Peer review file

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Reviewer A

Comment 1:

The first primary outcome is ACC and CPB. I would recommend these to order as secondary outcomes. In contrast to other primary outcomes such as PVL, PPI or Gradients, the ACC and CPB are highly confounded and very influenced from many factors, which in this study cannot be ruled out. First, the number of patients which underwent SU up to date worldwide as well as in the present study is clearly higher than RD. The gained experience of surgeons is greater with SU than with RD and this impact the ACC and CPB. Second, ACC and CPB are strongly approach influenced. The minimal invasive and conventional approaches are inconsistent throughout the studies. In isolated AVR, MICS and RAT approaches are unequally used. Moreover, only 4 studies report of MICS or RAT. Also in the discussion ACC and CPB should not be stated as main finding. The above facts should be mentioned in the discussion.

Reply 1:

As Reviewer indicated, we revised our manuscript to order ACC and CPB time as secondary outcomes, and also revised the Discussion section accordingly.

Changes in the text:

<***Statistical Analysis***> The primary outcomes were ~~ACC and CPB times,~~ the mean transvalvular pressure gradient of the aortic valve (AVMPG) after AVR, the need for PPI and the incidence of PVL. The secondary outcomes included ACC and CPB times, early mortality and postoperative complications such as bleeding reoperation and stroke.

<**Discussion**> The present study showed that the use of the SU valve could further shorten the ACC time by 6 minutes, although this result should be interpreted cautiously because the gained experience of surgeons is greater with SU valve than with RD valve and the proportion of minimally invasive procedures was different between the studies.

<Limitation> Fourth, regarding that the number of patients who underwent AVR using SU valve up to date worldwide is clearly higher than that of RD valve, procedural times could be biased by the gained experience of surgeons. The fact that the proportions of minimally invasive approaches and combined procedures were different between the studies would also confound the outcomes regarding procedural times.

Comment 2:

In the Abstract line 35 follow-up term is unusually used for early time period. The appropriate terminology would be …procedural and early outcomes.

Reply 2:

As Reviewer indicated, we revised our manuscript with the appropriate terminology.

Changes in the text:

This meta-analysis was conducted to compare the ~~early and follow-up~~ procedural and early outcomes of aortic valve replacement (AVR) using rapid deployment valve (RD group) versus sutureless valve (SU group).

Comment 3:

In the results section the Study Characteristics and Patient Populations lines 175-177 should be written more clearly: which studies? with numbers of patients and references.

Reply 3

As Reviewer indicated, we added the right reference numbers for the 7 studies.

Changes in the text:

All outcomes except AVMPG in matched valve sizes were extracted from 7 studies (5,11,13,16-19) with 2,228 patients (RD group = 842 patients and SU group = 1,386 patients); the largest study included 1418 patients (RD group and SU group = 407 and 1011 patients, respectively) (11) whereas only 43 patients (RD group and SU group = 27 and 16 patients, respectively) were included in the smallest study (17) (*Table 1*).

Comment 4:

In the abstract line 44 you state 8 studies RD=842; SU=1386 and in the results section line 176 you state 7 studies RD=842; SU=1386.--- please clarify.

Reply 4:

To clarify the description, we revised our abstract as follows.

Changes in the text 4:

Eight articles ~~(RD group = 842 patients, SU group = 1,386 patients)~~ were included, and all outcomes except MPG after AVR in matched valve sizes were extracted from 7 studies (RD group = 842 patients and SU group = 1,386 patients).

Reviewer B

Comment 1:

It would have been of value for the authors to report around rates of Regurgitation within the included studies, as opposed to just stenotics, this likely effects many of the reported outcomes.

Reply 1:

As Reviewer indicated, we revised our manuscript to report the proportion of aortic regurgitation for each of the included study.

Changes in the text:

The proportion of aortic regurgitation was added to the **Table 2**.

Comment 2:

My main concern regarding this paper is the different patient numbers extracted from various studies when contrasted with recent studies published by Williams and Flynn.

Flynn CD, Williams ML, Chakos A, Hirst L, Muston B, Tian DH. Sutureless valve and rapid deployment valves: a systematic review and meta-analysis of comparative studies. Ann Cardiothorac Surg 2020;9(5):364-374. doi: 10.21037/acs-2020-surd-27

Williams ML, Flynn CD, Mamo AA, Tian DH, Kappert U, Wilbring M, Folliguet T, Fiore A, Miceli A, D'Onofrio A, Cibin G, Gerosa G, Glauber M, Fischlein T, Pollari F. Long-term outcomes of sutureless and rapid-deployment aortic valve replacement: a systematic review and meta-analysis. Ann Cardiothorac Surg 2020;9(4):265-279. doi: 10.21037/acs-2020-surd-25

Whilst I appreciate that Dr Williams work was long-term and this may explain some of the differences in numbers, I don't understand why the reviewed work had such different numbers extracted compared to Dr Flynn's with relation to Pacemaker rates, etc. as a near-term outcome.

