Rationale and design for comparison of non-compliant balloon with drug-coating balloon angioplasty for side branch after provisional stenting for patients with true coronary bifurcation lesions: a prospective, multicentre and randomised DCB-BIF trial

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ABSTRACT

Introduction Provisional stenting using drug-eluting stent is effective for simple coronary bifurcation lesions. Kissing balloon inflation using conventional non-compliant balloon is the primary treatment of side branch (SB) after main vessel (MV) stenting. Drug-coating balloon (DCB) is reported to be associated with less frequent clinical events in in-stent restenosis and small vessel disease. The importance of DCB in bifurcation treatment is understudied. Accordingly, this trial is designed to investigate the superiority of DCB to non-compliant balloon angioplasty for SB after provisional stenting in patients with true coronary bifurcation lesions.

Methods and analysis The DCB-BIF trial is a prospective, multicentre, randomised, superiority trial including 784 patients with true coronary bifurcation lesions. Patients will be randomised in a 1:1 fashion to receive either DCB or non-compliant balloon with drug-coating balloon angioplasty for side branch after provisional stenting for patients with true coronary bifurcation lesions. The primary endpoint is the risk of stent thrombosis.

Strengths and limitations of this study

► This is the first randomised trial to investigate the superiority of drug-coating balloon for side branch (SB) after provisional stenting in patients with true coronary bifurcation lesions.
► We plan to enrol a total of 784 patients in at least 15 sites in 6 countries.
► Primary endpoint is clinical event (‘hard’ endpoint).
► This study will provide high-level evidence to help to create an algorithm for provisional stenting technique in coronary bifurcation lesions.
► True coronary bifurcation lesions with SB length less than 10 mm are included, which may not be reflective of complex bifurcation lesions.

BACKGROUND

Coronary bifurcation lesions are encountered in about 15%–20% of daily percutaneous coronary intervention (PCI) procedures, but with technical complexity and poor long-term outcomes.1 The systematic two-stent technique (mostly DK-CRUSH) has been demonstrated to improve the clinical outcomes for DEFINITION criteria-defined complex bifurcation lesions,2,3 while provisional stenting (PS) technique is regarded as the default strategy for simple bifurcation lesions.4,5 Routine side branch (SB) dilation with kissing balloon inflation (KBI) could not provide clinical benefits in PS, and SB ostium dilation is recommended only when severe...
ostial SB stenosis is present. Currently, non-compliant (NC) balloon is widely used in SB ostium dilation after stenting main vessel (MV) to restore normal blood flow in the SB, but it still yields more frequent restenosis and repeat revascularisation at the ostium of SB. Drug-coated balloon (DCB) is developed to deliver the antiproliferative agents into the vessel wall via a semicompliant balloon, which would suppress the proliferation of vascular smooth muscle cells (VSMCs) and reduce the restenosis by leaving no metal behind. The combined use of PS technique and DCB to treat the true bifurcation lesions is very attractive, which might improve the clinical outcomes. Previous studies showed that the combination of a stent in the MV and a DCB in the SB for the treatment of a bifurcation lesion could result in the lower late lumen loss (LLL) and less frequent SB ostium restenosis. However, those studies unlikely provide the benefits of clinical outcomes after SB dilation using a DCB in bifurcation lesions, mainly because of bare-metal stent (BMS) usage, small sample size (only 52, 35 or 28 patients), surrogate endpoint (LLL) and short follow-up duration (6 or 9 months). Therefore, we designed this prospective, multicentre, randomised trial to investigate the superiority of DCB to NC balloon angioplasty for SB after PS in patients with true coronary bifurcation lesions.

STUDY DESIGN AND METHODS

Study hypothesis

This study is designed to test the hypothesis that DCB dilation will lead to a lower rate of major adverse cardiac event (MACE), including cardiac death, myocardial infarction (MI) or clinically driven target lesion revascularisation (TLR), compared with conventional balloon angioplasty for SB after PS in patients with true coronary bifurcation lesions at 12-month follow-up.

Study design

The present study is a prospective, multicentre, randomised, superiority trial in at least 15 sites in 6 countries to enrol 784 patients with true coronary bifurcation lesions. The overall study flow chart is summarised in figure 1. This study has been registered at ClinicalTrials.gov, according to the statement of the International Committee of Medical Journal Editors. The study protocol and informed consent have been reviewed and approved by the Institutional Review Board at each participating centre. The written informed consent for participation in the trial will be obtained from all enrolled patients.

