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PREVENTION OF ATHEROSCLEROSIS WITH LDL-C LOWERING – LIPOPROTEIN CHANGES AND INTERACTIONS: THE SANDS STUDY

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Abstract

Background—Lowering low-density lipoprotein cholesterol (LDL-C) with statins reduces atherosclerosis. LDL and high-density lipoprotein (HDL) are commonly measured by their cholesterol content, but non-HDL cholesterol, LDL particle number (LDL-P), or total apolipoprotein B (apoB) may better predict cardiovascular risk. Few studies have examined relations among lipoprotein levels and composition before and after interventions to lower LDL-C and non-HDL-C.

Objective—To measure changes in carotid artery intimal media thickness (CIMT) and lipid concentration and composition during 36 months of statin therapy.

Methods—Analyses were conducted on 418 diabetic individuals, with complete data and no prior cardiovascular events, who were randomized to aggressive (AG) versus standard (STD) treatment

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for LDL-C, non-HDL-C, and systolic blood pressure (SBP) as part of the Stop Atherosclerosis in Native Diabetics Study (SANDS).

Results—The AG group achieved average LDL-C and non-HDL-C of 71mg/dL and 100mg/dL and a decrease in CIMT. No significant interactions were observed between treatment effect and initial levels of LDL-C, non-HDL-C, HDL-C, triglycerides, apoB, or LDL-P. Decreases in LDL-C ($p<.005$) and non-HDL-C ($p<.001$) were independently correlated with CIMT regression in the AG group. Changes in apoB and LDL-P showed borderline correlations with CIMT regression ($p=.07$ and $p=.09$).

Conclusions—In diabetic adults with no prior cardiovascular events, treatment to current targets for lipids and SBP reduces atherosclerosis progression and when more aggressive targets are met, atherosclerosis regresses. The aggressive targets for LDL-C and non-HDL-C appeared to be the main determinants of CIMT regression and were more predictive of this outcome than changes in LDL-P or apoB.

Keywords

atherosclerosis; cardiovascular disease; carotid arteries; cholesterol; lipoproteins

INTRODUCTION

Lipoproteins are known to be involved in the atherosclerotic process. Studies suggest that atherogenic lipoproteins are both necessary and sufficient for the development of atherosclerotic plaque (1). Almost all observational and interventional studies (2,3,4,5) implicate low-density lipoprotein (LDL) as the primary atherogenic lipoprotein, and high-density lipoprotein (HDL) appears to be the predominant anti-atherosclerotic lipoprotein (6). The most common method of measuring LDL and HDL is by determining their cholesterol content, which is designated as LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C). LDL-C has been shown in most clinical studies to be an independent predictor of cardiovascular events, while HDL-C is usually found to be an independent negative predictor. Low HDL often is accompanied by high triglycerides and altered lipoprotein particle distribution, a combination referred to as atherogenic dyslipidemia (1). However, in multivariate analyses, triglyceride concentration often is not predictive for cardiovascular disease (CVD) (1). Current debate has centered on more appropriate ways to measure LDL to improve the predictive value of this lipoprotein. In some studies, LDL particle number (LDL-P) or smaller LDL size (small, dense LDL) appears to be more predictive than concentrations of LDL (7). Another approach has been to derive a comprehensive measure of atherogenic particles, such as non-HDL-C or total apolipoprotein B (apoB) (1,8,9). These lipid measures have been shown in some studies to be superior to LDL-C level or other individual lipoprotein measures in predicting CVD (7, 8).

Lowering LDL-C with statin therapy reduces CVD and other atherosclerotic-related events. With such therapy, multiple changes occur in LDL composition and in other lipoproteins. Initial lipoprotein distribution also may influence response to lipid lowering therapy. Few interventional studies have examined the influence of initial lipoprotein levels and composition on the outcomes of lowering LDL-C. Additional information is needed on what changes statin therapy produces in lipoprotein composition and whether these changes influence the atherogenic process and resulting clinical outcomes.

The Stop Atherosclerosis in Native Diabetics Study (SANDS) was a randomized primary prevention trial in participants with diabetes to evaluate whether more aggressive goals for LDL-C, non-HDL-C, and blood pressure would reduce progression of atherosclerosis (10). In this 3-year interventional trial, one group was treated aggressively to targets of LDL-C ≤ 70

mg/dL, non-HDL-C ≤ 100 mg/dL, and systolic blood pressure (SBP) ≤ 115 mmHg, with the resulting changes in carotid atherosclerosis compared with a standard group treated to LDL-C ≤ 100 mg/dL, non-HDL-C ≤ 130 mg/dL, and SBP ≤ 130 mmHg. Compared with the standard group, the group treated to aggressive targets had a decrease in atherosclerosis as measured by a regression in carotid intimal medial thickness (CIMT) and a decrease in arterial cross-sectional area. Because the SANDS participants had type 2 diabetes with significant insulin resistance, many had elevations in triglyceride levels and decreased HDL-C levels. A current topic of debate is to what extent triglyceride and/or HDL concentration influences CVD outcomes when LDL-C is lowered to very low levels. In addition, few studies have examined changes in lipoprotein particle distribution with statin therapy. In this article, the SANDS dataset is used to examine these issues.

