Author's response to reviews

Title: Six sequence variants on chromosome 9p21.3 are associated with a positive family history of myocardial infarction: a multicenter registry

Authors:

Thomas Scheffold (th.scheffold@t-online.de)
Silke Kullmann (kullmann@herz-keislaufforschung.de)
Andreas Huge (andreas.huge@lifa-muenster.de)
Priska Binner (binner@herz-keislaufforschung.de)
Hermann R Ochs (h.r.ochs@gmx.de)
Wolfgang Schöls (wolfgang.schoels@ejk.de)
Joachim Thale (kardiologie@schuechtermann-klinik.de)
Wolfgang Motz (prof.motz@drguth.de)
Christoph Stellbrink (christoph.stellbrink@klinikumbielefeld.de)
Thomas Dorsel (t.dorsel@jhwaf.de)
Hartmut Gülker (hartmut.guelker@helios-kliniken.de)
Hubertus Heuer (heuer@joho-dortmund.de)
Monika Stoll (monika.stoll@lifa-muenster.de)
Franz Josef Hegge (dr.hegge@krankenhaus-werne.de)
Wilfried Dinh (wilfried.dinh@helios-kliniken.de)
Georg Haltern (georg.haltern@helios-kliniken.de)

Version: 5 Date: 17 January 2011

Author's response to reviews:

Dear Editors,

Thank you very much for extending the deadline and for giving us the opportunity to resubmit our thoroughly revised manuscript.

We would like to respond to the reviewers’ remarks and suggestions which we appreciate very much.

Rev. 1 Elmo Mannarino:

Ad 1

In fact – as acknowledged in our manuscript – the lack of an own control group may represent a limitation of the study. However, with purpose, we decided not to recruit an own control group because the heterogeneity of each SNP used in our study is abundantly documented and proofed in a sufficient number of chromosomes from other groups. We do not expect an own control group to differ significantly from the control groups recently published. So we believe that our results are only at a limited bias:

• Not all SNP’s used in our study where published in one single previous paper. Therefore, the data given for the different SNPs were taken into the analysis as
control groups from the appropriate papers. The criterion for choice of the appropriate control group was the disposability of data for each SNP analysed. Care was taken to confine to European studies to avoid genetic population bias.

- Four control groups were chosen ranging from 718 to 9053 control data, as given in the methods section.

Ad2

The association of the 9p21 genotypes with myocardial infarction in the presence of a positive family history has been statistically analysed. Results are added in the tables and figures showing indeed that the odds of experiencing MI in the presence of a positive family history is significantly raised over the odds of experiencing MI when the family history of MI is empty. As this is the key message of the paper we are happy to give you the appropriate data. Haplotype analysis was also added according to rev. 2, also revealing a significantly raised risk of MI in patients with 9p21 gene variants and a positive family history over patients with the same variants but without a positive family history. This also stresses the association of the 9p21 variants with the family history of MI.

Ad 3

Correct. The correct number of patients analysed is 976 all over the paper, and this was corrected.

Rev. 2 Jeffery Anderson

Ad 1

“Throughout the manuscript, an association of 9p21 with MI is stressed. Yet, numerous reports have shown that the association is with the initiation / development of coronary atherosclerosis but not directly with the precipitation of MI. Some recognition of this should be made.”

Often, myocardial infarction represents the first clinical manifestation of coronary atherosclerosis. The study group comprised a total of 976 patients aged < 65 years of age with acute MI as acute manifestation of coronary atherosclerosis. The phenotype to which genotypes are related in this study therefore is coronary atherosclerosis with manifestation of acute myocardial infarction.

Yet, the study was not designed to test the hypothesis that 9p21 is a precipitator of acute MI but – as stated in the title, the abstract and in the background, and as given in the analysis and discussion – was designed to find an association of the 9p21 genotype with a positive history of family disposition of CAD in younger patients experiencing myocardial infarction. The study therefore is more related to the familial aggregation of the disease, completely in line with the editorial of Anderson et al in JACC 56; 2010. Recognition of this is made by adding the statistical results (comparison of the OR (+/- CI) of MI patients with a positive family history of MI with the OR (+/s CI) of MI patients with negative family history of MI) and discussion of this topic in the discussion section.

Ad 2

Haplotype association with the phenotypes (MI with and without positive family
history) was actually significant; results are given in figure 2.

Ad 3

It is only few published regarding the familial aggregation of MI and the association of the 9p23.1 locus. To study familial aggregation was the major topic of our study. However, the focus of the current research efforts lies on the association of the 9p21.3 locus to the extent and progression of CAD, which is under controversial discussion (see Chen et al. BMC Cardiovascular Disorders 2009, 9:3 vs. Dandona et al. J Am Coll Cardiol 2010, 56(6):479-486.), but was not stressed with our study.

Ad 4

We would love to contribute to the question of how 9p21 modifies the prognosis of acute MI. However, the study was primarily planned in a cross-sectional design, therefore follow-up data are currently not available. In the current study we focused on the association of 9p21 genotype variation with a positive family history of MI in patients experiencing acute MI as manifestation of coronary artery disease.

Ad 5

The proportion of STEMI to NSTEMI patients do not reflect the clinical reality of patients with acute coronary syndrome. The cause of this is very simple: the study was initiated including only patients revealing STEMI. Because of a low inclusion number we amplified the inclusion criteria with patients having NSTEMI. The distribution of all parameters was the same, so we had no argument analysing both groups together. Secondly the 9p21.3 locus has been shown to be significant associated with coronary artery disease as well as with acute myocardial infarction. So we did not expect any differences between associations to any stage of coronary artery disease, including NSTEMI and STEMI patients.

Ad 6

See comment Rev. 1/ad 1

We hope that we could full fill all requirements for a positive vote.

If there is any question, please let us know for solving.

With kind regards