Treatment of drug-eluting stents in-stent restenosis with paclitaxel-coated balloon angioplasty: Insights from the French "real-world" prospective GARO Registry

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Abstract

Background: Data about paclitaxel-eluting balloon (PCB) angioplasty to treat drug-eluting stents (DES) in-stent restenosis (ISR) were mainly collected in selected patient populations in the setting of randomized trials. The main goal of this prospective registry was to confirm the positive findings of these studies in an unselected population in clinical practice.

Methods: Consecutive patients with DES-ISR treated by PCB angioplasty were recruited in this prospective real-world registry. The primary endpoint was clinically driven target-lesion revascularization (TLR) at 9 months. Secondary endpoints included acute technical success, in-hospital outcomes, 9-month major adverse cardiac events (MACE) a composite of death, myocardial infarction (MI) and TLR and the occurrence of target vessel revascularization.

Results: A total of 206 patients (67.7±10.2 years, 80.6% male, 41.3% diabetics) with 210 lesions were recruited. Unstable coronary artery disease was present in 55.3% of patients. The time from DES implantation to DES-ISR was 3.0±2.4 years. Quantitative analyses revealed that patterns of treated DES-ISR were focal in 55.7% and diffuse in 44.3%. The reference diameter was 2.76 ±0.64 mm. The 9-month follow-up rate was 90.8% (187/206). At 9 months, the TLR rate was 7.0% (13/187) whereas the rates for MACE, MI and cardiac death were 10.7% (20/187), 4.8% (9/187) and 2.1% (4/187) respectively. Results were consistent in patients with paclitaxel and non-paclitaxel-eluting stents (PES) ISR.

Conclusion: This large prospective registry demonstrated acceptable rates of TLR and MACE at 9 months after treatment of DES-ISR by PCB angioplasty. PCB angioplasty was equally effective in patients with PES-ISR and non PES-ISR.

Key words: drug-eluting stent in-stent restenosis, paclitaxel-coated balloon, target lesion revascularization

Introduction

The introduction of drug-eluting stents (DES), through the dramatically decreased incidence of in-stent restenosis (ISR) it yielded, is considered a revolution in the field of percutaneous coronary intervention (PCI)[1]. The further-improved safety profile of new-generation DES led to their unrestricted use in increasingly complex patients and lesions[2,3] so that latest European guidelines[4] state that DES should be considered by default in all clinical conditions and lesion subsets. However, DES have not eliminated the ISR issue as a recent angiographic study shown that these new-generation devices are still plagued by a 12% rate of angiographic ISR[5].

Paclitaxel-coated balloon (PCB) were initially studied in bare-metal stent (BMS) ISR against plain old balloon angioplasty (POBA)[6-9] or paclitaxel-eluting stent (PES)[10], since it appeared very attractive to locally deliver a drug without the introduction of additional stent layers. These studies showed an early and sustained benefit of PCB over POBA on angiographic and clinical outcomes whereas only a trend towards better clinical results was achieved against PES despite significantly improved angiographic findings with PCB. There are increasing data regarding treatment of DES-ISR by PCB angioplasty either compared to POBA[11,12], PES[13] or both techniques[14]. These studies demonstrated that late lumen loss (LLL), diameter stenosis (%) and major adverse cardiac events (MACE) were consistently and significantly lower in patients treated by PCB than in patients treated by POBA[11,12]. Moreover, PCB angioplasty matched the angiographic and clinical results of repeat stenting with PES[13,14]. These data recently led the European Society of Cardiology to give a class IA recommendation for the use of PCB in BMS and DES-ISR[4]. In this setting, the main goal of this observational study was to confirm these positive findings in an unselected French patient population under routine use.

Methods

Objectives

The aim of the GARO (Groupe des Angioplasticiens de la Région Ouest) registry was to evaluate the safety and efficacy of PCB angioplasty to treat DES-ISR in native coronary arteries. This was a non-randomized, open-label, single arm, observational registry conducted in 13 French centers (see list in Appendix). The protocol was approved by the French national ethics committee as part of the parent 'All-Comers Registry' which also included other indications beside DES-ISR. All patients gave written informed consent. Data were captured using an established electronic case report form with built-in plausibility checks previously proved useful and efficient in related observational PCB studies[15,16]. The two coordinating investigators (MB,JB) were responsible to contact co-investigators whenever the e-CRF plausibility checks indicated discrepancies.

Patients

All consecutive patients >18 years old with DES-ISR, treated by PCB angioplasty were enrolled in this registry. All Mehran types of ISR[17] in native coronary arteries with reference vessel diameters between ≤ 2.5 and ≤ 3.5 mm and ≤ 22 mm in length were eligible. ISR had to reduce the reference vessel diameter either by ≥70% or ≥50% with documented ischemia corresponding to the target lesion. Major exclusion criteria were: cardiogenic shock, Killip class III heart failure, pregnant/lactating women, severe valvular heart disease, patients with a life-expectancy < 5 years and patients with contraindications to dual-antiplatelet therapy or known hypersensitivity to acetylsalicylic acid, clopidogrel, paclitaxel, or heparin.

