Author's response to reviews

Title: SPECT myocardial perfusion imaging as an adjunct to coronary calcium score for the detection of hemodynamically significant coronary artery stenosis

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Author's response to reviews: see over
Dear Dr. Kruk,

Dear Editors,

we wish to re-submit the revised manuscript titled “SPECT myocardial perfusion imaging as an adjunct to coronary calcium score for the detection of hemodynamically significant coronary artery stenosis” to be considered for publication in your esteemed journal. We appreciate the possibility of revising our work according to the very helpful comments of the reviewers. Please find below the detailed answers to the reviewers remarks.

The study was conducted at the University of Munich, Department of Cardiology, Grosshadern Campus, Munich, Germany. The institutional review board approved the study protocol, which was in compliance with the Declaration of Helsinki. This is now explicitly stated in the Methods section. We additionally corrected a typo mistake in Table 1; the number of hypertensive patients was incorrectly summed up.

To Reviewer 1:
Thank you for your comments. We appreciate your help.

Major compulsory revisions.

It is true, that according to current guidelines coronary calcium scoring (CS) is not recommended as a diagnostic modality in symptomatic patients, but can be used in asymptomatic patients for risk stratification. Still there is...
evidence that also in symptomatic patients CS might be of certain diagnostic value. As reported by Haberl et al. a CS of 0 had a high negative predictive value above 97% for the exclusion of significant coronary artery disease (CAD). Also the prevalence of CAD rises with increasing CS values. Therefore the use of CS as a filter before invasive coronary angiography (ICA) or further non-invasive examinations might be useful. Aim of this study was to evaluate a combined non-invasive approach for the detection of significant CAD by utilizing CS in combination with an additional nuclear stress testing modality (in our study SPECT-MPI) in symptomatic patients with a moderate to high pre-test probability of having obstructive CAD. Significant CAD thereby was defined as luminal vessel obstruction ≥75% likely to cause ischemia in ICA serving as the gold standard. In this research setting we planned to answer the question in which clinical situation depending on the results of both, CS and SPECT-MPI, one or the other or both modalities in combination will lead to diagnose significant CAD leading to intervention non-invasively to develop a protocol for clinical routine use. This goal in now more emphasized in the introduction section in order to prevent misinterpretation of our data as also Reviewer 2 suggested clarification that this study was performed in a research setting. With respect to our results initial evaluation should be performed with CS to spare the patient radiation exposure compared to a nuclear study in first place. In case of exclusion of coronary calcifications no additional testing is necessary as discussed in the discussion section. The implications of our results for clinical use are now explicitly stated in the Conclusion section which was rephrased. We hope that our changes will now clarify methodology.

Minor essential revisions.

1. We defined significant CAD as luminal obstruction of ≥75% where stress induced ischemia can be assumed and therefore evaluated with SPECT-MPI. We agree with you that this approach increases the number of false-positive results resulting in lower specificity and positive predictive value. A luminal obstruction of 50% is unlikely to cause ischemia with its typical symptoms of chest-pain. As the title states we sought to evaluate the possibility to detect hemodynamically significant coronary artery stenosis. This approach reflects a real world setting as revascularization procedure in a 50% stenosis usually is not warranted. But we also feel that this should be more emphasized in the discussion section to prevent misinterpretation.

2. In order to guarantee a blinded study fashion with ICA being the gold standard for stenosis detection, revascularization was based on luminal coronary artery stenosis as evaluated by quantitative coronary analysis (QCA) reflecting clinical practice in the “pre-COURAGE era” when our study protocol was designed. The decision for coronary intervention was independently made by the examiner without recognition of stress induced ischemia, and thus being controversial nowadays. This limitation is now discussed detailed in the limitation section.

3. We again agree with you that a CS plus SPECT-MPI strategy is comparable to SPECT-MPI alone. By using CS as a filter before nuclear stress testing, a considerable amount of symptomatic patients (67/351; 19%) would have been prevented from further scanning with more radiation exposure. Moreover, CS provides additional information besides negative SPECT-MPI as it directly reflects coronary atherosclerosis and therefore can be used as an individual risk factor; although currently no general accepted recommendation exists concerning primary
prevention therapy in these particular patients based on their CS values. This was already mentioned in the discussion section, but it is now more pronounced.

4. The limitations are now discussed in more detail including the remarks of Reviewer 2.

To Reviewer 2:
Thank you for your helpful comments.

1. We now implemented CS and average number of cardiovascular risk factors into our Table 1. Additionally CS and average number of risk factors were stated in the Patients Section

2. To clarify that this study intended to evaluate in which clinical situation CS alone (with lower radiation exposure) or in combination with an established non-invasive modality for myocardial ischemia detection is useful this research setting needed to be established. Thereby ICA served as the gold standard. We feel according to your remarks that this needed to be more explicitly stated (see also below).

3. The ROC values are now given in the Results section. Thereby a significant increase of diagnostic accuracy could not be shown. Still it was not the primarily aim of the study to demonstrate a higher diagnostic accuracy of a combined approach. In fact we intended to examine in which clinical situations a combined approach of CS and SPECT-MPI is useful and more importantly in which situations we can refrain from one of the examinations. With this approach 19% of initially included patients theoretically would have been prevented from further non-invasive testing by exclusion of calcification. In 139/284 (49%) of patients with positive CS, additional SPECT-MPI excluded significant ischemic burden.

4. Your remarks were implemented in the Limitations Section. The utilization of different scanner technologies (MDCT and DSCT scanners) poses the risk of inconsistent calcium score values. A currently published head-to-head comparison of these two scanner types by Ghadri et al. revealed an excellent inter-scanner agreement for Agatston scores with a correlation coefficient of 0.976 despite relatively wide limits of agreement and a coefficient of variation 15.1% even in case of different vendors. Calcium mass score as well as calcium volume score were also evaluated showing also excellent correlation, but wider limits of agreement in Bland-Altman analysis. Interestingly the authors found that the use of different workstations had a greater influence on the comparability than the scanner technology. To account for those possible sources of error a comparable acquisition protocol for both scanner technologies routinely is used at our institution and the same workstation with the same software solution was utilized to calculate the Agatston score. Finally patients were grouped in accordance to the occurrence of coronary calcifications; CS=0 vs. CS>0. And this should be the same for both scanner types utilizing the same acquisition parameters.

5. Again the aim of the study was to evaluate a clinical scenario in which adding a nuclear stress study to prior CS provides additional useful information for the detection of hemodynamically relevant CAD. Thus evaluation took place in a research setting. For clarification the Background section was rephrased (see also comment to Reviewer 1; Major compulsory revisions).

The manuscript has not been published previously and it is also not under consideration for publication else-
where. All co-authors have read and agreed to the content of revised the manuscript. No author has financial interest in the subject matter or materials mentioned in the paper. The study was conducted at the Ludwig-Maximilians-University, Grosshadern Campus, Munich, Germany. All patients gave written informed consent and the study protocol was approved by the institutional review board.

Please find below my address and e-mail for correspondence.

Thank you for giving us the possibility to revise our manuscript.

Yours sincerely,

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