Effect of the Look AHEAD Study Intervention on Medication Use and Related Cost to Treat Cardiovascular Disease Risk Factors in Individuals With Type 2 Diabetes

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OBJECTIVE — To examine the effect of a lifestyle intervention to produce weight loss and increased physical fitness on use and cost of medications to treat cardiovascular disease (CVD) risk factors in people with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Look AHEAD is a multicenter randomized controlled trial of 5,145 overweight or obese individuals with type 2 diabetes, aged 45–76 years. An intensive lifestyle intervention (ILI) involving group and individual meetings to achieve and maintain weight loss through decreased caloric intake and increased physical activity was compared with a diabetes support and education (DSE) condition. Medications prescribed to treat diabetes, hypertension, and hyperlipidemia were compared at baseline and 1 year. Medication costs were conservatively estimated using prices from a national online pharmacy.

RESULTS — Participants randomized to an ILI had significantly greater improvements in CVD risk parameters and reduced medication use and cost compared with those assigned to DSE. At 1 year, average number of medications prescribed to treat CVD risk factors was 3.1 ± 1.8 for the ILI group and 3.6 ± 1.8 for the DSE group ($P < 0.0001$), with estimated total monthly medication costs of $143 and $173, respectively ($P < 0.0001$). DSE participants meeting optimal care goals at 1 year were taking an average of 3.8 ± 1.6 medications at an estimated cost of $194/month. ILI participants at optimal care required fewer medications (3.2 ± 1.7) at lower cost ($154/month) ($P < 0.001$).

CONCLUSIONS — At 1 year, ILI significantly improved CVD risk factors, while at the same time reduced medication use and cost. Continued intervention and follow-up will determine whether these changes are maintained and reduce cardiovascular risk.

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Type 2 diabetes is one of the most significant public health concerns in the U.S. due to its prevalence and adverse impact on life expectancy, quality of life, and cost. The increasing prevalence of obesity and type 2 diabetes in the U.S. further heightens the importance of diabetes as a chronic public health disease. Forecasts based on data from national health surveys ominously predict that continuation of current trends in obesity and diabetes will significantly and adversely impact the rate of future improvements in U.S. life expectancy and quality of life (1).

The excess morbidity and mortality experienced by people with type 2 diabetes is primarily due to increased cardiovascular disease (CVD) risk, and this risk is in turn driven by the triad of hyperglycemia, hypertension, and hyperlipidemia (2). Appropriately, interventions to reduce the adverse health outcomes of type 2 diabetes are primarily directed at these three CVD risk factors, and specific patient goals for parameters of hyperglycemia (A1C), hypertension (blood pressure), and hyperlipidemia (primarily LDL cholesterol) have been promulgated by various professional organizations (2,3).

Currently, only a minority of people with type 2 diabetes appear to be achieving optimal-care goals for CVD risk management (4). Lifestyle measures including weight loss and increased physical activity have been shown to improve CVD risk parameters and are therefore the initial interventions recommended for achieving glycemic, blood pressure, and lipid goals (5). However, in practice, most peo-

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ple are unable to implement significant lifestyle changes on a long-term basis and ultimately require multiple pharmacologic agents to achieve currently recommended treatment goals (6–8). Unfortunately, this polypharmacy is associated with decreased quality of life, increased risk of adverse medication effects, increased medication use, higher costs, and higher monitoring expenses (9,10).

Several studies (11–13) of weight loss interventions in people with type 2 diabetes have reported reductions in medication use and/or cost. These studies have typically been uncontrolled weight loss interventions applied to small groups of patients. Benefits have primarily been seen in diabetes medication requirements, with usually smaller effects when assessed on medications prescribed for treatment of hypertension and hyperlipidemia. These studies support the premise that effective programs for people with type 2 diabetes that achieve long-term weight loss and increase physical activity hold the promise of improving cardiovascular risk parameters while minimizing the use of pharmacologic agents.

Look AHEAD (Action for Health and Diabetes) is an National Institutes of Health–funded long-term (up to 11.5 years) clinical trial studying the effect of an intensive lifestyle intervention (ILI) on CVD morbidity and mortality in people with type 2 diabetes. The 1-year results of the Look AHEAD ILI on weight loss, glycemic control, blood pressure, lipid parameters, and medication use were recently reported (14). In this report, we examine the effect of the Look AHEAD intervention on medication requirements and estimated medication costs to treat CVD risk factors in the Look AHEAD cohort.

