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# Comparison of two different drug-coated balloons for the treatment of in-stent restenosis: A long-term single-centre experience☆

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ABSTRACT

*Objectives:* We aim to evaluate the long-term efficacy of two different paclitaxel-coated balloons (PCBs) for the treatment of coronary in-stent restenosis (ISR).
*Methods:* Between February 2011 and February 2012, all consecutive patients with ISR lesions treated with the SeQuent® Please (B. Braun, Melsungen, Germany) PCB or with the DIOR® (Eurocor GmbH, Bonn, Germany) PCB at our institution were prospectively included and followed up for 36 months by clinical observation. The primary endpoint was the clinically driven target lesion revascularization (TLR) rate at 36 months.
*Results:* 65 patients with 74 ISR lesions were included. 43 ISR lesions were treated with the SeQuent® Please PCB and 31 with the DIOR® PCB. Baseline clinical, lesion characteristics and procedural data did not significantly differ between the groups. The TLR rate was significantly lower in patients treated with the SeQuent® Please PCB compared with the DIOR® PCB (4.7% vs. 22. 6%, p = 0.03) at 36 months.
*Conclusions:* This registry suggests that there are differences in terms of TLR between two clinically available PCBs. The SeQuent® Please PCB demonstrated lower TLR rate compared to the DIOR® PCB at 36 months follow up.



## 1. Introduction

Paclitaxel-coated balloons (PCBs), a nonstent-based local antiproliferative drug-delivery system, are one of the most recently available tools among the different treatment options in percutaneous coronary revascularization. Coronary in-stent restenosis (ISR) is one of the challenging problems in the field of interventional cardiology. Compared with a standard uncoated balloon, a PCB significantly reduced neointimal proliferation and the need for target vessel revascularization (TVR) in an ISR setting [1]. PCBs have been demonstrated to be successful for the treatment of ISR after bare-metal stent (BMS) or drug-eluting stent (DES) implantation [1–5]. The potential advantage of PCB use as an alternative to DESs is that PCBs do not need a stent or durable polymer, reducing the risk of stent thrombosis and the need for prolonged dual antiplatelet therapy (DAPT) [6]. Currently there are several commercially available PEBs in Europe which all use paclitaxel as an active drug. However, the coating and release methods are quite different [7] so theoretically one cannot assume a class effect for all PCBs. This study aims to evaluate the long-term efficacy and safety of two second-generation PCBs for the treatment of coronary ISR in real life clinical practice.

## 2. Methods

The study is a prospective registry performed at one Spanish cardiology department in Jerez de la Frontera Hospital. The study was not sponsored and the design of the study, the analysis of the results and the preparation of the manuscript was made by the investigators. The institutional committee on human research approved the study protocol.

### 2.1. Patients

Between February 2011 and February 2012, all consecutive patients with ISR lesions treated with the SeQuent® Please (B. Braun, Melsungen, Germany) PCB or with the second generation DIOR® (Eurocor GmbH, Bonn, Germany) PCB at our institution were prospectively enrolled. Included patients were >18 years of age and presented with stable angina or acute coronary syndromes. Target lesions were coronary ISR lesions, defined as a stenosis assessed by angiographic visual estimation (>50%) in a previously stented segment identified by coronary angiography for any clinical indication. Additionally, patients

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with contraindications to DAPT and a life expectancy <12 months were not included.

### 2.2. The paclitaxel-coated balloons evaluated

The SeQuent® Please is a second generation drug-coated balloon that uses an antirestenotic drug (paclitaxel) in a concentration of 3 μg/mm$^2$ in a matrix with the hydrophilic contracts media, iopromide. Iopromide acts as a spacer and thereby makes the coating porous and paclitaxel bioavailable. The hydrophilic character of iopromide and the lipophilic properties of paclitaxel support the release of the drug from the balloon surface and its delivery into the vascular wall [8]. The recommended inflation time is 30 s to achieve optimal drug delivery to the vessel wall.

The first generation DIOR® PCB had a roughened balloon surface, containing a crystalline coating. One of the drawbacks of this PCB was the low delivery dose of paclitaxel into the vessel wall (25% of the dose loaded on the balloon) with an inflation time of 60 s. The currently available second generation DIOR® PCB is coated with 3 μg/mm$^2$ of paclitaxel using shellac as its excipient which is composed of a network of hydroxyl fatty acid esters and sesquiterpene acid esters. In contrast with SeQuent® Please, no plasma concentrations of paclitaxel can be detected after DIOR® inflation, indicating no systemic circulation release with the use of a DIOR®. This second generation DIOR® PCB showed significantly better properties of distribution into the vessel wall with an 5-to 20-fold higher tissue/drug concentrations in comparison to the first generation DIOR®, and around the same delivery dose of the SeQuent® Please PCB. The recommended inflation time is 30–45 s to achieve adequate drug delivery to the vessel wall [9].

### 2.3. Interventional procedure

The procedures were performed after obtaining written informed consent. All patients received pretreatment, commenced at least 1 day prior to the procedure, with aspirin (100–300 mg/day) and clopidogrel (a minimum of 300–600 mg load and 75 mg/day). During the procedure, the patients received anticoagulation with unfractionated heparin (70 UI/kg) to achieve an activated clotting time of 250–300 s or bivalirudin. Glycoprotein IIb/IIIa inhibitors were administered at operator's discretion. After the procedure, patients received DAPT with clopidogrel (75 mg/day) and aspirin (100 mg/day) for at least 1 month, or 6–12 months if an additional stent was implanted during the same session, followed by aspirin indefinitely.

