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CVN Interview

Impact of Drug Release Kinetics on Vascular Response to Different Zotarolimus-Eluting Stents Implanted in Patients With Long Coronary Stenoses

The LongOCT Study (Optical Coherence Tomography in Long Lesions)

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Objectives We assessed the in vivo vascular response to a new generation of zotarolimus-eluting stents (ZES) with prolonged drug release (Resolute ZES-SR, Medtronic Vascular, Santa Rosa, California) compared with ZES with faster kinetics (Endeavor ZES-FR, Medtronic Vascular) by optical coherence tomography.

Background Local drug release kinetics has been implicated with antirestenosis efficacy of drug-eluting stents. However, the impact of different release kinetics on vascular response of diseased human coronary arteries remains to be investigated.

Methods The study population consisted of 43 patients with long lesions in native coronary vessels treated with multiple overlapping ZES. Twenty-one patients treated with ZES-SR were compared with 22 patients treated with ZES-FR from the ODESSA (Optical coherence tomography for DES SAfety) study. The primary endpoint was in-stent neointimal hyperplasia as assessed by optical coherence tomography at 6-month follow-up. Coprimary endpoints were the percentage of uncovered and malapposed struts.

Results Strut-level median neointimal thickness was 0.11 mm (interquartile range [IQR]: 0.07 to 0.15 mm) in ZES-SR and 0.31 mm (IQR: 0.27 to 0.42 mm) in ZES-FR, respectively ($p < 0.001$). The 6-month rate of uncovered struts per patient was 7.38% (IQR: 3.06% to 12.72%) in ZES-SR and 0.00% (IQR: 0.00% to 0.00%) in ZES-FR ($p < 0.001$); rate of malapposed and uncovered struts was 1.47% (IQR: 0.32% to 4.23%) in ZES-SR and 0.00% (IQR: 0.00% to 0.00%) in ZES-FR ($p < 0.001$).

Conclusions This study demonstrated the impact of different release kinetics on human in vivo vascular response to ZES implantation. The new generation of ZES-SR compared with ZES-FR had better suppression of the neointimal response but higher proportion of uncovered and malapposed struts at 6-month optical coherence tomography follow-up. (Optical Coherence Tomography in Long Lesions [LongOCT]; NCT01133925) (J Am Coll Cardiol Intv 2011;4:778–85) © 2011 by the American College of Cardiology Foundation

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Drug-eluting stents (DES) significantly reduce restenosis and the need for repeat revascularization compared with bare-metal stents (BMS) across a broad range of patient and lesion subsets (1). Histopathological, preclinical, and clinical studies support significant disparities in neointimal response and vascular healing among leading polymeric DES (2,3). Long lesions are of particular concern, as these often require multiple stent implantations with more extensive vascular injury and have been associated with increased risk of stent thrombosis and restenosis (4).

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Zotarolimus-eluting stents (ZES) (Endeavor, Medtronic Vascular, Santa Rosa, California) have been associated with a more prompt, complete and homogeneous coverage, similar to BMS, but with higher percentage of neointimal hyperplasia (NIH) when compared with sirolimus- (SES) and paclitaxel-eluting stents (PES) (5–9). The Resolute stent (Medtronic Vascular) is a new generation of ZES that uses the same metallic platform (a thin-strut, cobalt-chromium alloy stent) and the same drug (zotarolimus) and dosage of the Endeavor stent with a newly developed biodurable polymer (BioLinx Polymer System). The new coating enables sustained drug elution compared with the Endeavor stent. No study has investigated the impacts of the 2 different release kinetics on in vivo vascular response to ZES. Optical coherence tomography (OCT) is able to detect subtle differences in coverage and vessel responses to DES implantation (10–12). Therefore, we designed this study to assess the in vivo, human coronary vascular response to ZES with sustained (ZES-SR) versus faster release kinetics (ZES-FR) in a subset of long lesions with overlapping stents.

