Effects of High-Dose Modified-Release Nicotinic Acid on Atherosclerosis and Vascular Function

A Randomized, Placebo-Controlled, Magnetic Resonance Imaging Study

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Objectives

Our aim was to determine the effects of high-dose (2 g) nicotinic acid (NA) on progression of atherosclerosis and measures of vascular function.

Background

NA raises high-density lipoprotein cholesterol (HDL-C) and reduces low-density lipoprotein cholesterol and is widely used as an adjunct to statin therapy in patients with coronary artery disease. Although changes in plasma lipoproteins suggest potential benefit, there is limited evidence of the effects of NA on disease progression when added to contemporary statin treatment.

Methods

We performed a double-blind, randomized, placebo-controlled study of 2 g daily modified-release NA added to statin therapy in 71 patients with low HDL-C (<40 mg/dl) and either: 1) type 2 diabetes with coronary heart disease; or 2) carotid/peripheral atherosclerosis. The primary end point was the change in carotid artery wall area, quantified by magnetic resonance imaging, after 1 year.

Results

NA increased HDL-C by 23% and decreased low-density lipoprotein cholesterol by 19%. At 12 months, NA significantly reduced carotid wall area compared with placebo (adjusted treatment difference: \(-1.64 \text{ mm}^2\) [95% confidence interval: \(-3.12 \text{ to } -0.16\); \(p = 0.03\)]. Mean change in carotid wall area was \(-1.1 \pm 2.6 \text{ mm}^2\) for NA versus \(+1.2 \pm 3.0 \text{ mm}^2\) for placebo. In both the treatment and placebo groups, larger plaques were more prone to changes in size (\(r = 0.4, p = 0.04\) for placebo, and \(r = -0.5, p = 0.02\) for NA).

Conclusions

In statin-treated patients with low HDL-C, high-dose modified-release NA, compared with placebo, significantly reduces carotid atherosclerosis within 12 months. (Oxford Niaspan Study: Effects of Niaspan on Atherosclerosis and Endothelial Function; NCT00232531) (J Am Coll Cardiol 2009;54:1787–94) © 2009 by the American College of Cardiology Foundation

Atherosclerosis is a systemic condition in which coronary, carotid, and peripheral arterial disease frequently coexist (1). In patients with atherosclerotic disease, low-density lipoprotein cholesterol (LDL-C) reduction with 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (“statins”) has consistently shown reduction in major cardiovascular events and mortality (2–4). However, treatment of LDL-C with statins prevents only a minority of cardiovascular events. Epidemiological studies indicate a strong inverse relationship between coronary heart disease risk and high-density lipoprotein cholesterol (HDL-C) at all levels of LDL-C (5–7). This relationship persists in patients who have been treated with statins, providing a rationale for additionally targeting low
HDL-C (3). Nicotinic acid (NA) raises HDL-C by approximately 20% to 25% and is the most effective clinically available drug for HDL-C elevation (8,9).

Magnetic resonance imaging (MRI) is a highly reproducible technique that allows the accurate quantification and characterization of plaque, and for changes in response to treatment to be identified in relatively small numbers of patients (10–14). In addition, MRI can assess central and peripheral arterial function in a single integrated examination (13,15).

This study was designed to investigate the effects of modified-release NA 2 g daily versus placebo on the progression of atherosclerosis, and vascular function, determined by MRI, in patients with pre-existing atherosclerosis and low HDL-C (<40 mg/dl) in whom LDL-C was treated to contemporary targets with statins (16).

