ORIGINAL ARTICLE

Effect of Ramipril on the Incidence of Diabetes

The DREAM Trial Investigators*

ABSTRACT

BACKGROUND

Previous studies have suggested that blockade of the renin–angiotensin system may prevent diabetes in people with cardiovascular disease or hypertension.

METHODS

In a double-blind, randomized clinical trial with a 2-by-2 factorial design, we randomly assigned 5269 participants without cardiovascular disease but with impaired fasting glucose levels (after an 8-hour fast) or impaired glucose tolerance to receive ramipril (up to 15 mg per day) or placebo (and rosiglitazone or placebo) and followed them for a median of 3 years. We studied the effects of ramipril on the development of diabetes or death, whichever came first (the primary outcome), and on secondary outcomes, including regression to normoglycemia.

RESULTS

The incidence of the primary outcome did not differ significantly between the ramipril group (18.1%) and the placebo group (19.5%; hazard ratio for the ramipril group, 0.91; 95% confidence interval [CI], 0.81 to 1.03; $P=0.15$). Participants receiving ramipril were more likely to have regression to normoglycemia than those receiving placebo (hazard ratio, 1.16; 95% CI, 1.07 to 1.27; $P=0.001$). At the end of the study, the median fasting plasma glucose level was not significantly lower in the ramipril group (102.7 mg per deciliter [5.70 mmol per liter]) than in the placebo group (103.4 mg per deciliter [5.74 mmol per liter], $P=0.07$), though plasma glucose levels 2 hours after an oral glucose load were significantly lower in the ramipril group (135.1 mg per deciliter [7.50 mmol per liter] vs. 140.5 mg per deciliter [7.80 mmol per liter], $P=0.01$).

CONCLUSIONS

Among persons with impaired fasting glucose levels or impaired glucose tolerance, the use of ramipril for 3 years does not significantly reduce the incidence of diabetes or death but does significantly increase regression to normoglycemia. (ClinicalTrials.gov number, NCT00095654.)

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DIABETES, RANKED AS THE FIFTH LEADing cause of death worldwide, is a major risk factor for various cardiovascular and renal disorders.[1] The prevalence of diabetes is increasing, which in turn increases the risk of premature cardiovascular disease and death.[2] Therefore, strategies to reduce the incidence of diabetes are needed.

Physical activity, weight loss,[3,4] and some glucose-lowering agents[4,5] reduce the incidence of diabetes in people with elevated glucose levels that are just below the diagnostic threshold for diabetes. Several trials involving people with hypertension or cardiovascular disease have suggested that agents that block or inhibit the renin–angiotensin system may also prevent diabetes.[6] The Heart Outcomes Prevention Evaluation (HOPE) study showed that, in a population at high risk for cardiovascular events, the use of ramipril reduced cardiovascular events by 22% and diabetes by 34%, as compared with placebo.[7] However, the presence of diabetes was ascertained by self-report in the HOPE study and was not a prespecified outcome. Other studies reported similar findings in people with cardiovascular disease or hypertension.[6,8] We conducted a prospective trial, the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study, to evaluate whether ramipril reduces the risk of diabetes in people who have impaired fasting glucose levels (after an 8-hour fast) or impaired glucose tolerance but who are at low risk for cardiovascular events.

METHODS

A detailed description of the design of the DREAM trial has been published previously.[9] Briefly, between July 2001 and August 2003, we enrolled 5269 persons 30 years of age or older who had impaired fasting plasma glucose levels (at least 110 mg per deciliter [6.1 mmol per liter] but less than 126 mg per deciliter [7.0 mmol per liter]) or impaired glucose tolerance (a plasma glucose level of at least 140 mg per deciliter [7.8 mmol per liter] but less than 200 mg per deciliter [11.1 mmol per liter] 2 hours after an oral glucose load) but who did not have a history of diabetes (not including gestational diabetes), cardiovascular disease, or intolerance of either angiotensin-converting–enzyme (ACE) inhibitors or thiazolidinediones. In early 2003, study eligibility was expanded to include persons with isolated impaired fasting glucose levels.

