Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

CARDIOVASCULAR EFFECTS OF INTENSIVE LIFESTYLE INTERVENTION IN TYPE 2 DIABETES

SUPPLEMENTARY APPENDIX

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DESIGN CONSIDERATIONS

Statistical Power and Rationale for Change in Definition of Primary Endpoint

The Look AHEAD trial was designed to have sufficient statistical power to detect an 18% reduction in the rate of major cardiovascular events among participants assigned to Intensive Lifestyle Intervention compared to Diabetes Support and Education over 10.5 years of follow-up. Originally, it was projected to provide 90% power based on an expected event rate of 3.125% per year in the Diabetes Support and Education group. The 3.125% per year event rate was based on data from Atherosclerosis Risk in Communities (ARIC) and the Cardiovascular Health Study (CHS),[1, 2] as discussed in the Look AHEAD Design paper [3] The 18% reduction was selected during the design stage based on the public health benefits of a 15-20% reduction and the feasibility of achieving this reduction. Prior data from an observational study of intentional weight loss in individuals with type 2 diabetes [4]suggested that intentional weight loss reduced mortality by 25%, with the greatest reduction (33%) occurring with a 20-29 pound intentional weight loss.

A lower-than-expected event rate in the first 24 months of follow-up prompted the Data and Safety Monitoring Board to express concern that the trial lacked the statistical power necessary to detect the originally hypothesized effect. To address this problem, the Steering Committee created an Endpoint Working Group, composed of Look AHEAD investigators with expertise in trials, representatives from NIH, and two senior consultants not otherwise affiliated with Look AHEAD, to investigate the possibility of modifying the study protocol in response to the unexpectedly low observed event rate. Many options were considered. Simply extending study follow-up appeared impractical, since many additional years would be required to compensate for an event rate far below that required for 80% power. Therefore, the Endpoint Working Group deliberated extensively about expanding the definition of the primary endpoint, in light of growing evidence of the many ill effects of obesity and widely recognized secular trends in the treated natural history of atherosclerotic cardiovascular disease. It recommended that the primary endpoint should be expanded to include hospitalized angina and the duration of the trial should be increased by two years. Together, these changes were projected to provide greater than 80% power for the trial. These recommendations were adopted by the Steering Committee and have led to revisions in the protocol document. The members of the Steering Committee and the Endpoints Working Group were masked to data on differences between intervention groups throughout the course of determining the revised endpoints. The Data and Safety Monitoring Board was not involved in choosing the revised endpoints, although they did approve the process by which the Endpoints Working Group developed the revised endpoints.

The Endpoint working group decided to include hospitalized angina in the primary outcome for the following reasons. Hospitalized angina would capture “aborted” MIs related to secular improvements in acute cardiac care and would be consistent in tone with recent thinking on CVD endpoints. [5] Look AHEAD defined hospitalized angina so as to clearly exclude chronic stable angina, which was considered susceptible to ascertainment bias in unblinded trial. Congestive heart failure was also considered but was not added to the primary outcome because it is a heterogeneous syndrome related not only to atherosclerosis but also to hypertension, renal disease, and other causes.

For a more complete discussion of the decisions involved in changing the primary endpoint, please see the reference by Brancati.[6]

Rationale for focusing on participants with type 2 diabetes and including participants with a history of cardiovascular disease.

Look AHEAD was conducted in overweight and obese individuals with type 2 diabetes. Diabetes is an increasingly prevalent health problem in the United States, and it has significant impact on cardiovascular morbidity and mortality. Patients with diabetes are typically advised to lose weight as the first step of treatment. The decision to include individuals with a history of cardiovascular disease was based on several considerations: the higher event rate in these individuals, the desire to be able to generalize to the type 2 diabetic population (29% of whom have a history of heart disease or stroke, based on NHANES III data),[7] and the fact that during screening many individuals without a known history of cardiovascular disease will be found to have evidence of cardiovascular disease. Moreover, it appears that lifestyle intervention can be effective in individuals with a history of heart disease. The Trial of Nonpharmacologic Interventions in the Elderly[8] found that weight losses between individuals with and without a history of cardiovascular disease were similar. Dietary intervention studies have successfully reduced mortality in individuals with a history of cardiovascular disease, as have cardiac rehabilitation programs.[9, 10]

Prior CVD was defined as history of myocardial infarction, stroke, congestive heart failure or CVD procedures (CABG, PTCA, carotid endarterectomy, angioplasty of a lower extremity artery, or aortic aneurysm repair).

Decision related to Medical Management by Participants Own Health Care Provider

The Look AHEAD trial was neither designed nor staffed to provide comprehensive medical care to all participants, nor was this necessary to address the principal study objective of the trial. Look AHEAD participants received their diabetes and general health care from providers outside of the study. This approach allowed the study to assess the benefits of weight loss compared to the medical care received in the general community. This approach also may have maximized the willingness of physicians to refer patients to the study (i.e., they would not have to worry about losing their patients).

Look AHEAD sought to facilitate effective medical management through participant education curricula, through providing clinical data on diabetes control and cardiovascular risk factors, through communication to physicians on current consensus recommendations for management of diabetes, lipids, and hypertension, and through communication concerning safety issues that arise in relation to interventions.

Feasibility evaluation and stopping rules

The progress of Look AHEAD and the study's potential of attaining its goals were regularly evaluated by the Data and Safety Monitoring Board (DSMB -- Section 10.9). Several key criteria that the DSMB used to inform its recommendations on the continuation of the Look AHEAD trial are summarized in this section.

Feasibility Evaluation. The feasibility of the trial was formally assessed by the DSMB early in the study to ensure that the trial interventions were being successfully delivered. Data on the first 25% of participants recruited into Look AHEAD were examined when these participants

all reached Year 1 and again when they reached Year 2. Three criteria were used to judge the success of the intervention.

1. To demonstrate success of the intervention at achieving a difference between study arms at one year, there must be at least a 5 percentage points difference in the average percentage point change in weight from Baseline to Year 1 between participants assigned to the Lifestyle Intervention compared to those assigned to Diabetes Support and Education.

2. Since the Look AHEAD goal is to achieve absolute weight loss (rather than diminished weight gain), a second feasibility criterion at Year 1 was also defined. The average absolute percent weight loss from Baseline among the first 25% of Lifestyle Intervention participants not using insulin at Baseline must be at least 5% at Year 1. Because insulin use may influence weight changes, the average percent weight loss from Baseline in insulin-using participants in the Lifestyle Intervention was also estimated, however the sample size is not sufficient to estimate this percentage precisely. Weight loss in this cohort was targeted to be at least 3% at Year 1.

3. To assess the ability of the Lifestyle Intervention to produce longer-term effects, feasibility criteria based on two-year changes also were defined. These acknowledge the potential that changes in fitness, as well as changes in weight, may have an impact on cardiovascular disease in the long term. The longer-term feasibility of the trial was assessed based on the following criterion. At Year 2, for the first 25% of participants there must be at least a 5% difference in the average percent change in weight or fitness from Baseline between participants assigned to the Lifestyle Intervention compared to those assigned to Diabetes Support and Education. The fitness measure at Year 2 was collected only in the subset of 25% of the study participants who were the first to reach their two-year post-randomization anniversary.

Stopping Rules For Efficacy and Futility. Incidence rates of the primary and secondary composite outcomes were monitored throughout the trial and used for interim analyses of efficacy and futility. Group sequential methods for events rates were used to control the Type I error to be 0.05 across these repeated analyses.[11-13] Critical values for interim testing were defined based on an O'Brien-Fleming type bound [14]and used a spending functions to allow flexibility in the number and timing of interim analyses. [15] With this approach, interim tests early in the trial are conservative and the reduction in the overall power of the trial caused by interim testing is small. Conditional power calculations was used to assess the futility of continuation in the presence of a negative treatment effect.[16]

The intervention was stopped for futility by the study sponsor based on a recommendation of the DSMB on September 14, 2012, at which point the trial was converted to an observational follow-up study.

Stopping Based On Safety Concerns. At each meeting, the DSMB reviewed data on adverse events and other safety issues to make an overall recommendation to the NIH concerning the safety of continuing Look AHEAD. Consistent with NIH policy, each Look AHEAD Principal Investigator received a report summarizing the DSMB review of the adverse event

data. Principal Investigators were responsible for providing this report to the IRB at their institution. Look AHEAD was not stopped for safety concerns.

Distinction between procedures for adverse events versus study outcomes

Adverse events, pre-existing conditions, and serious adverse events were defined by the Food and Drug Administration and other governing bodies. In the context of trials testing drugs, serious adverse events are defined by the FDA as: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse experiences if they might jeopardize the participant or might require medical or surgical intervention to prevent one of the outcomes in the definition. An example of this in Look AHEAD is treatment in the emergency room for severe hypoglycemia.

In the Look AHEAD safety monitoring system, participants who reported adverse events to any staff person at any time were referred to unmasked medical staff responsible for identifying, recording, and managing these events. Safety-related events were reported in a timely fashion as required by the Data and Safety Monitoring Board and the IRBs responsible for the study. Interventionists and other staff reporting or managing adverse events for safety purposes did not at any time communicate information regarding these events to study assessment personnel.

