Effects of Niacin Combination Therapy With Statin or Bile Acid Resin on Lipoproteins and Cardiovascular Disease

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Two large studies in populations selected for cardiovascular disease (CVD) demonstrated that raising high-density lipoprotein (HDL) cholesterol with niacin added to statin therapy did not decrease CVD. We examine the association of lipoprotein subfractions with niacin and changes in coronary stenosis and CVD event risk. One hundred and seven patients from 2 previous studies using niacin in combination with either statin or bile acid−binding resin were selected to evaluate changes in lipoproteins separated by density-gradient ultracentrifugation to progression of coronary artery disease as assessed by quantitative coronary angiography. Improvement in coronary stenosis was significantly associated with the decrease of cholesterol in the dense low-density lipoprotein (LDL) particles and across most of the intermediate density lipoprotein (IDL) and very low density lipoprotein particle density range, but, not with any of the HDL fraction or of the more buoyant LDL fractions. Event-free survival was significantly associated with the decrease of cholesterol in the dense LDL and IDL; there was no association with changes in cholesterol in the HDL and buoyant LDL fractions. Niacin combination therapy raises HDL cholesterol and decreases dense LDL and IDL cholesterol levels. Changes in LDL and IDL are related to improvement in CVD. Lipoprotein subfraction analysis should be performed in larger studies utilizing niacin in combination with statins. **(Am J Cardiol 2014;113:1494−1498)**

Although statins provide 25% to 40% reduction in cardiovascular disease (CVD) events, there is considerable residual risk of CVD events with this therapy.[1] Failure of recent trials[2−6] to provide evidence of additional clinical benefit by raising high-density lipoprotein cholesterol (HDL-C) levels, in addition to the conventional, statin-based strategy, supports a recent metaregression analysis suggesting that simply increasing the amount of circulating HDL-C with drugs does not reduce the risk of coronary heart disease events, coronary heart disease deaths, or total deaths.[7,8] No agent, however, solely increases HDL-C. For instance, niacin increases HDL-C up to 30% but concomitantly reduces low-density lipoprotein cholesterol (LDL-C), triglycerides, and lipoprotein(a), and small, dense LDL.[9] In several previous studies,[10−12] niacin therapy led to significant risk reductions in clinical events. In the present study, we analyzed pooled data from previous angiographic trials by us,[11,12] where niacin was used in combination with a second lipid-lowering agent, either colestipol or simvastatin, with the aim of evaluating lipoprotein subfractions as they might account for changes in coronary angiography and clinical benefits.

Methods

One hundred and seven subjects, of the initial 109 patients on niacin-based combination therapy, with clinically established or anatomically demonstrated coronary artery disease who participated in the Familial Atherosclerosis Treatment Study (FATS) in 146 men,[11] which was completed in 1989, and in the HDL-Atherosclerosis Treatment Study (HATS) in 160 men and women,[12] completed in 1999, were included in this analysis. No lipoprotein subclass analysis was available in 2 of the 109 original patients. Patient characteristics in FATS and HATS have been previously reported.[11,12] In this retrospective analysis, we included only those patients randomized to receive niacin (up to 4 g per day as tolerated) as part of their lipid-lowering strategy, which also included colestipol (up to 10 g tid; n = 36) in FATS or simvastatin (up to 20 mg per day; n = 73) in HATS. The prespecified primary clinical end point was the time to the first of the following events: death from coronary artery disease, enzymatically confirmed nonfatal myocardial infarction, stroke, or revascularization for worsening ischemia. These events were collected and documented as previously described.[11,12]

Coronary angiography was performed using a defined sequence of viewing angles.[11,12] A detailed coronary map was drawn that included all lesions causing a digital caliper-measured stenosis of ≥15% of luminal diameter. The lesion causing the most severe stenosis in each of 9 standard proximal segments was measured using computer-assisted methods in each patient at baseline and follow-up coronary angiography at 2.5 to 3 years. Mean change in severity (percent change) of 9 proximal stenoses between the 2

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See page 1497 for disclosure information.

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Table 1
Lipid parameters: baseline values and percent changes from baseline after therapy

	FATS: Niacin-Colestipol (n = 35)		HATS: Niacin-Simvastatin (n = 32)		HATS: Niacin-Simvastatin-Vit. (n = 40)	
	Baseline	% Change	Baseline	% Change	Baseline	% Change
CHOL (mg/dl)	270 ± 53	−23*	201 ± 48	−31*	199 ± 33	−27*
Triglycerides	194 ± 89	−30*	202 ± 85	−38*	236 ± 97	−31*
VLDL-C	42 ± 18	−45*	38 ± 18	−40*	43 ± 16	−28*
LDL-C	190 ± 54	−33*	132 ± 54	−43*	124 ± 46	−37*
HDL-C	39 ± 7	+41*	31 ± 15	+29*	30 ± 10	+20*

CHOL = cholesterol.
* p <0.001 versus baseline.

