JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 10, NO. 14, 2017
ISSN 1936-8798
http://dx.doi.org/10.1016/j.jcin.2017.05.004

CORONARY

First Report of the Resolute Onyx 2.0-mm Zotarolimus-Eluting Stent for the Treatment of Coronary Lesions With Very Small Reference Vessel Diameter

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ABSTRACT

OBJECTIVES The aim of this study was to explore the safety and efficacy of a dedicated drug-eluting stent for the treatment of coronary lesions with very small reference vessel diameter (RVD).

BACKGROUND Smaller RVD is associated with increased risk for restenosis and target lesion failure (TLF) after stent implantation.

METHODS This was a prospective, single-arm, multicenter trial of the Resolute Onyx 2.0-mm zotarolimus-eluting stent. The primary endpoint was 12-month TLF, which was compared with a pre-specified performance goal. Subjects with stable or unstable angina or ischemia, target lesions ≤27 mm in length, and RVD ≥2.0 and <2.25 mm were eligible for enrollment. A subset of subjects underwent follow-up angiography at 13 months post-procedure.

RESULTS A total of 101 subjects with 104 lesions were enrolled. The mean age was 67.3 ± 9.6 years, 47% of subjects had diabetes, the mean lesion length was 12.6 ± 6.3 mm, and the mean RVD was 1.91 ± 0.26 mm. The rate of TLF at 12 months was 5.0%, fulfilling the pre-specified performance goal of 19% ($p < 0.001$). The rates of target lesion revascularization and target vessel myocardial infarction were 2.0% and 3.0%, respectively. There were no episodes of stent thrombosis. In-stent late lumen loss was 0.26 ± 0.48 mm, and the rate of binary restenosis was 12.0%.

CONCLUSIONS In this first report of a drug-eluting stent with a dedicated size to treat lesions with RVD <2.25 mm, the Resolute Onyx 2.0-mm zotarolimus-eluting stent was associated with a low rate of TLF and late lumen loss, without a signal for stent thrombosis. This novel-sized drug-eluting stent appears to be a feasible option for the treatment of coronary lesions in extremely small vessels. (Medtronic Resolute Onyx 2.0 mm Clinical Study; NCT02412501) (J Am Coll Cardiol Intv 2017;10:1381–8) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

DES = drug-eluting stent(s)

MACE = major adverse cardiac event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

QCA = quantitative coronary angiography

R-Onyx = Resolute Onyx

RVD = reference vessel diameter

TLF = target lesion failure

TLR = target lesion revascularization

ZES = zotarolimus-eluting stent(s)

Reference vessel diameter (RVD) is a key determinant of restenosis and target lesion failure (TLF) after percutaneous coronary intervention (PCI) with stent implantation (1,2). Even in the drug-eluting stent (DES) era, smaller preprocedural RVD is associated with increased target lesion revascularization (TLR) and a lower rate of survival free from major adverse cardiac events (MACEs) (3). Furthermore, distal small-vessel disease is often seen in patients with multiple comorbidities, such as renal dysfunction and diabetes, which can further increase the risk for longer term cardiovascular events. Although the smallest sized DES commercially available in the United States is 2.25 mm in diameter, obstructive lesions with even smaller RVD (i.e., <2.25 mm) are frequently encountered and can be symptomatic (4,5). Furthermore, data suggest that side-branch occlusion of small coronary vessels can lead to myocardial infarction that in turn is associated with higher mortality and future adverse cardiac events (6,7). Coronary artery bypass grafting is performed successfully on vessels ≥1.5 mm in diameter, demonstrating the belief among the cardiac surgery community that coronary vessels with RVD between 1.5 and 2.25 mm may sustain important areas of myocardium (8).

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It is unclear whether the excellent outcomes with DES observed in smaller RVD (e.g., >2.25 mm) (9,10) are also seen with extremely small diameters. Therefore, the aim of the RESOLUTE ONYX 2.0 mm Clinical Study was to explore the safety and efficacy of the Resolute Onyx (R-Onyx) DES for the treatment of de novo lesions in native coronary arteries amenable to use of a 2.0-mm diameter DES.

