# Effects of Ramipril and Rosiglitazone on Cardiovascular and Renal Outcomes in People with Impaired Glucose Tolerance or Impaired Fasting Glucose: A Randomized, Controlled Trial. Results of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) study

## The DREAM Trial Investigators*

**Running Title:** Ramipril, Rosiglitazone, cardiovascular and renal disease

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# ABSTRACT

*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) study.

*RESEARCH DESIGN AND METHODS:* 5269 people aged $\geq$ 30 years, with IGT and/or IFG without known CVD or renal insufficiency were randomized to ramipril 15 mg/day vs. placebo, and rosiglitazone 8 mg/day vs. placebo. A composite cardio-renal outcome and its CVD and renal components were assessed during the 3-year follow-up.

*RESULTS:* Compared to placebo, neither ramipril [15.7%, (412/2623) vs. 16.0%, (424/2646)] [Hazard ratio (HR) 0.98 (95% CI, 0.84 - 1.13) $P = 0.75$], nor rosiglitazone [15.0% (394/2635) vs. 16.8% (442/2634)] [HR 0.87 (CI, 0.75 - 1.01) $P = 0.07$] reduced the risk of the cardio-renal composite outcome. Ramipril had no impact on the CVD and renal components. Rosiglitazone increased heart failure [0.53 vs. 0.08%, HR 7.04 (CI, 1.60 - 31.0) $P = 0.01$] but reduced the risk of the renal component [HR 0.80 (CI, 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 cardio-renal outcome or its components. Rosiglitazone, which reduced diabetes, also reduced the development of renal disease but not the cardio-renal outcome and increased the risk of heart failure.

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 angiotensin converting enzyme (ACE) inhibitor ramipril or placebo, and the thiazolidinedione rosiglitazone or placebo according to a 2 X 2 factorial design (1). After a median 3-year follow-up, ramipril did not significantly reduce the primary outcome of diabetes or death compared to placebo; however, it modestly reduced post-load 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 post-load 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 pre-specified a composite "cardio-renal" secondary outcome comprising either cardiovascular (CV) 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 or over with IFG [fasting plasma glucose between 110 and 126 mg/dL (6.1-7.0 mmol/L)] and/or IGT [2-hour 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 or less, uncontrolled hypertension requiring ACE inhibitors or angiotensin-2 receptor blockers; known renal artery stenosis; known creatinine clearance < 0.6 ml/s, a serum creatinine $\geq$ 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, cardiovascular and renal therapies. After randomization participants were allocated to either ramipril 5 mg/day for 2 months, 10 mg/day for 10 months and subsequently 15 mg/day, or matching placebo, or either rosiglitazone 4 mg/day for 2 months and 8 mg/day thereafter, or matching placebo. Study visits occurred at 2 months, 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, 2 years and 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/creatinine ratio. Estimated glomerular filtration rate (eGFR) was calculated according to Cockroft

and Gault based on the participant's serum creatinine, age, gender 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 (HPLC) method. As the HPLC method detects greater amount of albumin in the urine than the immunoassay and is less likely to underestimate albumin fragments in people with diabetes (7, 8), albumin/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 HPLC and immunoassay analysis of urine from the Heart Outcome Prevention Evaluation (HOPE) (9 - 11)

## STUDY OUTCOMES

The pre-specified composite cardio-renal outcome included either: a) a composite CV outcome defined as the first occurrence of any CV death, successful cardiac resuscitation, non-fatal myocardial infarction (MI), stroke, revascularization procedure, new stable or unstable angina with documented ischemia, or heart failure; or b) a composite renal outcome defined as any of: i) progression from normoalbuminuria to either microalbuminuria or proteinuria, or from microalbuminuria to proteinuria; ii) a decrease in eGFR of 30% or more; or iii) renal insufficiency requiring dialysis or transplantation. Microalbuminuria was defined as a single first morning albumin/creatinine ratio > 4.4 mg/mmol and < 36 mg/mmol. Clinical proteinuria was defined as either an albumin/creatinine ratio > 36 mg/mmol or an adjudicated report of clinical proteinuria. Regression from microalbuminuria to normoalbuminuria was also assessed.

