Reviewer's report

Title: Genetic Association Analysis of Coronary Collateral Circulation in Patients with Coronary Artery Disease Using 22 Single Nucleotide Polymorphisms Corresponding to 10 Genes Involved in Postischemic Neovascularization: Results of a 5-Year Prospective Study

Version: 2

Date: 26 January 2015

Reviewer: Niels van Royen

Reviewer's report:

The present study describes a large-scale study, searching for associations of coronary collateral artery growth and SNPs of several factors known to play a role in collateral artery growth. The rationale for the study is sound. A large heterogeneity in coronary collateral growth can be observed in patients, pointing to potential differences in genetic background.

The magnitude of the collateral circulation is measured angiographically rather than using pressure based collateral flow index. The angiographic Rentrop score is a qualitative rather than a quantitative technique.

Major Compulsory Revisions

For the original Rentrop score, contrast was injected in a donor artery, while occluding the recipient artery with a balloon. In the methodology section it is not described that the recipient artery is indeed occluded by balloon. If this is indeed not the case, in the present cohort, only in patients with a total occlusion a correct Rentrop classification could be obtained. Therefore, it might be of interest to repeat the analysis only in patients with a complete or sub-total occluded coronary artery.

The use of a “modified” Rentrop without occlusion of the recipient artery might also explain why such a relative low number of patients display well-developed collateral arteries in this cohort. Another explanation is the inclusion of a large portion of patients with intermediate lesions since the angiographic threshold was 70%. This should be addressed in a limitations section, together with the shortcomings of angiographic assessment of the collateral circulation.

Minor Essential Revisions

Did the authors perform a CASS or Gensini-score? It would be of interest to see whether the different SNP’s are related to the extent of CAD.

In the papers by Ozaki (Nature, 2004) and van der Laan (European Heart Journal, 2013) the rs7291467 polymorphism was found to be related to myocardial infarction and collateral growth respectively. Here, the authors at several instances (in text and table) refer to this polymorphism as rs1028728.
Please correct.

The paper by Zhang, looking at 54 SNPs in relation to collateral artery formation should be referenced and discussed. (Hum Hered. 2008;66(4):252-64.).

Discretionary Revisions
The role of TGF-beta in arteriogenesis was first described in: van Royen et al, FASEB J. 2002 Mar;16(3):432-4.

**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