Endpoints and definitions

The primary endpoint was clinically driven target lesion revascularization at 9 months (TLR) as a composite of re-PCI and coronary artery bypass grafting (CABG). Secondary endpoints included the procedural success rate, definite acute/subacute vessel thrombosis rates as defined by the ARC criteria[18]. Moreover, major adverse cardiac events (MACE), defined as the composite of TLR, death of cardiac or unknown origin and myocardial infarction (MI), were also documented. Myocardial infarction was diagnosed with corresponding ECG changes and/or cardiac enzyme elevations according to each institution's routine diagnostic algorithms.

Procedure

Patients received 500 mg of aspirin before the intervention or were receiving long-term treatment. A clopidogrel loading dose of 300-600 mg was administered. Heparin (50-100UI/kg) was administered upon insertion of the sheath. Intracoronary Nitrates (0.2 mg) were administered 2 minutes before baseline and final reference angiography performed in two near-orthogonal views. The paclitaxel-coated (3μg/mm²) PTCA catheter based on the Paccocath® Technology (SeQuent® Please, B.Braun Melsungen AG) was used accordingly to previously published guidelines[19]. Especially, special attention was given to proper predilation of the target lesion and PCB was not used unless residual diameter stenosis was ≤ 30% after balloon predilation. A 60s PCB inflation at a minimum of 10 bar was recommended unless not tolerated by the patient (hypotension and/or severe ventricular arrhythmia due to ischemia). Additional stents were implanted in case of significant recoil, residual stenosis or dissections after PCB therapy. Lesion length and vessel reference diameter were assessed using online quantitative coronary angiography or visual estimation. Dual-antiplatelet therapy was recommended for at least 9 months after the procedure.

Quantitative Coronary Angiography

Angiographic data were routinely collected pre- and post-procedure with the use of identical projections and analyses. Quantitative analysis of the coronary angiographic images was done by 2 independent operators in an independent angiographic core laboratory. A difference of ±3% of the relative stenosis between the two operators was deemed acceptable. If the discrepancy exceeded this value, a third operator decided upon the result of the assessment. In case of insufficient quality of the angiogram, the patient was rejected. The CAAS II research system (Quantcor QCA, Pie Medical Imaging, Maastricht, The Netherlands) was used for automated contour detection and quantification.

Statistical analysis

Continuous variables are expressed as mean±SD. Normality was tested using Kolmogorov-Smirnov test. Continuous variables were compared using unpaired t-test or Mann-Whitney U-test as appropriate. Categorical variables are presented as counts and percentages and were compared with the use of Fisher's exact or $\chi 2$ test, as appropriate. Time-to-event data are shown as Kaplan-Meier curves and were compared using the log-rank test. Kaplan-Meier curves reports end-points that were censored at the time of first event or at 9 months, whichever occurred first. All reported p-value are 2-sided and a p-value <0.05 was considered significant. Analyses were done with SAS version 9.2 (SAS Institute Cary, NC USA) and SPSS version 20.0 (IBM, Munich, Germany). Subgroup analyses were planned for DES-ISR subgroups consisting of PES-ISR and non-PES-ISR due to potential differences in clinical outcomes.

Results

Patients

From February 2011 to April 2013, a total of 206 consecutive patients (mean age: 67.7±10.2 years; male sex: 80.6%) were included in the present study. Diabetes mellitus was present in 85 patients (41.3%), 143 (69.4%) had hypertension, 156 (75.7%) had hyperlipidemia and 97 (47.1%) were current smokers. Thirty four patients (16.5%) presented with MI and a total of 114 patients (55.3%) had unstable coronary artery disease at presentation. The mean time from DES implantation to DES-ISR was 3.0±2.4 years. Table 1 summarizes baseline clinical characteristics of the study population and provides a comparison between patients with a PES-ISR (n=42) and a non PES-ISR (n=164). Both groups were comparable at the exception of a higher rate of unstable angina in the PES-ISR group (43.3% vs. 21.4%, p=0.009).

Baseline angiographic characteristics (Table 2)

The majority of patients had single-vessel disease (56.8%) with a target lesion located in the left anterior descending artery in the left anterior descending coronary artery in 37.6%, the left circumflex coronary artery in 27.6% and the right coronary artery in 29.0%. The most represented target stent types were PES (21.2%), sirolimus-eluting stent (SES, 38.4%) and new-generation everolimus-eluting stent (EES, 29.1%). Diffuse ISR pattern was present in 44.3% of patients.

