

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	A Randomized Comparison of Conventional Versus Intentional Strategy in Patients with High Risk Prediction of Side Branch Occlusion in Coronary Bifurcation Intervention: Rationale and Design of the CIT-RESOLVE trial
AUTHORS	Zhang, Dong; Yin, Dong; Song, Chenxi; Zhu, Chengang; Kirtane, Ajay; Xu, Bo; Dou, Kefei

VERSION 1 - REVIEW

REVIEWER	Soledad Ojeda Interventional Cardiology Department. Reina Sofía Hospital. Córdoba (Spain)
REVIEW RETURNED	11-Feb-2017

GENERAL COMMENTS	<p>The authors present the protocol of a randomized study. It has been designed to investigate if intentional strategy (elective two-stent strategy or jailed balloon technique) is associated with significant reduction of SB occlusion rate compared to conventional strategy (provisional two-stent strategy or jailed wire technique) in patients with high-risk of SB occlusion.</p> <p>The study is interesting and it will provide important information applicable to routine practice.</p> <p>However, in my opinion, the protocol has a limitation that the authors should clarify. It is confused if they want to compare two different strategies to protect the SB (jailed wire vs jailed balloon technique) or if the objective is to compare simple vs complex approach in bifurcations lesions with high risk of SB occlusion. The conventional group includes the usual stepwise. However, the intentional strategy includes two strategies: a more aggressive protection of the SB (jailed balloon technique), scantily reported and studied in bifurcation trials, and complex strategies which assure the SB from the beginning. As consequence, this group is more heterogeneous. I consider that it would be more interesting to focus the study on jailed balloon technique or on complex strategy to reduce the incidence of SB occlusion, but not in both.</p>
-------------------------	--

REVIEWER	Annapoorna Kini Mount Sinai Hospital, USA
REVIEW RETURNED	27-Feb-2017

GENERAL COMMENTS	Side branch (SB) occlusion is one of major complications of percutaneous coronary intervention (PCI), and a major cause of peri-procedural myocardial infarction. It remains an important issue how to predict this complication in advance as well as what procedure to be selected. The RESOLVE score which consists of six
-------------------------	---

angiographic parameters was developed to predict the risk of SB occlusion (1). In the V-RESOLVE score, four quantitative coronary angiography (QCA) analysis predictors in the RESOLVE score were replaced by visual estimation (2). Both of them seem to be useful to identify high-risk bifurcation lesion. The CIT-RESOLVE is a prospective, randomized (1:1), single-blind, and multicenter clinical trial comparing the rate of SB occlusion between conventional strategy and intentional strategy in a consecutive cohort of high-risk coronary bifurcation patients defined by V-RESOLVE score ≥ 12 . Although this study is of clinical interest, I have several concerns about the V-RESOLVE score and protocol.

(Specific comment)

1. In terms of SB size, SB ≥ 2 mm by visual estimation is contained in inclusion criteria (p.12, line 54). However, SB ≥ 1.5 mm by visual estimation was included in the analysis of previous study (1). Could they get the similar result by enrolling only lesions with SB ≥ 2 mm in previous analysis?

2. It is well-known that visual estimation of SB ostium is difficult and unreliable. Given that several hospitals are going to participate in this trial, it may be an important issue how to guarantee the quality of angiographic assessment.

3. It is also well accepted that visual estimation tends to evaluate the diameter stenosis as 10-15% greater than QCA analysis and the authors mentioned this fact in the discussion (2). However, when their angiographic results by QCA (1) and by visual estimation (2) are compared, diameter stenosis by QCA is greater in bifurcation core and SB. This is opposite to what they said in the discussion and quite confusing. Please give the reason why they got these results.

4. They are going to calculate V-RESOLVE score after predilatation according to the protocol (p.14, line 26). Why are they not going to calculate V-RESOLVE score at pre-procedure?

5. SB occlusion was defined as 'any decrease in TIMI flow grade or absence of flow in SB after main vessel (MV) stent well apposed'. The expression of 'after MV stent well apposed' is unclear (p.17, line 24). It should influence on the primary endpoint when they estimate TIMI flow grade in the SB. For example, when are they going to assess TIMI flow grade in the SB after MV stenting in jailed balloon technique group? Just after MV stenting? If so, is MV stent well apposed in this situation? They should define more clearly the timing of assessment of TIMI flow grade in the SB after MV stenting.

