Effects of a Mediterranean-Style Diet on the Need for Antihyperglycemic Drug Therapy in Patients With Newly Diagnosed Type 2 Diabetes

A Randomized Trial

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Background: Low-carbohydrate and low-fat calorie-restricted diets are recommended for weight loss in overweight and obese people with type 2 diabetes.

Objective: To compare the effects of a low-carbohydrate Mediterranean-style or a low-fat diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes.

Design: Single-center, randomized trial. Randomization was computer-generated and unstratified. Allocation was concealed in sealed study folders held in a central, secure location until participants gave informed consent. Participants and investigators were aware of treatment assignment, and assessors of the primary outcome were blinded.

Setting: Teaching hospital in Naples, Italy.

Patients: 215 overweight people with newly diagnosed type 2 diabetes who were never treated with antihyperglycemic drugs and had hemoglobin A_{1c} (HbA_{1c}) levels less than 11%.

Intervention: Mediterranean-style diet (<50% of daily calories from carbohydrates) ($n = 108$) or a low-fat diet (<30% of daily calories from fat) ($n = 107$).

Measurements: Start of antihyperglycemic drug therapy, defined by protocol as indicated for follow-up HbA_{1c} level greater than 7% (primary outcome), and changes in weight, glycemic control, and coronary risk factors (secondary outcomes).

Results: After 4 years, 44% of patients in the Mediterranean-style diet group and 70% in the low-fat diet group required treatment (absolute difference, −26.0 percentage points [95% CI, −31.1 to −20.1 percentage points]; hazard ratio, 0.63 [CI, 0.51 to 0.86]; hazard ratio adjusted for weight change, 0.70 [CI, 0.59 to 0.90]; $P < 0.001$). Participants assigned to the Mediterranean-style diet lost more weight and experienced greater improvements in some glycemic control and coronary risk measures than did those assigned to the low-fat diet.

Limitations: Investigators responsible for initiating drug therapy were not blinded to treatment assignment. Dietary intake was self-reported.

Conclusion: Compared with a low-fat diet, a low-carbohydrate, Mediterranean-style diet led to more favorable changes in glycemic control and coronary risk factors and delayed the need for antihyperglycemic drug therapy in overweight patients with newly diagnosed type 2 diabetes.

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The pandemic of type 2 diabetes is an enormous public health problem, with 380 million cases worldwide projected by 2025 (1, 2). Lifestyle intervention studies (3) have demonstrated large reductions in risk for type 2 diabetes that remain after lifestyle counseling is stopped (4, 5). Despite this beneficial effect, the American Diabetes Association (ADA) recommends that patients with newly diagnosed type 2 diabetes be treated with pharmacotherapy as well as lifestyle changes (6). The rationale for combination therapy is presumably that each form of treatment alone is imperfect. Lifestyle changes are often inadequate because patients do not lose weight or regain weight or their diabetes worsens independent of weight (6). Pharmacotherapy also often fails with time (7), and some drugs have associated cardiovascular and other risks (8, 9). For those reasons, lifestyle changes proven to be more effective than what is typically recommended would be welcome. For example, Mediterranean-style (MED) diets with a high proportion of monounsaturated fat provide cardiovascular benefits and increase insulin sensitivity (10–12), and the ADA recommends low-carbohydrate or low-fat, calorie-restricted diets for weight loss in overweight and obese patients with type 2 diabetes (13). However, few direct, long-term comparisons of the 2 diets in patients with diabetes have been done (11).

We conducted a randomized trial to compare the effectiveness, durability, and safety of a low-carbohydrate MED diet and a low-fat diet on glycemic control in patients with newly diagnosed type 2 diabetes.

See also:

METHODS

We conducted the trial between January 2004 (first patient enrolled) and September 2008 (end of follow-up of the last patient) at the research center of the Diabetes Clinic of the Azienda Ospedaliera Universitaria, Second University of Naples, Naples, Italy, in accordance with the Declaration of Helsinki and with the institutional review board's approval.

Screening Phase

We recruited men and women with newly diagnosed type 2 diabetes by ADA criteria who had never been treated with antihyperglycemic drugs from the clinical practices of trial investigators and screened them for eligibility.

Inclusion criteria were age 30 to 75 years, body mass index (BMI) greater than 25 kg/m^2, and hemoglobin A$_{1c}$ (HbA$_{1c}$) level less than 11%. Participants also had to be sedentary (<1 hour of physical activity per week) with no evidence of participation in weight-reduction programs and with a stable weight ($\pm$2 kg) in the past 6 months.

Exclusion criteria included pregnancy or breastfeeding, use of any investigational drug in the previous 3 months, use of agents affecting glycemic control (such as systemic glucocorticoids and weight loss drugs), and any condition that might compromise adherence to diet regimens. To minimize the likelihood of including participants with late-onset type 1 diabetes, we screened candidates by testing for antibodies to glutamate decarboxylase and measuring fasting plasma C-peptides. We excluded patients with positive antibodies or C-peptide levels less than 0.25 pmol/L (<0.76 ng/L). We also excluded patients with abnormal laboratory test results, including liver enzyme levels (alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase) greater than 3 times the upper limit of normal and serum creatinine levels greater than 123.8 μmol/L (>1.4 mg/dL).

We required that participants successfully self-monitor their diet and physical activity over a 2-week run-in period. We provided dietary education during that time that emphasized the importance of eating a healthy diet and being physically active for both weight loss and improvement of glycemic control. Participants were also taught to prepare their own meals at home. We encouraged all individuals who smoked to quit and provided self-help materials, referral to local programs, or both, as appropriate.

Randomization and Blinding

After obtaining informed consent, we randomly assigned patients to 1 of the 2 study diets by using a computer-generated random-number sequence (simple randomization). Allocation was concealed in sealed study folders that were held in a central, secured location until after informed consent was obtained. The nurses who scheduled the study visits did not have access to the randomization list, and laboratory staff did not know the participants' group assignments. Staff members involved in the intervention were aware of group assignments,

Context

Mediterranean-style diets improve control of coronary risk factors and hyperglycemia, but few direct comparisons of the diet with other standard diets have been done.

Contribution

In this randomized clinical trial, patients with newly diagnosed type 2 diabetes who were assigned to a low-carbohydrate, Mediterranean-style diet had better glycemic control and were less likely to need oral antihyperglycemic therapy than patients assigned to a low-fat diet.

