

Peer Review File

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Reviewer Comments

Comment 1: In Abstract/Background, you open with a discussion of high-risk patients, this should be updated to 2021 since TAVR is now approved for all levels of risk.

Reply 1: We gratefully appreciate for your valuable comment, and we feel very sorry for our ignorance. We have updated “high-risk patients” into “all levels of risk patients” as advised. **Transcatheter aortic valve replacement (TAVR) has been increasingly used in all levels of risk patients.** (see Page 2, line 24)

Changes in the text: Page 2, line 24 text in red.

Comment 2: In Introduction, you report a rapid increase in hypertension and diabetes being the main cause of CKD with the prevalence of CKD "expected to soar," please confirm this is what was discussed in reference #4. The way the sentence is worded seems that you are extrapolating.

Reply 2: Thanks for your professional review on our article. As you were concerned, reference #4 only discussed hypertension and diabetes are the main causes of CKD and the prevalence will be increased rapidly, in the section of Epidemiology of CKD, and did not mention the prevalence of CKD is expected to soar. We are very sorry for our inappropriate extrapolation. We have made corrections according to your precious comment as follows: **Although it is less clear the prevalence of CKD globally, with the rapid increase of hypertension and diabetes, the main causes of CKD (4), the number of CKD patients may be increased as well.** (see Page 3, line 60-62) Thanks again for your work on our article.

Changes in the text: Page 3, line 60-62 text in red.

Comment 3: In Introduction, confirm you mean "golden standard" and not "gold standard".

Reply 3: Thank you for your careful review. We have confirmed that we mean **golden standard** in introduction (Page 3, line 66-67).

Changes in the text: Page 3, line 66-67 text in red.

Comment 4: In Introduction, update to new ACC/AHA guidelines for AS published in 2020.

Reply 4: Thank you for your reminding. **We have already updated to 2020 ACC/AHA guidelines.** (see Page 4, line 78). Reference#7 **Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2021;143:e72-e227.** in Page 18, Line 590-593

Changes in the text: Page 4, line 78 and Page 18, line 590-593 text in red.

Comment 5: In Introduction, your blanket statement about advanced CKD making patients "high risk" for cardiac surgery is not accurate. Higher risk than if they did not have CKD, but not "high risk" by default.

Reply 5: We are very sorry for our inaccurate statement. We have made corrections according to your valuable comment as follows: **However, patients with advanced CKD (stage 3-5) are associated with high mortality and complications (8,9) and were regarded as having a higher risk for cardiac surgery than patients without CKD.** (see Page 4, line 78-80)

Changes in the text: Page 4, line 78-80 text in red.

Comment 6: In Introduction, TAVR has not been a "new option" since 2002 - 2002 was first in man.

Reply 6: It is really true as you suggested that TAVR was first reported in man in 2002. We have made corrections as follows: **The first successful transcatheter aortic valve replacement in man has been reported in 2002 (10), and it has been widely used for it is less invasive and has fewer complications.** (see Page 4, line 80-82)

Changes in the text: Page 4, line 80-82 text in red.

Comment 7: In Introduction, line 83, compared with medical management ... "both" strategies have improved clinical outcomes - you only mention 1 strategy when discussing TAVR.

Reply 7: We are terribly sorry that we may have not expressed it clearly. Both strategies mean SAVR and TAVR in the text. We have clarified it in the revised version. Here it is: **Compared with the medical management of severe AS both SAVR and TAVR improved clinical outcomes by reducing postoperative mortality (11,12).** (see Page 4, line 83-84)

Changes in the text: Page 4, line 83-84 text in red.

Comment 8: Somewhere in Introduction you need to define what you mean by "advanced CKD". Are you using a standard definition? Also needed in your methods section.

Reply 8: Thank you for your constructive comments. "advanced CKD" means CKD stage 3 to 5, and we used international guidelines to define advanced CKD. We have specified the scope of advanced CKD from CKD stage 3 to 5 in introduction. Here it is: **However, patients with advanced CKD (stages 3-5) are associated with high mortality and complications.** (see Page 4, line 79). And some details of this definition were reported in our methods section: **And advanced CKD (stage 3-5) defined as glomerular filtration rate of ≤ 59 ml/min/1.73m² (19).** #Reference 19: Kidney

Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013; 1–150. (see Page 5, line 133-134; reference in Page 20, line 628-630)

Changes in the text: Page 4, line 79 and Page 5, line 133-134; reference in Page 20, line 628-630 text in red.

Comment 9: In Study Selection, please confirm that all included studies were explicitly on TAVR vs SAVR "in adult with advanced CKD" - as opposed to all studies on TAVR vs SAVR that also included data on patients with advanced CKD.