METHODS

CLINICAL STUDY DESIGN AND STUDY POPULATION. The RESOLUTE ONYX 2.0 mm Clinical Study was a single-arm, open-label, multicenter study conducted at 20 sites in the United States and Japan. The Institutional Review Board or ethics committee at each study site approved the study protocol, and written informed consent was obtained from all subjects. Subjects who had evidence of ischemic heart disease were eligible to be enrolled if they had a single de novo target lesion or 2 target lesions located in separate target vessels, with at least 1 of the target lesions amenable to treatment with a 2.0-mm study stent. Specifically, the target lesion required an RVD ≥2.0 and <2.25 mm by visual estimate, TIMI (Thrombolysis in Myocardial Infarction) flow grade ≥2, and length ≤27 mm. For patients with multivessel disease, a positive functional study involving the area subtended by the target lesion (e.g., fractional flow reserve measurement) was required for the subject to be enrolled. Key exclusion criteria included evidence of an acute myocardial infarction within 72 h before the procedure, planned PCI of any vessel within 30 days after the index procedure, and planned PCI of the target vessel(s) within 12 months after the procedure.

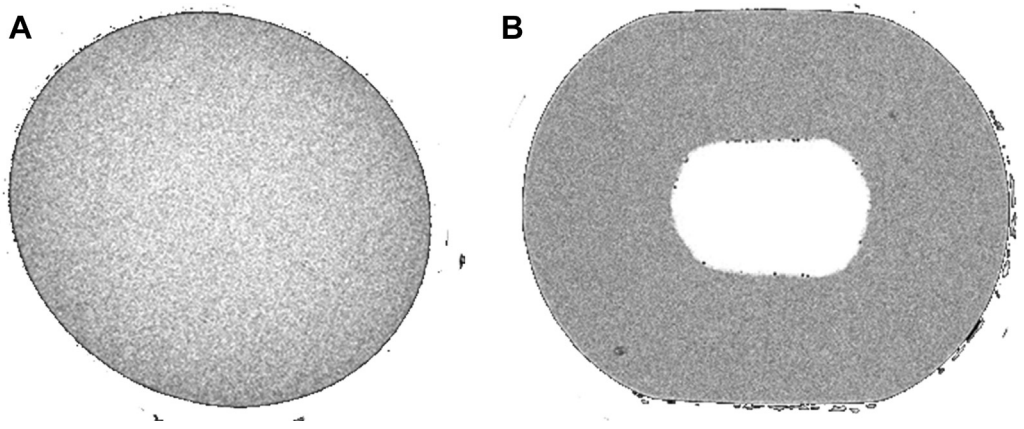
After the procedure, subjects received maintenance-dose aspirin 75 to 325 mg/day indefinitely and an oral $P2Y_{12}$ antagonist daily for at least 6 months and up to 12 months in subjects who were not at high risk for bleeding. Subjects were followed up at 30 days, 6 months, and 12 months post-procedure. Angiographic follow-up at 13 months was performed in the subset of subjects participating in an angiographic substudy. An independent core laboratory performed the quantitative coronary angiographic analyses (Beth Israel Deaconess Medical Center, Boston, Massachusetts). A data monitoring committee continuously monitored the ongoing safety of the study, and an independent clinical events committee adjudicated clinical endpoints.

R-ONYX ZOTAROLIMUS-ELUTING STENT. The R-Onyx zotarolimus-eluting stent (ZES) is composed of a single continuous wire with a swaged shape that is formed into a sinusoidal design, wound around a mandrel, and laser-fused at specific crowns to create its final configuration. The outer shell of this stent is the same cobalt alloy as the predecessors R-ZES and R-Integrity ZES (conforming to ASTM F562, material

grants from Medtronic, Boston Scientific, and Abbott Vascular. Dr. Mehran has received consulting honoraria from Medscape, Shanghai BraccoSine Pharmaceutical, and Abbott; has participated on the Data Safety Monitoring Board for Watermark Research Planners; has received research grants from Abbott Vascular, AstraZeneca, Bayer Healthcare Pharmaceuticals, Bristol-Myers Squibb Company, CSL Behring, DSI, Medtronic, Novartis Pharmaceuticals, OrbusNeich, and The Medicines Company; and has received other support from Janssen Pharmaceuticals and Wiley Blackwell. Dr. Brar, Dr. Liu, and Ms. Moe are employees of Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received April 10, 2017; revised manuscript received May 1, 2017, accepted May 4, 2017.

