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Abstract

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Keywords

American Indians; Atherosclerosis; Blood pressure; Cardiovascular disease; Cardiovascular system – Diseases; Carotid artery intimal medial thickness; Indians of North America; Lipids; Non-insulin-dependent diabetes

Cover Page Footnote

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Key words: lipids, blood pressure, carotid artery intimal medial thickness, cardiovascular disease, American Indians

INTRODUCTION

The aim of the Stop Atherosclerosis in Native Diabetics Study (SANDS) is to determine optimum strategies for cardiovascular disease (CVD) risk reduction in people with type 2 diabetes. SANDS is a randomized, open label, 3-year trial comparing the effects of aggressive low-density lipoprotein-cholesterol (LDL-C) (goal < 70 mg/dL) and blood pressure (BP) (goal < 115/75 mm Hg) reduction with the standard treatment goals of < 100 mg/dL for LDL-C and < 130/85 mm Hg for BP (1). The primary endpoint is a composite of progression of atherosclerosis as measured by common carotid artery intimal medial thickness (IMT) and clinical events. Secondary endpoints include other carotid and cardiac ultrasonographic measures. The group treated to lower targets had an improvement (decrease) in IMT, whereas the standard treatment group had a worsening (increase) in IMT. There was also a greater decrease in left ventricular mass index (LVMI) in the aggressive group. Few CVD events occurred overall, with no intergroup difference (2).

SANDS was initiated because of the increasing incidence of CVD in individuals with diabetes (1, 3 , 4) and the paucity of data on which to make evidence-based recommendations for optimal treatment targets for dyslipidemia and hypertension, established risk factors for CVD in diabetic individuals (5, 6, 7). SANDS is being conducted in American Indians, a population with high rates of diabetes and diabetes-related CVD (5). This is the first large, randomized interventional trial among American Indians with diabetes to assess CVD prevention strategies. The final sample, 499 men and women without baseline CVD, was randomized over a 15-month period and followed for 36 months, ending in July 2007.

This report describes the baseline characteristics of the 499 participants who were randomized into SANDS. To assess the applicability of the trial results to the American Indian population and other populations with diabetes, we compared the baseline characteristics of SANDS participants with three other groups. One was a population-based sample of American Indians as described by Strong Heart Study (SHS) data. The second group was representative of (8) the general U.S. population with diabetes as described in the 1999-2004 National Health and Nutrition Examination Survey (NHANES) data (9). NHANES 1999-2004 was designed to over sample Mexican Americans, non-Hispanic blacks, and children and adolescents. The final comparator group was the Translating Research Into Action for Diabetes (TRIAD) (10) registry, which examined racial/ethnic and socioeconomic variation in diabetes care in managed-care settings throughout the United States. The TRIAD cohort included five ethnic groups, Hispanic, Black/ Non-Hispanic, White/Non-Hispanic, Asian/Pacific Islander, and Other. The proportion of White/Non-Hispanic was more than twice than that of each of the other groups.

METHODS

Details of the study design and methods have been described elsewhere (5). The target population consisted of American Indians in four clinical centers in the United States: Lawton, OK; Phoenix, AZ; Chinle, AZ; and Rapid City, SD. Recruitment was initiated in May 2003. Each center developed community-specific recruitment plans that included informational mailings, community presentations, and referrals from local providers. Informed consent was obtained from all participants before screening, and the study was approved by the institutional review boards (IRBs) of all participating institutions and the Indian Health Service and by all participating tribal communities. At least one screening visit and a separate randomization visit were required to assess and confirm eligibility, complete randomization, and collect baseline data. Sonogram eligibility, defined as having adequate images for measurement of intimal-medial thickness, was required prior to randomization.

