CRM
CARDIOVASCULAR REVASCULARIZATION MEDICINE
INCLUDING VALVE AND STRUCTURAL HEART
THE OFFICIAL JOURNAL OF
CRT
THE CRT MEETING
CRTONLINE.ORG
2019
DOI: 10.1016/J.CARREV.2019.07.021
PUBLISHED 8 TIMES A YEAR

Reprinted from *Cardiovasc Revasc Med.* 2019. doi: 10.1016/j.carrev.2019.07.021

Angiography and optical coherence tomography assessment of the drug-coated balloon ESSENTIAL for the treatment of in-stent restenosis

Jose M. de la Torre Hernández, Tamara Garcia Camarero, Fernando Lozano Ruiz-Poveda, Cristóbal A. Urbano-Carrillo, Ignacio Sánchez Pérez, Macarena Cano-García, Roberto Saez, Abel Andrés Morist, Eduardo Molina, Eduardo Pinar, Alfonso Torres, Eduardo J. Lezcano, Hipolito Gutierrez, Roman J. Arnold and Javier Zueco

ELSEVIER
ISSN 1553-8389

INCLUDED IN INDEX MEDICUS / MEDLINE
www.cardiorevascmed.com

Reproduced by:
Elsevier España, S.L.U.
(A member of Elsevier)
Av. Josep Tarradellas, 20-30
08029 Barcelona
Tel.: 932 000 711
Fax: 932 091 136

Cardiovascular Revascularization Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

Angiography and optical coherence tomography assessment of the drug-coated balloon ESSENTIAL for the treatment of in-stent restenosis

Jose M. de la Torre Hernández [a,*], Tamara Garcia Camarero [a], Fernando Lozano Ruiz-Poveda [b], Cristóbal A. Urbano-Carrillo [c], Ignacio Sánchez Pérez [b], Macarena Cano-García [c], Roberto Saez [d], Abel Andrés Morist [d], Eduardo Molina [e], Eduardo Pinar [f], Alfonso Torres [g], Eduardo J. Lezcano [h], Hipolito Gutierrez [i], Roman J. Arnold [i], Javier Zueco [a]

[a] *Hospital Universitario Marques de Valdecilla, Dpt. of Interventional Cardiology, Santander, Spain*
[b] *Hospital Universitario de Ciudad Real, Dpt. of Interventional Cardiology, Ciudad Real, Spain*
[c] *Hospital Regional Universitario Carlos Haya, Dpt. of Interventional Cardiology, Malaga, Spain*
[d] *Hospital Universitario Basurto, Dpt. of Interventional Cardiology, Bilbao, Spain*
[e] *Hospital Universitario Virgen de las Nieves, Dpt. of Interventional Cardiology, Granada, Spain*
[f] *Hospital Universitario Virgen de la Arrixaca, Dpt. of Interventional Cardiology, Murcia, Spain*
[g] *Hospital Universitario de Araba, Dpt. of Interventional Cardiology, Vitoria, Spain*
[h] *Hospital San Pedro, Dpt. of Interventional Cardiology, Logroño, Spain*
[i] *Hospital Clinico de Valladolid, ICICOR/Imaging Core Lab, Valladolid, Spain*

ARTICLE INFO

Article history:
Received 2 April 2019
Received in revised form 8 July 2019
Accepted 18 July 2019
Available online xxxx

Keywords:
In-stent restenosis
Drug-eluting balloon
Optical coherence tomography

ABSTRACT

Objectives: This study sought to assess the efficacy of the drug-coated balloon (DCB) ESSENTIAL for the treatment of in-stent restenosis (ISR).

Background: DCBs have proven a valid therapeutic option for the management of ISR in several clinical trials, yet no class effect can be claimed. Accordingly, every new DCB model has to be individually evaluated through clinical studies.

Methods: This is a prospective, multicenter study including consecutive patients undergoing percutaneous coronary intervention for ISR with the ESSENTIAL DCB. A 6-month quantitative coronary angiography (QCA)/optical coherence tomography (OCT) follow-up was scheduled. The primary endpoint was OCT-derived in-segment maximal area stenosis. Secondary endpoints included QCA-derived in-segment late lumen loss (LLL) and target lesion failure (TLF) rates at 6, 12, and 24 months. TLF was defined as the composite of cardiac death, target vessel myocardial infarction, and target lesion revascularization.

Results: A total of 31 patients were successfully treated with DCB, with 67% of ISR corresponding to drug-eluting stents (DES). At 6 months, 26 patients underwent the scheduled angiographic follow-up. The mean value for in-segment maximal area stenosis was 51.4 ± 13% and the median value was 53% (IQR 46.4–59.5). In the DES-ISR subgroup, these parameters were 52.6 ± 10% and 55.2% (IQR 49.3–58.5), respectively. In-segment LLL was 0.25 ± 0.43 mm with only 2 (7.7%) patients showing binary restenosis (>50%). The incidence of TLF was 10% at 6 months, 13.3% at 12 months, and 13.3% at 24 months.

Conclusions: In this study, the ESSENTIAL DCB showed sustained efficacy in the prevention of recurrent restenosis after treatment of ISR.

Summary: We sought to assess the efficacy of the drug-coated balloon ESSENTIAL for the treatment of in-stent restenosis through a prospective, multicenter study including QCA and OCT assessment at 6-month follow-up. The primary endpoint was in-segment maximal area stenosis. Among the 31 patients successfully treated with the ESSENTIAL DCB, an angiographic follow-up was conducted in 26. Mean in-segment maximal area stenosis was 51.4 ± 13% and the median value was 53% (IQR 46.4–59.5). In the DES-ISR subgroup, corresponding values were 52.6 ± 10% and 55.2% (IQR 49.3–58.5), respectively. The observed in-segment LLL was 0.25 ± 0.43 mm and binary restenosis rate was 7.7%. TLF was 10% at 6 months and 13.3% at 12 and 24 months.

Abbreviations: BMS, bare metal stent; DES, drug-eluting stent; DCB, drug-coated balloon; ISR, in-stent restenosis; LLL, late lumen loss; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography; TLF, target lesion failure; TLR, target lesion revascularization.

* Corresponding author at: Hospital Universitario Marques de Valdecilla, 39012 Santander, Spain.
E-mail address: he1thj@humv.es (J.M. de la Torre Hernández).

https://doi.org/10.1016/j.carrev.2019.07.021
1553-8389/

1. Introduction

In-stent restenosis (ISR) has become less prevalent with the nearly systematic use of drug-eluting stents (DES) in percutaneous coronary interventions (PCI). Nonetheless, because of the increased complexity of lesions treated with DES, 5–10% of PCI are performed over ISR lesions [1]. However, treatment of ISR remains challenging, with a variable rate of recurrent restenosis [2].

Two network meta-analyses comparing existing transcatheter strategies for the treatment of ISR indicated, in the frequentist and Bayesian frameworks, that everolimus-eluting stents and drug-coated balloons (DCB) are the most effective devices [3,4]. Based on this evidence, the European Society of Cardiology issued a class I recommendation (level of evidence A) for DCB use in the treatment of in-stent restenosis of bare metal stents (BMS) or DES in their latest guidelines on myocardial revascularization [5].

The vast majority of currently-approved DCBs are coated with paclitaxel because of its lipophilicity and tissue retention characteristics [6]. However, the various paclitaxel DCB systems differ widely in drug-delivery technology and excipients used, thereby resulting in differences in specific elution kinetics and tissue retention. Therefore, no class effect can be claimed for all DCBs, and new designs need to be individually assessed through preclinical and clinical studies. While quantitative coronary angiography (QCA) is by far the most commonly used technique to assess neointimal inhibition after DCB treatment in such studies, it provides only rudimentary capability for detecting the real diameter stenosis, mainly due to limitations inherent to bi-dimensional imaging, foreshortening effects, and overlapping of vessel segments. These limitations account for the lower accuracy and usefulness of QCA for the assessment of microscopic phenomena such as neointimal proliferation. Thus, QCA is unable to distinguish neointimal hyperplasia from neoatherosclerosis or to detect mild/moderate degrees of stent underexpansion. On the contrary, optical coherence tomography (OCT) allows a precise and highly reliable evaluation of neointimal proliferation. Even so, because imaging evaluation is conducted at mid-term timepoints (6–12 months), a longer clinical follow up is also required to confirm the sustained clinical efficacy of the DCB in assessment studies.

The present study aimed to assess the efficacy of the ESSENTIAL DCB (iVascular, Barcelona, Spain) [7,8] for the treatment of ISR using QCA and OCT assessment at 6 months and clinical evaluation up to 24 months. The ESSENTIAL DCB has a uniform coating of paclitaxel in a 3 μg/mm^2 eluting formulation and incorporates the proprietary TransferTech™ technology, which is based on the ultrasonic deposition of nanodrops leading to a homogenous drug coating.

2. Methods

This study is a prospective, multicenter, single-arm investigation, aiming primarily to assess the efficacy of the ESSENTIAL DCB in ISR lesions by means of QCA and OCT examination at 6-month follow-up and secondarily to evaluate clinical outcomes up to 24 months following treatment. The study was carried out according to the Declaration of Helsinki; it was approved by the clinical investigation ethics committees of all participating centers. Accordingly, all included patients provided written informed consent.

2.1. Population

All consecutive patients scheduled to undergo PCI for a first significant ISR of a BMS or DES were deemed eligible. Significant restenosis was defined by standard angiographic and/or fractional flow reserve criteria. Angiographic inclusion criteria included focal or diffuse ISR (Mehran Patterns I and II). Angiographic exclusion criteria was comprised of the following: totally occlusive or proliferative ISR; ISR involving inter-stents gaps and stent margins; ISR within the left main coronary level; angiographic findings suggestive of stent thrombosis or neoatheroma plaque rupture; and visualization of an overt stent underexpansion by conventional angiography, angiography-based enhancing technologies, or intravascular imaging. Clinical exclusion criteria included age >75 years, left ventricular ejection fraction <40%, moderate or severe kidney function impairment, unsuitable vascular accesses, and known contrast allergies.

2.2. Procedures

After obtaining coronary angiograms, ISR deemed to be significant was treated with a non-compliant plain angioplasty balloon inflated to attain optimal expansion. Balloon diameter was chosen to be the same or up to 0.5 mm greater than the nominal diameter size of the original stent; the balloon length was selected to be similar to or slightly shorter than the underlying stent. After ruling out a significant dissection which could indicate a need for a new stent, the DCB was then employed.

