Reviewer's report

Title: HbA1c and cardiovascular and renal risk in an adult Mediterranean population

Version: 1 Date: 27 March 2013

Reviewer: Navin Jaipaul

Reviewer's report:

The manuscript is very well written and flows smoothly. As the authors point out, degree of glycemic control is known to be associated with risk for microalbuminuria and CAD, and a natural extension of the literature and biologic plausibility would be to investigate whether HbA1c levels are associated with CKD, particularly among non-diabetics. The findings of an independent and linear association of HbA1c with CKD are interesting but not surprising. Unfortunately, even if valid, they may not be justified based on the study design.

Major Compulsory Revisions

1. In general, prevalence rate ratio is preferable to prevalence odds ratio for a cross-sectional design study. In this study, the two may be similar because CKD prevalence among non-diabetic HbA1c tertiles was low. However.....

2. One could make the argument that a cross-sectional study design is not suitable for studying a disease with a protracted risk period or low prevalence, such as CKD in this case, especially if the exposure is modifiable over time, such as HbA1c in this case. Under this context, effect measures such as the prevalence odds ratio may provide misleading estimates about exposure “risk” which would be better evaluated via a longitudinal cohort design. The authors should address this limitation in their discussion of the results and urge caution about inferring risk of CKD from increasing HbA1C levels based on the study design.

3. Similarly, statements concluding increased risk or relative risk should be avoided as they convey matter-of-fact interpretations, when in fact, they are not justified based on the study design and data, and need further validation

4. The low prevalence rates of CVD and CKD among HbA1c tertiles should be acknowledged as they relate to the above limitations

5. Conclusions may be more robust if the data is demonstrated to validate known prevalences and associations of exposures/outcomes in the direction and degree expected in the studied population.

6. Would use a 130/80 mmHg blood pressure target for defining hypertension when considering CKD patients, especially in the adjusted analysis

7. Some of the inclusion criteria are prone to misclassification bias which may
make the data less robust and should be addressed (e.g., How were patients with previous diagnoses of various conditions identified, by chart review or ICD-classification? A patient with eGFR below 60 ml/min might have acute kidney injury rather than CKD but still be included as a CKD case according to the inclusion criteria, leading to an overestimation of the prevalence rate. This is especially concerning given the low prevalence rates observed and makes the interpretation of the results more problematic as mentioned above)

8. A cross-sectional study design cannot capture the appropriate case definition of patients with CKD which is defined as eGFR below 60 ml/min for at least 3 months

9. The findings may not be generalizable to all Caucasians as the authors conclude. It is limited to a Spanish subset and may not apply, for example, to Western Caucasians whose diet and lifestyle is very different from a Mediterranean one

Minor Essential Revisions

1. Abstract methods section, line 2: should be was undertaken rather than undertook

2. Table 1, male gender: n missing; only percentages are shown. Would include n for consistency.

Conclusion

The manuscript is well written and the study has been generally well conducted, but the conclusions are too far-reaching based on the cross-sectional study design. As long as these limitations are acknowledged and modifications are made as suggested, it should be considered for publication.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests