BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016044
Article Type:	Protocol
Date Submitted by the Author:	25-Jan-2017

Complete List of Authors:	Zhang, Dong; State Key Laboratory of Cardiovascular Disease, Department of Cardiology, Cardiovascular Institute, Fuwai Hospital and National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College Yin, Dong; State Key Laboratory of Cardiovascular Disease, Department of Cardiology, Cardiovascular Institute, Fuwai Hospital and National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College Song, Chenxi; State Key Laboratory of Cardiovascular Disease, Department of Cardiology, Cardiovascular Institute, Fuwai Hospital and National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College Zhu, Chengang; State Key Laboratory of Cardiovascular Disease, Department of Cardiology, Cardiovascular Institute, Fuwai Hospital and National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College Kirtane, Ajay; Columbia University Medical Center / New York Presbyterian Hospital Xu, Bo; State Key Laboratory of Cardiovascular Disease, Department of Cardiology, Cardiovascular Institute, Fuwai Hospital and National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College Dou, Kefei; State Key Laboratory of Cardiovascular Disease, Department of Cardiology, Cardiovascular Institute, Fuwai Hospital and National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	coronary bifurcation intervention, side branch occlusion, randomized comparison, conventional strategy, intentional strategy

A Randomized Comparison of **C**onventional Versus **I**ntentional Stra**T**egy in Patients with High **R**isk Pr**E**diction of **S**ide Branch **O**cc**L**usion in Coronary Bifurcation Inter**VE**ntion: Rationale and Design of the **CIT-RESOLVE** trial

Dong Zhang*, MD; Dong Yin*, MD; Chenxi Song*, MD; Chengang Zhu*, MD; Ajay J. Kirtane†, MD, SM; Bo Xu*, MBBS; Kefei Dou*, MD

The first two authors (Dong Zhang and Dong Yin) contributed equally to this work.

From *State Key Laboratory of Cardiovascular Disease, Department of Cardiology, Cardiovascular Institute, Fuwai Hospital and National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, 100037, China.

From †Columbia University Medical Center / New York Presbyterian Hospital, New York, NY.

Corresponding Author:
Bo Xu, MBBS, FESC
Fuwai Hospital, National Center for Cardiovascular Diseases
A 167, Beilishi Road, Xicheng District, Beijing, 100037, China
Tel: +86-10-8832-2562
E-mail: bxu@citmd.com

Kefei Dou, MD, PhD, FSCAI
Fuwai Hospital, National Center for Cardiovascular Diseases
A 167, Beilishi Road, Xicheng District, Beijing, 100037, China
Tel: +86-10-8839-6590
E-mail: drdoukefei@126.com

Keywords: coronary bifurcation intervention; randomized comparison; conventional strategy; intentional strategy; side branch occlusion

Word Count: 3905 (excluding title page, abstract, references, figures and tables.); Tables: 2; Figures: 1

Keywords: coronary bifurcation intervention; side branch occlusion; randomized comparison; conventional strategy; intentional strategy

This study is registered on www.clinicaltrials.gov, and the registration number is NCT 02644434.

Protocol version identifier: 15.0
Protocol date: 18. September, 2016.

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 ≥ 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.

Ethics and dissemination: The protocol has been approved by all local Ethics Committee. Written informed consent would be acquired from all participants. The findings of the trial will be shared by the participant hospitals and disseminated through peer-reviewed journals.

Trial registration number: NCT02644434.

Strengths and limitations of this study

CIT-RESOLVE is the leading trial which intends to investigate if intentional strategy could decrease the rate of SB occlusion in patients with high-risk of SB occlusion.

This study enrolls high-risk patients by using an inclusion criteria of SB occlusion risk (V-RESOLVE score ⩾12 points).

This study would provide evidence for interventionalists in strategy selection when treating bifurcation with high risk of SB occlusion.

Not all bifurcation lesions are included in the present study, left main diseases are excluded.

Abbreviations list

CK-MB=**C**reatine **K**inase-**M**yocardial **B**and

ECG=Electrocardiography

ITT=**I**ntention-**T**o-**T**reat population

LAD=**L**eft **A**nterior **D**escending coronary artery

MACE=**M**ajor **A**dverse **C**ardiac **E**vents

MI=**M**yocardial **I**nfarction

MV=**M**ain **V**essel

PCI=**P**ercutaneous **C**oronary **I**ntervention

PP=**P**er-**P**rotocol population

QCA=**Q**uantitative **C**oronary **A**ngiography analysis

RVD= **R**eference **V**essel **D**iameter

SB=**S**ide **B**ranch

TIMI=**T**hrombolysis **I**n **M**yocardial **I**nfarction 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.

Previous randomized clinical trials performed randomization of all categories of bifurcation lesions by using computer-generated random sequence, totally ignored the individual lesion anatomical characteristics and the risk of SB occlusion. Now, we have developed an angiographic tool for risk prediction of SB occlusion, the V-RESOLVE score, which can help risk stratification of SB occlusion and could also be used as a tool to select high-risk patients in randomized study. The SB occlusion rate was significantly higher in the high-risk group (V-RESOLVE score ≥12, rate of SB occlusion: 16.7%) than the non-high-risk group (V-RESOLVE score <12, rate of SB occlusion: 4.3%) as assessed by the V-RESOVLE score[14].

Bifurcation lesions with high-risk of SB occlusion may need intentional interventional strategy, which is more aggressive in SB protection than conventional strategy and considered to be associated with lower SB occlusion rate. However, no randomized trials were performed to compare the rate of SB occlusion between intentional strategy and conventional strategy in high-risk patients.

Accordingly, the present study is designed to enroll patients with high-risk of SB occlusion (V-RESOLVE score ≥12), and investigate if intentional strategy is associated with significant reduction of SB occlusion rate compared to conventional strategy in patients with high-risk of SB occlusion.

Methods and analysis

Hypothesis to be test. We hypothesized that for patients at high risk of SB occlusion (V-RESOLVE score ≥12), intentional strategy (a more aggressive SB

protection strategy: elective two-stent strategy or jailed balloon technique) is associated with significant reduction of SB occlusion rate compared to conventional strategy (provisional two-stent strategy or jailed wire technique). Thus the hypothesis to be decided upon are as follows: H_0, for patients with high risk prediction of SB occlusion, there is no difference in the rate of side branch occlusion between intentional strategy group and the conventional strategy group, versus H_1, the rate of side branch occlusion in intentional strategy group would be significantly lower than that of conventional strategy group.

Study design. The CIT-RESOLVE is a prospective, randomized (1:1), single-blind, multicenter clinical trial comparing the rate of side branch occlusion between the conventional strategy group and the intentional strategy group in a consecutive cohort of high-risk coronary bifurcation patients. Although operators are not blinded, all individuals analyzing data are masked to treatment assignment. A total of 21 centers in China will enroll patients. This study is registered on www.clinicaltrials.gov, and the registration number is NCT 02644434. The study flowchart is shown in figure 1.

This trial is conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. The conduct of the trial has been approved by the Ethics Committee. Written informed consent would be acquired from all participants. Patient data in the Data Management System are protected by password and only available to users designated by the study with appropriate authorization levels. De-identified data will be used for data analysis.

Risk prediction of side branch occlusion. V-RESOLVE score would be used for risk prediction of SB occlusion. The RESOLVE (**R**isk pr**E**diction of **S**ide branch **O**cc**L**usion in coronary bifurcation inter**VE**ntion) score, which is developed on the basis of quantitative coronary angiography (QCA), is a validated angiographic scoring system to evaluate the risk of SB occlusion in bifurcation intervention[9]. The QCA-based RESOLVE score system contains six independent risk factors of SB occlusion: including two visual estimation predictors (plaque distribution and MV thrombolysis in myocardial infarction [TIMI] flow grade before stenting), and four QCA analysis predictors (pre-procedural diameter stenosis of bifurcation core, bifurcation angle, diameter ratio between MV/SB and diameter stenosis of SB before MV stenting).

Although QCA provides a more objective determination of the extent and severity of coronary artery disease, it may be more time-consuming and/or not immediately available in real-time. As a result, the inclusion of QCA data within the QCA-based RESOLVE score limits its ability to be used at the time of bifurcation intervention[15]. Therefore, we evaluated the ability of a visually estimated RESOLVE (V-RESOLVE) score to predict the risk of side branch occlusion during bifurcation intervention. We found that the V-RESOLVE score, an easy-to-use score system based on visual estimation, can help risk stratification of SB occlusion during coronary bifurcation intervention. The rate of SB occlusion was significantly higher in high-risk group (V-RESOLVE score ≥12, rate of SB occlusion: 16.7%) than that in non-high-risk group (V-RESOLVE score ≤11, rate of SB occlusion: 4.3%) ($p<0.01$). V-RESOLVE

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 ≥ 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 ≥ 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
Clinical Inclusion Criteria:	***Clinical Exclusion Criteria:***
1. Subject must be male or nonpregnant female ≥18 years of age and ≤75 years of age;	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 $P2Y_{12}$ inhibitors, or aspirin);
2. Subject has symptomatic coronary artery disease with objective evidence of ischemia or silent ischemia;	2. Planned surgery within 6 months after the
3. Subject is eligible for PCI;	
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; 5. Subject is willing to comply with all protocol-required follow-up evaluation.	index procedure; 3. Subject has one of the following (as assessed prior to the index procedure): • Other serious medical illness (e.g., cancer, congestive heart failure) with estimated life expectancy of less than 12 months； • Current problems with substance abuse (e.g., alcohol, cocaine, heroin, etc.); • Planned procedure that may cause non-compliance with the protocol or confound data interpretation; 4. Subject has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions; 5. Subject is participating in another investigational drug or device clinical trial that has not reached its primary endpoint; 6. Subject intends to participate in another investigational drug or device clinical trial within 12 months after the index procedure; 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 method of contraception from the time of screening through 12 months after the index procedure); 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); 9. Subject with left ventricular ejection fraction < 35%; 10. Subject has preoperative renal dysfunction: serum creatinine>2.0mg/dl (176.82umol/L).
Angiographic Inclusion Criteria: 1. Subjects have coronary bifurcation lesions requiring PCI with stent implantation according to clinical guidelines and/or the operator's judgement; 2. Visually estimated reference vessel diameter (RVD) of target main vessel ≥2.5 mm and ≤4.0 mm; 3. Visually estimated RVD of target side branch ≥ 2.0mm;	***Angiographic Exclusion Criteria:*** 1. Left main lesions; 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>2.5mm]) which is proximal to occluded LAD segment should be excluded.

