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First-in-Human Evaluation of a Novel Polymer-Free Drug-Filled Stent: Angiographic, IVUS, OCT, and Clinical Outcomes from the RevElution Study

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ABSTRACT

Objectives. We sought to assess the safety and effectiveness of the drug-filled stent (DFS) in the treatment of patients with coronary artery disease.

Background. Polymer-free drug-eluting stents have the potential to improve clinical outcomes and facilitate shorter durations of dual anti-platelet therapy. The polymer-free DFS is made from a tri-layered continuous wire with an outer cobalt chromium layer, a middle tantalum layer, and an inner lumen coated with sirolimus. Small laser-drilled holes on the abluminal stent surface control drug elution.

Methods. RevElution enrolled 100 patients with *de novo* coronary lesions 2.25-3.50 mm in diameter and length ≤27 mm in 2 50-patient cohorts for angiographic, intravascular ultrasound, and clinical assessment at 9 or 24 months, with optical coherence tomography (OCT) performed in a subset of 30 patients at each time period. The primary endpoint was angiographic in-stent late lumen loss at 9 months compared with Resolute zotarolimus-eluting stent historical control data.

Results. Fifty patients with 56 lesions were treated with DFS in the 9-month cohort. In-stent late lumen loss was 0.26±0.28 mm for DFS and 0.36±0.52 mm for Resolute ($P_{noninferiority}$<0.001). The binary angiographic restenosis rate was 0%. Median stent strut coverage by OCT was 91.4%, 95.6%, and 99.1% at 1, 3, and 9 months, respectively. One non-Q-wave myocardial infarction occurred, with a 9-month target lesion failure rate of 2.1%. No stent thrombosis occurred.

Conclusions. At 9 months, the polymer-free DFS was safe and effective with high rates of early strut coverage and non-inferior late lumen loss compared to Resolute.

KEY WORDS: drug-filled stent, polymer-free stent, drug-eluting stent, percutaneous coronary intervention

CONDENSED ABSTRACT

The novel polymer-free drug-filled stent (DFS) comprises a multi-layered wire with a continuous sirolimus-containing lumen within the stent structure. The drug elutes from small, abluminal laser-drilled holes on the stent surface. In the RevElution trial, the 9-month primary endpoint of in-stent late lumen loss was met (DFS 0.26±0.28 vs 0.36±0.52 mm for Resolute stent historical control; $P_{noninferiority}$ <0.001). Median stent strut coverage after DFS by optical coherence tomography was 91.4%, 95.6%, and 99.1% at 1, 3 and 9 months respectively. At 9 months the target lesion failure rate was 2.1%, and no stent thromboses occurred.

ABBREVIATIONS

DAPT = dual antiplatelet therapy

DES = drug-eluting stent

DFS = drug-filled stent

IVUS = intravascular ultrasound

MACE = major adverse cardiac events

MI = myocardial infarction

OCT = optical coherence tomography

QCA = quantitative coronary angiography

TLR = target lesion revascularization

TLF = target lesion failure

INTRODUCTION

Most drug-eluting stents (DES) utilize a polymer to control the elution of an antiproliferative drug, and significantly reduce neointimal hyperplasia and restenosis compared with bare metal stents (BMS) (1). However, first-generation DES have been associated with high rates of very late (>1 year) stent thrombosis (ST) (2-4). Human autopsies and clinical evaluation by optical coherence tomography (OCT) demonstrated incomplete endothelialization and late acquired malapposition (ie, positive remodeling) as strong correlates of very late ST (5-7). These histopathological findings have been associated with chronic inflammation and hypersensitivity responses which are most likely due to the polymers used with first-generation DES (5,8-10).

Second-generation DES utilize more biocompatible polymers with reduced inflammation, improved healing, and lower rates of ST and repeat revascularization compared to first generation DES (11-15). Partly as a result, the mandatory duration of dual antiplatelet therapy (DAPT) after DES implantation has recently been reduced in societal guidelines from 12 to 6 months in patients with stable ischemic heart disease (16,17). However, longer duration DAPT decreases the risk for ischemic events even with second-generation DES, and as such the optimal duration of DAPT remains controversial (18). In additions, all polymer coatings on DES are prone to bonding, webbing, cracking, and peeling during stent expansion and delivery, defects which may serve as a thrombogenic nidus and decrease the uniformity of drug delivery, resulting in thrombosis or restenosis (19,20). A polymer-free metal surface stent that is capable of controlled antiproliferative drug elution may avoid the adverse effects of polymer-induced inflammation, thrombosis and non-uniformity, and could potentially allow for a shorter DAPT duration (21).

The polymer-free drug-filled stent (DFS, Medtronic, Santa Rosa, CA) was designed to provide controlled and sustained drug elution from an internal stent lumen without utilization of a polymer coating. We herein report the primary endpoint results from the RevElution trial, the first-in-human clinical experience with the DFS.

METHODS

Device description. The polymer-free DFS is formed from a tri-layered wire with the core material removed to create a continuous lumen within the stent structure that is coated throughout with sirolimus. The inner layer is tantalum, which enhances radiopacity, while the outer layer of cobalt chromium maintains stent strength despite a thin strut thickness of 81 μm. Based on a drug density of ~1.1 μg/mm^2 and the circumferential outer stent surface area, the total drug load is 99 μg for a 3.0 mm diameter x 18 mm long stent. Small laser-drilled holes (~20 μm diameter, ~6 per strut, ~1800 holes for an 18 mm stent) on the abluminal surface of the stent determine the rate of drug elution directly into the arterial wall (Figure 1).

Study Design. The RevElution trial enrolled planned to enroll 100 patients at 14 sites in Australia, Latin America, and Singapore to evaluate the clinical safety and efficacy of DFS for the treatment of *de novo* coronary lesions. Treatment was permitted in up to 2 lesions in 2 separate native coronary arteries with a reference vessel diameter between 2.25 and 3.50 mm and length ≤27 mm. Key exclusion criteria were myocardial infarction (MI) within 72 hours of the intended procedure, target lesion in a bypass graft, previous stenting in the target vessel within 9 months, the target lesion within 15 mm of a previously placed stent, planned percutaneous coronary intervention (PCI) of any vessel within 30 days post-index procedure, and planned PCI of the target vessel within 12 months post procedure. Additional angiographic exclusion criteria are shown in the Online Supplemental Appendix Table 1.

Patients were divided into 2 cohorts in which quantitative coronary angiography (QCA), intravascular ultrasound (IVUS), and clinical outcomes were assessed at 9 months (N=50) or 24 months (N=50). Subgroups of patients in the 9-month cohort underwent OCT at post-procedure, 1 month, 3 months, and 9 months, and subgroups of patients in the 24-month cohort undergo OCT at post-procedure, 2 months, 6 months, and 24 months (Figure 2). All patients are followed annually to 5 years. The primary endpoint was in-stent late lumen loss by QCA at 9 months in the 9-month cohort compared with a historical control (in-stent late lumen loss at 8 months from the RESOLUTE US Angio/IVUS sub-study) (22,23). The present report describes results through 9 months in the 9-month cohort, all of whom were enrolled in Australia. Follow-up in the 24-month cohort is ongoing.

Patients were prescribed the same DAPT regimen as in the RESOLUTE US study; a minimum of 75 mg of aspirin daily indefinitely and at least 75 mg of clopidogrel daily for a minimum of 6 months in all patients and for up to 12 months in those not at high-risk of bleeding per investigator discretion. All patients provided written informed consent, and the protocols were approved by the institutional review board or ethics committee at all sites.

