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History of cardiovascular disease, intensive lifestyle intervention, and cardiovascular outcomes in the Look AHEAD Trial

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Abstract

OBJECTIVE-—To examine intensive lifestyle intervention (ILI) effects on cardiovascular disease (CVD), Look AHEAD randomized 5145 participants with Type 2 diabetes and overweight/obesity to ILI or Diabetes Support and Education (DSE). While the primary outcome did not differ, there was suggestive evidence of heterogeneity for pre-specified baseline CVD history subgroups (interaction p=0.063). Event rates were higher in ILI among those with CVD history (hazard ratio [HR] 1.13 [95% CI 0.90-1.41]) and lower without CVD (HR, 0.86 [95% CI 0.72-1.02]).

METHODS-—*Post-hoc* analyses of rates of primary composite outcome and components: adjudicated cardiovascular death, nonfatal myocardial infarction (MI), stroke, and hospitalization for angina; and three secondary composite 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 non-fatal 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 CVD history, statin use was high and similar by group. In those without, LDL-C levels were higher (p=0.003) and statin use lower (p=<0.001) in ILI.

CONCLUSIONS: Intervention response heterogeneity was significant for non-fatal MI. Response heterogeneity may need consideration in CVD outcome trial design.

Keywords

Look AHEAD (Action for Health in Diabetes); outcome; myocardial infarction; diabetes; lifestyle; Diabetes, type 2; Lipids and Cholesterol; Obesity; Risk Factors

Introduction

Lifestyle interventions have been shown to reduce cardiovascular disease (CVD) risk factors and to have other health benefits for overweight or obese individuals with type 2 diabetes (1). However, there have been few studies evaluating the long-term effects of lifestyle intervention on CVD morbidity or mortality. The Look AHEAD trial randomized 5,145 volunteers with type 2 diabetes to either intensive lifestyle intervention (ILI) or Diabetes Support and Education (DSE), the usual care control condition. Participants were followed 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 Safety Monitoring Board (DSMB).

The incidence of the primary outcome, a composite of fatal or non-fatal myocardial infarction, stroke, hospitalization for angina, or cardiovascular death, did not differ between 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 pre-specified subgroups; however, the interaction for the pre-specified 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 non-significantly higher incidence of the primary CVD outcome compared to DSE (6.59%/year vs 5.95%/year, 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 non-significantly lower incidence of the primary outcome (1.23%/year vs 1.41%/year, 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 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 vs. without 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://www.lookaheadtrial.org/public/LookAHEADProtocol.pdf. The study was conducted at 16 clinical centers in the US, and was approved by the institutional review board at each center. All participants gave written informed consent.

We determined that 5000 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 DSE, 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 Data and Safety Monitoring Board throughout the trial (3). Look AHEAD recruited participants from August 2001 through April 2004, randomizing 5145 participants to 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 online supplemental material methods). 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 myocardial infarction, 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 if they had other cardiovascular conditions or findings (eg, ischemia on exercise ECG) that could affect safety of the intervention.

Interventions.

Curricula for both ILI and DSE were developed centrally and have been described in detail (3; 5–7; see online supplemental materials). ILI aimed at achieving and maintaining at least a 7% weight loss by focusing on reduced caloric intake and increased physical activity. The program included frequent contact throughout the trial, with both group and individual sessions, a calorie goal of 1200-1800 kcal/day, and at least 175 minutes per week of moderate intensity physical activity by month 6 with a further increase to 200 minutes/week for those who met this goal. The DSE condition included three group education sessions per year during years 1-4 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 ILI and DSE and their health care providers received annual reports on the participants’ most recent blood pressure levels, fasting glucose, HbA1C, fasting lipid panel, and renal function measures, and the goals recommended by the American Diabetes Association (3).

Assessments.

Certified masked staff measured weight, waist circumference, and blood pressure, assessed medication use, obtained blood for analysis at the central laboratory annually (3). Maximal exercise tests were performed on the full cohort prior to randomization, submaximal tests 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 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 with 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, myocardial infarction, stroke, or hospitalized angina (2; 11). Hospitalized angina was added to the original primary composite outcome due to the lower than expected event rate in DSE during the first trial's two years (11). Three composite secondary cardiovascular outcomes were examined: 1) CVD death, myocardial infarction, or stroke (original primary); 2) death (all causes), myocardial infarction, stroke, or hospitalized angina; and 3) death (all causes), myocardial infarction, 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 dataset used for the main results report (2). Participants reported their history of CVD at 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 4431 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 median follow-up of 9.6 years (interquartile range 8.9 to 10.3 years).

Using the pre-specified 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 non-fatal 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 and chi-square 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 measurement and medication use from baseline through 10 years. In all longitudinal analyses, an unstructured covariance matrix was estimated. As these are exploratory analyses, results were not adjusted for multiple comparisons and $p<0.05$ was considered statistically significant using 2-tailed tests. We used S-Plus software, version 8.0 (Insightful) or SAS software version 9.1 (SAS Institute).

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 were similar at baseline (Table 1). However, most characteristics were different between those with and without CVD history. Those with CVD were somewhat older, more often white, had a longer duration of diabetes, were more often male, less fit but less obese, and more often used insulin, aspirin, lipid lowering statins, and antihypertensive medications. Those with CVD also had lower levels of LDL-C and diastolic blood pressure, but worse eGFR, HDL-C, HbA1c, and triglycerides. Only current smoking and systolic blood pressure 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 5-fold and 4-fold higher than did those without CVD in ILI and in DSE, 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 ($p=.063$). Among those without CVD history, ILI resulted in a non-significantly lower incidence of the primary outcome, while in those with CVD ILI resulted in a non-significantly higher incidence (Figure 2). To better understand this interaction, we examined the various components of the primary outcome (Table 2). Significant interaction p values were present for myocardial infarction ($p=0.043$), specifically non-fatal 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 (p=0.430).

