**Peer Review File**

**Reviewer A**

Dong et al included 138 patients on hemodialysis who underwent revascularization with rotablaror and stent or rotablator and POBA or DCB. One-year MACE (including all cause death, heart failure hospitalization, definite stent thrombosis or ischemic driven TLR) was quite high (44%) and the predictors of MACE was in-stent restenotic lesion and non-LAD lesion location and the independent predictors of TLR was in-stent restenotic lesion, non-LAD, and larger acute gain.

**Major comments:** Poor outcome of ISR revascularization (especially treated by POBA even with rota) is well known. Thus, the revascularization strategy (POBA, DCB, or new stent) should be adjusted. It is quite interesting that the greater acute gain or RCA location were associated with poorer outcome, which I strongly believe due to the presence of calcified nodule. Since you have 100% of imaging, this description would be beneficial for the readers.

*Reply: Thank you for the valuable suggestion. We tried to explore the association between PCI strategy and MACE among De novo and ISR patients, and found there was no statistical significance with univariate analysis (Table 6). Therefore, the variable of PCI strategy was not included in the multivariable analysis. To address the reviewer's concern, we conducted*

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*the sensitivity analysis to include the PCI strategy variable into the multivariable Cox regression, and showed similar finding with the original ones. This issue also existed for the analysis of risk factors for MACE and TLR. Therefore, we updated Table 4 - Table 6 to include the univariate analysis for PCI strategy (see Page 31, line4-7; Page 32, line4-7; Page 33, line4-7), added Supplementary Material Table 1 - Table 3 to show the sensitivity analysis results (see Supplementary Tables 1-3), and modified the description in the Results (see Page 13, line 1-6).*

*We also agreed with the reviewer that the association of the greater acute gain and RCA location with poorer outcome were partially due to the presence of calcified nodule. However, we regretted that the detail information of calcified nodule was not available in the image database. On the other hand, we also postulated there were other explanation for these two factors besides calcified nodule. To addressed this issue, we have modified the explanation in the text in Discussion (see Page 17, line 21, 22; Page 18, line 1-11).*

***Changes in the text:***

*Results (see Page 13, line 1-6):*

*Although the proportion of POBA in the MACE (+) group was slightly higher than the MACE (-) group (Table 3), the PCI strategy was not associated with the studied outcomes with univariate analysis (Table 4 - Table 6). Sensitivity analysis was conducted to furtherly adjust the PCI strategy in the multivariate models, and showed similar finding with the original results (Supplementary Material Table 1- Table 3), in spite of fluctuation in the confidence intervals due to small sample size.*

*Discussion (see Page 17, line 21, 22; Page 18, line 1-11):*

*RCA lesion was also an independent risk factor for MACE in de novo lesion, which could be explained by the frequent existence of calcified nodule, the hinge motion or excessive torsion stress this vessel, as well as the presence of ISR lesion. As reported by Toru Morofuji (31), HD patients tended to have calcified nodule in the coronary. Other studies reported calcified nodule is most frequently observed in the RCA (32), and well known to cause poor outcome. However, the lacking of detail information about calcified nodule limited further validation of this hypothesis in the current study. Besides, previous studies showed that hinge motion or excessive torsion stress in RCA is the maximal during the cardiac cycle (32-34). Furthermore, in the current study, RCA had 42.0% of the target lesion located in this vessel, and half of which was ISR lesion. As we known, ISR lesion revascularization was highly associated with poor outcome.*

*31. Toru Morofuji, Shoichi Kuramitsu, Tomohiro Shinozaki, et al. Clinical impact of calcified nodule in patients with heavily calcified lesions requiring rotational atherectomy. Catheter Cardiovasc Interv. 2021;97(1):10-19.*

**Minor comments:** there are many unclearness.

Page 5, Line 27,

Please clarify "under detailed fluoroscopic imaging".

**Reply:** *We have clarified the statements in the Methods, Definition (see Page 8, line 6-12) and added two new paper in Reference (see Page 21, line 16-21).*

**Changes in the text:** *Calcifications were classified as previously reported as mild with a single image or multiple images of non-linear well-defined calcium density located on the*

*target lesion, moderate with an image of linear calcium density located on one side of the target lesion that was not visible under detailed fluoroscopic imaging with 15 frame per second X-ray fluoroscopy with or without contrast filling, and severe with a linear calcium density image located on both sides of the target lesion that was visible under detailed fluoroscopic imaging (11,12).*

*11. Dahdouh Z, Roule V, Dugue AE, et al. Rotational atherectomy for left main coronary artery disease in octogenarians: Transradial approach in a tertiary center and literature review. J Interv Cardiol 2013;26:173-82.*

*12. Moussa I, Ellis SG, Jones M, et al. Impact of coronary culprit lesion calcium in patients undergoing paclitaxel-eluting stent implantation (a TAXUS-IV sub study). Am J Cardiol 2005;96:1242–7.*

Page 5, Line 20m

If MACE include all-cause death, cardiac death should not be listed as a component of MACE here.