Caution

The trial was unblinded, and dietary intake was self-reported.

Implication

A low-carbohydrate, Mediterranean-style diet seems to be preferable to a low-fat diet for glycemic control in patients with newly diagnosed type 2 diabetes.

—*The Editors*

but those who assessed achievement of the primary outcome were blinded to the intervention. Participants received no financial compensation or gifts.

Dietary Interventions

We randomly assigned patients to a low-carbohydrate MED diet or to a low-fat diet.

The MED diet was rich in vegetables and whole grains and low in red meat, which was replaced with poultry and fish. We restricted energy intake to 1500 kcal/d for women and 1800 kcal/d for men, with the goal of no more than 50% of calories from complex carbohydrates, based on evidence that, in the context of a MED diet, a carbohydrate content less than 50% of daily energy is more beneficial than higher content for weight loss and cardiovascular risk reduction (14). The diet had no less than 30% calories from fat. The main source of added fat was 30 to 50 g of olive oil.

The low-fat diet was based on American Heart Association guidelines (15); it was rich in whole grains and restricted additional fats, sweets, and high-fat snacks. We restricted energy intake to 1500 kcal/d for women and 1800 kcal/d for men, with the goal of no more than 30% of calories from fat and no more than 10% of calories from saturated fat.

Nutritionists and dietitians gave dietary advice to participants in both groups in monthly sessions in the first year and bimonthly sessions thereafter. Participants kept diet diaries after being instructed how to record their intake using food models as examples of portion size and using actual weights or amounts in terms of common measures (such as cups, teaspoons, and dessert spoons). We

assessed adherence to the diets by session attendance and review of the diaries.

Nondietary Interventions

Patients in both groups also received guidance on increasing their level of physical activity, mainly walking for a minimum of 30 minutes per day, but also swimming or aerobic ball games. The physical activity program relied heavily on home-based exercise with gradual progression toward a goal of 175 minutes of moderate-intensity physical activity per week. Although walking was encouraged, participants were allowed to choose other types of moderate-intensity physical activity, and programs were tailored on the basis of the results of a baseline physical fitness test and safety concerns.

We asked all patients to record occupational, household, and leisure time physical activity.

Outcomes

We followed patients for 4 years to assess trial outcomes. The primary outcome measure was time to introduction of antihyperglycemic drug therapy. Trial investigators were responsible for initiating drug therapy by the following protocol. As suggested by the ADA for clinical evaluation and management of diabetic patients (16), we measured HbA_{1c} at baseline and every 3 months thereafter. Participants who had a HbA_{1c} level greater than 7% were given an additional 3 months to reinforce dietary guidance and physical activity; if the HbA_{1c} level remained greater than 7%, a drug regimen was introduced. Participants with an HbA_{1c} level greater than 7% at baseline were counted as having experienced the primary outcome if they still had that level at first follow-up. Trial investigators were also responsible for initiating or titrating antihypertensive or lipid-lowering therapy.

Secondary outcome measures were changes in weight (including BMI and waist circumference), glycemic control (HbA_{1c}, glucose, serum insulin, and adiponectin levels and homeostasis model assessment of insulin sensitivity), coronary risk factors (lipid levels and blood pressure), and medications and meeting ADA coronary risk factor goals (HbA_{1c} level <7%, blood pressure <130/80 mm Hg, and low-density lipoprotein cholesterol level <2.59 mmol/L [<100 mg/dL]) (16).

Participants were weighed without shoes and in lightweight clothing to the nearest 0.1 kg at baseline and every month. Height at baseline (for calculation of BMI) was measured to the nearest millimeter with the use of a wall-mounted stadiometer (Seca, Hamburg, Germany). Waist circumference was measured halfway between the last rib and the iliac crest.

We measured HbA_{1c} levels with high-pressure liquid chromatography by using the fully automated Glycosylated Hemoglobin Analyzer System (Bio-Rad, Hercules, California) traceable to the Diabetes Control and Complications Trial reference method, with a reference range of 4.0% to 6.0%. Insulin sensitivity in the fasting state was assessed with homeostasis model assessment and calculated with the following formula, as described by Matthews and colleagues (17): fasting plasma glucose (mmol/L) × fasting serum insulin (μU/mL)/25. High scores indicate low insulin sensitivity (insulin resistance). We assayed plasma insulin and adiponectin levels by radioimmunoassay, as described elsewhere (18).

We performed assays for serum total and high-density lipoprotein cholesterol, triglyceride, and glucose levels in the hospital's chemistry laboratory.

Statistical Analysis

We calculated the sample size for the primary analysis on the basis of differences seen in a pilot study of 10 patients with newly diagnosed type 2 diabetes who received either the MED diet or the low-fat diet for 3 months. In this pilot study, HbA_{1c} levels differed by 0.3%, with similar SDs that averaged 0.7. Assuming an α level of 0.05 and 80% power, the required number of patients for each group to observe a HbA_{1c} difference of 0.25% is 87. To allow for a 25% drop-out rate, we randomly assigned 215 patients.

We analyzed the data by intention-to-treat. We compared risk factors and nutrient intakes by using a test based on the values at the end of follow-up and a t test based on differences from baseline. Results of the analysis omitting patients lost during follow-up did not differ from that including these patients' last available records; however, because few participants were lost during follow-up, we used a complete case analysis with respect to secondary end points. We used the Fisher exact test to analyze the percentage of patients achieving goals and to compare categorical safety variables. We calculated Kaplan–Meier survival curves to estimate the probability of remaining without antihyperglycemic drug therapy in the 2 groups with a 2-sided log-rank test for comparisons. The time-to-drug analysis used the number of days after randomization to the introduction of antihyperglycemic drug therapy for each patient. We performed Cox regression for time to antihyperglycemic drug therapy, first using treatment as the only dependent variable, then adding weight loss as an additional covariate (in categories of ≤1 to 2.5 kg, 2.6 to 5.0 kg, and >5 kg) to assess the effect of the dietary interventions independent of weight loss, and we treated participants lost during follow-up as censored observations. We verified the underlying assumption of proportional hazards for the Cox regression models by demonstrating no statistically significant interaction between treatment and the log of the follow-up time ($P = 0.90$). We performed the same analysis using HbA_{1c} levels greater than 7% as the primary outcome to test the possibility that investigators who were not blinded to treatment assignment might have made biased decisions to initiate or withhold drug therapy. All statistical tests were 2-sided, and we present the results as means and SDs. P values less than 0.05 were deemed statistically significant. We conducted all analyses using SPSS, version 10.05 (SPSS, Chicago, Illinois).