Study definitions. Lesion success was defined as attainment of <50% residual stenosis of the target lesion using any percutaneous method. Device success was defined as attainment of <50% residual stenosis of the target lesion using only the trial device. Procedure success was defined as lesion success without the occurrence of in-hospital major adverse cardiac events (MACE), defined as the composite of death, MI (Q-wave or non-Q wave), or clinically-driven target lesion revascularization (TLR) by PCI or coronary artery bypass graft surgery (CABG). Target lesion failure (TLF) was defined as the composite of cardiac death, target vessel MI, or clinically-driven TLR. Target vessel failure was defined as the composite of cardiac death, target vessel

MI, or clinically-driven target vessel revascularization (TVR). Clinically-driven TLR (or TVR) was defined as unplanned repeat revascularization of the target lesion (or target vessel) with positive functional ischemia study or ischemic symptoms and an angiographic diameter stenosis ≥50% by QCA, or revascularization of a target lesion (or target vessel) with diameter stenosis ≥70% by QCA without angina or a positive functional study. MI was defined using the Society of Cardiac Angiography and Interventions definition for periprocedural events and the extended historical definition for post-procedure MIs (24,25). Deaths were considered cardiac unless an unequivocal non-cardiac cause could be established. Stent thrombosis was categorized as definite or probable using the Academic Research Consortium criteria (26).

Data management and core laboratories. A clinical events adjudication committee (Cardiovascular Research Foundation [CRF], New York, NY) and core laboratories (OCT: Cardiovascular Research Centre, São Paulo, Brazil; angiographic: Beth Israel Deaconess Medical Center, Boston, MA; IVUS: CRF) independently assessed the data. The angiographic and IVUS core laboratories were the same as those used for the RESOLUTE US study. A Data Monitoring Committee (Harvard Clinical Research Institute [HCRI], Boston, MA) evaluated safety data throughout the trial. HCRI also independently analyzed and validated the outcomes data provided by Medtronic.

OCT Image Acquisition and Analysis. All OCT images were acquired with commercially available Fourier-Domain OCT Systems (Ilumien or Ilumien Optis, St. Jude Medical, St. Paul, MN) and were analyzed with dedicated validated software (QIvus version 3.0, Medis Medical Imaging, Leiden, The Netherlands). Procedures of imaging acquisition have been previously described (27). The details of imaging analysis are presented in the online supplement.

Statistical analysis. This trial was powered for non-inferiority testing of the primary endpoint, in-stent late lumen loss by QCA, compared between the 9-month DFS cohort and the 8-month Resolute™ ZES historical control (RESOLUTE US angio/IVUS substudy). The observed 8-month in-stent late loss of the historical control arm was 0.36 ± 0.52 mm (n=93). Assuming true equivalence of the means between the two groups, with a standard deviation of 0.38 mm for DFS and a non-inferiority margin of 0.20 mm, a total sample size of 50 patients yields 80% power for non-inferiority using a one-sided, two-sample t-test with alpha 0.05. Given possible differences in baseline characteristics between RevElution and the RESOLUTE US Angio/IVUS Sub-study, a prespecified propensity score-adjusted model (28) was used for the comparison of the primary endpoint. The following baseline variables were used in the propensity score calculations: lesion length, baseline reference vessel diameter, age, gender, history of diabetes mellitus, history of MI, and Canadian Cardiovascular Society worst angina class.

Continuous data are presented as mean±standard deviation or median (interquartile range [IQR]) as appropriate; categorical data are presented as counts and percentages. Analyses were performed using SAS software, version 9.1 or later (SAS Institute, Cary, NC). OCT results are presented per lesion. Generalized estimation equations (GEE) model with an assumed Gaussian distribution (link identity) or Gamma distribution (link log) when appropriate, with an autoregressive working correlation matrix was used to address the clustered nature of OCT data and the inherent correlation within each subject and lesion arising from multiple longitudinal analysis. OCT analysis was performed using the R software version 3.2.2 (R Core Team, 2015).

RESULTS

Study population and acute success. A total of 50 patients with 56 treated lesions were enrolled in the 9-month cohort between July 21, 2015 and December 23, 2015. The mean patient age was

66.2 years, 76% were male, diabetes was present in 30%, and 76.8% of the target lesions were American Heart Association /American College of Cardiology type B2/C (Table 1). Differences in baseline characteristics between DFS and the historical control Resolute used in the propensity-adjusted model are shown in Supplemental Appendix Table 3. All lesions were successfully crossed; device success and procedure success were both100%. Nine-month outcomes are available for 48 patients and 49 lesions.

Angiographic and IVUS outcomes. Nine-month angiographic and IVUS outcomes are shown in Table 2. The primary endpoint, in-stent late lumen loss, was 0.26 ± 0.28 mm at 9 months with DFS compared with 0.36 ± 0.52 mm at 8 months with the Resolute historical control; the upper bound of the 1-sided 95% confidence interval was 0.05 mm which is less than the prespecified noninferiority margin of 0.20 mm ($P_{noninferiority}<0.001$) (Figure 3). The cumulative frequency distribution curves of the in-stent late loss for the 2 devices are shown in Figure 4, demonstrating fewer patients having marked late loss with DFS compared to Resolute. In-stent and in-segment binary angiographic restenosis rates were 0%. By IVUS, neointimal hyperplasia volume obstruction at 9 months was 9.76 ± 5.57%. Six cases of stent malapposition were observed immediately post procedure; 4 resolved and 2 persisted at 9 months. No cases of late acquired stent malapposition were observed.

OCT outcomes. Mean stent expansion was 87.20 ± 15.45%, with a concentric configuration as depicted by the low stent eccentricity index (0.08 ± 0.02). The proportion of covered struts per lesion at one month post-procedure was 91.4%, increasing to 95.6% at 3 months and 99.1% at 9 months (P=0.002) (Figure 5). The proportion of malapposed struts decreased from 0.3% at 1 month to 0.2% at 3 months, to 0.0% at 9 months. Mean neointimal hyperplasia thickness and

percent volume obstruction were low at all 3 time points (Table 3). No cases of intracoronary thrombus were observed.

Clinical outcomes. Usage of DAPT at 1 and 9 months was 100% and 93.8%, respectively. One non-Q wave MI occurred on day 263 post-implant in a subject with lung cancer while undergoing a CT-guided lung biopsy. Elevated biomarkers were noted after the biopsy with a normal ECG. Angiography was not performed. There were no target lesion or target vessel revascularizations, no definite or probable STs, and no deaths. Thus, the 9-month rates of TLF, MACE and TVF were all 2.1% (Table 4).

DISCUSSION

This first clinical experience with the novel polymer-free DFS demonstrates low 9-month in-stent late lumen loss, non-inferior to a Resolute historical control. OCT demonstrated minimal neointimal hyperplasia and a high degree of stent strut coverage at 1 month (91.4%), with a low rate of malapposition (0.3% at 1 month, 0.0% at 9 months), indicative of a favorable early healing profile. With follow-up through 9 months only 1 patient developed an adverse clinical event (a non-Q-wave MI), and there were no cases of stent thrombosis or binary angiographic restenosis.

The low in-stent late lumen loss indicates potent suppression of neointimal hyperplasia consistent with current generation rapamycin-derivative DES, despite the absence of a polymer carrier (22,29,30). The right skew in the cumulative frequency distribution curve was less with DFS than Resolute, consistent with fewer cases with marked late loss and greater uniformity of drug delivery. Although the sample size was modest, the 0% angiographic restenosis rate is encouraging. Similarly, NIH thickness over covered struts at 9 months by OCT was low at 0.15

± 0.04 mm. By IVUS there were no cases of late acquired (9-month) malapposition, consistent with favorable vascular healing.

The RevElution trial is unique in its assessment of stent strut coverage by OCT at numerous time points. High rates (>90%) of stent strut coverage were observed as early as 1 month post-procedure, and increased progressively through 9 months. This rapid healing may be indicative of the lack of inflammatory response with DFS as seen in porcine studies (31), and is similar to that seen with a BMS (32). Endeavor™, Resolute, and Xience™ DES show near complete coverage by OCT at late time points (12 and 13 months) (33,34); however, given the desire for earlier discontinuation of DAPT to reduce risk for bleeding complications, healing at earlier time points is desirable. In this regard, mean 3-month stent strut coverage by OCT with Endeavor and Xience has been reported to be 81.5-87.1% and 77.1%, respectively (33,35). The near-complete healing of DFS at 1 month may allow for shorter duration of DAPT, a hypothesis warranting adequately powered clinical trials.

Strut coverage by OCT has recently been reported with other polymer-free DES. The polymer-free sirolimus-eluting stent Nano^{+} demonstrated overall median strut coverage at 3 months of 93% (83.2-96.5), with approximately 2/3 of lesions having >90% strut coverage. However, high heterogeneity in the healing process was observed, with three lesions exhibiting <50% strut coverage at 3 months (36). In contrast, in the current study the median 3-month DFS strut coverage was 95.6% (90.3 to 97.2), and 76.5% had >90% strut coverage. At 9 months all DFS-treated lesions had >90% strut coverage (Figure 5).

Independent bench testing has confirmed improved radial strength of DFS compared with Resolute Onyx™ DES despite the internal lumen in the DFS (37). Confirmation of this radial strength was observed by OCT and IVUS in the RevElution trial, in which the mean stent

diameter and minimal lumen diameter remained unchanged at 1, 3, and 9 months compared to post-procedure.

Limitations. Several limitations should be mentioned. First, the RevElution 9-month cohort was modest in size and not powered for clinical events. However, the sample size was adequately powered to compare in-stent late lumen loss with DFS and historical control Resolute, and showed no significant differences (indeed, a trend toward lower late loss with DFS). The sample size was also sufficient to analyze healing by OCT and inhibition of neointimal hyperplasia by IVUS and OCT. Additional data in this regard is forthcoming from the 24-month RevElution cohort. Direct comparison of DES and DFS strut coverage is limited by substantial variation between studies. Larger controlled studies with long-term follow-up are required to examine whether the favorable healing responses evident in the present study translate into improved clinical outcomes and the ability to safely discontinue DAPT at an early time point (e.g. 1 month). Second, patients in the 1-month and 3-month OCT cohorts were not the same, and thus serial healing between these two time points can only be indirectly addressed. Third, given the absence of a concurrent control, most comparisons to other devices should be considered hypothesis generating. Fourth, as an unblinded single-arm study, some degree of bias cannot be excluded, although the use of the propensity score method to balance covariates, imaging core laboratories, on-site study monitoring and independent clinical events adjudication adds rigor to the results. Finally, the present study excluded enrolment of the highest risk patients, such as those with ongoing STEMI, left main intervention, dual stent bifurcation lesions, etc. Also, treated lesions were relatively short and not severely stenotic. Demonstration of the safety and efficacy of DFS in such patients must await the results from large-scale real-world experiences.

CONCLUSIONS

When implanted in simple and moderately complex de novo coronary lesions, the DFS resulted in non-inferior 9-month in-stent late lumen loss to the historical Resolute DES data, little neointimal hyperplasia with 0% binary restenosis, and a high degree of early stent strut coverage with minimal malapposition, indicative of a favorable early healing profile. The 9-month TLF rate was low (only 2.1%), and none of the first 50 patients developed a stent thrombosis within this time frame. DFS may avoid polymer-associated adverse vascular responses, potentially improving clinical outcomes compared to polymer-based metallic DES and BRS, and allow for shorter duration of DAPT. Large-scale clinical trials are required, however, to demonstrate whether the favorable properties of DFS translate into improved event-free survival after PCI in patients with coronary artery disease.

PERSPECTIVES

WHAT IS KNOWN?

Polymers typically utilized in drug-eluting stents (DES) are associated with bonding, webbing, cracking, and peeling during stent expansion and delivery that can lead to thrombosis or restenosis.

WHAT IS NEW?

The polymer-free drug-filled stent provides controlled drug elution from an internal lumen and results in non-inferior 9-month in-stent late lumen loss to historical Resolute DES data, 0% binary restenosis, and a high degree of early stent strut coverage with minimal malapposition.

WHAT IS NEXT?

Further clinical trials are scheduled to confirm that the favorable properties of DFS translate into improved event-free survival after implantation in patients with coronary artery disease.

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FIGURE LEGEND

Figure 1. Construction and Abluminal Drug Elution From the Drug-Filled Stent

The antiproliferative drug sirolimus coats the internal lumen of the stent (left). The drug elution is controlled and sustained through natural diffusion from abluminal holes (center) via direct interaction with the vessel wall (right).

Figure 2. RevElution Study Design

The 9-month cohort is presented in the current analysis. Angio = angiography; IVUS = intravascular ultrasound. OCT = optical coherence tomography; RVD = reference vessel diameter.

Figure 3. The Powered Primary Endpoint, 9-Month Late Lumen Loss With the DFS Compared With 8-Month Late Lumen Loss From the Historical Control Resolute Zotarolimus-Eluting Stent

The DFS was non-inferior for late lumen loss to Resolute. The confidence interval is adjusted to propensity score based on lesion length, baseline reference vessel diameter, age, sex, diabetes mellitus, history of myocardial infarction and worse Canadian Cardiovascular Society Angina Class as independent variables. DFS = drug-filled stent.

Figure 4. Cumulative Distribution Curve for In-Stent Late Lumen Loss

DFS = drug-filled stent.

Figure 5. Strut Coverage and Apposition by OCT at 1, 3, and 9 months

OCT = optical coherence tomography.

TABLE 1: Baseline Characteristics in the 9-Month Cohort

	DFS
Patient characteristics	**N=50 patients**
Age, years	66.2±10.1
Male	76.0 (38)
Prior myocardial infarction	20.0 (10)
Prior PCI	16.0 (8)
Diabetes mellitus	30.0 (15)
Insulin-treated	10.0 (5)
Hyperlipidemia	84.0 (42)
Hypertension	76.0 (38)
Current smoking	12.0 (6)
Family history of CAD	42.6 (20/47)
Reason for revascularization	
Stable angina	56.0 (28)
Unstable angina	18.0 (9)
Silent ischemia	6.0 (3)
Positive functional study	30.0 (15)
Target vessel location (per patient)	
Left anterior descending	52.0 (26)
Left circumflex	32.0 (16)
Right coronary artery	26.0 (13)

Lesion characteristics*	**N=56 lesions**
TIMI flow grade 3	98.2 (55)
AHA/ACC type B2/C lesion	76.8 (43)
Reference vessel diameter, mm	2.70±0.43
Minimum lumen diameter, mm	0.97±0.28
% Diameter stenosis	63.82±9.51
Lesion length, mm	12.85±5.21

Values are % (n) or mean±SD. AHA/ACC = American Heart Association/American College of Cardiology; CAD = coronary artery disease; PCI = percutaneous coronary intervention; TIMI = thrombolysis in myocardial infarction.

TABLE 2: 9-Month Angiographic and Intravascular Ultrasound Outcomes

	DFS (N=49 lesions)
Angiography	
Reference vessel diameter, mm	2.68±0.39
Late lumen loss, mm	
In-stent	0.26±0.28
In-segment	0.11±0.22
Late lumen loss index	
In-stent	0.17±0.20
In-segment	0.07±0.21
Minimum lumen diameter, mm	
In-stent	2.30±0.41
In-segment	2.05±0.36
Diameter stenosis, %	
In-stent	13.69±12.09
In-segment	23.28±8.02
Binary angiographic restenosis, %	
In-stent	0.0
In-segment	0.0
Intravascular Ultrasound	
Neointimal hyperplasia volume, mm^3	14.81±8.96
Volume obstruction, %	9.76±5.57

Stent malapposition, %	
After procedure	12.5 (6/48)
Persistent	4.1 (2)
Late-acquired	0.0 (0)

Values are % (n/N) or mean±SD. DFS = drug-filled stent.

TABLE 3: Optical Coherence Tomography Outcomes at 1, 3, and 9 Months

Variable	1-Month Cohort			3-Month Cohort		
	Post-procedure (N=14 patients, 17 lesions, 19 stents)	**1 Month** (N=14 patients, 17 lesions, 19 stents)	**9 Months** (N=13 patients, 16 lesions, 18 stents)	**Post-procedure** (N=15 patients, 17 lesions, 19 stents)	**3 Months** (N=15 patients, 17 lesions, 19 stents)	**9 Months** (N=12 patients, 13 lesions, 14 stents)
CROSS-SECTION LEVEL ANALYSIS						
Analyzed stent length, mm	22.12±7.55	20.88±7.25	21.44±7.91	23.20±6.63	22.46±6.14	23.44±5.57
Cross-sections analyzed per stent	38.06±12.93	35.59±12.37	36.62±13.19	40.12±10.73	38.29±10.37	39.69±9.27
Stent analysis						
Mean stent area, mm^2	8.07±1.64	8.21±1.76	8.24±1.81†	7.10±2.30	7.15±2.50	7.15±2.19
Mean stent diameter, mm	3.18±0.33	3.21±0.34	3.22±0.36†	2.97±0.48	2.97±0.51	2.98±0.46
Mean stent eccentricity index	0.09±0.02	0.09±0.03	0.09±0.03	0.08±0.02	0.07±0.02	0.08±0.03
Focal stent expansion, %	81.58±8.12	81.36±6.26	78.89±7.05	81.77±8.56	80.87±7.83	78.82±9.89
ISA Quantification						
No. of lesions with ISA, n (%)	15/17 (88.2%)	9/17 (52.9%)	3/16 (18.7%)‡	16/17 (94.1%)	9/17 (52.9%)	3/13 (23.1%)†

Mean ISA volume, mm^3	3.68±4.78	1.87±3.27	0.16±0.41*	5.24±8.10	2.29±5.82	0.49±1.53†
NIH Quantification						
Neointimal hyperplasia area, mm^2	N/A	0.46±0.18	1.34±0.48‡	N/A	0.52±0.20	1.30±0.45‡
Neointimal hyperplasia obstruction, %	N/A	5.82±2.40	16.560±6.54‡	N/A	7.59±2.47	18.52±5.35‡
Lumen Quantification						
Mean lumen area, mm2	8.10±1.71	7.97±1.88‡	6.96±1.74‡	7.20±2.32	6.81±2.39‡	5.90±1.92‡
Minimum lumen area, mm2	6.48±1.54	6.24±1.67‡	5.39±1.51‡	5.98±2.23	5.41±2.14‡	4.48±1.74‡
STRUT LEVEL ANALYSIS						
Total struts analyzed	7918	7403	7025	7838	7451	5794
Analyzed struts per lesion	465.76±156.81	435.47±151.25	439.06±159.28	461.06±145.35	438.29±147.09	445.69±109.44
Analyzed strut per cross-section	12.29±0.83	12.25±0.59	12.00±0.96	11.43±1.38	11.32±1.51	11.25±1.17
Covered struts per lesion, %						
Median [IQR]	N/A	91.40 [84.80; 93.20]	98.95 [97.88; 99.78]	N/A	95.60 [90.30; 97.20]	99.50 [98.30; 100.00]
Mean±SD		89.33±6.31	98.07±2.65‡		92.92±5.97	98.76±2.04‡
Malapposed struts per lesion, %						

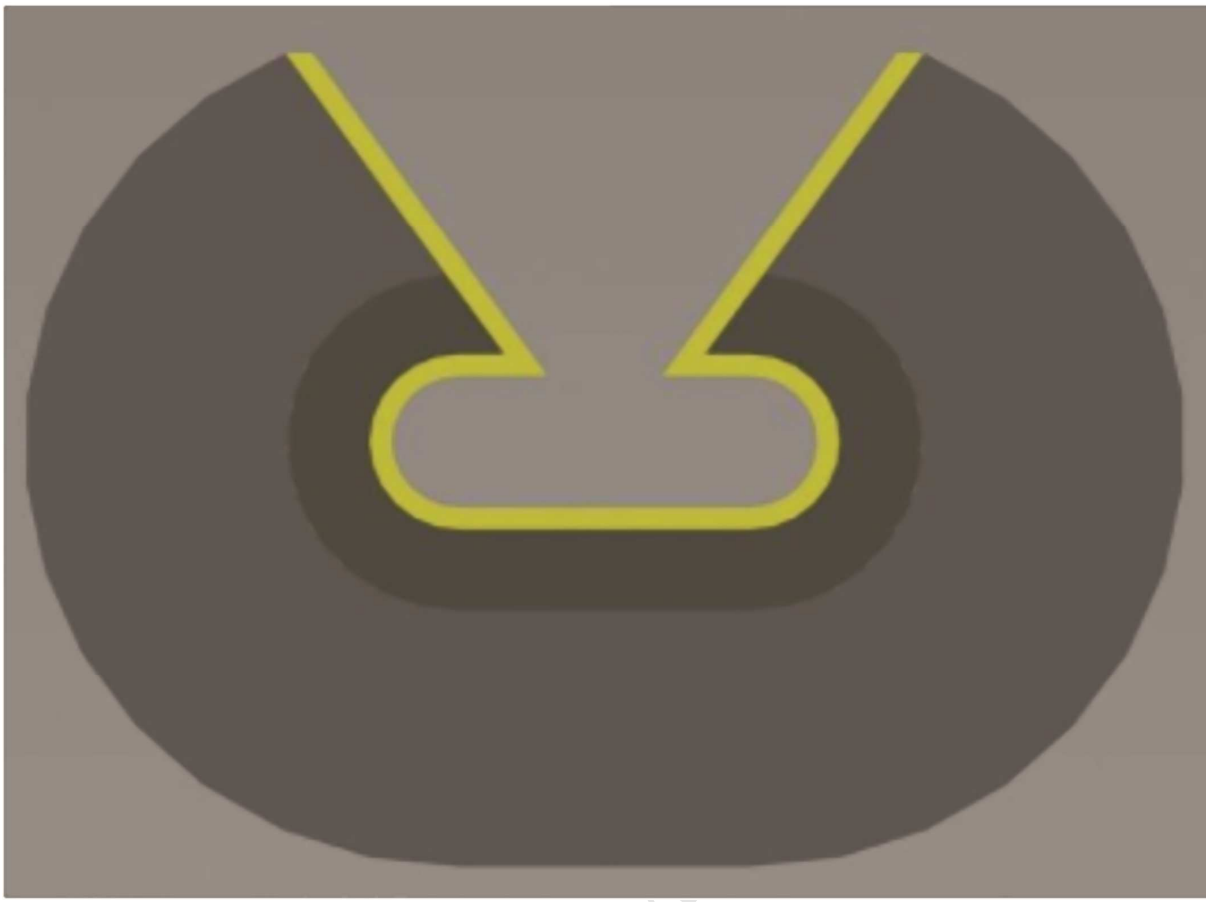
Median [IQR]	3.00 [1.50;	0.30 [0.00; 2.30]	0.00 [0.00; 0.00]	4.10 [0.70;	0.20 [0.00; 0.70]	0.00 [0.00; 0.00]
Mean±SD	8.20]	1.50±2.29	0.14±0.36*	9.90]	1.07±2.22	0.32±0.83
	4.81±4.86			6.35±7.78		
Neointimal thickness over covered struts, mm	N/A	0.06±0.02	0.15±0.05‡	N/A	0.07±0.01	0.16±0.04‡
Frequency of cross-sections with >30% uncovered struts, %	N/A	9.13±9.25	1.02±2.86†	N/A	5.52±6.30	0.34±0.83†
Frequency of cross-sections with >30% malapposed struts, %	3.84±5.74	0.77±2.49	0.00±0.00‡	7.22±11.86	0.39±1.22	0.00±0.00‡
Maximum length of consecutive segments of uncovered struts, mm	N/A	4.23±2.32	1.13±1.04‡	N/A	3.47±2.64	0.86±1.04†

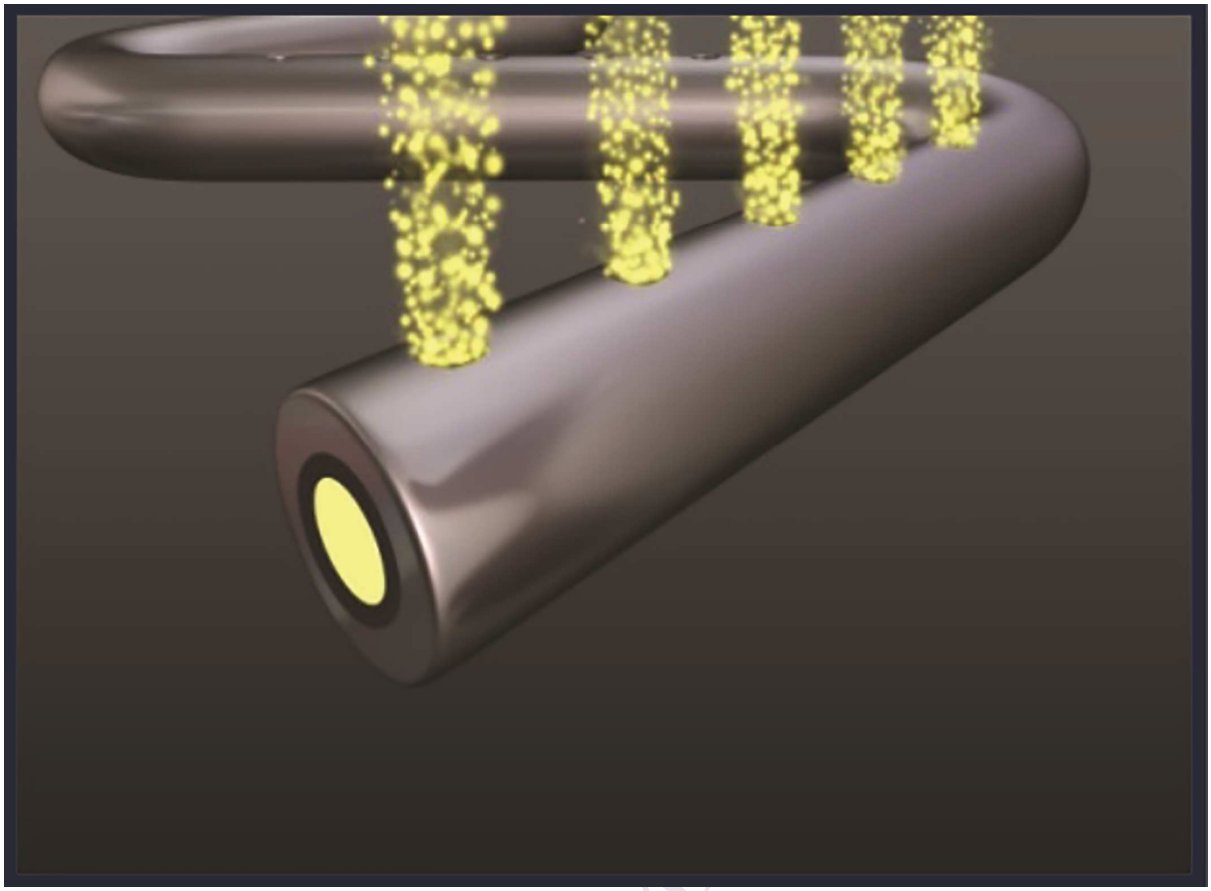
Values are mean±SD or n (%). p value calculated by analysis of variance method for three-way comparison between post-procedure vs 1- or 3-month vs 9-month follow-up or by paired t test for comparison between 1- or 3-month vs 9-month follow-up. *p<0.05; †p<0.01; ‡p<0.001. IQR = interquartile range; ISA = incomplete stent apposition; NIH = neointimal hyperplasia.
Fifteen patients were entered into each of the 1-month and 3-month OCT subgroups. The number of patients and stents differs over time and between groups because only evaluable OCT images are included.

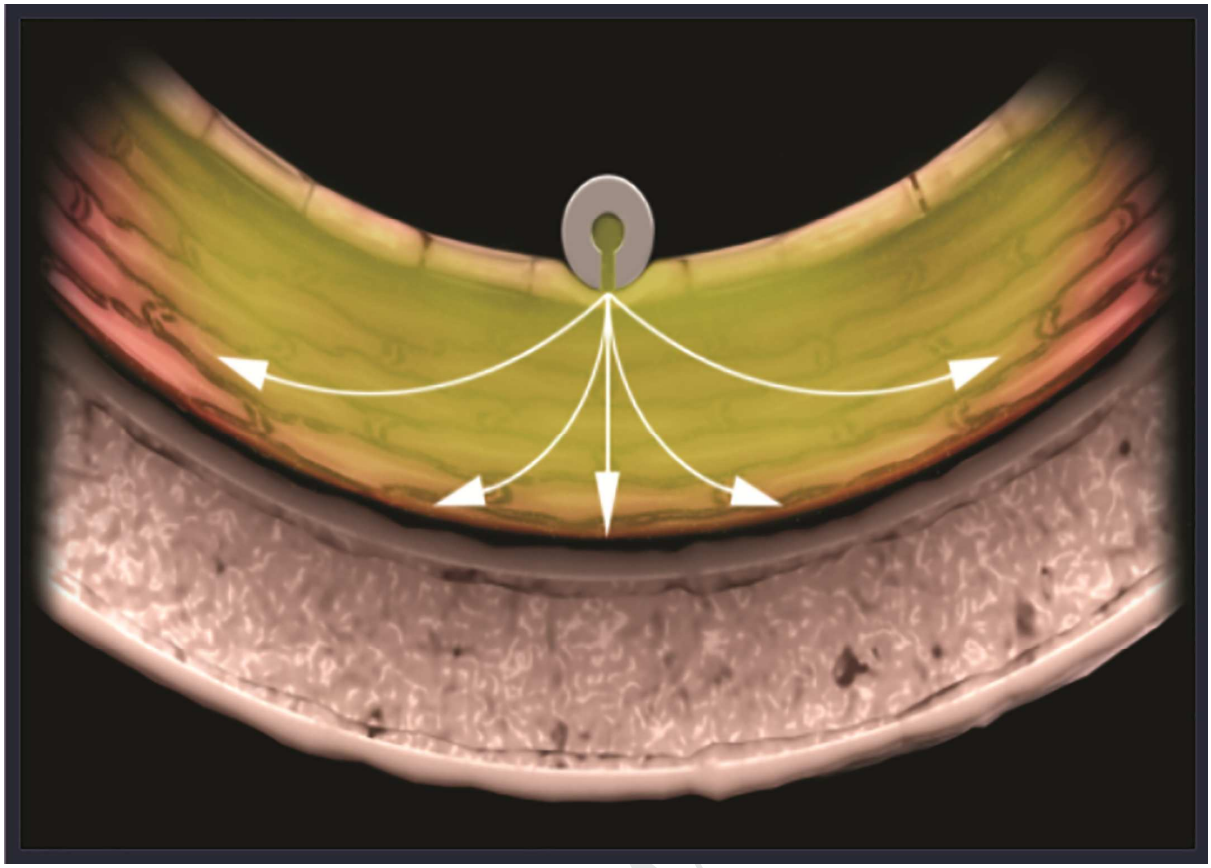
TABLE 4: 9-Month Incidence of Cardiovascular Events

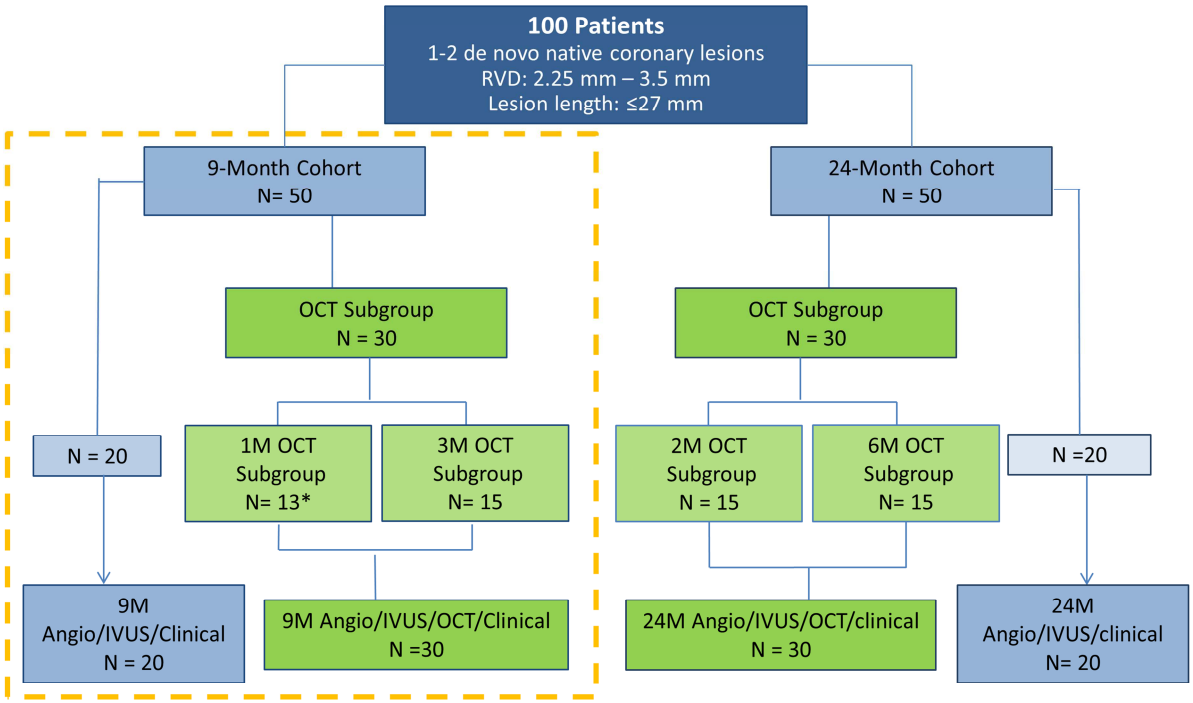
	DFS (N=48)
Major adverse cardiac events	2.1 (1)
Target vessel failure	2.1 (1)
Target lesion failure	2.1 (1)
Death	0.0
Cardiac death	0.0
Myocardial infarction	2.1 (1)
Target vessel myocardial infarction	2.1 (1)
Q wave	0.0
Non-Q wave	2.1 (1)
Non-target vessel myocardial infarction	0.0
Clinically driven target lesion revascularization	0.0
Clinically driven target vessel revascularization	0.0
Definite or probable stent thrombosis	0.0

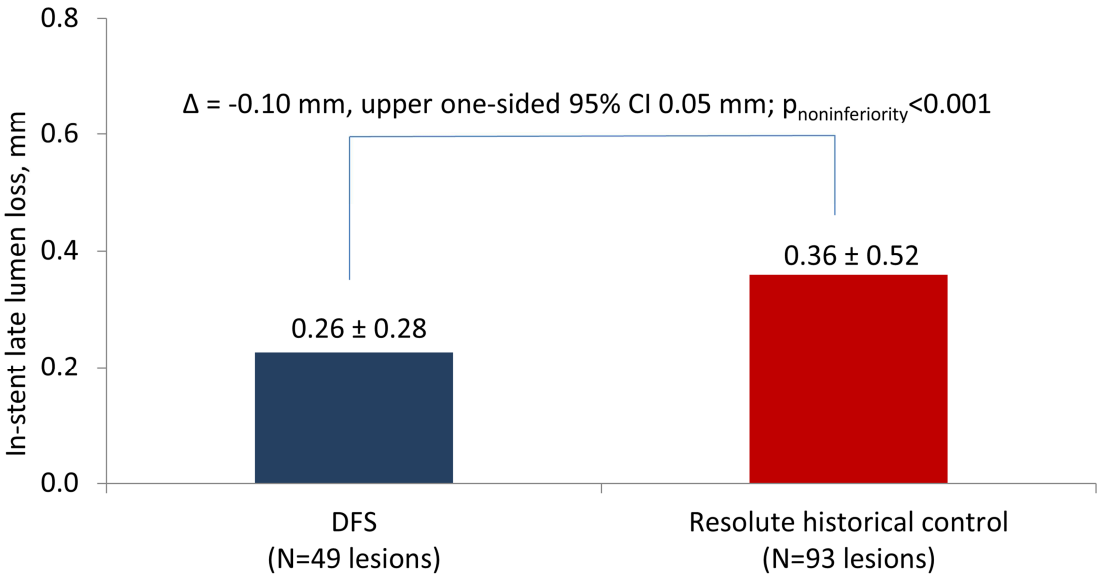
DFS = drug-filled stent.