RESEARCH DESIGN AND METHODS

— Trial design, methods, and baseline characteristics of the Look AHEAD study cohort have been previously described (15,16). In Look AHEAD, 5,145 overweight or obese people with type 2 diabetes were recruited in 16 centers in the U.S. Participants were aged 45–76 years, had a BMI >25 kg/m^2 (>27 kg/m^2 if taking insulin), A1C <11%, blood pressure <160/100 mmHg, and fasting triglyceride level <600 mg/dl. Participants had to successfully complete a baseline maximal graded exercise test reaching a workload of at least four metabolic equivalents (METS).

Interventions

Participants were randomly assigned to a usual-care cohort, which received a program of general diabetes support and education (DSE), or the ILI cohort, which received a program of diet, behavior modification, and increased physical activity with goals of a minimum weight loss of 7% of initial body weight and at least 175 min/week of moderate physical activity (e.g., walking). The initial year of the ILI used frequent individual and group meetings with intervention teams that included registered dietitians, behavior psychologists, and exercise specialists. To assist participants in reducing caloric intake, participants were prescribed portion-controlled diets that included the use of meal-replacement products. Dietary counseling included information on healthy diet composition, including adequate intake of fruits and vegetables and avoidance of excessive caloric intake from fat. After 6 months, participants who had difficulty meeting study weight loss goals received additional study intervention including additional behavior strategies and use of the weight loss medication orlistat in accord with specific study protocols. All study participants received a general diabetes education session prior to randomization. The DSE cohort was offered three additional diabetes education sessions during the first year. Informed consent was obtained from all participants before screening and at enrollment, consistent with the Helsinki Declaration and the guidelines of each center's institutional review board.

Clinical care

All participants in Look AHEAD were required to have a primary physician or physicians providing diabetes and general medical care. Participants and their physicians were provided results of the participant's baseline weight, blood pressure, A1C, fasting lipid values, serum creatinine, urinary albumin-to-creatinine ratio from spot urine samples, and results of the baseline maximal graded exercise test. All medical management and any changes in medications were made by the participant's primary physician, with the exception of temporary reductions in certain hyperglycemic medications during periods of intensive weight loss intervention for the ILI cohort. These temporary adjustments were made by Look AHEAD study physicians and nurses using a standard protocol in order to prevent serious hypoglycemia during aggressive caloric reduction. In these instances, the study protocol provided that hyperglycemic medications would be returned to the original regimen when the period of the intensive caloric restriction was completed (16).

Assessments

Baseline and 1-year assessments were made as previously described and included subject height, weight, seated blood pressure after a 5-min rest, A1C, and fasting lipid levels (14). Laboratory analyses were conducted by the central biochemistry laboratory (Northwest Lipid Research Laboratories, University of Washington, Seattle, WA). Cardiovascular fitness was assessed as estimated METS during baseline and 1-year treadmill exercise tests when >80% of age-predicted maximal heart rate was attained.

Participants brought all prescription medications to the baseline and 1-year visits to insure recording accuracy. Study staff entered prescription medications into the study database by medication name, but specific medication dosage was not entered. Medication costs were estimated as the cost of a 1-month supply of medication as listed on the Web site of a national online pharmacy (www.walgreens.com/library/finddrug/druginfosearch.jsp) (online appendix 1, available at http://care.diabetesjournals.org/cgi/content/full/dc09-2090/DC1) on 1 November 2007.

When cost varied by drug dose, a dosage of ~50% of the maximal recommended or effective dose was used. For diabetes medications, medication-specific drug costs were used. For blood pressure and lipid medications, the class of medication, but not the specific drug, was available from the database; therefore, a representative medication from each drug class was arbitrarily selected and the cost for this medication was assigned as the drug cost for drugs in this class. Generic drug costs were used whenever an appropriate generic drug was available.

Participants were defined to be at optimal care at their Look AHEAD baseline or 1-year visit if they met all three of the following criteria at the visit: *1*) A1C <7%, *2*) blood pressure <130/80 mmHg, and *3*) fasting LDL cholesterol <100 mg/dl (5).