METHODS

Details of the SANDS study design and methods have been published (10). All participants provided written informed consent and the study was approved by the SANDS institutional review board, the National Institutes of Health, and all participating American Indian communities.

Recruitment

Briefly, 499 men and women with type 2 diabetes older than age 40 years, with no history of a prior CVD event were enrolled between May 2003 and July 2004 at four clinical centers in Oklahoma, Arizona, and South Dakota. The participants were randomly assigned to one of two intervention groups: an aggressive group (n=252) or a standard group (n=247), using the urn method stratified by center and gender. All participants were American Indians as defined by Indian Health Service criteria. Eligibility criteria included documented Type 2 diabetes (per 1997 American Diabetes Association [ADA] criteria), a successfully measured CIMT, LDL-C ≥ 100 mg/dL, and SBP > 130 mmHg. If the screening LDL-C was < 100 mg/dL, clinic records were reviewed. If they had begun lipid lowering medication within the past year and the LDL-C was > 100 mg/dL prior to the initiation of this medication, they were admitted to the study provided the field physician felt the participant could be safely managed to meet target goals of either randomization group using the study lipid intervention algorithm. Major exclusion criteria included New York Heart Association class III or IV congestive heart failure, SBP > 180 mmHg, triglycerides ≥ 400 mg/dL, hepatic transaminase levels more than twice the upper limit of normal, diagnosis of primary hyperlipidemia or secondary hypercholesterolemia due to hypothyroidism or nephrotic syndrome. Other traditional exclusion criteria included medical conditions that predicted survival of less than 3 years and concerns about potential adherence that might affect completion of the study.

Lipid and Blood Pressure Interventions

Study personnel performed blood pressure and lipid management with equal frequency of contact for both groups. All other medical care, including diabetes management, was performed by the participants' Indian Health Service providers.

The algorithm for hypertension management was based on the recommendations of the Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (11); a full description of strategies and results are presented in Weir et al. (12). The algorithm for achieving lipid goals was based on the recommendations of the National Cholesterol Education Program Adult Treatment Panel III (1). If lifestyle modification was unsuccessful, statin therapy was initiated. If the LDL-C goal was not reached, adjunctive therapy with ezetimibe or colesvelam was added. The non-HDL-C goal was then addressed

using fenofibrate, omega-3 fatty acids, and/or niacin. Details of the intervention procedures and targets have been published (10).

Baseline and follow-up visits

All procedures followed standardized methods performed by trained, certified personnel and are described in detail in the initial SANDS publication (10). Based on the intention-to-treat criteria, participants were followed from the date of entry until death, loss to follow up, or request for no further contact regardless of their adherence to the medication intervention. All participants were scheduled for initial follow-up visits at 1 month, with subsequent visits every 3 months from the randomization date to 36 months. At all follow-up visits, seated blood pressure measurements were obtained and a lipid profile was measured using a Cholestec apparatus (Cholestec Corp., Hayward, CA) standardized against laboratory assay. Medications were adjusted to meet treatment goals, side effects were assessed, and information on health outcomes was obtained.

Fasting blood and urine samples were obtained at 18 and 36 months and forwarded to the core laboratory for repeat of all measures obtained at baseline. Lipoprotein particle number and distribution was measured by NMR spectroscopy using a rapid, automated commercially available assay (LipoScience Inc, Raleigh, NC). Details of this method have been published (13). Apo B concentration was measured using the Hitachi 717 autoanalyzer (14). Lipoprotein particle number and ApoB were determined in baseline and 36-month samples. In addition, at 6, 12, 24, and 30 months, a fasting blood sample was obtained for a complete lipoprotein profile.

Outcomes Ascertainment

At the baseline, 18-, and 36-month visits, carotid and cardiac ultrasound studies were performed using standardized protocols (15). These were performed by centrally trained ultrasonographers and interpreted by a single skilled physician reader who was blinded to all participant characteristics. For carotid ultrasound, B-mode imaging from multiple angles was performed to determine the presence and location of plaque (focal protrusion of the vessel $\geq 50\%$ greater than the surrounding wall), as well as arterial wall dimensions. Plaque score (0–8) was determined as the number of arterial segments (left and right common carotid, bulb, internal and external carotid arteries) containing plaque; a participant with plaque was anyone with a score of at least 1. End-diastolic B-mode images of the distal right and left common carotid artery (CCA) were acquired in real-time, and a 1-cm segment of each far wall was measured using an automated system employing an edge detection algorithm with manual override capacity. One hundred separate dimensional measurements were obtained from the 1-cm segment and averaged to obtain mean CIMT and lumen diameter. Carotid arterial cross-sectional area was calculated as $3.1416 ([\text{diameter}/2 + \text{CIMT}]^2 - [\text{diameter}/2]^2)$ using end-diastolic CIMT and lumen diameter measurements.

