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Randomized comparison between 3-month Cre8 DES vs. 1-month Vision/Multilink8 BMS neointimal coverage assessed by OCT evaluation: The DEMONSTRATE study

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ABSTRACT

Background: It has been hypothesized that incomplete endothelialization and delayed vascular healing may trigger stent thrombosis events after drug-eluting stent (DES) implantation. We aimed to demonstrate non-inferiority in terms of neointimal coverage of novel Cre8 DES at 3 months, compared to Vision/Multilink8 Bare Metal Stent (BMS) at 1 month.

Methods: The ranDomizEd coMparisOn betweeN novel Cre8 DES and BMS to assess neoinTimal coveRAge by OCT Evaluation (DEMONSTRATE) was a multicenter, randomized, parallel group study. Thirty-eight patients undergoing angioplasty of de-novo coronary lesion were randomized to Cre8 (19) or Vision/Multilink8 (19) stent placement at 6 OCT-experienced centers. Primary end-point was the Ratio of Uncovered to Total Stent Struts Per Cross Section (RUTTS) score of <30%, determined by OCT at 3 and 1 months for Cre8 and Vision/Multilink8, respectively. Percentage of uncovered/malapposed stent struts, neointimal growth and thickness were the main secondary end-points.

Results: The primary end-point of RUTTS score <30% occurred in 99.8% (899/901) of Cre8 struts and in 99.6% (1116/1121) of Vision/Multilink8 struts (difference 0.2, CI 95% −0.2 to 0.6, p for noninferiority <0.001). The percentage of uncovered/malapposed struts was comparable (0.36 ± 0.64 vs. 0.12 ± 0.24, p = 0.145) in the two study groups, while both neointimal percentage area (8.46 ± 5.29 vs. 19.84 ± 15.93, p < 0.001) and thickness (0.07 ± 0.04 vs. 0.16 ± 0.12, p < 0.001) were significantly reduced by Cre8 stent.

Conclusions: The Cre8 DES at 3 months has comparable strut coverage to Vision/Multilink8 BMS at 1 month while preserving a greater efficacy in neo-intima formation reduction. Further studies to assess clinical implication of these Cre8 characteristics are warranted.

1. Introduction

Although drug-eluting stents (DES) remarkably reduce the rate of in-stent angiographic restenosis and subsequent target lesion revascularization (TLR) compared with bare-metal stents (BMS) [1–3], concerns about the long term safety of DES exist [4,5]. In fact, the drug-induced delay in vascular healing results in unpredictable and incomplete endothelialization possibly leading to an increased risk of late and very late stent thrombosis. Thus, while in case of BMS implantation the guidelines recommend only one month of dual antiplatelet therapy (DAPT) [6], there is a paucity and controversy of evidence regarding the optimal duration of DAPT [7,8] with DES; moreover, it is also unclear whether DAPT duration should be the same for the different DES brands.

In this context, frequency domain optical coherence tomography (FD-OCT) with its innovative high-resolution imaging system allows in vivo characterization of intraluminal and endothelial structures [9,10]; in particular, it permits semi-automated accurate insights regarding

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stent apposition, strut coverage and neointimal growth. Indeed, previous studies demonstrated an association between lack of neointimal strut coverage and thrombus formation, with the greatest thrombotic risk for uneven healed DES (as indicated by the number of uncovered struts per cross section) [11–13].

Recently a new DES generation, the Cre8 (CID, Saluggia, Italy), has entered the market. Its Cobalt–Chromium polymer free platform with abluminal reservoir technology for drug release and the iCarbofilm (commercially named Bio Inducer Surface — BIS) coating assure high biocompatibility/thromboresistance and promise accelerated strut endothelialization after implantation [14,15]. Thus, the purpose of this study is to demonstrate the noninferiority in terms of vessel healing and strut coverage evaluated with OCT of the novel DES Cre8 at 3 months as compared to a standard renowned BMS at 1 month.

