Landmark Look AHEAD Trial Finds Successful Weight Loss But No Reduction in Cardiovascular Events

The Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369:145–54.

Study Overview

Objective. To examine the effect of intensive lifestyle intervention on long-term cardiovascular outcomes among overweight or obese diabetics.

Design. Randomized controlled trial, conducted in 16 centers in the United States, with enrollment from 2001 to 2004 [1]. Participants in the intervention arm were instructed to lose 10% of their body weight (trial goal of 7% average weight loss) and increase their physical activity to a goal of 175 minutes per week. They were aided in this goal by weekly group or individual counseling sessions during the first 6 months followed by less frequent contact but at least once per month thereafter for the duration of the study. Calorie reduction was augmented by use of meal replacements, especially during weeks 3 to 19. The pancreatic lipase blocker medication orlistat was encouraged for participants not achieving their goal body weight by 6 months, but the limited effect of this medication over time led to its abandonment as a trial component. Participants in the control arm received only 3 to 4 groups sessions annually for years 1 through 4 and annually thereafter. Research staff conducted annual visits with all participants, where they collected biometric and laboratory data, and participants had submaximal exercise tests in years 1 and 4.

Setting and participants. 5145 diabetic patients 45 to 75 years old with a BMI ≥ 25 kg/m^2. Participants were required to have a relationship with a primary care physician and be able to complete an exercise test, demonstrating safety with moderate intensity exercise. Exclusions included hemoglobin A1c > 11%, systolic blood pressure ≥ 160 mm Hg, diastolic blood pressure ≥ 100 mm Hg, triglyceride level ≥ 600 mg/dL, use of weight loss medications, history of bariatric surgery or extensive bowel resection, and medical or psychiatric conditions deemed substantial enough to limit a person's ability to adhere to the trial.

Main outcome measures. Composite cardiovascular outcome (death from cardiovascular cause, nonfatal myocardial infarction, nonfactor stroke, hospitalization for angina) over a 13.5-year follow-up period (later changed to a mean follow-up of approximately 10 years after the trial terminated early).

Main results. In each of the groups at baseline, mean age was 59 years, nearly 60% were female, and 63% were white, 16% black, 13% Hispanic, and 5% Native American. Mean body weight was 101 kg, and hemoglobin A1c 7.3/7.2. 13.5% and 14.2% in the control and intervention

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arms had a history of cardiovascular disease, and 16.5% and 15.4% used insulin. After a mean follow-up of 9.6 years (interquartile range, 8.9–10.3), the data and safety monitoring board recommended terminating the study because of expected lack of intervention efficacy on the primary outcome. 403 patients in the intervention group and 418 in the control group reached the composite outcome, corresponding to 1.83 and 1.92 events per 100 person-years (hazard ratio 0.95, 95% confidence interval 0.84–1.09; $P = 0.51$). No significant differences were evident for any of the individual components of the composite endpoint or all-cause mortality. This lack of efficacy was apparent despite the intervention's success with weight loss and other cardiovascular risk factors. In the intervention group, weight loss was 8.6% of baseline body weight after year 1 compared with 0.7% in the control group; a difference persisted through the end of the trial, with 6% mean baseline body weight lost in the intervention group compared with 3.5% in the control group. Waist circumference and hemoglobin A1c also were persistently lower in the intervention group throughout the trial, and physical fitness was greater; however, these differences, while large after year 1, were small though still statistically significant for most of the trial (difference of 1 cm in waist circumference, 0.11% in A1c, 1 mm Hg in systolic blood pressure, and 0.36 METS in physical fitness by the end of the trial). LDL was higher in the intervention group than in the control group (89.5 vs. 88.3 mg/dL at the end of the trial). Antihypertensive, insulin, and statin use was somewhat lower among intervention patients.

Conclusion. An intensive lifestyle intervention among diabetics did not decrease cardiovascular events over an approximately 10-year follow-up period. The intervention was successful in promoting weight loss and improving most cardiovascular risk factors.

