The OCT-ORION Study

A Randomized Optical Coherence Tomography Study Comparing Resolute Integrity to Biomatrix Drug-Eluting Stent on the Degree of Early Stent Healing and Late Lumen Loss

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Background—Durable polymers used in drug-eluting stents are considered a potential cause of hypersensitivity inflammatory response adversely affecting stent healing. Using a sequential follow-up with optical coherence tomography, we compared the differences in healing profiles of 2 drug-eluting stents with a biodegradable or durable polymer.

Methods and Results—Sixty patients with multivessel disease were prospectively enrolled to receive both study stents, which were randomly assigned to 2 individual vessels, a Resolute Integrity zotarolimus-eluting stent with a durable BioLinx polymer and a BioMatrix NeoFlex Biolimus A9–eluting stent with a biodegradable polylactic acid polymer. Optical coherence tomography was performed at baseline, then in 5 randomly assigned monthly groups at 2 to 6 months, and at 9 months in all patients. The primary end point was the difference in optical coherence tomography strut coverage at 9 months. Key secondary end points included angiographic late lumen loss and composite major adverse cardiac events (cardiac death, myocardial infarction, target lesion revascularization, and definite or probable stent thrombosis) at 9 months. Resolute Integrity zotarolimus-eluting stent showed significantly better strut coverage than BioMatrix NeoFlex Biolimus A9–eluting stent at 2 to 6 months ($P<0.001$) and less variance of percent coverage at 9 months, 99.7% (interquartile range, 99.1–100) versus 99.6% (interquartile range, 96.8–99.9; difference, 0.10; 95% confidence interval, 0.00–1.05; $P<0.001$). No significant difference was observed in major adverse cardiac events or angiographic end points.

Conclusions—Despite having a durable polymer, Resolute Integrity zotarolimus-eluting stent exhibited better strut coverage than BioMatrix NeoFlex Biolimus A9–eluting stent having a biodegradable polymer; both showed similar antiproliferative efficacy. This novel, longitudinal, sequential optical coherence tomography protocol using each patient as own control could achieve conclusive results in small sample size.

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Key Words: drug-eluting stents ■ myocardial infarction ■ polymers ■ sirolimus ■ zotarolimus

Drug-eluting stents (DES) reduce restenosis, but first-generation DES have been associated with higher rates of late (>1 year) stent thrombosis (ST) compared with bare-metal stents[1–3] and the late catch-up phenomenon.[4,5] Patients who have developed very late ST have often shown uncovered or malapposed stent struts and lipid-laden neointima when examined by optical coherence tomography (OCT); these were not observed in subjects without very late ST.[6] A delayed hypersensitivity healing response toward the durable polymer was identified as a potential culprit in very late ST with DES.[7–9] Autopsy examinations also identified polymer hypersensitivity as a risk factor causing death by ST in the first-generation DES.[10,11] Such concerns of delayed healing and very late ST have led to the prolonged use of dual antiplatelet therapy (DAPT) and initiatives searching for better polymer technologies aiming at allowing a DES to eventually become a bare-metal stents.

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WHAT IS KNOWN

- Durable polymer used in drug-eluting stents may cause hypersensitivity reaction in vessel wall and potentially affects stent healing.
- Biodegradable polymer or polymer-free drug-eluting stents may reduce or eliminate polymer hypersensitivity and are postulated to improve vascular healing response after stent implantation.
- The high spatial resolution of optic coherence tomography allows meticulous assessment of stent coverage and neointimal evolution.

WHAT THE STUDY ADDS

- Using a novel longitudinal and sequential optic coherence tomography protocol using each patient as his or her own control, a durable polymer drug-eluting stents (Resolute Integrity) exhibited better strut coverage and healing than a biodegradable polymer drug-eluting stents (BioMatrix NeoFlex) in short and medium term.
- This innovative study design may serve to examine vascular healing in new stent platforms in a small sample size to potentially predict safety and efficacy.

Polylactic acid (PLA) has been used in degradable sutures and is now used as a polymer coating material. The BioMatrix NeoFlex Biolimus A9 (BA9)–eluting stent (BX; Biosensors International, Singapore) uses PLA as a biodegradable polymer coating, leading to a polymer-free stent in several months' time after drug release[12] to reduce polymer hypersensitivity. The PLA polymer is applied solely to the abluminal surface of the stainless steel stent and impregnated with a highly lipophilic, semisynthetic sirolimus analog, BA9.[13] In vivo studies showed that PLA would be fully converted to lactic acid at 6 months.[12] Compared with bare-metal stents, BX significantly reduced lumen late loss and neointimal volume (NIV).[14] In the LEADERS trial (Limus Eluted From a Durable Versus Erodable Stent Coating) comparing BX with a durable polymer sirolimus-eluting stent, no difference was found in clinical events up to 4 years.[12,15]

The Resolute Integrity zotarolimus-eluting stent (RI; Medtronic, Minneapolis, MN) is a representative of a contemporary DES, having a durable polymer (BioLinx) eluting zotarolimus over a longer period of 180 days. RI was extensively reported to have similar safety and efficacy compared with other second-generation DES with durable polymers.[16–19]

Using an innovative clinical trial design that used longitudinal sequential OCT follow-ups with each patient receiving both study stents and acting as his or her own control, we examined the potential benefits of the biodegradable polymer approach as used in BX and compared it with RI. We postulated that BX, by changing to a bare-metal stents in a few months' time, would achieve better healing and early strut coverage, whereas RI would have better neointimal suppression at 9 months. Furthermore, we sought to determine whether this new protocol could enable us to identify subtle differences between stent platforms using a much smaller sample size in predicting safety and efficacy of any new stent platforms.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design and Procedures

The OCT-ORION study (A Randomized Optical Coherence Tomography Study Comparing Resolute Integrity to Biomatrix Drug-Eluting Stent on the Degree of Early Stent Healing and Late Lumen Loss) was a prospective, randomized, single-center study conducted at Queen Mary Hospital, the University of Hong Kong. This study was designed to enroll a real-world, all-comers population with symptomatic multivessel disease requiring stenting. Exclusion criteria included acute ST-elevation myocardial infarction or unstable hemodynamics, left main disease, bifurcation lesions requiring 2 stents, chronic total occlusion, vessels <2.5 mm in diameter or >38 mm in length, or planned surgery within 12 months of stenting.

