Effects of Ramipril and Rosiglitazone on Cardiovascular and Renal Outcomes in People With Impaired Glucose Tolerance or Impaired Fasting Glucose

Results of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial

THE DREAM TRIAL INVESTIGATORS*

OBJECTIVE — Impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) are risk factors for diabetes, cardiovascular disease (CVD), and kidney disease. We determined the effects of ramipril and rosiglitazone on combined and individual CVD and renal outcomes in people with IGT and/or IFG in the Diabetes REduction Assessment With ramipril and rosiglitazone Medication (DREAM) trial.

RESEARCH DESIGN AND METHODS — A total of 5,269 people aged ≥30 years, with IGT and/or IFG without known CVD or renal insufficiency, were randomized to 15 mg/day ramipril versus placebo and 8 mg/day rosiglitazone versus placebo. A composite cardiorenal outcome and its CVD and renal components were assessed during the 3-year follow-up.

RESULTS — Compared with placebo, neither ramipril (15.7% [412 of 2,623] vs. 16.0% [424 of 2,646]; hazard ratio [HR] 0.98 [95% CI 0.84–1.13]; $P = 0.75$) nor rosiglitazone (15.0% [394 of 2,635] vs. 16.8% [442 of 2,634]; 0.87 [0.75–1.01]; $P = 0.07$) reduced the risk of the cardiorenal composite outcome. Ramipril had no impact on the CVD and renal components. Rosiglitazone increased heart failure (0.53 vs. 0.08%; HR 7.04 [95% CI 1.60–31.0]; $P = 0.01$) but reduced the risk of the renal component (0.80 [0.68–0.93]; $P = 0.005$); prevention of diabetes was independently associated with prevention of the renal component ($P < 0.001$).

CONCLUSIONS — Ramipril did not alter the cardiorenal outcome or its components. Rosiglitazone, which reduced diabetes, also reduced the development of renal disease but not the cardiorenal outcome and increased the risk of heart failure.

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The Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial randomly allocated people with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) without known cardiovascular disease (CVD) or significant renal disease to the ACE inhibitor ramipril or placebo and the thiazolidinedione rosiglitazone or placebo, according to a 2 × 2 factorial design (1). After a median 3-year follow-up, ramipril did not significantly reduce the primary outcome of diabetes or death compared with placebo; however, it modestly reduced postload glucose levels and increased regression of IGT or IFG to normoglycemia (2). During the same period, rosiglitazone reduced the primary outcome by 60%, decreased fasting and postload glucose levels, and increased regression to normoglycemia (3). Neither medication affected CVD events overall; however, 0.5% of participants allocated to rosiglitazone vs. 0.1% of those allocated to placebo developed congestive heart failure.

IFG and IGT are both risk factors for CVD (4,5); however, people with IFG or IGT with CVD were excluded from this trial because of the known cardiovascular benefits of ACE inhibitors (6). As such, few CVD events were expected to accrue and the protocol prespecified a composite cardiorenal secondary outcome comprising either cardiovascular or renal events. The effects of ramipril and rosiglitazone on this composite outcome and its components are described herein.

RESEARCH DESIGN AND METHODS

— The DREAM trial design has been reported previously (1–3). Briefly, nondiabetic men and women aged ≥30 years with IFG (fasting plasma glucose between 110 and 126 mg/dl [6.1–7.0 mmol/l]) and/or IGT (2-h post 75-g oral load with plasma glucose between 140 and 200 mg/dl [7.8–11.0 mmol/l]) were recruited from 191 centers between July 2001 and August 2003. Key exclusion criteria were known left ventricular ejection <40% or congestive heart failure, documented CVD defined as ischemic heart disease, stroke, intermittent claudication with an ankle/arm pressure index of ≤0.8, uncontrolled hypertension requiring ACE inhibitors or angio-

