PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to the BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	A cost-utility analysis of transcatheter aortic valve implantation (TAVI) in Belgium: focusing on a well-defined and identifiable population
AUTHORS	Mattias Neyt, Hans Van Brabandt, Stephan Devriese and Stefaan Van de Sande

VERSION 1 - REVIEW

REVIEWER	Ken Redekop Erasmus University Rotterdam

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript describing a study of the cost-effectiveness of transcatheter aortic valve implantations (TAVIs) for two types of aortic stenosis (AS) patients in Belgium: "high-risk" operable patients and inoperable patients. The primary source for the effectiveness of TAVI was the PARTNER trial, a randomised controlled trial with two strata (cohort A, high-risk patients; cohort B, inoperable patients). The comparators used in the study differed between the strata: high-risk patients underwent either TAVI or surgical aortic valve replacement, while inoperable patients underwent either TAVI or 'standard therapy' (which often included balloon valvuloplasty). The incremental effectiveness of TAVI for high-risk patients was very small (0.03 quality-adjusted life-years, QALYS), much lower than that seen for inoperable patients (0.74 QALYs). Not surprisingly, the incremental cost-effectiveness ratio (ICER) for high-risk patients was therefore much greater than the ICER for inoperable patients (750,000 euros per QALY gained vs. 44,900 euros per QALY gained). The authors concluded that TAVI was certainly not cost-effective for high-risk patients but could be cost-effective for inoperable patients, depending on the willingness to pay. It appears like the authors have done a good job of combining the results of clinical trials (particularly the PARTNER trial) with "local" (i.e. Belgian) data. Moreover, the cost-effectiveness estimates probably correspond with what most would have expected from the outset. I have a few comments regarding the quality and relevance of this manuscript for the BMJ. In my opinion, this article is original and I think that the analyses described in the article were performed responsibly. My main concerns relate not so much to the quality of the analysis itself, but rather to the type of paper and the way in which the paper was written. GENERAL COMMENTS

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	1. What kind of article is particularly suitable for the BMJ? This article focused on the cost-effectiveness analysis of TAVI versus the alternatives and the conclusion primarily relates to these aspects. Despite my role as a reviewer (and not as an editor), I can't help wondering whether there are two papers to be written on this topic: 1) a paper describing the methods and results of the cost-effectiveness (and cost-utility) analysis of TAVI in Belgium; and 2) a paper which discusses the cost-effectiveness of TAVI (and perhaps similar high-cost devices and procedures) and ways to improve it. (Personally, I'd think that the second one would be more suitable for BMJ.) This paper is essentially the first type of paper, although there are a few points in the paper where elements of the second appear. For example, the authors concluded that TAVI could be a more acceptable treatment alternative (from an economic standpoint) for anatomically inoperable patients than for medically inoperable patients. Particularly important from a policymaking viewpoint would be the ability to distinguish these patients from other patients in daily practice (page 15, paragraph 1, final sentence). If the ultimate goal is to determine whether or not TAVI represents 'value for money', it would be important to describe what other countries have decided and how they came to their conclusion. For example, the Health Care Insurance Board in the Netherlands (CVZ) recently recommended that TAVI for inoperable patients be included in the basic reimbursement package. Their conclusion was based in part on the PARTNER trial results and cost-effectiveness analyses. Moreover, they also discussed with surgeons how their advice could be implemented in practice. Here is a quote from their summary statement: « Pour être retenues, les études (portant sur les générations de valves évaluées en 2008 par la HAS) devaient être multicentriques et renseigner : - les données procédurales - les données de sécurité à 1 mois et à 1 an en termes de mortalité, d'infarctus du myocarde, d'accident vasculaire cérébral, de saignements, de complications vasculaires, d'insuffisance rénale - les données d'efficacité à 1 mois et 1 an de suivi en termes de performances hémodynamiques et d'évolution des symptômes. » "The distinction between insured persons who are operable and those who are inoperable is made by the attending physicians and will depend on several factors including a risk-score and a clinical estimation involving numerous disciplines. The scientific associations of cardiologists and cardiosurgeons (the NVVC and the NVT) have jointly drawn up an indication protocol." http://www.cvz.nl/binaries/content/documents/cvzinternet/en/documents/assessments/asm1110-transcatheter-aortic-valve-replacement.pdf Incidentally, the comments found here correspond somewhat with those made by the authors in the Discussion section (page 15, para. 1, sent.1). Will every country have the same attitude towards TAVI? No. As the authors know, the attitude in Germany towards the reimbursement of TAVI is completely different, primarily because of the interests in promoting innovation in the health care industry. This means that the cost-effectiveness of TAVI will not always have a bearing on its reimbursement. 2. Writing style, documentation and choice of figures and tables In general, the authors have done a good job of describing what they did and I can appreciate the difficulty of fitting all relevant information in a limited space. There are a couple of opportunities to improve this manuscript. The two patient populations of interest are usually referred to in the paper as cohort A and cohort B, since these were the labels used in the PARTNER study. I would suggest referring to these populations as high-risk patients and inoperable patients throughout the paper. Not only would this improve readability, but it would also

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	remind the reader that the ultimate aim of this study was to estimate the cost-effectiveness of TAVI in Belgian patients using a combination of the PARTNER study results and Belgian data. It's not clear at the start of the paper that this study focused on the cost-effectiveness of TAVI in Belgium; in fact, Belgium is not mentioned until the mortality subsection in the Methods. All told, there are 7 figures and 5 tables in the paper (including the Supplement). I think that some are not needed at all (Figure 3), some may be combined, and others are missing. For example, it might be useful to have one table showing the cost-effectiveness results for both patient populations (à la Table 5), which also includes the results for the subgroups (particularly anatomically inoperable patients). Regardless of the limitations, choices will have to be made about which are to be included in the main paper. The Results section is too brief in places ("anatomically inoperable patients have a more favourable ICER...") and relies too heavily on results found only in the Supplement. Lastly, grammar can be improved upon although in most cases there's no unambiguity about what is meant. SPECIFIC COMMENTS Discussion One paragraph in this section (page 14, paragraph 2) discusses the cost-effectiveness of TAVI in the UK (versus Belgium). It's not quite clear why the NICE thresholds are discussed here, unless the authors assume that the ICERs found in their study can be seen as estimates of the ICERs in other countries like England. If so, this should be made explicit. Alternatively, the authors might have used the NICE threshold just to illustrate how unlikely it is that TAVI will be cost-effective at a given threshold. However, that's already addressed in the Results section. Figure 1: I'm not convinced that this figure will be understood by most readers. In addition, it's unclear what exactly is meant by hospitalisation and 'etc.'. Table 2: The costs of major stroke strike me as awfully low, unless they only refer to acute care. However, a higher estimate of costs would only increase the ICER for TAVI!

