combined dyslipidaemia and type 2 diabetes mellitus. Trials on CV endpoints evaluating the effect of statins with Niaspan are urgently needed to settle whether this combination can confirm the high expectations for cardiovascular outcome.

INTRODUCTION

During the last two decades the beneficial effect of statin therapy on cardiovascular morbidity and mortality has been confirmed in numerous large primary and secondary prevention trials that included an unprecedented number of patients, exceeding 65,000 subjects. Recent reports continue to extend the importance of low-density lipoprotein cholesterol (LDL-C) lowering in showing that even subjects with apparently 'normal' cholesterol benefit from statin treatment.[1] However, in spite of this breakthrough, between 65 and 80% of all coronary events cannot be prevented by statin therapy, at least not during the intervention period of most trials. This disappointing percentage has intensified the search for novel drug targets to further improve cardiovascular outcome. Amongst these, strategies aimed at increasing high-density lipoprotein cholesterol (HDL-C) levels hold great promise.

The importance of HDL-C as a pivotal defence mechanism against atherosclerosis has been substantiated by population studies, showing that the level of HDL-C is a powerful and independent inverse predictor of premature CHD.[2-4] In line, low levels of HDL-C are the most commonly encountered dyslipidaemia in patients with premature myocardial infarction, ranging up to 40% in prevalence.[5,6] The impact of low HDL-C as atherogenic risk factor increases dramatically when viewed against the background of the worldwide epidemic of obesity and the metabolic syndrome. Based on available data, it can be calculated that coronary risk increases by 1 to 2% for every 1% reduction in HDL-C level.[7] In spite of these strong observational findings, the implications of increasing HDL-C levels for cardiovascular outcome remain to be established. The lack of selective and efficacious drugs to increase HDL-C forms the main

reason for the lack of intervention studies. Lifestyle interventions, such as smoking cessation, exercise and alcohol use, are associated with only a modest increase of HDL-C.

Pharmacological modalities that raise HDL-C are statins, fibrates and nicotinic acid and its derivates. Statins increase the concentration of HDL-C by up to 5 to 10%. Fibrates lower plasma triglyceride by up to 50% and increase HDL-C by 5 to 25%, mainly through activation of the PPARα nuclear receptor. Indeed, intervention studies using fibrates have provided evidence that increasing HDL-C may constitute an important pharmaceutical target for cardiovascular prevention. Thus, in the VA-HIT trial, gemfibrozil significantly reduced CHD events from 21.7% in the placebo group to 17.3% in the active treatment group.[8] In this trial, LDL-C levels were not significantly lowered, whereas HDL-C levels were increased significantly. In addition, multivariate regression analysis showed that the increase in HDL-C was the only lipoprotein change that predicted benefit.[9] These data are supported by the outcome of the Helsinki Heart Study (HHS).[10] In this study, the primary endpoint (CHD events) was significantly reduced in the gemfibrozil group (2.7%), compared with the control group (4.1%). The results of these studies stress the need for further studies on the effects of pharmacological interventions resulting in increased HDL-C levels on CHD.

One of the oldest and most potent HDL-C increasing drugs is niacin. Niacin was first introduced as a lipid-lowering agent in 1954.[11] The mechanism by which niacin affects lipids and lipoproteins involves several pathways. Niacin stimulates the synthesis of both apo A-I and apo A-II.[12] In addition, it has been suggested that niacin reduces hepatic lipase activity, resulting in reduced hepatic removal of this particle.[13] Niacin also decreases the rate of hepatic very-low-density lipoprotein cholesterol (VLDL-C) and LDL-C synthesis, without affecting faecal excretion of fats, sterols, or bile acids. Shortly after its introduction, immediate-release niacin (IR-niacin) was shown to have beneficial effects on cholesterol and lipid metabolism. Despite its efficacy in increasing HDL-C and lowering triglycerides (TG), its side effects precluded broader clinical use of IR-niacin in patients.[14] The most common side effects were flushing and skin rash.[15] In an attempt to minimise potential side effects, slow-release formulations of niacin (SR-niacin) have been developed without great success.[14,16] Besides an unfavourable side-effect profile, SR-niacin also proved to be less efficacious in treating dyslipidaemias compared with IR-niacin.[17] The most recently developed compound in this class is Niaspan, an extended-release form of niacin. During the last five to six years, Niaspan was tested in numerous clinical trials, addressing safety and efficacy, both as monotherapy and in combination with other lipid-lowering drugs, such as statins and fibrates. In the next section, we will discuss the clinical trials conducted with Niaspan from 1996 until January 2004.

