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Niacin improves lipid profile but not endothelial function in patients with coronary artery disease on high dose statin therapy

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ABSTRACT

Aims: To determine the effect of extended release (ER) niacin on endothelial and vascular function assessed by brachial flow-mediated dilatation (FMD), peak hyperemic velocity (VTiRH) and pulse arterial tonometry (PAT) in patients with established coronary artery disease (CAD), already treated with high dose statins. Endothelial dysfunction is common in patients with established coronary artery disease (CAD) and has prognostic implications. Niacin has proven clinical benefit in patients with CAD, but its additive effect in patients on statin therapy is being evaluated. The effect of niacin on endothelial function, in the presence of optimal LDL cholesterol is unclear.

Methods and results: Sixty-six patients with CAD (mean age 57.9 ± 8.5 yrs) received ER niacin (1500 mg per day) and placebo in a randomized crossover fashion for 3 months of each therapy. All patients received atorvastatin 80 mg per day. FMD, VTiRH and PAT measurements were performed at baseline and after each treatment period. Treatment with niacin improved dyslipidemia parameters (LDL placebo 1.52 ± 0.51 vs. niacin 1.30 ± 0.43; $p = 0.004$; HDL placebo 0.95 ± 0.16 vs. niacin 1.11 ± 0.22; $p < 0.001$). However, there was no observed improvement in endothelial function as assessed by FMD (placebo 6.1 ± 4.9 vs. niacin 6.6 ± 4.8%; $p = 0.48$), VTiRH (placebo 75 ± 28 vs. niacin 78 ± 26 cm; $p = 0.23$) or PAT (placebo 1.8 ± 0.42 vs. niacin 1.79 ± 0.5; $p = 0.43$).

Conclusion: Niacin as add-on treatment to high dose statins in patients with established CAD significantly improves lipid profile. However, these changes were not associated with improved endothelial or microvascular function.

Registered clinical trial with clinicaltrials.gov: NCT00150722.

1. Introduction

Despite aggressive LDL lowering therapy with statins, annual event rates for high risk patients remain above 3 percent. Strategies aimed at adjuvant lipoprotein modification have been actively studied. Currently there is a lack of evidence that therapeutic elevation of HDL per se improves cardiovascular outcomes, however modulation of low HDL levels has attracted attention due to the strong epidemiological evidence demonstrating an inverse relationship between HDL and cardiovascular risk. Mechanisms that mediate this relationship remain speculative, but do include effects on endothelial function. HDL has been suggested to maintain endothelial function through antioxidant, anti-inflammatory, and other direct endothelial effects [1–3].

Recent results of HDL modification with Acyl-CoA cholesterol acyltransferase (ACAT) [4] and cholesterol ester transfer protein (CETP) [5] inhibitors have been disappointing. Niacin therefore currently remains the most effective therapy to raise HDL, but has not gained widespread popularity due to perceived side effects. The relatively recent introduction of a more tolerable intermediate release form of niacin (Niacin ER) may allow more widespread patient use. Recent studies have suggested a favorable effect of niacin on carotid intima-media thickness (CIMT) [6,7]. In addition, the Coronary Drug Project demonstrated a reduced mortality [8] in patients with coronary disease, but this was prior to the statin era. In the setting of background statin therapy, the utility of HDL elevation with niacin, and effects on endothelial function and inflammation is uncertain. The purpose of the present study was to assess the effect of Niacin ER on markers of vascular function in patients with documented coronary disease on optimal statin therapy.

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2. Methods

2.1. Patient population

We report a single center, randomized, placebo controlled, crossover design study of subjects with stable coronary disease on high dose statin therapy, measuring the effect of intermediate release niacin (niacin ER) on endothelial and microvascular function. Patients were recruited from the Foothills Hospital cardiac service and associated cardiac clinics. A total of 110 patients underwent screening. Of those 75 patients were randomized and 66 have complete data (Table 1). There were no differences in baseline characteristics between those who withdrew and the final cohort. Of those completing the study 98% achieved full dose niacin therapy, mean niacin dose was 1481 ± 100 mg/day. Finally, 82% of patients completed the study on the maximal 80 mg dose of atorvastatin (mean dose 74 ± 14 mg).