REVIEWER	Ingrid Zechmeister-Koss Ludwig Boltzmann Institute for Health Technology Assessment

GENERAL COMMENTS	This is a scientifically sound and well written paper. It addresses the important topic of cost-effectiveness of TAVI that has to my knowledge not been addressed in this form so far. According to the checklist for economic evaluations, the paper fulfils the core quality criteria for economic evaluations: In the paper the research question is well defined, the alternatives that are addressed in the analysis have been adequately described. Addtionally, the relevant costs and consequences have been included in the analysis, they have been measured appropriately and valued credibly. The results have been adjusted for timing and

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	they have been presented as incremental analysis. The authors have appropriately discussed the results and they have addressed uncertainty by doing appropriate sensitivity analyses. I have the following recommendations for minor changes: 1) The objective of the study, as stated by the authors, is to do a cost-effectiveness analysis of TAVI. For their calculation of costs they use Belgian data on resource use and unit costs. Hence, it needs to be made more transparent that this is a cost-effectiveness analysis that is primarily valid for the Belgian health care system. The way it is presented now gives the impression of a general cost-effectiveness analysis that is valid for any jurisdiction. 2) The authors use data from the PARTNER trial to generate their parameters on effectiveness of TAVI. I would prefer to read a bit more about the overall quality of those data/the trial quality, limitations... 3) table 5 in the appendix mixes 'comma' and 'dots' (e.g. 0,65 instead of 0.65)

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

1. What kind of article is particularly suitable for the BMJ?
This article focused on the cost-effectiveness analysis of TAVI versus the alternatives and the conclusion primarily relates to these aspects. Despite my role as a reviewer (and not as an editor), I can't help wondering whether there are two papers to be written on this topic: 1) a paper describing the methods and results of the cost-effectiveness (and cost-utility) analysis of TAVI in Belgium; and 2) a paper which discusses the cost-effectiveness of TAVI (and perhaps similar high-cost devices and procedures) and ways to improve it. (Personally, I'd think that the second one would be more suitable for BMJ.) This paper is essentially the first type of paper, although there are a few points in the paper where elements of the second appear. For example, the authors concluded that TAVI could be a more acceptable treatment alternative (from an economic standpoint) for anatomically inoperable patients than for medically inoperable patients. Particularly important from a policymaking viewpoint would be the ability to distinguish these patients from other patients in daily practice (page 15, paragraph 1, final sentence).

- We understand the comment of the reviewer. In the current situation, as suggested by the reviewer, our paper describing the methods and results of the cost-effectiveness (and cost-utility) analysis of TAVI in Belgium is submitted to BMJ Open. Other more general concerns about the TAVI and the PARTNER trial are submitted to BMJ.

If the ultimate goal is to determine whether or not TAVI represents 'value for money', it would be important to describe what other countries have decided and how they came to their conclusion. For example, the Health Care Insurance Board in the Netherlands (CVZ) recently recommended that TAVI for inoperable patients be included in the basic reimbursement package. Their conclusion was based in part on the PARTNER trial results and cost-effectiveness analyses. Moreover, they also discussed with surgeons how their advice could be implemented in practice. Here is a quote from their summary statement:

- We know that the selection criteria of other HTA institutes to include studies were strict. For example in HAS (in French):
  « Pour être retenues, les études (portant sur les générations de valves évaluées en 2008 par la HAS) devaient être multicentriques et renseigner :
  - les données procédurales
  - les données de sécurité à 1 mois et à 1 an en termes de mortalité, d'infarctus du myocarde, d'accident vasculaire cérébral, de saignements, de complications vasculaires, d'insuffisance rénale
  - les données d'efficacité à 1 mois et 1 an de suivi en termes de performances hémodynamiques

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et d'évolution des symptômes. »

As a result of restricting information to published data with one year of follow-up, the non-published negative results of the randomized continued access trial were not included. We are convinced that such selection criteria creates a bias since e.g. non-published negative results or discontinued trials (due to safety reasons) are not taken into account.

- It is not clear what the exact reasons are for (not) reimbursing TAVI in specific patient populations in different countries. We do not wish to criticize the decisions taken by other policy makers in our manuscript (although it would be interesting to criticize the selection criteria in some systematic reviews in general). We do not know to what extent other policy makers have taken account of the unbalanced patient characteristics in the published PARTNER results for inoperable patients or the non-published negative randomized trial results. We prefer to transparently present our economic evaluation and provide balanced arguments to the reader.
- In our conclusion, we added the following:
  "*Finally, the study sponsor should be more willing to share all relevant data in due time, i.e. before important policy decisions are taken. Both positive and negative study results providing details on all relevant outcomes (mortality, adverse events and QoL) for the most important subgroups should be revealed. This will enable more balanced evaluations and well-founded policy recommendations. Payers should insist to have full information before taking reimbursement decisions.*"

"The distinction between insured persons who are operable and those who are inoperable is made by the attending physicians and will depend on several factors including a risk-score and a clinical estimation involving numerous disciplines. The scientific associations of cardiologists and cardiosurgeons (the NVVC and the NVT) have jointly drawn up an indication protocol."
http://www.cvz.nl/binaries/content/documents/cvzinternet/en/documents/assessments/asm1110-transcatheter-aortic-valve-replacement.pdf

Incidentally, the comments found here correspond somewhat with those made by the authors in the Discussion section (page 15, para. 1, sent.1).

Will every country have the same attitude towards TAVI? No. As the authors know, the attitude in Germany towards the reimbursement of TAVI is completely different, primarily because of the interests in promoting innovation in the health care industry. This means that the cost-effectiveness of TAVI will not always have a bearing on its reimbursement.

