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COST-EFFECTIVENESS OF LOWER TARGETS FOR BLOOD PRESSURE AND LDL CHOLESTEROL IN DIABETES: THE STOP ATHEROSCLEROSIS IN NATIVE DIABETICS STUDY (SANDS)

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Abstract

Background—The Stop Atherosclerosis in Native Diabetics Study (SANDS) reported cardiovascular benefit of aggressive versus standard treatment targets for both low-density lipoprotein cholesterol (LDL-C) and blood pressure (BP) in diabetic individuals.

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Objective—In this analysis, we examined within trial cost-effectiveness of aggressive targets of LDL-C ≤ 70 mg/dL and systolic blood pressure (SBP) ≤ 115 mmHg vs. standard targets of LDL-C ≤ 100 mg/dL and SBP ≤ 130 mmHg.

Design—Randomized, open label blinded-to-endpoint 3-year trial.

Data Sources—SANDS clinical trial database, Quality of Wellbeing (QWB) survey, Centers for Medicare and Medicaid Services, Wholesale Drug Prices.

Target Population—American Indians $\geq$ age 40 years with type 2 diabetes and no prior cardiovascular events.

Time Horizon—April 2003-July 2007.

Perspective—Health payer.

Interventions—Participants were randomized to aggressive vs. standard groups with treatment algorithms defined for both.

Outcome Measures—Incremental cost-effectiveness.

Results of Base-Case Analysis—Compared with the standard group, the aggressive group had slightly lower costs of medical services (\$-116), but a 54% higher cost for BP medication (\$1,242) and a 116% higher cost for lipid-lowering medication (\$2,863), resulting in an increased cost of \$3,988 over 3 years. Those in the aggressively treated group gained 0.0480 quality-adjusted life-years (QALY) over the standard group. Using a 3% discount rate for costs and outcomes, the resulting cost per QALY was \$82,589.

Results of Sensitivity Analysis—Using a 25%, 50%, and 75% reduction in drug costs resulted in a cost per QALY of \$61,329, \$40,070, and \$18,810, respectively.

Limitations—This study was limited by use of a single ethnic group and by its 3-year duration.

Conclusions—Within this 3-year study, treatment to lower BP and LDL-C below standard targets was not cost-effective due to the cost of the additional medications required to meet the lower targets. With the anticipated availability of generic versions of the BP and lipid-lowering drugs used in SANDS, cost-effectiveness of this intervention should improve.

INTRODUCTION

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 higher prevalence of other major CVD risk factors, such as dyslipidemia and hypertension (4,5). Consequently, there is interest in treatment strategies for controlling these CVD risk factors in diabetic individuals.

Most research addressing CVD risk factor control has focused on low-density lipoprotein cholesterol (LDL-C) or blood pressure (BP) lowering as isolated interventions, often using fixed doses of lipid- or BP-lowering agents to compare treatment efficacy against a placebo (6,7,8,9,^{10,11},12,13,14,15). In clinical practice, patients frequently present with multiple risk factors (16) and instead of deciding between treatment versus no treatment, the clinical question is what level of treatment will result in a favorable balance of risk versus benefit to the patient. The Stop Atherosclerosis in Native Diabetics Study (SANDS) was the first to specifically evaluate the treatment efficacy and safety of aggressive versus standard treatment targets for both LDL-C and BP in diabetic individuals (17). It was a randomized open-label 3-year trial examining the effects of aggressive LDL-C (goal < 70 mg/dL) and systolic (SBP) (goal $< 115/75$ mm Hg) reduction versus standard goals of < 100 mg/dL and $< 130/80$ mm Hg, respectively, on carotid artery intimal-medial thickness (CMT) and echocardiographic left

ventricular mass index (LVMI) in 499 adults with type 2 diabetes. Using these endpoints, SANDS demonstrated that the aggressively treated group had both a regression of CIMT and greater decrease in LVMI compared with the standard treatment group. Over a 3-year period, mean target LDL-C and SBP levels for both groups were reached and maintained. The number of clinical events was lower than expected and did not differ significantly between groups. While the aggressively treated group had an increased frequency of adverse events, serious adverse events were rare.

In addition to treatment efficacy, it is important to consider the cost-effectiveness of various treatment options (18,19). Incremental cost-effectiveness analyses allow for description of the resources required to implement one intervention relative to another and can provide outcome information in terms of quality-adjusted life-years (QALYs). Such analyses can help in decision making across various treatment options and disease conditions. In this article, we examine the incremental cost-effectiveness of the two treatment strategies used in the SANDS trial.