The DCB ESSENTIAL balloon is a paclitaxel-coated balloon with a uniform 3 μg/mm^2 eluting formulation. The balloon incorporates the proprietary TransferTech™ technology, which is based on the ultrasonic deposition of nanodrops, following the dry-off process, leading to a homogenous drug coating. This allows more uniform and complete treatment of the vessel, in addition to rapid and optimal drug transfer due to its microcrystalline structure and the lipophilic nature of both paclitaxel and the excipient. The manufacturer estimates a theoretical drug release total time of 30 to 60 s (mostly at 45 s), which means that balloon inflation for longer than 60 s would not lead to any additional drug release. The preclinical efficacy and safety of the device have been successfully addressed in a swine model [7]. The ESSENTIAL DCB has been clinically evaluated in the setting of de novo lesions in small coronary vessels, showing favorable results [8].

The DCB diameter was recommended by protocol to be the same or 0.5 mm greater than the nominal diameter size of the original stent. The length of the DCB was also similar to that of the previous plain balloon used, but at least 4 mm longer than the ISR length. A first inflation at a pressure >8 atm was maintained for 45 s, followed by a second inflation lasting for 30 additional seconds.

Final bailout stenting was left to operator discretion if a suboptimal angiographic outcome was observed after DCB inflation. A suboptimal result was defined as residual stenosis >30%, National Heart, Lung, and Blood Institute dissection type ≥C, or a Thrombolysis in Myocardial Infarction (TIMI) flow <3 [9]. After the procedure, the prescribed duration of dual antiplatelet therapy was at least 6 months.

2.3. Endpoints

The primary endpoint was OCT-derived maximal area stenosis 6 months after intervention. Secondary endpoints included QCA-derived in-segment late lumen loss (LLL) at 6 months and target lesion failure (TLF) incidence at 6, 12, and 24 months post-intervention. TLF was defined as the composite of cardiac death, target vessel myocardial infarction, and target lesion revascularization (TLR).

2.4. Quantitative coronary angiography

Baseline coronary angiography was performed at 30 frames per second in 2 different views with at least 30° difference using 6 F catheters. Pre-procedural and post-procedural angiograms were obtained during breath hold without a guide wire in the coronary artery. Projections were selected without overlap of the target lesion, minimizing foreshortening of the segment of interest. Intracoronary nitroglycerine was administered before acquisition of the angiogram. Follow-up angiography was performed using the same projections as baseline coronary angiography.

All study baseline and follow-up coronary angiograms were analyzed in an independent QCA Core Lab (ICICOR, Valladolid, Spain).

Please cite this article as: J.M. de la Torre Hernández, T. Garcia Camarero, F. Lozano Ruiz-Poveda, et al., Angiography and optical coherence tomography assessment of the drug-coated balloon ESSENTIAL..., Cardiovascular Revascularization Medicine, https://doi.org/10.1016/j.carrev.2019.07.021

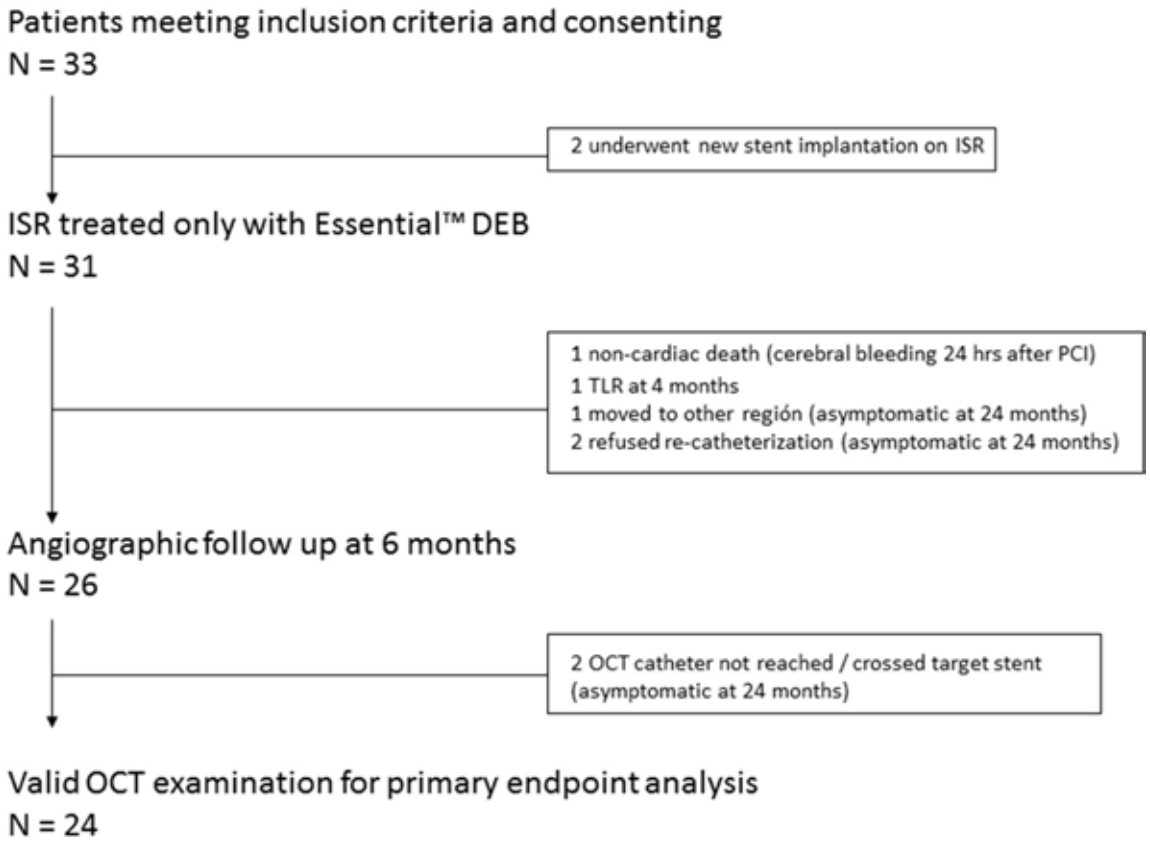

Fig. 1. Flow chart of the study.