From the DREAM Trial Study Group, Population Health Research Institute, Hamilton, Canada.
Corresponding author: Gilles R. Dagenais, MD, Laval University Heart and Lung Institute, 2725 Chemin Ste-Foy, Quebec, Quebec City, Canada G1V 4G5. E-mail: gilles.dagenais@crhl.ulaval.ca.
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*A complete list of the DREAM Trial Investigators can be found in the APPENDIX.
Abbreviations: CVD, cardiovascular disease; DREAM, Diabetes REduction Assessment with ramipril and rosiglitazone Medication; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HOPE, Heart Outcomes Prevention Evaluation; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MI, myocardial infarction.

tensin-2 receptor blockers, known renal artery stenosis, known creatinine clearance <0.6 ml/s, a serum creatinine ≥2.26 mg/dl (200 μmol/l), or clinical proteinuria. The protocol was approved by each center's ethics committee, and all participants provided written informed consent.

Evaluation, randomization, and follow-up

At baseline, participants were briefly examined and answered a standardized questionnaire regarding their medical history, current CVD symptoms, medication use, and cardiovascular and renal therapies. After randomization, participants were allocated to either 5 mg/day ramipril for 2 months, 10 mg/day for 10 months and subsequently 15 mg/day, or matching placebo and either 4 mg/day rosiglitazone for 2 months and 8 mg/day thereafter or matching placebo. Study visits occurred at 2 and 6 months and every 6 months subsequently. The median follow-up period was 3 years.

Clinical events were ascertained at each visit. Supine resting blood pressure and heart rate were measured at baseline, 2 months, 12 months, and every 12 months thereafter; electrocardiograms (ECGs) were recorded at baseline, at 2 years, and at study end. A serum and first-morning urine sample were taken at baseline and study end and sent to the central laboratory for measurement of serum creatinine and a urinary albumin-to-creatinine ratio. Estimated glomerular filtration rate (eGFR) was calculated according to Cockroft and Gault based on the participant's serum creatinine, age, sex, and weight.

Urine and serum creatinine were measured with a Roche Hitachi 917 analyzer, and urine albumin was measured by a Federal Drug Administration–approved size exclusion high-performance liquid chromatography method. Because the high-performance liquid chromatography method detects greater amounts of albumin in the urine than the immunoassay and is less likely to underestimate albumin fragments in people with diabetes (7,8), albumin-to-creatinine ratio thresholds for microalbuminuria and clinical proteinuria that corresponded to immunoassay thresholds of 2.0 and 36 mg/mmol, respectively (prespecified in the DREAM protocol), were identified by comparing high-performance liquid chromatography and immunoassay analysis of urine from the Heart Outcome, Prevention Evaluation (HOPE) (9–11)

Study outcomes

The prespecified composite cardiorenal outcome included either *1*) a composite cardiovascular outcome defined as the first occurrence of any cardiovascular death, successful cardiac resuscitation, nonfatal myocardial infarction (MI), stroke, revascularization procedure, new stable or unstable angina with documented ischemia, or heart failure or *2*) a composite renal outcome defined as any of the following: progression from normoalbuminuria to either microalbuminuria or proteinuria or from microalbuminuria to proteinuria, a decrease in eGFR of ≥30%, or renal insufficiency requiring dialysis or transplantation. Microalbuminuria was defined as a single first-morning albumin-to-creatinine ratio >4.4 mg/mmol and <36 mg/mmol. Clinical proteinuria was defined as either an albumin-to-creatinine ratio ≥36 mg/mmol or an adjudicated report of clinical proteinuria. Regression from microalbuminuria to normoalbuminuria was also assessed.

