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Prevention of atherosclerosis with low-density lipoprotein cholesterol lowering—lipoprotein changes and interactions: the SANDS study

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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 be better predictors of cardiovascular risk. Few studies have examined the relationship among lipoprotein levels and composition before and after interventions to lower LDL-C and non-HDL-C.

OBJECTIVE: We sought 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 previous cardiovascular events, who were randomized to aggressive (AG) versus standard treatment for LDL-C, non-HDL-C, and systolic blood pressure as part of the Stop Atherosclerosis in Native Diabetics Study (SANDS).

RESULTS: The AG group achieved average LDL-C and non-HDL-C of 71 mg/dL and 100 mg/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 demonstrated borderline correlations with CIMT regression ($P = .07$ and $P = .09$).

CONCLUSIONS: In diabetic adults with no previous cardiovascular events, treatment to current targets for lipids and systolic blood pressure 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

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the main determinants of CIMT regression and were more predictive of this outcome than changes in LDL-P or apoB.

Lipoproteins are known to be involved in the atherosclerotic process. The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Studies[1] suggest that atherogenic lipoproteins are both necessary and sufficient for the development of atherosclerotic plaque. Almost all observational and interventional studies[2–5] implicate low-density lipoprotein (LDL) as the primary atherogenic lipoprotein, and high-density lipoprotein (HDL) appears to be the predominant antiatherosclerotic 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, whereas HDL-C is usually found to be an independent negative predictor. Low HDL often is accompanied by high levels of 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 mm Hg, 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 mm Hg.

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 increased 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

In brief, 499 men and women older than age 40 years with type 2 diabetes and with no history of a previous CVD event were enrolled between May 2003 and July 2004 at 4 clinical centers in Oklahoma, Arizona, and South Dakota. The participants were randomly assigned to 1 of 2 intervention groups: an aggressive group (n = 252) or a standard group (n = 247), by use of the urn method stratified by center and sex. All participants were American Indians as defined by Indian Health Service criteria. Eligibility criteria included documented type 2 diabetes (per 1997 American Diabetes Association 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 the patient had begun taking lipid-lowering medication within the past year and the LDL-C was >100 mg/dL before the initiation of this medication, they were admitted to the study provided the field physician thought the participant could be safely managed to meet target goals of either randomization group by use of the study lipid intervention algorithm.

Major exclusion criteria included New York Heart Association functional class III or IV congestive heart failure, SBP >180 mm Hg, triglycerides ≥400 mg/dL,