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

DREAM Trial Overview

- An international multi-center prospective, randomized, double-blinded, placebo-controlled trial 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 (intent to treat analysis).
- Excluded patients who had diabetes (except gestational diabetes), CV disease or intolerant to insulinotropic or thiazolidinediones.
- IGT & IGF definitions in DREAM study have some variation from 2003 CDA Guidelines (as outlined below).
- This overview is for Ramipril 15mg od vs. placebo & Rosiglitazone 8mg od vs. placebo over a median follow up of 3yrs

Table 1: DREAM Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>ROSI %</th>
<th>N=2635</th>
<th>PI %</th>
<th>N=2634</th>
<th>ARR %</th>
<th>NNT 3yrs</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Newly diagnosed diabetes or death</td>
<td>11.6 (325 events)</td>
<td>26.0 (595 events)</td>
<td>0.40 (0.35-0.46)</td>
<td>14.4</td>
<td>7</td>
<td>&lt;0.0001</td>
<td>18.1 (47 events)</td>
</tr>
<tr>
<td>2 Regression (FPG &lt; 6.1 mmol/L)</td>
<td>50.5 (613 events)</td>
<td>30.3 (380 events)</td>
<td>1.71 (1.57-1.87)</td>
<td>20.2</td>
<td>6</td>
<td>&lt;0.0001</td>
<td>42.5 (82 events)</td>
</tr>
<tr>
<td>3 Confirmation of Heart Failure^</td>
<td>0.5 (14 events)</td>
<td>0.1 (2 events)</td>
<td>7.03 (16.30-39)</td>
<td>↑ 0.4</td>
<td>250 (NNH)</td>
<td>0.01</td>
<td>0.5</td>
</tr>
</tbody>
</table>

* 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

† 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

Note of 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 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/m2 to 68% in people with BMI > 32 kg/m2 (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% 71.7% in the rosiglitazone group and 75.1% in the placebo group were at least 80% adherent at the end of the study

What we know 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 CV patients.
- AKarsho10mg bid had the least effect (ARR=10%, NNT=11 in 3.3 yrs) and metformin 500mg bid × 1 weight (ARR=7.2%, NNT=14 in 3 years) reduce the incidence of diabetes by 25-30%.
- Lifestyle interventions that target diet and physical activity reduced the incidence of diabetes by more than 50% (7.8% ARR=14.5%, NNT = 7 for 3 years in DPP-lifestyle study) 10
- Pioglitazone Acts directly to improve insulin sensitivity in patients with type 2 diabetes who has an incidence of 6% heart failure requiring hospital admission compared to 4% on placebo PL Proactive

DREAM

- Rosiglitazone for 3 years does not significantly reduce the incidence of diabetes or death in patients with IGF or IGT & low risk CV disease (but NS effect on death 1.1 vs 1.3%)
- Ramipril for 3 years NS does not significantly reduce the incidence of diabetes or death in patients with IGF 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 IGF, IGT or both & low risk CV disease) treated with rosiglitazone 8mg/d for 3 years
- Magnitude of harm: 2 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: P<0.01

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 costs ~$340/100 days).
- Continues lifestyle intervention encouragement for patients at risk of being diagnosed with diabetes (25% of these patients within 5yrs will progress to diabetes without 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 2nd outcome of renal events and a composite cardiovascular outcome were not published (although mentioned as a secondary outcome)

Fractures have been recently reported for rosiglitazone 15mg od & pioglitazone 15mg od (eg. hands/feet esp. in women), as well as rare reports of macula edema

DREAM was stopped 5 months earlier than originally anticipated due to the monitoring committee’s recommendation.

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 CV risk factors
Rosiglitazone, an oral hypoglycaemic reduced glucose, thus less newly diagnosed diabetes. Awaiting results to show whether the diagnosis of diabetes is truly delayed.
Dream website: http://www.dtu.ox.ac.uk/dream


On the horizon:
- NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research)
- TRANSCEND (Telmisartan Randomized Assessment Study in aCE I 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)