2019 euro PCR

Angiographic and optical coherence tomography assessment in follow up of a new paclitaxel-eluting balloon, with an ultrasonic nanotechnology drop dosage system, for the treatment of in-stent restenosis

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On behalf of the ESSENTIAL study investigators

Conflicts of interest

Speaker's name : Jose M De La Torre Hernandez

☑ I have the following potential conflicts of interest to declare:

Receipt of grants / research supports: Abbott Medical, BMS / Pfizer Alliance, Amgen

Receipt of honoraria or consultation fees: Biotronik, Boston Scientific, Medtronic, AstraZeneca, Daiichi-Sankyo, Abbott Medical

Study funded by iVascular therapies for living

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BACKGROUND

-In-stent restenosis (ISR) has become less prevalent with the nearly systematic use of drug-eluting stent (DES) in PCI. Nonetheless, because the increased complexity of lesions treated with DES, yet a 5-10% of PCI are performed over in-stent restenotic lesions.

-Treatment of ISR remains challenging, with a variable rate of recurrent restenosis.

-Drug-coated balloons (DCB) have shown to be a valid treatment option in many trials, nonetheless no class-effect should be claimed, so every new DCB has to be evaluated through clinical studies.

OBJECTIVES

-This study sought to assess the efficacy of a new DCB, the paclitaxel-eluting balloon ESSENTIAL™ (iVascular, Spain) in the setting of ISR and cross-comparing results with those reported for other currently available DCB for ISR.

-Efficacy was assessed by means of quantitative angiography (QCA) and optical coherence tomography (OCT) evaluation at 6 months follow up.

-Clinical outcomes were evaluated at 6 months and 24 months.

-Results were cross-compared with those reported for the currently available DCB best supported by evidence.

METHODS

-This study is a prospective, multicenter (8 public hospitals), single-arm study that included consecutive patients undergoing PCI on in-stent restenosis lesions (ISR).

-All patients were treated with the ESSENTIAL™ balloon

-This is a paclitaxel-eluting balloon with a concentration of 3 µg/mm2 and a proprietary coating technology TransferTech™ (iVascular, Spain) consisting in a nanotechnology drop dosage system that yields a multilayer microcrystalline thin coating for a faster drug absorption rate.

METHODS: inclusion/exclusion criteria

All consecutive patients scheduled to undergo PCI on a first significant ISR of a BMS or DES.

Angiographic inclusion criteria:
Focal or diffuse ISR (Mehran Patterns I and II).
No evidence of overt stent subexpansion (angiography or intravascular imaging)

Angiographic exclusion criteria:
Totally occlusive or proliferative ISR
ISR involving inter-stents gaps and stent margins
ISR in the left main coronary artery
Angiographic findings suggestive of stent thrombosis or neo-atheroma plaque rupture

Clinical exclusion criteria:
Age > 75 years, left ventricular ejection fraction < 40%, moderate or severe kidney function impairment, unsuitable vascular accesses and known contrast allergies.

METHODS: endpoints / sample size

Primary end-point:

OCT derived maximal area stenosis at 6 months.

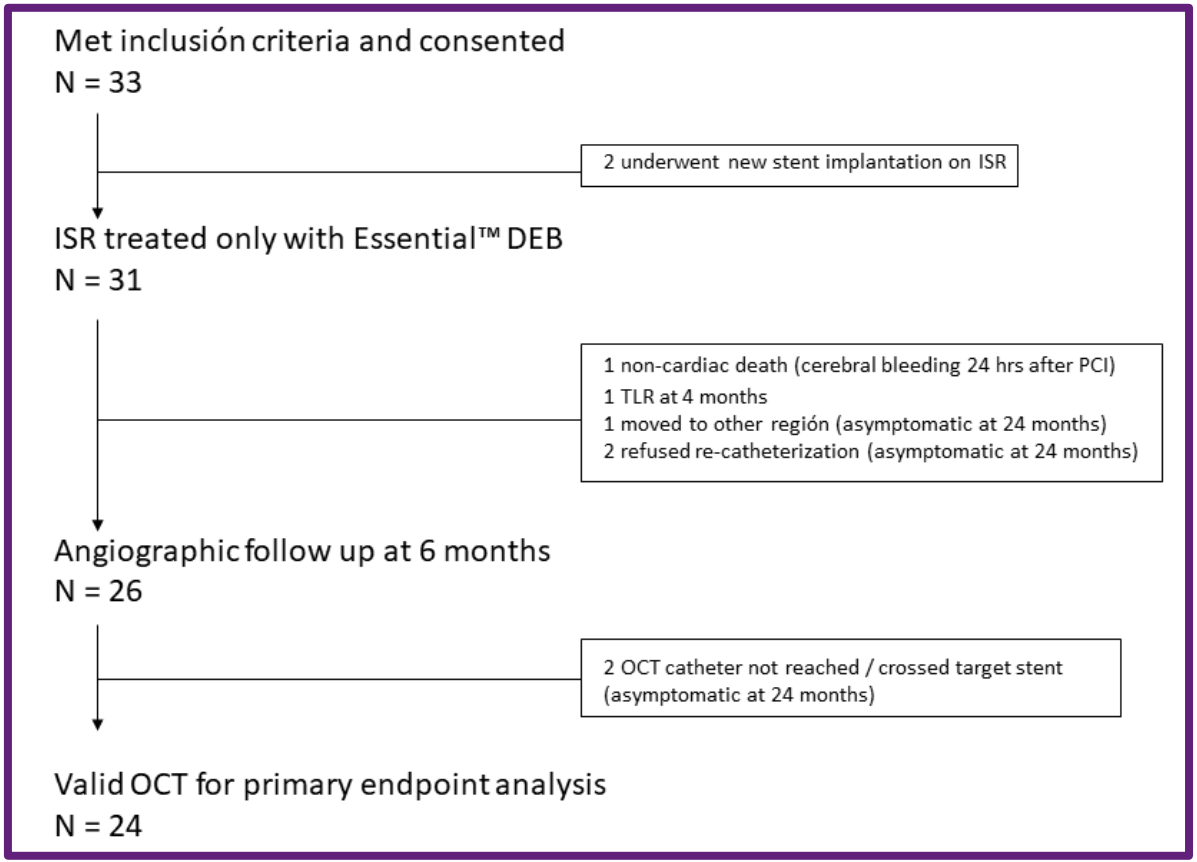
Secondary endpoints:

QCA-derived in-segment late lumen loss (LLL) at 6 months
TLF at 6 and 24 months (TLF= cardiac death/TV-MI/TLR)
TLR at 6 and 24 months

Sample estimation

Our primary analysis was a non-inferiority cross-comparison of the ESSENTIAL™ (iVascular) DEB with other currently available DEB for the primary endpoint of OCT-derived maximal area stenosis. In addition, a secondary analysis was a non-inferiority comparison of the ESSENTIAL™ (iVascular) DEB compared with the other currently available DEB for the secondary endpoint of in-segment LLL at 6-month angiographic follow-up. Based on these sample calculations and assuming a 15-20% loss to imaging follow-up rate, we thus planned to enroll a minimum of 30 patients.

Flow chart


Met inclusión criteria and consented
N = 33
2 underwent new stent implantation on ISR
ISR treated only with Essential™ DEB
N = 31
1 non-cardiac death (cerebral bleeding 24 hrs after PCI)
1 TLR at 4 months
1 moved to other región (asymptomatic at 24 months)
2 refused re-catheterization (asymptomatic at 24 months)
Angiographic follow up at 6 months
N = 26
2 OCT catheter not reached / crossed target stent (asymptomatic at 24 months)
Valid OCT for primary endpoint analysis
N = 24

RESULTS

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%)**

RESULTS

Procedural characteristics

ISR lesions treated	**N = 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
DCB diameter, mm	**3.02 ± 0.51**
DCB length, mm	19.83 ± 4.9
Max. balloon diameter to index stent nominal diameter ratio	0.98 ± 0.29
Additional stenting	2 (6%)
DCB angiographic success	**31 (94%)**
Procedural success	33 (100%)

2 patients crossover to DES

Quantitative coronary angiography analysis

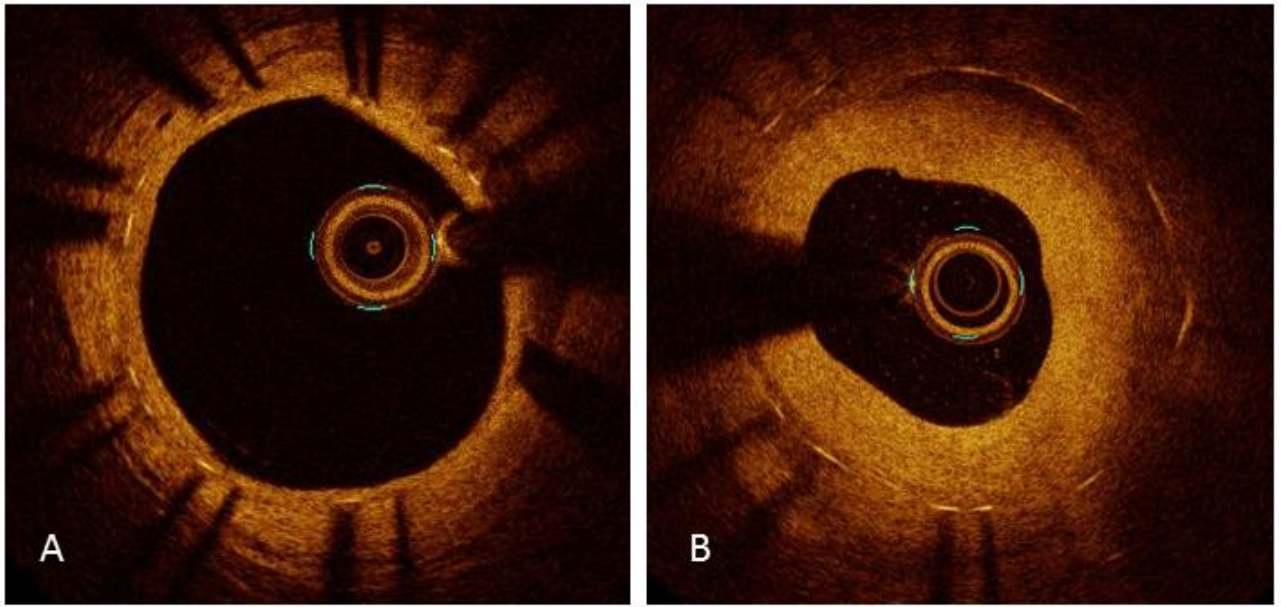
	Baseline N=33	**Post-DCB N = 31**	**6 m follow-up n =26**
Lesion length, mm	11.6±5.5	-	-
Reference vessel diameter, mm	2.69 ± 0.41	2.87±0.31	2.73 ± 0.44
Minimal lumen diameter, mm	0.94 ± 0.39	2.46±0.31	2.18 ± 0.56
Diameter stenosis, %	64.2± 14.7	13.75 ±5.7	20.60 ± 14.8
In-stent acute gain, mm	-	1.61 ± 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%)*
Binary restenosis in-segment	-	-	2 (7.7%)*