The study sample size was predefined at a minimum of 60 consecutive patients, estimated based on previous study results showing adequate data under longitudinal sequential OCT protocol.[20] Each patient received at least 1 RI and 1 BX stent, randomly assigned by computer to 2 separate diseased vessels in the same index procedure, enabling each patient to serve as his or her own control, thereby canceling all other confounding factors.

The study protocol prespecified 3 longitudinal sequential OCT assessments for each patient: (1) at baseline to ensure optimal stent implantation and for future reference; (2) at 2, 3, 4, 5, or 6 months in 5 randomly assigned monthly groups for early strut coverage and healing profile guiding future DAPT duration; and (3) at 9 months for OCT neointimal metrics and quantifications (Figure 1). Percutaneous coronary intervention (PCI) was performed in the usual manner after administration of DAPT (aspirin 80 mg and clopidogrel 75 mg) and unfractionated heparin. Study stents were deployed from normal-to-normal segment, with a stent:vessel diameter ratio of 1.1:1. Overlapping stents were allowed for long lesions. At baseline, meticulous optimization strategies were adopted under full OCT guidance, ensuring minimal stent undersizing, underexpansion, malapposition, and edge dissection. Serum cardiac enzymes were monitored as usual and as required. Patients were discharged with DAPT for 12 months and then aspirin indefinitely. Prespecified staged PCI to remaining lesion(s) in a nonstudy vessel (if any in 3-vessel disease) was allowed and performed during the first OCT follow-up. Clinical follow-ups were at 1, 6, 9, 12, and 24 months.

All OCT and quantitative coronary angiography data analyses were performed by core laboratories (Cardiovascular Research Foundation, New York, NY) in a blinded fashion to the time points and stent randomization details; all clinical events were adjudicated by independent clinical event committee. The study protocol received full ethics committee approval, and written informed consent was obtained from all patients.

Longitudinal Sequential OCT Assessments

OCT images were collected by the C7-XR frequency-domain OCT system and Dragonfly imaging catheter (St. Jude Medical, St. Paul, MN) at a pullback frame interval of 5 frames/mm (0.2 mm thickness per slice) and length of 54 mm, using 14 to 16 mL of contrast. Details of OCT analysis have been described previously.[20] In brief, a stringent prespecified 6-category classification was adopted by the core laboratory (Figure 2) to ensure consistency and reproducibility of visual assessment of early strut coverage. Categories in Figure 2D through 2F were classified as covered struts. All strut coverage was evaluated in a frame-by-frame manner (each and every 0.2-mm slice). OCT metrics, including strut neointimal thickness, cross-sectional lumen area, and stent area, were analyzed at every 1-mm interval (1 in each 5 frames). Neointimal area was calculated as stent area minus lumen area. NIV was calculated using Simpson's rule and reported as total NIV, mean NIV (total NIV divided by length), and percentage NIV (NIV divided by stent volume×100). Other OCT findings including intramural thrombi and neointimal characteristics were reported as previously described.[20]

Study End Points

The primary end point was the between-group percentage strut coverage at 9 months as assessed by OCT. The secondary end points

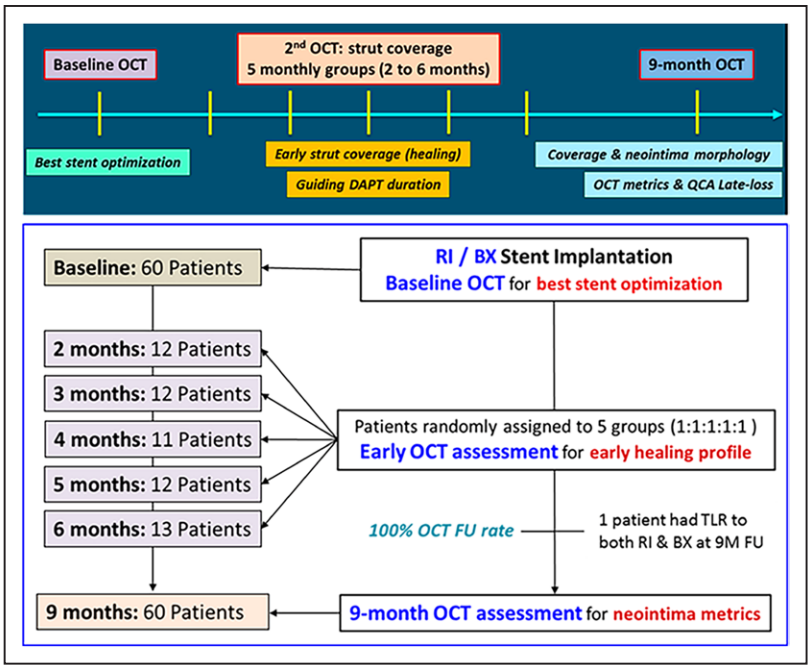

Figure 1. Study design and flow chart. **Upper**, Study design and objectives. **Lower**, Flow chart of enrollment from baseline to 9-month optical coherence tomography (OCT) follow-up. BX indicates BioMatrix NeoFlex Biolimus A9–eluting stent; DAPT, dual antiplatelet therapy; FU, follow-up; QCA, quantitative coronary angiography; RI, Resolute Integrity zotarolimus-eluting stent; and TLR, target lesion revascularization.

included (1) all OCT metrics (median neointimal thickness, neointimal area, and NIV) at different time points, (2) angiographic quantitative coronary angiography parameters including binary restenosis, minimal lumen diameter, and late lumen loss at 9 months, and (3) composite major adverse cardiac event rate including cardiac death, myocardial infarction, target lesion revascularization, and Academic Research Consortium–defined definite or probable ST.