Cardiovascular death included sudden cardiovascular death, death due to MI, stroke, heart failure, arrhythmia, vascular disease (pulmonary embolism or aortic rupture), presumed CVD (death not fulfilling all criteria for MI or stroke), or death of unknown cause. The diagnosis of MI required *1*) a troponin level that was at least twice the lower level signifying necrosis or a creatine kinase MB isoenzyme level that was ≥1.5 times the upper-normal limit or other cardiac enzymes at least twice the upper-normal limit and *2*) either acute ischemic ECG changes or ischemic chest pain lasting at least 10 min. The diagnosis of stroke required an acute localized neurological deficit lasting at least 24 h and imaging for its etiologic type. Heart failure required hospitalization or an emergency stay during 2 consecutive calendar days due to heart failure with two of the three following criteria: *1*) signs and/or symptoms of heart failure, *2*) radiological evidence of pulmonary congestion, or *3*) use of diuretics or inotropes or vasodilator agents. All events were adjudicated by cardiologists and endocrinologists blinded to the study medications, including three new CVD cases of angina (one on rosiglitazone alone, one on ramipril alone, and one on double placebo) that were not listed in the original DREAM publications as they occurred during the active phase but were only identified during the final closeout of the clinical sites following the posttrial washout phase.

Statistical analysis

Student's *t* test and χ^2 tests were used for univariate comparisons of continuous and categorical variables, respectively. Participants without urine and serum samples at the end of the study were considered to have values that did not differ from baseline. Individuals for whom CVD status was unavailable at the final visit were censored at the time of their last visit. Cox proportional hazards models were used to estimate the effect of each of the study drugs stratified for the other drug on the hazard ratios (HRs) of CVD outcomes, and the possibility of statistical interaction between the two study drugs on these outcomes was assessed by including an interaction term in the model. HRs and 95% CIs were calculated with corresponding two-sided *P* values. The HRs for cardiorenal and renal outcomes were calculated using logistic regression models adjusting for the effect of the other drug. Cox models for these outcomes could not be used because the cardiorenal and renal outcomes were only assessed in all participants at the end of the study. Logistic regression models were also constructed to determine whether prevention of diabetes with rosiglitazone may have also prevented the composite renal outcome (the dependent variable). In the first model, incident diabetes (during the DREAM median follow-up period of 3 years) and rosiglitazone allocation were included as independent variables. In the second model, diabetes was replaced by time of diabetes development, classified as either occurring in the first 1.5 years of follow-up, after 1.5 years, or never. Ramipril allocation, baseline albumin-to-creatinine ratio, and baseline calculated eGFR were also included as independent variables in these two models. Interactions were tested by including an interaction term in the model.

RESULTS — CVD status at trial end was available for 98% of randomized participants. A final visit urine albumin-to-creatinine value and a serum creatinine value were available for 4,106 (78%) and 4,236 (80%) participants, respectively. Compared with the participants who had a final renal ascertainment, those who did not were younger (53.5 vs. 55.0 years, $P = 0.0013$), more likely to be women

Table 1—*Baseline characteristics of participants with and without cardiorenal, cardiovascular, and renal outcomes*