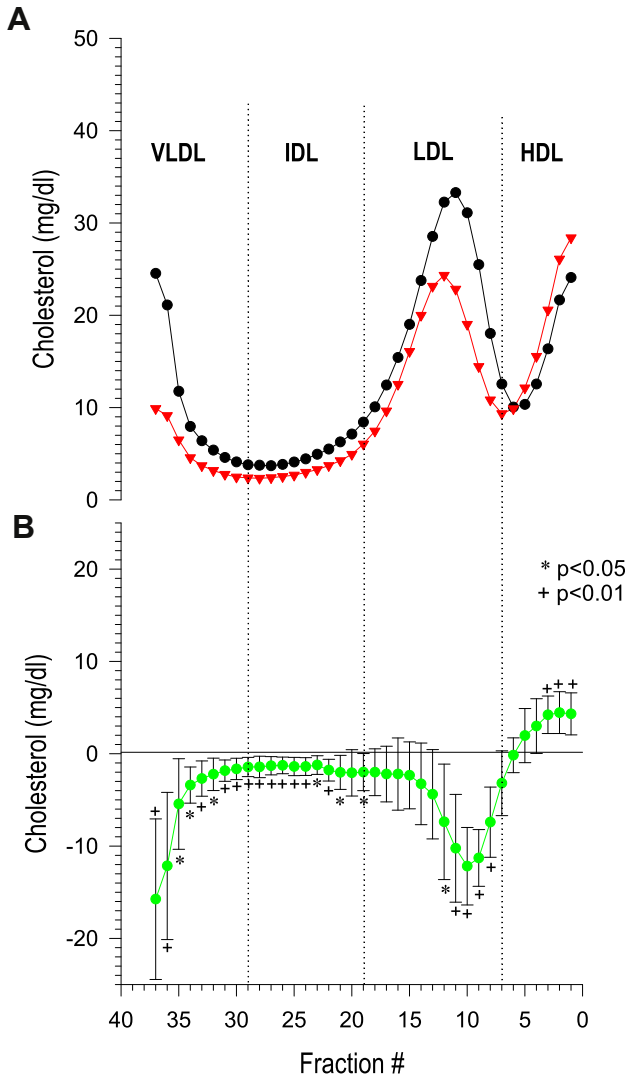

Figure 1. Cholesterol distribution profile in niacin-treated patients from FATS and HATS at baseline and after treatment (n = 107). Cholesterol (mg/dl) is expressed as absolute value in each fraction. *Panel A:* cholesterol content of each lipoprotein subfraction at baseline *(black circles)* and on niacin combination therapy *(red triangles). Panel B:* mean difference profile of cholesterol content of each lipoprotein subfraction on therapy versus baseline—values were obtained by subtracting cholesterol of each single fraction at baseline from the corresponding fraction on therapy. DGUC profiles were compared by calculating the mean and 95% confidence intervals of the difference for each fraction.[18] *p <0.05; $^{+}$p <0.01.

angiograms was the prespecified primary end point of these studies.

Nonequilibrium density-gradient ultracentrifugation (DGUC) for apo B−containing lipoproteins: this technique, designed to optimize the resolution of apo B−containing lipoproteins, is a modification of a previous method.[9] Cholesterol was measured as the absolute value in 37 fractions. Each lipoprotein subclass elution range was defined as previously described.[13] DGUC data on lipoprotein physicochemical properties parallel those made using the nuclear magnetic resonance spectroscopy for very low density lipoprotein (VLDL) and LDL; however, DGUC does not discriminate as well as nuclear magnetic resonance for HDL subfractions.[14]

Blood samples were collected and centrifuged (for 10 minutes at 1,600 rpm) at 4°C shortly after collection; plasma was immediately aliquoted, snap frozen, and stored at −80°C for later analyses. Plasma triglycerides (Wako Chemical GmbH, Richmond, Virginia) and cholesterol (CHOD-Pap by Roche Diagnostics, Mannheim, Germany) were evaluated by standardized enzymatic methods.

Data were analyzed using SPSS 11.0 for Windows (Chicago, Illinois). Results are reported as mean ± SD, if not otherwise stated. Group differences in continuous variables were determined using Student *t* test. Logistic regression or multiple linear regression analysis was carried out depending on the presence of a dichotomous or continuous linear dependent variable. Group differences or correlations with p <0.05 were deemed as statistically significant.

Results

Clinical and baseline biochemical parameters in niacin-treated patients from FATS and HATS have been previously described.[11,12] The baseline lipid phenotypes are, at least partly, dependent on the study inclusion criteria. Specifically, total and LDL-C levels were higher in FATS, and similarly HDL-C was significantly lower in HATS (Table 1). Changes in each lipoprotein level on therapy were significant (p <0.001) compared with baseline values.

Patients from the 2 angiographic studies who were on niacin-based combination therapy (n = 107) were pooled for the DGUC analysis of cholesterol distribution across the lipoprotein density range. Cholesterol distribution profiles at baseline and on therapy (Figure 1, panel A) and the mean difference profile (on vs off therapy; Figure 1, panel B) showed a significant increase on treatment in most of the HDL (fractions 1 to 3, p <0.01 for all), whereas LDL