Study population and randomisation

A total of 784 patients with true coronary bifurcation lesions (Medina 1,1,1 or 0,1,1 or 1,0,1) suitable for drug-eluting stent implantation are randomised in a 1:1 fashion to DCB or NC balloon angioplasty for SB after stenting main vessel. The detailed inclusion and exclusion criteria are presented in box 1.

Figure 1  Study flow chart. DCB, drug-coated balloon; DS, diameter stenosis; MACE, major adverse cardiac event; NC, non-compliant; NCB: non-compliant balloon; POT, proximal optimisation technique; SB, side branch; TIMI, thrombolysis and thrombin inhibition in myocardial infarction.
Box 1 Inclusion and exclusion criteria

Inclusion criteria:
1. Subject must be aged $\geq$ 18 years.
2. Subject has silent ischaemia, or stable/unstable angina, or acute MI (>7 days from the onset of chest pain to admission).
3. Subject (or legal guardian) understands the trial design and treatment procedures and provides written informal consent before any trial-specific tests or procedures are performed.
4. Subject is willing to comply with all protocol-required follow-up evaluations.
5. Target lesion must be a true bifurcation lesion on coronary angiogram (defined as Medina 0,1,1, Medina 1,0,1, or Medina 1,1,1 coronary bifurcation lesions) and is eligible for PCI.
6. Target lesion reference vessel diameter (both main vessel and side branch) $\geq$ 2.5 mm by visual estimation.
7. Target lesion must have visually estimated stenosis $\geq$ 50%.
8. Target lesion length of side branch must be $< 10$ mm by visual estimation.
9. Ostium side branch must have visually estimated stenosis $\geq$ 70% after proximal optimisation technique for the main vessel stenting.

Exclusion criteria:
1. Pregnant and breastfeeding mothers.
2. Comorbidity with an estimated life expectancy of $< 50\%$ at 12 months.
3. Scheduled major surgery in the next 12 months.
4. Inability to follow the protocol and comply with follow-up requirements or any other reason that the investigator feels would place the patient at increased risk.
5. Previous enrolment in this study or treatment with an investigational drug or device under another study protocol in the past 30 days.
6. Known allergy against ticagrelor, or against clopidogrel, or aspirin in a dose of 100 mg/day will be prescribed. Duration of clopidogrel treatment with 75 mg/day (or ticagrelor with 90 mg two times per day) is at least 6 months for stable patients or at least 12 months for patients with acute coronary syndrome.

at nominal pressure for 60 s. The ratio of the DCB diameter to the nominal diameter of the SB is recommended to be between 0.8 and 1.0. DCB should be delivered to the lesion within 2 min after entering human body. After DCB angioplasty, further kissing inflation using two NC balloons is performed. RePOT and SB stenting are in line with previous description in PS technique.

PS-NC balloon group
All procedures are consistent with technical requirements in the PS technique.

Intracoronary imaging and study stents
Intracoronary imaging tools (intravascular ultrasound or optical coherence tomography) are at the discretion of the interventional cardiologists. Stents for all implanted lesions are limus-eluting stents, including BuMA stent (Sino Medical, Tianjin, China); Firebird2 or Firehawk (Microport Co, Shanghai, China); EXCEL (Jiwei Co, Shandong, China); GuReater, Partner or Nano (Lepu Med, Beijing, China); Endeavor Resolute or Resolute Integrity (Medtronic, Minneapolis, Minnesota, USA); and Xience or Xience Prime (Abbott Vascular, Santa Clara, California, USA).

Medications
All patients in this trial are treated according to contemporary guidelines and local practice. A loading dose of aspirin (300 mg) and clopidogrel (300 mg, or ticagrelor 180 mg) is recommended at least 6 hours before PCI procedure. Heparin or an alternative antithrombotic (such as bivalirudin) must be used during the interventional portion of the procedure to maintain the activated clotting time $> 250$ s throughout the interventional portion of the procedure. After procedure, lifelong aspirin in a dose of 100 mg/day will be prescribed. Duration of clopidogrel treatment with 75 mg/day (or ticagrelor with 90 mg two times per day) is at least 6 months for stable patients or at least 12 months for patients with acute coronary syndrome.

Biomarker assessment
Total creatine kinase (CK), CK-myocardial band isoenzyme (MB) and troponin T/I are dynamically measured before the procedure and until 48 hours after procedure.

