Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial

*The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators**

Published Online
September 15, 2006
DOI:10.1016/S0140-6736(06)69420-8

*Group members are listed at the end of the report

Correspondence to:
DREAM Project Office, Population Health Research Institute, 237 Barton Street East, 2nd Floor, Hamilton, Ontario L8L 2X2, Canada
dream@cardio.on.ca

Summary

Background **Rosiglitazone is a thiazolidinedione that reduces insulin resistance and might preserve insulin secretion. The aim of this study was to assess prospectively the drug's ability to prevent type 2 diabetes in individuals at high risk of developing the condition.**

Methods **5269 adults aged 30 years or more with impaired fasting glucose or impaired glucose tolerance, or both, and no previous cardiovascular disease were recruited from 191 sites in 21 countries and randomly assigned to receive rosiglitazone (8 mg daily; n=2365) or placebo (2634) and followed for a median of 3 years. The primary outcome was a composite of incident diabetes or death. Analyses were done by intention to treat. This trial is registered at ClinicalTrials.gov, number NCT00095654.**

Findings **At the end of study, 59 individuals had dropped out from the rosiglitazone group and 46 from the placebo group. 306 (11·6%) individuals given rosiglitazone and 686 (26·0%) given placebo developed the composite primary outcome (hazard ratio 0·40, 95% CI 0·35–0·46; p<0·0001); 1330 (50·5%) individuals in the rosiglitazone group and 798 (30·3%) in the placebo group became normoglycaemic (1·71, 1·57–1·87; p<0·0001). Cardiovascular event rates were much the same in both groups, although 14 (0·5%) participants in the rosiglitazone group and two (0·1%) in the placebo group developed heart failure (p=0·01).**

Interpretation **Rosiglitazone at 8 mg daily for 3 years substantially reduces incident type 2 diabetes and increases the likelihood of regression to normoglycaemia in adults with impaired fasting glucose or impaired glucose tolerance, or both.**

Introduction

Type 2 diabetes mellitus affects about 5% of adults worldwide; this prevalence is rising rapidly.[1] People with type 2 diabetes are at high risk of serious eye, kidney, nerve, and vascular complications, which cause substantial morbidity and mortality. People with impaired fasting glucose or impaired glucose tolerance are asymptomatic but are at high risk of future diabetes and vascular disease.[2]

Type 2 diabetes develops when pancreatic insulin secretion is insufficient to maintain normal glucose homoeostasis. Acarbose and metformin[3,4] reduce incident diabetes by 25–30%; lifestyle interventions that target diet and physical activity[4–7] reduce incident diabetes by more than 50%, but are difficult to sustain. Rosiglitazone is a thiazolidinedione that is approved for treatment of hyperglycaemia in patients with established type 2 diabetes. The drug activates peroxisome proliferator-activated gamma receptors, increases hepatic and peripheral insulin sensitivity,[8] preserves insulin secretion,[9] and might promote pancreatic β-cell health.[10,11] These properties, together with data from trials with troglitazone[12,13] (another thiazolidinedione that has been withdrawn because of hepatotoxicity), suggest that rosiglitazone could reduce the frequency of diabetes in high-risk individuals.

The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial was designed to assess prospectively whether rosiglitazone can reduce the frequency of diabetes in individuals with impaired glucose tolerance or impaired fasting glucose, or both.

Methods

Patients

A detailed description of the design of the DREAM trial has been published previously.[14] Briefly, 24592 people aged 30 years or more were assessed for eligibility with a 75 g oral glucose tolerance test between July, 2001, and August, 2003, at 191 sites in 21 countries. Inclusion criteria included either impaired fasting glucose (fasting plasma glucose concentration ≥6·1 mmol/L and <7·0 mmol/L and 2-h plasma glucose concentration <11·1 mmol/L during the oral glucose tolerance test) or impaired glucose tolerance (fasting plasma glucose concentration <7·0 mmol/L and 2-h plasma glucose concentration ≥7·8 mmol/L and <11·1 mmol/L). People with a history of diabetes (except gestational diabetes), cardiovascular disease (including heart failure and known low ejection fraction), or intolerance to either angiotensin-converting enzyme inhibitors or thiazolidinediones were excluded.

In 2003, the steering committee expanded the original eligibility criteria from impaired glucose tolerance to also include individuals with isolated impaired fasting glucose (fasting plasma glucose concentration ≥6·1 mmol/L and

<7·0 mmol/L and 2-h plasma glucose concentration <7·8 mmol/L) to broaden the generalisability of the study results.[14]

If deemed to be eligible, patients entered a 17-day single-blind placebo run-in period; participants who took at least 80% of run-in medication were subsequently enrolled for randomisation.

All participants were provided with advice by the local research staff about healthy diets and lifestyle habits to reduce diabetes. The study protocol and consent forms were reviewed and approved by the ethics committees of the participating centres, and all participants provided written informed consent.

Procedures

Eligible patients were randomly assigned (stratified by site) by a concealed, computerised telephone randomisation system to receive either rosiglitazone (4 mg once daily for the first 2 months and then 8 mg once daily) or matching placebo. The dose of 8 mg per day was chosen to achieve maximum ability to identify whether the drug prevents diabetes and to ensure that a negative study would not be attributed to an inadequate dose. Patients were concurrently randomly assigned to receive either ramipril (titrated to 15 mg once daily) or matching placebo with a 2×2 factorial design. Detailed results for the ramipril arm are described elsewhere.[15]

Participants attended visits 2 months and 6 months after randomisation and every 6 months thereafter. At all visits, the importance of healthy diet and lifestyle was emphasised, drugs were dispensed, and adherence was assessed and reinforced. A 75 g oral glucose tolerance test with local fasting and 2-h plasma glucose concentration measurements was done after 2 years and at final visit, and at other yearly visits local fasting plasma glucose and glycated haemoglobin concentrations were measured. If at any visit the fasting plasma glucose concentration was 7·0 mmol/L or greater or the 2-h plasma glucose concentration was 11·1 mmol/L or greater (ie, suggesting possible diabetes), an oral glucose tolerance test was scheduled within the next 3 months to either confirm or refute the diagnosis. If the second confirmatory oral glucose tolerance test was negative, participants then had yearly repeat measurements taken until the end of the study or until diabetes was diagnosed. If the fasting plasma glucose concentration was greater than 5·3 mmol/L and less than 7·0 mmol/L, and the glycated haemoglobin concentration was more than 93% of the upper limit of normal for the assay at any visit at which an oral glucose tolerance test was not done, such a test was scheduled for the next 6-month visit to test for possible diabetes as described above. If diabetes was diagnosed during the study and needed pharmacological therapy, the study drug was continued and antidiabetic agents other than a thiazolidinedione were allowed. Individuals who were not diagnosed with diabetes at the final active therapy visit entered a washout period to assess whether any diabetes-prevention properties of the study drug(s) persisted after discontinuation. They were switched to single-blind placebo and scheduled for a repeat oral glucose tolerance test after 2–3 months (results to be reported separately).

Participants had local measurements of alanine aminotransferase (ALT) concentrations every 2 months during the first year of therapy; subsequent ALT measurements were done at the discretion of the site physician. Waist and hip circumference and weight were measured and an electrocardiograph was done at study entry, after 2 years, and at the end of the study. Blood pressure was measured at 2 months, 6 months, 12 months, and yearly thereafter.

The composite primary outcome was incident diabetes or death from any cause during the active treatment period; death was included to account for the possibility that diabetes might develop at a different rate in individuals who die than in those who survive. Diabetes was diagnosed if (1) a locally measured fasting plasma glucose concentration of 7·0 mmol/L or greater or 2-h plasma glucose concentration of 11·1 mmol/L or greater during a 75 g oral glucose tolerance test was confirmed by a second test on a different day; (2) a single test was consistent with diabetes, no confirmatory test was done, and the masked adjudicator had no reason to reject the diagnosis; or (3) a physician diagnosed diabetes outside the study and the diagnosis was supported by the prescription of an antidiabetic agent and either a fasting plasma glucose concentration of 7·0 mmol/L or greater or any glucose concentration of 11·1 mmol/L or more. Diabetes status and date of diagnosis were established by masked adjudication of all relevant data.

