An Overview of DREAM – Diabetes REduction Assessment with Ramipril and Rosiglitazone Medication

DREAM Trial Overview [1,2]

- An international multi-center prospective, randomized, doubled blinded, placebo-controlled trial [2 x 2 Factorial Design] evaluating the effects of ramipril or rosiglitazone on the development of diabetes or death in people who have impaired fasting glucose (IFG) levels or impaired glucose tolerance (IGT) & who are at **low risk** for cardiovascular events (intention to treat analysis). Excluded patients who had diabetes (except gestational diabetes), CV disease or intolerant to angiotensin inhibitors or thiazolidinediones.
- IGT & IFG definitions in DREAM study have some variation from 2003 CDA Guidelines (as outlined below).
- This overview is for Ramipril 15mg od [5mg od x 2mos; 10mg od x 10mos→ 15mg od] vs. placebo & Rosiglitazone 8mg od [4mg od x 2mos→8mg od] vs. placebo over a median follow up of 3yrs

IFG=FPG ≥6.1 to < 6.9 mmol/L[Same as CDA] and 2hPG < 11.1mmol/L[In 2003, <7.8mmol/L was included, CDA uses < 7.8];
IGT=FPG<7.0mmol/L[CDA uses <6.1] and 2hPG≥7.8mmol/L to < 11.1mmol/L[Same as CDA]; CDA=Canadian Diabetes Association guidelines, 2003

- 5269 patients were followed for 3 years (range 2.5-4.7) with the following **baseline characteristics**:
  - Mean age ~ 55 years, males[~40%] & females with isolated IGT[~57%], isolated IFG[~14%] or both[~29%], mean FPG = 5.8 mmol/L, mean 2h PG = 8.7 mmol/L
  - History of hypertension[~44%], gestational diabetes in women[~9%], current or former tobacco use[~44%], > 3 alcoholic drinks/week[~21%] and sedentary[~26%]
  - Mean Weight: ~85kg; BMI: ~31 kg/m^2; waist: hip (men): 0.96; waist:hip (women): 0.86; waist (men): 101cm, waist (women): 96cm; BP: ~136/83 mm Hg
  - Drug use: ASA or antiplatelets[~14%], thiazides[~9%], angiotensin receptor blocker[~6%], beta blocker[~17%], calcium channel blocker[~13%], statin or fibrate[~14%], weight loss drugs[~0.6%]

Table 1: DREAM Results

Endpoint	ROSI % N=2635	PI % N=2634	HR (95% CI)	ARR %	NNT 3 years	P value	RAMI % N=2623	PI % N=2646	HR (95%CI)	ARR %	NNT 3 years	P value
1° Newly diagnosed diabetes or death	11.6 (306 events)	26.0 (686 events)	0.40 (0.35-0.46)	14.4	7	<0.0001	18.1 (475 events)	19.5 (517 events)	0.91 (0.81-1.03)	1.4	NS	0.15
Diabetes	10.6	25.0	0.38 (0.33-0.44)	14.4	7	<0.0001	17.1	18.5	0.91 (0.80-1.03)	1.4	NS	NA
Death	1.1	1.3	0.91 (0.55-1.49)	0.2	NS	0.7	1.2	1.2	0.98 (0.60-1.60)	0	NS	NA
2° Regression (FPG < 6.1 mmol/L)	50.5	30.3	1.71 (1.57-1.87)	20.2	5	<0.0001	42.5	38.2	1.16 (1.07-1.27)	4.3	23	0.001
2° Regression (FPG < 5.6 mmol/L)	38.6	20.5	1.83 (1.65-2.04)	18.1	6	<0.0001	NA	NA	NA	NA	NA	NA
2° CVD events composite*	2.9	2.1	1.37 (0.97-1.94)	↑ 0.8	NS	0.08	2.6	2.4	1.08 (0.76-1.52)	↑ 0.2	NS	0.68
2°Confirmed Heart Failure^	0.5 (14 events)	0.1 (2 events)	7.03 (1.60-30.9)	↑ 0.4	250 (NNH)	0.01	0.5	0.2	NA	↑ 0.3	NS	NA

