Author’s response to reviews

Title: Comparison of drug-eluting balloon versus drug-eluting stent for treatment of coronary artery disease: A meta-analysis of randomized controlled trials

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Author’s response to reviews:

Francesco Gallo (Reviewer 1):

The purpose of this meta-analysis consists in compare the safety and the efficacy of DEB and DES for treatment of CAD.

This meta-analysis is characterized by several errors in methods and rationale.

1- Analysis of EP: in your analysis you shouldn't compare a device oriented MACEs, such as ST and ISR, considering patients undergoing to DEB only PTCA in de novo coronary lesions and patients undergoing to a new DES implantation. How can you talk about ISR after a DEB PTCA only? Pg 8 chapter 3.2.1.

Response: Thank you for your thoughtful suggestion. We have removed the result of ST from the revised manuscript as suggested. However, the binary restenosis we used was defined as diameter stenosis > 50% by quantitative coronary angiography (QCA) at the follow-up angiogram, thus, we thought this could be able to be considered as an endpoint. Besides, we extracted the data from the studies we included and almost all studies had reported binary restenosis no matter DEB or DES.
2- The trials that you have considered in your analysis concern about different type of deseases (biforcation lesions, patients affected by DM, ISR, small coronary vessels), so the analysis of the primary endpoint is not trustworthy.

Response: As for addressing this issue, we have done subgroup analysis by the type of diseases to reduce heterogeneity. And the result showed that no difference between DEB and DES in terms of MACE.

3- You shouldn't consider old studies.

Response: We aimed to include all valuable data to guarantee data reliability when we designed this study. Besides, we did exclude the relatively old studies as suggested and the results did not significantly change.

Ahmed Mahmoud (Reviewer 3):

Major concerns:

1- The authors chose to evaluate 2 co-primary end-points instead of one. This approach would result in a considerable impact regarding the power of the study. I do recommend choosing the clinical outcome of MACE as the primary outcome and the rest of outcomes as secondary ones.

Response: Thank you for your insightful suggestion. Accordingly, we have changed LLL as a secondary endpoint.

2- I don’t believe that the conclusion of the authors is accurate; they concluded inferiority of DEB bases on a subgroups analysis of MLD, with all other outcomes appearing similar. I recommend rephrasing the conclusion to indicate that current evidence do not show any differences between both methods and that larger RCTs are required to assess for hard clinical outcomes such as death, MI or ST with adequate power. Also “There is a trend towards better
clinical outcomes with DEB in long-term follow-up” is not a correct statistical statement, P value of 0.09 indicated similar effect and the word “trend” is subjective.

Response: As suggested, several sentences have been revised in the Conclusion of the revised manuscript (Page 2, lines 16 - 17; Page 14, lines 15 - 19).

3- It is unclear why the authors included the BMS group in their analysis. I would suggest removing the part comparing DEB+BMS to DES from all the results. The main advantage of DEB compared with DES is lack of permanent foreign body in the coronary as stated by the authors in their introduction, using BMS would be a strong confounder in TLR, MACE, LLL and binary stenosis outcomes.

Response: Thank you for your thoughtful suggestion. In the revised manuscript, we have removed the comparison between DEB+BMS and DES from all results. Also, a statement has been added in the Introduction of the revised manuscript to explain why the DEB+BMS group was included (Page 3, lines 16 - 18).

4- The authors have a wide follow-up range from 6 months to 24 months. This would affect all outcomes of interest and could be a potential reason for the large degree of heterogeneity seen in the current analysis. I suggest correcting this by performing multiple subgroups for the primary outcome according to the follow up duration <12 months vs. >12 months.

Response: As suggested, we performed subgroup analysis using the followup duration < 12 months and > 12 months.

5- Most of the studies included in the current analysis are old and were using first generation DES that were rarely used at the current time. Thus comparing DEB to these stents do not appear to be important in the current PCI practice and would add little information regarding the
comparative effectiveness of both methods in the contemporary era. I suggest to at least perform a subgroup analysis according to the generation of DES to assess for any interaction by the type of DES used.

Response: Thank you for raising this critical issue. In the revised manuscript, we performed a subgroup analysis based on the generation of DES regarding all outcomes.

Other comments:

Abstract:

1- This part in the abstract is not essential and just adds more space recommend removal: “Statistical analysis was performed using the Review Manager 5.1 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).”

Response: The sentence has been removed in the revised manuscript.

Introduction:

1- Line 36, P3: PACCOCATH-ISR: Needs to be full sentence.

Response: This correction has been made in the revised manuscript (Page 10, lines 18 - 19).

2- 2nd paragraph in the introduction is better suited in the discussion section, consider removal or replacement in the discussion.
Response: As suggested, we addressed this point in the Introduction of our revised manuscript (Page 3, lines 12 – 18; Page 10, lines 18 - 21).

3- “It is remains unknown if DEB or DES is better for treating coronary stenosis” consider a stronger sentence like: “the superiority of either therapy for treating coronary stenosis remains unknown”.

Response: This correction has been made in the revised manuscript (Page 3, line 19).

Methods:

1- The authors need to comment on the date of ending of search and whether conferences e.g. AHA and ACC abstracts were reviewed as well.

Response: This correction has been made in the revised manuscript (Page 4, lines 12 - 13 and line 15).