Study endpoints
The primary endpoint is MACE at 12 months after the indexed procedure, defined by the composite of cardiac death, MI and clinically driven TLR. The major secondary endpoints include all-cause death, periprocedural MI, spontaneous MI, clinically driven target vessel revascularisation, ISR, stroke and each individual component of the primary endpoint. The safety endpoint is the risk of Academic Research Consortium-defined stent thrombosis. Other endpoints are listed in box 2. The detailed definitions of study endpoints are described in the online supplemental appendix 1.

Box 2 Study endpoints

Primary endpoint:
- Major adverse cardiac events at 12 months, composite of cardiac death, myocardial infarction (MI) or clinically driven target lesion revascularisation (TLR).

Secondary endpoints:
- All-cause death: cardiac death, non-cardiac death.
- MI: periprocedural MI, spontaneous MI or target vessel MI.
- Revascularisation: TLR, target vessel revascularisation.
- In-stent restenosis.
- Periprocedural endpoints: angiographic success rate; clinical procedural success rate; crossover rate from single-stent technique to two-stent technique.

Safety endpoint:
- Stent thrombosis.
All endpoints are site reported in an electronic web-based capture system with additional submission of supporting medical documents. All clinical events will be assessed by an independent committee who was blinded to the patient’s allocation.

**Follow-up**

After hospital discharge, clinical follow-up is performed with visits (preferred) or telephone contact at 1, 6 and 12 months. Follow-up will be continued to 3 years after procedure annually. Angiographic follow-up at 13 months is optional for all patients.

**Quantitative coronary analysis**

Quantitative coronary angiographic analysis at baseline, post-procedure and follow-up will be performed off-site by the Core lab (Rodebern Research Institute, Nanjing, China) using Cardiovascular Angiographic Analysis System II software V.5.0 (Pie Medical Imaging, Maastricht, the Netherlands). Basic angiography for all lesions should include at least two injections after intracoronary injection of 100–200 µg nitroglycerin. There should be an angulation difference (at least 30°) between the two-baseline angiography. The diagnostic/guiding catheter and the index lesions should be well visible without foreshortening, near the centre of the angiogram. All balloon inflations and stent implantations from the preprocedure and post-procedure should be recorded by short cine runs. The images are analysed by two experienced technicians who are blinded to the study design, with the interobserver and intraobserver variability under 5% (kappa test).

**Statistical analysis**

All statistical analyses will be performed in the intention-to-treat population, regardless of the treatment actually received. We hypothesised that the rate of a 1-year MACE would be 10% in PS-DCB group and 17% in the PS-NC balloon group based on the previous studies.\(^3\)\(^-\)\(^6\) A total sample size of 746 is needed to detect a power of 0.8 (type II error=0.2–0.05, two tailed). Because of the considerable uncertainty, the enrolment is extended to 784 patients with 5% increment.

The distribution of continuous variables will be assessed by the Kolmogrov-Smirnov test. Continuous variables are expressed as mean±SD or median, and compared by Student’s t-test (for normal data) and Mann-Whitney U test (for non-normally distributed variables). Categorical variables are summarised as frequencies or percentages, and compared by the Chi-square or Fisher’s exact test. Survival curves with time-to-event data are generated by the Kaplan-Meier method and compared by the log-rank test. Comparison between two groups will be performed using the Cox proportional hazard model with reporting HR and 95% CI. A p value of <0.05 is considered statistically significant. All analyses are performed with the use of the statistical program SPSS V.24.0 (SPSS Institute).

The extensive subgroup analysis will be performed to assess the variation of treatment effects, as well as a test of interaction with treatment for each subgroup variable. The substudies of clinical factors include age (age ≥75 years old), sex, diabetes mellitus, chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m\(^2\)), acute coronary syndrome, cardiac dysfunction, left main bifurcation lesion or non-left main bifurcation lesion, intracoronary images guidance and multivessel disease. Therefore, there are at least nine prespecified subgroup analyses to explore the consistency of effects of DCB treatment on primary endpoint for coronary bifurcation lesions.

**ETHICS AND DISSEMINATION**

This protocol is conducted following the Guidelines of Standard Protocol Items: Recommendations for Interventional Trials (online supplemental appendix 2). The study will be performed in compliance with the Declaration of Helsinki of the World Medical Association. The study protocol and informed consent have been reviewed and approved by the Institutional Review Board of Nanjing First Hospital (KY20200110-01) and all other participating centres (online supplemental appendix 3). The written informed consent for participation in the trial will be obtained from all participants. The results of this study will be published in a peer-reviewed journal and disseminated at conferences.