Eligibility criteria included age ≥ 40 years, type 2 diabetes documented by medical record, LDL-C > 100 mg/dL, and systolic BP > 130/85 mm Hg. Because lipid and BP measurements are variable, up to four screening visits within a 3-month period were allowed to confirm eligibility. Those taking BP or lipid lowering medications with elevations in systolic BP or LDL-C documented in the medical record were admitted at the discretion of the field physician if it was felt that the participant could safely adhere to the study algorithms. Major exclusions included medical conditions that would preclude participation in a 3-year trial or a history of serious adverse effects from the major study drugs. Participants with prevalent CVD were randomized during the early months of recruitment. After release of the National Cholesterol Education Program - Adult Treatment Panel III (NCEP-ATP III) (11) guidelines, which recommended an LDL-C treatment goal of 70 mg/dL for patients with CVD and other risk factors, such as diabetes, the steering committee determined, and the Data and Safety Monitoring Board (DSMB) concurred, that all participants with clinical CVD would be treated to an LDL-C goal of 70 mg/dL and removed from the primary analysis. Randomization concluded in September 2004 with 548 participants, 499 of whom had no prevalent CVD.

Physical Measures

Anthropometric measurements were performed using standardized methods, with the participant fasting and having an empty bladder, and included height, waist circumference measured to the nearest quarter inch and weight measured to the nearest tenth pound. Sitting BP was measured on the right brachial artery, and the mean of the second and third measurements was used. Behavioral risk factors were assessed using standardized interviewer-administered questionnaires, and medical history and medication assessment were performed by both interview and chart review. Clinic staff were certified in all measurements and interviews, and quality control was maintained through periodic monitoring of duplicate measures and data entry.

Laboratory Measures

Blood and urine samples were collected after a 12-hr overnight fast, and plasma and serum samples were shipped to the core lab (Penn Medical Lab). All samples were shipped and stored at -70° C. Baseline measurements included fasting glucose, complete metabolic profile, A1c, C-reactive protein (CRP), lipid profile, and urine for creatinine, albumin, and sodium. Details of assay standardization and quality control have been described elsewhere (5).

Carotid Ultrasound and Echocardiographic Measures

Carotid ultrasound and echocardiographic studies were obtained at baseline before randomization. All ultrasound studies were performed using standardized protocols developed and refined by the Ultrasound Reading Center at Weill Medical College of Cornell University in New York (12). Skilled physician-readers blinded to participant characteristics interpreted all studies. Extensive B-mode imaging from multiple angles was performed to determine the presence and location of plaque, defined as the presence of focal protrusion at least 50% greater than the surrounding wall thickness (13). Pulsed Doppler sampling of the common carotid artery (CCA), carotid bifurcation, and internal and external carotid arteries was performed to quantify the presence of significant obstruction (14). The procedure was repeated on the contralateral artery. Plaque severity was graded as obstructive (> 50% occlusion based on peak Doppler systolic velocity) or non-obstructive. A plaque score (0-8) was determined based on the number of segments of each carotid artery containing plaque (15). IMT of the far wall of the distal left and right common carotid arteries 1-2 cm proximal to the carotid bifurcation was measured at end diastole using a semi-automated system, which averages 100 individual measurements over a 1-cm length of the vessel. Right and left IMTs were averaged. Vascular mass of the arteries was calculated as cross-sectional area, using end-diastolic diameter and wall thickness.

Echocardiographic performance and interpretation adhered to published methods (16, 17). Briefly, participants were examined in a partial left decubitus position, using phased-array echocardiographs. Attention was paid to correct orientation of imaging planes. The entire study was recorded on videotape and sent to the Reading Center for interpretation. Left ventricular end-diastolic and end-systolic wall thicknesses and diameters were measured from parasternal images using American Society of Echocardiography recommendations (18 ,19). Derived variables from these linear measurements included assessment of left ventricular structure (mass and relative wall thickness) and function (fractional shortening and ejection fraction [EF]). The location and severity of segmental wall motion abnormalities were noted.

Data Management and Analysis

Data collected in the field center were entered by staff certified in using a web-based system developed by the Data Coordinating Center (DCC).

