Author’s response to reviews

Title: Modified balloon-stent kissing technique avoid side-branch compromise for simple true bifurcation lesions

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Author’s response to reviews:

Cover Letter
Date: 31 Oct 2018
To: "BMC Cardiovascular Disorders Editorial Office" hassee.echanes@biomedcentral.com

From: Bing-Chen Liu" liubingchen111@126.com
Subject: The submission to BMC Cardiovascular Disorders - BCAR-D-18-00482

Executive Editors of BMC Cardiovascular Disorders Editorial Office
RE: BCAR-D-18-00482
Balloon-stent kissing technique avoid side-branch compromise for simple true bifurcation lesions
Wenbo Qu, M.D.; Wei Zhang; Junyan Liu; Fan Zhang; Shuainan Mu; Hao Tang; Xiqian Liu; Xueqi Li,
Dear Editor(s) at BMC Cardiovascular Disorders:

Thank you for your editorial efforts regarding our manuscript and for your offer to accept a suitably revised version. In addition, we thank the referees for their constructive comments. We have introduced changes to strengthen the manuscript by responding to the points and concerns raised by the referees. In particular, we have made the following major revisions:

1. We had changed the article title to “Modified balloon-stent kissing technique avoid side-branch compromise for simple true bifurcation lesions”. Reviewing the angiography programs, we find out that routine POT after rewiring was used as a regular operation in all patients. It could be a novelty to balloon-stent kissing technique. Thus, we proposed it as a modified balloon-stent kissing technique. (page2,18-21; page5,79-84; page18,345-351)

2. We accept the referee’s suggestions and explain the problems in our revised manuscript.

3. In order to reveal M-BSKT clearer and more valuable, we submit a figure that illustrates the above process in a simplified sequence flow diagram. The detailed angiography images about how to do M-BSKT were added to this manuscript. (page7,line129-page8,line160)

4. We added subgroup analysis of patients with acute coronary syndrome, the advantages of M-BSKT were showed prominently. We put a modification of the manuscript with more data that were illustrated by table and figures. (page3,line38-41; page14,line256-page15,line272; page15,line276-280; page18,line338-344; page20,line383-386)

Our point-by-point responses to the referees’ comments and revisions are given below. Any changed text in the revised manuscript and responses to referees has been marked in RED. The revised manuscript and our responses to the referees have been reviewed by several professionals.

We believe the manuscript to be greatly strengthened by the critique of the referees and hope that you will now find it acceptable for publication. Again, we thank you and the referees for your careful review and helpful comments on our work.

Respectfully yours,

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Reply to Editor

Technical Comments:

1. Author contributions
   - The individual contributions of ALL authors to the manuscript should be specified in this section.

2. Headings
   - Please change "Introduction" to "Background"

3. Ethics approval and consent to participate
   - A statement is required in this section detailing the name of the specific ethics board that approved your study and also that consent was provided.

4. STROBE guidelines
   In accordance with BioMed Central editorial policies (http://www.biomedcentral.com/submissions/editorial-policies#standards+of+reporting), could you please ensure your manuscript reporting adheres to STROBE guidelines (http://www.strobe-statement.org/) for reporting observational research. This is so your methodology can be fully evaluated and utilised. Can you please include a completed STROBE checklist as an additional file when submitting your revised manuscript.

Please complete the checklist in full by inserting the page number/paragraph and section of your manuscript which reports the information that meets the criteria of the checklist. For example, “Methods, paragraph 2”. If a criterion is not applicable for your particular manuscript/study, we can accept “N/A”.

Please note that checklists completed incorrectly will be returned for revision as we cannot progress your manuscript to peer review until the checklist has been completed.

REPLY: We appreciate the editor’s suggestion. The manuscript has been revised according to technical comments.

1) We had list all authors contributions to the manuscript: W-Z, JY-L and F-Z contributed to the data collection and analysis. SM-Z and H-T modified the charts. (page21,line424-425)

2) We had changed "Introduction" to "Background"

3) We submit the ethics approval as an additional file

4) We had completed STROBE checklist as an additional file

Reply to Referee 1

Toshiya Muramatsu (Reviewer 1): This paper shows that efficacy of BSKT for bifurcation lesions. However, it is necessary to revise as below.
1. Table and figure is so poor and few. it is necessary to describe how to do BSKT and PS. And more details of data shoud be necessary.