2. Methods

2.1. Study design and end-points

The ranDomizEd coMparisOn betweeN a DES and a BMS to assess neoinTimal coveR-Age by OCT Evaluation (DEMONSTRATE) was a multicenter, prospective, randomized, parallel group study designed to investigate with FD-OCT the vascular healing pattern of Cre8 DES, compared with a BMS having a similar 80 μm strut thickness, the Vision/Multilink8.

All subjects undergoing coronary angioplasty of de novo lesion in native coronary arteries assessable with OCT were eligible for the study. Inclusion/exclusion criteria adopted in this study are reported in Appendix 1. At the end of diagnostic exam, all enrolled patients were randomized (1:1 ratio) to receive Cre8 or Vision/Multilink8 stent on the basis of a central randomization system; random assignment was stratified for acute coronary syndrome to prevent imbalance between groups. By protocol all patients underwent OCT-guided angioplasty and received scheduled clinical examination at 1, 3 and 12 months after the procedure in order to verify clinical status and occurrence of any adverse event. In addition, patients in Vision/Multilink8 and Cre8 arms underwent angiographic and OCT evaluations at 1 and 3 months after the procedure, respectively. For BMS the choice of an OCT follow-up length of 1 month was based on the current standard guidelines for DAT duration, while for Cre8 the 3 month OCT follow-up length was based on in vivo randomized study data, showing a completed drug-elution within 3 months from implant [15].

The study protocol received ethical committee approval and all patients provided written informed consent to the procedure. The DEMONSTRATE trial is registered with ClinicalTrials.gov, NCT01543373.

As primary objective of the study we appraised the Ratio of Uncovered to Total Stent Struts Per Cross Section (RUTTS) score of <30%, determined by OCT at 1 or 3 months, according to the randomization group. Secondary objectives were percentage of uncovered and malapposed stent struts, neointimal growth and neointimal thickness, minimal lumen diameter, restenosis percentage and late lumen loss at the pre-specified OCT follow-ups. As clinical endpoint we also assessed the composite rate of cardiac death, target vessel-related myocardial infarction (MI) and clinically driven target lesion revascularization (TLR) at 1 and 3 months from the index procedure. The end-points were analyzed on the basis of an intention to treat principle by a blinded central independent clinical-event committee.

2.1.1. Core laboratory analyses

All OCT and Quantitative Coronary Analyses (QCA) were performed by an independent Core laboratory (Rome Heart Research s.r.l.) with specific expertise in intravascular imaging. All assessments were performed off-line by personnel blinded to procedural data and clinical outcome.

In particular, lesion and vessel parameters were obtained by means of QCA measurements using an automated edge detection algorithm (Medis 7 Cardiovascular angiography Analysis System II, The Netherlands). Similarly, all OCT frames were digitally stored and analyzed using an off-line software (LightLab Consolle, Westford, Massachusetts, USA) applying a 0.20-mm intervals, on all available frames. Assessment of strut tissue coverage, malapposition and neointimal thickness was done at stent level (per-stent analysis). The count of struts with uncoverage/malapposition and cross-sections with RUTTS score <30% was done in each single stent and expressed as the average of measurements calculated for each stent. Stent with suboptimal strut visualization (i.e. inability of OCT to address all stent struts in a specific cross-section) in more than 10% of total stent struts was excluded from final analysis.

2.2. Population and procedures

Patient enrolment was carried out in a prospective and sequential way, so that all consecutive patient candidates to percutaneous revascularization angioplasty could theoretically participate into the trial (Fig. 1). Patient preparation and percutaneous access were performed according to the standard local hospital practice. All patients were pretreated with acetylsalicylic acid plus loading dose of thienopyridine while procedural anticoagulation was achieved with unfractionated heparin maintaining an activated clotting time of >300 s or 200 s in case of GP IIa/IIIb inhibitors use. Standardized angiographic and OCT acquisitions were performed in order to obtain a more accurate evaluation of the QCA and intravascular parameters. Predilation of target lesion was mandatory and stents were selected in order to exceed the lesion length by 5 mm (2.5 mm for each stent side). Post-dilation with shorter non-compliant balloon was performed when needed, to obtain a residual stenosis <30% with TIMI flow III and a stent diameter/reference vessel diameter ratio ≥ 1.1. By protocol, only one study stent could be used per lesion. However, in case of documented major dissection and/or complication (e.g. lesion mismatch) additional stent(s) were allowed using the same stent type, according to the randomization protocol. After the procedure, all antithrombotic agents were discontinued according to local hospital practice depending on stent implanted.