Interaction effects for non-fatal 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 non-fatal MI by further adjusting the protocol-defined model for the variables in Table 1. This baseline adjustment did not change the within-subgroup hazard ratio in those without baseline CVD. In those with CVD history, the estimated hazard ratio 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), ILI produced sustained reductions in body weight, HbA1C, and systolic blood pressure, and through year 4 improvements in fitness, 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 (Table S1). For example, in those with CVD history the median weight loss at year 1 in ILI was 7.5% of body weight and 0.1% in DSE, and among those without CVD the median loss was 8.0%, and 0.5%, respectively, indicating similar weight loss in ILI and ILI-DSE differences. Fitness improvement at year 1 in ILI was 12.2% in those with and 15.6% in those without CVD, while both DSE groups experienced no change (Table S1, Figure S1). At year 4, fitness decreased in all groups, except the ILI group without baseline CVD (median change 0.0 METs); both CVD subgroups in ILI experienced similar differences relative to DSE. The interactions of treatment by CVD history were not significant for either percent weight change (p=0.85) or fitness change (METS, 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 DSE, but differences were not numerically large. For example, in ILI mean LDL-C level at year 4 was 97.3 mg/dL and 59% of participants reported statin use while in DSE these were 94.0 mg/dL and 62%, respectively. Aspirin use in those without CVD was significantly lower in ILI in years 1 and 2, but differences were not numerically large (Figure S2). Among those with CVD history, LDL-C levels and statin use did not differ between ILI and DSE during follow-up. At year 4 and beyond in those with CVD history, statins were used by approximately 80% or more of both ILI and DSE, 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 ILI and DSE and was also high at all time points.

HbA1c was significantly improved by ILI early in follow-up, with similar effects in CVD subgroups (overall p< 0.001 in both, Figure S3). Among those with baseline CVD, insulin use was nonsignificantly greater in DSE during follow-up, while in those without baseline CVD, insulin use was significantly more common in DSE (p<0.001, Figure S4). For HDL-C

(p=0.003, Figure S5) and SBP (p<0.001, Figure S6), 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 (Figure S7) and TG (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, Figure S9). There were similar hypoglycemia rates in those without CVD, but non-significantly greater rates in ILI compared in those with baseline CVD. However, only 24 participants had both a non-fatal MI and a hypoglycemic event and of those, only 8 participants had a hypoglycemic event before a non-fatal MI, and 6 of those were at least 200 days before the MI. The two 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 ILI did not reduce the rate of CVD events in overweight or obese adults with type 2 diabetes compared with DSE control (2). However, there was evidence of potential heterogeneity of response to ILI for the pre-specified subgroup of baseline CVD history, with a nominal unadjusted p value 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 hazard ratio for ILI compared to DSE was nonsignificantly decreased among those without CVD history, and nonsignificantly increased for ILI among those with CVD history. Among the components of the primary composite only non-fatal 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 ILI among those without CVD at baseline and increased risk in those with CVD. The effect was due to higher rates of non-fatal MI in ILI, which contained a physical activity component, among the group with baseline CVD. The DSMB viewed this finding as having biologic plausibility due to 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 group without baseline CVD, leading to the eventual recommendation to cease intervention due to 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 CVD history differed from those without CVD history on a number of baseline variables. However, within CVD history groups, there were no baseline

differences between those randomized to ILI vs DSE. Adjusting for baseline variables strengthened the interaction for nonfatal MI, suggesting benefit for ILI among those without CVD at baseline and no significant ILI vs DSE difference among those with baseline CVD.

We also considered differences in response to ILI as possible explanations. However, the overall effect of ILI relative to DSE on weight loss, improvements in fitness level, and on 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. Postrandomization confounding due to statin use was reported in the Women's Health Initiative hormone therapy trials (15), and in the diet modification trial (16). In the dietary modification trial, CVD outcome results were uninterpretable in women with baseline CVD due to high statin use. Women without baseline CVD or hypertension infrequently used statins, and in them coronary heart disease (CHD) outcome rates were significantly lower in the intervention group (HR 0.70 [95% CI 0.56-0.87]). In Look AHEAD participants without 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 ILI, 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, ILI had a nominally significant benefit compared to DSE for nonfatal acute MI (0.44%/year vs 0.61%/year, p=0.016). This is consistent with the findings for non-fatal acute MI from pharmacologic trials of tight glycemic control in type 2 diabetes, including ACCORD (17), the trial phase of UKPDS (18), and 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 (SGLT2i; 21) and glucagonlike 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 CVD history, there was a non-significantly greater incidence of nonfatal MI in ILI (2.47%/year) compared with DSE (2.18%/year). As noted, physical activity bouts, undertaken as part of ILI, have been associated with increased risk of acute CHD events (12; 13). The Lifestyle Interventions and Independence for Elders (LIFE) study, a randomized trial of structured physical activity in older adults at risk for mobility disability, found a non-significantly higher rate of MI/chest pain/acute coronary syndrome events (HR 1.32 [95% CI 0.79-2.20]), in the physical activity intervention group compared to the health education control group (23). In Look AHEAD, however, the hazard curves did not begin to separate until approximately 3 years after 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 in order 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 similar impact on cardiovascular outcomes in these two groups. For example, in the Sibutramine Cardiovascular Outcomes (SCOUT) trial (24), sibutramine resulted in greater weight loss, higher blood pressure, and significantly higher nonfatal MI and stroke rates than placebo; the increased event rates were observed in those with CVD history with or without diabetes, but not in those with diabetes without CVD history.