Look AHEAD maintained an outcome database that was completely separate and distinct from the safety monitoring system. This was necessary because many of the Look AHEAD staff members were not masked to intervention assignment, and it is critical that the identification and reporting of serious adverse events for safety reasons not bias the study's collection of outcome data. Thus, for outcome purposes, all Look AHEAD participants were systematically queried at clinic visits or on clinic phone calls scheduled according to the protocol to capture outcome data on study outcomes, medical events, or adverse experiences. This separate outcome database contained solely those adverse events that were reported through these regularly scheduled event interviews conducted by designated outcome assessment staff who were masked to intervention assignment.

ELIGIBILITY CRITERIA

Gender Men and women are eligible. Look AHEAD will endeavor to recruit approximately equal numbers of men and women.

Type 2 diabetes mellitus Diabetes mellitus will be determined by self-report with verification (medical records, current treatment, verification from personal health care provider, or test results meeting the 1997 American Diabetes Association criteria of fasting glucose > 126 mg/dl, symptoms of hyperglycemia with casual plasma glucose > 200 mg/dl or two-hour plasma glucose > 200 mg/dl after a 75 gram oral glucose load). In an effort to identify individuals with type 2 diabetes (the population that would be most responsive to weight loss), individuals who have a clinical history strongly suggestive of Type 1 diabetes will be excluded. Individuals taking oral hypoglycemic medication or insulin and those who are treated with diet and exercise are eligible. No more than 30% of the study population will be using insulin at entry into the study.

Body mass index Overweight individuals, with body mass index of 25 kg/m^2 or greater (27 kg/m^2 if currently taking insulin) are eligible. Weight loss is recommended for overweight individuals with one or more cardiovascular risk factors, including diabetes mellitus. There is no upper eligibility criterion for body mass index, however an upper limit on weight has been set (Section 4.2.1).

Age Individuals aged 45-75 years old are eligible. Individuals older than 75 years of age are excluded due to their increased risk of competing mortality and potential safety concerns related to weight loss.

Ethnicity All ethnic groups are eligible for the study. Look AHEAD has the goal of recruiting 33% of the study cohort from ethnic minority groups including African Americans, Hispanic Americans, American Indians, and Asian Americans. Data from NHANES III indicate that approximately 23% of individuals meeting the eligibility criteria for Look AHEAD will be from ethnic minorities.[7]

Blood pressure Look AHEAD will enroll individuals whose blood pressure is under at least moderate control: treated or untreated resting systolic/diastolic blood pressure less than 160/100 mmHg. Individuals whose blood pressure exceeds these levels during screening will be told to seek treatment. Such individuals may be rescreened after three months to re-assess blood pressure eligibility.

Glycemic control Look AHEAD will enroll individuals whose HbA1c is less than 11% or equal to 11%. Individuals whose HbA1c exceeds this level may require more urgent care and will be told to seek treatment. Such individuals may be re-screened after three months to re-assess HbA1c eligibility.

Lipid control Individuals with a fasting triglycerides concentration less than 600 mg/dl are eligible. Individuals whose fasting triglycerides concentration exceeds this level may be re-screened after three months to re-assess triglycerides eligibility.

History of cardiovascular disease Look AHEAD will recruit individuals both with and without a history of cardiovascular disease. Data from NHANES III indicate that approximately 29% of individuals meeting the eligibility criteria defined by the trial will have a history of cardiovascular disease. Cardiovascular event rates in diabetic individuals with heart disease are expected to be approximately twice those of diabetic individuals without a history of heart disease.[17]

Eligible participants include those with a history of uncomplicated myocardial infarction, coronary artery bypass surgery, percutaneous coronary angiography, atherectomy or stent placement, chronic stable angina pectoris, no resting or exercise induced complex arrhythmias, and stable NYHA Class I or Class II congestive heart failure if they are beyond three months. Participants with a history of carotid or peripheral artery atherectomy, angioplasty, or bypass surgery are also eligible for inclusion if they meet functional criteria for inclusion.

All participants will undergo a supervised maximum exercise stress test using the established study protocol. The exercise stress test will be conducted while the participant is continued on any prescribed medication for cardiovascular disease. Abnormalities will result in exclusion or in further evaluation. Individuals who develop exercise induced angina pectoris or significant ST segment depression of 1.5 mm or greater at low to moderate workloads (less than 7 METs) may be included if they have been evaluated by a cardiologist and considered safe for participation in the Lifestyle Intervention protocol.

Willingness to participate Participants must be willing to be randomized to either Diabetes Support and Education or the Lifestyle Intervention and to follow the protocol to which they have been assigned. Individuals who are unwilling to consider using weight loss medications are eligible for the study, however they must be willing to modify their diet and their activity and to attempt to lose 7% of their body weight if they are assigned to the Lifestyle Intervention.

EXCLUSION CRITERIA

The following criteria are used to exclude individuals for whom weight loss might not be safe, those who may have difficulty adhering to the lifestyle intervention, or those with medical conditions that might interfere with the intervention goals.

Exclusion Criteria for Factors That May Limit Adherence To Interventions or Affect Conduct of the Trial

- Unable or unwilling to give informed consent or communicate with local study staff
- Current diagnosis of schizophrenia, other psychotic disorders, or bipolar disorder
- Hospitalization for depression in past six months
- Self-report of alcohol or substance abuse within the past twelve months, current consumption of more than 14 alcoholic drinks per week, and/or current acute treatment or rehabilitation program for these problems (Long-term participation in Alcoholics Anonymous is not an exclusion.)
- Plans to relocate to an area not served by Look AHEAD or travel plans that do not permit full participation in the study
- Lack of support from primary health care provider or family members
- Failure to complete the run-in for dietary intake and exercise (see Section 4.6)
- In past three months, weight loss exceeding 10 lbs (Such individuals may have difficulty losing additional weight.)
- Current use of medications for weight loss
- Self-reported inability to walk two blocks
- History of bariatric surgery, small bowel resection, or extensive bowel resection
- Chronic treatment with systemic corticosteroids (Weight gain associated with steroids may interfere with the intervention goals. Use of hormone replacement therapy or oral contraceptives will not lead to exclusion.)
- Another member of the household is a participant or staff member in Look AHEAD
- Weight greater than 350 pounds unless equipment is available to conduct maximal exercise test for heavier individuals
- Other medical, psychiatric, or behavioral factors that in the judgment of the Principal Investigator may interfere with study participation or the ability to follow the intervention protocol

Exclusion Criteria for Underlying Diseases Likely to Limit Lifespan and/or Affect the Safety of the Interventions

- Currently pregnant or nursing (These individuals can be re-contacted for screening after delivery or when finished nursing.)
- Cancer requiring treatment in the past five years, except for non-melanoma skin cancers or cancers that have clearly been cured or in the opinion of the investigator carry an excellent prognosis (e.g., Stage 1 cervical cancer)
- HIV positive (self-report), due to effects on weight and body composition of HIV and medications used to treat HIV
- Active tuberculosis (self-report)
- Cardiovascular disease (heart attack or procedure within the past three months or participation in a cardiac rehabilitation program within last three months, stroke or

- Participants also will be excluded if they meet any of the following criteria:
  - unstable angina pectoris or angina pectoris at rest
  - a history of cardiac arrest
  - complex ventricular arrhythmia at rest or with exercise (e.g., ventricular tachycardia)
  - uncontrolled atrial fibrillation (heart rate of 100 beats per minute or more)
  - NYHA Class III or IV congestive heart failure
  - acute myocarditis, pericarditis or hypertrophic myocardopathy
  - clinically significant aortic stenosis
  - left bundle branch block or cardiac pacemaker unless evaluated and cleared for participation by a cardiologist
  - cardiac defibrillator
  - heart transplant
  - history of aortic aneurysm of at least 7 cm in diameter or aortic aneurysm repair
  - resting heart rate less than 45 beats per minute or greater than 100 beats per minute
- Any abnormality during the maximum exercise stress test that indicates that it would be unsafe to participate in the Lifestyle Intervention (This includes angina pectoris or significant ST segment depression at low levels of exercise, unless evaluated and cleared for participation by a cardiologist; exercise induced ventricular arrhythmias; abnormal hemodynamics, such as flat or decreasing systolic blood pressure with increasing workload; and an abnormal response to exercise which, in the opinion of the exercise physiologist or physician, would make it unsafe for the individual to participant.)
- Those at moderate to high risk for cardiac complications during exercise and/or who are unable to self-regulate activity or understand the recommended activity level (The phrase moderate to high risk is defined according to AHA/ACSM criteria. Information for this determination is available from the medical history and the ECG performed during maximal exercise stress testing.)
- Renal disease: urine dipstick protein of 4+ (equivalent to approximately > 1 g/day), serum creatinine exceeding 1.4 mg/dl (women) or 1.5 mg/dl (men), or currently receiving dialysis
- Chronic obstructive pulmonary disease that would limit ability to follow the protocol (investigator judgment)
- Self-reported chronic hepatitis B or C or cirrhosis
- Inflammatory bowel disease requiring treatment in past year
- Cushing's syndrome (clinic diagnosis or self-report)
- Acromegaly (clinical diagnosis or self-report)
- Amputation of lower limbs as result of non-traumatic causes
- Any major organ transplant (does not include cornea or hair transplants)
- Conditions not specifically mentioned above may serve as criteria for exclusion at the discretion of the clinical site

MORE DETAILED DESCRIPTION OF THE TRIAL INTERVENTIONS

Intensive Lifestyle Intervention

The lifestyle intervention used in Look AHEAD was based on the most recent research on the strategies for inducing and maintaining weight loss [18]. The intervention was similar to that used in the Diabetes Prevention Program (DPP), but differed in the following ways: the Look AHEAD intervention included both group and individual sessions, participants were given a weight loss goal of 10% (rather than 7%), meal replacement products were provided to improve adherence, weight loss medication was used as an option for a short period of time, the physical activity goal was 175 minutes (compared to 150 minutes in DPP), and a specific algorithm for adjustment of diabetes medications was followed to reduce the risk of hypoglycemia.