* includes myocardial infarction, stroke, cardiovascular death, revascularization procedures, heart failure, new angina with objective evidence of ischaemia, or ventricular arrhythmia needing resuscitation ^Only confirmed Heart Failure showed statistical significance in rosiglitazone arm; all other individual components of the cardiovascular composite showed no significant difference in both rosiglitazone and ramipril arm. 1°=primary outcome 2°=secondary outcome ARR=absolute risk reduction BMI=body mass index BP=blood pressure CV=cardiovascular FPG=fasting plasma glucose HR=hazard ratio IFG=impaired fasting glucose IGT=impaired glucose tolerance NNT=number needed to treat to benefit 1 patient NA=results not available NNH=number needed to treat to harm 1 patient NS= not statistically significant PG=plasma glucose pl=placebo RAMI=ramipril ROSI=rosiglitazone

Of Note (Rosiglitazone Arm):

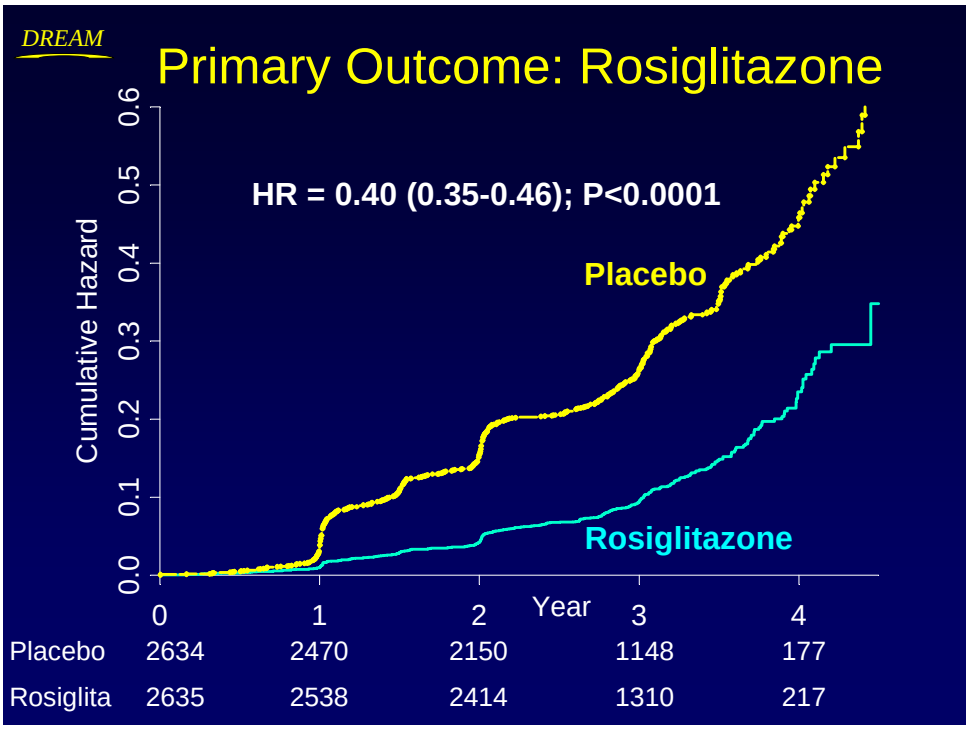
- Median FPG was 0.5mmol/L lower in the rosiglitazone group (p<0.0001); 2h PG was 1.6mmol/L lower (p<0.0001) at the final visit
- Mean systolic and diastolic blood pressure were 1.7 mmHg and 1.4 mmHg lower, respectively, in the rosiglitazone group (p<0.0001) at the final visit
- Increasing baseline weight or waist:hip ratio predicted a higher frequency of diabetes in individuals in the placebo group; this relation was NOT seen in the rosiglitazone group. The relative hazard reduction for the primary outcome increased from 40% in people whose BMI < 28 kg/m^2 to 68% in people with BMI > 32 kg/m^2 (p for heterogeneity 0.0004)
- 71.7% in the rosiglitazone group and 75.1% in the placebo group were at least 80% adherent at the end of the study
- Patients stopped medications by their last visit: 23.6% [18.9% refusal, 4.8% edema, 1.9% physician's advice, 1.9% weight gain, 1 pt hypoglycemia] in rosiglitazone arm; 20.2% [16.7% refusal, 1.6% edema, 1.5% physician's advice, 0.6% weight gain, 3 pt hypoglycemia] in placebo arm
- SAFETY:
  - **Heart Failure**: NNH = 250 [0.5 vs 0.1%] in 3 years p=0.01 (The overall CVD events, although not significant were ↑ with rosiglitazone; 2.9 vs 2.1% p=0.08 HR 0.97-1.94)
  - **Weight Gain**: 2.2kg more in the rosiglitazone group than placebo (p<0.0001) at the final visit. This was associated with a lower waist:hip ratio (p<0.0001) because of an increase in hip circumference of 1.8cm over 3 years. There was no effect on waist circumference.
  - **Edema**: 4.8% of the rosiglitazone group discontinued treatment compared to 1.6% on placebo