Quantitative coronary angiographic analysis and procedural characteristics

The mean lesion length and reference vessel diameter were 12.59±8.87mm and 2.77±0.78mm respectively (Table 3). The mean residual stenosis diameter was 15.6±12.5% post-index procedure (Table 3). Diameter stenosis was smaller in the PES-ISR group

(57.5±17.2% vs. 67.2±16.4%, p=0.002). However, this difference was not observed after the intervention (14.6±11.1% vs. 15.9±12.8%, p=0.575). There were also no post-procedural differences between groups in terms of reference vessel diameter (p=0.446) and MLD (p=0.262).

The mean PCB length and diameter were 19.5±4.9mm and 3.0±0.36mm respectively. For treatment of 210 lesions, 227 PCB were used (1.07 PCB per lesion).The mean inflation pressure was 12.6±3.7 bar. After PCB therapy, dissections were documented in 3 lesions (1.4%) and 6 patients (2.9%) necessitated additional stenting. Procedural characteristics are summarized in Table 4. Procedural success of the PCB interventions was reported for 207 lesions (98.6%) with a borderline significant difference (p=0.046) between the PES-ISR and non-PES-ISR groups (Table 4).

In-hospital and accumulated 9-months clinical events

There were no differences between the PES-ISR and the non PES-ISR groups during hospitalization (Table 5). Overall there was only one cardiac death and one TLR up to the point of discharge. Complete follow-up (by telephone: 79.7% or by hospital visit: 20.3%) was achieved in 187 patients (90.8%) at a mean of 8.9±0.84 months. The primary endpoint of TLR occurred in 13 patients (7.0%) whereas 10.7% of patients suffered a MACE. 9-month rates of MI and cardiac death were 4.8% and 2.1% respectively (Figure 1, Table 5).

There was no difference between the PES-ISR and the non PES-ISR groups in the 9-month rates of TLR (3.6% vs. 7.0%, p=0.314), MACE (7.2% vs. 9.2%, p=0.738), MI (4.8% vs. 4.4%, p=0.772), cardiac death (4.8% vs. 1.4%, p=0.791) as assessed by Kaplan-Meier method (Figure 2). Regarding TLR rates, these results were consistent across various subgroups. However, patients with a delay between DES implantation and DES-ISR < 12

months presented a clear trend towards higher rate of MACE (Figure 3). Although, treatment of new-generation EES-ISR resulted in higher absolute 9-months rates of TLR (9.7% vs. 4.7%) and MACE (15.3% vs. 6.8%), these differences did not reach statistical significance.

Discussion

The main finding of the present study is that PCB angioplasty to treat DES-ISR achieved acceptably low rates of TLR and MACE at 9 months in a French unselected patient population which is in agreement with previously conducted DES-ISR trials.

DES-ISR and BMS-ISR share some common mechanisms such as stent underexpansion, stent fracture, stent malapposition, and non-uniform strut distribution but DES-ISR also presents specific stimuli of neointimal thickening like localized hypersensitivity, non-uniform drug deposition, polymers and drug resistance[20,21]. This may explain why treatment of DES-ISR remains highly challenging. Indeed, a recent multicenter retrospective analysis of 392 patients with 481 DES-ISR lesions, which were treated with repeat DES stenting in 66% of cases, showed rates of recurrent restenosis ranging from 29.0 to 65.6% depending on the initial pattern of DES-ISR[21]. Some authors[9,22] suggested that DES-ISR identifies a high-risk group of patients in which the best available antirestenotic therapy to date has failed and PCB angioplasty in this setting, like repeat DES stenting, has shown worse results than in the treatment of BMS-ISR[9,12]. The results of the present study showing higher absolute rates of TLR and MACE after treatment of new-generation EES-ISR support this idea of a very challenging group of patients exhibiting signs of resistance to our current "gold-standard".

Previous studies investigating the efficacy and safety of PCB angioplasty to treat DES-ISR reported rates of TLR ranging from 2.9% at 6 months[9] to 22.1% at 12 months[14] and rates