METHODS

Details of the SANDS study design and methods of the clinical interventions have been published (20). Briefly, 548 diabetic men and women $\geq$ age 40 years 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. The participants were randomized to the aggressive (n=276) or standard treatment group (n=272) using the urn method stratified by center and gender. For this analysis, we excluded 49 subjects with baseline CVD because their treatment was changed to meet new clinical practice recommendations that arose during the study (21). Patients who died of non-CVD events were considered lost to follow up and were excluded, as were patients who had missing data. All participants provided written informed consent, and the study was approved by all participating institutional review boards, the National Institutes of Health, and all participating American Indian communities. Subjects with missing values or lost to follow-up at the end of the trial were excluded.

Lipid and BP Interventions

Study personnel performed BP and lipid management for both groups, with equal frequency of clinic visits. 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 $\leq$ 115 mmHg and $\leq$ 130 mmHg in the aggressive and standard groups, respectively. Secondary goals were diastolic BP (DBP) of $\leq$ 75 mmHg and $\leq$ 85 mmHg, respectively. The algorithm for achieving lipid goals was based on recommendations of the National Cholesterol Education Program – Adult Treatment Panel III (NCEP-ATP III) (6). LDL-C goals were $\leq$ 70 mg/dL and $\leq$ 100 mg/dL and non-high-density lipoprotein cholesterol (non-HDL-C) goals were $\leq$ 100 mg/dL and $\leq$ 130 mg/dL in the aggressive and standard groups, respectively.

Intervention-Related Treatment and Direct Medical Costs

After screening and randomization, patients were seen at monthly intervals until they achieved LDL-C and BP goals. Patients were seen every 3 months thereafter, unless there were problems with side effects or adjustments in intervention medications were required because of other medical conditions. 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.

Each center had a physician investigator who was knowledgeable and familiar with care in the community. The centers also had a physician assistant and a nurse or nurse practitioner who implemented the algorithm in consultation with the study physician. All centers employed community members when possible to carry out the study protocol. Local resources, including translators and drivers, were identified as needed. Additional consultants worked with each study site to review treatment plans and address individual patient's problems or barriers to achieving the target goals, using a mixture of regularly scheduled and ad hoc telephone consultations. These resources were available for participants in both treatment arms.

Every treatment-related patient encounter was recorded in a database. While a wide range of issues could be addressed at each encounter, all encounters were classified into one of two types for the purpose of attributing cost: scheduled baseline/follow-up visit versus medication adjustment/side effect management visit. Scheduled and unscheduled visits were attributed a cost based on medical billing procedures and Centers for Medicare/Medicaid Services U.S. cost estimates (22).

All intervention-related medications were recoded at each visit. Medication dosage and frequency were used in conjunction with average wholesale prices to establish a pharmaceutical cost for each participant (23).

All hospitalizations or invasive procedures were reviewed for potential relationships with the study intervention. Methods for ascertaining and classifying clinical outcomes have been described (20). Medical records for all hospitalizations and procedures were reviewed centrally by six physician adjudicators blinded to treatment assignment. Hospitalizations and procedures were attributed to either a related or non-study related adverse event or to a composite CVD endpoint, defined as fatal CHD or stroke, nonfatal myocardial infarction (MI) or stroke, unstable angina, coronary revascularization, and carotid arterial revascularization.

Non-Intervention Related Treatment

All other medical care, including diabetes management, dietary and exercise counseling, and smoking cessation, was performed by the participants' regular health care providers. Because the primary care was not affected by trial participation, those treatment costs were not quantified. Because of the random allocation process used for group assignment, non-intervention-related health care use and costs were presumed to be equivalent for the two groups.

Study-Related Testing

The costs of study-related tests were equivalent in both groups. Study-related measures not routinely used in clinical practice were excluded from the cost analysis.

Outcomes Ascertainment

All study participants completed the self-administered Quality of Well Being survey (QWB) at baseline and 36 months (24,25,26). The QWB is a generic quality of life instrument that is widely used in clinical trials to evaluate medical and surgical interventions. The scores on the QWB were used for the determination of a quality-adjusted life-year (QALY). A QALY is a measure of the length of life, adjusted for the quality of life, calculated as the sum of the product of the number of years of life and the quality of life in each of those years. The numerical value assigned to quality of life reflects the public's judgment of the desirability of the outcome and is called a health utility. Health utilities are placed on a continuum where perfect health is assigned a value of 1.0 and health judged equivalent to death is assigned a value of 0.0 (18).