Statistical Analysis

Analysis of the primary end point was based on the intention-to-treat principle, which included all patients enrolled in the study. Normally distributed continuous variables are expressed as mean±SD and compared using a paired *t* test between 2 stents, otherwise shown as median [first quartile, third quartile] and compared using Wilcoxon signed-ranks test. Categorical data are presented as frequencies and compared by McNemar test or exact McNemar test when <20 discordant pairs. A regression line including log-transformed follow-up days at early time points (2–6 months), stent type, and the interaction between stent type and log-transformed follow-up days predicted strut coverage, in which patient was included as a random effect with a compound symmetrical structure. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, NC), Excel (Microsoft, Redmond, Washington), or R version 3.2.2 (R Foundation, Vienna, Austria). A 2-sided *P* value <0.05 is considered statistically significant.

Results

Patient Population

Between April 2012 and July 2014, 60 consecutive patients with multivessel disease requiring stent treatment and consented to complete 3 sequential OCT follow-ups were enrolled (Figure 1); the enrollment process was slow because of inclusion criteria limitations with advanced disease. The mean age was 63±12 years; 83% were men, and 55% had diabetes mellitus (Table 1).

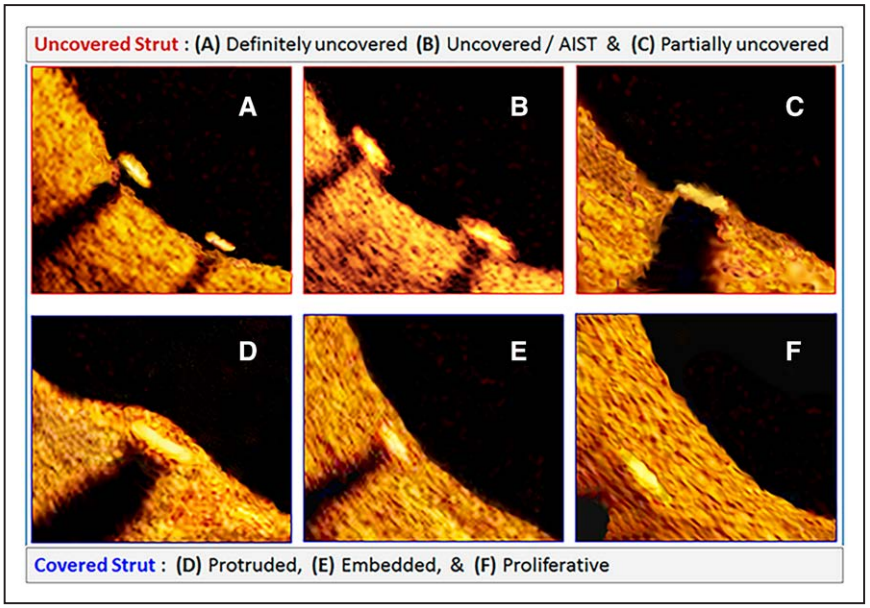

Figure 2. Six categories of strut coverage classification with representative optical coherence tomography (OCT) images. **A–C**, Uncovered struts, and (**D–F**) covered (refer to the Appendix for details). AIST indicates abnormal intrastent tissue.

Table 1. Baseline Characteristics

	n=60
Age, y	63±12
Men	50 (83.3)
Diabetes mellitus	33 (55)
History of hypertension	46 (76.7)
History of hyperlipidemia	37 (61.7)
History of smoking	29 (48.3)
Prior myocardial infarction	16 (26.7)
Prior percutaneous coronary intervention	8 (13.3)
Clinical presentation	
Stable angina	52 (86.7)
Non–ST-segment–elevation myocardial infarction or unstable angina	8 (13.3)

Results presented as mean±SD or n (%).

Procedural Characteristics and Quantitative Coronary Angiography Results

A total of 120 lesions in 60 pairs of separate vessels were treated using 73 RI and 71 BX randomly assigned to the vessels. Thirteen patients with 3-vessel disease having lesions on the remaining nonstudy artery (prespecified during the index procedure) received further staged PCI during the first OCT follow-up. Lesions were equally advanced in both stent arms, with 45% type C lesions (Table 2). Baseline angiographic characteristics were similar (Table 3), with percentage diameter stenosis of 66.1±10.8% in RI versus 67.6±11.3% in BX, *P*=0.43, and lesion length 19.6±7.6 versus 19.4±7.4 mm, *P*=0.88. The stent parameters were also similar (Table 2). Between-group characteristics among the 5 monthly groups were also similar and are presented in the Table in the Data Supplement.

