Examination of lower targets for low-density lipoprotein cholesterol and blood pressure in diabetes—the Stop Atherosclerosis in Native Diabetics Study (SANDS)

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Diabetes incidence is increasing rapidly in the United States. Diabetes increases the risk for cardiovascular disease, the major cause of death in diabetic individuals. The conventional cardiovascular risk factors of hyperlipidemia and hypertension worsen diabetic vascular disease. Treatment targets for low-density lipoprotein cholesterol (LDL-C) and blood pressure in diabetic individuals are being debated. The SANDS is a randomized, open-label, 3-year trial to examine the effects of aggressive LDL-C (goal <70 mg/dL) and blood pressure (BP) (goal <115/75 mm Hg) reduction versus the standard goals of <100 mg/dL for LDL-C and <130/85 mm Hg for BP. Five hundred forty-nine American-Indian men and women 40 years old with type 2 diabetes were randomized to 1 of 2 groups. Lipids and BP are managed using Food and Drug Administration-approved medications in an algorithmic approach. The presence and progression of atherosclerosis are evaluated by carotid ultrasonography; echocardiography assesses cardiac function. The primary end point is the composite outcome of change in carotid artery intimal medial thickness and fatal/nonfatal cardiovascular events. These outcomes are combined by using a ranked analysis for carotid thickness and assigning a “worst rank” for a cardiovascular event. Secondary end points include carotid plaque score, left ventricular geometry and function, serum C-reactive protein, and safety measures. Unique aspects of the study design and analysis plan involve the use of a composite outcome and changes during the trial of LDL-C treatment goals for participants with baseline or incident cardiovascular disease in the conventional group because of changes in the standard of care. Study results will further understanding of the effects of aggressive risk factor reduction on atherosclerosis burden and cardiac function in diabetic individuals in US populations and will help determine optimal LDL-C and BP treatment goals for diabetic patients. (Am Heart J 2006;152:867-75.)

Diabetes and CVD

The prevalence of diabetes in the United States is rising rapidly. Individuals with diabetes are at higher risk for developing cardiovascular disease (CVD). Cardiovascular disease is the cause of death for most individuals with diabetes. Increased diabetes-associated CVD is due in part to the higher prevalence of traditional risk factors, such as dyslipidemia and hypertension in diabetic individuals.

Controversy exists concerning the optimum levels of low-density lipoprotein cholesterol (LDL-C) and blood pressure (BP) to minimize risks for CVD in diabetes. The goal for LDL-C, as recommended by the National Cholesterol Education Program-Adult Treatment Panel III, is <100 mg/dL, and goals for BP control, as recommended by the Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI), are 130/85 mm Hg in diabetes. However, recent reports of secondary
prevention studies in high-risk patients showed that LDL-C lowering to below current targets improved outcomes.9 Two studies using statin therapy in high-risk diabetic patients also have suggested that reduction of CVD events can be achieved in diabetic individuals who are at current LDL goals.10,11 Furthermore, recent trials of antihypertensive agents also have suggested that achieving BP targets below 130/85 mm Hg might be beneficial.12,13 Because all these studies were designed to evaluate specific pharmacologic agents and their dose ranges, clinically feasible interventions are necessary to specifically evaluate targets for LDL-C and BP control. Because of their high prevalence of diabetes and diabetes-associated CVD, American Indians have a particular need to address diabetic CVD. Although American Indians in the past had low CVD rates,14 CVD today is their leading cause of death, and CVD largely occurs in diabetic individuals.15 Low-density lipoprotein cholesterol is the strongest lipid predictor of CVD in this population.16 Hypertension rates are also high in diabetic individuals in this population; hypertension also is a strong risk factor for CVD events, both directly and because of its enhancement of albuminuria, another strong predictor of CVD.15,16

Previous studies have shown that carotid artery intimal medial thickness (IMT) and plaque are reasonable surrogates for coronary artery disease and predict future events in many populations,17 including American Indians.18 In addition, echocardiographic measures of left ventricular structure and function are potent predictors of future CVD in this population.19 The SANDS trial aims to examine lower targets for LDL-C and BP in diabetic individuals using a combination of subclinical disease and clinical events. This article presents the study design and methods.

