ORIGINAL ARTICLE

Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

The Look AHEAD Research Group*

ABSTRACT

BACKGROUND

Weight loss is recommended for overweight or obese patients with type 2 diabetes on the basis of short-term studies, but long-term effects on cardiovascular disease remain unknown. We examined whether an intensive lifestyle intervention for weight loss would decrease cardiovascular morbidity and mortality among such patients.

METHODS

In 16 study centers in the United States, we randomly assigned 5145 overweight or obese patients with type 2 diabetes to participate in an intensive lifestyle intervention that promoted weight loss through decreased caloric intake and increased physical activity (intervention group) or to receive diabetes support and education (control group). The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina during a maximum follow-up of 13.5 years.

RESULTS

The trial was stopped early on the basis of a futility analysis when the median follow-up was 9.6 years. Weight loss was greater in the intervention group than in the control group throughout the study (8.6% vs. 0.7% at 1 year; 6.0% vs. 3.5% at study end). The intensive lifestyle intervention also produced greater reductions in glycated hemoglobin and greater initial improvements in fitness and all cardiovascular risk factors, except for low-density-lipoprotein cholesterol levels. The primary outcome occurred in 403 patients in the intervention group and in 418 in the control group (1.83 and 1.92 events per 100 person-years, respectively; hazard ratio in the intervention group, 0.95; 95% confidence interval, 0.83 to 1.09; P=0.51).

CONCLUSIONS

An intensive lifestyle intervention focusing on weight loss did not reduce the rate of cardiovascular events in overweight or obese adults with type 2 diabetes. (Funded by the National Institutes of Health and others; Look AHEAD ClinicalTrials.gov number, NCT00017953.)

The authors and their affiliations are listed in the Appendix. Address reprint requests to Dr. Rena Wing at the Weight Control and Diabetes Research Center, Warren Alpert Medical School of Brown University and Miriam Hospital, 196 Richmond St., Providence, RI 02903, or at rwing@lifespan.org.

*A complete list of participants in the Look AHEAD (Action for Health in Diabetes) Research Group is provided in the Supplementary Appendix, available at NEJM.org.

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Weight loss is recommended for overweight or obese patients with type 2 diabetes.[1] This recommendation is based on short-term studies showing numerous benefits of weight loss, including improvements in glycemic control, risk factors for cardiovascular disease, quality of life, and other obesity-related coexisting illnesses.[2] However, it is unknown whether weight loss reduces the risk of cardiovascular morbidity and mortality in patients with type 2 diabetes. Epidemiologic studies involving patients with diabetes have had conflicting results, perhaps because of confounding from unintentional weight loss.[3] A meta-analysis[4] of cohort studies concluded that moderate intentional weight loss was associated with reduced mortality among patients who were classified as "unhealthy," including those with diabetes. The Swedish Obese Subjects (SOS) study[5] showed reduced rates of cardiovascular events during a mean follow-up of 13.3 years among patients with type 2 diabetes who had undergone bariatric surgery. However, the study was not randomized, and the results achieved through surgery cannot be generalized to other methods of weight loss.

Thus, a critical question remains: Would an intensive lifestyle intervention designed to achieve weight loss through caloric restriction and increased physical activity decrease cardiovascular morbidity and mortality among overweight or obese adults with type 2 diabetes? The Look AHEAD (Action for Health in Diabetes) researchers addressed this question in a multicenter, randomized clinical trial.

Methods

Study Design

The study methods have been published previously.[6,7] The study was conducted at 16 clinical sites in the United States (for details, see the Supplementary Appendix, available with the full text of this article at NEJM.org). It was designed and conducted by the authors, and all analyses were completed by the coordinating center. The study was approved by the institutional review board at each center. The trial was not blinded, but clinical assessors and end-point adjudicators were unaware of study-group assignments. The authors vouch for the accuracy and completeness of the data and all analyses and for the fidelity of this report to the trial protocol, available at NEJM.org.

The study was sponsored by the National Institutes of Health, with additional support from other federal partners and the clinical research centers of several participating institutions. None of the corporate supporters, listed below, had any role in the trial design, data analysis, or reporting of results.