Data Analysis

An incremental cost-effectiveness ratio was calculated to compare the two interventions. Because the numbers of subjects differed between the two groups, average cost and QALY for each group were used for comparison. The numerator of the ratio was the difference in average cost between standard treatment and aggressive treatment. The denominator of the ratio was the difference in the average QALYs between standard treatment and aggressive treatment. Therefore, the ratio was interpreted as the incremental cost required for an individual to gain one QALY if switched from standard to aggressive treatment. Both cost and outcomes were converted to net present value using a 3% discount rate, where noted. A sensitivity analysis was conducted to estimate the variation of the results if the cost of medicine was reduced. Cost reductions of 25%, 50%, and 75% were tested.

All major treatment comparisons between the two groups were performed according to the principle of intention-to-treat, regardless of participant adherence to the assigned treatment. All analyses were performed using Intercooled Stata 9.2 (Stata Corporation Lp, College Station, TX) or SAS version 9.1 (Cary, NC). A two-tailed p-value < 0.05 was required to reject the null hypothesis.

Role of the Funding Source

The National Heart, Lung, and Blood Institute has representation on the SANDS Steering Committee, which governed the design and conduct of the study, interpretation of the data, and preparation and approval of the manuscript. The National Heart, Lung, and Blood Institute Project Office and all participating community review boards reviewed the manuscript.

RESULTS

Of the SANDS trial participants, 394 had complete data for inclusion in a cost-effectiveness analysis. Analyses were performed to identify whether the subjects excluded, due to missing data, differed from those included in the study. Participants excluded due to missing data were on average 3 years younger, more likely to smoke, and had smaller waist circumferences, but otherwise showed no significant differences in demographic or clinical characteristics (Table 1). The final sample consisted of 200 subjects in the aggressive group and 194 in the standard group.

Incremental costs for each major cost category are shown for each group (Table 2). Participants in the aggressive group incurred on average \$2,681 of care for scheduled and unscheduled medical evaluation and treatment, and participants in the standard group incurred \$2,797. Clinical endpoints, including invasive procedures, did not differ between groups. While adverse events were statistically more common in the aggressive group, serious events were similarly rare in both groups, and overall visits were not increased in the aggressively treated group vs. the standard group. However, to achieve the treatment goals, the aggressive group required more medications and higher dosages. The mean (SD) numbers of lipid-lowering and antihypertensive drugs used in the aggressive and standard groups were 1.5 (0.8) vs. 1.2 (0.7), $p < 0.05$ and 2.3 (1.3) vs. 1.6 (1.2), $p < 0.001$. To achieve the aggressive lipid targets, \$5,319 in lipid lowering drugs was required over the 3-year period, while \$2,457 was required to reach the conventional targets. Most of this cost differential is due to the greater use of non-generic agents, such as atorvastatin and ezetimibe, in the aggressive group. Similarly, to achieve the aggressive BP targets, \$3,561 in antihypertensive drugs was required over the 3 years, while \$2,319 was required to reach the conventional BP targets. For the aggressive BP and lipid targets, the combined cost of all care was \$11,561 per participant; for the standard targets, the cost was \$7,573 per participant. Thus, incremental costs of \$3,988 more per participant were

required to achieve the aggressive targets. Using a 3% discount rate, the incremental cost difference was \$3,846.

Health utility increased slightly in the aggressively treated group compared with baseline and with the standard treatment group (Table 3). Compared with the standard group, those in the aggressive group gained 0.0480 QALY during the study. The resulting cost per QALY was \$83,028. Discounting both costs and outcomes using a 3% discount rate resulted in a cost per QALY of \$82,589.

Because the incremental costs were entirely attributable to the cost of the study medications, we performed a sensitivity analysis using 25%, 50%, and 75% reductions in drug costs (Table 4). This resulted in a cost per QALY of \$61,329, \$40,070, and \$18,810, respectively.

DISCUSSION

SANDS randomized men and women with type 2 diabetes to two groups: one treated to aggressive targets of LDL-C ≤ 70 mg/dL and SBP ≤ 115 mmHg and the other treated to the standard LDL-C and SBP targets. As previously reported (17), the group treated to more aggressive targets had an improvement (decrease) in CIMT and thus a regression of atherosclerosis, whereas the group treated to standard targets had a worsening (increase) in CIMT. LVMI also decreased more in the aggressive group. Clinical endpoints did not differ between treatment groups. The current report expanded on the primary study endpoint to examine the cost-effectiveness of the intervention. Over the 3-year study, aggressive treatment of LDL-C and BP achieved a statistically significant effect on ultrasound measures of carotid atherosclerosis and cardiac mass but achieved only a small, statistically non-significant improvement on health utility. At an incremental cost of \$82,589 per QALY gained, the aggressive treatment did not meet the conventional criteria for cost-effectiveness of \$50,000 per QALY (27). Therefore, the cost to achieve this outcome per QALY is higher than is generally considered cost-effective.

