Original Article
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

History of Cardiovascular Disease, Intensive Lifestyle Intervention, and Cardiovascular Outcomes in the Look AHEAD Trial

Look AHEAD Research Group, Cora E. Lewis [1], John P. Bantle[2], Alain G. Bertoni[3], George Blackburn[4], Frederick L. Brancati[5], George A. Bray[6], Lawrence J. Cheskin[5], Jeffrey M. Curtis[7], Caitlin Egan[8], Mary Evans[9], John P. Foreyt[10], Siran Ghazarian[11], Bethany Barone Gibbs[12], Stephen P. Glasser[1], Edward W. Gregg[13], Helen P. Hazuda[14], Louise Hesson[15], James O. Hill[16], Edward S. Horton[17], Van S. Hubbard[9], John M. Jakicic [12], Robert W. Jeffery[2], Karen C. Johnson [18], Steven E. Kahn[19], Abbas E. Kitabchi[18], Dalane Kitzman[3], William C. Knowler[20], Edward Lipkin[19], Sara Michaels[21], Maria G. Montez[14], David M. Nathan[22], Ebenezer Nyenwe[18], Jennifer Patricio[23], Anne Peters[11], Xavier Pi-Sunyer[23], Henry Pownall[10], David M. Reboussin[3], Donna H. Ryan [6], Thomas A. Wadden [15], Lynne E. Wagenknecht[3], Holly Wyatt[16], Rena R. Wing [8], and Susan Z. Yanovski[9]

Objective: To examine the effects of an intensive lifestyle intervention (ILI) on cardiovascular disease (CVD), the Action for Health in Diabetes (Look AHEAD) trial randomized 5,145 participants with type 2 diabetes and overweight/obesity to a ILI or diabetes support and education. Although the primary outcome did not differ between the groups, there was suggestive evidence of heterogeneity for prespecified baseline CVD history subgroups (interaction $P=0.063$). Event rates were higher in the ILI group among those with a CVD history (hazard ratio 1.13 [95% CI: 0.90-1.41]) and lower among those without CVD (hazard ratio 0.86 [95% CI: 0.72-1.02]).
Methods: This study conducted post hoc analyses of the rates of the primary composite outcome and components, adjudicated cardiovascular death, nonfatal myocardial infarction (MI), stroke, and hospitalization for angina, as well as three secondary composite cardiovascular outcomes.
Results: Interaction *P* values for the primary and two secondary composites were similar (0.060-0.064). Of components, the interaction was significant for nonfatal MI ($P=0.035$). This interaction was not due to confounding by baseline variables, different intervention responses for weight loss and physical fitness, or hypoglycemic events. In those with a CVD history, statin use was high and similar by group. In those without a CVD history, low-density lipoprotein cholesterol levels were higher ($P=0.003$) and statin use was lower ($P\leq0.001$) in the ILI group.
Conclusions: Intervention response heterogeneity was significant for nonfatal MI. Response heterogeneity may need consideration in a CVD-outcome trial design.

Study Importance

What is already known?

- Lifestyle interventions promoting weight loss have been shown to improve cardiovascular disease (CVD) risk factors; however, there are few data on long-term effects of lifestyle intervention on CVD morbidity or mortality.

What does this study add?

- The Look AHEAD trial found no overall difference in the rates of a composite cardiovascular outcome between participants randomized to intensive lifestyle intervention (ILI) compared with those assigned to the control condition of diabetes support and education, but there was suggestive evidence ($P=0.063$) of treatment response heterogeneity by baseline CVD.
- In Look AHEAD participants with CVD at baseline, there was a reduction in nonfatal myocardial infarction among ILI participants, compared with the control condition ($P=0.035$).

Obesity (2020) **28**, 247-258.

[1] University of Alabama at Birmingham, Birmingham, Alabama, USA. Correspondence: Cora E. Lewis (celewis@uabmc.edu) [2] University of Minnesota, Minneapolis, Minnesota, USA [3] Wake Forest University, Winston-Salem, North Carolina, USA [4] Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA [5] Johns Hopkins University, Baltimore, Maryland, USA [6] Pennington Biomedical Research Center, Baton Rouge, Louisiana, USA [7] Southwestern American Indian Center, National Institute of Diabetes and Digestive and Kidney Diseases and St. Joseph's Hospital and Medical Center, Phoenix, Arizona, USA [8] The Miriam Hospital, Brown Medical School, Providence, Rhode Island, USA [9] National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland, USA [10] Baylor College of Medicine, Houston, Texas, USA [11] University of Southern California, Los Angeles, California, USA [12] University of Pittsburgh, Pittsburgh, Pennsylvania, USA [13] Centers for Disease Control and Prevention, Atlanta, Georgia, USA [14] University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA [15] University of Pennsylvania, Philadelphia, Pennsylvania, USA [16] University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA [17] Joslin Diabetes Center, Boston, Massachusetts, USA [18] The University of Tennessee Health Science Center, Memphis, Tennessee, USA [19] US Department of Veterans Affairs Puget Sound Health Care System, University of Washington, Seattle, Washington, USA [20] Southwestern American Indian Center, National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, Arizona, USA [21] Southwestern American Indian Center, Shiprock, New Mexico, USA [22] Massachusetts General Hospital, Boston, Massachusetts, USA [23] St. Luke's Roosevelt Hospital Center, Columbia University, New York, New York, USA.

 Received: 19 February 2019; **Accepted:** 11 September 2019; **Published online 3 January 2020. doi:10.1002/oby.22676**

Introduction

Lifestyle interventions have been shown to reduce cardiovascular disease (CVD) risk factors and have other health benefits for individuals with overweight or obesity and type 2 diabetes (1). However, there have been few studies evaluating the long-term effects of a lifestyle intervention on CVD morbidity or mortality. The Action for Health in Diabetes (Look AHEAD) trial randomized 5,145 volunteers with type 2 diabetes to either an intensive lifestyle intervention (ILI) or diabetes support and education (DSE), the usual-care control condition. Participants were observed for a median of 9.6 years until September 14, 2012 (2). At that time, study investigators terminated the intervention on the basis of a futility analysis, as recommended by the trial data and safety monitoring board (DSMB).

The incidence of the primary outcome, a composite of fatal or nonfatal myocardial infarction (MI), stroke, hospitalization for angina, or cardiovascular death, did not differ between the ILI and DSE groups, nor did any of the components of the primary outcome (2). There were no conventionally significant interactions between treatment assignment and the primary outcome in prespecified subgroups; however, the interaction for the prespecified subgroup of self-reported history of CVD at baseline approached significance ($P=0.063$). Among participants with a history of CVD, the ILI group had a nonsignificantly higher incidence of the primary CVD outcome compared with the DSE group (6.59%/y vs. 5.95%/y, respectively; hazard ratio [HR] for ILI vs. DSE 1.13 [95% CI: 0.90-1.41]). In contrast, among participants without CVD at baseline, the ILI group had a nonsignificantly lower incidence of the primary outcome (1.23%/y vs. 1.41%/y, respectively; HR 0.86 [95% CI: 0.72-1.02]). Because this interaction did not reach conventional levels of statistical significance, it was not discussed further in the report. However, the interaction had been nominally significant during trial monitoring and was of concern to the DSMB.

Therefore, the suggestion that ILI may have had heterogeneous effects in participants with and without a history of CVD could have implications for clinical care in high-risk populations, including patients with type 2 diabetes and CVD, and for the design of clinical trials. Therefore, we performed exploratory data analyses to examine the impact of treatment assignment on the components of the composite primary and secondary CVD outcomes among participants with versus without a history of CVD at baseline and to examine the potential effects of baseline covariates, responses to intervention, and hypoglycemia events.