Methods

Study background and population. This was an investigator-initiated, single-center, randomized, double-blind, placebo-controlled study examining the effect of modified release NA, 2 g daily, (Niaspan, Merck KGaA, Darmstadt, Germany). The study protocol was approved by the local research ethics committee. Study reporting follows principles recommended by the revised CONSORT statement (17). All patients provided written informed consent. Inclusion criteria were: 1) HDL-C <40 mg/dl in the previous 12 months together with either: 2a) carotid atherosclerosis (30% to 70% stenosis identified using carotid ultrasound); 2b) peripheral arterial disease (ankle-brachial pressure index <0.9); or 2c) type 2 diabetes with coronary artery disease (>50% stenosis of major epicardial vessel at angiography). There was no specific LDL-C inclusion criterion, but all patients were already taking statins, the dosage of which was determined by their own physician. Exclusion criteria were standard contraindications to MRI or to NA (e.g., elevated liver enzymes or known intolerance); severe carotid stenosis (>70%); existing treatment with fibrates, nicorandil, or oral nitrates; recent acute coronary syndrome; uncontrolled diabetes; fasting triglyceride level >500 mg/dl; active peptic ulcer disease; and cardiac failure requiring diuretic treatment. A computer generated randomization sequence was performed by Merck KGaA to generate study numbers in a ratio of 1:1, NA to placebo. Study medication was supplied by Merck KGaA in the form of NA tablets and identical placebo tablets. Patients were randomized to NA or placebo for 1 year. In keeping with clinical dosing regimens, NA (or placebo) was increased on a weekly basis from 375 mg to 500 mg, and then to 750 mg daily. Patients subsequently received 1,000 mg for 4 weeks, 1,500 mg for a further 4 weeks, and then 2,000 mg daily for the remainder of the study. Participants were advised to take study medication at night, together with aspirin, if taking this already, to reduce potential for flushing. MRI scans were performed at baseline, 6 months, and 12 months, and fasting blood samples were obtained before each scan. Further visits were scheduled after 7 and 15 weeks for safety review. Medication compliance was determined by pill counts. The primary end point was absolute change in carotid artery wall area at 12 months. Further pre-specified MRI end points were: change in aortic wall area, aortic distensibility, and brachial artery reactivity (flow-mediated dilation after forearm cuff occlusion and response to sublingual glyceryl trinitrate).

MRI. The MRI protocols (including sequence parameters) used in this study have been described in detail previously (13,15). To summarize, scans were performed on a 1.5-T MRI system (Sonata, Siemens, Erlangen, Germany) using a combination of surface and spine coils. Blood pressure was monitored during the MRI study using a cuff on the left arm. Electrocardiogram-gated turbo spin echo images with blood and fat suppression were acquired to yield between 9 and 11 axial images of the aorta (5-mm slice thickness and 5-mm interslice gap) and carotid arteries (3-mm slice thickness and no interslice gap). Images of the aorta were obtained from the level of the right pulmonary artery downwards. For the carotid arteries, the caudal most point of the bifurcation was used to define the region covering the distal 2 cm of the common carotid artery and the carotid bulb. Distensibility was assessed in the ascending and descending aorta at the level of the right pulmonary artery and at a level 11 cm below this in the descending aorta—calculated by the maximum relative change in cross-sectional area divided by the pulse pressure. Brachial artery endothelial function (flow-mediated dilation) was assessed by the maximum percent change in cross-sectional area after 5 min forearm ischemia. Endothelium independent response to 400 μm sublingual glyceryl trinitrate was also determined.

Image analysis. Semiautomated edge detection algorithms based in Matlab (Mathworks Inc., Natick, Massachusetts) were used to contour vessel boundaries to determine wall areas, as previously described (18). All images were analyzed by a single experienced observer (J.L.) blinded to patient identity, scan time point, and treatment allocation. Intraobserver variation was determined by repeat analysis of 6 randomly selected patients yielding coefficients of variation of 3% for carotid wall area and 2% for aortic wall area. For quality control, a second blinded observer (T.B.) repeated analyses in 10 randomly selected patients. Interobserver (J.L. and T.B.) coefficient of variation was 5% for the carotid and 2% for the aorta. Carotid wall area was expressed as the mean of all images including and below the carotid bulb. Aortic wall area was expressed as the mean of all images from the level of the right pulmonary artery.

Serum assays. Fasting blood samples were obtained at baseline, 6 months, and 12 months. For safety monitoring,
liver enzymes (aspartate aminotransferase) and creatine kinase were measured at each time point and also during up-titration of medication at 7 and 15 weeks. If significantly elevated, they were repeated after 2 weeks. Further plasma and serum samples were stored at \(-80^\circ\text{C}\) pending batch analyses. Total cholesterol, HDL-C, and triglycerides were measured, and LDL-C was calculated using the Friedwald equation. Apolipoprotein A1, apolipoprotein B, and lipoprotein(a) were assayed using immunoturbidimetric methods (ABX Diagnostics, Horiba ABX, Montpellier, France). C-reactive protein (CRP) and adiponectin were determined by Luminex multiplex bead assay using Milliplex MAP kits on a Bio-Plex system (Bio-Rad, Hercules, California).