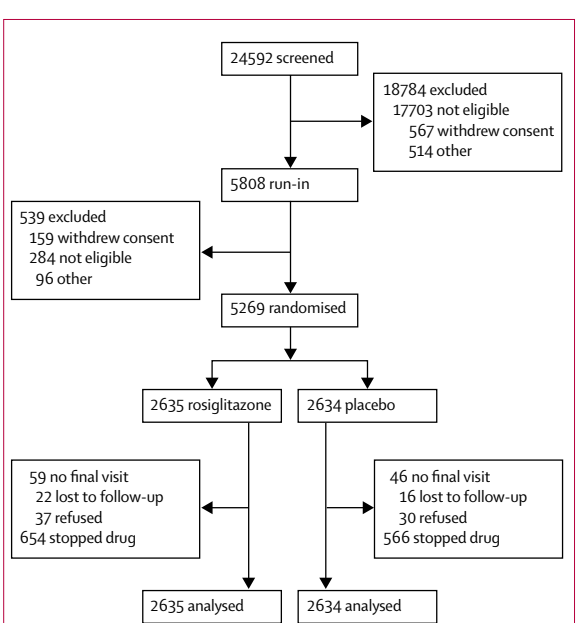

Figure 1: **Trial profile**
Data were censored at time of last follow-up for all participants.

	Rosiglitazone group (n=2635)	Placebo group (n=2634)
Mean age (years)	54·6 (10·9)	54·8 (10·9)
Women	1536 (58·3%)	1584 (60·1%)
Isolated IGT	1504 (57·1%)	1524 (57·9%)
Isolated IFG	369 (14·0%)	370 (14·1%)
Both IGT and IFG	762 (28·9%)*	740 (28·1%)*
Geographic distribution		
North America	1082 (41·1%)	1067 (40·5%)
South America	564 (21·4%)	572 (21·7%)
Europe	549 (20·8%)	555 (21·1%)
India	330 (12·5%)	332 (12·6%)
Australia	110 (4·2%)	108 (4·1%)
Medical history		
Gestational diabetes in women	139 (9·1%)	147 (9·3%)
History of hypertension	1159 (44·0%)	1132 (43·0%)
Current or former tobacco use	1157 (43·9%)	1193 (45·3%)
More than three alcoholic drinks per week	556 (21·1%)	503 (19·1%)
Sedentary	696 (26·4%)	717 (27·2%)
Drug use		
Aspirin or antiplatelet agent	378 (14·4%)	376 (14·3%)
Thiazide diuretics	246 (9·3%)	267 (10·1%)
Other diuretics or aldosterone antagonist	158 (6·0%)	145 (5·5%)
Angiotensin receptor blocker use	153 (5·8%)	133 (5·1%)
Beta-blocker	470 (17·8%)	442 (16·8%)
Calcium channel blockers	328 (12·5%)	349 (13·3%)
Alpha-blocker	43 (1·6%)	65 (2·5%)
Statin or fibrate	391 (14·8%)	389 (14·8%)
Weight loss drugs	16 (0·6%)	14 (0·5%)
Examination		
Weight (kg)	84·8 (19·0)	85·0 (18·9)
Body-mass index (kg/m^2)	30·8 (5·6)	31·0 (5·6)
Waist/hip ratio (men; women)	0·96 (0·07); 0·86(0·07)	0·96 (0·07); 0·87 (0·09)
Waist (cm) (men; women)	101 (14); 96 (14)	102 (13); 96 (14)
Systolic blood pressure (mm Hg)	135·9 (17·9)	136·3 (18·8)
Diastolic blood pressure (mm Hg)	83·3 (10·6)	83·5 (10·9)
Investigations		
Mean fasting plasma glucose concentration (mmol/L)	5·8 (0·7)	5·8 (0·7)
Mean 2-h plasma glucose concentration (mmol/L)	8·7 (1·4)	8·7 (1·5)
Left ventricular hypertrophy on ECG	118 (4·5)	129 (4·9)

Data are mean (SD) or number (%). ECG=electrocardiograph. IFG=impaired fasting glucose (fasting plasma glucose concentration >6·1 mmol/L and <7 mmol/L and 2-h plasma glucose concentration <7·8 mmol/L). IGT=impaired glucose tolerance. *One individual in the rosiglitazone group and three in the placebo group who were randomised despite a fasting plasma glucose concentration >7 mmol/L were assumed to have developed diabetes on day 1.

Table 1: **Baseline clinical and biochemical characteristics of participants**

Secondary outcomes included: (1) regression to normal fasting and 2-h post-load glucose concentrations, defined as a fasting plasma glucose concentration of less than 6·1 mmol/L and a 2-h plasma glucose concentration of less than 7·8 mmol/L; (2) a composite of cardiovascular events (myocardial infarction, stroke, cardiovascular death, revascularisation procedures, heart failure, new angina with objective evidence of ischaemia, or ventricular arrhythmia needing resuscitation); (3) individual components of this cardiovascular composite; (4) renal events and a composite cardiorenal outcome; and (5) glucose concentrations. Clinical outcomes were assessed by masked adjudication by a committee in accordance with prespecified diagnostic criteria.

Statistical analysis

A sample size of at least 5000 individuals with impaired glucose tolerance or impaired fasting glucose was estimated on the basis of a predicted incidence of the primary outcome in the placebo group of 4·5% or greater per year, a mean follow-up exceeding 3 years, a type 1 error rate of 5%, 10% subadditivity between the two interventions, and 90% power to identify a risk reduction of 22% or greater. Interim results were reviewed every year by an independent trial monitoring committee whose role was to unblind and advise the principal investigators if there was evidence of clear benefit or harm. Statistical guidelines for benefit were a reduction in the primary outcome by 4 SD or more in the first half of the trial or 3 SD in the second half that was maintained during two consecutive analyses at least 3 months apart in the original cohort of participants with impaired glucose tolerance. Guidelines for harm included a sustained excess of cardiovascular events or death of 3 SD or more in the first half and 2 SD in the second half. The committee also took emerging information from other studies into account in their deliberations. In April, 2005, the committee informed the principal investigators that these criteria had been met for the subgroup of participants with impaired glucose tolerance in the rosiglitazone arm and unblinded them to that arm only. However, the principal investigators and the committee agreed that the study should continue because the average follow-up was short, the full 2-year data were not available, and the long-term safety data were inadequate. After its review of all the data in October, 2005, as well as new results from a large cardiovascular outcome trial of another thiazolidinedione,[16] the committee was sufficiently convinced that the study question had been clearly and robustly answered that it unblinded the principal investigators to the entire study results and recommended an accelerated but orderly close-out of the DREAM trial. This recommendation was agreed and final visits were started about 5 months earlier than originally anticipated.

All results were analysed at the Population Health Research Institute at McMaster University (Hamilton, Ontario, Canada), on the basis of intention to treat. Cox's proportional hazards models were used to estimate the effect of rosiglitazone on the hazard of the primary and other outcomes (stratified by ramipril allocation) and the significance of the effect. Interaction of the effect of rosiglitazone and ramipril on the primary outcome was assessed by including an interaction term in the Cox model. Individuals for whom diabetes status was unavailable at the end of the study were censored at the

time of their last glucose measurement. Kaplan-Meier curves for the primary and secondary outcome were constructed for rosiglitazone and placebo and compared with stratified log-rank tests. Statistical heterogeneity of treatment effects within key subgroups was also assessed. The effect of study drugs on glucose concentrations was assessed by calculating the median fasting and 2-h plasma glucose concentrations noted at every scheduled measurement time. Since an oral glucose tolerance test was not done after diabetes was diagnosed, and because any post-diabetes fasting plasma glucose measurements could have been lowered by diabetes management, a calculation of the median or mean values with every available measurement would have failed to accurately assess the effect of the interventions on glucose concentrations. Instead, median values were calculated by assigning people with diabetes the worst rank score for both the 2-h and fasting plasma glucose measurements,[17] and the groups were compared with a Wilcoxon rank-sum analysis. Analysis of variance (with adjustment for the baseline value) was used to assess differences between groups in the mean change in ALT after 1 year, and in systolic and diastolic blood pressure from the beginning to the end of the trial, and the slope of change of body-mass index, weight, waist-to-hip ratio, and waist and hip circumference during the course of the study. We used SAS version 9.1 (2002) for analyses.

This trial is registered at ClinicalTrials.gov, number NCT00095654.

Role of the funding source

All sponsors were represented on the steering committee and, together with the other members, provided feedback on study design, analysis, interpretation, and the final report. The sponsors had no role in the collection, storage, or analysis of the data, and were not involved in the decision to submit the data for publication. The Steering Committee decided to submit for publication, and the Hamilton Project office had full access to the data.