Figure 1. Study flow diagram.
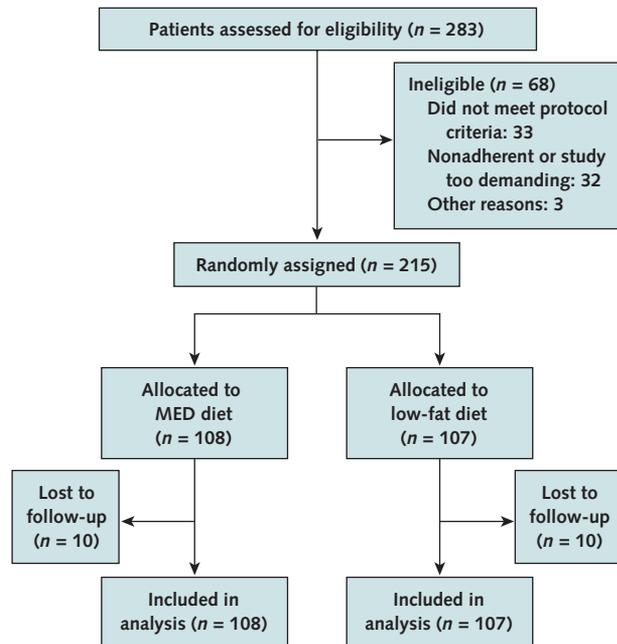
MED = low-carbohydrate, Mediterranean-style.

Role of the Funding Source

This study was funded in part by the Second University of Naples. The funding source had no role in the design, conduct, and analysis of the study or in the decision to submit the article for publication.

RESULTS

Patient Characteristics

We screened 283 participants and randomly assigned 215 to either the MED diet or the low-fat diet (**Figure 1**). Exclusions were for high HbA_{1c} levels ($n = 15$), BMI of 25 kg/m^2 or less ($n = 10$), nonadherence to dietary regimens ($n = 15$), high creatinine or liver enzyme levels ($n = 5$), other diseases ($n = 3$), finding the study too demanding ($n = 17$), and other ($n = 3$). Equal numbers of patients withdrew from the groups during the trial for reasons that included patient preference (3 MED diet participants, 4 low-fat diet participants), loss to follow-up (6 MED diet participants, 5 low-fat diet participants) or other reasons (1 MED diet participant, 1 low-fat diet participant). Baseline demographic and clinical characteristics were similar between treatment groups (**Table 1**). One hundred fifty-five patients had a baseline HbA_{1c} level greater than 7%.

Antihyperglycemic Drug Therapy

We found a statistically significant difference in the need for antihyperglycemic drug therapy at 18 months (12% [95% CI, 8% to 16%] of MED diet participants vs. 24% [CI, 18% to 31%] of low-fat diet participants required treatment) and at the end of the trial (44% [CI,

34% to 53%] vs. 70% [CI, 62% to 79%]; absolute difference, −26.0 percentage points [CI, −31.1 to −20.1 percentage points]; hazard ratio [HR], 0.63 [CI, 0.51 to 0.86]; $P <0.001$) (**Table 2** and **Figure 2**). The findings were essentially unchanged in analyses that adjusted for change in body weight (adjusted HR, 0.70 [CI, 0.59 to 0.90]). Nearly all patients with a follow-up HbA_{1c} level greater than 7% were given antihyperglycemic drug therapy (44 [97%] MED diet participants, 69 [97%] low-fat diet participants), so a sensitivity analysis using HbA_{1c} elevation greater than 7% as the primary outcome gave comparable results (absolute differences in proportions with HbA_{1c} levels greater than 7%, −25.0 percentage points (CI, −31.8 to −19.2 percentage points); HR, 0.64 [CI, 0.50 to 0.82]; $P < 0.001$).

Body Weight

Participants in both groups lost weight in the first year, but the reductions were greater in the MED diet group than the low-fat diet group (absolute between-group difference in weight loss, −2.0 kg [CI, −3.0 to −0.9 kg]) (**Table 2**). Participants in the MED diet group also experienced greater reductions in BMI (absolute between-group difference, −1.0 kg/m^2 [CI, −1.7 to −0.4 kg/m^2]) and waist circumference (absolute between-group difference, −1.3 cm [CI, −1.9 to −0.7 cm]) after 1 year. The response

Table 1. Participant Characteristics*

Characteristic	MED Diet (n = 108)	Low-Fat Diet (n = 107)
Age, y	52.4 (11.2)	51.9 (10.7)
Male, n (%)	54 (50.0)	52 (48.5)
Body weight, kg	86.0 (10.4)	85.7 (9.9)
Body mass index, kg/m²	29.7 (3.4)	29.5 (3.6)
Waist circumference, cm	98 (10.1)	98 (10)
HbA₁c level, %	7.75 (0.9)	7.71 (0.9)
HbA₁c level >7%, n (%)	77 (71)	78 (73)
Plasma glucose level		
mmol/L	9.0 (1.9)	8.8 (1.8)
mg/dL	162 (34)	159 (33)
Serum insulin level, pmol/L	108 (43)	115 (50)
HOMA of insulin sensitivity	5.2 (1.7)	5.3 (1.8)
Adiponectin level, µg/mL	6.1 (2.1)	6.3 (2.3)
Total cholesterol level		
mmol/L	5.7 (0.9)	5.6 (0.9)
mg/dL	221 (35)	216 (33)
HDL cholesterol level		
mmol/L	1.1 (0.2)	1.1 (0.2)
mg/dL	43 (10)	43 (10)
Triglyceride level		
mmol/L	1.9 (0.8)	1.9 (0.8)
mg/dL	171 (71)	168 (69)
Systolic BP, mm Hg	139 (12)	140 (12)
Diastolic BP, mm Hg	87 (8)	86 (8)
Smoking, n (%)	23 (21.3)	23 (21.49)
Current medication use, n (%)		
Antihypertensive therapy	26 (24.0)	25 (23.3)
Lipid-lowering therapy	16 (15)	15 (16)

BP = blood pressure; HbA_{1c} = hemoglobin A_{1c}; HDL = high-density lipoprotein; HOMA = homeostasis model assessment; MED = low-carbohydrate, Mediterranean-style.
* Data are presented as means (SDs), unless indicated otherwise.