QCA measurements were performed on a single "worst" projection (i.e., the projection in which the stenosis looked most severe).

Analyses were performed for in-stent and in-segment vascular regions. Acute gain was calculated from the difference between post- and pre-procedure minimum lumen diameter (MLD). LLL was calculated from the MLD difference between post-procedure and follow-up measurements, either for in-stent or in-segment analysis. Diameter stenosis (DS) was defined with respect to reference vessel diameter (RVD) as $\%DS = [1 - (MLD/RVD)] \times 100$.

Angiographic success was defined as achievement of final residual stenosis <30% and TIMI flow grade ≥3. Device success was defined as angiographic success using the DCB. Binary restenosis was defined as stenosis >50%.

2.5. Optical coherence tomography

OCT images were acquired at the 6-month follow-up. Investigators used currently available optical frequency domain imaging systems (Ilumien or Optis Imaging System™, Abbott Vascular, USA) with a pull-back speed of 20 mm/s. The imaging catheter was advanced 10 mm distal to the target stent, and the amount and rate of contrast injection was as previously tested in order to attain a complete wash-out of the vessel lumen.

All analysis was blinded to the coronary angiogram and performed offline by an independent core lab, which performed measurements every other millimeter from the entire stented and adjacent segments (5 mm proximal and distal). Values measured were minimal lumen

Table 1
Clinical characteristics.

	N = 33
Age, years	57.72 ± 9.6
Female	7 (21.2)
Diabetes	9 (27.3)
Hypertension	10 (30.3)
Hypercholesterolemia	19 (57.6)
Current smoker	9 (27.3)
Previous myocardial infarction	18 (54.5)
LVEF (%)	54.6 ± 10.5
Previous CABG	1 (3)
Stable angina	22 (66.6)
Acute coronary syndrome	11(33.3)
DES restenosis	22 (66.6)
BMS restenosis	11 (33.3)

Values are presented as mean ± SD or n (%).
BMS = Bare metal stent; CABG = coronary artery bypass grafting; DES = Drug eluting stent; LVEF = Left Ventricular ejection fraction; MI = Myocardial infarction.

Table 2
Procedural characteristics.

ISR lesions treated	33
Mehran I pattern	14 (42%)
Mehran II pattern	19 (58%)
Target vessel LAD	12 (36.3)
Target vessel LCx	11 (33.3)
Target vessel RCA	10 (30.4)
Predilatation balloon diameter, mm	2.93 ± 0.52
Predilatation balloon length, mm	16.12 ± 5.3
Peak predilatation pressure, atm	17.12 ± 3.5
DEB diameter, mm	3.02 ± 0.51
DEB length, mm	19.83 ± 4.9
Max. balloon diameter to index stent nominal diameter ratio	0.98 ± 0.29
Additional stenting	2 (6)
DEB angiographic success	31 (94%)
Procedural success	33 (100)

Values are presented as mean ± SD or n (%).
DEB = drug eluting balloon; ISR = in-stent restenosis; LAD = left anterior descending artery; LCx = left circumflex artery; RCA = right coronary artery.

Please cite this article as: J.M. de la Torre Hernández, T. Garcia Camarero, F. Lozano Ruiz-Poveda, et al., Angiography and optical coherence tomography assessment of the drug-coated balloon ESSENTIAL..., Cardiovascular Revascularization Medicine, https://doi.org/10.1016/j.carrev.2019.07.021

Table 3
Findings in quantitative coronary angiography at index procedure and 6 months follow up.

	Baseline	Post-DEB	Follow-up
	N = 33	N = 31	n = 26
Lesion length, mm	11.6 ± 5.5		
Reference vessel diameter, mm	2.69 ± 0.41	2.87 ± 0.31	2.73 ± 0.44
Minimal lumen diameter, mm	0.94 ± 0.39	2.46 ± 0.31	2.18 ± 0.56
Diameter stenosis, %	64.2 ± 14.7	13.75 ± 5.7	20.60 ± 14.8
In-stent acute gain, mm		1.61 ± 0.64	
In-segment acute gain, mm		1.52 ± 0.58	
In-stent-late lumen loss, mm			0.33 ± 0.45
In-segment-late lumen loss, mm			0.25 ± 0.43
In-stent net luminal gain, mm			1.21 ± 0.69
In-segment net luminal gain, mm			1.16 ± 0.71
Binary restenosis in-stent			2 (7.7%)[a]
Binary restenosis in-segment			2 (7.7%)[a]

Values are presented as mean ± SD or n (%). DEB = drug eluting balloon.
[a] Among the 26 patients who underwent the scheduled angiographic follow up at 6 months. Not included here the patient showing restenosis 4 months after index procedure.

area, minimal stent area, maximal neointimal thickness, maximal neointimal area, and maximal area stenosis. Area stenosis was calculated as the difference between stent area and lumen area, divided by stent area. This parameter was calculated along the entire length of the examined target region (stented and adjacent segments) at 1 mm intervals. For calculation of this parameter in the 5 mm stent margins (adjacent segments), the stent area was assumed to be that of the corresponding stent edge. The highest value for the maximal area stenosis was obtained for each coronary segment.