Methods

Study design. The study design followed the ODESSA (Optical coherence tomography for DES SAfety) trial, which has been reported previously (8). In the present prospective controlled study, 21 consecutive patients with long lesion (>20 mm) were treated with the implantation of multiple overlapping ZES-SR (Resolute). The ZES-SR–treated patients were compared with the ZES-FR (Endeavor) arm from the ODESSA trial. The study was conducted under Good Clinical Practice conditions and in compliance with the Medical Device Regulations for Italy. The Ethics Review Committee of Ospedali Riuniti di Bergamo approved the protocol; patients provided written informed consent before enrollment.

Drug-eluting stents. The ZES-SR is coated with a 6-μm BioLinx, a blend of 3 polymers that results in sustained drug elution in the first 30 days (approximately 85% in 30 days and 100% by 180 days). In contrast, the ZES-FR is coated with a 4-μm phosphorylcholine coating that results in rapid drug elution (approximately 80% in 1 week and 95% in 2 weeks). Both ZES-FR and ZES-SR are loaded with same concentration of zotarolimus (1.6 μg/mm^2 of stent surface).

Patient selection, procedure, and follow-up. The inclusion criteria were the same as for the ODESSA trial. In brief, eligible subjects (≥18 years of age) had a de novo lesion in a native coronary artery with length ≥20 mm, diameter stenosis (DS) ≥75%, reference vessel diameter of 2.5 to 3.5 mm by visual estimation, requiring percutaneous coronary intervention with overlapping stents. Exclusion criteria were ongoing/recent myocardial infarction, left main disease, previous target vessel stenting, ejection fraction ≤30%, creatinine ≥2.5 mg/dl, no suitable anatomy for OCT (ostial lesions and extreme vessel tortuosity), and inability to comply with dual antiplatelet therapy and follow-up requirements. Intracoronary nitroglycerin (200 μg) was administered before imaging procedures. Aspirin (100 mg daily) was mandated per protocol for 12 months and recommended indefinitely. All patients received clopidogrel (75 mg) daily for a minimum of 6 months but recommended for 12 months. Angiographic, OCT, and intravascular ultrasound (IVUS) follow-up were performed 6 months after stent implantation and clinical outcomes were followed for 12 months.

Abbreviations and Acronyms

AIT = abnormal intraluminal tissue
BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
DM = diabetes mellitus
DS = diameter stenosis
IQR = interquartile range
ISA = incomplete stent apposition
IVUS = intravascular ultrasound
NIH = neointimal hyperplasia
OCT = optical coherence tomography
PES = paclitaxel-eluting stent(s)
SES = sirolimus-eluting stent(s)
ZES = zotarolimus-eluting stent(s)
ZES-FR = zotarolimus-eluting stent(s) with faster release kinetics
ZES-SR = zotarolimus-eluting stent(s) with sustained release kinetics

Quantitative coronary angiography. Quantitative coronary angiography was done at baseline, after index percutaneous coronary intervention, and at follow-up. Digital coronary angiograms were analyzed offline by an independent core laboratory (Cardiovascular Imaging Core Laboratory, University Hospitals Case Medical Center, Cleveland, Ohio) using validated quantitative methods (7).

Intravascular ultrasound. IVUS was performed after index percutaneous coronary intervention and at 6-month follow-up using the Atlantis SR Pro 40-MHz catheter (Boston Scientific, Natick, Massachusetts) and the iLab ultrasound console (Boston Scientific). IVUS images were recorded with a motorized pullback at 1 mm/s throughout the stent and at least 5 mm distal and proximal to the stent. All IVUS data were digitally stored for subsequent analysis. Quantitative volumetric IVUS analysis was performed using a validated semiautomated detection algorithm (Curad,

version 4.32, Curad, Wijk bij Duurstede, the Netherlands) and previously described methodology (7). The cross-sectional areas and associated volumes were determined for the stent, lumen, vessel, and neointimal areas. Qualitative analysis included stent malapposition, defined as blood speckle behind the struts, categorized as persistent, resolved, and late acquired (7).