Our analysis has a number of strengths, including exploration of effects in a pre-specified 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 non-significant 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 CVD history was small, and the much larger subgroup without CVD history was also underpowered by itself, particularly as the event rate in this group was significantly lower than 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 initial telephone screening and at their first in-person screening visit.

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 non-fatal MI. We did not find specific baseline predictors that explained the suggestive heterogeneity in response to ILI vs DSE; however, adjusting our model for baseline covariates strengthened evidence for heterogeneity for non-fatal 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 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 may have affected our power to detect differences between randomized groups. We recognize that treatment response heterogeneity may reflect chance, given the interaction p value was not statistically significant for the primary outcome at the time intervention ceased. The findings nonetheless have implications for clinical trial design since trials generally assume homogeneous results

among subgroups. Investigators may wish to consider this potential heterogeneity of response when designing CVD outcome trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing: Look AHEAD data may be requested from the NIDDK Central Repository https://repository.niddk.nih.gov/studies/look-ahead. In addition to datasets, the Central Repository makes available the study protocol, forms, summary statistics, and data dictionary.

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Importance questions:

- Lifestyle interventions promoting weight loss have been shown to reduce cardiovascular disease (CVD) risk factors; however, there are few data on long-term effects of CVD morbidity or mortality.
- 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 to those assigned to the control condition of diabetes support and education (DSE); however, there was suggestive evidence (p=0.063) of treatment response heterogeneity by baseline cardiovascular disease (CVD).
- The overall heterogeneity was due to myocardial infarction (Ml; p=0.035), and strengthened when controlled for baseline variables that differed between those with and without baseline CVD.

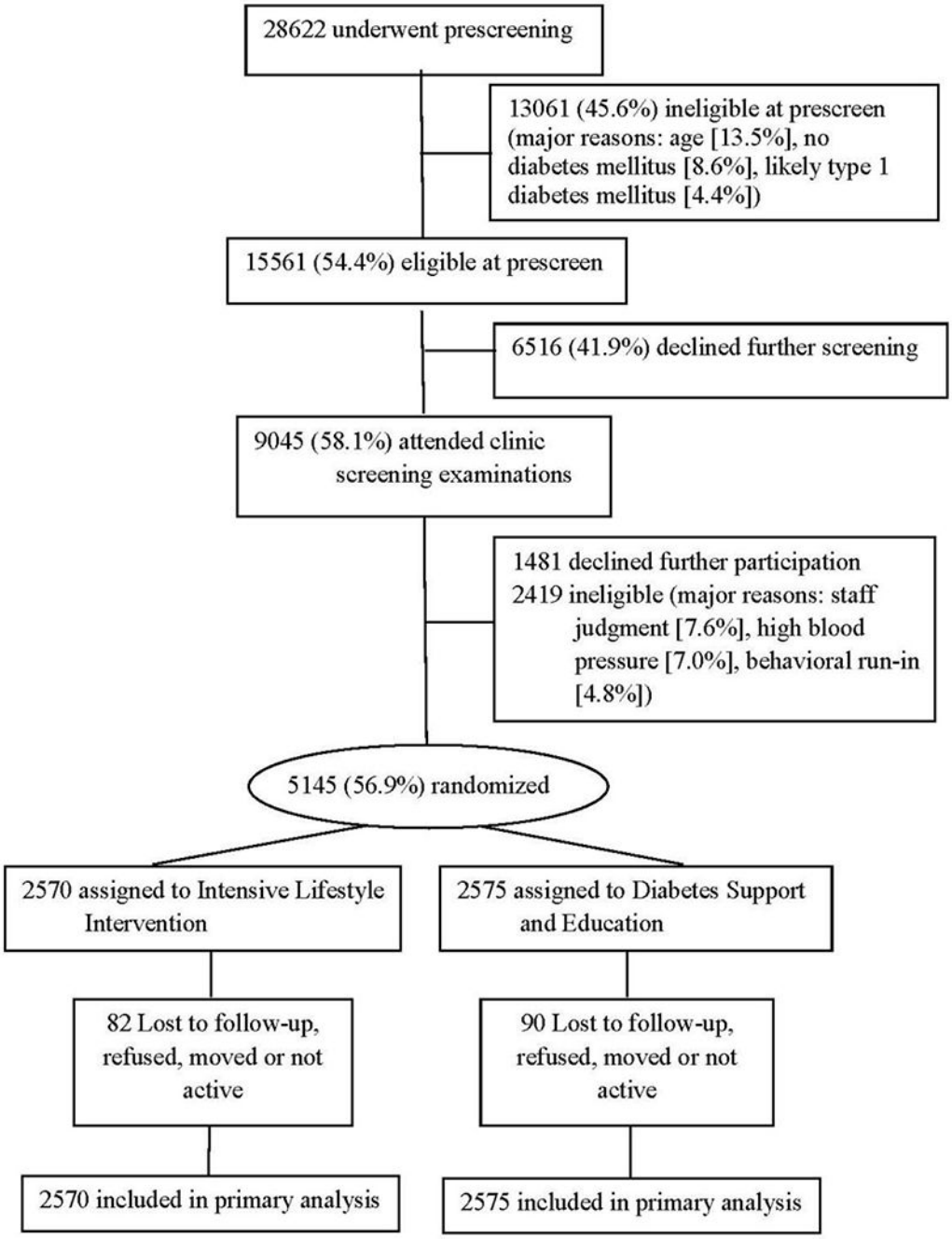


Figure 1.
Consort diagram for the Look AHEAD trial.