2. Clinical impact is not strong. Benefit of BSKT is not significanct. Suggetst more appopriate indication.

3. What is negative side of BSKT. For example, complication, costly , technical isuue etc.

4. Anyway, what types of bifurcation lesion is necessary to protect side branch? Most of side branch is not need protect wire.

REPLY: We sincerely appreciate this positive feedback. First, we could like to apologize for that we had changed the article title to “Modified balloon-stent kissing technique avoid side-branch compromise for simple true bifurcation lesions”. Reviewing the angiography programs, we find out that routine POT after rewiring was used as a regular operation in all patients. It could be a novelty to balloon-stent kissing technique. Thus, we proposed it as a modified balloon-stent kissing technique. (page2,18-21;page5,79-84; page18,345-351)

Minor comments:

1. Table and figure is so poor and few. it is necessary to describe how to do BSKT and PS. And more details of data shoud be necessary.

REPLY: We thank the referee for this helpful suggestion.

a) In order to reveal M-BSKT clearer and more valuable, we submit a figure that illustrates the above process in a simplified sequence flow diagram. The detailed angiography images about how to do M-BSKT were added to this manuscript. (page7,line129-page8,line160)

b) We added subgroup analysis of patients with acute coronary syndrome, the advantages of M-BSKT were showed prominently. We put a modification of the manuscript with more data that were illustrated by table and figures. (page3,line38-41; page14,line256-page15,line272; page15,line276-280; page18,line338-344 ;page20,line383-386)

2. Clinical impact is not strong. Benefit of BSKT is not significanct. Suggetst more appopriate indication.

REPLY: We thank the referee for this comment.

a) We agree that benefit of M-BSKT is not significanct what referee mentioned. In theory, it could avoid plaque or carina shift into the SB. Scientists have begun to approve, but argue for additional study, that M-BSKT may protect SB for bifurcation lesions. We only study the type of simple true bifurcation lesion, because of it do not need to be stent, but do need to be protected. Our findings showed that M-BSKT were similar to PS in every aspect except the incidence of immediate SB deterioration. However, given what has shown, we can see clearly that M-BSKT protected SB in some degree.

b) Consider the insufficient of evidence, we conducted subgroup analyses for ACS patients. Interestingly, when we conducted subgroup analysis of patients with acute coronary syndrome, the advantages of M-BSKT were showed prominently. It just made a clarity conclusion that M-BSKT may provide more protection of SB. Patients with ACS are likely to have multiple vulnerable plaques that are liable to rupture or shift[1, 2]. According to ACS patients with special bifurcation lesions, M-BSKT may reduce thrombosis and plaque shift towards to SB
more effectively, which avoid the impact on TIMI flow and reduce the application of FKBI. (page3,line38-41; page14,line256-page15,line272; page15,line276-280; page18,line338-344 ; page20,line383-386)

3. What is negative side of BSKT. For example, complication, costly , technical issue etc.
REPLY: We thank the referee for this comment.

a) As far as M-BSKT concerned, it may increase a balloon as medical disposable material. But when we take full consideration about integrated operation, reduced the total numbers of FKBI used is materially reduced the cost.

b) 95% of surgeries adopted the insertion of a 6F radial sheath into the right radial artery. SB dilation with a balloon may shift the carina to the MV and reduce the MV stent volume as well as area, and distort the MV stent symmetry in the bifurcation segment, but it was improved by the POT strategy which was mandated to achieve optimization. All the wires and balloons were not entrapment during the operations. Thus, we did not find any technical problems or complications with M-BSKT.

4. Anyway, what types of bifurcation lesion is necessary to protect side branch? Most of side branch is not need protect wire.
REPLY: We thank the referee for this comment.

a) There are no established guidelines for the treatment of SB stenosis and the visual assessment of SB stenosis is a challenge. Patients with true bifurcation lesions had worse clinical outcomes than those with non-true bifurcation lesions. Procedural and long-term clinical outcomes differed according to the type of bifurcation lesion.