Results

5269 (21·4%) people with a mean age of 54·7 (SD 10·9) years (59·2% women) were randomly assigned to receive either placebo or rosiglitazone (figure 1). The baseline characteristics of the participants are shown in table 1. Of note, 3028 (57%) participants had isolated impaired glucose tolerance, 739 (14%) had isolated impaired fasting glucose, and 1502 (29%) had both.

Participants were followed for a median of 3·0 years (range 2·5–4·7). During the trial 992 (18·8%) individuals experienced the primary outcome: 63 (1·2%) people died and 938 (17·8%) people developed diabetes on the basis of either study-related glucose concentrations (n=786) or other criteria (152). Of the remaining participants, 3961 completed a final visit, 218 provided a verbal report of their diabetes status, and 98 did not respond. Vital status could not be ascertained in 105 (2·0%) people by the end of the trial; in these individuals, vital status was known for 2 years or more in 56 people, in 22 for 1–2 years, and in 27 for less than 1 year.

In surviving participants for whom adherence to study drug was recorded by the research staff (2604 individuals assigned rosiglitazone and 2600 assigned placebo), 1868 (71·7%) in the rosiglitazone group and 1952 (75·1%) in the placebo group were at least 80% adherent at the end of the study; two individuals in the rosiglitazone group and one in the placebo group were taking 4 mg daily; four receiving rosiglitazone and 16 receiving placebo were taking open-label rosiglitazone or

	Rosiglitazone group (n=2635)	Placebo group (n=2634)	HR (95% CI)	p
Composite primary outcome*	306 (11·6%)	686 (26·0%)	0·40 (0·35–0·46)	<0·0001
Diabetes	280 (10·6%)	658 (25·0%)	0·38 (0·33–0·44)	<0·0001
Diagnosed by FPG/OGTT	231 (8·8%)	555 (21·1%)	0·38 (0·33–0·44)	<0·0001
Physician diagnosed	49 (1·9%)	103 (3·9%)	0·47 (0·33–0·66)	<0·0001
Death	30 (1·1%)	33 (1·3%)	0·91 (0·55–1·49)	0·7
Regression (FPG <6·1 mmol/L)†	1330 (50·5%)	798 (30·3%)	1·71 (1·57–1·87)	<0·0001
Regression (FPG <5·6 mmol/L)†	1016 (38·6%)	540 (20·5%)	1·83 (1·65–2·04)	<0·0001
Cardiovascular events composite*	75 (2·9%)	55 (2·1%)	1·37 (0·97–1·94)	0·08
Myocardial infarction	15 (0·6%)	9 (0·3%)	1·66 (0·73–3·80)	0·2
Stroke	7 (0·3%)	5 (0·2%)	1·39 (0·44–4·40)	0·6
Cardiovascular death	12 (0·5%)	10 (0·4%)	1·20 (0·52–2·77)	0·7
Confirmed heart failure‡	14 (0·5%)	2 (0·1%)	7·03 (1·60–30·9)	0·01
New angina	24 (0·9%)	20 (0·8%)	1·20 (0·66–2·17)	0·5
Revascularisation	35 (1·3%)	27 (1·0%)	1·29 (0·78–2·14)	0·3
Myocardial infarction, stroke, or cardiovascular death	32 (1·2%)	23 (0·9%)	1·39 (0·81–2·37)	0·2

Data are number (%). *Rows are not mutually exclusive for components of the composite—if a participant had more than one component of the composite then they are counted in the relevant row. †Regression implies achieving a normal fasting glucose concentration (as defined in both rows) and 2-h plasma glucose level. ‡Defined as acute treatment with at least two of the following criteria: typical signs and symptoms, typical radiological evidence, use of diuretics, vasodilators, or inotropes. FPG=fasting plasma glucose. OGTT=oral glucose tolerance test.

Table 2: **Primary and other outcomes**

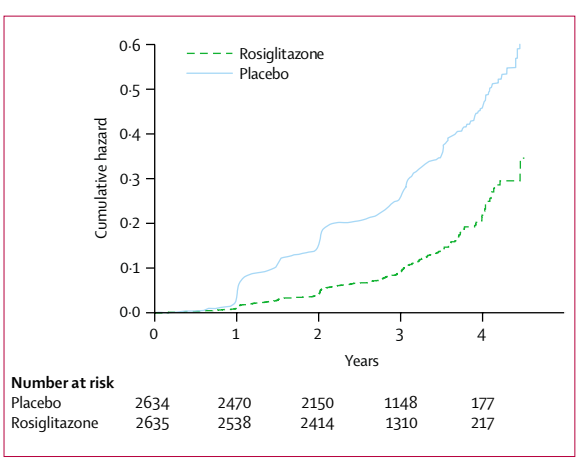

Figure 2: **Time to occurrence of primary outcome**

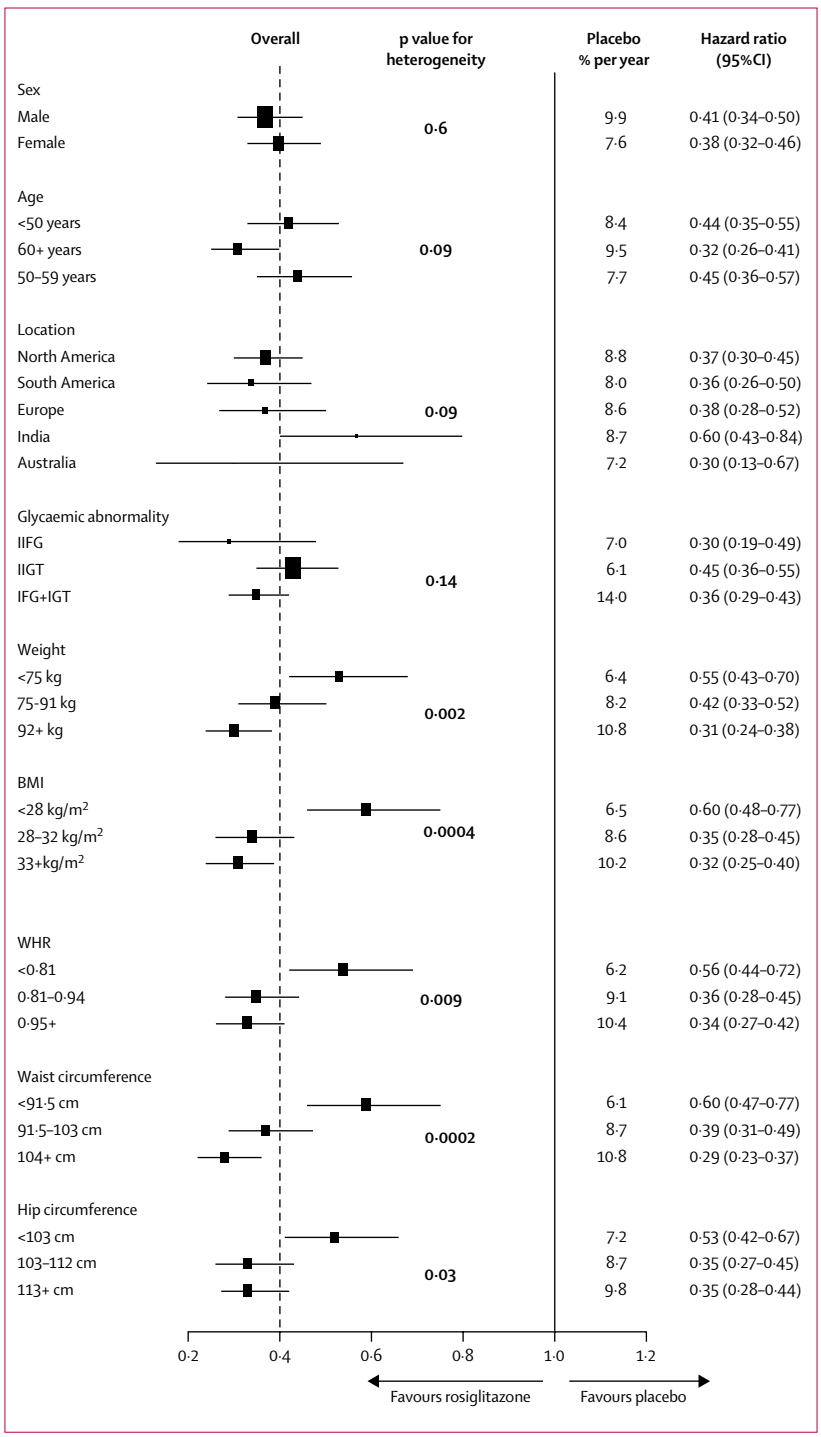

Figure 3: **Effect of rosiglitazone on the primary outcome in key subgroups**
BMI=body-mass index. IIFG=isolated impaired fasting glucose. IIGT=isolated impaired glucose tolerance. WHR=waist-to-hip ratio.