Methods

Target population

The target population consisted of American Indians located in 4 areas, including southwestern Oklahoma; Phoenix, AZ; southwestern and northeastern Arizona; and South Dakota. Recruitment was initiated in May 2003 with a goal of 498 subjects. In March 2004, the Steering Committee voted, with the approval of the Data and Safety Monitoring Board (DSMB), to overrecruit by about 10% to compensate for the possible need for more aggressive treatment for participants with baseline CVD, as suggested by an update to the National Cholesterol Education Program–Adult Treatment Panel III (NCEP-ATP III) treatment guidelines.20 Randomization concluded in September 2004 with 549 participants.

Eligibility criteria were intended to identify American Indians (defined as eligible for Indian Health Service [IHS] care) ≥40 years old with documented type 2 diabetes, defined using 1997 American Diabetes Association (ADA) criteria21 and/or previously diagnosed by former ADA or World Health Organization criteria,22 and who would likely be compliant with the protocol. To assure that the primary outcome would be measurable, a qualifying carotid ultrasound performed by study investigators was required no earlier than 3 months before randomization. Inclusion and exclusion criteria are listed in Table I. All participants provided informed consent. Approvals were obtained from the institutional review boards of all participating institutions and Indian communities. The protocol was approved by a National Heart, Lung, and Blood Institute (NHBLI)–appointed independent DSMB. All centers employed community members when possible to carry out the study protocol; they also served as translators in the case of language barriers.

<table>
<thead>
<tr>
<th>Table I. Eligibility criteria</th>
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<tr>
<td><strong>Inclusion criteria</strong></td>
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<tr>
<td>Native American (IHS-eligible or Tribal Health Care–eligible)</td>
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<tr>
<td>≥40 years old</td>
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<tr>
<td>Type 2 diabetes, per ADA criteria</td>
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<td>LDL-C ≥100 mg/dL within previous 12 m</td>
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<tr>
<td>SBP &gt;130 mm Hg within previous 12 m</td>
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<tr>
<td><strong>Exclusion criteria</strong></td>
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<tr>
<td>New York Heart Association Class III-IV congestive heart failure</td>
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<tr>
<td>SBP &gt;180 mm Hg or patients with known reversible causes of hypertension</td>
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<tr>
<td>History of angioedema</td>
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<td>Mental incapacity and/or cognitive impairment that might preclude adequate understanding of, or cooperation with, the study protocol</td>
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<tr>
<td>Serum hepatic transaminase levels ≥2 × the upper limit of normal</td>
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<tr>
<td>Participation in any clinical trial of any investigational medication within previous 3 m</td>
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<tr>
<td>Renal insufficiency as indicated by serum creatinine ≥2.0 for women and ≥2.4 for men</td>
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<tr>
<td>Diagnosis of primary hyperlipidemia in medical record (homozygous FH or types I, IV, or V)</td>
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<tr>
<td>Secondary hypercholesterolemia due to hypothyroidism or nephrotic syndrome</td>
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<td>Malignancy or history of any cancer except skin cancer within the past 5 y</td>
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<td>Pregnancy or lactation</td>
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<td>Unable to obtain quantifiable carotid measure during screening examination</td>
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<tr>
<td>Concomitant long-term use of the following drugs: cyclosporin, macrolide antibiotics, and azole antifungals</td>
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<tr>
<td>Orthostatic hypotension assessed at baseline</td>
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<tr>
<td>Triglycerides ≥350 mg/dL</td>
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<tr>
<td>Arm circumference ≥42 cm</td>
</tr>
<tr>
<td>Any medical condition that might interfere with study participation or evaluation of results</td>
</tr>
<tr>
<td>Previous or ongoing issues that might affect the conduct of SANDS</td>
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</table>

FH, Familial hyperlipidemia
Subcommittees within the steering committee include quality control, morbidity and mortality, and publications and presentations. A community relations/ethics committee was formed to ensure proper communication with, and sensitivity to, the American Indian communities and to advise on community issues.