CV death included sudden CV death, death due to MI, stroke, heart failure, arrhythmia, vascular disease (pulmonary embolism, aortic rupture), presumed CVD (death not fulfilling all criteria for MI or stroke) or death of unknown cause. The diagnosis of MI required: a) a troponin level that was > twice the lower level signifying necrosis or a creatine kinase MB level that was > 1.5 times the upper normal limit or other cardiac enzymes > twice the upper normal limit; and b) either acute ischemic ECG changes or ischemic chest pain lasting at least 10 minutes. The diagnosis of stroke required an acute localized neurological deficit lasting at least 24 hours and imaging for its etiologic type. Heart failure required hospitalization or an emergency stay during two consecutive calendar days due to heart failure with 2 of the 3 following criteria: a) signs and/or symptoms of heart failure, b) radiological evidence of pulmonary congestion or c) use of diuretics or inotropes or vasodilator agents. All events were adjudicated by cardiologists and endocrinologists blinded to the study medications, including 3 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 close-out of the clinical sites following the post-trial washout phase.

## STATISTICAL ANALYSIS

Student's t test and chi square tests were used for univariate comparisons of continuous and categorical variables respectively. Participants without urine and serum sample 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 (HR) 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. HR and 95% confidence intervals (CI) were calculated with corresponding two-sided $P$ values. The HRs for cardio-renal 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 as the cardio-renal and renal outcomes were only assessed in all participants at the end of the study. Logistic regression models were also constructed to determine if 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/creatinine ratio and baseline calculated eGFR were also included as independent variables in these 2 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/creatinine value and a serum creatinine value were available for 4106 (78%) and 4236 (80%) participants respectively. In comparison to 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 (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-hour 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%, $P = 0.004$), took less aspirin (12.1 vs 14.8%, $P = 0.023$) , and lipid lowering agents (12.5 vs. 15.4%, $P = 0.020$).

***Cardio-renal outcome.*** During the 3-year follow-up, 836 participants had a first occurrence of the composite cardio-renal outcome, comprising 133 (2.5%) CV composite outcomes and 718 (13.6%) renal composite outcomes. The composite cardio-renal outcome occurred in a) 412/2623 (15.7%) participants allocated to ramipril and 424/2646 (16.0%) allocated to placebo [HR 0.98 (95% CI, 0.84 - 1.13) $P = 0.75$] and b) 394/2635 (15.0%) participants allocated to rosiglitazone and 442/2634 (16.8%) allocated to placebo [HR 0.87 (0.75 - 1.01) $P = 0.07$]. The baseline characteristics of the participants with and without cardio-renal events and their components are shown in Table 1. There was no statistically significant interaction between the effects of ramipril and rosiglitazone on the cardio-renal outcome ($P = 0.09$). Event rates by each cell of the factorial design were: a) 15.6% (204/1310) for rosiglitazone and ramipril; b) 15.7% (207/1313) for ramipril and placebo; c) 14.3% (189/1325) for rosiglitazone and placebo; and d) 17.8% (235/1321) for placebo and placebo.

***Cardiovascular component.*** Ramipril did not alter the rate of CV events or the composite of CV death, non-fatal MI or stroke, or any individual CV event. Similarly, rosiglitazone did not reduce the overall risk of CV events but significantly increased the risk for heart failure (Table 2). There was no interaction for the CV component outcomes between ramipril and rosiglitazone ($P = 0.07$). Event rates by each cell of the factorial design were: a) 3.4% (45/1310) for rosiglitazone and ramipril; b) 1.8% (24/1313) for ramipril and placebo; c) 2.4% (32/1325) for rosiglitazone

and placebo; and d) 2.4% (32/1321) for placebo and placebo.

The 16 patients who had heart failure were at greater risk for CV 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), 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, betablockers, angiotensin receptor blockers, lipid lowering agents and calcium channel blockers. Data extracted from the documentation provided for adjudication of the 16 participants with heart failure showed that a) 3 cases were associated with severe valvular heart disease, b) 4 with an acute coronary syndrome, c) 2 with a left ventricular ejection fraction < 40%, and d) 2 with atrial fibrillation. Of the 14 participants who developed heart failure on rosiglitazone, medication was discontinued in 9, 2 died (one post–operatively following aortic valve replacement and coronary artery bypass graft surgery, and one death due to acute MI associated with the heart failure); one patient 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 (1.16 - 1.74) $P < 0.001$] and allocation to rosiglitazone [HR 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 [(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: a) 12.7% (166/1310) for rosiglitazone and ramipril; b), 14.2% (186/1313) for ramipril and placebo; c) 11.8% (157/1325), for rosiglitazone and placebo; and d) 15.7% (208/1321) 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: a) it was recognized that there would be a low CVD event rate which would not provide sufficient power to detect even modest effects on CVD – an assumption confirmed by the low 2.5% CVD incidence; and b) a composite cardio-renal secondary outcome that would yield a higher event rate was prespecified. Neither ramipril nor rosiglitazone significantly affected this cardio-renal composite outcome, and ramipril did not alter its CV 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 CV 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-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 CV death, MI or stroke was documented in only 1% (56/5269) compared to 16% (1477/9297) in HOPE] and the relatively short follow-up of 3 years compared to 4.5 years in 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 mellitus 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 these findings: 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 showed that rosiglitazone did not significantly reduce left systolic ventricular function (22,23). 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 CV 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 CV 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 cardio-renal benefit (due to no effect on the CV 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 CV outcome incidence were insufficient to allow a modest CV effect to emerge. Alternatively, rosiglitazone may have a neutral effect on ischemic CVD events. Indeed, recent concerns that it may increase the risk of ischemic CVD (25) but the absence of any clear CV benefit or harm of rosiglitazone in an interim analysis of a large CV 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 study showed no significant impact of ramipril on the composite cardio-renal outcome or its cardiovascular or renal components. It also did not show an effect of rosiglitazone on the cardio-renal 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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# REFERENCES

