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EFFECT OF LOWER TARGETS FOR BLOOD PRESSURE AND LDL CHOLESTEROL ON ATHEROSCLEROSIS IN DIABETES:

THE STOP ATHEROSCLEROSIS IN NATIVE DIABETICS STUDY (SANDS)

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Abstract

Context—Individuals with diabetes are at greatly increased risk for developing cardiovascular disease (CVD), but more aggressive targets for risk factor control have not been tested.

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Independent Statistical Analyses: Statistical analysis was performed by statisticians at MedStar, under the direction of Dr. Barbara V. Howard, PhD, and the direction of Nawar Shara, PhD, department chair, and by statisticians at the University of Oklahoma under the direction of Dr. Elisa T. Lee.

Objective—To compare the progression of subclinical atherosclerotic disease in diabetic adults treated to aggressive targets of low-density lipoprotein cholesterol (LDL-C) ≤ 70 mg/dL and blood pressure (BP) ≤ 115/75 mm Hg (aggressive) versus treatment to standard targets of LDL-C ≤ 100 mg/dL and BP ≤ 130/85 mm Hg (standard).

Design—Randomized, open label, blinded-to-endpoint 3-year trial in individuals with diabetes conducted April 2003-July 2004.

Setting—Four clinical centers in southwestern Oklahoma; Phoenix, AZ; northeastern Arizona; and South Dakota.

Participants—499 American Indian men and women ≥ age 40 with type 2 diabetes and no prior CVD events.

Interventions—Participants were randomized to aggressive vs. standard treatment. The same treatment algorithms were followed for both groups.

Main Outcome Measures—Primary endpoint was a composite of progression of atherosclerosis as measured by common carotid artery intimal medial thickness (IMT) and clinical events. Secondary endpoints included other carotid and cardiac ultrasonographic measures.

Results—LDL-C and systolic BP (SBP) goals for both groups were reached within 12 months and maintained to 36 months. LDL-C and SBP in the last 12 months averaged 72 and 104 mg/dL and 116 and 129 mm Hg in the aggressive and standard groups, respectively. Regression of IMT (-0.017 vs. 0.041 mm, $p < .0001$) and arterial mass (-0.14 vs. 1.14 mm^2, $p < .0001$) and greater decrease in left ventricular mass (-2.4 vs. -1.3 $g/m^{2.7}$, $p = .05$) were observed in the aggressive group. Clinical CVD events were lower than expected and did not differ between groups

Conclusions—Reducing LDL-C and SBP to lower targets resulted in regression of carotid IMT and greater decrease in left ventricular mass in individuals with type 2 diabetes. Clinical events were lower than expected and did not differ significantly between groups. Further follow-up is needed to determine whether these improvements will result in lower long-term CVD event rates and costs and favorable risk-benefit outomes.

Individuals with diabetes are at increased risk for developing cardiovascular disease (CVD), and coronary heart disease (CHD) is the leading cause of death in diabetic adults.1 2 3 The increased diabetes-associated CVD risk is due in large part to the higher prevalence of other major CVD risk factors, such as dyslipidemia and hypertension, in diabetic individuals.4 5 Prevention of CVD and control of CVD risk factors in diabetic individuals has become a priority. Expert panels have defined targets for low-density lipoprotein cholesterol (LDL-C)6 and blood pressure (BP)7 in diabetic patients based on epidemiological and clinical trial data. However, a number of secondary prevention studies in high-risk patients have suggested that LDL-C lowering beneath the current target may be associated with improved outcomes in diabetic individuals.8 9 10 11 12 13 14 15 16 17 18 Several studies using statin therapy in high-risk diabetic patients also have suggested that further reduction in CVD events may be achieved in individuals who are at or below current LDL-C targets. 18 19 20 21 22 23 24 25 In addition, antihypertensive treatment to levels below recommended goals may delay progression of microalbuminuria to clinical proteinuria in diabetes.26 Because no

studies have specifically evaluated the benefits and risks of aggressive treatment targets for both LDL-C and BP in diabetic individuals, the optimal treatment targets remain elusive.

A large body of epidemiologic data in American Indians, a population with high prevalence of diabetes and diabetes-related CVD, documents strong relations between LDL-C and BP levels and CVD events.27 28 These data suggest that lowering LDL-C and BP beyond current targets could help retard or reverse CVD in diabetic patients. Thus, the present study was undertaken to compare progression of subclinical atherosclerotic disease, as evaluated by carotid ultrasound, in diabetic American Indians ages ≥ 40 years, randomly assigned to either aggressive targets of LDL-C ≤ 70 mg/dL plus BP ≤ 115/75 mm Hg or current standard targets of LDL-C ≤ 100 mg/dL and BP ≤ 130/85 mm Hg. Impact on cardiac structure and function was also evaluated.

METHODS

Details of this study design and methods have been published.29 30 All participants provided written informed consent, and the study was approved by all participating institutional review boards (IRBs), the National Institutes of Health, and all participating American Indian communities.

Recruitment

Briefly, 548 diabetic men and women ≥ age 40 were enrolled between May 2003 and July 2004 at four clinical centers in the United States: southwestern Oklahoma; Phoenix, AZ; northeastern Arizona; and South Dakota. Participants were randomly assigned to the aggressive (n = 276) or standard treatment group (n = 272), stratified by center and gender. All participants were American Indians as defined by Indian Health Service (IHS) criteria.31 Eligibility criteria included documented type 2 diabetes,32 33 plus LDL-C ≥ 100 mg/dL and systolic BP (SBP) > 130 mm Hg within the previous 12 months. Major exclusion criteria included Class III or IV heart failure, SBP > 180 mm Hg, liver transaminase levels > twice the upper limit of normal, or diagnosis of primary hyperlipidemia or hypercholesterolemia due to hyperthyroidism or nephrotic syndrome.

Lipid and BP Interventions

Study personnel performed BP and lipid management for both groups, with equal frequency of clinic visits. All other medical care, including diabetes management, was performed by the participants' IHS health care providers.

The algorithm for hypertension management was based on the Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI).7 The goals of therapy were SBP ≤ 115 mm Hg and ≤ 130 mm Hg in the aggressive and standard groups, respectively. Secondary goals were diastolic BP (DBP) of ≤ 75 and ≤ 85 mm Hg, respectively. Step 1 drugs were angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) in the case of intolerance to ACE inhibitors. Step 2 was hydrochlorothiazide. Steps 3-5 added calcium channel blockers, beta-blockers, and then alpha-blockers and other vasodilators.