The DSMB was appointed by the NHLBI and reports to them; its charge is to recommend whether the study should be continued, evaluate the study’s safety, and recommend other changes as necessary.

The BP and lipid treatment protocols are overseen by study physicians who are specialists in these areas. These specialists facilitate training of study coordinators and research personnel and have regularly scheduled phone calls with the field centers to discuss treatment issues.

Study design

SANDS is a 2-arm, open label, multicenter, randomized trial comparing aggressive to standard treatment of elevated BP and LDL-C (see Table II for the schedule of visits and procedures performed at each visit). After screening, randomization, and 1-month visits, participants will be seen every 3 months during the follow-up period. Carotid ultrasonography and echocardiography will be repeated at 18 and 36 months. The primary end point is carotid IMT, with fatal and nonfatal CVD events included, using a ranked analysis (see below). Secondary end points will include carotid plaque score, echocardiographic parameters of left ventricular geometry and function, and C-reactive protein (CRP).

Screening

Each of the 4 centers was responsible for designing and implementing its own plan to identify and randomize participants. At least 1 screening visit and a separate randomization visit were required to assess and confirm eligibility, collect baseline data, and complete randomization. Carotid sonography tapes were sent to the Ultrasound Reading Center (Cornell University) to confirm sonogram eligibility, defined as adequate images, before randomization. Participants with fasting triglyceride levels >400 mg/dL were referred to their primary care provider for further management and asked to return so that their lipid profile could be reevaluated. Average systolic BP was measured sitting and standing to detect orthostatic hypotension.

A potential participant had to have LDL-C >100 mg/dL and systolic BP >130/85 mm Hg. Because lipid and BP measurements are variable, a participant could undergo 4 screening visits within a 3-month period to confirm eligibility, defined as absence of all exclusion criteria (Table I) and having LDL-C and BP values above entry criteria during at least 1 visit. Participants taking cholesterol or BP medications at screening were admitted if the field physician felt the participant could...
be managed to meet target goals of either randomization group using the study algorithm.

At either the final screening or baseline visit, a physical exam, ankle/brachial index, electrocardiogram, echocardiogram, and monofilament sensory test were performed, and demographic data, health history, and medication use were recorded. Food frequency, physical activity, and quality of life questionnaires were administered, and fasting blood and urine samples were collected and sent to the biochemistry core laboratory (Penn Medical Lab). Baseline assays included fasting glucose, hemoglobin A1c, CRP, lipid profile, and urine for creatinine, albumin, and sodium.

Randomization
Participants were randomly assigned to standard treatment targets (LDL-C <100 mg/dL and systolic BP <130/85 mm Hg) or aggressive targets (LDL-C <70 mg/dL and systolic BP <115/75 mm Hg). Participants were randomized using the urn method, stratified by site and sex.

Interventions and follow-up
All participants receive nutrition counseling and physical activity recommendations consistent with IHS guidelines for people with diabetes, hypertension, and dyslipidemia, and they are referred regularly to their IHS provider for management of diabetes and other health problems (Table II). The current IHS guideline for glucose control is hemoglobin A1c <7.0 mg/dL. Hemoglobin A1c and fasting glucose values collected by IHS are recorded in the study record, and all participants are
encouraged to attend diabetes clinic regularly and adhere to diabetes care regimens. The hypertension algorithm was developed based on JNC VI recommendations\(^8\) and the lipid algorithm on the NCEP-ATP III recommendations.\(^7\) The goal was to standardize the approach and provide medications not only known to be effective in lowering BP and cholesterol but also reported as helpful in reducing cardiovascular morbidity and mortality in patients with type 2 diabetes. The algorithms were designed to be used as general guidelines, and stepwise progression could be altered based on the needs and disease processes of each participant. Separate papers will be written on the safety and efficacy of the 2 algorithms.