MI risk ↑ with rosiglitazone: Nissen, NEJM, May 21, 2007. (OR 1.43; CI: 1.03-1.98). Death from CV cause also trend toward ↑ (OR 1.64; CI: 0.98-2.74). Metaanalysis of all trials and data.
http://content.nejm.org/cgi/content/full/NEJMoa072761

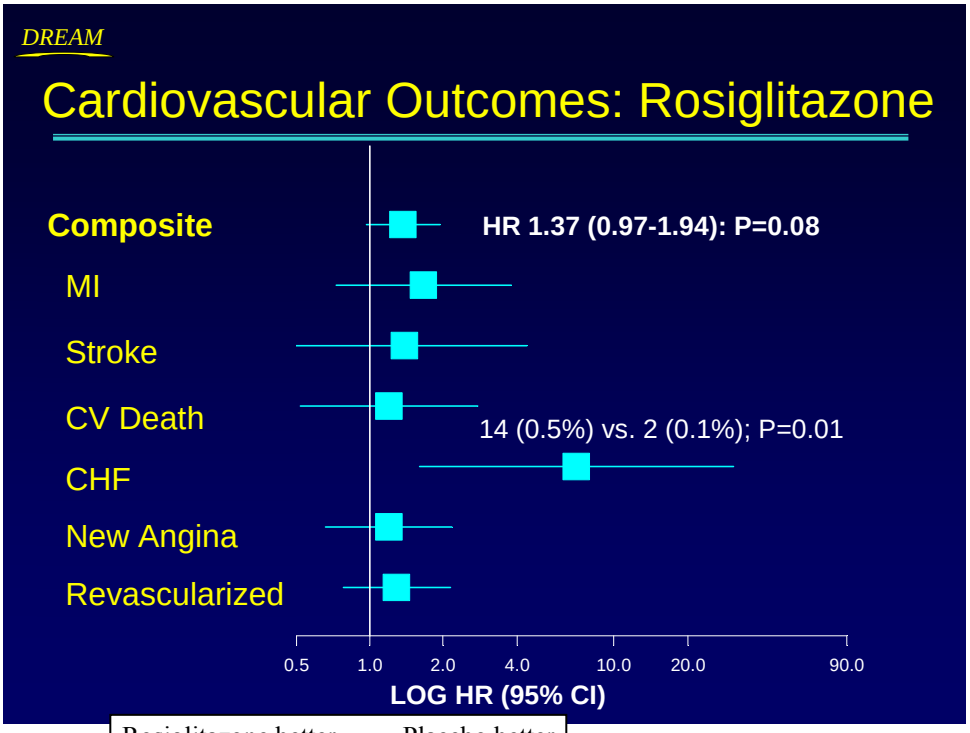
What we knew and what these results add to that knowledge:

- In the Heart Outcomes Prevention Evaluation (HOPE) study, ramipril ↓ the risk of CV events by 22% and diabetes by 34% (ARR=1.8%, NNT=56) in high risk CVD patients. [3]
- Acarbose[100mg tid but had ↑ GI side effects] (ARR=10%, NNT=11 in 3.3 yrs) and metformin [850mg bid & ↓ weight] (ARR=7.2%, NNT=14 in 3 years) reduce the incidence of diabetes by 25-30% [4,5]
- Lifestyle interventions that target diet and physical activity reduced the incidence of diabetes by more than 50% [6,7,8,9]; (ARR=14.5%, NNT = 7 for 3 years in DPP-lifestyle study) [10]
- Pioglitazone [Actos 45mg/d] given to patients with type 2 diabetes had an incidence of 6% heart failure [requiring hospital admission] compared to 4% on placebo [11 Proactive]
- DREAM:
  - Rosiglitazone for 3 years DOES significantly reduce the incidence of diabetes or death in patients with IFG and/or IGT & low risk CV disease (but NS effect on death [1.1 vs 1.3%])
  - Ramipril for 3 years DOES NOT significantly reduce the incidence of diabetes or death in patients with IFG and/or IGT & low risk CV disease (& CV events also neutral NS)
- Magnitude of benefit: 1 less diagnosis of diabetes or death for every 7 patients (with IFG, IGT or both & low risk CV disease) treated with rosiglitazone 8mg/d for 3 years
- Magnitude of harm: 1 more heart failure for every 250 patients treated with rosiglitazone 8mg/d for 3 years. Note also that all CV endpoints were on the side of harm [(HR: 0.97-1.94)].
- *Heads-Up*:
  - Risk of heart failure with rosiglitazone would be further increased, in patients at even higher risk
  - Unclear about the cost:benefit ratio for rosiglitazone 8mg/d in the prevention of diabetes (Avandia cost= $340/100 days) [Metformin [850mg bid] costs $42/100 day supply].
  - Continue lifestyle intervention encouragement for patients at risk of being diagnosed with diabetes (25% of these patients within 3yrs will progress to diabetes without intervention)
  - The long-term effects of rosiglitazone have not been established but ↑weight, edema & heart failure is of concern. (Also seen with pioglitazone in the Proactive trial.)
  - Awaiting the wash out period results (repeat oral glucose tolerance test after 2-3 months) of rosiglitazone to determine sustainability of the intervention. If it can be shown that treating for a period of time with rosiglitazone and then stopping, decreases or delays diabetes over time, this would be clinically important.
  - The results of the 2° outcome of renal events and a composite cardiorenal outcome were not published (although mentioned as a secondary outcome)
  - Fractures have been recently reported for rosiglitazone [13 ADOPT] & pioglitazone [14] (eg. hands/feet esp. in women), as well as rare reports of macular edema[15,16].
  - DREAM was stopped 5 months earlier than originally anticipated because the monitoring committee was sufficiently convinced the study question had been clearly and robustly answered. However, heart failure was significantly ↑ (ARR=0.4%, NNH = 250, p=0.01) and the composite CV event rate was higher [trend] in the rosiglitazone group [p=0.08, HR=1.37(0.97-1.94)]; it would have been prudent to complete the study as planned to determine the long-term outcome effects of rosiglitazone (eg. CV outcomes).

Bottom Line: Lifestyle has proven benefits, metformin is effective in preventing diabetes & has proven CV benefits, & rosiglitazone prevents diabetes without proven CV benefits. Counsel & encourage weight loss, physical activity, monitor for the development of diabetes every 1-2yrs & treat CVD risk factors [eg. tobacco use, hypertension & dyslipidemia ADA 2007]



Rosiglitazone, an oral hypoglycaemic reduced glucose, thus less newly diagnosed diabetes. Awaiting results to show whether the diagnosis of diabetes is truly delayed.



Rosiglitazone is trending on the side of **harm** for all cardiovascular outcomes versus placebo. The only statistically significant result was the ↑ **heart failure** with rosiglitazone. Unfortunately, trial stopped early though composite cardiovascular outcome was close to reaching statistical significance for harm.

[1] The Dream Trial Investigators. Effect of Ramipril on the Incidence of Diabetes. N Engl J Med 2006;355. 10.1056/NEJMoao65061