Inclusion criteria were as follows. Subjects with either angiographic evidence of coronary disease of greater than 50% severity in one or more vessels documented within 5 years, previous myocardial infarction or acute coronary syndrome greater than 1 month prior to commencement of the study, or coronary artery bypass grafting (CABG) (>3 months) or coronary angioplasty (PCI) (>1 month) prior to commencement of the study. We included male subjects with an HDL <1.10 and females <1.30 mmol/L. Exclusion criteria included current niacin use, PCI within one month or CABG within 3 months, planned revascularization in the next year, blood pressure >160/95 mm Hg, glucose >7.0 mmol/L or active diabetes, active gout, hepatic or gallbladder disease, creatinine >200 μmol/L, ALT >2× upper limit of normal, change in endothelial modulating medications within one month or need to change these during the study, or inability to provide informed consent. This study was approved by the ethics committee of the University of Calgary, and was registered as a clinical trial with clinicaltrials.gov (NCT00150722).

2.2. Study protocol

Sixty two subjects (94%) had been on statins prior to study and were not washed out prior to the screening blood work. Subjects first commenced a 4 week open label run-in treatment with atorvastatin 80 mg/day (Lipitor, Pfizer Canada). Patients then underwent baseline assessment of endothelial function and repeat blood work. Patients were randomized in double-blind fashion to receive either escalating doses of niacin ER (1st week 250 mg, second week 500 mg, 3rd week 750 mg, 4th week 1000 mg, and 5th week 1500 mg) or matching placebo. Data monitoring was performed by an experienced investigator, blinded to randomization status. To avoid unblinding, the placebo contained 50 mg nicotinic acid to induce modest flushing symptoms without affecting lipid parameters or endothelial function. After 12 weeks of Niacin ER (Niaspan, Sepracor Pharmaceuticals) or placebo, patients underwent repeat assessment of endothelial function and blood work, and then crossed over to the opposite arm of the study. The same process was repeated for an additional 12 weeks. A washout period between arms of the study was not utilized given the three-month treatment phases in this study. A safety visit was performed and blood taken after 6 weeks in each arm of the study. In patients who did not tolerate the drug/placebo due to flushing, dose escalation could be delayed, aborted, or dose reduction could be used if required (Fig. 1).

Table 1
Baseline characteristics.

	Mean ± SD ($n = 66$)
Age yrs	58 ± 8.5
Male gender (%)	55 (83)
Systolic blood pressure mmHg	120 ± 15
Diastolic blood pressure mm Hg	77 ± 9
Body mass index kg/m^2	29.9 ± 4.4
Current smokers (%)	16 (24)
Family history of cardiovascular disease < 50years of age (%)	9 (23)
History of peripheral vascular disease (%)	6 (9)
History of percutaneous coronary intervention or coronary artery bypass surgery (%)	61 (92.4)
ACE inhibitor or angiotensin receptor blocker (%)	58 (88)
Calcium channel blocker (%)	16 (24)
Statin therapy (%)	64 (97)
Aspirin (%)	66 (100)

2.3. Assessment of vascular function

Vasoactive medications (including ACE-inhibitors, angiotensin receptor blockers, calcium channel blockers and nitrates) with the exception of beta-blockers were held on the morning of baseline and subsequent endothelial function evaluations. The study medications (niacin and atorvastatin) were taken on the night before the studies occurred.

2.4. Endothelial function – flow-mediated dilatation

Measures of brachial artery flow-mediated dilatation were performed as previously published by our group [9]. Subjects were all analysed while fasting early in the working hours of the morning. Assessment of endothelial function occurred in a dedicated. quiet temperature controlled environment. Subjects were requested to abstain from exercise, tobacco, caffeine, or high fat foods for at least 6 h prior to the study. All measurements were taken by the same experienced technician, blinded to the randomization. In brief, the flow occlusion was produced by inflating a forearm cuff to 50 mm Hg above systolic pressure for 5 min. Peak hyperemic velocity, expressed as the velocity time integral (VTiRH) was measured for the first 15 s post cuff release and brachial artery dilation was measured for 3 min. Nitroglycerin mediated dilatation was induced with 0.3 mg NTG sublingually, and the artery imaged for 90 s commencing 2.5 min after administration.