OCT imaging acquisition and analyses. OCT images were obtained at 6-month follow-up according to a previously described procedure (8). In brief, a time-domain OCT system (M2CV OCT Imaging System, LightLab Imaging, Westford, Massachusetts) was used, and an occlusive technique was adopted. Images were acquired with an automated pullback at a rate of 1.0 mm/s, then digitally stored and submitted to the core laboratory for offline analysis. A dedicated software (OCT system software B.0.1, LightLab) was used for measurements. All cross-sectional images were initially screened for quality assessment and excluded if images were not suitable for analysis according to a previously described method (13). Qualitative assessment was performed in every frame (i.e., every 0.06 mm), whereas quantitative strut level analysis and morphometric analysis were performed at every 10 frames (i.e., 0.6-mm intervals) along the entire target segment. Strut-level intimal thickness was determined based on automated measurements performed from the center of the luminal surface of each strut blooming and its distance to the lumen contour. Strut malapposition was defined when the negative value of strut-level intimal thickness was higher than the sum of strut thickness plus abluminal polymer thickness, according to the stent manufacturer's specifications plus a compensation factor of 20 μm to correct for strut blooming (8). Qualitative imaging assessment included detection of abnormal intraluminal tissue (AIT), defined as any irregular mass protruding beyond the stent strut into the lumen. Highly reproducible measurements for strut apposition, strut coverage, and AIT qualitative assessment using the described methodology have been already reported (14).

Endpoints and data management. The primary prespecified OCT endpoint was the degree of in-stent NIH at 6-month follow-up. Coprimary OCT endpoints included the proportion of uncovered and malapposed struts per patient at 6-month follow-up. The secondary endpoint was the percentage of cross sections where >30% of struts were uncovered. Data on clinical outcomes included major adverse cardiac events (a composite of cardiac death, myocardial infarction, and target vessel revascularization), target lesion revascularization, and stent thrombosis as per the Academic Research Consortium definitions of definite/probable (15) and were to be evaluated at 1, 6, and 12 months.

Procedural success was defined as success stent implantation (<20% residual stenosis) without any in-hospital events.

Statistical methods. The analysis sample for the primary endpoint was the intent-to-treat population. Patient, lesion, and procedural characteristics and event rates were analyzed using descriptive statistics with SAS (version 9.1 or higher, SAS Institute Inc., Cary, North Carolina) with statistical significance at the 0.05 level. Continuous variables were expressed as mean ± SD or median (interquartile range), and categorical variables were expressed as counts and percentages. For per-patient analysis, the difference between 2 stent types was evaluated by nonparametric Mann-Whitney *U* test for continuous variables, and Fisher exact test for categorical variables. For segmental analysis, continuous variables were compared using generalized estimating equations model with exchangeable correlation structure to account for the clustering of values within each subject, and generalized estimating equations model or Fisher exact test were used for the comparison of categorical variables between 2 stent types or overlapping versus nonoverlapping segment when appropriate.

Results

Patient, lesion, and procedural characteristics. Baseline clinical and procedural characteristics are reported in Table 1. The 2 groups (ZES-SR, n = 21; ZES-FR, n = 22) were not significantly different from each other except with respect to higher prevalence of diabetes mellitus in the ZES-FR group (p = 0.02). Procedural success was 95.2% for ZES-SR and 100% for ZES-FR. All patients underwent angiography, IVUS, and OCT imaging at 6 months successfully and without complications.

Table 1. Clinical and Procedural Characteristics

	ZES-FR (n = 22)	ZES-SR (n = 21)	p Value
Men	15 (68)	15 (71)	0.62
Age, yrs	64.1 ± 9.65	68.7 ± 10.5	0.14
Diabetes mellitus	11 (50)	3 (14)	0.02
Hyperlipidemia	12 (54)	12 (57)	1.00
Hypertension	11 (50)	10 (48)	0.92
Prior MI	7 (32)	8 (38)	0.81
Prior PCI	5 (23)	8 (38)	0.22
Lesion treated			0.11
LAD	17 (77)	12 (57)	0.16
Cx/obtuse marginal	1 (5)	3 (14)	0.27
RCA	4 (18)	6 (29)	0.42
Stent/patient	2.5 ± 0.7	2.5 ± 0.6	0.98
Maximum inflation pressure, atm	18.3 ± 2.3	18.0 ± 1.6	0.72
Post-dilation performed	11 (50)	16 (76)	0.44

Values are n (%) or mean ± SD.