Study Patients

To be eligible for participation in the trial, patients were required to be 45 to 75 years of age and to meet all the following criteria: self-reported type 2 diabetes, as verified by the use of glucose-lowering medication, a physician's report, or glucose levels; a body-mass index (the weight in kilograms divided by the square of the height in meters) of 25.0 or more (27.0 or greater in patients taking insulin); a glycated hemoglobin level of 11% or less; a systolic blood pressure of less than 160 mm Hg; a diastolic blood pressure of less than 100 mm Hg; a triglyceride level of less than 600 mg per deciliter (6.77 mmol per liter); the ability to complete a valid maximal exercise test, suggesting it was safe to exercise; and an established relationship with a primary care provider. Patients could be using any type of glucose-lowering medication, but the percentage of those receiving insulin allowed in the trial was limited to less than 30%. Patients with and those without a history of cardiovascular disease were included to increase the generalizability of the results. Additional eligibility criteria are described elsewhere[6] and in the Supplementary Appendix.

Study Interventions

Eligible patients were randomly assigned to participate in an intensive lifestyle intervention (intervention group) or to receive diabetes support and education (control group), with stratification according to clinical site. Curricula for the two study groups were developed centrally and have been described in detail previously[6,8] (see the Supplementary Appendix).

The intensive lifestyle intervention was aimed at achieving and maintaining weight loss of at least 7% by focusing on reduced caloric intake and increased physical activity. The program included both group and individual counseling sessions, occurring weekly during the first 6 months, with decreasing frequency over the course of the trial. Specific intervention strategies included a calorie goal of 1200 to 1800 kcal per day (with <30%

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of calories from fat and >15% from protein), the use of meal-replacement products, and at least 175 minutes of moderate-intensity physical activity per week. A toolbox of strategies was available for patients having difficulty achieving the weight-loss goals (see the Supplementary Appendix).

Diabetes support and education featured three group sessions per year focused on diet, exercise, and social support during years 1 through 4. In subsequent years, the frequency was reduced to one session annually.

All medication adjustments were made by the patient's health care provider, with the exception of temporary changes in glucose-lowering medications made by study staff to reduce the risk of hypoglycemia in the intervention group. Patients and their health care providers received annual reports on the patients' updated cardiovascular risk factors and the goals recommended by the American Diabetes Association.[1]

STUDY ASSESSMENTS

At annual visits, certified staff members who were unaware of study-group assignments measured weight, waist circumference, and blood pressure, along with assessing medication use and obtaining blood for analysis at a central laboratory.[6] Maximal-exercise tests were performed in the full cohort before randomization. Submaximal-exercise tests were performed in the full cohort at years 1 and 4 and in a subset of patients at year 2.

During annual visits and telephone calls every 6 months, staff members who were unaware of study-group assignments queried patients about all medical events and hospitalizations. These queries were augmented with searches of national databases for deaths. Hospital and other records were reviewed for potential cardiovascular events, with adjudication according to standard criteria by reviewers who were unaware of study-group assignments (see the Supplementary Appendix).

STUDY END POINTS

The primary end point was the first occurrence of a composite cardiovascular outcome. Initially, the composite outcome included death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke, and the anticipated maximal follow-up period was 11.5 years. During the first 2 years of the trial, the primary-event rate in the control group was lower than expected.[9] Therefore, hospitalization for angina was added to the primary outcome, and planned follow-up was extended to a maximum of 13.5 years.

Three composite secondary cardiovascular outcomes were also examined: death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (the original primary outcome); death from any cause, myocardial infarction, stroke, or hospitalization for angina; and death from any cause, myocardial infarction, stroke, hospitalization for angina, coronary-artery bypass grafting, percutaneous coronary intervention, hospitalization for heart failure, or peripheral vascular disease.

STATISTICAL ANALYSIS

We determined that an enrollment of 5000 patients would provide a power of more than 80% to detect a between-group difference of 18% in the rate of major cardiovascular events, with a two-sided alpha level of 0.05, a primary outcome rate of 2% per year in the control group, and a planned maximum follow-up of 13.5 years. The 18% between-group difference was chosen on the basis of reductions in mortality among patients with type 2 diabetes and voluntary weight loss in an observational study,[10] effect sizes chosen for trials with similar outcomes,[11] feasibility, and public health significance.

On September 14, 2012, on the basis of a futility analysis and recommendation from the data and safety monitoring board, the study's primary sponsors instructed the study investigators to terminate the intervention. All data were censored on this date. At that time, the probability of observing a significant positive result at the planned end of follow-up (i.e., a hazard ratio of 0.82 in the intervention group) was estimated to be 1%.