- We agree that promoting innovation can be one of the reasons to support the use of a new intervention. However, in order to support science and avoid patients being exposed to unnecessary risks, policy makers should strive to support innovation in an appropriate research setting. Patient registries are not sufficient to prove an intervention's safety or efficacy. This is shown with the transapical TAVI: no transapical approach was evaluated in the inoperable patient group and the cessation of the independent Danish STACCATO trial for safety reasons. This while the transapical intervention is still applied in daily practice. We added the following in the discussion of our manuscript:
  "*It should be noted that the evidence from the PARTNER trial for inoperable patients only applies to the transfemoral approach. Although the FDA proposed to do so, the PARTNER study sponsor did not include a transapical arm in inoperable patients.*[4] *In high-risk operable patients, a subgroup analysis suggests that the transapical approach is not inferior to surgery, but doubles the stroke risk. Recently, the results from the STACCATO trial, an independent RCT of transapical TAVI in operable elderly patients have been presented.*[8] *The primary endpoint (30-day all cause mortality, major stroke, and/or renal failure) was reached in 5/34 TAVI and 1/36 surgically treated patients, and the study was prematurely terminated after advice from the Data Safety Monitoring Board. Given the fact that operative risk estimation is a highly subjective matter, it is as yet unclear to what extent the operative risk of patients enrolled in STACCATO is different from that of PARTNER patients or from patients currently treated all over Europe. These observations once more put into question the appropriateness for the European regulators granting the transapical Sapien valve a CE label in 2007.*[9] *It also shows the importance of performing high quality randomised trials with clinically relevant endpoints prior to granting marketing approval of innovative high-risk devices.*[9]"

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2. Writing style, documentation and choice of figures and tables In general, the authors have done a good job of describing what they did and I can appreciate the difficulty of fitting all relevant information in a limited space. There are a couple of opportunities to improve this manuscript.
The two patient populations of interest are usually referred to in the paper as cohort A and cohort B, since these were the labels used in the PARTNER study. I would suggest referring to these populations as high-risk patients and inoperable patients throughout the paper. Not only would this improve readability, but it would also remind the reader that the ultimate aim of this study was to estimate the cost-effectiveness of TAVI in Belgian patients using a combination of the PARTNER study results and Belgian data.

- We agree with this remark and replaced the 'cohort A' and 'cohort B' label by 'high-risk operable' and 'inoperable' patients.

It's not clear at the start of the paper that this study focused on the cost-effectiveness of TAVI in Belgium; in fact, Belgium is not mentioned until the mortality subsection in the Methods.

- We added Belgium in the title, abstract and text.

All told, there are 7 figures and 5 tables in the paper (including the Supplement). I think that some are not needed at all (Figure 3), some may be combined, and others are missing. For example, it might be useful to have one table showing the cost-effectiveness results for both patient populations (à la Table 5), which also includes the results for the subgroups (particularly anatomically inoperable patients). Regardless of the limitations, choices will have to be made about which are to be included in the main paper.
The Results section is too brief in places ("anatomically inoperable patients have a more favourable ICER...") and relies too heavily on results found only in the Supplement.

- If the editor allows to publish more tables and figures in the text, than we would be very happy to move Table 3 (input on QoL), table 5 and figure 6 from the supplements to the main paper. Table 5 and figure 6 contain all results the reviewer refers to. If it is not possible to include this amount of figures and tables, than we hope this additional information can be published in an online appendix.

Lastly, grammar can be improved upon although in most cases there's no unambiguity about what is meant.

SPECIFIC COMMENTS

Discussion
One paragraph in this section (page 14, paragraph 2) discusses the cost-effectiveness of TAVI in the UK (versus Belgium). It's not quite clear why the NICE thresholds are discussed here, unless the authors assume that the ICERs found in their study can be seen as estimates of the ICERs in other countries like England. If so, this should be made explicit. Alternatively, the authors might have used the NICE threshold just to illustrate how unlikely it is that TAVI will be cost-effective at a given threshold. However, that's already addressed in the Results section.

- Belgium does not have an explicit threshold value (see KCE report: "Cleemput I, Neyt M, Thiry N, De Laet C, Leys M. Threshold values for cost-effectiveness in health care Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE); 2008. KCE reports 100C (D/2008/10.273/96)"
  we added the following in our text:
  "*In most countries, as well as in Belgium, there is no explicit ICER threshold. Only NICE (National Institute for Health and Clinical Excellence) has explicitly mentioned this in their Guide to the Methods of Technology Appraisal.*[10] *Applying NICE's threshold values of £20,000 (£1 = €1.14, August 25, 2011) and £30,000 per QALY, results in a 9.2% and 36.7% chance, respectively, that TAVI is considered as being a cost-effective intervention. …*"

Figure 1: I'm not convinced that this figure will be understood by most readers. In addition, it's unclear what exactly is meant by hospitalisation and 'etc.'.

- The text under the title 'costs' mentions the following: "events with a possible incremental impact were selected from the published PARTNER trial. Included events are: repeat hospitalizations, minor/major stroke and TIA, and cardiac reintervention."

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- We added the following under the figure to explain what is meant with 'etc.':
  "Etc.: this indicates that if the patient survives, he goes to the next cycle in the Markov model. In each cycle, the patient is again at risk of dying, being hospitalized, having other events or no event."

Table 2: The costs of major stroke strike me as awfully low, unless they only refer to acute care. However, a higher estimate of costs would only increase the ICER for TAVI!
- This is indeed a correct interpretation of the reviewer. We prefer to include this explicitly in our discussion by adding the following:
  "*…This rather is an optimistic estimate due to several factors: the unbalanced patient characteristics in the PARTNER trial in favor of the TAVI group (see next paragraph), the lifelong extrapolation assumption on survival (see FDA remark in the Supplementary Appendix (Figure 7)), keeping QoL at a high level in the long-term in this ageing population, and the possible long-term consequences and costs of stroke.*"

Reviewer 2

This is a scientifically sound and well written paper. It addresses the important topic of cost-effectiveness of TAVI that has to my knowledge not been addressed in this form so far.

According to the checklist for economic evaluations, the paper fulfils the core quality criteria for economic evaluations: In the paper the research question is well defined, the alternatives that are addressed in the analysis have been adequately described. Addtionally, the relevant costs and consequences have been included in the analysis, they have been measured appropriately and valued credibly. The results have been adjusted for timing and they have been presented as incremental analysis. The authors have appropriately discussed the results and they have addressed uncertainty by doing appropriate sensitivity analyses.

I have the following recommendations for minor changes:
1) The objective of the study, as stated by the authors, is to do a cost-effectiveness analysis of TAVI. For their calculation of costs they use Belgian data on resource use and unit costs. Hence, it needs to be made more transparent that this is a cost-effectiveness analysis that is primarily valid for the Belgian health care system. The way it is presented now gives the impression of a general cost-effectiveness analysis that is valid for any jurisdiction.
- We added Belgium in the title, abstract and text.