pioglitazone. 752 (28·5%) participants in the rosiglitazone group and 641 (24·3%) in the placebo group stopped taking their assigned treatment at any time; and 602 (23·6%) people assigned to receive rosiglitazone and 517 (20·2%) assigned to receive placebo were not taking the allocated drug at their last visit. The most common reasons for stopping rosiglitazone and placebo included participant refusal (503 [18·9%] in the rosiglitazone group and 439 [16·7%] in the placebo group); oedema (439 [4·8%] and 41 [1·6%]), physician's advice (50 [1·9%] and 39 [1·5%]), and weight gain (50 [1·9%] and 15 [0·6%]). One patient in the rosiglitazone group and three in the placebo group stopped because of hypoglycaemia.

There was no statistical evidence of an interaction between the rosiglitazone and ramipril arms of the DREAM study for the primary outcomes, secondary outcomes, or their components (interaction p>0·11 for all; data not shown). The primary outcome of diabetes or death was seen in significantly fewer individuals in the rosiglitazone group than in the placebo group (hazard ratio [HR] 0·40, 95% CI 0·35–0·46; p<0·0001; table 2). There was no difference in the number of deaths (0·91, 0·55–1·49; p=0·7) and a large difference in the frequency of diabetes (0·38, 0·33–0·44; p<0·0001) between the two groups (table 2). The event curves for the primary outcome diverged by the time of the first assessment (after 1 year of follow-up; figure 2).

Effects on the primary outcome were much the same irrespective of the glycaemic abnormality that was present at the time of randomisation. Thus, an HR for the primary outcome of 0·30 (0·19–0·49) was recorded in individuals with isolated impaired fasting glucose, of 0·45 (0·36–0·55) in those with isolated impaired glucose tolerance, and 0·36 (0·29–0·43) in those with combined impaired fasting glucose tolerance and impaired glucose tolerance (p value for heterogeneity 0·14; figure 3). When analysed on the basis of the fasting plasma glucose alone (ie, irrespective of whether or not impaired glucose tolerance was also present), participants with any impaired fasting glucose tolerance (ie, isolated impaired fasting glucose or impaired fasting glucose plus impaired glucose tolerance) had an HR of 0·35 (0·29–0·42) for the primary outcome. If impaired fasting glucose is defined as a fasting plasma glucose of 5·6 mmol/L to 6·9 mmol/L[18] the hazard for these participants (who in this study also had impaired glucose tolerance) was 0·41 (0·30–0·55).

The effect of rosiglitazone was much the same in all regions of the world, different ethnic groups, in both sexes, and across all ages (figure 3). Rosiglitazone was also effective irrespective of baseline weight or fat distribution, albeit to a different degree. Whereas increasing baseline weight or waist-to-hip ratio (ie, abdominal fat distribution) predicted a higher frequency of diabetes in individuals in the placebo group, this relation was not seen in those in the rosiglitazone group. Consequently the relative hazard reduction for the primary outcome increased from 40% in people whose body-mass index was less than 28 kg/m² to 68% in people whose body-mass index was greater than 32 kg/m² (p for heterogeneity 0·0004; figure 3).

A significantly larger number of participants receiving rosiglitazone regressed to normoglycaemia (defined as a 2-h plasma glucose concentration <7·8 mmol/L and fasting plasma glucose concentration <6·1 mmol/L) than did individuals receiving placebo (1330 individuals on rosiglitazone *vs* 798 on placebo; HR 1·71, 1·57–1·87; p<0·0001; table 2). The effect on regression was also evident when a more stringent definition of normal fasting plasma glucose concentration (<5·6 mmol/L) was used (1·83, 1·65–2·04; p<0·0001; table 2 and figure 4).

Both treatment groups had much the same frequency of the composite cardiovascular outcome and of every component of the composite except for heart failure (table 2). There were no cases of fatal heart failure; one person in the rosiglitazone group died of a myocardial infarction 1 month after a diagnosis of heart failure and one person died after a procedure done 2 years after stopping treatment with rosiglitazone. Increases in the risk of heart failure in the presence or absence of ramipril were much the same and were distributed throughout the follow-up period (data not shown). 174 (6·8%) of 2547 people in the rosiglitazone group reported peripheral oedema at the final visit versus 124 (4·9%) of 2554 people in the placebo group (p=0·003).

Figure 5 shows the effect of rosiglitazone on fasting and 2-h plasma glucose concentrations. The median fasting plasma glucose concentration was 0·5 mmol/L lower in the rosiglitazone group than in the placebo group (p<0·0001); the 2-h plasma glucose concentration was 1·6 mmol/L lower (p<0·0001). Mean systolic and diastolic blood pressure were 1·7 mm Hg and 1·4 mm Hg lower, respectively, in the rosiglitazone group than in the placebo group (p<0·0001). Furthermore, mean hepatic ALT concentrations during the first year of therapy were 4·2 U/L lower in patients treated with rosiglitazone than those in the placebo group (p<0·0001). All results are for the final visit apart from the ALT difference, which was at 1 year. Of note, there was no difference in the use of antihypertensive agents in the two groups during the trial. Finally, by the final visit mean bodyweight was increased by 2·2 kg more in the rosiglitazone group than in the placebo group (p<0·0001). This increase in bodyweight in the rosiglitazone group was associated with a lower waist-to-hip ratio (p<0·0001) because of an increase in hip circumference of 1·8 cm; there was no effect on waist circumference (figure 6).

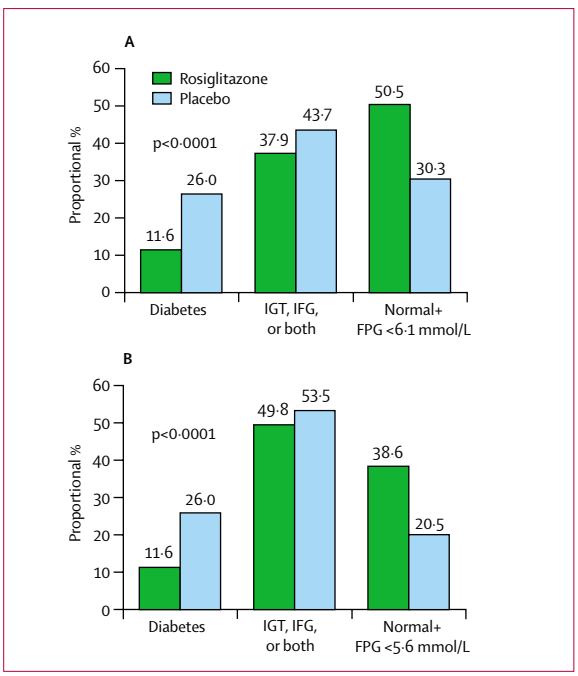

Figure 4: **Proportion of participants who either developed diabetes, regressed to normal, or had impaired fasting glucose or impaired glucose tolerance, or both, at the last assessment**
(A) FPG defined as concentration <6·1 mmol/L or (B) <5·6 mmol/L. The p value for the likelihood that the distribution across categories would have occurred by chance using both FPG cutoffs was <0·0001.