We used the chi-square test, Fisher's exact test, the Wilcoxon rank-sum test, two-sample t-tests, and Poisson regression to compare the baseline characteristics and key safety outcomes in the two study groups. Physical and laboratory measurements and medication use from baseline through 10 years were modeled with generalized linear regression and generalized estimating equations. The study center was included as a covariate, the covariance was unstructured, and linear contrasts were used to compare groups throughout follow-up. We performed analyses of primary and secondary outcomes using time-to-event methods according to the intention-to-treat principle, as

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prespecified in the protocol. Kaplan–Meier estimates were used to calculate the cumulative proportion of patients who had an event. First occurrences of primary and secondary outcomes in the two groups were compared with hazard ratios and 95% confidence intervals. Two-sided P values were calculated with likelihood-ratio tests from Cox proportional-hazards regression, with models containing terms for clinical site, history of cardiovascular disease, and study-group assignment. The consistency of intervention effects on the primary outcome among three prespecified subgroups (based on sex, race or ethnic group, and presence or absence of cardiovascular disease at baseline) was evaluated with the use of interaction tests. Results were not adjusted for multiple comparisons, and a P value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were conducted with the use of S-Plus software, version 8.0 (Insightful), or SAS software, version 9.1 (SAS Institute).

Table 1. Characteristics of the Patients at Baseline.*

Variable	Control Group (N=2575)	Intervention Group (N=2570)
Age — yr	58.9±6.9	58.6±6.8
Female sex — no. (%)	1537 (59.7)	1526 (59.4)
Race or ethnic group — no. (%)†		
Black	404 (15.7)	400 (15.6)
Native American	128 (5.0)	130 (5.1)
Asian or Pacific Islander	21 (0.8)	29 (1.1)
White	1631 (63.3)	1621 (63.1)
Hispanic	340 (13.2)	340 (13.2)
Other	51 (2.0)	50 (1.9)
History of cardiovascular disease — no. (%)‡	348 (13.5)	366 (14.2)
Use of insulin — no. (%)§	410 (16.5)	382 (15.4)
Current smoking — no. (%)	110 (4.3)	117 (4.6)
Median duration of diabetes (interquartile range) — yr	5.0 (2.0–10)	5.0 (2.0–10)
Weight — kg	101±19	101±20
Body-mass index¶	36.0±5.8	35.9±6.0
Waist circumference — cm	114±14	114±14
Glycated hemoglobin — %	7.3±1.2	7.2±1.1
Blood pressure — mm Hg		
Systolic	129±17	128±17
Diastolic	70.4±9.6	69.9±9.5
Cholesterol — mg/dl		
High-density lipoprotein	43.5±12	43.4±12
Low-density lipoprotein	112±32	112±32
Median triglycerides (interquartile range) — mg/dl	152 (107–218)	155 (110–221)

* Plus–minus values are means ±SD. There was no significant difference between the two study groups in any baseline characteristic except systolic blood pressure (P<0.01). To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.
† Race was self-reported.
‡ A history of cardiovascular disease was defined as a previous myocardial infarction or stroke, congestive heart failure, or a previous cardiovascular procedure (coronary-artery bypass grafting, percutaneous coronary intervention, carotid endarterectomy, angioplasty of a lower-extremity artery, or aortic-aneurysm repair).
§ The use of insulin was measured in 2479 patients in the control group and 2485 patients in the intervention group.
¶ The body-mass index is the weight in kilograms divided by the square of the height in meters.

RESULTS

STUDY PATIENTS

From August 2001 through April 2004, a total of 5145 patients were enrolled and randomly assigned to participate in the intensive lifestyle intervention (2570) or to receive diabetes support and education (2575) (Fig. S1 in the Supplementary Appendix). The characteristics of the patients in the two groups were similar at baseline (Table 1). The average age was 58.7 years, 60% of the patients were women, and the mean body-mass index was 36.0. The median duration of diabetes was 5 years, and 14% of patients reported a history of cardiovascular disease. Additional baseline data have been published previously.[12]

When the intervention was stopped on September 14, 2012, the median follow-up was 9.6 years (interquartile range, 8.9 to 10.3), and less than 4% of all patients randomly assigned to a study group had been lost to follow-up.