Despite very advanced disease, with 55% of patients having diabetes mellitus, both stents showed equivalent antiproliferative efficacy at 9 months, with median diameter stenosis of 11.2% [5.3, 16.2] for RI and 9.5% [3.7, 16.4] for BX, *P*=0.61. At 9 months, binary restenosis occurred in 3 patients (5.0%) with RI and 2 patients (3.3%) with BX, *P*>0.99. In-stent late loss was similar at 0.18±0.50 versus 0.14±0.38 mm, *P*=0.99 (Table 3).

Longitudinal Sequential OCT Assessment Results

At the index procedure, final OCT pullbacks were obtained after the stent optimization procedures were undertaken. These served as the baseline OCT reference, and no statistical differences were observed between the 2 arms (Table 4). All 60 patients had complete follow-up and longitudinal sequential OCT results from 2 to 9 months (Table 5). At most time

Table 2. Procedural Characteristics

	All Patients (n=60)	Lesions Treated With Resolute Integrity Stent (n=60)	Lesions Treated With BioMatrix Stent (n=60)	*P* Value
Vessel location (per lesion)				
Left anterior descending	50 (41.7)	25 (41.7)	25 (41.7)	>0.99
Left circumflex	41 (34.2)	14 (23.3)	15 (25.0)	0.85
Right coronary artery	29 (24.2)	21 (35.0)	20 (33.3)	0.88
Lesion location				
Proximal	42 (35.0)	19 (31.7)	23 (38.3)	0.39
Mid	64 (53.3)	33 (55.0)	31 (51.7)	0.82
Distal	14 (11.7)	8 (13.3)	6 (10.0)	0.77
Moderate tortuosity	16 (13.3)	8 (13.3)	8 (13.3)	>0.99
Severe tortuosity	2 (1.7)	1(1.7)	1 (1.7)	>0.99
Preprocedure TIMI flow 0	2 (1.7)	0 (0.0)	2 (3.3)	0.69
AHA/ACC class C lesion	54 (45.0)	27 (45.0)	27 (45.0)	>0.99
Thrombus present	1/112 (0.8)	0/56 (0.0)	1/56 (0.8)	…
Bifurcation lesion	35 (29.2)	19 (31.7)	16 (26.7)	0.61
Lesions with 1 stent	96 (80)	47 (78.3)	49 (81.7)	0.64
Lesions with 2 stents	24 (20)	13 (21.7)	11 (18.3)	0.64
Maximum stent size, mm	2.84±0.35	2.84±0.36	2.85±0.33	0.79
Total stent length, mm	27.1±8.23	27.5±8.5	27.1±8.2	0.79
Dissection	2 (1.7)	0 (0.0)	2 (3.3)	…
Post-PCI TIMI III flow	113 (94.2)	55/55 (100)	53/55 (96.4)	>0.99

Values presented as n (%) of observations or mean±SD. ACC indicates American College of Cardiology; AHA, American Heart Association; PCI, percutaneous coronary intervention; and TIMI, Thrombolysis in Myocardial Infarction.

Table 3. Quantitative Coronary Angiography Analyses

	Resolute Integrity (n=60)	BioMatrix (n=60)	*P* Value
Baseline			
Reference vessel diameter, mm	2.8±0.4	2.7±0.4	0.29
Minimum lumen diameter, mm	0.9±0.3	0.9±0.4	0.27
Diameter stenosis, %	66.1±10.8	67.6±11.3	0.43
Lesion length, mm	18.2 [14.7, 22.9]	17.9 [14.1, 23.8]	0.94*
Post-procedure			
In-segment minimum lumen diameter, mm	2.3±0.4	2.3±0.5	0.42
In-stent minimum lumen diameter, mm	2.6±0.4	2.6±0.4	0.51
In-stent diameter stenosis, %	8.4±8.1	7.0±8.3	0.31
In-stent acute gain, mm	1.6±0.4	1.7±0.40	0.14
9-mo follow-up			
Reference diameter, mm	2.7±0.4	2.8±0.4	0.77
In-segment minimum lumen diameter, mm	2.1±0.6	2.2±0.5	0.39
In-stent minimum lumen diameter, mm	2.5 [2.2, 2.7]	2.4 [2.2, 2.8]	0.69*
In-stent diameter stenosis, %	11.2 [5.3, 16.2]	9.5 [3.7, 16.4]	0.61*
In-stent binary restenosis	3 (5.0%)	2 (3.3%)	0.99
In-stent late lumen loss, mm	0.08 [−0.05, 0.26]	0.09 [−0.02, 0.24]	0.99*

Values are mean±SD for normally distributed variables and median [first quartile, third quartile] for *non-normally distributed variables or n (%).

points, percent strut coverage was significantly higher in RI compared with BX, with better healing profile (curve of percentage coverage over time; *P*=0.0005 for test of equality of slopes in Figure 3), signifying better healing of RI despite the presence of a durable polymer. Despite only minor difference in median percent strut coverage between RI and BX at 9 months, (99.7% [99.1, 100] versus 99.6% [96.8, 99.9]; difference, 0.10; 95% confidence interval, 0.00–1.05; *P*=0.001), much wider scattering (refer to green circle in Figure 4) was observed in BX, indicating incomplete healing even at 9 months, despite the disappearance of the biodegradable polymer. In patients with type 2 diabetes mellitus (n=33), better median strut coverage was also observed in the RI arm. Neointimal suppression seemed to be better in the BX arm in terms of OCT neointimal thickness, neointimal area, and NIV parameters (Table 5), but clinically driven target lesion revascularization was observed in only 1 patient (both RI and BX stents had restenosis; Figure 1) at 9 months.