The algorithm for achieving lipid goals was based on recommendations of the National Cholesterol Education Program - Adult Treatment Panel III (NCEP-ATP III). 6 34 LDL-C goals were ≤ 70 and ≤ 100 mg/dL and non high-density lipoprotein cholesterol (non-HDL-C) goals were ≤ 100 and ≤ 130 mg/dL in the aggressive and standard groups, respectively. If lifestyle modification was unsuccessful, a statin was initiated. If the LDL-C goal was not reached with a statin, combination therapy with ezetimibe was used. In addition, the non-HDL-C goals were addressed using fish oil, fenofibrate, or niacin. Details of the intervention procedures and targets have been published.29

Baseline and Follow-up Visits

All procedures followed standardized methods performed by trained, certified personnel. The baseline visit included a physical exam, electrocardiogram, carotid artery ultrasound, echocardiogram, and collection of demographic data, health history, and current medication use. Height, weight, waist circumference, and seated BP were measured, and fasting blood samples were collected to measure chemistry panel, lipoprotein profile, glucose, hemoglobin A1c, C-reactive protein (CRP), and creatinine, and urine samples for urinary albumin and creatinine.29

Participants were followed from date of entry until death, loss-to-follow up, request for no further contact, or completion of the study, regardless of adherence to the medication intervention. At follow-up visits after 1 month, and then every 3 months until 36 months, seated and standing BP (with orthostatic hypotension defined as a SBP fall of > 20 mm Hg after 2 minutes of standing and with symptoms lasting longer than 1 minute) and a lipid profile (using a Cholestech apparatus [Cholestech Corporation, Hayward, CA] standardized against the laboratory assay)35 were measured. 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 36 months to repeat all baseline measurements; additionally, fasting blood samples for complete lipoprotein profile and urine samples for albumin and creatinine were obtained at 6, 12, 24, and 30 months.

Outcomes Ascertainment

At the baseline, 18-, and 36-month visits, carotid and cardiac ultrasound studies were performed following standardized protocols36 by centrally trained sonographers and interpreted at a core reading center by physician readers blinded to treatment assignment. For carotid ultrasound studies, B-mode imaging from multiple angles was performed to determine the presence and location of plaque (focal protrusion of the vessel ≥ 50% greater than the surrounding wall), as well as arterial wall dimensions. Plaque score (0-8) was determined as the number of segments of each artery containing plaque. End-diastolic B-mode images of the distal right and left common carotid artery were acquired in real-time, and a 1-cm segment of the 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 intimal medial thickness (IMT) and lumen diameter. Arterial mass (cross-sectional area) was calculated using end-diastolic IMT and diameter measurements.37

Echocardiographic measures included assessment of left ventricular (LV) structure and function.38 39 Methods for ascertaining and classifying clinical outcomes have been described.29 Medical records for all hospitalizations and outpatient coronary revascularization procedures were reviewed centrally by a panel of six physician adjudicators blinded to treatment assignment. The primary CVD endpoint included fatal and non-fatal CVD events, defined as fatal CHD or stroke, nonfatal myocardial infarction (MI) or stroke, unstable angina, cardiac revascularization, and carotid arterial revascularization.

Data Analysis

The primary endpoint (identified at the beginning of the trial) was defined as a composite outcome of change from baseline to 36 months in common carotid artery (CCA) IMT and/or a primary CVD event. The primary hypothesis was that, compared with standard ATP III and JNC VI goals, achieving lower targets for LDL-C and BP will retard progression of atherosclerosis, as measured by change in carotid IMT and CVD events. Changes in carotid and ECHO measures were defined as secondary endpoints. The treatment effects on IMT at 18 or 36 months testing the primary hypothesis were compared in an intent-to-treat analysis using the worst-rank score method of Wei and Lachin40 for differences in IMT from baseline to 36 months after adjustment for baseline IMT and center. Participants who had a primary CVD event prior to 18 or 36 months were assigned a worse rank score than those with the greatest increase in IMT. Fatal events were ranked worse than non-fatal ones, and earlier events had worse ranks. The 36-month IMT measures of participants who died from non-CV causes or were lost to follow-up prior to 18 months were considered missing at random, and these participants (n = 10) were excluded from the analysis. For those who had 18- but not 36-month values (n = 18 for carotid measures and 47 for ECHO measures) and no primary event, the 18-month value was used in the 36-month analyses.

Because few CVD events occurred, standard parametric procedures were also used. Mean changes in the aggressive vs. standard groups for carotid and echocardiographic parameters and differences between changes in the two groups were evaluated with log-transformation as needed. Predefined secondary endpoints included CCA mass, plaque score, LV geometry and function, and CRP; safety measures were also examined.

Additional intention-to-treat analyses compared changes in IMT and LV mass index (LVMI) between the treatment groups stratified by predefined baseline characteristics, including age, gender, obesity, SBP, LDL-C, non-HDL-C, CRP, and hemoglobin A1c. Comparisons of means for each stratum across treatment groups, and tests for interactions between baseline characteristics and treatment were conducted. In addition, secondary analyses of factors influencing changes in endpoints were evaluated using change in IMT or LVMI as dependent variables in ordinary least squares regression models. Time of treatment effect was explored using models that included number of months at LDL-C or SBP target. A sensitivity analysis was performed to compare those in the aggressive group who maintained either the LDL-C goal of ≤ 70 mg/dL or the SBP goal of ≤ 115 mm Hg during the last 6 months of follow up with those in the standard group. Finally, ordered logit analyses compared the influence of LDL-C and SBP changes on categorical changes in IMT and LVMI variables; in these models the effect of changes in LDL-C and SBP on the probability

of observing no change (defined as no change within the variance of the measurement), a decrease, or an increase was tested in models that also controlled for baseline characteristics (i.e., age, body mass index [BMI], gender, and center).

RESULTS

Recruitment and Baseline Characteristics

Between April 2003 and July 2004, 548 diabetic men and women ≥ age 40 were randomized (Figure 1). Four months after initiation of recruitment, the Steering Committee voted (with concurrence of the Data and Safety Monitoring Board) to change the LDL-C goal to ≤ 70 mg/dL for those with baseline CVD (n = 49) who had been already randomized into the study to comply with the newly released ATP III recommendations.34 Recruitment was limited thereafter to persons who had not had a prior CVD event, and recruitment continued until the pre-specified sample size was reached. Thus, 499 participants without baseline CVD were included in the analyses (Figure 1). After 36 months, physical examination and blood measurements were obtained on 99%, and carotid ultrasound data were collected on 92% of those alive. Only 4 were lost to follow-up, and CVD endpoints were ascertained in 99%.

