**Title:** Prognostic Value of Dual-Source Computed Tomography (DSCT) Angiography Characteristics in Anomalous Coronary Artery from the Opposite Sinus (ACAOS) Patients: A Large-Scale Retrospective Study

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**Author’s response to reviews:**

Dear Prof. Ciaran Martin Fitzpatrick and Prof Michiel Voskuil:

Thank you very much for carefully reviewing our revised manuscript (manuscript ID: BCAR-D-18-00759R1, entitled "Prognostic Value of Dual-Source Computed Tomography (DSCT) Angiography Characteristics in Anomalous Coronary Artery from the Opposite Sinus (ACAOS) Patients: A Large-Scale Retrospective Study". These priceless comments are exceptionally inspiring and constructive for our work. We’re horned and grateful for your decision in the letter dated the 3rd, September considering a revised version of our manuscript, addressing all the issues brought up by editors and the reviewers.

The majority of the comments were amended by providing information in our manuscript. These changes were highlighted with different color (red to Editor and green for reviewer 1 (Prof Michiel Voskuil)).
Responses to the Editor:

Many thanks for the positive view of our work and the warm recommendation and kind remind. Below, I will detail how we revised our manuscript according to each of the comment (in italic). Corrections made in the text in response to these comments are highlighted in red.

- For table 2 and table S1, i.e. where you did not acquire the full data recommended by the reviewers to include, please include a limitations section in the discussion detailing that you did not record this data.

Thanks for the precious advice and kind remind. The reviewer suggested we add more information for the patients with MACE (including exercise testing and other evidence to better understand the clinical path, table S1), and more detailed classification of the clinical symptoms of the patients referred to CCTA (exertional and non-exertional, table 2). In the revised manuscript, we tried our best to be more detailed on the patients’ information in table S1 but failed to better classify the chest pain patients due to the innate drawbacks of the retrospective study. Actually we have already added some comments in the limitation section in the revised section to discuss over this issue. Following the editor’s suggestion, we have strengthened this part by directly detailing that we did not record this data in this newly revised one, and hope this one would look better. (DISCUSSION, line 413-417,419-422).

- For any data which could identify patients, e.g. table S1, please ensure that "consent for publication" has been acquired. Otherwise, remove data that could potential identify the patient, i.e. age and sex of patient

We agree with the editor’s comment. Thanks for your warm remind and we have deleted the “age and sex” from the table S1 in the revised manuscript.

Responses to Reviewer #1 (Prof Michiel Voskuil):

Thanks for the reviewer’s positive comments and we feel very appreciative for your constructive opinions, as well as the kind indication of our pitfalls. Below, I will detail how we revised our manuscript according to each of the comment (in italic). Corrections made in the text in response to these comments are highlighted in green.
One major important message should be to make a clear distinction between L-ACAOS and R-ACAOS throughout the paper. As stated previously, patients with R-ACAOS generally have a benign clinical course. In contrast, as we know, patients with L-ACAOS are more prone for arrhythmias and sudden cardiac death. Already in the first sentences of the abstract I would suggest to state this difference:

"Most reported cases of right anomalous coronary artery from the opposite sinus (R-ACAOS) have a benign clinical outcome. However, patients with left ACAOS (L-ACAOS) are more at risk for arrhythmias and sudden cardiac death."

Also, in the conclusions of the abstract:

"Patients with L-ACAOS and severe stenosis were at higher risk of adverse clinical events in the mid-term follow-up, and positive clinical intervention might be needed to help them avoid the malignant clinical events."

Introduction:

"Although this anomaly has been considered as relatively "friendly," compared with other congenital diseases, epidemiological studies have identified L-ACAOS as a major factor of…"

Finally, in the discussion section, the distinction between L-ACAOS and R-ACAOS should be emphasized much more.