FIGURE 1 Cross-Sectional Strut of the Resolute Integrity and Resolute Onyx



(A) Resolute Integrity, **(B)** Resolute Onyx. Cobalt alloy is shown in **gray** and platinum-iridium alloy in **white** (not shown to scale).

density of 8.4 g/cm^3), and R-Onyx uses the same zotarolimus dose and polymer. However, R-Onyx has an inner core composed of a 90% platinum and 10% iridium alloy with a material density of 21.5 g/cm^3 (Figure 1). The higher density of the platinum-iridium alloy inner core used in R-Onyx improves visibility on radiography despite having thinner stent struts than the predecessor ZES. The swaged shape of struts increases the strut width-to-thickness ratio (strut width 91 μm and thickness 81 μm) compared with R-Integrity ZES, with the aim to maintain radial strength.

FIGURE 2 Patient Disposition: Baseline Enrollment and Evaluable Patients at 12 Months for Clinical Follow-Up and at 13 Months for the Angiographic Cohort

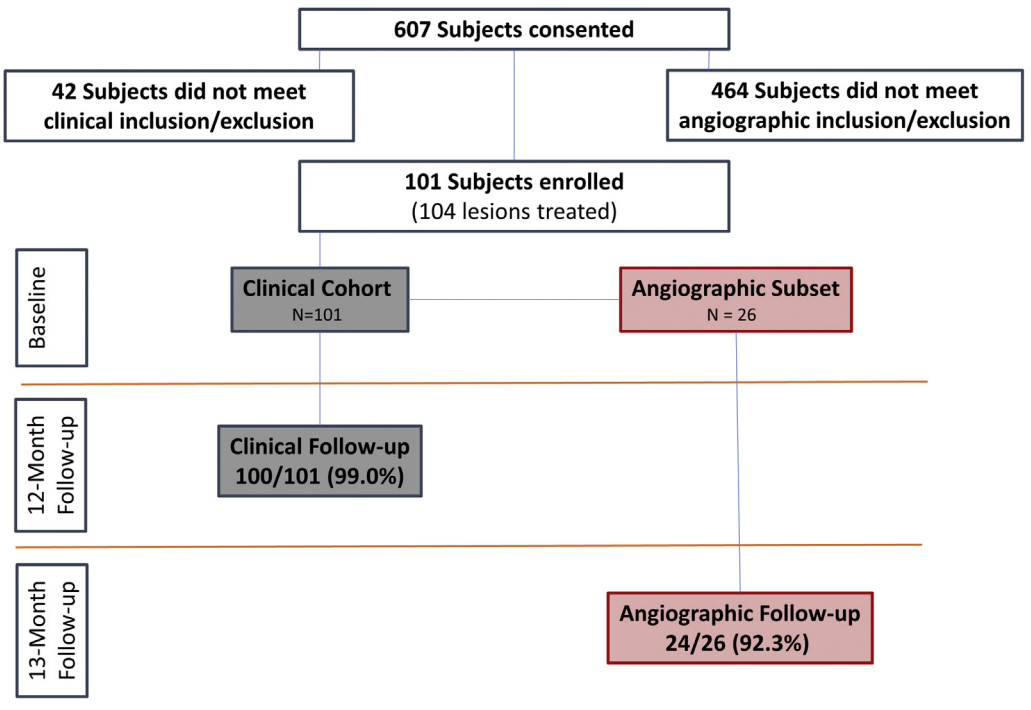


TABLE 1 Baseline Demographics and Clinical Characteristics of the Study Population (N = 101)

Age, yrs	67.3 ± 9.6
Male	70.3 (71/101)
BMI, kg/m^2	29.0 ± 6.5
Diabetes mellitus	46.5 (47/101)
Insulin-dependent diabetes mellitus	11.9 (12/101)
Hyperlipidemia	94.1 (95/101)
Hypertension	82.2 (83/101)
Previous MI	35.7 (35/98)
Prior PCI	59.4 (60/101)
Prior CABG	17.8 (18/101)
History of stroke or TIA	9.9 (10/101)
Current smoker	11.9 (12/101)
Reason for revascularization	
Stable angina	62.4 (63/101)
Unstable angina	27.7 (28/101)
MI	1.0 (1/101)
Silent angina	0.0 (0/101)
Positive functional study result*	46.5 (47/101)

Values are mean ± SD or % (n/N). *Subjects could have positive functional study results and other reasons for revascularization.

