Author’s response to reviews

Title: Single-center evaluation of a next generation fully repositionable and retrievable Transcatheter Aortic Valve Replacement

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Rebuttal

Dear Dr Mockridge,

Thank you very much for considering a revised version of our manuscript (original manuscript number: BCAR-D-17-00621R1) to be published in the BMC Cardiovascular Disorders. We would like to thank you and the reviewers for the comments and suggestions that we feel have improved the overall quality of the manuscript. We have replied to each comment below and edited the manuscript according to the proposals. We hope that you will find the manuscript suitable for publication in BMC Cardiovascular Disorders.
On behalf of the authors,

Best regards

Karolina Berntorp, MD

Reviewer #1, Ibrahim Akin:
1. Congratulation. All comments were addressed.

Reviewer #2, Josef Bis:
1. Congratulation to the authors for improvement of implantation of Lotus valve to reduce number of permanent pacemakers implantation.

Reviewer #3, Joëlle M Kefer, PhD:
1. The affiliation of the authors could be simplified as number 1 for the author 1,2, 4 and 6 - number 2 for the author 3 and 5

Author response: We have simplified the affiliation of the authors as proposed. The submitting guidelines addresses a list of full names, institutional addresses and email addresses. Therefore a list of the email addresses follows after the affiliation. The manuscript has been adjusted as follows, first page; Karolina Berntorp, MD, 1) Sasha Koul, MD, PhD, 1) Shahab Nozohoor, MD, PhD, 2) Jan Harnek, MD, PhD, 1) Henrik Bjursten, MD, PhD, 2) Matthias Götberg, MD, PhD. 1)
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2. The authors stated that the population of patients of the present study were at high risk for SAVR. However, the mean STS score is 6.5%, which ranges in the intermediate risk according to the American guidelines (4-8%). High risk are defined as an STS > 8%. The authors should precise how many patients are at high risk (>8%) and how many are intermediate (between 4 and 8%).

Author response: We thank the reviewer for this important comment. All our patients were deemed to be high or extreme risk patients by two multidisciplinary heart team meetings. At our institution, TAVI in intermediate risk patients has not been implemented yet (due to lack of reimbursement). Several comorbidities and patient characteristics such as porcelain aorta or severe pulmonary hypertension are not adequately reflected by STS-score. Since these patients constitute a significant portion of our patients, this may explain the observed STS-score. For all patients the mean Euroscore I were also calculated and it was 25.3%, suggesting a high risk cohort. We have therefore corrected our manuscript and added Euroscore to better demonstrate that this is a high risk cohort. The first correction is found in the Abstract, subheading 2, first sentence; "Mean age was 82.7 ± 5.6 years, mean Euroscore I was 25.3 ± 14.5%, mean STS-score was 6.5 ± 4.1% and mean aortic valve area was 0.6 ± 0.1 cm²." The second correction is found in the Methods, subheading 2 "Patient selection, procedure and follow-up"; "All patients were assessed to have severe symptomatic aortic stenosis with an indication for TAVI by two multidisciplinary heart team meetings consisting of at least one cardiologist and a cardiac surgeon. Patient risk for surgical valve replacement was based on the Society of Thoracic Surgeons (STS) score for mortality and Euroscore I."
The third correction is found in the Results, subheading 1 ”Patients”; "Mean Euroscore I was 25.3 ± 14.5%, and mean STS-score was 6.5 ± 4.1%.” We have also added the Euroscore I to Table 1 and the baseline characteristics.

3. The echo follow-up is limited to 50% of the population. Grading PVL was not verified by a core lab. Therefore, this valve performance is probably not really reliable. The number of patients should be mentioned in the Table 4. The authors should mention in the paper that the PVL evaluation was only done in 50% of cases without a central core lab.

Author response: We thank the reviewer for these two observations. First, it is correct that we have not had the opportunity to use a central core lab in this single-center study. Therefore we have added this to the manuscript and adjusted the Methods to clarify how the TTE has been performed. The changes are found in the Methods, subheading 2 ”Patients selection, procedure and follow-up”, paragraph 1 where we have moved the previous paragraph 3 and incorporated it into the new paragraph 1; ”Three different independent experienced cardiologists performed transthoracic echocardiogram (TTE) measurements. PVL and measurements of mean aortic gradient and left ventricular ejection fraction (LVEF) were performed on all patients before discharge. PVL was graded into no/trace, mild, moderate and severe as described elsewhere. [15] Follow-up was conducted according to local clinical practice at the referring hospital. TTE was not performed by a central core lab.”