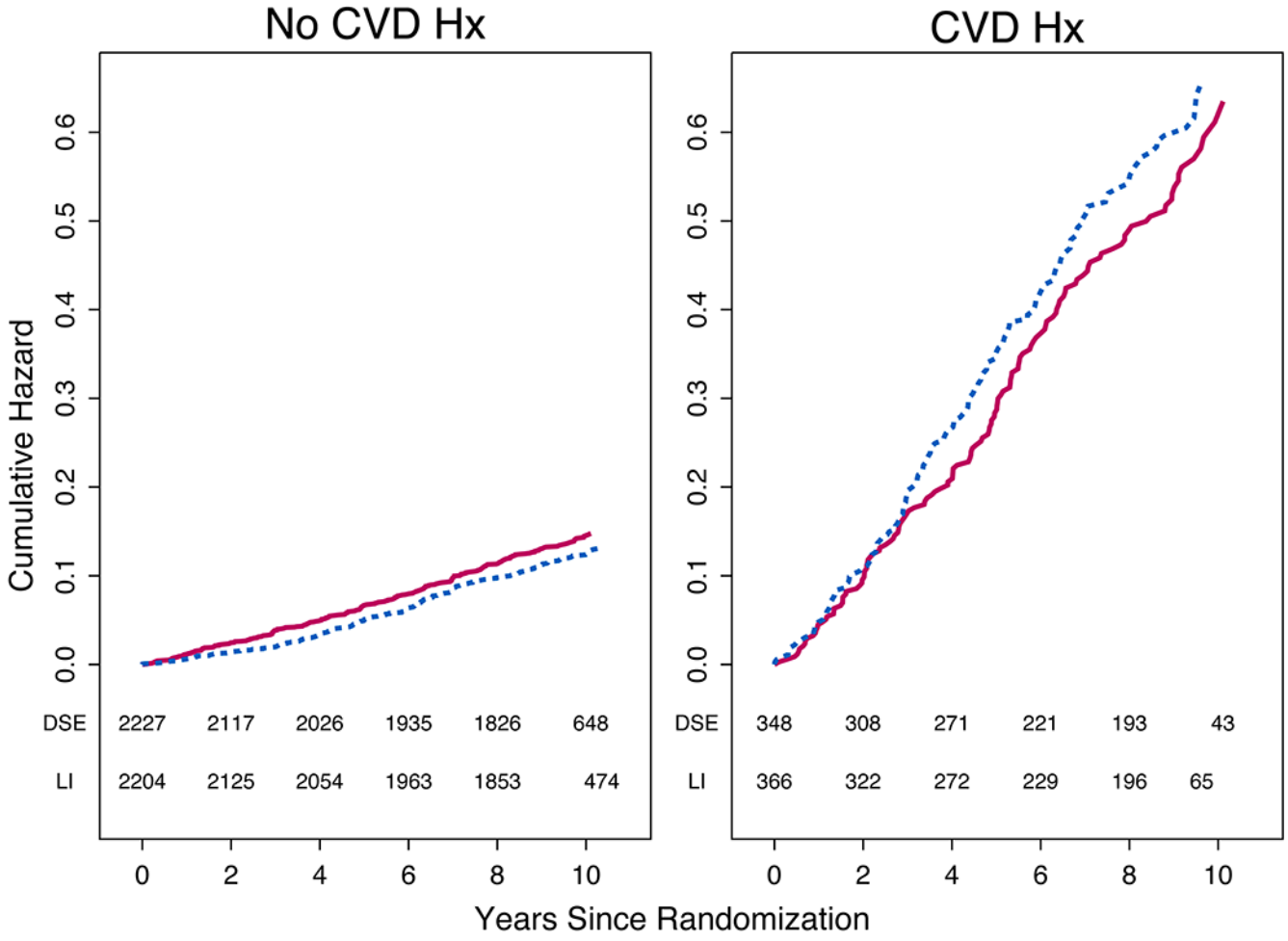


Figure 2.

Cumulative hazard plots for 821 primary composite outcomes including cardiovascular death, MI, stroke, or hospitalized angina, by history of CVD at baseline subgroup and randomized treatment assignment.*

* P value for interaction 0.063. The event rates were 1.23%/year and 1.41%/year for ILI vs DSE in those without CVD at baseline and 6.59%/year vs 5.95%/year in 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).