Analysis was performed as previously described [9]. Briefly, automated edge detection software was utilized to measure baseline diameter and peak diameter post reactive hyperemia (generally between 45 and 90 s) for the calculation of flow-mediated dilation. Two end-diastolic frames were averaged for each intervention. In our laboratory the intra-observer coefficient of variation for repeated measurements on the same image using the above approach is 4–5%.

2.5. Microvascular function – peripheral artery tonometry and hyperemic velocity

Concurrently with the FMD procedure, patients underwent assessment of pulsatile blood volume responses by pulse arterial tonometry (PAT) to measure the pulse volume amplitude (PVA) [10]. PAT measurements (EndoPat, Itamar, Israel) were simultaneously measured from the index finger of both hands. Results are expressed as an index calculated between the active and control fingers at baseline and during reactive hyperemia. The variable measured is therefore the ratio of PVA index in hyperemia to PVA index at baseline.

We and others have recently described the utility of blood velocity in reactive hyperemia (calculated as part of FMD

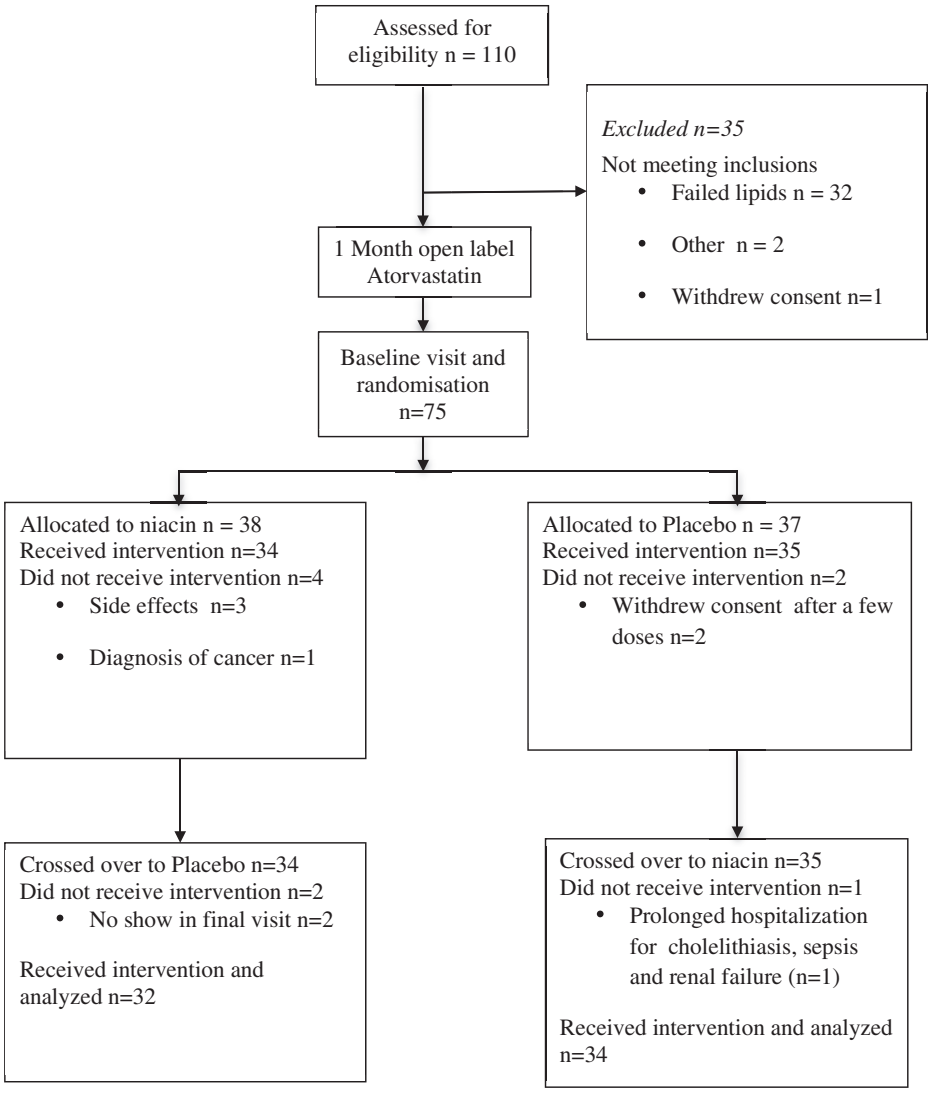

Fig. 1. Study protocol: schema for randomization and participation in study.

measurements) as another surrogate marker of microvascular function, and associated this with the presence of cardiovascular risk factors more strongly than FMD [11,12]. We therefore also report the effect of niacin on VTiRH, the first full velocity envelope following cuff release. Higher values for both PAT and VTiRH are felt to reflect better microvascular function. In our laboratory the intra-observer coefficient of variation for repeated measurements of VTiRH on the same image using the above approach is 2%.

