Author's response to reviews

Title: Cost-utility analysis of percutaneous mitral valve repair in inoperable patients with functional mitral regurgitation in German settings

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Author's response to reviews: see over
To: Executive Editor of the BMC Cardiovascular Disorders  
Timothy Shipley  

Dear Editor,

We are pleased to submit revised version of the manuscript entitled “Cost-Utility Analysis of Percutaneous Mitral Valve Repair in Inoperable Patients with Functional Mitral Regurgitation in German Settings” for your consideration for publication in the *BMC Cardiovascular Disorders* as a research article.

We are grateful for thorough review of our manuscript by two Journal’s reviewers. We believe that the changes made on the basis of the comments have helped to improve manuscript significantly. Response to reviewer’s comments is presented below.

We are submitting both clean version of the manuscript and version with tracked changes.

On behalf of authors,

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Response to reviewer’s comments for the manuscript

"Cost-utility analysis of percutaneous mitral valve repair in inoperable patients with functional mitral regurgitation in German settings"

(MS: 7570371911503754)

Reviewer #1

Comment 1: In line 103 you did not specify the source of the excessive all-cause mortality.
Response: The source of the excessive all-cause mortality is provided in the Table 1. We agree with the comment and will include reference 19 into the main text.

Actions: Reference is added.

Comment 2: What is the high prevalence of patients with heart failure and FMR? Can you support this with any data?
Response: Prevalence of functional mitral regurgitation is extensively reported in the literature. In the introduction to the manuscript we are citing four studies (references 1-4), which determined prevalence and burden of FMR in patients with heart failure. Additional study of Koeling et al. (Am Heart J. 2002 Sep;144(3):524-9.) estimated prevalence of severe mitral regurgitation of 18.9% and moderate mitral regurgitation of 29.7%.

Actions: No actions required.

Comment 3: In line 58 you mention the QRS interval. Since I don't have a medical background, I am not familiar with this term. Maybe you should explain this shortly?
Response: QRS interval stands for combination of the graphical deflections seen on a typical electrocardiogram. It corresponds to the depolarization of the right and left ventricles of the heart. In the context of the manuscript normal QRS interval means that there is no dissynchrony between ventricles, which can be the reason for heart failure and which is effectively treated with cardiac resynchronization therapy (CRT).

Actions: No actions required.

Comment 4: In Table 1 there is no transition probability for the optical medical treatment arm (cycles 2-11) to go from NYHA class II to III, while it is possible to go from II to II or II to IV. I wonder if this is correct? Shouldn't there be a probability to go from II to III as well?
Response: Transition probabilities were obtained from the limited sample of TITAN trial, in which progression from NYHA class II to III was not observed. We acknowledged this
limitation in the discussion section of the manuscript. Uncertainty about variable was included into probabilistic sensitivity analysis.

**Actions:** No actions required.

**Comment 5:** There were two long sentences (40-42 and 205-209) that were difficult to read. I would suggest splitting them up in two separate sentences.

**Response:** We agree with the comment.

**Actions:** Sentences were corrected.

**Reviewer #2:**

**Comment 1:** This study estimates the cost-effectiveness of PMVR for a time horizon of 10 years. The time horizon should be long enough to reflect all important differences in costs or outcomes between the technologies being compared. PMVR and OMT do lead to differences in survival or benefits that persists for the remainder of a person’s life and thus I think that a lifetime time horizon is required. It is not clear from the study what the life expectancy is after PMVR and therefore it is not possible to check if the time horizon of 10 years is justified.

**Response:** Selection of the time horizon of 10 years was made in order to ensure comparability of the results of analysis with other health economic studies on alternative technologies to treat functional mitral regurgitation in Europe and the fact that data about impact of functional mitral regurgitation on mortality is limited to 2-5 years, as it is shown in the validation of the model. We accept the comment about relevance of lifetime horizon and included analysis from lifetime horizon in the analysis. In the analysis from a lifetime perspective PMVR was more cost-effective with incremental cost-effectiveness ratio of €7,914/QALY.

