Percutaneous coronary intervention for treating de-novo lesions in small coronary vessels: initial experience with the Essential paclitaxel-coated balloon

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Background **Paclitaxel-coated balloon (PCB) coronary angioplasty is an alternative treatment for de-novo coronary lesions in small vessels. This study with the new Essential PCB aimed to evaluate early and mid-term clinical outcomes following angioplasty with the Essential PCB in the treatment of de-novo lesions in small vessels.**

Patients and methods **We included all patients who underwent PCB angioplasty for treating de-novo coronary lesions in small vessels (reference diameter <2.5 mm) between October 2015 and June 2016 in 2 centres. The primary endpoint was the 12-month target lesion failure (TLF) rate: a composite of cardiac death, target vessel-related myocardial infarction, and target lesion revascularization. The secondary endpoints were rates of target vessel failure and global major adverse cardiac events (MACE).**

Results **A total of 71 patients (comprising 71 lesions) were included, with a mean age of 66 ± 11 years. A 56% were diabetic and 70% had an acute coronary syndrome as an indication for coronary revascularization. The mean vessel diameter and lesion length were 2.21 ± 0.41 and 20.7 ± 9.2 mm, respectively. Predilatation was performed in 85.9% of patients. The median diameter, length, and inflation pressure of the Essential balloon were 2.0 [interquartile range (IQR): 2.0–2.5] mm, 20 (IQR: 15–30) mm, and 12 ± 2 atmospheres, respectively. Angiographic success was achieved in 97.2% of cases, and bail-out stenting was required in nine (12.7%) cases. The incidence of TLF at the 12-month follow-up was 4.2%, with a target lesion revascularization rate of 4.2%. Target vessel failure and global MACE rates were 4.2 and 9.9%, respectively.**

Conclusion **Use of the Essential PCB for treating de-novo coronary lesions in small vessels was safe, with low TLF and MACE rates at the 12-month follow-up.** *Coron Artery Dis* **00:000–000**

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Keywords: angioplasty, paclitaxel-coated balloon, de-novo lesions, small vessels

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Introduction

Stent implantation during a percutaneous coronary intervention (PCI) with either bare-metal stents (BMS) or drug-eluting stents (DES), optimizes procedural success and long-term lesion patency compared with plain old balloon angioplasty (POBA) as they prevent elastic recoil. However, permanent metallic caging of the vessel remains the main drawback of these devices as it may induce chronic inflammatory responses that can lead to late stent thrombosis and/or re-estenosis [1]. In the setting of in-stent restenosis (ISR), the use of paclitaxel-coated balloon (PCB) angioplasty has been shown to be safe and effective, with acceptable major adverse cardiac events (MACE) and target lesion revascularization (TLR) rates [2–4].

Achievement of optimal outcomes following PCI in small (< 2.5 mm diameter) coronary vessels remains challenging, with reports of higher rates of ISR [5]. PCB angioplasty is considered a valid alternative for treating diseased small vessels [6], with acceptable MACE and TLR rates [7,8]. The Essential balloon is a drug-coated balloon with a uniform coating of paclitaxel in a 3 μg/mm^2 eluting formulation. The balloon incorporates the TransferTech technology (iVascular, Barcelona, Spain), leading to a homogenous drug coating. This allows a more uniform and complete treatment of the vessel, in addition to rapid and optimal drug transfer (within just 30–60 s) thanks to its microcrystalline structure. The aim of this study was to evaluate the clinical outcomes associated with the initial experience with the Essential

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balloon following treatment of de-novo coronary lesions in small coronary vessels.

Patients and methods

The study included a total of 71 consecutive patients from two centers who underwent PCI with the Essential balloon (iVascular, Barcelona, Spain) for treating native coronary lesions in small vessels (< 2.5 mm lumen diameter). Patients were recruited from October 2015 to June 2016. The PCI strategy was based on the decision of the treating interventional cardiologist responsible for the procedure, and there were no prespecified exclusion criteria on lesion characteristics or complexity. All baseline and procedural characteristics and follow-up data were recorded in a dedicated database. A systematic 12-month follow-up was assured by clinical visits or phone contact. No patient was lost to follow-up. There was no systematic coronary angiography at follow-up, and repeat coronary angiography/PCI at follow-up was clinically driven in all cases. All patients provided signed informed consent for the procedures.

