Author’s response to reviews

Title: Influence of Mitroflow Bioprosthesis Structural Valve Deterioration on Cardiac Morbidity

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Regarding the manuscript: "Influence of Mitroflow Bioprosthesis Structural Valve Deterioration on Cardiac Morbidity" Journal of Cardiothoracic Surgery - JCTS-D-18-00215

Dear Prof. Vipin Zamvar

We thank the editors and reviewers for a qualified and constructive review of our paper. We attempted to answer specific reviewer comments. Hopefully, this will qualify our manuscript for publication in Journal of Cardiothoracic Surgery. Changes in the manuscript are highlighted with color red.

Reviewer comments:

Reviewer #1:

1. Five-year follow-up data suggesting a significant increase in heart failure and infective endocarditis due to bioprolierative failure. Your heart center also uses other company bio-valves. Why not compare between different bio-valves?

Answer: We thank this reviewer for this relevant comment. We agree that the suggested approach would be of utmost importance; especially if the objective were to identify differences between different bioprosthesis. A previous study from our institution has already investigated this issue (Nielsen PH et al 2016). It was a registry-based study observing increased reoperation
rates for Mitroflow prostheses size 19 and 21 compared with Carpentier-Edwards (CE) Perimount 19 and 21 mm valves.

However, cause of death related to known structural valve deterioration in Mitroflow bioprosthesis and the impact of living with a dysfunctional Mitroflow bioprosthesis on cardiac morbidity remain unclear. Our objective was to determine the cause of mortality in these specific patients who received a Mitroflow bioprosthesis and developed structural valve deterioration. In line with our conclusion we only address these issues in patients with Mitroflow bioprosthesis and recommend that these should be systematically and routinely followed with echocardiography, and reoperation should be considered if structural valve deterioration has developed.

2. Compare the differences in cancer between the three groups during follow-up. What is your main purpose?

Answer: We acknowledge the reviewer for this comment. As stated in the discussions section: “Contrary to our expectations, this study found no significant difference in all-cause mortality between any of the three groups. When we adjusted for cause of death, we found that, at 5 and 10 years, significantly more died in group 3 than in group 1 and group 2. The higher mortality in group 3 might be related to concurrent non-cardiac morbidities, such as cancer, that naturally increased the death rate”. Furthermore, given the small sample size in each group this statement might be caused by “chance finding”. Other different factors, as stated in the manuscript, could cause the differences.

Reviewer #2:

1. Congratulation to the author for an accurate data analysis in this paper. Although this article is not contribute for a new challenge data and treatment, however, the article has a strong data in accurate collection and analysis.

Answer: We thank this reviewer for the precise and accurate analysis of our study. It has been of utmost importance for us to use a strong methodology, collection of data and reporting. We are well aware of the missing novelty however; we still believe our study to be important as a large scale confirmatory study supporting previously published data.

Reviewer #3:

1. My recommendation to the authors relates to the relationship between the high incidence of Mitroflow bioprosthesis structural valve deterioration and its structural properties. If there are any specific reason that would explain its pathogenesis, that would be helpful.
Previous studies have demonstrated that age (below 70 years and above 80 years), Mitroflow valve size 19, ejection fraction below 35% and poor New York Heart Association functional class were independent risk factors for developing SVD [5,18,19]. Other studies have not identified small valve size as a risk factor [20]. However, the present study found no clinical variables that could predict the development of SVD. A possible explanation could be that the problem of developing SVD does not reside within the patient but in the structure of the Mitroflow valve itself [21]. In contrast to a previous case series [18], Lus F et al. found that the DLA Mitroflow model with its anticalcification treatment did not emerge as a protective factor against SVD in their study [20]. However, it has been mentioned that the pathologic mechanisms of SVD, concerning the degenerated LA/LXA Mitroflow prostheses shows more often calcification than cusp tear, in accordance with the results reported by Luk et al. [22]. Patients with a degenerated Mitroflow prosthesis developed prosthesis stenosis more often than regurgitation. This fact has important clinical consequences since patients with SVD withstand more easily a pressure than a volume overload. This is also in agreement with our long-term observations regarding more hospitalizations for congestive heart failure caused by the pressure overload observed.

2. It would be helpful for readers to insert a small paragraph describing the pathogenesis of bioprosthetic structural valve deterioration in the Discussion section.

Answer: Again, we thank the reviewer for this relevant comment – please see the above-mentioned extension of the discussion.

Kind regards on the behalf of corresponding author and co-authors

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