Statistical methods

Differences between participants assigned to the ILI and DSE treatments were compared at baseline and 1-year using Stu-

Table 1—*All participants: characteristics, cardiovascular risk parameters, medication use, and monthly cost at baseline and 1 year*

	Baseline			Year 1		
	ILI	DSE	*P* value	ILI	DSE	*P* value
n	2,496	2,502	0.93	2,182	2,176	0.93
Women (%)	1,480 (59)	1,491 (60)	0.84	1,301 (60)	1,288 (59)	0.80
Age at randomization (years)	59 ± 7	59 ± 7	0.13	—	—	—
Duration of diabetes (years)	7 ± 7	7 ± 6	0.62	—	—	—
BMI (kg/m^2)	35.9 ± 6.0	36.0 ± 5.8	0.42	32.8 ± 6.1	35.7 ± 5.9	<0.0001
Fitness (METS)	5.2 ± 1.5	5.1 ± 1.5	0.07	6.2 ± 2	5.4 ± 1.6	<0.0001
Diabetes						
A1C (%)	7.3 ± 1.1	7.3 ± 1.2	0.07	6.6 ± 1.0	7.1 ± 1.2	<0.0001
Number of prescribed medications	1.5 ± 0.9	1.5 ± 0.9	0.53	1.2 ± 0.9	1.6 ± 0.9	<0.0001
Monthly cost ($)	87 (55)	88 (55)	0.74	72 (33)	98 (55)	<0.0001
Hypertension						
Systolic blood pressure (mmHg)	128 ± 17	130 ± 17	0.011	122 ± 17	126 ± 17	<0.0001
Diastolic blood pressure (mmHg)	70 ± 9	70 ± 10	0.10	67 ± 9	68 ± 10	<0.0001
Number of prescribed medications	1.3 ± 1.1	1.3 ± 1.1	0.91	1.3 ± 1.1	1.4 ± 1.1	0.19
Monthly cost ($)	36 (23)	37 (23)	0.55	35 (28)	38 (65)	0.11
Hyperlipidemia						
LDL cholesterol (mg/dl)	112 ± 32	112 ± 32	0.91	107 ± 32	106 ± 32	0.54
HDL cholesterol (mg/dl)	43 ± 12	43 ± 12	0.99	47 ± 13	45 ± 12	<0.0001
Triglycerides (mg/dl)	182 ± 116	180 ± 118	0.59	152 ± 93	166 ± 95	<0.0001
Non-HDL cholesterol (mg/dl)	148 ± 38	147 ± 37	0.53	137 ± 37	139 ± 36	0.06
Number of prescribed medications	0.5 ± 0.6	0.5 ± 0.6	0.88	0.5 ± 0.6	0.6 ± 0.6	0.003
Monthly cost ($)	32 (0)	32 (0)	0.96	36 (24)	38 (24)	0.008
Total medications						
Number of prescribed medications	3.3 ± 1.8	3.3 ± 1.8	0.72	3.1 ± 1.8	3.6 ± 1.8	<0.0001
Monthly cost ($)	155 (129)	157 (134)	0.44	143 (120)	173 (152)	<0.0001

Data are mean ± SD or frequency (%) and monthly cost data are mean (median), unless otherwise specified. Fitness is exercise level attained at >80% of age-predicted maximal heart rate.

dent *t* test for unpaired data for continuous variables and a χ^2 test for categorical variables. Comparison of medication costs between the two groups was assessed using the Wilcoxon rank sum test for two-sample medians.

RESULTS

Participants' baseline characteristics

Of 5,145 individuals who were randomized into the trial, 4,998 (97%) had complete data to determine medication use at baseline (online appendix Fig. 1). As previously reported, 4,959 participants attended the 1-year exam (14). Of these, 4,358 (88%) had complete data at 1-year to determine medication use. The percentage of participants with evaluable data did not differ between the two groups either at baseline or year 1 (Fig. 1).

Table 1 shows characteristics of the two groups at baseline and year 1. As previously reported, the groups were similar at baseline, but at 1-year the ILI group had significantly greater weight loss (8.7 vs. 0.8 kg), lower BMI, and significantly greater fitness level than the DSE group (Table 1) (14).