WEIGHT, WAIST CIRCUMFERENCE, AND FITNESS

Patients in the intervention group had significantly greater reductions in weight and waist circumference and greater improvement in fitness than did those in the control group (Fig. 1A, 1B, and 1C, and Table S1 in the Supplementary Appendix). Differences in mean weight loss were largest at 1 year (8.6% in the intervention group vs. 0.7% in the control group) but remained significant throughout the trial. When the study ended, the mean weight loss from baseline was 6.0% in the intervention group and 3.5% in the control group.

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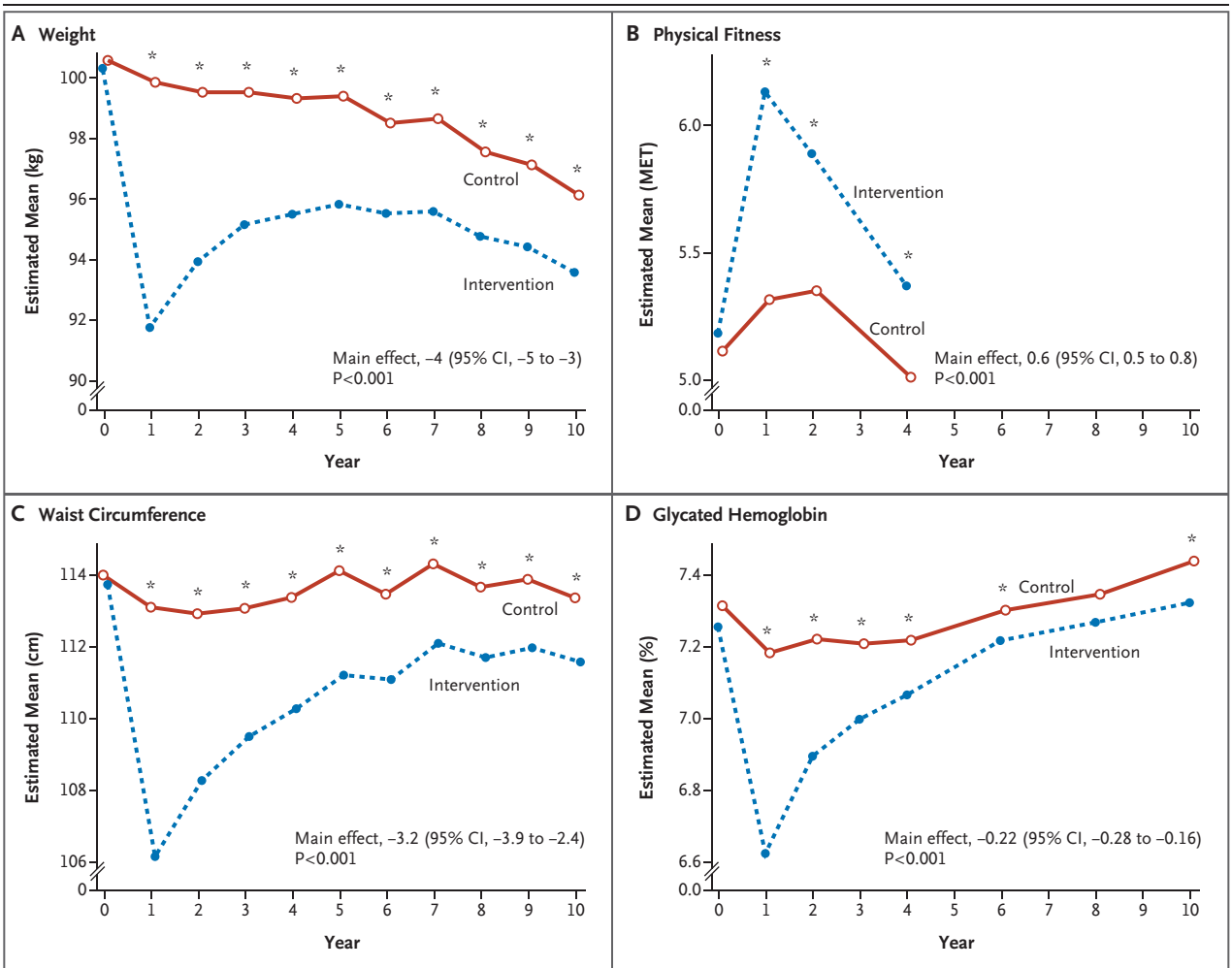


Figure 1. Changes in Weight, Physical Fitness, Waist Circumference, and Glycated Hemoglobin Levels during 10 Years of Follow-up.
Shown are the changes from baseline in overweight or obese patients with type 2 diabetes who participated in an intensive lifestyle intervention (intervention group) or who received diabetes support and education (control group). The reported main effect is the average of all between-group differences after baseline. Means were estimated with the use of generalized linear models for continuous measures. MET denotes metabolic equivalents; asterisks indicate P<0.05 for the between-group comparison. Data from 107 visits during year 11 were not included in the analyses.

