Author's response to reviews

Title: Association of angiotensin-converting enzyme inhibitor therapy and comorbidity in diabetes: results from the Vermont Diabetes Information System

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Author's response to reviews: see over
Dear Dr. Robin Cassady-Cain:

The authors appreciate the careful review of the manuscript by Ramos-Nino, MacLean and Littenberg entitled “Association of angiotensin-converting enzyme inhibitor therapy and comorbidity in diabetes: results from the Vermont Diabetes Information System”. We have responded to each of the reviewers’ comments below and in the text as follows:

**Reviewer 1:**

**Major Compulsory Revisions**

1.- An alternative interpretation of the results of this study including the “treatment-risk paradox” theory is suggested.

   We have reframe the discussion to present ours (there may be a causative association, but the study is not designed to test it) and the reviewers’ alternative explanations (treatment-risk paradox).

2.- A Table with ACE inhibitors and all other variables used is suggested.

   We have added an univariate table with ACE-I use vs. and all variable tested in the study. The multivariable tables are: Tables 4 and 6.

3.- Did the authors model any interaction?

   No, we did not model interactions. We are not sure which interactions the reviewer thinks would make an impact in the present study.

4.- How did the authors build their logistic models?

   The variables selected to built up these models are variables known to be confounders of the outcome variable and important in diabetic populations. The selection of these potential
confounding conditions was based on clinical and epidemiologic judgment and not on statistical determinants. We have included this explanation in Material and Methods.

5.- Was the analysis hypothesis-driven?

It has been our effort to establish the bases for further studies on the effect of chronically use medications in diabetics on comorbidities. We a priori hypothesized that ACE inhibitors may be protective against several comorbidities found in diabetics, particularly cancer. ACE inhibitors, as well as other chronically used medication (like TZDs, already published by the authors), have proven in vitro and in animal models to be useful in reducing cancer progression. The long term goal is to find preliminary data that allow us to propose longitudinal studies to prove these hypothesis-driven studies. The optimal use of these medications would be beneficial for diabetics with high risk of certain conditions.

Reviewer 2:

Major Compulsory Revisions

Problems between the nature of the study and the claimed hypothesis/conclusion

We have re-written the discussion and conclusions to address this comment.

On behalf of my co-authors, thank you for your consideration.

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