Reviewer's report

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

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Reviewer: Gilberto Velho

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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 dysglycaemia, but not in normoglycaemic subjects. No association was observed after 5 years of follow-up.

This is an improved version of manuscript MS 6144397646368746. However, some important points still need to be addressed.

Comments:

- Major Compulsory Revisions

1. Methods / Statistical analysis. The authors should adjust the threshold of statistical significance to take into account the stratification of the comparisons by the glycaemic status (analyses performed separately in dysglycaemic subjects and in subjects with normal glucose tolerance). Applying a simple Bonferroni correction, authors should consider significant p<0.025.

2. Results. Text and tables 2, 3 and 4: It is not clear which statistical test was used and when it was used. P-values in tables 2, 3 and 4 seem to be derived from chi-square tests. This test is not appropriate for incidence studies. In the methods section the authors state that "Survival curves were calculated with the Kaplan–Meier method and differences between the curves were evaluated with the log-rank statistic. We assessed the relationship between baseline variables and composite end-point events using a Cox proportional hazards survival model. Hazard ratios (relative risks) with 95% confidence intervals (CI) demonstrate the risk for combined events." In the results section, which comparison was tested by log-rank statistics and which by Cox? In the last paragraph of results, some odds ratios are given. How were they computed? If they are derived from Cox analyses, they should be given as hazard ratios.

3. The genotype frequencies and number of subjects (AA, AV and VV) at baseline, and at 2 and 5 years of follow-up should be given for subjects with or without CAD, with stratification by glycaemic status. A proper analysis of the data might help to understand what happens between 2 and 5 years of follow-up. It is important to describe what's going on with the data (AA/AV incidence of CAD...
truly catching up, different rates of lost to follow-up for different genotypes including mortality bias) before considering other possible causes for the lack of association (impact of duration of diabetes). Tables 2-4 are difficult to understand because the total number of subjects at each time point is not given. For instance, if we consider table 3, 32.5% of VV carriers had a CAD event after 2 years of follow-up, but only 8.9% of them had a CAD event after 5 years of follow-up. This presentation does not make much sense. Moreover, if the number of subjects was greatly reduced at year 5 of follow-up your comparisons might have lacked power to detect an allelic association at this time point.

- Minor Essential Revisions
The manuscript still needs a writing revision.

**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