Author’s response to reviews

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

Authors:

kaiyue Diao (kaiyuediao@qq.com)
Qin Zhao (zhaoqin626@foxmail.com)
Yue Gao (gaoyue815@foxmail.com)
Ke Shi (kshi0110@qq.com)
Min Ma (foundhope@foxmail.com)
Hua-yan Xu (xuhuayan89@sina.com)
Ying-kun Guo (gykpanda@163.com)
Zhi-gang Yang (yangzg666@163.com)

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Author’s response to reviews:

Dear Prof. Tomasz Plonek:

Here we submit our revised manuscript (manuscript ID: BCAR-D-18-00759_R1), 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" to editorial office via online submission. According to the recommendations of editor office and suggestions of reviewers, we have carefully amended the manuscript and made a point-by-point respond to the concerns as below:

The majority of the comments were amended by providing information in our manuscript. These changes were highlighted with different color (red to reviewer 1 and green for reviewer 2). Some questions or comments from editor and reviewers were answered or stressed as follows:
Responses to Reviewer #1:

We thank the reviewer for this positive view of our work and the thoughtful and constructive comments. What’s more, we feel very appreciative for the raised questiones, the constructive opinions, and 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 red.

- The manuscript is written in poor English, which makes the paper difficult to read. Please let it edit by a native English-speaking person

We have re-edited the manuscript for typing and grammatical errors in the text with the aid of two native English speakers from Enago Services Co.ltd.

- In general, it is known that patients with ACAOS, especially of the right coronary artery, have a benign clinical outcome. However, in the current cohort they describe a mortality of almost 4 percent (8 patients)! This would justify an aggressive approach of this patient subset. This is not comparable to our data and that known in literature. Is the patient selection for surgery sufficient? Are high-risk patients missed? They also describe a large subgroup of patients with simultaneous atherosclerotic coronary artery disease. Most likely, the mortality can be explained by largely by this patient subgroup with CAD? This does not reflect the true outcome of ACAOS.

We agree with the reviewer’s comment that most of the ACAOS patients have a benign clinical outcome. However, in this cohort, according to our telephone follow-up, there were truly 8 patients died (one with rectal cancer, one with lung cancer and 6 without specific reasons). Firstly, we were sorry we were not clear enough in the previous manuscript about the cause of the dead patients, and more details have been given in the revised one (RESULTS, line 282-283, and Table S1); Secondly previous study by Ghoshhajra B, et al showed a similar mortality with us (7/103, 7.0%). And we were both the studies focusing on the natural history of ACAOS, namely, no surgical intervention was given at the first place. We were sorry for these patients and did feel astonished hearing from their families. And we cannot agree with you more that maybe surgery should be considered at the beginning. And that come to the next question which is also the truth for most of the Chinese patients (BACKGROUND, line 134-136), who are usually not that willing to accept the vascular reconstruction surgery if they find it not necessary or they don’t suffer from this frequently, or for economic reasons. And that’s also why we feel it necessary to report this and let more patients and doctors, especially those from developing countries, be conscious of this disease! Another possible reason might be that the patient died because of other systems in stead of ACAOS. As we indicated in our revised manuscript, two patients died with the history of malignant tumor. However, we admitted that this is one of the limitation that the biopsy is not available in this study (Discussion, line 415-417).
As for the last question, to avoid the influence from CAD, we excluded these group of patients in our prognosis analysis (Methods-Clinical information, Line 203-204) thus their death were not likely to be the atherosclerotic plaques.

- Also, they describe adverse clinical outcome (MACE) in 54 of 108 non-CAD cases (50%). However, this MACE contains interventions that are not related to ACAOS like pacemaker implantations and catheter ablation. A new definition of MACE should be used: only adverse events that can (likely) be attributed to ACAOS: surgery (by the way: the authors describe surgery on page 8 (‘clinical informations’): how was clinical decision making done? Please describe), VT/VF, typical anginal complaints, acute coronary syndromes and acute deaths; all in non-atherosclerotic patients.