Baseline characteristics of the participants have been described previously (Table 1).30 Mean age was 56 years, 66% were women, average BMI was 33, and 21% were current smokers. At entry, 38% of participants were taking lipid-lowering medication, and 73% were on antihypertensive therapy. Baseline LDL-C averaged 104 mg/dL and systolic BP averaged 131 mm Hg. The majority was on some form of hypoglycemic therapy; hemoglobin A1c averaged 8.1%, and mean duration of diabetes was 8.7 years in the standard group and 9.2 years in the aggressive group.

The two treatment groups were well matched, with no meaningful differences in baseline characteristics, except that average clinic SBP was 5 mm Hg lower in the group randomized to aggressive therapy. No significant differences were observed in any carotid ultrasound or echocardiographic parameter.

Intervention

On average, the aggressive group achieved the LDL-C goal of ≤ 70 mg/dL within 12 months of randomization, maintaining it consistently throughout 36 months of follow-up. They reached the SBP goal of ≤ 115 mm Hg after 9 months of therapy, also maintaining that goal throughout follow up (Figure 2). Comparable decreases were observed in non-HDL-C, and DBP averaged < 70 mm Hg in the aggressive group (Table 2) throughout the study. LDL-C and BP goals were also maintained in the standard treatment group, with LDL-C at 100 mg/dL during follow up and SBP at 130 mm Hg (Figure 2). During the last 12 months, the difference in LDL-C between the groups was 32 mg/dL and that in SBP was 13 mm Hg (Table 2). Mean weight, average BMI, waist circumference, and fasting glucose also remained unchanged in both groups, but CRP tended to decrease in the aggressive group (p = 0.12 for difference between group changes) at 36 months (Table 2).

To achieve the treatment goals in both groups, the mean (SD) numbers of lipid-lowering and antihypertensive drugs used in the aggressive and standard treatment groups were 1.42 (.65) vs. 1.15 (.51) and 2.35 (1.33) vs. 1.62 (1.03), respectively. Rates of adverse events (AEs) and serious adverse events (SAEs) were low (Table 3). No difference was observed between groups in AEs related to lipid lowering drugs ($p = .216$), but more AEs related to BP drugs occurred in the aggressive group ($p = .002$). Orthostatic hypotension occurred in two participants in each group. One SAE judged to be possibly related to the interventions occurred in the standard group (hypotension) and four in the aggressive group (two hypotension and two hyperkalemia). All recovered after reduction or withdrawal of medication.

Outcomes

Primary CVD events occurred in 11 and 8 participants in the aggressive and standard treatment groups, respectively ($p = .511$) (Table 3). Other CV events and non-CVD death occurred in one vs. three and two vs. four participants in the two groups, respectively. The total number of CVD endpoints, either primary or secondary, did not differ significantly between treatment groups.

Carotid IMT progressed slightly in the standard treatment group and regressed in the aggressive group (Table 4). At 36 months, there was a significant difference between the standard vs. aggressive groups by both the worst-rank score method and t-test (both $p < .0001$). There were also significant differences in arterial mass (cross-sectional area, $p < .0001$ for both tests). Plaque score increased slightly in both groups at 36 months, with no difference between groups. Similarly, the percentage of individuals with at least one discrete plaque increased slightly in both groups at 36 months without significant intergroup difference.

Changes in echocardiographic measures of LV structure (Table 4) also differed significantly between the aggressive and standard groups. LV mass and LV mass normalized for height$^{2.7}$ decreased in both groups at 36 months, but to a greater degree in the aggressive treatment group ($p = 0.069$ and 0.050 respectively).

When both treatment groups were divided into those individuals whose measures decreased (improved), remained the same ($\pm$ 0.01 mm for IMT or $\pm$ 0.5 gm/m$^{2.7}$ for LVMI), or worsened over the treatment period (Figure 3), participants in the aggressive group were more likely to have a decrease in IMT ($p < .0001$) and a trend toward decreased LVMI ($p = .25$).

Secondary Analyses

Intention-to-treat analyses compared groups stratified by pre-specified characteristics, including age, BMI, baseline LDL-C, non-HDL-C, baseline SBP, gender, A1c, smoking, CRP, and estimated glomerular filtration rate. No significant quantitative interactions were observed between treatment and any of the variables (Appendix Table A).

A sensitivity analysis was performed by evaluating IMT and LVMI changes in individuals in the aggressive group who achieved either the LDL-C goal of $\leq$ 70 mg/dL (n = 126) or

SBP ≤ 115 mm Hg (n = 119) consistently during the last 6 months of the intervention compared with those in the standard treatment group. For IMT and arterial mass, there was a bigger difference in the adherent group compared to the whole aggressive group (Appendix Table B vs. Table 4) (changes of -.025 mm and -.39 mm^2, respectively, both $p < .0001$ compared to the standard group). For differences in LVMI, there was only a marginally greater decrease (-2.7 $g/m^{2.7}$ in the adherent group, $p < .04$ compared with the standard group). Participants achieving the aggressive SBP target had greater mean decreases in LVMI (-3.0 $g/m^{2.7}$ in the adherent group, $p < .01$ vs. the standard group) compared with the aggressive group as a whole (Appendix Table B vs. Table 4).

Ordered logit analyses were performed on the combined cohort (Appendix Table C). The probability of a decrease in IMT was significantly related to decrease in LDL-C but not related to a decrease in SBP, even when the two factors were present in a combined model ($p < .0005$). Conversely, probability of decreases in LVMI were significantly related to decreases in SBP ($p = .002$) but not to LDL-C. In these models, age was a significant positive predictor of IMT increase, and BMI was a significant positive predictor of LVMI increase. To explore the time dependence of the treatment effects on changes in IMT and LVMI, regression models were run for the combined groups, with IMT or LVMI changes as dependent variables, including all other potential covariates plus the number of months the treatment goal was maintained for LDL-C, SBP, or both. The proportion of months at LDL-C goal or at both LDL-C and BP goals in the aggressive group was a significant determinant of IMT changes ($p = .022$ and $p = .010$, respectively). For LVMI, the proportion of months at BP or at both LDL-C and BP goals tended to be related to change in LVMI, but the trends were not significant.

COMMENT

This randomized trial in American Indian men and women with type 2 diabetes compared groups treated aggressively to target levels of LDL-C ≤ 70 mg/dL and SBP ≤ 115 mm Hg with a group treated to current LDL-C and SBP targets. The group treated to lower targets had an improvement (decrease) in IMT, whereas the standard treatment group had a worsening (increase) in IMT, a measure of atherosclerosis. There was also a greater decrease in LVMI in the aggressive group. Few CVD events occurred overall, with no intergroup difference.