4. Coronary anatomy is likely to allow delivery of a study device to the target lesion(s); 5. V-RESOLVE score ≥ 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 ≥ 800. Operators with a minimum annual volume of 200 cases are allowed to participate in the PCI procedure.

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 substantial or grater (Fleiss Kappa > 0.80) after training. Once the investigators are

not sure that the V-RESOLVE score ≥ 12 points or not, we recommend them to send the cineangiograms by internet to the angiographic core laboratory in Fuwai Hospital, where cineangiograms would be assessed by two experienced technicians together and the V-RESOLVE score was generated by consensus.

Patient enrollment and randomization. Subjects must be ≥18 years and ≤75 years of age at the time of enrollment in the study. Coronary angiography would be performed to confirm that angiographic inclusion criteria are met. Then, wiring and pre-dilation would be performed at the discretion of the interventional cardiologists in the conventional manner. A mobile APP specialized for V-RESOLVE calculation will be used to calculate the V-RESOLVE score after pre-dilation. Bifurcation lesions with V-RESOLVE score ≥12 points will be enrolled. Patients that meet all the inclusion criteria and had no exclusion criteria would be included in this study. Patient enrollment has been started on 1st, December, 2016 and anticipated to be completed before December, 2017.

Patient randomization will be performed centrally by internet after signing an informed consent form. The randomization will be stratified by the diameter of side branch (diameter of side branch<2.5mm and ≥2.0mm vs. diameter of side branch≥2.5mm), with a randomization ratio of 1:1 to either conventional strategy group or intentional strategy group.

Intervention and procedure. PCI is undertaken via the access site of operators' choice. Coronary angioplasty is performed in the conventional manner and coronary 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 (creatine 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 ≥2.0mm) or provisional two-stent strategy (diameter of side branch≥2.5mm).

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.

Intentional strategy group. Patients randomized to the intentional strategy group

would undergo either jailed balloon technique (diameter of side branch<2.5mm and ≥2.0mm) or elective two-stent strategy (diameter of side branch≥2.5mm).

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.

No matter there is SB compromise or not, final kissing balloon technique could be performed at the discretion of the interventional cardiologists.

Elective two-stent strategy. Patients in this subgroup would undergo crush procedure (e.g. Crush, Balloon Crush or DK-Crush)[16-18] or any other elective

two-stent strategy like Culotte and T stent[19, 20], which stenting SB before MV stenting. These techniques were detailed in previous studies.[16-20]

For both the conventional and intentional strategy groups, proximal or distal dissections could be treated with further stenting at any stage. Post-dilations could be performed to optimize stent expansion. In all cases, an additional vessel with other lesions could be treated if required.

Primary and secondary endpoint(s). The primary endpoint is side branch occlusion, which is defined as any decrease in TIMI flow grade or absence of flow in side branch after main vessel stent well opposed.

The secondary endpoints are: 1) the elevation of biomarkers of peri-procedural myocardial injury (CK-MB and Troponin); Peri-procedural MI is defined as biomarkers elevation ≥10 × upper reference limit (URL) for CK-MB and/or ≥70 × URL for troponin[21]; 2) 12-month major adverse cardiac events (MACE, including all cause death, all MI and target vessel revascularization).

Follow-up. Subjects had either a telephone call or clinic visit at 30 days (±7 days), 3 months (±14 days), 6 months (±14 days), 12 months (±30 days) by the enrolling site for outcome evaluation. For all patients, MACE at 12-month will be reported. MACE will be defined as a composite of all cause death, all MI (defined by the Third Universal Definition[22]), and target vessel revascularization (defined by the Academic Research Consortium [ARC][23]).

Data collection. Profession trained staffs who are independent of patient treatment will be responsible for data collection and entering. The data collected for

each new CIT-RESOLVE patient include baseline information; sociodemographic characteristics; symptoms and signs of the presenting coronary disease; medical history, biomarker findings (CK-MB and Troponin activity will be determined by using an immunoinhibition assay and confirmed by mass spectrometry), electrocardiographic, and treatments administered prior to admission during hospitalization. Final diagnosis, major in-hospital clinical events (death, peri-procedural MI, major bleeding, stroke), and discharge status will also be recorded.

Baseline and procedural coronary angiography will be reviewed and analyzed by physicians and interventionalists to calculate the V-RESOLVE score. Coronary angiography findings, including bifurcation location, baseline and post MV stenting 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 (±7 days)	3 months[7] (±14 days)	6 months (±14 days)	12 months (±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	•[1]		•[2]				
Cardiac enzymes (CK-MB, Troponin)	•[3]		•[4]				
Serious Adverse Events[5]		•	•	•	•	•	•
V-RESOLVE score calculation		•					

Notes:

[1] Electrocardiography (ECG) at time of screening should be performed within 72 hours prior to PCI procedure.

[2] ECG within 24 hours post-procedure or at discharge, whichever comes first.

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

[4] 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.

[5] 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 ≥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

the written informed consent and are randomized, regardless which strategy was selected. The primary analysis is a superiority ITT analysis of the primary clinical endpoint. Normal approximation test for the difference between two proportions (pooled proportion) or Fisher's exact test (if applicable) will be used to test the two-sided hypothesis of superiority in proportions. If the P value from the two-sided test is <0.05, the intentional strategy (test) will be concluded to be superior to conventional strategy. If required, an additional analysis of the Per-Protocol (PP) population will be conducted of the primary and secondary endpoints.

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

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 ≥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 anatomical characteristics and risk factors of SB occlusion. Thus, a substantial part of bifurcation lesions may not undergo proper intervention strategy though some patients have crossed over to another group. This may be the major reason why the results of previous studies remain controversial.

Previous studies enrolled patients by using the inclusion criteria of either unselected bifurcation lesions, specific Medina classifications or true bifurcation lesions. However, neither “Medina classification” nor “true bifurcation lesion” could

predict the risk of SB occlusion accurately[34, 35]. The SB occlusion risk is not considered as an important criterion when enrolling patients. CIT-RESOLVE is the first trial which only enrolls high-risk patients by using a risk prediction tool (V-RESOLVE score ≥12 points).

Numerous classifications and definitions of coronary bifurcation lesions have been proposed to simplify the hard topic of bifurcation lesion in interventional cardiology[36-45]. Among them, "Medina classification" as well as "true bifurcation lesion" are straightforward and widely used. However, none of these classifications or definitions could accurately predict the risk of SB occlusion[35]. One of our previous researches has shown that "true bifurcation lesion" could not be regarded as an independent predictor of SB occlusion[34]. RESOLVE score and V-RESOLVE score is the first attempt to stratify the risk of SB occlusion during coronary bifurcation intervention. V-RESOLVE score, which contains 6 independent predictors of SB occlusion, is a validated score system to evaluate the risk of side branch occlusion[14] and a useful tool for risk prediction of SB occlusion in the present study. V-RESOLVE score ≥12 points is considered as high risk in SB occlusion, which may trigger interventional SB protection, and set as one of the inclusion criteria of CIT-RESOLVE trial.

The intentional strategy is more aggressive in SB protection: jailed wire may help SB reopen; stenting the SB before MV stenting may avoid SB occlusion. Thus, the intentional strategy is thought as a more suitable strategy for high-risk bifurcation lesion. CIT-RESOLVE is the leading trial which intends to investigate if intentional

strategy could decrease the rate of SB occlusion in patients with high-risk of SB occlusion. Comparing the rate of SB occlusion between intentional and conventional strategy would provide evidence for interventionalists in strategy selection when treating bifurcation with high risk of SB occlusion. 12-month follow-up would investigate if SB occlusion could impact the clinical outcome directly.

The limitation of the trial design is that not all high-risk bifurcation lesions are included in the present study. When treating left main diseases, left anterior descending artery or left circumflex artery occlusion may lead to serious outcome, thus, left main diseases are excluded in the consideration of ethic. Also, in case of acute MI of which the culprit vessel located at the LAD, the bifurcation lesion (LAD/diagonal branch [RVD>2.5mm]) which is proximal to occluded LAD segment is excluded.

Conclusion

The CIT-RESOLVE study is the first large randomized trial which enrolls only high-risk patients by using an inclusion criteria of SB occlusion risk (V-RESOLVE score ≥12 points), and it has sufficient power to assess the effect of intentional strategy in decreasing the SB occlusion rate in patients at high risk of SB occlusion.