MATERIALS AND METHODS

A literature search of the MEDLINE database (1996 to January 2004), using the keywords niacin, nicotinic acid, lipoproteins, statins and coronary artery disease, was performed. The search was restricted to studies published in English-language journals, conducted in human subjects, and classified as clinical trials in the MEDLINE database. For inclusion, a study had to meet the following criteria: (1) random allocation of study participants to extended-release niacin *vs* a placebo-control group or random allocation of study participants to extended-release niacin *vs* extended-release niacin in combination with a statin, (2) changes in lipid profile as the primary endpoint, and (3) studies which included patients treated with an HMG-CoA reductase inhibitor were required to have an LDL-C level of at least 3.4 mmol/L (≥130 mg/dl). The contents of 138 abstracts or full-text manuscripts identified during our literature search were reviewed by one author (R.B.) for inclusion. Of these abstracts and manuscripts, 18 Niaspan treatment trials were identified. Other publications included reviews and secondary analysis of data from the 18 published trials. Four RCTs and four CCTs studies matched the inclusion criteria. The highest dose and the longest treatment period were selected to calculate the pooled effect on serum lipids in this analysis. The data collected for the measurement of the weighted mean difference for continuous data were: (1) the mean change in serum lipids (LDL-C, TG, lipoprotein(a) (Lp(a)) and HDL-C) from baseline to follow-up in millimoles per litre (mmol/l), (2) the standard deviation (SD) of the mean difference, and (3) the number in each comparison group (n) at follow-up. Estimates of the average effect of Niaspan on serum lipid values and 95% confidence intervals (95% CI) were calculated with models based on random-effects model.

RESULTS

Efficacy and safety of Niaspan in randomised, placebo-controlled trials

The general characteristics of the four randomised, placebo-controlled, double-blind trials included in this analysis are presented in *table 1*.[10,18,19,21] A total of 522 patients met the inclusion criteria for RCTs with Niaspan. The total duration of treatment was 70 weeks with a mean follow-up time of 18 weeks. The mean age was 55 years with a male-to-female ratio of 1.8. The mean dosage was 1.5 g Niaspan per day (1-3 g/d). One trial was conducted in patients with secondary dyslipidaemia in type 2 diabetics,[21] whereas the other

Table 1
General characteristics of randomised controlled trials and comparative cohort trials with Niaspan

SOURCE	YEAR	n, M/F	AGE (YEARS)	DOSE PER DAY	DURATION (WEEKS)	DYSLIPIDAEMIA
RCT						
Goldberg *et al.*[18]	1998	149 (3.1)	54	N 1.5 g	16	HC
Morgan *et al.*[19]	1998	96 (1.6)	50	N 1 & 2 g	16	HC
Knopp *et al.*[20]	1998	149 (3.1)	54	N 1.5 g	16	HC
Grundy *et al.*[21]	2002	146 (1.4)	60	N 1 g & N1.5 g	16	DM type 2
Pooled		**522 (1.9)**	**55**		**16**	
CCT						
Capuzzi *et al.*[23]	1998	723 (2.3)	54	N 2 g & S 10-20 mg	96	HC
Hunninghake *et al.*[24]	2002	175 (1.1)	59	N 2 g & L 20-40 mg	28	HC
Van *et al.*[25]	2002	31 (5.9)	59	N 2.8 g & A 80 mg	16	DM type 2
Capuzzi *et al.*[26]	2003	224 (2.6)	5	N 1.3 g & R 10-40 mg	24	(F)CH
Pooled		**1153 (2.9)**	**57**		**41**	

RCT = randomised placebo controlled trial, CCT = comparative cohort trial, n = number of subjects, M/F = male/female ratio, N = Niaspan, A= atorvastatin, L= lovastatin, R= rosuvastatin, S = (any) statin, HC = hypercholesterolaemia, DM type 2 = secondary dislipidaemia in patients with diabetes mellitus type 2, (F)CH = (familial) combined hyperlipidaemia.