This trial, the first to test predefined treatment targets for both LDL-C and SBP, answered several questions. First, it showed that lower targets for LDL-C and BP can be successfully and safely achieved. Previous trials of LDL-C lowering8 18 19 20 21 22 23 24 25 26 41 42 43 using fixed doses of statins showed reduced CVD in those achieving targets lower than the standard goals, but in none of these trials were lower targets pre-specified; thus those who achieved lower targets may have had lower LDL-C at baseline or may have been more adherent or responsive to the regimen. One previous trial that targeted DBP below standard goals achieved fewer CVD events in the aggressive treatment arm.41 In our trial both LDL-C and BP were treated to aggressive targets, low-dose aspirin therapy was maintained in the majority of both groups, and few individuals smoked.

We used surrogate endpoints for this trial because of a number of practical constraints, including the trial cost, rapidly evolving evidence in this field, and concern about the feasibility of conducting a long-term intervention in a vulnerable population. However, the endpoints selected have been validated as having prognostic significance for CVD events. Carotid ultrasound measures of IMT also have been validated against pathologic specimens. In addition, the carotid and echocardiographic measures used have been demonstrated to be potent predictors of CVD outcomes in the Strong Heart population of American Indians, which closely resembles the current cohort.29 Furthermore, at least twelve lipid lowering trials44 45 46 47 48 49 50 51 52 53 54 55 have employed carotid ultrasound measures as endpoints and showed correlations between changes in carotid measures and reduction in CVD events.

Although the standard treatment group showed progression of carotid IMT, average IMT in the aggressive group decreased. This trial is one of the few to show regression of IMT.49 55 56 More commonly, clinical trials have observed less IMT progression in the treatment versus control group.46 47 54 57 58 59 60 61 This may suggest that intensive control of both lipids and BP may be necessary to reverse the atherosclerotic process. In contrast to IMT, plaque score and percentage of individuals with plaque did not differ between the two groups in the current study. These endpoints are less quantitative measures than IMT and reflect established atherosclerotic lesions. Thus, a longer period of therapy might be needed for improvement to be reflected in these measures of more advanced disease. More importantly, aggressive control of CVD risk factors at younger ages may prevent or retard development of advanced lesions.

LV hypertrophy and/or greater LVMI have been shown to predict CVD outcomes in both observational studies62 and clinical trials.63 64 Echocardiographic measures have not been used as commonly as surrogate endpoints in trials of risk factor reduction. However, lower echocardiographic LV mass and ECG estimates thereof during antihypertensive treatment have recently been shown to predict, independently of changes in BP and other covariates, lower rates of major cardiovascular events;63 64 as well as of incident heart failure,65 sudden death,66 and atrial fibrillation.67 Although LV mass measures declined in both groups, there was a significantly greater reduction in the aggressively treated group. Both treatment arms had normal mean LV ejection fraction upon study entry, and no changes were observed; a longer period of treatment would probably be necessary to detect a treatment effect in such a population.

Because we targeted both BP and lipid goals, the trial was not designed to distinguish which intervention was responsible for the improved measures of atherosclerosis and cardiac structure. Sensitivity analyses exploring the changes in those who met or exceeded LDL-C and SBP goals confirm the results of the intention-to-treat analyses, suggesting that the observed changes in endpoints could be attributable to the interventions on LDL-C and BP. Secondary analyses suggested that the IMT changes appeared to correlate more closely with the extent of lipid lowering. However, BP lowering also correlated with IMT changes, and it is difficult in secondary analyses to rule out confounding by compliance. Conversely, the changes in LVMI appeared more closely related to changes in SBP, although this analysis has the same limitation.

Additional analyses suggested that length of time at LDL-C and SBP targets in the aggressive group were determinants of both IMT and LVMI changes. Stratified analyses suggested that the effects were broadly applicable, regardless of age, obesity, gender, and baseline CVD risk factors.

An important finding was that few CVD events occurred in either treatment group. The rate of events in the combined sample was approximately 1.3 per 100 person-years. In the Strong Heart Study (SHS) population-based longitudinal follow-up of American Indians of comparable age with diabetes, CVD incidence rates were 2.8 to 3.6 per 100 person-years.27 68 In addition, progression of IMT in the standard treatment group in this trial was much lower than expected. A meta-analysis of trials using carotid IMT as an endpoint showed a 3-fold higher rate of progression in control groups than in our standard group,69 and rates of progression of IMT and LVMI in diabetic individuals of comparable ages in the SHS were also much higher (data not shown). Our findings may be the result of achieving defined targets in both groups at or better than current levels and the fact that all participants had frequent access to general medical care. In previous primary prevention studies that suggested major improvements in CVD rates at lower LDL-C targets resulting from statin therapy, BP was not controlled, aspirin use was low, and smoking rates tended to be higher. To our knowledge, no prior trials have had an SBP target as low as ≤ 115 mm Hg. In the Hypertension Optimal Treatment (HOT) trial, 41 the group in which DBP was lowered to 70 mm Hg had the lowest incidence of CVD events, although lipid levels were not targeted.

Our study suggests the possibility of incremental CV benefit of achieving more aggressive LDL-C and BP targets. Our data show significant retardation of atherosclerosis progression and regression of LV hypertrophy through more intensive therapy, suggesting that if these targets were achieved and sustained longer, incidence of CVD events would be reduced.

The strength of this study includes it being the first trial to test specific targets for both LDL-C and BP in individuals with diabetes. These targets were reached in each group, and adherence and follow-up were excellent. Subclinical ultrasound measures of atherosclerosis and cardiac function were assessed with standardized protocols. Observational data obtained using this methodology are available from a population-based sample of comparable diabetic American Indians,29 allowing comparison of progression rates as well as disease outcomes.

A reason to be cautious in interpreting this study is that only a single ethnic population was studied, American Indians. Although this group has high rates of CVD, their average LDL-C and BP levels are slightly lower than in other U.S. populations; other treat-to-target studies are needed to assess the safety and feasibility of achieving aggressive targets for LDL-C and BP in groups with higher levels. A second limitation is that surrogate endpoints were used. As the effectiveness of therapy improves and new treatment strategies are widely applied, it is becoming more difficult to conduct a trial in which adequate numbers of endpoints are achievable in a reasonable length of time for individuals without CVD at baseline. Thus, it may become increasingly important in the future to rely upon surrogate endpoints. We are planning an extended follow-up of these individuals to determine whether the improvements

in atherosclerosis and cardiac structure are maintained in the aggressive group and whether they are reflected in fewer clinical CVD outcomes.