2.6. Biochemical data

Fasting venous blood samples for hs CRP, lipid profile, and glucose were obtained at screening, after 12 weeks on the treatment phase 1, and after completion of treatment phase 2. Additional safety venous blood samples for creatinine kinase and ALT were obtained after 6 weeks treatment in each phase of the study.

2.7. Statistical analysis

The data were expressed as means ± SD except where indicated. Non-parametric data including triglycerides and hs CRP were medians (25, 75% CI). The primary efficacy analysis was the effect of niacin on flow-mediated dilation. The secondary analyses evaluated the effect of niacin on the microvascular responses of pulse arterial tonometry and hyperemic velocity. Differences in baseline characteristics were compared with unpaired Student *t*-tests, Wilcoxon or Chi squared where appropriate. The effect of atorvastatin 80 mg on biochemical parameters during the run-in period was evaluated by comparing the screening and baseline blood work for the entire cohort by paired *t*-tests. The effect of niacin on the biochemical and vascular parameters was determined by comparing the difference between active therapy and its preceding baseline with that same difference obtaining while on placebo by two way repeated measures ANOVA. Carry-over effects were evaluated by comparing the biochemical and vascular parameters on placebo in those subjects who received niacin for the first 12-week period followed by placebo.

The sample size of 75 patients was based on an assumption of a 2% change in FMD, 5% standard deviation of change in FMD with 80% power and alpha of 0.05. We allowed for a 15% drop-out rate. Statistical analysis was performed with PASW Statistics (version 18.0) with analysis at alpha of 5%.

Table 2
Effect of atorvastatin.

	Screening	Baseline	*p*-Value for pair *t*-test or Wilcoxon[a]
HsCRP[a]	1.23 (0.70, 2.86)	0.95 (0.64, 2.85)	0.302
Total cholesterol	3.85 ± 1.29	3.11 ± 0.74	<0.001
HDL cholesterol	0.99 ± 0.14	0.92 ± 0.15	<0.001
Triglycerides[a]	1.61 (1.14, 2.21)	1.17 (0.89, 1.87)	<0.001
LDL cholesterol	2.01 ± 1.02	1.52 ± 0.50	<0.001

Mean ± SD, values in mmol/L. $n = 64–66$.
[a] Median (25%, 75%tile) and Non-parametric Wilcoxon signed rank *p*-value.

3. Results

3.1. Baseline characteristics

Baseline characteristics are shown in Table 1. The LDL was 2.0 ± 1.0 mmol/L but HDL was low by design at 0.99 ± 0.14 mmol/L.

3.2. Effect of atorvastatin during run-in-phase

Although patients were on statins at screening, there was a further change in biochemistry during the 4-week run-in-phase of atorvastatin 80 mg (Table 2). There was a significant ($p < 0.001$) fall in total, LDL and HDL cholesterol as well as triglycerides. There was also a fall in hs CRP but this did not achieve statistical significance. The final HDL cholesterol on high dose atorvastatin was 0.92 ± 0.15 mmol/L prior to niacin randomization.

3.3. Carry over effects

Carry-over effects of niacin were evaluated by comparing the placebo values with the baseline for those who received niacin first and then crossed over to placebo. No significant carry-over effect was demonstrated for the vascular or biochemical end-points.

3.4. Effect of niacin ER on lipid levels and hs CRP

HDL cholesterol rose from 0.92 ± 0.15 mmol/L to 1.11 ± 0.22 mmol/L with niacin. This 21% increase in HDL was statistically different than the placebo effect ($p < 0.001$) or the baseline values. LDL cholesterol was further lowered by 14% with niacin to 1.30 ± 0.44 mmol/L ($p = 0.004$). Triglycerides were significantly reduced as well by 19% ($p < 0.001$). The median hs CRP did not change with niacin therapy. Glucose increased from 5.6 ± 0.5 mmol/L to 5.8 ± 0.7 mmol/L while on niacin ($p = 0.003$) (Table 3).