The primary endpoint of the study was the target lesion failure (TLF) rate at the 12-month follow-up, defined as the composite of cardiac death, target vessel-related myocardial infarction (MI), and TLR. TLR was defined as any repeat revascularization in the previously treated coronary segment or 5 mm proximally or distally. The secondary endpoints were the target vessel failure (TVF) rate and global MACE at the 12-month follow-up. TVF was defined as the composite of cardiac death, target vessel-related MI, and target vessel revascularization (TVR). MACE was defined as cardiac death, any MI, and any coronary revascularization.

Device characteristics and percutaneous coronary intervention procedure

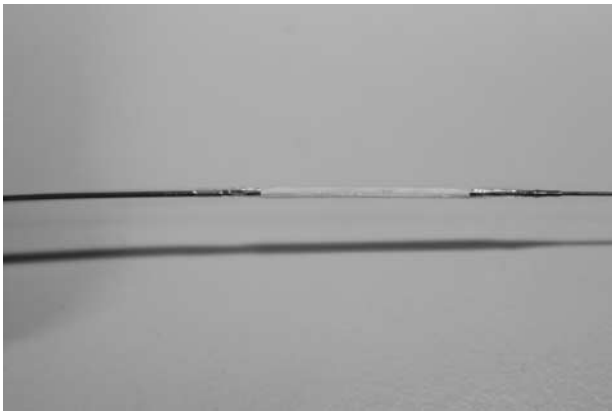
The main characteristics of the Essential balloon are shown in Table 1. Balloon coating comprised of paclitaxel (80%) and a biocompatible, lipophilic excipient (20%) (Fig. 1). Homogeneity of the final coating is ensured with the TransferTech technology, with a paclitaxel concentration of 3 μg/mm^2. As this technology is based on the ultrasonic deposition of drug nanodrops, following the dry-off process, the antiproliferative drug is presented in a microcrystalline structure. This combination, coupled to the lipophilic nature of both paclitaxel and the excipient, leads to a rapid release rate of paclitaxel with faster drug absorption rates (complete transfer to the vessel in 30–60 s). The Essential balloon has been designed with a smooth transition and a very low tip profile of just 0.016 inch, which markedly improves flexibility, trackability, and device crossability. The balloon is compatible with 5 F sheaths in all available diameters.

PCI was performed according to current standards. A minimum of 30 s was required for the balloon to be inflated. Predilatation with a noncoated balloon was recommended. Stenting was just performed as a bail-out indication to achieve optimal angiographic results in cases of dissection or acute recoil following PCB angioplasty. In these cases, BMS or DES was suitable. Angiographic success was defined as a residual stenosis less than 30% with final thrombolysis in myocardial infarction III flow at the end of the procedure. Dual antiplatelet therapy (DAPT) for at least 1 month was recommended after PCB angioplasty, followed by indefinite aspirin. For cases in which stenting was performed, DAPT duration was decided on the basis of stent type and the reason for coronary angiography/PCI [stable angina or acute coronary syndrome (ACS)].

Table 1 Characteristics of the Essential paclitaxel-eluting coronary balloon

Characteristics	Essential paclitaxel-eluting coronary balloon
Balloon material	Latex free: nylon/pebax
Coating	80%: paclitaxel 3 μg/mm^2 20%: biocompatible, lipophilic excipient
Balloon properties	Semicompliant (10–15%) 2 radiopaque polymeric markers of high-flexible tungsten base
Balloon inflation pressure	Nominal inflation pressure: 6 atm Rated burst pressure: 16 atm Average burst pressure: 20 atm
Catheter properties	Useful length: 142 cm Body diameters: 2.0 F proximal, 2.4–2.6 F medium, 2.3 F distal
Recommended guide wire	0.014 inch
Guiding catheter compatibility	5 F in all diameters 6 F in case of kissing-balloon technique
Available balloon lengths (mm)	10, 15, 20, 25, 30, and 40
Available balloon diameters (mm)	1.50, 2.00, 2.25, 2.50, 2.75, 3.00, 3.25, 3.50, 3.75, 4.00, and 4.50

Fig. 1



The Essential paclitaxel-eluting coronary balloon. Picture of a 3.0 × 20 mm Essential paclitaxel-eluting coronary balloon.