2) The authors use data from the PARTNER trial to generate their parameters on effectiveness of TAVI. I would prefer to read a bit more about the overall quality of those data/the trial quality, limitations...
- We included our main concerns in the manuscript: not publishing the negative results of the continued access PARTNER trial and the non-balanced distribution of patient characteristics (in contrast to what is mentioned in the original publication) in favor of TAVI.
  1) the non-publication of the negative Continued Access RCT is mentioned in the main text and discussion.
  2) imbalanced patient characteristics (included in the discussion):
  "*In the PARTNER trial, baseline characteristics of inoperable patients were unevenly distributed among the two study groups, most if not all imbalances favoring survival in the TAVI treated patients. The logistic EuroSCORE was higher in the control arm (30.4 vs. 26.4, p=0.04), and both chronic obstructive pulmonary disease (52.5% vs. 41.3%) and atrial fibrillation (48.8% vs. 32.9%) were statistically significantly (p<0.05) more prevalent. "Frailty" patients (28% vs. 18.1%, p=0.09) were also overrepresented. In general, patients that are inoperable due to co-morbidities were overrepresented in the control arm. The PARTNER study protocol stipulates that both medical and anatomic conditions may lead to the surgeons' conclusion of inoperability and that the surgeons' consult notes shall specify the medical or anatomic factors.11 Patients with co-existing anatomic conditions (extensively calcified aorta, deleterious effects of chest-wall irradiation, and chest-wall deformity) were better represented in the TAVI group than in the control group (29.6% vs. 20.7%, p=0.05). These anatomically inoperable patients probably have a better prognosis and quality of life after solving the aortic valve stenosis. Because of the imbalance in patient characteristics and the possibly better*

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prognosis, this one subgroup analysis for this specific patient characteristic was asked to the study sponsor."

- As suggested by the first reviewer, we also submitted a more detailed manuscript to the BMJ with our concerns on the PARTNER trial.

3) table 5 in the appendix mixes 'comma' and 'dots' (e.g. 0,65 instead of 0.65)

- We corrected this in table 5.

VERSION 2 – REVIEW

REVIEWER	Claudia Wilde Ludwig Boltzmann Institute for Health Technology Assessment
REVIEW RETURNED	05/03/2012

GENERAL COMMENTS	Thank you for the possibility to review this manuscript on TAVI, a cost-effectiveness analysis, based on Belgium data. TAVI – as an intervention in an aged and multi-morbid patient group - is a highly relevant (for health care systems/ solidarity payers) medical intervention in an aging western society – that is to say broad diffusion, huge markets. It is an easy task (to review), since I have not read such a clear manuscript for a long time. The analysis is based on published data (Leon et al/ 2 publications, 2 cohorts: A and B) and unpublished data from the Continued Access study. The authors have done a very good job concerning transparent and systematic quality research, fulfilling all criteria of quality publishing checklists. This manuscript is a very thorough piece of research. Some important informations are not stressed enough/ must be mentioned more often: In the Continued Access study (not published) the mortality was higher in the Intervention group was 12,7% (p 7/32) higher. This important information underlines other results of unpublished studies, that only positive results are published. Later (p 15/32) it is mentioned that the STACCATO trial was –prematurely – terminated, because of worse results in the intervention group (TAVI). This manuscript should be published – fast !

REVIEWER	Ken Redekop (Associate professor) and Saskia de Groot (Research fellow) Institute for Medical Technology Assessment Erasmus University Rotterdam The Netherlands There are no conflicts of interest to report.
REVIEW RETURNED	09/03/2012

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript. The aim of this study was to assess the cost-effectiveness of transcatheter aortic valve implantations (TAVIs) in Belgium. Two patient groups

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were studied: “high-risk” operable patients and inoperable patients. The primary source for effectiveness data was the PARTNER trial, a randomised controlled trial with two strata (cohort A, high-risk patients; cohort B, inoperable patients). The comparators used in the study differed between the strata: high-risk patients underwent either TAVI or surgical aortic valve replacement, while inoperable patients underwent either TAVI or ‘standard therapy’ (which often included balloon valvuloplasty).

The incremental cost-effectiveness ratio (ICER) of TAVI for high-risk patients was very high, particularly because the gain in quality-adjusted life-years (QALYS) was very small. In contrast, the ICER for inoperable patients was much lower (44,900 euros per QALY gained), mainly since the QALY gain was more substantial (0.74 QALYs). The authors concluded that TAVI was certainly not cost-effective for high-risk patients but could be cost-effective for inoperable patients, depending on society’s willingness to pay. Moreover, the authors stress the need for the study sponsor to be more forthcoming about the results of trials that have been performed.

The authors appear to have done a good job of combining the results of clinical trials (particularly the PARTNER trial) with "local" (i.e. Belgian) data. In my opinion, this article is original, the topic is quite relevant, and I think that the analyses described in the article were performed responsibly.

GENERAL COMMENTS

In general, the authors have done a good job of describing what they did. Some of these are specific comments and are found below. One general issue relates to the choice of figures and tables. All told, there are 7 figures and 5 tables right now, including those found in the supplements. I think that some are not needed at all. For example, figure 3 may not be necessary (see specific comments below). It might be useful to have one table showing the cost-effectiveness results for both patient populations (like Table 5), which also includes the results for the subgroups (particularly anatomically inoperable patients). In addition, the figures in the supplement on pages 26-28 (Figures 1, 1, and 2) are already found in the main paper. I’m not that familiar with BMJ Open’s policy regarding the use of supplements, so choices about what to include where may or may not have to be made. Note that the results section sometimes refers to results found only in the Supplement.

Minor improvements to grammar can be made here and there (e.g., solving the stenosis appears twice; reference is made to ‘“frailty” patients’).

SPECIFIC COMMENTS

Methods
Page 5 (Methods, paragraph 1): @Risk “adds-on” should read “add-in”

Page 5 (Intervention and comparator, paragraph 1): the PARTNER-US study was introduced. Was the PARTNER study meant here?

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	Page 6 (Time horizon): No significant difference in survival after one year was found in the high risk operable patients, and therefore the time horizon for that cost-effectiveness analysis was restricted to this period. However, there were differences found in secondary outcome measures, for example a twofold increase in stroke risk after TAVI. Could this have an influence on the costs after one year? Note however that a longer time horizon would only lead to a higher cost-effectiveness ratio. Page 6: Figure 1 shows the Markov model that was used. Here we see that a patient can die (absorbing state), be hospitalized, have an adverse event or have no event. Table 4 shows the percentage of observed events after 30 days and one year which are used in the economic model. How exactly were the values shown in table 4 used to fit into the health states shown in figure 1, since it seems like most events in table 4 will lead to hospitalization. Also, many readers won't understand what is meant by 'etc.'. Page 7: Since the utility values of high-risk operable patients were not provided, it was assumed that the utility difference found in inoperable patients could apply to high-risk operable patients as well. However, from the manuscript it's unclear whether the reduction in symptoms to NYHA class II or lower was comparable to the reduction seen in inoperable patients. Page 11: One-way sensitivity analysis was performed based on several uncertain parameters. However, from the methods it's unclear how the ranges were selected, for example a QoL improvement of 0.1. It would help to specify the reasons for these ranges. Page 14: What is the reason behind figure 3 and how are the limits of both inoperability and high risk operable patients determined? It's not likely that the range in ICERs for the high risk patient population (indicated along the X-axis) is based on any statistics (e.g. 95% confidence interval). Instead, it seems like the aim is to emphasise that there's an important overlap between medically inoperable patients and high-risk operable patients, and that TAVI has a high ICER with both patient populations. I would therefore suggest the text just below the figure be put in the main text. Page 24: Figure 6 shows the tornado graph. Minor comment here: this figure is technically not quite correct, since the most influential variable on the ICER should be placed on top, i.e. 3-year time horizon followed by (non-)technical inoperable patients. It might help to have the vertical line present the ICER in the base-case and not based on the pivotal PARTNER trial.