3.5. Effect of niacin ER on endothelial function

The baseline brachial artery diameter did not change during the study period. There was no significant difference between Niacin ER and placebo on FMD. There was a small increase in FMD (niacin Δ 0.24 ± 4.7% vs. placebo Δ −0.3 ± 5.0%), but this was not statistically significant (Fig. 2). Similarly, our measures of microvascular function were not statistically different with niacin therapy. The difference in VTiRH for niacin compared with placebo (5.9 ± 40 cm) was not significant ($p = 0.23$) (Fig. 2). PAT-index was attenuated at baseline and was not augmented with active therapy (Fig. 2). In addition, those in the lowest tertile of baseline HDL levels did not show any change in vascular parameters as has been suggested by a previous study [13].

4. Discussion

In patients with coronary disease and optimal statin therapy, 12 weeks of Niacin ER resulted in a significant increase in HDL and decrease in LDL cholesterol. Despite this, there was no improvement in conduit or resistance vessel vascular function. Endothelial dysfunction was not improved with niacin in subjects with LDL cholesterol well below current target levels.

Patients with coronary disease have impaired brachial artery flow-mediated vasodilatation as was demonstrated in the current study, and a correlation exists between measures of endothelial function in the coronary and peripheral circulation [14]. There is emerging evidence for the prognostic capacity of endothelial function measurement through several techniques including FMD and VTiRH [15–17]. A number of pharmacological interventions that improve cardiovascular outcomes, including lipid lowering therapy with statins, have been shown to also improve endothelial function in a variety of patient populations [18,19]. Thus, measures of endothelial function are now accepted surrogates of atherosclerosis activity and are used as end-points in research studies of cardiovascular interventions.

Until recently, evidence of clinical effects from HDL raising therapy with niacin was limited to the pre-statin era. Canner et al found a modest reduction in non fatal MI after niacin therapy compared with placebo, and at 15 years follow up this group had 11% reduction in mortality [8]. Recently the “Atherothrombosis intervention in Metabolic syndrome with low HDL/High triglycerides: impact on global health” (AIM-High) study using similar treatment to that tested here, albeit in a patient population of generally lower risk, was halted due to lack of clinical benefit in the niacin treated group [20]. Thus even though there were subtle differences between the inclusion criteria and the dose of niacin used in the current study and AIM-HIGH, the results are congruent between the two studies.

This study was designed recognizing that most patients with coronary artery disease now receive intensive statin therapy. Many of these patients will have low HDL levels despite this therapy and have substantial residual risk. Consequently we only included patients in this study who had low HDL (and this level remained

Table 3
Vascular function and biochemical measures in baseline and after placebo or niacin ($N = 66$).

	Baseline	Placebo	Niacin ER	2 Way Anova *p*-value
FMD	6.4 ± 4.3	6.1 ± 4.9	6.6 ± 4.8	0.48
NMD	19.0 ± 7.0	19.1 ± 8.5	18.8 ± 8.6	0.92
VTiRH	85 ± 30	75 ± 28	78 ± 26	0.23
PAT-Index	1.67 ± 0.35	1.8 ± 0.42	1.79 ± 0.5	0.44
HsCRP[a] (mg/L)	0.95 (0.64, 2.85)	0.91 (0.45, 1.95)	0.78 (0.44, 1.6)	0.89
LDL cholesterol (mmol/L)	1.52 ± 0.5	1.52 ± 0.51	1.3 ± 0.43	0.004
Triglyceride[a] (mmol/L)	1.17 (0.89, 1.87)	1.31 (0.9, 1.7)	0.95 (0.67, 1.34)	<0.001
HDL cholesterol (mmol/L)	0.92 ± 0.15	0.95 ± 0.16	1.11 ± 0.22	<0.001
Fasting glucose (mmol/L)	5.6 ± 0.5	5.5 ± 0.6	5.8 ± 0.7	0.003

$n = 64–66$. Mean ± SD; FMD, flow-mediated dilation (%); NMD, nitroglycerin mediated dilation (%); VTiRH, velocity time integral (cm); PAT, peripheral arterial tonometry.
[a] Median (inter-quartile range) and non-parametric Wilcoxon signed rank *p*-value.