b) Meanwhile, SB occlusion occurred more frequently in patients with true bifurcation lesions than in those with non-true bifurcation lesions[3]. Medina 1,1,1 1,0,1 and 0,1,1 coronary bifurcation lesions with an SB diameter ≥2.0mm based on visual estimation were included in our experiment. The occlusion of a SB N1.0 mm has been associated with a 14% incidence of myocardial infarction, and the occlusion of a SB N2.0 mm during the simple strategy can be associated with a large periprocedural myocardial infarction. Therefore, for true bifurcation lesions with large SB, it is necessary to protect SB. (page15,283-285)

c) Inclusion of lesion complexity as a parameter in previous studies might have otherwise led to different stenting strategies, and consequently, the final clinical results might have been different. This experiment adapt the classification to differentiate simple from complex bifurcation lesions proposed by Chen SL[4]. Besides, 2-stent techniques for complex lesions elicited a lower rate of cardiac death and in-hospital MACE but higher rates of in-hospital ST and revascularization at 1 year for simple lesions. Based on previous research, we eliminated complex bifurcation lesions that may get the maximum benefit from 2-stent techniques [4] (page15,290- page19,298)

d) Since a proportion of patients with a severe big SB lesions (simple true bifurcation lesions) would remain ischemic after MV stenting, the jailed SB wire or balloon facilitated rewiring of the SB by widening the angle between the MV and SB and prevent SB occlusion after MV stenting.

e) Patients with ACS are likely to have multiple vulnerable plaques that are liable to rupture or shift According to the result from subgroup analysis, we concluded that SB was more liable to
deterioration in ACS patients with a severe SB lesions (simple true bifurcation lesions).


Reply to Referee 2

Kenji Sakata (Reviewer 2): Comments to the Author

The manuscript entitled "Balloon-stent kissing technique avoid side-branch compromise for simple true bifurcation lesions" was reviewed. The concept of this study is interesting and important for therapeutic strategy of coronary bifurcation lesions, however, there are several issues that the authors should address as indicated in the Specific Comments.

Specific Comment:
In Table 3, the authors described that the incidence of immediate SB deterioration was significantly lower in BSKT than PS. This statistical significance between the two groups was mainly due to the difference in SB ostial pinching≥90% by angiography. Previous studies suggested that angiographic visual assessment of jailed SB lesions tended to overestimate the severity of jailed SB lesions compared to functional assessment by FFR (J Am Coll Cardiol, 46 (2005), pp. 633-637, J Am Coll Cardiol Cardiol Intv, 5 (2012), pp. 155-161, J Am Coll Cardiol Intv, 5 (2012), pp. 409-415, Eur Heart J, 29 (2008), pp. 726-732). Therefore, because most of angiographic significant stenosis might not show functional ischemia, the difference between long-term clinical outcomes did not differ between patients treated with BSKT and PS at 12 months. The authors should discuss about this issue.

REPLY: We thank the referee for this comment.
First, we could like to apologize for that we had changed the article title to “Modified balloon-stent kissing technique avoid side-branch compromise for simple true bifurcation lesions”. Reviewing the angiography programs, we find out that routine POT after rewiring was used as a regular operation in all patients. It could be a novelty to balloon-stent kissing technique. Thus, we proposed it as a modified
balloon-stent kissing technique. (page2,18-21;page5,79-84; page18,345-351)
We submit a figure that illustrates the above process in a simplified sequence flow diagram. The detailed angiography images about how to do M-BSKT were added to this manuscript. (page7,line129-page8,line160)

Lesions of vascular bifurcation and their treatment outcomes have been evaluated by anatomical and physiological methods, such as fractional flow reserve (FFR). It has been proposed as the gold standard to assess functional severity of coronary artery stenosis and to stratify which lesions should be subjected to intervention. We admitted that angiographic visual assessment of jailed SB lesions tended to overestimate the severity of jailed SB lesions compared to functional assessment by FFR. But for this experiment, we have some different points of view.

1) Regrettably, there was no application of FFR in this study. For non-left main bifurcation lesions, it would be impractical to apply FFR for all patients. It also means a waste of medical resources. So, considering the limitation of visual assessment which tended to overestimate the severity of jailed SB lesions, this manuscript used SB ostial pinching ≥90% by angiography as indication for SB intervention. It was reduced the unnecessary intervention of SB in the maximum limit.(page19, 362-371)
a) Previous studies does support the concept that angiographic evaluation may overestimate the severity of SB lesions resulting in unnecessary intervention, but these experiments aimed at special side branch lesions (percent stenosis >50% by visual estimation)[3-6].