CIT-RESOLVE Study Group

Principal investigator: Kefei Dou (Fuwai Hospital and National Center for Cardiovascular Diseases).

Co-principal investigator: Bo Xu (Fuwai Hospital and National Center for Cardiovascular Diseases).

Coordinating center: Fuwai Hospital and National Center for Cardiovascular Diseases, Beijing, China.

Advisory Chairmen: Yuejin Yang (Fuwai Hospital and National Center for Cardiovascular Diseases), Shaoliang Chen (Nanjing First Hospital and Nanjing Medical University) and Ajay J. Kirtane (Columbia University Medical Center and New York Presbyterian Hospital).

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.

Funding

The CIT-RESOLVE trial is physician-initiated and supported by Investigator

Sponsored Studies (Abbott Cardiovascular, Study No.: COR-10498) and Peking Union Medical College Youth Fund and Fundamental Research Funds for the Central Universities (Grant number: 3332016130). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

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 purpose or research cooperation will be provided.

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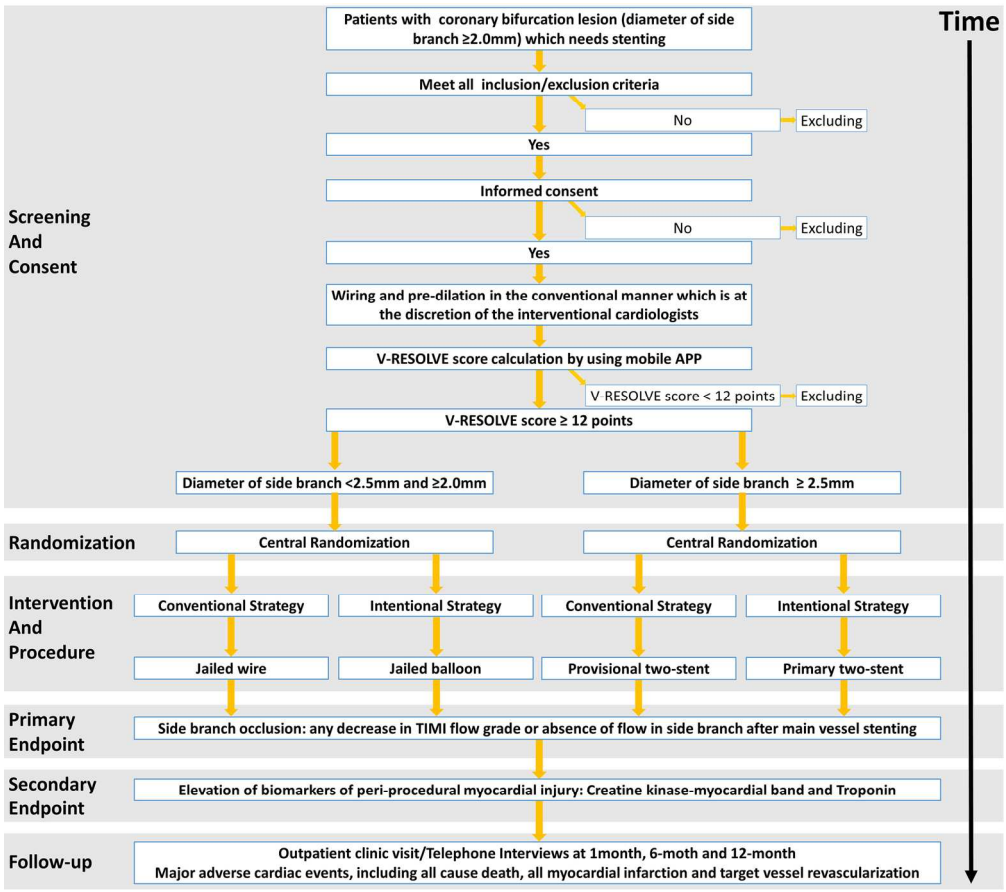

Figure 1. Study flowchart

179x159mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **(Title page)**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **(Title page)**
Protocol version	3	Date and version identifier **(Title page)**
Funding	4	Sources and types of financial, material, and other support **(Page 24-25)**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **(Page 23-24)**
	5b	Name and contact information for the trial sponsor **(Page 24-25)**
	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 **(Page 24-25)**
	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) **(Page 24-25)**
Introduction		
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 **(Page 5-6)**
	6b	Explanation for choice of comparators **(Page 5-6)**
Objectives	7	Specific objectives or hypotheses **(Page 6)**

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:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **(Page 13)**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **(Page 13)**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **(Page 13)**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **(Page 7)**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **(Page 7)**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **(Page 16-17)**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols (**Page 16-17)**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol (**Page 16-18)**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol (**Page 19-20)**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **(Page 19-20)**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **(Page 19-20)**

Methods: Monitoring

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 (**Page 7)**
	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 (**Page 19-20)**
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 (**Page 19-20)**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **(Page 7)**

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **(Page 7)**
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) **(Page 7)**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **(Page 7)**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **(Page 7)**
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 **(Page 7)**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **(Page 24)**
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 **(Page 25)**
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

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 **(Page 25)**
	31b	Authorship eligibility guidelines and any intended use of professional writers **(Page 24-25)**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **(Page 25)**

*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

The First Affiliated Hospital of Dalian Medical University	Liaoning	Dalian
Shengjing Hospital of China Medical University	Liaoning	Shenyang
The First Affiliated Hospital of Guangxi Medical University	Guangxi	Nanning
Hunan Provincial People's Hospital	Hunan	Changsha
Cangzhou Central Hospital	Hebei	Cangzhou

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:	*BMJ Open*
Manuscript ID	bmjopen-2017-016044.R1
Article Type:	Protocol
Date Submitted by the Author:	28-Mar-2017

Complete List of Authors:	Zhang, Dong; State Key Laboratory of Cardiovascular Disease, Department of Cardiology, Cardiovascular Institute, Fuwai Hospital and National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College Yin, Dong; State Key Laboratory of Cardiovascular Disease, Department of Cardiology, Cardiovascular Institute, Fuwai Hospital and National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College Song, Chenxi; State Key Laboratory of Cardiovascular Disease, Department of Cardiology, Cardiovascular Institute, Fuwai Hospital and National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College Zhu, Chengang; State Key Laboratory of Cardiovascular Disease, Department of Cardiology, Cardiovascular Institute, Fuwai Hospital and National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College Kirtane, Ajay; Columbia University Medical Center / New York Presbyterian Hospital Xu, Bo; State Key Laboratory of Cardiovascular Disease, Department of Cardiology, Cardiovascular Institute, Fuwai Hospital and National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College Dou, Kefei; State Key Laboratory of Cardiovascular Disease, Department of Cardiology, Cardiovascular Institute, Fuwai Hospital and National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	coronary bifurcation intervention, side branch occlusion, randomized comparison, conventional strategy, intentional strategy

A Randomized Comparison of **C**onventional Versus **I**ntentional Stra**T**egy in Patients with High **R**isk Pr**E**diction of **S**ide Branch **O**cc**L**usion in Coronary Bifurcation Inter**VE**ntion: Rationale and Design of the **CIT-RESOLVE** trial

Dong Zhang*, MD; Dong Yin*, MD; Chenxi Song*, MD; Chengang Zhu*, MD; Ajay J. Kirtane†, MD, SM; Bo Xu*, MBBS; Kefei Dou*, MD

The first two authors (Dong Zhang and Dong Yin) contributed equally to this work.

From *State Key Laboratory of Cardiovascular Disease, Department of Cardiology, Cardiovascular Institute, Fuwai Hospital and National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, 100037, China.

From †Columbia University Medical Center / New York Presbyterian Hospital, New York, NY.

Corresponding Author:
Bo Xu, MBBS, FESC
Fuwai Hospital, National Center for Cardiovascular Diseases
A 167, Beilishi Road, Xicheng District, Beijing, 100037, China
Tel: +86-10-8832-2562
E-mail: bxu@citmd.com

Kefei Dou, MD, PhD, FSCAI
Fuwai Hospital, National Center for Cardiovascular Diseases
A 167, Beilishi Road, Xicheng District, Beijing, 100037, China
Tel: +86-10-8839-6590
E-mail: drdoukefei@126.com

Keywords: coronary bifurcation intervention; randomized comparison; conventional strategy; intentional strategy; side branch occlusion

Word Count: 4102 (excluding title page, abstract, references, figures and tables.); Tables: 2; Figures: 1

Keywords: coronary bifurcation intervention; side branch occlusion; randomized comparison; conventional strategy; intentional strategy

This study is registered on www.clinicaltrials.gov, and the registration number is NCT 02644434.

Protocol version identifier: 15.0
Protocol date: 18. September, 2016.

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 ≥ 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.

Ethics and dissemination: The protocol has been approved by all local Ethics Committee. Written informed consent would be acquired from all participants. The findings of the trial will be shared by the participant hospitals and disseminated through peer-reviewed journals.

Trial registration number: NCT02644434.

Strengths and limitations of this study

CIT-RESOLVE is the leading trial which intends to investigate if intentional strategy could decrease the rate of SB occlusion in patients with high-risk of SB occlusion.

This study enrolls high-risk patients by using an inclusion criteria of SB occlusion risk (V-RESOLVE score ⩾12 points).

This study would provide evidence for interventionalists in strategy selection when treating bifurcation with high risk of SB occlusion.

Not all bifurcation lesions are included in the present study, left main diseases are excluded.