Reply 9: Thanks for your reminding. We have confirmed that all included studies were explicitly on TAVR vs SAVR in adult with advanced CKD, and made corresponding corrections: **All published studies that included TAVR vs SAVR in adult with advanced CKD were identified and included.** (see Page 5, line 132-133).

Changes in the text: Page 5, line 132-133 text in red.

Comment 10: In outcomes, please define your outcomes. You mention the definition of bleeding, stroke, or major vascular complication, but what about cardiac tamponade "requiring treatment"; acute kidney injury as defined as "?"

Reply 10: Thank you for your professional review work on our article. We were really sorry for our negligence. And the definition of cardiac tamponade, AKI and AKI requiring dialysis have been added in outcomes as follows:

1. Cardiac tamponade was defined as pericardial effusion discovered by doppler echocardiography post-procedure.
2. Acute kidney injury was defined as an absolute increase in serum creatinine concentration of ≥ 0.3 mg/dL (≥ 26.5 μ mol/L) within 48 hours post-procedure or a relative increase of $> 50\%$ within 7 days from baseline.
3. The definition of AKI requiring dialysis was an AKI necessitating dialysis during the index hospitalization.

4. PPMI requirement was defined as patients with atrioventricular block, bradycardia, sick sinus syndrome or any other situations need permanent pacemaker implantation post-procedure. (see Page 6, line 153-160)

Changes in the text: Page 6, line 153-160 text in red.

Comment 11: General comment, the entire manuscript needs language editing and medical editing - example line 264, Since the first commercially available transcatheter valve "put into practice," consider change to "implant". Line 267, However, severe CKD "patients" were excluded... "It seems like for dialysis patient it is too risky to do SAVR," poorly worded.

Reply 11: Thanks for your suggestion. We feel sorry for our poor writings. We have made some corrections as you suggest as follows:

1. Since the first commercially available transcatheter valve was implanted. (see Page 12, line 305)
2. However, patients with severe CKD were excluded from these studies. (see Page 13, line 319)
3. It seems like for dialysis patient it is too risky to do SAVR changed into "Our study indicated that SAVR is of great risk for dialysis patients" (see Page 13, line 331-332)

Besides, we tried our best to improve the manuscript and made some other changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in red in revised paper. We appreciate for your warm work earnestly, and hope that the correction will meet with approval.

Changes in the text: Page 12, line 305; Page 13, line 319; and Page 13, line 331-332 text in red.

Comment 12: Discussion, general comment, this section is too long and not focused. You introduce too many new ideas. What did you find? why is it important? why is it different than the current body of knowledge? how does it help us care for patients?

Reply 12: We sincerely appreciate your valuable comments. It is really true as you suggested that the Discussion part is too long and not focused. Therefore, we followed your instructions and made a major revision on this part. (see Page 12-15, Line 298-463) What's more, we made point-by-point responses to your kind comments.

- What did you find?
 1. Even through the patients of TAVR group were older and more likely to have preoperative comorbidities, it could significantly reduce the incidence of in-hospital mortality, stroke and some other postoperative complications such as AKI, AKI requiring dialysis, bleeding, blood transfusion, infection, major vascular damage, new-onset atrial fibrillation, and cardiac tamponade.
 2. Compared to TAVR, SAVR have a much greater impact on renal function.

- Why is it important?
 1. Since large RCTs excluded patients with severe CKD, it remains unclear whether TAVR is comparable to SAVR in patients with advanced CKD. The findings of this latest meta-analysis may help clinicians make a better decision for AS patients with advanced CKD under different situations.
 2. A large number of AS patients with advanced CKD need aortic valve replacement treatment, the findings of our study may help the cardiologist to choose a better way to maximize the benefit of the surgery.

- Why is it different than the current body of knowledge?
 1. Because our study focused on patients with advanced CKD (stage 3-5) to do SAVR or TAVR, which has not been reported in large RCTs, and this meta-analysis included 38,989 patients with advanced CKD to reach a credible conclusion.
 2. With the advancements in delivery-system, procedural experience, multidisciplinary engagement, and valvular design, some complications have been decreased in TAVR such as stroke, PPMI requirements and major vascular damage.

- How does it help us care for patients?
 1. TAVR is preferable to SAVR for dialysis patients since TAVR has less damage to renal function.
 2. For patients with advanced CKD the function of blood coagulation should be improved before procedure since these patients often appear to be associated with platelet dysfunction and hemostatic abnormalities, which could increase the risk of post-procedure bleeding and blood transfusion.
 3. Although TAVR is less invasive and has fewer complications, it should be discreetly used for patients with arrhythmia, because TAVR is associated with a higher risk of post-procedure PPMI requirement.

Changes in the text: Page 12-15, Line 298-463 text in red.