Lipid lowering

An LDL-C <100 mg/dL is the goal for the standard group. The original LDL-C goal for the aggressive group was <75 mg/dL. However, in November 2004, because of the NCEP advisory\(^20\) and with the concurrence of the DSMB, the steering committee voted to lower the LDL-C target for the aggressive group to <70 mg/dL and the non-HDL cholesterol target for the aggressive group to <100 mg/dL. Based on this same advisory,\(^20\) the LDL-C goal for those individuals in the standard group with baseline CVD (defined by a history of prior documented myocardial infarction, stroke, coronary or peripheral arterial revascularization, or significant stenosis) was changed to <70 mg/dL. Because this change necessitated removing individuals with baseline CVD from the standard treatment group for LDL, all participants with baseline CVD were excluded from the primary analysis; they will be included in some secondary analyses. Figure 1 shows the algorithms for achieving lipid goals.

**Table III. Algorithm for hypertension management**

<table>
<thead>
<tr>
<th>Step</th>
<th>Medication</th>
<th>Minimal starting dose</th>
<th>Usual starting dose</th>
<th>Titration sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Lisinopril or losartan</td>
<td>10 mg QD/50 mg QD</td>
<td>10 mg QD/50 mg QD</td>
<td>10-20-40 mg QD/50 mg QD</td>
</tr>
<tr>
<td>2. Add</td>
<td>HCTZ or losartan/HCTZ</td>
<td>12.5 mg QD/50/12.5 mg QD</td>
<td>12.5 mg QD/50/12.5 mg QD</td>
<td>12.5-25 mg QD/100/25 mg QD</td>
</tr>
<tr>
<td>3. Add</td>
<td>Atenolol or nifedipine SR</td>
<td>25 mg QD/30 mg QD</td>
<td>50 mg QD/30 mg QD</td>
<td>25-50-100 mg QD/30-60-90 mg QD</td>
</tr>
<tr>
<td>4. Add alternate no. 3 agent at specified doses: if on atenolol, can add nifedipine and vice versa. Do not use atenolol and diltiazem combination.</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>5. Add</td>
<td>Doxazosin</td>
<td>1 mg QD</td>
<td>1 mg QD</td>
<td>1-2-3-4-5-6-7-8 mg QD</td>
</tr>
<tr>
<td>6. Add</td>
<td>Hydralazine, minoxidil, or reserpine</td>
<td>10 mg BID/2.5 mg QD/0.1 mg QD</td>
<td>25 mg BID/2.5 mg QD/0.1 mg QD</td>
<td>10-25-50-100 mg BID/2.5-5-10-20 mg BID/0.1-0.2 mg QD</td>
</tr>
</tbody>
</table>

HCTZ, Hydrochlorothiazide; SR, slow release.

**Table IV. Adverse events possibly related to treatment**

<table>
<thead>
<tr>
<th>Symptomatic orthostatic hypotension</th>
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<tbody>
<tr>
<td>Hyperkalemia from ACE inhibitors/ARBs</td>
</tr>
<tr>
<td>Fatigue from any SANDS medication</td>
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<tr>
<td>Allergy or severe dermatitis from any SANDS medication</td>
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<tr>
<td>Nightmares from (\beta)-blockers</td>
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<tr>
<td>Angioedema, neutropenia, or necrotizing vasculitis from ACE inhibitors</td>
</tr>
<tr>
<td>Clinical hepatitis from dihydropyridine calcium-channel blockers</td>
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<tr>
<td>Diffuse muscle pain or weakness from statins/fibric acid</td>
</tr>
<tr>
<td>ALT levels exceeding 3 times the upper limit of normal from statins, fenofibrate, or ezetimibe</td>
</tr>
<tr>
<td>Medication changes caused by adverse effects</td>
</tr>
<tr>
<td>Myositis</td>
</tr>
<tr>
<td>Elevated ALT</td>
</tr>
<tr>
<td>Elevated CK</td>
</tr>
</tbody>
</table>

ACE, Angiotensin-converting enzyme; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; CK, creatine kinase.

the standard group and <115 mm Hg in the aggressive group; secondary goals are diastolic BPs of <85 mm Hg in the standard group and <75 mm Hg in the aggressive group.

Follow-up visits and monitoring of side effects

All SANDS participants were scheduled for a 1-month visit and follow-up visits every 3 months from the randomization date for 36 months to adjust medications to meet treatment goals, ensure participant safety, assess side effects, document clinical events, and encourage compliance with study treatments. Interim visits are scheduled as necessary to adjust medication or assess side effects.