Table 2. **Trial Outcomes at 1 Year and End of Trial (4 Years)***

Variable	MED Diet	Low-Fat Diet	Difference (95% CI)	Hazard Ratio (95% CI)
Patients requiring treatment, %†				
Year 1	5.5	9.4	−3.9 (−7.8 to 1.2)	
Year 4	44.0	70.0	−26.0 (−31.1 to −20.1)	
Hazard ratio				
Unadjusted				0.63 (0.51 to 0.86)
Adjusted‡				0.70 (0.59 to 0.90)
Unadjusted§				0.64 (0.50 to 0.82)
Weight				
Weight, *kg*				
Year 1	−6.2 (3.2)	−4.2 (3.5)	−2.0 (−3.0 to −0.9)	
Year 4	−3.8 (2.0)	−3.2 (1.9)	−0.6 (−1.6 to 1.2)	
Body mass index, *kg/m²*				
Year 1	−2.4 (1.6)	−1.4 (0.9)	−1.0 (−2.2 to −0.3)	
Year 4	−1.2 (0.7)	−0.9 (0.6)	−0.3 (−0.9 to 0.4)	
Waist circumference, *cm*				
Year 1	−4.8 (3.0)	−3.5 (2.8)	−1.3 (−1.7 to −0.5)	
Year 4	−3.0 (1.7)	−2.6 (2.0)	−0.4 (−0.9 to 0.5)	
Glycemic control				
HbA$_{1c}$ level, *%*				
Year 1	−1.2 (1.0)	−0.6 (0.6)	−0.6 (−0.9 to −0.3)	
Year 4	−0.9 (0.6)	−0.5 (0.4)	−0.4 (−0.9 to −0.1)	
Plasma glucose level, *mmol/L*				
Year 1	−2.3 (1.9)	−1.1 (1.1)	−1.2 (−1.7 to −0.72)	
Year 4	−1.7 (1.1)	−0.8 (0.8)	−0.9 (−1.6 to −0.2)	
Serum insulin level, *pmol/L*				
Year 1	−14.0 (13.6)	−12.9 (12.9)	−1.1 (−6.9 to 7.4)	
Year 4	−9.8 (8.9)	−5.6 (4.3)	−4.2 (−10.7 to 3.4)	
HOMA of insulin sensitivity				
Year 1	−1.9 (0.5)	−0.9 (0.4)	−1.0 (−1.6 to −0.5)	
Year 4	−1.5 (1.0)	−0.9 (0.6)	−0.6 (−1.1 to −0.1)	
Adiponectin level, *μg/mL*				
Year 1	2.7 (0.9)	0.7 (0.4)	2.0 (0.9 to 3.2)	
Year 4	1.9 (10)	0.8 (0.7)	1.1 (0.1 to 1.9)	
Coronary risk factors				
Total cholesterol level, *mmol/L*				
Year 1	−0.39 (0.38)	−0.15 (0.17)	−0.24 (−0.36 to −0.12)	
Year 4	−0.25 (0.20)	−0.10 (0.18)	−0.15 (−0.39 to 0.05)	
HDL cholesterol level, *mmol/L*				
Year 1	0.10 (0.12)	0.025 (0.02)	0.08 (0.04 to 0.12)	
Year 4	0.09 (0.08)	0.02 (0.02)	0.07 (0.02 to 0.14)	
Triglyceride level, *mmol/L*				
Year 1	−0.44 (0.57)	−0.22 (0.45)	−0.22 (−0.32 to –0.10)	
Year 4	−0.28 (0.28)	−0.07 (0.10)	−0.21 (−0.36 to –0.02)	
Systolic BP, *mm Hg*				
Year 1	−5.1 (4.2)	−2.0 (1.9)	−3.1 (−4.9 to –1.2)	
Year 4	−2.5 (2.6)	−1.0 (1.0)	−1.5 (−4.5 to 1.2)	
Diastolic BP, *mm Hg*				
Year 1	−4.0 (3.0)	−3.0 (4.0)	−1.0 (−4.0 to −1.0)	
Year 4	−2.9 (1.9)	−1.5 (1.4)	−1.4 (−4.0 to 1.8)	

BP = blood pressure; HbA$_{1c}$ = hemoglobin A$_{1c}$; HDL = high-density lipoprotein; HOMA = homeostasis model assessment; MED = low-carbohydrate, Mediterranean-style.
* Data are presented as means (SDs), unless otherwise indicated. Annual changes, including years 2 and 3, are detailed in **Appendix Table 1** (available at www.annals.org). To convert cholesterol, triglyceride, or glucose values to mg/dL, divide by 0.0259, 0.0113, or 0.0555, respectively.
† The number of participants eligible for the outcome (HbA$_{1c}$ level ≤7%) each year (MED diet/low-fat diet) was 102/97 for year 1, 85/64 for year 2, 72/50 for year 3, and 50/29 for year 4. These numbers were the same for all variables except adiponectin level and waist circumference, which were 100/96, 83/63, 70/49, and 47/28, respectively. At each time point, values were compared with respective baseline values.
‡ Adjusted for weight change.
§ Using HbA$_{1c}$ level >7% as the outcome.

did not differ between men and women (data not shown). The between-group differences were attenuated in the second year, and there were no statistically significant between-group differences in weight variables at years 3 and 4 (**Appendix Table 1**, available at www.annals.org).

Glycemic Control

Of the 155 patients with an HbA$_{1c}$ level greater than 7% at baseline, 22 maintained that level at the 3-month follow-up and none had that level at 6 months. Participants in both groups experienced decreases in fasting

plasma glucose and HbA$_{1c}$ levels, but the reductions were statistically significantly greater in the MED diet group than in the low-fat diet group in all 4 trial years (**Table 2** and **Appendix Table 1** [available at www.annals.org]). Participants in both groups experienced decreases in serum insulin levels, but the differences were not statistically significant in any trial year. Participants in the MED diet group experienced greater increases in insulin sensitivity (declines in homeostasis model assessment of insulin sensitivity scores) and in adiponectin levels that were statistically significant in most trial years and greater declines in serum insulin levels that were not statistically significant in any trial year.

Coronary Risk Factors

Throughout the trial, participants in the MED diet group experienced statistically significantly greater increases in high-density lipoprotein cholesterol levels and decreases in triglyceride levels than those in the low-fat diet group. Total cholesterol levels decreased more in the MED diet group, but the between-group differences were statistically significant only in the first 2 years (**Table 2**).