Discussion

This large, prospective, blinded international clinical trial shows that 8 mg of rosiglitazone daily, together with lifestyle recommendations, substantially reduces the risk of diabetes or death by 60% in individuals at high risk for diabetes. The absolute risk difference between treatment groups of 14·4% means that for every seven people with impaired fasting glucose or impaired glucose tolerance who are prescribed rosiglitazone for 3 years, one will be prevented from developing diabetes. Moreover, rosiglitazone significantly increased the likelihood of regression to normoglycaemia by about 70–80% compared with placebo. The reduction in diabetes reported here is of much the same magnitude as the reduction achieved with lifestyle approaches[4,5] and greater than the reductions reported previously with drugs such as metformin[4] or acarbose.[3] The effect on regression is

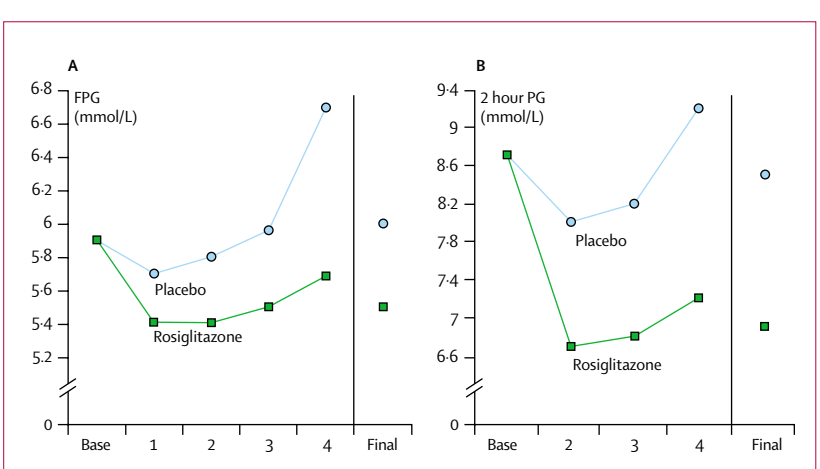

Figure 5: **Effect of rosiglitazone on the point estimates of (A) fasting plasma glucose (FPG) and (B) 2-h plasma glucose (PG) concentrations**

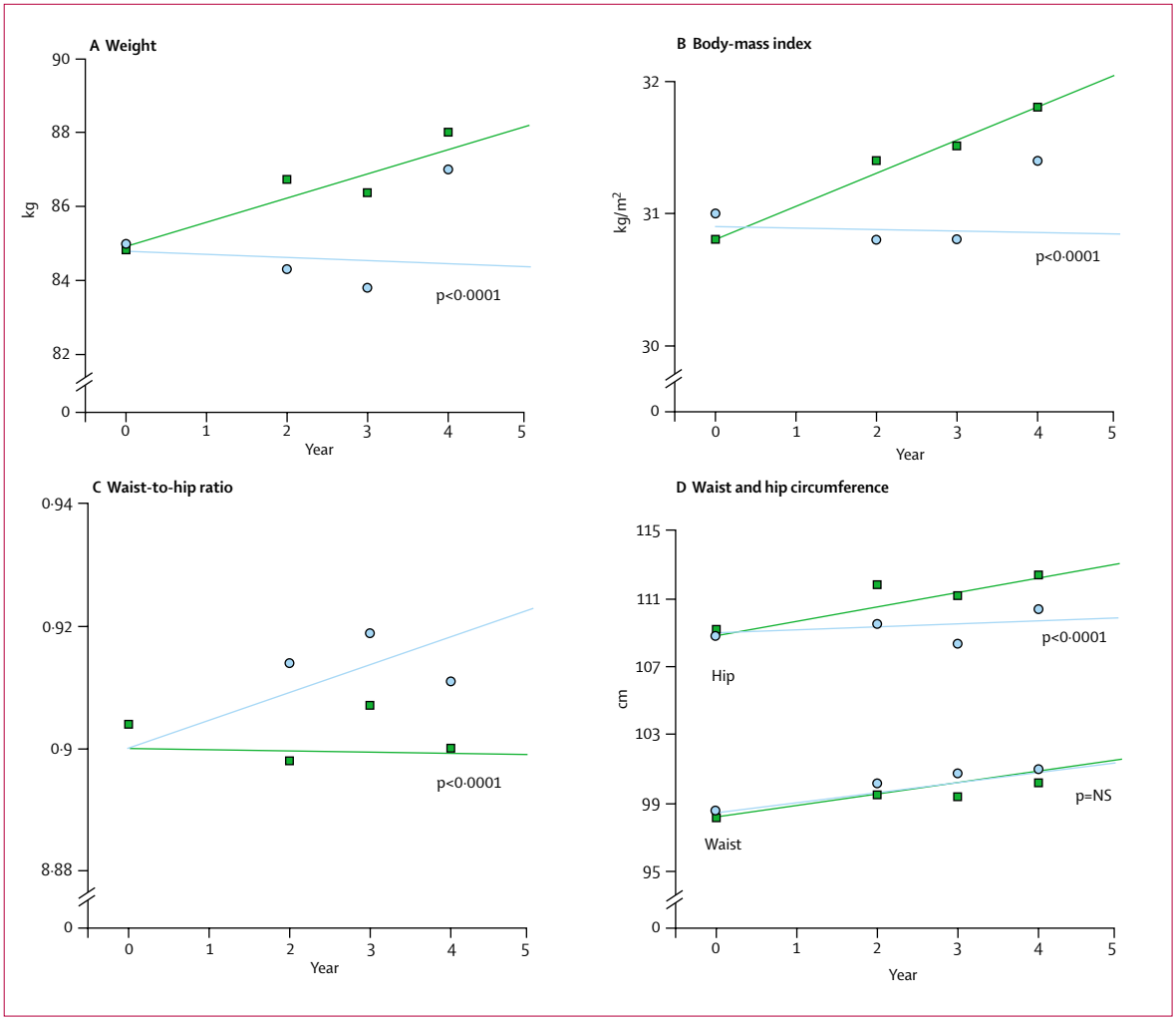

Figure 6: **The effect of rosiglitazone on weight and fat distribution**
Overall effect of rosiglitazone and placebo on the slope of (A) weight and (B) body-mass index, (C) waist-to-hip ratios in all participants, and (D) waist and hip separately. p values indicate the differences in slope and the markers indicate the mean values for rosiglitazone (square) and placebo (circle) at every time point. Weight, waist, and hip circumference were recorded at baseline, 2 years, and study end (3 or 4 years for most participants). NS=not significant.

much the same or larger than that of lifestyle approaches or acarbose, but larger than that with metformin, which did not promote more regression than placebo.[3,4] These results support findings from smaller clinical trials of troglitazone in people with either impaired glucose tolerance[12] or women with a history of gestational diabetes.[13]

A consistent reduction in the primary outcome was noted in people with impaired fasting glucose and those with impaired glucose tolerance, in men and women, in all participating regions of the world (consisting of many ethnic groups), in patients of all ages, and in participants of varying weight and fat distribution. Participants with a higher body-mass index or abdominal fat distribution who were allocated to receive rosiglitazone all had the same 3–4% per year incidence of the primary outcome, despite progressively higher rates in the corresponding control participants (data not shown); this finding accounts for the observation of higher risk reduction with higher baseline obesity (figure 3). Rosiglitazone therefore seems to reduce or eliminate the relation between increasing obesity and a higher risk of diabetes.

Several explanations could account for these findings. Rosiglitazone might simply reduce the raised glucose concentrations of dysglycaemic participants by increasing the effectiveness of endogenous insulin. If true, the effect on glucose concentrations should be largely eliminated upon withdrawal or washout of the drug; this will be formally tested during the post-trial washout period. Data from one previous troglitazone trial suggests that the benefits of a thiazolidinedione persist even after the drug is stopped;[19] this was not seen in another trial.[12] Alternatively, rosiglitazone could slow the fall in β-cell function with time by reducing the physiological demand

for basal as well as prandial insulin secretion (ie, through insulin sensitisation) or by a direct β-cell cytoprotective effect.[11] Another explanation is offered by the observation that the frequency of diabetes was lower in the rosiglitazone group than in the placebo group, despite a 2·2 kg increase in weight in the rosiglitazone group. The preferential deposition of fat in the hip versus the abdomen and the reduction in ALT concentrations noted during the first year of therapy suggests that this modest weight gain could have been due to fat accumulation in non-visceral compartments and an increase in subcutaneous adipocyte mass.[20] Such an effect could be accompanied by increased secretion of adiponectin and reduced levels of inflammatory cytokines, and is associated with less diabetes.[21,22]

Epidemiological studies and at least one clinical trial of people with cardiovascular disease suggest that thiazolidinediones might reduce cardiovascular events.[16,23] However, such a reduction was not the focus of this trial and the short observation period and low event rates (table 2) preclude drawing reliable conclusions with regard to the cardiovascular effects of rosiglitazone. Indeed, the DREAM trial explicitly excluded individuals with previously diagnosed cardiovascular disease because of clear evidence that ramipril reduced cardiovascular events in these individuals.[24] The effect of rosiglitazone on atherosclerosis, measured by sequential carotid ultrasounds in a subset of DREAM participants, will be reported elsewhere.

