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Study Protocol · **Open Access** ·

Comparison of the safety and efficacy of two types of drug-eluting balloons (RESTORE DEB and SeQuent® Please) in the treatment of coronary in-stent restenosis: study protocol for a randomized controlled trial (RESTORE ISR China)

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1 Introduction

In-stent restenosis (ISR), characterized by neointimal proliferation and/or neoatherosclerosis in the vessel of the stent, can cause a reduction in lumen diameter after stent implantation, which can directly induce the recurrence of angina symptoms or an acute coronary syndrome in patients and is usually life-threatening.[1–3] ISR has also been considered as formidable clinical problem for the interventional cardiologists.

In recent years, many remarkable improvements in medical technology of percutaneous coronary intervention (PCI), such as first-generation bare metal stents (BMS) and newer-generation drug-eluting stents (DES) have been achieved, which significantly reduce ISR occurrence in patients with PCI.[4,5] For example, growing evidence has suggested that the safety and efficacy of revascularization procedures of newer-generation DES was greatly superior to those of first generation DES and BMS.[6–10] However, ISR rate remains as high as 5% to 10% for patients treated with newer-generation DES at two years.[11] More recently, a newly developed drug-eluting balloon (DEB) coated with paclitaxel, an antiproliferative drug that could inhibit neointimal hyperplasia, had emerged as an alternative therapeutic tool for ISR disease.[12,13] DEB plays the anti-restenosis efficacy through a high-concentration, rapid local delivery of paclitaxel without the use of polymers on a stent. To date, there are numerous randomized trials performed to compare the safety and efficacy among plain old balloon angioplasty (POBA), DES and DEB for the treatment of ISR.[14] One recent meta-analysis enrolled eight randomized controlled trials and indicated that DEB was a better option for treatment of ISR when compared to POBA.[15] Another meta-analysis showed that DEB and DES have similar efficacy and safety for the treatment of ISR.[16]

SeQuent® Please DEB is the only approved product utilized for ISR treatment in China.[17] Currently, a novel paclitaxel-coated balloon (RESTORE DEB) has been invented for the treatment of ISR. However, clinical information on the two different types of DEB in treatment of ISR is limited. This trial aims to compare the safety and efficacy of the RESTOREDEB versus SeQuent® Please DEB for the treatment of coronary ISR in Chinese patients.

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2 Methods

2.1 Study protocol

The RESTORE ISR China: RESTORE DEB *vs*. SeQuent® Please study is a multicenter, prospective, controlled, randomized clinical trial which compares the results of RESTORE DEB versus SeQuent® Please in patients with ISR (Clinical Trials.gov Identifier: NCT02944890). The inclusion criteria are: (1) patients > 18 years of age presenting with angina or ischaemia and showing ISR (≥ 70% diameter stenosis on visual assessment, or ≥ 50% diameter stenosis and with ischemic symptoms) on coronary angiography, and suitable to receive any types of coronary revascularization (including balloon angioplasty, stent implantation or coronary artery bypass grafting). (2) Patients in whom the stent ISR patterns are Mehran type Ⅰ-Ⅲ and the stent diameter of ISR is 2.5–4.0 mm. (3) Patients with ≤ 2 episode of ISR and those with ≤ 2 balloons at the target lesion. The exclusion criteria are: (1) patients with not only two target lesions (less than 10 mm) and the distant lesions, but also multiple lesions (≥ 3) requiring PCI treatment in the same artery; (2) patients with lesions requiring intervention treatment in three vessels and branch lesions diameter more than 2.5 mm in the target lesion; (3) patients who had cerebral stroke, a history of peptic ulcer, gastrointestinal bleeding in the past six months, or bleeding tendency; (4) patients with evidence of extensive thrombosis in the target vessel before intervention, and contraindication to use anticoagulation agents or anti-platelet drugs, or intolerance to aspirin or clopidogrel); (5) patients with severe systemic illnesses (including severe renal and hepatic dysfunction) or a life expectancy < 1 year; and (6) patients with severe heart disease potentially unable to coordinate with angiographic follow-up.

After patients are enrolled in the study, central randomization process is being preceded via the Interactive Web Respond System (IWRS) after all procedural and angiographic eligibility criteria have been met, including the requirements that all non-target lesions have been successfully treated. Randomization is layered according to whether patients are concomitant with diabetes or not.

This trial is conducted in accordance with the principles of the Declaration of Helsinki, ISO 14155 and Good Clinical Practices guidelines. The Ethics Committees of all investigational sites have approved the trial protocol, and written informed consent will be obtained from all patients before enrollment. Patients retain the right to withdraw from the trial during follow-up at any time without prejudice.