1.      The DREAM Trial Investigators: Rationale, design and recruitment characteristics of a large simple, international trial of diabetes prevention: the DREAM trial. *Diabetologia* 47: 1519-1527, 2004

2.      The DREAM Trial Investigators: Effect of ramipril on the incidence of diabetes. *N Engl J Med* 355: 1551-1562, 2006

3.      The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators: Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 368: 1096-1105, 2006

4.      Asia Pacific Cohort Studies Collaboration: Blood glucose and risk of cardiovascular disease in the Asia Pacific region. *Diabetes Care* 27: 2836-2842, 2004

5.      Petersen JL, McGuire DK:  Impaired glucose tolerance and impaired fasting glucose – a review of diagnosis, clinical implications and management.  *Diab Vasc Res* 2: 9-15, 2005

6.      Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S: Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. *Lancet* 368: 581-588, 2006

7.      Brinkman JW, Bakker SJ, Gansevoort RT, Hillege HL, Kema IP, Gans RO, de Jong PE, de Zeeuw D:  Which method for quantifying urinary albumin excretion gives what outcome?  A comparison of immunonephelometry with HPLC.  *Kidney Int Suppl* 92: s69-75, 2004.

8.      Polkinghome KR, Su Q, Chadban SJ, Shaw JE, Zimmet PZ, Atkins RC:  Population prevalence of albuminuria in the Australian Diabetes, Obesity, and Lifestyle (AusDiab) Study: immunonephelometry compared with high performance liquid chromatography.  *Am J Kid Dis* 47:  604-613, 2006

9.      McQueen MJ, Gerstein HC, Pogue J, Mann JFE, Yusuf S: Re-evaluation by high-performance liquid chromatography:  clinical significance of microalbuminuria in individuals at high risk of cardiovascular disease in the Heart Outcomes Prevention Evaluation (HOPE) Study.  *Am J Kidney Dis* 48: 889-896, 2006

10.      The Heart Outcomes Prevention Evaluation Study Investigators: Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 342: 145–153, 2000

11.      The Heart Outcomes Prevention Evaluation (HOPE) Study Investigators:  Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus:  results of the HOPE study and Micro-HOPE substudy.  *Lancet* 355: 253-259, 2000

12.      Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O'Neill MC, Zinman B, Viberti G:  Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 355: 2427-2443, 2006

13.      Kermani S, Garg A**:** Thiazolidinedione-associated congestive heart failure and pulmonary edema. *Mayo Clin Proc* 78: 1088-1091, 2003

14.      Hartung DM, Touchette DR, Bultemeier NC, Haxby DG: Risk of hospitalization for heart failure associated with thiazolidinedione therapy: a Medicaid claims-based case-control study. *Pharmacotherapy* 25: 1329-1336, 2005

15.      Home PD, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefield M, Jones NP, Komajda M, McMurray JJV: Rosiglitazone evaluated for cardiovascular outcomes – an interim analysis. *N Engl J Med* 357: 28-38, 2007

16.     Dormandy J, Charbonnel B, Eckland DJA, Erdmann E, Massi-Benedetti M, Moules IHK, Skene AM, Tan MH, Lefèbvre, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Koranyi L, Laakso M, Mokan M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J: Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomized controlled trial. *Lancet* 366: 1279-1289, 2005

17.     Semenkovich CF: TZDs and diabetes: testing the waters. *Nat Med* 11: 822-824, 2005

18.     Song J, Knepper MA, Hu X, Vedrbalis JG, Ecebarger CA: Rosiglitazone activates renal sodium- and water reabsorptive pathways and lowers blood pressure in normal rats. *J Pharmacol ExpTher* 308: 426-433, 2004