**Reply:** *We have modified the definition of MACE in the text as advised (see Page 8, line 2).*

**Changes in the text:** *Follow-up MACE included all-cause death, hospitalization due to heart failure, definite stent thrombosis (ST), and ischemia-driven TLR.*

Page 6, Line 4,

Please clarify "inelastic tissue"

**Reply:** *Sorry for the confusing. "inelastic tissue" means fibrous calcification compound. We*

*have clarified the definition in the text (see Page 8, line 15-17).*

***Changes in the text:*** *1) lesions with moderate to severe superficial calcification or fibrous calcification compound,*

Page 6, Line 9,

Please cite your reference for "standard method". Your angiographic definition of calcium is not standard.

***Reply:*** *"Standard method" meant the QCA analysis method used before in previously reported, which we modified "standard method" to "previously reported method". (see Page 9, line 2-5). In concern with the angiographic definition of calcium, we used the classification previously reported in other paper, and cited the reference for the method as suggested (see Page 8, line 6-12; Page 21, line 16-21; Page 22, line 1-4).*

***Changes in the text:*** *Quantitative coronary angiography (QCA) analysis was performed according to the previously reported method using CAAS software ver. 5.9.1. (Pie Medical Imaging, Maastricht, the Netherlands) (13).*

*Calcifications were classified as previously reported as mild with a single image or multiple images of non-linear well-defined calcium density located on the target lesion, moderate with an image of linear calcium density located on one side of the target lesion that was not visible under detailed fluoroscopic imaging with 15 frame per second X-ray fluoroscopy with or without contrast filling, and severe with a linear calcium density image located on both sides of the target lesion that was visible under detailed fluoroscopic imaging (11,12).*

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12. Moussa I, Ellis SG, Jones M, et al. Impact of coronary culprit lesion calcium in patients undergoing paclitaxel-eluting stent implantation (a TAXUS-IV sub study). Am J Cardiol 2005;96:1242–7.

13. Lansky A J, Dangas G, Mehran R, et al. Quantitative angiographic methods for appropriate end-point analysis, edge-effect evaluation, and prediction of recurrent restenosis after coronary brachytherapy with gamma irradiation. J Am Coll Cardiol. 2002; 39: 274-280.

Page6, Line 27,

"Stepwise univariate logistic regression analysis". If you use stepwise method, then this should be multivariable logistic regression analysis.

MACE (+) patients include more men, whereas men was negatively associated with MACE in the univariate logistic model. This is very strange. Similar comment for BMI.

**Reply :** We apologized for the confusion. Actually, both univariate and multivariate Cox regression analysis was performed to evaluate the independent predictors of MACE. We have corrected the description in Methods, Statistical analysis. (see Page 10, line 2-4).

It was true that MACE (+) patients include more men and higher BMI level in the current study. Therefore, both indicates were positively associated with MACE in the Pearson $\chi2$ test (Table 1) and univariate logistic model (Table 4), which was rational.

**Changes in the text:** Univariate and multivariate Cox regression analysis was performed to

*evaluate the independent predictors of MACE.*

**Reviewer B**

**Comments:** Patients on dialysis have an increased risk of cardiovascular disease and tend to develop more diffuse and complex lesions in the coronaries. In addition, dialysis patients tend to have more calcified lesions which may be associated with an increased risk of adverse clinical outcomes. Calcified lesions are associated with prolonged procedure time, reduced deliverability of coronary devices such as stents, reduced stent expansion and potentially need more aggressive lesion preparation such as rotational atherectomy which is a form of calcium debulking device.

Cardiovascular disease is also one of the main causes of mortality and morbidity in ESRD patients. While percutaneous coronary intervention (PCI) forms the mainstay of treatment options in patients with ischaemic heart disease, this treatment modality has been shown to be associated with high periprocedural mortality and poor clinical outcome, when compared to patients without ESRD.

Yet there is limited data on the risk factors that may influence outcomes in this group of patients in particular the group of patients who undergo high risk complex PCI requiring rotational atherectomy.