Cx = circumflex; LAD = left anterior descending artery; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery; ZES-FR = zotarolimus-eluting stent(s) with faster release kinetics; ZES-SR = zotarolimus-eluting stent(s) with sustained release kinetics.

Quantitative coronary angiography. Angiographic assessments pre-procedure, post-procedure, and at 6 months are shown in Table 2. Pre- and post-procedural angiographic measurements were similar for ZES-SR and ZES-FR. However, at follow-up, in-stent late lumen loss and % DS were significantly different between the 2 groups (late lumen loss: 0.17 mm [interquartile range (IQR): 0.00 to 0.33 mm] in ZES-SR vs. 0.46 mm [IQR: 0.11 to 0.62 mm] in ZES-FR, p = 0.01; 18.0% DS [11.0% to 23.0%] and 25.3% DS [19.0% to 41.0%], p = 0.01, respectively). In-stent binary restenosis was 0% for ZES-SR and 18.2% for ZES-FR (p = 0.11).

Optical coherence tomography. Using OCT, 23,091 struts were analyzed. Of 2,791 frames, 392 (14.1%) were excluded from analysis due to: location of bifurcation level (n = 196, 7.0%); presence of sew-up artifact (n = 15, 0.5%); strut was out of screen (n = 71, 2.6%); or presence residual blood (n = 110, 4.0%). At 6 months, NIH was significantly lower in the ZES-SR group than in the ZES-FR group (0.11 mm vs. 0.31 mm, p < 0.01) (Table 3). However, the median proportion of uncovered struts per patient ranged from 0% in the ZES-FR group to 7.4% in the ZES-SR group (p < 0.01) (Fig. 1). The rate of cross sections with ≥30% uncovered struts was 0.0% in the ZES-FR group versus 6.4% in the ZES-SR group (p < 0.01). The longitudinal distribution of covered struts is depicted in Figure 2. Three patients (14.3%) in the ZES-SR group had AIT related to uncovered struts compared with none (0.0%) in the ZES-FR group. Similar proportions of uncovered struts were measured by OCT at overlap compared with nonoverlapping sites in both groups (Table 4). The length of overlap was 4.32 ± 2.28 mm in the ZES-FR group versus 3.58 ± 1.47 mm in the ZES-SR group (p = 0.13).

Table 2. Core Laboratory Angiographic Assessment Through 6 Months

	ZES-FR (n = 22)	ZES-SR (n = 21)	p Value
Pre-procedure			
RVD, mm	2.59 (2.38–3.08)	2.54 (2.13–2.74)	0.25
MLD, mm	0.65 (0.43–0.85)	1.01 (0.57–1.08)	0.17
DS, %	76.0 (65.0–82.0)	63.0 (58.0–76.0)	0.11
Lesion length, mm	34.80 (32.82–48.62)	31.72 (28.80–53.18)	0.90
Post-procedure*			
In-stent MLD, mm	2.18 (1.90–2.46)	2.18 (1.95–2.43)	0.90
In-segment MLD, mm	1.87 (1.62–2.17)	1.88 (1.68–2.05)	0.87
In-segment acute gain, mm	1.19 (0.94–1.55)	0.99 (0.80–1.44)	0.38
In-stent DS, %	14.5 (10.0–24.0)	13.0 (7.0–18.0)	0.33
Stent length, mm	39.54 (31.80–47.96)	37.89 (31.46–59.61)	0.75
6 months*			
In-stent MLD, mm	1.76 (1.41–1.99)	2.03 (1.84–2.37)	0.02
In-segment MLD, mm	1.70 (1.36–1.95)	1.88 (1.63–2.11)	0.09
In-stent DS, %	25.25 (19.00–41.00)	18.00 (11.00–23.00)	0.01
In-stent late loss, mm	0.46 (0.11–0.62)	0.17 (0.00–0.33)	0.01
In-stent binary restenosis, n (%)	4 (18.18)	0 (0.00)	0.11

Values are median (interquartile range) or n (%). *In-segment analysis included the segment covered by the stent (in-stent) plus 5-mm segments proximal and distal to the stent edge.
DS = diameter stenosis; MLD = minimum lumen diameter; RVD = reference vessel diameter; other abbreviations as in Table 1.