The Look AHEAD intervention sought to achieve and maintain at least a mean 7% weight loss. In order to achieve this, each individual participant was encouraged to lose and maintain at least 10% of their body weight. Weight loss was attained through decreased caloric intake and increased physical activity.

Participants attended both group and individual sessions, with decreasing frequency of contact over the course of the trial. The sessions were conducted by nutritionists, exercise specialists, and behavior therapists certified by Look AHEAD. All participants were assigned a lifestyle counselor who worked with the individual throughout the program. Participants completed the first year of treatment with an assigned group of 10-20 persons. For months 1-6, participants were provided weekly treatment, with three group sessions and one individual session each month; for months 7-12, they were provided two group sessions and one individual session each month. During Years 2 to 4, the intervention was delivered more on an individual basis, with at least one in-person contact each month and an additional monthly phone or email contact. After year 4, there was one individual contact each month. In addition, participants were offered two or three group classes and courses each year to help maintain interest and the weight and activity goals.

ILI participants were given a calorie goal of 1200-1500 kcal/day for those who weighed less than 114 kg (250 lbs) and 1500 to 1800kcal/day for those over 114 kg. They were encouraged to consume 30% of total calories from fat and at least 15% of calories from protein. Meal replacement products were provided at no cost to help participants adhere to their dietary goals. During weeks 3 to 19 of the program, individuals were encouraged to replace two meals each day with a liquid shake and one snack with a bar. The other meal (typically dinner) consisted of conventional foods; fruits and vegetables were added to reach the calorie goal. From week 20 on, meal replacements were typically used for one meal per day with conventional foods consumed at the other times.

Physical activity was gradually increased to a goal of at least 175 minutes/week. This activity goal was achieved in bouts of at least 10 minutes in duration and used moderate intensity activities such as brisk walking. Group sessions discussed methods for exercising safely and reducing barriers to exercise and introduced participants to strength training which could comprise up to 25% of the weekly goal. In addition to structured activity done in bouts of at least 10 minutes, participants were also encouraged to increase their lifestyle activity. They were provided with pedometers and encouraged to walk 10,000 steps each day.

Behavioral strategies were stressed throughout the program. Self-monitoring of food and physical activity was emphasized as the most important behavioral strategy, and self-monitoring logs were reviewed regularly by the lifestyle counselors to assist participants with their behavior changes. Participants were weighed at each session, self-monitoring books were reviewed, and a new lesson topic presented. Lessons were prepared centrally and are available at the web address provided at the end of this appendix.. These lessons included topics such as limiting times and places of eating, coping with negative thoughts, and relapse prevention.

Hypoglycemia was of particular concern during the first 6 months of the program when caloric restriction and meal replacement products were started. To minimize the risk of hypoglycemia, participants taking insulin or other medications that might cause hypoglycemia, monitored their blood sugar for at least one week. These readings were used by the medical staff to adjust medications following a preset algorithm [18]. The same approach to adjusting medications was used in later years when campaigns or refresher groups included more structured dietary approaches and meal replacement products.

To maximize weight loss, a tool box of additional strategies was available for use with participants after month 6 if the individual had not achieved the 10% weight loss. The tool box included orlistat, a weight loss medication. However, since minimal weight loss benefit was observed with orlistat, the use of this medication was discontinued in 2008.

From Year 2 on, participants were invited to participate in a periodic group refresher courses and national campaigns. (Refreshers typically lasted 4-6 weeks, while campaigns were usually 8-10 weeks.) Both were designed to re-engage participants and increase commitment of lifestyle changes. The national campaigns were implemented at all sites and the same time and often included a small prize (e.g. a windbreaker or stadium blanket) for achieving campaign goals. Monthly open group meetings and reunion groups, where participants met with the members of their original year 1 treatment group, were also provided.

Note: The Lifestyle Counselor Guide and Participant Handouts for the first year of the intervention may be found at:
https://www.lookaheadtrial.org/public/dspMaterials.cfmhttps

Diabetes Support and Education

The goal of the Diabetes Support and Education program is to offer a valuable educational experience to these participants and to respond to their interest in education and support, thereby helping to retain them in the trial.

Contact Mode and Frequency
Participants assigned to Diabetes Support and Education are invited to attend three group educational / social support sessions each year for 4.0 to 6.5 years after study randomization begins. One educational or social support session annually will continue to be offered beginning with year 5 until the end of the trial. Attendance is strongly encouraged but not required at these sessions. These participants also attend regularly scheduled clinic visits for annual assessment and participate in telephone calls for data collection and safety monitoring.

Content of Educational Sessions

The educational sessions offered for Diabetes Support and Education include one session each year on diet/nutrition and one session related to exercise. These sessions are informational and do not teach behavioral self-regulation skills. The content of these sessions are developed by the Diabetes Support and Education committee to standardize the intervention across clinics. Different nutrition and exercise topics are covered each year. Sessions are conducted by an individual with a background in diabetes education, exercise, or nutrition.

Content of Support Sessions

Support sessions are also offered annually to participants assigned to Diabetes Support and Education. These provide an opportunity for participants to discuss issues related to living with diabetes. These sessions will involve open discussion, facilitated by a member of the Look AHEAD staff.

DEFINITION OF THE PRIMARY AND SECONDARY OUTCOME MEASURES

Primary Outcome Measure

The primary outcome measure of the Look AHEAD clinical trial is the combined incidence of cardiovascular deaths (including fatal myocardial infarctions and strokes, and other cardiovascular causes), non-fatal myocardial infarctions, non-fatal strokes, and hospitalization for angina according to the definitions below.

Myocardial Infarction

The algorithm for classifying MI includes elements of the history, results of cardiac enzyme determinations, and ECG readings, and includes MI that occurred during surgery/procedure and MI aborted by thrombolytic therapy or procedure. The definition and differentiation of definite vs probable vs possible MI followed published consensus criteria [5] on case definitions of acute coronary heart disease (CHD [Table B1]), with classification at the highest level of the combinations of the three characteristics.

Table B1. Algorithm for classification of MI

	Biomarker findings							
	Cardiac signs or symptoms present				Cardiac signs or symptoms absent			
ECG findings	Diagnostic**	Equivocal**	Missing**	Normal	Diagnostic	Equivocal	Missing	Normal
Evolving diagnostic	Definite	Definite	Definite	Definite	Definite	Definite	Definite	Definite
Positive	Definite	Probable	Probable	No	Definite	Probable	Possible	No
Nonspecific	Definite	Possible	No	No	Definite*	Possible	No	No
Normal or other ECG	Definite	Possible	No	No	Definite*	No	No	No

* in the absence of diagnostic troponin, downgrade to possible.

Cardiac symptoms were defined as presence of acute chest pain, epigastric, neck jaw, or arm pain or discomfort or pressure without apparent noncardiac source. More general, atypical symptoms, such as fatigue, nausea, vomiting, diaphoresis, faintness, and back pain, were not used as diagnostic criterion. Cardiac signs included acute congestive heart failure or cardiogenic shock in the absence of non-CHD cause.

The adjudicators interpreted serial tracings, with the ECG series assigned the highest category for which criteria were met. Evolving diagnostic included new major Q wave in the absence of Q wave in previous ECG, or the presence of an equivocal Q wave in previous ECG followed by the appearance of major Q wave and either major ST-segment depression, T wave inversion, or ST-segment elevation. Positive ECG included evolving ST elevation alone, evolving equivocal Q wave plus evolving ST-T depression/inversion, or new left bundle block. Nonspecific ECG included evolving non-ST elevation non-Q wave pattern (eg ST depression alone) or evolving minor Q wave alone. Findings other than these or normal ECGs were classified as negative for ischemia. Look AHEAD clinical centers provided copies of the 12 lead ECG obtained at study visits in the adjudication packet.