2- I don’t believe that limiting the search key to RCTs and not including keywords for PVD was a correct approach by the authors and this might exclude a considerable number of records that compared DEB with DES and did not state RCT or CT in the title/abstract section. It would have been better to include everything initiation and then exclude after reviewing the titles and abstracts by the authors. (https://www.ncbi.nlm.nih.gov/pubmed/20820050)

Response: This correction has been made in the revised manuscript and the detailed search strategy is shown in Additional File 1.

3- Line 30, P5: The authors need to add the word “Loss” after late lumen in LLL.
Response: This correction has been made in the revised manuscript (Page 5, line 7).

4- The authors need to define their outcomes and state which outcomes were considered safety outcomes and which one are considered efficacy ones. I would suggest to use procedural outcomes and clinical outcomes instead of safety and efficacy as the authors are looking into multiple procedure related outcomes such as LLL and MLD and other clinical outcomes such as MACE, MI and ST. The definition of efficacy here is very important as the authors conclude that DEB is inferior regarding this outcome.

Response: A statement has been added to address this issue in the revised manuscript (Page 5, lines 11 - 13).

5- Why did the authors choose to perform a hybrid MH method rather than a pure random effects method. I would suggest to use random effects method such as Der-Simonian and Liard as a primary method then confirm that with a fixed effects MH. This is especially important for outcomes with high level of heterogeneity such as MACE and TLR in the current analysis.

Response: We used either the Mantel-Haenszel random-effect model or the Inverse Variance random-effect model as a primary method then confirmed the findings using the corresponding fixed-effect model. We have added this information in the revised manuscript (Page 6, lines 7 - 8).

6- Line 40-41, P6: The authors need to further clarify what they meant by “or on the basis of factors that may lead to heterogeneity.”

Response: We have further clarified this issue in the revised manuscript (Page 6, lines 14 - 15).

Results:

7- Line 64, P6: Please add IQR to the median of 8 months reported.
Response: We have corrected this issue in the revised manuscript (Page 6, line 22).

8- Line 38, P7: Again the authors are using statistically incorrect wording such as trend towards, I strongly recommend to rephrase the whole paragraph to no significant differences instead.

Response: This correction has been made in the revised manuscript for each outcome.

9- The authors need to include the I2 test numbers in every effect size reported.

Response: This correction has been made in the revised manuscript for each outcome.

10- Line 61 P7: how was the % of MACE calculated? Was it weighted or non-weighted? Better to use random effects inverse variance weighting in calculation of such incidences with inclusion of 95% CI.

Response: This correction has been made in the revised manuscript.

11- I do recommend starting the results with MACE and other clinical endpoints followed by procedural endpoints. As the final efficacy and safety of any intervention depends on its impact on clinical outcomes.

Response: This correction has been made in the revised manuscript.
12- The authors state in the abstract that binary stenosis is a co-primary outcome, however in the results section it was presented as 2ry outcome. Please correct.

Response: This correction has been made in the revised manuscript (Page 8 line 6 - 11).

13- Line 28 P9: I do not fully understand what the authors meant by “subset analysis” If this is a comparison of immediate post procedural characteristic rather than an outcome, I would recommend to report this earlier before the report of endpoints (after Table1).

Response: We removed the MLD subgroup, and the long-term follow-up subgroup has been moved to the secondary outcomes.

14- Line 14 P10: The authors report one Egger’s test, they need to specify this P value is for which outcome and report the Egger’s for at least all primary outcomes if not all outcomes analysed.

Response: This correction has been made in the revised manuscript (Page 9, line 18).

Discussion:

1- The first paragraph of the discussion needs to be rephrased to reflect lack of differences between both methods regarding both primary and secondary outcomes of interest assessed.

Response: As suggested, we rephrased the first paragraph (Page 10, lines 1 - 12).
2- Paragraph 2 concentrates on the weakness of DES regarding bifurcational lesions and small vessel disease, however, the current analysis did not add much regarding these topics as the study numbers were not enough to conduct any subgroup analyses according to there factors. I recommend down-tuning this paragraph. The authors did indeed compare denovo CAD with ISR however they did not look into small vessel disease, bifurcational lesion or DM patients.

Response: As suggested, we modified this paragraph.

3- Line 33-44, P12: better suited for conclusion section.

Response: As suggested, we moved this section to the Conclusion of the revised manuscript (Page 15, lines 2 - 6).

4- Line 44, P13: Need to state that the simple size and power of the current analysis is not adequate to evaluate for rare outcomes such as death and ST.

Response: This correction has been made in the revised manuscript (Page 13 lines 8 - 9).

5- Line 47, P14: The authors should state that the current evidence is not in favour of BRS and reference available evidence showing increased risk of TLR, MACE and ST with BRS such as Mahmoud et al. in Circulation: Cardiovascular interventions http://circinterventions.ahajournals.org/content/10/5/e005286.full.pdf?download=true

Response: This correction has been made in the revised manuscript (Page 14 lines 11 - 12).
Figure 1: The structure is confusing; it would appear as if 9+9 records lead to 383+9 records. I suggest changing the position of the upper two boxes to be at the same level of the 389+9 box. Also to rewrite that box to 398 instead. And to include the initial number of records retrieved from each database without removal of the duplicates.

Response: We have researched the databases again and the new flow diagram is shown in Figure 1 in the revised manuscript.

Figure 2: Using the word Favours is rather confusing as MLD is less with DEB compared to DES. I suggest changing the wording to something easier to interpret.

Response: We have removed this outcome from the revised manuscript as suggested.