Abbreviations list

CK-MB=**C**reatine **K**inase-**M**yocardial **B**and

ECG=Electrocardiography

ITT=**I**ntention-**T**o-**T**reat population

LAD=**L**eft **A**nterior **D**escending coronary artery

MACE=**M**ajor **A**dverse **C**ardiac **E**vents

MI=**M**yocardial **I**nfarction

MV=**M**ain **V**essel

PCI=**P**ercutaneous **C**oronary **I**ntervention

PP=**P**er-**P**rotocol population

QCA=**Q**uantitative **C**oronary **A**ngiography analysis

RVD= **R**eference **V**essel **D**iameter

SB=**S**ide **B**ranch

TIMI=**T**hrombolysis **I**n **M**yocardial **I**nfarction 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.

Previous randomized clinical trials performed randomization of all categories of bifurcation lesions by using computer-generated random sequence, totally ignored the individual lesion anatomical characteristics and the risk of SB occlusion. Now, we have developed an angiographic tool for risk prediction of SB occlusion, the V-RESOLVE score, which can help risk stratification of SB occlusion and could also be used as a tool to select high-risk patients in randomized study. The SB occlusion rate was significantly higher in the high-risk group (V-RESOLVE score ≥12, rate of SB occlusion: 16.7%) than the non-high-risk group (V-RESOLVE score <12, rate of SB occlusion: 4.3%) as assessed by the V-RESOVLE score[14].

Bifurcation lesions with high-risk of SB occlusion may need intentional interventional strategy, which is more aggressive in SB protection than conventional strategy and considered to be associated with lower SB occlusion rate. However, no randomized trials were performed to compare the rate of SB occlusion between intentional strategy and conventional strategy in high-risk patients.

Accordingly, the present study is designed to enroll patients with high-risk of SB occlusion (V-RESOLVE score ≥12), and investigate if intentional strategy is associated with significant reduction of SB occlusion rate compared to conventional strategy in patients with high-risk of SB occlusion.

Methods and analysis

Hypothesis to be test. We hypothesized that for patients at high risk of SB occlusion (V-RESOLVE score ≥12), intentional strategy (a more aggressive SB

protection strategy: elective two-stent strategy or jailed balloon technique) is associated with significant reduction of SB occlusion rate compared to conventional strategy (provisional two-stent strategy or jailed wire technique). Thus the hypothesis to be decided upon are as follows: H_0, for patients with high risk prediction of SB occlusion, there is no difference in the rate of side branch occlusion between intentional strategy group and the conventional strategy group, versus H_1, the rate of side branch occlusion in intentional strategy group would be significantly lower than that of conventional strategy group.

Study design. The CIT-RESOLVE is a prospective, randomized (1:1), single-blind, multicenter clinical trial comparing the rate of side branch occlusion between the conventional strategy group and the intentional strategy group in a consecutive cohort of high-risk coronary bifurcation patients. Although operators are not blinded, all individuals analyzing data are masked to treatment assignment. A total of 21 centers in China will enroll patients. This study is registered on www.clinicaltrials.gov, and the registration number is NCT 02644434. The study flowchart is shown in figure 1 and its legend.

This trial is conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. The conduct of the trial has been approved by the Ethics Committee. Written informed consent would be acquired from all participants. Patient data in the Data Management System are protected by password and only available to users designated by the study with appropriate authorization levels. De-identified data will be used for data analysis.

Risk prediction of side branch occlusion. V-RESOLVE score would be used for risk prediction of SB occlusion. The RESOLVE (**R**isk pr**E**diction of **S**ide branch **O**cc**L**usion in coronary bifurcation inter**VE**ntion) score, which is developed on the basis of quantitative coronary angiography (QCA), is a validated angiographic scoring system to evaluate the risk of SB occlusion in bifurcation intervention[9]. The QCA-based RESOLVE score system contains six independent risk factors of SB occlusion: including two visual estimation predictors (plaque distribution and MV thrombolysis in myocardial infarction [TIMI] flow grade before stenting), and four QCA analysis predictors (pre-procedural diameter stenosis of bifurcation core, bifurcation angle, diameter ratio between MV/SB and diameter stenosis of SB before MV stenting).

Although QCA provides a more objective determination of the extent and severity of coronary artery disease, it may be more time-consuming and/or not immediately available in real-time. As a result, the inclusion of QCA data within the QCA-based RESOLVE score limits its ability to be used at the time of bifurcation intervention[15]. Therefore, we evaluated the ability of a visually estimated RESOLVE (V-RESOLVE) score to predict the risk of side branch occlusion during bifurcation intervention. We found that the V-RESOLVE score, an easy-to-use score system based on visual estimation, can help risk stratification of SB occlusion during coronary bifurcation intervention. The rate of SB occlusion was significantly higher in high-risk group (V-RESOLVE score ≥12, rate of SB occlusion: 16.7%) than that in non-high-risk group (V-RESOLVE score ≤11, rate of SB occlusion: 4.3%) ($p<0.01$). V-RESOLVE

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 ≥ 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 ≥ 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
Clinical Inclusion Criteria:	***Clinical Exclusion Criteria:***
1. Subject must be male or nonpregnant female ≥18 years of age and ≤75 years of age;	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 $P2Y_{12}$ inhibitors, or aspirin);
2. Subject has symptomatic coronary artery disease with objective evidence of ischemia or silent ischemia;	2. Planned surgery within 6 months after the
3. Subject is eligible for PCI;	
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; 5. Subject is willing to comply with all protocol-required follow-up evaluation.	index procedure; 3. Subject has one of the following (as assessed prior to the index procedure): • Other serious medical illness (e.g., cancer, congestive heart failure) with estimated life expectancy of less than 12 months； • Current problems with substance abuse (e.g., alcohol, cocaine, heroin, etc.); • Planned procedure that may cause non-compliance with the protocol or confound data interpretation; 4. Subject has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions; 5. Subject is participating in another investigational drug or device clinical trial that has not reached its primary endpoint; 6. Subject intends to participate in another investigational drug or device clinical trial within 12 months after the index procedure; 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 method of contraception from the time of screening through 12 months after the index procedure); 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); 9. Subject with left ventricular ejection fraction < 35%; 10. Subject has preoperative renal dysfunction: serum creatinine>2.0mg/dl (176.82umol/L).
Angiographic Inclusion Criteria: 1. Subjects have coronary bifurcation lesions requiring PCI with stent implantation according to clinical guidelines and/or the operator's judgement; 2. Visually estimated reference vessel diameter (RVD) of target main vessel ≥2.5 mm and ≤4.0 mm; 3. Visually estimated RVD of target side branch ≥ 2.0mm;	***Angiographic Exclusion Criteria:*** 1. Left main lesions; 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>2.5mm]) which is proximal to occluded LAD segment should be excluded.

4. Coronary anatomy is likely to allow delivery of a study device to the target lesion(s); 5. V-RESOLVE score ≥ 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 ≥ 800. Operators with a minimum annual volume of 200 cases are allowed to participate in the PCI procedure.

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 substantial or greater (Fleiss Kappa >0.60) after training. Once the investigators are

not sure that the V-RESOLVE score ≥ 12 points or not, we recommend them to send the cineangiograms by internet to the angiographic core laboratory in Fuwai Hospital, where cineangiograms would be assessed by two experienced technicians together and the V-RESOLVE score was generated by consensus.

Patient enrollment and randomization. Subjects must be ≥18 years and ≤75 years of age at the time of enrollment in the study. Coronary angiography would be performed to confirm that angiographic inclusion criteria are met. Then, wiring and pre-dilation would be performed at the discretion of the interventional cardiologists in the conventional manner. A mobile APP specialized for V-RESOLVE calculation will be used to calculate the V-RESOLVE score after pre-dilation. Bifurcation lesions with V-RESOLVE score ≥12 points will be enrolled. Patients that meet all the inclusion criteria and had no exclusion criteria would be included in this study. Patient enrollment has been started on 1st, December, 2016 and anticipated to be completed before December, 2017.

Patient randomization will be performed centrally by internet after signing an informed consent form. The randomization will be stratified by the diameter of side branch (diameter of side branch<2.5mm and ≥2.0mm vs. diameter of side branch≥2.5mm), with a randomization ratio of 1:1 to either conventional strategy group or intentional strategy group.

Intervention and procedure. PCI is undertaken via the access site of operators' choice. Coronary angioplasty is performed in the conventional manner and coronary 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 (creatine 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 ≥2.0mm) or provisional two-stent strategy (diameter of side branch≥2.5mm).

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.

Intentional strategy group. In the present trial, we would enroll high-risk SB

with diameter ≥2.0mm, which would critically impact the prognosis. However, elective two-stent strategy is not appropriate for all SB with diameter ≥2.0mm. Thus, we use two aggressive strategies in intentional strategy group: jailed balloon technique (for SB with diameter <2.5mm and ≥2.0mm) or elective two-stent strategy (for SB with diameter ≥2.5mm).

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.

No matter there is SB compromise or not, final kissing balloon technique could

be performed at the discretion of the interventional cardiologists.

Elective two-stent strategy. Patients in this subgroup would undergo crush procedure (e.g. Crush, Balloon Crush or DK-Crush)[16-18] or any other elective two-stent strategy like Culotte and T stent[19, 20], which stenting SB before MV stenting. These techniques were detailed in previous studies.[16-20]

For both the conventional and intentional strategy groups, proximal or distal dissections could be treated with further stenting at any stage. Post-dilations could be performed to optimize stent expansion. In all cases, an additional vessel with other lesions could be treated if required.