VERSION 2 – AUTHOR RESPONSE

Reviewer: Claudia Wild
Ludwig Boltzmann Institut

Thank you for the possibility to review this manuscript on TAVI, a cost-effectiveness analysis, based on Belgium data. TAVI – as an intervention in an aged and multi-morbid patient group - is a highly relevant (for health care systems/ solidarity payers) medical intervention in an aging western society – that is to say broad diffusion, huge markets.

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It is an easy task (to review), since I have not read such a clear manuscript for a long time.

The analysis is based on published data (Leon et al/ 2 publications, 2 cohorts: A and B) and unpublished data from the Continued Access study.

The authors have done a very good job concerning transparent and systematic quality research, fulfilling all criteria of quality publishing checklists. This manuscript is a very thorough piece of research.

Some important informations are not stressed enough/ must be mentioned more often:

In the Continued Access study (not published) the mortality was higher in the Intervention group was 12,7% (p 7/32) higher. This important information underlines other results of unpublished studies, that only positive results are published. Later (p 15/32) it is mentioned that the STACCATO trial was – prematurely – terminated, because of worse results in the intervention group (TAVI).

- We agree with this comment from the reviewer.
  We changed the following sentence in the introduction:
  "*After the publication of the pivotal trial results, additional data from the PARTNER trial became available. Among them are non-published negative mortality data from the Continued Access study*"
  We added the following paragraph in the discussion:
  "*Not publishing negative or prematurely terminated studies is problematic for assessing clinical efficacy and supporting rational decision making. Manufacturers should reveal all relevant or requested information to health technology assessment bodies. If this does not work on a voluntary basis, then, policymakers should have the courage to take more drastic measures. For example, government could refuse to take a reimbursement decision as long as not all relevant data are provided. The German Institute for Quality and Efficiency in Health Care (IQWiG) assessment report on the antidepressant reboxetine has shown this can be a very effective measure: Pfizer did not submit a complete list of unpublished trials as requested by IQWiG. IQWiG therefore issued the preliminary conclusion that because of the high risk of publication bias, no meaningful assessment of reboxetine was possible and thus no benefit of the drug could be proved.*[13] *Pfizer then decided to provide most of the missing data and the subsequent assessment showed that, overall, reboxetine had no benefit.*[14-16] *Unfortunately, several other examples of publication bias exist that could have influenced policy recommendations and decisions if full information was available. The non-availability of complete information is, as mentioned in a BMJ editorial, "a disservice to research participants, patients, health systems, and the whole endeavour of clinical medicine".*[17]"

This manuscript should be published – fast !

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Reviewer: Ken Redekop (Associate professor) and Saskia de Groot (Research fellow)
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There are no conflicts of interest to report.

Thank you for the opportunity to review this manuscript. The aim of this study was to assess the cost-effectiveness of transcatheter aortic valve implantations (TAVIs) in Belgium. Two patient groups were studied: “high-risk” operable patients and inoperable patients. The primary source for effectiveness data was the PARTNER trial, a randomised controlled trial with two strata (cohort A, high-risk patients; cohort B, inoperable patients). The comparators used in the study differed between the strata: high-risk patients underwent either TAVI or surgical aortic valve replacement, while inoperable patients underwent either TAVI or ‘standard therapy’ (which often included balloon valvuloplasty).

The incremental cost-effectiveness ratio (ICER) of TAVI for high-risk patients was very high, particularly because the gain in quality-adjusted life-years (QALYS) was very small. In contrast, the ICER for inoperable patients was much lower (44,900 euros per QALY gained), mainly since the QALY gain was more substantial (0.74 QALYs). The authors concluded that TAVI was certainly not cost-effective for high-risk patients but could be cost-effective for inoperable patients, depending on society’s willingness to pay. Moreover, the authors stress the need for the study sponsor to be more forthcoming about the results of trials that have been performed.

The authors appear to have done a good job of combining the results of clinical trials (particularly the PARTNER trial) with "local" (i.e. Belgian) data. In my opinion, this article is original, the topic is quite relevant, and I think that the analyses described in the article were performed responsibly.

GENERAL COMMENTS

In general, the authors have done a good job of describing what they did. Some of these are specific comments and are found below. One general issue relates to the choice of figures and tables. All told, there are 7 figures and 5 tables right now, including those found in the supplements. I think that some are not needed at all. For example, figure 3 may not be necessary (see specific comments below). It might be useful to have one table showing the cost-effectiveness results for both patient populations (like Table 5), which also includes the results for the subgroups (particularly anatomically inoperable patients). In addition, the figures in the supplement on pages 26-28 (Figures 1, 1, and 2) are already found in the main paper. I’m not that familiar with BMJ Open’s policy regarding the use of supplements, so choices about what to include where may or may not have to be made. Note that the results section sometimes refers to results found only in the Supplement.

- We included 5 tables and figures in the main text. The other 7 tables and figures are in the supplements. As such, we try to provide the necessary information in the main text, and extra information for the interested reader in the supplements. This should make the manuscript very transparent. We think it is more a personal taste that determines which figures or tables to include in the main text or supplements. We hope that 5 tables and figures is not too much for the main text.
- The reviewer suggests that figure 3 may not be necessary. However, in our opinion, figure 3 gives a very good overview of results and several important issues that are discussed in the manuscript:
    - 1) the subjective (non-)distinction between high-risk operable and inoperable patients, with exception of anatomic inoperable patients.
    - 2) the very high ICERs (€750.000/QALY) for high-risk operable patients and the lower (but still relatively high) ICERs (>€45.000/QALY) for inoperable patients.

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- And 3) within the latter category, the better ICERs for anatomic inoperable patients.

We made this more clear by adding the following under the figure:
"*The x-axis indicates the operability of patients. There is an overlap between medically inoperable and high risk operable patients. Anatomically inoperable patients are readily identifiable. For high-risk operable patients, the ICERs are very high (€750.000/QALY). For inoperable patients, the ICER was on average €45.000/QALY. Within the latter category, ICERs are better for anatomic inoperable patients and worse for medical inoperable patients.*"

- We also added the reference to this figure in the text:
"*With an average ICER of about €750,000 per QALY (Figure 3), it is hard to defend a reimbursement for TAVI in high-risk operable patients as an efficient use of limited resources."*
"For inoperable patients, combining the mortality data from both the pivotal and Continued Access trial results in an ICER of about €45,000 per QALY (Figure 3)."
"Anatomically inoperable patients, who benefit most from the intervention, can easily be distinguished from other patients (Figure 3)."

