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"Puzzling" *Lancet* Paper Posits Low-Dose Rosiglitazone/Metformin for Diabetes Prevention

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June 3, 2010 (Toronto, Ontario)— With just over a month to go before **rosiglitazone** (Avandia, GlaxoSmithKline) makes its reappearance in front of an **FDA** review panel, a surprising study--in the *Lancet*, no less--suggests that half-dose rosiglitazone combined with half-dose **metformin** may help prevent progression to diabetes [1].

The paper, published online June 2, 2010, will no doubt raise some eyebrows, given mounting calls to remove rosiglitazone from the market. Experts not involved with the study were quick to point out to **heartwire** that the new study does nothing to alleviate concerns about the drug.

The paper was published within hours of [news](#) that the drug maker had settled the first US court case to go to trial, alleging that rosiglitazone causes MI.

Lead author on this new paper, however, **Dr Bernard Zinman** (University of Toronto, ON), stressed in an interview with **heartwire** that the study was not powered to look at cardiovascular outcomes and that the main point of the research was that reduced doses of available drugs--not necessarily rosiglitazone--may help reduce progression to diabetes.

"We chose these two agents [rosiglitazone and metformin] when we started this because they were available in a single pill--**Avandamet** [GlaxoSmithKline]. We felt that compliance with the study medication would be better if it were a fixed-dose combination--we could equally have chosen **pioglitazone** (Actos, Takeda) and metformin, and I think the results would be the same."

While lifestyle changes are "very effective" in preventing progression to full-blown diabetes in people with impaired glucose tolerance, they are "very, very difficult to implement, and on a society level, we've failed to do that," Zinman explained. Previous studies looking at pharmacological interventions to prevent diabetes have proven effective, but at the expense of major side effects.

Thus, the rationale for the **Canadian Normoglycemia Outcomes Evaluation** (CANOE) trial was to try for the same benefits, with lower drug strength, he said. "The notion here is to use low doses, in combination, because diabetes and prediabetes are complex diseases, and you need to target various aspects of the pathophysiology, and that's exactly what we've done. We used a combination of half-dose metformin and half-dose rosiglitazone to improve insulin sensitivity, decrease hepatic glucose production, and have what we hope would be a robust effect on preventing diabetes. And we achieved that."

Journey by CANOE

In CANOE, 207 patients with impaired glucose tolerance were randomized equally to either placebo or a combination of rosiglitazone (2 mg) and metformin (500 mg) as a twice-daily dose over a median of almost four years. Doses of both drugs were half the maximum recommended dose, the authors note in the paper, and both patients and physicians were blinded to treatment type.

At follow-up, occurrence of incident diabetes (established by oral glucose tolerance or two fasting glucose values of 7.0 mmol/L or higher) was significantly lower in patients assigned to the combination drug, 14%, than the placebo group, 39%, a relative risk reduction of 66% ($p < 0.0001$) and an absolute risk reduction of 26%.

Overall, 70 patients (80%) in the combination-drug arm regressed to "normal glucose tolerance" by the end of the study, compared with 52 in the placebo group (53%; $p = 0.0002$). Insulin sensitivity, likewise, remained unchanged in the drug-combination group but decreased in the placebo group; beta-cell function, however remained unchanged in both study arms.

In terms of side effects, incidence of diarrhea increased significantly in the drug group only, but there were no signs of swollen ankles, fluid retention, gastrointestinal symptoms, or hypoglycemia.

"The adverse effects were really not there," Zinman stressed in the interview. There was no weight gain--something seen in the **DREAM** study of rosiglitazone--no edema or fluid retention, and the fracture rate was the same in both groups.

"This is a small study designed to show efficacy and not long-term safety, so there was no evidence on the effects on cardiovascular outcomes, but [the study] was way too small to look at that," he said. "I think this means--and I've been telling family physicians this all along--that what we should be doing with respect to managing diabetes is using thiazolidinediones (TZDs) at half maximal dose. These drugs at full maximal dose have too much risk and at half maximal dose combined with other agents are very effective."