2.3. Data collection and definitions

By design, specific database and explicit definitions for outcomes were adopted. Data about clinical follow-up were obtained by direct visit or contact with referring physician. In case of any adverse clinical occurrence documentation was collected and analyzed by the central clinical-event committee.

Strut coverage was defined as a measured tissue thickness >0 μm on the luminal surface of the strut [10,11]. Strut malapposition was defined as a distance ≥80 μm from the inner edge of the strut to the vessel wall [10,11].

Cardiac death was defined as any death due to cardiac cause, procedure-related deaths, and death of unknown cause. MI was defined as new ischemic symptoms lasting >20 min and new or recurrent ST-segment elevation or depression >1 mm in at least 2 contiguous leads, associated with an increase of the cardiac biomarker [16]. Clinically indicated TLR was defined as any revascularization procedure performed because of angiographic restenosis/thrombosis >70% at the site of the culprit lesion or restenosis >50% (core lab QCA assessment) associated with clinical or objective evidence of inducible myocardial ischemia. Stent thrombosis was classified utilizing the Academic Research Consortium (ARC) definition [17].

2.4. Statistical analysis

In the DEMONSTRATE trial we hypothesized that the grade of endothelialization of Cre8 stent at 3 months would not be inferior to Vision/Multilink8 at 1 month (BMS with comparable strut thickness). The sample size was calculated assuming a 95% of cross sections with a Ratio of Uncovered to Total Stent Struts Per Cross Section (RUTTS) score of <30% in Vision/Multilink8 group after 1 month, and using an absolute delta non-inferiority margin of 5% with a 97.5% one-sided significance level of the risk differences. Thus, we computed that 1792 cross sections were required to have 90% power to detect the non-inferiority of the Cre8 when compared to Vision/Multilink8, in terms of strut coverage. Taking into account a cross-sectional OCT image analysis at 0.2 mm intervals and assuming a mean length of stented segment of 20 mm per patient, we figured that at least 18 patients (9 per arm) should be enrolled to obtain the 1792 cross sections required. In order to have a more sample representative of the overall population and to minimize bias due to randomization, the enrolment was extended to a total of 40 patients (20 per arm). Analyses were conducted on intention-to-treat basis.

Data were reported as means (±standard deviation) for continuous variables normally distributed, as median (±inter-quartile range) for continuous variable that failed the normal distribution test and as counts and percentages for categorical variables. Levene's test or Brown–Forsythe test were used for comparison according to homogeneity of variances between groups; Student t or Mann–Whitney *U* test for continuous and Fisher exact tests for bivariate analyses were computed when appropriate.

For the non-inferiority primary endpoint the confidence limit of the risk difference and a single tailed (alpha = 0.025) test was performed, while for all other comparisons a two tailed (alpha = 0.05) test was adopted.

3. Results

The final study population included 38 patients undergoing OCT-guided angioplasty of de novo coronary lesion at six European high-volume centers. Two patients (one per arm) who had a baseline OCT assessment refused the follow-up control and were therefore excluded from the final analysis. Each Investigational Center enrolled a minimum of 5 patients and the recruitment was competitive among the centers involved.

Patients enrolled in the two study groups were similar for demographic and clinical characteristics (Table 1). Baseline angiographic and procedural data addressed with QCA and OCT were also well balanced. Finally, there were no differences in the rate of angiographic complication (e.g. dissection at edge stent) and procedural success between the two study arms (Table 2).