Minor improvements to grammar can be made here and there (e.g., solving the stenosis appears twice; reference is made to '"frailty" patients').

- "*after ~~solving~~ remediating the aortic valve stenosis*" and "*after ~~solving~~ correction of the aortic stenosis*"
- *"~~"~~Frail~~ty"~~ patients"*

SPECIFIC COMMENTS

Methods
Page 5 (Methods, paragraph 1): @Risk "adds-on" should read "add-in"

- *"The @Risk add~~s~~ in~~on~~ tool"*

Page 5 (Intervention and comparator, paragraph 1): the PARTNER-US study was introduced. Was the PARTNER study meant here?

- There is the distinction between the PARTNER-US study, which is an RCT, and the PARTNER-EU study, which is a registry without control group. We changed the text as follows:
  - 1) Remove the 'US' indication in the text: "*The Edwards SAPIEN heart-valve system (Edwards Lifesciences) is used in the PARTNER ~~US~~ study.*"
  - 2) We added this distinction in our discussion: "*The contrast between the US and EU regulation is striking. Evidence of clinical efficacy is required before market entry in the US but not in Europe.[9] This is also the case with TAVI. In the US, the PARTNER-US study design is an RCT to demonstrate efficacy. In contrast, in Europe, the PARTNER-EU and other studies are mere registries with no control group. Despite European data from thousands of patients, it remains unclear from these registries for whom the intervention is beneficial due to a lack of a proper research design. For innovative high-risk devices the future EU Device Directive should move away from requiring clinical safety and "performance" data only to also require pre-market data that demonstrate "clinical efficacy".[9]*"

Page 6 (Time horizon): No significant difference in survival after one year was found in the high risk

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operable patients, and therefore the time horizon for that cost-effectiveness analysis was restricted to this period. However, there were differences found in secondary outcome measures, for example a twofold increase in stroke risk after TAVI. Could this have an influence on the costs after one year? Note however that a longer time horizon would only lead to a higher cost-effectiveness ratio.

- We added the following in our discussion:
  "*From an economic point of view, the less invasive nature of the TAVI procedure does not weigh against the extra costs. With an average ICER of about €750,000 per QALY (Figure 3), it is hard to defend a reimbursement for TAVI in high-risk operable patients as an efficient use of limited resources. This can be altered if TAVI costs become similar to those of AVR. The long-term consequences of stroke on both QoL and costs should also not be underestimated and would probably worsen the ICER of TAVI.*"

Page 6: Figure 1 shows the Markov model that was used. Here we see that a patient can die (absorbing state), be hospitalized, have an adverse event or have no event. Table 4 shows the percentage of observed events after 30 days and one year which are used in the economic model. How exactly were the values shown in table 4 used to fit into the health states shown in figure 1, since it seems like most events in table 4 will lead to hospitalization. Also, many readers won't understand what is meant by 'etc.'.

- There is indeed no clarity about the possible double counting of events in the published trial data. Therefore, we focused on the events with an incremental impact (i.e. those that differed between the treatment and control group). The model has calculated results with exactly the input values as shown in table 4. To be able to estimate the impact of possible double counting, a scenario analysis was made with "*in- or exclusion of events in the model (major/minor stroke or TIA)*". This analysis showed the results remained robust. In the full HTA report, even more scenarios were modeled. However, in the manuscript, we preferred to present the most important ones.
- The 'etc.' is explained under the figure: "*Etc.: this indicates that if the patient survives, he goes to the next cycle in the Markov model. In each monthly cycle, the patient is again at risk of dying, being hospitalized, having other events or no event.*"

Page 7: Since the utility values of high-risk operable patients were not provided, it was assumed that the utility difference found in inoperable patients could apply to high-risk operable patients as well. However, from the manuscript it's unclear whether the reduction in symptoms to NYHA class II or lower was comparable to the reduction seen in inoperable patients.

- We are not in favour of using NYHA class to determine utilities. We have written this in a comment reflecting on TAVI that will be published in Heart. Therefore, we would prefer not to go into detail on this issue in this manuscript.
  A quote from the article that will be published in Heart: "*Although the NYHA class is a very subjective measure, it is very often used in clinical trials to evaluate symptoms in heart failure patients. A literature survey showed that 99% of research papers do not reference or describe their methods for assigning NYHA classes and an interoperator comparison on NYHA class II and III patients gave a result that was little better than chance.(Raphael et al., Heart, 2007; Spertus, BMJ, 2008) The link between NYHA class and utility is also unclear with wide differences depending on the underlying study.(Van Brabandt et al., HTA report, 2010) The patient's QoL depends also on his co-morbidities that often occur in the elderly PARTNER population.*"

Page 11: One-way sensitivity analysis was performed based on several uncertain parameters.

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However, from the methods it's unclear how the ranges were selected, for example a QoL improvement of 0.1. It would help to specify the reasons for these ranges.

- All sources for ranges are explained in the text. Only the 0.1 improvement is an optimistic assumption to prevent criticism on our analysis: even with this optimistic assumption, the result remains unfavourable.
- The information on uncertainty is mentioned as follows in the manuscript:
- First of all, a general description is given under the heading "Sensitivity and scenario analyses"
  "The impact of uncertainty around all the model's input parameters on the results was modeled probabilistically. The applied distribution depends on the type of variable:6 transition probabilities (mortality or chance for another event) and utilities are modeled as beta distributions. This distribution is limited to the 0-1 scale and reflects the possible outcomes for these variables. The alpha parameter of this distribution equals the number of events in the PARTNER RCT. The beta parameter is adjusted to equal the published percentage of events. Strict correlation is imposed between the modeled probabilities at 30 days and 1 year to avoid irrational modeled outcomes. Relying on the central limit theorem, TAVI and AVR costs are modeled as normal distribution around the mean. Due to the large uncertainty around follow-up costs, a uniform distribution (+/- 50%) is applied. Finally, publicly available TCT cost data are published with P5 and P95 values. For these cost variables, gamma distributions reflecting the same mean, P5 and P95 values are modeled."

- For costs, details are provided in Table 2, inclusive the uncertainty, applied probability distributions, and sources for all variables. Further details are provided in the footnotes under the table.
  "Table 1: Overview of cost data.