In conclusion, in this first trial to evaluate lower targets for both LDL-C and BP compared with standard targets in adults with diabetes, regression of IMT and greater decrease in LV mass were observed in the aggressive treatment group. Although there were no differences in clinical CVD outcomes, event rates were low in both groups, and progression of subclinical disease in the standard treatment group was lower than expected. The data suggest that targeted treatment of LDL-C and SBP improved surrogate measures of CVD, with greater benefits being attributable to the lower target levels. Whether these improvements will result in lower long-term CVD event rates or economic benefit remains to be determined.

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APPENDIX

Table A

Change in IMT Mean (Columns 1-5) and LV Mass Index (Columns 6-10), by Strata of Baseline Characteristics

	IMT (1)	Aggressive (2)	Standard (3)	Group Dif. (4)	p-val. (5)	LVMI (6)	Aggressive (7)	Standard (8)	Group Dif. (9)	p-val. (10)
	N	Mean (SD)	Mean (SD)		Inter.	N	Mean (SD)	Mean (SD)		Inter.
Age (yrs) <51	145	-.010 (.12)	.046 (.12)	.05		140	-3.43 (5.3)	-1.76 (5.5)	1.67	
51-60	173	-.035 (.14)	.028 (.13)	.06	*.70*	164	-1.38 (6.5)	-.73 (6.9)	.65	*.86*
>60	151	-.007 (.11)	.052 (.16)	.05		141	-2.37 (6.7)	-1.46 (5.4)	.91	
BMI (kg/m^2) <30	146	-.013 (.13)	.044 (.15)	.06		142	-2.26 (5.2)	-1.96 (5.6)	.31	
30-35	159	-.019 (.14)	.029 (.14)	.05	*.64*	151	-2.84 (5.8)	-1.63 (5.5)	1.21	*.28*
>35	163	-.020 (.11)	.052 (.12)	.07		152	-2.14 (7.4)	-.08 (7.0)	2.06	
Gender Male	159	-.029 (.12)	.038 (.16)	.07	*.47*	148	-2.20 (5.2)	-.40 (5.9)	1.8	*.35*
Female	310	-.011 (.13)	.042 (.13)	.05		297	-2.50 (6.7)	-1.68 (6.1)	.82	
LDL-C (mg/dl) <100	222	-.021 (.12)	.047 (.13)	.07		212	-2.37 (6.6)	-1.33 (6.2)	1.05	
100-130	159	-.011 (.12)	.040 (.12)	.05	*.94*	135	-2.61 (6.13)	-1.16 (6.27)	1.44	*.72*
>130	81	-.016 (.15)	.021 (.19)	.04		74	-2.26 (5.6)	-1.05 (5.3)	1.21	

	IMT (1)	Aggressive (2)	Standard (3)	Group Dif. (4)	p-val. (5)	LVMI (6)	Aggressive (7)	Standard (8)	Group Dif. (9)	p-val. (10)
	N	Mean (SD)	Mean (SD)		Inter.	N	Mean (SD)	Mean (SD)		Inter.
Non-HDL (mg/dl) <130	194	-.023 (.12)	.029 (.12)	.05		186	-2.56 (6.4)	-1.35 (6.5)	1.21	
130-160	158	-.012 (.12)	.057 (.13)	.07	*.85*	151	-3.01 (6.9)	-.91 (6.2)	2.1	*.95*
>160	110	-.010 (.14)	.030 (.18)	.04		101	-1.44 (5.2)	-1.54 (5.2)	.10	
SBP (mm Hg) <120	129	-.003 (.11)	.046 (.11)	.05		125	-2.03 (6.3)	-2.28 (5.8)	.24	
120-130	108	-.019(.11)	.039 (.13)	.07	*.28*	101	-2.43 (6.7)	-.44 (6.7)	1.99	*.59*
>130	231	-.027 (.14)	.039 (.16)	.07		218	-2.64(6.0)	-1.21 (5.8)	1.44	
A1c <7	162	-.027 (.12)	.042 (.14)	.07		153	-2.27 (6.5)	-1.26 (5.6)	1.00	
7-8	107	-.024 (.11)	.063 (.15)	.09	*.40*	99	-1.98 (7.0)	-2.26 (5.6)	.28	*.20*
>8	193	-.010(.13)	.022 (.13)	.03		186	-2.76 (5.7)	-.59(6.8)	2.17	
CRP (mg/dl) <1.7	133	-.009 (.10)	.053 (.17)	.06		127	-2.30 (5.3)	-.33 (5.3)	1.98	
1.7-4.5	138	-.032(.14)	.032(.12)	.06	*.41*	128	-2.05 (6.7)	-1.48 (6.9)	.57	*.66*
>4.5	142	-.017(.13)	.041(.14)	.06		136	-2.68 (5.4)	-2.09 (6.0)	.60	
eGFR <78	138	.004 (.10)	.038 (.17)	.03		155	-2.64(6.2)	.45(5.7)	2.19	
78-96	160	-.023 (.13)	.040 (.12)	.06	*.53*	151	-2.56 (5.5)	-1.25 (6.7)	1.32	*.09*
>96	161	-.023(.13)	.041 (.13)	.06		155	-2.64 (6.2)	-.45 (5.7)	2.18	
Current smoker Yes	96	-.040(.16)	.045 (.14)	.09	*.22*	87	-1.96 (6.6)	-1.73 (7.6)	.23	*.38*
No	373	-.010(.11)	.040 (.14)	.05		358	-2.51 (6.2)	-1.15 (5.6)	1.45	

Abbreviations: BMI = body mass index; CRP = c-reactive protein; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; IMT = intimal medial thickness; LDL-C = low-density lipoprotein cholesterol; LV = left ventricular; SBP = systolic blood pressure.

Note: A non-parametric test of trend for the ranks of across-ordered groups was used for trends within groups. BMI exhibited a trend for LVMI within the standard group at p = .05. All other trends were non-significant. P-values for interaction terms were obtained by an ordinary least squares equation of IMT mean change variable on each variable of interest and its interaction with the treatment group, controlling for baseline IMT mean and data center.