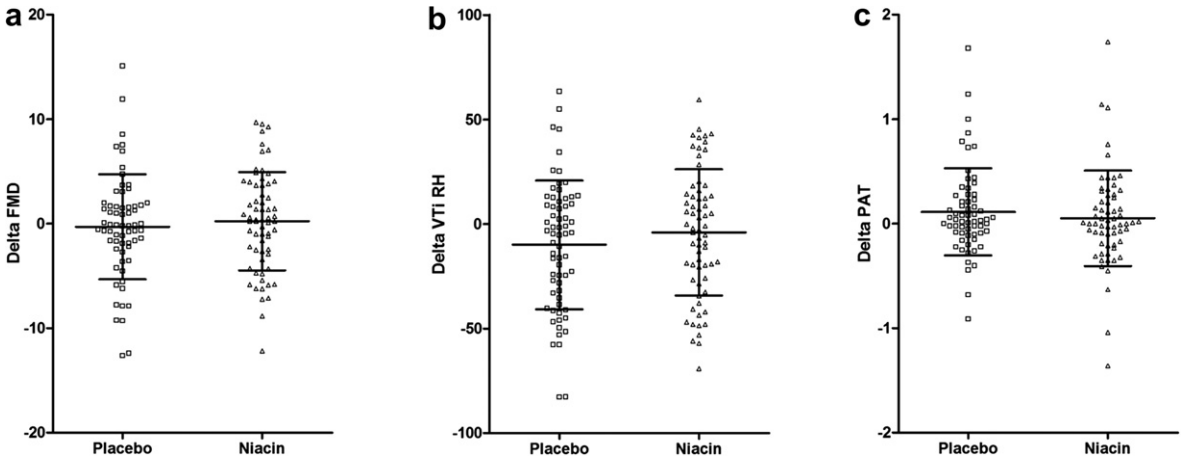

Fig. 2. Effect of niacin on FMD, VTiRH, and PAT: change (delta) in (a) FMD, (b) VTiRH, and (c) PAT (mean ± SD) after 3 months treatment with placebo or niacin.

low during the placebo arm of the study). The optimal approach in these patients has not been established. Evidence regarding the effects of niacin therapy in this setting on vascular and endothelial function is lacking however some imaging data exists regarding progression of atherosclerosis [6,7,21].

This is the largest study to assess the endothelial and microvascular function effects of niacin in patients with cardiovascular disease on optimal LDL lowering therapy. Several small studies have previously assessed the effect of HDL therapy with niacin on endothelial function in patients with coronary disease. Kuvin et al. noted an improvement in brachial endothelial function in 11 subjects treated with niacin [22]. Benjo et al. studied 30 patients with isolated low HDL and also found improved FMD after three months therapy with niacin [23]. In a subgroup of a recent study of 41 patients by Sorrentino et al., niacin ER increased radial artery flow-mediated dilatation by approximately 4% after three months [24]. In contrast Westphall et al. found no change in brachial artery FMD in 20 patients with metabolic syndrome treated with niacin for 6 weeks [25]. More recently, Warnholtz et al. reported a larger study of 106 patients with normal HDL levels and impaired FMD. Unlike our study, these patients had suboptimal LDL levels (baseline LDL 2.6 vs 1.5 in this study), and less patients received statin therapy (87% vs 97%). Half of these patients were randomized to receive niacin for 3 months, and no effect on FMD was found although post hoc analysis suggested an effect on the patients with the lowest tertile of HDL at baseline [13].

HDL has an accepted role in mediating reverse cholesterol transport. In vitro data shows that HDL stimulates eNOS activity, NO bioavailability and vasorelaxation [22] and may therefore be expected to improve endothelial dysfunction as measured by FMD. Understanding the mechanism of niacin effects has been advanced in the last decade with identification of specific niacin receptors [26]. However, Niacin is understood to raise HDL through multiple mechanisms. Niacin receptors are not limited to hepatic tissue, and non-lipid vascular protective and anti-inflammatory effects have been proposed [27]. In vitro human studies have shown niacin to have anti-inflammatory properties mediated through multiple pathways [28]. HDL is the most complex lipoprotein fraction in mammals with over 75 different modifiable proteins identified in the proteosome [29]. It is apparent from recent clinical studies of ACAT inhibition that raising HDL-C per se does not necessarily confer clinical benefit [4]. Niacin therefore remains the only clinically available therapy to specifically increase HDL levels.