Intravascular ultrasound and clinical outcomes. IVUS results are reported in Table 5. Higher percentage of IVUS-derived net volume obstruction was also found in the ZES-FR group compared with the ZES-SR group. Late-acquired incomplete stent apposition (ISA) was observed in only 1 case (4.8%) treated with ZES-SR and in 3 cases (13.6%) treated with ZES-FR. Follow-up through 1 year was obtained in 41 of 43 patients (95.3%). There were 2 deaths in the ZES-SR group (1 cardiac at 240 days, possible stent thrombosis based on Academic Research Consortium definition, and 1 of noncardiac origin). One-year major adverse cardiac event rates were 18.2% in the ZES-FR group, including 3 target lesion revascularizations (2 ischemic-driven and 1 angiographic-driven) and 1 myocardial infarction, and in the ZES-SR group, the rate was 9.5% (2 deaths) (p = 0.41).

Discussion

This study provides the first detailed comparative analysis of in vivo human vascular responses to DES with the same platform and drug dosage but different drug release kinetics. The study revealed that ZES-SR was more effective for suppressing neointimal proliferation than ZES-FR was, but it resulted in significantly higher proportion of patients, frames, and stent segments with uncovered and malapposed struts at 6-months follow-up.

DES platforms were developed to suppress neointimal proliferation, an exaggerated healing response common to BMS that leads to frequent repeat procedures and negative clinical consequences (8,11,16). The potent inhibition of cellular proliferation promoted by DES, compared with BMS, has also been associated with delayed vascular healing, with higher percentage of uncovered strut, and increased risk of very late stent thrombosis (15,17). ZES-FR has shown less suppression of neointima growth compared with SES and PES (18), but potentially it has a better safety profile (5). The OCT findings observed in different lesion and patient cohorts confirmed that ZES-FR has a more complete, uniform, and prompt stent coverage than SES and PES do (6–8). To increase potency in suppressing NIH, a second generation of ZES was designed with slower drug release kinetics, while preserving the flexible stent platform, drug properties, and dosage (19). The present study confirms the greater efficacy in inhibition of neointimal proliferation of a sustained versus a fast release of ZES, which was associated with larger lumen area and reduced NIH across all imaging modalities (angiography, IVUS, and OCT).

ZES-SR seems to improve ZES results even in long lesions requiring multiple stents in overlap. We recently

Table 3. Optical Coherence Tomography Findings at 6 Months

Result	ZES-FR (n = 22)	ZES-SR (n = 21)	p Value
Analyzed frames/imaged frames per patient, %	55.5 (49.0–67.0)	60.0 (53.0–95.0)	0.14
Strut level analysis			
Struts per patient, n	493.5 (353.0–589.0)	566.0 (415.0–623.0)	0.16
Analyzed struts/cross section, n	9.66 (7.82–10.66)	9.59 (8.63–10.97)	0.64
Uncovered struts per patient, %	0.00 (0.00–0.00)	7.38 (3.06–12.72)	<0.01
Uncovered, nonmalapposed struts, %	0.00 (0.00–0.00)	5.85 (2.18–8.19)	<0.01
Uncovered, malapposed struts, %	0.00 (0.00–0.00)	1.47 (0.32–4.23)	<0.01
Patients with any uncovered struts	3 (13.6)	19 (90.5)	<0.01
Patients with any malapposed struts	0 (0.0)	18 (85.7)	<0.01
Frames with >30% uncovered stent struts, %	0.00 (0.00–0.00)	6.35 (0.00–16.90)	<0.01
Maximum length of uncovered segment, mm	0.00 (0.00–0.00)	3.91 (1.92–6.35)	<0.01
Maximum length of malapposed segment, mm	0.00 (0.00–0.00)	1.28 (0.64–3.27)	<0.01
NIH, mm	0.31 (0.27–0.42)	0.11 (0.07–0.15)	<0.01
AIT related to uncovered struts	0 (0.0)	3 (14.3)	0.11
AIT related to malapposed struts	0 (0.0)	0 (0.0)	NA
Morphometric analysis			
Stent area, mm^2	6.85 (6.14–7.65)	7.23 (6.22–8.41)	0.46
Lumen area, mm^2	3.91 (3.43–4.75)	6.37 (5.29–7.34)	<0.01
Neointimal area, mm^2	2.60 (2.01–3.06)	0.86 (0.65–1.32)	<0.01
Stent volume, mm^3	248.07 (196.33–285.34)	292.91 (226.66–409.23)	0.12
Lumen volume, mm^3	150.97 (121.53–200.53)	269.42 (169.30–394.53)	<0.01
Neointimal volume, mm^3	96.28 (73.39–108.89)	32.43 (25.00–70.95)	<0.01
Net volume obstruction (%)	36.89 (32.67–43.47)	12.49 (7.86–20.23)	<0.01