2.6. Clinical events

All deaths were considered cardiac death unless an unequivocal non-cardiac cause could be established. Myocardial infarction was defined according to the fourth Universal Definition by the European Society of Cardiology and the American College of Cardiology Foundation. TLR was defined as either repeat percutaneous or surgical revascularization for a lesion anywhere within the stent or the 5 mm margins. Stent thrombosis was defined according to the Academic Research Consortium criteria. A clinical events committee adjudicated all reported outcomes.

Table 4
Findings in optical coherence tomography at 6 months follow up.

	N = 24	
Minimal stent area, mm^2	7.96 ± 2.72	
Minimal lumen area, mm2	5.11 ± 1.96	
Minimal neointimal thickness, mm	0.14 ± 0.10	
Maximal neointimal thickness, mm	0.54 ± 0.29	
Mean neointimal thickness, mm	0.33 ± 0.19	
Maximal intimal area, mm2	2.86 ± 1.84	
Mean in-segment area stenosis, %	34 ± 16	
DES-ISR	N = 15	
Mean in-segment area stenosis, %	36.1 ± 16	
BMS-ISR	N = 9	
Mean in-segment area stenosis, %	31.2 ± 15	
Maximal in-segment area stenosis, %	51.4 ± 13	53 (46.4–59.5)[a]
DES-ISR	N = 15	
Maximal in-segment area stenosis, %	52.6 ± 10	55.2 (49.3–58.5)[a]
BMS-ISR	N = 9	
Maximal in-segment area stenosis, %	50.5 ± 13	51 (44.6–59.5)[a]

Values presented as mean ± SD.
[a] Median (interquartile range) values are included despite normal distribution for the purpose of comparison with previous studies [10,11].

2.7. Statistical analysis

In order to evaluate the sample, analyses performed non-inferiority cross-comparisons between the ESSENTIAL balloon and other currently available DCBs for the primary endpoint of OCT-derived maximal area stenosis. We assumed as reference the reported values for maximal in-stent area stenosis for other DCBs in the setting of ISR (median values 45–65%) with a standard deviation for this outcome being up to 20% [10,11]. On these grounds, with a power of 80%, a lower limit of a one-sided 95% confidence interval, and a non-inferiority limit of −15% for maximal area stenosis, 22 patients were required for the study group. In addition, a secondary analysis was a non-inferiority comparison of the ESSENTIAL balloon with the SeQuent Please balloon (Braun, Germany) for the secondary endpoint of in-segment LLL at 6 months. Based on reported values for in-segment LLL of 0.1–0.4 mm with SeQuent Please and a standard deviation of 0.4–0.5 [12–16], a non-inferiority limit of −0.2 mm, and the aforementioned statistical parameters, a 25-patient study group was required. Accordingly, assuming a 15–20% loss to imaging follow-up, a minimum target of 30 patients was planned for enrollment.

Continuous variables are presented as mean ± standard deviation or median (interquartile range), as appropriate. Categorical variables are reported as counts and percentages. Distribution was assessed for each variable with the Kolmogorov-Smirnov test. Comparison of continuous variables was performed using the Mann–Whitney *U* test, considering the small group sizes. Categorical variables were compared by means of chi-squared or Fisher's exact test. A two-tailed p-value < 0.05 was regarded as statistically significant. The IBM SPSS Statistics 19.0 package was used.

3. Results

Overall, a total of 33 patients fulfilling the study criteria were included. The flow chart of the study is shown in Fig. 1. DCB angiographic success was achieved in 31 patients (93.9%); 2 patients required stent placement due to a suboptimal angiographic result after balloon dilatation. Baseline clinical, angiographic, and procedural features are shown in Tables 1–3. Most ISR corresponded to DES (67%), and 58% showed Mehran ISR pattern II. Lesion length was 11.6 ± 5.5 mm and reference vessel diameter was 2.7 ± 0.4 mm.

QCA analysis at baseline, post-intervention, and at follow-up is detailed in Table 3. At 6 months, 26 patients underwent the scheduled angiographic examination. In these patients, in-segment LLL was 0.25 ± 0.43 mm and in-stent LLL was 0.33 ± 0.45 mm, with only 2 (7.7%) patients showing binary restenosis (not including the patient undergoing TLR 4 months after the index procedure). Among the 26 patients, an adequate OCT examination could be obtained for 24. Findings in OCT are presented in Table 4 and some illustrative images are shown in Fig. 2. The mean in-segment maximal area stenosis was 51 ± 13% with a median value of 53% (interquartile range 46.4–59.5). This parameter was comparable between DES-ISR and BMS-ISR subgroups: 52.6 ± 10%, 55.2% (49.3–58.5) and 50.5 ± 13%, 51% (44.6–59.5), respectively.

Clinical outcomes at 6-, 12-, and 24-month follow-up are presented in Table 5. No patients were lost for clinical follow-up. TLF occurred in 10% at 6 months, 13.3% at 12 months, and 13.3% at 24 months. Of note, TLR accounted for all TLF events, since no cardiac death, myocardial infarction, or thrombosis occurred. TLR was performed in one patient at 4 months, in two additional patients during the planned angiographic follow-up (at 6 months), and in one patient within the period from 6 to 12 months. One patient died shortly after the procedure due to cerebral bleeding, and four patients underwent revascularizations of non-target vessels.