In view of the Reviewer’s comment, we rewrote the definition of MACE and rewrote the corresponding results and methods part (Methods-Clinical information, Line 212-213, Results-Analysis of clinical events in non-CAD patients, Line 284-286). We were sorry that we misused the words “MACE”, for which we originally meant to express the cardiovascular relevant clinical event we were concerned about. By the new and correct definition of “MACE”, a total of 8 patients could be considered as having MACE. We feel so grateful for your kind consideration and pointing out the misuse of “MACE” and the added information in the method part. Considering the relatively small number of patients with MACE, we didn’t do further prognosis for these group of patients (Hope we could do further analysis in the future). And since one of the main purposes of this study was the “potential high-risk CTA characteristics to predict a relatively poor prognosis”, we choose to keep our original analysis results on predicting cardiovascular clinical events and we also give details following the reviewer’s suggestion (Methods-Clinical information, Line 204-211)

Regarding “how the clinical decision would be made for surgery”, we consulted the cardiac experts in our hospital and added the part to describe how the clinical decisions were made in our center in the revised version (Methods-Clinical information, Line 207-209).

-I believe atherosclerotic patients should be excluded from the analysis.

Thank you very much for adding the comment that atherosclerotic patients should be excluded from the analysis, we did exclude atherosclerotic patients in this part (Methods-Clinical information, Line 203-204), for which no atherosclerotic plaques were observed on CTA images, to exclude the influence of the CAD disease on patients.
They claim that 44 patients (40%) have clinical symptoms. In a lot of patients, complaints are present. Question is: how typical are these complaints? Has exercise testing been performed? Non-invasive ischemia detection (myoview, adenosine-MR)? Even better would be invasive evaluation like FFR/IVUS, like has been described previously.*

Thank you very much for adding this comment. It’s truly an important question and we were sorry that we failed to stress it in the previous manuscript. We have added this point and emphasized it in different parts in our revised version. Typical clinical symptoms included chest pain, syncope, dyspnea, and palpitation (METHODS-Clinical information, line 201-202). And one thing we hate but have to mention here is that our hospital don’t widely perform exercise testing for patients with suspicion of ischemia disease unless the clinicians asked before surgery. Usually coronary CTA (especially for the old and current-smokers), cardiovascular magnetic resonance (not many considering the relatively high cost), ultrasound, PCI (not the first choice since it is invasive) might be considered but not necessarily and since the coronary anomalies were confirmed on CCTA the patients usually won’t receive further examinations. Thus, we could not give a summarized results for the patients reported chest pain for the limited data. Anyway, we agreed that these items need to be mentioned in the manuscript and we added the part in the METHODS (line 178-180) and DISCUSSION part (line 345-349).

Like said above, a clear distinction throughout the manuscript should be made concerning atherosclerotic patients and non-atherosclerotic patients, R-ARCAOS and L-ACAOS (the latter with known poor outcome; were the deaths (untreated) L-ACAOS patients? Thanks for your kind remind. We were sorry for the obscure description of atherosclerotic patients and non-atherosclerotic patients and we revised this in the revised version (METHODS-Image analysis, Line 177-178).

We rewrote the definition of the ALCA-R and ARCA-L (BACKGROUND, line 128-133). According to the newest adult congenital heart disease guideline and studies in recent years, Malignant, potentially lethal forms of anomalous coronary artery origin should include right coronary artery origin from the left and left main coronary artery origin from the right, with the course of the artery between the main pulmonary artery and the ascending aorta.

Many thanks for your pointing out our missing details of our follow-up in the methods part. We did telephone follow-up on only the ARCA-L patients and without atherosclerotic plaques (METHODS-Clinical information, Line 203-204). The anatomy details of the MACE patients were given in table S1.
- How were the atherosclerotic patients treated: PCI, CABG. Has FFR been performed in these cases etc?

We totally agree with the reviewer that all the atherosclerotic patients, especially those with aggressive atherosclerotic plaques and narrowed lumens (or CAD-RID 4 or 5) should be treated. And thanks for your kind comment we added this part in the “Method” part (line 178-180). All the patients with observed atherosclerotic plaques were classified using the latest guidelines and referred for downstream investigations following the guideline. However, FFR was not available in our hospital, and not all the patients would be willing to take the downstream investigations. And that’s also one reason we excluded these patients in our prognosis analysis.

- The title and abstract suggests a large patient population. However, only the incidence of ACAOS has been calculated from this large database. Despite the fact that 211 patients is still a nice cohort, it is a little different from >30,000 patients...