BMI = body mass index; CABG = coronary artery bypass grafting; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

TABLE 2 Procedural and Lesion Characteristics of the Study Population (N = 101 Patients, N = 104 Lesions)

Vessel location (per patient)	
Left anterior descending coronary artery	36.6 (37/101)
Left circumflex coronary artery	36.6 (37/101)
Right coronary artery	28.7 (29/101)
Modified ACC/AHA lesion type	
A	5.8 (6/104)
B1	28.8 (30/104)
B2	44.2 (46/104)
C	21.2 (22/104)
Tortuosity	
None	94.2 (98/104)
Moderate	4.8 (5/104)
Severe	1.0 (1/104)
Calcification	
Mild	76.0 (79/104)
Moderate	18.3 (19/104)
Severe	5.8 (6/104)
Lesion measurements, pre-procedure*	
Lesion length, mm	12.6 ± 6.3
Reference vessel diameter, mm	1.91 ± 0.26
Minimum luminal diameter, mm	0.65 ± 0.22
Mean % stenosis	65.8 ± 10.9
Number of lesions treated per subject	1.1 ± 0.3
Number of lesions with pre-dilatation	99.0 (103/104)
Stent post-dilated	39.8 (43/108)
Lesion success	99.0 (103/104)
Device success	96.2 (100/104)
Procedure success	97.0 (98/101)

Values are % (n/N) or mean ± SD. *Baseline lesion measurements according to quantitative coronary angiographic analysis.

ACC = American College of Cardiology; AHA = American Heart Association.

STUDY ENDPOINTS. The primary endpoint was TLF at 12 months post-procedure, defined as the composite of cardiac death, target vessel myocardial infarction (Q-wave or non-Q-wave) or TLR. Secondary clinical endpoints included the individual components of the primary endpoint, clinically driven target vessel revascularization, target vessel failure, stent thrombosis, and MACEs (defined as the composite of death from any cause, myocardial infarction, emergency coronary bypass surgery, or TLR). Angiographic endpoints included late lumen loss, binary angiographic restenosis defined as ≥50% in-stent diameter stenosis, and percentage diameter stenosis.

Device success was defined as the achievement of <30% residual stenosis by quantitative coronary angiography (QCA) (or <20% by visual assessment) and TIMI flow grade 3 after the procedure, using only the study device. Lesion success was defined as the achievement of <30% residual stenosis by QCA (or <20% by visual assessment) and TIMI flow grade 3 after the procedure using any percutaneous method. Procedural success was defined as the achievement of lesion success without the occurrence of MACEs during the hospital stay.

STATISTICAL ANALYSES. The primary endpoint of TLF at 12 months post-procedure was compared with a performance goal of 19%. The trial would be considered to have fulfilled its primary objective if the observed primary endpoint was significantly lower than the performance goal. Accounting for a 10% clinical loss to follow-up and a 1-sided 0.05 level of significance, a sample size of 100 subjects was calculated to yield >80% power to reject the null hypothesis in favor of the alternative, assuming the true R-Onyx 2.0-mm ZES 12-month TLF rate is 9.4%. The expected rate of 9.4% was estimated from the weighted average of TLF rates observed with 2.25-mm DES (10–15) and the known association between smaller RVD and increased event rates. The performance goal was set at 19%, approximately twice the point estimate of the expected TLF rate.

Categorical variables are expressed as counts and percentages and were compared using the chi-square or Fisher exact test. Continuous variables are presented as mean ± SD, and were compared using the Student *t* test or Wilcoxon rank sum test. A p value <0.05 was considered to indicate statistical significance. All analyses were performed using SAS for Windows version 9.2 or higher (SAS Institute, Cary, North Carolina).