**Statistical analysis.** Sample size was estimated from our MRI-based measurements (subsequently reported [13]) of plaque change in statin-treated patients. A minimum of 26 patients per group was required to detect a mean difference (SD) in the change in vessel wall area of 7.9 (10.3) mm\(^2\) (power = 0.8, alpha = 0.05). Allowing for a 20% patient drop-out rate (e.g., due to side-effects of study medication or claustrophobia in magnetic resonance scanner), we planned to recruit 70 patients to retain a total sample size of 56. We carried out an intention-to-treat analysis. Patients with at least 1 follow-up measure were included in the analysis. Our primary analysis was a mixed-effect model of the primary outcome, with adjustment of side (within subject), time (within side), corresponding baseline measures, and baseline prognostic covariates such as peripheral vascular disease, diabetes, HDL-C, total cholesterol, glucose, and blood pressure.
A similar approach was used for the other secondary outcomes. Values are reported as mean ± SD or median (interquartile range) if they are skewed data. Data were log-transformed to meet the normal distribution assumption where stated. Pearson’s method was used to assess correlation. Statistical significance was assigned at a value of p < 0.05. Only the statistician was aware of the treatment allocation when performing the final analysis, and it was unblinded to the investigators after the analysis. All statistical methods used in the analysis and choice of covariates for adjustments were determined before the unblinding of the data to the statistician.

Results

A total of 71 patients were randomized, mean age 65 years. Baseline characteristics were similar between groups (Table 1). Figure 1 illustrates the flow of participants through the study. Seven patients randomized to NA withdrew from the study citing side effects that were possibly attributable to NA: gastrointestinal (n = 3), skin flushing or itching (n = 3), and hyperglycemia (n = 1). Medication adherence assessed by pill count in those who completed the study was similar between NA (93%) and placebo (92%) groups. Of the patients who completed the study, 2 patients in each group had carotid images of insufficient quality for wall area analysis. All patients had adequate image quality for assessment of aortic and brachial parameters.

Table 2 summarizes the data from blood samples. No statin dose alteration occurred during the study. In the NA-treated group, mean HDL-C increased by 23% and LDL-C was reduced by 19% at 12 months. Triglycerides, apolipoprotein B, and lipoprotein(a) were significantly decreased by NA compared with placebo. CRP was decreased by NA compared with placebo (p = 0.03 at 6 months, p = 0.1 at 12 months). Adiponectin was significantly increased at both 6 and 12 months (p < 0.01). From the safety perspective, minor transient elevations were noted in creatine kinase and liver enzymes, but no significant, sustained elevations (>3× the upper limit of normal for 2 weeks) were observed in any subjects. Fasting glucose did not change significantly, but glycated hemoglobin showed a
small increase in the NA group versus placebo ($p = 0.02$ at 6 months, $p = 0.07$ at 12 months). Blood pressure and body mass index did not change significantly in either group.

For the primary end point, the NA group had significantly greater change in carotid wall area at 12 months, compared with placebo (adjusted treatment difference: $-1.64 \text{ mm}^2$ [95% confidence interval (CI): $-3.12$ to $-0.16$]; $p = 0.03$). Within group, the mean change in carotid wall area was $-1.1 \pm 2.6 \text{ mm}^2$ for NA and $+1.2 \pm 3.0 \text{ mm}^2$ for placebo (Fig. 2). Similarly, at 12 months change in carotid plaque index (wall area normalized to total vessel area) was also reduced by NA treatment (estimated treatment difference $-0.016$ [95% CI: $-0.03$ to $-0.0022$]; $p = 0.02$). At the earlier time point of 6 months, change in carotid plaque index was lower in the NA-treated group (treatment difference $-0.016$ [95% CI: $-0.03$ to $0.0019$]; $p = 0.03$), although change in absolute carotid wall area did not reach statistical significance at that point (treatment difference $-0.98 \text{ mm}^2$ [95% CI: $-2.45$ to $0.49$]; $p = 0.2$). Representative images of carotid plaque at 0 and 12 months, in each treatment group, are shown in Figure 3. We examined the relationship between baseline carotid wall area and change in wall area at 12 months. In both the treatment and placebo groups, larger plaques were more prone to changes in size ($r = 0.4$, $p = 0.04$ for placebo, and $r = -0.5$, $p = 0.02$ for NA). Since NA treatment raised HDL-C and lowered LDL-C, we also show the relationships between these lipid measures and change in carotid wall area (Fig. 4).

There was significant reduction in aortic wall area at 6 months in the NA-treated group compared with placebo (estimated treatment difference $-6.40 \text{ mm}^2$ [95% CI: $-12.27$ to $-0.54$]; $p = 0.03$). At 12 months, the estimated treatment difference was $-5.08 \text{ mm}^2$ (95% CI: $-12.83$ to $2.67$; $p = 0.2$). Neither aortic distensibility nor flow-mediated dilation of the brachial artery was significantly affected by NA treatment (Table 3).