We were sorry for the misunderstanding. We originally want to express we investigated the ACAOS in a relatively big group in our area since one of the main purposes of this study is to provide epidemiological data of ACAOS patients. And we did report the epidemiologic characteristics in a big group. We changed the title and some of the description in the abstract and hope this would look better. (TITLE; ABSTRACT, Line 62-63)

- On page 14 it is stated: Considering a higher myocardial bridge frequency in patients without CAD in our population, chest pain might not be the sole factor when ranking the risk of MACE for the patients.... Myocardial bridging in general is believed not to cause ischemia / adverse clinical events. Maybe leave out?

Thanks for your great suggestion. We agree that myocardial bridging is generally believed not to cause ischemia/adverse clinical events. We changed the description in this part and left out the words on myocardial bridge. (DISCUSSION, Line 341-343)

- In the abstract it is stated that 30,597 patients have been evaluated. On page 6 they mention 30,593...

Sorry for the wrong numbers we put in the previous “ABSTRACT” section. We have carefully reviewed the data and the final number should be 30953. (Line 62)
- How was mortality gathered; is there a national database of the government?

Thanks for your comment. As we mentioned in our “METHOD” part, all the follow-up data was acquired through telephone (Line 203-204). The mortality was confirmed through the families. I really wish but I don’t think we have such a database available for everyone.

Responses to Reviewer #2:

We really thank the reviewer’s positive comments of our study and the warm words, which help us to rejudge the value of our manuscript and what to do for the future study. We thank the reviewer for his thoughtful and constructive comments. Corrections made in the text in response to these comments are highlighted in GREEN.

-The authors briefly discuss about intramural segment of a coronary artery in the discussion. This is believed to be one of the most important risk factors for adverse events associated with anomalous origin of a coronary artery. Although intramural length can be confirmed at surgery or pathology, it can be assessed very well using two signs on CT angiograms. Firstly, the pericoronary fat sign and the cross-sectional shape of the lumen which has been described in the article below


It will be good to reanalyze the data to look for the presence or absence of intramurality and also to look at the correlation between length of intramurally with adverse events.

Thanks for your precious suggestions and generous guide! We read the article carefully and watched the online video, in which the author concluded that the oval-to-round shape and the pericoronary fat could be used to diagnose the “intramural course” of the abnormal artery. To be honest, we really don’t think this would be a perfect way to “diagnose” the “intramural course”. We agreed that this might be a screening method to exclude those without intramural course. For the former one, the author defined “oval” shape to be “transverse diameter is 50-90% of AP diameter”, which was also used by some other studies using the word “elliptical”. We used the “Height-to-width” index to try to be more quantitative. We tried this index while no significance was found in our univariate regression analysis in our prognosis data. Patients presented oval shape during the path between aorta and pulmonary artery, and the “fat sign” is really too subjective and we were not able to reach a good reproducibility when trying to assess this sign. We had add some comments in our discussion part, and if the reviewer further asked we could did further revision but we were truly not confident in presenting this analysis results. (DISCUSSION, Line 375-380). Besides, we put this classification into use when giving the anatomical details of the MACE patients (table S1)
- In the abstract and introduction, the authors have referred to anomalous origin of a coronary artery as a hemodynamically stable lesion. I would refrain from using such a term due to its association with sudden cardiac death.

Thank you for your suggestions! We initially used the word “hemodynamically” for trying to differentiating it from the more life-threatening cardiac disease. And we changed the description in the new version. (ABSTRACT, Line 56-57; BACKGROUND, Line 104-105)

- In the table 2 which provides the data on symptoms. Is it possible to break down symptoms into exertional and non-exertional to be more specific.

Thanks for your kind remind. We intended to be more specific on this issue but since the history taking was all done by review the database in our hospital (which is actually a single sheet with a few words on why the patients came to the hospital), we couldn’t further classify the complaints to be exertional or non-exertional.

- A major limitation of the outcomes is that the authors do not provide any further details on the cause of death for the patients. It will be good to know any co-morbidities present in these patients.

Exactly! Thanks for your suggestion, which is also mentioned by the reviewe 1. We did try to record more details of the patient clinical outcomes while very limited data could be traced in China, especially some patients from rural area usually would not be willing to take further examinations. We followed the suggestions and give more details in Table S1 and wish this could be better.

Additionally, we have changed the order of “References” due to some sections of text were revised, especially the “Discussion”.

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 chance to make the substantial revisions according to your comment! 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