Author's response to reviews

Title: The CYP2J2 G-50T Polymorphism and Survived Myocardial Infarction in Patients with Cardiovascular Risk Profile

Authors:

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Author's response to reviews: see over
To the editor:

We are herewith sending to you the revision of our manuscript: “The CYP2J2 G-50T Polymorphism and Survived Myocardial Infarction in Patients with Cardiovascular Risk Profile”.

You can find a List of Corrections, based on the Comments of the three Reviewers:

Reviewer 1, Daniel Petrovic:

Major compulsory revisions:

Reviewer:
The MS "The CYP2J2 G-50T Polymorphism and Survived Myocardial Infarction in Patients with Cardiovascular Risk Profile" by the authors Jan Börgel, Daniel Bulut, Christoph Hanefeld, Horst Neubauer, Andreas Mügge, Jörg, T Epplen, Tim Holland-Letz and Martin Spiecker is is well-written manuscript. The study demonstrates that the CYP2J2 G-50T polymorphism might increase the risk for myocardial infarction.

The problem of the study is its design. Namely, half of patients with CAD originates from OSA group (in which coronary angiography was not performed), whereas the other half of the patients originates from the CAR group (in which coronary angiography was performed). In the CAR group the difference was not statistically significant in genotype distribution (Table 2) (GT + TT vs. GG: 29.2% vs. 23.9%, P=0.351), whereas in the OSA group the difference was of borderline significance (GT + TT vs. GG: 10.9% vs. 4.5%, P=0.06); both groups together demonstrate the association between the T allele and MI (GT + TT vs. GG: 21.6% vs. 13.7%, P=0.026).

Answer of Author:
The authors are aware about the fact, that coronary angiography was performed consequently in the CAR-group only. Therefore the diagnosis coronary heart diseases was not analysed. However, the aim of the study was the risk myocardial infarction in the past (history of myocardial infarction = survived myocardial infarction). This risk is not defined by coronary angiography. The diagnosis of myocardial infarction in the past was defined by anamnesis and chart history of the patients in both study groups. Therefore, according to myocardial infarction, the methods were the same in both groups.

Reviewer 2, Winfried Renner:

Major Compulsory Revisions

Reviewer:
1) The aim of the study is not very clearly stated. The target phenotype “survived myocardial infarction” is a bit puzzling: Do the authors suggest that CYP2J2 genotypes increase the risk for MI, or is the CYP2J2 genotype improving your chances to survive a MI? This should be clarified in the introduction and results sections.
**Answer of Author:**
Since a myocardial infarction which is diagnosed by anamnesis of the patient must be a survived infarction and since fatal myocardial infarction cannot be diagnosed by this method, we called the target “survived myocardial infarction”. In the revised manuscript, this inappropriate phrase was either changed into “a history of myocardial infarction” or deleted.

**Reviewer:**
2) After correction for classical risk factors, the CYP2J2 T allele is NOT significantly associated with survived MI (p = 0.073). Thus, the main finding is negative and should be presented and discussed as such. When the authors conclude the CYP2J2 variant is indeed associated with MI, they thereby suggest that their own finding is false negative. This should be clarified.

**Answer of Author:**
The manuscript was reviewed and changed. The results are now discussed as not significant more clearly.

**Reviewer 3, VA Cameron:**

**Major Comments:**

**Reviewer:**
This manuscript reports a possible association between the CYP2J2 G-50T polymorphism and survival after myocardial infarction. The study group is heterogeneous, being a combined cohort of sleep apnoea study patients and coronary angiography patients.

**Major Comments:**

1. It is not clear whether the authors are claiming that the CYP2J2 polymorphism T-allele is associated with an increased risk of having a myocardial infarction (MI) or of being a survivor of MI. They state that fatal cardiac events could not be considered in this study, and hence it is difficult to determine whether the gene polymorphism has a beneficial association with survival or an adverse association with increased risk of MI.

**Answer of Author:**
The manuscript was changed according to the reviewer´s comments, see also Reviewer 2.

**Reviewer:**
2. Univariate analyses suggested that carriers of the T-allele were more likely to be among those who had survived myocardial infarction (p=0.026). However, with multivariate regression analysis the relationship did not reach significance (p=0.073) when corrected for other risk factors (diabetes, hypertension, dyslipidemia, age, smoking and gender). Thus it is uncertain whether any genetic association has been demonstrated.