We have also extended the paragraph about our limitations to highlight the limitation this brings to our manuscript and other limitations that follows. The paragraph is found last in the Discussion section; “There are several limitations to this study. First, this was a single-center non-randomized study. Second, TTE measurements were not performed by a central core lab, and follow-up TTE were not available in all patients. The main findings of this small study need to be verified in a larger study.”
Second, it is correct that the one year follow-up TTE was performed in 52% of the patients. However, before discharge all patients had a TTE performed with all measurements which brings a good reliability to the discharge results which are the results we compare with literature in the Discussion section. Therefore we are afraid that there has been a misunderstanding regarding TTE follow-up. The number of patients is mentioned in the Results. However, we have adjusted the Results to add clarity to the reader. The changes are found in subheading 3 "Echocardiographic follow-up"; "The TTE examination at discharge was performed in 100% of the patients and LVEF, mean aortic gradient and PVL were measured. One year follow-up TTE examination measurements and follow-up were not available for all patients due to differences in follow-up routines between referring hospitals. After one year TTE measurements were available in 52% of the patients. The mean aortic gradient was 47.2 ± 0.1 mmHg at baseline, 9.9 ± 3.4 mmHg at discharge and 12.2 ± 4.6 mmHg at one year, p = 0.08 (Table 4). The mean LVEF was 44.1 ± 11.1% at baseline, 48.9 ± 9.6% at discharge and 50.5 ± 7.9% at one year, p = 0.17.

The rate of PVL after TAVI was no/trace in 87% and mild in 12% of the patients at discharge (Table 4). One patient had a moderate PVL due to an annular calcified nodule (9x7 mm). Similar rates of PVL were observed at one year with no/trace in 94.1% and mild in 3.9% of patients."

We would also like to thank the reviewer for mentioning that the number of patients should be mentioned in Table 4, this was previously only mentioned for the PVL follow-up. Therefore we have made adjustments by adding a "*" to better reflect the follow-up rate. Table 4 is found in the Results, after subheading 3 "Echocardiographic follow-up".

4. One patient suffered from an aortic root abscess: do you think that it can be due to a delayed complication of the transcatheter valve procedure?

Author response: This is an interesting observation we found out of when investigating the patients follow-up TTE. The patient presented 5 months post TAVI with an aortic root abscess, verified by TEE. Blood culture demonstrated growth of streptococcus Gallolyticus and Bovis. The patient was successfully treated with antibiotics, and is currently doing well. Given the time interval between the procedure and the presentation, it is however difficult to know whether the abscess was related to the procedure or not. We have added a comment about the outcome to what was previously mentioned in the Results, subheading 3 "Echocardiographic follow-up", last sentences; "One patient presented 5 months post TAVI with a severe PVL due to an aortic root abscess. The patient was successfully treated by antibiotics with good outcome."
5. PCMK : Table 5 is not included in the paper. Please add it. The authors should mention in the paper and in the abstract that the rate of new pacemaker after lotus valve implantation is 14.8%.

How many patients developed new LBBB after TAVI. Patients requiring delayed pcmk implant after discharge had normal ECG at discharge or not ?

Author response: To start with we would like to apologize for mistakenly mentioning Table 5. We did not have the intention to include Table 5 in the manuscript, as it does not bring further knowledge to the paper.

When collecting our data for PPM calculations we used the national pacemaker registry which is supposed to cover 100% of the PPM implanted in Sweden since the late 80s. When given the very interesting question about the patients ECG post TAVI we went through all the patients’ medical records and found out that data were missing in the national pacemaker registry. Therefore we have made new calculations regarding PPM rates. The new results are found in the Results, subheading 4 ”Pacemaker and Conduction disturbances”; ”Before implantation 15% of the patients had a preexisting pacemaker. After implantation, but before discharge, 13 patients (13%) received a new PPM according to ESC guidelines. Among patients who did not have a PPM prior to TAVI, the PPM rate was 15.3% (13/85 patients). The majority of patients (12/13) received a PPM due to peri- or post-procedural 3rd degree AV block and one due to 2nd degree type II AV block. After one year 4 more patients had received a new PPM. Three patients due to 3rd degree AV block and one due to an unspecified AV block.” The PPM rate 15.3% is added to the Abstract, subheading ”Results”, last sentence; ”Among patients who did not have a PPM before the procedure, the PPM rate was 15.3%.”