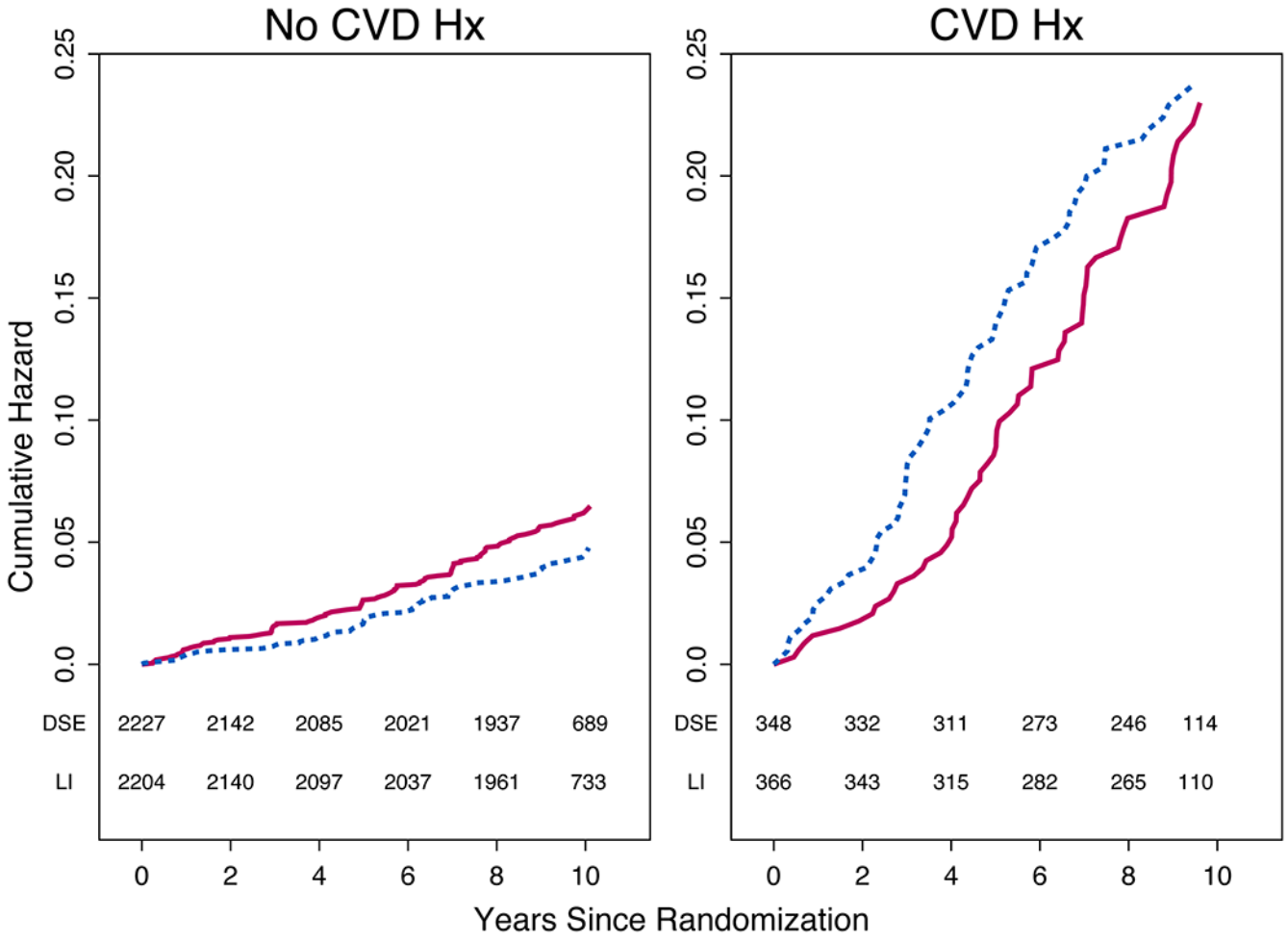


Figure 3.

Cumulative hazard plots for 354 non-fatal myocardial infarction by history of CVD at baseline and randomized treatment assignment.*

*P value for interaction 0.035. The event rates were 0.44%/year and 0.61%/year for ILI vs DSE in those without CVD at baseline, and 2.47%/year vs 2.18%/year in 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).