Table B

Baseline and Follow-up Carotid and Cardiac Measures: Participants who Achieved the LDL-C Goal of ≤ 70 (N = 126) or the SBP Goal of ≤ 115 (N = 119) vs the Standard Treatment Group

	LDL-C Goal			SBP Goal		
	Adherent Aggressive	Standard		Adherent Aggressive	Standard	
	Mean (SD)	Mean (SD)	p-value	Mean (SD)	Mean (SD)	p-value
Carotid						
IMT (mm) Baseline	.830 (.21)	.797 (.17)		.803(.21)	.797 (.17)	
36 mo	.802 (.19)	.834 (.20)		.785 (.20)	.833 (.20)	
Mean Change	-.025(.13)	.041 (.14)	<.001	-.018(.12)	.041 (.14)	<.001
Art. Mass Baseline	18.1 (5.5)	17.3(4.6)		16.80(5.2)	17.3(4.6)	
36 mo	17.5(5.3)	18.2 (5.0)		16.6(5.0)	18.2 (5.0)	

	LDL-C Goal			SBP Goal		
	Adherent Aggressive	Standard		Adherent Aggressive	Standard	
	Mean (SD)	Mean (SD)	p-value	Mean (SD)	Mean (SD)	p-value
Mean Change	-.39 (2.5)	1.1 (2.7)	<.001	-.32 (2.4)	1.1 (2.7)	<.001
Plaque Score Baseline	2.02 (1.63)	1.83 (1.56)		1.76 (1.59)	1.83 (1.56)	
36 mo	2.58 (1.77)	2.33 (1.71)		2.27 (1.75)	2.33 (1.71)	
Mean Change	.54(1.14)	.50 (1.16)	.73	.50 (1.10)	.50 (1.16)	.97
% Plaque Baseline	78.6	76.4	.64	73.1	76.4	.49
36 mo	89.5	84.3	.17	86.2	84.3	.63
Percentage Point Difference	10.9	7.9		13.1	7.9	
Cardiac						
LV Mass (g) Baseline	160.2(40.1)	156.1(38.3)		155.7(38.3)	156.1(38.3)	
36 mo	150.5(37.5)	150.9(38.5)		144.8(36.6)	150.9(38.5)	
Mean Change	-8.8 (24.7)	-4.2 (22.4)	.08	-10.1(22.3)	-4.2 (22.4)	.02
LVMI($g/m^{2.7}$) Baseline	41.8 (9.2)	40.6 (8.5)		40.7 (9.3)	40.6 (8.5)	
36 mo	39.0 (8.2)	39.3(8.4)		37.6 (8.2)	39.3 (8.4)	
Mean Change	-2.7 (6.7)	-1.3(6.0)	.04	-3.0 (5.9)	-1.3 (6.1)	.01
EF (%) Baseline	60.5 (5.9)	59.8 (5.8)		60.5 (5.0)	59.8 (5.8)	
36 mo	60.2 (4.5)	59.2(5.6)		60.0 (4.6)	59.2 (5.6)	
Mean Change	-.17 (5.8)	-.70 (5.6)	.41	-.43 (4.2)	-.70 (5.6)	.46

Table C

Ordered Logistic Regression Analyses of Determinants of Change Category for IMT and LV Mass Index Between Baseline and 36 Months

MODELS	1. With Change in LDL-C		2. With Change in SBP		3. With Changes in LDL-C and SBP	
	Coefficient (SE)	p-value	Coefficient (SE)	p-value	Coefficient (SE)	p-value
Dependent Variable: IMT Change Category*						
Baseline IMT mean	-3.82 (0.71)	.000	-3.88 (0.69)	.000	-3.84 (0.72)	.000
Change in LDL-C	0.008 (0.0025)	.002			0.007 (0.003)	.005
Change in SBP			0.008 (0.005)	.127	0.005 (0.006)	.345
Age	0.029 (0.012)	.016	0.032 (0.012)	.006	0.030 (0.012)	.012
BMI	0.014 (0.015)	.38	0.019 (.015)	.214	0.016 (0.0016)	.29
N	445		458		444	
LR chi-sq	54.2	.000	50.4	.000	56.3	.000
Dependent Variable: LV Mass Index Change Category						

MODELS	1. With Change in LDL-C		2. With Change in SBP		3. With Changes in LDL-C and SBP	
	Coefficient (SE)	p-value	Coefficient (SE)	p-value	Coefficient (SE)	p-value
Baseline LV mass	-0.096 (.015)	.000	-0.105 (0.016)	.000	-0.101 (0.016)	.000
Change in LDL-C	0.006 (0.003)	.042			0.004 (0.003)	.169
Change in SBP			0.021 (0.006)	.001	0.020 (0.006)	.002
Age	0.014 (0.012)	.24	0.015 (0.012)	.20	0.019 (0.012)	.13
BMI	0.078 (0.019)	.000	0.095 (0.020)	.000	0.091(0.020)	.000
N	423		436		422	
LR chi-sq	57.5	.000	72.4	.000	70.4	.000

Note: Gender and site were not significant.

Abbreviations: BMI = body mass index; IMT = intimal medial thickness; LDL-C = low-density lipoprotein cholesterol; LR chi-sq = Likelihood ratio chi-square statistic for the overall model; LV = left ventricular; SBP = systolic blood pressure.

* Change Categories: 1 = Decrease, 2 = No Change, 3 = Increase

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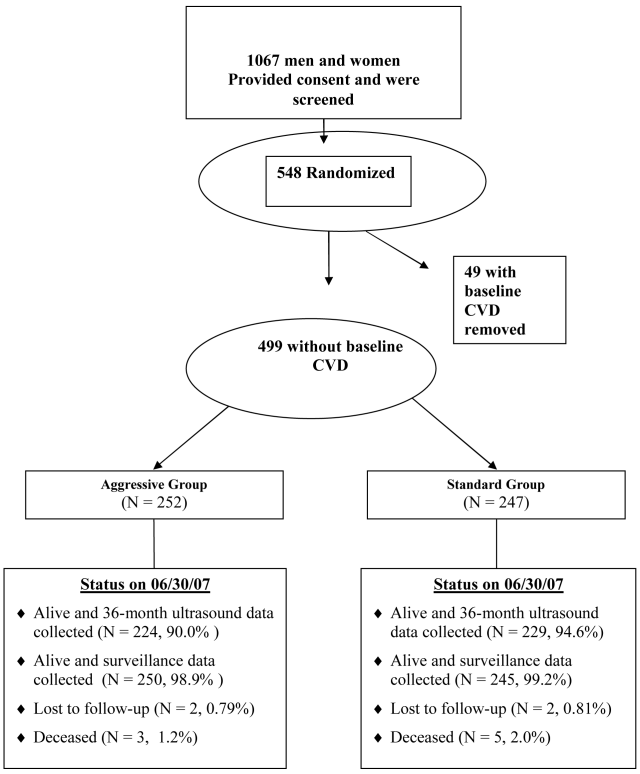