19.     Zanchi A, Chiolero A, Maillard M, Nussaberger J, Brunner HR, Burnbier HR: Effects of the peroxisomal proliferator-activated receptor-gamma agonist pioglitazone on renal and hormonal responses to salt in healthy men. *J Clin Endocrinol Metab* 89: 1140-1145, 2004

20.     Bennett SMA, Agrawal A, Elasha H, Heise M, Jones NP, Walker M, Wilding JPH: Rosiglitazone improves insulin sensitivity, glucose tolerance and ambulatory blood pressure in subjects with impaired glucose tolerance. *Diabet Med* 2: 415-422, 2004

21.     Sarafidis PA, Lasaridis AN: Actions of peroxisome proliferator-activated receptors-gamma agonists explaining a possible blood pressure-lowering effect. *Am J Hypertens* 19**:** 646-653, 2006

22.     St. John Sutton M, Rendell M, Dandona P, Dole JF, Murphy K, Patwardhan R, Patel J, Freed M:  A comparison of the effects of rosiglitazone and glyburide on cardiovascular function and glycemic control in patients with type 2 diabetes. *Diabetes Care* 25: 2058-2064, 2002

23.     Dargie HJ, Hildebrandt PR, Riegger GAJ,  McMurray JJV, McMorn SO, Roberts JN, Zambanini A, Wilding JPH: A randomized, placebo-controlled trial assessing the effects of rosiglitazone on echocardiographic function and cardiac status in type 2 diabetic patients with New York Heart Association Functional class I or II heart failure. *J Am Coll Cardiol* 49: 1696-1704, 2007

24.     Bakris G, Viberti G, Weston Wm, Heise M, Porter LE, Freed MI: Rosiglitazone reduces urinary albumin excretion in type II diabetes. *J Hum Hypertension* 17: 7-12, 2003

25.     Nissen SE, Wolski K: Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 356:2457-2471, 2007

**TABLE 1.** *Baseline characteristics of participants with and without cardio-renal, cardiovascular and renal outcomes*

| Characteristic | Cardio-renal | | Cardiovascular | | Renal | |
|---|---|---|---|---|---|---|
| | Yes | No | Yes | No | Yes | No |
| Numbers | 836 (100) | 4433 (100) | 133 (100) | 5136 (100) | 718 (100) | 4551 (100) |
| Age (years) | 57.4 ± 11.2 | 54.2 ± 10.8[a] | 62.9 ± 10.0 | 54.5 ±10.9[a] | 56.4 ± 11.1 | 54.4 ± 10.9[a] |
| Women | 521 (62.3) | 2599 (58.6)[d] | 60 (45.1) | 3060 (59.6)[b] | 472 (65.7) | 2648 (58.2)[a] |
| 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) | 2568 (57.9) | 62 (46.6) | 2965 (57.7)[c] | 408 (56.8) | 2619 (57.6) |
| IFG+IGT | 267 (32.0) | 1236 (27.9)[d] | 54 (40.6) | 1449 (28.2)[c] | 215 (29.9) | 1288 (28.3) |
| Fasting blood sugar (mmol/L) | 5.88 ± 0.67 | 5.82 ± 0.66[d] | 6.01 ± 0.66 | 5.83 ± 0.66[c] | 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 [0] | 72.9 ± 22.0 | 75.9 ± 16.7[b] |
| Microalbuminuria | 96 (11.6) | 895 (20.9) [a] | 37 (29.1) | 954 (19.1) [c] | 62 (8.7) | 929 (21.1) [a] |
| Hypercholesterolemia | 307 (36.7) | 1564 (35.3) | 64 (48.1) | 1807 (35.2)[c] | 249 (34.7) | 1622 (35.6) |
| History of hypertension | 428 (51.2) | 1863 (42.0)[a] | 87 (65.4) | 2204 (42.9)[a] | 355 (49.4) | 1936 (42.5)[c] |
| Systolic blood pressure (mmHg) | 138.4 ±17.9 | 135.7± 18.4[b] | 142.2 ± 18.4 | 135.9 ±18.3[a] | 137.7 ±17.6 | 135.8± 18.5[d] |
| Diastolic blood pressure (mm/Hg) | 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 |
| Body mass index (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 U/L | 27.2 ±14.6 | 29.2 ± 16.5[c] | 26.9 ± 13.6 | 28.9 ± 16.3 | 27.2 ± 14.8 | 29.1 ± 16.5[c] |
| ECG – LVH  with ST-T changes | 25 (3.0) | 51 (1.2)[a] | 11 (8.3) | 65 (1.3)[a] | 18.0 (2.5) | 58.0 (1.3)[c] |
| Aspirin or antiplatelets | 150 (18.0) | 604 (13.6)[b] | 33 (24.8) | 721 (14.0)[b] | 120 (16.7) | 634 (13.9)[d] |
| Thiazide | 94 (11.3) | 419 (9.5) | 25 (18.8) | 488 (9.5)[b] | 72 (10.0) | 441 (9.7) |
| Other diuretics | 71 (8.5) | 203 (4.6)[a] | 20 (15.0) | 254 (5.0)[a] | 52 (7.3) | 222 (4.9)[c] |
| Aldactone | 10 (1.2) | 30 (0.7) | 4 (3.0) | 36 (0.7)[c] | 8 (1.1) | 32 (0.7) |
| Angiotensin receptor blockers | 48 (5.7) | 238 (5.4) | 14 (10.5) | 272 (5.3)[c] | 36 (5.0) | 250 (5.5) |
| Beta blockers | 174 (20.8) | 738 (16.6)[c] | 36 (27.1) | 876 (17.1)[c] | 143 (19.9) | 769 (16.9)[d] |
| Calcium channel blockers | 152 (18.2) | 525 (11.8)[a] | 35 (26.3) | 642 (12.5)[a] | 122 (17.0) | 555 (12.2)[b] |
| Alpha 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)[c] | 102 (14.2) | 678 (14.9) |

