

## A comment on ‘the risk of coronary heart disease in type 2 diabetic patients exposed to thiazolidinediones compared to metformin and sulfonylurea therapy’<sup>†</sup>

To the Editor

We read with interest the recently published article by Johannes *et al.*<sup>1</sup> evaluating whether the risk of coronary heart disease differs among type 2 diabetic patients treated with thiazolidinediones (TZDs) compared to those treated with combined oral metformin and sulfonylurea (M + S) therapy. This report represents an important contribution to the field, but we would like to comment on some of the authors’ methods.

Our primary concern with this study is the definition of study population. Although, according to the title and the introduction, the targeted study population was type 2 diabetic patients, it is not clear that Johannes *et al.*<sup>1</sup> excluded type 1 diabetic patients and specifically selected type 2 diabetic patients.

Although type 1 diabetes mellitus most commonly develops before the age of 30,<sup>2</sup> in contrast to previous studies targeting type 2 diabetic patients,<sup>3,4</sup> the authors did not include information regarding how patients with type 1 diabetes were excluded which is especially important in the case of patients under the age of 35. Moreover, a previous study observed that the majority of cases of death in diabetic participants was attributable to acute coronary events, and that the 5-year mortality rate for type 2 diabetes (18.9%) was higher than that for type 1 (5.5%).<sup>4</sup> Likewise, type 1 and type 2 diabetes may differ in several aspects, such as their complications. Therefore, the authors should give details of the criteria of the study population.

Another concern is that among 12570 TZD initiators, in the ‘as balanced’ analyses, 56% began TZD monotherapy, 16% added a TZD to metformin, 22% added a TZD to sulfonylurea and 6% added a TZD to combination M + S therapy; only 38% remained on TZD monotherapy throughout the study period.<sup>1</sup> This leaves us wondering how different the results would have been if the TZD

initiators included in the ‘as balanced’ analyses would have been restricted to those who began TZD monotherapy, especially to those who remained on TZD monotherapy throughout the study period.

Our third concern with this study is that the authors did not clearly define the non-user group. If non-use was a substitute for ‘no exposure’, which the authors defined, it would be helpful if a different definition were to be used because no exposure, which the authors defined, might result in a different outcome than that seen for patients who have never used TZD. This leaves us wondering whether the results would have been different for as treated analyses if the reference group would have been defined as those who have never used TZD.

Finally, the reason that the authors chose as the comparison group patients receiving M + S therapy to evaluate ‘the effects of TZD therapy as prescribed in routine clinical practice on coronary heart disease in comparison with other oral antidiabetic therapy’ remains unclear, although authors explained that patients started on TZDs might be more advanced in their disease progression than diabetics started on other oral antidiabetic therapy.<sup>1</sup> Recent studies have shown that the combination of sulfonylureas and metformin might result in a higher risk of adverse cardiovascular outcomes than treatment with metformin alone.<sup>3</sup> In addition, different sulfonylurea derivatives could lead to different outcomes, in particular as regards cardiovascular outcome.<sup>5,6</sup> Among sulfonylurea derivatives included in final analysis, it would be helpful to include information on what kinds of sulfonylurea derivatives were included.

### REFERENCES

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<sup>†</sup>There is no conflict of interest.

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## Response to a comment on ‘the risk of coronary heart disease in type 2 diabetic patients exposed to thiazolidinediones compared to metformin and sulfonylurea therapy’

Dear Editor

We welcome the opportunity to respond to the letter from Chang and colleagues<sup>1</sup> with questions relating to our study of the risk of coronary heart disease in patients with type 2 diabetes exposed to thiazolidinediones (TZD) compared with metformin and sulfonylurea (M+S) therapy.<sup>2</sup> To address the primary concern about our study population definition and whether patients with type 1 diabetes were excluded, we would like to clarify that we defined the study cohorts on the basis of a pharmacy claim for a dispensing of one of the relevant oral antidiabetic drugs, not on the basis of diagnosis codes on health services claims. Because the drugs under investigation, the TZDs, metformin and sulfonylureas, are only indicated for treatment of type 2 diabetes (they have no role in the treatment of type 1 diabetes), cohorts formed on the dispensing of these drugs will be devoid of patients with type 1 diabetes. In addition, due to the uncertainty in ICD-9 coding in claims data, particularly at the 5th digit level that is required to distinguish type 1 from type 2 diabetes, selecting the cohort based on claims for dispensings of drugs indicated only for type 2 diabetes (a TZD or M+S dispensing) was a more accurate way to restrict the study population to patients with type 2 diabetes and to a population that is relevant for study inferences (i.e. persons

with type 2 diabetes using oral antidiabetic drugs). The fact that few people under 30 are present in our study (less than 5%) serves as an implicit validation of our definition as it accords with the expected low prevalence of type 2 diabetes in this age group.<sup>3</sup> In addition, the propensity matching resulted in study cohorts that are well balanced at baseline on complications of diabetes and baseline insulin use.

Chang and coauthors were also concerned that the results may have differed had we restricted the TZD initiators in the ‘as balanced’ analyses to monotherapy users. We would point out that changes in therapy during follow-up are notoriously difficult to account for because the changes in therapy may be a function of therapy (adverse effects or therapy failure) or may be related to changes in the patient’s underlying clinical status. Accordingly, while it is entirely plausible that a cohort of people who remain on TZD monotherapy throughout follow-up may have a different risk of outcomes, they may have a different risk of outcomes due to either a drug effect or a selection effect. In our ‘as treated’ analyses, we examined TZD monotherapy-exposed person-time relative to M+S exposed person time and the results were the same (IRR from Poisson regression = 1.02) as the results from the as-balanced analysis: (HR from Cox proportional hazards model = 1.02).<sup>2</sup> In addition, Chang and coauthors question what the results would have been had we used a