Clinical Events

There was no difference in target-vessel adverse cardiovascular events between RI and BX. No death was recorded. One

Table 4. Baseline OCT Characteristics at Index PCI Procedure After Final Stent Optimization

	Resolute Integrity	BioMatrix	*P* Value
Reference luminal area, mm^2	6.19±1.25	6.23±1.54	0.93
Minimal in-stent luminal area, mm^2	5.38±1.51	5.42±1.63	0.74
Percentage of struts with malapposition (%)*	5.33±4.32	4.79±5.13	0.68
Malapposed distance, mm*	0.14±0.08	0.15±0.16	0.38
Malapposed area, mm^{2*}	0.21±0.23	0.24±0.21	0.73
Percentage of frames with underexpansion (%)†	8.69±5.21	8.38±7.69	0.66
Unattended edge dissection (n)‡	0	2	N/A
Micro-thrombus (n)	2	0	N/A

Mean±SD. OCT indicates optical coherence tomography; and PCI, percutaneous coronary intervention.

*Malapposition is defined as a distance of strut artifact to intimal surface (a) >97 μm for Resolute Integrity (strut thickness 91 μm+polymer thickness 6 μm), and (b) >130 μm for BioMatrix (strut thickness 120 μm+polymer thickness 10 μm), excluding analyses of those frames near side branch openings. Malapposition analyses were performed after the unblinding process.

†Defined as frames with stent area <80% of the mean reference luminal area.

‡Defined as circumferential intimal tear of >120° in >10 consecutive frames.

Table 5. Longitudinal Sequential Optical Coherence Tomographic Analyses

	2 mo (n=12)	3 mo (n=12)	4 mo (n=11)	5 mo (n=12)	6 mo (n=13)	9 mo (n=60)
No. of OCT frames analyzed						
BioMatrix	167±48	149±28	156±41	133±30	161±45	150 [115, 183]
Resolute integrity	141±32	150±39	168±54	136±39	169±47	147 [115, 186]
P value	0.04	0.92	0.19	0.71	0.43	0.88*
No. of struts analyzed						
BioMatrix	1201±383	1054±238	1053±265	913±205	1161±369	1083±325
Resolute integrity	1409±282	1543±552	1885±789	1409±491	1760±600	1597±584
P value	0.03	0.002	0.002	0.002	<0.001	<0.001
Stent struts covered, %						
BioMatrix	87.2±8.1	87.0±5.9	94.8±3.9	99.0 [93.9, 99.4]	98.2 [95.5, 99.5]	99.6 [96.8, 99.9]
Resolute integrity	91.6±5.9	94.2±5.3	96.9±3.0	99.3 [98.0, 99.8]	99.7 [97.3, 99.9]	99.7 [99.1, 100]
P value	0.06	0.004	0.23	0.13*	0.002*	0.001*
Neointimal area, mm^2						
BioMatrix	0.40±0.46	0.23±0.18	0.33±0.18	0.44±0.30	0.34±0.26	0.50 [0.27, 0.84]
Resolute integrity	0.39±0.38	0.30±0.27	0.52±0.34	0.69±0.35	0.58±0.45	0.82 [0.46, 1.14]
P value	0.99	0.24	0.14	0.006	0.02	<0.001*
Neointimal thickness, mm						
BioMatrix	0.046±0.04	0.047±0.03	0.050±0.02	0.061±0.03	0.051 [0.039, 0.064]	0.073 [0.052, 0.097]
Resolute integrity	0.046±0.03	0.032±0.02	0.066±0.03	0.086±0.03	0.076 [0.048, 0.094]	0.094 [0.069, 0.133]
P Value	0.98	0.03	0.20	0.02	0.002*	<0.001*
Neointimal volume, mm^3						
BioMatrix	11.50±13.06	6.12±4.66	8.66 [4.06, 10.83]	10.99±9.00	10.41±10.04	16.52±12.22
Resolute integrity	9.87±8.95	7.72±7.08	18.74 [4.28, 24.30]	16.70±10.11	17.60±14.42	25.81±17.28
P value	0.61	0.35	0.15*	0.008	0.02	<0.001
Neointimal volume, %						
BioMatrix	4.54±4.66	3.87±3.14	4.44±2.61	6.69±4.90	5.26±5.13	8.07 [4.51, 11.26]
Resolute integrity	4.77±3.82	5.28±5.35	7.06±5.52	10.25±6.17	9.12±7.44	12.19 [7.35, 17.54]
P value	0.84	0.25	0.16	0.18	0.004	<0.001*

Values are mean±SD for normally distributed variables and median [first quartile, third quartile] for *non-normally distributed variables. For primary end point of percentage coverage, every single frame (at 0.2 mm slice) was analyzed. For other OCT metrics, frames at every 1 mm interval (1 out of every 5 frames) were analyzed. OCT indicates optical coherence tomography.

patient (mentioned above) developed non–ST-segment–elevation myocardial infarction within 9 months with significant in-stent restenosis in both study stents and was treated accordingly. Another patient had clinical restenosis in the RI stent during the 24-month clinical follow-up period. Two patients had nonfatal bleeding. No patient had definite or probable ST or stroke.

