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## 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

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4 Patients with High Risk Prediction of Side Branch Occlusion in Coronary  
5 Bifurcation Intervention: Rationale and Design of the CIT-RESOLVE trial  
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40 **Keywords:** coronary bifurcation intervention; randomized comparison; conventional  
41 strategy; intentional strategy; side branch occlusion  
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48 **Keywords:** coronary bifurcation intervention; side branch occlusion; randomized  
49 comparison; conventional strategy; intentional strategy  
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52 This study is registered on [www.clinicaltrials.gov](http://www.clinicaltrials.gov), and the registration number is NCT  
53 02644434.  
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55 **Protocol version identifier:** 15.0

56 **Protocol date:** 18. September, 2016.  
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### Abstract

**Introduction:** The intentional strategy (aggressive side branch [SB] protection strategy: elective two-stent strategy or jailed balloon technique) is thought to be associated with lower SB occlusion rate than conventional strategy (provisional two-stent strategy or jailed wire technique). However, most previous studies showed comparable outcomes between the two strategies, probably due to no risk classification of SB occlusion when enrolling patients. There is still no randomized trial compared the intentional and conventional strategy when treating bifurcation lesions with high risk of SB occlusion. We aim to investigate if intentional strategy is associated with significant reduction of SB occlusion rate compared to conventional strategy in high-risk patients.

**Methods and analysis:** The CIT-RESOLVE is a prospective, randomized, single-blind, multicenter clinical trial comparing the rate of SB occlusion between the intentional strategy group and the conventional strategy group (positive control group) in a consecutive cohort of patients with high risk of side branch occlusion defined by V-RESOLVE score, which is a validated angiographic scoring system to evaluate the risk of SB occlusion in bifurcation intervention and used as one of the inclusion criteria to select patients with high SB occlusion risk (V-RESOLVE score  $\geq 12$ ). A total of 21 hospitals from 10 provinces in China participated in the present study. 566 patients meeting all inclusion/exclusion criteria are randomized to either intentional strategy group or conventional strategy group. The primary endpoint is SB occlusion (defined as any decrease in TIMI flow grade or absence of flow in SB after main vessel stenting). All patients are followed up for 12-month post discharge.

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4 **Ethics and dissemination:** The protocol has been approved by all local Ethics  
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6 Committee. Written informed consent would be acquired from all participants. The  
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8 findings of the trial will be shared by the participant hospitals and disseminated  
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10 through peer-reviewed journals.  
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14 **Trial registration number:** NCT02644434.  
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### 17 18 19 **Strengths and limitations of this study**

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21 CIT-RESOLVE is the leading trial which intends to investigate if intentional strategy  
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23 could decrease the rate of SB occlusion in patients with high-risk of SB occlusion.  
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28 This study enrolls high-risk patients by using an inclusion criteria of SB occlusion  
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30 risk (V-RESOLVE score  $\geq 12$  points).  
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36 This study would provide evidence for interventionalists in strategy selection when  
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38 treating bifurcation with high risk of SB occlusion.  
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43 Not all bifurcation lesions are included in the present study, left main diseases are  
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45 excluded.  
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**Abbreviations list**

**CK-MB=Creatine Kinase-Myocardial Band**

**ECG=Electrocardiography**

**ITT=Intention-To-Treat population**

**LAD=Left Anterior Descending coronary artery**

**MACE=Major Adverse Cardiac Events**

**MI=Myocardial Infarction**

**MV=Main Vessel**

**PCI=Percutaneous Coronary Intervention**

**PP=Per-Protocol population**

**QCA=Quantitative Coronary Angiography analysis**

**RVD= Reference Vessel Diameter**

**SB=Side Branch**

**TIMI=Thrombolysis In Myocardial Infarction flow grade**

## Introduction

Approximately 15% to 20% of percutaneous coronary interventions (PCI) are performed to treat coronary bifurcation lesions[1-3]. Previous studies have shown similar short and long term clinical outcomes between the conventional strategy (e.g. provisional two-stent strategy or jailed wire technique[4-6]) and the intentional strategy (e.g. elective two-stent strategy or jailed balloon technique)[7, 8], thus, the conventional strategy is generally preferred for its easy use and reduced procedure time. However, the optimal interventional strategy selection for complex coronary bifurcation lesions remains somewhat controversial because of the variability in side branch (SB) disease and the desire to preserve patency of large diseased side branches. SB occlusion after main vessel (MV) stenting is one of the most serious complications during the procedure and may be the major reason why operators prefer more aggressive strategy in the complex bifurcation lesions. Our study has shown that the rate of SB occlusion was 7.37% in patients underwent conventional strategy[9], which was in accordance with previous studies (SB occlusion rate: 8.4%-19%)[10-12]. SB occlusion can result in vessel closure and ischemia, with clinically significant myocardial infarction (MI) and even death depending upon the size of the SB (and the myocardial territory subtended by it)[12, 13].

The risk and incidence of SB occlusion are important factors impacting the interventional strategy selection and clinical outcome[9]. However, since the lack of useful tool for risk prediction of SB occlusion, no previous studies have considered the risk of SB occlusion as one of the inclusion criteria during patient enrollment.

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4 Previous randomized clinical trials performed randomization of all categories of  
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6 bifurcation lesions by using computer-generated random sequence, totally ignored the  
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8 individual lesion anatomical characteristics and the risk of SB occlusion. Now, we  
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10 have developed an angiographic tool for risk prediction of SB occlusion, the  
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12 V-RESOLVE score, which can help risk stratification of SB occlusion and could also  
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14 be used as a tool to select high-risk patients in randomized study. The SB occlusion  
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16 rate was significantly higher in the high-risk group (V-RESOLVE score  $\geq 12$ , rate of  
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18 SB occlusion: 16.7%) than the non-high-risk group (V-RESOLVE score  $< 12$ , rate of  
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20 SB occlusion: 4.3%) as assessed by the V-RESOVLE score[14].  
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26 Bifurcation lesions with high-risk of SB occlusion may need intentional  
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28 interventional strategy, which is more aggressive in SB protection than conventional  
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30 strategy and considered to be associated with lower SB occlusion rate. However, no  
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32 randomized trials were performed to compare the rate of SB occlusion between  
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34 intentional strategy and conventional strategy in high-risk patients.  
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39 Accordingly, the present study is designed to enroll patients with high-risk of SB  
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41 occlusion (V-RESOLVE score  $\geq 12$ ), and investigate if intentional strategy is  
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43 associated with significant reduction of SB occlusion rate compared to conventional  
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45 strategy in patients with high-risk of SB occlusion.  
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## 51 **Methods and analysis**

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54 **Hypothesis to be test.** We hypothesized that for patients at high risk of SB  
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56 occlusion (V-RESOLVE score  $\geq 12$ ), intentional strategy (a more aggressive SB  
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4 protection strategy: elective two-stent strategy or jailed balloon technique) is  
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6 associated with significant reduction of SB occlusion rate compared to conventional  
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8 strategy (provisional two-stent strategy or jailed wire technique). Thus the hypothesis  
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10 to be decided upon are as follows:  $H_0$ , for patients with high risk prediction of SB  
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12 occlusion, there is no difference in the rate of side branch occlusion between  
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14 intentional strategy group and the conventional strategy group, versus  $H_1$ , the rate of  
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16 side branch occlusion in intentional strategy group would be significantly lower than  
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18 that of conventional strategy group.  
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24 **Study design.** The CIT-RESOLVE is a prospective, randomized (1:1),  
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26 single-blind, multicenter clinical trial comparing the rate of side branch occlusion  
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28 between the conventional strategy group and the intentional strategy group in a  
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30 consecutive cohort of high-risk coronary bifurcation patients. Although operators are  
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32 not blinded, all individuals analyzing data are masked to treatment assignment. A total  
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34 of 21 centers in China will enroll patients. This study is registered on  
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36 www.clinicaltrials.gov, and the registration number is NCT 02644434. The study  
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38 flowchart is shown in figure 1.  
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44 This trial is conducted in accordance with the Declaration of Helsinki and good  
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46 clinical practice guidelines. The conduct of the trial has been approved by the Ethics  
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48 Committee. Written informed consent would be acquired from all participants. Patient  
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50 data in the Data Management System are protected by password and only available to  
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52 users designated by the study with appropriate authorization levels. De-identified data  
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54 will be used for data analysis.  
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4 **Risk prediction of side branch occlusion.** V-RESOLVE score would be used for  
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6 risk prediction of SB occlusion. The RESOLVE (**R**isk **p**r**E**diction of **S**ide **b**ranch  
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8 **O**cc**L**usion in coronary bifurcation inter**V**Ention) score, which is developed on the  
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10 basis of quantitative coronary angiography (QCA), is a validated angiographic scoring  
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12 system to evaluate the risk of SB occlusion in bifurcation intervention[9]. The  
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14 QCA-based RESOLVE score system contains six independent risk factors of SB  
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16 occlusion: including two visual estimation predictors (plaque distribution and MV  
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18 thrombolysis in myocardial infarction [TIMI] flow grade before stenting), and four  
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20 QCA analysis predictors (pre-procedural diameter stenosis of bifurcation core,  
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22 bifurcation angle, diameter ratio between MV/SB and diameter stenosis of SB before  
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24 MV stenting).  
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31 Although QCA provides a more objective determination of the extent and severity  
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33 of coronary artery disease, it may be more time-consuming and/or not immediately  
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35 available in real-time. As a result, the inclusion of QCA data within the QCA-based  
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37 RESOLVE score limits its ability to be used at the time of bifurcation intervention[15].  
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39 Therefore, we evaluated the ability of a visually estimated RESOLVE (V-RESOLVE)  
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41 score to predict the risk of side branch occlusion during bifurcation intervention. We  
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43 found that the V-RESOLVE score, an easy-to-use score system based on visual  
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45 estimation, can help risk stratification of SB occlusion during coronary bifurcation  
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47 intervention. The rate of SB occlusion was significantly higher in high-risk group  
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49 (V-RESOLVE score  $\geq 12$ , rate of SB occlusion: 16.7%) than that in non-high-risk  
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51 group (V-RESOLVE score  $\leq 11$ , rate of SB occlusion: 4.3%) ( $p < 0.01$ ). V-RESOLVE  
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score makes precision medicine possible in the daily practice of coronary bifurcation intervention for its easy use. The development, validation and calculation methods are detailed in our previous study[14]. The V-RESOLVE score is calculated by using a dedicate APP, which is available in both the iTunes store and Google play store. Only patients with V-RESOLVE score  $\geq 12$  would be enrolled.

**Study population.** A total of 566 patients with coronary bifurcation lesions (at high risk of SB occlusion), requiring PCI with stent implantation, are studied. V-RESOLVE score  $\geq 12$  points are defined as lesions with high risk of SB occlusion. This implies the application of only few angiographic exclusion criteria (Table 1). All patients provide written informed consent.

**Table 1. Inclusion and exclusion criteria.**

Inclusion criteria	Exclusion criteria
<p><b><i>Clinical Inclusion Criteria:</i></b></p> <ol style="list-style-type: none"> <li>Subject must be male or nonpregnant female <math>\geq 18</math> years of age and <math>\leq 75</math> years of age;</li> <li>Subject has symptomatic coronary artery disease with objective evidence of ischemia or silent ischemia;</li> <li>Subject is eligible for PCI;</li> <li>Subject (or legal guardian) understands the trial requirements and the treatment procedures and provides written informed consent before any</li> </ol>	<p><b><i>Clinical Exclusion Criteria:</i></b></p> <ol style="list-style-type: none"> <li>Subject has a known allergy to contrast (that cannot be adequately pre-medicated) and/or the trial stent system or protocol-required concomitant medications (e.g., stent alloy, stainless steel, sirolimus, everolimus or structurally related compounds, polymer or individual components, all P2Y<sub>12</sub> inhibitors, or aspirin);</li> <li>Planned surgery within 6 months after the</li> </ol>

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<p>trial-specific tests or procedures are performed;</p> <p>5. Subject is willing to comply with all protocol-required follow-up evaluation.</p>	<p>index procedure;</p> <p>3. Subject has one of the following (as assessed prior to the index procedure):</p> <ul style="list-style-type: none"><li>• Other serious medical illness (e.g., cancer, congestive heart failure) with estimated life expectancy of less than 12 months;</li><li>• Current problems with substance abuse (e.g., alcohol, cocaine, heroin, etc.);</li><li>• Planned procedure that may cause non-compliance with the protocol or confound data interpretation;</li></ul> <p>4. Subject has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions;</p> <p>5. Subject is participating in another investigational drug or device clinical trial that has not reached its primary endpoint;</p> <p>6. Subject intends to participate in another investigational drug or device clinical trial within 12 months after the index procedure;</p> <p>7. Subject with known intention to procreate within 12 months after the index procedure (women of child-bearing potential who are</p>
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<p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32</p>	<p>sexually active must agree to use a reliable method of contraception from the time of screening through 12 months after the index procedure);</p> <p>8. Subject is a woman who is pregnant or nursing (a pregnancy test must be performed within 7 days prior to the index procedure in women of child-bearing potential);</p> <p>9. Subject with left ventricular ejection fraction &lt; 35%;</p> <p>10. Subject has preoperative renal dysfunction: serum creatinine&gt;2.0mg/dl (176.82umol/L).</p>
<p>33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58</p> <p><b><i>Angiographic Inclusion Criteria:</i></b></p> <ol style="list-style-type: none"> <li>1. Subjects have coronary bifurcation lesions requiring PCI with stent implantation according to clinical guidelines and/or the operator's judgement;</li> <li>2. Visually estimated reference vessel diameter (RVD) of target main vessel <math>\geq 2.5</math> mm and <math>\leq 4.0</math> mm;</li> <li>3. Visually estimated RVD of target side branch <math>\geq 2.0</math>mm;</li> </ol>	<p>33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58</p> <p><b><i>Angiographic Exclusion Criteria:</i></b></p> <ol style="list-style-type: none"> <li>1. Left main lesions;</li> <li>2. In case of acute myocardial infarction (MI) of which the culprit vessel located at the left anterior descending coronary artery (LAD), the bifurcation lesion (LAD/diagonal branch [RVD&gt;2.5mm]) which is proximal to occluded LAD segment should be excluded.</li> </ol>