The authors of this present study sought to determine the clinical outcomes and independent predictors of major adverse cardiac events in a group of dialysis patients in an Asian geopolitical setting that underwent high risk PCI as characterized by the need to perform rotational atherectomy.

A retrospective analysis of clinical outcomes was conducted in a single centre database consisting of patients who were on maintenance hemodialysis with severe calcified lesions and treated with rotational atherectomy-facilitated percutaneous coronary intervention. The main limitation of the study was that it involved a relatively small sample size and appears to be a single centre study. This was partially addressed in the study limitations section (pg 11). Also outcomes are best compared with cohorts of similar patients treated with medical therapy only and those that underwent surgical revascularization. The selection bias was appropriately acknowledged.

Pg 3 line 5: In this relatively small study, cumulative all-cause death at 30-day and 1-year follow-up were 6.52% and 18.8%, respectively.

Overall the findings from the study further reinforces the fact that despite advancements in PCI and the usage of intracoronary imaging (Table 3), progress in improving clinical outcomes for this group of patients appear limited and an in depth discussion of the possible outcomes and risks with an emphasis on discussing the risk benefit balance of going for such a high risk complex procedure in Asian dialysis patients with an option to explore surgical

revascularization especially when there is more extensive disease. The diagrams, tables and figures were appropriate and clear.

Pg 3 line 6: The study shows that male gender, higher body mass index, more insulin use, more hypertension, and old myocardial infarction were risk factors of increased MACE. These findings may form the basis of an eventual risk score to be further evaluated in future studies that may be used to guide patient and physician decision making regarding the treatment modalities available. This is also consistent with another earlier study (Singapore Med J 2021; 62(6): 300-304) that suggest that DM was a significant independent predictor of adverse clinical outcomes following PCI in Asian dialysis patients. Other studies that may be considered for reference include paper from Hertzog et al (Circulation 2002; 106:2207-11); Rubertsein et al (Eur Heart J 2000; 21 [Suppl]: 168) as well as ULTIMATE study involving outcomes after PCI guided by intracoronary imaging in patients with renal disease.

*Reply:* T*hank you for your positive comments on our work and we all learnt a lot from your comments. We would also further design other studies to guide patient and physician decision making regarding the treatment modalities available in future studies as you suggested. Furthermore, we had reviewed the paper you mentioned and added two of them as reference. (see Page 21, line 9-15)*

*Changes in the text:*

*9. Charles A Herzog, Jennie Z Ma, Allan J Collins. Comparative survival of dialysis patients in the United States after coronary angioplasty, coronary artery stenting, and coronary artery bypass surgery and impact of diabetes. Circulation. 2002 Oct 22;106(17):2207-11.*

*10. Jiang Ming Fam, Chun Yuan Khoo, Yee How Lau, Weng Kit Lye, Xinzhe James Cai, Lina Hui Lin Choong, John Carson Allen, Khung Keong Yeo. Age and diabetes mellitus associated with worse outcomes after percutaneous coronary intervention in a multi-ethnic Asian dialysis patient population. Singapore Med J 2021; 62(6): 300-304.*

**Reviewer C**

In this original manuscript entitled, "Predictors of clinical outcome after rotational atherectomy-facilitated percutaneous coronary intervention in hemodialysis patients", Dong et al. discuss an important aspect of complex PCI. This is a timely manuscript, and I congratulate the authors for their choice. I have a few comments for their consideration.

1. Can the authors comment on their choice of calcium-modification techniques available? Do they have access to alternate techniques such as orbital atherectomy, high pressure non-compliant balloon inflations, and intravascular lithotripsy? What criteria did they use to decide on rotational atherectomy?

*Reply: Thank you for the question. In SCVC, we have ROTA, DCA, ECLA, cutting/ soring balloon and high pressure non-compliant balloon for calcium-modification on hand. And we did not have orbital atherectomy or intravascular lithotripsy yet. As suggested, we added the comment on the choice of calcium-modification techniques available in SCVC in Discussion (see Page 14, line 3-11). We also added the rationale to use ROTA and introduced the criteria in Methods (see Page 8, line 15-22; Page 9, line 1).*

*Change in the text:*

*Discussion (see Page 14, line 3-11):*

*In SCVC, we have ROTA, directional coronary atherectomy (DCA), excimer laser coronary angioplasty (ECLA), cutting/ soring balloon and high pressure non-compliant balloon for calcium-modification on hand. And we did not have orbital atherectomy or intravascular lithotripsy yet. As the indication mentioned above, rotational atherectomy is the first choice for the calcium-modification technique in severe calcification cases in our routinely clinical practice. For the moderate and severe calcified lesion, ROTA has the three advantages of device passing, creating crack and plaque debulking. DCA was easy to cause hematoma for deep cutting and, ECLA or cutting balloon were not effective in passing and cracking in severe calcification.*