Changes in medications and cardiovascular risk parameters

Table 1 and online appendix Fig. 2 show CVD risk parameters and related medication use by participants at baseline and 1 year by treatment group. At baseline, medication use was not different between the groups. At 1 year, medication use for ILI was significantly lower than DSE (Table 1 and online appendix Fig. 2). Although medication use was less for all three risk factor categories for ILI compared with DSE participants, the difference was most pronounced for diabetes medications. At 1 year, 52% of DSE participants were taking two or more diabetes medications compared with only 37% of ILI participants (online appendix Fig. 2). Also at 1 year, almost 25% of ILI participants were taking no diabetes medications compared with only 12% of DSE participants. Insulin was prescribed for 15 and 16% of ILI and DSE participants, respectively, at baseline ($P = 0.18$) and 13 and 17%, respectively, at 1-year ($P < 0.0001$). Medication use for treatment of hypertension and hyperlipidemia was also lower at 1 year for ILI participants compared with DSE subjects (Table 1 and online appendix Fig. 2), although for hypertensive medications the difference was not statistically significant (Table 1). After 1 year of the Look AHEAD intervention, ILI participants were taking an average of 3.1 ± 1.8 medications for treatment of diabetes, hypertension, and hyperlipidemia compared with 3.6 ± 1.8 medications for DSE participants ($P < 0.0001$).

Table 1 also shows estimated monthly medication cost by risk factor category and total cost for each group at baseline and 1 year. At baseline, combined mean (median) medication costs for the three risk categories were approximately $155 ($130) per month and were not different between the two groups ($P = 0.44$ for comparison of medians). At 1 year, total medication costs actually decreased in the ILI group compared with baseline but increased in the DSE group. Mean (median) total medication costs at 1 year were $143 ($120) and $173 ($152) for ILI and DSE, respectively ($P < 0.0001$ for comparison of medians). This cost difference was primarily due to significantly lower cost of diabetes medications for ILI compared with DSE. Thiazolidinedione medications are particularly expensive and were pre-

Table 2—*Participants meeting optimal-care goals: cardiovascular risk parameters, medication use, and monthly cost at baseline and 1 year*

	Baseline			Year 1		
	ILI	DSE	*P* value	ILI	DSE	*P* value
n (% of total cohort)	269 (11)	239 (10)	0.93	517 (24)	359 (16)	<0.0001
Diabetes						
A1C (%)	6.3 ± 0.4	6.3 ± 0.5	0.92	6.1 ± 0.5	6.3 ± 0.4	<0.0001
Number of prescribed medications	1.3 ± 0.9	1.4 ± 0.9	0.28	1.1 ± 0.5	1.5 ± 0.9	<0.001
Monthly cost ($)	74 (33)	86 (33)	0.13	70 (33)	101 (55)	<0.001
Hypertension						
Systolic blood pressure (mmHg)	114 ± 10	115 ± 10	0.68	112 ± 10	114 ± 10	<0.0001
Diastolic blood pressure (mmHg)	65 ± 8	65 ± 8	0.90	63 ± 8	64 ± 8	0.20
Number of prescribed medications	1.4 ± 1.1	1.3 ± 1.1	0.34	1.4 ± 1.1	1.5 ± 1.1	0.05
Monthly cost ($)	40 (24)	35 (24)	0.39	37 (24)	40 (24)	0.08
Hyperlipidemia						
LDL cholesterol (mg/dl)	80 ± 15	81 ± 14	0.49	80 ± 15	79 ± 14	0.84
HDL cholesterol (mg/dl)	43 ± 12	43 ± 12	0.99	47 ± 13	45 ± 12	<0.0001
Triglycerides (mg/dl)	183 ± 116	180 ± 118	0.40	152 ± 93	166 ± 95	<0.0001
Non-HDL cholesterol (mg/dl)	114 ± 24	117 ± 24	0.26	107 ± 23	110 ± 21	0.03
Number of prescribed medications	1.4 ± 1.1	1.3 ± 1.1	0.48	1.4 ± 1.1	1.5 ± 1.1	0.009
Monthly cost ($)	48 (65)	52 (65)	0.62	47 (65)	54 (65)	0.008
Total medications						
Number of prescribed medications	3.4 ± 1.8	3.5 ± 1.7	0.86	3.2 ± 1.7	3.8 ± 1.6	<0.001
Monthly cost ($)	163 (139)	172 (142)	0.86	154 (128)	194 (177)	<0.001