The primary end-point of RUTTS score <30% occurred in 99.6% (2015/2022) of sections analyzed with no difference between the Cre8 (99.8%, 899/901) at 3-month follow-up and the Vision/Multilink8 (99.6%, 1116/1121) at 1-month follow-up (difference 0.2, CI 95% −0.2

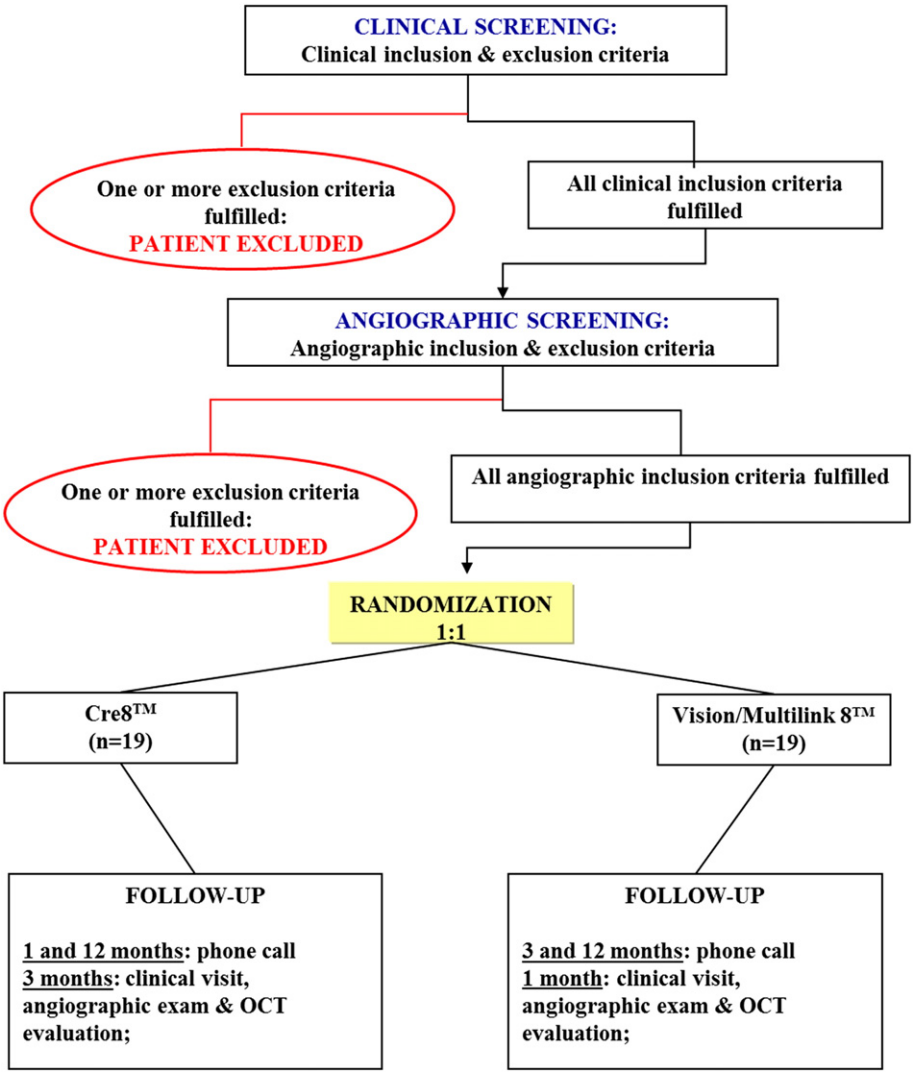

Fig. 1. Study flow chart.

to 0.6, p for noninferiority < 0.001) (Table 3). Accordingly, the mean percentage of uncovered stent struts was comparable in Cre8 (1.59 ± 2.10) and in Vision/Multilink8 (0.86 ± 1.38, p = 0.228) groups, with no difference also in the presence of two overlapping stents (0.00 ± 0.00 vs. 1.39 ± 2.41, p = 0.670).

Although a comparable strut malapposition rate (7.57 ± 7.78 vs. 5.63 ± 6.30, p = 0.450) was appreciated at OCT post-implantation a significant higher percentage was found at the 3-month follow-up in the Cre8 arm (4.18 ± 5.09 vs. 1.21 ± 1.72, p < 0.001) confined to the non-overlapping stent segments. Nevertheless, the rate of uncovered and malapposed stent struts did not differ between the two study groups (0.36 ± 0.64 vs. 0.12 ± 0.24, p = 0.145). No significant differences or inconsistent data were observed among the enrolling centers. None of the baseline clinical characteristic (e.g. NSTEMI diagnosis) or of the peri-procedural variables (Tables 1–2) showed a significant correlation with the primary and secondary endpoints.

