



Lifestyle Intervention Fails to Reduce Rate of CV Events in T2DM but Has Favorable Effect on Other Measures

Written by Wayne Kuznar

An intensive lifestyle intervention (ILI) designed for weight loss did not reduce the risk of cardiovascular (CV) events after a decade in overweight/obese patients with type 2 diabetes mellitus (T2DM) compared with diabetes support and education (DSE). The ILI did, however, reduce the risk of developing advanced kidney disease and depression, and resulted in a lower rate of hospitalizations and a lower expenditure for medications.

Details of the Action for Health in Diabetes study [Look AHEAD; NCT00017953] were presented by four of the study's authors. Observational studies of the effects of weight loss in overweight and obese persons with T2DM have produced conflicting results, said Rena Wing, PhD, Alpert Medical School Brown University, Providence, Rhode Island, USA. She provided an overview of Look AHEAD and its outcomes related to CV disease [Look AHEAD Research Group. *N Engl J Med* 2013]. In Look AHEAD, conducted at 16 centers in the United States, 5145 overweight and obese patients with T2DM were randomly assigned to ILI promoting weight loss or DSE. A composite outcome of death from CV causes, nonfatal myocardial infarction (MI), nonfatal stroke, or hospitalization for angina during a maximum of 13.5 years follow-up comprised the primary endpoint.

The mean age of study participants at baseline was 58.7 years, their mean body mass index was 36 kg/m², their median duration of diabetes was 5 years, and 14% had a history of CV disease. All participants had annual visits during which weight, blood pressure (BP), and lipid levels were measured. A maximum fitness test was performed at baseline; submaximal tests were performed at Years 1, 2, and 4. At the annual visits and during phone calls every 6 months, participants reported medical events and hospitalizations. Medication changes were made by the subjects' own physicians.

The study was stopped prematurely after a maximum follow-up of 11 years (median, 9.6 years); short of the planned maximum follow-up of 13.5 years on the basis of futility for finding a difference between groups on the primary outcome.

Patients in the ILI group lost more weight compared with the DSE group. At 1 year, mean weight loss was 8.6% versus 0.7% for the ILI and DSE groups, respectively ($p < 0.001$). By the end of the study, mean weight loss was 6% and 3.5% in the ILI and DSE groups, respectively ($p < 0.001$).

Improvement in physical fitness, as measured in metabolic equivalents, was significantly greater with ILI than with DSE ($p < 0.001$). Patients assigned to ILI had significantly greater reductions in HbA1C ($p < 0.001$ from Years 1 to 6) and sustained improvements in systolic BP and high-density lipoprotein cholesterol levels relative to those assigned to DSE. Levels of low-density lipoprotein cholesterol, however, decreased significantly more in the DSE participants ($p < 0.05$ from Years 3 to 6), who also had greater use of statins, said Dr. Wing, who added that use of antihypertensive drugs and insulin was also significantly greater in the DSE group.

Occurrence of the primary outcome was not significantly different between the groups—1.83 events per 100 person-years in the ILI group versus 1.92 per 100 person-years in the DSE group (HR, 0.95; 95% CI, 0.83 to 1.09; $p = 0.505$). ILI and DSE did not differ significantly in the event rates for death from all CV causes, MI, hospitalization for angina, stroke, congestive heart failure, and rates of carotid endarterectomy and coronary artery bypass graft surgery.

The education sessions and the greater use of statins in the DSE group, along with intensive medical management of CV risk factors, may have obscured differences in outcomes between the two groups, said Dr. Wing.

RATE OF MICROVASCULAR COMPLICATIONS REDUCED WITH ILI

William C. Knowler, MD, DrPH, National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, Arizona, USA, spoke about the effects of ILI on microvascular complications of diabetes. As part of Look AHEAD, participants had annual measurements of urine albumin, urine creatinine, and serum creatinine for 4 years, and then every other year. Their level of chronic kidney disease (CKD) was classified using estimated glomerular filtration rate and measures of urine albumin excretion.

Over the course of the study, very-high-risk CKD developed in 123 participants in the ILI group versus 172 in the DSE group, corresponding to a 31% risk reduction with ILI (HR, 0.69; 95% CI, 0.55 to 0.87; $p = 0.002$). There were no significant differences in the effects of ILI on this endpoint according to age, race/ethnicity, diabetes duration, or other medical conditions, although ILI was significantly more effective in women than in men (p for interaction=0.02).

The rate of self-reported retinopathy was 14% lower in the ILI group relative to DSE (HR, 0.86; 95% CI, 0.75 to 0.98; $p=0.027$); there was no significant difference between groups in the occurrence of neuropathy symptoms (HR, 1.13; 95% CI, 0.92 to 1.38; $p=0.23$).

MOST QUALITY OF LIFE MEASURES FAVOR ILI

Lucy Faulconbridge, PhD, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA, reported that ILI ameliorated symptoms of depression and better protected participants against an age-related decline in physical health-related quality of life (HRQoL) measures than DSE. Look AHEAD participants completed the Beck Depression Inventory (BDI) and brought antidepressant medications to their yearly assessment visits. They also completed the Short Form-36 (SF-36) to gauge HRQoL.

The rate of incident mild or greater levels of depressive symptoms as determined by scores on the BDI was 20% lower in participants randomized to ILI compared with DSE (17.5% vs 20.9%; HR, 0.807; 95% CI, 0.704 to 0.924; $p=0.0019$), which suggests that weight loss protected against the development of elevated depressive symptoms, said Dr. Faulconbridge.

Resolution of significant symptoms of depression was not significantly different between the groups, with remission rates of 83.7% in the ILI group and 87.2% in the DSE. Initiation of antidepressant medications also did not differ over the course of the study (23.0% with ILI vs 21.3% with DSE; HR, 1.082; 95% CI, 0.951 to 1.230; $p=0.2315$).

Physical HRQoL was significantly better ($p<0.05$) in the ILI group versus the DSE during the first 8 years of the study, although the Physical Component Summary HRQoL score on the SF-36 declined in both groups as the participants aged.

Henry A. Glick, PhD, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA, reported that the rate of hospitalizations was 11.9% lower in the ILI group relative to the DSE group (hospitalizations per year, 0.193 versus 0.170; $p=0.003$), which translated into an annual reduction in cost of \$294 ($p=0.03$).

The number of medications per participants was reduced by 6.3%, from 4.92 to 4.61 per year ($p<0.001$), leading to a 10-year cost-offset of \$2487. The largest relative reductions in medication use in the ILI group were for diabetes drugs (13.3%; $p<0.0001$), lipid-lowering drugs (6.1%; $p=0.003$), and antihypertensive drugs (4.9%; $p=0.02$). The ILI group had greater increases in use of psychiatric/neurologic medications.

Average overall costs per year were \$8205 for the ILI group versus \$8807 for the DSE group ($p=0.001$).

The data do not include the cost of interventions, making it unclear whether ILI reduced total costs, said Dr. Glick.

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