All medication prescriptions are filled through local IHS pharmacies to avoid drug interactions and duplication of medications. All medications are provided to the clinic pharmacy by the TCC.

Study-defined adverse events (AEs) that may be related to treatment are listed in Table IV AEs (Table IV), and
serious AEs are reviewed by the morbidity and mortality committee and the DSMB. All AE and serious AE reports are blinded to treatment arm for the morbidity and mortality committee but unblinded for the DSMB.

**Training/equipment**

Examinations and follow-up are performed by qualified personnel overseen by field physicians and the site coordinator. Field staff are certified in performance of standard clinical measurements and administration of questionnaires. To ensure proper measurements and completion of survey forms, the site coordinator observes the field personnel quarterly for proficiency.

The Cholestech LDX device (Cholestech Corporation, Hayward, CA) is used to monitor lipids from fingertip blood. This device was chosen for its ability to provide point of service lipid measurements. A standardized procedure is used to obtain fingertip capillary blood. Instruction in operation of the Cholestech LDX analyzer and performance of quality assurance procedures is provided to the research coordinator through the Cholestech LDX User Manual and in-service education provided by the TCC and Cholestech.

The Omron 907 (OMRON Healthcare, Inc, Kyoto, Japan) device is used to measure BP. This device was chosen for its accuracy in obtaining BP readings in the low-to-moderate range.

**Carotid ultrasound and echocardiographic studies**

All ultrasound studies are performed using standardized protocols developed and refined by the Ultrasound Reading Center, Weill Cornell Medical College, NY. Before study initiation, field ultrasonographers were trained at the reading center. Readers are blinded to all participant characteristics. Clinical alerts, such as high-grade carotid or aortic stenosis, are identified at the field sites and immediately transmitted for review at the reading center. Reports are sent to the local medical provider for follow-up, as necessary.

**Carotid ultrasound performance and interpretation protocol**

Extensive B-mode imaging from multiple angles is performed to determine the presence and location of plaque, defined as focal protrusion of the vessel at least 50% greater than the surrounding wall. Pulsed Doppler sampling of the common carotid arteries (CCAs), carotid bifurcations, and internal and external carotid arteries is performed with angle correction ≤60° to quantify obstruction. An end-diastolic (minimum dimension) frame containing the distal 2 cm of the CCA is recorded for several seconds.

At the reading center, end-diastolic B-mode images of the distal CCA are acquired in real time, and a 1-cm segment of the far wall is measured using an automated system using an edge detection algorithm with manual override capacity. One hundred measurements are averaged to obtain mean IMT and lumen diameter. Plaque severity is graded as obstructive (>50% occlusion based on peak Doppler systolic velocity) or nonobstructive. A plaque score (0-8) is based on the number of segments of each carotid artery containing plaque.

**Echocardiogram performance and interpretation protocol**

Echocardiographic performance and interpretation adhere to published methods. The entire study is recorded on videotape and sent to the reading center for interpretation. Left ventricular end-diastolic and end-systolic wall thicknesses and diameters are measured from parasternal images according to established recommendations. Derived variables from these linear measurements include assessment of left ventricular structure (mass and relative wall thickness) and function (fractional shortening and ejection fraction). Location and severity of segmental wall motion abnormalities are noted. Pulsed wave, continuous wave, and color flow Doppler imaging are performed to detect and quantify valvular regurgitation and stenosis and to characterize left ventricular diastolic filling.

**Sample size determination and analysis plan**

The primary end point for SANDS is a composite outcome that includes change in carotid artery IMT and fatal and nonfatal CVD events (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, unstable angina, cardiac revascularization, and incident peripheral arterial disease).