I think it would be worth the authors clarifying the data extraction strategy given the differences between two otherwise very similarly conducted searches.

The manner in which the outcomes have been calculated based on size is novel and I would still recommend publication on this basis is it is likely of broad interest, however the nature of the data extraction and the difference between this and recently published works needs to be clarified or reconsidered.

Reply 2:

Compared with the meta-analysis by Flynn et al, our meta-analysis did not include the work by Chiariello et al [Innovations (Phila) 2019;14:27-36] because the participated institution in Chiariello et al was duplicated with that in Berretta et al.

For outcomes whose confounding-adjusted results were available, we extracted data from the adjusted results. Of the included studies in this meta-analysis, two studies (D'Onofrio et al and Ensminger et al) presented results for both all patients and propensity-score matched patients. We extracted data from PSM results when available whereas Flynn et al extracted data from results for all patients. That is why the patient numbers in Flynn et al were greater than those in this study. We presented which data were used in forest plots with analysis column (PSM vs UV).

Additionally, there were slight differences in patient numbers for ACC and CPB times because Berretta 2019 only reported the patient number of both groups with data available (n=1375 for ACC time, n=1369 for CPB time). Flynn et al used each group patient number without considering missing cases (n=1011 for Perceval group, 407 for Intuity) whereas we estimated patient numbers by multiplying its total number with data available and each group's patient proportion. For the case of ACC time, we used patient numbers (n=983 for Perceval group from 1375*(0.715=1011/1418), n=392 for Intuity from 1375*(0.285= 407/1418))

We briefly discussed this at "Discussion" section.

Changes in the text:

<***Data Extraction***> For outcomes whose confounding-adjusted results were available, data were extracted from adjusted results, otherwise from unadjusted results.

<***Statistical Analysis***> In one study (14), where the number of patients in both groups was reported for each of CPB and ACC times, the number of patients in each group for each time outcome was estimated by multiplying its total number by the proportion of patients in each group.

<**Discussion**>

A meta-analysis (34) comparing results after the RD and SU valves was recently published while the present study was being prepared. There were some differences in included studies and total number of patients between that study and ours. It might be due to the differences in inclusion criteria such as the duplication, and data extraction strategy in studies where propensity score matching was performed. Most of all, it would be novel and distinctive that we compared the mean transvalvular pressure gradient between the groups based on the prosthesis size, considering two possible matchings.

Reviewer C

Comment 1:

I suggest removing "follow-up outcomes" form abstract or replacing with early postoperative outcomes, as there is no long-term follow-up data.

Reply 1:

As Reviewer indicated, we revised our manuscript with the appropriate terminology.

Changes in the text:

This meta-analysis was conducted to compare the ~~early and follow-up~~ procedural and early outcomes of aortic valve replacement (AVR) using rapid deployment valve (RD group) versus sutureless valve (SU group).

Comment 2:

In terms of analysing and comparing two valves and your primary endpoints, ACC and CPB times should not be the most important factors. Therefore, I suggest early mortality as one of the primary endpoints if possible. ACC and CPB time should be secondary endpoints, particularly as your references consist of significant proportion of combined procedures. In addition, when defining aim of your study and comparing early outcomes of AVR, I am not certain that CPB time is the most important. This is more related to the surgeon's performance and technical skills.

Reply 2:

As Reviewer indicated, we revised our manuscript to reorder ACC and CPB time as secondary endpoints, remaining mean transvalvular pressure gradient, the incidence of paravalvular leak

and the need for a permanent pacemaker implantation as primary endpoints. Regarding early mortality, we left this as the secondary endpoint because the incidence was very low and it was expected to be similar between the groups.

Changes in the text:

<***Statistical Analysis***> The primary outcomes were ~~ACC and CPB times,~~ the mean transvalvular pressure gradient of the aortic valve (AVMPG) after AVR, the need for PPI and the incidence of PVL. The secondary outcomes included ACC and CPB times, early mortality and postoperative complications such as bleeding reoperation and stroke.