Biomarkers were interpreted in the clinical context, with evaluation of pattern and timing. An adequate set of biomarkers was defined as at least two measurements of the same marker taken at least 6 hours apart. The general classification pertained to cases without defibrillation/cardioversion, CPR, or intervention. Diagnostic biomarkers were defined as at least 1 positive biomarker in an adequate set showing a rising or falling pattern in the setting of clinical cardiac ischemia and the absence of noncardiac (absence of overt ischemic heart disease) causes of biomarker elevation. Positive biomarkers were defined as at least one value of 2 or more times the upper limit of normal in the lab performing the measurement, as described below. Equivocal biomarkers were defined as only 1 available measurement that was positive, or a rising or falling pattern not in the setting of clinical cardiac ischemia or in the presence of nonischemic causes of biomarker elevation. Equivocal also included the range between "above normal" and "twice the upper limit of normal. Normal biomarkers did not meet criteria for positive or equivocal biomarkers. In the first 48 hours following percutaneous angioplasty, levels of CK or MB or troponin above 3 times the upper limit of normal were characterized as positive. Troponin took precedence over CK-MB, and CK-MB took precedence over CK if both were available. Similarly for coronary artery bypass graft surgery, levels of troponin or MB above 5 times the upper limit of normal within 48 hours of the procedure were categorized as positive.

The consensus criteria [5] defined "positive" as at least one value exceeding the 99th percentile of the distribution in healthy populations or the lowest level at which a 10% coefficient of variation can be demonstrated for that value. Additional literature described an array of assay specific values for the cutpoint of the 99th percentile [19]. In practice, the adjudication committee could not operationally define these cutpoints due to variation in the assays used by clinical labs and the lack of available information on these ranges specific to the large number of clinical labs performing biomarkers on Look AHEAD participants. The committee continued to use the cutpoint of 2 times the upper limit of normal for positive, and the range between less than 2 times the upper limit of normal and the upper limit of normal for equivocal, since these levels closely corresponded to the 99th percentile where that could be ascertained.

Stroke

The minimum criterion for definite or probable stroke is evidence of sudden or rapid onset of focal neurological symptoms lasting more than 24 hours or leading to death, in the absence of evidence for a non-stroke cause [20]. Exclusionary conditions for stroke included major brain trauma, intracranial neoplasm, coma due to metabolic disorders or disorders of fluid or electrolyte balance, peripheral neuropathy, or central nervous system infections. Major stroke symptoms were hemiparesis of two or more body parts, homonymous hemianopia, or aphasia. Minor stroke symptoms were diplopia, vertigo and gait disturbance (both together), dysarthria, dysphagia, dysphonia, or unilateral numbness of one or more body parts.

Strokes were further subdivided into ischemic and hemorrhagic. Definite ischemic stroke required: autopsy or surgical evidence of a non-hemorrhagic (ischemic) infarct of the brain (cerebral thrombosis or cerebral embolism); or evidence from the hospital record of one major or two minor neurologic signs or symptoms lasting at least 24 hours or until the participant died without CT or MRI scan, or lumbar puncture evidence of blood; or deficit lasting more than 24 hours with evidence of brain infarction (mottled cerebral pattern or decreased density in a compatible location by CT or MRI); and absence of a nonvascular condition which would satisfactorily explain the participant's symptom. Ischemic stroke subtypes were adjudicated

using published [21] criteria into large artery atherosclerosis, cardioembolic, small artery occlusion (lacunar), ischemic stroke of undetermined etiology, and ischemic stroke of other determined etiology (eg, hypercoagulable state). Hemorrhagic stroke subtypes were primary intracerebral hemorrhage and subarachnoid hemorrhage using methods from the Multi-Ethnic Study of Atherosclerosis (MESA) study.

A transient ischemic attack (TIA), and not stroke, was defined as one major or two minor neurologic symptoms of sudden onset lasting less than 24 hours and CT or MRI findings within the first 48 hours were negative or nonspecific, with no sign of hemorrhage; or a lumbar puncture yielded clear, colorless spinal fluid or bloody fluid with the characteristics of a traumatic tap.

Hospitalization for Angina

Look AHEAD based adjudication of hospitalization for the diagnosis and/or treatment of angina on methods developed by the Women's Health Initiative [22]. Angina was not defined initially as a component of the primary outcome, but was added after the low event rate experienced in the first two years of follow-up [6].

Angina was considered when patients experienced symptomatic events involving ischemic chest, left arm, or jaw pain; however, atypical anginal symptoms, including shortness of breath, exertional dyspnea, epigastric discomfort, or pain isolated to the arm or the jaw, could also be considered. An indication of new or increasing symptoms was considered supportive. Typically, cases of angina had a discharge diagnosis of unstable angina/acute coronary syndrome, the participant was treated for angina and had a treatment response, the clinical picture was consistent with angina, and the participant was discharged on medications for angina. Other criteria in support of angina included previous history of coronary heart disease documented by revascularization or catheterization, catheterization showing ≥ 70% obstruction at the time of the event; revascularization occurring at the time of the event; exercise or pharmacologic stress test showing abnormal exercise ECG (ST depression or elevation≥ 1 mm) with pain; scintigraphic or echocardiographic stress test positive for ischemia associated with the admission; or resting ECG with pain showing horizontal or down-sloping ST depression or abnormal elevation ≥ 1 mm not present without pain during the admission. In the presence of multiple documented negative tests (eg, catheterization, nuclear stress test), the diagnosis of angina was not be assigned.

Angina could be assigned if the participant was admitted for treatment of symptoms (ie, chest pain consistent with cardiac ischemia) due to atherosclerosis, such as a scheduled admission for CABG following an outpatient evaluation of chest pain, even if the participant was not admitted for an acute episode of angina. Due to changes in medical care practices during follow-up of Look AHEAD participants, a participant with the clinical picture of new or increasing symptom episodes with outpatient evaluation and percutaneous intervention could be classified as having hospitalized angina. Angina was not assigned when the participant experienced a myocardial infarction, including in cases of intervention-associated MI.

Cardiovascular Death

Coronary heart disease deaths were classified using the case definitions for acute CHD [5], separating into inpatient and out of hospital deaths and classified into hierarchical order. CHD death occurring in the hospital included definite fatal MI, probable fatal MI, and possible fatal coronary event. Definite fatal MI was defined as death within 28 days of hospital admission in MI cases, defined as definite MI above; or postmortem findings consistent with MI within 28 days. Probable fatal MI was defined as death within 28 days of hospital admission in MI cases defined as probable MI above; or death within 6 hours of hospital admission with cardiac symptoms and/or signs and other confirmatory information (biomarkers, ECG) were absent or not diagnostic. Possible fatal coronary event was defined as death within 28 days of hospital admission in case defined as possible MI or angina; or postmortem findings show old infarct and/or $\geq$ 50% atherosclerotic narrowing of coronary arteries. Out of hospital CHD deaths included definite fatal MI, definite fatal CHD, and possible fatal CHD. Definite fatal MI (outpatient) was defined as documented definite or probable MI in the previous 28 days and no evidence of a non-coronary cause of death; or autopsy evidence of recent coronary occlusion or MI less than 28 days old. Definite fatal CHD was defined as a history of CHD and/or documented cardiac pain within 72 hours before death; and no evidence of a non-coronary cause of death; or autopsy evidence of chronic CHD, including coronary atherosclerosis and myocardial scarring. Possible fatal CHD was defined as an ICD code for underlying cause of death (ICD 9 410 to 414, 427.5, 429.2, and 799; ICD 10 I20 to 25 and 146) and no evidence of a non-coronary cause of death.

Look AHEAD clinical staff blinded to randomization assignment were trained to conduct a structured interview with a knowledgeable informant to collect data on circumstances, symptoms, and other information useful for determining cause of death in cases of outpatient death (including participants pronounced death in the emergency department) not obviously due to a non-CHD cause. Informant interviews were available for adjudicators, who also had access to the records from the most recent prior hospitalization, and a summary report of all prior outcomes cases reported, and the adjudicated outcome, during the course of the study.

Cardiovascular disease (CVD) deaths also included deaths due to congestive heart failure, documented arrhythmia, stroke, and other CVD. Congestive heart failure death was defined as death due to clinical, radiological or postmortem evidence of congestive heart failure without clinical or postmortem evidence of an acute ischemic event (cardiogenic shock included). Documented arrhythmia death was defined as death due to bradyarrhythmias or tachyarrhythmias not associated with an acute cardiac ischemic event. Stroke death was defined as death due to stroke, any subtype, occurring within seven days of the signs and symptoms of a stroke and/or prior to hospital discharge. Other CVD death was defined as death due to other vascular diseases including abdominal aortic aneurysm rupture.

Secondary Outcome Measures

Secondary outcome measures of the Look AHEAD clinical trial included heart failure, coronary revascularization procedures, peripheral vascular (arterial) disease.