Despite the present findings, there is reason to believe that this intervention will prove cost-effective in the future. If the effect on surrogate measures persists over time and if the costs of maintaining the lower targets do not rise, the intervention may eventually result in improved mortality and quality of life outcomes that could meet cost-effectiveness and willingness-to-pay thresholds. The current study, however, found no evidence for cost-effectiveness of aggressive vs. standard targets over 3 years.

Both LDL-C and BP lowering have been the subject of a number of cost-effectiveness studies (28). In longer-term studies, the incremental cost-effectiveness ratio for LDL-C lowering has been estimated at \$51,889 per QALY, comparable with cost-effectiveness ratios for commonly funded interventions (29). For intensified BP control over prolonged periods, the cost-effectiveness ratio is $-\$1959$ per QALY (28), meaning that the intervention results in costs savings. Thus, LDL-C and BP lowering interventions are accepted as cost-effective over the long term. In SANDS we have shown that it is possible to reach specific aggressive targets for both BP and LDL-C in people with diabetes, but it does not appear to be cost-effective over the intermediate-term at the current prices for the medications used.

It is also possible to compare relative cost per QALY of intensive lowering of LDL-C and BP in SANDS with various conditions, such as heart transplantation, hypertension screening and therapy among asymptomatic 20-year-old men, neonatal intensive care vs. standard neonatal care among premature infants, and dual air bags vs. driver-side air bag only, which result in costs per QALY ranging from \$40,000 to \$69,000 (27,30).

This study has several strengths. It is the first trial to examine the incremental costs of achieving specific targets for both LDL-C and BP in individuals with diabetes. Furthermore, this trial was conducted in a setting similar to routine clinical practice. While there were some aspects of care that may not be available in all clinical settings, such as community support and access to specialty consultation and case review, these targets were reached in each group largely with protocol-driven treatment algorithms implemented by primary care providers and their team of medical personnel. Interestingly, there was no incremental cost of medical care required to achieve either target. The primary cost differential was attributable to the cost of medications, particularly lipid-lowering medications. Compared with the standard group, the aggressive group had slightly lower costs of medical evaluation and care (\$-116), but a 54% higher incremental cost for BP medication (\$1,242) and a 116% higher cost for lipid lowering medication (\$2,863) over the 3 years, resulting in an incremental cost of \$3,988. Using sensitivity analysis, the cost of medications would need to be lowered by approximately 50% from the average wholesale price to reach cost-effectiveness and willingness-to-pay thresholds.

This study is limited by the single ethnic population studied. Although American Indians have high rates of CVD, their LDL-C and BP levels are slightly lower than other U.S. populations. Other treat-to-target studies may be needed to assess the cost-effectiveness of achieving aggressive targets for LDL-C and BP in groups with higher initial LDL-C and BP. Another weakness of this study is its modest 3-year duration. Extended follow up of these individuals to determine whether the improvements in subclinical atherosclerosis and cardiac structure are maintained in the aggressive group and whether they are reflected in fewer clinical CVD outcomes and sustained improvement in health utility could result in more favorable cost-effectiveness estimates. The report from the STENO-2 extension showing reduction in CVD events 7.8 years after intense risk factor management ceased suggests that improvement in CVD outcomes may be found upon long-term follow-up (31).

In conclusion, over a 3-year period, aggressive targets for both LDL-C and BP compared with standard targets in adults with diabetes resulted in added costs with beneficial effects on subclinical, but not clinical or health utility outcomes. The principal driver of the cost differential between the two treatment strategies was the cost of the BP and lipid-lowering medications required to achieve the lower targets. Once more generic versions of these medications become available, the cost differential between aggressive and standard treatment targets will decrease, thereby improving the cost-effectiveness of this strategy.

