

# Intensive Lifestyle Intervention in Type 2 Diabetes

**TO THE EDITOR:** Wing et al. (July 11 issue)<sup>1</sup> report that significant reductions in cardiovascular risk factors were achieved in the Look AHEAD (Action for Health in Diabetes) trial, yet no significant difference in clinical end points was evident. Table 1 of their article perhaps indicates the reason for this apparent discrepancy. More than 59% of the patients in each treatment group were women, and in both groups, the serum low-density lipoprotein and high-density lipoprotein cholesterol values of 112 mg per deciliter and 43 mg per deciliter, respectively, and smoking prevalence rates of less than 5% suggest that this was indeed an elite cohort of patients. Fewer than 15% of the patients had previous cardiovascular disease. The use of current risk-prediction tools such as the Systematic Coronary Risk Evaluation<sup>2</sup> for patients without diabetes who have this profile (e.g., women who do not smoke) suggests a (crude) 10-year rate of fatal cardiovascular events of 1%. Even doubling this risk in a population with diabetes suggests a risk of 2% over the same period, which was close to that observed in the trial (Table 2 of the article). The expectation that lifestyle intervention would exert a positive effect on this already low baseline risk over 10 years was optimistic, and this trial was surely underpowered to detect significant differences in outcome.

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No potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** The failure of intensive lifestyle modification to achieve cardiovascular benefits in patients with diabetes, as reported by the Look AHEAD Research Group, may be due to the high burden of cardiovascular disease in the trial participants at baseline. The median duration of diabetes was 5 years, and 14% of the patients had a

history of cardiovascular disease. Early treatment and intervention, before clinically significant cardiovascular changes have set in, are crucial to achieve macrovascular benefits.<sup>1</sup> In the United Kingdom Prospective Diabetes Study, patients who had tight glycemic control in the initial stages of the disease had significant cardiovascular benefits during the post-study follow-up phase. However, tight glycemic control did not result in significant cardiovascular benefits in the Action to Control Cardiovascular Risk in Diabetes study, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation study, or the Veterans Affairs Diabetes Trial; this was attributed to the inclusion of patients who had already been receiving treatment for several years.<sup>2</sup> It might be interesting to have a separate analysis of the outcomes in those patients who had a shorter duration of diabetes in the Look AHEAD study. Lifestyle modification, which is basically a preventive measure, would be expected to yield good results in patients with newly diagnosed disease rather than in patients with established vascular complications.

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No potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** The conclusions of the Look AHEAD trial, which are misleading for obese persons who are trying to achieve a healthy weight, are likely to induce complacency. The mean weight of patients in the group of patients who were assigned to participate in an intensive lifestyle intervention decreased by only 6.0%, with the largest mean weight loss of 8.6%. Although the end-of-study body-mass index (the

weight in kilograms divided by the square of the height in meters) was not reported, is likely to have been in the obese range (approximately 32.5). The mean waist circumference decreased by only 2 cm (to 112 cm) in the intervention group. The Swedish Obese Subjects study showed that a weight loss of more than 20% achieved by bariatric surgery, with a sustained weight loss of 17% at 10 years, reduced cardiovascular events in patients with diabetes.<sup>1,2</sup> Moreover, greater reductions in weight and waist circumference than those in the present study are achievable by means of dietary intervention.<sup>3</sup> The reason for negative outcomes in this study was the lack of significant weight loss (which unfortunately was not hypothesized) achieved with the intensive lifestyle intervention. The conclusions should have clearly reflected this fact.

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**TO THE EDITOR:** In the Look AHEAD trial, an intervention to decrease caloric and fat intake (with <30% of calories from fat) and to increase physical activity did not reduce cardiovascular events among patients with type 2 diabetes.

However, among 3614 patients with type 2 diabetes included in our Prevención con Dieta Mediterránea trial, a Mediterranean diet, as compared with a control (low-fat) diet, was associated with a significant 29% relative reduction in cardiovascular events.<sup>1</sup> Among our participants with diabetes, we observed that patients who reduced their total intake to less than 30% of calories from fat during the trial, as compared

with patients who did not reduce their total fat intake, did not have a reduction in cardiovascular events (multivariable-adjusted relative risk, 0.95; 95% confidence interval, 0.47 to 1.91;  $P=0.89$ ). This is consistent with the null results for low-fat diets in Look AHEAD and another trial.<sup>2</sup>

In our experience, the long-term compliance with and sustainability of low-fat diets are not ideal. In any case, nutritional quality should be a higher priority than reducing fat intake.<sup>3</sup> The Mediterranean diet has passed the tests of long-term sustainability, effectiveness,<sup>1</sup> and nutritional quality.<sup>4</sup> A low-calorie Mediterranean diet might be the most sensible approach for weight loss and prevention of cardiovascular disease in patients with diabetes.

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No other potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** The results of the Look AHEAD trial showed that a very intervention-focused and

expensive weight-loss program (which included 46 visits with a health professional in the first year alone, the use of meal-replacement products daily, and the use of orlistat) did not achieve any of its prespecified cardiovascular objectives.