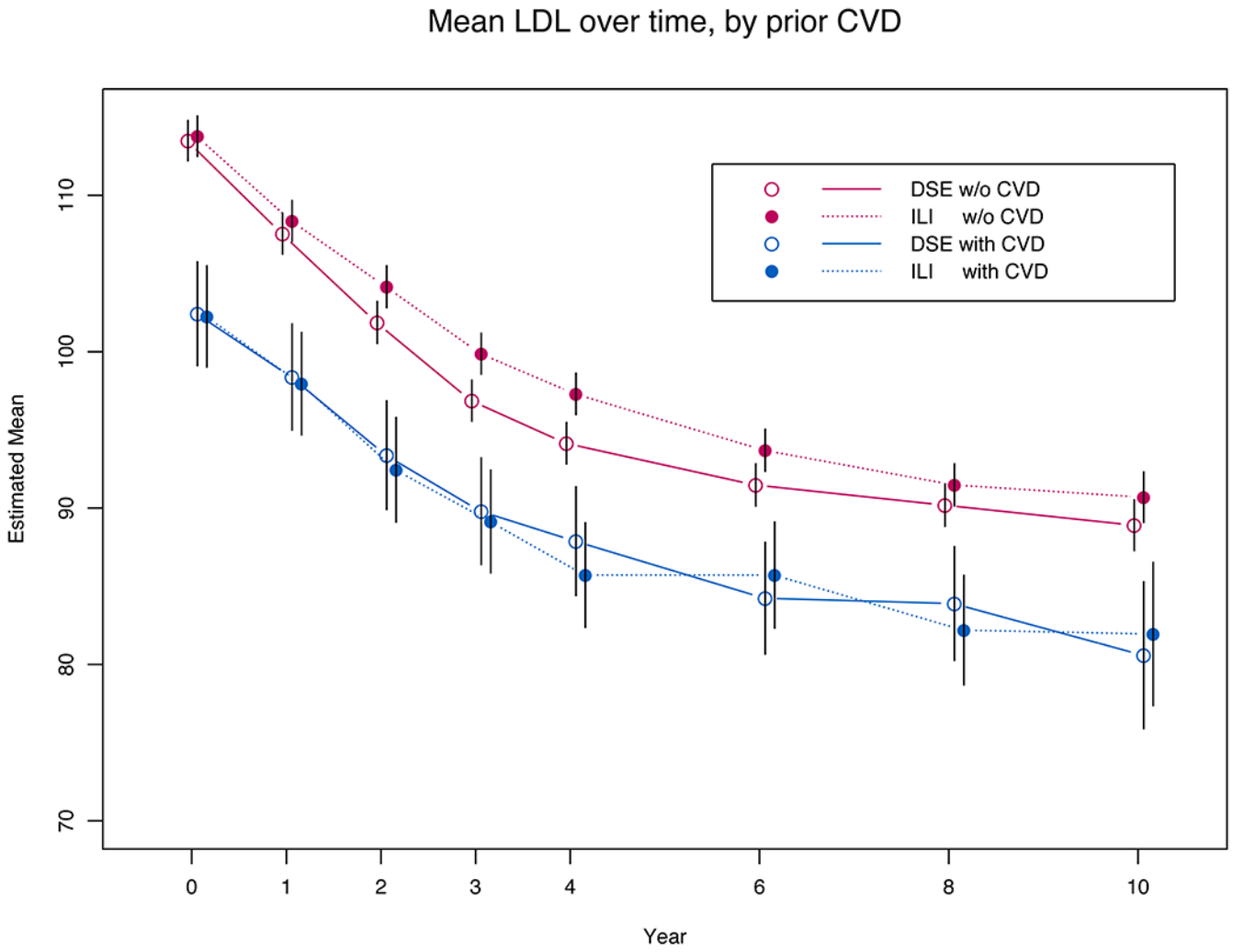
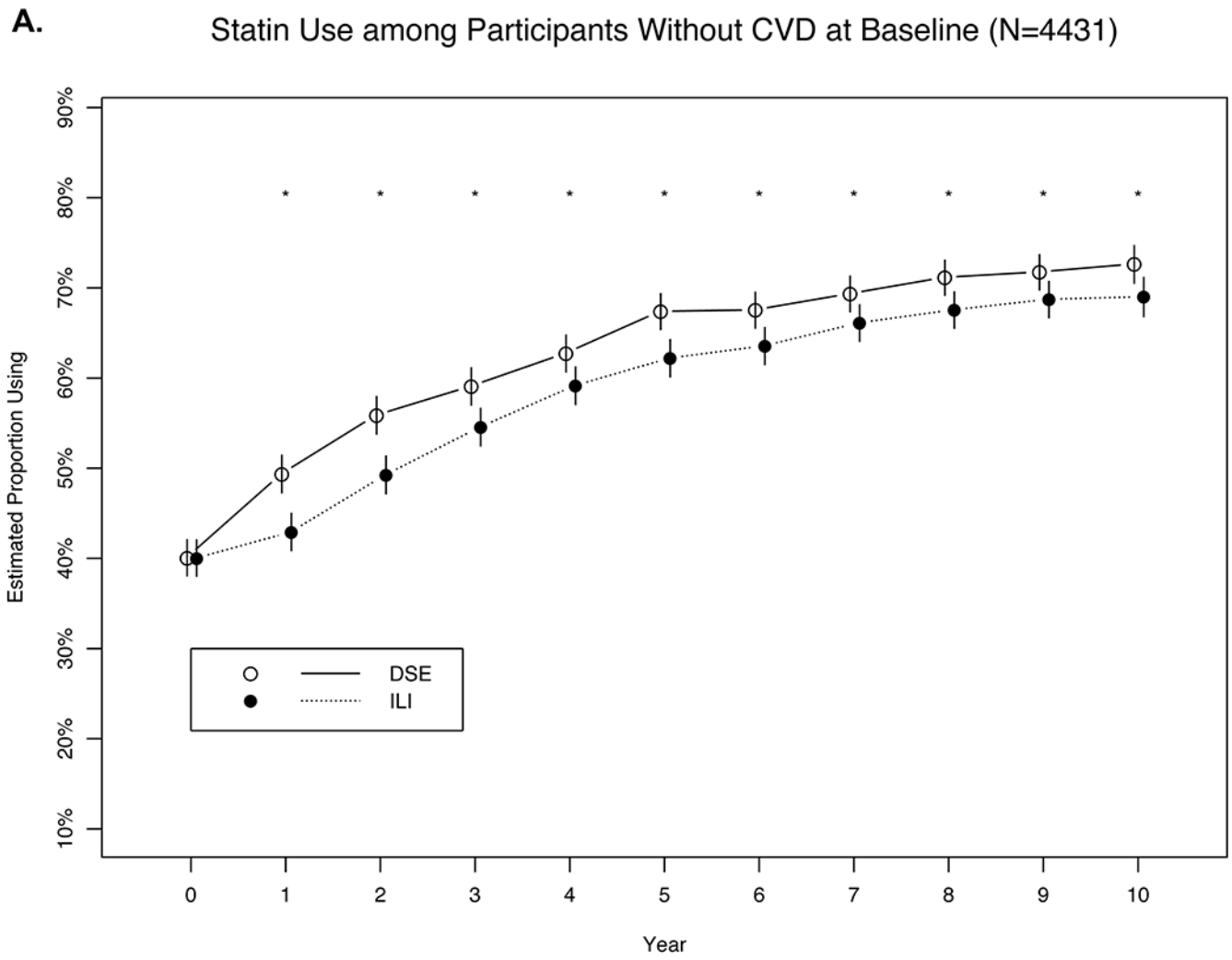


Figure 4.