**Discussion**

The addition of high-dose NA (2 g daily) to statin treatment reduced mean carotid artery wall area, within 12 months, in patients with low HDL-C (<40 g/dl) and atherosclerosis. This is the first demonstration of an incremental effect of NA, added to statin treatment, when compared with placebo.

In the 1970s, the Coronary Drug Project demonstrated a reduction in cardiovascular events with NA treatment at
initial follow-up and in mortality after 15 years (19). However, statins have since become the pre-eminent class of LDL-C-lowering drugs in secondary prevention, and the effects of NA in this context are unknown. The HATS (HDL-Atherosclerosis Treatment Study) trial demonstrated a reduction in events and coronary atheroma for the combination of NA and simvastatin, but this study did not have a statin monotherapy group for comparison, and the treatment group. The additional benefit apparent in the current study may have both biological and technical explanations.

First, in the current study, NA 2 g daily both raised HDL-C by 23% and also reduced LDL-C by 19%. This is in line with previous reports of use of NA at the 2-g dose (23,24). Our data cannot establish with certainty the relative contributions of each of these potentially beneficial effects on plasma lipoprotein profile. Second, assessment with MRI may bring enhanced sensitivity over other modalities for the detection of relatively small changes in atheroma burden. A particular advantage of MRI is the ability to interrogate multiple arteries noninvasively and to obtain volumetric data. Measurements are less sensitive to inter-study variability along the length and circumference of the artery and to spatially selective measurements that fail to identify the full extent of disease (25,26). As a result, changes in arterial wall can be detected in a relatively small numbers of patients (11,27). Aortic wall area was also significantly reduced at 6 months. The absence of a significant difference at 12 months, despite a persistent numeric reduction, may reflect insufficient statistical power.

A likely mechanism for the benefit of NA observed is HDL-C elevation and enhanced reverse cholesterol transport (28). Further benefits might arise through anti-inflammatory effects as reductions in CRP were observed at 6 months, or through elevation of the ‘atheroprotective’ adipokine adiponectin (29).

As well as measuring plaque burden, we used the multimodal capabilities of MRI to examine pre-specified secondary end points in: 1) flow-mediated vasodilation of the forearm, a marker of endothelial function; and 2) aortic distensibility. We observed a trend towards improvement in brachial endothelial function with NA treatment in this study (p = 0.07 and p = 0.1 after 6 and 12 months, respectively). Some studies using ultrasound-based methods have reported improvement in endothelial function after NA treatment either as monotherapy or in combination with other lipid medication, although this finding has not been universally confirmed (30–34). Assessment of brachial artery reactivity by MRI has been evaluated against and modal capabilities of MRI to examine pre-specified secondary endpoints. Some studies using ultrasound-based methods have reported improvement in endothelial function after NA treatment either as monotherapy or in combination with other lipid medication, although this finding has not been universally confirmed (30–34). Assessment of brachial artery reactivity by MRI has been evaluated against and demonstrated to be at least equivalent to established ultrasound methods (35,36).

Aortic stiffness is associated with the presence of atherosclerosis and an independent predictor of cardiovascular events (37). We and others have demonstrated beneficial effects of statins on aortic stiffness in patients with hypertension (38) and coronary artery disease (13). In this study, despite effects of NA therapy on both HDL-C and LDL-C, there was no effect of NA on arterial stiffness. It is possible that vessels of patients in the current study, who were pre-selected for peripheral arterial disease, were less susceptible to improvement or that the full extent of any improvement had been achieved by the pre-existing statin therapy.

