

# Look Action for Health in Diabetes trial: What we have learned in terms of real world practice and clinical trials

Type 2 diabetes is the most common form of diabetes, affecting more and more people all over the world. Complications of type 2 diabetes include heart disease, stroke, blindness, nephropathy, neuropathy and amputations. It has long been known that lifestyle intervention is beneficial for the prevention and treatment of type 2 diabetes. Short-term studies have shown that weight loss improves control of blood sugar, and mitigates risk factors for heart disease and stroke in overweight and obese individuals with type 2 diabetes. However, the longer-term effects of weight loss have not been well studied, and a critical question remains: would an intensive lifestyle intervention (ILI) to lose bodyweight through caloric restriction and increased physical activity decrease cardiovascular morbidity and mortality among overweight or obese adults with type 2 diabetes? Recently, the results of the Look Action for Health in Diabetes (AHEAD) trial, the largest landmark study aimed to fill the gap in existing data about whether ILI would decrease cardiovascular disease (CVD), came up with interesting findings. ILI was unable to reduce cardiovascular events and mortality<sup>1</sup>. Initiated in 2001, the trial enrolled more than 5,000 adults at 16 clinical centers across the USA. It is the longest intervention study of its type ever undertaken for diabetes. A total of 5,145 diabetic patients with body mass index (BMI) >25 were randomly assigned to either the ILI arm, in which patients were provided with individual sessions with a nutritionist, group sessions and refresher courses; or the diabetes support

and education (DSE) arm, in which patients were given education and attended meetings twice a year, but they did not receive the intervention that was provided to the ILI group. The goal of the intervention was achieving and maintaining weight loss of at least 7%. The primary outcome of that study consisted of non-fatal myocardial infarction, non-fatal stroke, death or hospitalization for angina. After 11 years, the results showed no significant difference in the primary outcome between the two groups despite substantial reductions in bodyweight and improvements in many CVD risk factors, including treadmill fitness, blood pressure, high-density lipoprotein cholesterol and hemoglobin A1c<sup>1,2</sup>. Indeed, the trial concluded in 2012 after a median follow up of 9.6 years, when interim analyses suggested that it was very unlikely that further follow up would yield a different result.

Why did weight loss fail to reduce the rate of CVD or mortality in this trial? There are several possible explanations. First, although the weight loss achieved in the ILI group was one of the best that has been achieved with current lifestyle approaches, it is not enough to reduce the rate of CVD, and sustained larger weight loss might be required. Second, the rate of cardiac events was lower than expected in both groups (DSE 1.92, ILI 1.83 events/100 person-years). In fact, the study investigators had to expand the definition of the study outcome so they would have enough events to measure<sup>1</sup>. Third, the increased use of statins in the DSE group might have lessened the difference in CVD rates between the two groups, probably by decreasing the blood levels of low-density lipoprotein cholesterol and C-reactive protein, both are risk factors for atherosclerosis progression and CVD. This notion is supported by the results showing

that reductions in low-density lipoprotein cholesterol levels averaged across the first 4 years of the trial were greater in DSE than ILI participants ( $-12.84$  vs  $-11.27$  mg/dL;  $P = 0.009$ )<sup>2</sup>. In addition, the median C-reactive protein levels after 1 year of the trial were 2.6 mg/L for participants receiving statins in the DSE group and 2.9 mg/L for those randomized to ILI, but not receiving statins<sup>3</sup>. Fourth, as the 1-year and 4-year findings of the trial were already published and well publicized, the participants in the DSE group might have taken more action to lose weight and eat a healthy diet. Therefore, the CVD risks for all participants might have been reduced at a comparable rate. Fifth, it is also possible that ILI might cause a real reduction in CVD risks, but that it requires more than 10 years to become apparent. Indeed, the results of the United Kingdom Prospective Diabetes Study showed no difference in CVD at 12 years, but a significant difference at 20 years. Look AHEAD will now change into an observational cohort study in which patients will be followed over time and then the 'legacy effect' might become apparent later. Sixth, although weight loss and exercise can prevent diabetes in adults with prediabetes, once diabetes is established, they are not going to reduce the risk for macrovascular complications (Table 1).