Please cite this article as: J.M. de la Torre Hernández, T. Garcia Camarero, F. Lozano Ruiz-Poveda, et al., Angiography and optical coherence tomography assessment of the drug-coated balloon ESSENTIAL..., Cardiovascular Revascularization Medicine, https://doi.org/10.1016/j.carrev.2019.07.021

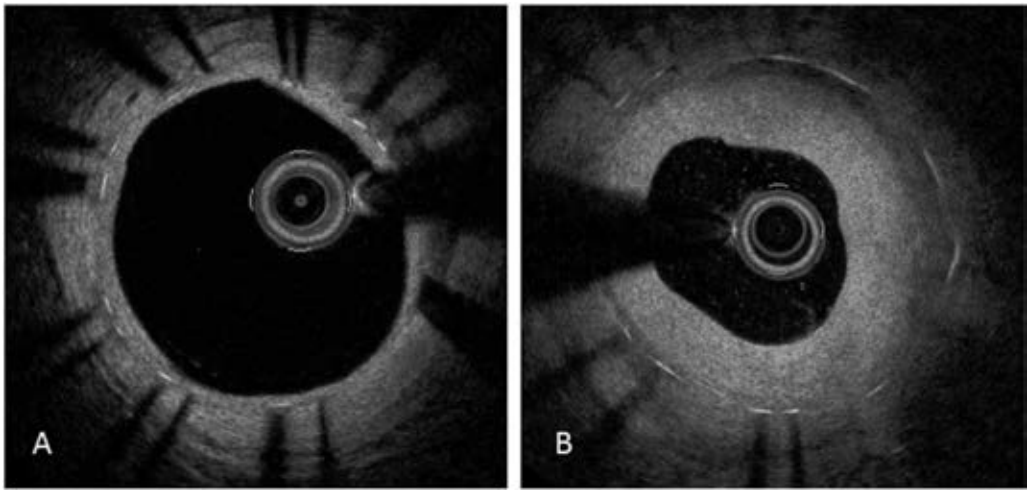

Fig. 2. Illustrative images from OCT analysis at 6 months. A) Mild neointimal proliferation. B) Moderate neointimal proliferation.

4. Discussion

The main findings of this study are summarized as follows: a) In a consecutive cohort of patients showing significant ISR (mostly of DES), use of the ESSENTIAL DCB was associated with a low maximal area stenosis and a low in-segment LLL at 6 months; b) The rate of TLF remained low up to 24 months, though the study is underpowered for clinical endpoints.

The treatment of BMS-ISR with the most evidence-supported DCB, SeQuent Please, has been associated with a mean in-segment LLL at 6–9 months of 0.11–0.28 mm [12–14]. In studies addressing DES-ISR, the reported in-segment LLL at 6 months with SeQuent Please was somehow higher: 0.18–0.43 mm [15,16]. The RIBS IV and V trials compared the SeQuent Please balloon with everolimus-eluting stents in the treatment of DES-ISR and BMS-ISR, respectively [17,18]. The pooled analysis showed in-segment LLL of 0.24 mm at 9 months [19]. In the recently published randomized DARE trial the SeQuent Please DCB was compared with everolimus-eluting stents in 278 patients, of whom 56% had DES-ISR. At 6 months the reported in-segment LLL was 0.17 ± 0.41 mm [20]. The in-segment LLL at 6 months observed for the ESSENTIAL DCB in our study (0.25 ± 0.43 mm) appears to be comparable to that reported in studies with the SeQuent Please balloon including a similar proportion of BMS/DES ISR [19,20].

Table 5
Incidences of clinical outcomes.

At 6 months	N at risk 30
Target lesion failure	3 (10%)
Cardiac death	0%
Target-vessel myocardial infarction	0%
Target lesion revascularization	3 (10%)
All cause death	1 (3.2%)
Myocardial infarction	0%
Thrombosis	0%
Non-TLR revascularization	2 (6.6%)
At 12 months	**N at risk 30**
Target lesion failure	4 (13.3%)
Cardiac death	0%
Target-vessel myocardial infarction	0%
Target lesion revascularization	4 (13.3%)
All cause death	1 (3.2%)
Myocardial infarction	0%
Thrombosis	0%
Non-TLR revascularization	3 (10%)
At 24 months	**N at risk 30**
Target lesion failure	4 (13.3%)
Cardiac death	0%
Target-vessel myocardial infarction	0%
Target lesion revascularization	4 (13.3%)
All cause death	1 (3.2%)
Myocardial infarction	0%
Thrombosis	0%
Non-TLR revascularization	4 (13.3%)

TLR = Target lesion revascularization.

While angiography is commonly used to assess recurrent restenosis after DCB treatment, it remains "lumenography" and cannot be used to differentiate neointimal inhibition from neoatherosclerosis. QCA results are somewhat vulnerable to observer subjectivity, so precision and reproducibility are limited. On the other side, OCT provides separate measurements of lumen, neointimal, and stent dimensions, allowing a precise and highly reliable calculation of neointima, lumen, and stent areas. Maximal area stenosis was selected as the endpoint instead of minimal in-stent lumen area because the former is a relative parameter that takes into account the influence of the vessel (stent) size, and as such is more indicative of the potential flow compromise imposed by the ISR.

Nonetheless, there are only a few studies that include OCT assessment during follow-up after treatment of ISR with DCB. Regarding OCT maximal area stenosis, the results reported herein seem to be comparable to those published for the IN.PACT Falcon (Medtronic, US)—median 47.7% (37.3–60.7)—but better compared to those published for the DIOR (Eurocor, Germany)—median 66.4% (49.9–76.6) [10,11]. In the SEDUCE trial, 50 patients with BMS-ISR were randomized to treatment with the SeQuent Please balloon or everolimus-eluting stent [14]. In this trial the main goal was to evaluate healing characteristics through a strut-level OCT analysis performed at 9 months. Thus, the maximal area stenosis was not reported as such, but the mean value can be inferred from data provided (minimum lumen area of 4.2 ± 1.86 mm^2 and stent area of 8.34 ± 2.76 mm^2 for the DCB subgroup) as being roughly 45–50%. Of note, the maximal area stenosis reported in our study for ESSENTIAL DCB was similar in BMS and DES subgroups.