Discussion

Most previous reports have suggested that DES with biodegradable polymers show at least equivalent, if not better efficacy than the second-generation DES with durable polymers. BA9-eluting stents have been shown to be noninferior to everolimus-eluting stents.[21,22] The BX stent, which elutes BA9 but has a biodegradable PLA polymer, was reported to be effective too.[12–15] Comparing 2 everolimus-eluting DES from the same manufacturer, Synergy (using a different PLA–glycolic acid biodegradable polymer) and Promus Element (with a durable polymer; both Boston Scientific, Marlborough, MA) were reported to show similar results in the EVOLVE (A Prospective Randomized Multicenter Single-Blind Non-Inferiority Trial to Assess the Safety and Performance of the Evolution Everolimus-Eluting Monorail Coronary Stent System [Evolution Stent System] for the Treatment of a De Novo Atherosclerotic Lesion) and EVOLVE II trials (A Prospective Multicenter Trial to Assess the Safety and Effectiveness of the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System [SYNERGY Stent System] for the Treatment of Atherosclerotic Lesions)[23,24]; however, in the recently published SORT OUT VI trial[25] in which 2999 patients were randomized to receive RI or BX, no significant differences in safety or efficacy outcomes were observed after 3

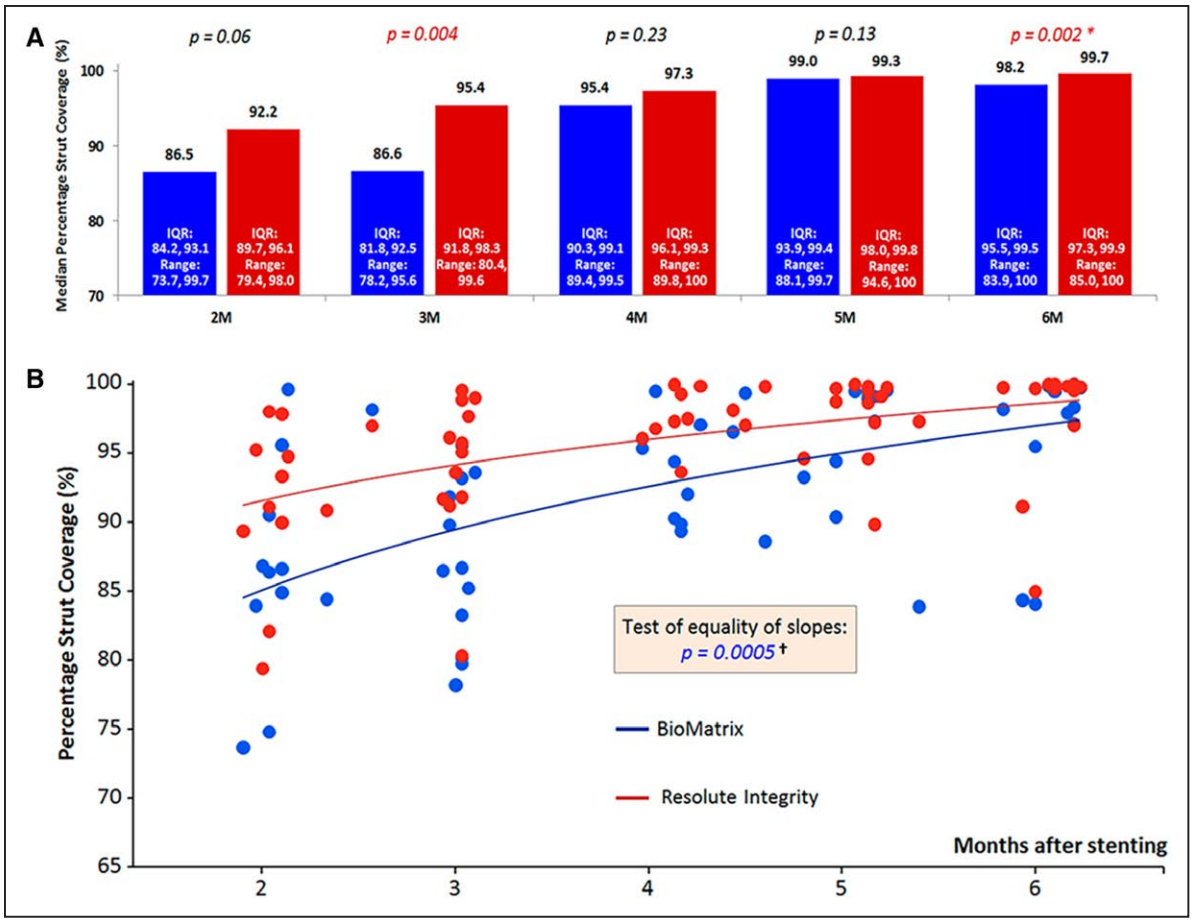

Figure 3. Percent strut coverage of the Resolute Integrity vs BioMatrix Stent in early follow-up periods. **A**, The bar chart shows the median percent coverage and interquartile range (IQR) over time for the Resolute Integrity (red) and BioMatrix NeoFlex (blue) stents. **B**, The curves compare the healing profiles (percent coverage over time) of the 2 stent platforms, revealing significantly better coverage over time in Resolute Integrity compared with BioMatrix (P=0.0005). *Data failed assumption for normality per the Shapiro–Wilk test; P value and interquartile range derived from Wilcoxon signed-rank test. †An ANCOVA with random effects for subjects was used to test equality of slopes. The P value was taken from the type III SS for the interaction between stent type and log time.

years, suggesting that the presence of a durable polymer is not as disadvantageous as previously thought. This is in full concordance with the findings in our OCT-ORION study.

