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## Results of the DREAM TRIAL (Diabetes REDuction Assessment with ramipril and rosiglitazone Medication)

Originally presented by: Jackie Bosch, MSc; Salim Yusuf, MD; and Hertzel Gerstein, MD

Based on the Late-breaking Clinical Trial Presentation at the  
42<sup>nd</sup> European Association for the Study of Diabetes (EASD) Meeting

September 15, 2006 Copenhagen-Malmö, Denmark-Sweden

By LAWRENCE A. LEITER MD, FRCPC, FACP

Over the past decade, various trials have demonstrated that diabetes mellitus (DM) risk can be reduced with lifestyle and pharmacological intervention. The primary endpoint of the recent Diabetes REDuction Assessment with ramipril and rosiglitazone Medication (DREAM) trial was the effect of ramipril and rosiglitazone in preventing new-onset diabetes mellitus (DM) and death, while the secondary endpoint was the effect of these drugs on regression from impaired glucose tolerance/impaired fasting glucose (IGT/IFG) to normal over a median 3-year follow-up in over 5000 patients. The results of DREAM were presented at the recent EASD. This issue of *Endocrinology Scientific Update* presents an overview of the findings of the DREAM trial and how they may affect future pharmacological recommendations for the prevention and treatment of DM.

It is estimated that DM currently affects approximately 230 million individuals worldwide and it is estimated that, by the year 2025, this number will increase to more than 350 million.<sup>1</sup> This epidemic will be associated with an increase in the so-called "chronic complications of diabetes," including cardiovascular disease (CVD), retinopathy, neuropathy, and nephropathy. In addition, there is evidence that even individuals who are "pre-diabetic" (ie, with IFG and IGT) are also at increased risk for CVD.<sup>2</sup> Because of this epidemic, increasing attention has focused on ways of preventing DM.

Over the last few years, we have seen the results of a number of successful preventive interventions for DM. The American Diabetes Prevention Program (DPP) reported that

an intensive lifestyle intervention was associated with a 58% reduced risk of developing DM over 3 years,<sup>3</sup> while the Finnish Diabetes Prevention Study (DPS), using a somewhat less intensive lifestyle program, revealed an identical 58% risk reduction. There has also been evidence for a benefit associated with pharmacologic interventions. In the DPP, use of metformin was associated with a 31% risk reduction,<sup>4</sup> whereas in the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial, the use of acarbose was associated with a 25% reduced risk of developing DM.<sup>5</sup> There has also been some limited data with troglitazone (a thiazolidinedione [TZD] that was never released in Canada and which is no longer currently available), suggesting that TZDs can also reduce the risk for DM. In the DPP, there was a 75% risk reduction in a relatively small number of patients tested for a short period of time before the drug was withdrawn.<sup>6</sup> Similarly, in the TRogliitazone In the Prevention Of Diabetes (TRIPOD), a study in 266 women with post-gestational diabetes, the use of troglitazone was associated with a 55% reduced risk.<sup>7</sup>

There has also been a belief that blockade of the renin-angiotensin system (RAS) may also prevent DM.<sup>8</sup> Studies with both angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have suggested benefit. For example, in the Heart Outcomes Prevention Evaluation (HOPE) study, the use of ramipril 10 mg daily was associated with a 34% reduced risk of developing DM.<sup>9</sup> A recent meta-analysis of the HOPE, PEACE and EUROPA studies demonstrated an overall 14% reduced risk of developing DM associated with the use of ACE inhibitors.<sup>10</sup> It should be noted, however, that the prevention of DM was not the primary outcome in any

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of these studies and glucose tolerance tests were not routinely performed, either at baseline, or at the end of the studies and, therefore, prevalent DM at baseline and new-onset DM on follow-up may have been missed. Furthermore, the subjects in these studies were at high cardiovascular risk and intermediate diabetes risk.

### The DREAM study

The DREAM trial was a 2 × 2 factorial, double-blind, randomized, controlled trial that included 5,269 subjects in 191 sites across 21 countries.<sup>11,12</sup> It examined 2 questions:

- Does ramipril 15 mg per day prevent DM?
- Does rosiglitazone 8 mg per day prevent DM?

In contrast to previous diabetes prevention trials that focused on individuals with IGT, DREAM included subjects aged >30 years with both IGT, as well as IFG. The primary outcome was new-onset DM or death (death was included because diagnosed DM may be more frequent in those who die than in those who do not). A total of 24,592 subjects were screened and 5,269 were randomized. The major reason for ineligibility was “out of range” glucose levels. The glucose or primary outcome status was determined in 94% of the study subjects at study end and vital status was reported in 98% of subjects.