*Methods (see Page 8, line 15-22; Page 9, line 1):*

*The general indications for ROTA in HD included: 1) lesions with moderate to severe superficial calcification or fibrous calcification compound, identified using imaging methods such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT); 2) calcified lesions with difficulty in passing devices, such as a balloon catheter, imaging catheter, or stent; 3) residual indentation was identified, even when utilizing high-pressure balloon dilatation;4) chronic total occlusion lesions, in which the guidewire has been correctly positioned but low-profile balloons cannot be advanced; 5) selected cases of diffuse in-stent restenosis.*

2. Can the authors justify why CCTA was performed in the subsequent 12 months? If this

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was a part of a scientific protocol, please highlight the rationale and references. This seems

rather excessive, even though these patients were on hemodialysis and therefore may not be

as affected by contrast dosing as the non-ESRD population.

*Reply : Thank you for your comments and we admitted the CCTA for these patients was very*

*positive and necessary but not excessive. Patients with HD and ROTA-needed CAD should be*

*followed up carefully because of their poor prognosis. And the CCTA was an accurate method*

*for vessel assessment. Furthermore, contrast dose was low for CCTA in SCVC. We have*

*addressed this issue in the Discussion and added more reference paper (see Page 14, line 11-*

*18; Page 22, line 8-10).*

*Change in the text: Patients with HD and ROTA-needed CAD should be followed up carefully*

*because of their poor prognosis. And the MACE and TLR rates were so high in the first year*

*that early screening and treatment of ISR or ischemia was indispensable before ACS attacked.*

*CCTA presents as an accurate and ideal diagnostic method for vessel noninvasive assessment*

*(15), and limited contrast (less than 20ml) was needed for CCTA in SCVC clinical practice*

*even though contrast dosing was not that influential for HD patients. Therefore, CCTA was*

*positive and necessary for such group of patients.*

*15. Li Ru, Pengxun Lan, Chengcheng Xu, et al, The value of coronary CTA in the diagnosis of*

*coronary artery disease . Am J Transl Res. 2021 May 15;13(5):5287-5293. eCollection 2021.*

3.    There is an intrinsic issue with the study design. Are the authors intending to perform a

cohort study or a case control study? They start the research question as a cohort study, the

abstract conclusion is that of a cohort study, but the study itself is executed like a case control

study. I'm not sure why that change happened.

*Reply：We apologized for the confusion. The current study was indeed a retrospective cohort study that was part of the work we done before (Dong H et al, J Interv Cardiol, 2020,2020:9190702). A total of 138 patients with HD requiring ROTA-PCI and were followed up for at least one year. We collected the baseline demographics, angiographic characteristics and clinical outcome from all of the enrolled 138 patients. In order to identify the potential risk factors for MACE in the cohort, we presented the characteristics of the patients and lesions, the PCI procedure and QCA data by MACE (+) group (n=61) and MACE (-) group(n=77). We also showed the survival curve for the cohort. We have the indicative sentence in the text to guide the reader to understand our cohort study design, such as following:*

***Methods (Page 6, line 5-7)***

*"During the period from January 2013 to December 2015, a consecutive series of patients undergoing maintenance HD owing to end-stage renal failure who were treated with ROTA-facilitated PCI were retrospectively included."*

***Page 7, line 1-3***

*All patients underwent a routine clinical follow-up at least once within 2 years in the outpatient clinic that involved an interview with the interventionist.*

***Page 9, line 16,17***

*The individual outcomes of MACE and TLR were prespecified end points, presented as Kaplan–Meier percentages.*

*In addition, we corrected the expression of odds ratio (OR) to hazard ratio (HR), logistic regression to Cox regression throughout the text, and modified some of the statements to clarify the cohort study design as follows in Abstract (see Page 3, line 20,21; Page 4, line 1) and Methods (see Page 6, line 12-14).*

**Change in the text:**

**Abstract (Page 3, line 20-22; Page 4, line 1)**

*61 patients in the cohort had MACE, most of which were TLR (47.5%, 29/61).*

**Abstract (Page 3, line 15-17)**

*The individual outcomes of MACE and TLR in the cohort were presented as Kaplan–Meier percentages. Cox regression analyses were performed to identify independent predictors of MACE.*

**Methods (Page 9, line 14-16)**

*Baseline patient characteristics, angiographic data, and parameters during each procedure were compared between patients in the MACE (+) vs. MACE (-) groups in the cohort.*

**Page 10, line 2-4**

*Univariate and multivariate Cox regression analysis was performed to evaluate the independent predictors of MACE.*

4.   What is the rationale for selection of the two groups as those with and without MACE? Clinically, the question the authors choose to address should ideally be a cohort study – i.e. groups with and without HD, requiring rota and therefore to see what their long-term outcomes are. The current study design does not help understand the study question at all.