of MACE ranging from 6.6%[9] to 23.5%[14] at the same time points (Table 6). Thus, the clinical outcomes of the present study are in agreement with previously published trials[9,11-14]. Post-procedural diameter stenosis (Table 6) was 15.6±12.5% in our series which agrees well with the findings in the ISAR DESIRE 3[14] (18.5±8.3%) and the PEPCAD DES[12] (12.6%±6.2%) trials. Even lower procedural diameter stenoses were reported by Xu et al.[13] (10.5%±7.2%) whereas Habara and coworkers documented the highest remaining degree of stenosis (25.7%±7.2%). These discrepancies seems attributable to lower post-procedural MLD in studies by Habara et al.[9,11] which highlights the adamant importance of a proper pre-dilation of the lesion before using a PCB with regard to angiographic outcomes. These procedural results does not necessarily relate to clinical outcomes (Table 6) however they greatly influence the conclusion of studies using an angiographic measure at follow-up as their primary end-point. Intermodality studies comparing PCB angioplasty to repeat DES stenting might especially be prone to this bias as repeat stenting usually results in higher post-procedural MLD[13,14,23]. Moreover, the number of stent layers may introduce additional bias. Rittger et al[12] reported that 53.6% of the ISR lesions treated in their patient population had at least 2 metal layers the latest being a DES which may explain the relatively high late lumen loss in the PCB and POBA groups (0.43± 0.61 mm vs. 1.03± 0.77 mm, p<0.001). Our belief is that a proper pre-dilation is of adamant importance in the setting of DES-ISR. Cutting and especially the more flexible and deliverable scoring balloons may be particularly attractive as they allow device anchoring in the lesion, deep incision of neointimal tissue and prevent "watermelon seeding" effect which might be responsible for edge dissection and unplanned stent implantation. Whether these devices provide better results in the treatment of DES-ISR is currently the subject of ongoing clinical trials (21).

Our finding that PCB angioplasty results in similar clinical outcomes after treatment of PES-ISR and non PES-ISR is in line with the conclusion of the ISAR-DESIRE 2 study[24]. In

this trial, 450 patients with 483 SES-ISR lesions were randomized to repeat DES stenting with either a SES or a PES. No differences were seen between the two strategies with regard to angiographic or clinical outcomes. On the contrary, the RIBS III (Restenosis Intra-Stent: Balloon Angioplasty Versus Drug-Eluting Stent) trial, a prospective multicenter registry including 363 patients with DES-ISR, demonstrated, after adjustment using propensity score analyses, a significant reduction of the composite of cardiac death, MI and TLR (hazard ratio: 0.56, 95% CI: 0.33 to 0.96, p=0.038) with the use of a switch strategy[25]. If overall data about the switch strategy remain inconclusive, an interesting point in the RIBS III trial is the suggestion of a superiority of second-generation DES over first-generation DES. Indeed, so far, studies and meta-analyses support non-inferiority of PCB angioplasty against first-generation DES[10,13,14,26,27] but little is known about the comparative effectiveness of PCB and new-generation DES in DES-ISR. A recent study by Almalla et al.[28] compared PCB angioplasty to EES implantation in an DES-ISR study population using a historic control arm and showed significantly lower TLR and MACE rates in the PCB group. Contrarily, in the setting of BMS-ISR, the RIBS V (Restenosis Intra-stent: Drug-eluting Balloon vs. Everolimus-eluting Stent) trial[23], which recently provided the first randomized comparison of PCB angioplasty with second-generation EES in 189 patients, demonstrated improved angiographic results (LLL, diameter stenosis) after EES. However, binary restenosis rates were low and similar in both groups (4.7% vs. 9.5%, p =0.22) and these better angiographic results did not translate into improved clinical outcomes. Therefore, additional data are needed to define the respective roles of PCB angioplasty and EES implantation in the treatment of DES-ISR.

The time course between DES implantation and ISR seems to be an important factor to consider when addressing the issue of DES-ISR. We showed a higher rate of MACE in patients with a delay between DES implantation and DES-ISR < 12 months. The shorter the

time frame from DES implantation to DES-ISR is, the less likely ISR is to be caused by neointimal hyperplasia whereas mechanical factors probably play a crucial role. It has also been shown that early ISR presentation was correlated to diffuse ISR patterns which may explain the worse results we observed in the sub-group of patients with a short delay between DES implantation and ISR as the morphological pattern of DES-ISR is an important predictor of clinical outcomes, especially TLR[20].

By definition a study limitation of all-comers registries is a less stringent control of data collection. Moreover, source data monitoring was only conducted whenever discrepancies were detected by the electronic data capture system. As a consequence, some under-reporting may have occurred in the present study. Owing to the evaluation of PCB angioplasty in routine clinical practice, we did not provide an angiographic follow-up and the database did not include information about intracoronary imaging techniques as their use to identify underlying mechanical factors was left to the discretion of the operator in this real-life setting. However, rates of 20% and even 42% of stent under-expansion were reported respectively in the setting of BMS-ISR (29) and DES-ISR (30). Thus, the crucial importance of identifying these mechanical issues cannot be enough emphasized to reach better results when dealing with DES-ISR.

Conclusion

PCB angioplasty to treat DES-ISR delivered an acceptably low 9-month TLR rate in a French unselected patient population which is in agreement with previously conducted DES-ISR trials. No difference was seen between PES-ISR and non-PES-ISR patients treated with PCB-angioplasty. Cardiovascular and lesion related risk factors were not predictors of MACE. However, if DES-ISR occurred within 12 months the risk of MACE at 9 months was higher in these early DES-ISR patients after PCB angioplasty.

Acknowledgements

Conflict of interest

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Figure legends

Figure 1-Rates of major adverse cardiac events, target lesion revascularization, myocardial infarction and cardiac death according to the type of drug-eluting stent in-stent restenosis.

