

## Spotlight on the Low dose Rosiglitazone/ Metformin Combination In Prevention of Type 2 Diabetes

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**D**iabetes mellitus is one of the major challenges to public health with global prevalence of 6.6% (285 million) and annual cost of 376 billion US dollars [1]. Pharmacological and non pharmacological interventions which target either to delay the onset of diabetes or to prevent its complications have been the focus of clinical research. Recently, a double blind randomized controlled trial, CANOE (Canadian Normoglycemia Outcomes Evaluation), compared efficacy of a fixed- low-dose combination of rosiglitazone (2mg) and metformin (500mg) given twice daily against matched placebo [2]. Time to the development of diabetes being the primary outcome measure the investigators reported a relative risk reduction of 66% (95% CI 41–80) and the absolute risk reduction of 26% (14–37) in the treatment group. In addition, the only significant side effect observed in the treatment group compared with placebo was increase in diarrhea (16 [16%] vs 6 [6%];  $p = 0.0253$ ). The trial design is unique as it is the first trial to use fixed low dose combination of rosiglitazone and metformin but certain issues in its design cannot be overlooked.

Surprisingly, in spite of well documented cardiovascular and other side effects such as; fluid retention, increased risk of heart failure, risk of bone fracture and weight gain associated with the use of rosiglitazone [3,4], the current study was not powered enough to establish cardiovascular safety. Both efficacy and long term safety are equally important for any intervention intended for primary prevention, as it allows the physician to estimate the benefit against potential risk in clinical practice. Delaying the onset of diabetes at the cost of cardiovascular events is certainly not desirable. The choice of a placebo controlled trial over an active controlled trial (against high dose monotherapy) is debatable, when ADOPT (A Diabetes Outcome Progression Trial) [3] and DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) [4] trials of rosiglitazone, and DPP (Diabetes Prevention Programme) [5] study of metformin, have already proven their efficacy in delaying the onset of diabetes.

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In addition, the sample size was too small to detect which group i.e in terms of gender, age group, ethnicity and socioeconomic class is most likely to benefit from primary prevention. Furthermore, it still remains unclear whether delaying the onset of diabetes is a “class-effect” of thiazolidinediones or a unique characteristic of rosiglitazone. Nonetheless, CANOE trial has laid a solid foundation for future research to extensively evaluate the efficacy, long term safety and pharmacoeconomic aspects of rosiglitazone-metformin combination. Until, the long term safety of this low dose combination is established, it is unlikely to be used in clinical practice

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### Authors' contribution:

Hadi MA has compiled the initial and final draft

### Conflict of interest:

Not disclosed