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| 1<br>2<br>3<br>4<br>5<br>6<br>7<br>8<br>9 | 4. Coronary anatomy is likely to allow delivery of<br>a study device to the target lesion(s);<br>5. V-RESOLVE score $\geq$ 12 points. |  |
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14 **Hospitals selection.** A total of 21 hospitals from 10 provinces (Beijing, Shanghai,  
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16 Guangdong, Shanxi, Heilongjiang, Jilin, Liaoning, Guangxi, Hunan, and Hebei,  
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18 detailed in supplementary file) are chosen. The annual PCI volume of each of these  
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20 hospitals  $\geq$  800. Operators with a minimum annual volume of 200 cases are allowed  
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22 to participate in the PCI procedure.  
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26 **Investigator Training.** All investigators received comprehensive training on the  
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28 standard definition of elements, protocol, APP using, calculation of V-RESOLVE  
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30 score, randomization, standard procedure of PCI, and data management.  
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34 Although there are only 6 variables in the V-RESOLVE score, intra- and  
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36 inter-observer variability for visual estimation is always a question for every visual  
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38 score system and is also a major concern of us. To minimize the intra- and  
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40 inter-observer variability in the calculation of V-RESOLVE score, all investigators  
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42 have undergone an extensive training session by a group of experienced technicians  
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44 from the angiographic core laboratory in Fuwai Hospital on August 13th, 2016. The  
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46 training session included: 1) calculate the V-RESOLVE score of low and high risk  
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48 bifurcation lesions; 2) a comprehensive review of bias, discrepancies and pitfalls  
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50 related to these cases. The investigator interobserver agreement was found to be  
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52 substantial or grater (Fleiss Kappa  $>$  0.80) after training. Once the investigators are  
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4 not sure that the V-RESOLVE score  $\geq 12$  points or not, we recommend them to send  
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6 the cineangiograms by internet to the angiographic core laboratory in Fuwai Hospital,  
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8 where cineangiograms would be assessed by two experienced technicians together  
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10 and the V-RESOLVE score was generated by consensus.  
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14 **Patient enrollment and randomization.** Subjects must be  $\geq 18$  years and  $\leq 75$   
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16 years of age at the time of enrollment in the study. Coronary angiography would be  
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18 performed to confirm that angiographic inclusion criteria are met. Then, wiring and  
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20 pre-dilation would be performed at the discretion of the interventional cardiologists in  
21  
22 the conventional manner. A mobile APP specialized for V-RESOLVE calculation will  
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24 be used to calculate the V-RESOLVE score after pre-dilation. Bifurcation lesions with  
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26 V-RESOLVE score  $\geq 12$  points will be enrolled. Patients that meet all the inclusion  
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28 criteria and had no exclusion criteria would be included in this study. Patient  
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30 enrollment has been started on 1<sup>st</sup>, December, 2016 and anticipated to be completed  
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32 before December, 2017.  
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39 Patient randomization will be performed centrally by internet after signing an  
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41 informed consent form. The randomization will be stratified by the diameter of side  
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43 branch (diameter of side branch  $< 2.5$ mm and  $\geq 2.0$ mm vs. diameter of side  
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45 branch  $\geq 2.5$ mm), with a randomization ratio of 1:1 to either conventional strategy  
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47 group or intentional strategy group.  
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51 **Intervention and procedure.** PCI is undertaken via the access site of operators'  
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53 choice. Coronary angioplasty is performed in the conventional manner and coronary  
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55 stents or other procedures/devices are used only when required. The administration of  
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4 peri-procedural antiplatelet and antithrombotic medications is based on the operator's  
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6 discretion and current guidelines. Intravenous unfractionated heparin is used to  
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8 maintain an activated clotting time between 250s and 300s through the whole  
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10 procedure. Cardiac enzymes (creatinine kinase-myocardial band [CK-MB] and  
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12 Troponin) are dynamically measured until 48h post-procedure. Lifelong aspirin (100  
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14 mg/d) is prescribed to all patients. At least 12 months of clopidogrel (75 mg/d) would  
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16 be recommended to all patients.  
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21 ***Conventional strategy group.*** Patients randomized to the conventional strategy  
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23 group would undergo either jailed wire technique (diameter of side branch <2.5mm  
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25 and  $\geq 2.0$ mm) or provisional two-stent strategy (diameter of side branch  $\geq 2.5$ mm).  
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29 ***Jailed wire technique.*** Both MV and SB are wired, with lesion preparation at the  
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31 operator's discretion. The MV is stented with wire protection in SB. The SB is not  
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33 further treated unless there is threatened SB closure, severe ostial pinching of SB  
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35 (>90%), TIMI flow grade decrease in SB, or SB dissection greater than type A. If one  
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37 of these criteria exists, the SB would be rewired and a kissing balloon inflation is  
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39 undertaken with anatomically appropriate sizing for each vessel.  
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44 ***Provisional two-stent strategy.*** Both vessels are wired, with lesion preparation  
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46 and MV stenting the same as the jailed wire technique. Provisional T stenting of the  
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48 SB could be undertaken if one of the following criteria exists after SB rewiring and a  
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50 kissing balloon inflation is undertaken: threatened SB closure, severe ostial pinching  
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52 of SB (>90%), TIMI flow grade decrease in SB, or SB dissection greater than type A.  
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57 ***Intentional strategy group.*** Patients randomized to the intentional strategy group  
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4 would undergo either jailed balloon technique (diameter of side branch < 2.5mm and  
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6  $\geq 2.0$ mm) or elective two-stent strategy (diameter of side branch  $\geq 2.5$ mm).  
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9 *Jailed balloon technique.* The technique has been detailed in previous studies[4,  
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11 5]. To be brief, vessel wiring and lesion preparation are the same as the jailed wire  
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13 technique. A balloon that is appropriately sized to approximate the RVD of SB is  
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15 advanced into the SB. A stent is then advanced into correct position over the target  
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17 lesion in the MV. To prevent entrapment of the SB balloon, the proximal marker of  
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19 the balloon is positioned approximately 2mm proximal to the MV stent. Adequate  
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21 length of balloon is advanced into SB to project the ostium. Then, the stent in MV is  
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23 deployed to nominal pressures, jailing the SB balloon and wire. If the SB is not  
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25 compromised, then the jailed SB balloon is inflated to low pressure (<3 atmospheres),  
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27 deflated, and the SB wire and balloon removed. Then the SB is rewired, followed by  
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29 mandatory proximal optimisation technique (POT).  
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37 However, if there is TIMI flow grade decrease in SB, the balloon is inflated to try  
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39 to reopen the SB. After the SB is rewired, the SB balloon is removed. Ballooning or T  
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41 stenting of the SB could be undertaken. POT is mandated to achieve good apposition  
42  
43 of the proximal MV stent after the SB is reopened. The wire in SB will not be  
44  
45 removed until the POT is completed.  
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48  
49 No matter there is SB compromise or not, final kissing balloon technique could  
50  
51 be performed at the discretion of the interventional cardiologists.  
52

53  
54 *Elective two-stent strategy.* Patients in this subgroup would undergo crush  
55  
56 procedure (e.g. Crush, Balloon Crush or DK-Crush)[16-18] or any other elective  
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3  
4 two-stent strategy like Culotte and T stent[19, 20], which stenting SB before MV  
5  
6 stenting. These techniques were detailed in previous studies.[16-20]  
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8  
9 For both the conventional and intentional strategy groups, proximal or distal  
10  
11 dissections could be treated with further stenting at any stage. Post-dilations could be  
12  
13 performed to optimize stent expansion. In all cases, an additional vessel with other  
14  
15 lesions could be treated if required.  
16

17  
18 **Primary and secondary endpoint(s).** The primary endpoint is side branch  
19  
20 occlusion, which is defined as any decrease in TIMI flow grade or absence of flow in  
21  
22 side branch after main vessel stent well opposed.  
23  
24

25  
26 The secondary endpoints are: 1) the elevation of biomarkers of peri-procedural  
27  
28 myocardial injury (CK-MB and Troponin); Peri-procedural MI is defined as  
29  
30 biomarkers elevation  $\geq 10 \times$  upper reference limit (URL) for CK-MB and/or  $\geq 70 \times$   
31  
32 URL for troponin[21]; 2) 12-month major adverse cardiac events (MACE, including  
33  
34 all cause death, all MI and target vessel revascularization).  
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39 **Follow-up.** Subjects had either a telephone call or clinic visit at 30 days ( $\pm 7$  days),  
40  
41 3 months ( $\pm 14$  days), 6 months ( $\pm 14$  days), 12 months ( $\pm 30$  days) by the enrolling site  
42  
43 for outcome evaluation. For all patients, MACE at 12-month will be reported. MACE  
44  
45 will be defined as a composite of all cause death, all MI (defined by the Third  
46  
47 Universal Definition[22]), and target vessel revascularization (defined by the  
48  
49 Academic Research Consortium [ARC][23]).  
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54 **Data collection.** Profession trained staffs who are independent of patient  
55  
56 treatment will be responsible for data collection and entering. The data collected for  
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4 each new CIT-RESOLVE patient include baseline information; sociodemographic  
5  
6 characteristics; symptoms and signs of the presenting coronary disease; medical  
7  
8 history, biomarker findings (CK-MB and Troponin activity will be determined by  
9  
10 using an immunoinhibition assay and confirmed by mass spectrometry),  
11  
12 electrocardiographic, and treatments administered prior to admission during  
13  
14 hospitalization. Final diagnosis, major in-hospital clinical events (death,  
15  
16 peri-procedural MI, major bleeding, stroke), and discharge status will also be  
17  
18 recorded.  
19  
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23  
24 Baseline and procedural coronary angiography will be reviewed and analyzed by  
25  
26 physicians and interventionalists to calculate the V-RESOLVE score. Coronary  
27  
28 angiography findings, including bifurcation location, baseline and post MV stenting  
29  
30 TIMI flow grade in MV and SB will be recorded. Procedural characteristics including  
31  
32 interventional strategy, the presence of jailed wire/balloon, successful final kissing or  
33  
34 not, will be collected. All investigators are required to collect, recheck and input all  
35  
36 these data and submit the completed electronic case report form (eCRF) upon the  
37  
38 patient's discharge or death. The investigation scheduling is detailed in table 2.  
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44 One follow-up survey (by outpatient clinic visit or telephone) will be conducted  
45  
46 at 12 months after discharge, to collect information on medications, MACE, and any  
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48 rehospitalizations after discharge.  
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Table 2. Investigation Scheduling

Schedule of Investigations	Baseline (prePCI)	Procedure	Post-procedure\ Discharge	30 days ( $\pm 7$ days)	3 months <sup>7</sup> ( $\pm 14$ days)	6 months ( $\pm 14$ days)	12 months ( $\pm 30$ days)
				Visit or Phone contact	Visit or Phone contact	Visit or Phone contact	Visit or Phone contact
Inclusion/Exclusion Criteria	•						
Informed Consent	•						
History & Risk Factors	•						
Physical examination	•						
Anginal status	•		•	•	•	•	•
Recording of Medications	•		•	•	•	•	•
12-Lead Electrocardiography	• <sup>1</sup>		• <sup>2</sup>				
Cardiac enzymes (CK-MB, Troponin)	• <sup>3</sup>		• <sup>4</sup>				
Serious Adverse Events <sup>5</sup>		•	•	•	•	•	•
V-RESOLVE score calculation		•					

Notes:

<sup>1</sup> Electrocardiography (ECG) at time of screening should be performed within 72 hours prior to PCI procedure.

<sup>2</sup> ECG within 24 hours post-procedure or at discharge, whichever comes first.

<sup>3</sup> Cardiac biomarkers per standard of care and local practice is drawn prior to the index PCI procedure (within 24 hours prior to PCI).

<sup>4</sup> CK-MB and Troponin in the post-procedure hospitalization period should be taken approximately 3-6 hours post procedure). If cardiac enzymes are elevated (according to local upper limit of normal), serial measurements of cardiac enzymes must be taken until a decline is noted.

<sup>5</sup> For all revascularizations (including stent thrombosis, etc.), the angiogram must be sent to the Monitor organization.

Note: In the event of undercurrents illnesses, interventions, adverse events, or treatment failure, effort should be made to complete the required observations as much as possible.

### Statistical considerations.

*Sample size calculations.* Sample size parameters for the primary endpoint:

- A 1:1 treatment allocation ratio of intentional strategy group and the conventional strategy group
- A two-side significance level (alpha) of 0.05
- 80% power to show differences in the rate of side branch occlusion between intentional strategy group and conventional strategy group
- The rate of side branch occlusion in intentional strategy group: 4.0%
- The rate of side branch occlusion in conventional strategy group: 10.0%
- The primary endpoint would be reached immediately after the main vessel stenting, therefore, the attrition rate is 0%
- Sample size formula:

$$n = \frac{\left[ \mu_{1-\alpha/2} \sqrt{2\bar{p}(1-\bar{p})} + \mu_{1-\beta} \sqrt{p_T(1-p_T) + p_C(1-p_C)} \right]^2}{(p_T - p_C)^2}$$

The 10% rate of side branch occlusion in conventional strategy group is based on the V-RESOLVE study[15]. It is reasonable to assume that, with an intentional strategy for bifurcation lesions with V-RESOLVE score  $\geq 12$  points, the rate of side branch occlusion would decrease to 4% in intentional strategy group. Thus, the present study requires 283 subjects in intentional strategy group and 283 in conventional strategy group, and the total number will be 566.

*Analysis plan.* The statistical analyses of the full analysis set will follow the intention-to-treat (ITT) principle. The ITT set will consist of all subjects who signed

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4 the written informed consent and are randomized, regardless which strategy was  
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6 selected. The primary analysis is a superiority ITT analysis of the primary clinical  
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8 endpoint. Normal approximation test for the difference between two proportions  
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10 (pooled proportion) or Fisher's exact test (if applicable) will be used to test the  
11  
12 two-sided hypothesis of superiority in proportions. If the P value from the two-sided  
13  
14 test is <0.05, the intentional strategy (test) will be concluded to be superior to  
15  
16 conventional strategy. If required, an additional analysis of the Per-Protocol (PP)  
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18 population will be conducted of the primary and secondary endpoints.  
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24 The conventional  $\chi^2$  test or Fisher exact test will be used for the analysis of  
25  
26 categorical variables. The treatment group differences will be evaluated with student t  
27  
28 or Wilcoxon rank sum scores for continuous variables. The 2 strategies will be  
29  
30 compared by Kaplan-Meier estimates for survival analysis. Statistical significance  
31  
32 will be declared if the 2-sided P value is <0.05. All analyses will be performed with  
33  
34 the use of the statistical program SAS version 9.4 (SAS Institute Inc, Cary, NC).  
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## 42 Discussion

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44 During coronary bifurcation intervention, one of the most serious complications  
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46 is side branch occlusion. Keeping the SB open is the major principle during PCI.  
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48 However, no previous randomized trials tried to address the problem of decreasing SB  
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50 occlusion rate in patients with high-risk of SB occlusion. The intentional strategy,  
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52 which is more aggressive in SB protection, is thought to have lower SB occlusion rate.  
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54 However, there is no concrete evidence confirming that intentional strategy is  
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4 associated with significant reduction of SB occlusion rate compared to conventional  
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6 strategy in patients with high risk of SB occlusion. CIT-RESOLVE is the leading  
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8 randomized trial which attempts to clarify this issue. To the best of our knowledge,  
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10 CIT-RESOLVE will be the first trial which 1) enrolls high-risk patients by using an  
11  
12 inclusion criteria of SB occlusion risk (V-RESOLVE score  $\geq 12$  points); 2) compares  
13  
14 the rate of SB occlusion between intentional strategy and conventional strategy in  
15  
16 patients with high-risk of SB occlusion.  
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20  
21 Series randomized clinical trials have attempted to address the problem of  
22  
23 whether bifurcation lesions require stenting both the MV and SB or not[2, 6, 19,  
24  
25 24-33]. However, the results of previous studies remain controversial: the BBC ONE  
26  
27 study showed significant lower incidence of MACE in simple strategy group[29],  
28  
29 while the DKCRUSH-II study showed a significant reduction of target lesion  
30  
31 revascularization and target vessel revascularization in DK crush group[6]. Most of  
32  
33 the randomized clinical trials performed randomization of all bifurcation lesions by  
34  
35 using computer-generated random sequence, totally ignored the individual lesion  
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37 anatomical characteristics and risk factors of SB occlusion. Thus, a substantial part of  
38  
39 bifurcation lesions may not undergo proper intervention strategy though some patients  
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41 have crossed over to another group. This may be the major reason why the results of  
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43 previous studies remain controversial.  
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51 Previous studies enrolled patients by using the inclusion criteria of either  
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53 unselected bifurcation lesions, specific Medina classifications or true bifurcation  
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55 lesions. However, neither “Medina classification” nor “true bifurcation lesion” could  
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4 predict the risk of SB occlusion accurately[34, 35]. The SB occlusion risk is not  
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6 considered as an important criterion when enrolling patients. CIT-RESOLVE is the  
7  
8 first trial which only enrolls high-risk patients by using a risk prediction tool  
9  
10 (V-RESOLVE score  $\geq 12$  points).  
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14 Numerous classifications and definitions of coronary bifurcation lesions have  
15  
16 been proposed to simplify the hard topic of bifurcation lesion in interventional  
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18 cardiology[36-45]. Among them, “Medina classification” as well as “true bifurcation  
19  
20 lesion” are straightforward and widely used. However, none of these classifications or  
21  
22 definitions could accurately predict the risk of SB occlusion[35]. One of our previous  
23  
24 researches has shown that “true bifurcation lesion” could not be regarded as an  
25  
26 independent predictor of SB occlusion[34]. RESOLVE score and V-RESOLVE score  
27  
28 is the first attempt to stratify the risk of SB occlusion during coronary bifurcation  
29  
30 intervention. V-RESOLVE score, which contains 6 independent predictors of SB  
31  
32 occlusion, is a validated score system to evaluate the risk of side branch occlusion[14]  
33  
34 and a useful tool for risk prediction of SB occlusion in the present study. V-RESOLVE  
35  
36 score  $\geq 12$  points is considered as high risk in SB occlusion, which may trigger  
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38 interventional SB protection, and set as one of the inclusion criteria of CIT-RESOLVE  
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40 trial.  
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49 The intentional strategy is more aggressive in SB protection: jailed wire may help  
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51 SB reopen; stenting the SB before MV stenting may avoid SB occlusion. Thus, the  
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53 intentional strategy is thought as a more suitable strategy for high-risk bifurcation  
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55 lesion. CIT-RESOLVE is the leading trial which intends to investigate if intentional  
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4 strategy could decrease the rate of SB occlusion in patients with high-risk of SB  
5  
6 occlusion. Comparing the rate of SB occlusion between intentional and conventional  
7  
8 strategy would provide evidence for interventionalists in strategy selection when  
9  
10 treating bifurcation with high risk of SB occlusion. 12-month follow-up would  
11  
12 investigate if SB occlusion could impact the clinical outcome directly.  
13  
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15  
16 The limitation of the trial design is that not all high-risk bifurcation lesions are  
17  
18 included in the present study. When treating left main diseases, left anterior  
19  
20 descending artery or left circumflex artery occlusion may lead to serious outcome,  
21  
22 thus, left main diseases are excluded in the consideration of ethic. Also, in case of  
23  
24 acute MI of which the culprit vessel located at the LAD, the bifurcation lesion  
25  
26 (LAD/diagonal branch [RVD>2.5mm]) which is proximal to occluded LAD segment  
27  
28 is excluded.  
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### 36 **Conclusion**

37  
38 The CIT-RESOLVE study is the first large randomized trial which enrolls only  
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40 high-risk patients by using an inclusion criteria of SB occlusion risk (V-RESOLVE  
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42 score  $\geq 12$  points), and it has sufficient power to assess the effect of intentional  
43  
44 strategy in decreasing the SB occlusion rate in patients at high risk of SB occlusion.  
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### 51 **CIT-RESOLVE Study Group**

52  
53 Principal investigator: Kefei Dou (Fuwai Hospital and National Center for  
54  
55 Cardiovascular Diseases).  
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5  
6 Cardiovascular Diseases).