2.2 Procedures

All patients received aspirin (either100 mg/day for at least three days before PCI or with a pre-PCI 300 mg loading dose), and clopidogrel (300 or 600 mg as a loading dose, followed by 75 mg daily) or ticagrelor (180 mg as a loading dose, followed by 90 mg twice a day) following clinical indication. During the procedure, all patients were administered unfractionated heparin with an initial bolus of 100 mg/kg, followed by additional boluses as necessary, or bivalirudin (bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg per hour for the duration of the procedure). The protocol mandated careful lesion pre-dilation before randomization. Initially, lesions should be pre-dilated with relatively short balloons and low pressures to ensure balloon stabilization at the lesion site and to avoid any damage to the adjacent segments. Once adequate lesion pre-dilation was obtained, patients without severe coronary dissection were randomized and received the allocated treatment. The DEB was inflated for 45 to 60 s at normal pressure, according to the morphological characteristics of the lesion (e.g., degree of calcification, length, and tortuosity).

2.3 Definitions and clinical and angiographic follow-up

All patients will be followed up at 1, 3, 6, 9, 12 months, and angiographic follow-up will be scheduled at nine months. Data will be collected via electronic clinical report form during treatment at all investigational centers and will be completed prospectively during the hospital admission and follow-up. Data capture takes place via web application on the servers of the Center for Clinical Studies at Fuwai Hospital (Beijing, China) with "DataTrack®", a study management software. DataTrack® meets all regulatory requirements. Patient files and other source data (particularly with regard to informed consent, date of angiography and outcomes) must be kept for at least 10 years after the study finished. A Clinical Events Committee (CEC) is comprised of independent, interventional cardiologists who are not participants in the study. The CEC is charged with the development of specific criteria used for the categorization of clinical events and clinical endpoints in the study that are based on protocol. The CEC will meet regularly to review and adjudicate all clinical events in which the required minimum data are available. All members of the CEC will be blinded to the primary results of the trial. Deaths will be considered as cardiac unless a non-cardiac cause is demonstrated. The diagnosis of myocardial infarction has been in accordance with Third Universal Definition of Myocardial Infarction. Case report forms clearly separate target lesion from target vessel revascularization. However, all the angiograms of patients requiring target vessel revascularization will be analyzed at the core lab to determine the exact site of revascularization. The Consensus Report From the

Bleeding Academic Research Consortium will be used to evaluate bleeding.

2.4 Angiographic analysis

All coronary angiograms will be analyzed at the central angiographic core laboratory. Studies will be analyzed by trained personnel blinded to treatment allocation and using a standard methodology. An automatic edge-detection system (CAAS II System; Pie Medical Imaging BV, Maastricht, the Netherlands) will be used for offline quantitative measurements. After intracoronary administration of nitroglycerine, orthogonal views (three separate projections) will be selected by the operator (avoiding vessel foreshortening and the overlap of major side branches) and matched projections will be repeated immediately after the intervention and at late follow-up. Both in-lesion and in-segment (lesion + complete treated segment + 5 mm adjacent margins) analyses will be performed. The same measurements will be obtained after the procedure and at follow-up.

2.5 Main outcome measurements

The primary endpoint is in-segment late loss at nine months follow-up as measured by quantitative coronary angiography. Major secondary endpoints include procedural success, such as device success, lesions success and clinical success, and binary restenosis rate (> 50% diameter stenosis) at nine months. The main clinical outcomes are all-cause mortality, myocardial infarction, and total repeat revascularization during follow-up.

2.6 Statistical analyses

The primary objective is to demonstrate the non-inferiority of the in-segment late loss after a novel paclitaxel-coated balloon (RESTORE DEB) angioplasty compared with the corresponding late loss following current con-generic product (SeQuent® Please) angioplasty in Chinese ISR patients. Based on the study results of PEPCAD China ISR, we postulated the late lumen loss level is 0.46 mm in the test group and the control group, and the conservative estimation of combined standard deviation is ± 0.48 mm. To claim the investigational DEB non-inferior to the control DEB, we assumed the non-inferiority margin of 0.195 mm as acceptable difference, which is referred to the SPIRIT Ⅲ study, α = 5% (two-sided), and a statistical power of 80%, grouped according to the ratio of 1: 1. It is calculated that the required sample size is 192 patients (with 96 patients in each group). In consideration of possible 20% drop-out from the angiography follow-up, it is planned to include 240 patients in total, with 120 patients in each group. The trial design is presented in Figure 1.