Values are median (interquartile range) or n (%).
AIT = abnormal intraluminal tissue; NA = not analyzable; NIH = neointimal hyperplasia; other abbreviations as in Table 1.

demonstrated that the site of overlapping DES have greater neointimal proliferation compared with nonoverlapping segments across all types of DES (8). Overlapping DES have also been associated with increased rates of repeat revascularization at 3-year follow-up (20). The degree of NIH response in the ZES-SR group was similar between overlapping and nonoverlapping segments (Table 4). Interestingly, this favorable result was not accompanied by higher rate of uncovered or malapposed struts at the overlap site. Rather, the incidence of ISA was higher in the nonoverlapping ZES-SR versus overlapping segments. ISA after DES has been linked to tissue necrosis, washout of friable thrombus or plaque material, and positive vessel remodeling. Due to the lack of OCT assessment immediately after stent implantation, no clear mechanistic explanation of ISA can be drawn from our study.

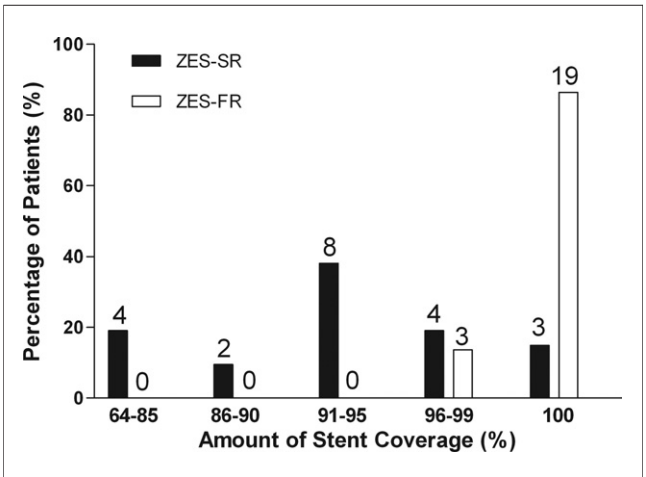

Figure 1. Distribution of Stent Strut Coverage in Patients

Distribution of percentage strut coverage measured by optical coherence tomography at 6 months, in patients treated with zotarolimus-eluting stent with sustained release kinetics (ZES-SR) (n = 21) **(solid bars)** and zotarolimus-eluting stent with faster release kinetics (ZES-FR) stents (n = 22) **(open bars).** Significant difference in distribution was detected between the 2 ZES types ($p < 0.001$).

Conversely, in the present study, a higher proportion of uncovered struts was found in the ZES-SR group (Fig. 1). In addition, the frequency of analyzed frames with ≥30% uncovered struts, a morphometric predictor of late stent thrombosis in histological study (17), was significantly higher in the ZES-SR group. A previous OCT study (21) demonstrated a substantial decrease of the frequency of uncovered SES struts (from 10.4% to 5.7%, $p < 0.01$) between 6 and 12 months. A minimum increase of NIH in the ZES-SR group, between 4 and 9 months, was also reported in an IVUS study (22). As a result, the 6-month