Primary and secondary endpoint(s). The primary endpoint is side branch occlusion, which is defined as any decrease in TIMI flow grade or absence of flow in side branch after main vessel stent well opposed. For lesions underwent conventional strategy, TIMI flow grade is assessed immediately after the main vessel stent is deployed and post-dilation (if post-dilation is performed), then, the SB could be further treated if required. For lesions underwent jailed balloon technique, TIMI flow grade is assessed after POT is performed. For lesions underwent elective two-stent strategy, TIMI flow grade is assessed immediately after the main vessel stent is deployed and post-dilation (if post-dilation is performed), then rewiring the SB or final kissing balloon is performed if required.

The secondary endpoints are: 1) the elevation of biomarkers of peri-procedural myocardial injury (CK-MB and Troponin); Peri-procedural MI is defined as biomarkers elevation ≥10 × upper reference limit (URL) for CK-MB and/or ≥70 ×

URL for troponin[21]; 2) 12-month major adverse cardiac events (MACE, including all cause death, all MI and target vessel revascularization).

Follow-up. Subjects had either a telephone call or clinic visit at 30 days (±7 days), 3 months (±14 days), 6 months (±14 days), 12 months (±30 days) by the enrolling site for outcome evaluation. For all patients, MACE at 12-month will be reported. MACE will be defined as a composite of all cause death, all MI (defined by the Third Universal Definition[22]), and target vessel revascularization (defined by the Academic Research Consortium [ARC][23]).

Data collection. Profession trained staffs who are independent of patient treatment will be responsible for data collection and entering. The data collected for each new CIT-RESOLVE patient include baseline information; sociodemographic characteristics; symptoms and signs of the presenting coronary disease; medical history, biomarker findings (CK-MB and Troponin activity will be determined by using an immunoinhibition assay and confirmed by mass spectrometry), electrocardiographic, and treatments administered prior to admission during hospitalization. Final diagnosis, major in-hospital clinical events (death, peri-procedural MI, major bleeding, stroke), and discharge status will also be recorded.

Baseline and procedural coronary angiography will be reviewed and analyzed by physicians and interventionalists to calculate the V-RESOLVE score. Coronary angiography findings, including bifurcation location, baseline and post MV stenting 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 (±7 days)	3 months[7] (±14 days)	6 months (±14 days)	12 months (±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	•[1]		•[2]				
Cardiac enzymes (CK-MB, Troponin)	•[3]		•[4]				
Serious Adverse Events[5]		•	•	•	•	•	•
V-RESOLVE score calculation		•					

Notes:

[1] Electrocardiography (ECG) at time of screening should be performed within 72 hours prior to PCI procedure.

[2] ECG within 24 hours post-procedure or at discharge, whichever comes first.

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

[4] 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.

[5] 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:

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

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 ≥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 the written informed consent and are randomized, regardless which strategy was selected. The primary analysis is a superiority ITT analysis of the primary clinical endpoint. Normal approximation test for the difference between two proportions (pooled proportion) or Fisher's exact test (if applicable) will be used to test the two-sided hypothesis of superiority in proportions. If the P value from the two-sided test is <0.05, the intentional strategy (test) will be concluded to be superior to conventional strategy. If required, an additional analysis of the Per-Protocol (PP) population will be conducted of the primary and secondary endpoints.

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

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 ≥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

anatomical characteristics and risk factors of SB occlusion. Thus, a substantial part of bifurcation lesions may not undergo proper intervention strategy though some patients have crossed over to another group. This may be the major reason why the results of previous studies remain controversial.

Previous studies enrolled patients by using the inclusion criteria of either unselected bifurcation lesions, specific Medina classifications or true bifurcation lesions. However, neither "Medina classification" nor "true bifurcation lesion" could predict the risk of SB occlusion accurately[34, 35]. The SB occlusion risk is not considered as an important criterion when enrolling patients. CIT-RESOLVE is the first trial which only enrolls high-risk patients by using a risk prediction tool (V-RESOLVE score ≥12 points).

Numerous classifications and definitions of coronary bifurcation lesions have been proposed to simplify the hard topic of bifurcation lesion in interventional cardiology[36-45]. Among them, "Medina classification" as well as "true bifurcation lesion" are straightforward and widely used. However, none of these classifications or definitions could accurately predict the risk of SB occlusion[35]. One of our previous researches has shown that "true bifurcation lesion" could not be regarded as an independent predictor of SB occlusion[34]. RESOLVE score and V-RESOLVE score is the first attempt to stratify the risk of SB occlusion during coronary bifurcation intervention. V-RESOLVE score, which contains 6 independent predictors of SB occlusion, is a validated score system to evaluate the risk of side branch occlusion[14] and a useful tool for risk prediction of SB occlusion in the present study. V-RESOLVE

score ≥12 points is considered as high risk in SB occlusion, which may trigger interventional SB protection, and set as one of the inclusion criteria of CIT-RESOLVE trial.

The intentional strategy is more aggressive in SB protection: jailed wire may help SB reopen; stenting the SB before MV stenting may avoid SB occlusion. Thus, the intentional strategy is thought as a more suitable strategy for high-risk bifurcation lesion. CIT-RESOLVE is the leading trial which intends to investigate if intentional strategy could decrease the rate of SB occlusion in patients with high-risk of SB occlusion. Comparing the rate of SB occlusion between intentional and conventional strategy would provide evidence for interventionalists in strategy selection when treating bifurcation with high risk of SB occlusion. 12-month follow-up would investigate if SB occlusion could impact the clinical outcome directly.

One limitation of the trial design is that not all high-risk bifurcation lesions are included in the present study. When treating left main diseases, left anterior descending artery or left circumflex artery occlusion may lead to serious outcome, thus, left main diseases are excluded in the consideration of ethic. Also, in case of acute MI of which the culprit vessel located at the LAD, the bifurcation lesion (LAD/diagonal branch [RVD>2.5mm]) which is proximal to occluded LAD segment is excluded. Another limitation is that jailed balloon technique, which has not been proven by randomized clinical trials and widely used in clinical practice, is used in the interventional group. Although jailed balloon technique has been reported to be associated with very low rate of SB occlusion[4], its effect in SB protection warrant

further studies. In future studies, we would compare the rate of SB occlusion between provisional two-stent strategy and elective two-stent strategy in patients at high risk of SB occlusion.

Conclusion

The CIT-RESOLVE study is the first large randomized trial which enrolls only high-risk patients by using an inclusion criteria of SB occlusion risk (V-RESOLVE score ≥12 points), and it has sufficient power to assess the effect of intentional strategy in decreasing the SB occlusion rate in patients at high risk of SB occlusion.

CIT-RESOLVE Study Group

Principal investigator: Kefei Dou (Fuwai Hospital and National Center for Cardiovascular Diseases).

Co-principal investigator: Bo Xu (Fuwai Hospital and National Center for Cardiovascular Diseases).

Coordinating center: Fuwai Hospital and National Center for Cardiovascular Diseases, Beijing, China.

Advisory Chairmen: Yuejin Yang (Fuwai Hospital and National Center for Cardiovascular Diseases), Shaoliang Chen (Nanjing First Hospital and Nanjing Medical University) and Ajay J. Kirtane (Columbia University Medical Center and New York Presbyterian Hospital).

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.

Funding

The CIT-RESOLVE trial is physician-initiated and supported by Investigator Sponsored Studies (Abbott Cardiovascular, Study No.: COR-10498) and Peking Union Medical College Youth Fund and Fundamental Research Funds for the Central Universities (Grant number: 3332016130). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

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

purpose or research cooperation will be provided.

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Figure legend

Figure 1. Study flowchart

Screening, randomization, intervention, procedure, study endpoint and follow-up of CIT-RESOLVE trial.

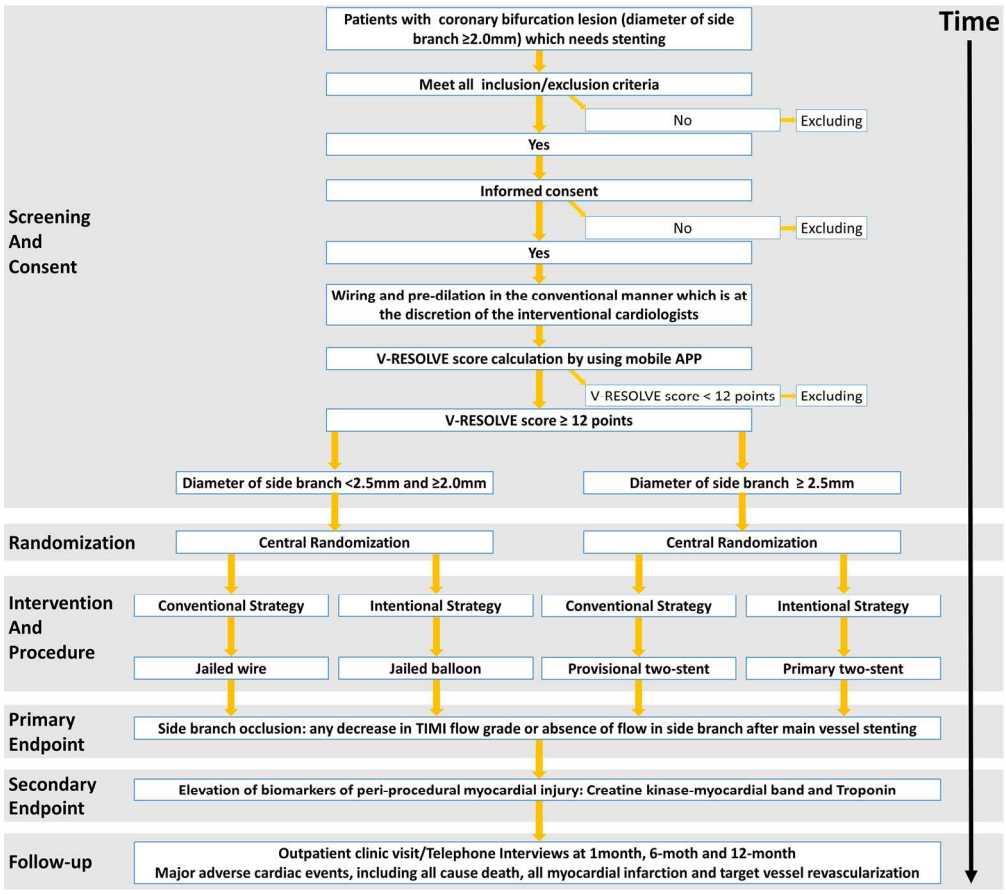

Figure 1. Study flowchart: screening, consent, randomization, intervention, procedure, study endpoint and follow-up.