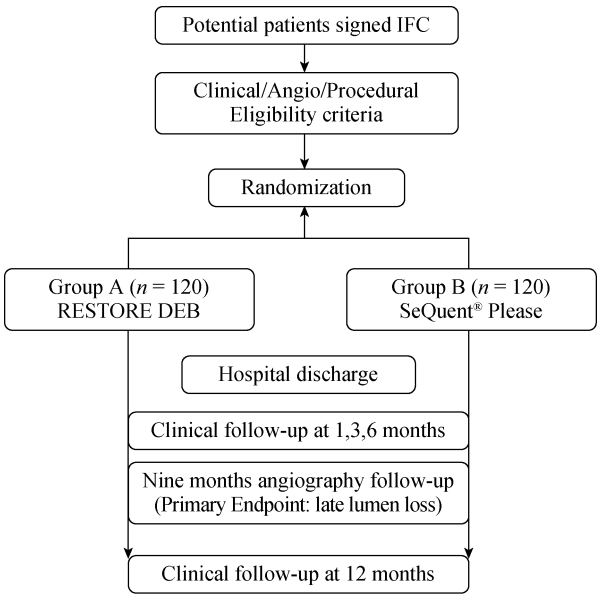

Figure 1. Study flow chart detailing randomisation of patients and patients with late angiography and clinical follow-up. IFC: informed consent form.

Baseline characteristics of study patients will be summarized in terms of frequencies and percentages for categorical variables and by means ± SD and median with quartile for continuous variables. Categorical variables will be compared with chi-square test or Fisher's exact test. Continuous variables will be compared using the Student's *t*-test or the Mann-Whitney test. Main effect estimated will be presented with the corresponding 95% confidence interval (CI). Multivariate predictors of all primary and secondary endpoints will be determined using covariance analysis. After correction of the homogeneity of variance, minimum mean square of dependent variable, minimum mean square error and its 95% CI between groups will be calculated. Whether the hypothesis will be established will be determined by comparing the 95% CI and the assumed non-inferiority margin. The statistical analysis will be conducted by Medical statistics department, National Center for Cardiovascular Diseases. All analyses with be performed according to the intention-to-treat principle unless otherwise specified. The SAS®9.4 statistical software will be used. A value of $P < 0.05$ will be considered as statistically significant.

3 Discussion

Although the rate of ISR has greatly decreased with the remarkable improvements in medical technology, there were also numerous patients which were required target vessel revascularization.[1,2,18] DEB has emerged as a novel

therapeutic tool for ISR. The advantages of DEB include effective anti-proliferative drugs delivery in the vessel wall, reduced duration of dual antiplatelet therapy without polymers and the avoidance of the stent implant.[14,19,20] The most commonly used DEB was the SeQuent® Please DEB and there were numerous studies have reported the safety and efficacy of SeQuent® Please DEB compared with other strategies for the treatment of ISR.[17,21,22] However, due to the lipophilicity and prolonged tissue retention rate of paclitaxel, the drug chemical status (crystalline or amorphous), the excipient or carrier used (different for each DEB), varied delivering balloon surface and the technology used to assemble all these components are equally important for the efficacy and contribute to each unique final DEB product.

RESTORE DEB is the newer-generation coronary balloon catheter coated with paclitaxel. The RESTORE DEB catheter is a double lumen catheter for rapid exchange use with semi-compliant balloon and two radiopaque markers, proximal and distal, to aid in the balloon positioning under fluoroscopy. The coating of RESTORE DEB for the balloon consists of a degradable, drug-eluting Ammonium Salt-Paclitaxel composite, which could avoid drug washing off and the potential risk of micro embolization during catheter tracking to the lesion site. The coating layer of the RESTORE DEB catheter is applied to release an effectual proportion of paclitaxel to the vessel wall of the artery at the dilated stenosis. The drug substance paclitaxel is known to reduce the risk of restenosis by inhibition of smooth muscle cell proliferation. During the insertion of the balloon catheter and the coronary lesion tracking, the multi-folded balloon protects the loaded drug substance from early wash-off effect. The anti-proliferative drug substance paclitaxel will be immediately released at the lesion site within 30-60 s. Bioavailability of paclitaxel is guaranteed because the drug substance is an integral part of the coating. Although there were a number of advantages in RESTORE DEB, few clinical trials have been conducted to study the safety and efficacy of this newer-generation DEB.

