Title: The Impact of Coronary Artery Disease Risk Loci on Ischemic Heart Failure Severity and Prognosis: Data from the COntrolled ROsvastatin multiNAtional trial in heart failure (CORONA)

Authors:

Vincent G Haver (v.g.haver@umcg.nl)
Niek Verweij (n.verweij@umcg.nl)
John Kjekshus (john.kjekshus@medisin.uio.no)
Jayne C Fox (jayne.fox@astrazeneca.com)
Hans Wedel (hans.wedel@biostat.se)
John Wikstrand (john.wikstrand@wlab.gu.se)
Wiek H van Gilst (w.h.van.gilst@umcg.nl)
Rudolf A de Boer (r.a.de.boer@umcg.nl)
Dirk J van Veldhuisen (d.j.van.veldhuisen@umcg.nl)
Pim van der Harst (p.van.der.harst@umcg.nl)

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Author's response to reviews: see over
Date October 29th, 2014

Dear Dr. Tregouet,

In response to your letter of 9th October 2014 we wish to consider submitting a new manuscript to the journal addressing the all of the Editors’ concerns as suggested in the paragraph of the SECTION EDITOR.

We like to emphasize that this data is derived from the CORONA trail involving 3,320 ischemic heart failure patients, the largest heart failure cohort with DNA available to date. We also like to note that this work has been performed in collaboration with AstraZeneca and that a lot of effort has gone in to establishing public-private collaboration to enable the determination of the genetic variants of interest to the community. We agree with the associate editor that it would be of interest to continue genotyping the additionally reported 46 variants from the latest CARDIoGRAMplusC4D Nature Genetics paper but without the DNA in our possession (not allowed due to ethical restrictions because of informed consent restraints) and the ongoing reorganisation at AstraZeneca genotyping facility, it is not realistic to embark on additional genotyping and have available data within a reasonable timeframe. We feel, however, that we should publish the existing data to ensure it becomes recognised in the public domain and we do not ‘sit on’ this relevant data and deleteriously biasing the ‘weight of evidence’ in favour of positive associations. Everyone is aware of the publication bias in genetics has caused a lot of unmet expectations. We therefore would like to resubmit a revised version addressing the Editor’s concerns.

SECTION EDITOR:
"The Associate Editor is not completely satisfied by the whole response made by the authors as she noticed that one main issue still remains; The one related to the selection of variants. If the authors can add a paragraph in the discussion about the limitation of their work related to this point, I could consider a re-revision of the manuscript.

We agree with the Section Editor that our experiment is limited by the number of variants tested.

We have added a paragraph in the discussion in which we address these limitations:
“Among the strengths of the present study are the size and quality of the study cohort, which is the largest heart failure cohorts with DNA available to date. Patient characteristics and outcomes have been collected and documented systematically within the framework of a clinical trial. However, there are some limitations which we need to address. At first, we have limited the variants tested to the N.J. Samani paper published in 2007 [5] and the variants reported by the Coronary Artery Disease Consortium in 2009 [7]. Recent GWA studies have identified additional variants involved in CAD development. The recent publication by the CARDIoGRAMplusC4D consortium reported 46 genetic variants associated with CAD risk [19]. We cannot exclude that there might be variants among these 46 that are related to heart failure outcomes and this remains an objective for further study.”

The re-revised version should also include a limitation paragraph in the discussion about the power considerations related to the lack of association observed in the primary composite endpoint analysis. I will recommend the authors to provide power calculations not at the 0.05 statistical threshold as they used in their responses to reviewers but with the 0.0071 threshold they have used in their primary endpoint analysis."

We performed a post-hoc power calculation with $P$ value threshold of 0.0071 and found that the power ranged from 0.90 to 0.91 (depending on the frequency of the risk allele ranging from 0.25 to 0.55), assuming that the effect size of the risk variant is comparable to the CAD discovery GWAS (genotype relative risk Aa = 1.3; genotype relative risk AA = 1.6).

We have included the following paragraph to the discussion:
“The performed a post-hoc power calculation to consider whether our study might have had lack of power [20]. Assuming an effect size of the risk variant comparable to the CAD discovery GWAS (genotype relative risk Aa = 1.3; genotype relative risk AA = 1.6) [5, 7], we calculated the power to detect a significant effect for a variant (prevalence cases = 0.175; number of cases = 581; control:case ratio = 4.7). The power of our analyses ranged from 0.90 to 0.91 depending on the frequency of the risk allele (ranging from 0.25 to 0.55).”

ASSOCIATE EDITOR:
“Although the manuscript has been improved in some aspects, the most critical issue of variant selection for these analyses has not been addressed adequately. It is not correct to state that the used variants are the ones that are most robustly associated, and time and cost reasons are not seen to be sufficient. If the analyses are performed more comprehensively, i.e., using all relevant variables, the results might be interesting and relevant.”

We agree with the associate editor that it would be of interest to continue genotyping the additionally reported 46 variants from the latest CARDIoGRAMplusC4D Nature Genetics paper but without the DNA in our possession (not allowed due to ethical restrictions because of informed consent restraints) and the ongoing reorganisation at AstraZeneca genotyping facility, it is not realistic to embark on additional genotyping. However, we feel we should publish the existing data to ensure it becomes recognised in the public domain and we do not ‘sit on’ this relevant data and deleteriously biasing the ‘weight of evidence’ in favour of positive associations. Everyone is aware of the publication bias in genetics has caused a lot of unmet expectations. We feel that our analyses, of the first 7 variants, will still be valuable and of interest for the readership of BMC Medical Genetics due to the size of the CORONA cohort and the intriguing hypothesis which we have investigated.

We have added the following paragraph to the discussion of the manuscript, stating our reflections according to the limitations of the study:

We added the following paragraph to the discussion of the manuscript, stating our reflections according to the limitations of the study:
“Among the strengths of the present study are the size and quality of the study cohort, which is the largest heart failure cohorts with DNA available to date. Patient characteristics and outcomes have been collected and documented systematically within the framework of a clinical trial. However, there are some limitations which we need to address. At first, we have limited the variants tested to the N.J. Samani paper published in 2007 [5] and the variants reported by the Coronary Artery Disease Consortium in 2009 [7]. Recent GWA studies have identified additional variants involved in CAD development. The recent publication by the CARDIoGRAMplusC4D consortium reported 46 genetic variants associated with CAD risk [19]. We cannot exclude that there might be variants among these 46 that are related to heart failure outcomes and this remains an objective for further study.”

We are grateful to you for considering this re-revised manuscript for publication.

Yours sincerely,

Pim van der Harst,
on behalf of the co-authors
Additional references included in the manuscript