179x159mm (300 x 300 DPI)

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

The First Affiliated Hospital of Dalian Medical University	Liaoning	Dalian
Shengjing Hospital of China Medical University	Liaoning	Shenyang
The First Affiliated Hospital of Guangxi Medical University	Guangxi	Nanning
Hunan Provincial People's Hospital	Hunan	Changsha
Cangzhou Central Hospital	Hebei	Cangzhou

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **(Title page)**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **(Title page)**
Protocol version	3	Date and version identifier **(Title page)**
Funding	4	Sources and types of financial, material, and other support **(Page 24-25)**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **(Page 23-24)**
	5b	Name and contact information for the trial sponsor **(Page 24-25)**
	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 **(Page 24-25)**
	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) **(Page 24-25)**
Introduction		
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 **(Page 5-6)**
	6b	Explanation for choice of comparators **(Page 5-6)**
Objectives	7	Specific objectives or hypotheses **(Page 6)**

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:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **(Page 13)**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **(Page 13)**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **(Page 13)**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **(Page 7)**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **(Page 7)**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **(Page 16-17)**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols (**Page 16-17)**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol (**Page 16-18)**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol (**Page 19-20)**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **(Page 19-20)**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **(Page 19-20)**

Methods: Monitoring

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 (**Page 7)**
	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 (**Page 19-20)**
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 (**Page 19-20)**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **(Page 7)**

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **(Page 7)**
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) **(Page 7)**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **(Page 7)**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **(Page 7)**
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 **(Page 7)**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **(Page 24)**
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 **(Page 25)**
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

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 **(Page 25)**
	31b	Authorship eligibility guidelines and any intended use of professional writers **(Page 24-25)**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **(Page 25)**

*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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016044.R2
Article Type:	Protocol
Date Submitted by the Author:	10-May-2017

Complete List of Authors:	Zhang, Dong; State Key Laboratory of Cardiovascular Disease, Department of Cardiology, Cardiovascular Institute, Fuwai Hospital and National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College Yin, Dong; State Key Laboratory of Cardiovascular Disease, Department of Cardiology, Cardiovascular Institute, Fuwai Hospital and National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College Song, Chenxi; State Key Laboratory of Cardiovascular Disease, Department of Cardiology, Cardiovascular Institute, Fuwai Hospital and National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College Zhu, Chengang; State Key Laboratory of Cardiovascular Disease, Department of Cardiology, Cardiovascular Institute, Fuwai Hospital and National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College Kirtane, Ajay; Columbia University Medical Center / New York Presbyterian Hospital Xu, Bo; State Key Laboratory of Cardiovascular Disease, Department of Cardiology, Cardiovascular Institute, Fuwai Hospital and National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College Dou, Kefei; State Key Laboratory of Cardiovascular Disease, Department of Cardiology, Cardiovascular Institute, Fuwai Hospital and National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	coronary bifurcation intervention, side branch occlusion, randomized comparison, conventional strategy, intentional strategy

A Randomized Comparison of **C**onventional Versus **I**ntentional Stra**T**egy in Patients with High **R**isk Pr**E**diction of **S**ide Branch **O**cc**L**usion in Coronary Bifurcation Inter**VE**ntion: Rationale and Design of the **CIT-RESOLVE** trial

Dong Zhang*, MD; Dong Yin*, MD; Chenxi Song*, MD; Chengang Zhu*, MD; Ajay J. Kirtane†, MD, SM; Bo Xu*, MBBS; Kefei Dou*, MD

The first two authors (Dong Zhang and Dong Yin) contributed equally to this work.

From *State Key Laboratory of Cardiovascular Disease, Department of Cardiology, Cardiovascular Institute, Fuwai Hospital and National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, 100037, China.

From †Columbia University Medical Center / New York Presbyterian Hospital, New York, NY.

Corresponding Author:
Bo Xu, MBBS, FESC
Fuwai Hospital, National Center for Cardiovascular Diseases
A 167, Beilishi Road, Xicheng District, Beijing, 100037, China
Tel: +86-10-8832-2562
E-mail: bxu@citmd.com

Kefei Dou, MD, PhD, FSCAI
Fuwai Hospital, National Center for Cardiovascular Diseases
A 167, Beilishi Road, Xicheng District, Beijing, 100037, China
Tel: +86-10-8839-6590
E-mail: drdoukefei@126.com

Keywords: coronary bifurcation intervention; randomized comparison; conventional strategy; intentional strategy; side branch occlusion

Word Count: 4121 (excluding title page, abstract, references, figures and tables.); Tables: 2; Figures: 1

Keywords: coronary bifurcation intervention; side branch occlusion; randomized comparison; conventional strategy; intentional strategy

This study is registered on www.clinicaltrials.gov, and the registration number is NCT 02644434.

Protocol version identifier: 15.0
Protocol date: 18. September, 2016.

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 ≥ 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.

Ethics and dissemination: The protocol has been approved by all local Ethics Committee. The Ethics Committee have approved the study protocol, evaluated the risk to benefit ratio, allowed operators with a minimum annual volume of 200 cases to participate in the PCI procedure, and permitted them to perform both conventional and intentional strategies. Written informed consent would be acquired from all participants. The findings of the trial will be shared by the participant hospitals and disseminated through peer-reviewed journals.

Trial registration number: NCT02644434.

Strengths and limitations of this study

CIT-RESOLVE is the leading trial which intends to investigate if intentional strategy could decrease the rate of SB occlusion in patients with high-risk of SB occlusion.

This study enrolls high-risk patients by using an inclusion criteria of SB occlusion risk (V-RESOLVE score ≥12 points).

This study would provide evidence for interventionalists in strategy selection when treating bifurcation with high risk of SB occlusion.

Not all bifurcation lesions are included in the present study, left main diseases are excluded.

Abbreviations list

CK-MB=**C**reatine **K**inase-**M**yocardial **B**and

ECG=Electrocardiography

ITT=**I**ntention-**T**o-**T**reat population

LAD=**L**eft **A**nterior **D**escending coronary artery

MACE=**M**ajor **A**dverse **C**ardiac **E**vents

MI=**M**yocardial **I**nfarction

MV=**M**ain **V**essel

PCI=**P**ercutaneous **C**oronary **I**ntervention

PP=**P**er-**P**rotocol population

QCA=**Q**uantitative **C**oronary **A**ngiography analysis

RVD= **R**eference **V**essel **D**iameter

SB=**S**ide **B**ranch

TIMI=**T**hrombolysis **I**n **M**yocardial **I**nfarction 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.

Previous randomized clinical trials performed randomization of all categories of bifurcation lesions by using computer-generated random sequence, totally ignored the individual lesion anatomical characteristics and the risk of SB occlusion. Now, we have developed an angiographic tool for risk prediction of SB occlusion, the V-RESOLVE score, which can help risk stratification of SB occlusion and could also be used as a tool to select high-risk patients in randomized study. The SB occlusion rate was significantly higher in the high-risk group (V-RESOLVE score ≥12, rate of SB occlusion: 16.7%) than the non-high-risk group (V-RESOLVE score <12, rate of SB occlusion: 4.3%) as assessed by the V-RESOVLE score[14].

Bifurcation lesions with high-risk of SB occlusion may need intentional interventional strategy, which is more aggressive in SB protection than conventional strategy and considered to be associated with lower SB occlusion rate. However, no randomized trials were performed to compare the rate of SB occlusion between intentional strategy and conventional strategy in high-risk patients.

Accordingly, the present study is designed to enroll patients with high-risk of SB occlusion (V-RESOLVE score ≥12), and investigate if intentional strategy is associated with significant reduction of SB occlusion rate compared to conventional strategy in patients with high-risk of SB occlusion.

Methods and analysis

Hypothesis to be test. We hypothesized that for patients at high risk of SB occlusion (V-RESOLVE score ≥12), intentional strategy (a more aggressive SB protection strategy: elective two-stent strategy or jailed balloon technique) is

associated with significant reduction of SB occlusion rate compared to conventional strategy (provisional two-stent strategy or jailed wire technique). Thus the hypothesis to be decided upon are as follows: H_0, for patients with high risk prediction of SB occlusion, there is no difference in the rate of side branch occlusion between intentional strategy group and the conventional strategy group, versus H_1, the rate of side branch occlusion in intentional strategy group would be significantly lower than that of conventional strategy group.

