Rosiglitazone Reduced the Incidence of Diabetes in Patients With Impaired Glucose Tolerance

Reviewed by Michael Pignone, MD, MPH

STUDY

DREAM (Diabetes REduction Assessment with ramipril and rosiglitizone Medication) Trial Investigators; Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, Hanefeld M, Hoogwerf B, Laakso M, Mohan V, Shaw J, Zinman, B, Holman RR: 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

SUMMARY

Design. A randomized, placebo-controlled, double-blind trial.

Subjects. Adults > 30 years of age with impaired fasting glucose (IFG; fasting plasma glucose [FPG] > 110 mg/dl and < 126 mg/dl and 2-hour plasma glucose < 200 mg/dl during oral glucose tolerance test [OGTT]) or impaired glucose tolerance (IGT; FPG < 126 mg/dl and 2-hour plasma glucose 140–200 mg/dl and no previous history of diabetes or cardiovascular disease).

Methods. Potentially eligible patients entered a placebo run-in period; those who were successful in taking 80% of doses were then randomized to rosiglitazone and 4 mg/day for 2 months then 8 mg/day. Follow-up visits were scheduled at 2 months, 6 months, and then every 6 months thereafter. FPG was used for monitoring; those with results suggestive of diabetes were scheduled for an OGTT to determine the presence or absence of diabetes. The main outcome of interest was incident diabetes or death, as assessed by blinded outcome adjudicators.

Results. A total of 5,269 patients were enrolled. The mean age was 54.7 years, and 59% were women. Most participants (86%) had IGT with or without IFG; 14% had IFG only. Median follow-up was 3.0 years. The incidence of diabetes was 10.6% in the intervention group and 25.0% in the control group (hazard ratio [HR] 0.38, 95% CI 0.33–0.44). Deaths did not differ between groups. The median FPG was 9 mg/dl lower in the intervention group. Adverse effects were uncommon, but incidence of heart failure (0.5 vs. 0.1%, HR 7.0, 95% CI 1.6–30.9) and incidence of total cardiovascular events (2.9 vs. 2.1%, 1.37, 0.97–1.94) were increased in the intervention group. Intervention patients also gained on average 2.2 kg of additional weight compared with control subjects.

Conclusions. Rosiglitazone reduces the incidence of diabetes and mean FPG levels but is associated with a small excess risk of heart failure and with weight gain.

COMMENTARY

The DREAM trial suggests that rosiglitazone can be effective in reducing the risk of clinical diabetes among patients with IGT or IFG. The observed reduction in the risk of developing clinical diabetes was large in magnitude: seven patients would need to be treated to prevent one case of incident diabetes. Rosiglitazone was also associated with an increased risk of heart failure, although the underlying incidence of heart failure was low in this population.

These findings add to existing evidence suggesting that lifestyle intervention,[1] and to a lesser extent metformin or acarbose,[2] can delay or prevent progression to diabetes. They also add to accumulating evidence about the increased risk of heart failure with thiazolidinediones.[3] A separate arm of the DREAM trial also examined the effect of ACE inhibitors on diabetes incidence, but it did not find a reduction in incidence.[4]

What are the clinical implications of these trials? First, it should be recognized that the end point of diabetes prevention is a somewhat artificial construct. The adverse microvascular and macrovascular effects of elevated plasma glucose levels behave in a linear or exponential manner and do not change dramatically when patients' FPG or OGTT results pass the threshold we have defined as "diabetes." As such, the net beneficial effects of "diabetes prevention" in this context may be more modest than the large reduction in the hazard ratio seems to suggest.

The benefits of prevention must be balanced against any adverse effects and costs of interventions used to achieve it. Lifestyle interventions, such as the changes in dietary and physical activity patterns used in the Diabetes Prevention Program, may have important collateral benefits beyond the reductions in diabetes incidence. Increased effort should be devoted to identifying effective and relatively inexpensive ways to implement such programs in wider practice.[5]

For now, the best choice of pharmacological agent (if any) to be used as an adjunct to lifestyle intervention or when lifestyle change is not effective in patients with IGT remains unclear. Further evidence from head-to-head studies and economic analyses is required.

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