Eligible participants entered a 17-day, single-blind, double-placebo run-in period. If they showed adherence to their study medications during that period, participants were randomly assigned to receive either ramipril (Altace, Sanofi-Aventis, King Pharmaceuticals) (5 mg daily for the first 2 months, with an increase to 10 mg at the 2-month visit and 15 mg after 1 year) or matching placebo (and rosiglitazone or matching placebo [Avandia, GlaxoSmithKline]) (4 mg once daily for the first 2 months and then 8 mg thereafter). In a 2-by-2 factorial design, patients were randomly assigned to a study group with the use of a concealed, computerized telephone randomization system, stratified according to center, with a permuted block size of 8. Detailed results for the rosiglitazone group are reported separately.[10]

Visits were scheduled 2 months and 6 months after randomization and then every 6 months until the common termination window between February and April 2006. Alanine aminotransferase levels were measured every 2 months during the first year. At each visit, study drugs were dispensed, and adherence was assessed and reinforced, as was a healthy diet and lifestyle. Electrocardiograms were recorded at baseline, at 2 years, and at the end of the study.

At the 2-year and final visits, a glucose-tolerance test was performed 2 hours after a 75-g oral glucose load in participants in whom diabetes had not developed. At other annual visits, fasting plasma levels of glucose and glycated hemoglobin were measured locally, and an oral glucose-tolerance test was performed if the fasting plasma glucose level was 126 mg per deciliter (7.0 mmol per liter) or higher, to confirm or refute the diagnosis of diabetes, or if the fasting plasma glucose level exceeded 95 mg per deciliter (5.3 mmol per liter) and the glycated hemoglobin value exceeded 93% of the upper limit of the normal range for the assay. If diabetes was diagnosed during the study and required pharmacologic therapy, the study medications were continued and antihyperglycemic agents other than thiazolidinediones could be prescribed. Participants who had not received a diagnosis of diabetes by the end of the study entered a single-blind placebo washout period and underwent a glucose-tolerance test (2 hours after an oral glucose load) 2 to 3 months later. The study protocol and consent forms were

approved by the ethics committees at all centers, and all participants provided written informed consent.

OUTCOMES

The primary outcome was newly diagnosed diabetes or death. Death was included to account for the possibility that diabetes may develop at different rates in people who die and in those who survive. Diabetes was diagnosed if a locally measured fasting plasma glucose level was at least 126 mg per deciliter (7.0 mmol per liter) or a 2-hour post-load glucose level was at least 200 mg per deciliter (11.1 mmol per liter), with confirmation by a second test on a different day. In the event that a confirmatory second result could not be obtained, diabetes was diagnosed on the basis of one abnormal result, provided there was no clinical reason to refute the diagnosis. Diabetes was also diagnosed if a physician outside of the study diagnosed diabetes on the basis of a fasting plasma glucose level of at least 126 mg per deciliter (7.0 mmol per liter) or any plasma glucose level of at least 200 mg per deciliter (11.1 mmol per liter) and prescribed an antidiabetic agent.

The key secondary outcomes were a composite of cardiac and renal events, defined as either cardiovascular events (clinical or silent myocardial infarction, stroke, death from cardiovascular events, revascularization procedures, heart failure, newly diagnosed angina with objective evidence of ischemia, or ventricular arrhythmia requiring resuscitation) or renal events (on the basis of measurements in urine and blood at a central laboratory). Both the composite of the cardiac and renal events and the renal events alone have yet to be analyzed. Other secondary outcomes included glucose levels and regression to normal glucose levels (fasting plasma glucose level, less than 110 mg per deciliter [6.1 mmol per liter]; 2-hour post-load glucose level, less than 140 mg per deciliter [7.8 mmol per liter]). A committee that was unaware of the study-group assignments adjudicated the diagnoses of diabetes and clinical outcomes according to predefined definitions (see the Supplementary Appendix, available with the full text of this article at www.nejm.org).

STATISTICAL ANALYSIS

We calculated that we would need to enroll at least 5000 persons with impaired fasting glucose levels or impaired glucose tolerance for the study

to have a statistical power of 90% to detect a risk reduction exceeding 22% in the ramipril group. The calculation was based on an estimated annual incidence of the primary outcome in the placebo group of 4.5%, a mean follow-up of 3 years, a two-sided type 1 error rate of 5%, and a combined effect of both interventions that was 10% less than that for either intervention.

All data were collected and analyzed at the Population Health Research Institute, McMaster University, with the use of an intention-to-treat approach, under the supervision of the steering committee. Data for participants whose diabetes status was unavailable at the end of the study were censored at the time of the last glucose assessment. Kaplan–Meier curves for the primary outcome as well as regression to normoglycemia were constructed for the treatment and placebo groups and were compared with the use of log-rank tests. The outcome of regression was based on available values. If glucose levels were not available (e.g., because tests were not completed), we assumed that glycemic status had not changed since the last known value. Cox proportional-hazards models were used to estimate the effect of ramipril on the hazard ratio for the primary and secondary outcomes (with stratification according to whether treatment included rosiglitazone or placebo). Interaction between the ramipril and rosiglitazone treatments was assessed with the inclusion of an interaction term in the model.