Laboratory and ultrasound data were transmitted electronically to the DCC. The central database was maintained using standardized methods for ensuring security and verifying accuracy and consistency.

This paper presents descriptive statistics for all variables of interest in the form of means and standard deviations for continuous variables and number of observations and percentages for categorical variables. In addition, two-sample comparisons are provided to examine if there are significant differences between the conventional and aggressive groups. Differences in the means are tested using two-sample t-tests for means, and differences in the proportions are tested using two-sample tests of proportions. Positively skewed variables such as carotid measures, CRP, and triglyceride levels are log-transformed prior to the application of the two-sample tests, and geometric means or medians and inter-quartile ranges are presented for these variables.

RESULTS

Demographic and Physical Characteristics

Of the 1097 men and women who underwent screening, 548 were randomized into the trial. Forty-nine with documented CVD at baseline were excluded based on the recommendation of the DSMB, leaving 499 participants (Table 1). Mean age was 56 years; 66% were women. A large proportion (66%) was obese, with an average BMI of 33 kg/m^2 in both men and women (Table 1). Average duration of diabetes was 10 years. No significant differences were found in baseline characteristics between the treatment groups, other than slightly higher systolic BP in the conventional treatment group (133 vs. 128 mm Hg, $p < .002$) and age (56.9 years vs. 55.3 years, $p = 0.05$). No significant differences were found between the groups in baseline laboratory measures (Table 2). Serum LDL-C averaged 104 mg/dL in both groups. A1c averaged 8.0 %. Less than 1% had macroalbuminuria, defined as urine albumin/creatinine > 300 mg/g.

Baseline Medications

Baseline medication usage is listed in Table 3. Seventy-three percent of the cohort took anti-hypertensive medications at baseline; angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB) were used by 64%, with no other single agent used by more than 21%. Only 38% of participants were taking a lipid-lowering agent at baseline. Statins were the most commonly used lipid-lowering agents (34%), while fibrates were used by 5%. Ezetimibe was not readily available at the time of randomization. Sixteen percent of participants took no anti-diabetic agent at baseline. Most participants took oral medications only for diabetes (61%), with 6% using insulin only and 17% using both.

Cardiovascular Measures

Carotid IMT and mass and presence and extent of carotid atherosclerosis (Table 4) were similar between the two groups. Echocardiographic measures of LV structure and function were also similar between the groups.

Table 1. Baseline Characteristics of Participants Without CVD at Baseline

Analysis Variables	Conventional	Aggressive	P-value*
Participants (N)	247	252	
Female	160 (64.8)	167 (66.3)	.73
Age at randomization (yrs)	56.9 (8.9)	55.3 (9.3)	.05
SBP (mm Hg)	133 (16.6)	128 (14.9)	.002
DBP (mm Hg)	76 (10.4)	74.4 (10.3)	.04
Duration of hypertension (yrs)	10.4 (8.5)	9.4 (8.2)	.26
Duration of diabetes (yrs)	9.6 (8.1)	9.8 (7.6)	.82
BMI (kg/m^2) Men	32.8 (5.5)	33.5 (6.4)	.44
BMI (kg/m^2) Women	33.4 (6.5)	33.5 (6.7)	.88
BMI (kg/m^2) < 30	75 (30.5)	80 (31.8)	.74
BMI (kg/m^2) > 30	172 (69.5)	172 (68.2)	.74
Total daily calories (Kcal)	2098 (1547)	1880 (1190)	.15
Waist circumference (cm) Men	111.4 (13.4)	113.1 (16.1)	.45
Waist circumference (cm) Women	109.3 (14.3)	108.8 (14.9)	.74
Smoking status (N)	244	243	
Never	123 (51)	109 (45)	.20
Current	48 (20)	54 (22)	.58
Former	73 (30)	80 (33)	.60

SBP = systolic blood pressure; DBP = diastolic blood pressure. Percentages may not add up to 100 because of rounding. Data presented in this table are means with standard deviations in parentheses for continuous variables and N and percentages for categorical variables.