In this prospective, randomized study simultaneously comparing 2 second-generation DES, the RI stent with a durable polymer eluting zotarolimus for 180 days, and the BA9-eluting BX stent with a biodegradable PLA polymer which should disappear in 6 to 9 months, we postulated that BX would heal better in terms of stent strut coverage than RI, especially at early months (2–6 months), but RI might show better neointimal suppression (durable polymer with long eluting kinetics) in the long run. Contrary to our postulations, RI exhibited better healing and less incomplete strut coverage than BX at all study time points (Figures 3 and 4; Table 3), together with more mature (bright and homogenous) neointima as revealed by OCT. Both stents had comparable neointimal suppression efficacy and clinical restenosis similar to reported series for other DES,[21–25] but with no ST observed throughout the 24-month follow-up period in our series. These findings again suggested that the presence of durable polymer is not as disadvantageous as previously thought. On stent healing and early OCT strut coverage, 2 contemporary DES with biodegradable polymers (everolimus-eluting Synergy versus BA9-eluting BX) were compared at 1 and 3 months and presented in the SORT OUT VIII OCT study.[26] Synergy was reported to show better strut coverage compared with BX at 3 months (median, 88.6% versus 80.7%; P=0.02). Our OCT-ORION study generated similar results of 86.5% median coverage of BX at 3 months (Table 5); however, RI had significantly better median coverage than BX at all time points (Table 5), in particular at 3 months RI versus BX were 95.4% [91.8, 98.3] versus 86.5% [81.8, 92.5], P=0.004. The better healing observed in RI may be attributed to many factors. RI was designed to improve the safety of first-generation DES using the proprietary BioLinx polymer system, which is a blend of 3 polymers.[27] The hydrophilic polymer coating mimics the body's biological chemistry, and BioLinx has been shown to reduce local inflammation and vascular cell proliferation.[27,28] These factors may account for the safety of RI, with a lack of association between DAPT use and ST between 1 and 12 months.[29] Although other factors like different drugs and different strut thickness may also affect healing,[30,31] the presence of a durable polymer as in RI may not be as disadvantageous. Further studies are needed, and the role of polymer degradation will continue to be a topic of debate.

Although OCT cannot delineate endothelialization, it can provide very high in vivo resolution allowing

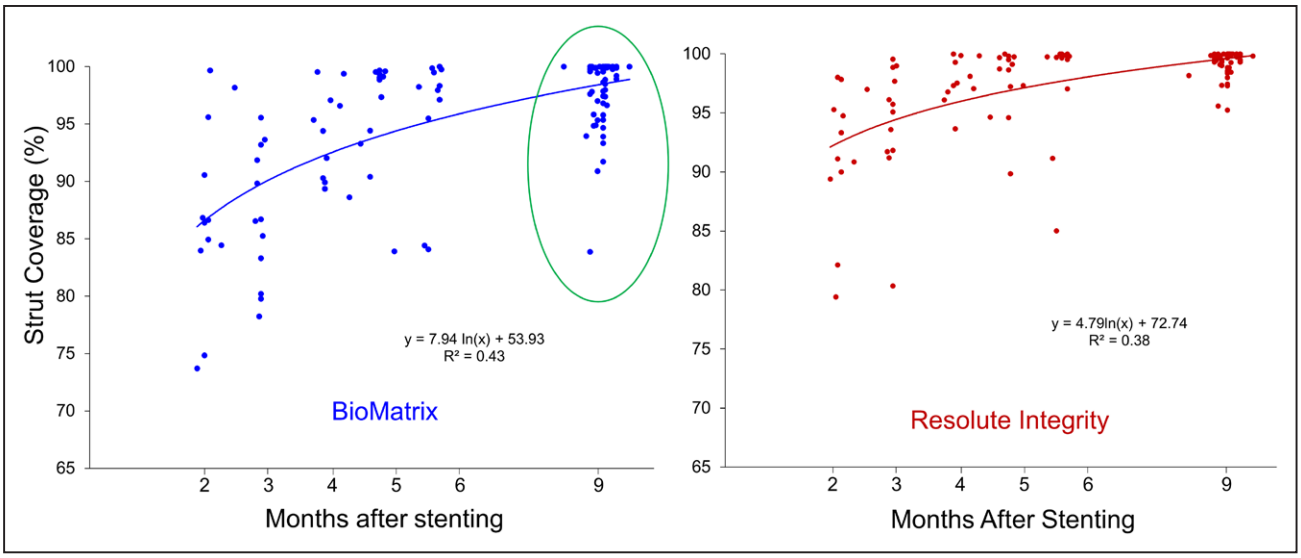

Figure 4. Percent strut coverage between Resolute Integrity and BioMatrix Stents from 2 to 9 months. Nonlinear regression plots showing less coverage in the BioMatrix NeoFlex stent, with much wider scattering even at 9 months (green circle), implying incomplete healing. Primary end point median strut coverage at 9 months: Resolute Integrity 99.7% [99.1, 100] vs BioMatrix 99.6% [96.8, 99.9]; *P*=0.001.

quantification of very thin neointima (around 10 µm or 3 cell layers); however, caution must be exercised on the interpretation of strut coverage in every time points as tissue prolapse, abnormal in-stent fibrin deposition, and thrombus formation may all be mistakenly interpreted as neointimal coverage. A stringent and reproducible category classification is, therefore, important (Figure 2; Appendix) to ensure valid interpretations.

To the best of our knowledge, this is the first study using patients as a self-control (2 study stents randomized to 2-target vessels in each patient) and a longitudinal sequential OCT protocol. Most confounding factors and data contaminations were then canceled out, allowing statistically significant and conclusive results to be generated even with a smaller sample size. In the randomized SORT OUT VI trial recently reported,[25] it took 36 months and 2999 patients to show that the durable polymer RI and the biodegradable polymer BX stents were similar in clinical outcomes, with no significant difference in safety and efficacy outcomes, including ST. Such outcomes findings are indeed predicted by our OCT-ORION study in just 9-month follow-up with only 60 patients; the better neointimal maturation of RI under OCT and the better healing curves (Figures 3 and 4) all suggested at least equal, if not better outcomes with the durable polymer RI.