RISK FACTORS FOR CARDIOVASCULAR DISEASE

During the first year of follow-up, patients in the intervention group had greater improvements than the control group in glycated hemoglobin levels (Fig. 1D) and in all other measured cardiovascular risk factors, except for low-density lipoprotein (LDL) cholesterol levels (Fig. S2 and Table S1 in the Supplementary Appendix). The between-group difference in cardiovascular risk factors diminished over time, with the glycated hemoglobin level and systolic blood pressure showing the most sustained differences. LDL cholesterol levels were lower in the control group than in the intervention group (mean difference, 1.6 mg per deciliter [0.04 mmol per liter] during 10 years of follow-up). The use of antihypertensive medications, statins, and insulin was lower in the intervention group than in the control group (Fig. S2 and S3 and Table S1 in the Supplementary Appendix).

CLINICAL OUTCOMES

The composite primary outcome — the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina — occurred in 403

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patients in the intervention group and 418 in the control group, with no significant between-group difference (1.83 and 1.92 events per 100 person-years, respectively; hazard ratio in the intervention group, 0.95; 95% confidence interval, 0.83 to 1.09; P=0.51) (Table 2 and Fig. 2). There were also no significant between-group differences with respect to the prespecified composite secondary outcomes or any of the individual cardiovascular events making up the composite outcomes (Table 2). There were no significant interactions among the prespecified subgroups (Fig. 3).

ADVERSE EVENTS

Severe hypoglycemia, gallstones, fractures, amputations, and congestive heart failure were monitored, as plausibly being affected by the intensive lifestyle intervention. Although the rate of self-reported fractures differed significantly between groups (2.51 per 100 person-years in the intervention group vs. 2.16 per 100 person-years in the control group, P=0.01), there was no significant difference in the rate of adjudicated fractures (1.66 and 1.64 per 100 person-years, respectively; P=0.83) (Table S2 in the Supplementary Appendix).

Table 2. Primary and Secondary Outcomes and Other Cardiovascular Outcomes.*

Outcome	Patients with Event	Control Group	Intervention Group	Hazard Ratio (95% CI)	P Value
	no.	*no. of events (rate/100 person-yr)*			
Primary outcome					
Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina	821	418 (1.92)	403 (1.83)	0.95 (0.83–1.09)	0.51
Secondary outcomes					
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	550	283 (1.25)	267 (1.17)	0.93 (0.79–1.10)	0.42
Death from any cause, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina	1025	529 (2.43)	496 (2.25)	0.93 (0.82–1.05)	0.23
Death from any cause, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, CABG, PCI, hospitalization for heart failure, carotid endarterectomy, or peripheral vascular disease	1177	600 (2.81)	577 (2.67)	0.94 (0.84–1.05)	0.29
Other cardiovascular outcomes					
Death					
Any cause	376	202 (0.86)	174 (0.73)	0.85 (0.69–1.04)	0.11
Cardiovascular cause	109	57 (0.24)	52 (0.22)	0.88 (0.61–1.29)	0.52
Myocardial infarction					
Fatal or nonfatal†	354	191 (0.84)	163 (0.71)	0.84 (0.68–1.04)	0.11
Fatal	16	11 (0.05)	5 (<0.02)	0.44 (0.15–1.26)	0.13
Nonfatal	342	183 (0.80)	159 (0.69)	0.86 (0.69–1.06)	0.16
Hospitalization for angina	390	196 (0.87)	194 (0.85)	0.97 (0.80–1.19)	0.79
Stroke	165	80 (0.34)	85 (0.36)	1.05 (0.77–1.42)	0.78
Heart failure	218	119 (0.51)	99 (0.42)	0.80 (0.61–1.04)	0.10
CABG	525	269 (1.21)	256 (1.14)	0.93 (0.78–1.10)	0.41
Carotid endarterectomy	54	25 (0.11)	29 (0.12)	1.10 (0.64–1.87)	0.74

* CABG denotes coronary-artery bypass grafting, and PCI percutaneous coronary intervention.
† Patients who had both nonfatal and fatal myocardial infarctions were counted only once.