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17  
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19  
20 New York Presbyterian Hospital).

### 21 22 23 24 25 26 27 **Contributorship statement**

28  
29 All listed authors fulfil the International Committee of Medical Journal Editors  
30  
31 (ICMJE) guidelines for authorship. Dong Zhang drafted the manuscript. Dong Yin,  
32  
33 Chenxi Song and Chengang Zhu revised it critically for important intellectual content.  
34  
35 Ajay J. Kirtane were responsible for editing and providing guidance on the paper.  
36  
37  
38 Concept and supervision of the protocol was conducted by Bo Xu and Kefei Dou. All  
39  
40 authors have offered final approval of this manuscript.  
41  
42  
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### 46 47 **Competing interests**

48  
49 No authors have any potential competing interest related to this manuscript.  
50  
51  
52  
53

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56  
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58  
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9  
10 design and conduct of this study, all study analyses, the drafting and editing of the  
11  
12 manuscript, and its final contents.  
13  
14

### 15 16 17 18 **Data sharing statement** 19

20  
21 Since this is a protocol of an ongoing prospective study, the data are not fully gathered  
22  
23 or published. After the publication of major outputs, requested data for scientific  
24  
25 purpose or research cooperation will be provided.  
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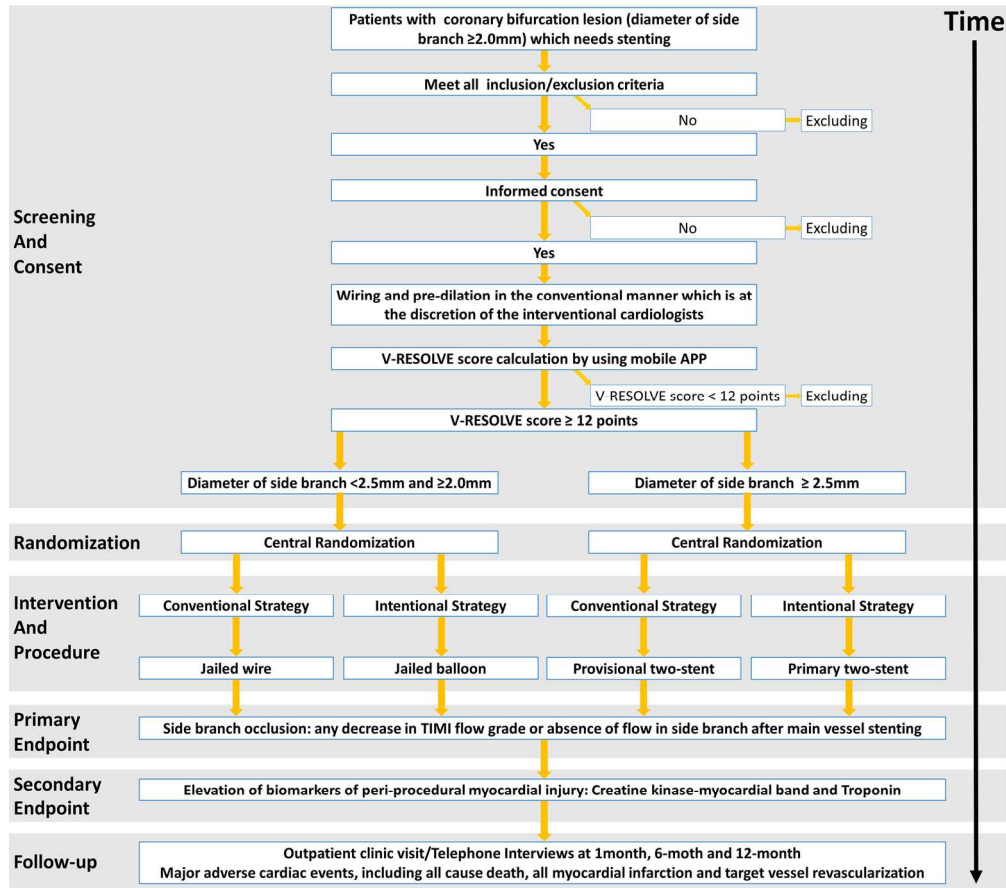


Figure 1. Study flowchart

179x159mm (300 x 300 DPI)

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description
<b>Administrative information</b>		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym ( <b>Title page</b> )
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry ( <b>Title page</b> )
Protocol version	3	Date and version identifier ( <b>Title page</b> )
Funding	4	Sources and types of financial, material, and other support ( <b>Page 24-25</b> )
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors ( <b>Page 23-24</b> )
	5b	Name and contact information for the trial sponsor ( <b>Page 24-25</b> )
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities ( <b>Page 24-25</b> )
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) ( <b>Page 24-25</b> )
<b>Introduction</b>		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention ( <b>Page 5-6</b> )
	6b	Explanation for choice of comparators ( <b>Page 5-6</b> )
Objectives	7	Specific objectives or hypotheses ( <b>Page 6</b> )

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Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (**Page 6-7**)

### Methods: Participants, interventions, and outcomes

Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained (**Supplementary File**)

Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) (**Page 9-12**)

Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (**Page 13-16**)

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) (**Page 13-16**)

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (**Page 13-16**)

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial (**Page 13-16**)

Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (**Page 16**)

Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (**Page 18 & Figure 1**)

Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (**Page 19**)

Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size (**Page 13**)

### Methods: Assignment of interventions (for controlled trials)

Allocation:

1			
2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions ( <b>Page 13</b> )
8			
9	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
10	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
11	mechanism		describing any steps to conceal the sequence until interventions are
12			assigned ( <b>Page 13</b> )
13			
14	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
15			and who will assign participants to interventions ( <b>Page 13</b> )
16			
17	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
18	(masking)		participants, care providers, outcome assessors, data analysts), and
19			how ( <b>Page 7</b> )
20			
21		17b	If blinded, circumstances under which unblinding is permissible, and
22			procedure for revealing a participant's allocated intervention during
23			the trial ( <b>Page 7</b> )
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### Methods: Data collection, management, and analysis

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28	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
29	methods		trial data, including any related processes to promote data quality (eg,
30			duplicate measurements, training of assessors) and a description of
31			study instruments (eg, questionnaires, laboratory tests) along with
32			their reliability and validity, if known. Reference to where data
33			collection forms can be found, if not in the protocol ( <b>Page 16-17</b> )
34			
35		18b	Plans to promote participant retention and complete follow-up,
36			including list of any outcome data to be collected for participants who
37			discontinue or deviate from intervention protocols ( <b>Page 16-17</b> )
38			
39	Data	19	Plans for data entry, coding, security, and storage, including any
40	management		related processes to promote data quality (eg, double data entry;
41			range checks for data values). Reference to where details of data
42			management procedures can be found, if not in the protocol ( <b>Page</b>
43			<b>16-18</b> )
44			
45	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
46	methods		Reference to where other details of the statistical analysis plan can be
47			found, if not in the protocol ( <b>Page 19-20</b> )
48			
49		20b	Methods for any additional analyses (eg, subgroup and adjusted
50			analyses) ( <b>Page 19-20</b> )
51			
52		20c	Definition of analysis population relating to protocol non-adherence
53			(eg, as randomised analysis), and any statistical methods to handle
54			missing data (eg, multiple imputation) ( <b>Page 19-20</b> )
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**Methods: Monitoring**

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| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed ( <b>Page 7</b> ) |
|                 | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial ( <b>Page 19-20</b> )   |
| Harms           | 22  | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct ( <b>Page 19-20</b> )   |
| Auditing        | 23  | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor ( <b>Page 7</b> )   |

**Ethics and dissemination**

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| Research ethics approval      | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval ( <b>Page 7</b> )  |
| Protocol amendments           | 25  | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) ( <b>Page 7</b> ) |
| Consent or assent             | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) ( <b>Page 7</b> )   |
|                               | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable ( <b>Page 7</b> )  |
| Confidentiality               | 27  | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial ( <b>Page 7</b> )   |
| Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site ( <b>Page 24</b> )   |
| Access to data                | 29  | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators ( <b>Page 25</b> )   |
| Ancillary and post-trial care | 30  | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation  |

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| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions <b>(Page 25)</b> |
|                      | 31b | Authorship eligibility guidelines and any intended use of professional writers <b>(Page 24-25)</b>   |
|                      | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code <b>(Page 25)</b>   |
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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.



## Supplementary File

## List of Hospitals in the CIT-RESOLVE Trial

Hospital	Province/Municipality	City
Fuwai Hospital	Beijing	Beijing
Peking Union Medical College Hospital	Beijing	Beijing
Peking University Third Hospital	Beijing	Beijing
Beijing Xuanwu Hospital	Beijing	Beijing
Chinese PLA General Hospital	Beijing	Beijing
Beijing Anzhen Hospital	Beijing	Beijing
Shanghai Tongji Hospital	Shanghai	Shanghai
Shanghai Dongfang Hospital	Shanghai	Shanghai
Renji Hospital, Shanghai Jiaotong University of Medicine	Shanghai	Shanghai
Shanghai Chest Hospital	Shanghai	Shanghai
Guangdong General Hospital	Guangdong	Guangzhou
The First Affiliated Hospital of Xi'an Jiaotong University	Shanxi	Xi'an
Xijing Hospital	Shanxi	Xi'an
Daqing Oilfield General Hospital	Heilongjiang	Daqing
The First Affiliated Hospital of Haerbin Medical University	Heilongjiang	Haerbin
The Second Hospital of Jilin University	Jilin	Changchun

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4	The First Affiliated Hospital of Dalian		
5		Liaoning	Dalian
6	Medical University		
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9	Shengjing Hospital of China Medical		
10		Liaoning	Shenyang
11	University		
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14	The First Affiliated Hospital of Guangxi		
15		Guangxi	Nanning
16	Medical University		
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19	Hunan Provincial People's Hospital	Hunan	Changsha
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21	Cangzhou Central Hospital	Hebei	Cangzhou
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# BMJ Open

## 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-016044.R1
Article Type:	Protocol
Date Submitted by the Author:	28-Mar-2017
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<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	coronary bifurcation intervention, side branch occlusion, randomized comparison, conventional strategy, intentional strategy

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For peer review only

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3 A Randomized Comparison of Conventional Versus Intentional Strategy in  
4 Patients with High Risk Prediction of Side Branch Occlusion in Coronary  
5 Bifurcation Intervention: Rationale and Design of the CIT-RESOLVE trial  
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40 **Keywords:** coronary bifurcation intervention; randomized comparison; conventional  
41 strategy; intentional strategy; side branch occlusion  
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44 **Word Count:** 4102 (excluding title page, abstract, references, figures and tables.);

45 Tables: 2; Figures: 1  
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48 **Keywords:** coronary bifurcation intervention; side branch occlusion; randomized  
49 comparison; conventional strategy; intentional strategy  
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52 This study is registered on [www.clinicaltrials.gov](http://www.clinicaltrials.gov), and the registration number is NCT  
53 02644434.  
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55 **Protocol version identifier:** 15.0

56 **Protocol date:** 18. September, 2016.  
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### Abstract

**Introduction:** The intentional strategy (aggressive side branch [SB] protection strategy: elective two-stent strategy or jailed balloon technique) is thought to be associated with lower SB occlusion rate than conventional strategy (provisional two-stent strategy or jailed wire technique). However, most previous studies showed comparable outcomes between the two strategies, probably due to no risk classification of SB occlusion when enrolling patients. There is still no randomized trial compared the intentional and conventional strategy when treating bifurcation lesions with high risk of SB occlusion. We aim to investigate if intentional strategy is associated with significant reduction of SB occlusion rate compared to conventional strategy in high-risk patients.

**Methods and analysis:** The CIT-RESOLVE is a prospective, randomized, single-blind, multicenter clinical trial comparing the rate of SB occlusion between the intentional strategy group and the conventional strategy group (positive control group) in a consecutive cohort of patients with high risk of side branch occlusion defined by V-RESOLVE score, which is a validated angiographic scoring system to evaluate the risk of SB occlusion in bifurcation intervention and used as one of the inclusion criteria to select patients with high SB occlusion risk (V-RESOLVE score  $\geq 12$ ). A total of 21 hospitals from 10 provinces in China participated in the present study. 566 patients meeting all inclusion/exclusion criteria are randomized to either intentional strategy group or conventional strategy group. The primary endpoint is SB occlusion (defined as any decrease in TIMI flow grade or absence of flow in SB after main vessel stenting). All patients are followed up for 12-month post discharge.

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4 **Ethics and dissemination:** The protocol has been approved by all local Ethics  
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6 Committee. Written informed consent would be acquired from all participants. The  
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8 findings of the trial will be shared by the participant hospitals and disseminated  
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10 through peer-reviewed journals.  
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14 **Trial registration number:** NCT02644434.  
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### 17 18 19 **Strengths and limitations of this study**

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21 CIT-RESOLVE is the leading trial which intends to investigate if intentional strategy  
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23 could decrease the rate of SB occlusion in patients with high-risk of SB occlusion.  
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28 This study enrolls high-risk patients by using an inclusion criteria of SB occlusion  
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30 risk (V-RESOLVE score  $\geq 12$  points).  
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36 This study would provide evidence for interventionalists in strategy selection when  
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38 treating bifurcation with high risk of SB occlusion.  
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43 Not all bifurcation lesions are included in the present study, left main diseases are  
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**Abbreviations list**

**CK-MB=Creatine Kinase-Myocardial Band**

**EKG=Electrocardiography**

**ITT=Intention-To-Treat population**

**LAD=Left Anterior Descending coronary artery**

**MACE=Major Adverse Cardiac Events**

**MI=Myocardial Infarction**

**MV=Main Vessel**

**PCI=Percutaneous Coronary Intervention**

**PP=Per-Protocol population**

**QCA=Quantitative Coronary Angiography analysis**

**RVD= Reference Vessel Diameter**

**SB=Side Branch**

**TIMI=Thrombolysis In Myocardial Infarction flow grade**



## Introduction

Approximately 15% to 20% of percutaneous coronary interventions (PCI) are performed to treat coronary bifurcation lesions[1-3]. Previous studies have shown similar short and long term clinical outcomes between the conventional strategy (e.g. provisional two-stent strategy or jailed wire technique[4-6]) and the intentional strategy (e.g. elective two-stent strategy or jailed balloon technique)[7, 8], thus, the conventional strategy is generally preferred for its easy use and reduced procedure time. However, the optimal interventional strategy selection for complex coronary bifurcation lesions remains somewhat controversial because of the variability in side branch (SB) disease and the desire to preserve patency of large diseased side branches. SB occlusion after main vessel (MV) stenting is one of the most serious complications during the procedure and may be the major reason why operators prefer more aggressive strategy in the complex bifurcation lesions. Our study has shown that the rate of SB occlusion was 7.37% in patients underwent conventional strategy[9], which was in accordance with previous studies (SB occlusion rate: 8.4%-19%)[10-12]. SB occlusion can result in vessel closure and ischemia, with clinically significant myocardial infarction (MI) and even death depending upon the size of the SB (and the myocardial territory subtended by it)[12, 13].

The risk and incidence of SB occlusion are important factors impacting the interventional strategy selection and clinical outcome[9]. However, since the lack of useful tool for risk prediction of SB occlusion, no previous studies have considered the risk of SB occlusion as one of the inclusion criteria during patient enrollment.