Data Analysis

Complete baseline and 36-month data were available for only 418 of the 499 participants for lipid levels, lipid particle number and size, and change in mean CIMT. Therefore, all analyses were conducted with these 418 cases. CVD risk factors, carotid and cardiac ultrasound measures, and changes in these measures during the study were compared between the standard and aggressive groups using two-sided t-tests. In addition, variables detailing lipid size and particle number were similarly compared between the two groups. Significant changes at the end of the study were noted ($p\text{-value} < .05$). Variables that violated the normality assumption of the t-test were log-transformed and then tested. Their geometric means with 95% confidence intervals are presented to provide a better description of the distributions. The available number of cases for the change in apoB measurement was 381. Additional analyses compared changes in CIMT between the treatment groups stratified by baseline lipoprotein characteristics: very

low-density lipoprotein cholesterol (VLDL-C); LDL-C; HDL-C; non-HDL-C; apoB; and VLDL, LDL, and HDL particle number (HDL-P). Tests were performed to determine interactions between baseline characteristics and treatment method.

Sensitivity analyses of carotid measures were performed to compare those in the aggressive group who maintained an LDL-C goal of ≤ 73 mg/dL during the last 12 months of follow up with those in the standard group. Changes in all lipid levels and particle size and number in these subgroups were compared with each other and with the standard group using analysis of variance (ANOVA). Bonferroni-adjusted p-values were reported for comparisons in which the F-test for ANOVA was significant ($p < .05$). Finally, ordered logit analyses were conducted to test the effects of changes in LDL-C, non-HDL-C, HDL-C, apoB, and VLDL-P and LDL-P on the probability of observing no change, a decrease, or an increase in mean CIMT by controlling for baseline characteristics (i.e., lipid levels, CIMT, age, body mass index [BMI], gender, and SBP). All analyses were performed using Intercooled Stata 9.2 (Stata Corporation Lp, College Station, TX) or SAS version 9.1 (Cary, NC).

RESULTS

Table 1 summarizes the key characteristics of the study participants at the beginning and end of the trial. Sixty-six percent were women. All participants had a history of LDL-C > 100 and SBP > 130 , with 38% taking lipid lowering and 75% taking anti-hypertensive medications prior to randomization. Randomization groups were well matched except for a slightly lower SBP in the aggressive group at baseline. Average age was 56 years, average BMI was 33, and average A1c was 8.0. Weight and A1c did not change during the 36 months of the trial; participants maintained an average SBP of 116 mmHg in the aggressive group and 129 mmHg in the standard group. Mean CIMT, the primary endpoint, progressed slightly in the standard group and regressed in the aggressive group; the difference in the CIMT change between the aggressive and standard groups at the end of the study was significant ($p < .0001$) (Table 1). Details of the trial intervention and endpoints have been reported (10).

Targets for mean LDL-C and non-HDL-C were met in both groups (Table 2). At the end of the study, the aggressive group LDL-C averaged 71 mg/dL and non-HDL-C averaged 100 mg/dL, compared with 104 mg/dL and 138 mg/dL, respectively, in the standard group (all $p < .0001$). At baseline, both the standard and aggressive groups had elevated triglyceride levels; at the end of the study, the decline was somewhat greater in the aggressive group ($p = .08$). HDL-C was low in both groups at baseline, averaging 46 mg/dL and did not change significantly during the study. ApoB averaged 93 mg/dL and 97 mg/dL in the aggressive and standard groups, respectively, at baseline. There was a large decrease in apoB (24 mg/dL) in the aggressive group and a small change in the standard group; the two differed significantly at study end ($p < .0001$). Major changes also occurred in lipoprotein particle concentrations and size. VLDL-P and concentration of medium and small particles were significantly lower in the aggressive group at the end of the study ($p < .001$, $.0002$, and $.0001$, respectively). LDL-P, and concentrations of large and small LDL, also decreased in both groups and were significantly lower in the aggressive group (all $p < .0001$); LDL size did not differ between groups at the end of the study. No significant changes were observed in HDL-P or particle distribution. Changes in CIMT were compared in the two groups, stratified by baseline lipoprotein levels and composition (Table 3).

There were no significant interactions between treatment and initial levels of LDL-C, non-HDL-C, HDL-C, triglycerides, or apoB in this study. This indicates that the treatment effect did not differ by baseline levels of any of the measured lipid parameters. Moreover, there were no significant interactions with lipoprotein particle number or distribution.