We assessed the effect of the study drugs on glucose levels by calculating the median fasting plasma glucose level and the 2-hour post-load plasma glucose level at each scheduled measurement time. Since an oral glucose-tolerance test was not performed after diabetes was diagnosed, and since any fasting plasma glucose level measured after diabetes was diagnosed might have been lowered as a result of diabetes management, a calculation of the medians or means with the use of every available value would have failed to assess accurately the effect of the treatment on glucose levels. Instead, we calculated the medians by assigning people with diabetes the worst rank score, in Wilcoxon rank-sum analyses, for both the 2-hour post-load and fasting plasma glucose levels.[11] Analysis of variance (with adjustment for the baseline level) was used to assess the differences between groups in the mean change in alanine aminotransferase levels and in systolic

and diastolic blood pressures at the end of the trial. All reported P values are two-sided, and they were not adjusted for multiple testing.

An independent trial monitoring committee reviewed the data at least annually. The committee could inform the principal investigators of the study results and recommend study termination if there was a consistent reduction (i.e., a reduction that was evident after two consecutive analyses performed more than 6 months apart) in the hazard ratio for the primary outcome of 4 SD in the first half of the planned follow-up or of 3 SD in the second half, or if there was an excess of cardiovascular events of 3 SD in the first half of the trial or of 2 SD in the second half. In October 2005, after confirming the first interim analysis, the trial monitoring committee informed the principal investigators of the results of the entire study after determining that the study question regarding rosiglitazone had been clearly answered. The committee recommended an early and orderly close-out of the study. The principal investigators agreed, and the study was terminated 5 months early.

The DREAM trial was funded by the Canadian Institutes of Health Research, Sanofi-Aventis, GlaxoSmithKline, and King Pharmaceuticals through the University Industry grant program. Sanofi-Aventis and King Pharmaceuticals provided ramipril and placebo, and GlaxoSmithKline provided rosiglitazone and placebo. The trial was designed, implemented, and analyzed by the steering committee, which also wrote and reviewed the paper. The data were held by the investigators at the Population Health Research Institute, Mc-Master University. Representatives of the study sponsors were nonvoting members of the steering committee.

RESULTS

BASELINE AND FOLLOW-UP

A total of 24,592 participants were screened at 191 centers in 21 countries. Of those screened, 5808 entered the run-in phase of the trial. The most common reasons for exclusion were ineligibility (94.2%) and refusal to participate (3.0%). Of those entering the run-in phase, 5269 participants were randomly assigned to treatment (739 had impaired fasting glucose levels alone and 4530 had impaired glucose tolerance with or without impaired fasting glucose levels). The most common reasons for exclusion during the run-in period were ineligibility (284 participants) and refusal to participate (159 participants). Table 1 summarizes the baseline characteristics of the 5269 participants, which were similar in the ramipril and placebo groups.

Participants were followed for a median of 3.0 years. At 1 year, 86.6% of participants randomly assigned to receive ramipril and 89.9% of those randomly assigned to receive placebo were still taking the study medication. The corresponding proportions at 2 years were 81.3% and 84.8%; at 3 years, 75.4% and 80.9%; and at the end of the study, 72.7% and 78.0%. Throughout the study, the most common reasons for the discontinuation of study medications among participants in the ramipril group and those in the placebo group were the participant's decision to stop taking the medication (17.4% and 17.7%, respectively), cough (9.7% and 1.8%), advice from a physician (2.3% and 2.5%), and peripheral edema (1.0% and 1.1%) (Table 1 in the Supplementary Appendix). Angioedema occurred in three participants receiving ramipril (0.1%) and in four participants receiving placebo (0.2%). Open-label ACE inhibitors were used by 2.7% and 4.0% of participants in the ramipril and placebo groups, respectively.

The mean systolic blood pressure at baseline was 136.1 mm Hg in the ramipril group and 136.0 mm Hg in the placebo group (Table 1). This value decreased by 8.2 mm Hg among those receiving ramipril, as compared with 3.9 mm Hg among those receiving placebo at 2 months (P<0.001). This difference persisted throughout the trial. The mean diastolic blood pressure at baseline was the same in the two groups (83.4 mm Hg). At 2 months, the mean value had decreased by 4.3 mm Hg in the ramipril group, as compared with 1.6 mm Hg in the placebo group (P<0.001), and by the end of the study, the mean had decreased by 5.4 mm Hg in the ramipril group and 3.0 mm Hg in the placebo group (P<0.001).