Methods

Study design and participants

Detailed study methods have been published previously (3), and the protocol is available at https://repository.niddk.nih.gov/studies/look-ahead/?query=Look%20AHEAD. The study was conducted at 16 clinical centers in the United States and was approved by the institutional review board at each center. All participants gave written informed consent.

We determined that 5,000 participants would provide more than 80% power to detect a between-group difference of 18% in the rate of major CVD events, with two-sided $\alpha=0.05$, a primary outcome rate of 2% per year in the DSE group, and a planned maximum follow-up of 13.5 years (2). Incidence rates of the primary and secondary composite outcomes were monitored for efficacy and futility by a DSMB throughout the trial (3). Look AHEAD recruited participants from August 2001 to April 2004, randomizing 5,145 participants to either a ILI or DSE in a 1:1 ratio, stratified by clinical center (Figure 1). Treatment group assignment was not blinded to participants or investigators, but outcome assessors and adjudicators were masked to intervention assignment.

Eligibility and recruitment details have been previously reported (3,4) (see the Methods section of the online Supporting Information). In brief, participants had type 2 diabetes, verified by self-report of use of hypoglycemic medications, physician or medical record report, or fasting plasma glucose value ≥ 126 mg/dL confirmed on a subsequent day.

We recruited individuals with and without a prior history of CVD to increase the generalizability of our results to the overall population of patients with type 2 diabetes and to increase the event rate. We defined CVD history at baseline as self-reported history of MI, coronary revascularization, stroke, transient ischemic attack, heart failure, or peripheral arterial revascularization. We screened potential participants with a maximum symptom-limited graded treadmill exercise test to assess fitness and safety of physical activity. We excluded those who reported an acute CVD event within 3 months of screening or had other cardiovascular conditions or findings (e.g., ischemia on exercise electrocardiogram [ECG]) that could affect the safety of the intervention.

Interventions

Curricula for both the ILI and DSE were developed centrally and have been described in detail (3,5-7) (see the online Supporting Information). The ILI aimed to achieve and maintain at least 7% weight loss by focusing on reduced caloric intake and increased physical activity. The program included frequent contact throughout the trial using both group and individual sessions, a calorie goal of 1,200 to 1,800 kcal/d, and at least 175 min/wk of moderate-intensity physical activity by month 6, with a further increase to 200 min/wk for those who met this goal. The DSE condition included three group education sessions per year during years 1 to 4 that focused on diet, exercise, and social support and one session annually in later years.

All medication adjustments were made by the participant's health care provider, except for temporary changes in glucose-lowering medications made by study staff according to an algorithm designed to reduce the risk of hypoglycemia in the ILI group during periods of weight loss. Participants in the ILI and DSE groups and their health care providers received annual reports on the participants' most recent blood pressure levels, fasting glucose levels, hemoglobin A_{1C} (HbA_{1C}) levels, fasting lipid panel, and renal function measures as well as the goals recommended by the American Diabetes Association (3).

Assessments

Certified masked staff measured weight, waist circumference, and blood pressure; assessed medication use; and obtained blood for analysis at the central laboratory annually (3). Maximal exercise tests were performed on the full cohort prior to randomization, and submaximal tests were performed at years 1 and 4. A subset had submaximal testing at year 2 (8). Self-reported physical activity was assessed by questionnaire (9).

At annual visits and 6-month phone calls, for which participants received a stipend, ILI and DSE participants were queried by masked staff about all medical events and hospitalizations using a structured outcomes interview. Searches of various databases were used to identify deaths and track participants. Hospital and other records were obtained

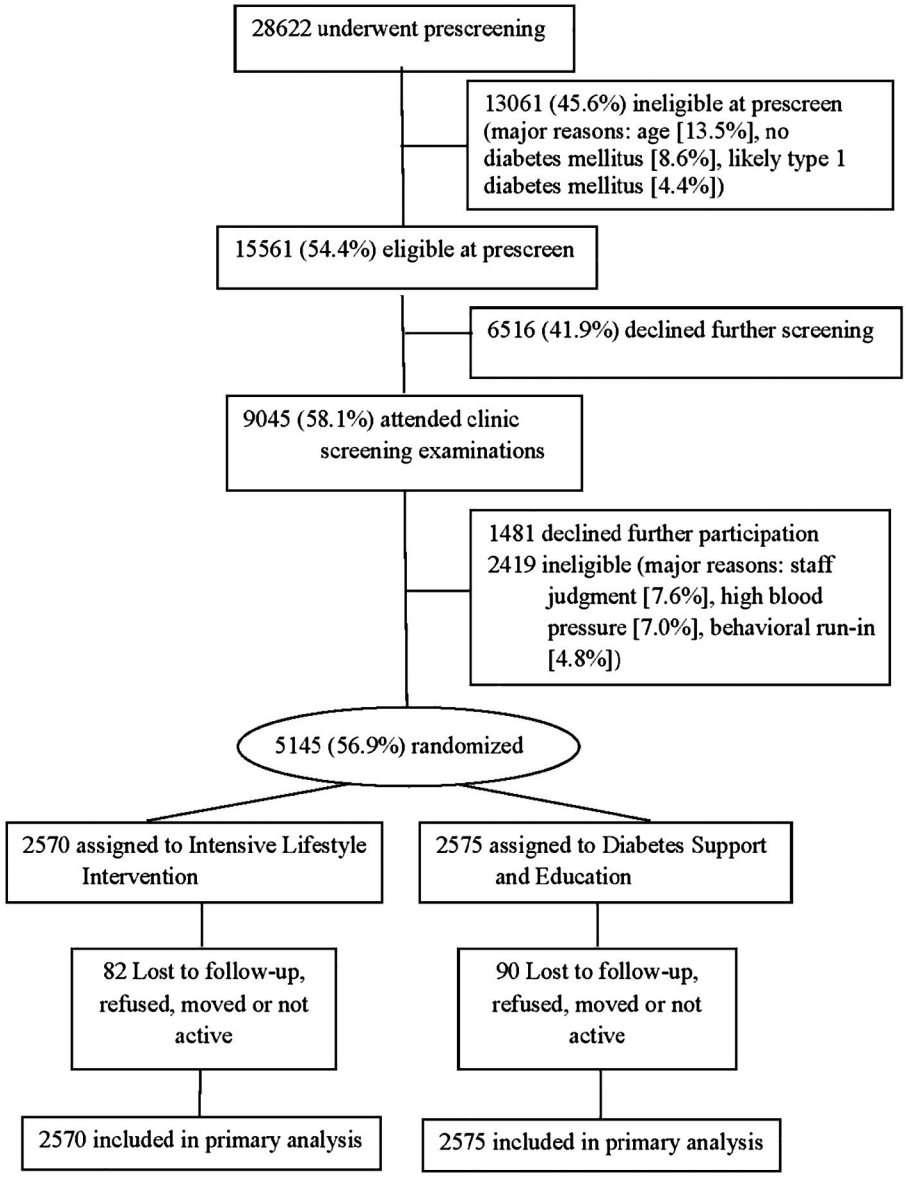

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) diagram for the Look AHEAD trial. Republished from Wing et al. (2).

for potential CVD events that were adjudicated according to standard criteria by masked reviewers (2).

Hypoglycemia events

Serious hypoglycemia was defined as any episode of loss of consciousness or level of confusion that prevented self-treatment or required hospitalization or emergency care (10). All participants were assessed for emergency department and/or doctor visits for hypoglycemia by the structured outcomes interview. However, participants could report hypoglycemia events at any contact. In these cases, unmasked staff collected information about hypoglycemia events and implemented safety protocols.