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4 Previous randomized clinical trials performed randomization of all categories of  
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6 bifurcation lesions by using computer-generated random sequence, totally ignored the  
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8 individual lesion anatomical characteristics and the risk of SB occlusion. Now, we  
9  
10 have developed an angiographic tool for risk prediction of SB occlusion, the  
11  
12 V-RESOLVE score, which can help risk stratification of SB occlusion and could also  
13  
14 be used as a tool to select high-risk patients in randomized study. The SB occlusion  
15  
16 rate was significantly higher in the high-risk group (V-RESOLVE score  $\geq 12$ , rate of  
17  
18 SB occlusion: 16.7%) than the non-high-risk group (V-RESOLVE score  $< 12$ , rate of  
19  
20 SB occlusion: 4.3%) as assessed by the V-RESOVLE score[14].  
21  
22  
23  
24

25  
26 Bifurcation lesions with high-risk of SB occlusion may need intentional  
27  
28 interventional strategy, which is more aggressive in SB protection than conventional  
29  
30 strategy and considered to be associated with lower SB occlusion rate. However, no  
31  
32 randomized trials were performed to compare the rate of SB occlusion between  
33  
34 intentional strategy and conventional strategy in high-risk patients.  
35  
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39 Accordingly, the present study is designed to enroll patients with high-risk of SB  
40  
41 occlusion (V-RESOLVE score  $\geq 12$ ), and investigate if intentional strategy is  
42  
43 associated with significant reduction of SB occlusion rate compared to conventional  
44  
45 strategy in patients with high-risk of SB occlusion.  
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## 51 **Methods and analysis**

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54 **Hypothesis to be test.** We hypothesized that for patients at high risk of SB  
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56 occlusion (V-RESOLVE score  $\geq 12$ ), intentional strategy (a more aggressive SB  
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4 protection strategy: elective two-stent strategy or jailed balloon technique) is  
5  
6 associated with significant reduction of SB occlusion rate compared to conventional  
7  
8 strategy (provisional two-stent strategy or jailed wire technique). Thus the hypothesis  
9  
10 to be decided upon are as follows:  $H_0$ , for patients with high risk prediction of SB  
11  
12 occlusion, there is no difference in the rate of side branch occlusion between  
13  
14 intentional strategy group and the conventional strategy group, versus  $H_1$ , the rate of  
15  
16 side branch occlusion in intentional strategy group would be significantly lower than  
17  
18 that of conventional strategy group.  
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23  
24 **Study design.** The CIT-RESOLVE is a prospective, randomized (1:1),  
25  
26 single-blind, multicenter clinical trial comparing the rate of side branch occlusion  
27  
28 between the conventional strategy group and the intentional strategy group in a  
29  
30 consecutive cohort of high-risk coronary bifurcation patients. Although operators are  
31  
32 not blinded, all individuals analyzing data are masked to treatment assignment. A total  
33  
34 of 21 centers in China will enroll patients. This study is registered on  
35  
36 www.clinicaltrials.gov, and the registration number is NCT 02644434. The study  
37  
38 flowchart is shown in figure 1 and its legend.  
39  
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43  
44 This trial is conducted in accordance with the Declaration of Helsinki and good  
45  
46 clinical practice guidelines. The conduct of the trial has been approved by the Ethics  
47  
48 Committee. Written informed consent would be acquired from all participants. Patient  
49  
50 data in the Data Management System are protected by password and only available to  
51  
52 users designated by the study with appropriate authorization levels. De-identified data  
53  
54 will be used for data analysis.  
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4 **Risk prediction of side branch occlusion.** V-RESOLVE score would be used for  
5  
6 risk prediction of SB occlusion. The RESOLVE (**R**isk **p**r**E**diction of **S**ide branch  
7  
8 **O**cc**L**usion in coronary bifurcation inter**V**Ention) score, which is developed on the  
9  
10 basis of quantitative coronary angiography (QCA), is a validated angiographic scoring  
11  
12 system to evaluate the risk of SB occlusion in bifurcation intervention[9]. The  
13  
14 QCA-based RESOLVE score system contains six independent risk factors of SB  
15  
16 occlusion: including two visual estimation predictors (plaque distribution and MV  
17  
18 thrombolysis in myocardial infarction [TIMI] flow grade before stenting), and four  
19  
20 QCA analysis predictors (pre-procedural diameter stenosis of bifurcation core,  
21  
22 bifurcation angle, diameter ratio between MV/SB and diameter stenosis of SB before  
23  
24 MV stenting).  
25  
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30  
31 Although QCA provides a more objective determination of the extent and severity  
32  
33 of coronary artery disease, it may be more time-consuming and/or not immediately  
34  
35 available in real-time. As a result, the inclusion of QCA data within the QCA-based  
36  
37 RESOLVE score limits its ability to be used at the time of bifurcation intervention[15].  
38  
39 Therefore, we evaluated the ability of a visually estimated RESOLVE (V-RESOLVE)  
40  
41 score to predict the risk of side branch occlusion during bifurcation intervention. We  
42  
43 found that the V-RESOLVE score, an easy-to-use score system based on visual  
44  
45 estimation, can help risk stratification of SB occlusion during coronary bifurcation  
46  
47 intervention. The rate of SB occlusion was significantly higher in high-risk group  
48  
49 (V-RESOLVE score  $\geq 12$ , rate of SB occlusion: 16.7%) than that in non-high-risk  
50  
51 group (V-RESOLVE score  $\leq 11$ , rate of SB occlusion: 4.3%) ( $p < 0.01$ ). V-RESOLVE  
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score makes precision medicine possible in the daily practice of coronary bifurcation intervention for its easy use. The development, validation and calculation methods are detailed in our previous study[14]. The V-RESOLVE score is calculated by using a dedicate APP, which is available in both the iTunes store and Google play store. Only patients with V-RESOLVE score  $\geq 12$  would be enrolled.

**Study population.** A total of 566 patients with coronary bifurcation lesions (at high risk of SB occlusion), requiring PCI with stent implantation, are studied. V-RESOLVE score  $\geq 12$  points are defined as lesions with high risk of SB occlusion. This implies the application of only few angiographic exclusion criteria (Table 1). All patients provide written informed consent.

**Table 1. Inclusion and exclusion criteria.**

Inclusion criteria	Exclusion criteria
<p><b><i>Clinical Inclusion Criteria:</i></b></p> <ol style="list-style-type: none"> <li>1. Subject must be male or nonpregnant female <math>\geq 18</math> years of age and <math>\leq 75</math> years of age;</li> <li>2. Subject has symptomatic coronary artery disease with objective evidence of ischemia or silent ischemia;</li> <li>3. Subject is eligible for PCI;</li> <li>4. Subject (or legal guardian) understands the trial requirements and the treatment procedures and provides written informed consent before any</li> </ol>	<p><b><i>Clinical Exclusion Criteria:</i></b></p> <ol style="list-style-type: none"> <li>1. Subject has a known allergy to contrast (that cannot be adequately pre-medicated) and/or the trial stent system or protocol-required concomitant medications (e.g., stent alloy, stainless steel, sirolimus, everolimus or structurally related compounds, polymer or individual components, all P2Y<sub>12</sub> inhibitors, or aspirin);</li> <li>2. Planned surgery within 6 months after the</li> </ol>

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<p>trial-specific tests or procedures are performed;</p> <p>5. Subject is willing to comply with all protocol-required follow-up evaluation.</p>	<p>index procedure;</p> <p>3. Subject has one of the following (as assessed prior to the index procedure):</p> <ul style="list-style-type: none"><li>• Other serious medical illness (e.g., cancer, congestive heart failure) with estimated life expectancy of less than 12 months;</li><li>• Current problems with substance abuse (e.g., alcohol, cocaine, heroin, etc.);</li><li>• Planned procedure that may cause non-compliance with the protocol or confound data interpretation;</li></ul> <p>4. Subject has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions;</p> <p>5. Subject is participating in another investigational drug or device clinical trial that has not reached its primary endpoint;</p> <p>6. Subject intends to participate in another investigational drug or device clinical trial within 12 months after the index procedure;</p> <p>7. Subject with known intention to procreate within 12 months after the index procedure (women of child-bearing potential who are</p>
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<p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32</p>	<p>sexually active must agree to use a reliable method of contraception from the time of screening through 12 months after the index procedure);</p> <p>8. Subject is a woman who is pregnant or nursing (a pregnancy test must be performed within 7 days prior to the index procedure in women of child-bearing potential);</p> <p>9. Subject with left ventricular ejection fraction &lt; 35%;</p> <p>10. Subject has preoperative renal dysfunction: serum creatinine&gt;2.0mg/dl (176.82umol/L).</p>
<p>33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58</p> <p><b><i>Angiographic Inclusion Criteria:</i></b></p> <ol style="list-style-type: none"> <li>1. Subjects have coronary bifurcation lesions requiring PCI with stent implantation according to clinical guidelines and/or the operator's judgement;</li> <li>2. Visually estimated reference vessel diameter (RVD) of target main vessel <math>\geq 2.5</math> mm and <math>\leq 4.0</math> mm;</li> <li>3. Visually estimated RVD of target side branch <math>\geq 2.0</math>mm;</li> </ol>	<p>33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58</p> <p><b><i>Angiographic Exclusion Criteria:</i></b></p> <ol style="list-style-type: none"> <li>1. Left main lesions;</li> <li>2. In case of acute myocardial infarction (MI) of which the culprit vessel located at the left anterior descending coronary artery (LAD), the bifurcation lesion (LAD/diagonal branch [RVD&gt;2.5mm]) which is proximal to occluded LAD segment should be excluded.</li> </ol>

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|---|---|--|
| 1<br>2<br>3<br>4<br>5<br>6<br>7<br>8<br>9 | 4. Coronary anatomy is likely to allow delivery of<br>a study device to the target lesion(s);<br>5. V-RESOLVE score $\geq$ 12 points. |  |
|---|---|--|

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14 **Hospitals selection.** A total of 21 hospitals from 10 provinces (Beijing, Shanghai,  
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16 Guangdong, Shanxi, Heilongjiang, Jilin, Liaoning, Guangxi, Hunan, and Hebei,  
17  
18 detailed in supplementary file) are chosen. The annual PCI volume of each of these  
19  
20 hospitals  $\geq$  800. Operators with a minimum annual volume of 200 cases are allowed  
21  
22 to participate in the PCI procedure.  
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24

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26 **Investigator Training.** All investigators received comprehensive training on the  
27  
28 standard definition of elements, protocol, APP using, calculation of V-RESOLVE  
29  
30 score, randomization, standard procedure of PCI, and data management.  
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34 Although there are only 6 variables in the V-RESOLVE score, intra- and  
35  
36 inter-observer variability for visual estimation is always a question for every visual  
37  
38 score system and is also a major concern of us. To minimize the intra- and  
39  
40 inter-observer variability in the calculation of V-RESOLVE score, all investigators  
41  
42 have undergone an extensive training session by a group of experienced technicians  
43  
44 from the angiographic core laboratory in Fuwai Hospital on August 13th, 2016. The  
45  
46 training session included: 1) calculate the V-RESOLVE score of low and high risk  
47  
48 bifurcation lesions; 2) a comprehensive review of bias, discrepancies and pitfalls  
49  
50 related to these cases. The investigator interobserver agreement was found to be  
51  
52 substantial or greater (Fleiss Kappa  $>0.60$ ) after training. Once the investigators are  
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4 not sure that the V-RESOLVE score  $\geq 12$  points or not, we recommend them to send  
5  
6 the cineangiograms by internet to the angiographic core laboratory in Fuwai Hospital,  
7  
8 where cineangiograms would be assessed by two experienced technicians together  
9  
10 and the V-RESOLVE score was generated by consensus.  
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13  
14 **Patient enrollment and randomization.** Subjects must be  $\geq 18$  years and  $\leq 75$   
15  
16 years of age at the time of enrollment in the study. Coronary angiography would be  
17  
18 performed to confirm that angiographic inclusion criteria are met. Then, wiring and  
19  
20 pre-dilation would be performed at the discretion of the interventional cardiologists in  
21  
22 the conventional manner. A mobile APP specialized for V-RESOLVE calculation will  
23  
24 be used to calculate the V-RESOLVE score after pre-dilation. Bifurcation lesions with  
25  
26 V-RESOLVE score  $\geq 12$  points will be enrolled. Patients that meet all the inclusion  
27  
28 criteria and had no exclusion criteria would be included in this study. Patient  
29  
30 enrollment has been started on 1<sup>st</sup>, December, 2016 and anticipated to be completed  
31  
32 before December, 2017.  
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39 Patient randomization will be performed centrally by internet after signing an  
40  
41 informed consent form. The randomization will be stratified by the diameter of side  
42  
43 branch (diameter of side branch  $< 2.5$ mm and  $\geq 2.0$ mm vs. diameter of side  
44  
45 branch  $\geq 2.5$ mm), with a randomization ratio of 1:1 to either conventional strategy  
46  
47 group or intentional strategy group.  
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51 **Intervention and procedure.** PCI is undertaken via the access site of operators'  
52  
53 choice. Coronary angioplasty is performed in the conventional manner and coronary  
54  
55 stents or other procedures/devices are used only when required. The administration of  
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4 peri-procedural antiplatelet and antithrombotic medications is based on the operator's  
5  
6 discretion and current guidelines. Intravenous unfractionated heparin is used to  
7  
8 maintain an activated clotting time between 250s and 300s through the whole  
9  
10 procedure. Cardiac enzymes (creatinine kinase-myocardial band [CK-MB] and  
11  
12 Troponin) are dynamically measured until 48h post-procedure. Lifelong aspirin (100  
13  
14 mg/d) is prescribed to all patients. At least 12 months of clopidogrel (75 mg/d) would  
15  
16 be recommended to all patients.  
17  
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21 ***Conventional strategy group.*** Patients randomized to the conventional strategy  
22  
23 group would undergo either jailed wire technique (diameter of side branch <2.5mm  
24  
25 and  $\geq 2.0$ mm) or provisional two-stent strategy (diameter of side branch  $\geq 2.5$ mm).  
26  
27

28  
29 ***Jailed wire technique.*** Both MV and SB are wired, with lesion preparation at the  
30  
31 operator's discretion. The MV is stented with wire protection in SB. The SB is not  
32  
33 further treated unless there is threatened SB closure, severe ostial pinching of SB  
34  
35 (>90%), TIMI flow grade decrease in SB, or SB dissection greater than type A. If one  
36  
37 of these criteria exists, the SB would be rewired and a kissing balloon inflation is  
38  
39 undertaken with anatomically appropriate sizing for each vessel.  
40  
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42

43  
44 ***Provisional two-stent strategy.*** Both vessels are wired, with lesion preparation  
45  
46 and MV stenting the same as the jailed wire technique. Provisional T stenting of the  
47  
48 SB could be undertaken if one of the following criteria exists after SB rewiring and a  
49  
50 kissing balloon inflation is undertaken: threatened SB closure, severe ostial pinching  
51  
52 of SB (>90%), TIMI flow grade decrease in SB, or SB dissection greater than type A.  
53  
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56  
57 ***Intentional strategy group.*** In the present trial, we would enroll high-risk SB  
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4 with diameter  $\geq 2.0$ mm, which would critically impact the prognosis. However,  
5  
6 elective two-stent strategy is not appropriate for all SB with diameter  $\geq 2.0$ mm. Thus,  
7  
8 we use two aggressive strategies in intentional strategy group: jailed balloon  
9  
10 technique (for SB with diameter  $< 2.5$ mm and  $\geq 2.0$ mm) or elective two-stent strategy  
11  
12 (for SB with diameter  $\geq 2.5$ mm).  
13  
14

15  
16 *Jailed balloon technique.* The technique has been detailed in previous studies[4,  
17  
18 5]. To be brief, vessel wiring and lesion preparation are the same as the jailed wire  
19  
20 technique. A balloon that is appropriately sized to approximate the RVD of SB is  
21  
22 advanced into the SB. A stent is then advanced into correct position over the target  
23  
24 lesion in the MV. To prevent entrapment of the SB balloon, the proximal marker of  
25  
26 the balloon is positioned approximately 2mm proximal to the MV stent. Adequate  
27  
28 length of balloon is advanced into SB to project the ostium. Then, the stent in MV is  
29  
30 deployed to nominal pressures, jailing the SB balloon and wire. If the SB is not  
31  
32 compromised, then the jailed SB balloon is inflated to low pressure ( $< 3$  atmospheres),  
33  
34 deflated, and the SB wire and balloon removed. Then the SB is rewired, followed by  
35  
36 mandatory proximal optimisation technique (POT).  
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44 However, if there is TIMI flow grade decrease in SB, the balloon is inflated to try  
45  
46 to reopen the SB. After the SB is rewired, the SB balloon is removed. Ballooning or T  
47  
48 stenting of the SB could be undertaken. POT is mandated to achieve good apposition  
49  
50 of the proximal MV stent after the SB is reopened. The wire in SB will not be  
51  
52 removed until the POT is completed.  
53  
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55  
56 No matter there is SB compromise or not, final kissing balloon technique could  
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4 be performed at the discretion of the interventional cardiologists.