Statistical analyses

Categorical variables were expressed as number (percentage) and continuous variables as mean (SD) or

median (interquartile range) according to variable distributions. The Kaplan–Meier curves were used to present the time to first event over time. Statistical analyses were carried out using SPSS software, version 17 (SPSS Inc., Chicago, Illinois, USA).

Results

Patient and procedural characteristics

The baseline characteristics of the study population are described in Table 2. The mean age of the study population was 66 ± 11 years; 67.6% were men. A history of diabetes mellitus was present in 56.3% of patients, and ACS was the most common cause for coronary angiography/PCI. Lesion characteristics and procedural data are presented in Table 3. A total of 71 lesions were treated. A total of 30 (42.3%) lesions were located in the left anterior descending artery, with 17 and 13 lesions in the mid-distal segment and diagonal branches, respectively. A total of 23 lesions were located in the left circumflex artery, with 10 and 13 lesions in the proximal-mid segment and marginal branches, respectively. Balloon predilation with a non-coated balloon was performed in the vast majority of cases (85.9%), and the median diameter and length of the PCB were 2.0 (interquartile range: 2.0–2.5) mm and 20 (interquartile range: 15–30) mm, respectively. Bail-out stenting was required in nine (12.7%) cases: four for coronary dissection and five for acute recoil. Angiographic success was achieved in 69 (97.2%) lesions. The mean duration of DAPT was 10 ± 5 months, and 12 (17%) patients received DAPT for just 1 month.

Clinical outcomes

The main clinical outcomes at the 12-month follow-up are shown in Table 4. At the 12-month follow-up, there were two noncardiac deaths (secondary to hemorrhagic stroke and cancer). One target vessel MIs occurred during the follow-up period. A total of three (4.2%) patients who had undergone simple PCB angioplasty (with no

Table 2 Baseline characteristics of the study population

Characteristics	*N* = 71
Age (years)	66 ± 11
Male	48 (67.6)
Hypertension	53 (74.6)
Diabetes mellitus	40 (56.3)
Dyslipidemia	40 (56.3)
Smoker	29 (40.8)
Chronic kidney disease[a]	12 (16.9)
Peripheral artery disease	10 (14.1)
Atrial fibrillation	10 (14.1)
Previous myocardial infarction	11 (15.5)
Previous CABG	4 (5.6)
Previous PCI	19 (26.8)
Mean LVEF (%)	56 ± 11.4
LVEF <50%	20 (28.2)
Indication for coronary angiography	
Stable angina	21 (29.6)
Unstable angina-NSTEMI	39 (54.9)
STEMI	11 (15.5)

Values are expressed as *n* (%) or mean ± SD.
CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.
[a]Chronic kidney disease was defined as an estimated glomerular filtration rate less than 60 ml/min/1.73 m^2 (Levey-modified MDRD formula).

Table 3 Lesion characteristics and procedural characteristics

Angiographic lesion characteristics	*N* = 71
Radial approach	61 (85.9)
Target vessel	
LAD	30 (42.3)
LCX	23 (32.4)
RCA	17 (23.9)
Saphenous graft	1 (1.4)
AHA lesion classification	
A	7 (9.9)
B1	35 (49.3)
B2	23 (32.4)
C	6 (8.5)
'De-novo' lesions	71 (100.0)
CTO	2 (2.8)
Bifurcations	23 (32.4)
Ostial lesions	11 (15.5)
Lesions calcification	
None	33 (46.5)
Mild	27 (38.0)
Moderate	6 (8.5)
Severe	5 (7.0)
TIMI flow before PCI	
0	8 (11.3)
I	1 (1.4)
II	5 (7.0)
III	57 (80.3)
Mean lesion length (mm)	20.7 ± 9.20
Mean vessel diameter (mm)	2.21 ± 0.41
Procedural characteristics	
DEB	62 (87.3)
DEB + BMS	5 (7.0)
DEB + DES	4 (5.6)
Predilatation	61 (85.9)
Mean number of used DEB	1.01 ± 0.12
Median DEB length (mm)	20 (15–30)
Median DEB diameter (mm)	2 (2.0–2.5)
Mean balloon inflation pressure (atm)	12.35 ± 2.32
Median balloon inflation time (s)	30 (30–60)
Bail-out stenting	9 (12.7)
Angiographic success	69 (97.2)

