Author’s response to reviews

Title: Three-years outcomes of diabetic patients treated with coronary bioresorbable scaffolds

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Version: 2 Date: 18 Feb 2018

Author’s response to reviews:

Ref.: Ms. No. BCAR-D-18-00018R1 - Three-years outcomes of diabetic patients treated with coronary bioresorbable scaffolds

Dear Dr Biscaglia,

We appreciate the wise and thoughtful comments made by the Editor and Reviewers, which have helped improve our manuscript.

We provide below a point-by-point response to the issues raised by the Editorial Board and Reviewers.
Please note that we changed “BVS” in the tables to “BRS” as well as changed the list of abbreviations into alphabetical order. Furthermore, we added “diabetes” to the key words and erased “complex coronary lesion”.

Any other change in the text as well as the above mentioned are highlighted using a bold font.

We also changed the number of words given in the title page.

Looking forward to your response,

Sincerely,

Tommaso Gori

A Technical Comments:

1) Different corresponding author in the manuscript and system

Corresponding authorship for this paper remains Prof Dr Tommaso Gori. However, Mr Remzi Anadol was given responsibility for submitting the paper and, thus, was stated as corresponding author in the online submission process. Changes in the text were done and approved by all authors.

2) Please provide Background sub-section in Abstract section

We provided a Background sub-section in the Abstract section. It now says:

“Diabetes is among the strongest predictors of outcome after coronary artery stenting and the incidence of negative outcomes is still high in this specific group. Data of long-term outcomes comparing diabetic patients with non-diabetic patients treated with bioresorbable scaffolds are still incomplete.”
B Reviewer 1 (Rossella Ruggiero):

1) The main issue of the study is represented by the description of the outcome in two groups with different baseline CV risk (diabetics vs non diabetics). In fact, although partially corrected by PS-matching, diabetic patients are still at higher risk of CV events compared with non diabetic patients. This finding is not new neither interesting. The same operation has been made in a GHOST-EU subgroup analysis of patient receiving BRS in overlap vs receiving BRS not in overlap (doi: 10.1016/j.jcin.2016.12.013; doi: 10.1016/j.jcin.2017.04.001). Thus, the interesting comparison is not between diabetic and non diabetic patients, but between diabetic patients treated with BRS with a correct implantation technique vs diabetic patients treated with 2nd generation DES, as it was performed for overlapping BRS (doi: 10.1016/j.ijcard.2016.01.202). Authors should comment these issues and papers in discussion.

It is true that an analysis of the role of diabetes in determining the prognosis after BRS implantation has already been performed in the GHOST-EU database and other databases (mentioned in the discussion section), however there are important differences among the previous papers and the current one:

1. Follow-up: in the previous papers, except for the one by Wohrle et al, follow-up was limited to one year. Since the most frequent complication associated with diabetes (restenosis) only occurs at a later timepoint, our data remain original and important. Of note, the paper of Wohrle et al included a group that was ~25% the size of the one in our paper. This allows us to evaluate relatively rare endpoints, and to perform subanalyses (eg the one on implantation technique).

2. Endpoints (see point 1): we provide a more thorough analysis of all separate endpoints. In the GHOST-EU paper and the paper by Muramatsu, the endpoint was a composite one. The paper by Wohrle had a small sample size which does not allow investigating separate endpoints.

3. Propensity score analysis: this was not performed in previous papers for the comparison of non-diabetics with diabetics.

Your point regarding the comparison between well-implanted BRS and newer generation DES is important. Our database does not include DES patients, and we cannot conclude about it. This limitation has been added. For the sake of comparison, however, we have introduced a small paragraph providing information on the incidence of stent restenosis and thrombosis in modern DES:
Finally, although we show a difference in the outcomes in association with appropriate implantation technique, we cannot provide a direct comparison between BRS and newer generation drug eluting stents as recently performed in the UNDERDOGS study for long lesions(23). For comparison, however, our reported incidence of no scaffold restenosis and 1.2% scaffold thrombosis at two years in the group of diabetics with appropriate implantation technique are in the same range (if not lower than) of those previously reported in patients treated with everolimus-eluting metallic stents(24).

2) Authors should better detail how the propensity score was performed (ie: what was the calliper).

Please note that we did not use a propensity score-based method for traditional matching, ie there is no caliper. The method used here, “inverse probability of treatment weighting (IPTW)” uses propensity score-based weights to create an „adjusted“ (synthetic) sample. In this sample (we used here the ATE method because all subjects were treated) the distribution of covariates is independent of the group. More detail has been added to the statistical methods section. The results of the weighting are presented in the supplemental tables. In order to avoid confusion, we have eliminated the term „matching“ from the paper.

3) Authors state that, after 1 year, diabetic patients receiving BRS showed a higher risk of CV death, ScR and TLR compared to non diabetic patients. However, diabetic patients did not show a higher incidence of TVMI or MI. Authors should explain at least a theoretical mechanism for this CV death increase, since it is not related to MI and an excess in ScR is hardly related to an increased CV death.