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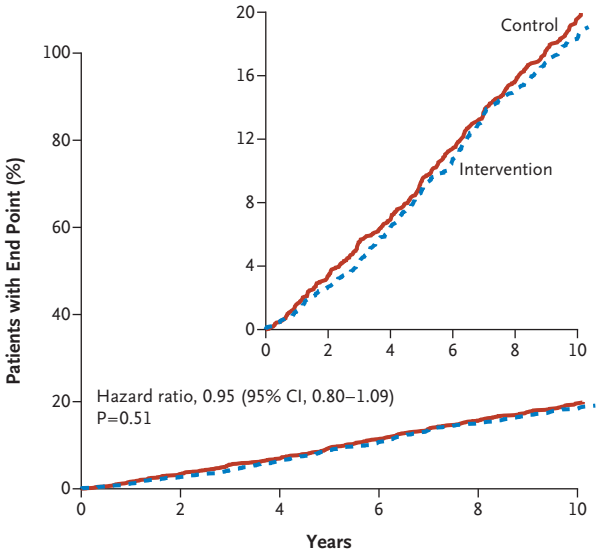
DISCUSSION

In this study, we compared the effect of an intensive lifestyle intervention with a control regimen of diabetes support and education among overweight or obese patients with type 2 diabetes. At a median follow-up of almost 10 years, there was no significant difference between the two groups in cardiovascular morbidity and mortality.

Our findings showed that overweight or obese adults with type 2 diabetes can lose weight and maintain modest weight loss during a 10-year period. Multicomponent lifestyle interventions in clinical trial settings typically achieve an initial weight loss of 7 to 10%,[13,14] with maximal weight loss at 1 year, followed by gradual regain.[13-15] However, few studies have provided an ongoing intervention for an extended period.[16] In our trial, the initial mean weight loss in the intervention group was 8.6%. This was followed by weight regain through year 5 and then a subsequent gradual decrease in weight, resulting in an average weight loss of 6.0% at the end of the trial. The control group had a gradual but consistent weight loss throughout the study, resulting in an average weight loss of 3.5% at the end of the trial. The intervention group also had greater improvements in fitness, particularly at 1 year.

We have considered several possible explanations for the lack of a significant difference in the rates of cardiovascular events between groups. One possibility is that the study lacked sufficient power. However, we do not believe that this explains the negative result; the 95% confidence interval for the primary outcome excluded the benefit of 18% or more targeted in the trial's design. Another possibility is that a sustained weight loss of more than that achieved in the intervention group may be required to reduce the risk of cardiovascular disease. In this regard, it is noteworthy that the differential weight loss between the two trial groups averaged 4% over the course of the study but only 2.5% at the end. However, our trial was planned to test the effects of an intensive lifestyle intervention, and the weight loss achieved in the intervention group is representative of the best that has been achieved with current lifestyle approaches. Third, the provision of educational sessions and the increased use of statins in the control group, as compared with the intervention group, may have lessened the difference between the two groups. In addition, the intensification of medical management of cardiovascular risk factors[17] in routine medical care in the two study groups may have made the relative benefit of the intensive lifestyle intervention more difficult to demonstrate. The intervention may also have had different effects in different subgroups. Although none of the interactions with subgroups were significant, our data suggest that the event rate for the primary outcome was nonsignificantly lower in the intervention group than in the control group among patients with no history of cardiovascular disease at baseline but that it was nonsignificantly higher in the intervention group than in the control group among those with cardiovascular disease at baseline.

There are several limitations to these findings. We used a specific lifestyle intervention that focused on achieving weight loss through caloric restriction and increased physical activity. It is unclear whether an intervention focused on changes in dietary composition (e.g., the Mediterranean diet[18]) might have different outcomes. In addition,



No. at Risk

Control	2575	2425	2296	2156	2019	688
Intervention	2570	2447	2326	2192	2049	505

Figure 2. Cumulative Hazard Curves for the Primary Composite End Point.
Shown are Kaplan–Meier estimates of the cumulative proportion of patients with a primary event. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina. The numbers below the graph are the numbers of patients at risk in each study group at years 2, 4, 6, and 8 and at 10.4 years, when the last observed event occurred. The inset shows the same data on an expanded y axis.