Values are expressed as *n* (%), mean ± SD, or median (interquartile range).
AHA, American Heart Association; BMS, bare-metal stent; CTO, chronic total occlusion; DEB, drug-eluting balloon; DES, drug-eluting stent; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

Table 4 Clinical outcomes at 12-month follow-up

Outcomes	*N* = 71
Target lesion failure	3 (4.2)
Cardiac death	0 (0)
Target vessel-related myocardial infarction	1 (1.4)
TLR	3 (4.2)
Target vessel failure	3 (4.2)
Target vessel revascularization	3 (4.2)
Nontarget vessel revascularization	5 (7.0)
Target lesion thrombosis	0 (0)
Death from any cause	2 (2.8)
Global MACE	7 (9.9)
Cardiac death	0 (0)
Any myocardial infarction	2 (2.8)
Any coronary revascularization	8 (11.3)

Values are expressed as *n* (%).
MACE, major adverse cardiac events; TLR, target lesion revascularization.

bail-out stenting) had TLR at follow-up and the cumulative TLF rate (primary endpoint) was 4.2%. The TVF and global MACE rates at the 12-month follow-up were 4.2 and 9.9%, respectively. The Kaplan–Meier curves for clinical events at the 12-month follow-up are shown in Fig. 2.

Discussion

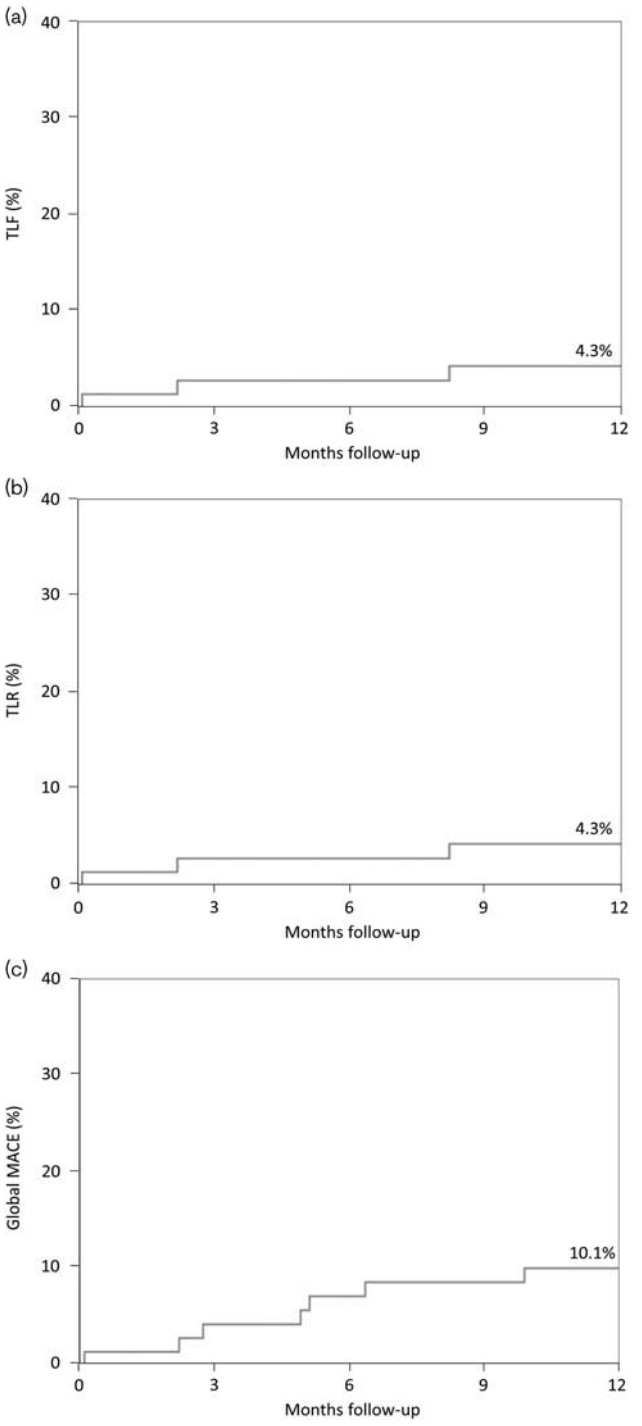
PCI with the Essential PCB for treating de-novo coronary lesions in small vessels in a consecutive cohort of unselected patients was associated with (a) low rates of bail-out stenting or periprocedural complications, (b) low rates of TLF (~4%), and overall MACE (~10%) at the 12-month follow-up. The present analysis represents the initial clinical experience with this novel PCB.