Systolic and diastolic blood pressure decreased more in the MED diet group than in the low-fat diet group, but the between-group differences were no longer statistically significant by the fourth year for systolic blood pressure and by the second year for diastolic blood pressure.

ADA Goals

The proportion of participants who met ADA goals for HbA$_{1c}$, blood pressure, and low-density lipoprotein cholesterol increased in both groups, but the between-group difference in the increase was statistically significantly greater only for HbA$_{1c}$ in the MED diet group (**Table 3** and **Appendix Table 2** [available at www.annals.org]). The increase in proportion of participants who met

Table 3. **Participants Meeting American Diabetes Association Goals for HbA$_{1c}$, Blood Pressure, and LDL Cholesterol at 1 Year and End of Trial (4 Years)***

Variable	MED Diet, %	Low-Fat Diet, %	Difference (95% CI), percentage points
HbA$_{1c}$ level ≤7%†			
Year 1	72	53	19 (14 to 23)
Year 4	37	24	13 (8 to 17)
BP <130/80 mm Hg			
Year 1	66	59	7 (−4 to 12)
Year 4	65	63	2 (−4 to 8)
LDL cholesterol level <2.59 mmol/L (<100 mg/dL)			
Year 1	39	36	3 (−2 to 6)
Year 4	38	35	3 (−4 to 7)
All 3 goals			
Year 1	34	23	11 (4 to 16)
Year 4	32	28	4 (−1 to 6)

BP = blood pressure; HbA$_{1c}$ = hemoglobin A$_{1c}$; LDL = low-density lipoprotein; MED = low-carbohydrate, Mediterranean-style.
* Annual changes, including years 2 and 3, are detailed in **Appendix Table 2** (available at www.annals.org).
† The number of participants eligible for the outcome (HbA$_{1c}$ level ≤7%) each year (MED diet/low-fat diet) was 102/97 for year 1, 85/64 for year 2, 72/50 for year 3, and 50/29 for year 4. At each time point, values were compared with respective baseline values.

all 3 goals was statistically significantly greater in the MED diet group in the first 3 years of the trial.

Dietary Intake

The composition of the diets consumed by participants in the MED diet and low-fat diet groups did not statistically significantly differ at baseline. Daily energy intake decreased in both groups during the study without statistically significant between-group differences in any trial year (**Table 4** and **Appendix Table 3** [available at www.annals.org]). The percentage of carbohydrate intake decreased in the MED diet group compared with the low-fat diet group, and the percentage of monounsaturated and polyunsaturated fatty acid intake increased. Between-group differences in these variables were statistically significant throughout the trial.

Physical Activity

Participants in both groups increased the time they spent being physically active (from 45 min/wk [SD, 12] to 125 min/wk [SD, 41] in the MED diet group and from 43 min/wk [SD, 13] to 119 min/wk [SD, 48] in the low-fat diet group), with no statistically significant between-group difference in the amount of increase (absolute between-group difference, 4 min/wk [CI, −5 to 6 min/wk], favoring the MED diet).

Use of Concurrent Medications

Equal proportions of patients used antihypertensive and lipid-lowering agents at the start of the trial (**Table 1**), and no statistically significant within- or between-group

Figure 2. **Probability of remaining free of antihyperglycemic drug therapy.**
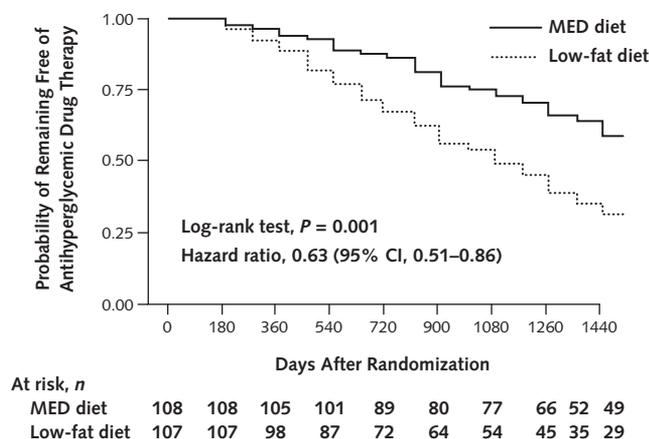
MED = low-carbohydrate, Mediterranean-style.

change in these proportions occurred during the trial (absolute between-group difference in the proportion using antihypertensive drugs, −1.5 percentage points [CI, −3.5 to 2.3 percentage points], favoring the MED diet; absolute between-group difference in the proportion using lipid-lowering drugs, −2.6 percentage points [CI, −4.6 to 3.4 percentage points], favoring the MED diet).

Adverse Events

No participant died during the study. The incidence of adverse events during the treatment phase was similar in both groups: 23 participants (21%) in the MED diet group and 25 participants (23%) in the low-fat diet group reported at least 1 adverse event. One patient in each group had a serious adverse event (atrial fibrillation in a MED diet participant and pneumonia in a low-fat diet participant), which was considered to be unrelated to the study medications (**Appendix Table 4**, available at www.annals.org).

DISCUSSION

In this trial comparing a low-carbohydrate, Mediterranean-style diet with a low-fat diet in people with newly diagnosed type 2 diabetes, we found that the MED diet delayed the need for antihyperglycemic drug therapy. There were no differences in the degree to which participants in each group increased their physical activity or decreased their ca-

loric intake, so the effect seems specific to the MED diet and is probably, although not exclusively, linked to its ability to induce greater weight loss, in accord with results of a recent trial (11). The between-group difference in the proportion of people needing antihyperglycemic drug therapy increased over the course of the trial and favored the MED diet, whereas the between-group differences in weight loss decreased. Analyses adjusted for weight change suggested a statistically significant reduced rate of needing drug therapy, so the effect of the MED diet goes beyond weight reduction. Consumption of monounsaturated fatty acids is thought to increase insulin sensitivity (10–12), and this component of the diet might explain the favorable effect of the MED diet on the need for drug therapy.