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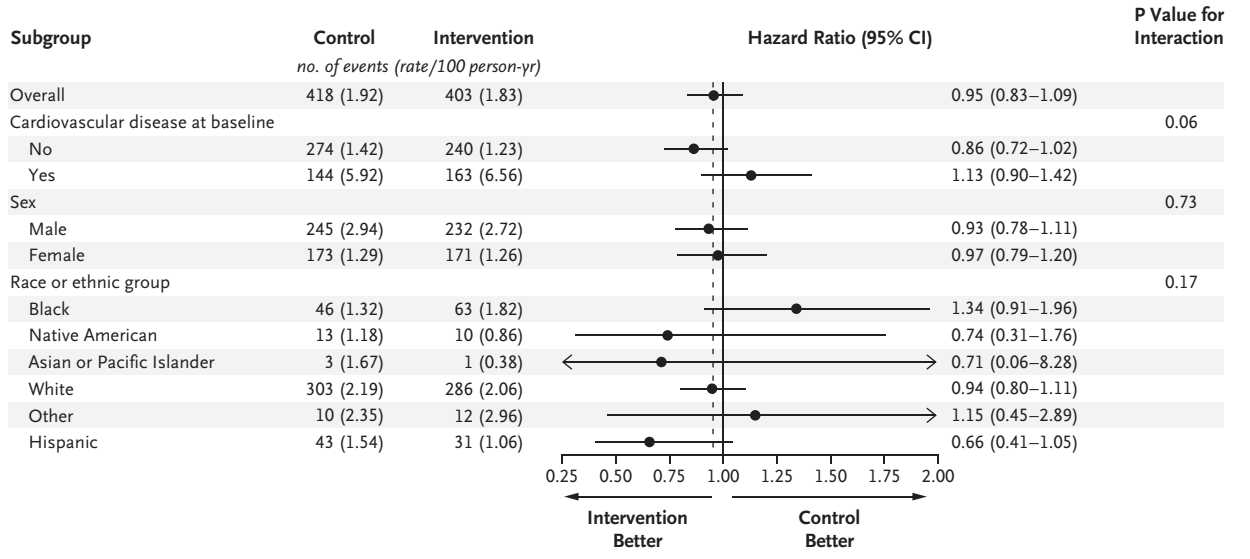


Figure 3. Primary Outcome in Prespecified Subgroups.

Shown are hazard ratios for three prespecified subgroups — defined according to the presence or absence of cardiovascular disease at baseline, sex, and race or ethnic group — in the intervention group and the control group. The dashed vertical line indicates the overall hazard ratio (0.95), and the solid vertical line indicates no effect (hazard ratio, 1.00).

we recruited patients with type 2 diabetes who were motivated to lose weight through lifestyle intervention and who could successfully complete a maximal-fitness test at baseline. Thus, the results cannot be generalized to all patients with type 2 diabetes.

The finding that the intensive lifestyle intervention, as compared with diabetes support and education, did not reduce the risk of cardiovascular morbidity and mortality must be considered in the context of other positive effects observed with this intervention. Patients in the intervention group had clinically meaningful improvements in glycated hemoglobin levels, which were greatest during the first year but were at least partly sustained throughout follow-up. This positive effect may explain why patients in the intervention group were less likely to be treated with insulin during this period. Furthermore, we recently reported that patients in the intervention group were more likely to have a partial remission of diabetes during the first 4 years of the trial than were those in the control group.[19] Other benefits that were identified during the early years of the trial included reductions in urinary incontinence,[20] sleep apnea,[21] and depression[22] and improvements in quality of life,[23] physical functioning,[24] and mobility.[25] Intensive lifestyle intervention has also been shown to prevent or delay the development of type 2 diabetes in other studies.[15,26]

In conclusion, our study showed that an intensive lifestyle intervention did not reduce the risk of cardiovascular morbidity or mortality, as compared with a control program of diabetes support and education, among overweight or obese patients with type 2 diabetes.

The opinions expressed in this article are those of the authors and do not necessarily reflect the views of the funding sources.