Among the 138 diabetic patients, 7 died at least one year after implantation of device versus 5 in the non-diabetic group. Although this comparison is significant, the small numbers advocate caution when analyzing for differences. Of the 7 patients, 1 patient died because of target vessel-myocardial infarction and another one had a TVMI during previous follow-up (<365 days). In the other patients, death occurred at a median of 928 days after index. Three were older than 80 years, and died of heart failure. The remaining two were young subjects (55 and 56 years of age), and the reason of death was unknown. One of these patients had received BRS implantation with optimal implantation technique, the other not. In both cases, the postimplantation result was suboptimal (33 and 46% residual stenosis). Any conclusion regarding these cases remains however speculative. Since a cardiovascular event (including device-related ones) cannot be excluded, we categorized these as cardiovascular deaths. However, since deaths occurred after
365 days and stent thrombosis was classified according to the ARC definitions, we did not consider these as possible ScT.

We have entered a note to this regard in the limitation section.

4) Interestingly, diabetic group's residual stenosis per lesion was statistically increased compared to non diabetic patients. However, authors did not correlate this observation with lesion characteristics. Was residual stenosis correlated with degree of calcification? Indeed, presence of severe calcification could influence the sizing (inability to obtain a stent-like predilatation), as well as lead to a suboptimal final result.

You are absolutely right. Because angiography is not adequate to truly assess the extent, severity and type of coronary calcification, data regarding the degree of calcification was not collected in the database, and thus cannot be correlated with residual stenosis. However, the complexity of the lesion according to ACC/AHA was recorded, in which – besides e.g. tortuosity of lesion - calcification of the lesion is also implemented. The two groups – diabetic and non-diabetic patients – were not statistically different with regards to lesion complexity.

5) The data regarding implantation technique are really interesting, especially the highly significant impact of correct implantation technique on ScR in diabetic patients. At the same time, the lack of ScT increase in diabetic patients without proper implantation technique is quite counterintuitive and contradicts previous evidence. Authors should comment this finding. Is it due to the low number of patients? Are there other confounders?

Among the 28 patients suffering from a ScT there were only 4 patients with diabetes. Among those 4 patients, 2 had received a BRS using the proper implantation technique and 2 did not. Given the small number of patients, any conclusion is dangerous.

6) Were all TLR clinically driven? Were there any angiographic programmed follow-up? - Authors should acknowledge that their follow-up is long (3 years) but not sufficient to detect to theoretical benefit due to scaffold reabsorption (>5 years).

All TLR were either clinically driven as defined by typical symptoms/evidence of ischemia in the territory of interest or incidental findings of a stenosis >75%. A comment regarding the resorption time has been added (very last sentence of the manuscript).
7) Minor issue In methods section: "QCA data are reported in?". Please correct.

We changed the sentence to

“…; detailed methods, reproducibility and repeatability data have already been published before (17)” , with the number in parenthesis indicating the publication that is referred to.

8) Authors showed a U-shaped relationship between RVD and ScR incidence. However, RVD did not result a ScR predictor at Cox regression. In discussion, authors should clarify that the point is not small or large RVD (as showed by Cox regression), rather BRS under or oversizing (corresponding to small or large RVD vessels) (Figure 3B).

This is absolutely right, thank you. This sentence has been added/changed:

Taken as a continuous variable RVD was not a predictor of events. However, in patients with diabetes, the risk of ScR was progressively higher for both smaller and larger RVDs, describing a U-shaped curve with lowest incidence for RVDs between 2.75 and 3.5mm. This evidence demonstrates that sizing is indeed important.

C Reviewer 2 (Andrea Erriquez):

1) The authors conclude that diabetic patients treated with scaffolds have a higher rate of events than non-diabetics. However, the message of the present study could be misleading. Indeed, diabetes is already known to be one of the strongest predictors of negative outcomes after coronary stenting, so this study, that compared diabetic with non-diabetic patients treated with the same device, reports results that are consistent with those already known for diabetic patients. Therefore, the higher rate of events in the diabetic group is due to diabetes itself rather than to the scaffold implantation.

This is correct. We have made this point clear in the abstract (the point has already been made in the very first sentence) and conclusion. We do however still believe that our data regarding implantation technique, sizing and vessel size remain important. These data are unique, even when compared to DES papers.

2) Furthermore, the outcomes could be influenced by unbalanced baseline characteristics between the 2 different groups of the study, with a higher prevalence of hypertension,
hyperlipidemia, prior stroke/TIA and impaired renal function in diabetic group, that are all cardiovascular risk factors.

In order to correct for these differences, we performed a propensity score adjustment. All data are presented based on this type of analysis. Of course, we cannot exclude that other variables, beyond those captured here, might have determined a difference between the groups. This is however valid for any study.

3) Another important issue of the manuscript is that the authors reported, one year after scaffold implantation, a higher rate of cardiovascular death in diabetic group without an increased rate of myocardial infarction, without finding a pathophysiological reason, at least theoretically, that can explain this outcome.

This is an important point, please see our rebuttal to the same question from reviewer 1 above.