Patients with type 2 diabetes and overweight or obesity might ask whether they can stop exercising and go out to eat anything they wish. The answer is of course 'no,' because there is an overwhelming amount of evidence from this study and others that have shown that weight loss and physical activity were associated with numerous health benefits. For instance, nephropathy, which is a major factor associated with worse qual-

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**Table 1** | Reasons to explain why weight loss failed to reduce the rate of cardiovascular disease and findings supporting health benefits in overweight diabetic patients in the Look Action for Health in Diabetes trial

Findings that support health benefits in overweight diabetic patients	Reasons to explain why weight loss failed to reduce the rate of CVD
<ol style="list-style-type: none"> <li>1. Greater likelihood of partial remission of type 2 diabetes.</li> <li>2. Decrease in kidney diseases and diabetic retinopathy.</li> <li>3. Less sleep apnea.</li> <li>4. Improved sexual dysfunction in female patients.</li> <li>5. Less urinary incontinence.</li> <li>6. Reduction in cases of new depression.</li> <li>7. Better physical function and mobility.</li> <li>8. Fewer hospitalization.</li> <li>9. Reduced medication use.</li> </ol>	<ol style="list-style-type: none"> <li>1. Not enough weight loss.</li> <li>2. Low cardiac events in both groups.</li> <li>3. Increased use of statins in DSE group.</li> <li>4. Participants in the DSE group might have taken more action to lose weight and eat a healthy diet when they knew the 1- and 4-year findings of the trial, which were publicized.</li> <li>5. Reduction in CVD requires more than 10 years to become apparent.</li> <li>6. Weight loss and exercise cannot reduce the risk for the macrovascular complications of established diabetes.</li> </ol>

CVD, cardiovascular disease; DSE, diabetes support and education.

ity of life and higher mortality in diabetic patients, was 31% lower in the ILI group. Other benefits of weight loss and exercise include 14% decrease in eye disease, less obstructive sleep apnea, improved sexual dysfunction in women, fewer hospitalizations, less urinary incontinence and reduced medication use<sup>1</sup>. All these continue to be reasons to recommend overweight diabetic patients to adopt a healthy lifestyle.

Finally, how about diet composition? The achieved dietary changes are not reported in the Look AHEAD trial. The role of dietary composition is not completely clear. Interest in the possible benefits of a Mediterranean-style diet rich in monounsaturated and polyunsaturated fat and lower in saturated fat started in the 1950s, and was boosted in 1994 when a large French trial found that it reduced mortality in patients after myocardial infarction. Since then, a persuasive body of evidence from observational studies has documented that Mediterranean-style diets are associated with a substantially reduced risk of CVD. Furthermore, the adoption of the Mediterranean diet has been associated with a significant reduction in new cancers. Recently, the results of a large randomized controlled trial extended the findings to persons at high risk for CVD<sup>4</sup>. Thus, the Mediterranean diet pattern can be considered an effective approach for the prevention of fatal and non-fatal CVD complications. This diet pattern is rich in monounsaturated fat, polyphenols and polyunsaturated fat,

including alpha-linolenic acid. Further studies are warranted to examine in more detail what the important components are and how they work.

Another issue worth mentioning is fructose. Fructose is a major component of added sugars. In the last 100 years, intake of fructose has increased dramatically, and correlates closely with the rise in obesity, metabolic syndrome and diabetes. Fructose is distinct from other sugars in its ability to cause intracellular adenosine triphosphate depletion, nucleotide turnover and the generation of uric acid. The discovery provides new insights into the pathogenesis and therapies for this important disease<sup>5</sup>. Furthermore, a low-fat diet, as adopted in this trial, might be accompanied by increasing the portion size of carbohydrate intake to be isocaloric in the ILI group, which might contribute a confounding factor in dietary impacts.

In conclusion, although intensive lifestyle therapy did not decrease the rate of CVD in the Look AHEAD trial, it is reasonable to recommend overweight people to increase physical activity, eat healthily and to lose weight. The earlier this is done the better. Furthermore, the possible benefits of individual food components require further investigation. Lifestyle therapy might have to focus not only on bodyweight, but also on diet composition. As for evidence on beneficial CVD outcomes, mega-trials with stratified control in confounding factors, especially 'cardioprotective' drugs, remain to be seen.

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