After routine coronary angiography, patient's target lesion was either predilated with conventional non-coated balloons or underwent direct treatment with the PCB. The choice between SeQuent® Please and DIOR® PCB was at the discretion of the treating physicians (no randomization was performed). These PCBs were the two available in our hospital during the study period. The length of the PCB was chosen to exceed the target lesion for at least 2 to 3 mm on each side. It should also have a balloon to vessel ratio of 0.8–1.0 and be inflated for 30 s with a minimum of 10 atm. Additional stent was implanted if the result after PCB therapy alone was not satisfactory because recoil, residual stenosis, or dissections.

### 2.4. Clinical follow up and study endpoints

Patients were followed up for 36 months by clinical observation after the index procedure. The primary endpoint was the target lesion revascularization (TLR) rate at 36 months. TLR was defined as any repeat revascularization (percutaneous or surgical) due to a restenosis in the PCB-treated segment (which included 5 mm beyond the treated segments proximally a distally). Restenosis was defined as a diameter stenosis of at least 50%. Quantitative analysis of the angiographic images was performed using the QCA-CMS® 6.1 system (MEDIS, Medical Imaging Systems, Leiden, The Netherlands).TLR was based on symptoms of coronary ischaemia, angiographic findings at scheduled or unscheduled follow-up, or both. The secondary endpoint was the occurrence of major adverse cardiac events (MACE), defined as a composite of cardiac death, myocardial infarction (MI), and TLR at 36 months. Deaths were classified as either cardiac or non-cardiac. Deaths from unascertained causes were assumed to be cardiac. MI was assumed to have occurred if two of the following five criteria were present: chest pain lasting longer than 30 min; electrocardiographic changes typical of acute myocardial infarction (ST-segment elevation of 0.1 mV in at least two adjacent ECG leads or new occurrence of a complete left bundle branch block); increase of creatine kinase concentration or its MB isoform to at least three times the upper normal value; new, clinically significant Q-waves; and chest pain leading to angiography up to six hours after the onset of the chest pain with angiographic evidence of an occluded vessel. The definition for vessel thrombosis follows the Academic Research Consortium criteria for stent thrombosis [10]. Angiographic success was defined as a residual final stenosis <30% with TIMI 3 flow after PCB treatment and possible bail-out stenting. Procedural success was defined by the presence of angiographic success without in-hospital MACE.

### 2.5. Statistical analysis

Baseline clinical, angiographic and procedural variables were entered prospectively into a computerized database and retrospectively analyzed. The statistical analysis was done with the SPSS 19.0 package (SPSS, Inc., Chicago, Illinois).Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables as absolute counts and percentages. Student's t test was used for continuous variables and categorical variables were compared with chi-square test or, when appropriate, Fisher's exact test. A p value of less than 0.05 was considered statistically significant.

## 3. Results

### 3.1. Patient and procedural characteristics

Between February 2011 and February 2012, a total of 65 consecutive patients with 74 ISR lesions treated with PCB at our institution were included. 43 ISR lesions (21 BMS, 22 DES) were treated with the SeQuent® Please PCB and 31 (11 BMS, 20 DES) with the DIOR® PCB. The mean age was 66.2 ± 10.8 years and 56.9% were diabetic patients. The majority of patients presented with stable angina (63.1%).Baseline clinical characteristics are summarized in Table 1. The target lesion was mainly located in

**Table 1**
Baseline Clinical Characteristics.

| Variable | ALL | DIOR ® | SEQUENT PLEASE ® | p Value |
|---|---|---|---|---|
| Number of patients | 65 | 27 | 38 | — |
| Number of lesions | 74 | 31 (46.6%) | 43 (53.4%) | — |
| Age (years) | 66.2 ± 10.8 | 64.9 ± 10.9 | 67.2 ± 10.8 | 0.42 |
| Male | 45 (69.2%) | 18 (66.7%) | 27 (71.1%) | 0.71 |
| Cardiac risk factors | | | | |
| Diabetes mellitus | 37 (56.9%) | 14 (51.9%) | 23 (60.5%) | 0.49 |
| Hypertension | 56 (86.2%) | 21 (77.8%) | 35 (92.1%) | 0.15 |
| Hyperlipidemia | 38 (58.5%) | 12 (44.4%) | 26 (68.4%) | 0.053 |
| History of Smoking | 32 (49.2%) | 13 (48.1%) | 19 (50%) | 0.88 |
| Chronic renal failure | 8 (12.3%) | 3 (11.1%) | 5 (13.2%) | 0.56 |
| Previous MI | 32 (49.2%) | 13 (48.1%) | 19 (50%) | 0.88 |
| Previous CABG | 5 (7.7%) | 1 (3.7%) | 4 (10.5%) | 0.39 |
| Clinical presentation | | | | |
| Stable angina | 41(63.1%) | 19 (70.4%) | 22 (57.9%) | 0.30 |
| Non-ST ACS | 22 (33.8%) | 7 (25.9%) | 15 (39.5%) | 0.26 |
| STEMI | 2 (3.1%) | 1 (3.7%) | 1 (2.6%) | 0.80 |
| LVEF | 57.2 ± 12.2 | 57.2 ± 12.2 | 57.2 ± 12.4 | 0.99 |

Values are n (%) or mean ± SD. DES = drug-eluting stent (s); BMS = bare-metal stent (s); MI = myocardial infarction; CABG = coronary artery by-pass grafting; ACS = acute coronary syndrome; STEMI = ST-elevation myocardial infarction; LVEF = Left ventricular ejection fraction.