Study outcomes

The primary outcome was the first occurrence of a composite consisting of CVD death, MI, stroke, or hospitalized angina (2,11). Hospitalized angina was added to the original primary composite outcome because of the lower-than-expected event rate in the DSE group during the first two years of the trial (11). Three composite secondary cardiovascular outcomes were examined: (1) CVD death, MI, or stroke (original primary outcome); (2) death (all causes), MI, stroke, or hospitalized angina; and (3) death (all causes), MI, stroke, hospitalized angina, coronary artery revascularization, hospitalization for heart failure, or procedures to address peripheral artery disease (bypass or angioplasty), including carotid procedures. For this

exploratory data analysis, we also examined individual components of the primary outcome and total mortality.

Statistical analysis

We used the same data set used for the main results report (2). Participants reported their history of CVD at the initial telephone screening and during their first in-person screening visit; our main analyses included participants reporting CVD at either assessment. A total of 714 reported CVD history, and 4,431 did not. Analyses of primary and secondary outcomes using time-to-event methods according to the intention-to-treat principal included all available data through September 14, 2012, with a median follow-up of 9.6 years (interquartile range 8.9-10.3 y).

Using the prespecified subgroup of CVD history, we performed additional post hoc exploratory data analyses to examine the interaction between treatment assignment and baseline history of CVD for the primary outcome, its components, and secondary composites. Three groups of analyses were undertaken. We assessed whether baseline covariates that could influence the incidence of events might be unbalanced by intervention arm within subgroups defined by baseline CVD history, especially those expected to be different in participants with and without CVD. We tested for CVD subgroup effects on the components of the primary outcome and on other CVD outcomes. We assessed whether additional adjustment for an array of baseline covariates affected the estimation of CVD subgroup effects, adjusting for baseline factors not balanced between groups. We conducted these models on nonfatal MI given that it was the primary outcome component with a significant CVD subgroup interaction. Additional summaries were performed on post-randomization changes in risk factors, medication use, and hypoglycemia incidence.

Differences in baseline covariates between groups were tested using two-sample *t* tests for continuous variables and χ^2 statistics for categorical variables. Proportional hazards models stratified by clinical center were used to estimate effects on time-to-event outcomes. We used mixed-effects models or generalized estimating equations for physical and laboratory measurements and medication use from baseline to 10 years. In all longitudinal analyses, an unstructured covariance matrix was estimated. Because these are exploratory analyses, results were not adjusted for multiple comparisons, and $P<0.05$ was considered statistically significant using two-tailed tests. We used S-PLUS software version 8.0 (Insightful Corporation, Seattle, Washington) or SAS software version 9.1 (SAS Institute, Inc., Cary, North Carolina).

Results

Baseline differences by CVD history

CVD history was reported by 714 (14%) of Look AHEAD participants. Overall and within CVD subgroups, the ILI and DSE groups

TABLE 1 Baseline characteristics by history of CVD at baseline and randomization assignment

	CVD history at baseline present		No CVD history at baseline		
Variable	DSE (*n* = 348)	ILI (*n* = 366)	DSE (*n* = 2,227)	ILI (*n* = 2,204)	CVD history difference, *P* value
Age, y, mean (SD)	62.3 (6.6)	62.0 (6.7)	58.3 (6.8)	58.0 (6.6)	< 0.001
Female sex, %	37.9	39.1	63.1	62.7	< 0.001
Race/ethnicity, %					< 0.001
White	72.4	72.1	61.9	61.6	…
African American	10.6	11.5	16.5	16.3	…
Hispanic	9.2	9.3	13.8	13.9	…
Other	7.8	7.1	7.8	8.3	…
Duration of diabetes, y, mean (SD)	9.0 (8.4)	9.0 (8.0)	6.5 (6.0)	6.4 (6.3)	< 0.001
Insulin treatment, %	23.4	25.9	15.5	13.6	< 0.001
Current smoking, %	4.9	5.7	4.2	4.4	0.202
Weight, kg, mean (SD)	101.6 (18.7)	103.1 (18.9)	100.7 (18.9)	100.1 (19.8)	0.014
BMI, kg/m^2, mean (SD)	35.0 (5.5)	35.8 (5.6)	36.1 (5.8)	35.9 (6.1)	0.012
Fitness (METs), mean (SD)	6.8 (2.0)	6.7 (1.8)	7.2 (2.0)	7.3 (2.0)	< 0.001
Use of statins, %	72.4	71.5	40.6	40.7	< 0.001
Use of any antihypertensive drug, %	87.8	91.8	69.8	69.6	< 0.001
Use of aspirin, %	81.6	81.4	51.3	50.4	< 0.001
SBP, mm Hg, mean (SD)	128.8 (19.0)	128.3 (18.3)	129.6 (16.7)	128.2 (17.1)	0.641
DBP, mm Hg, mean (SD)	69.3 (10.2)	68.4 (9.7)	70.5 (9.5)	70.2 (9.5)	< 0.001
HbA_{1C}, %	7.4 (1.2)	7.4 (1.1)	7.3 (1.2)	7.2 (1.2)	0.010
eGFR, mL/min/1.73 m^2, mean (SD)	83.4 (16.5)	84.2 (16.5)	91.0 (15.7)	91.4 (16.0)	< 0.001
LDL-C, mg/dL, mean (SD)	102.4 (33.4)	102.3 (30.4)	113.5 (31.8)	113.8 (32.3)	< 0.001
HDL-C, mg/dL, mean (SD)	41.2 (11.5)	41.0 (10.9)	43.9 (11.8)	43.8 (11.9)	< 0.001
Triglycerides, mg/dL, mean (SD)	197.3 (132.6)	183.6 (111.5)	179.2 (119.2)	180.1 (113.2)	0.020

CVD, cardiovascular disease; DBP, diastolic blood pressure; DSE, diabetes support and education; eGFR, estimated glomerular filtration rate; HbA_{1C}, hemoglovin A_{1C}; HDL-C, high-density lipoprotein cholesterol; ILI, intensive lifestyle intervention; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent; SBP, systolic blood pressure.

were similar at baseline (Table 1). However, most characteristics were different between those with and without a CVD history. Those with CVD were somewhat older, were more often white, had a longer duration of diabetes, were more often male, were less fit but with less obesity, and more often used insulin, aspirin, lipid-lowering statins, and antihypertensive medications. Those with CVD also had lower levels of low-density lipoprotein cholesterol (LDL-C) and diastolic blood pressure (DBP) but a worse estimated glomerular filtration rate and worse high-density lipoprotein cholesterol (HDL-C), HbA_{1C}, and triglyceride levels. Only current smoking and systolic blood pressure (SBP) were not significantly different between CVD history subgroups.

Association between CVD history at baseline and CVD outcomes

The 14% of participants with baseline CVD experienced 37% of the primary outcomes over the course of follow-up and had outcome rates more than fivefold and fourfold higher than did those without CVD in the ILI and DSE groups, respectively (Table 2). Although the overall event rates between DSE and ILI were not significantly different, we noted suggestive evidence of a CVD history–treatment assignment interaction ($P=0.063$). Among those without a CVD history, the ILI resulted in a nonsignificantly lower incidence of the primary outcome, whereas in those with CVD, the ILI resulted in a nonsignificantly higher incidence (Figure 2). For better understanding of this interaction, we examined the various components of the primary outcome (Table 2). Significant interaction P values were present for MI ($P=0.043$), specifically nonfatal MI ($P=0.035$; Figure 3). There was no evidence of interaction for other primary outcome components and total mortality.

We next examined whether interactions between treatment group and CVD history were seen for the secondary composite outcomes (Table 2). The interaction terms approached significance for the first ($P=0.060$) and second ($P=0.064$) composite outcomes but was not significant for the third composite outcome ($P=0.430$).