The mean (±SD) creatinine values at baseline were 0.85±0.20 mg per deciliter (76.0±17.7 μmol per liter) for the ramipril group and 0.85±0.20 mg per deciliter (75.1±17.7 μmol per liter) in the placebo group. At the end of the study, creatinine values were 0.89±0.25 mg per deciliter (78.7±22.1 μmol per liter) in the ramipril group and 0.88±0.23 mg per deciliter (77.8±20.3 μmol

Table 1. Baseline Characteristics of the Study Participants.*

Characteristic†	Ramipril (N = 2623)	Placebo (N = 2646)	P Value
Age — yr	54.7±10.9	54.7±10.9	0.88
Median local fasting plasma glucose level — mg/dl			
Median	106.3	106.5	0.46
Interquartile range	97.3–113.5	97.3–115.3	
2-Hr local plasma glucose level — mg/dl			
Median	155.6	157.6	0.06
Interquartile range	144.1–173.7	144.1–175.6	
Weight — kg	84.8±18.9	85.0±19.0	0.69
Body-mass index	30.9±5.6	30.9±5.7	0.76
Waist-to-hip ratio			
Men	0.96±0.07	0.96±0.07	0.31
Women	0.86±0.08	0.87±0.08	0.28
Blood pressure — mm Hg			
Systolic	136.1±18.6	136.0±18.1	0.80
Diastolic	83.4±10.8	83.4±10.8	0.88
Female sex — no. (%)	1567 (59.7)	1553 (58.7)	0.45
Previous gestational diabetes — no. (%)	131 (8.4)	155 (10.0)	0.12
Isolated impaired glucose tolerance — no. (%)	1513 (57.7)	1515 (57.3)	0.76
Isolated IFG — no. (%)	366 (14.0)	373 (14.1)	0.91
Impaired glucose tolerance and IFG — no. (%)‡	744 (28.4)	758 (28.6)	0.83
Current or previous tobacco use — no. (%)§	1158 (44.1)	1192 (45.0)	0.52
History of hypertension — no. (%)	1136 (43.3)	1155 (43.7)	0.82
History of dyslipidemia — no. (%)	933 (35.6)	938 (35.4)	0.93
Aspirin or antiplatelet therapies — no. (%)	376 (14.3)	378 (14.3)	0.97
Thiazide diuretics — no. (%)	248 (9.5)	265 (10.0)	0.52
Nonthiazide diuretics — no. (%)	155 (5.9)	148 (5.6)	0.64
Angiotensin-receptor blockers — no. (%)	146 (5.6)	140 (5.3)	0.67
Beta-blockers — no. (%)	450 (17.2)	462 (17.5)	0.77
Calcium-channel blockers — no. (%)	336 (12.8)	341 (12.9)	0.93
Alpha-blockers — no. (%)	51 (1.9)	57 (2.2)	0.63
Statins — no. (%)	325 (12.4)	357 (13.5)	0.23
Fibrates — no. (%)	56 (2.1)	61 (2.3)	0.71
Weight-loss drugs — no. (%)	16 (0.6)	14 (0.5)	0.72

* Plus–minus values are means ±SD. To convert values for plasma glucose to millimoles per liter, multiply by 0.05551.
† The body-mass index is the weight in kilograms divided by the square of the height in meters. Impaired glucose toler-ance was defined as a 2-hour post-load plasma glucose level between 140 and 199 mg per deciliter; an impaired fasting glucose level (IFG) was defined as a fasting plasma glucose level of at least 110 but less than 126 mg per deciliter; and "isolated" indicates the existence of only one of the two glycemic categories.
‡ Four participants in the placebo group with fasting glucose levels in the diabetic range were enrolled inappropriately and were included in this category.
§ Tobacco use was defined as the use of cigarettes, beedies, pipe tobacco, cigars, chewing tobacco, or snuff.

per liter) in the placebo group. There was a small difference in weight gain each year, which did not differ significantly between the two groups (mean, 0.22 kg in the ramipril group and 0.36 kg in the placebo group; P=0.07), and an even smaller increase in the body-mass index (the weight in kilograms divided by the square of the height in meters; mean, 0.09 in the ramipril group and 0.14 in the placebo group; P=0.06).

Vital status was ascertained at the end of the study in 5164 participants. Of the 4277 participants who did not reach the primary outcome by the end of the study, fasting or 2-hour post-load glucose levels, or both, were measured in 3961 participants (92.6%). Of the remaining 316 participants, 218 reported that they did not have diabetes.