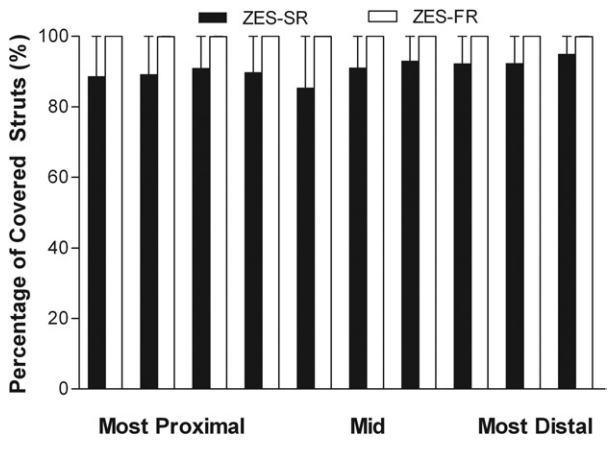

Figure 2. Longitudinal Pattern of Percent Strut Coverage in Different ZES Types

Longitudinal pattern of percent strut coverage in ZES-SR (n = 21) **(solid bars)** and ZES-FR stents (n = 22) **(open bars)** as measured by optical coherence tomography at 6-month follow-up. Data are from 10 subsegments covering the entire length of the stent. The rate of coverage among different subsegments does not change significantly in both ZES-FR (p = 0.54) and ZES-SR stents (p = 0.32). Abbreviations as in Figure 1.

OCT time point selected in our study might have been too early for judging the extent of vascular response after ZES-SR implantation. In the ODESSA trial, ZES-FR showed homogenous coverage in OCT compared with SES and PES. The present study confirmed similar homogenous coverage after ZES-FR and ZES-SR implantation (Fig. 2).

In the present study, the historical control ZES-FR had a 50% incidence of diabetes mellitus (DM), compared with 14% in the ZES-SR group (p = 0.02), with possible impact on the observed OCT findings. Although DM resulted in a greater amount of NIH and strut coverage in SES (23), no significant differences were observed in strut coverage and NIH between DM and non-DM patients in our study (strut coverage: ZES-FR: 0% in DM vs. 0% in non-DM, p = 0.51; ZES-SR: 7.28% in DM vs. 7.70% in non-DM, p = 0.51; and NIH: ZES-FR: 0.30 mm in DM vs. 0.34 mm in non-DM, p = 0.47; ZES-SR: 0.07 mm in DM vs. 0.12 mm in non-DM, p = 0.06).

ISA has been related to late stent thrombosis observed with DES (24). ZES-FR were not associated with late-acquired ISA, and there was very low incidence of persistent ISA even at 3 months after the implant, in either stable or unstable patients (9). Minimal post-stent malapposition, not detected on IVUS but visualized by OCT, completely disappeared or significantly decreased in the first 6 months after ZES-FR implantation, with a residual malapposition area of only 0.04 ± 0.11 mm (25). In our study, a higher rate of ISA was observed by OCT in the ZES-SR group compared with the ZES-FR group. However, the maximum length of malapposed segment was limited to approximately 1 mm. Although a small amount of ISA does not seem to influence clinical outcome, the higher rate of ISA and uncovered struts observed by OCT might suggest a less prompt and favorable vessel response to ZES-SR. In accordance, a higher rate of AIT related to uncovered struts was observed in the ZES-SR group (14.3%) compared with the ZES-FR group (0%), although it was not statistically significant. In a large clinical study (Resolute All-Comers trial) that randomized patients to ZES-SR or everolimus-eluting stents, ZES-SR was found to be as safe and effective as everolimus-eluting stents, with low late loss, target lesion revascularization, and similar major adverse cardiac event rates (26). However at 12 months, the rate of definite stent thrombosis was significantly higher in the ZES-SR group, primarily driven by 30-day stent thrombosis.

The biocompatibility of ZES-SR polymer system was tested in vitro and in pre-clinical models, with evidence of low inflammatory response, similar to that observed in BMS and ZES-FR (19). In our study, no significant enlargement of external elastic membrane by IVUS was observed in the ZES-SR group compared with the ZES-FR group.

Study limitations. The nonrandomized design of this study imposes some limitations on the conclusions. The higher incidence of diabetes in 1 of the groups may have contributed to the findings. The lack of OCT imaging immediately after stent implantation represents an important limitation to further evaluate the mechanisms of strut malapposition. Finally, current intravascular OCT cannot detect <15 μm of tissue deposition and cannot differentiate tissue characteristics.