ISR= in-stent restenosis; MACE= major adverse cardiac events; MI= myocardial infarction; PES= paclitaxel-eluting stent; TLR= target lesion revascularization.

Figure 2-Kaplan Meier time-to-event curves showing cumulative rates of major adverse cardiac events, target lesion revascularization, myocardial infarction and cardiac death with comparison of cumulative rates according to the type of drug-eluting stent in-stent restenosis.

ISR= in-stent restenosis; MACE= major adverse cardiac events; MI= myocardial infarction; PES= paclitaxel-eluting stent; TLR= target lesion revascularization.

Figure 3- Adjusted odds-ratio and corresponding 95% confidence intervals for major adverse cardiac events.

CI= confidence interval; DES= drug-eluting stents; ISR= in-stent restenosis; MACE= major adverse cardiac events; OR=odds-ratio PES= paclitaxel-eluting stent.

Reference categories are: non PES-ISR; DES-ISR delay < 1 year; focal ISR, no diabetes mellitus, no hypertension, no hyperlipidemia.

Appendix

List of participating centers: Centre Hospitalier Universitaire d'Angers; Centre Hospitalier d'Avignon ; Centre Hospitalier de Bourges; Centre Hospitalier de Chartres ; Centre Hospitalier de Colmar ; Centre Hospitalier Universitaire Nord de Marseille ; Centre Hospitalier Universitaire de Montpellier ; Polyclinique les Fleurs Ollioules ; Centre Hospitalier de Pau ; Centre Hospitalier Universitaire de Rennes ; Centre Hospitalier Universitaire de Rouen ; Clinique Saint-Hilaire Rouen ; Centre Hospitalier Universitaire de Toulouse.
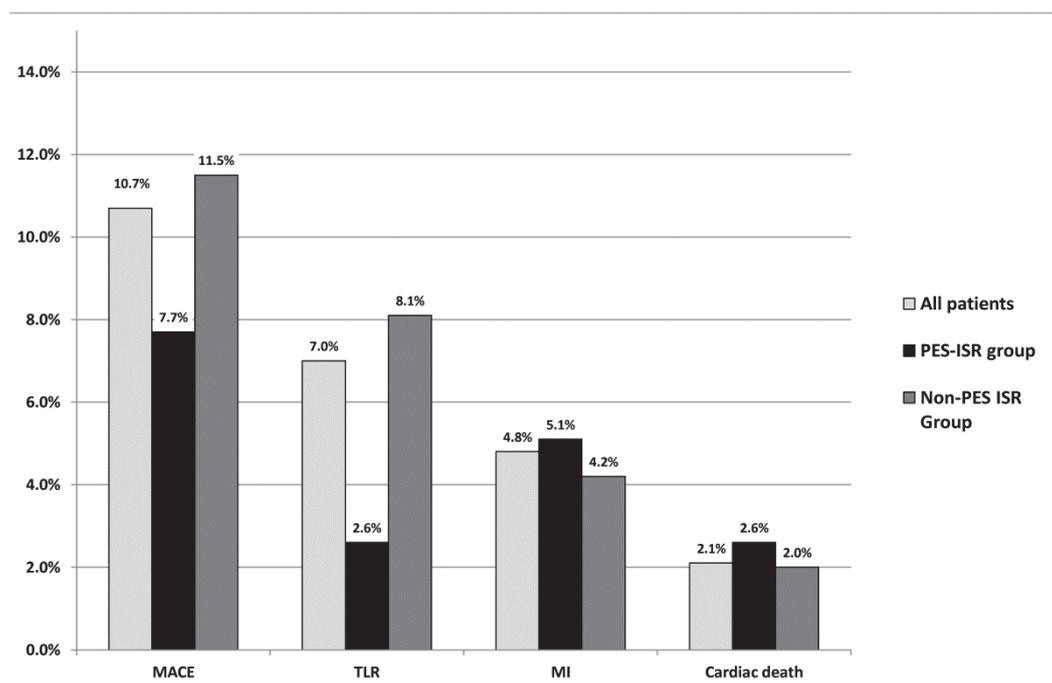
Fig. 1
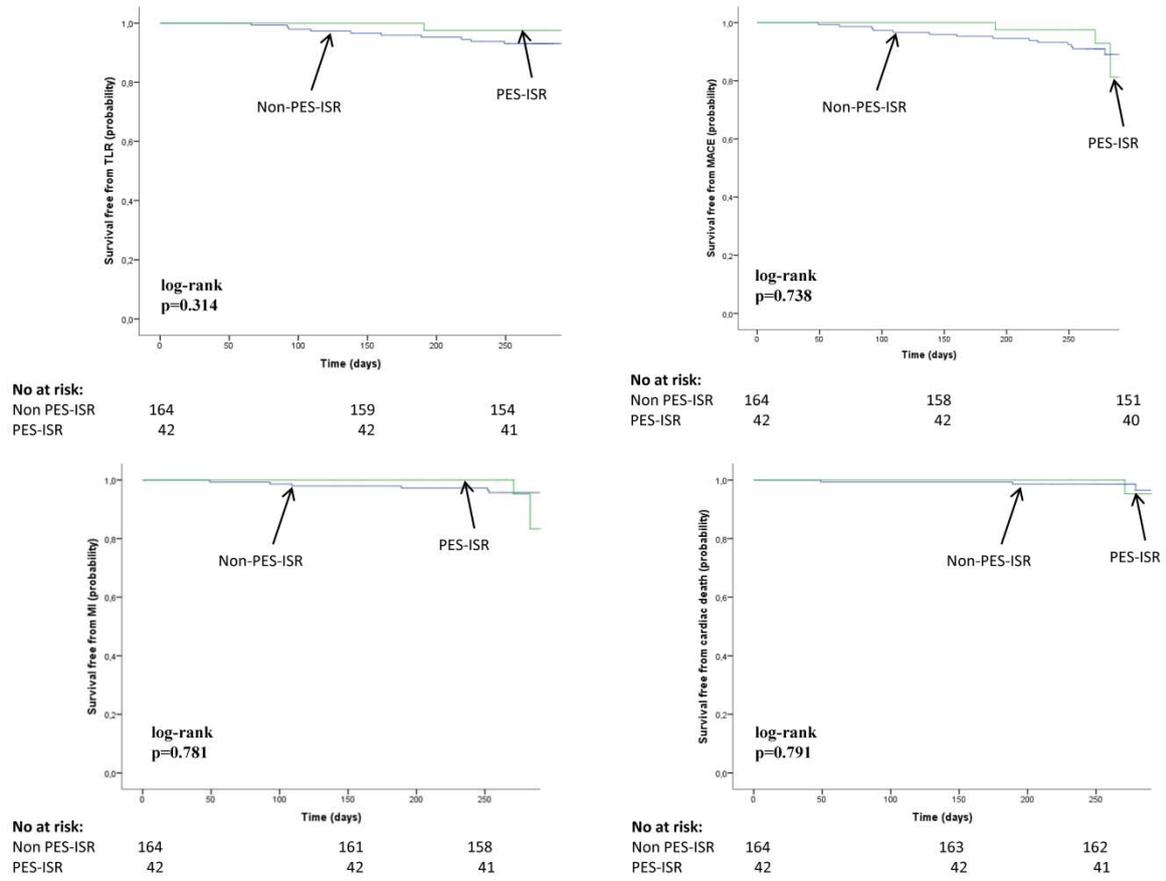
Fig. 2
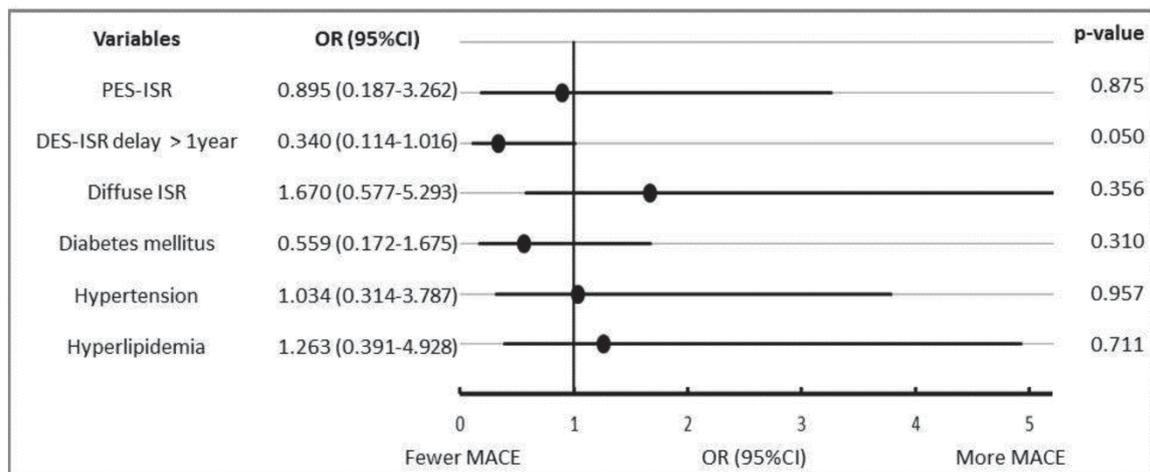
Fig. 3

Table 1 Baseline demographic characteristics.