6. Intuitively, the rate of SB occlusion just after MV stenting should be higher in provisional strategy compared with primary two-stent strategy. I think that post-procedural SB occlusion is more clinically important and should be assessed as well as SB occlusion after MV stenting. In reference 13, myocardial infarction was associated with post-procedural SB occlusion, not after MV stenting.

7. I do not think that jailed balloon technique has been widely accepted as an established procedure. I am concerned about the safety and efficacy of this technique, especially in terms of rewiring to the SB after MV stenting, because the proximal part of MV stent may not be well apposed.

8. "Substantial or greater" should be used as Fleiss Kappa >0.60

	(p.13, line 56). (References) 1. Dou K, Zhang D, Xu B et al. An angiographic tool for risk prediction of side branch occlusion in coronary bifurcation intervention: the RESOLVE score system (Risk prEdiction of Side branch OccLusion in coronary bifurcation interVEntion). JACC Cardiovasc Interv 2015;8:39-46. 2. Dou K, Zhang D, Xu B et al. An angiographic tool based on Visual estimation for Risk prEdiction of Side branch OccLusion in coronary bifurcation interVEntion: the V-RESOLVE score system. EuroIntervention 2016;11:e1604-11.
--	---

REVIEWER	Dario Buccheri San Giovanni di Dio Hospital, Agrigento, Italy.
REVIEW RETURNED	01-Mar-2017

GENERAL COMMENTS	Congratulations to authors for this interesting protocol of a prospective ongoing study. I think the results will be really important for the daily practice of coronary bifurcation treatment strategies. I have no request for review of this manuscript.
-------------------------	---

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

The authors present the protocol of a randomized study. It has been designed to investigate if intentional strategy (elective two-stent strategy or jailed balloon technique) is associated with significant reduction of SB occlusion rate compared to conventional strategy (provisional two-stent strategy or jailed wire technique) in patients with high-risk of SB occlusion.

The study is interesting and it will provide important information applicable to routine practice. However, in my opinion, the protocol has a limitation that the authors should clarify. It is confused if they want to compare two different strategies to protect the SB (jailed wire vs jailed balloon technique) or if the objective is to compare simple vs complex approach in bifurcations lesions with high risk of SB occlusion. The conventional group includes the usual stepwise. However, the intentional strategy includes two strategies: a more aggressive protection of the SB (jailed balloon technique), scantily reported and studied in bifurcation trials, and complex strategies which assure the SB from the beginning. As consequence, this group is more heterogeneous. I consider that it would be more interesting to focus the study on jailed balloon technique or on complex strategy to reduce the incidence of SB occlusion, but not in both.

Response: Thanks for the reviewer's question. In the CIT-RESOLVE trial, we would enroll high-risk SB with diameter ≥ 2.0 mm, which would critically impact the prognosis. However, elective two-stent strategy is not appropriate for some SB with diameter < 2.5 mm. Thus, we have to use two aggressive strategies in intentional group. We will discuss this limitation in our manuscript.

As for the efficacy of jailed balloon technique, one previous study has reported that jailed balloon technique was associated with a very low rate of SB occlusion (1%) [1], which is significantly lower than previously reported rate of SB occlusion (7.4%-19%) [2-4]. A retrospective analysis, which we have just finished in Fuwai Hospital, showed SB occlusion occurred in 1 (0.36%) of 280 bifurcation lesions underwent jailed balloon technique. By far, 20 patients have been randomized to jailed balloon technique in CIT-RESOLVE trial and no SBs occluded, indicating its efficacy in protecting SB. As jailed balloon technique has not been proven by randomized clinical trials and widely used in clinical practice, we would explain the reason why we use the jailed balloon technique and clarify this

limitation in the manuscript:

In the present trial, we would enroll high-risk SB with diameter $\geq 2.0\text{mm}$, which would critically impact the prognosis. However, elective two-stent strategy is not appropriate for all SB with diameter $\geq 2.0\text{mm}$. Thus, we use two aggressive strategies in intentional strategy group: jailed balloon technique (for SB with diameter $< 2.5\text{mm}$ and $\geq 2.0\text{mm}$) or elective two-stent strategy (for SB with diameter $\geq 2.5\text{mm}$). (Page14-15)