Had there been a surgical group in the study, it seems likely that there would not only have been a reduction in adverse cardiovascular outcomes, but there would also have been fewer deaths.<sup>1-3</sup> Several studies have shown that bariatric surgery results in marked reductions in the incidence of other obesity-related conditions such as diabetes, gastroesophageal reflux disease, sleep apnea,<sup>1,2,4</sup> and cancer, as well as marked reductions in mortality.<sup>2-4</sup>

This trial does not answer the question as to whether lifestyle interventions such as weight loss and exercise improve outcomes in patients with diabetes. They almost certainly do. It simply addresses the question of whether a medically supervised weight-loss program can achieve those outcomes, and it almost certainly cannot.

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**THE AUTHORS REPLY:** The lack of a significant effect of lifestyle intervention on cardiovascular outcomes has led to concerns about our approach. Our trial addressed a very important question: whether an intensive lifestyle intervention focused on weight loss reduces cardiovascular morbidity and mortality in overweight and obese

adults with type 2 diabetes. We believe the trial succeeded in addressing this question and that our findings are valid, although our results may have been unexpected. This should raise questions not about the study design, but about the ways in which lifestyle interventions do and do not benefit persons with type 2 diabetes.

Meleady suggests that the participants in the trial were too healthy to see benefits, whereas Mahabala suggests that their disease was too advanced; we stress that we recruited the cohort specified in our protocol and observed a sufficient number of events (i.e., power) to detect clinically meaningful effects.

Dhooria et al. and Martínez-González et al. raise concerns about our intervention. We know of no study examining long-term lifestyle interventions that achieved better weight loss and maintenance than ours. Dhooria et al. cite the results of the Diet, Obesity, and Genes study,<sup>1</sup> which examined weight loss at week 26 in a subgroup of patients who had successful weight loss initially; in contrast, our trial examined weight loss over 9 to 10 years in all participants who were randomly assigned to participate in the intensive lifestyle intervention. Martínez-González et al. note that we did not test a Mediterranean diet; we agree and encourage research on a full range of dietary options for persons with diabetes. Similarly, as Eliosoff and Christou observe, our study did not include a group that was randomly assigned to bariatric surgery. To our knowledge, there has never been a trial comparing cardiovascular outcomes in participants with type 2 diabetes who were randomly assigned to bariatric surgery or lifestyle intervention. Although our trial showed no evidence of beneficial effects with respect to cardiovascular morbidity and mortality in the intention-to-treat analyses, other analyses to compare outcomes within subgroups of participants categorized according to baseline level of disease and weight loss achieved would be of interest.

We agree with Eliosoff and Christou that lifestyle intervention has many positive effects. Although our trial showed no beneficial effect of lifestyle intervention on cardiovascular morbidity and mortality, it produced many important benefits, including improvements in glycemic control, physical functioning, and quality of life, as

well as reductions in sleep apnea, urinary incontinence, and depression symptoms. Thus, we believe weight loss remains important for overweight and obese patients with type 2 diabetes.

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## Carotid Stenosis

**TO THE EDITOR:** We are less certain than Grotta (Sept. 19 issue)<sup>1</sup> that the female patient with recently symptomatic internal-carotid-artery stenosis described in the case vignette of his Clinical Practice article should be treated with carotid endarterectomy or stenting. On the basis of a published risk-prediction model<sup>2</sup> (available at [www.stroke.ox.ac.uk](http://www.stroke.ox.ac.uk)), her 5-year risk of recurrent ipsilateral stroke could be as high as 25% but is probably considerably lower. This model is based on data from large, randomized trials that enrolled patients from 1981 through 1996. These trials showed the benefit of early carotid endarterectomy over medical treatment alone in cases such as hers.<sup>3</sup> However, medical treatment has improved substantially in the meantime and may now be as effective as early carotid revascularization in reducing the risk of recurrent stroke<sup>4</sup>; this is supported by findings from a recent randomized trial involving patients with symptomatic intracranial-artery stenosis in which aggressive medical management was superior to stenting.<sup>5</sup> We would therefore recommend to this patient randomization to carotid revascularization or optimized medical treatment alone in the ongoing European Carotid Surgery Trial 2 ([www.ecst2.com](http://www.ecst2.com)).

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Drs. van der Worp and Bonati report being members of the steering committee and Dr. Brown reports being the chief investigator of the European Carotid Surgery Trial 2. Dr. van der Worp reports receiving a grant (2010T075) from the Dutch Heart Foundation, speaking fees from Sanofi-Aventis and GlaxoSmith-Kline, and consulting fees from Bristol-Myers Squibb; and Dr. Brown, receiving grants from the National Institute for Health Research in the United Kingdom. No other potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** Grotta recommends carotid-artery stenting over carotid endarterectomy for the treatment of a 53-year-old woman with stroke symptoms lasting 48 hours. The reasons given were the patient's "relatively young age" and "recent stroke, which increases the risks associated with surgery and general anesthesia." We disagree with that rationale. Even in the best academic centers, rates of stroke and rates of stroke