Both the median neo-intimal area percentage (8.46 ± 5.29 vs. 19.84 ± 15.93, p < 0.001) and median neo-intimal thickness (0.07 ± 0.04 vs. 0.16 ± 0.12, p < 0.001) were significantly reduced in Cre8 group when compared to Vision/Multilink8 group (Figs. 2 and 3). The inhibition of neo-intimal formation in terms of area and thickness was evident also in the presence of a double strut layer (14.67 ± 3.99 vs. 32.58 ± 12.86, p < 0.001 and 0.14 ± 0.03 vs. 0.19 ± 0.04, p < 0.001, respectively).

Furthermore thin and homogenous tissue coverage was appreciated in all cases treated with the Cre8 (Fig. 2). Consistently the QCA minimum

Table 1
Baseline clinical patients' characteristics.

	Cre8 (19)	Vision/Multilink8 (19)	p
Age (years)[a]	69.2 (±8.6)	65.0 (±8.6)	0.1406
Male gender	84.2% (16/19)	63.2% (12/19)	0.2691
Hypertension	84.2% (16/19)	68.4% (13/19)	0.4470
Hyperlipidemia	68.4% (13/19)	47.4% (9/19)	0.3245
Smoke habit	47.4% (9/19)	57.9% (11/19)	0.7459
Family history of CAD	15.8% (3/19)	42.1% (8/19)	0.1510
Diabetes mellitus	26.3% (5/19)	15.8% (3/19)	0.6928
Prior myocardial infarction	26.3% (5/19)	36.8% (7/19)	0.7281
Prior revascularization	26.3% (5/19)	31.6% (6/19)	1.0000
Diagnosis			
Silent ischemia	31.6% (6/19)	26.3% (5/19)	1.0000
Stable angina	57.9% (11/19)	47.4% (9/19)	0.7459
Unstable Angina	5.3% (1/19)	15.8% (3/19)	0.6039
NSTEMI	5.3% (1/19)	10.5% (2/19)	1.0000

NSTEMI = non ST-elevation myocardial infarction; CAD = coronary artery disease.
[a] Expressed as mean and standard deviation.

Table 2
Baseline and post implantation angiographic and OCT lesions' characteristics.

	Cre8 (19)	Vision/Multilink8 (19)	p
Target vessel			
Left main trunk	0.0% (0/19)	0.0% (0/19)	1.000
Left descending artery	42.1% (8/19)	36.8% (7/19)	0.998
Left circumflex artery	31.6% (6/19)	31.6% (6/19)	0.727
Right coronary artery	26.3% (5/19)	31.6% (6/19)	0.998
Lesion classification ACC/AHA			
Type A	5.2% (1/19)	0 (0/19)	0.959
Type B1	47.4% (9/19)	42.1% (8/19)	0.998
Type B2	36.8% (7/19)	47.4% (9/19)	0.739
Type C	10.5% (2/19)	10.5% (2/19)	0.597
Stent implantation			
No. stent per lesion (range)[a]	1.3 ± .05 (1–3)	1.2 ± .04 (1,2)	0.547
Mean stent diameter (mm)[a]	3.1 ± 0.4	3.0 ± 0.4	0.240
Mean stent length (mm)[a]	19.3 ± 4.9	19.8 ± 6.3	0.780
Maximum inflation pressure (atm)[a]	14.7 ± 3.7	16 ± 2.3	0.168
Basal QCA/OCT			
Minimum lumen diameter (mm)[a]	0.70 ± 0.38	0.74 ± 0.32	0.728
Reference vessel diameter (mm)[a]	2.75 ± 0.49	2.55 ± 0.33	0.200
Diameter stenosis (%)[a]	73.86 ± 14.36	70.28 ± 14.33	0.447
Post intervention QCA/OCT			
Minimum lumen diameter (mm)[a]	2.71 ± 0.32	2.67 ± 0.48	0.764
Reference diameter (mm)[a]	3.05 ± 0.40	2.91 ± 0.52	0.390
Diameter stenosis (%)[a]	10.90 ± 4.90	8.23 ± 3.41	0.070
Mal-apposition (%)[a]	7.57 ± 7.78	5.63 ± 6.30	0.450
Edge dissection 200 μ (%)	6.8% (7/19)	6.8% (7/19)	0.737