**Sample size estimate**

The power calculations were conservatively based only on IMT change. Based on data from the SHS, one would anticipate a mean between-groups difference of 0.05 mm in CCA IMT for an 8-mm Hg difference in SBP. Data from PLAC II for the effect of statin treatment versus no statin treatment (calculated by multiplying effect/year in their 3-year study) would yield a similar estimate of 0.05-mm mean group IMT difference (which can be of clinical significance) related to LDL-C-lowering drugs. We assumed that the difference would be reduced by 15% because starting levels of LDL-C will be lower in diabetic individuals in the SHS than in PLAC II participants and to allow for some attrition. Based on the SHS, we assume an IMT SD of 0.16. A 2-sided test at α = .05, 80% power, and 10% loss to follow-up would
result in a total sample size of 498. These calculations take into account only the individual effects of SBP or LDL-C lowering rather than their likely additive effects and are likely to be conservative. The expected CVD event rate in those with diabetes and no CVD at baseline is 6.7% per 3 years in the conventional group and 5% (25% reduction) in the intensive group.

As described above, additional participants without pre-existing CVD were recruited. This adjustment increased the sample size to 548. This sample size maintains adequate power, even after participants with prevalent CVD at baseline are excluded from the analysis.

Analysis plan

All major treatment comparisons between the 2 randomized groups in this trial will be performed according to “intention-to-treat,” that is, patients will be analyzed according to the treatment arm to which they were randomized, regardless of adherence to the assigned treatment.

The primary hypothesis is as follows: compared with standard ATP III and JNC VI goals (LDL-C <100 mg/dL and BP <130/85 mm Hg), achieving lower targets for LDL-C and BP (LDL-C <70 mg/dL and BP <115/75 mm Hg) in American Indians with diabetes will retard the progression of atherosclerosis as measured by CCA IMT and reduce CVD events. Because it is expected that the treatment effect will not reach maximum until 36 months, primary analysis will be based on a univariate nonparametric test of change in IMT from baseline to 36 months, using an “untied worst-rank score” imputation approach for participants with a fatal or nonfatal study end point event before 36 months. This combined end point was chosen because a missing observation of a cardiovascular event is informative and not random.

Change in IMT will be adjusted for baseline IMT and center using a regression analysis. The adjusted IMT will be ranked, and the Wilcoxon rank test will be used to test the primary hypothesis. Participants with a fatal or nonfatal study end point event before 36 months will be assigned a worse rank or Wilcoxon score. Fatal events will be ranked worse than nonfatal events and the earlier an event, the worse the rank. In the presence of informatively missing observations, as in this study, the worst score analysis provides an unbiased test against a restricted alternative.

Participants with prevalent CVD at randomization, as defined earlier, will be excluded from the primary analysis because of the change in treatment goals. They will be included in secondary analyses. The 36-month IMT measurements of participants who die of a non-CVD cause or are lost to follow-up before 18 months will be considered missing at random, and these patients will be excluded from the primary analysis; if death or loss to follow-up occurs after 18 months, 36-month IMT will be imputed using baseline and 18-month values.

To compare treatment effects at 18 and 36 months, a secondary analysis of the primary hypothesis will be conducted using the multivariate rank test of Wei and Lachin with the adjusted changes of IMT from baseline at 18 and 36 months. A test of stochastic ordering will be used to test differences between the 2 treatment groups. It is assumed that the changes at 18 and 36 months will both have positive effects but not necessarily of the same magnitude. Under these assumptions, the test of stochastic ordering is more powerful than other multivariate methods (eg, the omnibus test [multivariate analysis of variance] and the test of association). Missing values will be handled as described above in the primary analysis.

Several secondary hypotheses for the secondary end points, including carotid plaque score, left ventricular function and geometry, CRP, and safety measures, also will be tested. Interim data analysis for monitoring safety will be conducted every 6 months. Chemistry and lipid profiles, urinalysis, and BP in the 2 treatment groups will be compared to evaluate possible side effects of the treatments. Severity of adverse effects will be reported to the DSMB in the interim study reports.

Discussion

SANDS is the first primary prevention trial for CVD that will systematically examine more aggressive targets for BP and lipid management in diabetic patients. We hypothesize that more aggressive BP and LDL-C control will decrease the progression of atherosclerotic disease in adults with diabetes.