Another limitation is that jailed balloon technique, which has not been proven by randomized clinical trials and widely used in clinical practice, is used in the interventional group. Although jailed balloon technique has been reported to be associated with very low rate of SB occlusion, its effect in SB protection warrant further studies. In future studies, we would compare the rate of SB occlusion between provisional two-stent strategy and elective two-stent strategy in patients at high risk of SB occlusion. (Page23-24)

Reviewer #2

Side branch (SB) occlusion is one of major complications of percutaneous coronary intervention (PCI), and a major cause of peri-procedural myocardial infarction. It remains an important issue how to predict this complication in advance as well as what procedure to be selected. The RESOLVE score which consists of six angiographic parameters was developed to predict the risk of SB occlusion (1). In the V-RESOLVE score, four quantitative coronary angiography (QCA) analysis predictors in the RESOLVE score were replaced by visual estimation (2). Both of them seem to be useful to identify high-risk bifurcation lesion. The CIT-RESOLVE is a prospective, randomized (1:1), single-blind, and multicenter clinical trial comparing the rate of SB occlusion between conventional strategy and intentional strategy in a consecutive cohort of high-risk coronary bifurcation patients defined by V-RESOLVE score ≥ 12 . Although this study is of clinical interest, I have several concerns about the V-RESOLVE score and protocol.

(Specific comment)

1. In terms of SB size, SB $\geq 2\text{mm}$ by visual estimation is contained in inclusion criteria (p.12, line 54). However, SB $\geq 1.5\text{mm}$ by visual estimation was included in the analysis of previous study (1). Could they get the similar result by enrolling only lesions with SB $\geq 2\text{mm}$ in previous analysis?

Response: Thanks for the reviewer's question. Although side branches with diameter $\geq 1.5\text{mm}$ are considered as significant SB [5], the CIT-RESOLVE trial would enroll SB with diameter $\geq 2.0\text{mm}$, which would critically impact the prognosis. Occlusion of SB with diameter $\geq 2.0\text{mm}$ can result in vessel closure and ischemia, with clinically significant myocardial infarction and even death depending upon the myocardial territory subtended by it.

In our previous study (V-RESOLVE trial), SB occlusion occurred in 66 (16.67%) of 396 high-risk bifurcation lesions. SB with diameter $\geq 2.0\text{mm}$ accounts for 44.4% (176/396) of all high-risk bifurcation lesions. The occlusion rate of SB with diameter $< 2.0\text{mm}$ is 22.27% (49/220) and the occlusion rate of SB with diameter $\geq 2.0\text{mm}$ is 9.66% (17/176). Our previous study has shown that V-RESOLVE score is accurately predictive in occlusion of SB with diameter $\geq 2.0\text{mm}$.

Considering the difference in SB diameter between V-RESOLVE trial and the CIT-RESOLVE study, we calculated the sample size according to the occlusion rate (9.66%) of SB (diameter $\geq 2.0\text{mm}$) in V-RESOLVE trial. Sample size calculations are detailed in the manuscript (Page 19-20). 566 subjects would ensure sufficient power of CIT-RESOLVE trial. We have considered the difference of SB diameter and calculated the sample size according to the event incidence in SB $\geq 2.0\text{mm}$. Thus, we believe the present study could get the similar result and has enough power to test the hypothesis.

2. It is well-known that visual estimation of SB ostium is difficult and unreliable. Given that several hospitals are going to participate in this trial, it may be an important issue how to guarantee the quality of angiographic assessment.

Response: Thanks for the reviewer's question. Intra- and inter-observer variability for visual estimation and angiographic assessment is always a question for every angiographic-based score system and is also a major concern of us. To minimize the intra- and inter-observer variability in the calculation of V-RESOLVE score, all investigators have undergone an extensive training session by a group of experienced technicians from the angiographic core laboratory in Fuwai Hospital on August 13th, 2016. The training session included: 1) calculate the V-RESOLVE score of low and high risk bifurcation lesions; 2) a comprehensive review of bias, discrepancies and pitfalls related to these cases. The investigator interobserver agreement was found to be substantial or greater (Fleiss Kappa > 0.60) after training. During trial randomization, once the investigators are not sure that the V-RESOLVE score \geq 12 points or not, we recommend them to send the cineangiograms by internet to the angiographic core laboratory in Fuwai Hospital, where cineangiograms would be assessed by two experienced technicians together and the V-RESOLVE score was generated by consensus. Investigator training and support of core laboratory would guarantee the quality of angiographic assessment.