### Table 3 MRI Data

<table>
<thead>
<tr>
<th>MRI Data</th>
<th>Baseline</th>
<th>6 Months</th>
<th>12 Months</th>
</tr>
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<tbody>
<tr>
<td><strong>Carotid wall area (mm²)</strong></td>
<td></td>
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<tr>
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<td>35.3 ± 9.5</td>
<td>34.5 ± 8.6</td>
<td>34.2 ± 8.5</td>
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<td>29.9 ± 4.8</td>
<td>30.6 ± 5.9</td>
<td>31.0 ± 6.6</td>
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<td>p value*</td>
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</tr>
<tr>
<td><strong>Aortic wall area (mm²)</strong></td>
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<tr>
<td>NA</td>
<td>194.2 ± 44.4</td>
<td>195.3 ± 44.2</td>
<td>197.3 ± 43.6</td>
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<td>173.8 ± 30.8</td>
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<tr>
<td>p value*</td>
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<td><strong>Ascending aorta distensibility (× 10⁻² mm Hg⁻¹)</strong></td>
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<tr>
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<td>1.8 (1.2–2.4)</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.7 (0.9–2.8)</td>
<td>1.9 (0.9–3.3)</td>
<td>1.7 (1.1–2.3)</td>
</tr>
<tr>
<td>p value*†</td>
<td></td>
<td></td>
<td>0.5</td>
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<td><strong>Proximal descending aorta distensibility (× 10⁻² mm Hg⁻¹)</strong></td>
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<td>2.6 (1.8–3.8)</td>
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</tr>
<tr>
<td>p value*†</td>
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<tr>
<td><strong>Distal descending aorta distensibility (× 10⁻² mm Hg⁻¹)</strong></td>
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<td></td>
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<tr>
<td>NA</td>
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<tr>
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<tr>
<td>p value*†</td>
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<td><strong>Brachial FMD response (%)</strong></td>
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<tr>
<td><strong>Brachial GTN response (%)</strong></td>
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<td></td>
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Summary statistics reported as mean ± SD or median (interquartile range). *p values derived from mixed-effect model on outcomes defined as change from 6 (or 12 months) from baseline, adjusting for baseline prognostic covariates; †analysis was carried out on log-transformed data. FMD = flow-mediated dilation; GTN = glyceryl trinitrate; other abbreviations as in Table 1.
As anticipated, some patients withdrew from the study due to drug side effects. However, at 7 of 35 (20%), the rate of drop out in the NA group was similar to previous studies of modified release NA at 2 g per day (8,39,40) and had been allowed for in the sample size calculation. Although, in common with all studies of this drug, flushing and other side effects of NA could potentially have affected patient and investigator ‘blinding,’ all analysis was undertaken blind to patient identity and time point.

Our study provides further evidence for a beneficial effect from addition of NA to statin therapy. Although in epidemiological studies HDL-C is inversely related to cardiovascular risk, a beneficial effect of therapeutic HDL-C elevation cannot be assumed. For example, treatment with the cholesteryl ester transfer protein inhibitor, torcetrapib, raised HDL-C by 72% but resulted in excess total mortality (41). Treatment with torcetrapib was not associated with a reduction in carotid IMT assessed by ultrasound (42,43) or coronary atheroma quantified by intravascular ultrasound (44). Had the results of these studies been available before the clinical outcome studies, the dissociation between plasma HDL-C and clinical events might have been anticipated. In the case of NA, 2 large outcome trials are underway. The AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes) study has projected completion in 2011, while the HPS2-THRIVE (Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events) study, will assess a new combination therapy containing extended-release niacin and a specific blocker of prostaglandin D2 to prevent flushing (projected completion 2013). Our findings that HDL-C elevation with NA reduces carotid plaque further intensify interest in the outcome of these studies.

Study limitations. In addition to measuring plaque size, MRI can also determine plaque composition (e.g., lipid-rich necrotic core). Underhill et al. (14) have recently demonstrated regression of this plaque component over 24 months in patients with pre-existing carotid plaques who were treated with rosuvastatin. Data from experimental animal models suggest that high-density lipoprotein elevation can favorably modify atherosclerotic plaque composition, reducing lipid content (45–47). Although magnetic resonance analysis of plaque lipid-rich cores was intended as a secondary end point, the prevalence of this feature in this study was too low to allow meaningful analysis. This study enrolled mainly male and Caucasian patients, so applicability to other populations may be limited. It was not powered to detect changes in clinical event rates. Mild disturbance in glycemic control with NA observed here is well recognized with NA (9); the clinical significance will be determined by large ongoing outcome studies.

Secondary prevention in atherosclerosis with statin drugs has proved a successful approach in multiple patient groups but prevents only a minority of events. Progressively higher doses of statins are associated with diminishing clinical benefits and increased side effects (48). Epidemiological and experimental observations recommend HDL-C elevation as a compelling additional target. Our study shows, for the first time, that in patients with low HDL-C and existing atherosclerotic disease, addition of NA 2 g daily to contemporary therapy reduces atherosclerosis compared with placebo. The findings support current recommendations for the use of NA and strongly underpin the rationale for the large clinical outcome studies that are ongoing.

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REFERENCES


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