A number of potential explanations may be proposed for the lack of vascular or anti-inflammatory effects in our study despite improved lipid parameters. The high dose statin therapy used in this study through lipid, nitric oxide dependent, and anti-inflammatory mechanisms may have attenuated any niacin induced effects [30].

Further, despite favourably modifying lipid levels, niacin may not have affected this increase through subfractions of HDL capable of endothelial benefit.

The small increase we observed in fasting glucose is consistent with previous reports that describe a 4–5% increase in fasting glucose with niacin therapy [31]. While it could be suggested that this effect may counteract improvements in vascular function measures, the change appears too small to be clinically significant in this setting.

The median LDL levels of 1.5 mmol/L or less while on niacin is the lowest level reported in studies that have assessed the effect of niacin on vascular function. In patients whose LDL cholesterol is very well treated, it may be that niacin therapy is unable to confer further beneficial effects on vascular function. This is consistent with the recently terminated AIM-HIGH study [20].

4.1. Limitations

Although appropriately powered, this is a single center study of 66 patients utilizing measures of vascular function that entail some variability. Our subjects were also predominantly male (88%), and we cannot exclude gender based differences in results in this study.

A washout period between phases of the study would have excluded any concern of carry-over effects between treatment arms. It is also possible that a beneficial effect of this intervention might not occur within the 3 month time frame of this study. The Arbiter-2 and Arbiter-6 studies reported reduced progression of CIMT after twelve months therapy with niacin added to simvastatin [7], while the Coronary Drug Project did not reveal a mortality benefit early after treatment, but was associated with significant reduction in mortality at 15 years follow up [8].

The current study only addresses one aspect of atherosclerosis biology, measures of vascular function, with one duration of therapy and a maximum dose of 1500 mg/day. The Heart Protection Study 2, will add to the recently published “AIM-HIGH” study [20] and provide further data on clinical outcomes in the next 2 years.

5. Summary

Our results suggest that ER Niacin is well tolerated and effective in improving lipid parameters in patients with CAD on high dose

statin therapy. However, they do not support evidence that this effect improves endothelial or microvascular function after three months treatment. Whether the improved lipid parameters confer a clinical benefit in this patient population via other mechanisms remains to be determined.

Conflict of interest

Philpott and Anderson have received speakers honorariums from Pfizer less than ten thousand dollars, and Anderson unrestricted grants of greater than ten thousand dollars. Anderson has received speakers honorariums from sepracor less than ten thousand dollars. There are no other industry affiliations to disclose.