Figure 1. Participant Flow in SANDS

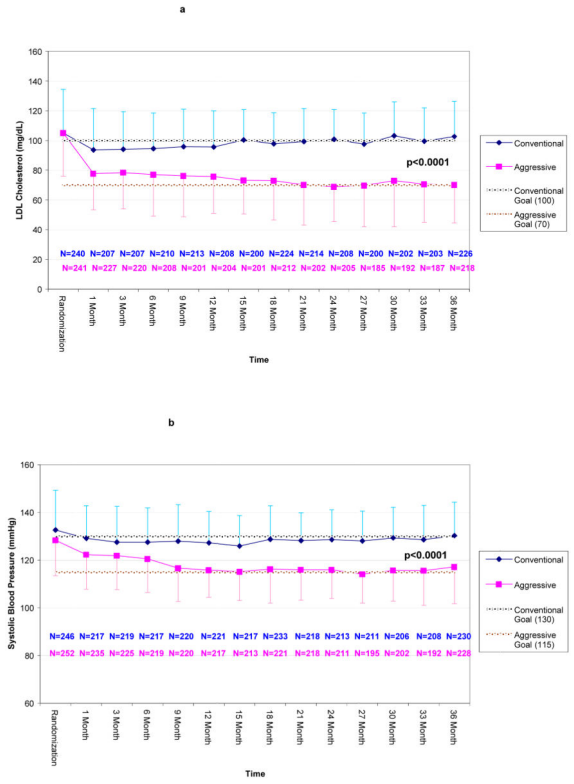

Figure 2. Panel A. Mean (SD) LDL cholesterol by treatment group (vertical axis) at 3-month intervals (horizontal axis) throughout the study. Panel B. Mean (SD) systolic blood pressure (vertical axis) by treatment group at 3-month intervals throughout the study

Note. LDL values were obtained from capillary blood using Cholestech apparatus. For 2292 samples having both laboratory and Cholestech measures, the means (SD) were 89.2 (31.2) and 87.9 (29.1) mg/dL, respectively

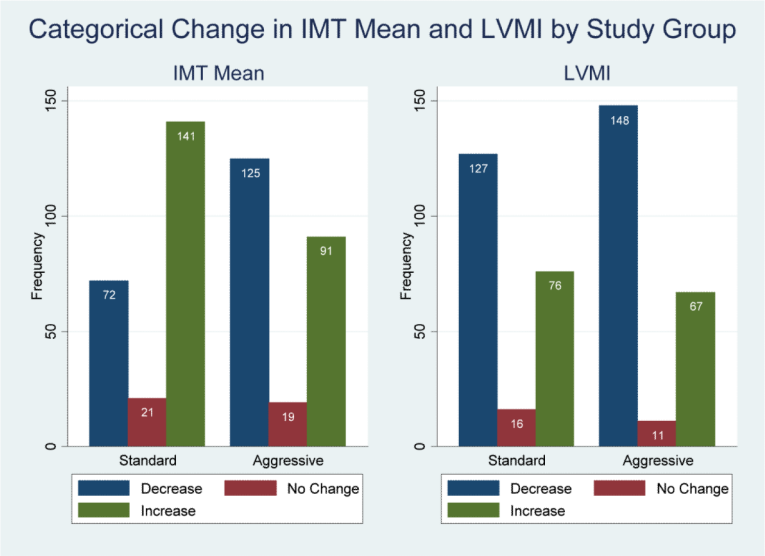

Figure 3. Categorical Changes in IMT Mean (a) and LVMI (b) by Randomization Group

N for IMT data is 469, p-value <.0001. N for LVMI is 445, p-value = .25.

No change category was defined as ± 0.01 mm for IMT or ± 0.5 gm/m$^{2.7}$ for LVMI.

Table 1

Baseline Characteristics of the SANDS Participants (N = 499)

	Aggressive (N = 252)	Standard (N = 247)	P-value
	N (%)	N (%)	
Age (years)	55.3 (9.3)	56.9 (8.9)	.05
Gender, women N, %)	167 (66)	160 (65)	.73
Body mass index (BMI), kg/m^2	33.5 (6.6)	33.2 (6.2)	.57
Waist (cm)	110.2 (15.4)	110.1 (14.0)	.90
Cholesterol (mg/dL)			
Total	184 (33)	185 (33)	.56
LDL	104 (30)	104 (29)	.95
HDL	46 (13)	46 (12)	.90
Non-HDL	138 (32)	140 (32)	.50
Triglycerides (mg/dL)**	158 (149-167)	168 (159-177)	.10*
Systolic blood pressure (mm Hg)	128 (15)	133 (17)	.002
Diastolic blood pressure (mm Hg)	74 (10)	76 (10)	.04
A1c	8.2 (1.8)	7.9 (1.8)	.10
Diabetes Therapy			
Lifestyle	27 (11.0)	34 (13.9)	.33
Oral hypoglycemics	206 (82)	180 (73)	.02
Insulin	70 (28.6)	53 (22.0)	.10
Insulin plus oral	247 (98)	227 (92)	.002
eGFR	91 (24)	88 (23)	.21
Smoking	243	244	
Never	109 (45)	123 (51)	.20
Current	54 (22)	48 (20)	.58
Former	80 (33)	73 (30)	.60
Aspirin use (≥ 80 mg)			
Yes	177 (70)	168 (69)	.74
CRP (mg/dL)**	2.7 (2.3-3.1)	2.8 (2.4-3.3)	.56*
Carotid			
IMT (mm)	.810 (.19)	.797 (.17)	.48*
Arterial area (mm^2)	17.4 (5.0)	17.3 (4.6)	.85
Plaque score (1-8)	1.85 (1.6)	1.83 (1.7)	.89*
Plaque (N, %)	188 (75)	188 (76)	.64
Cardiac			
LV mass	156.7 (38.3)	156.1 (38.3)	.56*
LV mass index (g/m$^{2.7}$)	41.2 (9.5)	40.6 (8.5)	.87*

	Aggressive (N = 252)	Standard (N = 247)	P-value
LV ejection fraction	60.5 (5.7)	59.8 (5.8)	.26*

Abbreviations: eGFR = estimated glomerular filtration rate; IMT = intimal medial thickness; LV = left ventricular.

* Two-sample comparison t-tests were calculated based on log-transformed variables.