*Not included here the patient undergoing TLR at 4 months after index procedure.

Optical Coherence Tomography at 6 months follow up

	N = 24
Minimal stent area, mm2	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**
DES-ISR	*N=15*
Maximal in-segment area stenosis, %	52.6 ± 10
BMS-ISR	*N=9*
Maximal in-segment area stenosis, %	50.5 ± 13

Optical Coherence Tomography at 6 months follow up



A) Mild neointimal proliferation. B) Moderate neointimal proliferation.

Clinical outcomes at 6 and at 24 months

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%)

1 patient: non-cardiac death before 6 months

TLF at 6 months **10%**

TLF at 24 months **13.3%**

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%)

Primary endpoint: Cross-comparison with previous studies

	mean ± SD	*median (IQR)*
Maximal in-segment area stenosis, %	**51.4 ± 13**	**53 (46.4-59.5)**
DES-ISR		
Maximal in-segment area stenosis, %	52.6 ± 10	55.2 (49.3-58.5)
BMS-ISR		
Maximal in-segment area stenosis, %	50.5 ± 13	51 (44.6-59.5)

IN.PACT Falcon, **median 47.7% (37.3-60.7)**
DIOR, **median 66.4% (49.9-76.6**)
SeQuent Please, **mean 45-50%** (value inferred)

Agostoni P, et al. J Am Coll Cardiol Intv. 2013;6:569-576
Nijhoff F, et al. Clin Res Cardiol. 2016;105:401-411.
Adriaenssens T, et al. EuroIntervention. 2014;10:439-448.

Secondary endpoints: Cross-comparison with previous studies

In-segment late lumen loss at 6 months, mm	**0.25 ± 0.43**
TLR at 6 months	**3 (10%)**
TLR at 24 months	**4 (13.3%)**

Pooled analysis RIBS IV + V (SeQuent Please), in-segment LLL at 9 months was **0.24 mm**
DARE trial (SeQuent Please) in-segment LLL at 6 months was **0.17 mm**

Alfonso F, et al. Am J Cardiol. 2016;117:546-554.
Baan J Jr, et al. J Am Coll Cardiol Intv. 2018;11:275-283.

SeQuent Please: TLR rates at 12 months from 4-6% in BMS-ISR to 13-16.5% with DES-ISR, **11%** in a pooled analysis with a similar proportion of BMS/DES ISR as in our study.

Scheller B et al. J Am Coll Cardiol Intv. 2012;5:323-330. Unverdorben M etal. Circulation. 2009;119:2986-2994.
Alfonso F et al. J Am Coll Cardiol 2014;63:1378–86. Alfonso F et al. J Am Coll Cardiol 2015;66:23–33.
Xu B et al. J Am Coll Cardiol Intv. 2014;7:204-211. Alfonso F et al. Am J Cardiol. 2016;117:546-554

Limitations

Non-randomized design of our study confers the most important limitation.

Even applying similar inclusion and exclusion criteria and primary outcomes definition, a cross-comparison between studies is of limited value.

Underpowered for clinical endpoints.

Results applicable to the types of ISR treated according to inclusion-exclusion criteria.

No systematic OCT at baseline

Conclusions

-In this study, the drug-coated balloon ESSENTIAL showed a good efficacy in the treatment of ISR (mostly of DES) in terms of OCT and QCA assessment, which appear to be comparable to the provided by other drug-coated balloons well supported by evidence.

-Clinical efficacy seems to be good and maintained on the very long term.

-Larger studies are warranted to confirm clinical efficacy.