A sensitivity analysis was performed by comparing the change in CIMT in individuals in the aggressive group who achieved an LDL-C level of ≤ 73 mg/dL (n=132) with those in the standard group, and a bigger improvement was observed in CIMT in the group that achieved the goals for LDL-C and non-HDL-C (changes of -0.027 mm for both compared with -0.020 mm for the entire aggressive group).

An ordered logit analysis (Figure 1) was performed to determine the influence of the change in each lipid parameter and the change in CIMT at 36 months. The decreases in LDL-C and non-HDL-C were both independently correlated with CIMT regression in the aggressive group (Figure 1a). The change in apoB and LDL-P showed borderline significance related to CIMT regression (Figure 1b).

DISCUSSION

The SANDS trial was the first to establish regression of atherosclerosis, as indicated by the reduction of CIMT in diabetic men and women, with lipid and blood pressure lowering to targets below current standards. Secondary analyses suggested the improvement in carotid parameters was attributable mainly to the decreases in LDL-C and non-HDL-C. Further analyses of aggressive group participants showed that in addition to decreases in LDL-C to 71 mg/dL and non-HDL-C to ≤ 100 mg/dL, comparable decreases occurred in plasma apoB, LDL particle number, and in the number and size of VLDL particles. No change was observed in LDL size. Our analyses showed that the differences in CIMT between treatment groups were independent of baseline levels for any of the lipoprotein parameters.

LDL-C has been the target for most interventional trials of lipid lowering and was designated as the primary goal of therapy by all three ATP panels (1). The evidence for making LDL-C the primary target of therapy is based on the outcomes of trials which have confirmed a reduction in CVD risk that is directly proportional to reduction in LDL-C. The ATPIII indicated that non-HDL-C should be a secondary target of therapy, after LDL-C targets are achieved (1). This recommendation also was based on evidence from clinical trials (1,16,17); however, it has been largely ignored. SANDS is one of few trials to make non-HDL-C as well as LDL-C the target of interventional therapy. The results of SANDS confirm the importance of this strategy for diminishing the progression of atherosclerosis in individuals with type 2 diabetes. Because LDL-C is the predominant component of non-HDL-C, it is difficult to separate the contribution of each to the regression seen in the aggressive group in this study. However, the significant decrease in non-HDL-C in the standard group with only minimal change in LDL-C indicates that the decrease in progression observed in CIMT in the standard group is probably attributable to the change in non-HDL-C. In addition, logit models examining determinants of change in CIMT showed that both LDL-C and non-HDL-C were significant predictors.

Although LDL particle size did not change over the 36 months of this trial, LDL-P concentration for both large and small LDL particles decreased significantly in the aggressive group, with a small change occurring in the standard group. The decrease in LDL-P was of borderline significance as a determinant of the observed regression in CIMT. This is contrary to other studies (7,8), which indicated that LDL-P is a better predictor than LDL-C of baseline risk and of risk reduction with statin therapy. However, no interventional trials have treated individuals with type 2 diabetes to pre-determined LDL-P targets. Alternatively, the differences between LDL-C and LDL-P may be a reflection of differences in the precision of the measurements. Significant changes also were observed in VLDL-P in the aggressive group, which were reflected in VLDL medium and small subfractions.

ApoB decreased in the aggressive group by a percentage similar to the decrease in LDL-C and LDL-P. The decrease in apoB, however, was not significantly related to the primary outcome

of CIMT regression. As with the LDL-P findings, this finding is contrary to some previous studies (7,8), which showed apoB to be more predictive than LDL-C and non-HDL-C of CVD risk reduction with statin therapy. It has been proposed (8) that apoB is the most accurate measure of the atherogenicity of an individual's CVD risk, because there is one apoB for each LDL and VLDL particle in the circulation and, thus, the apoB level represents the total circulating atherogenic lipoprotein pool. Some studies have indicated that statins deplete the LDL particle of cholesterol to a greater extent than they decrease the number of LDL particles, thus resulting in relatively cholesterol-poor LDL particles that are present in increased numbers and which may be more atherogenic than the LDL-C level would indicate. However, in SANDS, the aggressive goals for LDL-C and non-HDL-C resulted in similar reductions in apoB and LDL-P and, thus, no increase in the accumulation of small, cholesterol-poor particles was observed. Non-HDL-C was proposed as the secondary target of lipid management because it approximates the sum of all of the apoB-containing atherogenic lipoproteins; therefore, it acts as a surrogate for the measurement of apoB. Non-HDL-C level is a more accurate measure of risk than LDL-C in a diabetic population with metabolic syndrome, as was seen in the present study, because it also reflects atherogenic VLDL-containing lipoproteins.