Commentary

Since the Diabetes Prevention Program demonstrated modest long-term weight loss (5.6 kg after 2.8 years; 2 kg after 10 years) [2,3] and a reduction in diabetes incidence (58% lower incidence than placebo at 2.8 years and 34% lower at 10 years), an assumption has persisted that long-term weight loss should correspond to a reduction in cardiovascular events and perhaps mortality. However, despite multiple studies showing weight loss and cardiovascular risk reductions with intensive lifestyle interventions, none have demonstrated reductions in cardiovascular events. Primarily funded by the National Institutes of Health, the Look AHEAD trial set forth to examine the effect of an intensive lifestyle intervention encouraging weight loss and physical activity among diabetics. The planned primary endpoint was a composite of cardiovascular outcomes over 11.5 years. Because of a low number of cardiovascular events in the first 2 years of the trial, the length of follow-up was extended by 2 years and the additional cardiovascular endpoint of hospitalization with angina was added to the composite. Ultimately, because of expected futility of the trial on the primary outcome, the study was stopped after a mean of 9.6 years of follow-up. This lack of benefit occurred despite a large sample size, a robust retention rate, clearly articulated and objectively verifiable outcomes, and a straightforward protocol and study design.

This study did find clear success with intermediate outcomes. Weight loss in intervention patients was 6% of baseline body weight at the end of the trial, 2.5% more than in the placebo group, with small but significant reductions in most cardiovascular outcomes. LDL cholesterol was typically higher in the intervention group than the control throughout follow-up. Prior publications from the Look AHEAD study team demonstrated the intervention's success with weight loss through 4 years of follow-up with a higher rate of partial or complete remission from diabetes (3.5% in the intervention group, 0.5% in the control) [4]. Further, obstructive sleep apnea was decreased in this interim follow-up period, and physical mobility and quality of life were improved [5–8]. Yet, the holy grail of success for a lifestyle intervention, a reduction in cardiovascular events and mortality, never materialized.

The question is why. Were the patients too healthy at baseline, thus leading to a very low rate of cardiovascular events? Among patients, hemoglobin A1c was near goal at baseline and a history of cardiovascular disease and insulin use were present in less than 20%. Perhaps doing such an intervention in a higher-risk group would yield successful results. However, a study of this size and duration is unlikely to be repeated, and virtually no signal of benefit from the intervention on cardiovascular events emerged. Was the study follow-up too short? Again, this is possible, considering that the effect of weight loss, better glycemic control, and cardiovascular risk reduction may take some time to manifest. But, 10

years should be long enough to see the emergence of differences, and the Data and Safety Monitoring Board stopped this study early because of a nearly impossible chance that differences would emerge between groups by 13.5 years. Was the sample size too small? This study had 80% power to detect an 18% difference in the primary outcome event rate between the intervention and control groups. A larger study may have found smaller differences between groups. Was the weight loss too limited? Observational studies of bariatric surgery patients have found that greater weight loss—an average of 25% of baseline body weight lost over 10 years with gastric bypass—was associated with a reduction in cardiovascular events and mortality [9,10]. However, even if greater weight loss were required to achieve a reduction in cardiovascular events, intensive weight loss interventions have rarely achieved more weight loss than seen in this trial.

Other relevant data came from the PREDIMED study [11]. This study found small but significant reductions in cardiovascular events for patients adhering to a Mediterranean-type diet, with free daily provisions of olive oil or mixed nuts (walnuts, almonds, and hazelnuts). After nearly 5 years of follow-up, subjects on the Mediterranean diet had 13 and 26 fewer events in the olive oil and nut diet arms compared with a control, low-fat diet, despite high total calorie consumption in the Mediterranean diet groups.

Perhaps our expectations for intensive lifestyle interventions have been too high. Such interventions can be successful and can achieve weight loss, increasing mobility and quality of life, and cardiovascular risk reduction without any evidence of harm. These are outcomes that can stand alone, even without a reduction in cardiovascular events. However, after Look AHEAD, we should be careful about how we communicate to patients the likely outcomes of weight loss and increasing physical activity. Patients may live better but not longer. Of course, these results should always be considered with the typical caveats for studies, which is that these results only apply to the population under study. A similar study in higher-risk patients may be more successful and life-saving, and studies with large sample sizes might detect more subtle differences. Studies that achieve greater weight loss also may lead to more success with cardiovascular events. Presently, Look AHEAD speaks loudest, and we should use its results to guide clinical practice.

Applications for Clinical Practice

Physicians should continue recommending intensive lifestyle education programs when appropriate for patients. However, they should understand and counsel patients that such interventions may not lead to a reduction in cardiovascular outcomes or mortality. Bariatric surgery and a Mediterranean diet might be considerations for patients most interested in a reduction in cardiovascular outcomes as their primary goal.

—Review by Jason P. Block, MD, MPH

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