Table 4. Optical Coherence Tomography Comparing Overlap Versus Nonoverlap Segments

	ZES-FR (n = 22)			ZES-SR (n = 21)				
	OLP 26 Segments	Non-OLP 48 Segments	p Value	OLP 26 Segments	Non-OLP 48 Segments	p Value	p Value OLP ZES-FR vs. ZES-SR	p Value Non-OLP ZES-FR vs. ZES-SR
Analyzed struts/cross section	14.72 ± 3.48	8.57 ± 1.62	<0.001	15.65 ± 3.13	9.31 ± 1.72	<0.001	0.32	0.21
Strut-level NIH, mm	0.39 ± 0.16	0.33 ± 0.12	0.004	0.12 ± 0.06	0.12 ± 0.07	0.497	<0.001	<0.001
Malapposed struts, %	0.00 ± 0.00	0.00 ± 0.00	NA	2.01 ± 4.19	3.78 ± 7.09	0.017	0.02	0.01
Uncovered struts, %	0.03 ± 0.16	0.04 ± 0.19	0.859	9.70 ± 12.00	9.43 ± 11.18	0.716	<0.001	0.001

Values are mean ± SD.
OLP = overlap; other abbreviations as in Tables 1 and 3.

Table 5. Intravascular Ultrasound Analysis Through 6 Months

Result	ZES-FR (n = 22)	ZES-SR (n = 21)	p Value
Post-procedural stent segment			
Mean EEM CSA, mm^2	11.81 (11.30 to 13.36)	13.06 (11.72 to 14.67)	0.19
Mean lumen CSA, mm^2	6.49 (5.73 to 7.47)	7.00 (5.89 to 7.68)	0.52
Mean stent CSA, mm^2	6.49 (5.73 to 7.50)	6.80 (5.89 to 7.47)	0.61
Mean plaque + media CSA, mm^2	5.17 (4.90 to 5.91)	6.12 (5.19 to 6.83)	0.07
Stent length, mm	41.53 (38.15 to 54.18)	45.16 (38.66 to 74.09)	0.43
Follow-up stent segment			
Mean EEM CSA, mm^2	13.39 (11.91 to 14.52)	13.44 (12.21 to 14.56)	0.60
Mean lumen CSA, mm^2	4.52 (3.99 to 5.56)	7.77 (5.78 to 8.17)	<0.01
Mean stent CSA, mm^2	6.79 (6.12 to 7.51)	7.90 (6.89 to 8.47)	0.02
Mean plaque + media CSA, mm^2	6.17 (5.67 to 6.99)	5.66 (4.64 to 6.75)	0.33
Net volume obstruction, %	26.93 (21.72 to 35.48)	3.01 (0.00 to 9.83)	<0.01
Change from index to follow-up			
Mean change in EEM CSA, mm^2	1.27 (0.49 to 1.92)	0.87 (0 to 1.98)	0.61
Mean change in plaque + media CSA, mm^2	1.15 (0.63 to 1.45)	−0.05 (−1.01 to 0.71)	0.01
Mean change % in EEM CSA, mm^2	8.86 (4.18 to 13.94)	6.23 (0.02 to 16.49)	0.58
Stent malapposition			
Post-procedure	3 (14.3)	2 (10.0)	1.00
Persistent at follow-up	1 (4.6)	0 (0.0)	1.00
Late acquired	3 (13.6)	1 (4.8)	0.61

Values are median (interquartile range) or n (%).
CSA = cross-sectional area; EEM = external elastic membrane, other abbreviations as in Table 1.

Conclusions

The present study demonstrated the impact of drug release kinetics on human coronary vessel response to DES. Although 2 similar stent platform and drug concentrations were compared, differences in drug release had profound impacts in vessel response as detected by OCT. The new generation of ZES-SR, Resolute, has better control of the in-stent neointimal tissue growth but a higher proportion of uncovered and malapposed struts at 6 months compared with the Endeavor stent. The relationship between these surrogate OCT imaging findings and clinical outcomes remains to be clarified.

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