Congestive Heart Failure

Criteria for hospitalized congestive heart failure (CHF) were adapted from the Women's Health Initiative, and did not include cardiogenic shock complicating MI. CHF was adjudicated

when the participant was hospitalized for new onset or worsened heart failure. Criteria included physician diagnosis of CHF, favoring discharge over admitting diagnosis, and medical therapy for CHF on admission (eg, diuretics), past medical history documenting previous imaging procedure showing impaired systolic or diastolic left ventricular function, pulmonary edema or congestion on chest x-ray during admission, and/or documentation of imaging during the admission showing dilated or poor left- or right-sided ventricular function or evidence of left ventricular diastolic dysfunction.

Peripheral vascular (arterial) disease

Peripheral vascular disease was adjudicated when there was documentation of a revascularization procedure or amputation. This included one or more of the following: carotid angioplasty/stenting; carotid endarterectomy; surgery, angioplasty, or thrombolysis for peripheral vascular disease (including renal artery); amputation of one or more toes or part of the lower extremity because of ischemia or gangrene (including toes); surgical or vascular procedure for abdominal aortic aneurysm.

Adjudication Process

Adjudication was conducted centrally, by an adjudication committee consisting of physicians, including those with certification in internal medicine/subspecialists (cardiology, endocrinology, gastroenterology), preventive medicine, and neurology. Individual adjudicators were masked to participant assignment and did not adjudicate outcomes reported from the Look AHEAD center with which they were affiliated.

Fig S1. Consort Diagram

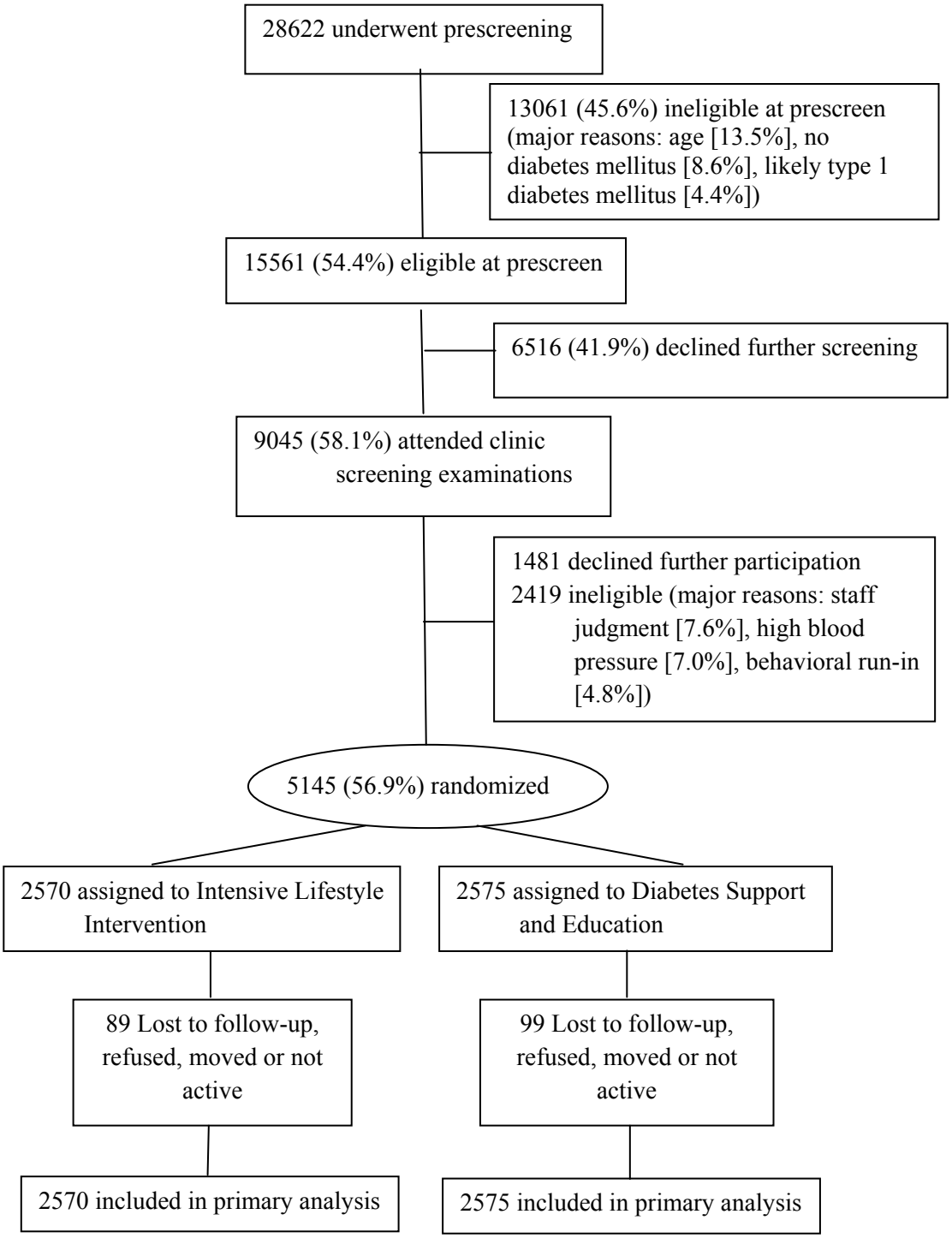
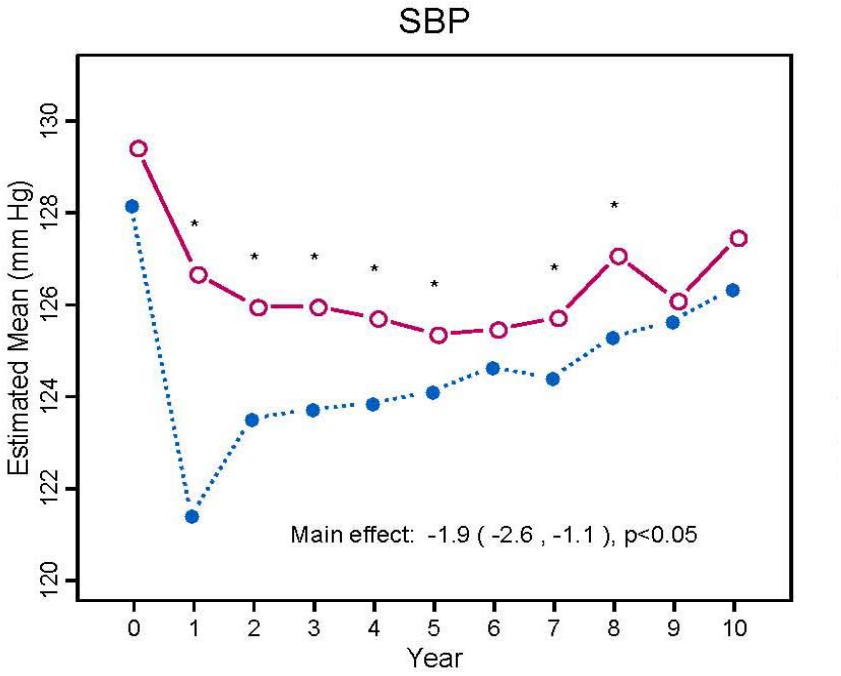
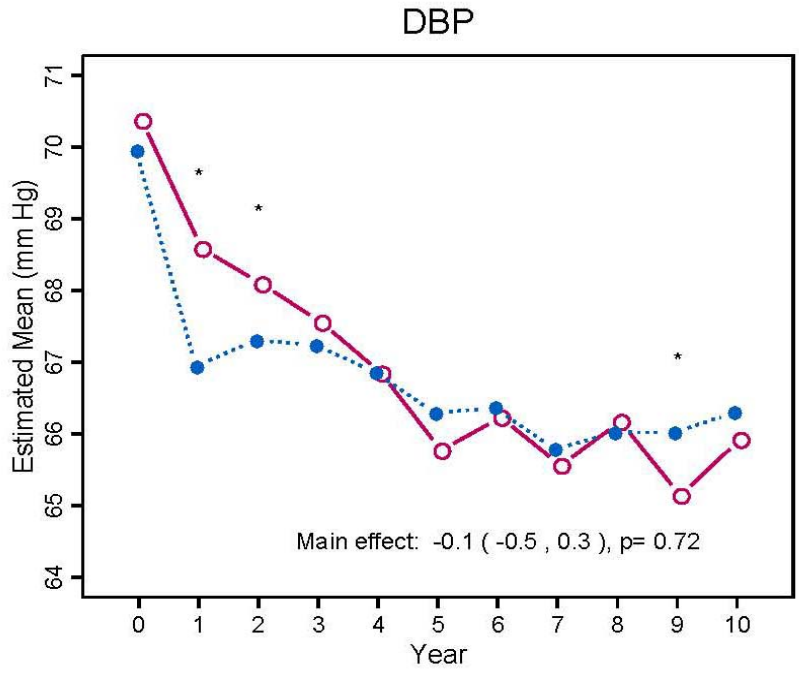
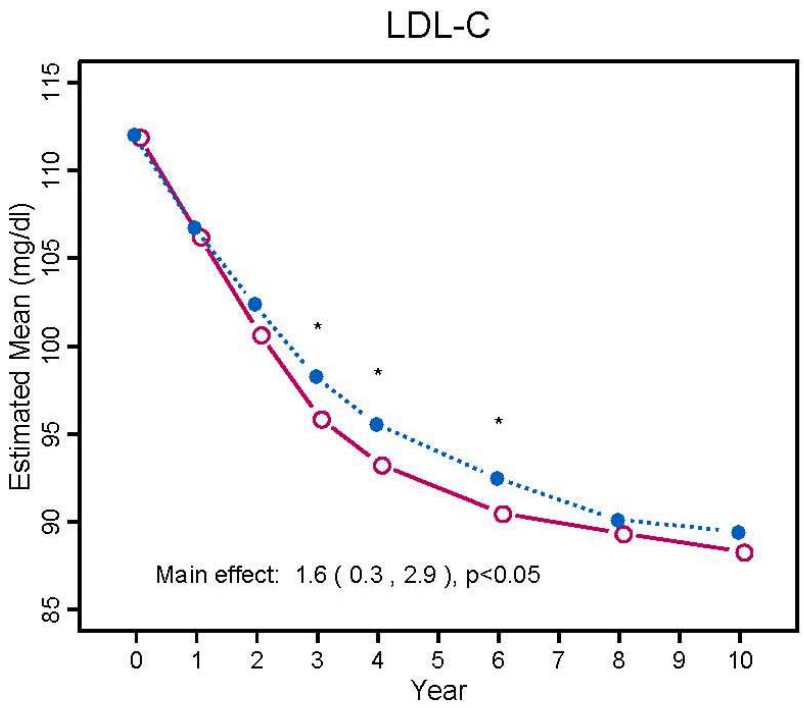