Data are mean ± SD or frequency (%) and monthly cost data are mean (median), unless otherwise specified. Participants at optimal care defined as participants with A1C <7%, blood pressure <130/80 mmHg, and LDL cholesterol <100 mg/dl as measured at the applicable study visit.

scribed for 25 and 27% of ILI and DSE participants, respectively, at baseline ($P = 0.24$) and 22 and 31%, respectively, at 1 year ($P = 0.0001$). Median costs of blood pressure and lipid medications were also lower in ILI compared with DSE at 1 year, although the differences were smaller and, in the case of blood pressure medications, was not statistically significant.

Participants meeting optimal-care goals

We also analyzed cardiovascular risk parameters and medication costs for the subgroup of participants who met optimal-care goals for diabetes, blood pressure, and lipid control (Table 2). As previously reported, ~10% of participants in both the ILI and DSE groups met all three optimal-care goals at baseline (Table 2) (14). At study entry, participants at optimal care had a shorter duration of diabetes, had lower BMI, and were more fit than participants not at optimal care (data not shown). Medication use and cost was slightly higher at baseline for participants meeting optimal-care goals compared with the overall study cohorts.

As shown in Table 2, cardiovascular risk parameters, medication use, and cost were not different between the two optimal-care groups at baseline. After 1 year of the Look AHEAD intervention, more ILI participants met optimal-care goals, and ILI participants at optimal care had significantly lower A1C, systolic blood pressure, triglycerides, and non-HDL cholesterol and higher HDL cholesterol compared with the DSE optimal-care cohort. LDL cholesterol was lower in both groups at 1 year compared with baseline and was not different between groups. Notably, medication use and cost decreased in the ILI optimal-care group at 1 year compared with baseline but increased in the DSE group. At 1 year, average medication costs to reach optimal-care goals were almost $200/month for DSE participants compared with approximately $155/month for the ILI cohort (median costs $177 vs. $128, respectively, $P < 0.001$).

CONCLUSIONS — We found that at randomization into the Look AHEAD study, participants were taking an average of 3.3 medications, costing an estimated $155/month for management of the CVD risk factor triad of hyperglycemia, hypertension, and hyperlipidemia. Despite this, only 10% of participants at entry into the study were meeting optimal goals for diabetes, blood pressure, and lipid control. After 1 year of an ILI focused on weight loss and increased physical activity, participants in the ILI group had significant improvements in A1C, blood pressure, and lipid parameters, while at the same time reduced medication use and cost. The DSE group experienced a more modest improvement in these parameters, and this occurred in the setting of increased medication use and cost. The total cost of diabetes, blood pressure, and lipid prescription medications for DSE participants at 1 year was an estimated $173/month compared with approximately $143/month for ILI participants. Compared with baseline, medication costs increased by 10% in the DSE group and decreased by almost 10% in ILI participants. At 1 year, almost 40% of ILI participants were taking two or fewer total medications to manage their diabetes, hypertension, and hyperlipidemia compared with only 28% of DSE participants. Over 50% of DSE participants were prescribed four or more medications at 1 year compared with 41% of ILI participants.

Participants meeting optimal-care goals at baseline were taking more medications with increased cost relative to the overall study cohort. The Look AHEAD intervention more than doubled the percentage of participants achieving optimal-care goals, while at the same time reduced medication use and cost.

The beneficial effects of the ILI intervention were seen primarily in diabetes

and blood pressure parameters. No further improvement in LDL cholesterol values was observed. This latter observation is not surprising since weight reduction programs with diet and exercise typically show greater reductions in triglyceride levels with more modest reductions in total and LDL cholesterol (17). Non-HDL cholesterol may be a better predictor of cardiovascular risk in people with type 2 diabetes than LDL cholesterol (18), and current lipid guidelines suggest targeting non-HDL cholesterol as a secondary goal after LDL cholesterol (5). At 1 year, non-HDL cholesterol was lower in the ILI cohort compared with the DSE subjects, and this was achieved without additional medication use.