Finally, with respect to clinical outcomes, several comparative data are available. The rate of TLR at 6–9 months in previous studies conducted with the SeQuent Please balloon and including only or mostly BMS-ISR was 3–4% [14,21]. In trials including DES-ISR the rate of TLR at 6–9 months has been as low as 4.3% [15], but was notably higher in most other studies: 15.3%, 16.5%, and 22% [16,22,23]. Regarding TLR rates at 12 months, previously published incidences range from 4 to 6% in BMS-ISR [12,13,17] to 13–16.5% in DES-ISR [18,22], and was 11% overall in a pooled analysis with a similar proportion of BMS/DES ISR cases as in our study [19]. Thus, a TLR of 13.3% at 24 months with

Please cite this article as: J.M. de la Torre Hernández, T. Garcia Camarero, F. Lozano Ruiz-Poveda, et al., Angiography and optical coherence tomography assessment of the drug-coated balloon ESSENTIAL..., Cardiovascular Revascularization Medicine, https://doi.org/10.1016/j.carrev.2019.07.021

ESSENTIAL DCB appears quite comparable to the aforementioned incidences at 12 months with SeQuent Please.

5. Limitations

The non-randomized design confers the most important limitation to this study. Even though we applied similar inclusion and exclusion criteria and primary outcome definitions, a cross-comparison between studies is of limited value. The number of patients included in this study is small. Nonetheless, the sample size was calculated according to the selected QCA- and OCT-derived endpoints, though it is clearly underpowered for any kind of clinical endpoint. The results presented are applicable to the types of ISR treated according to the inclusion-exclusion criteria. The angiographic follow-up was set at 6 months, as in many of the referenced studies, however a later time point might have been more appropriate to evaluate the DCB performance.

There was an absence of baseline OCT imaging. As such, the impact of OCT findings at 6-month follow-up is relatively limited. The absolute value for maximal area stenosis in follow-up, though still informative of the DCB efficacy, is not as much so as the change in maximal area stenosis with respect to the post-procedural value. The lack of systematic OCT examination at baseline did not allow the contribution of the different ISR mechanisms (underexpansion vs. neointimal proliferation) to be established. Nonetheless, the visualization of an overt stent underexpansion, either through angiography or by intravascular imaging (modality left to operator's discretion), was an exclusion criterion. The detection of this finding is commonly facilitated during angiography by means of enhancing technologies. However, these imaging modalities are sensitive only for extreme cases of underexpansion, and thus stent underexpansion is a diagnosis properly made by intravascular imaging. Also, baseline lesion characteristics of ISR such as neointimal hyperplasia, calcification, and lipid plaque presence may impact the effectiveness of the DCB.

6. Conclusions

In this study, the ESSENTIAL DCB proved effective in the prevention of recurrent restenosis after treatment of ISR in terms of OCT and QCA assessment. These results seem to be comparable to those produced by the most evidence-supported DCB. Clinical efficacy appears favorable and is maintained over the very long term, though the study is underpowered for clinical endpoints.

Funding statement

The study was funded by iVascular (Barcelona, Spain).

Study design, selection of participating centers, collection, management, and interpretation of data, and manuscript preparation were exclusive responsibilities of the investigators with no involvement/interference of the funding company.

Declaration of Competing Interest

Jose M. de la Torre Hernández

Receipt of grants/research support: Abbott Medical; Biosensors; Bristol Myers Squibb; and Amgen. Receipt of honoraria or consultation fees: Boston Scientific; Medtronic; Biotronik; Astra Zeneca; and Daiichi-Sankyo.

This work has not been published previously and it is not under consideration for publication elsewhere.

The manuscript has been approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