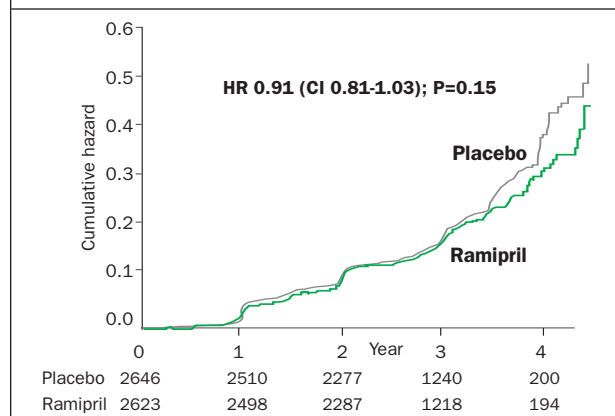
The subjects had a mean age of 54.7 years and 59.2% were female. Isolated IGT was present in 57.5%, 14% had isolated IFG, and 28.5% had both IGT and IFG. Hypertension was present in 43.5% of subjects, while 44.6% were current or prior smokers, and 26.8% were self-described as being sedentary.

### DREAM: Results of the ramipril arm

At the end of the median 3-year follow-up, 75.4% of ramipril-treated patients and 80.9% of those allocated to placebo were still on study medication. Cough occurred in 9.7% of the ramipril-treated patients versus 1.8% of those on placebo, similar to that seen in the HOPE trial. Despite the 15 mg dosage of ramipril in a study population who were not all hypertensive, hypotension was seen in only 0.8% of the subjects on ramipril versus 0.4% on placebo. Interestingly, increases in body weight and body mass index (BMI) were somewhat less in the patients on ramipril, although this did not quite reach statistical significance ( $p=0.07$  and  $0.06$ , respectively). Blood pressure was significantly lower in the subjects on ramipril, 128.3/78.0 mm Hg versus 132.3/80.3 mm Hg,  $p<0.0001$  for those on placebo. Alanine aminotransferase (ALT) was also significantly lower ( $p=0.04$ ) in ramipril-treated patients, although the mean values were in the normal range. It is interesting to note that there is increasing literature suggesting that ALT is an independent predictor of cardiovascular risk.<sup>13</sup>

The primary outcome (ie, new-onset DM plus death) in the DREAM study was reduced by a nonstatistically significant 9% ( $p=0.15$ ) (Figure 1). Regression from IGT/IFG to normal (fasting glucose <6.1 mmol/L), a secondary endpoint, was increased by a significant 16% ( $p=0.001$ ) (Figure 2).

**Figure 1: Primary outcome of new-onset DM and death: Ramipril**

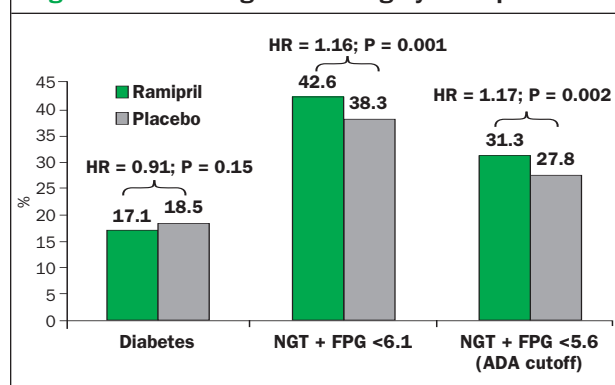


Adapted from reference 11

If one utilizes the newer American Diabetes Association cut-off for normal values (<5.6 mmol/L), regression to normal was increased by 17% ( $p=0.002$ ). The median final fasting plasma glucose was 5.7 mmol/L in those on ramipril versus 5.74 mmol/L in those on placebo, whereas the plasma glucose 2 hours after a glucose load was 7.50 mmol/L in those on ramipril vs. 7.80 mmol/L in those on placebo ( $p=0.01$ ). The risk for a cardiovascular composite was not altered by ramipril therapy. It is important to note, however, that this population was at low cardiovascular risk. Given the previous evidence regarding the significant benefits associated with ramipril 10 mg daily treatment in patients at high risk for CVD, these subjects were excluded from the DREAM trial.