Variable	Mean	Uncertainty	
TAVI (high-risk operable patients)			
TF	€40,917	Normal (mean: 40917; SD mean 1204)	Gov. Health Ins
TA	€49,799	Normal (mean: 49799; SD mean 1994)	Gov. Health Ins
All	€43,571[a]		
TAVI (inoperable patients)	€40,057[b]		
Standard therapy	€3,170[c]		
AVR	€23,749[d]	Normal (mean: 23749; SD mean 191)	Gov. Health Ins
Balloon aortic valvuloplasty	€489[e]	Fixed fee	Belgian Nomen
Repeat hospitalization	€5,983	Gamma (mean: 5983; P5: 1339; P95: 15596)	TCT, APR-DRG
Stroke			TCT, APR-DRG
minor	€4,679[f]	Gamma (mean: 3292; P5: 932; P95: 6842)	minor
		Gamma (mean: 6066; P5: 1574; P95: 17285)	moderate
major	€12,493[f]	Gamma (mean: 9593; P5: 1630; P95: 27526)	major

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		Gamma (mean: 15392; P5: 2631; P95: 40079)	extreme
TIA	€3,946	Gamma (mean: 3946; P5: 974; P95: 9942)	TCT, APR-DRG
follow-up fees	€43.2/month[g]	Uniform (+/- 50%)	Expert opinion
follow-up drugs	€20.5/month[h]	Uniform (+/- 50%)	Gov. Health Ins

- For Utilities in inoperable patients, the details are available in the supplement. We also added a sentence in the footnote:
  "Table 2: EQ-5D values for inoperable patients.

EQ-5D Utilities	TAVI	Standard therapy
Baseline	0.59 ± 0.23	0.57 ± 0.23
1 month	0.71 ± 0.23	0.64 ± 0.22
6 months	0.72 ± 0.26	0.66 ± 0.24
12 months	0.72 ± 0.24	0.62 ± 0.23

Source: information provided by the study sponsor.
These variables were modeled as beta distributions with the same mean and standard deviation."

- For Utilities in high-risk operable patients, the following is mentioned in the text:
  "*The PARTNER study protocol mentions QoL was measured with the EQ-5D questionnaire in both the high-risk operable and inoperable patients. …*
  Unfortunately, although requested from the study sponsor, no EQ-5D results were provided for high-risk operable patients. At 30 days, more patients in the transcatheter group than in the surgical group had a reduction in symptoms to NYHA class II or lower (P<0.001). Among patients who could perform a 6-minute walk test, patients in the transcatheter group walked farther than those in the surgical group (P = 0.002).2 Therefore, a similar difference as observed during the first month in inoperable patients was assumed. The NYHA functional class was no longer different at 6 months. At 1 year, there were no significant between-group differences in cardiac symptoms and the 6-minute walk distance.2 Therefore, in the base case, no further differences in QoL were included in the model for high-risk operable patients. This assumption was altered in a sensitivity analysis."
  in the scenario we added that improving the QoL with 0.1 during the first year is optimistic. Even doing so, the result remains unfavourable.
  "The following scenarios are modeled for high-risk operable patients: TAVI device cost of €10,000, and an optimistic QoL improvement of 0.1 during the whole first year."

- In our conclusion, we also write the following:
  "*the study sponsor should be more willing to share all relevant data in due time, i.e. before important policy decisions are taken. Both positive and negative study results providing details on all relevant outcomes (mortality, adverse events and QoL) for the most important subgroups should be revealed. This will enable more balanced evaluations and well-founded policy recommendations. Payers should insist to have full information before taking reimbursement decisions.*"

- For mortality we also added an example under the table:
  "Table 3: Early and late mortality in the PARTNER trial

	High-risk operable patients	Inoperable patients

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				PIVOTAL TRIAL			CONT. ACCESS		COMBINED*	
	TAVI	AVR	p-value	TAVI	Stand.	p-value	TAVI	Stand.	TAVI	Stand.
N	348	351		179	179		41	49	220	228
30-d. mort.	3.4%	6.5%	0.07	5.0%**	2.8%	0.41	9.8%	2.1%	5.9%	2.7%
1-yr. mort.	24.0%	26.8%	0.44	30.7%	50.7%	<0.001	34.3%	21.6%	31.4%	43.7%

- AVR: aortic valve replacement; Cont.: Continued; Stand.: standard therapy; TAVI: transcatheter aortic valve implantation.
  Sources: high-risk operable patients: Smith et al.[2]; inoperable patients: pivotal trial: Leon et al.[1]; Continued Access: FDA.[4]
  * The weights are based on the number of participants in the pivotal and Continued Access trials.
  ** Uncertainty surrounding mortality is modeled with beta distributions with the same mean. The alpha parameter of these distributions equals the number of events in the PARTNER RCT. For example: 5% mortality on a total of 179 patients is reflected with a beta distribution with the alpha parameter being 9 (i.e. 5% of 179 = 9 patients) and the beta parameter being 170 (i.e. 179 – 9)."

Page 14: What is the reason behind figure 3 and how are the limits of both inoperability and high risk operable patients determined? It's not likely that the range in ICERs for the high risk patient population (indicated along the X-axis) is based on any statistics (e.g. 95% confidence interval). Instead, it seems like the aim is to emphasise that there's an important overlap between medically inoperable patients and high-risk operable patients, and that TAVI has a high ICER with both patient populations. I would therefore suggest the text just below the figure be put in the main text.

- The ICER is not indicated on the x-axis, but on the y-axis. The x-axis indicates the operability of patients. This is shown in the figure and explained in the footnote under the figure.
  See remark above: we are of the opinion that this is a good figure that presents the overall result of the manuscript and we prefer this figure to stay in the main manuscript. We made this figure more clear by adding information in the footnote under the table:
  "Figure 1: TAVI's cost effectiveness.