Table 2. Baseline Laboratory Values by Treatment Group			
Analysis Variables	**Conventional**	**Aggressive**	**P-value***
Fasting glucose (mg/dL) (SD)	156.5 (71.1)	159.3 (69.3)	.66
CRP* (95% CI)	2.84 (2.43-3.31)	2.66 (2.27-3.11)	.56
Serum creatinine (mg/dL) (SD)	0.85 (0.2)	0.83 (0.2)	.34
Cholesterol (mg/dL) (SD)			
Total	185 (33)	184 (33)	.56
LDL	104 (29)	104 (30)	.95
HDL	46 (12)	46 (13)	.90
Non-HDL	140 (32)	138 (32)	0.50
Triglycerides (mg/dL)* (95% CI)	168 (159-177)	158 (149-167)	.10
Microalbumin/creatinine ratio (urine)			
(N) % normal (< 30 mg/g)	(139) 87	(148) 94	.09
(N) % with micro-albuminuria (30-300 mg/g)	(19) 12	(14) 5	
Estimated GFR (MDRD)			
Mean (SD)	88.2 (23.3)	90.9 (24.1)	.21
(N) % < 60 ml/min	(18) 11.1	(3) 9.3	.51
Urinary sodium (mmol/L) (SD)	99.4 (50.6)	98.3 (48.2)	.84

CRP = C-reactive protein; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease. *Geometric mean with 95% confidence interval in parenthesis. Two-sample comparison t-tests are calculated based on log-transformed variables.

Comparison with Population-Based Data

Compared with the population-based cohort of American Indians in the SHS (7), SANDS participants had similar values for lipids, BP, and CRP, as well as degree of obesity, smoking rates, and renal function as estimated by glomerular filtration rate (GFR) (Table 5). The SANDS cohort was slightly younger, with a shorter duration of diabetes, but average A1c was similar. Compared with men and women with diabetes in NHANES (9), SANDS participants were slightly younger with slightly shorter diabetes duration and slightly higher A1cs. BPs in the two groups were similar. LDL-C, high density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were lower among the SANDS participants, but smoking rates were similar. Compared with participants in TRIAD, SANDS participants were somewhat younger, more likely to be female, and had somewhat lower mean systolic BP and LDL-C.

Table 3. Baseline Medication Use			
	Conventional (%)	**Aggressive (%)**	**P-value***
N	**242**	**252**	
Anti-hypertensive			
ACE inhibitor/ARB	155 (63)	163 (65)	.65
Thiazide diuretic	29 (12)	20 (8)	.15
Beta blocker	24 (10)	19 (8)	.38
Calcium blocker	48 (20)	43 (17)	.48
Other anti HTN rx	56 (23)	50 (20)	.43
Any	185 (75)	179 (71)	.28
Lipid lowering			
Statin	90 (37)	80 (32)	.26
Fibrate	13 (5)	12 (5)	.48
Ezetimibe	2 (0.8)	1 (0.4)	.49
Any	101 (41)	90 (36)	.23
Diabetes			
Insulin only	12 (5)	18 (7)	.28
Oral agent only	145 (59)	158 (63)	.62
Both (oral and insulin)	38 (15)	48 (19)	.28
Lifestyle only	52 (21)	28 (11)	.003
Aspirin	89 (36)	77 (31)	.18

Entries are numbers of observations; percentages are in parentheses.