three trials were conducted in patients with hypercholesterolaemia.[18-20,22] In the trial by Grundy *et al.*[21] participants were included if they were taking statins, provided that their LDL-C was at least 3.4 mmol/l (130 mg/dl). Analysis showed significant changes in lipid profile: 13% mean reduction in LDL-C (95% CI -12.76 [-2.96 to -22.55]), 26% mean reduction in triglycerides (95% CI -25.91 [-20.89 to -30.93]), 17% mean reduction in Lp(a) (95% CI -17.36 [-17.81 to -16.90]), and an 18% mean increase in HDL-c (95% CI 17.86 [13.39 to 22.32]). The highest dose of Niaspan (3 g/day) resulted in an HDL-C increase of 28% (95% CI [27.59 to 39.66]). The effects of various doses of Niaspan on HDL-C or shown in *table 2*. Overall 69% of the study participants experienced flushes *vs* 10% of the participants who were allocated to placebo (RR 6.12, 95% CI 4.10-9.13, p<0.00001).
In the Niaspan treatment group, 22 patients (RR 6.87, 95% CI 1.53-30.85) experienced pruritus and/or rash whereas one patient in the placebo group complained of this symptom. There were seven patients with increased transaminase levels (>2 times the upper reference limit) in the Niaspan treatment group (RR 3.51, 95% CI 0.63 to 19.49, p=0.15) and none in the placebo group. Myopathy (defined as CPK >10 times the upper reference limit with myalgia) was not evident in either group. Twenty subjects (10%) in the placebo group discontinued the study compared with 116 patients (34%) in the Niaspan treatment group (p<0.00001). The most common reason for discontinuation of the drug was the occurrence of skin flushes.

Efficacy and safety of Niaspan in comparative cohort studies
Four comparative, uncontrolled, open-label trials with Niaspan were included in this analysis.[23-26] The general characteristics are presented in *table 1*. A total of 1153 patients met the inclusion criteria for CCTs with Niaspan *vs* Niaspan and statins. The total duration of treatment was 164 weeks with a mean follow-up time of 41 weeks. The mean age was 57 years with a male-to-female ratio of 2.9. The mean dosage was 2 g Niaspan per day (1.3 to 2.8 g/d). One trial was conducted in patients with diabetes type 2 and secondary dyslipidaemia,[25] whereas in two trials patients with hypercholesterolaemia and in one trial patients with combined hyperlipidaemia were included. Analysis showed significant changes in lipid profile: 22% more reduction of LDL-C in favour of the Niaspan and statin combination treatment group *vs* the Niaspan monotherapy group (95% CI 21.99 [21.75, 22.41], p<0.00001), 8% more reduction in TG in favour of the Niaspan and statin combination treatment group (95% CI 8.28 [7.89, 8.67], p<0.00001), 6% more reduction in Lp(a) in favour of the Niaspan monotherapy group (95% CI -5.91 [-6.93, -4.88]; p=0.10), and a modest change of a 1% higher increase in HDL-C (p<0.0001) in favour of the Niaspan and statin combination treatment groups (95% CI 0.81 [0.60 to 1.02]). Overall 65% of patients who received Niaspan monotherapy experienced flushes *vs* 60% of patients who were allocated to the Niaspan and statin combination treatment group. A total of 33% of patients experienced pruritus and/or rash in the Niaspan monotherapy group *vs* 13% of patients in the Niaspan and statin combination treatment group (p=0.006). There were 14 patients with increased transaminase levels (>2 times the upper reference limit) in the Niaspan monotherapy group compared with six patients in the Niaspan and statin treatment group (NS). In the Niaspan monotherapy group, 323 subjects (50%) discontinued the study compared with 138 patients (29%) in the

Table 2
Net change and percent change in HDL-C in randomised controlled trials with various doses of Niaspan