[a] Expressed as mean and standard deviation.

lumen diameter (2.61 ± 0.34 mm vs. 2.24 ± 0.60 mm, p = 0.033), in-stent late loss (0.10 ± 0.33 mm vs. 0.43 ± 0.36 mm, p < 0.001) and residual diameter stenosis (9.26 ± 4.98% vs. 19.07 ± 12.67%, p = 0.005) were significantly improved in the Cre8 stent group at the pre-specified angiographic follow-up.

No outcome difference, in terms of cardiac death, target vessel-related MI and clinically-driven TLR was found at the 3-month clinical follow-up. In particular, only one TLR due to early restenosis was recorded in the Vision/Multilink8 group one month after the index procedure.

Table 3
Angiographic, OCT and clinical outcome at follow-up.

	Cre8 (19)	Vision/Multilink8 (19)	p
Follow-up QCA (3 vs. 1 month)			
MLD (mm) [a]	2.61 ± 0.34	2.24 ± 0.60	0.033
REF (mm) [a]	2.89 ± 0.42	2.76 ± 0.58	0.480
Late loss (mm) [a]	0.10 ± 0.33	0.43 ± 0.36	<0.001
Diameter stenosis (%)[a]	9.26 ± 4.98	19.07 ± 12.67	0.005
Follow-up OCT (3 vs. 1 month)			
RUTTS score <30% (%)	99.8 (899/901)	99.6 (1116/1121)	<0.001[b]
Uncovered struts (%)[a]	1.59 ± 2.10	0.86 ± 1.38	0.228
Strut mal-apposition (%)[a]	4.18 ± 5.09	1.21 ± 1.72	<0.001
Uncovered and malapposed struts (%)[a]	0.36 ± 0.64	0.12 ± 0.24	0.145
Neointima area (%)[c]	8.46 ± 5.29	19.84 ± 15.93	<0.001
Neointima thickness (mm) [c]	0.07 ± 0.04	0.16 ± 0.12	<0.001
Follow-up MACE (3 months)			
Cardiac death (%)	0 (0/19)	0 (0/19)	1.000
Myocardial infarction (%)	0 (0/19)	0 (0/19)	1.000
Clinical TLR (%)	0 (0/19)	5.2 (1/19)	0.959

QCA = quantitative coronary angiography. OCT = optical coherence tomography. RUTTS = Ratio of Uncovered to Total Stent Struts Per Cross Section. TLR = target lesion revascularization.
[a] Expressed as mean and standard deviation.
[b] p for noninferiority.
[c] Expressed as median and interquartile range.

4. Discussion

The results of the present multi-center randomized clinical trial can be summarized as follows: 1) the high biocompatibility of the Cre8 DES led to a homogenous tissue coverage after 3 months, comparable to that achievable with BMS at 1 month, opening therefore a door for possible improvement of the long-term DES safety and for reconsideration of DAPT duration and 2) the Cre8 DES showed an excellent neo-intima suppression, similar to that achieved with other DES and much greater than that obtained in the BMS group.

A recent network meta-analysis has shown as stent strut thickness, thromboresistant properties of polymer and reduced drug load may contribute to increase long term DES safety [18]. In particular, some second generation DES seem not to be associated with a significant increase in stent thrombosis risk over time, also when compared to BMS. Nevertheless, the effective role of single DES components (e.g. stent platform, polymer or drug) in determining such a reassuring result remains to be determined [19].