Interaction effects for nonfatal MI after adjusting for baseline characteristics

Given the baseline differences between CVD subgroups, we examined whether controlling for these variables modified the CVD history–treatment assignment interaction for nonfatal MI by further adjusting the protocol-defined model for the variables in Table 1. This baseline adjustment did not change the within-subgroup HR in those without baseline CVD. In those with a CVD history, the estimated HR increased from 1.14 to 1.23, and the interaction P value strengthened from 0.035 to 0.010, providing greater evidence for heterogeneity (Table 3).

Intervention effects by CVD history

As previously reported (2), the ILI produced sustained reductions in body weight, HbA_{1C} levels, and SBP as well as sustained improvements in fitness through year 4, relative to DSE. We considered the possibility that the CVD subgroups might have responded differently to ILI, resulting in the interaction effects. We found little evidence to support this (Supporting Information Table S1). For example, in those with a CVD history, the median weight loss at year 1 in the ILI group was 7.5% of body weight, compared with 0.1% in the DSE group; among those without CVD, the median loss was 8.0% and 0.5%, respectively, indicating similar weight loss in the ILI group and ILI-DSE differences. Fitness improvement at year 1 in the ILI group was 12.2% in those with CVD and 15.6% in those without CVD, whereas those in both DSE subgroups experienced no change (Supporting Information Table S1, Supporting Information Figure S1). At year 4, fitness decreased in all groups except the ILI group without baseline CVD (median change 0.0 metabolic equivalents); both CVD subgroups in the ILI experienced similar differences relative to DSE. The interactions between treatment and CVD history were not significant for either percent weight change ($P=0.85$) or fitness change (metabolic equivalents; $P=0.51$).

Changes in CVD risk factors and use of statins, insulin, and aspirin differed by CVD subgroup and, in some cases, by randomization assignment. Among those without baseline CVD, the ILI group had significantly higher LDL-C levels ($P=0.003$; Figure 4) and lower statin use ($P<0.001$; Figure 5) than did the DSE group, but differences were not numerically large. For example, in the ILI group, the mean LDL-C level at year 4 was 97.3 mg/dL, and 59% of participants reported statin use, whereas in the DSE group, these were 94.0 mg/dL and 62%, respectively. Aspirin use in those without CVD was significantly lower in the ILI group in years 1 and 2, but differences were not numerically large (Supporting Information Figure S2). Among those with a CVD history, LDL-C levels and statin use did not differ between the ILI and DSE during follow-up. At year 4 and beyond, in those with a CVD history, statins were used by approximately 80% or more of both ILI and DSE group participants, and mean LDL-C levels were less than 90 mg/dL in both groups at each time point. Aspirin use in those with CVD did not differ between the ILI and DSE and was also high at all time points.

HbA_{1C} was significantly improved by the ILI early in follow-up, with similar effects in CVD subgroups (overall $P<0.001$ in both; Supporting Information Figure S3). Among those with baseline CVD, insulin use was nonsignificantly greater in the DSE group during follow-up, whereas in those without baseline CVD, insulin use was significantly more common in the DSE group ($P<0.001$; Supporting Information Figure S4). For HDL-C ($P=0.003$; Supporting Information Figure S5) and SBP ($P<0.001$; Supporting Information Figure S6), the ILI had greater improvements than DSE among those without CVD at baseline, especially early in follow-up. Among those with baseline CVD, ILI had nonsignificant improvements for both HDL-C and SBP. DBP (Supporting Information Figure S7) and triglyceride levels (Supporting Information Figure S8) were not significantly different between treatment groups in either CVD subgroup.

Hypoglycemia

We found that the interaction between randomization assignment and CVD history for hypoglycemia events was not significant ($P=0.106$; Supporting Information Figure S9). There were similar hypoglycemia rates in those without CVD but nonsignificantly greater rates in the ILI group when compared with DSE in those with baseline CVD. However, only 24 participants had both a nonfatal MI and a hypoglycemic event; of those, only 8 participants had a hypoglycemic event before a nonfatal MI, and 6 of those were at least 200 days before the MI. The 2 hypoglycemic events occurring less than 60 days before an MI were too few to influence a CVD history–treatment group interaction.

Discussion

Look AHEAD showed that a ILI did not reduce the rate of CVD events in adults with overweight or obesity and type 2 diabetes, compared with a DSE control (2). However, there was evidence of potential

TABLE 2 Primary and secondary outcome event rates and HRs overall and according to CVD history at baseline for subgroups

	Overall			CVD history			No CVD history			
	Event rate		HR (95% CI), *P*	Event rate		HR (95% CI), *P*	Event rate		HR (95% CI), *P*	*P* for interaction
	DSE	ILI		DSE	ILI		DSE	ILI		
Primary outcome[a]	418, 1.92%	403, 1.83%	0.95 (0.83-1.09), *P*=0.505	144, 5.95%	163, 6.59%	1.13 (0.90-1.41), *P*=0.305	274, 1.41%	240, 1.23%	0.86 (0.72-1.02), *P*=0.090	0.063
Secondary outcome[b]	283, 1.25%	267, 1.17%	0.93 (0.79-1.10), *P*=0.416	99, 3.63%	114, 4.11%	1.15 (0.87-1.50), *P*=0.330	184, 0.93%	153, 0.77%	0.82 (0.66-1.02), *P*=0.069	0.060
Secondary outcome[c]	529, 2.43%	496, 2.25%	0.93 (0.82-1.05), *P*=0.229	163, 6.73%	179, 7.23%	1.10 (0.88-1.36), *P*=0.404	366, 1.89%	317, 1.62%	0.85 (0.73-0.99), *P*=0.038	0.064
Secondary outcome[d]	600, 2.81%	577, 2.67%	0.94 (0.84-1.05), *P*=0.293	190, 8.59%	200, 8.58%	1.01 (0.82-1.23), *P*=0.961	410, 2.15%	377, 1.95%	0.91 (0.79-1.04), *P*=0.179	0.430
CVD death	57, 0.24%	52, 0.22%	0.88 (0.61-1.29), *P*=0.519	28, 0.92%	24, 0.74%	0.80 (0.46-1.39), *P*=0.428	29, 0.14%	28, 0.14%	0.97 (0.58-1.64), *P*=0.920	0.600
MI (all)	191, 0.84%	163, 0.71%	0.84 (0.68-1.04), *P*=0.107	65, 2.32%	73, 2.54%	1.11 (0.79-1.55), *P*=0.557	126, 0.63%	90, 0.45%	0.71 (0.54-0.93), *P*=0.012	0.043
MI (nonfatal)	183, 0.80%	159, 0.69%	0.86 (0.69-1.06), *P*=0.156	61, 2.18%	71, 2.47%	1.14 (0.81-1.62), *P*=0.443	122, 0.61%	88, 0.44%	0.71 (0.54-0.94), *P*=0.016	0.035
MI (fatal)	11, 0.05%	5, 0.02%	0.44 (0.15-1.26), *P*=0.126	7, 0.23%	3, 0.09%	0.42 (0.11-1.68), *P*=0.220	4, 0.02%	2, 0.01%	0.50 (0.09-2.72), *P*=0.421	0.852
Stroke (all)	80, 0.34%	85, 0.36%	1.05 (0.77-1.42), *P*=0.776	30, 1.02%	31, 0.99%	1.01 (0.61-1.67), *P*=0.979	50, 0.25%	54, 0.27%	1.07 (0.73-1.57), *P*=0.730	0.834
Hospitalization for angina	196, 0.87%	194, 0.85%	0.97 (0.80-1.19), *P*=0.785	83, 3.17%	83, 2.97%	0.94 (0.70-1.28), *P*=0.717	113, 0.57%	111, 0.56%	0.97 (0.75-1.27), *P*=0.847	0.934
Total mortality	202, 0.86%	174, 0.73%	0.85 (0.69-1.04), *P*=0.111	62, 2.05%	55, 1.70%	0.83 (0.58-1.21), *P*=0.334	140, 0.68%	119, 0.58%	0.86 (0.67-1.09), *P*=0.209	0.930

[a]Primary composite outcomes were CVD death, MI, stroke, and hospitalization for angina.
[b]CVD death, MI, or stroke.
[c]Death (all causes), MI, stroke, or hospitalized angina.
[d]Death (all causes), MI, stroke, hospitalized angina, coronary artery bypass grafting, percutaneous coronary angioplasty, hospitalization for heart failure, or peripheral vascular disease.
CVD, cardiovascular disease; DSE, diabetes support and education; ILI, intensive lifestyle intervention; MI, myocardial infarction.