Study design. The CIT-RESOLVE is a prospective, randomized (1:1), single-blind, multicenter clinical trial comparing the rate of side branch occlusion between the conventional strategy group and the intentional strategy group in a consecutive cohort of high-risk coronary bifurcation patients. Although operators are not blinded, all individuals analyzing data are masked to treatment assignment. A total of 21 centers in China will enroll patients. This study is registered on www.clinicaltrials.gov, and the registration number is NCT 02644434. The study flowchart is shown in figure 1 and its legend.

This trial is conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. The conduct of the trial has been approved by the Ethics Committee. Written informed consent would be acquired from all participants. Patient data in the Data Management System are protected by password and only available to users designated by the study with appropriate authorization levels. De-identified data will be used for data analysis.

Risk prediction of side branch occlusion. V-RESOLVE score would be used for

risk prediction of SB occlusion. The RESOLVE (**R**isk pr**E**diction of **S**ide branch **O**cc**L**usion in coronary bifurcation inter**VE**ntion) score, which is developed on the basis of quantitative coronary angiography (QCA), is a validated angiographic scoring system to evaluate the risk of SB occlusion in bifurcation intervention[9]. The QCA-based RESOLVE score system contains six independent risk factors of SB occlusion: including two visual estimation predictors (plaque distribution and MV thrombolysis in myocardial infarction [TIMI] flow grade before stenting), and four QCA analysis predictors (pre-procedural diameter stenosis of bifurcation core, bifurcation angle, diameter ratio between MV/SB and diameter stenosis of SB before MV stenting).

Although QCA provides a more objective determination of the extent and severity of coronary artery disease, it may be more time-consuming and/or not immediately available in real-time. As a result, the inclusion of QCA data within the QCA-based RESOLVE score limits its ability to be used at the time of bifurcation intervention[15]. Therefore, we evaluated the ability of a visually estimated RESOLVE (V-RESOLVE) score to predict the risk of side branch occlusion during bifurcation intervention. We found that the V-RESOLVE score, an easy-to-use score system based on visual estimation, can help risk stratification of SB occlusion during coronary bifurcation intervention. The rate of SB occlusion was significantly higher in high-risk group (V-RESOLVE score ≥12, rate of SB occlusion: 16.7%) than that in non-high-risk group (V-RESOLVE score ≤11, rate of SB occlusion: 4.3%) ($p<0.01$). V-RESOLVE 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 ≥ 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 ≥ 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
Clinical Inclusion Criteria:	***Clinical Exclusion Criteria:***
1. Subject must be male or nonpregnant female ≥18 years of age and ≤75 years of age;	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 $P2Y_{12}$ inhibitors, or aspirin);
2. Subject has symptomatic coronary artery disease with objective evidence of ischemia or silent ischemia;	2. Planned surgery within 6 months after the index procedure;
3. Subject is eligible for PCI;	
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;	

5. Subject is willing to comply with all protocol-required follow-up evaluation.	3. Subject has one of the following (as assessed prior to the index procedure): • Other serious medical illness (e.g., cancer, congestive heart failure) with estimated life expectancy of less than 12 months； • Current problems with substance abuse (e.g., alcohol, cocaine, heroin, etc.); • Planned procedure that may cause non-compliance with the protocol or confound data interpretation; 4. Subject has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions; 5. Subject is participating in another investigational drug or device clinical trial that has not reached its primary endpoint; 6. Subject intends to participate in another investigational drug or device clinical trial within 12 months after the index procedure; 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

	method of contraception from the time of screening through 12 months after the index procedure); 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); 9. Subject with left ventricular ejection fraction < 35%; 10. Subject has preoperative renal dysfunction: serum creatinine>2.0mg/dl (176.82umol/L).
Angiographic Inclusion Criteria: 1. Subjects have coronary bifurcation lesions requiring PCI with stent implantation according to clinical guidelines and/or the operator's judgement; 2. Visually estimated reference vessel diameter (RVD) of target main vessel ≥2.5 mm and ≤4.0 mm; 3. Visually estimated RVD of target side branch ≥ 2.0mm; 4. Coronary anatomy is likely to allow delivery of	***Angiographic Exclusion Criteria:*** 1. Left main lesions; 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>2.5mm]) which is proximal to occluded LAD segment should be excluded.

a study device to the target lesion(s); 5. V-RESOLVE score ≥ 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 ≥ 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

substantial or greater (Fleiss Kappa >0.60) after training. Once the investigators are not sure that the V-RESOLVE score ≥ 12 points or not, we recommend them to send the cineangiograms by internet to the angiographic core laboratory in Fuwai Hospital, where cineangiograms would be assessed by two experienced technicians together and the V-RESOLVE score was generated by consensus.

Patient enrollment and randomization. Subjects must be ≥18 years and ≤75 years of age at the time of enrollment in the study. Coronary angiography would be performed to confirm that angiographic inclusion criteria are met. Then, wiring and pre-dilation would be performed at the discretion of the interventional cardiologists in the conventional manner. A mobile APP specialized for V-RESOLVE calculation will be used to calculate the V-RESOLVE score after pre-dilation. Bifurcation lesions with V-RESOLVE score ≥12 points will be enrolled. Patients that meet all the inclusion criteria and had no exclusion criteria would be included in this study. Patient enrollment has been started on 1st, December, 2016 and anticipated to be completed before December, 2017.

Patient randomization will be performed centrally by internet after signing an informed consent form. The randomization will be stratified by the diameter of side branch (diameter of side branch<2.5mm and ≥2.0mm vs. diameter of side branch≥2.5mm), with a randomization ratio of 1:1 to either conventional strategy group or intentional strategy group.

Intervention and procedure. PCI is undertaken via the access site of operators' choice. Coronary angioplasty is performed in the conventional manner and coronary

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 (creatine 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 ≥2.0mm) or provisional two-stent strategy (diameter of side branch≥2.5mm).

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.

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

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.

No matter there is SB compromise or not, final kissing balloon technique could be performed at the discretion of the interventional cardiologists.

Elective two-stent strategy. Patients in this subgroup would undergo crush procedure (e.g. Crush, Balloon Crush or DK-Crush)[16-18] or any other elective two-stent strategy like Culotte and T stent[19, 20], which stenting SB before MV stenting. These techniques were detailed in previous studies.[16-20]

For both the conventional and intentional strategy groups, proximal or distal dissections could be treated with further stenting at any stage. Post-dilations could be performed to optimize stent expansion. In all cases, an additional vessel with other lesions could be treated if required.

Primary and secondary endpoint(s). The primary endpoint is side branch occlusion, which is defined as any decrease in TIMI flow grade or absence of flow in side branch after main vessel stent well opposed. For lesions underwent conventional strategy, TIMI flow grade is assessed immediately after the main vessel stent is deployed and post-dilation (if post-dilation is performed), then, the SB could be further treated if required. For lesions underwent jailed balloon technique, TIMI flow grade is assessed after POT is performed. For lesions underwent elective two-stent strategy, TIMI flow grade is assessed immediately after the main vessel stent is deployed and post-dilation (if post-dilation is performed), then rewiring the SB or final kissing balloon is performed if required.

The secondary endpoints are: 1) the elevation of biomarkers of peri-procedural myocardial injury (CK-MB and Troponin); Peri-procedural MI is defined as

biomarkers elevation ≥10 × upper reference limit (URL) for CK-MB and/or ≥70 × URL for troponin[21]; 2) 12-month major adverse cardiac events (MACE, including all cause death, all MI and target vessel revascularization).

Follow-up. Subjects had either a telephone call or clinic visit at 30 days (±7 days), 3 months (±14 days), 6 months (±14 days), 12 months (±30 days) by the enrolling site for outcome evaluation. For all patients, MACE at 12-month will be reported. MACE will be defined as a composite of all cause death, all MI (defined by the Third Universal Definition[22]), and target vessel revascularization (defined by the Academic Research Consortium [ARC][23]).

Data collection. Profession trained staffs who are independent of patient treatment will be responsible for data collection and entering. The data collected for each new CIT-RESOLVE patient include baseline information; sociodemographic characteristics; symptoms and signs of the presenting coronary disease; medical history, biomarker findings (CK-MB and Troponin activity will be determined by using an immunoinhibition assay and confirmed by mass spectrometry), electrocardiographic, and treatments administered prior to admission during hospitalization. Final diagnosis, major in-hospital clinical events (death, peri-procedural MI, major bleeding, stroke), and discharge status will also be recorded.

Baseline and procedural coronary angiography will be reviewed and analyzed by physicians and interventionalists to calculate the V-RESOLVE score. Coronary angiography findings, including bifurcation location, baseline and post MV stenting

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 (±7 days)	3 months[7] (±14 days)	6 months (±14 days)	12 months (±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	•[1]		•[2]				
Cardiac enzymes (CK-MB, Troponin)	•[3]		•[4]				
Serious Adverse Events[5]		•	•	•	•	•	•
V-RESOLVE score calculation		•					

Notes:

[1] Electrocardiography (ECG) at time of screening should be performed within 72 hours prior to PCI procedure.

[2] ECG within 24 hours post-procedure or at discharge, whichever comes first.

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

[4] 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.