TABLE 3 Clinical Outcomes at 12-Month Follow-Up (N = 100)

TLF	5.0 (5/100)
TVF	5.0 (5/100)
TV-MI	3.0 (3/100)
MACE	5.0 (5/100)
Cardiac death	0.0 (0/100)
Noncardiac death	0.0 (0/100)
Cardiac death or TV-MI	3.0 (3/100)
TLR	2.0 (2/100)
TVR	2.0 (2/100)
Stent thrombosis (ARC) definite/probable	0.0 (0/100)
Early thrombosis (≤30 days)	0.0 (0/100)
Late thrombosis (31–360 days)	0.0 (0/100)

Values are % (n/N).

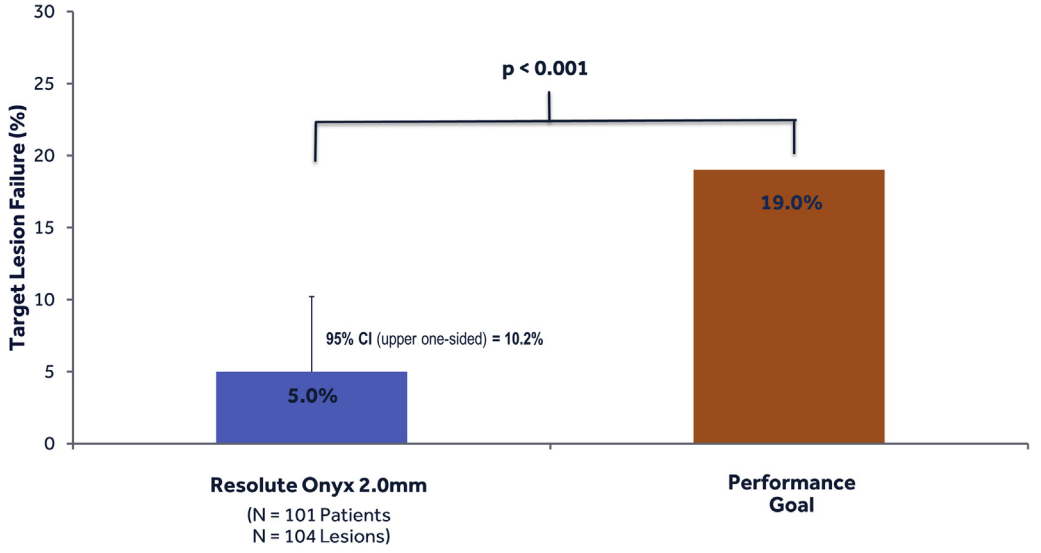
ARC = Academic Research Consortium; MACE = major adverse cardiac event(s); TLF = target lesion failure; TVF = target vessel failure; TV-MI = target vessel myocardial infarction.

RESULTS

BASELINE CHARACTERISTICS AND PROCEDURAL RESULTS. Study flow is shown in Figure 2. A total of 101 subjects with 104 lesions were enrolled (Tables 1 and 2). The mean subject age was 67.3 ± 9.6 years, 70% were men, and 47% had diabetes. The target lesion involved the left anterior descending coronary artery in 37%, the left circumflex coronary artery in 37%, and the right coronary artery in 29% of cases. The majority of lesions were anatomically complex (65% were type B2/C). The mean lesion length was 12.6 ± 6.3 mm and the mean RVD was 1.91 ± 0.26 mm by QCA. Per protocol, nearly all lesions (99%) were pre-dilated. Post-dilation was performed for 39% of implanted stents. Lesion success was 99.0%, device success was 96.2%, and procedure success was 97.0%. At 12 months, 88% of subjects reported taking dual-antiplatelet therapy.