5  
6 *Elective two-stent strategy.* Patients in this subgroup would undergo crush  
7  
8 procedure (e.g. Crush, Balloon Crush or DK-Crush)[16-18] or any other elective  
9  
10 two-stent strategy like Culotte and T stent[19, 20], which stenting SB before MV  
11  
12 stenting. These techniques were detailed in previous studies.[16-20]  
13  
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15  
16 For both the conventional and intentional strategy groups, proximal or distal  
17  
18 dissections could be treated with further stenting at any stage. Post-dilations could be  
19  
20 performed to optimize stent expansion. In all cases, an additional vessel with other  
21  
22 lesions could be treated if required.  
23  
24

25  
26 **Primary and secondary endpoint(s).** The primary endpoint is side branch  
27  
28 occlusion, which is defined as any decrease in TIMI flow grade or absence of flow in  
29  
30 side branch after main vessel stent well opposed. For lesions underwent conventional  
31  
32 strategy, TIMI flow grade is assessed immediately after the main vessel stent is  
33  
34 deployed and post-dilation (if post-dilation is performed), then, the SB could be  
35  
36 further treated if required. For lesions underwent jailed balloon technique, TIMI flow  
37  
38 grade is assessed after POT is performed. For lesions underwent elective two-stent  
39  
40 strategy, TIMI flow grade is assessed immediately after the main vessel stent is  
41  
42 deployed and post-dilation (if post-dilation is performed), then rewiring the SB or  
43  
44 final kissing balloon is performed if required.  
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51 The secondary endpoints are: 1) the elevation of biomarkers of peri-procedural  
52  
53 myocardial injury (CK-MB and Troponin); Peri-procedural MI is defined as  
54  
55 biomarkers elevation  $\geq 10 \times$  upper reference limit (URL) for CK-MB and/or  $\geq 70 \times$   
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4 URL for troponin[21]; 2) 12-month major adverse cardiac events (MACE, including  
5  
6 all cause death, all MI and target vessel revascularization).  
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9 **Follow-up.** Subjects had either a telephone call or clinic visit at 30 days ( $\pm 7$  days),  
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11 3 months ( $\pm 14$  days), 6 months ( $\pm 14$  days), 12 months ( $\pm 30$  days) by the enrolling site  
12  
13 for outcome evaluation. For all patients, MACE at 12-month will be reported. MACE  
14  
15 will be defined as a composite of all cause death, all MI (defined by the Third  
16  
17 Universal Definition[22]), and target vessel revascularization (defined by the  
18  
19 Academic Research Consortium [ARC][23]).  
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24 **Data collection.** Profession trained staffs who are independent of patient  
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26 treatment will be responsible for data collection and entering. The data collected for  
27  
28 each new CIT-RESOLVE patient include baseline information; sociodemographic  
29  
30 characteristics; symptoms and signs of the presenting coronary disease; medical  
31  
32 characteristics; symptoms and signs of the presenting coronary disease; medical  
33  
34 history, biomarker findings (CK-MB and Troponin activity will be determined by  
35  
36 using an immunoinhibition assay and confirmed by mass spectrometry),  
37  
38 electrocardiographic, and treatments administered prior to admission during  
39  
40 hospitalization. Final diagnosis, major in-hospital clinical events (death,  
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42 peri-procedural MI, major bleeding, stroke), and discharge status will also be  
43  
44 recorded.  
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49 Baseline and procedural coronary angiography will be reviewed and analyzed by  
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51 physicians and interventionalists to calculate the V-RESOLVE score. Coronary  
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53 angiography findings, including bifurcation location, baseline and post MV stenting  
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55 TIMI flow grade in MV and SB will be recorded. Procedural characteristics including  
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4 interventional strategy, the presence of jailed wire/balloon, successful final kissing or  
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6 not, will be collected. All investigators are required to collect, recheck and input all  
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8 these data and submit the completed electronic case report form (eCRF) upon the  
9  
10 patient's discharge or death. The investigation scheduling is detailed in table 2.  
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12

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14 One follow-up survey (by outpatient clinic visit or telephone) will be conducted  
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16 at 12 months after discharge, to collect information on medications, MACE, and any  
17  
18 rehospitalizations after discharge.  
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24 **Table 2. Investigation Scheduling**

Schedule of Investigations	Baseline (prePCI)	Procedure	Post-procedure\ Discharge	30 days ( $\pm 7$ days)	3 months <sup>7</sup> ( $\pm 14$ days)	6 months ( $\pm 14$ days)	12 months ( $\pm 30$ days)
				Visit or Phone contact	Visit or Phone contact	Visit or Phone contact	Visit or Phone contact
Inclusion/Exclusion Criteria	•						
Informed Consent	•						
History & Risk Factors	•						
Physical examination	•						
Anginal status	•		•	•	•	•	•
Recording of Medications	•		•	•	•	•	•
12-Lead Electrocardiography	• <sup>1</sup>		• <sup>2</sup>				
Cardiac enzymes (CK-MB, Troponin)	• <sup>3</sup>		• <sup>4</sup>				
Serious Adverse Events <sup>5</sup>		•	•	•	•	•	•
V-RESOLVE score calculation		•					

Notes:

<sup>1</sup> *Electrocardiography (ECG) at time of screening should be performed within 72 hours prior to PCI procedure.*

<sup>2</sup> *ECG within 24 hours post-procedure or at discharge, whichever comes first.*

<sup>3</sup> *Cardiac biomarkers per standard of care and local practice is drawn prior to the index PCI procedure (within 24 hours prior to PCI).*

<sup>4</sup> *CK-MB and Troponin in the post-procedure hospitalization period should be taken approximately 3-6 hours post procedure). If cardiac enzymes are elevated (according to local upper limit of normal), serial measurements of cardiac enzymes must be taken until a decline is noted.*

<sup>5</sup> *For all revascularizations (including stent thrombosis, etc.), the angiogram must be sent to the Monitor organization.*

*Note: In the event of undercurrents illnesses, interventions, adverse events, or treatment failure, effort should be made to complete the required observations as much as possible.*

**Statistical considerations.**

*Sample size calculations.* Sample size parameters for the primary endpoint:

- A 1:1 treatment allocation ratio of intentional strategy group and the conventional strategy group
- A two-side significance level (alpha) of 0.05
- 80% power to show differences in the rate of side branch occlusion between intentional strategy group and conventional strategy group
- The rate of side branch occlusion in intentional strategy group: 4.0%
- The rate of side branch occlusion in conventional strategy group: 10.0%
- The primary endpoint would be reached immediately after the main vessel stenting, therefore, the attrition rate is 0%
- Sample size formula:

$$n = \frac{\left[ \mu_{1-\alpha/2} \sqrt{2\bar{p}(1-\bar{p})} + \mu_{1-\beta} \sqrt{p_T(1-p_T) + p_C(1-p_C)} \right]^2}{(p_T - p_C)^2}$$

The 10% rate of side branch occlusion in conventional strategy group is based on

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3 the V-RESOLVE study[15]. It is reasonable to assume that, with an intentional  
4 strategy for bifurcation lesions with V-RESOLVE score  $\geq 12$  points, the rate of side  
5 branch occlusion would decrease to 4% in intentional strategy group. Thus, the  
6 present study requires 283 subjects in intentional strategy group and 283 in  
7 conventional strategy group, and the total number will be 566.

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16 *Analysis plan.* The statistical analyses of the full analysis set will follow the  
17 intention-to-treat (ITT) principle. The ITT set will consist of all subjects who signed  
18 the written informed consent and are randomized, regardless which strategy was  
19 selected. The primary analysis is a superiority ITT analysis of the primary clinical  
20 endpoint. Normal approximation test for the difference between two proportions  
21 (pooled proportion) or Fisher's exact test (if applicable) will be used to test the  
22 two-sided hypothesis of superiority in proportions. If the P value from the two-sided  
23 test is  $< 0.05$ , the intentional strategy (test) will be concluded to be superior to  
24 conventional strategy. If required, an additional analysis of the Per-Protocol (PP)  
25 population will be conducted of the primary and secondary endpoints.

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41 The conventional  $\chi^2$  test or Fisher exact test will be used for the analysis of  
42 categorical variables. The treatment group differences will be evaluated with student t  
43 or Wilcoxon rank sum scores for continuous variables. The 2 strategies will be  
44 compared by Kaplan-Meier estimates for survival analysis. Statistical significance  
45 will be declared if the 2-sided P value is  $< 0.05$ . All analyses will be performed with  
46 the use of the statistical program SAS version 9.4 (SAS Institute Inc, Cary, NC).  
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## Discussion

During coronary bifurcation intervention, one of the most serious complications is side branch occlusion. Keeping the SB open is the major principle during PCI. However, no previous randomized trials tried to address the problem of decreasing SB occlusion rate in patients with high-risk of SB occlusion. The intentional strategy, which is more aggressive in SB protection, is thought to have lower SB occlusion rate. However, there is no concrete evidence confirming that intentional strategy is associated with significant reduction of SB occlusion rate compared to conventional strategy in patients with high risk of SB occlusion. CIT-RESOLVE is the leading randomized trial which attempts to clarify this issue. To the best of our knowledge, CIT-RESOLVE will be the first trial which 1) enrolls high-risk patients by using an inclusion criteria of SB occlusion risk (V-RESOLVE score  $\geq 12$  points); 2) compares the rate of SB occlusion between intentional strategy and conventional strategy in patients with high-risk of SB occlusion.

Series randomized clinical trials have attempted to address the problem of whether bifurcation lesions require stenting both the MV and SB or not[2, 6, 19, 24-33]. However, the results of previous studies remain controversial: the BBC ONE study showed significant lower incidence of MACE in simple strategy group[29], while the DKCRUSH-II study showed a significant reduction of target lesion revascularization and target vessel revascularization in DK crush group[6]. Most of the randomized clinical trials performed randomization of all bifurcation lesions by using computer-generated random sequence, totally ignored the individual lesion

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3 anatomical characteristics and risk factors of SB occlusion. Thus, a substantial part of  
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5 bifurcation lesions may not undergo proper intervention strategy though some patients  
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7 have crossed over to another group. This may be the major reason why the results of  
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9 previous studies remain controversial.  
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14 Previous studies enrolled patients by using the inclusion criteria of either  
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16 unselected bifurcation lesions, specific Medina classifications or true bifurcation  
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18 lesions. However, neither “Medina classification” nor “true bifurcation lesion” could  
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20 predict the risk of SB occlusion accurately[34, 35]. The SB occlusion risk is not  
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22 considered as an important criterion when enrolling patients. CIT-RESOLVE is the  
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24 first trial which only enrolls high-risk patients by using a risk prediction tool  
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26 (V-RESOLVE score  $\geq 12$  points).  
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31 Numerous classifications and definitions of coronary bifurcation lesions have  
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33 been proposed to simplify the hard topic of bifurcation lesion in interventional  
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35 cardiology[36-45]. Among them, “Medina classification” as well as “true bifurcation  
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37 lesion” are straightforward and widely used. However, none of these classifications or  
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39 definitions could accurately predict the risk of SB occlusion[35]. One of our previous  
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41 researches has shown that “true bifurcation lesion” could not be regarded as an  
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43 independent predictor of SB occlusion[34]. RESOLVE score and V-RESOLVE score  
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45 is the first attempt to stratify the risk of SB occlusion during coronary bifurcation  
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47 intervention. V-RESOLVE score, which contains 6 independent predictors of SB  
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49 occlusion, is a validated score system to evaluate the risk of side branch occlusion[14]  
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51 and a useful tool for risk prediction of SB occlusion in the present study. V-RESOLVE  
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4 score  $\geq 12$  points is considered as high risk in SB occlusion, which may trigger  
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6 interventional SB protection, and set as one of the inclusion criteria of CIT-RESOLVE  
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8 trial.  
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11 The intentional strategy is more aggressive in SB protection: jailed wire may help  
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13 SB reopen; stenting the SB before MV stenting may avoid SB occlusion. Thus, the  
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15 intentional strategy is thought as a more suitable strategy for high-risk bifurcation  
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17 lesion. CIT-RESOLVE is the leading trial which intends to investigate if intentional  
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19 strategy could decrease the rate of SB occlusion in patients with high-risk of SB  
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21 occlusion. Comparing the rate of SB occlusion between intentional and conventional  
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23 strategy would provide evidence for interventionalists in strategy selection when  
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25 treating bifurcation with high risk of SB occlusion. 12-month follow-up would  
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27 investigate if SB occlusion could impact the clinical outcome directly.  
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34 One limitation of the trial design is that not all high-risk bifurcation lesions are  
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36 included in the present study. When treating left main diseases, left anterior  
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38 descending artery or left circumflex artery occlusion may lead to serious outcome,  
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40 thus, left main diseases are excluded in the consideration of ethic. Also, in case of  
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42 acute MI of which the culprit vessel located at the LAD, the bifurcation lesion  
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44 (LAD/diagonal branch [RVD>2.5mm]) which is proximal to occluded LAD segment  
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46 is excluded. Another limitation is that jailed balloon technique, which has not been  
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48 proven by randomized clinical trials and widely used in clinical practice, is used in the  
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50 interventional group. Although jailed balloon technique has been reported to be  
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52 associated with very low rate of SB occlusion[4], its effect in SB protection warrant  
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3 further studies. In future studies, we would compare the rate of SB occlusion between  
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6 provisional two-stent strategy and elective two-stent strategy in patients at high risk of  
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8 SB occlusion.  
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### 10 11 12 13 14 **Conclusion**

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16 The CIT-RESOLVE study is the first large randomized trial which enrolls only  
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18 high-risk patients by using an inclusion criteria of SB occlusion risk (V-RESOLVE  
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20 score  $\geq 12$  points), and it has sufficient power to assess the effect of intentional  
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22 strategy in decreasing the SB occlusion rate in patients at high risk of SB occlusion.  
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### 29 **CIT-RESOLVE Study Group**

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31 Principal investigator: Kefei Dou (Fuwai Hospital and National Center for  
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33 Cardiovascular Diseases).  
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36 Co-principal investigator: Bo Xu (Fuwai Hospital and National Center for  
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38 Cardiovascular Diseases).  
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41 Coordinating center: Fuwai Hospital and National Center for Cardiovascular  
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43 Diseases, Beijing, China.  
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46 Advisory Chairmen: Yuejin Yang (Fuwai Hospital and National Center for  
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48 Cardiovascular Diseases), Shaoliang Chen (Nanjing First Hospital and Nanjing  
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50 Medical University) and Ajay J. Kirtane (Columbia University Medical Center and  
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52 New York Presbyterian Hospital).  
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### Contributorship statement

All listed authors fulfil the International Committee of Medical Journal Editors (ICMJE) guidelines for authorship. Dong Zhang drafted the manuscript. Dong Yin, Chenxi Song and Chengang Zhu revised it critically for important intellectual content. Ajay J. Kirtane were responsible for editing and providing guidance on the paper. Concept and supervision of the protocol was conducted by Bo Xu and Kefei Dou. All authors have offered final approval of this manuscript.

### Competing interests

No authors have any potential competing interest related to this manuscript.

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### Data sharing statement

Since this is a protocol of an ongoing prospective study, the data are not fully gathered or published. After the publication of major outputs, requested data for scientific

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purpose or research cooperation will be provided.

For peer review only

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### 23 24 25 26 **Figure legend**

#### 27 28 **Figure 1. Study flowchart**

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31 Screening, randomization, intervention, procedure, study endpoint and follow-up of  
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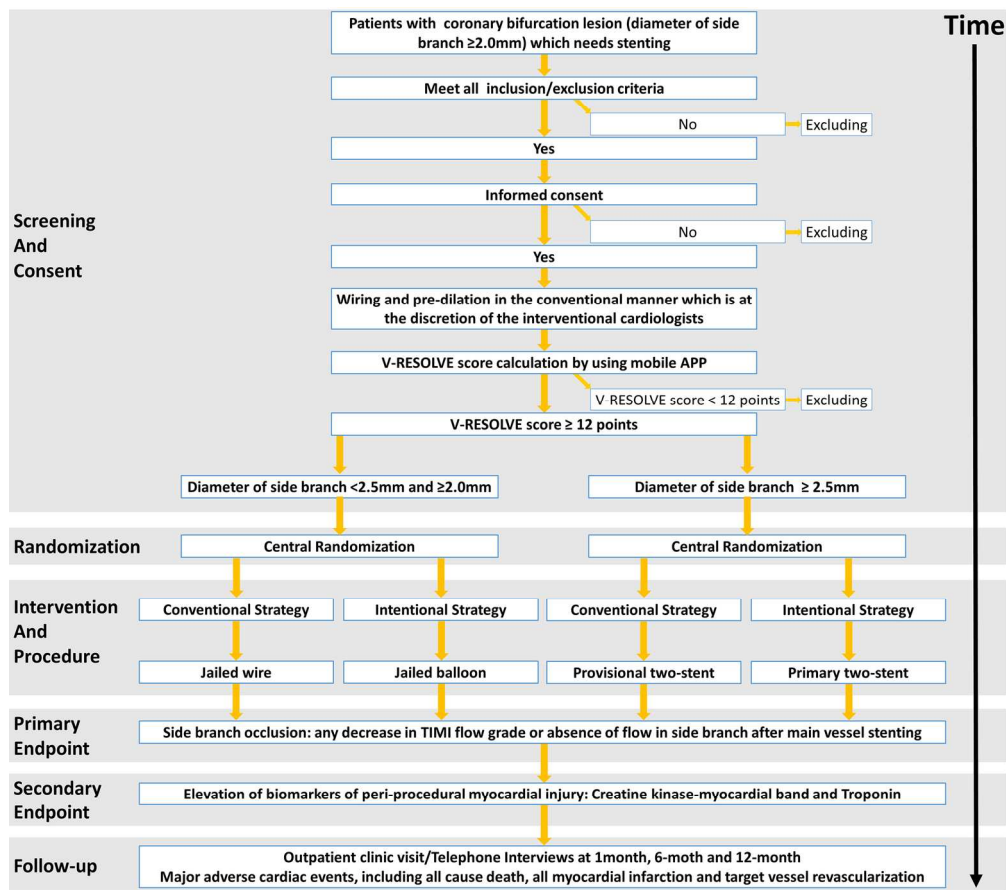


Figure 1. Study flowchart: screening, consent, randomization, intervention, procedure, study endpoint and follow-up.