PRIMARY OUTCOME

During the study, diabetes or death occurred in 475 participants (18.1%) in the ramipril group, as compared with 517 (19.5%) in the placebo group (hazard ratio, 0.91; 95% confidence interval [CI], 0.81 to 1.03; P=0.15) (Table 2 and Fig. 1A). There were 31 deaths in the ramipril group and 32 in the placebo group, whereas diabetes developed in 449 participants in the ramipril group (17.1%) and in 489 in the placebo group (18.5%; hazard ratio, 0.91; 95% CI, 0.80 to 1.03). The effect of ramipril on the development of diabetes was consistent, even after we controlled for the use of diuretics, beta-blockers, or angiotensin-receptor blockers. The results for the primary outcome were similar among participants with impaired fasting glucose levels and in those with impaired glucose tolerance, as they were for various other subgroups (Fig. 1 in the Supplementary Appendix).

SECONDARY GLUCOSE-RELATED OUTCOMES

By the end of the study, 1116 participants (42.5%) receiving ramipril, as compared with 1012 participants (38.2%) receiving placebo, had normal fasting plasma glucose levels (less than 110 mg per deciliter [6.1 mmol per liter]) and normal 2-hour plasma glucose levels (less than 140 mg per deciliter [7.8 mmol per liter]) (hazard ratio, 1.16; 95% CI, 1.07 to 1.27; P=0.001). These results were unchanged after adjustment for the use of diuretics or beta-blockers. The Kaplan–Meier estimates for the regression to normoglycemia are shown in Figure 1B. The proportions of participants at the end of the study who had diabetes, impaired fasting glucose levels, impaired glucose tolerance, and normal glucose levels are shown in Figure 2.

Median fasting plasma glucose levels and 2-hour post-load plasma glucose levels for the duration of the study are shown in Figure 3. At the end of the study, the median fasting plasma glucose level was not significantly lower in the ramipril group (102.7 mg per deciliter [5.70 mmol per liter]) than in the placebo group (103.4 mg per deciliter [5.74 mmol per liter], P=0.07). The median 2-hour post-load plasma glucose level was significantly lower in the ramipril group (135.1 mg per deciliter [7.50 mmol per liter]) than in the placebo group (140.5 mg per deciliter [7.80 mmol per liter], P=0.01). Alanine aminotransferase levels decreased more in the ramipril group than in the placebo group — by 3.4 U per liter and 2.3 U

Outcome	Ramipril (N=2623)	Placebo (N=2646)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Primary composite outcome	475 (18.1)	517 (19.5)	0.91 (0.81–1.03)	0.15
Diabetes	449 (17.1)	489 (18.5)	0.91 (0.80–1.03)	
Diagnosed on the basis of fasting plasma glucose level and 2-hr post-load glucose level	375 (14.3)	411 (15.5)	0.91 (0.79–1.04)	
Diagnosed by physician	74 (2.8)	78 (2.9)	0.95 (0.69–1.30)	
Death*	31 (1.2)	32 (1.2)	0.98 (0.60–1.60)	
Regression to normoglycemia	1116 (42.5)	1012 (38.2)	1.16 (1.07–1.27)	0.001

Table 2. Hazard Ratios for Primary Outcome and Regression to Normoglycemia.

* Before diabetes was diagnosed, 26 deaths occurred in the ramipril group and 28 occurred in the placebo group.