Lifestyle changes promote weight loss and increase activity levels and should, with rare exceptions, be included as part of diabetes management (6). In the UKPDS (United Kingdom Prospective Diabetes Study) (19), a total of 2906 patients with newly diagnosed type 2 diabetes each had 3 months of diet therapy before allocation to therapy with oral drugs or insulin. Weight decreased after diet by a mean of 4.5 kg, and HbA_{1c} levels decreased by 2% from a baseline 9% (19). A 2-year trial comparing 3 weight-loss diets in moderately obese participants (11) suggested that both MED and low-carbohydrate diets may be effective alternatives to low-fat diets. Among diabetic participants (14% of those included in the study), changes in fasting plasma glucose and insulin levels were more favorable in those assigned to the MED diet, whereas the reduction of HbA_{1c} levels was greatest (0.9%) in the low-carbohydrate diet group (11). A 1-year trial involving 311 obese women also suggests that a low-carbohydrate diet is a feasible alternative to a low-fat diet for weight loss and may have favorable metabolic effects (20). Also, we evaluated the effect of a Mediterranean-style diet on body weight in 190 overweight women who were followed for up to 2 years and found that women consuming a low-carbohydrate diet lost more weight and more centimeters off the waist than did those consuming a high-carbohydrate diet (14).

Prospective studies have shown that Mediterranean food patterns are associated with a reduction in the risk for type 2 diabetes, both in healthy participants (21) and in patients who had myocardial infarction in the previous 3 months (22). In 3 large prospective studies (23–25), consumption of vegetables and fruit, which are essential components of the Mediterranean diet, was associated with a modestly lower hazard of diabetes (15%, 18%, and 22%, respectively). A recent meta-analysis of prospective cohort studies with a total of 1 574 299 participants followed from 3 to 18 years showed that a 2-point increase in the adherence score to a Mediterranean diet was associated with a reduced risk for overall mortality (9%) and mortality from cardiovascular disease (9%) (26).

One of the most desirable features of MED diets is the ability to improve coronary risk factors (27). Beyond this, epidemiologic and interventional studies have revealed a

Table 4. **Changes From Baseline in Selected Nutrient Indexes at 1 Year and End of Trial (4 Years)***

Variable	MED Diet	Low-Fat Diet	Difference (95% CI)
Total energy, *kcal/d*			
Year 1	−570 (121)	−525 (111)	−45 (−120 to 30)
Year 4	−450 (100)	−409 (92)	−41 (−109 to 35)
Carbohydrates, %			
Year 1	−9.4 (3.1)	1.5 (1.8)	−9.9 (−14.0 to −5.0)
Year 4	−7.9 (4.1)	0.1 (0.3)	−8.0 (−13.1 to −3.8)
Protein, %			
Year 1	1.6 (1.5)	1.9 (1.7)	−0.3 (−0.9 to 0.6)
Year 4	1.3 (1.4)	1.5 (1.6)	−0.2 (−0.8 to 0.4)
Fat, %			
Saturated			
Year 1	−0.5 (0.5)	−0.8 (0.7)	0.3 (−0.5 to 1.1)
Year 4	−0.2 (0.3)	−0.4 (0.5)	0.2 (−0.5 to 0.6)
Monounsaturated			
Year 1	5.9 (3.7)	−1.4 (1.5)	7.3 (5.0 to 12.0)
Year 4	5.5 (3.3)	−1.0 (0.9)	6.5 (3.5 to 10.7)
Polyunsaturated			
Year 1	2.4 (1.7)	−1.4 (1.2)	3.8 (1.5 to 5.5)
Year 4	2.6 (1.9)	−1.1 (1.0)	3.7 (1.4 to 6.0)

MED = low-carbohydrate, Mediterranean-style.
* Data are presented as means (SDs), unless otherwise indicated. Annual changes, including years 2 and 3, are detailed in **Appendix Table 3** (available at www.annals.org). The number of participants eligible for the outcome (hemoglobin A_{1c} level ≤7%) each year (MED diet/low-fat diet) was 102/97 for year 1, 85/64 for year 2, 72/50 for year 3, and 50/29 for year 4. At each time point, values were compared with respective baseline values.

protective effect of MED diets against chronic inflammation (28), which is predictive of the future occurrence of type 2 diabetes (29). Two trials have shown that MED diets protect against insulin resistance and the metabolic syndrome (10, 30). In addition, a large cross-sectional study nested in the Nurses' Health Study found that increased adherence to a Mediterranean diet was associated with higher levels of adiponectin (31), which are associated with a reduced risk for type 2 diabetes (32). So, a mechanism through which MED diets may improve glycemic control may be through amelioration of insulin sensitivity mediated by increased circulating adiponectin levels.

Our study has several limitations. The investigators responsible for starting antihyperglycemic drug treatment were not blinded to trial assignment, and differences in assessment of patient information and patient management related to knowledge of that assignment cannot be totally excluded as contributing to the findings. Assessment of dietary adherence was based on self-report, and patients may have had incentives to misrepresent their adherence. Moreover, the study groups received intensive and frequent information about healthy diets, which may in part explain the high adherence rates to the 2 diets but makes it difficult to generalize the results to the general outpatient diabetic population.

Nevertheless, we believe our findings suggest that people with newly diagnosed type 2 diabetes who use a low-carbohydrate MED diet can lower their HbA_{1c} levels and delay the need for antihyperglycemic drug therapy compared with use of a low-fat diet. The differences in effect might have been greater if the need for drug therapy were linked to a less stringent threshold for HbA_{1c} level. Perhaps most important, the findings reinforce the message that benefits of lifestyle interventions should not be overlooked despite the drug-intensive style of medicine fueled by the current medical literature (33).