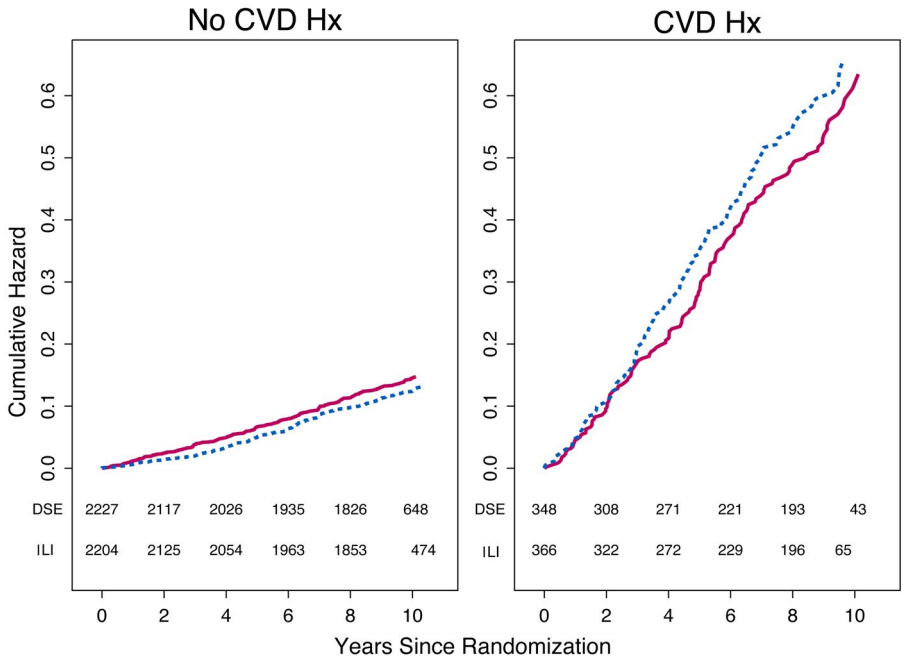

Figure 2 Cumulative hazard plots for 821 primary composite outcomes, including cardiovascular death, MI, stroke, and hospitalized angina, by history of CVD at baseline subgroup and randomized treatment assignment. Event rates were 1.23%/y vs. 1.41%/y for ILI vs. DSE in those without CVD at baseline and 6.59%/y vs. 5.95%/y for ILI vs. DSE in those with CVD at baseline. Numbers at risk at various follow-up time points are shown by randomized group above the x-axis, with the maximum follow-up time for each group indicated separately. ILI indicates the intensive lifestyle intervention group (dashed blue line), and DSE indicates the diabetes support and education control group (solid red line). *P* for interaction = 0.063. Hx, medical history. [Color figure can be viewed at wileyonlinelibrary.com]

heterogeneity of response to ILI for the prespecified subgroup of baseline CVD history, with a nominal unadjusted $P = 0.063$ for the primary outcome. This heterogeneity was present for two of three secondary composite outcomes, including the original trial primary outcome of fatal CVD, MI, and stroke (11). In each case, stratified analyses showed that the HR for ILI compared with DSE was nonsignificantly decreased among those without a CVD history and nonsignificantly increased for ILI among those with a CVD history. Among the components of the primary composite, only nonfatal MI demonstrated nominally statistically significant heterogeneity ($P = 0.035$).

During trial monitoring, the DSMB was aware of nominally significant interaction for the prespecified CVD history subgroup and was sequentially monitoring this subgroup. Analyses requested by the DSMB were consistent with results here, showing decreased risk of the primary outcome in the ILI group among those without CVD at baseline and increased risk in those with CVD. The effect was due to higher rates of nonfatal MI in the ILI group, which contained a physical activity component, among those with baseline CVD. The DSMB viewed this finding as having biologic plausibility because of the known acute MI–triggering effect of acute physical activity (12,13) and the lack of benefit of cardiac rehabilitation for acute MI present in the cardiac rehabilitation literature (14). With time, this interaction effect weakened somewhat, easing safety concerns somewhat, as did the signal for ILI benefit in the subgroup without baseline CVD, leading to the eventual recommendation to cease intervention because of futility.

Given this potentially important signal of heterogeneity, we conducted further analyses to identify variables that might be related to the observed effects as a hypothesis-generating effort. Participants with a CVD history differed from those without a CVD history on a number of baseline variables. However, within CVD history subgroups, there were no baseline differences between those randomized to the ILI versus DSE. Adjusting for baseline variables strengthened the interaction for nonfatal MI, suggesting a benefit of ILI among those without CVD at baseline and no significant ILI versus DSE difference among those with baseline CVD.

We also considered differences in response to the ILI as possible explanations. However, the overall effect of the ILI, relative to DSE, on weight loss, improvements in fitness level, several CVD risk factors, and glycemic control were similar regardless of CVD history. There were few hypoglycemic events, providing little evidence that hypoglycemia contributed to our findings.

We did observe differential changes in LDL-C levels and statin use during follow-up. Post-randomization confounding due to statin use was reported in the Women's Health Initiative hormone-therapy trials (15) and the diet modification trial (16). In the dietary modification

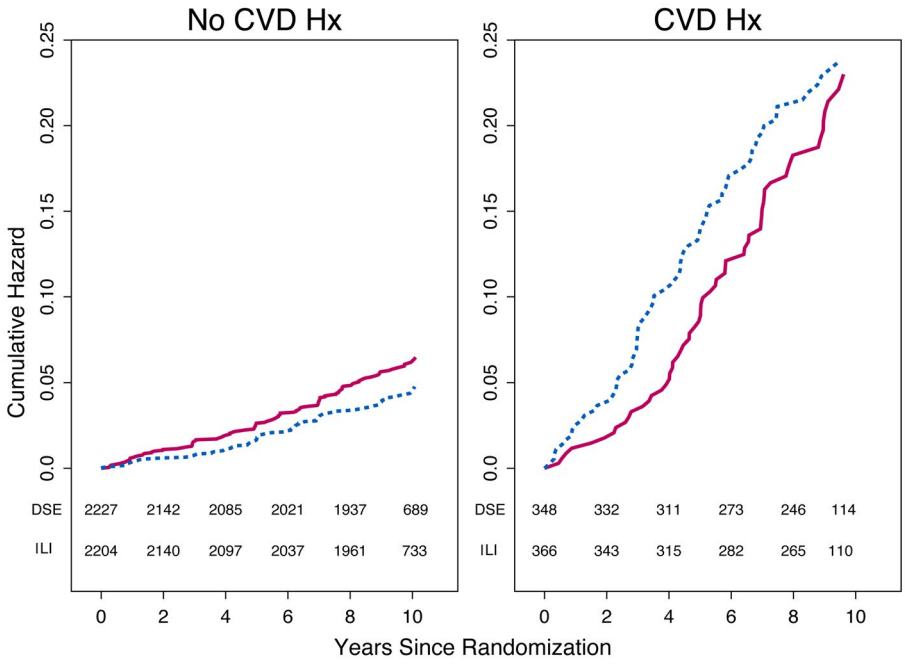

Figure 3 Cumulative hazard plots for 354 nonfatal MIs by history of CVD at baseline and randomized treatment assignment. Event rates were 0.44%/y vs. 0.61%/y for ILI vs. DSE in those without CVD at baseline and 2.47%/y vs. 2.18%/y for ILI vs. DSE in those with CVD at baseline. Numbers at risk at various follow-up time points are shown by randomized group above the x-axis, with the maximum follow-up time for each group indicated separately. ILI indicates the intensive lifestyle intervention group (dashed blue line), and DSE indicates the diabetes support and education control group (solid red line). *P* for interaction = 0.035. Hx, medical history. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Proportional hazards models for the nonfatal MI outcome with interaction terms for randomized assignment (ILI group vs. DSE [control] group) and baseline history of CVD subgroup, comparing protocol-defined proportional hazards model with protocol-defined proportional hazards model with further adjustment for baseline variables