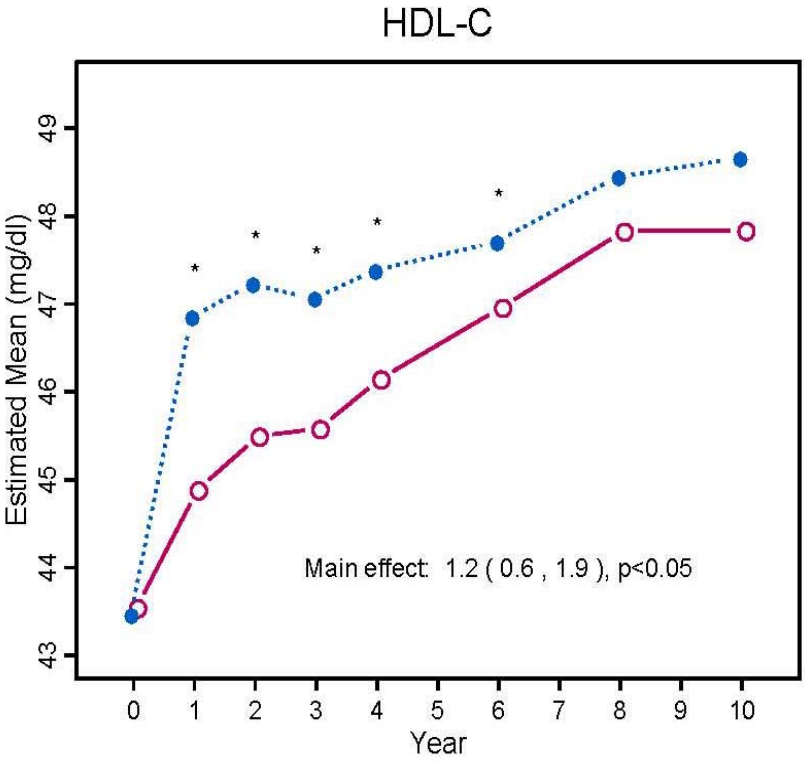
Fig S2. Cardiovascular Disease Risk Factors and Medication Summary

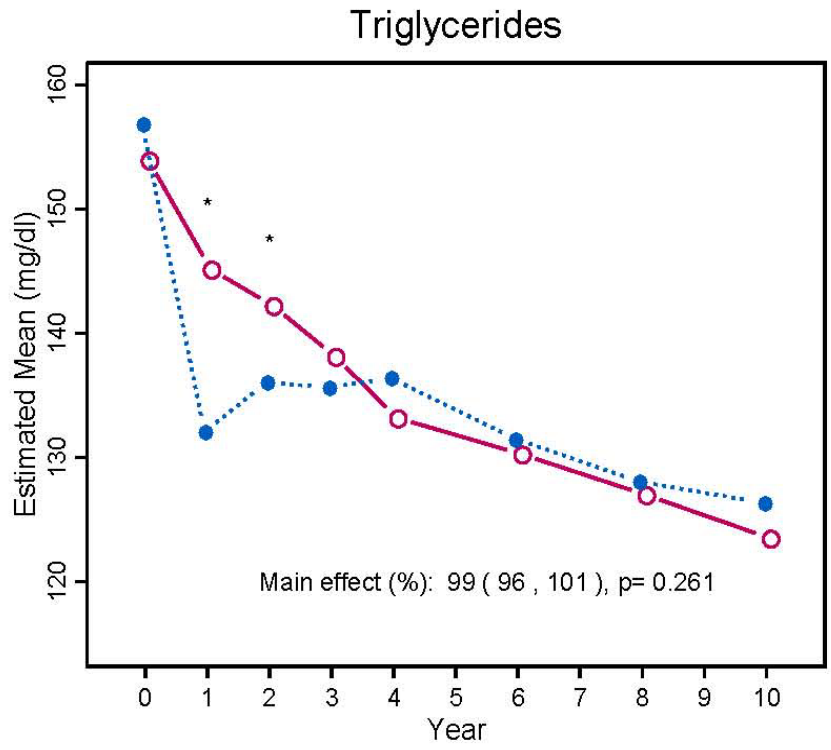
Blue line represents ILI group; pink line is DSE. The main effect is the average of post-baseline differences. Means are estimated using generalized linear models for continuous measures and GEE models for reported medication use. * indicates significant difference between arms with $p < 0.05$. Data from 107 year 11 visits were not included in these analyses.

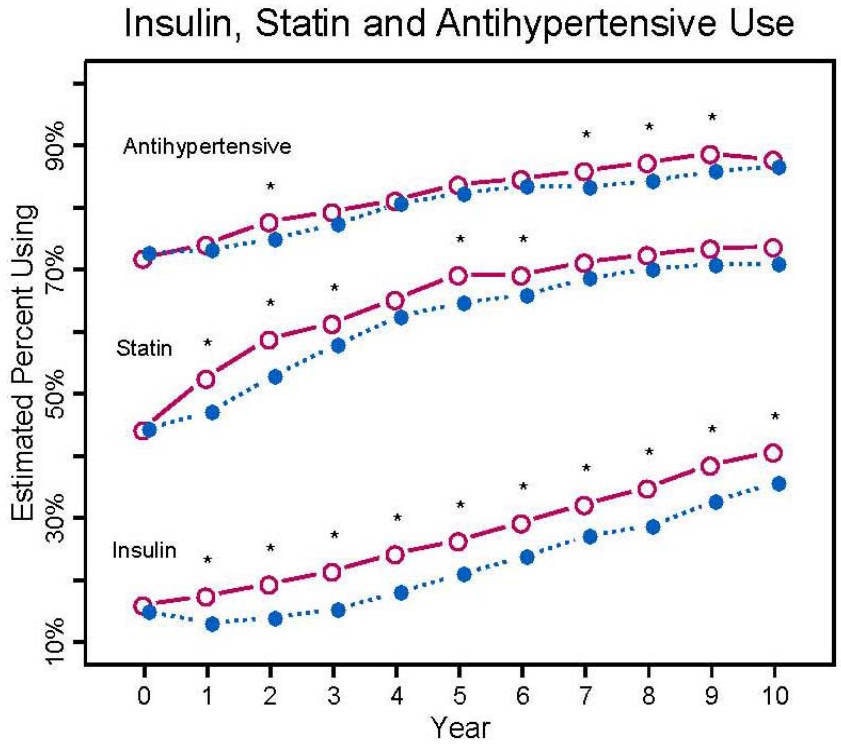





LDL-C
Estimated Mean (mg/dl)
85
90
95
100
105
110
115
0
1
2
3
4
5
6
7
8
9
10
Year
Main effect: 1.6 (0.3 , 2.9), p<0.05


HDL-C
Estimated Mean (mg/dl)
43
44
45
46
47
48
49
0
1
2
3
4
5
6
7
8
9
10
Year
Main effect: 1.2 (0.6 , 1.9), p<0.05