**Actions:** The following additions were made to the methods section: “In addition to the base-case analysis over 10-year time horizon, cost-effectiveness of PMVR was also estimated over lifetime horizon.” The following additions were made to the results section: “In the analysis over lifetime horizon PMVR led to incremental cost of €19,539, incremental life-years gained of 3.23 and QALYs gained of 2.47. PMVR was more cost-effective over lifetime (ICER of €7,914/QALY) compared with base-case analysis over 10-year time horizon.”

**Comment 2:** Figure 2 shows all-cause mortality only for the first 4.5 years after implantation, please show also the survival of the patients after 4.5 years. In addition, the survival of the OMT patients could be included in the figure.
Response: Figure 2 is presenting results of model validation against three epidemiological studies. In validation exercise, baseline patient characteristics in the model followed baseline characteristics of each individual study and cannot be interpreted as mortality, demonstrated in the base-case analysis. We accept the suggestion to include data about mortality in the model into the manuscript.

Actions: The following was added to the results section: “Cumulative mortality was 13.8% and 23.5% at 1 year, 20.0% and 33.0% at 2 years, 35.6% and 54.3% at 5 years, and 55.5% and 76.5% at 10 years in the PMVR and optimal medical treatment arm respectively.”

Comment 3: It is not clear how short term effectiveness is extrapolated to 10 years in the base-case analysis.

Response: Based on the available 3-year data, effectiveness was assumed constant over long-term. It is stated in the methods section: “The long-term follow-up of these patients (3 years) has demonstrated a stable and durable effect of PMVR over time and, therefore, a sustained FMR reduction was assumed. According to the results of the TITAN trial, the patients in the control group had no improvement in FMR.” We have tested alternative assumption about no effect of the PMVR after 3 years in the sensitivity analysis, which is also reported in the methods and results section.

Actions: No actions required.

Comment 4: Utility decrements for PCI, MI, CABG, heart transplant are not incorporated in the model.

Response: We have decided to incorporate utility decrement only for PMVR into the model. Utilities, associated with NYHA classes in the model, were obtained from the same study (CARE-HF study), which provided information about distribution of interventions (PCI, MI, CABG, heart transplant) during hospitalization due to worsening of heart failure. In our opinion, utilities associated with NYHA classes in this case take into account disutility associated with interventions during hospitalizations, as all these variables are obtained from the same study.

Actions: No actions required.

Comment 5: The deterministic results do not correspond with the probabilistic results, please clarify.
Response: Base-case results are obtained in the probabilistic mode of the model, in which only age and gender of the cohort varied within pre-determined distributions. Probabilistic sensitivity analysis reflects uncertainty around variables in the model. In the probabilistic sensitivity analysis PMVR was associated with lower incremental cost, but also with reduced gains of benefits (both life years gained and QALYs gained). This resulted in the higher value of incremental cost-effectiveness ratio in the analysis.
Actions: No actions required.

Comment 6: Table 2: Please explain why the percentage of patients being hospitalized with stay in ICU is not varied in the PSA. The same applies to the other percentages in this part of the table and for the disutility.
Response: Percentage of patients being hospitalized and received different interventions as well as disutility were added to the probabilistic sensitivity analysis. DRG tariffs were not included into PSA, as there is no uncertainty about these variables.
Actions: Percentage of patients being hospitalized and received different interventions as well as disutility were added to the probabilistic sensitivity analysis. Analysis was updated in the manuscript.

Comment 7: Since performing one-way sensitivity analyses of probabilities have often an effect on both the incremental costs and incremental effects it would be useful to show also the tornado diagrams for the incremental costs and incremental effects.
Response: We appreciate the suggestion, although our decision is to focus on the major outcome of the study (incremental cost-effectiveness ratio) to simplify interpretation of the study for readers. Also, it is more common for publications of the results of decision analytic modelling is to demonstrate only one Tornado diagram for the sake of space in the article. If Editors will suggest that it is necessary to include additional Tornado diagrams, we can include them.
Actions: No actions required.