<**Discussion**> The present study showed that the use of the SU valve could further shorten the ACC time by 6 minutes, although this result should be interpreted cautiously because the gained experience of surgeons is greater with SU valve than with RD valve and the proportion of minimally invasive procedures was different between the studies.

<Limitation> Fourth, regarding that the number of patients who underwent AVR using SU valve up to date worldwide is clearly higher than that of RD valve, procedural times could be biased by the gained experience of surgeons. The fact that the proportions of minimally invasive approaches and combined procedures were different between the studies would also confound the outcomes regarding procedural times.

Comment 3:

Is it possible to add success implant rate and known complication of re-deployment of the valve to the endpoints? This is one of the main concerns when using SU/RD valves. Also, most of these procedures were performed with minimally invasive approach, and there is no mention of conversion to sternotomy rate.

Reply 3:

Thank you for your valuable comment. However, the comparisons of device success rate or sternotomy conversion rate between sutureless and rapid deployment valve were demonstrated only in two studies with no differences between the two groups.

Comment 4:

Conclusion in terms of procedural time does not seem justified with the results. Between the two groups there was different proportion of minimally invasive approach (Di Eusanio et al.

2018), and furthermore of ministernotomy and minithoracotomy approach (Berretta et al 2019), which can influence outcomes such as CPB and ACC more than the actual type of valve. In addition, there was different proportion between isolated and combined AVR, and this is another significant bias. Authors do not mention these limitations. Can you please discuss?

Reply 4:

It is certain that CPB and ACC times would be strongly influenced by the minimally invasive approach and by the combined procedures, more than by the type of bioprosthesis. Following the Reviewer's comment, we rearranged the CPB and ACC time to be the secondary outcomes and mentioned the comments to the limitations.

Changes in the text:

<***Statistical Analysis***> The primary outcomes were ~~ACC and CPB times,~~ the mean transvalvular pressure gradient of the aortic valve (AVMPG) after AVR, the need for PPI and the incidence of PVL. The secondary outcomes included ACC and CPB times, early mortality and postoperative complications such as bleeding reoperation and stroke.

<**Discussion**> The present study showed that the use of the SU valve could further shorten the ACC time by 6 minutes, although this result should be interpreted cautiously because the gained experience of surgeons is greater with SU valve than with RD valve and the proportion of minimally invasive procedures was different between the studies.

<Limitation> Fourth, regarding that the number of patients who underwent AVR using SU valve up to date worldwide is clearly higher than that of RD valve, procedural times could be biased by the gained experience of surgeons. The fact that the proportions of minimally invasive approaches and combined procedures were different between the studies would also confound the outcomes regarding procedural times.

Comment 5:

Page 3, Line 64: Please use TAVR instead of T[AVR]

Reply 5:

We revised the manuscript.

Changes in the text:

Rapid deployment (RD) and sutureless (SU) valves ~~were introduced to overcome the limitations of~~ have emerged to have the best of transcatheter aortic valve replacement (~~T[AVR]~~TAVR) ~~as well as~~ and conventional surgical AVR (1,2).

Comment 6:

Page 3, Line 67: Please remove “favorable hemodynamic properties” as this is not demonstrated with the reference 3. Actually, there is more evidence that SU and RDV have inferior HD outcomes with higher MPG as compared to the conventional bioprosthesis.

Reply 6:

We revised our manuscript as “**acceptable** hemodynamic properties”.

Changes in the text:

Theoretically, RD and SU valves have advantages such as short operation time, ease of insertion even in limited operating fields and ~~favorable~~ acceptable hemodynamic properties

Comment 7:

Why cut off for the systematic review is 20.03.2020? There are important recent studies with a large sample size, and I suggest referring to them in your study:

a. Di Eusanio M, Berretta P. The sutureless and rapid-deployment aortic valve replacement international registry: lessons learned from more than 4,500 patients. Ann Cardiothorac Surg. 2020 Jul;9(4):289-297. doi: 10.21037/acs-2020-surd-21.

b. Sef D, Krajnc M, Klokocovnik T. Minimally invasive aortic valve replacement with sutureless bioprosthesis through right minithoracotomy with completely central cannulation-Early results in 203 patients. J Card Surg. 2020 Dec 12. doi: 10.1111/jocs.15257.

Reply 7:

20.03.2020 is the date when we searched all database. Most of the data presented in the review article "a" is already included in 2 studies of our meta-analysis (Berretta et al. and Di Eusanio et al.). The reference ‘b’ could not be added because it does not demonstrate any comparative result between the RD and SU valves.