*Reply : Thank you for the comments. As we have addressed in the Comment 3, the current study is a retrospective cohort study, which was mainly aimed to explore the risk factors for MACE in patients with HD requiring ROTA-PCI, instead of their long-term outcome. In our previous analysis reported, hemodialysis had been proved to be significantly related to higher incidence of MACE in ROTA-PCI patients. However, potential risk factors for MACE with ROTA-PCI in this high risk population, the HD patients, was unclear. To better identify the high risk patients, we therefore only enrolled HD patients with ROTA-facilitated PCI in the current study, compared the differences of potential factors between MACE group and non-MACE group. We further modified the text in Introduction for more clear study aim (see Page 5, line 18-21).*

*Change in the text: For better and earlier management of the contributing risk factors, we enrolled HD patients with ROTA-facilitated PCI, and retrospectively evaluated data and compared outcome to identify potential risk factors for MACE.*

5.  The fact that there were a higher volume of POBA in the MACE group and that this was not adjusted for is a significant issue. The fact that nearly 40% of all patients received POBA or DCB is a problem since the current concepts recommending stenting (including for ISR) unless the patient already has two layers of stent.

*Reply : Thank you for the suggestion. Although the proportion of POBA in the MACE (+) group was slightly higher than the MACE (-) group, there was not statistical difference with the univariate analysis (see updated Table 4- Table 6). Therefore, the variable of PCI strategy was not included in the multivariable analysis. To addressed the reviewer concern, we*

*conducted the sensitivity analysis to include the PCI strategy variable into the multivariable Cox regression, which was presented in Supplementary Table 1- Table 3, and showed similar finding with the original ones. We updated Table 4- Table 6 to include the univariate analysis for PCI strategy (see Page 31, line4-7; Page 32, line4-7; Page 33, line4-7), added Supplementary Material Table 1 - Table 3 to show the sensitivity analysis results (see Supplementary Tables 1-3), and modified the description in the Results (see Page 13, line 1-6).*

*We agreed with that the current concept recommends stenting (including for ISR) unless the patient already has two layers of stent. In our study, 66.7% (92/138) patients had previous stenting PCI and 34.1% (47/138) patients had ISR lesions. We believe that POBA would be an essential and effective technique to PCI and also DCB seems to be more useful option of treating ISR than DES implantation in some situation, reported by Manabu Moriya et (Cardiovasc Interv Ther. 2015;30(4):315-9) and Indermuehle A et al (Heart. 2013;99:327–33). So we tended to performed POBA or DCB as the first choice for previous PCI patients, especially for those with long term dual antiplatelet drugs intolerance. Therefore, 30% (40/138) and 8.7% (12/138) patients received POBA and DCB, respectively. We modified the text for the rationale of high portion of POBA or DCB in the study population in Discussion (see Page 15, line 18-22; Page 16, line 1-2).*

 ***Changes in the text:***

*Results (see Page 13, line 1-6):*

*Although the proportion of POBA in the MACE (+) group was slightly higher than the MACE (-) group (Table 3), the PCI strategy was not associated with the studied outcomes with*

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*univariate analysis (Table 4 - Table 6). Sensitivity analysis was conducted to furtherly adjust the PCI strategy in the multivariate models, and showed similar finding with the original results (Supplementary Material Table 1- Table 3), in spite of fluctuation in the confidence intervals due to small sample size.*

*Discussion (see Page 15, line 18-22; Page 16, line 1-2):*

*In concern with the PCI strategy, the current concept recommended stenting (including for ISR) unless the patient already had two layers of stent. In our study, 66.7% (92/138) patients had previous stenting PCI and 34.1% (47/138) patients had ISR lesions. We tended to performed POBA or DCB for previous PCI patients, especially for those with long term dual antiplatelet drugs intolerance. Therefore, the frequency of patients receiving POBA and DCB was relatively high in the studied cohort, with a rate of 30% (40/138) and 8.7% (12/138), respectively.*