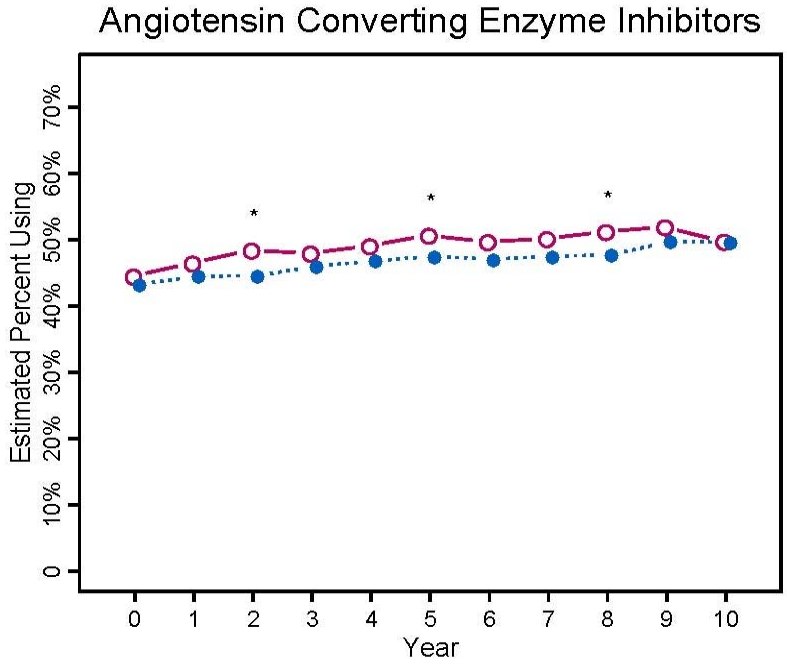


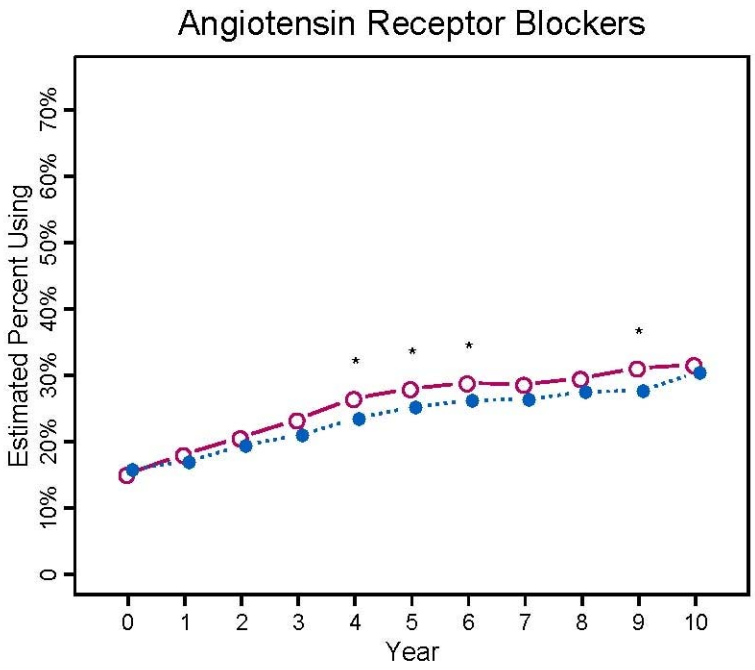


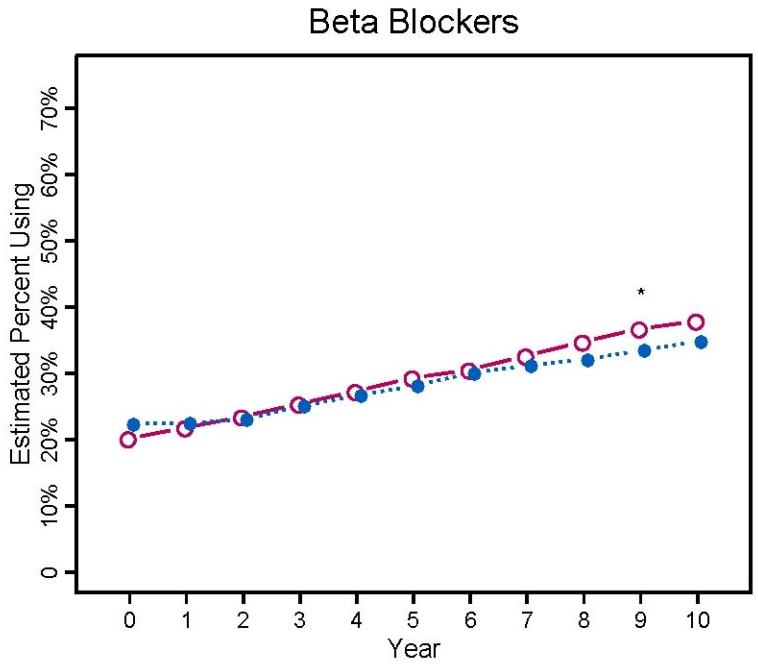
Odds ratios for medication use are: antihypertensive 0.88, 95% CI 0.78 to 0.89, p=0.026; insulin 0.74, 95% CI 0.66 to 0.82, p<0.001; statins 0.86, 95% CI 0.78 to 0.94, p=0.001.

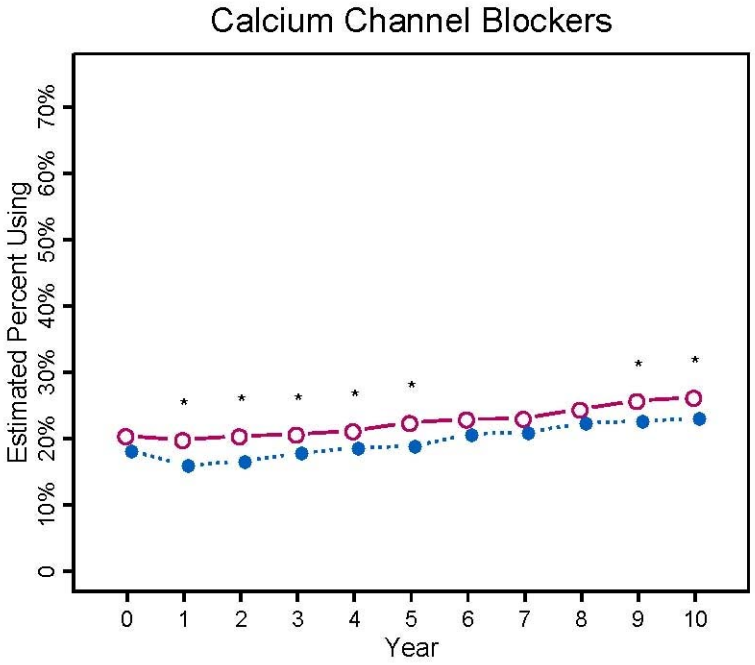
Fig S3. Details of Medication Use

Blue line represents ILI group; pink line is DSE. Means are estimated using GEE models.
* indicates significant difference between arms with $p < 0.05$.






Beta Blockers
Estimated Percent Using
0
10%
20%
30%
40%
50%
60%
70%
0 1 2 3 4 5 6 7 8 9 10
Year
*