SANDS will provide evidence for guiding future lipid and BP goals not only for American Indian populations but also for other diabetic patients. SANDS uses algorithms based on recommendations of NCEP-ATP III and JNC VI to regulate lipids and BPs, respectively. The primary end point of carotid artery IMT and the secondary measure of plaque score are surrogate markers for coronary artery disease. The echocardiographic measures will provide additional insight into the effect of the intervention on generalized cardiac and vascular function. Recently, there has been intense focus on lipid goals because of secondary prevention trials in patients with established CVD. The NCEP has recommended that providers consider lowering targets for individuals with high risk conditions, such as diabetes, because of their enhanced risk of CVD. Thus, SANDS, which specifically compares current lipid and BP targets to more aggressive targets for efficacy and safety, will not only advance our understanding of preventing atherosclerosis but will provide data that will be valuable in shaping future national guidelines.

We thank Apache, Caddo, Cheyenne River Sioux, Comanche, Delaware, Fort Sill Apache, Gila River,
Pima/Maricopa, Kiowa, Navajo, Oglala Sioux; Salt River Pima/Maricopa, and Wichita Indian communities for the assistance and cooperation; without their support, this study would not have been possible. We also thank the Indian Health Service hospitals and clinics at each center and Taqueer Ali, Damon Davis, JoAnne Detweiler, Lynne Dobrovolsky, and the directors of the SANDS clinics and their staffs and acknowledge the editorial assistance of Rachel Schaperow.

References


34. El Assaad MA, Topouchian JA, Darne BM, et al. Validation of the
Omron HEM-907 device for blood pressure measurement. Blood
and media thickness as a risk factor for myocardial infarction and stroke
36. Zwiebel WJ. Doppler evaluation of carotid stenosis. Introduction
to vascular sonography. 3rd ed. Philadelphia: W.B. Saunders;
computerized analyzing system simplifies readings and reduces the
variability in ultrasound measurement of intima-media thickness.
is greater in isolated systolic hypertension than in diastolic hyper-
tension: the Insufficienza Cardiaca negli Anziani Residenti
39. Devereux RB, Roman MJ. Evaluation of cardiac and vascular
structure by echocardiography and other noninvasive techniques.
In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology,
cardioc structure and function: The Strong Heart Study. Circulation
41. Sahin DJ, DeMaria A, Kisslo J, et al. Recommendations concern-
ing quantitation in M-mode echocardiography: results of a
survey of echocardiographic measurements. Circulation 1978;58:
1072 -83.
42. Schiller NB, Shah PM, Crawford M, et al. Recommendations for
quantitation of the left ventricle by two-dimensional echocardiog-
for the severity of native valvular regurgitation with
two-dimensional and Doppler echocardiography. J Am Soc Echo-
44. Quinones MA, Otto CM, Stoddard M, et al. Recommendations for
quantification of Doppler echocardiography: a report from the
Doppler quantification task force of the nomenclature and standards
committee of the American Society of Echocardiography. J Am Soc
45. Byington RP, Evans GW, Espeland MA, et al. Research effects of
lovastatin and warfarin on early carotid atherosclerosis. Circulation
1999;100:e14 -7.
46. Howard BV, Best LG, Galloway JM, et al. Coronary heart disease
risk equivalence in diabetes depends on concomitant risk factors.
47. Wittes J, Lakatos E, Probstfield J. Surrogate end points in clinical
48. Lachin JM. Worst-rank analysis with informatively missing
49. Waters DD, Alderman EL, Hsia J, et al. Effects of hormone
replacement therapy and antioxidant vitamin supplements on
coronary atherosclerosis in postmenopausal women: a randomized
50. Lachin JM. Some large-sample distribution-free estimators and tests
for multivariate partially incomplete data from two populations. Stat
51. Wei L, Lachin JM. Two-sample asymptotically distribution-free
tests for incomplete multivariate observations. J Am Stat Assoc
52. Ricotta JJ, Bryan FA, Bond MG, et al. Multicenter validation study of
real-time (B-mode) ultrasound, arteriography, and pathologic
heart disease incidence with carotid arterial wall thickness and
major risk factors: the Atherosclerosis Risk in Communities (ARIC)