Table 4. Echocardiographic and Carotid Measures			
	Conventional	**Aggressive**	**P-value**
CCA IMT (mm) *	.78 (.68-.87)	.78(.69-.90)	.48**
CCA mass (mm^2)*	16.7 (14.2-19.4)	16.6(13.9-19.5)	.99**
Plaque (%) ***	76	75	.64
Plaque score	2(1-3)	2 (0-3)	.89**
LV ejection fraction (%)	59.8 (5.8)	60.5 (5.7)	.19
LV mass (g)	156.1 (38.3)	156.7 (38.3)	.86
LV mass index ($g/m^{2.7}$)	40.6 (8.5)	41.2 (9.5)	.43
% LVH men, > $49.2/m^{2.7}$ ***	14	22	.15
% LVH women , > $46.7\ g/m^{2.7}$ ***	23	30	.14

*Medians and inter-quartile ranges (observations between 25th and 75th percentile) are provided for positively skewed variables. **p-values represent the results of two-sample means tests applied to the log-transformed continuous variables. The descriptive statistics for these continuous variables are based on actual values. *** indicates categorical variables. The entries in the means columns for these variables are percentages within each group. P-values are based on two-sample tests of proportions.

Table 5. Comparison of SANDS Cohort with Other Diabetic Cohorts				
	SANDS	**SHS (with diabetes)**	**NHANES* (1999-2004)**	**TRIAD****
N	**499**	**1733**	**1549**	**3707**
Male (%)	172 (34)	590 (34)	759 (49)	1838 (50)
Female (%)	327 (66)	1143 (66)	790 (51)	1869 (50)
Age (yrs) (SD)	56 (9.0)	63 (7)	59 (0.5)	62 (13)
BMI (kg/m^2)				
Men (SD)	33.1 (6.0)	31.4		
Women (SD)	33.5 (6.6)	33.3		
Men and women	33.3	32.7	31.8	31.5
HTN duration (yrs)	9.9 (8.3)	8.0		
SBP (mmHg)	130.4 (15.9)	132 (20.2)	132 (0.8)	136 (19.0)
DBP (mmHg)	75.3 (10.4)	75 (29.7)	69 (0.72)	76 (11.0)
Diabetes duration (yrs)	9.7 (7.8)	15.7 (12.2)	12.0 (0.5)	
A1c (%) (SD)	8.0 (1.8)	8.1 (1.9)	7.5 (0.2)	7.8 (1.7)
Total cholesterol (mg/dL) (SD)	184	182 (39)	205(2)	196 (43)
LDL-C (mg/dL) (SD)	104	110 (32)	115 (2)	110 (33)
HDL-C (mg/dL) (SD)	46	40 (12)	47 (1)	46 (13)
Non-HDL-C (mg/dL) (SD)	139 (32)	142 (39)	196 (9)	151 (42)
TG (mg/dL) (SD)	163 (geo mean)	162 (122)		220 (187)
eGFR % < 60 ml/min (SD)	89.6 (23.7) 10%	84.22 (28.6) 16%	NA	75.8 (25.2)
Smoking (% ever)	52.3	58.8	53.2	49
Mean IMT (mm)	0.80 ± 0.18	0.75 ± 0.16		
Mean CCA mass (mm^2)	17.3 ± 4.8	16.5 ± 4.5		
Plaque (%)	76	67		
Plaque score (n)	1.8 ± 1.6	1.7 ± 1.7		
LVMI (g/m$^{2.7}$)	40.9 (9.0)	40.4 (10.0)		

*The NHANES cohort excluded people who were pregnant or on dialysis. **The TRIAD cohort was white, non-Hispanic. HTN = hypertension; SBP = systolic blood pressure; DBP = diastolic blood pressure; LDL-C = low-density lipoprotein-cholesterol; HDL-C = high-density lipoprotein-cholesterol; TG = triglycerides; eGFR = estimated glomerular filtration rate; NA = not applicable.

DISCUSSION

Baseline BP levels in the SANDS participants were within the normal range, probably due to the use of antihypertension medications by over 70%. Of note, average BP levels in American Indians are lower than those in other U.S. populations and, even in those with diabetes, stage III or IV hypertension is rare (20). Nevertheless, BP is a strong predictor of CVD events in American Indians (20), even in those with pre-hypertension (21). Thus, it was postulated that risk would be considerably reduced with the intensive intervention.

