International Journal of Cardiology 203 (2016) 690–696

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

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

V. Auffret [a,b,c,1], J. Berland [d,1], P. Barragan [e,1], M. Waliszewski [f,1], L. Bonello [g,1], N. Delarche [h,1], A. Furber [i,1], F. Albert [j,1], D. Carrié [k,1], H. Eltchaninoff [l,1], M. Pansieri [m,1], M. Schneeberger [n,1], C. Piot [o,1], P. Marcollet [p,1], M. Bedossa [a,b,c,*,1]

[a] CHU Rennes, Service de Cardiologie et Maladies Vasculaires, Rennes, F-35000, France
[b] INSERM, U1099, Rennes, F-35000, France
[c] Université de Rennes 1, LTSI, Rennes, F-35000, France
[d] Clinique Saint Hilaire Rouen, Service de Cardiologie, F-76000, France
[e] Polyclinique Les Fleurs Ollioules, Service de Cardiologie, F-83190, France
[f] Medical Scientific Affairs, B. Braun Melsungen AG, Germany
[g] Département de Cardiologie Centre Hospitalo, Universitaire Nord, Marseille, F-13915, France
[h] Centre Hospitalier de Pau, Service de Cardiologie, F-64000, France
[i] Centre Hospitalier Universitaire Angers, Service de Cardiologie, F-49100, France
[j] Centre Hospitalier de Chartres, Service de Cardiologie, F-28018, France
[k] CHU de Toulouse, Service de Cardiologie, F-31059, France
[l] CHU de Rouen, Service de Cardiologie, F-76000, France
[m] Centre Hospitalier Avignon, Service de Cardiologie, F-84000, France
[n] Hôpital Albert Schweitzer, Colmar, Service de Cardiologie, F-68024, France
[o] CHU de Montpellier, Service de Cardiologie, F-34090, France
[p] Centre Hospitalier de Bourges, Service de Cardiologie, F-18000, France

ARTICLE INFO

Article history:
Received 11 December 2014
Received in revised form 3 August 2015
Accepted 4 November 2015
Available online 6 November 2015

Keywords:
Drug-eluting stent in-stent restenosis
Paclitaxel-coated balloon
Target lesion revascularization

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.

* Corresponding author at: Service de Cardiologie et Maladies Vasculaires, CHU Pontchaillou, 2 Rue Henri le Guilloux, Rennes, F-35000, France.
E-mail address: marc.bedossa@chu-rennes.fr (M. Bedossa).
[1] These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

http://dx.doi.org/10.1016/j.ijcard.2015.11.031
0167-5273/

1. 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 showed 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.

2. Methods

2.1. 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 0). The protocol was approved by the French national ethics committee as part of the parent 'All-Comers Registry' which also included other indications besides DES-ISR. All patients gave written informed consent. Data were captured using an established electronic case report form with built-in plausibility checks which previously proved useful and efficient in related observational PCB studies [15,16]. The two coordinating investigators (MB, JB) were responsible for contacting co-investigators whenever the e-CRF plausibility checks indicated discrepancies.

2.2. 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.

2.3. 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.

2.4. 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 (50–100 UI/kg) was administered upon insertion of the sheath. Intracoronary nitrates (0.2 mg) were administered 2 min before baseline and final reference angiography performed in two near-orthogonal views. The paclitaxel-coated (3 μg/mm^2) PTCA catheter based on the Paccocath® Technology (SeQuent® Please, B. Braun Melsungen AG) was used according 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.

2.5. 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.

2.6. 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 χ^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-values 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.

3. Results

3.1. 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

Table 1
Baseline demographic characteristics.

	All patients (n = 206)	PES-ISR group (n = 42)	Non PES-ISR group (n = 164)	p-Value
Age, years	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
Diabetes 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, years	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.