3. It is also well accepted that visual estimation tends to evaluate the diameter stenosis as 10-15% greater than QCA analysis and the authors mentioned this fact in the discussion (2). However, when their angiographic results by QCA (1) and by visual estimation (2) are compared, diameter stenosis by QCA is greater in bifurcation core and SB. This is opposite to what they said in the discussion and quite confusing. Please give the reason why they got these results.

Response: Thanks for pointing out this important issue. As previous studies described, visual estimation tends to evaluate the diameter stenosis greater than QCA analysis. However, in our previous studies, diameter stenosis by QCA is greater in SB and bifurcation core. Potential reasons of why we got these results are as follows:

1) As for the diameter stenosis of SB, the reason why we got severer stenosis by QCA analysis is that the most severe diameter stenosis when using QCA is determined by QCA software. However, when performing visual estimation, observer intended to evaluate only lesions adjacent to the ostium of SB which may affect the risk of SB occlusion.

2) A potential explanation of why diameter stenosis by QCA is greater in bifurcation core is that the definition of bifurcation core is different between QCA analysis and visual estimation. In QCA analysis, the bifurcation core is defined and mapped by the QCA software, however, bifurcation core is defined as the 5mm part of main vessel before the carina in visual estimation.

Bifurcation lesions are much more complex in both QCA analysis and visual estimation. That is why these results are not in conformity with non-bifurcation studies. We sincerely thank the reviewer for this question. The reviewer has pointed out a really important issue, which warrants intense researches. We would perform further studies to clarify this problem.

4. They are going to calculate V-RESOLVE score after predilatation according to the protocol (p.14, line 26). Why are they not going to calculate V-RESOLVE score at pre-procedure?

Response: Thanks for the reviewer's question. The V-RESOLVE score contains six independent risk predictors: plaque distribution, main vessel [MV] thrombolysis in myocardial infarction [TIMI] flow grade before stenting, pre-procedural diameter stenosis of bifurcation core, bifurcation angle,

diameter ratio between MV/SB and diameter stenosis of SB before MV stenting. Among them, MV TIMI flow grade before stenting and diameter stenosis of SB before MV stenting are variables which could only be acquired after lesion preparation (wiring, pre-dilation, et al) and before stenting. That is why we calculate V-RESOLVE score after predilatation.

5. SB occlusion was defined as 'any decrease in TIMI flow grade or absence of flow in SB after main vessel (MV) stent well apposed'. The expression of 'after MV stent well apposed' is unclear (p.17, line 24). It should influence on the primary endpoint when they estimate TIMI flow grade in the SB. For example, when are they going to assess TIMI flow grade in the SB after MV stenting in jailed balloon technique group? Just after MV stenting? If so, is MV stent well apposed in this situation? They should define more clearly the timing of assessment of TIMI flow grade in the SB after MV stenting.

Response: Thanks for pointing out this important issue. We have described the time of assessing SB TIMI flow grade in detail in the manuscript. (Page 16)

For lesions underwent conventional strategy, TIMI flow grade is assessed immediately after the main vessel stent is deployed and post-dilation (if post-dilation is performed), then, the SB could be further treated if required. For lesions underwent jailed balloon technique, TIMI flow grade is assessed after POT is performed. For lesions underwent elective two-stent strategy, TIMI flow grade is assessed immediately after the main vessel stent is deployed and post-dilation (if post-dilation is performed), then rewiring the SB or final kissing balloon is performed if required.

6. Intuitively, the rate of SB occlusion just after MV stenting should be higher in provisional strategy compared with primary two-stent strategy. I think that post-procedural SB occlusion is more clinically important and should be assessed as well as SB occlusion after MV stenting. In reference 13, myocardial infarction was associated with post-procedural SB occlusion, not after MV stenting.