Because we found that the national pacemaker registry does not have a 100% cover of PPM we have made an adjustment to the Methods, subheading 3 ”Data sources and statistical analysis”, sentence three; ”PPM rates were assessed using the national pacemaker registry and electronic medical records.” An adjustment is also made to the Abstract, subheading ”Methods”, second last sentence; ” Postoperative pacemaker rates were assessed using the national pacemaker registry and electronic medical records.”
Because literature differs in how they present PPM rates as either PPM of all patients or of all pacemaker-naïve patients we have made corrections to the Discussion section for a more representative presentation, paragraph 2; “The need of a PPM after TAVI has not been associated with any increased risk of mortality. [17, 18] It does however add costs of another invasive procedure with associated risk of complications, and delays in patient discharge. High PPM rates after implantation of a Lotus Valve System compared to first generation TAVI has been identified as a significant drawback of the technology. [19] [20] The PPM rates in all patients in the REPRISE I and II studies were 36% and 28.6% respectively. [7, 8] Two single-center studies using the Lotus Valve System have demonstrated an incidence of new PPM of 24.1% and 39.9% in pacemaker-naïve patients. [11] [20] A third single-center study presented 28% PPM rate in all patients. [21] Furthermore, the RESPOND post market evaluation study demonstrated 30% new PPM in all patients and 34.6% in pacemaker-naïve patients after implantation of the Lotus Valve System. [14] Krackhardt et al have previously reported 9.5% PPM in a small case series after using a high implantation technique. [22] We reported 13% PPM rate in all patients due to 2nd degree type II or 3rd degree AV block, and 15.3% in pacemaker-naïve patients. We have demonstrated low PPM rate confirming the benefit of limiting the implantation depth. In the Swedish Percutaneous Valve Registry, where all TAVI in Sweden are registered, the combined reported PPM rate after Lotus Valve implantation in all implanting hospitals in Sweden has been less than 17% since 2013. [23] A possible explanation for the observed low PPM-rates in this study is a careful pre-operative assessment using gated computer tomography to avoid oversizing the Lotus Valve, and the introduction of a new implantation technique where the valve is kept in a high position during the entire deployment aiming to avoid mechanical interaction with the LVOT. Ideal final Lotus Valve position was considered to be with minimal valve protrusion in LVOT while still allowing access of the coronary ostia.”

There were 37 patients who developed a LBBB. Regarding the 4 patients who had a PPM implanted after discharge their ECGs at discharge were as follows; two of them had 1st degree AV block and LBBB, one had 1st degree AV block and incomplete LBBB and one is not verified by an ECG of unknown reason. These results are added to the Result section, subheading 4 “Pacemaker and Conduction disturbances”; “There were 37 patients who developed a LBBB (left bundle branch block) post TAVI. Among the patients who had a PPM implanted after discharge their discharge ECG were as follows; two patients had a 1st degree AV block and LBBB, one had a 1st degree AV block and incomplete LBBB and in one patient the discharge ECG was missing.”
6. Stroke: the rate of stroke after TAVI is lower than after SAVR in the most recent studies; But you experienced two major strokes leading to death. What is the exact cause of these strokes: A Fib underanticoagulated? calcium dislodgement due to the lotus manipulation in the aortic valve? other? authors should provide more details about these fatal complications (timing: on the cath lab? later? - causes - imaging ischemic vs hemorrhagic - treatment: did you try a thrombectomy?)

Author response: Both patients were extreme risk patients with severe calcification of the aorta and the aortic valve. In both cases it was difficult to position the device. Both strokes were periprocedural and ischemic. Since both patients were under full anesthesia during the procedure, the ischemic strokes were detected at the ward, and the patients never regained consciousness. The stroke rates are similar to what has been observed in a previously published registry (Falk et al, Eur Heart J 2017 Dec 1;38(45):3359-3366). Since this is a fairly small sample size, it is difficult to speculate whether the rate of low frequency events differ from other studies. We have added information to the previously mentioned in the Results, subheading 2 "Device failure and secondary outcomes", second last sentence; "In addition, two patients suffered from periprocedural fatal ischemic strokes, probably from calcium dislodgement, resulting in an overall 30-day mortality rate of 3%.”

7. In the discussion, the authors compare their results to the previous series of Lotus device only. It is important to compare this new technique of Lotus deployment with the results of the others devices: Sapien 3, Evolut-R, Portico,… Are the authors totally convinced that the current results of their study are better than the last series of competitive devices? They should demonstrate that.

Author response: We are not certain whether we correctly understand the reviewer. We fully agree with the reviewer that a comparison with other devices would be beneficial, but it is not within the scope of this manuscript. The main purposes of this manuscript was to provide insight on the outcome in an unselected cohort of patients while evaluating a new implantation technique that lowers the PPM rate for the Lotus Valve. This has been perceived as the main limitation of the Lotus Valve, and these encouraging results provide specific insight into the issue of PPM.
Reviewer #4, Filippo Figin:

The article in its present form is clear and well explained; I only have two minor comments:

1. It would be interesting to know how many patients underwent TOE monitoring during valve deployment

Author response: We thank the reviewer for his valuable comment. TOE monitoring was performed in the first 10 patients. Because of the low rates of PVL observed, it was scrapped in favor of angiographic assessment of PVL as part of a more minimalistic approach.

2. Page 4 line 6: please correct "vale" into "valve"

Author response: Thank you for the observation. We have now edited grammatical errors and a native English speaking member of our research group has proof-read the manuscript and made corrections.