References

[1] Kim MS, Dean LS. In-stent restenosis. Cardiovasc Ther 2011;29:190–8.
[2] Alfonso F, Byrne RA, Rivero F, Kastrati A. Current treatment of in-stent restenosis. JACC 2014;63:2659–73.
[3] Siontis GC, Stefanini GG, Mavridis D, Siontis KC, Alfonso F, Perez-Vizcayno MJ, et al. Percutaneous coronary interventional strategies for treatment of in-stent restenosis: a network meta-analysis. Lancet 2015;386:655–64.
[4] Giacoppo D, Gargiulo G, Aruta P, Capranzano P, Tamburino C, Capodanno D. Treatment strategies for coronary in-stent restenosis: systematic review and hierarchical Bayesian network meta-analysis of 24 randomised trials and 4880 patients. BMJ 2015;351:h5392.
[5] Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al, ESC Scientific Document Group. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J 2019;40:87–165.
[6] Lunardi M, Zivelonghi C, van den Brink FS, Ghione M, Vinco G, Benfari G, et al. Drug eluting balloon for the treatment of patients with coronary artery disease: current perspectives. Cardiovasc Revasc Med 2018;19:215–20.
[7] Pérez de Prado A, Perez-Martinez C, Cuellas Ramón C, Regueiro Purriños M, Diego Nieto A, Gonzalo-Orden JM, et al. Safety and efficacy of different paclitaxel-eluting balloons in a porcine model. Rev Esp Cardiol (Engl Ed) 2014;67:456–62.
[8] Abellas-Sequeiros RA, Benezet J, Agarrado Luna A, Oneto Otero J, Déry JP, Cieza T, et al. Percutaneous coronary intervention for treating de-novo lesions in small coronary vessels: initial experience with the Essential paclitaxel-coated balloon. Coron Artery Dis 2018;29:477–81.
[9] Kleber FX, Rittger H, Bonaventura K, Zeymer U, Wöhrle J, Jeger R, et al. B. Drug-coated balloons for treatment of coronary artery disease: updated recommendations from a consensus group. Clin Res Cardiol 2013;102:785–97.
[10] Agostoni P, Belkacemi A, Voskuil M, Nathoe HM, Doevendans PA, Stella PR. Serial morphological and functional assessment of drug-eluting balloon for in-stent restenotic lesions. J Am Coll Cardiol Intv 2013;6:569–76.
[11] Nijhoff F, Stella PR, Troost MS, Belkacemi A, Nathoe HM, Voskuil M, et al. Comparative assessment of the antirestenotic efficacy of two paclitaxel drug-eluting balloons with different coatings in the treatment of in-stent restenosis. Clin Res Cardiol 2016;105:401–11.
[12] Scheller B, Clever YP, Kelsch B, Hehrlein C, Bocksch W, Rutsch W, et al. Long-term follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. J Am Coll Cardiol Intv 2012;5:323–30.
[13] Unverdorben M, Vallbracht C, Cremers B, Heuer H, Hengstenberg C, Maikowski C, et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. Circulation 2009;119:2986–94.
[14] Adriaenssens T, Dens J, Ughi G, Bennett J, Dubois C, Sinnaeve P, et al. Optical coherence tomography study of healing characteristics of paclitaxel-eluting balloons vs. everolimus-eluting stents for in-stent restenosis: the SEDUCE (Safety and Efficacy of a Drug elUting balloon in Coronary artery rEstenosis) randomised clinical trial. EuroIntervention 2014;10:439–48.
[15] Habara S, Mitsudo K, Kadota K, Goto T, Fujii S, Yamamoto H, et al. Effectiveness of paclitaxel-eluting balloon catheter in patients with sirolimus-eluting stent restenosis. J Am Coll Cardiol Intv 2011;4:149–54.
[16] Rittger H, Brachmann J, Sinha AM, Waliszewski M, Ohlow M, Brugger A, et al. A randomized, multicenter, single-blinded trial comparing paclitaxel-coated balloon angioplasty with plain balloon angioplasty in drug-eluting stent restenosis: the PEPCAD-DES study. J Am Coll Cardiol 2012;59:1377–82.
[17] Alfonso F, Pérez-Vizcayno MJ, Cárdenas A, García Del Blanco B, Seidelberger B, Iñiguez A, et al. A randomized comparison of drug-eluting balloon versus everolimus-eluting stent in patients with baremetal stent-in-stent restenosis: the RIBS V Clinical Trial (Restenosis Intrastent of Bare Metal Stents: paclitaxel-eluting balloon vs. everolimus-eluting stent). J Am Coll Cardiol 2014;63:1378–86.
[18] Alfonso F, Pérez-Vizcayno MJ, Cárdenas A, García del Blanco B, García-Touchard A, López-Minguéz JR, et al. A prospective randomized trial of drug-eluting balloons versus everolimus-eluting stents in patients with in-stent restenosis of drug-eluting stents: the RIBS IV randomized clinical trial. J Am Coll Cardiol 2015;66:23–33.
[19] Alfonso F, Pérez-Vizcayno MJ, García Del Blanco B, García-Touchard A, Masotti M, López-Minguez JR, et al. Comparison of the efficacy of everolimus-eluting stents versus drug-eluting balloons in patients with in-stent restenosis (from the RIBS IV and V randomized clinical trials). Am J Cardiol 2016;117:546–54.
[20] Baan Jr J, Claessen BE, Dijk KB, Vendrik J, van der Schaaf RJ, Meuwissen M, et al. A randomized comparison of paclitaxel-eluting balloon versus everolimus-eluting stent for the treatment of any in-stent restenosis: the DARE trial. J Am Coll Cardiol Intv 2018;11:275–83.
[21] Habara S, Iwabuchi M, Inoue N, Nakamura S, Asano R, Nanto S, et al. A multicenter randomized comparison of paclitaxel-coated balloon catheter with conventional balloon angioplasty in patients with bare-metal stent restenosis and drug-eluting stent restenosis. Am Heart J 2013;166:527–33.
[22] Xu B, Gao R, Wang J, Yang Y, Chen S, Liu B, et al, PEPCAD China ISR Trial Investigators. A prospective, multicenter, randomized trial of paclitaxel-coated balloon versus paclitaxel-eluting stent for the treatment of drug-eluting stent in-stent restenosis: results from the PEPCAD China ISR trial. J Am Coll Cardiol Intv 2014;7:204–11.
[23] Byrne RA, Neumann FJ, Mehilli J, Pinieck S, Wolff B, Tiroch K, et al, ISAR-DESIRE 3 investigators. Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial. Lancet 2013;381:461–7.

Please cite this article as: J.M. de la Torre Hernández, T. Garcia Camarero, F. Lozano Ruiz-Poveda, et al., Angiography and optical coherence tomography assessment of the drug-coated balloon ESSENTIAL..., Cardiovascular Revascularization Medicine, https://doi.org/10.1016/j.carrev.2019.07.021