Trials  FFR measurement

J Am Coll Cardiol. 2005 Aug 16;46(4):633-7.[3]
No lesion with a ≥50 and 75 % stenosis had a FFR less than 0.75. Among 73 lesions with >75 % stenosis only 20 lesions were functionally significant

In the FFR-guided SB treatment group, the functional restenosis (FFR <0.75) rates were only 8 % at 6 months, whereas the rates of angiographic binary restenosis rates (defined by >75 % diameter stenosis at follow-up) was 48 %. 
The application of the angiographic criterion of 75% stenosis would have resulted in 68, 32, and 48% of the lesions requiring additional side-branch intervention after main branch stent implantation, after kissing balloon dilatation and at follow-up, respectively. However, these were reduced to 31, 8, and 8% with the application of the functional criterion of FFR <0.75

SB stenting was performed for Thrombolysis In Myocardial Infarction flow grade<3, ostial SB stenosis>70%, or greater than type A dissection after main vessel stenting in the Angio-guided group and for SB-FFR<0.80 in the FFR-guided group.

JACC Cardiovasc Interv. 2015 Apr 20;8(4):564-74.[6]
Applying a threshold of ≥50% diameter stenosis, as assessed by the bifurcation model, to predict FFR≤0.80 resulted in 23 true positives, 27 true negatives, 17 false positives, and 11 false negatives. Meanwhile, there are several clinical, angiographic characteristics and a scoring system to guide the approach to intermediate lesions. Characteristics associated with FFR ≤0.8 include male gender, higher SYNTAX score, lesions ≥20 mm, stenosis >50%, bifurcation, calcification, absence of tortuosity and
smaller reference diameter[7].

b) On the subject of FFR, most experiments classify the side-branch lesion stenosis of 50% as a dividing point, concluding that angiographic visual assessment of jailed SB lesions tended to overestimate the severity of jailed SB lesions compared to functional assessment by FFR. According to the RESOLVE risk score that SB occlusion rates in the validation cohort increased significantly across different characteristics[8]. Diameter stenosis of SB 70–90% or≥90% means different risk score which provides a accurately predictive of the extent and severity of coronary artery disease. Thus, this manuscript used SB ostial pinching≥90% by angiography as indication for SB intervention.

c) Since the size of the SB in our patients was large enough to influence the survival of a large area of myocardial, final kissing balloon was applied to SB ostial pinching≥90%. Final kissing ballooning with good angiographic results may improve clinical outcomes[9]. Even if the use of FKBI did not improve clinical outcome, there was not a penalty for undertaking FKBI[10]. Though the findings of 1 year clinical follow-up were similar between the 2 techniques, we believe M-BSKT will play a safe and effective role for a longer period of time.

2) Consider the insufficient of evidence, we conducted subgroup analyses for ACS patients. Interestingly, when we conducted subgroup analysis of patients with acute coronary syndrome, the advantages of M-BSKT were showed prominently. It just made a clarity conclusion that M-BSKT may provide more protection of SB. Patients with ACS are likely to have multiple vulnerable plaques that are liable to rupture or shift[1, 2]. According to ACS patients with special bifurcation lesions, M-BSKT may reduce thrombosis and plaque shift towards to SB more effectively, which avoid the impact on TIMI flow and reduce the application of FKBI.

The immediate SB deterioration in the PS group [n=17(51.5%)] was significant higher compared to M-BSKT group [n=1(8.3%)] (p=0.014) (Figure5a). All situations of SB deterioration were not identical between two groups (Figure5c). The PS group displayed higher (p=0.042) rate [n=10(30.3%)] of SB TIMI flow<3 than M-BSKT. FKBI was more frequently performed in PS group [n=15(45.5%)] than M-BSKT group [n=1(8.3%)] (p=0.033) (Figure5b). Despite the SB loss in two groups showed no difference, there were 4 (12.1%) patients in ACS patients, which made a big proportion of all patients.


Minor comment:

In table 3, "Main-vessel TIMI flow≥3 after procedure" means "Main-vessel TIMI flow 3 after procedure"?

REPLY: We thank the referee for these comments and we apologize for our mistakes. We had changed it in table 3.