Very importantly, common practice of just quoting the median percentage coverage alone without revealing the actual scatter plot could be misleading and deceptive in assessing stent healing. Figure 4 shows similar (>99%) strut coverage for both RI and BX at 9 months; however, a closer look (green circle in Figure 4) reveals a much wider scattering of BX coverage at 9 months implying incomplete healing, predicting possible safety concerns of late ST. Indeed in the SORT OUT VI outcome trial,[25] definite very late ST occurred in 6 (0.4%) patients in RI but almost a double of 10 (0.7%) in BX at 3 years, even though the study was not powered to show statistical significance (*P*=0.33).

Limitations

The study was not powered for clinical end points; such end points have to be derived from other large-scale outcome studies. Besides, though patients act as their own control in our protocol, there were subtle differences between lesions/vessels treated by 2 groups of stents despite randomization owing to the small patient sample size. This can partially be circumvented by the similar baseline procedural characteristics and OCT-guided PCI optimization. Furthermore, although remote, the systemic dose effect of one drug impacting on the other on healing and coverage may not be fully understood. Moreover, the study results may not be applicable to other biodegradable polymers with different properties. The risk involved in enrolling patients with advanced diseases (2–3-vessel PCI, over 50% diabetics) requiring multiple OCT pullbacks may limit the application of this novel protocol.

Conclusions

Despite having a durable polymer, the zotarolimus-eluting RI stent exhibited better strut coverage and healing than the BA9-eluting BX stent having a biodegradable polymer; both stent platforms showed similar antiproliferative efficacy. This novel longitudinal sequential OCT protocol, with each patient serving as his or her own control, has the potential to achieve predictive and conclusive results in future stent studies using a much smaller sample size, thereby saving time and cost.

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Disclosures

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The OCT-ORION Study: A Randomized Optical Coherence Tomography Study Comparing Resolute Integrity to Biomatrix Drug-Eluting Stent on the Degree of Early Stent Healing and Late Lumen Loss

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Supplemental Table. Patient Demographics and Procedural Characteristics

	Total	2 Months	3 Months	4 Months	5 Months	6 Months
Number of patients	60	12	12	11	12	13
Age, years	62.5 ± 11.9	60.5 ± 10.9	64.6 ± 15.6	66.5 ± 9.4	59.6 ± 11.6	61.5 ± 11.4
Male (% within group)	50 (83.3)	10 (83.3)	10 (83.3)	9 (81.8)	10 (83.3)	11 (84.6)
Diabetes Mellitus	33 (55)	7 (58.3)	7 (58.3)	6 (54.5)	6 (50)	7 (53.8)
Hypertension	46 (76.7)	8 (66.7)	9 (75)	9 (81.8)	8 (66.7)	12 (92.3)
Hyperlipidemia	37 (61.7)	8 (66.7)	6 (50)	6 (54.6)	9 (75)	8 (61.5)
History of Smoking	29 (48.3)	6 (50)	5 (41.7)	6 (54.6)	6 (50)	6 (46.2)
Prior Myocardial Infarction	16 (26.7)	3 (25)	4 (33.3)	1 (9.1)	4 (33.3)	4 (30.8)
Prior percutaneous coronary intervention	8 (13.3)	2 (16.7)	1 (8.3)	0 (0)	3 (25)	2 (15.4)
Clinical Presentation						
Stable angina	52 (86.7)	12 (100)	10 (83.3)	8 (72.7)	10 (83.3)	12 (92.3)
NSTEMI or unstable angina	8 (13.3)	0 (0)	2 (16.7)	3 (27.3)	2 (16.7)	1 (7.7)
Number of lesions						
Total	120	24 (19.7)	24 (20)	22 (18.3)	24 (20)	26 (21.7)

Left anterior descending	50 (41.7)	9 (37.5)	11 (45.8)	10 (45.5)	10 (41.7)	10 (38.5)
Left circumflex	41 (34.2)	9 (37.5)	9 (37.5)	5 (22.7)	10 (41.7)	8 (30.8)
Right	29 (24.2)	6 (25)	4 (16.7)	7 (31.8)	4 (16.7%)	8 (30.8)
Number of stents implanted	144	30	27	28	24	35
Per lesion treated	1.2 ± 0.4	1.3 ± 0.4	1.1 ± 0.3	1.3 ± 0.5	1 ± 0	1.3 ± 0.6
Resolute Integrity	73	13	13	16	12	19
Per lesion treated	1.2 ± 0.5	1.1 ± 0.3	1.1 ±0.3	1.5 ± 0.5	1 ± 0	1.5 ± 0.7
BioMatrix	71	17	14	12	12	16
Per lesion treated	1.2 ± 0.4	1.4 ± 0.5	1.2 ± 0.4	1.1 ± 0.3	1 ± 0	1.2 ± 0.4
Mean stent length, mm						
Resolute Integrity	27.1 ± 8.2	24.4 ± 6.0	26.6 ± 7.4	30.4 ± 10.4	24.1 ± 6.8	30.1 ± 9.0
BioMatrix	27.5 ± 8.5	30 ± 11.7	27.2 ± 6.8	27.9 ± 7.9	23 ± 6.1	29.2 ± 8.4
Mean stent diameter, mm						
Resolute Integrity	2.79 ± 0.32	2.88 ± 0.27	2.71 ± 0.26	2.90 ± 0.27	2.83 ± 0.44	2.66 ± 0.30
BioMatrix	2.83 ± 0.37	3.02 ± 0.53	2.67 ± 0.20	2.86 ± 0.30	2.88 ± 0.33	2.75 ± 0.34

Values presented as numbers (%) of observations or mean ± standard deviation.