Mean LDL-C levels by baseline history of CVD and treatment assignment by year.*

*Overall difference between randomized assignment groups in the subset without CVD history at baseline (p = 0.003); significant differences between ILI and DSE were present at follow-up years 2, 3, 4, and 6 in this group. There were no differences by treatment assignment among those with baseline CVD history.



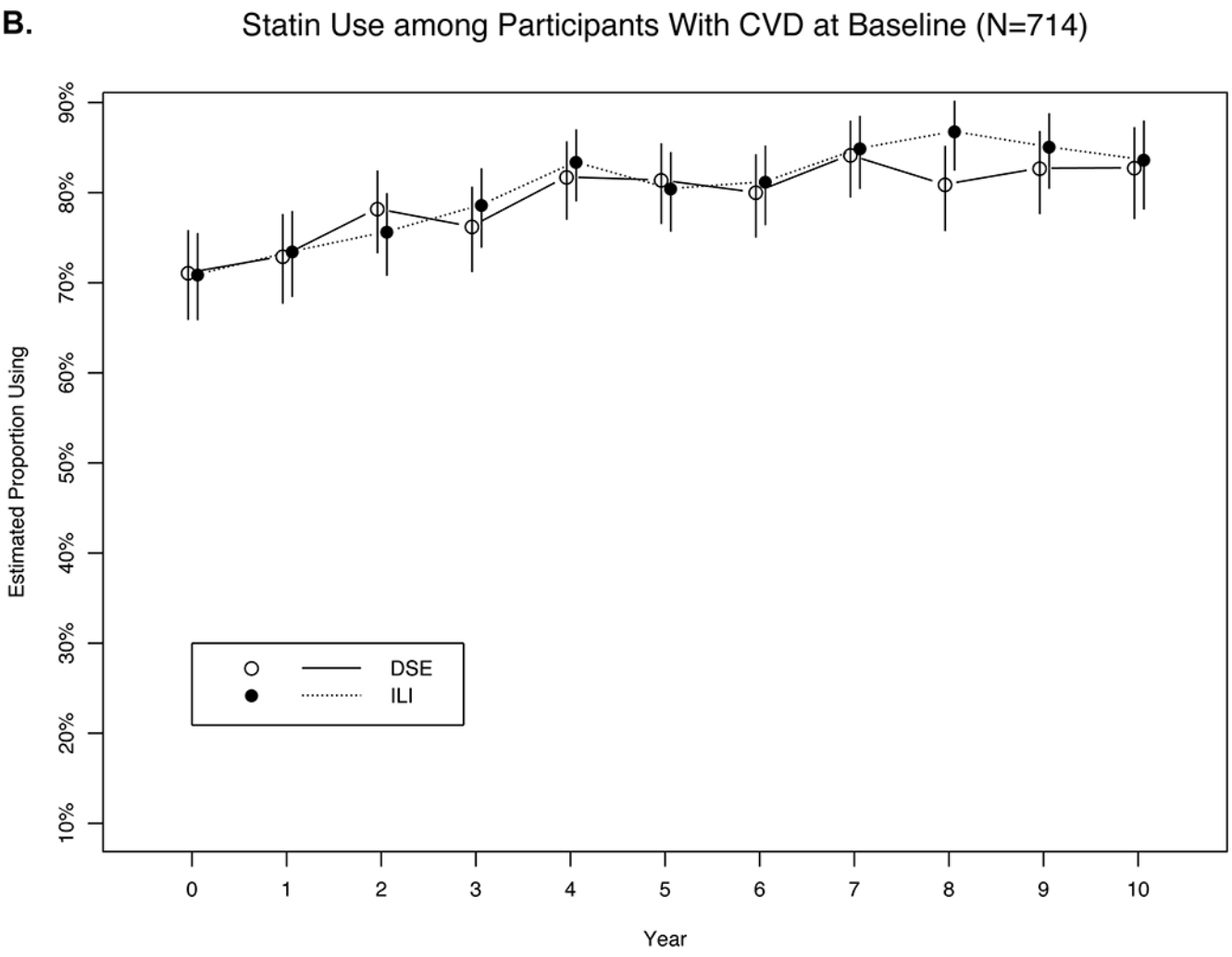


Figure 5.

Statin use by treatment assignment and by year, among those without CVD history (A) and with CVD history at baseline (B).* †

*p<0.05 for ILI vs DSE difference at time point with CVD subgroup

† Overall difference between randomized assignment groups in the subset without history of CVD at baseline p < 0.001; significant differences between ILI and DSE groups were present at all follow-up time points except year 10. There were no differences by treatment assignment among those with CVD history at baseline.

Table 1.