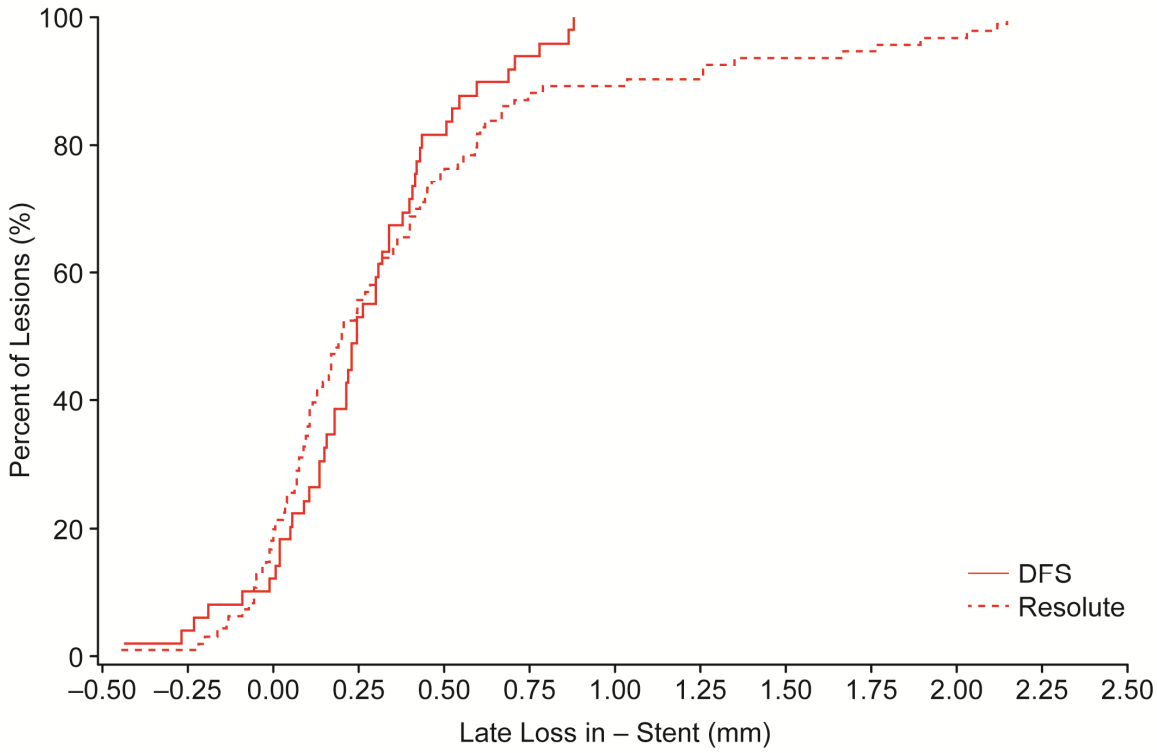


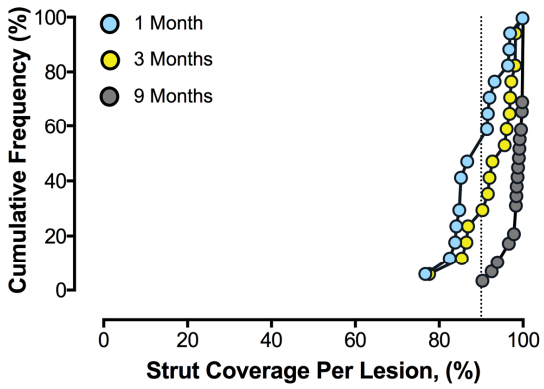


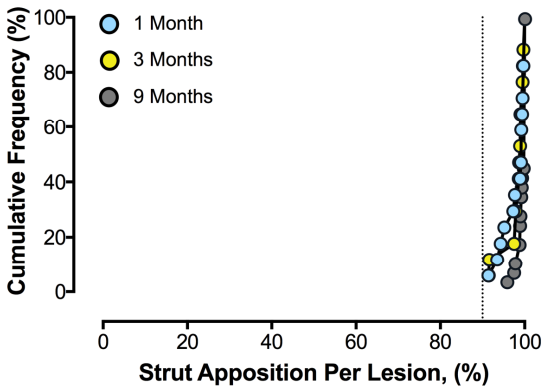












Online Appendix

First-in-Human Evaluation of a Novel Drug-Filled Stent:

Angiographic, IVUS, OCT, and Clinical Outcomes From the RevElution Study

Table of Contents

Stenting Procedure

The stent length should be adequate to cover the lesion with a single stent. In general, the stent size should match the diameter of the reference vessel (stent:vessel ratio of 1.0 to 1.1:1), and the stent should be ≥3 mm longer than the lesion to provide >1.5 mm of stent on either side of the lesion.

The Medtronic Polymer-Free Drug-Eluting Coronary Stent System was advanced over the guidewire, through the guiding catheter, to the target lesion site. The stent was positioned across the lesion and placement confirmed by fluoroscopic angiography. The stent was then deployed according to the instructions for use following the standard practice.

Post-dilatation was performed at the investigator's discretion to ensure that the stent was in full contact with the vessel wall. Post-stent dilatation with a non-compliant balloon at high pressure, sized 1 to 1.1:1 to the vessel, with length shorter than the stent to avoid edge dissections, was recommended unless the immediate post-stent result had an angiographic 0% diameter stenosis. Intravascular ultrasound (IVUS) and/or optical coherence tomography (OCT) was used to guide the interventional procedure at operator discretion and to aid in pre- and post-stent deployment decisions. Although the operators in the imaging substudies were not required to utilize IVUS or OCT in guiding stent implantation, the images were not blinded to the investigator and may have been used for stent optimization.

Angiographic Imaging

For angiographic assessment, ≥2 unforeshortened views of the stenosis with angiographic projections >30 degrees apart from one another were obtained before the index procedure. Immediately after the procedure, ≥2 unforeshortened views of the lesion identical to the pre-procedural angiograms were obtained. At 9 months, ≥2 unforeshortened views of the lesion identical to those of the post-procedural angiogram were obtained. Images were acquired at 15 to 30 frames per second.

Intravascular Ultrasound

An IVUS image was obtained post-procedurally after all interventions and before any intervention at the 9-month follow-up examination. Automatic pullback was performed at a rate of 0.5 mm/s. Operators recorded the entire segment (ie, the complete stent including at least 10 mm distal and proximal to the stent) in a single pullback without changing the zoom setting. Imaging was repeated as necessary to record the full segment.

OCT Methodology

After adjusting for the pullback speed, cross-sections were analyzed at 0.6-mm longitudinal intervals throughout the treated segment. Lumen contours were traced using semiautomatic algorithms. Detection of metallic stent struts was performed automatically with manual adjustments made as necessary. Stent area tracings were automatically performed by interpolated contours connecting the center point of the luminal surface of each detected metallic strut. Stent expansion was determined as the minimum stent area divided by the average reference lumen area and presented as a percentage. The stent eccentricity index was calculated in every analyzed cross-section as (maximum stent diameter – minimum stent diameter) / maximum stent diameter. Neointimal hyperplasia (NIH) area was determined in follow-up examinations as the area between the stent and lumen contours. The percentage of NIH obstruction of the stented area was automatically determined in each analyzed cross-section at follow-up as (NIH area / stent area) × 100. Incomplete stent apposition (ISA) area was determined as the area between the stent contour and the lumen contour at the site of malapposed struts, in a region not overlying a side branch ostium. ISA volume was automatically computed by the Simpson rule.