Response: Thanks for the reviewer's question. Post-procedural SB occlusion is surely more clinically important than transient SB occlusion after MV stenting. However, there are reasons that why we did not set post-procedural SB occlusion as the primary endpoint:

1) Though SB occlusion could be classified retrospectively as either post-procedural SB occlusion or transient SB occlusion after MV stenting, in real time it is difficult to predict which occluded SB is recoverable because it is highly depended on the experience of operators. The rate of successful SB blood flow restoration by intervention may vary significantly in different intervention centers.

2) Avoiding SB occlusion after MV stenting would be proactive in preventing post-procedural SB occlusion. It would leave room for SB blood flow restoration and prevent SB from post-procedural occlusion in the first place.

3) V-RESOLVE score is established to predict SB occlusion after MV stenting. Setting SB occlusion after MV stenting as the primary study endpoint would be consistent with the V-RESOLVE study.

As a result, we defined total occlusion and any TIMI flow grade decrease of SB after MV stenting as the primary study endpoint. We would like to assess the rate of post-procedural SB occlusion between intentional strategy and conventional strategy, nevertheless, it would not be set as the primary study endpoint.

7. I do not think that jailed balloon technique has been widely accepted as an established procedure. I am concerned about the safety and efficacy of this technique, especially in terms of rewiring to the SB after MV stenting, because the proximal part of MV stent may not be well apposed.

Response: Thanks for the reviewer's question. Jailed balloon technique is aggressive in SB protection. One previous study has reported that jailed balloon technique was associated with a very low rate (1%) of SB occlusion [1], which is significantly lower than previously reported rate of SB occlusion (7.4%-19%) [2-4]. A retrospective analysis, which we have just finished in Fuwai Hospital, showed SB occlusion occurred in 1 (0.36%) of 280 bifurcation lesions underwent jailed balloon technique. By far, 20 patients have been randomized to jailed balloon technique in CIT-RESOLVE trial and no SBs occluded. Even so, we are still concerning about the proximal part of MV stent may not be well apposed in using this technique. To achieve good apposition of the proximal MV stent, we recommend to use a pullback technique from distal MV to proximal with the aim of crossing the distal side cells of the MV stent when rewiring SB. Also, proximal optimisation technique (POT) is mandatory to achieve good apposition of the proximal MV stent. We believe POT would help struts of MV stent to be well apposed.

8. "Substantial or greater" should be used as Fleiss Kappa >0.60 (p.13, line 56).

Response: Thanks for pointing out the important issue. We have corrected this mistake in our manuscript. (Page 12)

The investigator interobserver agreement was found to be substantial or greater (Fleiss Kappa > 0.60) after training.

Reviewer #3

Congratulations to authors for this interesting protocol of a prospective ongoing study. I think the results will be important for the daily practice of coronary bifurcation treatment strategies. I have no request for review of this manuscript.

Response: Thank you so much for your review and your comments.

Reference:

- [1] Singh J, Patel Y, Depta JP, Mathews SJ, Cyrus T, Zajarias A, Kurz HI, Lasala JM, Bach RG. A modified provisional stenting approach to coronary bifurcation lesions: clinical application of the "jailed-balloon technique". J Interv Cardiol. 2012;25(3):289-96.
- [2] KraleV S, Poerner TC, Basorth D, et al. Side branch occlusion after coronary stent implantation in patients presenting with ST-elevation myocardial infarction: clinical impact and angiographic predictors. American heart journal. 2006;151:153-7.
- [3] Aliabadi D, Tilli FV, Bowers TR, et al. Incidence and angiographic predictors of side branch occlusion following high-pressure intracoronary stenting. Am J Cardiol 1997;80:994-7.
- [4] Hahn JY, Chun WJ, Kim JH, et al. Predictors and outcomes of side branch occlusion after main vessel stenting in coronary bifurcation lesions: results from the COBIS II Registry (COronary Bifurcation Stenting). J Am Coll Cardiol. 2013;62:1654-9.
- [5] Louvard Y, Medina A, Stankovic G. Definition and classification of bifurcation lesions and treatments. EuroIntervention 2010;6 Suppl J:J31-5.

VERSION 2 – REVIEW

REVIEWER	Ojeda, Soledad Interventional Cardiology Department Reina Sofía Hospital Córdoba (Spain)
REVIEW RETURNED	14-Apr-2017

GENERAL COMMENTS	The authors have answered my comments adequately
-------------------------	--