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Variable	MED Diet	Low-Fat Diet	Difference (95% CI)
Patients requiring treatment, %†			
Year 1	5.5	9.4	−3.9 (−7.8 to 1.2)
Year 2	22.0	39.8	−17.8 (−25.2 to −10.5)
Year 3	33.2	53.2	−20.0 (−26.1 to −13.7)
Year 4	44.0	70.0	−26.0 (−31.1 to −20.1)
Weight			
Weight, *kg*			
Year 1	−6.2 (3.2)	−4.2 (3.5)	−2.0 (−3.0 to −0.9)
Year 2	−4.9 (2.5)	−3.7 (2.1)	−1.2 (−2.1 to −0.3)
Year 3	−4.2 (2.4)	−3.4 (1.9)	−0.8 (−2.4 to 0.3)
Year 4	−3.8 (2.0)	−3.2 (1.9)	−0.6 (−1.6 to 1.2)
Body mass index, *kg/m²*			
Year 1	−2.4 (1.6)	−1.4 (0.9)	−1.0 (−2.2 to −0.3)
Year 2	−1.9 (0.9)	−1.1 (0.6)	−0.8 (−1.6 to −0.2)
Year 3	−1.5 (0.6)	−1.0 (0.6)	−0.5 (−1.2 to 0.3)
Year 4	−1.2 (0.7)	−0.9 (0.6)	−0.3 (−0.9 to 0.4)
Waist circumference, *cm*			
Year 1	−4.8 (3.0)	−3.5 (2.8)	−1.3 (−1.7 to −0.5)
Year 2	−4.4 (2.8)	−3.3 (2.5)	−1.1 (−1.8 to −0.3)
Year 3	−3.5 (2.2)	−2.9 (1.9)	−0.6 (−1.3 to 0.1)
Year 4	−3.0 (1.7)	−2.6 (2.0)	−0.4 (−0.9 to 0.5)
Glycemic control			
HbA_{1c} level, *%*			
Year 1	−1.2 (1.0)	−0.6 (0.6)	−0.6 (−0.9 to −0.3)
Year 2	−1.1 (0.9)	−0.5 (0.4)	−0.6 (−1.0 to −0.2)
Year 3	−1.0 (0.7)	−0.5 (0.4)	−0.5 (−0.9 to −0.1)
Year 4	−0.9 (0.6)	−0.5 (0.4)	−0.4 (−0.9 to −0.1)
Plasma glucose level, *mmol/L*			
Year 1	−2.3 (1.9)	−1.1 (1.1)	−1.2 (−1.7 to −0.72)
Year 2	−2.1 (1.6)	−1.1 (1.1)	−1.0 (−1.8 to −0.3)
Year 3	−1.9 (1.4)	−1.0 (15)	−0.9 (−1.5 to −0.2)
Year 4	−1.7 (1.1)	−0.8 (0.8)	−0.9 (−1.6 to −0.2)
Serum insulin level, *pmol/L*			
Year 1	−14.0 (13.6)	−12.9 (12.9)	−1.1 (−6.9 to 7.4)
Year 2	−10.7 (10.5)	−12.1 (10.4)	1.4 (−5.7 to 6.9)
Year 3	−12.2 (11.2)	−10.0 (9.4)	−2.2 (−6.5 to 4.9)
Year 4	−9.8 (8.9)	−5.6 (4.3)	−4.2 (−10.7 to 3.4)
HOMA of insulin sensitivity			
Year 1	−1.9 (0.5)	−0.9 (0.4)	−1.0 (−1.6 to −0.5)
Year 2	−2.1 (0.9)	−1.1 (0.7)	−1.0 (−1.8 to −0.3)
Year 3	−1.8 (1.1)	−1.2 (0.7)	−0.6 (−1.2 to −0.1)
Year 4	−1.5 (1.0)	−0.9 (0.6)	−0.6 (−1.1 to −0.1)
Adiponectin level, *μg/mL*			
Year 1	2.7 (0.9)	0.7 (0.4)	2.0 (0.9 to 3.2)
Year 2	2.4 (1.0)	0.8 (0.5)	1.6 (0.5 to 2.7)
Year 3	2.2 (1.1)	0.9 (0.5)	1.3 (0.2 to 2.2)
Year 4	1.9 (10)	0.8 (0.7)	1.1 (0.1 to 1.9)
Coronary risk factors			
Total cholesterol level, *mmol/L*			
Year 1	−0.39 (0.38)	−0.15 (0.17)	−0.24 (−0.36 to −0.12)
Year 2	−0.46 (0.32)	−0.20 (0.20)	−0.26 (−0.31 to −0.05)
Year 3	−0.39 (0.26)	−0.31 (0.20)	−0.08 (−018 to 0.08)
Year 4	−0.25 (0.20)	−0.10 (0.18)	−0.15 (−0.39 to 0.05)
HDL cholesterol level, *mmol/L*			
Year 1	0.10 (0.12)	0.025 (0.02)	0.08 (0.04 to 0.12)
Year 2	0.12 (0.12)	0.0 (0.02)	0.12 (0.05 to 0.14)
Year 3	0.11 (0.10)	0.01 (0.01)	0.10 (0.01 to 0.19)
Year 4	0.09 (0.08)	0.02 (0.02)	0.07 (0.02 to 0.14)
Triglyceride level, *mmol/L*			
Year 1	−0.44 (0.57)	−0.22 (0.45)	−0.22 (−0.32 to −0.10)
Year 2	−0.47 (0.52)	−0.28 (0.42)	−0.19 (−0.34 to −0.06)
Year 3	−0.35 (0.34)	−0.19 (0.22)	−0.16 (−0.36 to 0.00)
Year 4	−0.28 (0.28)	−0.07 (0.10)	−0.21 (−0.36 to −0.02)

Continued on following page

Appendix Table 1—Continued

Variable	MED Diet	Low-Fat Diet	Difference (95% CI)
Systolic BP, *mm Hg*			
Year 1	−5.1 (4.2)	−2.0 (1.9)	−3.1 (−4.9 to −1.2)
Year 2	−4.5 (3.7)	−1.4 (1.7)	−3.1 (−5.4 to −0.6)
Year 3	−3.9 (2.8)	−1.1 (1.2)	−2.8 (−4.9 to −0.3)
Year 4	−2.5 (2.6)	−1.0 (1.0)	−1.5 (−4.5 to 1.2)
Diastolic BP, *mm Hg*			
Year 1	−4.0 (3.0)	−3.0 (4.0)	−1.0 (−4.0 to −1.0)
Year 2	−3.2 (2.8)	−2.5 (2.3)	−0.7 (−2.4 to 1.7)
Year 3	−3.0 (2.6)	−2.1 (1.9)	−0.9 (−3.1 to 1.5)
Year 4	−2.9 (1.9)	−1.5 (1.4)	−1.4 (−4.0 to 1.8)

BP = blood pressure; HbA_{1c} = hemoglobin A_{1c}; HDL = high-density lipoprotein; HOMA = homeostasis model assessment; MED = low-carbohydrate, Mediterranean-style.
* Data are presented as means (SDs), unless otherwise indicated. To convert cholesterol, triglyceride, or glucose values to mg/dL, divide by 0.0259, 0.0113, or 0.0555, respectively.
† The number of participants eligible for the outcome (HbA_{1c} level ≤7%) each year (MED diet/low-fat diet) was 102/97 for year 1, 85/64 for year 2, 72/50 for year 3, and 50/29 for year 4. These numbers were the same for all variables except adiponectin level and waist circumference, which were 100/96, 83/63, 70/49, and 47/28, respectively. At each time point, values were compared with respective baseline values.