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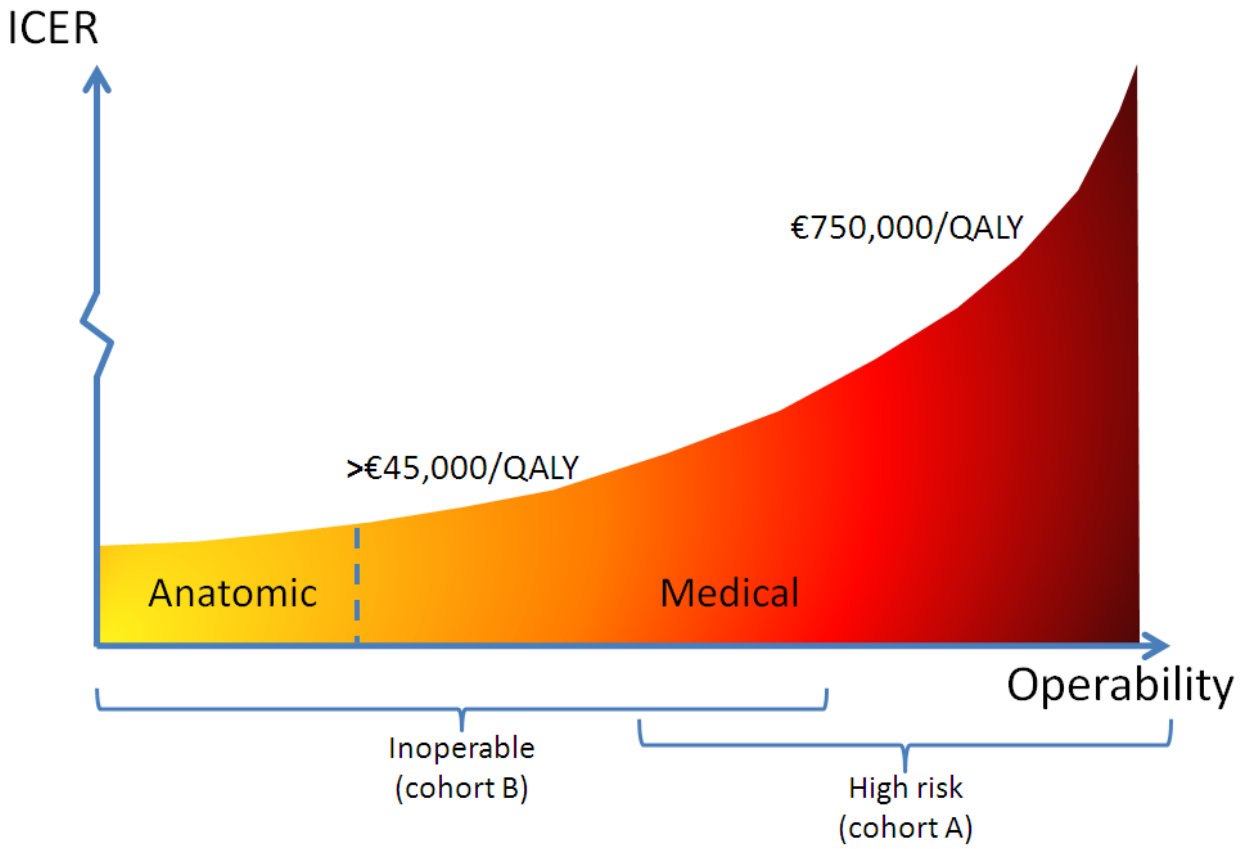

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year.
The x-axis indicates the operability of patients. There is an overlap between medically inoperable and high risk operable patients. Anatomically inoperable patients are readily identifiable. For high-risk operable patients, the ICERs are very high (€750.000/QALY). For inoperable patients, the ICER was on average €45.000/QALY. Within the latter category, ICERs are better for anatomic inoperable patients and worse for medical inoperable patients."

Page 24: Figure 6 shows the tornado graph. Minor comment here: this figure is technically not quite correct, since the most influential variable on the ICER should be placed on top, i.e. 3-year time horizon followed by (non-)technical inoperable patients. It might help to have the vertical line present the ICER in the base-case and not based on the pivotal PARTNER trial.

- Typically, the vertical line is put at the base case. However, in this analysis, it would not be correct to put the vertical line at the base case. The reason is that we did not receive all requested information for the Continued Access trial (although the study protocol was just the same for the pivotal and Continued Access RCT). As such we could not perform all sensitivity analyses starting from our base case. Therefore, our vertical line is put at the level of the analysis that only takes into account the results of the pivotal trial. We describe this as follows in the text:
  "*Only including results of the pivotal trial, without taking into account the conflicting mortality results of the smaller Continued Access trial results in a more favorable ICER of €37,400 per QALY gained (***Error! Reference source not found.***). Since detailed information was only available for the pivotal trial, sensitivity analyses are based on this analysis. Together with the other scenarios, the base case scenario (mortality pivotal trial + Continued Access) is presented on the tornado graph (***Error! Reference source not found.***).*"
- We agree to change the order of the variables in the tornado graph. The figure now looks as follows:

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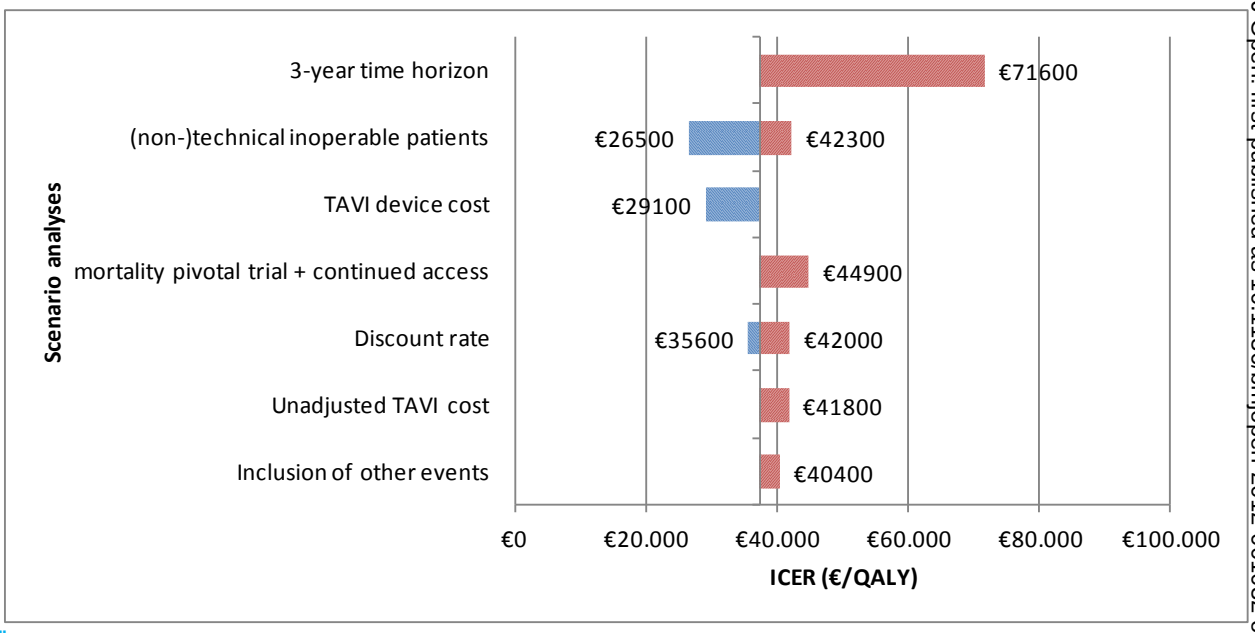

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