Rosiglitazone had no effect on the cardiovascular composite outcome, although blood pressure was significantly lower in those receiving the drug than those receiving placebo. However, as reported in thiazolidinedione studies done in people with diabetes,[25] there was a small excess in non-fatal congestive heart failure in those receiving rosiglitazone. These findings could be explained by the vascular and renal effects of the drug. Rosiglitazone-mediated vasodilation caused by both direct effects on blood vessels and increases in vascular insulin sensitivity accounts for the modest fall in blood pressure.[26] Sodium and water retention could occur as a result of a direct thiazolidinedione effect on the renal collecting duct and possibly in response to the modest fall in blood pressure.[25,27] The resulting fluid overload is probably responsible for congestive heart failure in susceptible individuals. The observation that the incidence of heart failure with a thiazolidinedione was about ten times lower in participants at low risk of cardiovascular events in the DREAM trial than in a cardiovascular prevention trial of participants at high risk[16] could be explained by a reduced susceptibility of lower risk people to heart failure. Nevertheless, since there were only 16 cases of heart failure, this estimate needs to be interpreted cautiously and further analyses of these data, together with data from other thiazolidinedione studies, are indicated to better identify people at risk.

More than 8% of adults worldwide have either impaired glucose tolerance or impaired fasting glucose.[1] Every year about 5–10% of these people will develop diabetes and acquire the disease burden related to its diagnosis, symptoms, need for surveillance for chronic consequences, and associated costs. They will also be at high risk for several chronic diseases. The results of this study suggest that the addition of rosiglitazone to basic lifestyle recommendations substantially reduces the risk of developing diabetes by about two-thirds, offering a novel preventive approach that could be as, or more, effective and sustained than previously reported lifestyle approaches alone.[4,5] Balancing both the benefits and risks suggests that for every 1000 people treated with rosiglitazone for 3 years, about 144 cases of diabetes will be prevented, with an excess of four to five cases of congestive heart failure. Finally, the observation that rosiglitazone increased the likelihood of regression to normoglycaemia by about 70–80% suggests that it is treating dysglycaemia as well as reducing the frequency of diabetes. Further work is needed to establish whether the beneficial metabolic effects seen with rosiglitazone will lead to a reduction in cardiovascular, renal, retinal, or other serious health consequences.[28]

DREAM trial investigators

Steering committee—H C Gerstein, S Yusuf, R R Holman, J Bosch, S Anand, A Avezum, A Budaj, J Chiasson, I Conget, G Dagenais, M Davis, R Diaz, N Dinccag, M Enjalbert, A Escalante, G Fodor, M Hanefeld, T Hedner, K Jolly, M Keltai, M Laakso, F Lanas, E Lonn, M McQueen, V Mohan, A Phillips, L Piegas, V Pirags, J Probstfield, J Shaw, I Schmid, K Teo, P Zimmet, B Zinman.

Writing committee—H C Gerstein, S Yusuf, J Bosch, J Pogue, P Sheridan, N Dinccag, M Hanefeld, B Hoogwerf, M Laakso, V Mohan, J Shaw, B Zinman, R R Holman, on behalf of the DREAM trial investigators.

Site investigators and study coordinators—ARGENTINA: R Diaz, R Ahuad Guerrero, J Albisu, M S Alvarez, V Arregui, H Avaca, H Baglivo, M Balbuena, F Bello, J Bono, M Botto, L Brandani, M Brandes, D Bruera, R Cabral Venere, A Caccavo, A Cacurri, G Caime, M Capozzi, A Carrique, P Carrique, L Cartasegna, J Casabe, G Casaccia, C Castellanos, L Castro, G Cendali, P Cerchi, M Cerdan, M Cinalli, M Cipullo, M Cismondi, N Citta, L Citta, C Crespo, P Crunger, C Cuneo, L De Loredo, S De Loredo, S del Cerro, R Denaro, E Esperatti, L Esposito, H Farras, A Fernandez, M Fernandez, S Fernandez, G Ferrari, M Focaccia, L Frontini, A Gabito, A Gambarte, M Garrido, I Garrido, V Guglielmotti, A Hershson, V Hoffman, G Juarisit, M Klyver, M Lagrutta, A Liberman, J Llanos, L Lobo Marquez, R Lopez, D Lowenstein, J Lowenstein, C Lucero, H Luciardi, E Luduena Clos, M Luna, C Luquez, I MacKinnon, M Maffia, C Mahfoud, C Majul, N Maldonado, O Manuale, G Marcucci, S Martin, G Martinez, M Martos, E Marzetti, R Memoli, M Molina, O Montana, S Morales, Y Morell, S Navarrete, F Nieto, L Ocampo, R Orce, A Orlandini, E Oteiza, C Pepa, J Piasentin, D Piskorz, M Plastino, J Pomposiello, G Quiroga, F Ramos, H Ramos, F Reissig, A Risolo, Z Riverso , H Rodrigues , C Rodriquez, S Saavedra, L Sago, R Sanchez, C Schwindt, P Schygiel, F Sebastian, G Sposetti, P Streitenberger, G Suarez, F Suzrez, M Vico, S Vignau, V Visco, A Vizcaya Castro, C Zaidman; *AUSTRALIA:* J Shaw, P Zimmet, C Allen, T Arsov, N Bartlett, B Batrouney, R Borger, B Brooks, P Buchanan, A Buckland, D Calvert, J Carr, Y Chan, H Ching, A Chronopoulos, P Coates, N Cohen, S Colagiuri, P Colman, M Correcha, M d'Emden, G Ding, W Edwards, K Estensen, B Fitzpatrick, J Freeborn, H Friebel, G Fulcher, C Garland, A Gauld, J Gein, C Glatthaar, J Graham, A Gronan, A Gunser, P Hackney, C Hall, L Hay, V Heazlewood, D Heyward, B Higgins, M Hines, A Hodge, S Honisett, A Jovanovska, J Karrasch, M Kean, M Lawton, C Lee, H Legg, F Long, E Lucas, L Lynch, A Marangou, F Margrie, L Martin, J McKenzie, A McKinnon, M McNamara, J Mencel, R Moses, C Murphy, V Naidu,