Baseline characteristics by history of CVD at baseline and randomization assignment (Mean (SD) or %)

Variable	CVD history at baseline present		No CVD history at baseline		P value CVD history difference
	DSE N=348	ILI N=366	DSE N=2227	ILI N=2204	
Age (years)	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 (years)	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)	101.6 (18.7)	103.1 (18.9)	100.7 (18.9)	100.1 (19.8)	0.014
BMI (kg/m^2)	35.0 (5.5)	35.8 (5.6)	36.1 (5.8)	35.9 (6.1)	0.012
Fitness (METS)	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
Systolic blood pressure (mm Hg)	128.8 (19.0)	128.3 (18.3)	129.6 (16.7)	128.2 (17.1)	0.641
Diastolic blood pressure (mm Hg)	69.3 (10.2)	68.4 (9.7)	70.5 (9.5)	70.2 (9.5)	<0.001
HbA1C (%)	7.4 (1.2)	7.4 (1.1)	7.3 (1.2)	7.2 (1.2)	0.010
eGFR ($ml/min/1.73\ m^2$)	83.4 (16.5)	84.2 (16.5)	91.0 (15.7)	91.4 (16.0)	<0.001
LDL-C (mg/dL)	102.4 (33.4)	102.3 (30.4)	113.5 (31.8)	113.8 (32.3)	<0.001
HDL-C (mg/dL)	41.2 (11.5)	41.0 (10.9)	43.9 (11.8)	43.8 (11.9)	<0.001
Triglycerides (mg/dL)	197.3 (132.6)	183.6 (111.5)	179.2 (119.2)	180.1 (113.2)	0.020

DSE: diabetes support and education

ILI: intensive lifestyle intervention

eGFR: estimate glomerular filtration rate

MET: metabolic equivalents

Table 2.

Primary and secondary outcome event rates and hazard ratios overall and according to CVD at baseline subgroups.

	Overall			CVD History			No CVD History			P value for Interaction
	Event rate		Hazard ratio	Event rate		Hazard ratio	Event rate		Hazard ratio	
	DSE	ILI		DSE	ILI		DSE	ILI		
Primary outcome *	418, 1.92%	403, 1.83%	0.95 (0.83, 1.09), p=.505	144, 5.95%	163, 6.59%	1.13 (0.90, 1.41), p=.305	274, 1.41%	240, 1.23%	0.86 (0.72, 1.02), p=.090	0.063
Secondary outcome 1†	283, 1.25%	267, 1.17%	0.93 (0.79, 1.10), p=.416	99, 3.63%	114, 4.11%	1.15 (0.87, 1.50), p=.330	184, 0.93%	153, 0.77%	0.82 (0.66, 1.02), p=.069	0.060
Secondary outcome 2†	529, 2.43%	496, 2.25%	0.93 (0.82, 1.05), p=.229	163, 6.73%	179, 7.23%	1.10 (0.88, 1.36), p=.404	366, 1.89%	317, 1.62%	0.85 (0.73, 0.99), p=.038	0.064
Secondary outcome 3†	600, 2.81%	577, 2.67%	0.94 (0.84, 1.05), p=.293	190, 8.59%	200, 8.58%	1.01 (0.82, 1.23), p=.961	410, 2.15%	377, 1.95%	0.91 (0.79, 1.04), p=.179	0.430
CVD death	57, 0.24%	52, 0.22%	0.88 (0.61,1.29), p=.519	28, 0.92%	24, 0.74%	0.80 (0.46, 1.39), p=.428	29, 0.14%	28, 0.14%	0.97 (0.58, 1.64), p=.920	0.600
Myocardial infarction - all	191,0.84%	163, 0.71%	0.84 (0.68, 1.04), p=.107	65, 2.32%	73, 2.54%	1.11 (0.79, 1.55), p=.557	126, 0.63%	90, 0.45%	0.71 (0.54, 0.93), p=.012	0.043
Myocardial infarction -nonfatal	183, 0.80%	159, 0.69%	0.86 (0.69, 1.06), p=.156	61,2.18%	71,2.47%	1.14 (0.81, 1.62), p=.443	122, 0.61%	88, 0.44%	0.71 (0.54, 0.94), p=.016	0.035
Myocardial infarction - fatal	11,0.05%	5, 0.02%	0.44 (0.15, 1.26), p=.126	7, 0.23%	3, 0.09%	0.42 (0.11, 1.68), p=.220	4, 0.02%	2, 0.01%	0.50 (0.09, 2.72), p=.421	0.852
Stroke - all	80, 0.34%	85, 0.36%	1.05 (0.77, 1.42), p=.776	30, 1.02%	31,0.99%	1.01 (0.61, 1.67), p=.979	50, 0.25%	54, 0.27%	1.07 (0.73, 1.57), p=.730	0.834
Hospitalization for angina	196, 0.87%	194, 0.85%	0.97 (0.80, 1.19), p=.785	83, 3.17%	83, 2.97%	0.94 (0.70, 1.28), p=.717	113, 0.57%	111,0.56%	0.97 (0.75, 1.27), p=.847	0.934
Total mortality	202, 0.86%	174, 0.73%	0.85 (0.69, 1.04), p=.111	62, 2.05%	55, 1.70%	0.83 (0.58, 1.21), p=.334	140, 0.68%	119, 0.58%	0.86 (0.67, 1.09), p=.209	0.930

*primary composite outcome was CVD death, myocardial infarction, stroke, and hospitalization for angina

†composite secondary cardiovascular outcomes were:

1. CVD death, myocardial infarction, or stroke;
2. death (all causes), myocardial infarction, stroke, or hospitalized angina; and
3. death (all causes), myocardial infarction, stroke, hospitalized angina, coronary artery bypass grafting, percutaneous coronary angioplasty, hospitalization for heart failure, or peripheral vascular disease

Table 3.

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

	CVD history at baseline present			No CVD history at baseline			
	HR	**95% CI**	**P value**	**HR**	**95% CI**	**P value**	**P value for Interaction†**
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 statin, use of any antihypertensive drug, use of aspirin, systolic blood pressure, diastolic blood pressure, HbA1C, eGFR, LDL-C, HDL-C, and triglycerides.

†interaction of randomized group and CVD history at baseline