In this context, the novel drug-eluting Cre8 stent has an innovative design, combining the previous demonstrated non-thrombogenic properties of the integral pure carbon coating [20–22] (BIS) with a new drug loading technology. The Cre8 has a polymer-free Cobalt–Chromium platform with abluminal reservoir providing controlled and directed elution exclusively targeted to the vessel wall. The drug is Sirolimus combined with an organic acid (Amphilimus formulation) that is an active drug carrier assuring enhanced drug bioavailability with sustained and homogenous distribution to the entire vessel wall. Preliminary study showed brilliant results both for the BIS in terms of tissue coverage [22] and for the Amphilimus formulation in terms of neo-intima suppression [14,15].

The present OCT study confirmed the excellent in vivo stent strut coverage of the BIS also in combination with the Sirolimus, which is a highly effective antiproliferative agent. Indeed, patients treated with Cre8 had no differences in terms of percentage of uncovered stent when compared to a BMS.

Early and complete re-endothelialization represents a crucial aspect for intracoronary devices, especially for DES. Indeed, the drug-induced delay of vessel healing and incomplete strut coverage have been advocated as the main causes of late and very late thrombosis recorded with first generation DES [12,13].

More importantly, the Cre8 showed that the almost complete stent coverage is associated with a marked reduction of neo-intimal formation. Indeed, all the OCT neo-intimal growth indexes, including the intimal area percentage, intimal thickness, minimum lumen diameter and residual diameter stenosis were significantly improved by Cre8 when compared to Vision/Multilink8. These data confirm the validity of the innovative drug loading system of Cre8. The absence of a permanent polymer, triggering a chronic inflammatory stimuli and the more complete and homogenous distribution of drug assured by the Amphilimus formulation, are probably the main determinants of these distinctive findings.

The small but significantly higher incidence of late malapposed struts, found in the Cre8 group with respect to Vision/Multilink8 group, is likely the inevitable consequence of the active drug-induced neo-intima suppression. Dissolution of thrombotic remnants between the abluminal strut side and the vessel wall or drug-induced positive plaque remodeling can generate empty spaces that require a marked neointima formation to be filled up during the follow-up. Nevertheless, the practical impact of late malapposition, frequently described with

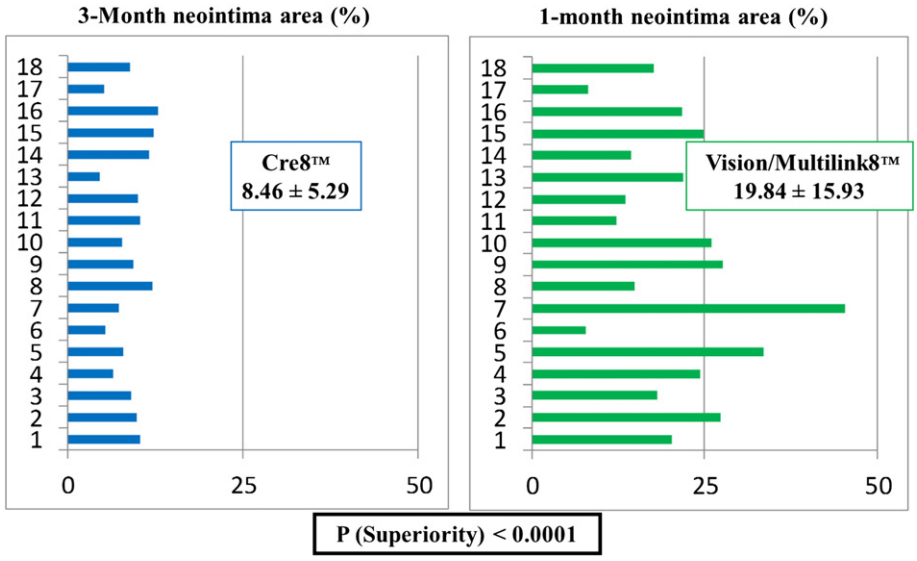

Fig. 2. Distribution of in stent neo-intima area of Cre8 and Vision/Multilink8 at 3-month and 1-month follow-up, respectively.

DES, remains uncertain, but it does not seem to be associated with an increased risk of adverse events (i.e. stent thrombosis) [12,13]. Furthermore, no difference in number of malapposed and uncovered struts was found between the two study groups.