per liter, respectively (P=0.004) — during the first year of the trial.
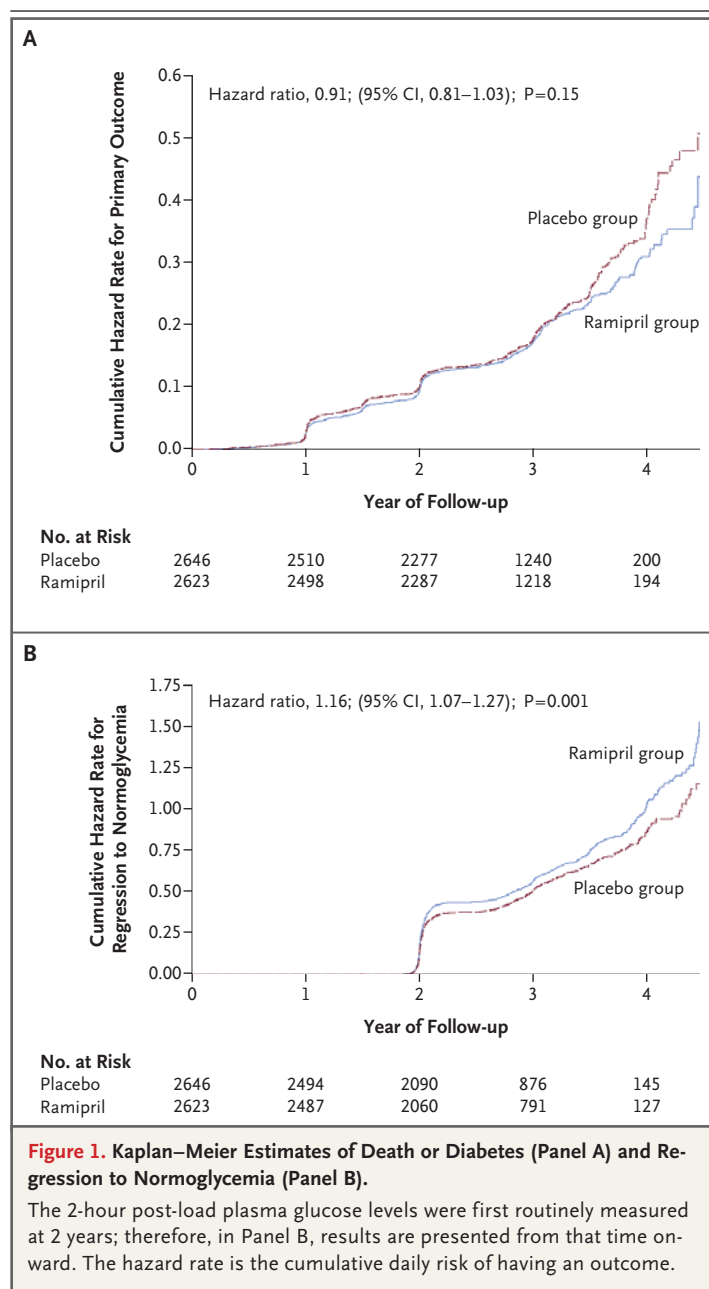
SECONDARY AND SUBGROUP OUTCOMES

The numbers of cardiovascular events were similar in the two groups (67 events in the ramipril group and 63 in the placebo group, P=0.68) (Table 3). The numbers of hospitalizations for all events were also similar (497 in the ramipril group and 489 in the placebo group, P=0.67).

Treatment with rosiglitazone significantly reduced the incidence of diabetes or death (hazard ratio, 0.40; 95% CI, 0.35 to 0.46; P<0.001).[10] There were no significant interactions indicating that the effect of ramipril was the same in the presence or absence of rosiglitazone with respect to the primary outcome, secondary outcomes, or their components (P>0.11 for all interactions). The absence of a significant interaction was further demonstrated by the similar hazard ratios for the primary outcome among participants receiving ramipril, regardless of whether they also received active rosiglitazone: the hazard ratio associated with ramipril, as compared with placebo, among participants receiving active rosiglitazone was 0.92 (95% CI, 0.74 to 1.15), and that among participants receiving placebo rosiglitazone was 0.91 (95% CI, 0.78 to 1.05). The results for the regression to normoglycemia were similar.
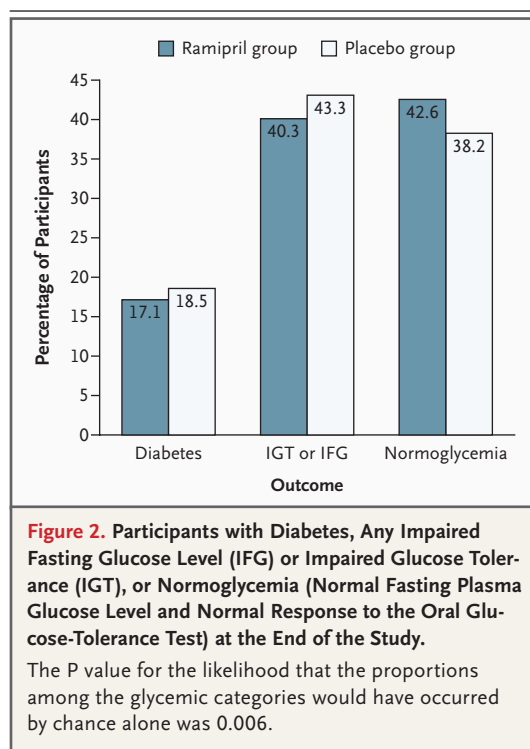
DISCUSSION

Our study suggests that the use of up to 15 mg of ramipril daily for 3 years does not significantly prevent diabetes or death in people without cardiovascular disease who have impaired fasting glucose levels or impaired glucose tolerance. However, significantly more participants receiving ramipril had normal fasting glucose levels and glucose tolerance than those receiving placebo, and the distribution of the glucose levels had shifted downward in the ramipril group by the end of the study. These significant effects suggest that a longer or larger study would be needed to detect a reduction in the rate of newly diagnosed diabetes in this population, if such a reduction exists.