	CVD history at baseline present			No CVD history at baseline			*P* for interaction[a]
	HR	95% CI	*P*	HR	95% CI	*P*	
Protocol-defined model	1.14	0.81-1.62	0.443	0.71	0.54-0.94	0.016	0.035
Protocol-defined model with further adjustment for baseline variables	1.23	0.86-1.76	0.248	0.68	0.51-0.90	0.008	0.010

Baseline variables include all those contained in Table 1: age, sex, race/ethnicity, diabetes duration, current smoking, weight, BMI, fitness, use of insulin, use of statins, use of any antihypertensive drug, use of aspirin, SBP, DBP, hemoglobin A_{1C}, estimated glomerular filtration rate, LDL-C, HDL-C, and triglycerides.
[a]Interaction of randomized group and cardiovascular disease (CVD) history at baseline.

trial, CVD-outcome results were uninterpretable in women with baseline CVD because of high statin use. Women without baseline CVD or hypertension infrequently used statins, and for them, coronary heart disease outcome rates were significantly lower in the intervention group (HR 0.70 [95% CI: 0.56-0.87]). In Look AHEAD participants without a CVD history, the ILI group had significantly higher mean LDL-C levels and lower statin use relative to DSE. This pattern would predispose to greater CVD risk in the ILI group, counter to the observed trends. On the other hand, there were no significant differences between intervention groups in LDL-C levels or statin use in those with baseline CVD, with most using these medications as well as aspirin, potentially making it difficult to detect an effect of a lifestyle intervention.

As noted, the suggestive heterogeneity was related to nonfatal acute MI rates. In participants without CVD at baseline (86% of Look AHEAD participants), the ILI had a nominally significant benefit compared with DSE for nonfatal acute MI (0.44%/y vs. 0.61%/y; $P = 0.016$). This is consistent with the findings for nonfatal acute MI in pharmacologic trials of tight glycemic control in type 2 diabetes, including ACCORD (17), the trial phase of the UK Prospective Diabetes Study (18), and

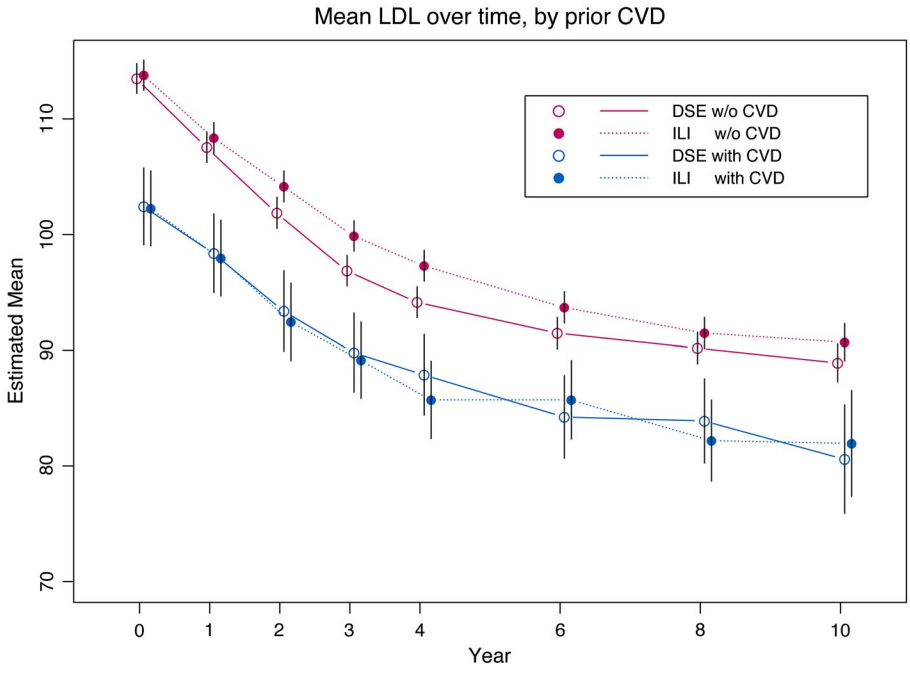

Figure 4 Mean LDL-C levels by baseline history of CVD and treatment assignment by year. Significant differences between ILI and DSE groups were present at follow-up years 2, 3, 4, and 6 in this subset. There were no differences by treatment assignment among those with a baseline CVD history. $P = 0.003$ for the overall difference between randomized assignment groups in the subset without (w/o) a CVD history at baseline. [Color figure can be viewed at wileyonlinelibrary.com]

in some meta-analyses of pharmacologic trials (19,20). Several recent CVD-outcome trials in type 2 diabetes, for example, of sodium-glucose cotransporter-2 inhibitors (21) and glucagon-like peptide-1 analogs (22), have found decreased rates of MI and CVD death in those with baseline CVD but not in those with multiple CVD risk factors and no prior clinical CVD. The mechanism for the beneficial effect in CVD is unclear.

In the 14% of Look AHEAD participants with a CVD history, there was a nonsignificantly greater incidence of nonfatal MI in the ILI group (2.47%/y) compared with the DSE group (2.18%/y). As noted, physical activity bouts, undertaken as part of the ILI, have been associated with increased risk of acute coronary heart disease events (12,13). The Lifestyle Interventions and Independence for Elders study, a randomized trial of structured physical activity in older adults at risk for mobility disability, found a nonsignificantly higher rate of MI, chest pain, and acute coronary syndrome events (HR 1.32 [95% CI: 0.79-2.20]) in the physical activity intervention group compared with the health education control group (23). In Look AHEAD, however, the hazard curves did not begin to separate until approximately 3 years after the ILI started.

Our findings are hypothesis-generating rather than definitive. However, they may have implications for cardiovascular-outcomes studies that aim to recruit a defined proportion of participants at high CVD risk to increase CVD event rates and statistical power. Often, these studies are not powered to examine intervention effects separately in both those with and without CVD history, therefore complicating outcomes reporting. Our study and others suggest that it is a mistake to assume that interventions will have a similar impact on cardiovascular outcomes in these two groups. For example, in the Sibutramine Cardiovascular Outcomes trial (24), sibutramine resulted in greater weight loss, higher blood pressure, and significantly higher nonfatal MI and stroke rates than the placebo; the increased event rates were observed in those with a CVD history with or without diabetes but not in those with diabetes without a CVD history.