This study has a number of strengths. First, the compliance rates were unusually high for a 3-year aggressive interventional trial (10). Second, treating both intervention groups to separate targets for LDL-C, non-HDL-C, and SBP allowed for comparisons unrelated to the use of a specific pharmacologic regimen. The use of surrogate clinical endpoints allowed for examination of early atherosclerosis. Finally, this is one of only a few clinical trials in which non-HDL-C as well as LDL-C levels were managed, thus potentially decreasing the residual risk which remains when the only goal of therapy is LDL-C.

This study was limited by the homogeneity and small size of the cohort. The modest sample size and short duration of the intervention provided inadequate statistical power to observe the effects of aggressive lipid and blood pressure management on clinical CVD events, thus necessitating the use of surrogate endpoint outcomes.

CONCLUSION

The SANDS trial, a prevention study of atherosclerosis progression in participants with type 2 diabetes and no history of CVD events, has shown that treatment to current targets for lipids and SBP decreases progression of atherosclerosis and when more aggressive targets are met, atherosclerosis regresses. Treating the aggressive group to significantly lower targets for LDL-C and non-HDL-C than currently recommended appears to be the main determinant of the observed regression of CIMT and was more predictive of this outcome than LDL-P or apoB. Long-term studies in other populations with diabetes are needed to determine the ultimate relation among LDL-C, non-HDL-C, and clinical outcomes.

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Abbreviations

ANOVA	analysis of variance
ApoB	apolipoprotein B
BMI	body mass index
CVD	cardiovascular disease
CIMT	carotid intimal medial thickness
CCA	common carotid artery
HDL-C	high-density lipoprotein cholesterol
HDL-P	high-density lipoprotein particle number
LDL-C	low-density lipoprotein cholesterol
LDL-P	low-density lipoprotein particle number
SANDS	Stop Atherosclerosis in Native Diabetics Study
SBP	systolic blood pressure
VLDL-C	very low-density lipoprotein cholesterol

References

1. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143–421. [PubMed: 12485966]
2. Kannel WB, Wilson PW. Efficacy of lipid profiles in prediction of coronary disease. *Am Heart J* 1992;124:768–74. [PubMed: 1514505]
3. Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 1986;256:2823–8. [PubMed: 3773199]
4. Lu W, Resnick HE, Jablonski KA, Jones KL, Jain AK, Howard WJ, Robbins DC, Howard BV. Non-HDL cholesterol as a predictor of cardiovascular disease in type 2 diabetes: the Strong Heart Study. *Diabetes Care* 2003;26:16–23. [PubMed: 12502653]
5. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R. Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267–78. [PubMed: 16214597]
6. 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. [PubMed: 193398]
7. Otvos JD, Jeyarajah EJ, Cromwell WC. Measurement issues related to lipoprotein heterogeneity. *Am J Cardiol* 2002 Oct 17;90(8A):22i–29i.
8. Sniderman AD. Differential response of cholesterol and particle measures of atherogenic lipoproteins to LDL-lowering therapy: implications for clinical practice. *Journal of Clinical Lipidology* 2008;2:36–42.
9. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ. National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association: Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;110:227–39. [PubMed: 15249516]

10. Howard BV, Roman MJ, Devereux RB, Fleg JL, Galloway JM, Henderson JA, Howard WJ, Lee ET, Mete M, Poolaw B, Ratner RE, Russell M, Silverman A, Stylianou M, Umans JG, Wang W, Weir MR, Weissman NJ, Wilson C, Yeh F, Zhu J. Effect of lower targets for blood pressure and LDL cholesterol on atherosclerosis in diabetes: the SANDS randomized trial. *JAMA* 2008;299:1678–89. [PubMed: 18398080]
11. National Institutes of Health. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program: The sixth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Bethesda, MD: National Institutes of Health; 1997. NIH Publication 98–4080
12. Weir MR, Yeh F, Silverman A, Galloway J, Henderson JA, Howard BV. Safety and efficacy of achieving lower blood pressure goals in Native Americans with type 2 diabetes. (in press).
13. Jeyarajah EJ, Cromwell WC, Otvos JD. Lipoprotein particle analysis by nuclear magnetic resonance spectroscopy. *Clin Lab Med* 2006 Dec;26:847–70. [PubMed: 17110242]
14. Albers, JJ.; Marcovina, SM. Apolipoprotein Measurements. In: Kreisberg, RA.; Segrest, JP., editors. *Plasma Lipoproteins and Coronary Artery Disease*. Boston: Blackwell Scientific; 1992. p. 265-88.
15. Devereux, RB.; Roman, MJ. Evaluation of cardiac and vascular structure by echocardiography and other noninvasive techniques. In: Laragh, JH.; Brenner, BM., editors. *Hypertension: Pathophysiology, Diagnosis, Management*. 2. New York, NY: Raven Press; 1995. p. 1969-1985.
16. Kastelein JJ, van der Steeg WA, Holme I, Gaffney M, Cater NB, Barter P, Deedwania P, Olsson AG, Boekholdt SM, Demicco DA, Szarek M, LaRosa JC, Pedersen TR, Grundy SM. TNT Study Group. IDEAL Study Group: Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. *Circulation* 2008;117:3002–9. [PubMed: 18519851]
17. Robinson JG, Wang S, Smith BJ, Jacobson TA. Meta-analysis of the relationship between non-high-density lipoprotein cholesterol reduction and coronary heart disease risk. *J Am Coll Cardiol* 2009;53:316–22. [PubMed: 19161879]

Figure 1 a

Figure 1b.

Figure 1.

- a. Percentage of participants in the aggressive group with CIMT decrease or no increase, by change in LDL-C and Non-HDL-C in quartiles
- b. Percentage of participants in the aggressive group with CIMT decrease or no increase, by change in apoB and LDL-P in quartiles

Table 1
Change in Baseline Characteristics from Baseline to 36 Months in Aggressive vs. Standard Groups

	Baseline		36 months		Mean Change at 36 months	
	Aggressive	Standard	Aggressive	Standard	Aggressive	Standard
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Weight, kg	90 (20)	90 (19)	92 (21)	91 (21)	.65 (12)	1.2 (10)
BMI, kg/m ²	33.7 (6.7)	33.3 (6.2)	34.0 (7.0)	33.8 (7.0)	.3 (4.7)	.5 (3.9)
Waist, cm	110 (15)	110 (14)	111 (16)	110 (16)	.7 (10)	.9 (10)
Systolic BP, mmHg	128 (15)	132 (16)*	116 (11)	129 (10)*	-11 (15)	-3 (15)
Diastolic BP, mmHg	73 (10)	76 (10)*	67 (8)	73 (8)*	-7 (8)	-2.3 (9)
CRP, mg/dL (geometric mean and 95% CI)	2.8 (2.3-3.3)	2.9 (2.4-3.4)	2.3 (1.9-2.7)	3.2 (2.8-3.8)*	-7(11)**	.9(9)**
Glucose, mg/dL	158 (70)	157 (74)	167(78)	170(81)	9 (86)	16(97)
A1c	8.1 (1.8)	7.9 (1.9)	8.2 (2.2)	8.2 (2.3)	.1(1.9)	.3(2.5)
<i>Carotid</i>						
IMT mean (mm)	.818 (.19)	.791 (.17)	.798 (.18)	.830 (.20)	-.020(.12)	.038 (.14)
Arterial area (mm ²)	17.46 (4.9)	17.04 (4.5)	17.14(5.0)	18.13 (5.0)	-.28 (2.5)	1.07 (2.7)
Plaque score (1-8)	1.93 (1.6)	1.79 (1.6)	2.46 (1.7)	2.33 (1.7)	.53 (1.3)	.54 (1.2)
% plaque	78	75	90	84*	12	9
<i>ECHO</i>						
LVMl(g/m ^{2.7})	41.5 (9.6)	40.4 (8.4)	39.2 (8.7)	39.5 (8.5)	-2.5 (6.7)	-1.1 (6.1)
Ejection fraction	60.0 (5.8)	60.3 (5.9)	59.8 (5.0)	59.3 (5.7)	-4 (5.3)	-9 (5.5)

Abbreviations: BMI = body mass index; BP = blood pressure; CRP = c-reactive protein; IMT = intimal medial thickness; LVMl = left ventricular mass index.

* Difference between the groups at baseline or 36-mo is significant at p<.05

** Based on arithmetic mean.

Table 2
Mean Change in Lipid Measures from Baseline to 36 months in the Aggressive vs. Standard Groups