INDEX	DOSE NIASPAN (MG/DAY)	NIASPAN (n)	PLACEBO (n)	HDL-C MMOL/L	NET CHANGE MMOL/L (95% CI)	PERCENT CHANGE (95% CI)
Goldberg *et al.*[18]	3000	46	34	1.16	0.32 0.17 to 0.46	28 15 to 42
Morgan *et al.*[19]	1000	39	37	1.11	0.14 -0.04 to 0.32	13 -4 to 30
Morgan *et al.*[19]	2000	41	37	1.11	0.17 0.002 to 0.3	15 0 to 30
Knopp *et al.*[20]	1500	74	72	1.16	0.18 0.05 to 0.32	16 4 to 28
Grundy *et al.*[21]	1000	45	49	1.06	0.16 0.06 to 0.25	15 6 to 24
Grundy *et al.*[21]	1500	52	49	1.06	0.24 0.14 to 0.34	23 13 to 32
Pooled		297	278	1.12	0.20 0.15 to 0.25	18 14 to 22

CI = 95% confidence interval, n = number of subjects treated with either Niaspan or placebo. To convert values for HDL cholesterol from millimoles per litre to milligram per decilitre, multiply by 38.7. Net change is expressed as the change during active treatment minus the change during control.

Niaspan treatment group (p<0.00001). The most common reason for discontinuation was the occurrence of skin flushes.

DISCUSSION

These pooled data show that Niaspan has a distinct beneficial effect on the lipid profile in patients with hypercholesterolaemia, combined hyperlipidaemia and secondary dyslipidaemia in type 2 diabetes, including a net change of 0.20 mmol/l (18%) increase in HDL-C as well as significant LDL-C, TG and Lp(a) lowering. Combination therapy of Niaspan and statin does not convey additional toxicity, whereas the efficacy of both drugs is additive. The most important side effect of Niaspan is skin flushing, the severity of which decreases significantly over time.[23] In spite of previous reports on insulin resistance during Niaspan therapy, this phenomenon appears to be clinically insignificant in the currently pooled studies, which also include a study in type 2 diabetic patients.[27] Overall, Niaspan has proven to be an efficacious HDL-C increasing drug, which is able to fill an important gap in the currently available lipid-modulating pharmacological arena.

Clinical perspective

In the past decade, large statin trials have proven to be beneficial for cardiovascular prevention. Despite these successes more than 70% of coronary events cannot be prevented by statins. This concerning number, plus the epidemiological findings in large-scale prospective studies demonstrating an inverse relation between HDL-C and CHD, has to some extent directed the search for new therapeutic targets. In recent years increasing HDL-C on top of statins has emerged as a therapeutic option that holds great promise for cardiovascular prevention. Especially patients with the metabolic syndrome consisting of a low HDL-C, patients with CHD and patients with genetically determined low isolated HDL-C are expected to benefit from this new and promising therapeutic option in the years to come. Expectations have increased after completion of surrogate endpoint studies, showing a significantly greater reduction of carotid arterial intima-media thickness (IMT) during statin/colestipol/niacin therapy compared with statin monotherapy.[28-30] In line, HDL-C increasing strategies have also been associated with improvements in endothelial function.[31] Unfortunately, clinical endpoint studies showing survival benefit during combination therapy are scarce. Available data from, for instance, the VA-HIT study have predicted a 1 to 2% additional reduction in cardiovascular events for every 1% increase in HDL-C level.[13] Extrapolation of these estimates would result in reductions in cardiovascular morbidity and mortality as high as 65 to 75% if statins are combined with drugs inducing a 20 to 30% increase in HDL-C.

Brown *et al.* reported outcome data from the FATS study, in which combinations of niacin/colestipol or lovastatin/colestipol were evaluated *vs* conventional therapy with placebo or colestipol, assessed in 176 patients.[32] In the Niacin combination therapy group, HDL-C increased by 41%, whereas cardiovascular event rate was reduced by 72% at ten-year follow-up. In the HATS study, 160 patients with CHD, low HDL-C and normal LDL-C levels, were treated with simvastatin combined with either niacin (SR-niacin or IR-niacin) or placebo. The combination of

statin and niacin was associated with a 26% increase in HDL-C and a 60% reduction in cardiovascular event rate during a three-year follow-up period of 160 subjects.[33] Notably, data from these relatively small intervention studies fit nicely with the calculated cardiovascular gain due to HDL-C increase, based on observational data.

In conclusion, randomised trials with Niaspan on top of statin therapy, evaluating the effect on clinical endpoints, are urgently awaited to settle whether this combination, having been proven safe and effective, can indeed live up to the high expectations for cardiovascular outcome.