	All patients (n=206)	PES-ISR group (n=42)	Non PES-ISR group (n=164)	p-value
Age, yrs	67.7±10.2	66.9±11.4	67.9±9.9	0.586
Male	166 (80.6)	36 (85.7)	130 (79.3)	0.341
Diabete mellitus	85 (41.3)	14 (33.3)	71 (43.3)	0.242
Hypertension	143 (69.4)	27 (64.3)	116 (70.7)	0.419
Hyperlipidemia	156 (75.7)	35 (83.3)	121 (73.8)	0.198
Current smoker	97 (47.1)	22 (52.4)	75 (45.7)	0.441
End stage renal disease	11 (5.3)	1 (2.4)	10 (6.1)	0.339
Stress test available	65 (31.6)	11 (26.2)	54 (32.9)	0.402
Positive stress test	63 (96.9)	11 (100)	52 (96.3)	0.517
Unstable angina	80 (38.8)	71 (43.3)	9 (21.4)	0.009
Non-STEMI	26 (12.6)	7 (16.7)	19 (11.6)	0.376
STEMI	8 (3.9)	0 (0.0)	8 (4.9)	0.144
ISR delay, yrs	3.0±2.4	3.2±2.2	3.0±2.4	0.558

Values are mean ± SD or n (%).

ISR= in-stent restenosis; PES= paclitaxel-eluting stent; STEMI= ST-elevation myocardial infarction.

Table 2 Baseline angiographic characteristics.

	All patients/lesions (n=206/210)	PES-ISR group (n=42/43)	Non PES-ISR group (n=164/167)	p-value
Diagnostic coronary findings				0.524
Single-vessel disease	117 (56.8)	27 (64.3)	90 (54.9)	
Two-vessel disease	53 (25.7)	8 (19.0)	45 (27.4)	
Three-vessel disease	36 (17.5)	7 (16.7)	29 (17.7)	
Target vessel				0.318
LAD	79 (37.6)	18 (41.9)	61 (36.5)	
LCX	58 (27.6)	13 (30.9)	45 (26.9)	
RCA	61 (29.0)	12 (27.2)	49 (29.3)	
Other	12 (5.7)	0 (0)	12 (7.2)	
Target stent[i]				<0.001
PES	43 (21.2)	43 (100)	0	
SES	78 (38.4)	0 (0)	78 (48.8)	
ZES	12 (5.9)	0 (0)	12 (7.5)	
EES	59 (29.1)	0 (0)	59 (36.9)	
BES	6 (3.0)	0 (0)	6 (3.7)	
Other	5 (2.5)	0 (0)	5 (3.1)	
ISR classification[ii]				0.706
Articulation/Gap	2 (1.0)	1 (2.4)	1 (0.6)	
Focal margin	21 (10.2)	4 (9.8)	17 (10.4)	
Focal body	79 (38.5)	14 (34.1)	65 (39.6)	
Multifocal	10 (4.9)	1 (2.4)	9 (5.5)	
Diffuse	71 (34.6)	18 (43.9)	53 (32.3)	
Proliferative	15 (7.3)	2 (4.9)	13 (7.9)	
Occlusive	7 (3.4)	1 (2.4)	6 (3.7)	
Diffuse ISR pattern	93 (44.3)	21(48.8)	72 (43.1)	0.606
Target lesion characteristics				
TIMI flow 0 or 1	16 (7.6)	3 (7.0)	13 (7.8)	1.000
B2-C lesion	72 (34.3)	18 (41.9)	54 (32.3)	0.281

Values are mean ± SD or n (%)

BES= biolimus-eluting stent; EES= everolimus-eluting stent; LAD= left anterior descending artery; LCX= left circumflex; RCA= right coronary artery; SES= sirolimus-eluting stent; TIMI= thrombolysis in myocardial infarction; ZES= zotarolimus-eluting stent. Other abbreviations as in table 1.

[i]Percentage of lesions with data available about target stent type (n=203).

[ii]Percentage of lesions with data available about ISR classification (n=205).

Table 3 Quantitative coronary analysis[*].

	All lesions (n=163/210)	PES-ISR group (n=36/43)	Non PES-ISR group (n=127/167)	p-value
Before index procedure				
Lesion length, mm	12.59±8.87	15.02±12.61	11.99±7.4	0.07
Reference vessel diameter, mm	2.77±0.78	2.74±0.55	2.78±0.84	0.033
Minimal lumen diameter, mm	0.98±0.47	1.13±0.40	0.92±0.48	0.021
Diameter stenosis, %	65.1±17.0	57.5±17.2	67.2±16.4	0.002
Post-index procedure				
Reference vessel diameter, mm	2.78±0.52	2.72±0.45	2.80±0.54	0.446
Minimal lumen diameter, mm	2.37±0.55	2.22±0.57	2.39±0.54	0.262
Diameter stenosis, %	15.6±12.5	14.6±11.1	15.9±12.8	0.575

[*]Based on angiographic data from patients with sufficient quality for analysis.

Table 4 Procedural and device characteristics.