Calcium Channel Blockers
Estimated Percent Using
0
10%
20%
30%
40%
50%
60%
70%
0 1 2 3 4 5 6 7 8 9 10
Year
*
*
*
*
*
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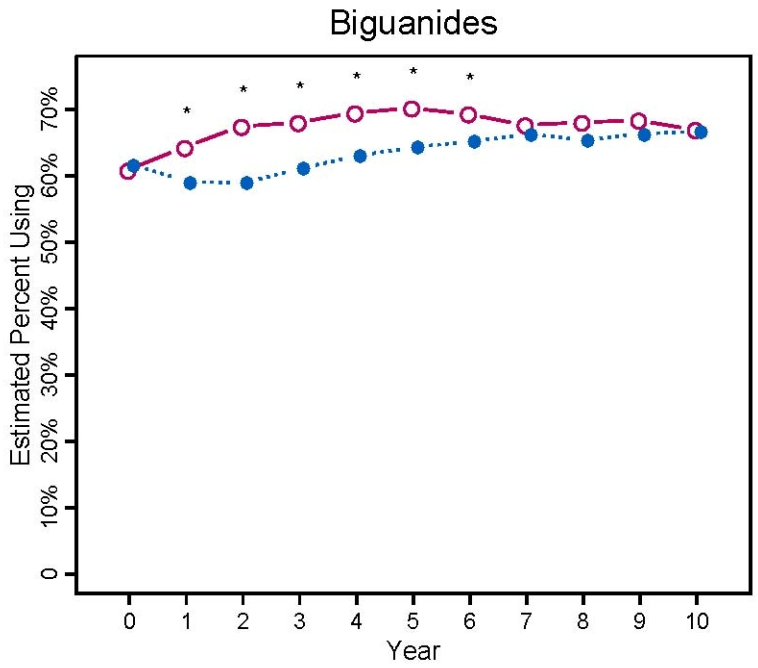
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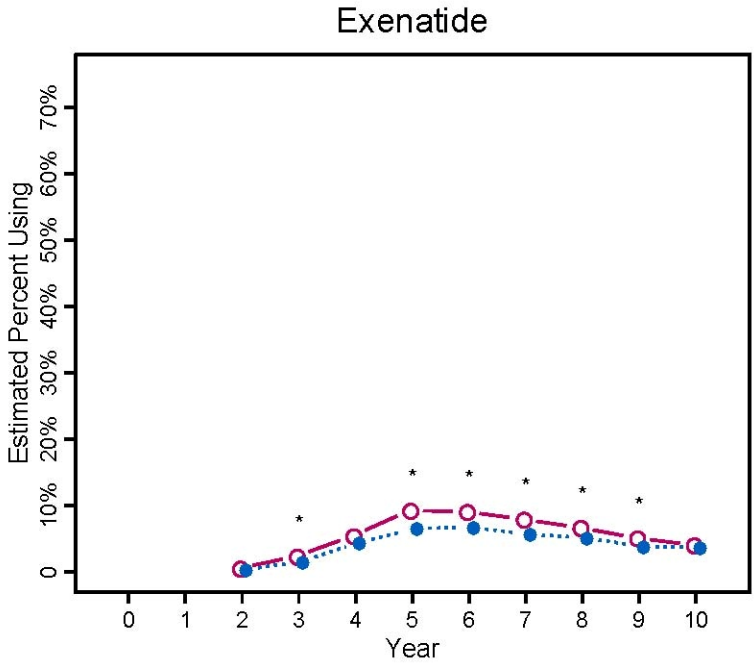
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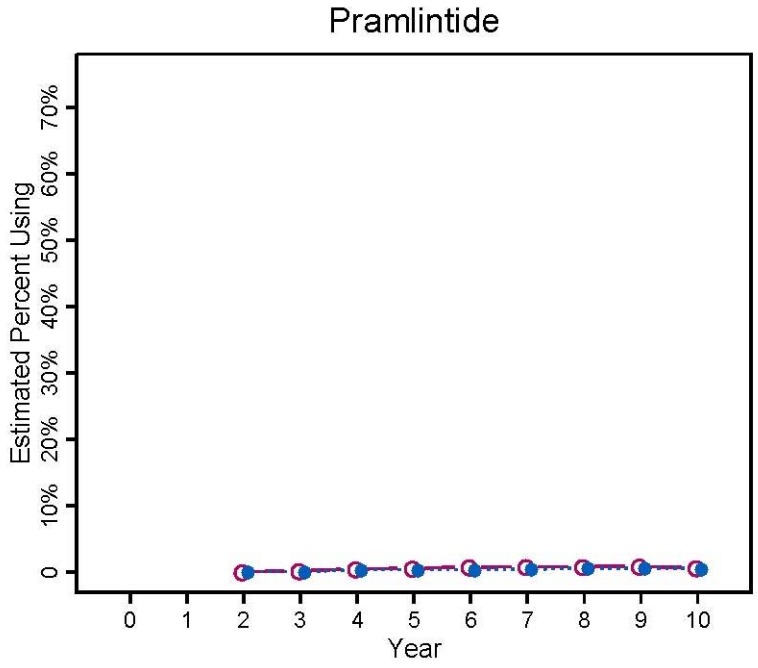
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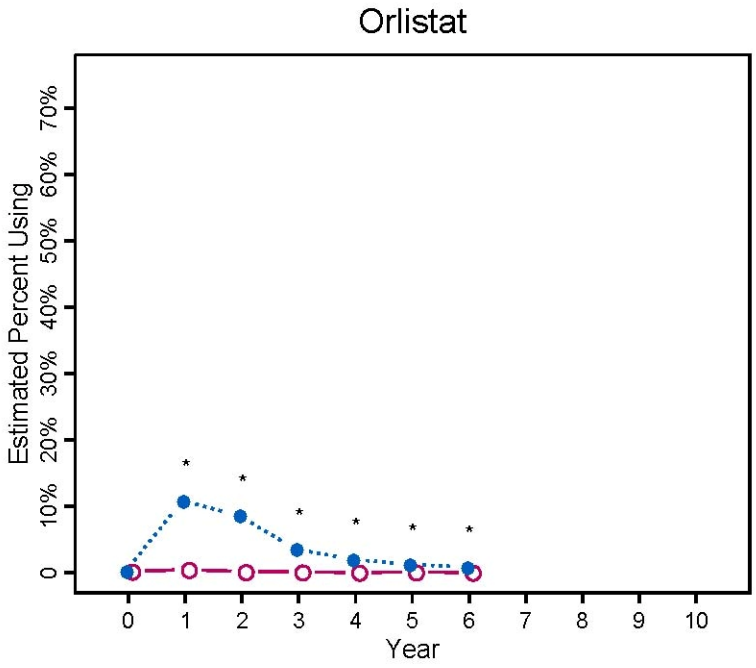
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Table S1. Comparison of Diabetes Support and Education (DSE) and Intensive Lifestyle Intervention (ILI) groups at baseline and end of study

	Baseline		End of Study	
	DSE Mean (95% CI)	ILI Mean (95% CI)	DSE Mean (95% CI)	ILI Mean (95% CI)
Weight (kg)	101 (100, 101)	100 (99.7, 101)	96.2 (95.4, 97)	93.6 (92.8, 94.4)
Waist circumference (cm)	114 (114, 115)	114 (113, 114)	113 (113, 114)	112 (111, 112)
A1c (%)	7.32 (7.27, 7.36)	7.26 (7.21, 7.3)	7.44 (7.37, 7.52)	7.33 (7.25, 7.41)
Systolic blood pressure (mmHg)	129 (129, 130)	128 (128, 129)	127 (127, 128)	126 (125, 127)
Diastolic blood pressure (mmHg)	70.4 (70, 70.7)	70 (69.6, 70.3)	65.9 (65.5, 66.4)	66.3 (65.8, 66.8)
HDL cholesterol (mg/dl)	43.5 (43.1, 44)	43.5 (43, 43.9)	47.8 (47.2, 48.5)	48.7 (48, 49.3)
Triglycerides (mg/dl)	154 (151, 157)	157 (154, 160)	124 (121, 126)	126 (123, 129)
LDL cholesterol (mg/dl)	112 (111, 113)	112 (111, 113)	88.3 (86.6, 90)	89.5 (87.8, 91.1)
METS**	5.12 (5.06, 5.18)	5.19 (5.13, 5.25)	5.02 (4.95, 5.09)	5.38 (5.31, 5.45)
Use of specific medications (%)				
Hypertension medications	0.72 (0.7, 0.74)	0.73 (0.71, 0.74)	0.88 (0.86, 0.89)	0.87 (0.85, 0.88)
Statins	0.44 (0.42, 0.46)	0.44 (0.42, 0.46)	0.74 (0.71, 0.76)	0.71 (0.69, 0.73)
Insulin	0.16 (0.15, 0.18)	0.15 (0.14, 0.16)	0.41 (0.38, 0.43)	0.36 (0.33, 0.38)
Angiotensin Converting Enzymes	0.45 (0.43, 0.46)	0.43 (0.41, 0.45)	0.5 (0.47, 0.52)	0.5 (0.47, 0.52)
Angiotensin Receptor Blockers	0.15 (0.14, 0.17)	0.16 (0.15, 0.17)	0.32 (0.29, 0.34)	0.31 (0.28, 0.33)
Beta Blockers	0.2 (0.19, 0.22)	0.22 (0.21, 0.24)	0.38 (0.36, 0.4)	0.35 (0.33, 0.37)
Calcium Chanel Blockers	0.2 (0.19, 0.22)	0.18 (0.17, 0.2)	0.26 (0.24, 0.28)	0.23 (0.21, 0.25)
Biguanides	0.61 (0.59, 0.63)	0.62 (0.6, 0.64)	0.67 (0.65, 0.69)	0.67 (0.64, 0.69)

* Data provided for End of Study are from Year 8 ** Data provided for End of Study are from Year 4

Table S2. Serious adverse events plausibly related to ILI: number of events reported over follow-up and rates per 100 person-years.

Events reported as SAEs	DSE 23567 person-years N (rate/100 pyrs)	ILI 23636 person-years N (rate/100 pyrs)	P-value
Severe hypoglycemia	146 (0.62)	158 (0.67)	0.508
Gallstones	51 (0.22)	57 (0.24)	0.574
All Reported Fractures*	508 (2.16)	594 (2.51)	0.011
All Adjudicated Fractures**	386 (1.64)	393 (1.66)	0.833
Amputations	29 (0.12)	41 (0.17)	0.157
Congestive heart failure	115 (0.49)	109 (0.46)	0.673

Differences in SAE rates between arms tested using Poisson regression. *All reported fractures are from data collected from participants' self-reports. ** Adjudication of fractures was only done for fractures in locations which might be most related to exercise: the hip, upper leg, pelvis, knee, lower leg, ankle, foot (but not toe), tailbone/coccyx, spine/back, lower arm/wrist, hand (not finger), elbow, upper arm or shoulder. Locations for fractures reported but not adjudicated include: ribs, chest, sternum, skull, face, nose, jaw, fingers, toes, cervical vertebrae and neck.

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