Our analysis has a number of strengths, including exploration of effects in a prespecified subgroup in a long-term randomized trial with high retention. The interaction tests for heterogeneity by CVD history for the primary and secondary composite outcomes were also prespecified. However, there are a number of important limitations, including the nonsignificant interaction for the primary and secondary composite outcomes and the post hoc exploratory analyses for individual components of the composite outcomes and potential mediating factors. Additionally, Look AHEAD was not powered to analyze effects within subgroups: the subgroup with a CVD history was small, and the much larger subgroup without a CVD history was also underpowered by itself, particularly because the event rate in this group was significantly lower than that in those with baseline CVD. A large proportion of participants were on statin and aspirin therapy and had well-controlled CVD risk factors, which challenged the ability of a lifestyle intervention to further affect CVD events, especially among the subgroup with CVD at baseline. Finally, we collected baseline history by self-report; however, we do not expect that any misclassification would be differential by treatment assignment, and more than 90% of participants consistently reported their history and specific CVD conditions when assessed during the initial telephone screening and at their first in-person screening visit.

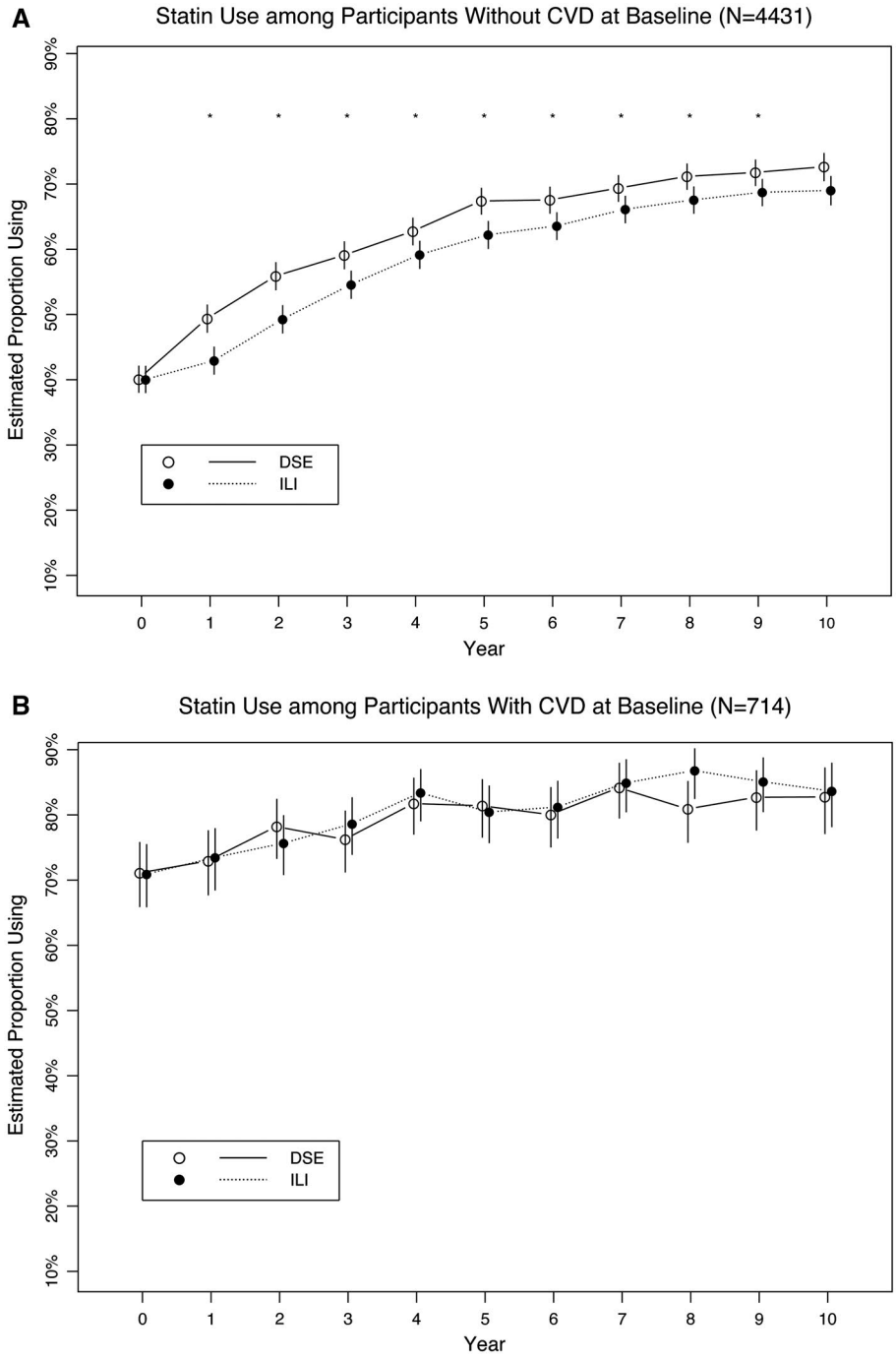

Figure 5 Statin use by treatment assignment and by year among (**A**) those without a CVD history and (**B**) those with a CVD history at baseline. Significant differences between ILI and DSE groups without CVD history were present at all follow-up time points except year 10. There were no differences by treatment assignment among those with a CVD history at baseline. *$P < 0.05$ for the ILI vs. DSE difference by time point in the without CVD subgroup. $P < 0.001$ for the overall difference between randomized assignment groups in the subset without a history of CVD at baseline.

Conclusion

Although the overall Look AHEAD results did not show differences in CVD rates by randomized treatment group, there was a suggestion of heterogeneity in response to ILI by the baseline history of CVD, specifically for nonfatal MI. We did not find specific baseline predictors that explained the suggestive heterogeneity in response to ILI versus DSE; however, adjusting our model for baseline covariates strengthened evidence for heterogeneity for nonfatal MI. The interactions between CVD history and treatment assignment were unlikely to be due to differences

in weight loss, fitness change, or hypoglycemic episodes. Differences in LDL-C levels and statin use were unlikely explanations for our findings in those without CVD. High use of statins and aspirin and well-controlled LDL-C levels among those with baseline CVD, regardless of Look AHEAD treatment assignment, might have affected our power to detect differences between randomized groups. We recognize that treatment response heterogeneity may reflect chance; given the interaction, the *P* value was not statistically significant for the primary outcome at the time intervention ceased. The findings nonetheless have implications for a clinical trial design because trials generally assume homogeneous results among subgroups. Investigators may wish to consider this potential heterogeneity of response when designing CVD-outcome trials. O

Acknowledgments

Coauthors George Blackburn, Frederick L. Brancati, and Abbas E. Kitabchi died during the production of this work. Some of the information contained herein was derived from data provided by the Bureau of Vital Statistics, New York City Department of Health and Mental Hygiene. Look AHEAD data may be requested from the National Institute of Diabetes and Digestive and Kidney Diseases Central Repository (https://repository.niddk.nih.gov/studies/look-ahead). In addition to data sets, the Central Repository makes available the study protocol, forms, summary statistics, and data dictionary.

Funding agencies: This research was funded by the NIH through cooperative agreements with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK): DK57136, DK57149, DK56990, DK57177, DK57171, DK57151, DK57182, DK57131, DK57002, DK57078, DK57154, DK57178, DK57219, DK57008, DK57135, and DK56992. Additional funding was provided by the National Heart, Lung, and Blood Institute, the National Institute of Nursing Research, the National Institute on Minority Health and Health Disparities, the NIH Office of Research on Women's Health, and the Centers for Disease Control and Prevention. This research was supported in part by the Intramural Research Program of the NIDDK. The Indian Health Service provided personnel, medical oversight, and use of facilities. The opinions expressed in this article are those of the authors and do not necessarily reflect the views of the Indian Health Service or the other funding sources. Additional support was received from The Johns Hopkins Medical Institutions Bayview General Clinical Research Center (M01RR02719); the Massachusetts General Hospital Mallinckrodt General Clinical Research Center and the Massachusetts Institute of Technology General Clinical Research Center (M01RR01066); the Harvard Clinical and Translational Science Center (RR025758-04); the University of Colorado Health Sciences Center General Clinical Research Center (M01RR00051) and Clinical Nutrition Research Unit (P30 DK48520); the University of Tennessee at Memphis General Clinical Research Center (M01RR0021140); the University of Pittsburgh General Clinical Research Center (M01RR000056) and the Clinical and Translational Research Center, funded by Clinical and Translational Science Award UL1 RR 024153 and NIH grant DK 046204; the US Department of Veterans Affairs Puget Sound Health Care System Medical Research Service; and the Frederic C. Bartter General Clinical Research Center (M01RR01346). The following organizations have committed to making major contributions to Look AHEAD: FedEx Corporation; Health Management Resources; LifeScan, Inc., a Johnson & Johnson Company; OPTIFAST of Nestle HealthCare Nutrition, Inc.; Hoffmann-La Roche Inc.; Abbott Nutrition; and Slim-Fast brand of Unilever, North America.