**Trial organisation**

The trial has been designed by the principal investigator and the executive committee. The executive committee members are also responsible for reporting the results and drafting the manuscripts. The executive committee, together with the steering committee, the data and safety monitoring board (DSMB) and the independent endpoints adjudication committee, are involved in the present trial. All data will be collected in paper-based case report form (CRF), and then entered into an electronic CRF. All data will also be carefully examined and verified by two trained investigators. Research assistants will regularly check adherence to the protocol and the accuracy of the data by on-site visits or remote monitoring. All severe adverse events will be recorded in detail and reported to the ethics committee. DSMB will review all adverse events regularly to evaluate the safety of DCB in treating the coronary bifurcation lesions.

**Patient and public involvement**

No patient involved in the development of the research question, study design, recruitment, outcome measures and conduct of the study.

**DISCUSSION**

The present study describes the methodology of a randomised trial on the effect of SB DCB treatment
after PS in patients with true coronary bifurcation lesion. Coronary bifurcation lesions account for 15%–20% of coronary lesions treated with PCI. PS technique has been considered as a default strategy for simple bifurcation lesions, due to no benefit of systematic two-stent approach but with higher procedure time, radiation exposure, contrast volume and cost. Technically, active SB protection could reduce the risk of SB occlusion in high-risk bifurcation lesions with a V-RESOLVE score ≥12 points. Routine KBI or SB dilation after main vessel stenting has failed to provide clinical benefits. If inadequate results of SB are present (TIMI <3, severe ostial SB stenosis or Fractional Flow Reserve<0.8), guidewire should be inserted into the SB through the distal cell, and then KBI or SB dilation is performed (POT-KBI-rePOT, or POT-SB dilation-rePOT). SB stenting should be considered by the Tstenting, T-stenting and minimal protrusion (TAP), or Culotte technique if SB TIMI <3, major SB dissection, or severe ostial SB stenosis after KBI or SB dilation. When the guidewire is inserted in the SB through the distal cell, T-stenting could be done; when SB access is performed through a proximal strut, TAP or Culotte is necessary to cover the SB ostium.

Although above-mentioned standard protocol of PS has been widely used in our daily clinical practice, the frequent restenosis at the SB ostium still remains an unsolved problem. In the DK-CRUSH V trial, it reported that the rate of ISR at the ostium of left circumflex coronary artery reached up to 12.0% with PS for treating true distal left main bifurcation lesions. DCB is a semicompliant balloon coated with antiproliferative drugs, which could be released into the vessel wall after balloon inflation to inhibit the VSMC proliferation. The efficacy and safety of DCB have been fully investigated for ISR and de novo small vessel disease, meanwhile emerging studies have indicated promising results of DCB in treating bifurcation lesions, de novo large vessel disease and patients at risk of high bleeding.

Because MB stenting with provisional SB stenting has been recommended as a default strategy for most bifurcation lesions, a stent in MB first following a DCB in SB is more preferable to be accepted for bifurcation lesions. BIOLUX-I and DEBSIDE Studies enrolled 35 patients and 52 patients, respectively, showing that the combination of a DCB in MB and a DCB in SB appeared to be a safe and effective treatment for bifurcation lesions with a very low LLL. However, these studies could not provide the enough power to establish the use of DCB in bifurcation lesions, due to the BMS usage, small sample size, surrogate endpoint and short follow-up duration. Currently, these data combined with our daily clinical practice could confirm the safety of DCB usage in bifurcation lesions, and our protocol also recommends that an additional SB stent will be implanted if SB TIMI flow <3 or 2type C dissection after DCB dilation in SB. Besides, DSMB will review all adverse events regularly to evaluate the safety of DCB in treating the coronary bifurcation lesions.

This study is the first prospective, randomised, active-controlled multicentre trial to assess the hypothesis that using DCB is more efficient than NC balloon angioplasty for SB after PS for patients with true coronary bifurcation lesion. Of note, true coronary bifurcation lesions with SB length less than 10 mm are included, which may not be reflective of complex bifurcation lesions. This well-designed, adequately powered randomised controlled trial with hard endpoint will provide high-level evidence to help to create an algorithm for PS technique in coronary bifurcation lesions.

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