At the strut level, the strut-to-lumen distance was automatically measured from the center point of the luminal surface of each analyzed strut to the lumen contour by a line projected through the gravitational center of the lumen. Covered struts had positive strut-to-lumen distances, a measure of the NIH thickness covering each strut. Uncovered and malapposed struts had negative strut-to-lumen distances. Malapposed struts were differentiated from uncovered struts when the negative value of the strut-to-lumen distance was higher than the sum of the strut thickness + a compensation factor of 20 μm

to correct for the strut blooming (1). Thus, a cutoff of 101 μm (81 μm for strut thickness + 20 μm for the compensation factor) was used for determination of DFS strut malapposition. The ratio of uncovered to total stent struts (RUTTS) was calculated in each analyzed cross-section as the number of uncovered struts divided by the total number of struts in that particular cross-section. The number of cross-sections in which the RUTTS was >30% was reported for each time point (2).

References

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Representative Case

OCT images of a 3.0 × 26 mm DFS stent in the mid left anterior descending (LAD) artery. Representative images at post-procedure, 1-month, and 9-month follow-up are shown. OCT images were taken from matched positions along the treated segment, and are presented from distal (left) to proximal (right). The position of matched OCT cross-sections along the stented segment is indicated in millimeters at the bottom of the image.

At post-procedure, 2.9% of the struts were malapposed. At 1 month, a favorable healing profile was observed, with 91.4% strut coverage and only 0.8% strut malapposition. At 9 months, nearly all struts were covered (98.8%) with no malapposed struts. A magnified view of an area of initial malapposition from the very proximal stent segment is shown in the right-most column (green borders). The magnified images correspond to the dashed green boxes in the fourth column.

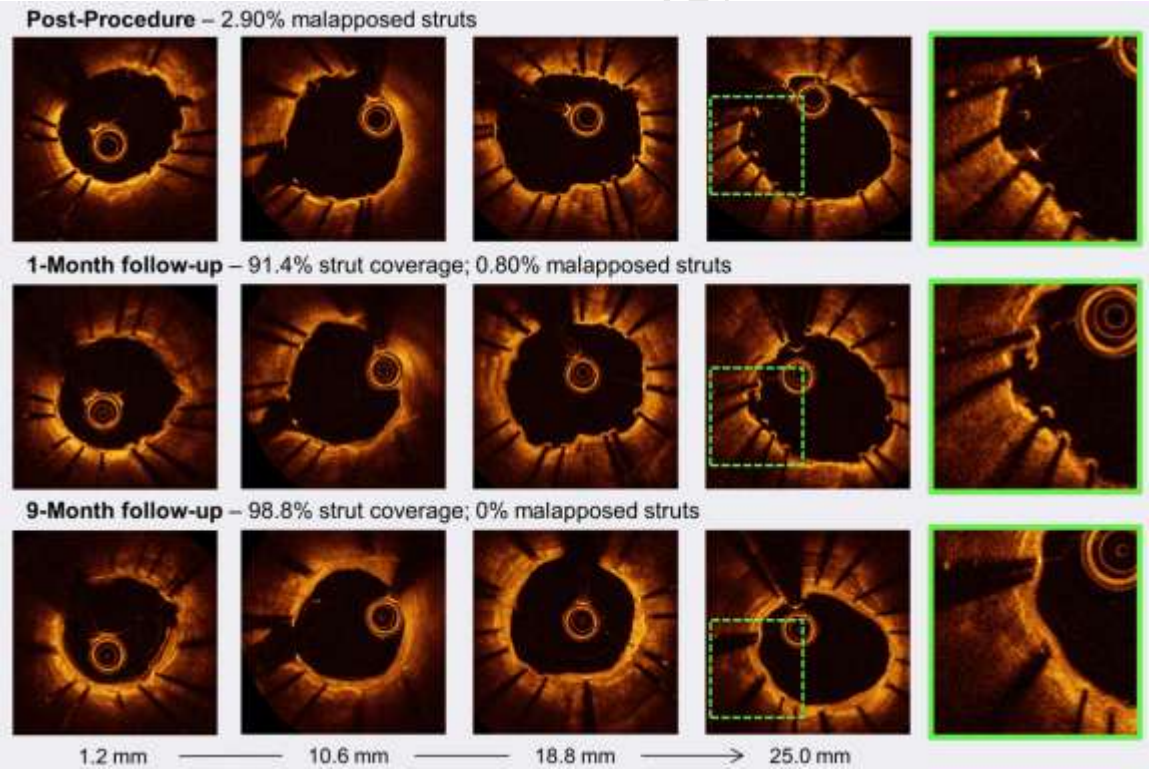

TABLE 1. Principal Investigators in the RevElution Trial

Principal Investigator	Clinical Site	Location
Stephen Worthley	Royal Adelaide Hospital and Saint Andrews Hospital	Adelaide, Australia
Sharad Shetty	Fiona Stanley Hospital	Murdoch, Australia
Ajay Sinhal	Flinders Medical Centre	Bedford Park, Australia
Ian Meredith	Monash Medical Centre	Clayton, Australia
Alexandre Abizaid	Instituto Dante Pazzanese de Cardiologia	São Paulo, Brazil
Nigel Jepson	Eastern Heart Clinic- Prince of Wales Hospital	Radwick, Australia
Ravinay Bhindi	Royal North Shore Public Hospital	St. Leonards, Australia
Soo Teik Lim	National Heart Centre Singapore	Singapore, Singapore
Peter Stewart	Royal Brisbane and Womens Hospital	Brisbane, Australia
Peter Barlis	The Northern Hospital	Epping, Australia
Darren Walters	The Prince Charles Hospital	Chermside, Australia
David Muller	Saint Vincent's Hospital (Sydney)	Darlinghurst, Australia
Stephen Cox	HeartCare Partners	Spring Hill, Australia
Rohan Bhagwandeen	John Hunter Hospital	New Lambton, Australia

TABLE 2. Angiographic Exclusion Criteria

Target vessel(s) has/have other lesions with >40% diameter stenosis based on visual estimate or online QCA

Target vessel(s) has/have evidence of thrombus

Target vessel(s) is/are excessively tortuous (any bend >90º to reach the target lesion)

Target lesion(s) has/have any of the following characteristics:

- Lesion location is aorto-ostial, an unprotected left main lesion, or within 5 mm of the origin of the left anterior descending or left circumflex
- Involves a side branch >2.0 mm in diameter
- Is at a >45º bend in the vessel
- Is severely calcified

Unprotected left main coronary artery disease is present (an obstruction greater than 50% in the left main coronary artery)

QCA = quantitative coronary angiography.

TABLE 3. Baseline Variables Included in the Propensity Score Calculation Used for the Primary Endpoint, In-Stent Late Lumen Loss of DFS in the 9-Month Cohort of RevElution Compared With In-Stent Lumen Loss of Resolute Historical Control at 8 Months in the RESOLUTE US Angiographic 2.25-3.5 mm Substudy

Subject Characteristic	DFS (N=50 Subjects, 56 lesion)	Resolute (N=100 Subjects, 104 lesions)	P value
Age, y	66.2±10.1	64.9±11.8	0.51
Male	76.0 (38)	62.0 (62)	0.09
Diabetes mellitus	30.0 (15)	35.0 (35)	0.54
Prior MI	20.0 (10)	22.0 (22)	0.78
CCSC			0.02
I	44.4 (16/36)	9.5 (6/63)	
II	33.3 (12/36)	69.8 (44/63)	
III	19.4 (7/36)	17.5 (11/63)	
IV	2.8 (1/36)	3.2 (2/63)	
Reference vessel diameter, mm	2.70±0.43	2.48±0.38	<0.001
Lesion length, mm	12.85±5.21	14.04±5.87	0.21

Values are mean±SD or % (n). CCSC = Canadian Cardiovascular Society angina class; MI = myocardial infarction.