[2] DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators; Gerstein HC, Yusuf S, Bosch J, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial.Lancet. 2006 Sep 23;368(9541):1096-105. Erratum: Lancet. 2006 Nov 18;368(9549):1770. (InfoPOEMs: Patients at increased risk of developing diabetes were less likely to develop diabetes if taking rosiglitazone than if given a placebo. We don't know how well rosiglitazone compares with other interventions also known to delay diabetes: diet & exercise, metformin, or acarbose. We also don't know if clinically relevant outcomes are improved.) (Xiang AH, et al. Effect of pioglitazone on pancreatic beta-cell function and diabetes risk in Hispanic women with prior gestational diabetes. (PIPOD)Diabetes. 2006 Feb;55(2):517-22. Buchanan TA, et al. Preservation of pancreatic beta-cell function & prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk hispanic women. (TRIPOD) Diabetes. 2002Sep;51(9):2796-803.)
See also Preventing the Development of Diabetes – The DREAM Trial. Pharmacist's Letter Oct 2006. (Montori VM, Isley WL, Guyatt GH. Waking up from the DREAM of preventing diabetes with drugs. BMJ. 2007 Apr 28;334(7599):882-4). (Nathan DM, Berkwits M. Trials that matter: rosiglitazone, ramipril, and the prevention of type 2 diabetes. Ann Intern Med. 2007 Mar 20;146(6):461-3.)

[3] Yusuf S, Gerstein H, Hoogwerf B, et al. Ramipril and the development of diabetes. JAMA 2001;286:1882-5

[4] Chiasson JL, Josse RG, Gomis R, et al. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomized trial. Lancet 2002;359:2072-7

[5] 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

[6] Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. Finnish Diabetes Prevention Study N Engl J Med 2001;344:1343-50 (Lindstrom J, et al. Finnish Diabetes Prevention Study Group. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study.Lancet. 2006 Nov 11;368(9548):1673-9.)

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[8] Ramachandran A, et al. 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

[9] 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

[10] 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

[11] Dormandy JA, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in teh PROactive Study (PROspective pioglitAzone Clinical Trial in macroVascular Events) : a RCT trial. Lancet 2005;366(9493):1279-89

[12] March 28, 2007 (New Orleans, LA) - The thiazolidinedione antidiabetes drug rosiglitazone (Avandia, GlaxoSmithKline) showed a trend toward a reduction in carotid intima media thickness (IMT) according to the primary end point measurement and a significant reduction according to the secondary end point measurement in the STARR study in patients with prediabetes. But the ACE inhibitor ramipril (Altace, King Pharmaceuticals) did not show any change in carotid IMT compared with placebo. The STARR study was a substudy of the larger DREAM trial, and the results are consistent with those of the parent trial, which showed that three years of treatment with rosiglitazone reduced the incidence of type 2 diabetes in patients with prediabetes (defined as impaired fasting glucose levels, impaired glucose tolerance, or both), but treatment with ramipril did not.

[13] Kahn SE, et al.; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006 Dec 7;355(23):2427-43. Epub 2006 Dec 4. Erratum in: N Engl J Med. 2007 Mar 29;356(13):1387-8. (6.3% vs 3.7%)

[14] Health Canada May 2007 Actos pooled data from 19 trials showed more fractures (2.6% versus 1.7%) http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/actos_hpc-cps_2_e.html

[15] Health Canada Dec/05 Association of AVANDIA & AVANDAMET with new onset and/or worsening of macular edema http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2005/avandia_avandamet_hpc-cps_e.html

[16] Kendall C, Wooltorton E. Rosiglitazone (Avandia) and macular edema. CMAJ. 2006 Feb 28;174(5):623. Epub 2006 Feb 8.
[17] American Diabetes Association (ADA). Standards of medical care in diabetes. IV. Prevention/delay of type 2 diabetes. Diabetes Care 2007 Jan;30(Suppl 1):S7-8. http://care.diabetesjournals.org/cgi/content/full/30/suppl_1/S4#SEC14

Dream website: http://www.dtu.ox.ac.uk/dream ;

Metaanalysis of rosiglitazone (Avandia) cardiovascular events / outcomes. See **Nissen, NEJM, May 21, 2007.** **http://content.nejm.org/cgi/content/full/NEJMoa072761**

On the horizon:

- **NAVIGATOR** (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research)
- **TRANSCEND** (Telmisartan Randomized Assessment Study in aCE iNtolerant subjects with cardiovascular Disease)
- **ONTARGET** (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial)
- **ACCORD**: Action to Control Cardiovascular Risk in Diabetes (standard therapy vs. intensive therapy of type 2 diabetes).
- **RAPSODI:** (rimonabant in diabetes prevention)