	Baseline			36 months			Mean Change at 36 months		
	Aggressive	Standard		Aggressive	Standard		Aggressive	Standard	Difference
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	Mean (95% CI) p-value
Total cholesterol, mg/dL	182 (32)	184 (32)		149 (29)	187 (27)*		-34(39)	3 (37)	37(30-44) .000
LDL cholesterol, mg/dL	103 (29)	102 (27)		71 (23)	104 (19)*		-33(36)	2(32)	34(28-41) .000
HDL cholesterol, mg/dL	46 (13)	46 (12)		48 (13)	48 (13)		3(9)	2(11)	.3(-2.2-1.6) .77
Total cholesterol/HDL-C	4.2 (1.2)	4.2 (1.1)		3.2 (1.0)	4.1 (1.0)*		-1(1.0)	-1(1.0)	.9(6-1.1) .000
Non-HDL cholesterol, mg/dL	136 (32)	137 (32)		100 (29)	138 (26)*		-36 (39)	9(36)	37(30-44) .000
Triglycerides (mg/dL)	173(94)	184(85)		148(66)	172(70)*		-25(78)	-12(81)	14(-1.8-29) .08
Triglycerides (geometric mean and 95% CI)	156(147-165)	168 (158-178)		136(129-144)	160 (152-169)				
VLDL particle total (nmol/L)	66.9(26.4)	66.3(22.9)		51.3(21.8)	69.3(21.8)		-15.6(30.2)	3.0(25.9)	18.6(13-24) .000
Large	4.3(4.1)	5.1(4.3)		2.4(2.2)	2.1(2.9)		-1.9(4.1)	-1.7(4.3)	.2(-.6-1.0) .63
Large (geometric mean and CI)	2.7(2.4-3.2)	3.4(3-3.9)		1.5(1.3-1.8)	2.2(1.9-2.6)				
Medium	21.3(14.9)	21.1(12.9)		15.5(8.7)	20.5(10.1)		-6.0(15.3)	-7(13.6)	5.2(2.4-8.0) .0002
Medium (geometric mean and CI)	17(15-19)	17(15-19)		13(12-14)	18(17-19)				
Small	41.3(14.9)	40.2(15.0)		33.4(14.8)	45.5(14.7)		-7.9(18.9)	5.3(17.6)	13.2(9.7-16.7) .000
VLDL size (nm)	54.4(9.1)	56.7(10.0)		51.5(8.1)	51.5(7.7)		-2.9(8.8)	-5.2(9.4)	-2.3(-4-(-5)) .01
LDL particle total (nmol/L)	1228(337)	1254(341)		860(312)	1159(347)		-369(379)	-95(387)	274(200-348) .000
Large	365(168)	363(170)		262(116)	326(160)		-104(170)	-37(179)	68(33-100) .0001
Small	804(385)	824(392)		561(327)	769(406)		-244(382)	-54(427)	189(111-267) .000
LDL size (nm)	20.8(.7)	20.8(.8)		21.0(.7)	20.8(.8)		.11(.7)	.00(.7)	.10(-.24-.04) .17
HDL particle total (umol/L)	30(5)	30(5)		31(5)	31(6)		1.8(5.1)	1.2(4.7)	.59(-1.5-.35) .22
Large	5(3)	5(2)		5.0(3)	5(3)		.39(2.3)	.10(2.5)	.3(-.8-.2) .21
Medium	2(3.0)	3(4)		4(4)	5(4)		2.0(4.3)	2.1(5.0)	.15(-.8-1.0) .75
Small	22.3(5)	22(5)		22(6)	21(6)		-6(5.6)	-1.0(5.6)	-.4(-1.5-.7) .43
HDL size (nm)	8.7(4)	8.8(4)		8.9(4)	8.9(4)		.17(.33)	.13(.35)	.04(-.1-.02) .22
ApoB (mg/dL)	93(21)	97(19)		69(22)	91(23)		-24.1(27.9)	-6.3(25.4)	17.9(12.5-23.2) .000

Notes:

Abbreviations: HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein.

¹ Lipid measurements at 36 months represent the averages for the last year of the study; lipid subfractions represent the measurements at the 36th month. Total sample size for all lipid variables is 418 except for the apoB (n = 381). The sample consists of all participants with available data for particles, lipids, and carotid IMT mean.

² Geometric means and 95% confidence intervals for the geometric mean are also presented if the variables were observed to be strongly positively skewed.

Table 3
Change in CIMT Mean between Baseline and 36 Months by Strata of Baseline Lipid Characteristics

			Aggressive	Standard	Group Diff. (mm)	p-value	Inter- action p-value
		N	Mean (SD)	Mean (SD)			
Age (yrs)	40–52	142	-.016 (.11)	.046 (.12)	.06	.002	
	53–60	144	-.038 (.15)	.027 (.13)	.07	.05	.29
	61–81	132	-.007 (.11)	.044 (.17)	.05	.04	
BMI (kg/m ²)	<30	139	-.014 (.13)	.048 (.15)	.06	.01	
	30–35	139	-.026 (.13)	.030 (.16)	.06	.03	.52
	>35	139	-.021 (.11)	.037 (.10)	.06	.002	
Gender	Male	143	-.035 (.12)	.036 (.16)	.07	.004	.45
	Female	275	-.012 (.12)	.039 (.12)	.05	.0007	
HDL-C (mg/dL)	<40	130	-.009(.12)	.051(.14)	.06	.009	
	40–50	154	-.036(.14)	.035(.13)	.07	.001	.24
	50–60	87	-.030(.12)	.031(.11)	.06	.013	
Non-HDL-C (mg/dl)	>60	47	.010(.11)	.026(.22)	.02	.75	
	<120	48	-.029(.10)	.031(.17)	.06	.15	
	120–140	134	-.024(.13)	.030(.11)	.05	.01	.92
LDL-C (mg/dL)	140–160	140	-.015(.12)	.050(.13)	.07	.003	
	>160	96	-.015(.13)	.033(.17)	.05	.13	
	<70	39	-.036(.10)	.036(.11)	.07	.04	
TG (mg/dL)	70–100	162	-.024(.12)	.049(.15)	.07	.0007	.78
	100–130	148	-.013(.12)	.035(.12)	.05	.02	
	>130	69	-.015(.14)	.025(.18)	.04	.31	
ApoB (mg/dL)	<100	50	-.058(.18)	.046(.11)	.10	.02	
	100–150	142	-.012(.11)	.022(.13)	.03	.09	.59
	150–200	103	-.024(.13)	.005(.13)	.03	.26	
ApoB (mg/dL)	>200	123	-.008(.11)	.076(.16)	.08	.001	
	<84.8	132	-.042(.12)	.018(.12)	.06	.006	
	85–102.2	127	-.009(.11)	.047(.13)	.06	.009	.46