179x159mm (300 x 300 DPI)

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## Supplementary File

## List of Hospitals in the CIT-RESOLVE Trial

Hospital	Province/Municipality	City
Fuwai Hospital	Beijing	Beijing
Peking Union Medical College Hospital	Beijing	Beijing
Peking University Third Hospital	Beijing	Beijing
Beijing Xuanwu Hospital	Beijing	Beijing
Chinese PLA General Hospital	Beijing	Beijing
Beijing Anzhen Hospital	Beijing	Beijing
Shanghai Tongji Hospital	Shanghai	Shanghai
Shanghai Dongfang Hospital	Shanghai	Shanghai
Renji Hospital, Shanghai Jiaotong University of Medicine	Shanghai	Shanghai
Shanghai Chest Hospital	Shanghai	Shanghai
Guangdong General Hospital	Guangdong	Guangzhou
The First Affiliated Hospital of Xi'an Jiaotong University	Shanxi	Xi'an
Xijing Hospital	Shanxi	Xi'an
Daqing Oilfield General Hospital	Heilongjiang	Daqing
The First Affiliated Hospital of Haerbin Medical University	Heilongjiang	Haerbin
The Second Hospital of Jilin University	Jilin	Changchun

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4	The First Affiliated Hospital of Dalian		
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6	Medical University		
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10		Liaoning	Shenyang
11	University		
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14	The First Affiliated Hospital of Guangxi		
15		Guangxi	Nanning
16	Medical University		
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18	Hunan Provincial People's Hospital	Hunan	Changsha
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23	Cangzhou Central Hospital	Hebei	Cangzhou
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description
<b>Administrative information</b>		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym ( <b>Title page</b> )
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry ( <b>Title page</b> )
Protocol version	3	Date and version identifier ( <b>Title page</b> )
Funding	4	Sources and types of financial, material, and other support ( <b>Page 24-25</b> )
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors ( <b>Page 23-24</b> )
	5b	Name and contact information for the trial sponsor ( <b>Page 24-25</b> )
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities ( <b>Page 24-25</b> )
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) ( <b>Page 24-25</b> )
<b>Introduction</b>		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention ( <b>Page 5-6</b> )
	6b	Explanation for choice of comparators ( <b>Page 5-6</b> )
Objectives	7	Specific objectives or hypotheses ( <b>Page 6</b> )

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Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (**Page 6-7**)

### **Methods: Participants, interventions, and outcomes**

Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained (**Supplementary File**)

Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) (**Page 9-12**)

Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (**Page 13-16**)

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) (**Page 13-16**)

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (**Page 13-16**)

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial (**Page 13-16**)

Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (**Page 16**)

Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (**Page 18 & Figure 1**)

Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (**Page 19**)

Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size (**Page 13**)

### **Methods: Assignment of interventions (for controlled trials)**

Allocation:

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2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions ( <b>Page 13</b> )
8			
9	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
10	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
11	mechanism		describing any steps to conceal the sequence until interventions are
12			assigned ( <b>Page 13</b> )
13			
14	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
15			and who will assign participants to interventions ( <b>Page 13</b> )
16			
17			
18	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
19	(masking)		participants, care providers, outcome assessors, data analysts), and
20			how ( <b>Page 7</b> )
21			
22		17b	If blinded, circumstances under which unblinding is permissible, and
23			procedure for revealing a participant's allocated intervention during
24			the trial ( <b>Page 7</b> )
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### Methods: Data collection, management, and analysis

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29	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
30	methods		trial data, including any related processes to promote data quality (eg,
31			duplicate measurements, training of assessors) and a description of
32			study instruments (eg, questionnaires, laboratory tests) along with
33			their reliability and validity, if known. Reference to where data
34			collection forms can be found, if not in the protocol ( <b>Page 16-17</b> )
35			
36		18b	Plans to promote participant retention and complete follow-up,
37			including list of any outcome data to be collected for participants who
38			discontinue or deviate from intervention protocols ( <b>Page 16-17</b> )
39			
40			
41	Data	19	Plans for data entry, coding, security, and storage, including any
42	management		related processes to promote data quality (eg, double data entry;
43			range checks for data values). Reference to where details of data
44			management procedures can be found, if not in the protocol ( <b>Page</b>
45			<b>16-18</b> )
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47			
48	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
49	methods		Reference to where other details of the statistical analysis plan can be
50			found, if not in the protocol ( <b>Page 19-20</b> )
51			
52		20b	Methods for any additional analyses (eg, subgroup and adjusted
53			analyses) ( <b>Page 19-20</b> )
54			
55		20c	Definition of analysis population relating to protocol non-adherence
56			(eg, as randomised analysis), and any statistical methods to handle
57			missing data (eg, multiple imputation) ( <b>Page 19-20</b> )
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**Methods: Monitoring**

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| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed ( <b>Page 7</b> ) |
|                 | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial ( <b>Page 19-20</b> )   |
| Harms           | 22  | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct ( <b>Page 19-20</b> )   |
| Auditing        | 23  | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor ( <b>Page 7</b> )   |

**Ethics and dissemination**

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| Research ethics approval      | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval ( <b>Page 7</b> )  |
| Protocol amendments           | 25  | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) ( <b>Page 7</b> ) |
| Consent or assent             | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) ( <b>Page 7</b> )   |
|                               | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable ( <b>Page 7</b> )  |
| Confidentiality               | 27  | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial ( <b>Page 7</b> )   |
| Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site ( <b>Page 24</b> )   |
| Access to data                | 29  | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators ( <b>Page 25</b> )   |
| Ancillary and post-trial care | 30  | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation  |

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| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions <b>(Page 25)</b> |
|                      | 31b | Authorship eligibility guidelines and any intended use of professional writers <b>(Page 24-25)</b>   |
|                      | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code <b>(Page 25)</b>   |
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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

# BMJ Open

## 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

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<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	coronary bifurcation intervention, side branch occlusion, randomized comparison, conventional strategy, intentional strategy

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For peer review only

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3 A Randomized Comparison of Conventional Versus Intentional Strategy in  
4 Patients with High Risk Prediction of Side Branch Occlusion in Coronary  
5 Bifurcation Intervention: Rationale and Design of the CIT-RESOLVE trial  
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40 **Keywords:** coronary bifurcation intervention; randomized comparison; conventional  
41 strategy; intentional strategy; side branch occlusion  
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44 **Word Count:** 4121 (excluding title page, abstract, references, figures and tables.);

45 Tables: 2; Figures: 1  
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48 **Keywords:** coronary bifurcation intervention; side branch occlusion; randomized  
49 comparison; conventional strategy; intentional strategy  
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52 This study is registered on [www.clinicaltrials.gov](http://www.clinicaltrials.gov), and the registration number is NCT  
53 02644434.  
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55 **Protocol version identifier:** 15.0

56 **Protocol date:** 18. September, 2016.  
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### Abstract

**Introduction:** The intentional strategy (aggressive side branch [SB] protection strategy: elective two-stent strategy or jailed balloon technique) is thought to be associated with lower SB occlusion rate than conventional strategy (provisional two-stent strategy or jailed wire technique). However, most previous studies showed comparable outcomes between the two strategies, probably due to no risk classification of SB occlusion when enrolling patients. There is still no randomized trial compared the intentional and conventional strategy when treating bifurcation lesions with high risk of SB occlusion. We aim to investigate if intentional strategy is associated with significant reduction of SB occlusion rate compared to conventional strategy in high-risk patients.

**Methods and analysis:** The CIT-RESOLVE is a prospective, randomized, single-blind, multicenter clinical trial comparing the rate of SB occlusion between the intentional strategy group and the conventional strategy group (positive control group) in a consecutive cohort of patients with high risk of side branch occlusion defined by V-RESOLVE score, which is a validated angiographic scoring system to evaluate the risk of SB occlusion in bifurcation intervention and used as one of the inclusion criteria to select patients with high SB occlusion risk (V-RESOLVE score  $\geq 12$ ). A total of 21 hospitals from 10 provinces in China participated in the present study. 566 patients meeting all inclusion/exclusion criteria are randomized to either intentional strategy group or conventional strategy group. The primary endpoint is SB occlusion (defined as any decrease in TIMI flow grade or absence of flow in SB after main vessel stenting). All patients are followed up for 12-month post discharge.

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4 **Ethics and dissemination:** The protocol has been approved by all local Ethics  
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6 Committee. The Ethics Committee have approved the study protocol, evaluated the  
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8 risk to benefit ratio, allowed operators with a minimum annual volume of 200 cases to  
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10 participate in the PCI procedure, and permitted them to perform both conventional  
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12 and intentional strategies. Written informed consent would be acquired from all  
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14 participants. The findings of the trial will be shared by the participant hospitals and  
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16 disseminated through peer-reviewed journals.  
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21 **Trial registration number:** NCT02644434.  
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### 24 25 26 **Strengths and limitations of this study** 27

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29 CIT-RESOLVE is the leading trial which intends to investigate if intentional strategy  
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31 could decrease the rate of SB occlusion in patients with high-risk of SB occlusion.  
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36 This study enrolls high-risk patients by using an inclusion criteria of SB occlusion  
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38 risk (V-RESOLVE score  $\geq 12$  points).  
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44 This study would provide evidence for interventionalists in strategy selection when  
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46 treating bifurcation with high risk of SB occlusion.  
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51 Not all bifurcation lesions are included in the present study, left main diseases are  
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53 excluded.  
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**Abbreviations list**

**CK-MB=Creatine Kinase-Myocardial Band**

**ECG=Electrocardiography**

**ITT=Intention-To-Treat population**

**LAD=Left Anterior Descending coronary artery**

**MACE=Major Adverse Cardiac Events**

**MI=Myocardial Infarction**

**MV=Main Vessel**

**PCI=Percutaneous Coronary Intervention**

**PP=Per-Protocol population**

**QCA=Quantitative Coronary Angiography analysis**

**RVD= Reference Vessel Diameter**

**SB=Side Branch**

**TIMI=Thrombolysis In Myocardial Infarction flow grade**

## Introduction

Approximately 15% to 20% of percutaneous coronary interventions (PCI) are performed to treat coronary bifurcation lesions[1-3]. Previous studies have shown similar short and long term clinical outcomes between the conventional strategy (e.g. provisional two-stent strategy or jailed wire technique[4-6]) and the intentional strategy (e.g. elective two-stent strategy or jailed balloon technique)[7, 8], thus, the conventional strategy is generally preferred for its easy use and reduced procedure time. However, the optimal interventional strategy selection for complex coronary bifurcation lesions remains somewhat controversial because of the variability in side branch (SB) disease and the desire to preserve patency of large diseased side branches. SB occlusion after main vessel (MV) stenting is one of the most serious complications during the procedure and may be the major reason why operators prefer more aggressive strategy in the complex bifurcation lesions. Our study has shown that the rate of SB occlusion was 7.37% in patients underwent conventional strategy[9], which was in accordance with previous studies (SB occlusion rate: 8.4%-19%)[10-12]. SB occlusion can result in vessel closure and ischemia, with clinically significant myocardial infarction (MI) and even death depending upon the size of the SB (and the myocardial territory subtended by it)[12, 13].

The risk and incidence of SB occlusion are important factors impacting the interventional strategy selection and clinical outcome[9]. However, since the lack of useful tool for risk prediction of SB occlusion, no previous studies have considered the risk of SB occlusion as one of the inclusion criteria during patient enrollment.

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4 Previous randomized clinical trials performed randomization of all categories of  
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6 bifurcation lesions by using computer-generated random sequence, totally ignored the  
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8 individual lesion anatomical characteristics and the risk of SB occlusion. Now, we  
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10 have developed an angiographic tool for risk prediction of SB occlusion, the  
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12 V-RESOLVE score, which can help risk stratification of SB occlusion and could also  
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14 be used as a tool to select high-risk patients in randomized study. The SB occlusion  
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16 rate was significantly higher in the high-risk group (V-RESOLVE score  $\geq 12$ , rate of  
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18 SB occlusion: 16.7%) than the non-high-risk group (V-RESOLVE score  $< 12$ , rate of  
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20 SB occlusion: 4.3%) as assessed by the V-RESOVLE score[14].  
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26 Bifurcation lesions with high-risk of SB occlusion may need intentional  
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28 interventional strategy, which is more aggressive in SB protection than conventional  
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30 strategy and considered to be associated with lower SB occlusion rate. However, no  
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32 randomized trials were performed to compare the rate of SB occlusion between  
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34 intentional strategy and conventional strategy in high-risk patients.  
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39 Accordingly, the present study is designed to enroll patients with high-risk of SB  
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41 occlusion (V-RESOLVE score  $\geq 12$ ), and investigate if intentional strategy is  
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43 associated with significant reduction of SB occlusion rate compared to conventional  
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45 strategy in patients with high-risk of SB occlusion.  
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### 49 **Methods and analysis**

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51 **Hypothesis to be test.** We hypothesized that for patients at high risk of SB  
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53 occlusion (V-RESOLVE score  $\geq 12$ ), intentional strategy (a more aggressive SB  
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55 protection strategy: elective two-stent strategy or jailed balloon technique) is  
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4 associated with significant reduction of SB occlusion rate compared to conventional  
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6 strategy (provisional two-stent strategy or jailed wire technique). Thus the hypothesis  
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8 to be decided upon are as follows:  $H_0$ , for patients with high risk prediction of SB  
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10 occlusion, there is no difference in the rate of side branch occlusion between  
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12 intentional strategy group and the conventional strategy group, versus  $H_1$ , the rate of  
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14 side branch occlusion in intentional strategy group would be significantly lower than  
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16 that of conventional strategy group.  
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21 **Study design.** The CIT-RESOLVE is a prospective, randomized (1:1),  
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23 single-blind, multicenter clinical trial comparing the rate of side branch occlusion  
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25 between the conventional strategy group and the intentional strategy group in a  
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27 consecutive cohort of high-risk coronary bifurcation patients. Although operators are  
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29 not blinded, all individuals analyzing data are masked to treatment assignment. A total  
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31 of 21 centers in China will enroll patients. This study is registered on  
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33 www.clinicaltrials.gov, and the registration number is NCT 02644434. The study  
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35 flowchart is shown in figure 1 and its legend.  
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41 This trial is conducted in accordance with the Declaration of Helsinki and good  
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43 clinical practice guidelines. The conduct of the trial has been approved by the Ethics  
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45 Committee. Written informed consent would be acquired from all participants. Patient  
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47 data in the Data Management System are protected by password and only available to  
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49 users designated by the study with appropriate authorization levels. De-identified data  
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51 will be used for data analysis.  
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57 **Risk prediction of side branch occlusion.** V-RESOLVE score would be used for  
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4 risk prediction of SB occlusion. The RESOLVE (**R**isk **pr**Ediction of **S**ide branch  
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6 **O**ccLusion in coronary bifurcation inter**V**Ention) score, which is developed on the  
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8 basis of quantitative coronary angiography (QCA), is a validated angiographic scoring  
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10 system to evaluate the risk of SB occlusion in bifurcation intervention[9]. The  
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12 QCA-based RESOLVE score system contains six independent risk factors of SB  
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14 occlusion: including two visual estimation predictors (plaque distribution and MV  
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16 thrombolysis in myocardial infarction [TIMI] flow grade before stenting), and four  
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18 QCA analysis predictors (pre-procedural diameter stenosis of bifurcation core,  
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20 bifurcation angle, diameter ratio between MV/SB and diameter stenosis of SB before  
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22 MV stenting).  
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29 Although QCA provides a more objective determination of the extent and severity  
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31 of coronary artery disease, it may be more time-consuming and/or not immediately  
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33 available in real-time. As a result, the inclusion of QCA data within the QCA-based  
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35 RESOLVE score limits its ability to be used at the time of bifurcation intervention[15].  
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37 Therefore, we evaluated the ability of a visually estimated RESOLVE (V-RESOLVE)  
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39 score to predict the risk of side branch occlusion during bifurcation intervention. We  
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41 found that the V-RESOLVE score, an easy-to-use score system based on visual  
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43 estimation, can help risk stratification of SB occlusion during coronary bifurcation  
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45 intervention. The rate of SB occlusion was significantly higher in high-risk group  
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47 (V-RESOLVE score  $\geq 12$ , rate of SB occlusion: 16.7%) than that in non-high-risk  
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49 group (V-RESOLVE score  $\leq 11$ , rate of SB occlusion: 4.3%) ( $p < 0.01$ ). V-RESOLVE  
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51 score makes precision medicine possible in the daily practice of coronary bifurcation  
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intervention for its easy use. The development, validation and calculation methods are detailed in our previous study[14]. The V-RESOLVE score is calculated by using a dedicate APP, which is available in both the iTunes store and Google play store. Only patients with V-RESOLVE score  $\geq 12$  would be enrolled.