	Cardiorenal		Cardiovascular		Renal	
Characteristic	Yes	No	Yes	No	Yes	No
n	836 (100)	4,433 (100)	133 (100)	5,136 (100)	718 (100)	4,551 (100)
Age (years)	57.4 ± 11.2	54.2 ± 10.8*	62.9 ± 10.0	54.5 ± 10.9*	56.4 ± 11.1	54.4 ± 10.9*
Women	521 (62.3)	2,599 (58.6)†	60 (45.1)	3,060 (59.6)‡	472 (65.7)	2,648 (58.2)*
Isolated IFG	110 (13.2)	629 (14.2)	17 (12.8)	722 (14.1)	95 (13.2)	644 (14.2)
Isolated IGT	459 (54.9)	2,568 (57.9)	62 (46.6)	2,965 (57.7)§	408 (56.8)	2,619 (57.6)
IFG + IGT	267 (32.0)	1,236 (27.9)†	54 (40.6)	1,449 (28.2)§	215 (29.9)	1,288 (28.3)
Fasting blood glucose (mmol/l)	5.88 ± 0.67	5.82 ± 0.66†	6.01 ± 0.66	5.83 ± 0.66§	5.85 ± 0.67	5.83 ± 0.66
2-h post 75-g glucose (mmol/l)	8.74 ± 1.43	8.67 ± 1.43	8.80 ± 1.49	8.68 ± 1.43	8.73 ± 1.43	8.68 ± 1.43
Serum creatinine (mmol/l)	74.5 ± 22.2	75.6 ± 16.5	83.7 ± 20.5	75.3 ± 17.4	72.9 ± 22.0	75.9 ± 16.7‡
Microalbuminuria	96 (11.6)	895 (20.9)*	37 (29.1)	954 (19.1)§	62 (8.7)	929 (21.1)*
Hypercholesterolemia	307 (36.7)	1,564 (35.3)	64 (48.1)	1,807 (35.2)§	249 (34.7)	1,622 (35.6)
History of hypertension	428 (51.2)	1,863 (42.0)*	87 (65.4)	2,204 (42.9)*	355 (49.4)	1,936 (42.5)§
Systolic blood pressure (mmHg)	138.4 ± 17.9	135.7 ± 18.4‡	142.2 ± 18.4	135.9 ± 18.3*	137.7 ± 17.6	135.8 ± 18.5†
Diastolic blood pressure (mmHg)	83.4 ± 10.4	83.4 ± 10.9	84.1 ± 10.6	83.4 ± 10.8	83.3 ± 10.4	83.4 ± 10.8
Ankle brachial index	1.21 ± 0.17	1.22 ± 0.18	1.19 ± 0.20	1.19 ± 0.20	1.21 ± 0.16	1.22 ± 0.18
BMI (kg/m^2)	31.0 ± 5.7	30.9 ± 5.6	30.5 ± 5.6	30.9 ± 5.6	31.0 ± 5.6	30.9 ± 5.6
Waist-to-hip ratio (men)	0.96 ± 0.06	0.96 ± 0.07	0.97 ± 0.06	0.96 ± 0.07	0.96 ± 0.06	0.96 ± 0.07
Waist-to-hip ratio (women)	0.87 ± 0.08	0.87 ± 0.08	0.88 ± 0.08	0.87 ± 0.08	0.87 ± 0.08	0.87 ± 0.08
Current smokers	110 (13.2)	532 (12.0)	18 (13.5)	624 (12.2)	94 (13.1)	548 (12.0)
Alanine aminotransferase units/l	27.2 ± 14.6	29.2 ± 16.5§	26.9 ± 13.6	28.9 ± 16.3	27.2 ± 14.8	29.1 ± 16.5§
ECG-LVH with sign of overload	25 (3.0)	51 (1.2)*	11 (8.3)	65 (1.3)*	18.0 (2.5)	58.0 (1.3)§
Aspirin or antiplatelets	150 (18.0)	604 (13.6)‡	33 (24.8)	721 (14.0)‡	120 (16.7)	634 (13.9)†
Thiazide	94 (11.3)	419 (9.5)	25 (18.8)	488 (9.5)‡	72 (10.0)	441 (9.7)
Other diuretics	71 (8.5)	203 (4.6)*	20 (15.0)	254 (5.0)*	52 (7.3)	222 (4.9)§
Aldactone	10 (1.2)	30 (0.7)	4 (3.0)	36 (0.7)§	8 (1.1)	32 (0.7)
Angiotensin receptor blockers	48 (5.7)	238 (5.4)	14 (10.5)	272 (5.3)§	36 (5.0)	250 (5.5)
β-Blockers	174 (20.8)	738 (16.6)§	36 (27.1)	876 (17.1)§	143 (19.9)	769 (16.9)†
Calcium channel blockers	152 (18.2)	525 (11.8)*	35 (26.3)	642 (12.5)*	122 (17.0)	555 (12.2)‡
α-Blockers	18 (2.2)	90 (2.0)	3 (2.3)	105 (2.0)	15 (2.1)	93 (2.0)
Lipid-lowering agents	132 (15.8)	648 (14.6)	32 (24.1)	748 (14.6)§	102 (14.2)	678 (14.9)

Data are means ± SD or *n* (%). *$P < 0.0001$; †$P < 0.05$; ‡$P < 0.001$; §$P < 0.01$. LVH, left ventricular hypertrophy.

(62.1 vs. 58.6%, $P = 0.042$), had a lower fasting plasma glucose (5.78 vs. 5.85 mmol/l, $P = 0.004$), a higher 2-h glucose level (8.80 vs. 8.66 mmol/l, $P = 0.006$), a lower serum creatinine (74.3 vs. 75.7 mg/dl, $P = 0.04$), were more likely to be smokers (14.8 vs. 11.6%, $P = 0.004$), and took less aspirin (12.1 vs. 14.8%, $P = 0.023$) and lipid-lowering agents (12.5 vs. 15.4%, $P = 0.020$).

Cardiorenal outcome

During the 3-year follow-up, 836 participants had a first occurrence of the composite cardiorenal outcome, comprising 133 (2.5%) cardiovascular composite outcomes and 718 (13.6%) renal composite outcomes. The composite cardiorenal outcome occurred in *1*) 412 of 2,623 (15.7%) participants allocated to ramipril and 424 of 2,646 (16.0%) participants allocated to placebo (HR 0.98 [95% CI 0.84–1.13]; $P = 0.75$) and *2*) 394 of 2,635 (15.0%) participants allocated to rosiglitazone and 442 of 2,634 (16.8%) allocated to placebo (0.87 [0.75–1.01]; $P = 0.07$). The baseline characteristics of the participants with and without cardiorenal events and their components are shown in Table 1. There was no statistically significant interaction between the effects of ramipril and rosiglitazone on the cardiorenal outcome ($P = 0.09$). Event rates by each cell of the factorial design were *1*) 15.6% (204 of 1,310) for rosiglitazone and ramipril, *2*) 15.7% (207 of 1,313) for ramipril and placebo, *3*) 14.3% (189 of 1,325) for rosiglitazone and placebo, and *4*) 17.8% (235 of 1,321) for placebo and placebo.

Cardiovascular component

Ramipril did not alter the rate of cardiovascular events or the composite of cardiovascular death, nonfatal MI or stroke, or any individual cardiovascualr event. Similarly, rosiglitazone did not reduce the overall risk of cardiovascular events but significantly increased the risk for heart failure (Table 2). There was no interaction for the cardiovascular component outcomes between ramipril and rosiglitazone ($P = 0.07$). Event rates by each cell of the factorial design were 3.4% (45 of 1,310) for rosiglitazone and ramipril, 1.8% (24 of 1,313) for ramipril and placebo, 2.4% (32 of 1,325) for rosiglitazone and placebo, and 2.4% (32 of 1,321) for placebo and placebo.

The 16 patients who had heart failure were at greater risk for cardiovascular events than the other DREAM participants. They were older (67.5 vs. 54.7 years), had higher systolic blood pressure (147.5 vs. 136.1 mmHg), and more often had a history of hypertension (94 vs. 43%) and left ventricular hypertrophy on ECG tracing (25 vs. 5%). They were also taking more antiplatelets, diuretics, β-blockers, angiotensin receptor blockers, lipid-lowering agents, and calcium channel blockers. Data extracted from the