**Answer of Author:**
The manuscript was changed. See also Reviewer 2

**Reviewer:**
3. The methods for ascertaining whether patients had dyslipidemia, diabetes,
hypertension and prior MI are unclear, and seemed to largely depend on self-reported recall, especially in the sleep study patients. Were lipid profiles assayed in all cases or only if the patient did not recall ever being diagnosed? Were lipid measurements fasting? Was the diagnosis of hypertension made on three independent occasions or just three sequential measurements?

**Answer of Author:**
Lipid profiles were assayed in all cases. The blood pressure measurements were performed in 3 different occasions during the day: 8:00 AM, 2:00 PM and 8:00 PM.

**Reviewer:**
4. The manuscript needs to be extensively rewritten into colloquial English. See below and manuscript.

**Reviewer:**
**Minor Comments:**

**Reviewer:**
5. The Title is poorly worded. Do the Authors mean: The CYP2J2 G-50T Polymorphism and Survival after Myocardial Infarction in Patients with High Cardiovascular Risk Profiles?

**Author:**
manuscript was changed (s. manuscript). The Study does not focus on survival after myocardial infarction, but on history of myocardial infarction. The was clarified as stated above. Therefore the phrase “survived myocardial infarction” is not used any more.

**Reviewer:**
6. The Abstract could be much more succinct. For example, the methods section of the Abstract could read: The CYP 2J2 polymorphism was genotyped in 512 patients with sleep apnoea (group: OSA) and with high cardiovascular risk profiles and in 488 patients admitted for coronary angiography (CAR group). The CYP 2J2 G-50T polymorphism was evaluated for a potential correlation with survival after myocardial infarction. Genotyping was performed by allele-specific restriction and Light-cycler analysis.

English usage – some examples of non-colloquial English (partial list)

**Title**

**Abstract**, last sentence of results- “In the multivariate logistic regression….while the significance for this relationship was barely reduced to the trend level (p=0.073).” This should read “In the multivariate logistic regression ….but this trend was not significant (p=0.073).”

**Background**, line 18 – change 17,3% to 17.3%.

**Background**, last line – delete the words “on average.” The patients had high cardiovascular risk profiles, and the words “on average” are superfluous.

**Methods**, line 7 and elsewhere - instead of “anamnesis” use “patient recall.”

**Methods**, line 10 – instead of “whenever” use “…and also if patients were taking…”

**Methods**, line 11 should read – “The diagnosis of hypertension was established if patients were…”

**Methods**, line 14 – instead of “controlled” use “confirmed.”

**Methods**, Statistical Analysis section is in a different font from the remaining text.

**Methods**, Statistical Analysis line 5 - “…considered significantly different if
p<0.05.”
Results, line 1 – (11.1%) appears to be repeated.
Results, line 9 – use “invalid” instead of “unfeasible.”
Discussion, line 12 – “…that OSA itself deteriorates conventional risk factors…”
is not correct. Possible alternatives are “worsen,” “aggravates” or “exacerbates”?
Discussion, line 18 – “…these findings…”
Discussion, page 2, line 5 – “Since the polymorphism has been detected
recently, there are currently few population-based studies…”
Discussion, page 2, line 6 – “found significantly more carriers…”
Discussion, page 2, line 8 – “in cells with the T-allele but not in wild-type cells,
nicotine significantly…”
Discussion, page 2, line 19 – “…large cohort of patients…” (not collective).
Discussion, page 2, line 21 – “Our previous experience has shown that
genotyping…” (not Previous own experience... and no comma after shown)
Discussion, page 2, line 23 – “Light-cycler analysis of the G-50T polymorphism is
more reliable…”
Discussion, page 3, line 1 – “genetic predisposition to…” (not “in”)
Discussion, page 3, line 6 – “Observing the overall group of 1000 patients…”
Limitations, line 5 – “…thus it is not as reliable as the clinical diagnosis available
in the CAR group.”

**Answer of Author:**
We appreciate the careful and exact analysis of the Reviewer and are pleased about
the constructive and helpful criticism. The Manuscript was reviewed and changed
according to the recommendation of Mr. Cameron.

Thank you very much, we are looking forward to your answer.

Best regards

Jan Börgel