There may be several reasons why these results differ from the reductions in the rates of newly diagnosed diabetes reported previously with ACE inhibitors.[7,12-20] First, our study was specifically designed to determine whether ramipril pre-

Figure 1. Kaplan–Meier Estimates of Death or Diabetes (Panel A) and Regression to Normoglycemia (Panel B).

The 2-hour post-load plasma glucose levels were first routinely measured at 2 years; therefore, in Panel B, results are presented from that time onward. The hazard rate is the cumulative daily risk of having an outcome.

vents diabetes, unlike previous studies[7,8,12,13] in which the analysis of the development of diabetes was either a secondary or post hoc outcome and in which glucose levels were not systematically recorded.

Second, fasting glucose levels and 2-hour post-load glucose levels below the diagnostic threshold for diabetes were required for entry into our study. In contrast, diabetes status was not explicitly established in several previous studies[7,8,12,13]; consequently, some participants in those studies who

Figure 2. Participants with Diabetes, Any Impaired Fasting Glucose Level (IFG) or Impaired Glucose Tolerance (IGT), or Normoglycemia (Normal Fasting Plasma Glucose Level and Normal Response to the Oral Glucose-Tolerance Test) at the End of the Study.

The P value for the likelihood that the proportions among the glycemic categories would have occurred by chance alone was 0.006.

inhibition may therefore have a greater effect in these people than in others.

We compared ramipril with placebo, whereas the comparison treatment in several other trials was with another antihypertensive agent, such as a beta-blocker or a diuretic.[14-16] Both of these medications may increase the risk of diabetes,[23] thereby leading to an overestimation of the effects of ACE inhibitors. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) compared the metabolically neutral calcium-channel blocker to an ACE inhibitor and reported an 17% reduction in the incidence of diabetes in the ACE-inhibitor group.[15] The combined data from three of the largest previous trials that compared ACE inhibitors with placebo in subjects with cardiovascular disease suggest a risk reduction in diabetes of 14% (95% CI, 5 to 22),[8] which appears to be consistent with the 9% lower rate of newly diagnosed diabetes in our study.

The duration of follow-up was shorter in our trial (median, 3 years) than in the previous studies of ACE inhibitors and angiotensin-receptor blockers (median, about 4.5 years). The Kaplan–Meier curves in our study suggest a benefit of ramipril in the prevention of diabetes after 3.5 years (Fig. 1A). Whether this apparent late divergence between the ramipril group and the placebo group is real (or simply due to chance) can be reliably ascertained only by further follow-up of the participants in our trial or by other trials with longer follow-up (e.g., the NAVIGATOR [Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research] trial or the ONTARGET/TRANSCEND [Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease] trials[24]).

Finally, the fact that our study detected a significant effect of ramipril on glucose metabolism but not a significant reduction in the incidence of diabetes may reflect the entry criteria, which led to the exclusion of anyone with glucose levels in the diabetic range. As a result, most participants had baseline glucose levels that were far from the diagnostic threshold for diabetes and close to the normal threshold, which is reflected in the median fasting plasma glucose level of approximately 106.3 mg per deciliter (5.90

were identified as not having diabetes may actually have had undiagnosed diabetes at baseline. The fact that participants also had preexisting cardiovascular disease, which is associated with a high prevalence of dysglycemia,[21,22] supports this possibility. Previous observations concerning the effects of ACE inhibition on newly diagnosed diabetes therefore arguably reflect reduced ascertainment or increased regression of preexisting diabetes in participants with undiagnosed diabetes at baseline, decreased progression to newly diagnosed diabetes, or both.

Third, participants in our trial differed from those in previous studies, who primarily had known cardiovascular disease, heart failure, hypertension, or a combination thereof. In our study, patients with cardiovascular disease and heart failure were excluded, and participants were relatively younger (mean age, 55 years, vs. 65 years in other trials). The mean blood pressure of 136/83 mm Hg at baseline in our study is substantially lower than that reported in the hypertension trials. It is possible that the degree of activation of the renin–angiotensin system is higher in people who are older or have known cardiovascular disease or hypertension and that ACE

mmol per liter) and the median 2-hour post-load glucose level of approximately 156.7 mg per deciliter (8.70 mmol per liter) among all participants at baseline. Therefore, a modest reduction in glucose levels resulting from the use of ramipril would allow more participants to cross into the normal range rather than into the more distant diabetic range, and there would be more power to detect an effect on regression to normal levels than progression to diabetic levels. This appeared to be the case, since diabetes developed in 938 participants, whereas 2128 participants had regression to normoglycemia. Thus, despite the fact that the DREAM trial did not detect a significant effect of ramipril on the incidence of diabetes, the effect with respect to regression to normoglycemia and the totality of the available data suggest that drugs that block the renin–angiotensin system may have a modest, favorable effect on glucose metabolism.