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References

[1] Fleisher LN, Tall AR, Witte LD, et al. Stimulation of arterial endothelial cell prostacyclin synthesis by high density lipoproteins. J Biol Chem 1982;257:6653–5.
[2] Yuhanna IS, Zhu Y, Cox BE, et al. High-density lipoprotein binding to scavenger receptor-BI activates endothelial nitric oxide synthase. Nat Med 2001;7:853–7.
[3] Noor R, Shuaib U, Wang CX, et al. High-density lipoprotein cholesterol regulates endothelial progenitor cells by increasing eNOS and preventing apoptosis. Atherosclerosis 2007;192:92–9.
[4] Nissen SE, Tuzcu EM, Brewer HB, et al. Effect of ACAT inhibition on the progression of coronary atherosclerosis. N Engl J Med 2006;354:1253–63.
[5] Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med 2007;357:2109–22.
[6] Taylor AJ, Sullenberger LE, Lee HJ, et al. 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;110:3512–7.
[7] 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.
[8] Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. J Am Coll Cardiol 1986;8:1245–55.
[9] Yan RT, Anderson TJ, Charbonneau F, et al. Relationship between carotid artery intima-media thickness and brachial artery flow-mediated dilation in middle-aged healthy men. J Am Coll Cardiol 2005;45:1980–6.
[10] Roifman I, Sun YC, Fedwick JP, et al. Evidence of endothelial dysfunction in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2009;7:175–82.
[11] Philpott AC, Lonn E, Title LM, et al. Comparison of new measures of vascular function to flow mediated dilatation as a measure of cardiovascular risk factors. Am J Cardiol 2009;103:1610–5.
[12] Mitchell GF, Vita JA, Larson MG, et al. Cross-sectional relations of peripheral microvascular function, cardiovascular disease risk factors, and aortic stiffness: the Framingham Heart Study. Circulation 2005;112:3722–8.
[13] Warnholtz A, Wild P, Ostad MA, et al. Effects of oral niacin on endothelial dysfunction in patients with coronary artery disease: results of the randomized, double-blind, placebo-controlled INEF study. Atherosclerosis 2009;204:216–21.
[14] Anderson TJ, Uehata A, Gerhard MD, et al. Close relation of endothelial function in the human coronary and peripheral circulations. J Am Coll Cardiol 1995;26:1235–41.
[15] Yeboah J, Crouse JR, Hsu FC, et al. Brachial flow-mediated dilation predicts incident cardiovascular events in older adults: the Cardiovascular Health Study. Circulation 2007;115:2390–7.
[16] Yeboah J, Folsom AR, Burke GL, et al. Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study: the multi-ethnic study of atherosclerosis. Circulation 2009;120:502–9.
[17] Anderson TJ, Charbonneau F, Title LM, et al. Microvascular function predicts cardiovascular events in primary prevention: long-term results from the Firefighters and Their Endothelium (FATE) study. Circulation 2011;123:163–9.
[18] Anderson TJ, Meredith IT, Yeung AC, et al. The effect of cholesterol-lowering and antioxidant therapy on endothelium-dependent coronary vasomotion. N Engl J Med 1995;332:488–93.
[19] Anderson TJ, Elstein E, Haber H, et al. Comparative study of ACE-inhibition, angiotensin II antagonism, and calcium channel blockade on flow-mediated vasodilation in patients with coronary disease (BANFF study). J Am Coll Cardiol 2000;35:60–6.
[20] 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.
[21] Lee JM, Robson MD, Yu LM, et al. Effects of high-dose modified-release nicotinic acid on atherosclerosis and vascular function: a randomized, placebo-controlled, magnetic resonance imaging study. J Am Coll Cardiol 2009;54:1787–94.
[22] Kuvin JT, Ramet ME, Patel AR, et al. A novel mechanism for the beneficial vascular effects of high-density lipoprotein cholesterol: enhanced vasorelaxation and increased endothelial nitric oxide synthase expression. Am Heart J 2002;144:165–72.
[23] Benjo AM, Maranhao RC, Coimbra SR, et al. Accumulation of chylomicron remnants and impaired vascular reactivity occur in subjects with isolated low HDL cholesterol: effects of niacin treatment. Atherosclerosis 2006;187:116–22.
[24] Sorrentino SA, Besler C, Rohrer L, et al. Endothelial-vasoprotective effects of high-density lipoprotein are impaired in patients with type 2 diabetes mellitus but are improved after extended-release niacin therapy. Circulation 2010;121:110–22.
[25] Westphal S, Borucki K, Taneva E, et al. Extended-release niacin raises adiponectin and leptin. Atherosclerosis 2007;193:361–5.
[26] Tunaru S, Kero J, Schaub A, et al. PUMA-G and HM74 are receptors for nicotinic acid and mediate its anti-lipolytic effect. Nat Med 2003;9:352–5.
[27] Kamanna VS, Kashyap ML. Mechanism of action of niacin. Am J Cardiol 2008;101:20B–6B.
[28] Nofer JR, Walter M, Kehrel B, et al. HDL3-mediated inhibition of thrombin-induced platelet aggregation and fibrinogen binding occurs via decreased production of phosphoinositide-derived second messengers 1,2-diacylglycerol and inositol 1,4,5-tris-phosphate. Arterioscler Thromb Vasc Biol 1998;18:861–9.
[29] Toth PP. Activation of intracellular signaling systems by high-density lipoproteins. J Clin Lipidol 2010;4:376–81.
[30] Ostad MA, Eggeling S, Tschentscher P, et al. Flow-mediated dilation in patients with coronary artery disease is enhanced by high dose atorvastatin compared to combined low dose atorvastatin and ezetimibe: results of the CEZAR study. Atherosclerosis 2009;205:227–32.
[31] Goldberg RB, Jacobson TA. Effects of niacin on glucose control in patients with dyslipidemia. Mayo Clin Proc 2008;83:470–8.