There were no cases of MI or heart failure in the combination-drug group (and one of each in the placebo group), although Zinman shied away from addressing the cardiovascular effects, noting for heart failure, he's "confident it's not a big risk" based on the lack of fluid retention with the combination low-dose pill. For MIs, the study "was too small" to draw any conclusions.

But acknowledging the concerns about rosiglitazone, he reiterated that pioglitazone could be used in its stead. "I think the results apply to pioglitazone as well. But again, I would not use pioglitazone at full maximum dose; I would use it at half."

He added that he currently prescribes pioglitazone at half-dosages, even to patients with established diabetes, and he also has some patients "doing well" on rosiglitazone, again at a half maximal dose.

"Pure Speculation at Best"

One of the most outspoken critics of rosiglitazone, **Dr Steven Nissen**, commented on the study for **heartwire**, noting: "This is a very small study--only about 200 patients--and its publication in the *Lancet* is puzzling."

Delay to onset of diabetes has previously been shown for rosiglitazone in the DREAM study, and earlier studies suggested a similar effect for metformin, Nissen observed in an email. But importantly, the FDA does not recognize delay in diabetes onset as a legitimate label claim.

"Delaying onset of diabetes is not particularly useful if you increase adverse cardiovascular events," he continued. "Despite the authors' claims, there is no evidence whatsoever that lower doses of rosiglitazone are 'safe.' Any suggestion that serious cardiovascular toxicity can be avoided by using a small dose represents pure speculation at best."

Also commenting on the study, **Dr Baiju Shah** (Sunnybrook Health Sciences Centre, Toronto, ON) pointed out that it's not surprising investigators saw no increased CV events with rosiglitazone, since the population was very low risk to begin with. "While there is no evidence of harm at all, I don't think this in any way 'exonerates' Avandia, since we wouldn't have expected to see anything in such a small study," he told **heartwire**. In addition, the study did not include higher doses of either metformin or rosiglitazone, leaving it unclear whether a high dose of a single drug would have had the same effect as the lower-dose combo, he added.

Shah was less perplexed by the study's high-profile publication: "It's still a well-conducted randomized controlled trial showing a positive result for an outcome that's 'sexy.' If you believe in drug therapy for diabetes prevention--although I don't--it's a good study!"

Other Questions

A Comment accompanying the Zinman paper points to additional unanswered questions, without addressing the choice of rosiglitazone specifically [2]. **Drs Thomas A Buchanan** (University of California, Los Angeles) and **Anny H Xiang** (Kaiser Permanente, Pasadena, CA) note that the lack of an effect on B-cell function is surprising in light of other TZD studies. The study also did not include information on off-drug testing, which could clarify whether drugs slowed or arrested "metabolic deterioration" beyond drug treatment, and whether these metabolic effects actually have an impact on long-term clinical outcomes.

"We need data on more intensive approaches, including high-dose combination therapy, to provide clinicians with a full range of evidence-based approaches to halt or reverse this progressive disease relatively early in its course," they conclude.

Asked for comment, a GlaxoSmithKline spokesperson called the results "interesting news for all of us seeking ways to advance the treatment of type 2 diabetes. . . . While CANOE examines the benefits of low-dose Avandamet in preventing diabetes, we are not able to draw conclusions about how these results will translate to the broader patient population already diagnosed with diabetes."

Zinman disclosed having received consulting fees, honoraria, and grant support from GlaxoSmithKline, which also provided funding for the study. Zinman stressed that GlaxoSmithKline had no role in the study design or write-up or any role in the data collection, analysis, or interpretation. Disclosures for study coauthors are listed in the paper.

References

1. Zinman B, Harris SB, Neuman J, et al. Low-dose combination therapy with rosiglitazone and metformin to prevent type 2 diabetes mellitus (CANOE trial): A

double-blind randomised controlled study. *Lancet* 2010; DOI: 10.1016/S0140-6736(10)60746-5. Available at: <http://www.thelancet.com>.

2. Buchanan TA and Ziang AH. Preventing type 2 diabetes with low-dose combinations. *Lancet* 2010; DOI: 10.1016/S0140-6736(10)60900-2. Available at: <http://www.thelancet.com>.