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REFERENCES

1. Collins R, Armitage J, Parish S, Sleigh P, Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003;361:2005-16.
2. Goldbourt U, Medalie JH. High density lipoprotein cholesterol and incidence of coronary heart disease-the Israeli Ischemic Heart Disease Study. Am J Epidemiol 1979;109:296-308.
3. Jacobs DR Jr, Mebane IL, Bangdiwala SI, Criqui MH, Tyroler HA. High density lipoprotein cholesterol as a predictor of cardiovascular disease mortality in men and women: the follow-up study of the Lipid Research Clinics Prevalence Study. Am J Epidemiol 1990;131:32-47.
4. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. Am J Med 1977;62:707-14.
5. Genest JJ Jr, Martin-Munley SS, McNamara JR, et al. Familial lipoprotein disorders in patients with premature coronary artery disease. Circulation 1992;85:2025-33.
6. Genest J Jr, Bard JM, Fruchart JC, Ordovas JM, Schaefer EJ. Familial hypoalphalipoproteinemia in premature coronary artery disease. Arterioscler Thromb 1993;13:1728-37.
7. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation 1989;79:8-15.
8. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med 1999;341:410-8.
9. Robins SJ, Collins D, Wittes JT, et al. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. JAMA 2001;285:1585-91.
10. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med 1987;317:1237-45.
11. Altscul R, Hoffeer A, Stephen JD. Influence of nicotinic acid on serum cholesterol in man. Arch Biochem 1955;54:558-9.
12. Shepherd J, Packard CJ, Patsch JR, Gotto AM, Jr, Taunton OD. Effects of nicotinic acid therapy on plasma high density lipoprotein subfraction distribution and composition and on apolipoprotein A metabolism. J Clin Invest 1979;63:858-67.
13. 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;21:1783-9.
14. McKenney JM, Proctor JD, Harris S, Chinchili VM. A comparison of the efficacy and toxic effects of sustained- vs intermediate-release niacin in hypercholesterolemic patients. JAMA 1994;271:672-7.
15. Keenan JM, Fontaine PL, Wenz JB, Myers S, Huang ZQ, Ripsin CM. Niacin revisited. A randomized, controlled trial of wax-matrix sustained-release niacin in hypercholesterolemia. Arch Intern Med 1991;151:1424-32.
16. Hodis HN. Acute hepatic failure associated with the use of low-dose sustained-release niacin. JAMA 1990;264:181.
17. Knopp RH, Ginsberg J, Albers JJ, et al. Contrasting effects of unmodified and time-release forms of niacin on lipoproteins in hyperlipidemic subjects: clues to mechanism of action of niacin. Metabolism 1985;34:642-50.
18. Goldberg A, Alagona P Jr, Capuzzi DM, et al. Multiple-dose efficacy and safety of an extended-release form of niacin in the management of hyperlipidemia. Am J Cardiol 2000;85:1100-5.
19. Morgan JM, Capuzzi DM, Guyton JR. A new extended-release niacin (Niaspan): efficacy, tolerability, and safety in hypercholesterolemic patients. Am J Cardiol 1998;82:29U-34U.
20. 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 1998;47:1097-104.
21. 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;162:1568-76.
22. Goldberg AC. Clinical trial experience with extended-release niacin (Niaspan): dose-escalation study. Am J Cardiol 1998;82:35U-38U.
23. Capuzzi DM, Guyton JR, Morgan JM, et al. Efficacy and safety of an extended-release niacin (Niaspan): a long-term study. Am J Cardiol 1998;82:74U-81U.
24. Hunninghake DB, McGovern ME, Koren M, et al. A dose-ranging study of a new, once-daily, dual-component drug product containing niacin extended-release and lovastatin. Clin Cardiol 2003;26:112-8.
25. Van JT, Pan J, Wasty T, Chan E, Wu X, Charles MA. Comparison of extended-release niacin and atorvastatin monotherapies and combination treatment of the atherogenic lipid profile in diabetes mellitus. Am J Cardiol 2002;89:1306-18.
26. Capuzzi DM, Morgan JM, Weiss RJ, Chitra RR, Hutchinson HG, Cressman MD. Beneficial effects of rosuvastatin alone and in combination with extended-release niacin in patients with a combined hyperlipidemia and low high-density lipoprotein cholesterol levels. Am J Cardiol 2003;91:1304-10.