Comment 8:

Page 4, Line 98: Under keywords/MESH terms you mention “sutureless” and “rapid”, would adding “rapid deployment” perhaps contribute to your search strategy?

Reply 8:

We used "rapid" instead of "rapid deployment" for our search strategy because this could minimize the chance of missing any relevant articles. All the articles searched with "rapid deployment" must be a part of studies searched with "rapid".

Comment 9:

Page 6, Line 184: “The proportions of isolated AVR ranged from 18.5% to 70.1% in the other 5 studies” – this is one of the most significant biases to your study, as it is well known that combined surgical procedures are higher risk with inferior postoperative outcomes and longer ACC and CPB time as compared to the isolated AVR. Type of the valve is less significant, and it would be much better to compare only isolated AVR procedures with SU and RD valves. Please discuss. Another bias is that among your references in the Table 1. there are several studies with different proportion of full sternotomy/ministernotomy/right minithoracotomy/ approach. (Di Eusanio et al. 2018), and furthermore of ministernotomy and minithoracotomy approach (Berretta et al 2019 consist of ministernotomy and RAT approach patients. Liakopoulos et al consist of combined procedures. It seems that Jiritano et al. do not mention precisely which approach was used? Di Eusanio et al. had 30% combined procedures and 35% full sternotomy. All in all, this makes the sum of patients unmatched and significantly contributes to bias of your analysis and conclusion.

Reply 9:

We agree with the Reviewer’s comment that different surgical approach could affect the outcomes, especially the procedural times. In the original manuscript, we performed subgroup analyses with isolated AVR patients for ACC and CPB times and for clinical outcomes including early mortality, bleeding reoperation and stroke. We revised ACC and CPB times as secondary outcomes, and reflected the Reviewer’s comment to the limitations.

Changes in the text:

<***Statistical Analysis***> The primary outcomes were ~~ACC and CPB times,~~ the mean transvalvular pressure gradient of the aortic valve (AVMPG) after AVR, the need for PPI and the incidence of PVL. The secondary outcomes included ACC and CPB times, early mortality and postoperative complications such as bleeding reoperation and stroke.

<**Discussion**> The present study showed that the use of the SU valve could further shorten the ACC time by 6 minutes, although this result should be interpreted cautiously because the

gained experience of surgeons is greater with SU valve than with RD valve and the proportion of minimally invasive procedures was different between the studies.

<Limitation> Fourth, regarding that the number of patients who underwent AVR using SU valve up to date worldwide is clearly higher than that of RD valve, procedural times could be biased by the gained experience of surgeons. The fact that the proportions of minimally invasive approaches and combined procedures were different between the studies would also confound the outcomes regarding procedural times.

Reviewer D

Comment 1:

Line 313 and following: These are theoretical considerations, I would shorten this and discuss the options to reduce pacemaker implantations in patients receiving RD valve (Coti et al, JTCVS 2020)

Reply 1:

We shortened the paragraph as Reviewer indicated, and cited Coti et al (JTCVS 2020) to discuss that preoperative right bundle branch block and concomitant procedures were the independent predictors for new pacemaker implantation after rapid deployment AVR.

Changes in the text:

Theoretically, the difference of PPI rate between RD and SU group would be explained by the followings: ~~After~~after AVR is performed ~~in patients with aortic stenosis and, consequently~~, the pressure gradient is decreased, the left ventricular hypertrophy regresses gradually, and ~~the myocardial hypertrophy at the left ventricular outflow tract also decreases. Myocardial~~ myocardial edema ~~that occurred during the operation~~ also resolved in the postoperative period. Because the skirt of the RD valve becomes a fixed structure with no more outward force after the balloon expansion is completed, the conduction status in the RD group has the chance of recovery ~~will take advantage of the processes mentioned above~~. However, the SU valve has a self-expanding nature and will constantly compress the conduction pathway with a persistent outward force (31). Clinically, Coti et al (32) reported that preoperative right bundle branch block and concomitant procedures were the independent predictors for new pacemaker implantation after RDAVR.

Comment 2:

I would suggest to add to the limitations that the SURD registry was the largest contribution to this analysis and the results are in the line with this published results.

Reply 2:

We added Reviewer's comment to the limitations.

Changes in the text:

Third, the SURD-IR (Sutureless and Rapid Deployment Aortic Valve Replacement International Registry) was the largest contribution to this analysis and the results are in the line with this published results.