Lipid levels are also low in this cohort, with a mean LDL-C of 104 mg/dL. Only 38% were taking statins or other hypolipidemic medication at baseline. LDL-C levels are lower among American Indians than in the general U.S. population and are slightly lower in diabetic than in non-diabetic individuals (22). Despite a relatively low mean level, LDL-C is the strongest lipid predictor of CVD in American Indians with diabetes; a 10-mg/dL increase in LDL-C is associated with a 12% increase in CVD risk (23). These data indicate that LDL-C has a particularly strong impact on CVD in this population, suggesting that the lower therapeutic target will be effective.

Carotid artery IMT is a widely accepted surrogate marker for atherosclerosis and is strongly associated with major CVD risk factors (24) and prevalent and incident CVD (25). Diabetes is associated with increased IMT (26,27). In other diabetic populations, carotid IMT predicted CVD and correlated with CVD risk factors, such as diabetes (28). Plaque and plaque score are independent predictors of incident CVD events in American Indians without pre-existing CVD. All four measures of sub-clinical carotid atherosclerosis in SANDS were slightly higher compared with the diabetic SHS participants studied a mean of 6 years earlier (Table 5), suggesting that sub-clinical disease among American Indians may be increasing, despite lower mean LDL-C and BP levels. Thus, differences in these surrogate measures in the aggressive and conventional therapy groups at the conclusion of the study may predict differences in the occurrence of CVD events in the two groups

Left ventricular hypertrophy (LVH) is a strong, independent risk indicator for CVD events. Reversal of LVH has prognostic benefit, independent of therapy and BP (28). Diabetes has been shown to be independently associated with greater absolute and relative LV wall thicknesses (but not larger chamber size) and with higher absolute and indexed LV mass independent of all confounders (17). Absolute LV mass, or LV mass indexed for measures of body size, was virtually identical in SANDS (41.0 gm/$m^{2.7}$, SD 9.2) and SHS participants with diabetes (40.4 gm/$m^{2.7}$, SD 10.0) (29). Echocardiographic structural and functional abnormalities are highly prevalent among American Indians with diabetes and appear to be predictors of clinical CVD events. In a regression analysis that considered other predictors of mortality, cardiovascular death in diabetic SHS participants was most strongly predicted by higher LV mass/height$^{2.7}$ ($p = 0.0001$) (30). When

analyses were restricted to participants with diabetes, all-cause mortality, cardiovascular death, and nonfatal cardiovascular events were all more common in those with LV hypertrophy (28). Thus, SANDS will have the added benefit of determining whether several abnormalities in cardiac structure and function also improve with risk-factor modification, an issue not previously addressed in any diabetes trials.

The SANDS cohort consisted of trial volunteers and thus is subject to the healthy volunteer bias in clinical trial participants. Additionally, individuals with CVD and renal failure were excluded from SANDS but not SHS. Thus, it was important to determine to what extent the SANDS cohort is representative of other diabetic groups. The baseline characteristics of the SANDS cohort are similar to those of the American Indian diabetic population from the Strong Heart Study and also resemble diabetic men and women of other ethnic groups. Although blood pressure and LDL-C in the SANDS cohort are not high, the carotid ultrasound and echocardiographic findings show much evidence of preclinical disease.

Traditional goals for blood pressure (< 130/80 mmHg) and LDL-C (< 100 mg/dL) for high-risk patients may be inadequate to reduce CVD risk in American Indians and other diabetic populations at high risk for CVD. The data obtained in this study have provided evidence to define therapeutic prevention strategies that can reverse the alarming increase in CVD among American Indians with diabetes and will guide treatment strategies for diabetic individuals from all U.S. ethnic groups and in other countries where diabetes rates are rising.

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