Comment 8: Is it possible that patients who had a device recapture undergo an additional intervention? If so, than it should be included in the model.
Response: In the model we have used intention-to-treat principle to determine course of actions for patients with recapture of device. In the model all patients with recapture of device did not undergo repeated procedure of insertion of PMVR.
Actions: No actions required.
Comment 9: People interested in this article without a medical background may have trouble reading it. It would be useful to make it easier to read. For example, for a reader without a medical background it is unclear that recapturing the device means that the intervention was unsuccessful. Please make clear that the 17 patients with a recaptured device are the controls.
Response: We agree with the comment.
Actions: The following was added to the methods section: “Thirty-six patients underwent permanent device implantation and seventeen patients had the device recaptured intra-operatively (i.e., device was removed) either for clinical indications (i.e., transient coronary compromise) or for a protocol defined indication (i.e., <1 grade FMR reduction). Both groups underwent serial follow-ups with the non-implanted cohort serving as a non-randomized, non-blinded comparator group. Data for 17 patients with device recaptured after unsuccessful implantation have been used to obtain transition probabilities in the optimal medical management (control) arm in the model.”

Comment 10: Please specify earlier in the model description that the decision tree estimates the cost-effectiveness for the first month after the intervention.
Response: We agree with the comment.
Actions: The following was added to the methods section: “Decision tree estimates the cost-effectiveness for the first month in the model.”

Comment 11: The discussion could elaborate more on the assumptions that were made.
Response: We agree with the comment, although major assumptions are addressed as limitations in the discussion section.
Actions: The following was added to the discussion section: “First, the transition probabilities between the different NYHA functional classes were based on a limited sample from the TITAN trial. Due to the limited sample size, not all transitions were possible in the base-case analysis. This limitation was addressed in the probabilistic sensitivity analysis.”

Comment 12: Abbreviation EROA is not introduced.
Response: We agree with the comment.
Actions: Abbreviation is explained in the text.

Comment 13: Please incorporate all items of the CHEERS statement (e.g. generalizability or identification of the used studies).
Response: We agree with the comment.
Actions: Changes were made throughout the manuscript.

Comment 14: Table 1 could use a column with source.
Response: All data in the table came from the TITAN trial.
Actions: Clarification about source of the data is made in the table.

Comment 15: Please provide a reference for the used threshold (35,000/QALY gained).
Response: We agree with the comment.
Actions: Reference has been provided.

Comment 16: Expand Table 3 with the fade-out effect analysis.
Response: We would like to clearly distinguish base-case and scenario analyses in the manuscript. We added extra details about results of fade-out effect analysis to the text.
Actions: The following was added to the results section: “Analysis of fade-out effect for effectiveness of PMVR showed that technology remains cost-effective with ICER of €23,582/QALY. In this analysis, PMVR led to an incremental cost of €20,662 (cost of €39,702 and €19,040 in the PMVR and optimal medical management arms respectively), an incremental life-years gained of 1.04 (life-years gained of 5.49 and 4.46 in the PMVR and optimal medical management arms respectively) and a QALYs gained of 0.88 (QALYs gained of 3.78 and 2.90 in the PMVR and optimal medical management arms respectively).”

Comment 17: Table 2: base case value ‘probability of MI, which lead to PCI’ and ‘probability of arrhythmia’ do not correspond with the beta distribution.
Response: We agree with the comment.
Actions: Base-case values were corrected.

Comment 18: Table 2: the beta distributions used for six months probability….. and monthly probability…. add all up to 100. Is this coincidence or were the exact alpha, beta’s or sample size unknown.
Response: That’s correct observation. Sample size was not known, that is why an assumption was used to develop distributions.
Actions: No actions required.
Comment 19: Maybe it is good to start the method section with a description of the population, intervention and comparator.
Response: We have introduced technology in the introduction section. Target population is described in the analysis section.
Actions: No actions required.

Comment 20: Some clinicians do not have experience with cost-effectiveness studies. It could be useful to refer to some health economic modelling papers: ISPOR, MDM or Cohen & Reynolds 2008 JACC.
Response: In the methods section we use reference to the handbook in health economics. We agree with the comment and will introduce additional references.
Actions: Several references are added in the methods section.