**Study population.** A total of 566 patients with coronary bifurcation lesions (at high risk of SB occlusion), requiring PCI with stent implantation, are studied. V-RESOLVE score  $\geq 12$  points are defined as lesions with high risk of SB occlusion. This implies the application of only few angiographic exclusion criteria (Table 1). All patients provide written informed consent.

**Table 1. Inclusion and exclusion criteria.**

Inclusion criteria	Exclusion criteria
<p><b><i>Clinical Inclusion Criteria:</i></b></p> <ol style="list-style-type: none"> <li>1. Subject must be male or nonpregnant female <math>\geq 18</math> years of age and <math>\leq 75</math> years of age;</li> <li>2. Subject has symptomatic coronary artery disease with objective evidence of ischemia or silent ischemia;</li> <li>3. Subject is eligible for PCI;</li> <li>4. Subject (or legal guardian) understands the trial requirements and the treatment procedures and provides written informed consent before any trial-specific tests or procedures are performed;</li> </ol>	<p><b><i>Clinical Exclusion Criteria:</i></b></p> <ol style="list-style-type: none"> <li>1. Subject has a known allergy to contrast (that cannot be adequately pre-medicated) and/or the trial stent system or protocol-required concomitant medications (e.g., stent alloy, stainless steel, sirolimus, everolimus or structurally related compounds, polymer or individual components, all P2Y<sub>12</sub> inhibitors, or aspirin);</li> <li>2. Planned surgery within 6 months after the index procedure;</li> </ol>



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<p>5. Subject is willing to comply with all protocol-required follow-up evaluation.</p>	<p>3. Subject has one of the following (as assessed prior to the index procedure):</p> <ul style="list-style-type: none"><li>• Other serious medical illness (e.g., cancer, congestive heart failure) with estimated life expectancy of less than 12 months;</li><li>• Current problems with substance abuse (e.g., alcohol, cocaine, heroin, etc.);</li><li>• Planned procedure that may cause non-compliance with the protocol or confound data interpretation;</li></ul> <p>4. Subject has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions;</p> <p>5. Subject is participating in another investigational drug or device clinical trial that has not reached its primary endpoint;</p> <p>6. Subject intends to participate in another investigational drug or device clinical trial within 12 months after the index procedure;</p> <p>7. Subject with known intention to procreate within 12 months after the index procedure (women of child-bearing potential who are sexually active must agree to use a reliable</p>
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	<p>method of contraception from the time of screening through 12 months after the index procedure);</p> <p>8. Subject is a woman who is pregnant or nursing (a pregnancy test must be performed within 7 days prior to the index procedure in women of child-bearing potential);</p> <p>9. Subject with left ventricular ejection fraction &lt; 35%;</p> <p>10. Subject has preoperative renal dysfunction: serum creatinine &gt; 2.0mg/dl (176.82umol/L).</p>
<p><b><i>Angiographic Inclusion Criteria:</i></b></p> <ol style="list-style-type: none"> <li>1. Subjects have coronary bifurcation lesions requiring PCI with stent implantation according to clinical guidelines and/or the operator's judgement;</li> <li>2. Visually estimated reference vessel diameter (RVD) of target main vessel <math>\geq 2.5</math> mm and <math>\leq 4.0</math> mm;</li> <li>3. Visually estimated RVD of target side branch <math>\geq 2.0</math>mm;</li> <li>4. Coronary anatomy is likely to allow delivery of</li> </ol>	<p><b><i>Angiographic Exclusion Criteria:</i></b></p> <ol style="list-style-type: none"> <li>1. Left main lesions;</li> <li>2. In case of acute myocardial infarction (MI) of which the culprit vessel located at the left anterior descending coronary artery (LAD), the bifurcation lesion (LAD/diagonal branch [RVD &gt; 2.5mm]) which is proximal to occluded LAD segment should be excluded.</li> </ol>

a study device to the target lesion(s);

5. V-RESOLVE score  $\geq$  12 points.

**Hospitals selection.** A total of 21 hospitals from 10 provinces (Beijing, Shanghai, Guangdong, Shanxi, Heilongjiang, Jilin, Liaoning, Guangxi, Hunan, and Hebei, detailed in supplementary file) are chosen. The annual PCI volume of each of these hospitals  $\geq$  800. Only operators with a minimum annual volume of 200 cases are allowed to participate in the PCI procedure. All these interventionalists are skilled in coronary bifurcation PCI and qualified to perform both conventional and intentional strategies.

**Investigator Training.** All investigators received comprehensive training on the standard definition of elements, protocol, APP using, calculation of V-RESOLVE score, randomization, standard procedure of PCI, and data management.

Although there are only 6 variables in the V-RESOLVE score, intra- and inter-observer variability for visual estimation is always a question for every visual 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

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4 substantial or greater (Fleiss Kappa >0.60) after training. Once the investigators are  
5  
6 not sure that the V-RESOLVE score  $\geq 12$  points or not, we recommend them to send  
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8 the cineangiograms by internet to the angiographic core laboratory in Fuwai Hospital,  
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10 where cineangiograms would be assessed by two experienced technicians together  
11  
12 and the V-RESOLVE score was generated by consensus.  
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16 **Patient enrollment and randomization.** Subjects must be  $\geq 18$  years and  $\leq 75$   
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18 years of age at the time of enrollment in the study. Coronary angiography would be  
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20 performed to confirm that angiographic inclusion criteria are met. Then, wiring and  
21  
22 pre-dilation would be performed at the discretion of the interventional cardiologists in  
23  
24 the conventional manner. A mobile APP specialized for V-RESOLVE calculation will  
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26 be used to calculate the V-RESOLVE score after pre-dilation. Bifurcation lesions with  
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28 V-RESOLVE score  $\geq 12$  points will be enrolled. Patients that meet all the inclusion  
29  
30 criteria and had no exclusion criteria would be included in this study. Patient  
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32 enrollment has been started on 1<sup>st</sup>, December, 2016 and anticipated to be completed  
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34 before December, 2017.  
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41 Patient randomization will be performed centrally by internet after signing an  
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43 informed consent form. The randomization will be stratified by the diameter of side  
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45 branch (diameter of side branch <2.5mm and  $\geq 2.0$ mm vs. diameter of side  
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47 branch  $\geq 2.5$ mm), with a randomization ratio of 1:1 to either conventional strategy  
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49 group or intentional strategy group.  
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54 **Intervention and procedure.** PCI is undertaken via the access site of operators'  
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56 choice. Coronary angioplasty is performed in the conventional manner and coronary  
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stents or other procedures/devices are used only when required. The administration of peri-procedural antiplatelet and antithrombotic medications is based on the operator's discretion and current guidelines. Intravenous unfractionated heparin is used to maintain an activated clotting time between 250s and 300s through the whole procedure. Cardiac enzymes (creatin kinase-myocardial band [CK-MB] and Troponin) are dynamically measured until 48h post-procedure. Lifelong aspirin (100 mg/d) is prescribed to all patients. At least 12 months of clopidogrel (75 mg/d) would be recommended to all patients.

***Conventional strategy group.*** Patients randomized to the conventional strategy group would undergo either jailed wire technique (diameter of side branch <2.5mm and  $\geq 2.0$ mm) or provisional two-stent strategy (diameter of side branch  $\geq 2.5$ mm).

***Jailed wire technique.*** Both MV and SB are wired, with lesion preparation at the operator's discretion. The MV is stented with wire protection in SB. The SB is not further treated unless there is threatened SB closure, severe ostial pinching of SB (>90%), TIMI flow grade decrease in SB, or SB dissection greater than type A. If one of these criteria exists, the SB would be rewired and a kissing balloon inflation is undertaken with anatomically appropriate sizing for each vessel.

***Provisional two-stent strategy.*** Both vessels are wired, with lesion preparation and MV stenting the same as the jailed wire technique. Provisional T stenting of the SB could be undertaken if one of the following criteria exists after SB rewiring and a kissing balloon inflation is undertaken: threatened SB closure, severe ostial pinching of SB (>90%), TIMI flow grade decrease in SB, or SB dissection greater than type A.

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

*Jailed balloon technique.* The technique has been detailed in previous studies[4, 5]. To be brief, vessel wiring and lesion preparation are the same as the jailed wire technique. A balloon that is appropriately sized to approximate the RVD of SB is advanced into the SB. A stent is then advanced into correct position over the target lesion in the MV. To prevent entrapment of the SB balloon, the proximal marker of the balloon is positioned approximately 2mm proximal to the MV stent. Adequate length of balloon is advanced into SB to project the ostium. Then, the stent in MV is deployed to nominal pressures, jailing the SB balloon and wire. If the SB is not compromised, then the jailed SB balloon is inflated to low pressure ( $< 3$  atmospheres), deflated, and the SB wire and balloon removed. Then the SB is rewired, followed by mandatory proximal optimisation technique (POT).

However, if there is TIMI flow grade decrease in SB, the balloon is inflated to try to reopen the SB. After the SB is rewired, the SB balloon is removed. Ballooning or T stenting of the SB could be undertaken. POT is mandated to achieve good apposition of the proximal MV stent after the SB is reopened. The wire in SB will not be removed until the POT is completed.

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4 No matter there is SB compromise or not, final kissing balloon technique could  
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6 be performed at the discretion of the interventional cardiologists.  
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9 *Elective two-stent strategy.* Patients in this subgroup would undergo crush  
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11 procedure (e.g. Crush, Balloon Crush or DK-Crush)[16-18] or any other elective  
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13 two-stent strategy like Culotte and T stent[19, 20], which stenting SB before MV  
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15 stenting. These techniques were detailed in previous studies.[16-20]  
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19 For both the conventional and intentional strategy groups, proximal or distal  
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21 dissections could be treated with further stenting at any stage. Post-dilations could be  
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23 performed to optimize stent expansion. In all cases, an additional vessel with other  
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25 lesions could be treated if required.  
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29 **Primary and secondary endpoint(s).** The primary endpoint is side branch  
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31 occlusion, which is defined as any decrease in TIMI flow grade or absence of flow in  
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33 side branch after main vessel stent well opposed. For lesions underwent conventional  
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35 strategy, TIMI flow grade is assessed immediately after the main vessel stent is  
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37 deployed and post-dilation (if post-dilation is performed), then, the SB could be  
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39 further treated if required. For lesions underwent jailed balloon technique, TIMI flow  
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41 grade is assessed after POT is performed. For lesions underwent elective two-stent  
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43 strategy, TIMI flow grade is assessed immediately after the main vessel stent is  
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45 deployed and post-dilation (if post-dilation is performed), then rewiring the SB or  
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47 final kissing balloon is performed if required.  
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54 The secondary endpoints are: 1) the elevation of biomarkers of peri-procedural  
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56 myocardial injury (CK-MB and Troponin); Peri-procedural MI is defined as  
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4 biomarkers elevation  $\geq 10 \times$  upper reference limit (URL) for CK-MB and/or  $\geq 70 \times$   
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6 URL for troponin[21]; 2) 12-month major adverse cardiac events (MACE, including  
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8 all cause death, all MI and target vessel revascularization).  
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11 **Follow-up.** Subjects had either a telephone call or clinic visit at 30 days ( $\pm 7$  days),  
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13 3 months ( $\pm 14$  days), 6 months ( $\pm 14$  days), 12 months ( $\pm 30$  days) by the enrolling site  
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15 for outcome evaluation. For all patients, MACE at 12-month will be reported. MACE  
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17 will be defined as a composite of all cause death, all MI (defined by the Third  
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19 Universal Definition[22]), and target vessel revascularization (defined by the  
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21 Academic Research Consortium [ARC][23]).  
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26 **Data collection.** Profession trained staffs who are independent of patient  
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28 treatment will be responsible for data collection and entering. The data collected for  
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30 each new CIT-RESOLVE patient include baseline information; sociodemographic  
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32 characteristics; symptoms and signs of the presenting coronary disease; medical  
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34 history, biomarker findings (CK-MB and Troponin activity will be determined by  
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36 using an immunoinhibition assay and confirmed by mass spectrometry),  
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38 electrocardiographic, and treatments administered prior to admission during  
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40 hospitalization. Final diagnosis, major in-hospital clinical events (death,  
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42 peri-procedural MI, major bleeding, stroke), and discharge status will also be  
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44 recorded.  
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51 Baseline and procedural coronary angiography will be reviewed and analyzed by  
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53 physicians and interventionalists to calculate the V-RESOLVE score. Coronary  
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55 angiography findings, including bifurcation location, baseline and post MV stenting  
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TIMI flow grade in MV and SB will be recorded. Procedural characteristics including interventional strategy, the presence of jailed wire/balloon, successful final kissing or not, will be collected. All investigators are required to collect, recheck and input all these data and submit the completed electronic case report form (eCRF) upon the patient's discharge or death. The investigation scheduling is detailed in table 2.

One follow-up survey (by outpatient clinic visit or telephone) will be conducted at 12 months after discharge, to collect information on medications, MACE, and any rehospitalizations after discharge.

**Table 2. Investigation Scheduling**

Schedule of Investigations	Baseline (prePCI)	Procedure	Post-procedure\ Discharge	30 days ( $\pm 7$ days)	3 months <sup>7</sup> ( $\pm 14$ days)	6 months ( $\pm 14$ days)	12 months ( $\pm 30$ days)
				Visit or Phone contact	Visit or Phone contact	Visit or Phone contact	Visit or Phone contact
Inclusion/Exclusion Criteria	•						
Informed Consent	•						
History & Risk Factors	•						
Physical examination	•						
Anginal status	•		•	•	•	•	•
Recording of Medications	•		•	•	•	•	•
12-Lead Electrocardiography	• <sup>1</sup>		• <sup>2</sup>				
Cardiac enzymes (CK-MB, Troponin)	• <sup>3</sup>		• <sup>4</sup>				
Serious Adverse Events <sup>5</sup>		•	•	•	•	•	•
V-RESOLVE score calculation		•					

Notes:

<sup>1</sup> *Electrocardiography (ECG) at time of screening should be performed within 72 hours prior to PCI procedure.*

<sup>2</sup> *ECG within 24 hours post-procedure or at discharge, whichever comes first.*

<sup>3</sup> *Cardiac biomarkers per standard of care and local practice is drawn prior to the index PCI procedure (within 24 hours prior to PCI).*

<sup>4</sup> *CK-MB and Troponin in the post-procedure hospitalization period should be taken approximately 3-6 hours post procedure). If cardiac enzymes are elevated (according to local upper limit of normal), serial measurements of cardiac enzymes must be taken until a decline is noted.*

<sup>5</sup> *For all revascularizations (including stent thrombosis, etc.), the angiogram must be sent to the Monitor organization.*

*Note: In the event of undercurrents illnesses, interventions, adverse events, or treatment failure, effort should be made to complete the required observations as much as possible.*

**Statistical considerations.**

*Sample size calculations.* Sample size parameters for the primary endpoint:

- A 1:1 treatment allocation ratio of intentional strategy group and the conventional strategy group
- A two-side significance level (alpha) of 0.05
- 80% power to show differences in the rate of side branch occlusion between intentional strategy group and conventional strategy group
- The rate of side branch occlusion in intentional strategy group: 4.0%
- The rate of side branch occlusion in conventional strategy group: 10.0%
- The primary endpoint would be reached immediately after the main vessel stenting, therefore, the attrition rate is 0%
- Sample size formula:

$$n = \frac{\left[ \mu_{1-\alpha/2} \sqrt{2\bar{p}(1-\bar{p})} + \mu_{1-\beta} \sqrt{p_T(1-p_T) + p_C(1-p_C)} \right]^2}{(p_T - p_C)^2}$$