Table 2—*Cardiovascular component of the cardiorenal composite*

Event	Ramipril	Placebo	HR (95% CI)	Rosiglitazone	Placebo	HR (95% CI)
Cardiovascular composite	69 (2.6)	64 (2.4)	1.09 (0.78–1.53)*	77 (2.9)	56 (2.1)	1.38 (0.98–1.95)†
Cardiovascular death	12 (0.5)	10 (0.4)	1.21 (0.52–2.80)	12 (0.5)	10 (0.4)	1.20 (0.52–2.77)
MI	14 (0.5)	11 (0.4)	1.29 (0.59–2.84)	16 (0.6)	9 (0.3)	1.78 (0.79–4.03)
Stroke	4 (0.2)	8 (0.3)	0.50 (0.15–1.66)	7 (0.3)	5 (0.2)	1.40 (0.44–4.40)
Congestive heart failure	12 (0.5)	4 (0.2)	3.06 (0.99–9.48)	14 (0.5)	2 (0.1)	7.04 (1.60–31.0)
Revascularization	28 (1.1)	38 (1.4)	0.74 (0.46–1.21)	37 (1.4)	29 (1.1)	1.27 (0.78–2.07)
New angina	24 (0.9)	20 (0.8)	1.21 (0.67–2.19)	24 (0.9)	20 (0.8)	1.20 (0.66–2.17)
Cardiovascular death, MI, or stroke	27 (1.0)	29 (1.1)	0.94 (0.56–1.59)*	33 (1.3)	23 (0.9)	1.43 (0.84–2.44)*
Total mortality	31 (1.2)	32 (1.2)	0.98 (0.60–1.61)*	30 (1.1)	33 (1.3)	0.91 (0.56–1.49)*

Data are *n* (%) unless otherwise indicated. Revascularization = interventions on either coronary or peripheral arteries. The cardiovascular composite outcome represents the first occurrence of cardiovascular death, MI, or stroke. For the other individual events, all participants with an event are included in each row. *$P >$ 0.1; †$P = 0.067$

documentation provided for adjudication of the 16 participants with heart failure showed that *1*) three cases were associated with severe valvular heart disease, *2*) four were associated with an acute coronary syndrome, *3*) two were associated with a left ventricular ejection fraction <40%, and *4*) two were associated with atrial fibrillation. Of 14 participants who developed heart failure on rosiglitazone, medication was discontinued in 9 subjects, 2 subjects died (1 postoperatively following aortic valve replacement and coronary artery bypass graft surgery and 1 due to acute MI associated with the heart failure), and 1 subject with renal failure had recurrent heart failure despite having discontinued rosiglitazone at the time of the first episode.

Renal component

Ramipril did not alter the renal component of the composite outcome (Table 3). Rosiglitazone reduced this component by 20% due to a reduction in progression of albuminuria, but the fall in eGFR by ≥30% was not significant (Table 3). In a logistic model that also included rosiglitazone allocation, ramipril allocation, baseline albumin/creatinine ratio, and the baseline eGFR, the renal outcome was independently associated with both incident diabetes (HR 1.42 [95% CI 1.16–1.74]; $P < 0.001$) and allocation to rosiglitazone (0.83 [0.70–0.98]; $P = 0.027$); this HR remained unchanged when incident diabetes was replaced by mean fasting plasma glucose in the equation. This possible relationship between prevention of diabetes with rosiglitazone and prevention of the renal outcome was explored by replacing diabetes by time of diabetes development. After controlling for allocation to rosiglitazone and the other variables, developing diabetes within the first 1.5 years of follow-up was associated with a 1.59-fold higher risk of the renal outcome (95% CI 1.16–2.17) ($P = 0.0039$) versus remaining free of diabetes; developing diabetes after 1.5 years was associated with a 1.34-fold higher risk (1.05–1.71) ($P = 0.0019$). There was no interaction for the renal component outcomes between ramipril and rosiglitazone ($P = 0.2$). Event rates by each cell of the factorial design were *1*) 12.7% (166 of 1,310) for rosiglitazone and ramipril, *2*) 14.2% (186 of 1,313) for ramipril and placebo, *3*) 11.8% (157 of 1,325) for rosiglitazone and placebo, and *4*) 15.7% (208 of 1,321) for placebo and placebo.

CONCLUSIONS — The DREAM trial excluded people with IFG and/or IGT who had CVD because of the known benefits of ramipril on CVD. As such, when the trial was designed *1*) it was recognized that there would be a low CVD event rate that would not provide sufficient power to detect even modest effects on CVD (an assumption confirmed by the low 2.5% CVD incidence) and *2*) a composite cardiorenal secondary outcome that would yield a higher event rate was prespecified. Neither ramipril nor rosiglitazone significantly affected this cardiorenal composite outcome, and ramipril did not alter its cardiovascular or renal components. However, rosiglitazone significantly reduced the renal component of this outcome but increased the risk of heart failure.