** Geometric mean with 95% confidence interval in parenthesis.

Table 2

Differences in Mean Changes from Baseline to 36 Months, Aggressive vs. Standard Group

	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
Weight, kg	90 (20)	90 (19)	91 (21)	91 (21)	1 (12)	1 (10)	.22 (-1.8-2.2)	.83
BMI, kg/m^2	33.5 (6.6)	33.2 (6.2)	33.8 (6.9)	33.6 (7.0)	.3 (4.5)	.4 (3.8)	.11 (-.6-.9)	.77
Waist, cm	110 (15)	110 (14)	110 (16)	110 (15)	.2 (11)	.6 (10)	.4 (-1.5-2.3)	.66
Systolic BP, mm Hg	128 (15)	133 (17)	116.5 (11)	129 (10)	-11 (15)	-3 (15)	8 (5.5-12)	.000
Diastolic BP, mm Hg	74 (10)	76 (10)	67 (8)	73 (8)	-7 (8)	-3 (9)	4 (2.5-5.5)	.000
Total cholesterol, mg/dL	184 (33)	185 (33)	150 (29)	187 (27)	-32(39)	3 (36)	35(28-42)	.000
LDL cholesterol, mg/dL	104 (30)	104 (29)	72 (24)	104 (20)	-31(35)	1(32)	32(26-38)	.000
HDL cholesterol, mg/dL	46 (13)	46 (12)	48 (13)	48 (13)	3(9)	3(11)	.1(-1.9-1.8)	.94
Total cholesterol/HDL-C	4.2 (1.1)	4.2 (1.1)	3.3 (1.0)	4.0 (1.0)	-1(1.0)	-.1(1.1)	.8(.6-1)	.000
Non-HDL cholesterol, mg/dL	138 (32)	140 (32)	102 (29)	138 (26)	-35 (38)	.2(36)	35(28-42)	.000
Triglycerides, mg/dL (geo mean and 95% CI)	158(149-167)	168 (159-177)	137(130-144)	160 (153-168)	-26(78)*	-12(84)*	14(-2.8-29)*	.06*
CRP mg/dL (geo mean and 95% CI)	2.7 (2.3-3.1)	2.8 (2.4-3.3)	2.2 (1.9-2.7)	3.3 (2.8-3.8)	-.7(11)*	.9(9)*	1.6(-.4-3.6)*	.12*
Glucose, mg/dL	159 (69)	156 (72)	169(78)	169(80)	11 (88)	14(97)	4 (-14-22)	.68
A1c	8.2 (1.8)	7.9 (1.8)	8.3 (2.2)	8.2 (2.3)	.1(2.0)	.3(2.4)	.2(-.3-.6)	.45

Note: N for the 36-month lipids variables was 458 and the means were based on the average of 24th, 30th and 36th month observations.

*Based on arithmetic mean.

Table 3

CVD Events and Adverse Events, by Randomization Group

	Aggressive (N = 252)	Standard (N = 247)	P-value
CVD EVENTS			
Primary endpoint	11	8	.51
Other CVD endpoints	1	3	.31
Total CVD	12	11	.87
Non-CVD deaths	2	4	.40
ADVERSE EVENTS			
Participants with AEs*	97 (38.5%)	66 (26.7%)	.005
Related to lipid drugs	46 (18.3%)	35 (14.2%)	.216
Related to BP drugs	67 (26.6%)	38 (15.4%)	.002
Participants with SAEs*	74 (29.4%)	55 (22.3%)	.070
Related to drugs	4	1	

Abbreviations: AE = adverse event; SAE = serious adverse event.

Note: Aggressive group primary events were 2 MI, 4 CABG/PTCA, 2 unstable angina, 1 definite stroke, 1 CHD death; the other CVD was a TIA. Standard group primary events were 2 MI, 4 CABG/PTCA, 1definite stroke, 1 CHD death; other CVD events were 2 possible nonfatal strokes and 1 SVT.

Table 4

Baseline and Follow-up Carotid and Cardiac Measures

	Aggressive	Standard	Group Difference	p-value
	Mean (SD)	**Mean (SD)**		
Carotid				
IMT (mm) Baseline	.810 (.19)	.797 (.17)		
18 mo	.806 (.18)	.801 (.18)		
36 mo	.795 (.18)	.834 (.20)		
Mean Change 18 mo	-.006 (.11)	.008 (.13)	.014	.218*
Mean Change 36 mo	-.017 (.12)X	.041 (.14)+	.058	<.0001*
Arterial Mass (mm^2) Baseline	17.36 (5.02)	17.28 (4.55)		
18 mo	17.04 (4.50)	17.42 (4.42)		
36 mo	17.14 (5.00)	18.24 (4.95)		
Mean Change 18 mo	-.16 (2.52)	.25 (2.98)	.41	.131*
Mean Change 36 mo	-.14 (2.60)	1.14 (2.70)+	1.29	<.0001*
Plaque Score Baseline	1.85 (1.64)	1.83 (1.56)		
18 mo	2.07 (1.64)	2.02 (1.58)		
36 mo	2.40 (1.73)	2.33 (1.71)		
Mean Change 18 mo	.19 (1.10)+	.19 (.89)+	0	1.00
Mean Change 36 mo	.53 (1.22)+	.50 (1.16)+	.03	.79
% Plaque Baseline	74.6	76.4		
18 mo	82.5	80.4		
36 mo	88.9	84.3		
Point Change 18 mo	7.9X	4.0	3.9	
Point Change 36 mo	14.3+	7.9X	6.4	
Cardiac				
LV mass (g) Baseline	156.7 (38.3)	156.1 (38.3)		
18 mo	142.2 (33.6)	147.2 (38.8)		
36 mo	147.7 (36.2)	150.9 (38.5)		
Mean Change 18 mo	-14.7 (23.3)+	-7.1 (26.3)+	7.6	.002
Mean Change 36 mo	-8.1(22.6)+	-4.2 (22.4)+	3.9	.069
LVM index ($g/m^{2.7}$) Baseline	41.2 (9.5)	40.5 (8.5)		
18 mo	37.4 (8.0)	38.7 (9.3)		
36 mo	38.6 (8.6)	39.3 (8.4)		

	Aggressive	Standard	Group Difference	p-value
	Mean (SD)	**Mean (SD)**		
Mean Change 18 mo	-3.9 (6.2)[+]	-1.7 (7.3)[+]	2.1	.002
Mean Change 36 mo	-2.4 (6.2)[+]	-1.3 (6.0)[+]	1.2	.050
EF Baseline	60.5 (5.7)	59.8 (5.8)		
18 mo	59.8 (5.0)	58.7 (6.3)		
36 mo	59.7 (4.9)	59.2 (5.6)		
Mean Change 18 mo	-.9 (5.2)[X]	-1.2 (5.6)[+]	.36	.50
Mean Change 36 mo	-.7 (5.3)	-.7 (5.6)	.04	.93

Abbreviations: EF = ejection fraction; IMT = intimal medial thickness; LV = left ventricular.

[*] P- values from the worst rank analyses for IMT were .691 and < .0001, and for arterial mass were .194 and < .0001 at 18 and 36 months, respectively.

[+] Significant within-group change (p-value < .01).

[X] Significant within-group change (p-value < .05).(**Mihriye's Nov 19 edit**)