The optimal approach in percutaneous revascularization of small coronary vessels remains challenging. POBA and BMS are not commonly used because of high TLR rates at the mid-term follow-up [9]. Although newer generation DES have been associated with major reductions in TLR, poorer outcomes along with higher rates of TLF, TLR, and target vessel-related MI have been associated with the use of DES in coronary vessels with reference diameters less than 2.5 mm [10].

PCB coronary angioplasty has shown reductions in excessive neointimal proliferation (without impacting strut endothelization) [11], with subsequent reductions in target vessel and TLR rates when used as a strategy for treating ISR-PCI [2–4]. PCB coronary angioplasty has also been tested as a feasible alternative for performing PCI in de-novo small vessels. Unverdorben *et al.* [8] reported an acceptable 6-month late lumen loss of 0.16 ± 0.38 mm after PCB angioplasty of de-novo lesions in small coronary vessels. In addition, PCB angioplasty has been shown to be noninferior to the use of DES, with no differences between groups (PCB alone vs. DES) in MACE or TLR rates at the 12-month follow-up [12,13].

The preclinical experience with the Essential PCB showed improved angiographic and histological results at 28 days after PCB use compared with POBA, with lower late lumen loss and angiographic/histologic stenosis [14]. Furthermore, no significant differences were observed between the Essential and In.Pact Falcon (Medtronic, Minneapolis, Minnesota, USA) PCBs, supporting the concept of a class effect [14]. The TLR rate at the 12-month follow-up was less than 5%, which is in agreement with previous studies with other PCBs [12,15,16]. This low TLR rate appears to be particularly promising if we consider that ostial and bifurcation lesions accounted for 48% of the total lesions treated in the present study. From these data, it may seem that PCB angioplasty could be a reliable treatment option instead of more difficult two-stent techniques for bifurcation lesions. Also, diabetes mellitus, a well-known risk factor for restenosis post-PCI, was present in more than 50% of the patients, a much higher rate compared with previous PCB studies [7,12,15,16]. Importantly, no target lesion thrombosis was observed at the 12-month follow-up. This result may be especially relevant taking into account that

Fig. 2



Kaplan–Meier curves of the clinical events at the 12-month follow-up. (a) Target lesion failure (TLF); (b) target lesion revascularization (TLR); (c) global major adverse cardiac events (MACE).

most patients in our study underwent PCI in the setting of an ACS (70.4%), which has been shown to increase thrombotic risk. Long-term DAPT was prescribed in most patients (mean duration of 10 ± 5 months), according to current guidelines that recommend 12-month DAPT after ACS [17]. However, it is remarkable that close to one-fifth of patients included in our study received just 1-month DAPT, with no secondary increase in thrombosis rates, cardiac death, or MI. These results are similar to those published previously by Waksman *et al*. [16], who reported 0% vessel thrombosis rate among 102 patients who received DAPT during 3 months after PCB angioplasty of de-novo lesions. These data suggest that PCB angioplasty could be an alternative treatment in patients with high bleeding and thrombosis risk in the presence of de-novo coronary lesions in small vessels. However, more evidence is needed.

Limitations

The study included a limited number of patients with a follow-up of 12 months, and the decision for using the PCB was made on the basis of the criteria of the interventional cardiologist performing the procedure. There was no systematic follow-up coronary angiography in this study.

Conclusion

Use of the Essential PCB for treating de-novo coronary lesions in small coronary vessels was safe and associated with low rates of clinical events at the 12-month follow-up. These results suggest that this treatment strategy may be a valid alternative in these cases. Larger studies with a longer follow-up duration are warranted.

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Conflicts of interest

Lluis Duocastella, Alex Gomez, and Maria Molina are full-time paid employees of iVascular. Josep Rodés-Cabau is a consultant for iVascular and received research grant support from iVascular. For the remaining authors there are no conflicts of interest.

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