Disclosure: AGB reports consulting with Merck unrelated to this work. LJC reports having served on a scientific advisory board (Medifast). JMJ reports receiving personal fees and grant support from Weight Watchers International. DK reports support from Gilead, grants and personal fees from Novartis, grants and personal fees from GlaxoSmithKline, personal fees from AstraZeneca, personal fees from Merck, grants and personal fees from Bayer, personal fees from Boehringer Ingelheim, and personal fees from Duke Clinical Research Institute, outside the submitted work. AP reports personal fees from Abbott Diabetes Care; personal fees from Becton Dickinson, Boehringer Ingelheim, Eli Lilly and Company, Lexicon, Livongo, MannKind, Medscape, Merck, Novo Nordisk, Omada Health, OptumHealth, Sanofi, and Zafgen; and grant support from AstraZeneca, Dexcom, and MannKind during the conduct of the study. XPS serves on scientific advisory boards of Novo Nordisk, AstraZeneca, and Zafgen. DHR reports serving on the steering committee for an industry-sponsored diabetes medication cardiovascular outcome trial (Novo Nordisk). DHR also reports serving on scientific advisory boards, with expenses reimbursed (Novo Nordisk, Phenomix, Janssen, and Sanofi) and serving as a speaker for industry (Novo Nordisk); she also reports holding stock/stock options (Scientific Intake Xeno Bioscience, Epitomee, and Gila Therapeutics). DHR reports personal fees from Novo Nordisk, Amgen, Janssen, Sanofi, IFA Celtics, Real Appeal, and KVK Tech and nonfinancial support from Epitomee, Gila Therapeutics, Xeno Bioscience, Phenomix, and Scientific Intake outside the submitted work. TAW reports receiving grants from Novo Nordisk as well as serving on the advisory board for both Novo Nordisk and Weight Watchers. HW reports grants from Novo Nordisk; equity ownership in Shakabuku LLC; a book, *The State of Slim*, with Rodale Publishing; grants and personal fees from the National Cattleman's Beef Association; personal fees from the Endocrine Society; royalties from Up to Date; personal fees from the North American Menopause Society and Haymarket Media; grants from Gelesis, the American Beverage Association, Dupont; and other support from Retrofit outside the submitted work. In addition, HW has a patent for Energy Gap issued. SZY reports that her spouse receives research project support to his institution from Rhythm Pharmaceuticals. The other authors declared no conflict of interest.

Writing group: CEL, AGB, LJC, DMR, SPG, KCJ, RRW, SZY, and XPS wrote the article.

Clinical trial registration: ClinicalTrials.gov identifier NCT00017953.

Supporting information: Additional Supporting Information may be found in the online version of this article.

References

1. Jensen MD, Ryan DH, Donato KA, et al. Guidelines (2013) for managing overweight and obesity in adults. *Obesity (Silver Spring)* 2014;22(S2):S1-S410.
2. Wing RR, Bolin P, Brancati FL, et al; Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *New Engl J Med* 2013;369:145-154.
3. Ryan DH, Espeland MA, Foster GD, et al; Look AHEAD Research Group. Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. *Control Clin Trials* 2003;24:610-628.
4. Bray G, Gregg E, Haffner S, Pi-Sunyer XF, Wagenknecht LE, Walkup M, Wing R; Look Ahead Research Group. Baseline characteristics of the randomised cohort from the Look AHEAD (Action for Health in Diabetes) study. *Diab Vasc Dis Res* 2006;3:202-215.
5. Wadden TA, West DS, Delahanty L, et al; Look AHEAD Research Group. The Look AHEAD study: a description of the lifestyle intervention and the evidence supporting it. *Obesity (Silver Spring)* 2006;14:737-752.
6. Look AHEAD Research Group. Eight-year weight losses with an intensive lifestyle intervention: the Look AHEAD study. *Obesity (Silver Spring)* 2014;22:5-13.
7. Wadden TA, West DS, Neiberg RH, et al; Look AHEAD Research Group. One-year weight losses in the Look AHEAD study: factors associated with success. *Obesity (Silver Spring)* 2009;17:713-722.
8. Jakicic JM, Jaramillo SA, Balasubramanyam A, et al; Look AHEAD Study Group. Effect of a lifestyle intervention on change in cardiorespiratory fitness in adults with type 2 diabetes: results from the Look AHEAD study. *Int J Obes (Lond)* 2009;33:305-316.
9. Paffenbarger RS, Wing AL, Hyde RT. Physical activity as an index of heart attack risk in college alumni. *Am J Epidemiol* 1978;108:161-175.
10. Greenway FL; Look AHEAD Research Group. Severe hypoglycemia in the Look AHEAD Trial. *J Diabetes Complications* 2016;30:935-943.
11. Brancati FL, Evans M, Furberg CD, et al; Look AHEAD Study Group. Midcourse correction to a clinical trial when the event rate is underestimated: the Look AHEAD (Action for Health in Diabetes) Study. *Clin Trials* 2012;9:113-124.
12. Willich SN, Lewis M, Löwel H, Arntz HR, Schubert F, Schröder R. Physical exertion as a trigger of acute myocardial infarction. Triggers and Mechanisms of Myocardial Infarction Study Group. *New Engl J Med* 1993;329:1684-1690.
13. Giri S, Thompson PD, Kiernan FJ, et al. Clinical and angiographic characteristics of exertion-related acute myocardial infarction. *JAMA* 1999;282:1731-1736.
14. Taylor RS, Brown A, Ebrahim S, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *Am J Med* 2004;116:682-692.
15. Manson JE, Shufelt CL, Robins JM. The potential for postrandomization confounding in randomized clinical trials. *JAMA* 2016;315:2273-2274.
16. Prentice RL, Aragaki AK, Van Horn L, et al. Low-fat dietary pattern and cardiovascular disease: results from the Women's Health Initiative randomized controlled trial. *Am J Clin Nutr* 2017;106:35-43.
17. Gerstein HC, Miller ME, Genuth S, et al; ACCORD Study Group. Long-term effects of intensive glucose lowering on cardiovascular outcomes. *New Engl J Med* 2011;364:818-828.
18. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-853.
19. Turnbull FM, Abraira C, Anderson RJ, et al; Control Group. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* 2009;52:2288-2298.
20. Hemmingsen B, Lund SS, Gluud C, et al. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2011:CD008143. doi:10.1002/14651858.CD008143

21. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* 2019;393:31-39.
22. Verma S, Poulter NR, Bhatt DL, et al. Effects of liraglutide on cardiovascular outcomes in patients with type 2 diabetes mellitus with or without history of myocardial infarction or stroke. *Circulation* 2018;138:2884-2894.
23. Pahor M, Guralnik JM, Ambrosius WT, et al; LIFE study investigators. Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial. *JAMA* 2014;311:2387-2396.
24. James WP, Caterson ID, Coutinho W, et al; SCOUT Investigators. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *New Engl J Med* 2010;363:905-917.