The 10% rate of side branch occlusion in conventional strategy group is based on

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3 the V-RESOLVE study[15]. It is reasonable to assume that, with an intentional  
4 strategy for bifurcation lesions with V-RESOLVE score  $\geq 12$  points, the rate of side  
5 branch occlusion would decrease to 4% in intentional strategy group. Thus, the  
6 present study requires 283 subjects in intentional strategy group and 283 in  
7 conventional strategy group, and the total number will be 566.  
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16 *Analysis plan.* The statistical analyses of the full analysis set will follow the  
17 intention-to-treat (ITT) principle. The ITT set will consist of all subjects who signed  
18 the written informed consent and are randomized, regardless which strategy was  
19 selected. The primary analysis is a superiority ITT analysis of the primary clinical  
20 endpoint. Normal approximation test for the difference between two proportions  
21 (pooled proportion) or Fisher's exact test (if applicable) will be used to test the  
22 two-sided hypothesis of superiority in proportions. If the P value from the two-sided  
23 test is  $< 0.05$ , the intentional strategy (test) will be concluded to be superior to  
24 conventional strategy. If required, an additional analysis of the Per-Protocol (PP)  
25 population will be conducted of the primary and secondary endpoints.  
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41 The conventional  $\chi^2$  test or Fisher exact test will be used for the analysis of  
42 categorical variables. The treatment group differences will be evaluated with student t  
43 or Wilcoxon rank sum scores for continuous variables. The 2 strategies will be  
44 compared by Kaplan-Meier estimates for survival analysis. Statistical significance  
45 will be declared if the 2-sided P value is  $< 0.05$ . All analyses will be performed with  
46 the use of the statistical program SAS version 9.4 (SAS Institute Inc, Cary, NC).  
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## Discussion

During coronary bifurcation intervention, one of the most serious complications is side branch occlusion. Keeping the SB open is the major principle during PCI. However, no previous randomized trials tried to address the problem of decreasing SB occlusion rate in patients with high-risk of SB occlusion. The intentional strategy, which is more aggressive in SB protection, is thought to have lower SB occlusion rate. However, there is no concrete evidence confirming that intentional strategy is associated with significant reduction of SB occlusion rate compared to conventional strategy in patients with high risk of SB occlusion. CIT-RESOLVE is the leading randomized trial which attempts to clarify this issue. To the best of our knowledge, CIT-RESOLVE will be the first trial which 1) enrolls high-risk patients by using an inclusion criteria of SB occlusion risk (V-RESOLVE score  $\geq 12$  points); 2) compares the rate of SB occlusion between intentional strategy and conventional strategy in patients with high-risk of SB occlusion.

Series randomized clinical trials have attempted to address the problem of whether bifurcation lesions require stenting both the MV and SB or not[2, 6, 19, 24-33]. However, the results of previous studies remain controversial: the BBC ONE study showed significant lower incidence of MACE in simple strategy group[29], while the DKCRUSH-II study showed a significant reduction of target lesion revascularization and target vessel revascularization in DK crush group[6]. Most of the randomized clinical trials performed randomization of all bifurcation lesions by using computer-generated random sequence, totally ignored the individual lesion

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3 anatomical characteristics and risk factors of SB occlusion. Thus, a substantial part of  
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5 bifurcation lesions may not undergo proper intervention strategy though some patients  
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7 have crossed over to another group. This may be the major reason why the results of  
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9 previous studies remain controversial.  
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14 Previous studies enrolled patients by using the inclusion criteria of either  
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16 unselected bifurcation lesions, specific Medina classifications or true bifurcation  
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18 lesions. However, neither “Medina classification” nor “true bifurcation lesion” could  
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20 predict the risk of SB occlusion accurately[34, 35]. The SB occlusion risk is not  
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22 considered as an important criterion when enrolling patients. CIT-RESOLVE is the  
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24 first trial which only enrolls high-risk patients by using a risk prediction tool  
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26 (V-RESOLVE score  $\geq 12$  points).  
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31 Numerous classifications and definitions of coronary bifurcation lesions have  
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33 been proposed to simplify the hard topic of bifurcation lesion in interventional  
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35 cardiology[36-45]. Among them, “Medina classification” as well as “true bifurcation  
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37 lesion” are straightforward and widely used. However, none of these classifications or  
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39 definitions could accurately predict the risk of SB occlusion[35]. One of our previous  
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41 researches has shown that “true bifurcation lesion” could not be regarded as an  
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43 independent predictor of SB occlusion[34]. RESOLVE score and V-RESOLVE score  
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45 is the first attempt to stratify the risk of SB occlusion during coronary bifurcation  
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47 intervention. V-RESOLVE score, which contains 6 independent predictors of SB  
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49 occlusion, is a validated score system to evaluate the risk of side branch occlusion[14]  
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51 and a useful tool for risk prediction of SB occlusion in the present study. V-RESOLVE  
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4 score  $\geq 12$  points is considered as high risk in SB occlusion, which may trigger  
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6 interventional SB protection, and set as one of the inclusion criteria of CIT-RESOLVE  
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8 trial.  
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11 The intentional strategy is more aggressive in SB protection: jailed wire may help  
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13 SB reopen; stenting the SB before MV stenting may avoid SB occlusion. Thus, the  
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15 intentional strategy is thought as a more suitable strategy for high-risk bifurcation  
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17 lesion. CIT-RESOLVE is the leading trial which intends to investigate if intentional  
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19 strategy could decrease the rate of SB occlusion in patients with high-risk of SB  
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21 occlusion. Comparing the rate of SB occlusion between intentional and conventional  
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23 strategy would provide evidence for interventionalists in strategy selection when  
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25 treating bifurcation with high risk of SB occlusion. 12-month follow-up would  
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27 investigate if SB occlusion could impact the clinical outcome directly.  
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34 One limitation of the trial design is that not all high-risk bifurcation lesions are  
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36 included in the present study. When treating left main diseases, left anterior  
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38 descending artery or left circumflex artery occlusion may lead to serious outcome,  
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40 thus, left main diseases are excluded in the consideration of ethic. Also, in case of  
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42 acute MI of which the culprit vessel located at the LAD, the bifurcation lesion  
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44 (LAD/diagonal branch [RVD>2.5mm]) which is proximal to occluded LAD segment  
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46 is excluded. Another limitation is that jailed balloon technique, which has not been  
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48 proven by randomized clinical trials and widely used in clinical practice, is used in the  
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50 interventional group. Although jailed balloon technique has been reported to be  
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52 associated with very low rate of SB occlusion[4], its effect in SB protection warrant  
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3 further studies. In future studies, we would compare the rate of SB occlusion between  
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6 provisional two-stent strategy and elective two-stent strategy in patients at high risk of  
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8 SB occlusion.  
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### 10 11 12 13 14 **Conclusion**

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16 The CIT-RESOLVE study is the first large randomized trial which enrolls only  
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18 high-risk patients by using an inclusion criteria of SB occlusion risk (V-RESOLVE  
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20 score  $\geq 12$  points), and it has sufficient power to assess the effect of intentional  
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22 strategy in decreasing the SB occlusion rate in patients at high risk of SB occlusion.  
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### 29 **CIT-RESOLVE Study Group**

30  
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32  
33 Cardiovascular Diseases).  
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52 New York Presbyterian Hospital).  
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### Contributorship statement

All listed authors fulfil the International Committee of Medical Journal Editors (ICMJE) guidelines for authorship. Dong Zhang drafted the manuscript. Dong Yin, Chenxi Song and Chengang Zhu revised it critically for important intellectual content. Ajay J. Kirtane were responsible for editing and providing guidance on the paper. Concept and supervision of the protocol was conducted by Bo Xu and Kefei Dou. All authors have offered final approval of this manuscript.

### Competing interests

No authors have any potential competing interest related to this manuscript.

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### Data sharing statement

Since this is a protocol of an ongoing prospective study, the data are not fully gathered or published. After the publication of major outputs, requested data for scientific



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purpose or research cooperation will be provided.

For peer review only

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### 23 24 25 26 **Figure legend**

#### 27 28 **Figure 1. Study flowchart**

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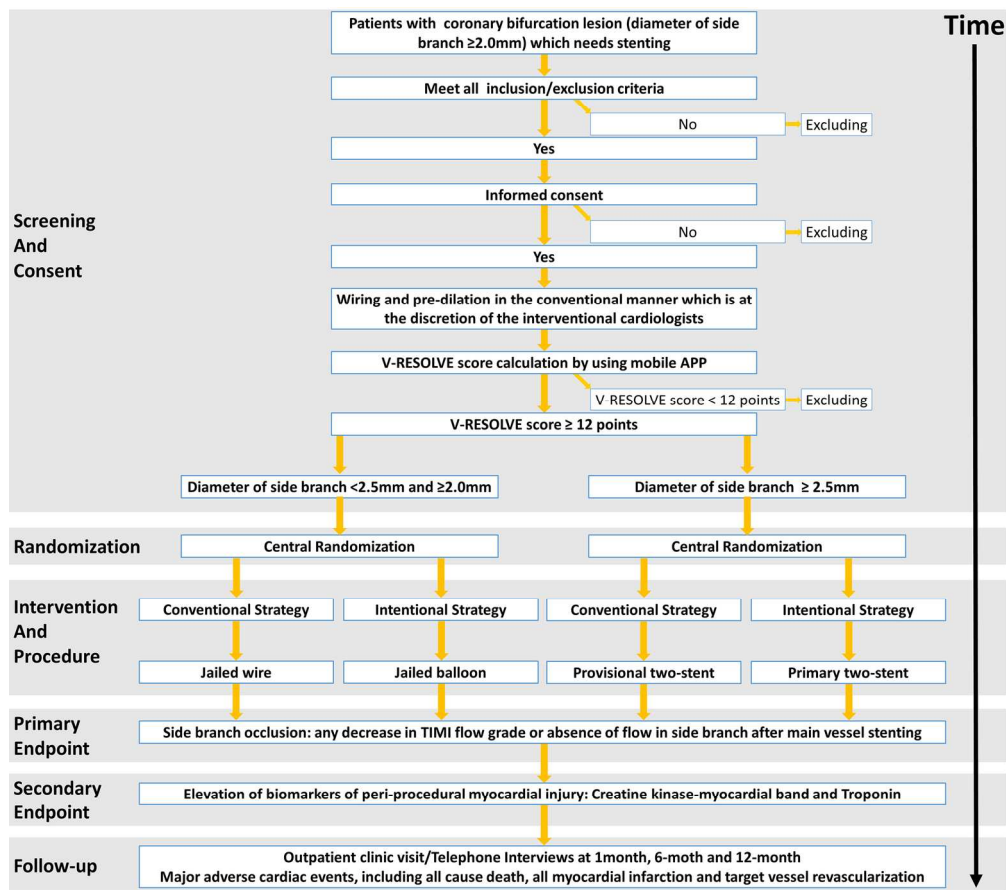


Figure 1. Study flowchart: screening, consent, randomization, intervention, procedure, study endpoint and follow-up.

179x159mm (300 x 300 DPI)

only

## Supplementary File

## List of Hospitals in the CIT-RESOLVE Trial

Hospital	Province/Municipality	City
Fuwai Hospital	Beijing	Beijing
Peking Union Medical College Hospital	Beijing	Beijing
Peking University Third Hospital	Beijing	Beijing
Beijing Xuanwu Hospital	Beijing	Beijing
Chinese PLA General Hospital	Beijing	Beijing
Beijing Anzhen Hospital	Beijing	Beijing
Shanghai Tongji Hospital	Shanghai	Shanghai
Shanghai Dongfang Hospital	Shanghai	Shanghai
Renji Hospital, Shanghai Jiaotong University of Medicine	Shanghai	Shanghai
Shanghai Chest Hospital	Shanghai	Shanghai
Guangdong General Hospital	Guangdong	Guangzhou
The First Affiliated Hospital of Xi'an Jiaotong University	Shanxi	Xi'an
Xijing Hospital	Shanxi	Xi'an
Daqing Oilfield General Hospital	Heilongjiang	Daqing
The First Affiliated Hospital of Haerbin Medical University	Heilongjiang	Haerbin
The Second Hospital of Jilin University	Jilin	Changchun

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4	The First Affiliated Hospital of Dalian		
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6	Medical University		
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9	Shengjing Hospital of China Medical		
10		Liaoning	Shenyang
11	University		
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14	The First Affiliated Hospital of Guangxi		
15		Guangxi	Nanning
16	Medical University		
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18	Hunan Provincial People's Hospital	Hunan	Changsha
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23	Cangzhou Central Hospital	Hebei	Cangzhou
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description
<b>Administrative information</b>		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym ( <b>Title page</b> )
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry ( <b>Title page</b> )
Protocol version	3	Date and version identifier ( <b>Title page</b> )
Funding	4	Sources and types of financial, material, and other support ( <b>Page 24-25</b> )
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors ( <b>Page 23-24</b> )
	5b	Name and contact information for the trial sponsor ( <b>Page 24-25</b> )
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities ( <b>Page 24-25</b> )
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) ( <b>Page 24-25</b> )
<b>Introduction</b>		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention ( <b>Page 5-6</b> )
	6b	Explanation for choice of comparators ( <b>Page 5-6</b> )
Objectives	7	Specific objectives or hypotheses ( <b>Page 6</b> )

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Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (**Page 6-7**)

### **Methods: Participants, interventions, and outcomes**

Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained (**Supplementary File**)

Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) (**Page 9-12**)

Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (**Page 13-16**)

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) (**Page 13-16**)

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (**Page 13-16**)

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial (**Page 13-16**)

Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (**Page 16**)

Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (**Page 18 & Figure 1**)

Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (**Page 19**)

Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size (**Page 13**)

### **Methods: Assignment of interventions (for controlled trials)**

Allocation:

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2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions ( <b>Page 13</b> )
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9	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
10	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
11	mechanism		describing any steps to conceal the sequence until interventions are
12			assigned ( <b>Page 13</b> )
13			
14	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
15			and who will assign participants to interventions ( <b>Page 13</b> )
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18	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
19	(masking)		participants, care providers, outcome assessors, data analysts), and
20			how ( <b>Page 7</b> )
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22		17b	If blinded, circumstances under which unblinding is permissible, and
23			procedure for revealing a participant's allocated intervention during
24			the trial ( <b>Page 7</b> )
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### Methods: Data collection, management, and analysis

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29	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
30	methods		trial data, including any related processes to promote data quality (eg,
31			duplicate measurements, training of assessors) and a description of
32			study instruments (eg, questionnaires, laboratory tests) along with
33			their reliability and validity, if known. Reference to where data
34			collection forms can be found, if not in the protocol ( <b>Page 16-17</b> )
35			
36		18b	Plans to promote participant retention and complete follow-up,
37			including list of any outcome data to be collected for participants who
38			discontinue or deviate from intervention protocols ( <b>Page 16-17</b> )
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41	Data	19	Plans for data entry, coding, security, and storage, including any
42	management		related processes to promote data quality (eg, double data entry;
43			range checks for data values). Reference to where details of data
44			management procedures can be found, if not in the protocol ( <b>Page</b>
45			<b>16-18</b> )
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48	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
49	methods		Reference to where other details of the statistical analysis plan can be
50			found, if not in the protocol ( <b>Page 19-20</b> )
51			
52		20b	Methods for any additional analyses (eg, subgroup and adjusted
53			analyses) ( <b>Page 19-20</b> )
54			
55		20c	Definition of analysis population relating to protocol non-adherence
56			(eg, as randomised analysis), and any statistical methods to handle
57			missing data (eg, multiple imputation) ( <b>Page 19-20</b> )
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**Methods: Monitoring**

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| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed ( <b>Page 7</b> ) |
|                 | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial ( <b>Page 19-20</b> )   |
| Harms           | 22  | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct ( <b>Page 19-20</b> )   |
| Auditing        | 23  | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor ( <b>Page 7</b> )   |

**Ethics and dissemination**

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| Research ethics approval      | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval ( <b>Page 7</b> )  |
| Protocol amendments           | 25  | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) ( <b>Page 7</b> ) |
| Consent or assent             | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) ( <b>Page 7</b> )   |
|                               | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable ( <b>Page 7</b> )  |
| Confidentiality               | 27  | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial ( <b>Page 7</b> )   |
| Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site ( <b>Page 24</b> )   |
| Access to data                | 29  | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators ( <b>Page 25</b> )   |
| Ancillary and post-trial care | 30  | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation  |

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| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions <b>(Page 25)</b> |
|                      | 31b | Authorship eligibility guidelines and any intended use of professional writers <b>(Page 24-25)</b>   |
|                      | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code <b>(Page 25)</b>   |
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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.