The fact that ramipril reduces cardiovascular outcomes and progression of albuminuria in people at high risk of CVD has been clearly shown in the HOPE study (10,11). This effect was attributed to the modulation of the renin-

Table 3—*Renal component of the cardiorenal composite*

Event	Ramipril	Placebo	HR (95% CI)	Rosiglitazone	Placebo	HR (95% CI)
Renal composite	353 (13.5)	365 (13.8)	0.97 (0.83–1.14)*	324 (12.3)	394 (15.0)	0.80 (0.68–0.93)†
Albuminuria progression	267 (10.2)	287 (10.9)	0.93 (0.78–1.11)*	253 (9.6)	301 (11.4)	0.82 (0.69–0.98)‡
Normal to microalbuminuria	253 (9.7)	273 (10.3)	0.93 (0.77–1.11)	241 (9.2)	285 (10.8)	0.83 (0.69–0.99)
Normal to proteinuria	5 (0.19)	4 (0.15)	1.26 (0.34–4.71)	6 (0.23)	3 (0.11)	2.00 (0.50–8.01)
MA to proteinuria	9 (0.34)	10 (0.39)	0.91 (0.37–2.24)	6 (0.23)	13 (0.49)	0.46 (0.18–1.21)
Decreased eGFR ≥30%	99 (3.8)	88 (3.3)	1.14 (0.85–1.53)*	82 (3.1)	105 (4.0)	0.77 (0.58–1.04)§
Microalbuminuria regression to normal	204 (53.7)	174 (47.3)	1.30 (0.98–1.74)‖	193 (52.5)	185 (48.7)	1.18 (0.88–1.57)*

Data are *n* (%) unless otherwise indicated. The renal component of the composite is the first occurrence of any of progression of albuminuria, decreased eGFR by ≥30%, or renal insufficiency requiring dialysis or transplantation. For the other individual events, all participants with this event are included in each row. *$P >$ 0.1; †$P = 0.005$; ‡$P = 0.031$; §$P = 0.087$; ‖$P = 0.073$.

angiotensin aldosterone system. The absence of such benefit in the DREAM trial may have been due to the low incidence of CVD (the composite of cardiovascular death, MI, or stroke was documented in only 1% [56 of 5,269] compared with 16% [1,477 of 9,297] in the HOPE study) and the relatively short follow-up of 3 years compared with 4.5 years in the HOPE. Moreover, as the low-risk DREAM participants may have low activation of the renin-angiotensin system, further inhibition with ramipril would be expected to have a minimal effect.

Diabetes is a strong risk factor for renal disease. As the glucose criteria used to diagnose diabetes represent thresholds above which the risk of retinal and renal disease rises rapidly, an intervention that reduces the incidence of diabetes (and therefore the rise of glucose levels past the diabetes thresholds) may also reduce renal disease. This possibility is strongly supported by the following finding: rosiglitazone, which clearly reduced the risk of diabetes, also reduced the risk of renal disease by 20% versus placebo, with consistent changes of the renal outcome. It is also supported by the regression models in which incident diabetes, time of development of diabetes (before or after 1.5 years), and rosiglitazone allocation were independently associated with the renal outcome. Whether additional effects beyond improved metabolic control contributed to the renal effects observed cannot be determined from the present findings.

Rosiglitazone clearly increased the risk of heart failure. Such an effect has been repeatedly noted in other thiazolidinedione studies (12–16) and appears to be due to sodium and water retention at the renal collecting duct noted above, an increased plasma renin activity (17–19) perhaps related in part to a modest fall in blood pressure (20,21), and increased insulin action (20). Two echocardiographic studies (22,23) showed that rosiglitazone did not significantly reduce left systolic ventricular function. Of note is the fact that the actual 0.5% incidence of heart failure with rosiglitazone during this 3-year trial of people at low risk for cardiovascular outcomes was lower than the 1.5% (12), 1.7% (15), and 5.7% (16) incidence reported in similar length thiazolidinedione trials of people at higher risk of cardiovascular outcomes. Nevertheless, the high relative risk of heart failure represents new evidence that low-risk people are not protected from this side effect.