Thanks for your generous suggestions! Following your guide, we have added the comments to better differentiate the R-ACAOS and L-ACAOS in the revised manuscript (ABSTRAC, Line 55-57, 79-80; INTRODUCTION, Line 104-105 DISCUSSION, Line 360-362, 431-434). Additionally, we changed the abbreviations for “right anomalous coronary artery from the opposite sinus” to R-ACAOS and “left anomalous coronary artery from the opposite sinus” to L-ACAOS at other places of the manuscript accordingly. However, considering that patients with R-ACAOS and L-ACAOS have completely different anatomic features, and the number of L-ACAOS was not good enough, our study’s prognosis analysis was only focused on patients with R-ACAOS (as we mentioned that “…L-ACAOS is considered malignant and more emphasis or surgical therapy is provided to the patients, treatment for patients with R-ACAOS has not been completely decided, and the prognosis of such patients with conservative therapy is also encouraged”) and thus we were not able to add the comments “patients with L-ACAOS were at higher risk for MACE” in our conclusion. We were sorry for the ambiguous words we used before and we have modified the conclusion part to make it more clear.
Moreover, it is important to distinguish the different anatomical types of L-ACAOS, since particular L-ACAOS with an interarterial course (between aorta and AP) are considered to be malignant. In lines 253-255 the authors describe

"A total of 6 types of ACAOS were recognized. The subpulmonic type (n = 97, 53.3%) was the most common for ARCA-L while the retroaortic type (n = 14, 48.3%) was the most common for ALCA-R (Figure 4(c))."

How many had an interarterial course? Were those the patients with adverse events / deaths during follow-up?? This anatomical distinction then should also be taken into account in the Cox proportional hazards model. Please

Thank you for your kind remind! We agree that the interarterial is one of the most malignant anatomic features, which is recorded as suprapulmonic type as we mentioned in our METHODS part. We have added the texts for describing the prevalence of this vessel route type for both R- and L- ACAOS in the revised RESULTS part. (RESULTS, Line 253-256) Simultaneously, we updated the table S1 to show the vessel routes of the patients with MACE. Nevertheless, only one of the patients with MACE was with a vessel route of interarterial route. In our prognosis analysis, all the anatomic features were considered (including the vessel type as we mentioned in our results part) but according to the results, the vessel route failed to have predictive value for MACE.

-A nice study has recently been published on the use of intracoronary physiological assessment and -imaging using FFR and IVUS bij Driesen et al. Maybe add this study in your references / Table 1.*

Thanks for your great suggestion! We have added it to the revised table 1 and discussed this manuscript in our revised DISCUSSION part. (DISCUSSION, Line 353-356). The order of references was changed accordingly.

- Table3: Table 3 CTA findings of the abnormal right coronary artery patients.

Most likely this should be: Table 3 CTA findings of the abnormal coronary artery patients.

Sorry for the misunderstanding title but we did only analyze the patients with R-ACAOS for detailed CTA features and the prognosis. As we have noted before, we finally chose to focus on R-ACAOS when analyzing and comparing the CTA findings in this study. Anyway we still changed the title of table 3 to be more specific and clear.
- The numbering of the Figures after the text does not fit with the numbering in the text… Please correct.

Thanks for your kind remind. We have re-checked and updated the order of the figures and tables in our revised manuscript and changed the corresponding order in the manuscript accordingly.

- Also please state in Figure 5 which ROC curve belongs to which entity (stenosis, HW ratio etc). The curves are quite blurry; please improve the image quality.

Thanks for your warm recommendations! We have added the corresponding title for the ROCs in the revised manuscript. We also uploaded a new one with better image quality for the new manuscript.

Additionally, we have changed the order of “References” due to some sections of text were revised, especially the “Discussion”. And we updated the funding information for the time interval between the first manuscript and this new one.

Now we would like to express again our most sincere gratitude for your extraordinary help to polish our work. Thanks again for giving us this second chance to make the substantial revisions according to your comments! We hope the above response can address your questions properly and please don’t hesitate to contact with us if you have any further questions. We will try our best to finish them.

Best regards,

Zhi-gang Yang, MD