	All lesions (n=210)	PES-ISR group (n=43)	Non PES-ISR group (n=167)	p-value
Balloon pre-dilation	195 (92.9)	41 (95.3)	154 (92.2)	0.477
Number of PCB used	227	45	182	-
Paclitaxel-coated balloon				
Diameter, mm	3.0±0.36	2.97±0.42	3.0±0.34	0.305
Length, mm	19.5±4.9	20.3±5.8	19.3±4.6	0.816
Inflation pressure, bar	12.6±3.7	13.4±4.8	12.4±3.4	0.075
Post-PCB dissection	3 (1.4)	2 (4.7)	1 (0.6)	0.046
Procedural success	207 (98.6)	2 (4.7)	1 (0.6)	0.046
Additional stenting	6 (2.9)	2 (4.7)	4 (2.4)	0.428
Multivessel PCI	28 (13.3)	5 (11.6)	23 (13.8)	0.712

Values are mean ± SD or n (%).

PCI= percutaneous coronary intervention; PCB= paclitaxel-coated balloon. Other abbreviations as in table 1 and 2.

Table 5 Clinical outcomes.

	All patients (n=206)	PES-ISR group (n=42)	Non PES-ISR group (n=164)	p-value
In-hospital events				
Death	1 (0.5)	0 (0.0)	1 (0.6)	0.612
Cardiac death	0 (0.0)	0 (0.0)	0 (0.0)	-
Myocardial infarction	1 (0.5)	0 (0.0)	1 (0.6)	0.612
Target lesion revascularization	2 (1.0)	0 (0.0)	0 (0.0)	0.472
PCI	2 (1.0)	0 (0.0)	2 (1.2)	0.472
CABG	0 (0.0)	0 (0.0)	0 (0.0)	-
Target vessel revascularization	9 (4.4)	2 (4.8)	7 (4.3)	0.889
Composite MACE	3 (1.5)	0 (0.0)	3 (1.8)	0.377
Events at 9 months	(n=187)	36 (92.3)	131 (88.5)	-
Death	5 (2.7)	2 (5.1)	3 (2.0)	0.279
Cardiac death	4 (2.1)	1 (2.6)	3 (2.0)	0.837
Myocardial infarction	9 (4.8)	2 (5.1)	7 (4.2)	0.918
Target lesion revascularization	13 (7.0)	1 (2.6)	12 (8.1)	0.226
PCI	11 (5.9)	1 (2.6)	10 (6.8)	0.322
CABG	3 (1.6)	0 (0.0)	3 (2.0)	0.370
Target vessel revascularization	19 (10.2)	3 (7.7)	16 (10.8)	0.566
Composite MACE	20 (10.7)	3 (7.7)	17 (11.5)	0.495

Values are n (%).

CABG= coronary artery bypass graft; MACE= major adverse cardiac events. Other abbreviations as in table 1 and 3.

Table 6 Comparison of pre- and post-procedural MLD, reference vessel diameters, diameter stenosis, TLR and MACE rates in PCB groups across studies investigating treatment of DES-ISR.

	GARO Registry	Habara et al.[11]	PEPCAD DES[12]	ISAR DESIRE 3[14]	Habara et al[9]	PEPCAD China ISR[13]
Pre-procedural MLD, mm	0.98±0.47	0.99±0.32	0.66±0.40	0.97±0.50	0.87 ± 0.40	0.85±0.38
Post-procedural MLD, mm	2.37 ±0.55	1.99±0.32	2.15±0.42	2.29±0.44	1.87 ± 0.37	2.39±0.37
Reference vessel diameter, mm	2.78±0.52	2.74±0.34	2.92±2.47	2.75±0.5	2.49 ± 0.50	2.59±0.40
Post-procedural diameter stenosis, %	15.6±12.5	25.7±7.2	12.6±6.2	18.5±8.3	23.6 ± 7.3	10.5±7.2
TLR, %[*]	7.0	4.3	15.3	22.1	2.9	14.7
MACE,%[*]	10.7	4.3	16.7	23.5	6.6	16.5

DES= Drug-eluting stent; ISAR-DESIRE 3= Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 3; MLD=Minimal lumen diameter; PEPCAD-China ISR= A Prospective, Multicenter, Randomized Trial of Paclitaxel-Coated Balloon versus Paclitaxel-Eluting Stent for the Treatment of Drug-eluting Stent In-Stent Restenosis; PEPCAD DES=Treatment of DES-In-Stent Restenosis With SeQuent® Please Paclitaxel Eluting PTCA Catheter; TLR=Target lesion revascularization. Other abbreviations as in tables 1, 2, 4 and 5.

[*]Time of follow-up was 6 months for Habara et al[9,11] and PEPCAD DES[12]; 9 months for PEPCAD China ISR[13] and the GARO registry and 12 months for ISAR-DESIRE 3[14].