Numbers in parentheses = %; [a] $P< 0.0001$; [b] $P < 0.001$; [c] $P < 0.01$; [d] $P < 0.05$; IFG=impaired fasting glucose, IGT=impaired glucose tolerance, ECG= electrocardiographic, LVH=left ventricular hypertrophy;

**TABLE 2.** *Cardiovascular Component of the Cardio-renal Composite*

| Event | Ramipril | Placebo | HR (95% CI) | Rosiglitazone | Placebo | HR (95% CI) |
|---|---|---|---|---|---|---|
| | N (%) | N (%) | | N (%) | N (%) | |
| CV composite | 69 (2.6) | 64 (2.4) | 1.09 (0.78-1.53)[a] | 77 (2.9) | 56 (2.1) | 1.38 (0.98-1.95)[b] |
|    CV 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) |
|    CHF | 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) |
| CV death, MI or stroke | 27 (1.0) | 29 (1.1) | 0.94 (0.56-1.59)[a] | 33 (1.3) | 23 (0.9) | 1.43 (0.84-2.44)[a] |
| Total mortality | 31 (1.2) | 32 (1.2) | 0.98 (0.60-1.61)[a] | 30 (1.1) | 33 (1.3) | 0.91 (0.56-1.49)[a] |

CV-cardiovascular; MI-myocardial infarction; CHF-congestive heart failure; Revascularization - interventions on either coronary or peripheral arteries. The CV composite outcome represents the first occurrence of CV death, MI or stroke. For the other individual events, all participants with an event are included in each row. [a]P>0.1; [b]P=0.067

**TABLE 3.** **Renal** *Component of the Cardio-renal Composite*

| Event | Ramipril | Placebo | HR (95% CI) | Rosiglitazone | Placebo | HR (95% CI) |
|---|---|---|---|---|---|---|
| | N (%) | N (%) | | N (%) | N (%) | |
| Renal composite | 353 (13.5) | 365 (13.8) | 0.97 (0.83-1.14)[a] | 324 (12.3) | 394 (15.0) | 0.80 (0.68-0.93)[c] |
| Albuminuria Progression | 267 (10.2) | 287 (10.9) | 0.93 (0.78-1.11)[a] | 253 (9.6) | 301 (11.4) | 0.82 (0.69-0.98)[d] |
| Normal to MA | 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 $\geq$ 30% | 99 (3.8) | 88 (3.3) | 1.14 (0.85-1.53)[a] | 82 (3.1) | 105 (4.0) | 0.77 (0.58-1.04)[e] |
| MA regression to normal | 204 (53.7) | 174 (47.3) | 1.30 (0.98-1.74)[b] | 193 (52.5) | 185 (48.7) | 1.18 (0.88-1.57)[a] |

eGFR-estimated glomerular filtration rate; MA-microalbuminuria. The renal component of the composite is the first occurrence of any of progression of albuminuria, decreased eGFR by $\geq$ 30% or renal insufficiency requiring dialysis or transplantation. For the other individual events, all participants with this event are included in each row. [a]P>0.1; [b]P=0.073 [c]P=0.005;[d]P=0.031;[e]P=0.087