The lack of a clear cardiorenal benefit (due to no effect on the cardiovascular component of the composite) was surprising in light of the many favorable effects of rosiglitazone on surrogate markers of CVD (15,20,21,24). It is possible that the short follow-up period and the low cardiovascular outcome incidence were insufficient to allow a modest cardiovascular effect to emerge. Alternatively, rosiglitazone may have a neutral effect on ischemic CVD events. Indeed, there have been recent concerns that it may increase the risk of ischemic CVD (25), but the absence of any clear cardiovascular benefit or harm of rosiglitazone in an interim analysis of a large cardiovascular trial (15) have fueled uncertainty regarding its effects on ischemic CVD and highlight the need for large trials with sufficient power to resolve this dilemma.

Strengths of our study include the fact that all of the measured outcomes were prospectively defined, collected, and adjudicated. The findings are limited by the fact that renal outcomes were only available in 78% of participants at study end.

In summary, the DREAM trial showed no significant impact of ramipril on the composite cardiorenal outcome or its cardiovascular or renal components. It also did not show an effect of rosiglitazone on the cardiorenal outcome or its cardiovascular component, but it increased heart failure. However, rosiglitazone did reduce the renal component of this outcome, one of the consequences of diabetes, in addition to reducing the incidence of diabetes itself.

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APPENDIX

Writing committee

G.R. Dagenais, H.C. Gerstein, R. Holman, A. Budaj, A. Escalante, T. Hedner, M. Keltai, E. Lonn, S. McFarlane, M. McQueen, K. Teo, P. Sheridan, J. Bosch, J. Pogue, S. Yusuf

Steering committee

H.C. Gerstein (Co-chair and Co-PI), S. Yusuf (Co-chair and Co-PI), R.R. Holman (European Co-chair), J. Bosch (Project Director), S. Anand, A. Avezum, A. Budaj, J.L. Chiasson, I. Conget, G. Dagenais, M. Davies, 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. Piegas, J. Probstfield, I. Schmid, J. Shaw, K. Teo, P. Zimmet, B. Zinman

Site investigators and study coordinators by country

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, S. Fernandez, M. Fernandez, A. 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, J. Llanos, A. Liberman, 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.

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Canada. G.R.D., C. Abbott, A. Abu-Bakare, R. Allison, S. Anand, T. Anderlic, D. Auger, A. Barnie, J Beauchef, S. Beers, A. Belanger, 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.L. 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

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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 Mo-

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DREAM project offices

Global. J.B., N. Barr, C. Choppick, D. Desai, J. George, H.C.G., P. Khatib, K. Killman, L. MacRae, S. MacRae, F. Pasha, J.P., U. Rangachari, V. Reiding, D. Robinson, L. Santarelli, J. Shannon, P.S., S.Y.; Argentina: A. Pascual, C. Rovito; Australia: B. Fricke, E. McBride, S. Richmond; Brazil: P. Smith; Canada: L. Frenette, A. Magi; Chile: A. Montecinos; Europe: R.R.H., J. Keenan, J. Starrett; Finland: J. Ramo, M. Tarvainen; Germany: A. Güth, B. Weise; Hungary: K. K.; India: V. Kumar H.G; Latvia: I. Balode, G. Zilgalve; Mexico: I. Garcia, P. Liceaga, A. Moreno; Norway: G. Bratten, I. Ronning; Poland: W. Nowak; Slovaki: W. West; Spain: B. Margo, O. Martinez; Sweden: G. Dahl; Netherlands: Y. Bookelmann, M. Schoonhoven; Turkey: Z. Cetin; U.S.: 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

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