				Aggressive Mean (SD)	Standard Mean (SD)	Group Diff. (mm)	p-value	Inter- action p-value
			N					
		>102.3	129	-.006(.14)	.042(.15)	.05	.07	
VLDL particle total (nmol/L)								
		<55	140	-.025(.14)	.029(.13)	.05	.03	
		55-73	139	-.022(.10)	.042(.11)	.06	.0007	.49
		>73	139	-.013(.13)	.044(.16)	.06	.03	
Large VLDL particles								
		<2.3	140	-.037(.12)	.026(.15)	.06	.008	
		2.3-4.8	139	-.013(.14)	.048(.12)	.06	.005	.801
		>4.8	139	-.007(.11)	.039(.15)	.05	.05	
Medium VLDL particles								
		<14	140	-.015(.13)	.023(.13)	.04	.08	
		14-25	139	-.022(.13)	.040(.10)	.06	.002	.22
		>25	139	-.023(.11)	.050(.17)	.07	.005	
Small VLDL particles								
		<34	140	-.024(.13)	.051(.16)	.08	.003	
		34-46	139	-.032(.11)	.013(.09)	.05	.009	.82
		>46	139	-.003(.13)	.049(.16)	.05	.04	
LDL particle total (nmol/L)								
		<1061	140	-.028(.10)	.033(.16)	.06	.006	
		1062-1362	139	-.025(.13)	.042(.11)	.07	.001	.67
		>1363	139	-.006(.14)	.039(.15)	.05	.07	
Large LDL particles								
		<281	140	-.015(.13)	.067(.13)	.08	.0003	
		282-439	139	-.026(.14)	.023(.15)	.05	.05	.34
		>440	139	-.019(.11)	.023(.12)	.04	.03	
Small LDL particles								
		<597	140	-.016(.10)	.029(.15)	.05	.04	
		598-972	139	-.031(.14)	.039(.12)	.07	.002	.49
		>973	139	-.012(.13)	.050(.15)	.06	.02	
HDL particle total (nmol/L)								
		<27.4	140	-.029(.13)	.025(.13)	.05	.02	

			Aggressive	Standard	Group Diff. (mm)	p-value	Inter- action p-value
		N	Mean (SD)	Mean (SD)			
	27.5–31.6	139	-.018(.12)	.064(.15)	.08	.0004	.38
	>31.6	139	-.012(.12)	.026(.14)	.04	.09	
Large HDL particles							
	<3.8	140	-.029(.13)	.025(.14)	.05	.02	
	3.8–5.8	139	-.045(.14)	.054(.16)	.10	.0001	.26
	>5.8	139	.012(.10)	.032(.12)	.02	.25	
Medium HDL particles							
	<3	140	-.014(.10)	.024(.14)	.04	.07	
	.3–2.9	139	-.019(.16)	.041(.13)	.06	.02	.76
	>2.9	139	-.027(.10)	.049(.14)	.08	.0005	
Small HDL particles							
	<21	140	-.024(.13)	.043(.13)	.07	.003	
	21–24	139	-.021(.12)	.035(.13)	.06	.007	.84
	>24	139	-.015(.12)	.036(.16)	.05	.04	
VLDL size(nm)							
	<51	140	-.031(.12)	.049(.17)	.08	.001	
	51–58	139	-.015(.15)	.044(.11)	.06	.007	.91
	>58	139	-.012(.10)	.023(.14)	.04	.09	
LDL size(nm)							
	<20.4	140	-.013(.13)	.048(.14)	.06	.009	
	20.4–21.2	139	-.030(.13)	.042(.16)	.07	.004	.25
	>21.2	139	-.015(.10)	.025(.12)	.04	.04	
HDL size(nm)							
	<8.5	140	-.013(.13)	.034(.14)	.05	.05	
	8.5–8.9	139	-.049(.11)	.040(.13)	.09	.0001	.46
	>8.9	139	-.002(.13)	.040(.14)	.04	.07	

Abbreviations: HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglyceride; VLDL = very low-density lipoprotein.