A limitation of our study was that, despite extensive efforts to obtain complete follow-up data, glucose levels were available for only 92.6% of those participants who had not reached a primary outcome by the end of the study. However, information on diabetes status was obtained from the histories of 97.7% of the participants. In addition, the 3 years of follow-up in our trial and the low rates of cardiovascular events during the trial are probably inadequate to provide reliable information on the ultimate prevention of cardiovascular outcomes.

Diet and lifestyle changes are typically recommended for the prevention of diabetes in people

with profiles similar to those of the participants in our study.[3,4] The DREAM trial did not show that ramipril prevents diabetes in this population; however, it did demonstrate an effect of ramipril on regression to normal glucose levels.
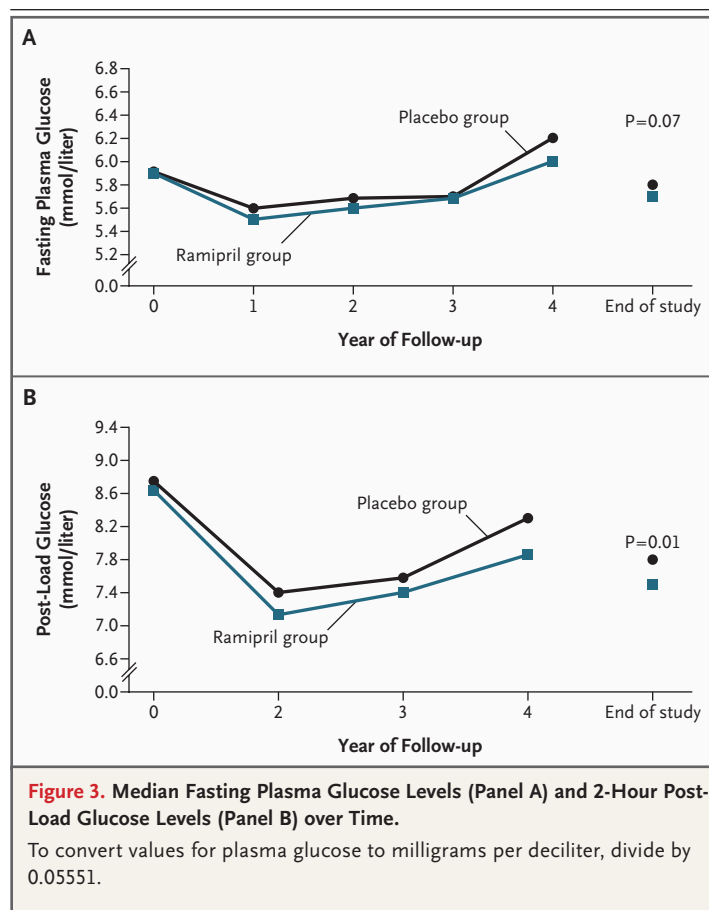

Figure 3. Median Fasting Plasma Glucose Levels (Panel A) and 2-Hour Post-Load Glucose Levels (Panel B) over Time.

To convert values for plasma glucose to milligrams per deciliter, divide by 0.05551.

Table 3. Cardiovascular and Noncardiovascular Outcomes.

Outcome	Ramipril (N=2623)	Placebo (N=2646)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Cardiovascular event (composite)	67 (2.6)	63 (2.4)	1.08 (0.76–1.52)	0.68
Myocardial infarction	13 (0.5)	11 (0.4)		
Stroke	4 (0.2)	8 (0.3)		
Death from cardiovascular event	12 (0.5)	10 (0.4)		
Confirmed heart failure	12 (0.5)	4 (0.2)		
Newly diagnosed angina	24 (0.9)	20 (0.8)		
Revascularization	27 (1.0)	35 (1.3)		
Ventricular arrhythmia requiring resuscitation	0	0		
Hospitalization for noncardiovascular events	155 (5.9)	180 (6.8)		

These results suggest that ramipril may have favorable effects on glucose metabolism, a finding that is consonant with other reports on studies of ACE inhibitors (when used for established indications).[16,23] However, not all trials have found such an association.[15] Further research will be required to clarify this effect. For now, the routine use of ramipril for the express purpose of preventing diabetes is not indicated.

APPENDIX

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