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Table 1
Characteristics of SANDS Subjects Included and Excluded from the Cost-Effectiveness Analysis

Characteristics at Baseline	Mean (S.D.)		P value for Difference
	Exclusion (n=105)	Inclusion (n=394)	
Age	53.76 (8.83) ²	56.74 (9.12)	0.003 ^{*1}
Female	65.71%	65.48%	0.965
Current smoker	27.62%	18.53%	0.040 [*]
Take aspirin	75.00%	68.11%	0.175
Waist, cm	107.22 (14.85)	110.89 (14.62)	0.025 [*]
Weight, kg	88.60 (18.88)	90.62 (19.91)	0.350
BMI	32.26 (6.10)	33.63 (6.46)	0.051
Glucose, mg/dL	149.49 (66.01)	160.68 (71.24)	0.092
Diabetes therapy—oral hypoglycemics or insulin	82.86%	86.04%	0.412
Diabetes therapy—diet and exercise alone	10.89%	12.89%	0.589
Diabetes therapy—oral hypoglycemics	75.24%	77.92%	0.560
Total cholesterol, mg/dL	184.79 (36.06)	184.35 (32.23)	0.905
Non-HDL-C, mg/dL	139.45 (33.60)	138.31 (31.56)	0.747
HDL-C, mg/dL	45.34 (11.94)	46.09 (12.36)	0.581
LDL-C, mg/dL	104.11 (30.10)	103.98 (28.83)	0.969
Total cholesterol/HDL-C	4.26 (1.09)	4.23 (1.18)	0.797
Systolic blood pressure, mm Hg	130.89 (18.08)	130.26 (15.24)	0.719
Diastolic blood pressure, mm Hg	76.66 (11.85)	74.95 (9.94)	0.133
Hemoglobin A1c	7.77 (1.62)	8.09 (1.88)	0.122
Glomerular filtration rate, mL/min	86.80 (19.89)	90.32 (24.58)	0.183
Triglycerides, mg/dL ³	169.10	161.17	N.S.
CRP, mg/L ³	2.58	2.80	N.S.
Intimal medial thickness	0.79 (0.18)	0.81 (0.18)	0.468
Years of diabetes	8.97 (7.77)	9.86 (7.84)	0.327

Characteristics at Baseline	Mean (S.D.)		P value for Difference
	Exclusion (n=105)	Inclusion (n=394)	
Left ventricular mass index	39.30 (7.93)	41.29 (9.24)	0.051

¹ denotes statistically significant.

* denotes statistically significant.

² The parentheses contain the standard deviations.

³ Geometric averages were presented for these variables.

Table 2
Costs of Care by Major Treatment Category to Achieve the Standard and Aggressive Targets

Cost/Case (Unit: U.S. Dollar)	Standard Group (N=194), \$	Aggressive Group (N=200), \$	Difference (\$)	95% CI of Difference
Cost of medical evaluation and management	2,797	2,681	-116	-248 ~ 15
Cost of physician visit per subject	1,331.	1,284	-46	-120 ~ 27
Cost of lab and exam per subject	1,420.	1,396	-23	-51 ~ 4
Other inpatient care related to CVD	47.	0.00	-47	-137 ~ 44
Cost of lipid medicine *	2,457	5,320	2,863	2456 ~ 3269
Cost of antihypertension medicine *	2,319	3,561	1,242	805 ~ 1678
Total direct medical cost *	7,573	11,561	3,988	3311 ~ 4665
Adjusted total direct medical cost (3% discount rate) *	7,364	11,210	3,846	3191 ~ 4502

Abbreviations: CVD = cardiovascular disease.

All results are means.

* Denotes a statistically significant difference in means between two groups ($P < 0.05$).

Table 3
Outcomes in Quality-Adjusted Life-Years Achieved by Standard and Aggressive Groups

Outcome	Standard Group (N=194)	Aggressive Group (N=200)	Difference	95% CI of Difference
QWB (Start)	0.6362	0.6471	0.0109	−0.0190 ~ 0.0412
QWB (End)	0.6394	0.6594	0.0200	−0.0140 ~ 0.0540
QALY	1.9094	1.9574	0.0480	−0.0340 ~ 0.1303
Adjusted QALY (3% discount rate)	1.8543	1.9009	0.0466	−0.0330 ~ 0.1264
Cost per QALY			\$ 83,028	
Adjusted Cost per QALY (3% discount rate)			\$ 82,589	

Abbreviations: QALY = quality-adjusted life-year; QWB = Quality of Well Being survey.

All results are means.

Table 4

Sensitivity Analysis Using Drug Cost Reductions

% reduction of drug cost	Total Medical Cost				Incremental Cost-Effectiveness Ratio	
	Standard Group		Aggressive Group		Cost per QALY gained	
	Non-adjusted (\$)	Adjusted (\$)	Non-adjusted (\$)	Adjusted (\$)	Non-adjusted (\$)	Adjusted (\$)
0	7,573	7,364	11,561	11,210	83,028	82,589
25	6,379	6,205	9,341	9,061	61,666	61,329
50	5,185	5,046	7,121	6,912	40,304	40,070
75	3,991	3,887	4,901	4,763	18,942	18,810

Dollars are U.S. dollars. All results are means. QALY = quality-adjusted life-year.