Appendix Table 2. Participants Meeting American Diabetes Association Goals for HbA_{1c}, Blood Pressure, and LDL Cholesterol at Baseline and Each Year of Follow-Up

Variable	MED Diet, %	Low-Fat Diet, %	Difference (95% CI), *percentage points*
HbA_{1c} level ≤7%*			
Baseline	19	18	1 (–3 to 6)
Year 1	72	53	19 (14 to 23)
Year 2	66	44	22 (15 to 25)
Year 3	53	38	15 (9 to 21)
Year 4	37	24	13 (8 to 17)
BP <130/80 mm Hg			
Baseline	43	44	–1 (–4 to 5)
Year 1	66	59	7 (–4 to 12)
Year 2	68	62	6 (–3 to 8)
Year 3	67	65	2 (–5 to 8)
Year 4	65	63	2 (–4 to 8)
LDL cholesterol level <2.59 mmol/L (<100 mg/dL)			
Baseline	31	28	3 (–3 to 6)
Year 1	39	36	3 (–2 to 6)
Year 2	42	40	2 (–3 to 5)
Year 3	36	35	1 (–3 to 4)
Year 4	38	35	3 (–4 to 7)
All 3 goals			
Baseline	7	8	–1 (–3 to 2)
Year 1	34	23	11 (4 to 16)
Year 2	36	26	10 (2 to 13)
Year 3	33	26	7 (1 to 14)
Year 4	32	28	4 (–1 to 6)

BP = blood pressure; HbA_{1c} = hemoglobin A_{1c}; LDL = low-density lipoprotein; MED = low-carbohydrate, Mediterranean-style.
* The number of participants eligible for the outcome (HbA_{1c} level ≤7%) each year (MED diet/low-fat diet) was 102/97 for year 1, 85/64 for year 2, 72/50 for year 3, and 50/29 for year 4. At each time point, values were compared with respective baseline values.

Appendix Table 3. Changes in Selected Nutrient Indexes*

Variable	MED Diet	Low-Fat Diet	Difference (95% CI)
Total energy, *kcal/d*			
Baseline	2345 (345)	2304 (298)	−41 (−125 to 33)
Year 1	−570 (121)	−525 (111)	−45 (−120 to 30)
Year 2	−505 (108)	−470 (98)	−30 (−99 to 41)
Year 3	−445 (101)	−430 (95)	−15 (−85 to 47)
Year 4	−450 (100)	−409 (92)	−41 (−109 to 35)
Carbohydrates, %			
Baseline	52.1 (7.6)	51.7 (8.1)	0.4 (−0.3 to 1.0)
Year 1	−9.4 (3.1)	1.5 (1.8)	−10.9 (−15 to −5.0)
Year 2	−8.9 (4.1)	0.4 (0.9)	−9.3 (−13.5 to −4.5)
Year 3	−8.2 (4.6)	−0.2 (0.5)	−8.0 (−14.7 to −2.9)
Year 4	−7.9 (4.1)	0.1 (0.3)	−8.0 (−13.1 to −3.8)
Protein, %			
Baseline	16.7 (3.3)	16.4 (3.4)	−0.3 (−0.8 to 0.5)
Year 1	1.6 (1.5)	1.9 (1.7)	−0.3 (−0.9 to 0.6)
Year 2	1.4 (1.4)	1.7 (1.6)	−0.3 (−1.0 to 0.5)
Year 3	1.5 (1.3)	1.8 (1.5)	−0.3 (−0.9 to 0.4)
Year 4	1.3 (1.4)	1.5 (1.6)	−0.2 (−0.8 to 0.4)
Fat, %			
Saturated			
Baseline	10.2 (2.8)	9.8 (2.7)	0.4 (−1.1 to 0.4)
Year 1	−0.5 (0.5)	−0.8 (0.7)	0.3 (−0.5 to 1.1)
Year 2	−0.3 (0.4)	−1.0 (0.7)	0.7 (−0.4 to 1.7)
Year 3	−0.4 (0.5)	−0.5 (0.4)	0.1 (−0.6 to 0.7)
Year 4	−0.2 (0.3)	−0.4 (0.5)	0.2 (−0.5 to 0.6)
Monounsaturated			
Baseline	12.1 (2.6)	13.4 (3.2)	−1.3 (−2.7 to 0.3)
Year 1	5.9 (3.7)	−1.4 (1.5)	7.3 (5 to 12)
Year 2	6.1 (3.5)	−1.3 (1.3)	7.2 (4.2 to 11.5)
Year 3	5.8 (4.1)	−1.4 (1.2)	7.2. (4 to 11.7)
Year 4	5.5 (3.3)	−1.0 (0.9)	6.5 (3.5 to 10.7)
Polyunsaturated			
Baseline	8.9 (2.1)	8.7 (2.4)	0.2 (−0.6 to 0.5)
Year 1	2.4 (1.7)	−1.4 (1.2)	3.8 (1.5 to 5.5)
Year 2	2.6 (1.8)	−1.2 (1.2)	3.8 (1.2 to 6.0)
Year 3	2.3 (1.9)	−1.3 (1.1)	3.6 (1.3 to 5.8)
Year 4	2.6 (1.9)	−1.1 (1.0)	3.7 (1.4 to 6)

MED = low-carbohydrate, Mediterranean-style.
* Data are presented as means (SDs), unless otherwise indicated. The number of participants eligible for the outcome (hemoglobin A_{1c} level ≤7%) each year (MED diet/low-fat diet) was 102/97 for year 1, 85/64 for year 2, 72/50 for year 3, and 50/29 for year 4. At each time point, values were compared with respective baseline values.

Appendix Table 4. Main Adverse Events During the Study

Adverse Event	MED Diet, *n*	Low-Fat Diet, *n*
Mild		
Gastroenteritis	9	13
Nausea	5	3
Vomiting	3	2
Headache	4	6
Fever	3	1
Fatigue	5	4
Serious		
Atrial fibrillation	1	0
Pneumonia	0	1

MED = low-carbohydrate, Mediterranean-style.