J Nairn, A Nankervis, N Nattrass, A Ngweso, T Nugent, R O'Brien, N Palmer, H Parry, K Pasculli, P Patrikios, S Perampalam, J Phillips, S Phillips, E Por, S Pringle, E Prior, J Proietto, L Rando, D Ridley, A Roberts, P Robertson, K Robinson, C Rodgers, G Ross, J Rowe, R Siddall, D Silva, R Simpson, R Slobodniuk, G Smith, L Socha, V Soden, M Speedy, E Spence, K Steed, C Stephens, R Stewart, B Stuckey, P Sumithran, J Sunderland, E Tapp, N Tejani, C Tong, D Topliss, H Tran, S Vanlint, J Wagner, J Walsh, J Warner, A Webb, T Welborn, J Wentworth, C White, S Wigg, V Willenberg, D Wilson, M Wood, S Wu, D Yue, R Yuen; Bermuda: S Marshall E Baillie, G Campbell, J Cressall, J Heir, D Jones, J Myrie, M Watlington, A West; *BRAZIL:* A Avezum, L Piegas, M Bertolami, J Borges, D Branco de Araujo, L Cartena, N de Campos Salvarani, A Faludi, D Fernades Telo, S Grespan, J Gross, A Halpern, A Hirota, S Maeda, O Monte, Y Nakamura, J Nunes Salles, O Oliveira, C Pinto, L Rabelo, A Rabelo Jr, S Silveiro, L Turatti, H Zatz, V Zoubel; *CANADA:* G Dagenais, C Abbott, A Abu-Bakare, R Allison, S Anand, T Anderlic, D Auger, A Barnie, J Beauchef, S Beers, L Beliveau, L Berard, H Bolduc, G Bondy, J Bradley, P Bragaglia, S Brault, M Brittain, R Brossoit, S Brown, S Capes, P Carmichael, D Caron, L Caruana, J Cha, P Champion, S Chan, Y Chan, I Chausse, R Cheung, J Chiasson, M Chilvers, S Chisholm, M Clearwaters, C Colborne, J Conway, T Czolpinski, S Dallaire, M David, A Davis, D DeAngelis, I Delpech, R Denton, A Dufour, P Dunn, H Duong, D Eddy, S Erickson-Nesmith, D Fay, G Fox J Frohlich, M Fyfe, S Galandzy, S Gauthier, J Gillett, G Girard, G Gosselin, M Gourgues, S Gray, D Grunbaum, M Gupta, J Halle, A Hanley, P Hardin, S Harris, N Harvey, G Hoag, M Hogard, R Houlden, D Hughes, D Hunt, L Janzen, O Jenkins, J Krider, S Kwan, C Lai, A Lam, L Lambing, D Lau, C Lavallee, P Lavallee, G LeDrew, H Lee, C Legare, W Leong, D Lesperance, H Lochnan, S Ludwig, D MacNair, S Mann, M Marin, J MacFadyen, S MacLean, J Marucci, C Masson, P Maurice, S Mawani, A McCarthy, G McCarthy, D McInnis, S McLean, A McLean, D Monier, S Montreuil, L Neal, S Newman, D O'Keefe, T Oprici, J Otis, G Ouellet, M Parmar, M Paul, R Petrella, S Petrella, R Phillips, D Poisson, S Prieur, R Rabasa-Lhoret, G Rajakumar, A Rajakumar, J Raymond, D Richard, G Rideout, C Robert, Y Robitaille, D Ross, S Ross, R Rowe, C Salmon, D Saunier, C Savard, D Savard, R Sayeed, Z Sayeed, F Sestier, J Shaban, D Shu, R Sigal, J Silverberg, E Smith, R Smith, J Soucy, R Starra, B Stearn, D Steel, D Steinson, B Sternberg, D Stewart, F Stone, B Sussex, D Tippe, A Toupin-Halle, D Trapsa, S Tremblay, N Troung, J van Buuren, L VanSickle, R Verdonk, P Whitsitt, R Wilson, L Winkler, W Wong, V Woo, P Wozniak, J Yale, D Zaniol, L Zaychkowsky, G Zimakas, B Zinman, T Zmijowskyj; *CHILE:* F Lanas, M Atkinson Altamirano, F Bello Murua, O Landaeta, G Larenas, V Raddatz Kiefer, L Roddriguez, G Torres Carrasco. *FINLAND:* M Laakso, P Harkonen, L Hiltunen, A Jantunen, S Keinanen-Kiukaanniemi, M M Laakso, E Lahdensuo, J Rutanen, E Saastamoinen, V Salaspuro, K Sivenius, T Valle; *GERMANY:* M Hanefeld, P Budziarek, S Engeli, K Fache, C Fischer, K Flehmig, A Gordalla, I Gottschalk, M Habel, R Hampel, E Henkel, S Höltzl, J Jordan, M Kletetschka, C Kresse, D Lehmann, H Mehling, C Otte, M Pein, B Pfeffer, B Ploog, F Schaper, G Scholz, G Stoffels, A Strauss, K Wilhelm; *HUNGARY:* M Keltai, B Balazs, E Balogh, Z Birkus, T Boros, G Gyarmati, K Hati, K Hati, Z Hermanyi, M Herold Benko, P Kempler, A Kohari, S Kornel, Z Laszlo, ZZ Laszlo, F Nagy, C Nemeth, F Poor, P Pusztai, K Sandor, A Somogyi, J Takacs, A Toth, E Varga, P Voros; *INDIA:* V Mohan, S Aravind, S R Aravind, V Ayyar, M Dharmalingam, B Ganapathi, R Gayatri, U Gopal, J Idiculla, U Kalaivani, K Karkuzhali, L Kavitha, S Krishnan, P Kumar, K Kumar, M Monika, M Muniswamy, M Padmalatha Devi, P Pais, S Poongothai, S Prakash, M Ramu, P V Rao, C Rao, K Shailaja, T Sreenivas, S Sudha, K Udayakumar, C Yajnik; *LATVIA:* V Pirags, A Erina, E Gailiss, S Gara, A Gozite, S Hansone, I Kreislere, L Liepa, M Ozolina, L Putane, J Raibarts, I Rasa, N Rozkova, E Rudzite, A Staka, I Veze; *MEXICO:* A Escalante, S Arellano, K Bañuelos, C Calvo, M Carbajal, E Cardona, R Castaneda, J Chavira, C Dominguez, M Escalante, E Flores, F Gómez, J Gonzalez, D González-Barcena, C Granados, J Illescas, M Jimenez, L Mancillas, L Mejia , C Mendoza, L Mendoza, M Muñoz, A Muñoz, V Padilla, S Pascoe, O Plascencia , C Ramos, A Reza, I Rubio, E Ruiz, M Vidrio; *NETHERLANDS:* M Alhakim, V Bemelmans, W de Backer, S Eelkman Rooda, F Guldemond, M Hulshof, J Jonker, H Koppeschaar, K Meinema, M Pondman-Mulder, S Ponteyn-Rose, K van Asten, V van de Walle, W van Kempen; *NORWAY:* B Bryne, B Enderle, K Furuseth, J Halse, T Henriksen, A Hertzenberg Faehn, O Knudsrod, S Lerssl, C Loennicken, K Murud, E Steinbo, S Vaaler; *POLAND:* A Budaj, A Baranowska, M Baranska, J Blaszak, M Bronisz, L Ceremuzynski, H Cywinska, E Czempik, M Gmytrasiewicz, A Grochola, O Grzegorz, P Ignaczak, K Janik, B Jankiewicz, G Kania, T Kawka-Urbanek, M Kolaczek, D Kopcik, M Kordys, A Krainska, J Majer, M Makuch, P Miekus, J Mormul, A Mrowczynska, D Nowak, P Nowakowski, M Ogorek, L Oleskowaska, L Paliszewska, B Przywoska-Para, S Pszonak, M Rozwodowska, M Rucinski, M Rzyman, M Sikora-Frac, J Stecka-Wierzbicka, M Swiatkowski, R Swierczynski, A Szczepanska, M Szpajer, M Ukleja-Adamowicz, A Urbaniak, D Winek, P Wojewoda, B Zaborksa, J Zadrosny, J Zak, B Zalska; *SLOVAKIA:* G Fodor, M Bilicky, M Caprnda, A Dukat, A Dukat, M Gajdosova, J Lietava, P Penz, M Thurzo, A Vachulova; *SPAIN:* I Conget, E Aguilera Hurtado, M Armayor, J Bernardino, C Campo Sien, R Carrarro, L de Teresa Pareno, L Diez, G Esteban, L Fernandez Lopez, R Gabriel, A Garcia Herola, C Girones, L Guerrero lamas, G Hermosa, P Lopez Fernandez, M Macia, D Mendez Morillejo, J Puig, C Roldan, L Ruilope Urioste, E Sanchez Carranza, J Segura, I Serrano, F Tudelilla; *SWEDEN:* T Hedner, M Anders, L Andrén, I Berndtson, G Dahlén, A Eriksson, M Escar, L Jungersten, G Lindh, H Nielsen, L Ny B Polhem, M Sandberg, S Skrtic, S Svensson, S Wallerstedt. *TURKEY:* N Dinccag, S Kaya, Z Oglagu, Y Tutuncu; UK: M Davies, J Barron, J Beaverstock, L Borthwick, B Bradford, L Bryan, N Capps, F Coates, S Dickson, D Donaldson, F Forbes, C Fox, K Hall, M Hollway, J Howe, J Jamieson, K MacLeod, M MacLeod, J Maiden, D Matthews, M McIntosh, S McQuaid, A Millward, G Nayani, A Neil, M Page, J Piper, M Ramell, T Reynolds, S Ross, A Shore, L Tonks, S White, J Wylie; *USA:* S Anderson, E Anteola, A Araghi, G Bahtyiar, S Baker, G Bakris, E Basta, A Bastien, D Bell, R Bergenstal, L Berrios Lopez, J Bigger, D Brautigam, N Bultermeier, R Burgos-Calderon, D Cacia, M Casale, C Charles, J Chiarot, M Cipolle, L Coley, B Cushman, J de Lemos, M Deshmukh, L DeVivo, D Donovan, W Elliott, A Farag, J Flack, P Fuste, S Garay, D Garcia De La Rosa, R Garcia De La Rosa, A Getaneh, H Ginsberg, R Goland, R Goldberg, S Griffin, L Griffith, R Grimm, H Guber, B Guzman Serrano, G Haddad, M Hagen, K Hall, A Hamrahian, D Herr, B Hoogwerf, M Izhar, L Joseph, S Kashyap, M Kelly, S Kempainen, A Khera, M Kringas, J Levin, P Linz, S List, C Lopez-Jimenez, E Los, M Manaiermam, K Margolis, M Matzinger, S McFarlane, J McGill, D McGuire, G Medina Caban, A Mehta, L Merkle, B Meyer, A Monk, L Montalvo-Burke, C Nelson, G Neri, J Nicasio, C Octaviani, F Ovalle, S Padilla, P Pepper, O Portalatin, J Probstfield, J Ramirez, S Rao Kashyap, M Riddle, A Rivera Cruz, G Saavedra, D Scharf, L Seibold, S Shah, D Shay, E Siraj, B Slavik, M Smith, S Solomon, J Spencer, E Stephens, L Thomas, E Vasquez, W Vega Ocasio, M Vetrano, S Walsh, R Zimmerman.