Our data on medication cost should be viewed as general estimates of the cost individuals with type 2 diabetes might incur if they paid out of pocket for their diabetes, blood pressure, and lipid medications. We did not factor in medication dosage or individual insulin requirements in the cost estimates. For blood pressure and lipid medications, we assigned a single drug cost for each drug class using cost data for a representative drug from that class. We used cost data for generic drugs whenever possible and assumed half-maximal drug dosage; therefore, our estimates very likely underestimate cost. As improvements in diabetes, blood pressure, and lipid parameters might prompt participants' personal physicians to reduce medication doses rather than discontinue medications altogether, our estimates would tend to underestimate cost differences between the ILI and DSE groups.

Our analysis is limited to a comparison of medication costs between ILI and DSE participants. The analysis does not include assessment of other costs associated with the respective interventions. Both the ILI and DSE participants received counseling related to healthy lifestyle and general diabetes care. Counseling sessions were more intensive and frequent for ILI participants and therefore would have greater cost. ILI participants also were provided with meal-replacement products to assist in weight loss, and some received the weight loss medication orlistat. This would also add to the overall cost of the ILI during the 1st year. On the other hand, we did not include in medication cost–related expenses such as cost of supplies for insulin administration, home glucose testing, and laboratory expenses related to medication monitoring. At 1 year, ILI participants were less likely to be using insulin and were taking fewer medications overall compared with DSE participants. It is therefore likely that these related expenses would also be lower for the ILI cohort compared with DSE. A comparison of intervention costs between the ILI and DSE approaches would need to be interpreted in the context of an overall cost/benefit analysis, which of necessity must await the completion of the Look AHEAD trial.

People with type 2 diabetes die on average 8 years earlier than their nondiabetic counterparts, primarily due to a two- to fourfold increased risk of CVD (2,19). Pharmacologic treatment of hyperglycemia, hypertension, and hyperlipidemia has been shown to reduce CVD risk in people with diabetes, and this triad is now the cornerstone of optimal-care goals in the chronic disease management of type 2 diabetes (5). Clinical trials and clinical experience show that polypharmacy is the rule in meeting current optimal-care goals (6,8). The term "triple therapy" has entered the lexicon of clinical diabetes care, and five or more prescription drugs are often required to adequately treat diabetes, hypertension, and hyperlipidemia (6,20). Unfortunately, polypharmacy comes at a price of increased cost, side effects, risk of adverse drug interactions, decreased compliance, and decreased quality of life (9,10,21,22). Moreover, recent results from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial raise questions about the benefits of aggressive glycemic control, at least when achieved through the use of multiple diabetes medications (23). At 1 year, DSE participants in the Look AHEAD study reaching optimal-care goals were taking, on average, almost four medications daily for management of diabetes, hypertension, and hyperlipidemia at an estimated cost of almost $200/month. Their ILI optimal-care counterparts were taking slightly more than three medications daily at an estimated cost of $155/month.

The total cost of diabetes in the U.S. in 2007 is estimated at $174 billion, with $25 billion of this cost attributed to outpatient retail prescriptions. Diabetes medications and supplies and medications to treat the complications of diabetes are estimated at 25% of the medical expenses attributed to diabetes, making this the second largest single cost after hospital inpatient care (24). An effective, long-term lifestyle intervention for people with type 2 diabetes that simultaneously reduces cardiovascular risk parameters and prescription medication cost would have major public health implications.

In conclusion, compared with a program of general DSE, the Look AHEAD study ILI program after 1 year resulted in greater improvements in diabetes, blood pressure, and lipid parameters, while at the same time reduced prescription medication requirements and cost. These benefits were seen for both the total study cohort as well as the subgroup of participants who met optimal-care goals for the CVD risk triad of diabetes, hypertension, and hyperlipidemia. Those participants meeting optimal-care goals took more medications with higher cost compared with the overall study cohort, but like the total study cohort, their medication requirements and costs were substantially reduced by the study intervention. If these changes can be sustained for the long term, the public health benefits would be substantial.

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