Thus, the Cre8 represents a promising device balancing efficacy, expressed in terms of restenosis reduction, and safety, expressed in terms of optimal stent coverage. The latter represents the main challenge for future DES generation. Indeed, to date, there is great uncertainty about long term vessel reaction to DES and the only data available derived from meta-analyses or post-mortem studies on patients experiencing fatal adverse events. In these autoptic studies, a tight correlation between drug efficacy in neo-intima suppression and incidence of incomplete or uneven stent re-endothelialization has been described [12,13]. Moreover, stent polymer represents a permanent target for inflammatory cells that can lead to a chronic inflammatory response and inadequate vessel healing of the stented segment [12,13]. The novel Cre8 design represents a possible solution to overcome both these problems and to reconsider DAPT duration requirement after DES implantation.

Finally, the modern OCT technology offers the possibility to explore in vivo the interplay between stents and vessel-wall reaction. In particular, the OCT resolution is able to describe with high level of accuracy superficial structures, depicting stent strut coverage and malapposition.

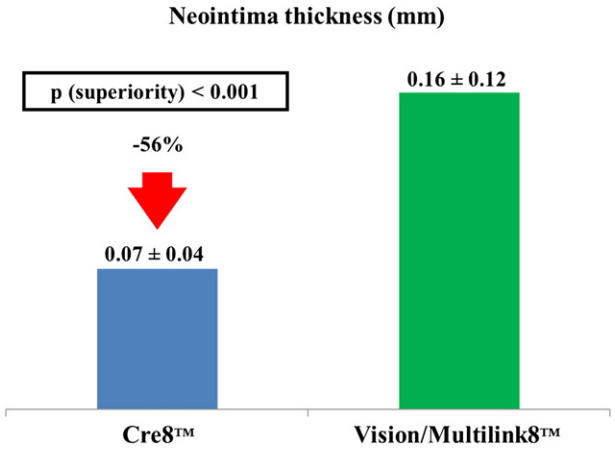

Fig. 3. Comparison of in stent neo-intima thickness of Cre8 and Vision/Multilink8 at 3-month and 1-month follow-up, respectively.

The present study was based on the concept that strut uncoverage could indicate a higher risk of stent thrombosis, particularly when this feature includes many struts closed to each other, leading to the presence of almost completely uncovered spots.

If confirmed, the information gained by this study will help in the future design of clinical trials to test the clinical outcome after Cre8 deployment in a regimen of reduced DAPT duration [22,23]. More generally, the DEMONSTRATE trial would corroborate, with a solid scientific basis, the recent reconsideration of DAPT duration proposed with modern DES (e.g. 3–6 months). Thus, the validity of this approach, with a systematic OCT DES evaluation, preceding large clinical studies to determine modern stent efficacy/safety and DAPT duration, is unique and should lead to further validation in larger cohort studies.

5. Conclusions

In conclusion the DEMONSTRATE trial showed an almost complete tissue coverage of the Cre8 DES after 3-months, comparable to that of Vision/Multilink8 BMS at 1 month, and a sustained efficacy in neointimal suppression. Larger cohort studies with long term follow-up are warranted to test the effective clinical impact of this promising innovative DES.

Funding

The DEMONSTRATE trial was sponsored by CID (C21101) S.p.A (Saluggia, Italy) who was responsible for selecting investigators, ethical committee approvals and to ensure that the study was conducted according to Good Clinical Practice (ICH-GCP), ISO 14155-1 (2009), Declaration of Helsinki, Study Protocol, or any conditions of approval imposed by regulatory authorities.

Conflict of interest

FP is a consultant for St. Jude Medical. PS is a consultant for Mentice and Physician Proctor for Edwards Lifesciences. MV has received honoraria for lectures/advisory board and research grants from Merck, Iroko, Eli Lilly and Medtronic; honoraria for advisory board and lectures from The Medicines Company and Eli Lilly Co; Daiichi Sankyo, Inc., St Jude and Abbott Vascular; lectures from Cordis, CID and Terumo.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2014.08.031.

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