[5] 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:

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

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 ≥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 the written informed consent and are randomized, regardless which strategy was selected. The primary analysis is a superiority ITT analysis of the primary clinical endpoint. Normal approximation test for the difference between two proportions (pooled proportion) or Fisher's exact test (if applicable) will be used to test the two-sided hypothesis of superiority in proportions. If the P value from the two-sided test is <0.05, the intentional strategy (test) will be concluded to be superior to conventional strategy. If required, an additional analysis of the Per-Protocol (PP) population will be conducted of the primary and secondary endpoints.

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

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 ≥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

anatomical characteristics and risk factors of SB occlusion. Thus, a substantial part of bifurcation lesions may not undergo proper intervention strategy though some patients have crossed over to another group. This may be the major reason why the results of previous studies remain controversial.

Previous studies enrolled patients by using the inclusion criteria of either unselected bifurcation lesions, specific Medina classifications or true bifurcation lesions. However, neither "Medina classification" nor "true bifurcation lesion" could predict the risk of SB occlusion accurately[34, 35]. The SB occlusion risk is not considered as an important criterion when enrolling patients. CIT-RESOLVE is the first trial which only enrolls high-risk patients by using a risk prediction tool (V-RESOLVE score ≥12 points).

Numerous classifications and definitions of coronary bifurcation lesions have been proposed to simplify the hard topic of bifurcation lesion in interventional cardiology[36-45]. Among them, "Medina classification" as well as "true bifurcation lesion" are straightforward and widely used. However, none of these classifications or definitions could accurately predict the risk of SB occlusion[35]. One of our previous researches has shown that "true bifurcation lesion" could not be regarded as an independent predictor of SB occlusion[34]. RESOLVE score and V-RESOLVE score is the first attempt to stratify the risk of SB occlusion during coronary bifurcation intervention. V-RESOLVE score, which contains 6 independent predictors of SB occlusion, is a validated score system to evaluate the risk of side branch occlusion[14] and a useful tool for risk prediction of SB occlusion in the present study. V-RESOLVE

score ≥12 points is considered as high risk in SB occlusion, which may trigger interventional SB protection, and set as one of the inclusion criteria of CIT-RESOLVE trial.

The intentional strategy is more aggressive in SB protection: jailed wire may help SB reopen; stenting the SB before MV stenting may avoid SB occlusion. Thus, the intentional strategy is thought as a more suitable strategy for high-risk bifurcation lesion. CIT-RESOLVE is the leading trial which intends to investigate if intentional strategy could decrease the rate of SB occlusion in patients with high-risk of SB occlusion. Comparing the rate of SB occlusion between intentional and conventional strategy would provide evidence for interventionalists in strategy selection when treating bifurcation with high risk of SB occlusion. 12-month follow-up would investigate if SB occlusion could impact the clinical outcome directly.

One limitation of the trial design is that not all high-risk bifurcation lesions are included in the present study. When treating left main diseases, left anterior descending artery or left circumflex artery occlusion may lead to serious outcome, thus, left main diseases are excluded in the consideration of ethic. Also, in case of acute MI of which the culprit vessel located at the LAD, the bifurcation lesion (LAD/diagonal branch [RVD>2.5mm]) which is proximal to occluded LAD segment is excluded. Another limitation is that jailed balloon technique, which has not been proven by randomized clinical trials and widely used in clinical practice, is used in the interventional group. Although jailed balloon technique has been reported to be associated with very low rate of SB occlusion[4], its effect in SB protection warrant

further studies. In future studies, we would compare the rate of SB occlusion between provisional two-stent strategy and elective two-stent strategy in patients at high risk of SB occlusion.

Conclusion

The CIT-RESOLVE study is the first large randomized trial which enrolls only high-risk patients by using an inclusion criteria of SB occlusion risk (V-RESOLVE score ≥12 points), and it has sufficient power to assess the effect of intentional strategy in decreasing the SB occlusion rate in patients at high risk of SB occlusion.

CIT-RESOLVE Study Group

Principal investigator: Kefei Dou (Fuwai Hospital and National Center for Cardiovascular Diseases).

Co-principal investigator: Bo Xu (Fuwai Hospital and National Center for Cardiovascular Diseases).

Coordinating center: Fuwai Hospital and National Center for Cardiovascular Diseases, Beijing, China.

Advisory Chairmen: Yuejin Yang (Fuwai Hospital and National Center for Cardiovascular Diseases), Shaoliang Chen (Nanjing First Hospital and Nanjing Medical University) and Ajay J. Kirtane (Columbia University Medical Center and New York Presbyterian Hospital).

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.

Funding

The CIT-RESOLVE trial is physician-initiated and supported by Investigator Sponsored Studies (Abbott Cardiovascular, Study No.: COR-10498) and Peking Union Medical College Youth Fund and Fundamental Research Funds for the Central Universities (Grant number: 3332016130). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

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

purpose or research cooperation will be provided.

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Figure legend

Figure 1. Study flowchart

Screening, randomization, intervention, procedure, study endpoint and follow-up of CIT-RESOLVE trial.

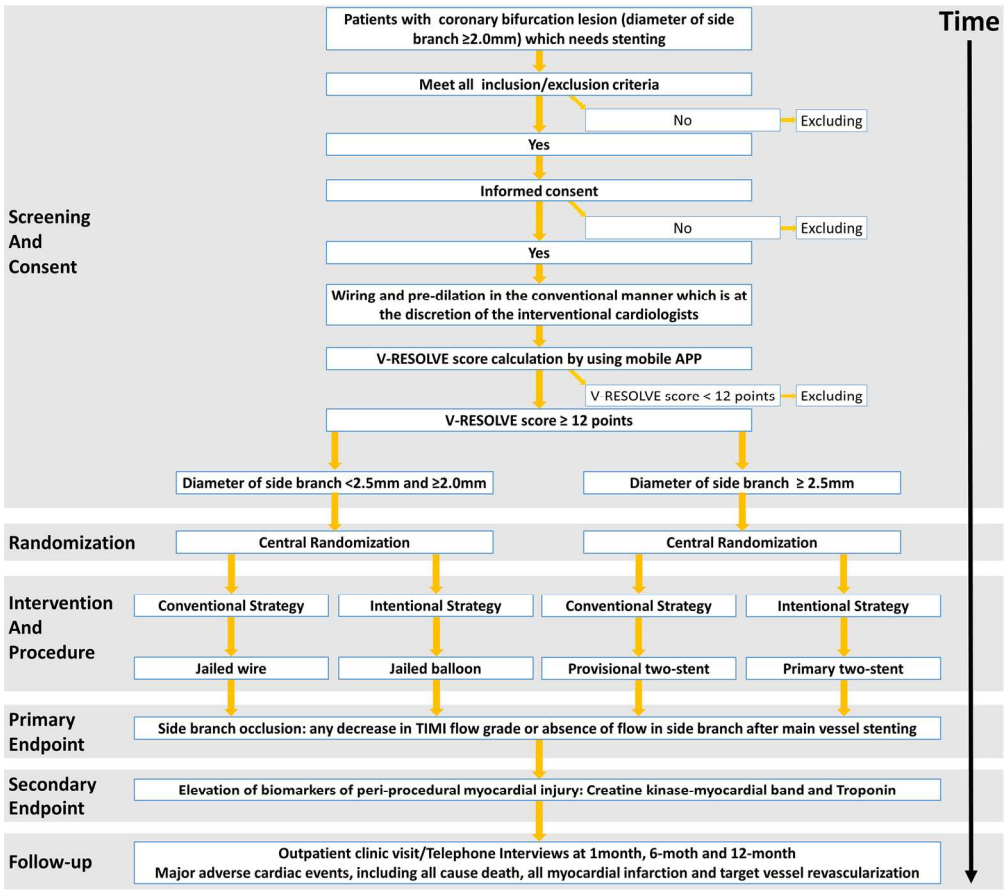

Figure 1. Study flowchart: screening, consent, randomization, intervention, procedure, study endpoint and follow-up.

179x159mm (300 x 300 DPI)

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

The First Affiliated Hospital of Dalian Medical University	Liaoning	Dalian
Shengjing Hospital of China Medical University	Liaoning	Shenyang
The First Affiliated Hospital of Guangxi Medical University	Guangxi	Nanning
Hunan Provincial People's Hospital	Hunan	Changsha
Cangzhou Central Hospital	Hebei	Cangzhou

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **(Title page)**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **(Title page)**
Protocol version	3	Date and version identifier **(Title page)**
Funding	4	Sources and types of financial, material, and other support **(Page 24-25)**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **(Page 23-24)**
	5b	Name and contact information for the trial sponsor **(Page 24-25)**
	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 **(Page 24-25)**
	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) **(Page 24-25)**
Introduction		
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 **(Page 5-6)**
	6b	Explanation for choice of comparators **(Page 5-6)**
Objectives	7	Specific objectives or hypotheses **(Page 6)**

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:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **(Page 13)**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **(Page 13)**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **(Page 13)**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **(Page 7)**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **(Page 7)**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **(Page 16-17)**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols (**Page 16-17)**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol (**Page 16-18)**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol (**Page 19-20)**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **(Page 19-20)**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **(Page 19-20)**

Methods: Monitoring

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 (**Page 7)**
	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 (**Page 19-20)**
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 (**Page 19-20)**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **(Page 7)**

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **(Page 7)**
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) **(Page 7)**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **(Page 7)**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **(Page 7)**
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 **(Page 7)**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **(Page 24)**
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 **(Page 25)**
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

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 **(Page 25)**
	31b	Authorship eligibility guidelines and any intended use of professional writers **(Page 24-25)**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **(Page 25)**

*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.