DREAM project offices—GLOBAL: J Bosch, N Barr, C Choppick, D Desai, J George, H C Gerstein, P Khatib, K Killman, L MacRae, S MacRae, F Pasha, J Pogue, U Rangachari, V Reiding, D Robinson, L Santarelli, J Shannon, P Sheridan, S Yusuf; *ARGENTINA:* A Pascual, C Rovito; *AUSTRALIA:* B Fricke, E McBride, S Richmond; *BRAZIL:* P Smith; *CANADA:* L Frenette, A Magi; Chile: A Montecinos, *EUROPE:* J Keenan, J Starrett; *FINLAND:* J Ramo, M Tarvainen; *GERMANY:* A Güth, B Weise; *HUNGARY:* K Keltai; *INDIA:* V Kumar HG; *LATVIA:* I Balode, G Zilgalve; *MEXICO:* I Garcia, P Liceaga, A Moreno; *NORWAY:* G Bratten, I Ronning; *POLAND:* W Nowak; *SLOVAKIA:* W West; *SPAIN:* B Margo, O Martinez, *SWEDEN:* G Dahl; *NETHERLANDS:* Y Bookelmann, M Schoonhoven; *TURKEY:* Z Cetin; *USA:* S Clare.

External trial monitoring committee (data safety and management board)— D L Sackett, D Altman, P Bennett, C M Clark, R Hamman, L Ryden.

Contributors

The members of the steering committee designed the trial, did the scientific review, and interpreted the data. The members of the writing committee wrote the manuscript and the people listed above by country contributed to recruitment and data collection. H C Gerstein and S Yusuf were co-principal investigators; R Holman was the European co-chair, and J Bosch was the project director.

Conflict of interest statement

H C Gerstein and S Yusuf have received honoraria for providing advice to, and speaking for, Sanofi-Aventis and GlaxoSmithKline. J Bosch has received honoraria for attending advisory committee meetings for Sanofi-Aventis. B Hoogwerf is a clinical investigator at GlaxoSmithKline and is involved in a phase III trial of a DDP-IV inhibitor. R R Holman has received honoraria from GlaxoSmithKline for attending advisory boards and speaking at symposia. M Laakso has been a consultant for Astra-Zeneca, GlaxoSmithKline, Merck Sharpe and Dohme, and Sanofi-Aventis, and has received speaker's fees from Bayer, Lilly, and Takeda, and travel or accommodation payments for consultancies and lectures. M Hanefeld has received honoraria for lectures from Sanofi-Aventis, Bayer, Takeda advisory board, Novo Nordisk, and GlaxoSmithKline. J Shaw has received honoraria from GlaxoSmithKline and Eli Lilly Australia for giving lectures and has received payment for being on the advisory board of Eli Lilly. B Zinman has received research support and honoraria for scientific advisory board and speaking from GlaxoSmithKline and honoraria for scientific advisory board and speaking from Sanofi-Aventis. The other members of the writing committee declare that they have no conflict of interest.

Acknowledgments

The DREAM trial is funded by the Canadian Institutes of Health Research (MCT41548) as well as by Sanofi-Aventis, GlaxoSmithKline, and King Pharmaceuticals.

References

1 Secree R, Shaw J, Zimmet P. Diabetes and impaired glucose tolerance: prevalence and projections. In: Allgot B, Gan D, King H, et al, eds. Diabetes atlas, 2nd edn. Brussels: International *Diabetes Federation*, 2003: 17–71.

2 Unwin N, Shaw J, Zimmet P, Alberti KG. Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. *Diabet Med* 2002; **19:** 708–23.

3 Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002; **359:** 2072–77.

4 Knowler WC, Barrett-Connor E, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346:** 393–403.

5 Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001; **344:** 1343–50.

6 Kosaka K, Noda M, Kuzuya T. Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males. *Diabetes Res Clin Pract* 2005; **67:** 152–62.

7 Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia* 2006; **49:** 289–97.

8 Yki-Jarvinen H. Thiazolidinediones. *N Engl J Med* 2004; **351:** 1106–18.

9 Lupi R, Del GS, Marselli L, et al. Rosiglitazone prevents the impairment of human islet function induced by fatty acids: evidence for a role of PPARgamma2 in the modulation of insulin secretion. *Am J Physiol Endocrinol Metab* 2004; **286:** E560–67.

10 Finegood DT, McArthur MD, Kojwang D, et al. Beta-cell mass dynamics in Zucker diabetic fatty rats. Rosiglitazone prevents the rise in net cell death. *Diabetes* 2001; **50:** 1021–29.

11 Leiter LA. Beta-cell preservation: a potential role for thiazolidinediones to improve clinical care in type 2 diabetes. *Diabet Med* 2005; **22:** 963–72.

12 Diabetes Prevention Program Research Group. Prevention of type 2 diabetes with troglitazone in the Diabetes Prevention Program. *Diabetes* 2005; **54:** 1150–56.

13 Buchanan TA, Xiang AH, Peters RK, et al. Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk hispanic women. *Diabetes* 2002; **51:** 2796–803.

14 DREAM Trial Investigators. Rationale, design and recruitment characteristics of a large, simple international trial of diabetes prevention: the DREAM trial. *Diabetologia* 2004; **47:** 1519–27.

15 DREAM Trial Investigators. Ramipril's effect on incident diabetes in impaired glucose regulation. *N Engl J Med* (in press).

16 Dormandy J, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005; **366:** 1279–89.

17 Lachin JM. Worst-rank score analysis with informatively missing observations in clinical trials. *Control Clin Trials* 1999; **20:** 408–22.

18 Genuth S, Alberti KG, Bennett P, et al. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003; **26:** 3160–67.

19 Xiang AH, Peters RK, Kjos SL, et al. Pharmacological treatment of insulin resistance at two different stages in the evolution of type 2 diabetes: impact on glucose tolerance and beta-cell function. *J Clin Endocrinol Metab* 2004; **89:** 2846–51.

20 Nakamura T, Funahashi T, Yamashita S, et al. Thiazolidinedione derivative improves fat distribution and multiple risk factors in subjects with visceral fat accumulation—double-blind placebo-controlled trial. *Diabetes Res Clin Pract* 2001; **54:** 181–90.

21 Snijder MB, Zimmet PZ, Visser M, Dekker JM, Seidell JC, Shaw JE. Independent and opposite associations of waist and hip circumferences with diabetes, hypertension and dyslipidemia: the AusDiab Study. *Int J Obes Relat Metab Disord* 2004; **28:** 402–09.

22 Yki-Jarvinen H. Fat in the liver and insulin resistance. *Ann Med* 2005; **37:** 347–56.

23 Masoudi FA, Inzucchi SE, Wang Y, Havranek EP, Foody JM, Krumholz HM. Thiazolidinediones, metformin, and outcomes in older patients with diabetes and heart failure: an observational study. *Circulation* 2005; **111:** 583–90.

24 HOPE Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; **342:** 145–53.

25 Nesto RW, Bell D, Bonow RO, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. *Circulation* 2003; **108:** 2941–48.

26 Sarafidis PA, Lasaridis AN. Actions of peroxisome proliferator-activated receptors-gamma agonists explaining a possible blood pressure-lowering effect. *Am J Hypertens* 2006; **19:** 646–53.

27 Semenkovich CF. TZDs and diabetes: testing the waters. *Nat Med* 2005; **11:** 822–24.

28 Buse JB, Rosenstock J. Prevention of cardiovascular outcomes in type 2 diabetes mellitus: trials on the horizon. *Endocrinol Metab Clin North Am* 2005; **34:** 221–35.