Reviewer E

Comment 1:

The authors wrote that "Rapid deployment (RD) and sutureless (SU) valves were introduced to overcome the limitations of transcatheter aortic valve replacement (T[AVR]) as well as conventional surgical AVR. This is not correct: the first sutureless valve which was the Enable from ATS and later Medtronic was developed as early than 2003 or 2004 and unfortunately taken back from the market for different reasons. At that times, sutureless valves were aimed to reduce cross-clamp time in complex multivalve operations and combined CABG and valve procedures or to facilitate the introduction of. valve through a minimal access. TAVR ans surgical AVR have practically no limitations!

Reply 1:

As Reviewer indicated, we revised the sentence.

Changes in the text:

Rapid deployment (RD) and sutureless (SU) valves ~~were introduced to overcome the limitations of~~ have emerged to have the best of transcatheter aortic valve replacement (~~T[AVR]~~TAVR) ~~as well as~~ and conventional surgical AVR (1,2).

Comment 2:

Since the pooled analyses using a random-effects model revealed that the ACC and CPB times were longer in the RD group than in the SU group, one could discuss if the terminology "rapid deployment" is really justified ... Please comment perhaps this point in the discussion.

Reply 2:

The terminology of “rapid deployment” might mean that this “rapid deployment” valve could be deployed rapider not than the sutureless (SU) valve but than the conventional stented bioprostheses. In this aspect, the terminology “rapid deployment”, we think, could be justified. Anyway, we added some comments regarding this point in the section Discussion.

Changes in the text:

This result might be expected because the SU valve does not need knot-tying or balloon inflation, whereas the RD valve needs knot-tying of at least 3 sutures, and manipulation of the balloon system and balloon inflation for 10 seconds are also mandatory. Because the procedural time of ‘rapid deployment’ valve is not faster than that of SU valve, opponents might argue whether the terminology "rapid deployment" could be really justified.

Comment 3:

I would personally recommend to delete the whole paragraph of the discussion "After AVR is performed in patients with aortic stenosis and, consequently, the pressure gradient is decreased, the left ventricular hypertrophy regresses gradually, and the myocardial hypertrophy at the left ventricular outflow tract also decreases. Myocardial edema that occurred during the operation also resolved in the postoperative period. Because the skirt of the RD valve becomes a fixed structure with no more outward force after the balloon expansion is completed, the conduction status in the RD group will take advantage of the processes mentioned above. However, the SU valve has a self-expanding nature and will constantly compress the conduction pathway with a persistent outward force." since it is rather hypothetic and does not have much to do with the main goal of the paper.

Reply 3:

Although hypothetic, the paragraph is discussing the theoretical explanation for the difference of pacemaker implantation rate between RD and SU valves. We condensed and revised the paragraph, also following the Comment 1 by Reviewer D.

Changes in the text:

Theoretically, the difference of PPI rate between RD and SU group would be explained by the followings: ~~After~~after AVR is performed ~~in patients with aortic stenosis and, consequently~~, the pressure gradient is decreased, the left ventricular hypertrophy regresses gradually, and ~~the myocardial hypertrophy at the left ventricular outflow tract also decreases. Myocardial~~ myocardial edema ~~that occurred during the operation~~ also resolved in the postoperative period.

Because the skirt of the RD valve becomes a fixed structure with no more outward force after the balloon expansion is completed, the conduction status in the RD group has the chance of recovery ~~will take advantage of the processes mentioned above~~. However, the SU valve has a self-expanding nature and will constantly compress the conduction pathway with a persistent outward force (31). Clinically, Coti et al (32) reported that preoperative right bundle branch block and concomitant procedures were the independent predictors for new pacemaker implantation after RDAVR.

Comment 4:

However, a short paragraph in the discussion could discuss the clamping and perfusion time of patients in such studies because from an overall point of view, I do not believe that they are really shorter than those obtained during conventional surgical AVR. One of the problems here may be that for comparison, sometimes data from large international registries like STS are used. In fact, the average clamping time in the US for a simple AVR is around 70 minutes what is really not very competitive. This should be commented.

Reply 4:

We included Reviewer's comment in the Discussion.

Changes in the text:

In contrast, other surgeons might think that it is controversial whether shortening ACC time by several minutes would indeed affect the clinical outcomes of AVR. The ACC time of RD and SU AVR from the studies included in this meta-analysis was around 40-60 minutes while that of isolated primary surgical AVR from the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database was around 70 minutes (33). Compared with this large international registry, it is not conclusive that the early clinical outcomes of RD and SU valves from this meta-analysis are superior to those of conventional valves. Thus, reduction of several minutes in the procedural times might be regarded as not very competitive to some surgeons.