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APPENDIX

The authors are as follows: Rena R. Wing, Ph.D., Weight Control and Diabetes Research Center, Warren Alpert Medical School of Brown University and Miriam Hospital, Providence, RI; Paula Bolin, R.N., M.C., National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; Frederick L. Brancati,* M.D., M.H.S., Johns Hopkins School of Medicine, Baltimore; George A. Bray, M.D., Pennington Biomedical Research Center, Baton Rouge, LA; Jeanne M. Clark, M.D., M.P.H., Johns Hopkins School of Medicine, Baltimore; Mace Coday, Ph.D., Department of Preventive Medicine, University of Tennessee Health Sciences Center, Memphis; Richard S. Crow,* M.D., Division of Epidemiology and Community Health, University of Minnesota, Minneapolis; Jeffrey M. Curtis, M.D., M.P.H., NIH/NIDDK Southwest American Indian Center, Phoenix, AZ; Caitlin M. Egan, M.S., Weight Control and Diabetes Research Center, Warren Alpert Medical School of Brown University and Miriam Hospital, Providence, RI; Mark A. Espeland, Ph.D., Department of Biostatistical Sciences, Wake Forest University School of Medicine, Winston-Salem, NC; Mary Evans, Ph.D., NIH/NIDDK, Bethesda, MD; John P. Foreyt, Ph.D., Department of Medicine, Baylor College of Medicine, Houston; Siran Ghazarian, M.D., Roybal Comprehensive Health Center, Los Angeles; Edward W. Gregg, Ph.D., Centers for Disease Control and Prevention, Atlanta; Barbara Harrison, M.S., NIH/NIDDK, Bethesda, MD; Helen P. Hazuda, Ph.D., Department of Clinical Epidemiology, University of Texas Health Science Center at San Antonio, San Antonio; James O. Hill, Ph.D., Center for Human Nutrition, University of Colorado Health Sciences Center, Aurora; Edward S. Horton, M.D., Joslin Diabetes Center, Boston; Van S. Hubbard, M.D., Ph.D., NIH/NIDDK, Bethesda, MD; John M. Jakicic, Ph.D., Department of Health and Physical Activity, University of Pittsburgh, Pittsburgh; Robert W. Jeffery, Ph.D., Division of Epidemiology and Community Health, University of Minnesota, Minneapolis; Karen C. Johnson, M.D., M.P.H., Department of Preventive Medicine, University of Tennessee Health Sciences Center, Memphis; Steven E. Kahn, M.B., Ch.B., Department of Medicine, University of Washington, Seattle; Abbas E. Kitabchi, Ph.D., M.D., Department of Preventive Medicine, University of Tennessee Health Sciences Center, Memphis; William C. Knowler, M.D., Dr.P.H., NIH/NIDDK Southwest American Indian Center, Phoenix, AZ; Cora E. Lewis, M.D., M.S.P.H., Division of Preventive Medicine, University of Alabama at Birmingham, Birmingham; Barbara J. Maschak-Carey, M.S.N., C.D.E., Weight and Eating Disorder Program, University of Pennsylvania, Philadelphia; Maria G. Montez, R.N., M.S.H.P., C.D.E., Department of Clinical Epidemiology, University of Texas Health Science Center at San Antonio, San Antonio; Anne Murillo, B.S., Department of Medicine, University of Washington, Seattle; David M. Nathan, M.D., Diabetes Unit, Massachusetts General Hospital, Boston; Jennifer Patricio, M.S., Department of Medicine, St. Luke's–Roosevelt Hospital, New York; Anne Peters, M.D., Roybal Comprehensive Health Center, Los Angeles; Xavier Pi-Sunyer, M.D., Department of Medicine, St. Luke's–Roosevelt Hospital, New York; Henry Pownall, Ph.D., Department of Medicine, Baylor College of Medicine, Houston; David Reboussin, Ph.D., Department of Biostatistical Sciences, Wake Forest University School of Medicine, Winston-Salem, NC; Judith G. Regensteiner, Ph.D., Center for Women's Health Research, University of Colorado Health Sciences Center, Aurora; Amy D. Rickman, Ph.D., R.D., L.D.N., Department of Health and Physical Activity, University of Pittsburgh, Pittsburgh; Donna H. Ryan, M.D., Pennington Biomedical Research Center, Baton Rouge, LA; Monika Safford, M.D., Division of Preventive Medicine, University of Alabama at Birmingham, Birmingham; Thomas A. Wadden, Ph.D., Weight and Eating Disorder Program, University of Pennsylvania, Philadelphia; Lynne E. Wagenknecht, Dr.P.H., Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC; Delia S. West, Ph.D., Department of Health Behavior and Health Education, College of Public Health, University of Arkansas for Medical Sciences, Little Rock; David F. Williamson, Ph.D., Centers for Disease Control and Prevention, Atlanta; and Susan Z. Yanovski, M.D., NIH/NIDDK, Bethesda, MD.

*Deceased.

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