In order to compare the safety and efficacy of the newer-generation DEB (RESTORE DEB) versus the most frequently used DEB (SeQuent® Please), we perform the first randomized clinical trial of the world to determine RESTORE DEB will be non-inferior to SeQuent® Please in Chinese ISR patients. As there was only one study showed the results of DEB in Chinese patients with ISR, we selected the parameter values in the PEPCAD China trial to calculate the sample size of this study and also consideration of possible 20% drop-out from the angiography follow-up. Finally, the sample size of this study is 240, larger than that in the PEPCAD China trial (220 patients), and will be compared for in-segment late loss, the primary endpoint. Moreover, our study will also be powered for the comparison of other secondary angiographic endpoint, binary restenosis rate. The in-segment late loss and binary restenosis rate has been widely used and validated in previous trials comparing between different therapeutic strategies in PCI. These variables will provide strong evidence into the relative efficacy of RESTORE DEB and SeQuent® Please. Furthermore, the randomization in this study is layered according to whether patients are concomitant with diabetes or not. We could further explore the treatment effects of different DEBs in pre-specified subgroup population.

3.1 Previous studies of DEB used in the treatment of ISR

In the management of BMS-ISR, the PACCOCATH-ISR trial first reported that DCB was superior to POBA in fifty-two patients with BMS-ISR.[23] Following the cohort, angiographic results at six month and clinical outcomes at five years also confirmed the same conclusion.[24] The PEPCAD Ⅱ trial enrolled 131 patients with BMS-ISR to compare the efficacy of DCB and DES, and showed that DCB was superior to paclitaxel DES in in-segment late lumen loss at 6 months.[25] However, the Ribs Ⅴ Clinical Trial demonstrated that DES (everolimus) provide superior late angiographic findings compared with DEB.[26] The two randomized trials both demonstrated clinical outcomes were similar in DEB and DES groups. Thus, all clinical data indicated that DEB was superior to POBA, and non-inferior to DES in the treatment of BMS-ISR.

Although the rate of DES-ISR is less than 10%, the treatment of DES-ISR is more therapeutic challenging than BMS-ISR. In patients with DES-ISR, Rittger and his colleagues demonstrated that DCB was superior to POBA not only in late lumen loss, but also in clinical outcomes.[27] Another randomized clinical trial also reported angiographic and clinical superiority of DCB compared with POBA in 90 DES-ISR patients.[28] In addition, when compared the efficacy of DCB versus first generation DES, the non-inferiority of DCB was suggested by ISAR-DESIRE 3 trials in 402 patients with DES-ISR and by PEPCAD China ISR Trial in 220 Chinese patients with DES-ISR.[17,29] Furthermore, several clinical trials were performed to compare the DCB with newer-generation DES in DES-ISR patients. However, the results were inconsistent or even contradictory. The RIBS Ⅳ randomized clinical trial enrolled 309 patients with DES-ISR to compare the DCB with DES (everolimus-eluting stents) and showed that newer-generation DES was superior to DCB in in-segment minimal lumen diameter at 9 months and clinical outcomes at 12 months.[30] Kawamoto, *et al*.[31] reported that there was no significant

difference of clinical outcomes at 12 months between DCB and newer-generation DES in 179 patients with DES-ISR. However, Almalla and his colleagues demonstrated that DEB was superior to newer-generation DES on the clinical outcomes in the treatment of DES-ISR. In this study a MACE rate of 8.6% was found in the DEB group at 12 months, which is much lesser than that in the newer-generation DES group in patients with DES-ISR.[32] These studies indicate that DEB is superior to POBA, but has similar efficacy for the treatment of DES-ISR.

3.2 Limitations

Some limitations of this trial should be addressed. First, this trial included only 240 patients with ISR, the sample size was relatively small which was not fully powered to detect differences in clinical outcomes. Regarding the analyses in which the patients were stratified by diabetes status, the sample sizes in the subgroups were too small to limit the ability to explore effects in these subgroups. Second, this study is not a double-blinded trial as the treating physician could not be blinded since the two types of DEB were obviously different. Third, some clinical or angiographic features should also be considered in the process of random grouping, which could be helpful to study on the interaction effects between these selected features and the main outcomes, which will be beneficial for patients favor to select one DEB over another.

3.3 Conclusions

This multi-center randomized clinical trial will compare the safety and efficacy of the RESTOREDEB versus SeQuent® Please DEB in Chinese patients with coronary ISR.

3.4 Impact on daily practice

Treatment of DES-ISR still remains a technical and clinical challenge. The results of this trial will help to elucidate the safety and efficacy of two types of DEB (RESTORE DEB and SeQuent® Please) in patients with coronary ISR. The results of this study will determine whether RESTORE DEB are able to obtain similar angiographic results compared with SeQuent® Please DEB in patients with coronary ISR. Furthermore, this study will also compare the late clinical outcome of these two DEBs, thus providing new evidence to inform clinical decision-making.

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