Reviewer's report

Title: Association between UCP2 A55V polymorphism and risk of cardiovascular events in patients with multi-vessel coronary arterial disease

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Reviewer: Gilberto Velho

Reviewer's report:

The authors investigated the association of UCP2 A55V variant with secondary cardiovascular events in subjects with coronary artery disease enrolled in a prospective randomized trial that compared different treatments. They report an association of A55V with increased cardiovascular risk in the first 2 years of follow-up in the subset of patients with dysglycemia, but not in normoglycemic subjects. No association was observed after 5 years of follow-up.

Revision 2 is a much-improved version of manuscript MS 6144397646368746. However, some important ("major compulsory") points of previous comments were not addressed.

Comments:

- Major Compulsory Revisions

1. Methods / Statistical analysis. Stratification of the comparisons by the glycemic status of the patients has a major impact in the results of the study. For this reason, I believe that the authors should not simply ignore it when defining the threshold of statistical significance. As the authors remarked in their response to the reviewers, even with a conservative correction (i.e. Bonferroni), most of their results would still be considered significant. So, there is no reason for not doing it. Moreover, a more elegant (and less conservative) alternative to Bonferroni's could be used. It would consist in nesting the genotype variable within the "glycemic status" variable in the Cox regression model. This would result in the computation of statistical effects for normoglycemic and dysglycemic subjects separately, adjusted for multiple comparisons due to the stratification by glycemic status.

2. Results: Text and table 2. As stated by the authors in their response to the reviewers "...we provide the reader with 3 different analyses showing the same results: a frequency comparison using a Chi-square test (used in Table 2). The same comparison using Kaplan-Meier curves (Figure 1) and a multivariate adjusted model provided in the results section". There's one too many. Particularly, because a chi-square test (Table 2) is not appropriate for incidence statistics in prospective studies. It does not take into account the impact of confounding covariable, nor the "time to event" effect. My suggestion regarding table 2 is to keep the genotype frequencies and give the hazard ratios (95% C.I.) and p-values of the Cox regression analyses.
Tables and text. It is now clear from the data shown in table 2 that the incidence of CAD (all events) between years 2 and 5 of follow-up is relatively stable in dysglycemic VV carriers (year 2: 32.5%; year 5: 36.3%), while it increases in dysglycemic AA/AV carriers (year 2: 20%; year 5: 31.7%). According to table 1, the age of VV and AV/AA carriers is similar at baseline. What about duration of diabetes? This parameter should be given in table 1. The discussion of this issue (page 10) is difficult to understand: "We speculate that the predictive effect of UCP2 genotype in dysglycemic patients could be related to the time since the dysglycemic status has been acquired. On the other hand, there is no experimental evidence suggesting that the duration of diabetes could play a role in this result."

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

'I declare that I have no competing interests'