The question arises as to why DREAM did not demonstrate the prevention of DM with ramipril therapy, when previous trials suggested such a benefit. Reasons may include the fact that diabetes was the primary outcome in DREAM, whereas it was not in the other trials and subjects with undiagnosed DM were excluded from DREAM. Furthermore, because subjects in DREAM were at low

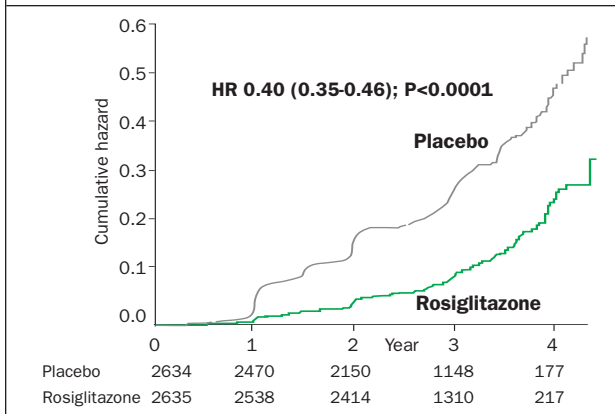
**Figure 2: Effect on glucose category: Ramipril**



NGT = normal glucose tolerance  
FPG = fasting plasma glucose

Adapted from reference 11

**Figure 3: Primary outcome of new-onset DM and death: Rosiglitazone**



Adapted from reference 12

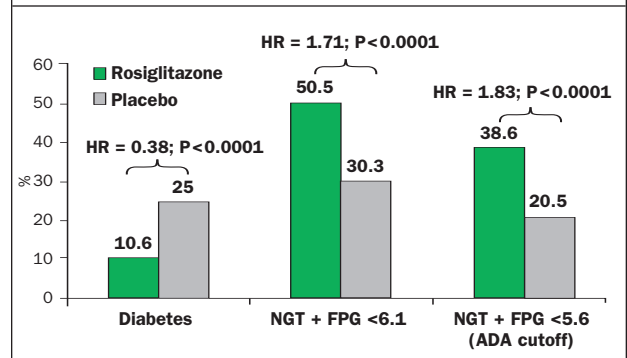
cardiovascular risk, they likely had a less activated RAS, which was perhaps less amenable to benefit from ACE inhibition. In addition, placebo-treated subjects in the DREAM trial were less likely to be on drugs that raise blood glucose (eg, thiazide diuretics and beta-blockers). Finally, there was low power to detect differences in cardiovascular events, given the relatively short duration of the trial and the low CV risk of the study participants.

### DREAM: Results of the rosiglitazone arm

At the end of the median 3-year follow-up, 79.5% of rosiglitazone-treated subjects and 84.0% of those on placebo were still on study medication. Edema was seen in 4.8% of those treated with rosiglitazone vs 1.6% in those treated with placebo. The use of rosiglitazone was also associated with improved blood pressures: 129.4/78.4 mm Hg versus 131.1/79.8 mm Hg ( $p=0.0001$ ). The effects on body weight and body fat distribution is of interest; patients on rosiglitazone had significantly greater increases in body weight and BMI. The increase in waist circumference, however, was not different between the two arms of the study and hip circumference was increased to a greater degree in rosiglitazone-treated patients. As a result, the waist-to-hip ratio (WHR), which some recent evidence suggests may be a better predictor of cardiovascular risk than waist circumference, was significantly decreased ( $p=0.0001$ ) in rosiglitazone-treated patients.

The primary composite endpoint of new-onset DM and death was reduced by an impressive 60% ( $p<0.0001$ ) in subjects treated with rosiglitazone (Figure 3). Regression to a normal fasting plasma glucose ( $<6.1$  mmol/L) was increased by 71% and regression to a normal fasting plasma glucose ( $<5.6$  mmol/L according to the ADA cutoff) was increased by 83% (all  $p<0.0001$ ; Figure 4). The median final plasma glucose in rosiglitazone-treated patients was 5.5 mmol/L vs. 6.0 mmol/L in those treated with placebo and the plasma glucose 2 hours after a glucose load was 6.9 mmol/L on rosiglitazone vs 8.5 mmol/L on placebo (both  $p<0.0001$ ).

**Figure 4: Effect on glucose category: Rosiglitazone**

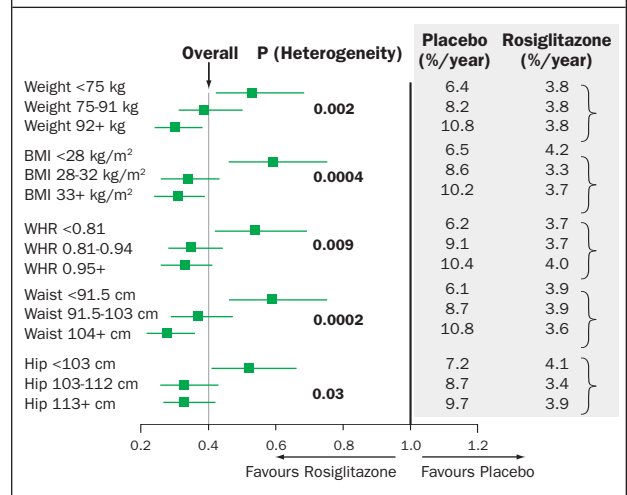


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With regard to subgroup analyses of the primary endpoint, no differential response was observed based on gender, age, region of the world, or whether the subject had isolated IFG, isolated IGT, or both. Subgroup analyses based on body weight and body fat distribution did, however, show evidence of heterogeneity. Patients with the greatest weight and most abnormal body fat distribution had the greatest benefit (Figure 5). In fact, treatment with rosiglitazone eliminated the gradient of diabetes risk typically associated with increasing weight.

Overall, there were no differences in cardiovascular outcomes between the patients treated with rosiglitazone versus those treated with placebo. However, 14 rosiglitazone-treated subjects (0.5% of participants) vs. only 2 placebo-treated subjects (0.1% of participants) developed congestive heart failure ( $p=0.01$ ). This outcome was adjudicated by an independent committee. To put this into perspective, however, the incidence of heart failure was about 10% of what was observed in the PROspective

**Figure 5: Rosiglitazone subgroups: primary**



WHR = waist-to-hip ratio

Adapted from reference 12

pioglitazone Clinical Trial In macroVascular Event (PROACTIVE) study, in which study subjects all had a history of DM plus coronary artery disease.<sup>14</sup>

### Implications for practice

In summary, the DREAM study demonstrated that in subjects with IGT or IFG, ramipril 15 mg daily for 3 years did not significantly reduce the risk for DM or death, but did significantly increase regression to normal. Rosiglitazone 8 mg daily reduced new-onset diabetes by >60% and promoted regression to normal of both fasting and 2-hour sugars by >70%. Although there was about a 3% increase in body weight, there was a favourable effect on the WHR. There was also an increased risk for congestive heart failure, although the numbers were small. There were too few events to draw any conclusions with regard to the effect of either of these treatments on other cardiovascular events or death. With regard to absolute risk reduction, it was calculated that for every 1,000 people treated with rosiglitazone for about 3 years, 144 cases of DM would be prevented, with an excess of about 4 cases of congestive heart failure.

The current Canadian Diabetes Association Clinical Practice Guidelines recommends that a structured program of lifestyle modification, including moderate weight loss and regular physical activity, be implemented in individuals with IGT, and that pharmacologic therapy with metformin or acarbose also be considered.<sup>15</sup> The DREAM results are important in that they add rosiglitazone to the list of medications proven to reduce the risk of type 2 DM and extend the benefit of pharmacologic intervention to patients with IFG as well. Although lifestyle modification has multiple additional benefits and must, therefore, remain our first choice for diabetes prevention, the type of intensive lifestyle program utilized in the DPP is expensive, not readily available, and not always successful. The DREAM study is important in that we now have another medication that has similar diabetes prevention efficacy as intensive lifestyle intervention. Based on the DREAM results, ramipril cannot currently be recommended for the prevention of DM. Nonetheless, in patients, with an indication for ACE inhibitors (eg, those with hypertension, congestive heart failure, or high cardiovascular risk [prior atherosclerotic disease or high-risk diabetes]), the favourable effects of ramipril on glycemia may be an added benefit.

The durability of the glycemic effect of these drugs was assessed in DREAM with repeat glucose tolerance tests following a 2-3 month washout period. These results are expected to be presented at the International Diabetes Federation meeting that will be held in December, 2006, in Cape Town, South Africa. In addition, the effects of these drugs on carotid atherosclerosis (as assessed by carotid ultrasound) are expected to be presented at the American Heart Association meeting in Chicago in November 2006.

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