CLINICAL OUTCOMES. At discharge, the rate of TLF was 2.0% (2 of 101), driven by target vessel myocardial infarction (Table 3). There were no new events between discharge and 30 days. Follow-up at 12 months was available in 100 subjects (99%) (Figure 2). The rate of 12-month TLF was 5.0% (5 of 100), fulfilling the pre-specified performance criterion ($p < 0.001$) (Central Illustration). TLR occurred in 2.0%, target vessel myocardial infarction in 3.0%, target vessel failure in 5.0%, and MACEs in 5.0% of subjects. There were no episodes of stent thrombosis and no deaths. The 12-month rates of TLF and TLR were similar for subjects with and without diabetes mellitus (TLF: 6.4% [3 of 47] for patients with diabetes vs. 3.8% [2 of 53] for those without diabetes, $p = 0.664$; TLR: 4.3% [2 of 47] vs. 0.0% [0 of 53], respectively, $p = 0.218$).

CENTRAL ILLUSTRATION Primary Endpoint of Target Lesion Failure at 12 Months



Price, M.J. et al. J Am Coll Cardiol Intv. 2017;10(14):1381–8.

CI = confidence interval.

TABLE 4 Measurements at Baseline and 13 Months Follow-Up for the Angiographic Cohort

Baseline (N = 26 patients, N = 27 lesions)	
Lesion length, mm	12.38 ± 6.43
Reference vessel diameter, mm	1.98 ± 0.25
Minimum luminal diameter, mm	0.68 ± 0.20
Mean % stenosis	65.28 ± 9.85
13-month follow-up (N = 24 patients, N = 25 lesions)	
Reference vessel diameter, mm	2.02 ± 0.28
Minimum luminal diameter, mm	
In-stent	1.55 ± 0.52
In-segment	1.25 ± 0.46
Diameter stenosis, % of luminal diameter	
In-stent	22.49 ± 26.89
In-segment	37.92 ± 21.54
Binary restenosis	
In-stent	12.0 (3/25)
In-segment	20.0 (5/25)
Late loss, mm	
In-stent	0.26 ± 0.48
In-segment	0.25 ± 0.41

Values are mean ± SD or % (n/N).

ANGIOGRAPHIC OUTCOMES. A total of 26 subjects with 27 lesions participated in the angiographic substudy. The baseline characteristics of the subjects enrolled in the substudy were similar to those of the subjects who did not undergo angiographic follow-up, with the exception of hypertension and unstable angina, which were less frequently present (Online Table 1). Evaluable follow-up angiographic data were available for 24 subjects and 25 lesions (**Table 4**). More than one-half of these subjects (57.7%) had diabetes. Angiographic follow-up occurred a median of 391 days post-procedure (range 301 to 427 days). In-stent late lumen loss was 0.26 ± 0.48 mm, in-stent percentage diameter stenosis was 22.5 ± 26.9%, and in-stent binary restenosis occurred in 12.0% of subjects (3 of 25).

DISCUSSION

Small RVD has historically identified a particularly challenging lesion subset to treat successfully with percutaneous revascularization. In this first report of a DES with a dedicated size to treat lesions with RVD <2.25 mm, the R-Onyx 2.0-mm ZES was associated with a low rate of TLF at 1-year follow-up (5%) and a degree of late lumen loss consistent with that of prior generation ZES implanted in lesions with larger, "standard" RVD. These results were achieved safely, without a signal for increased stent thrombosis, and despite the presence of diabetes in nearly one-half of the study population.

Current management options for the percutaneous treatment of symptomatic coronary artery disease involving target vessels <2.25 mm in diameter include plain old balloon angioplasty, implanting a bare-metal stent, or oversizing with a 2.25-mm DES, as no dedicated 2.0-mm DES is commercially available within the United States. However, small RVD is among the strongest predictors of restenosis and TLR after PCI, particularly following bare-metal stent or plain old balloon angioplasty (16,17), for which repeat revascularization rates are in excess of 25% (18,19). Although repeat revascularization rates are reduced with a drug-eluting balloon, outcomes may be worse than with DES (20), bailout stenting in small vessels is sometimes required (21), and at present, a drug-eluting balloon is not commercially available in the United States. Post hoc analyses of clinical trials suggest that implantation of contemporary DES in vessels with diameter <2.25 mm is associated with similar rates of TLF in target vessels of 2.25 to <2.50 mm, but with higher MACE rates compared with vessel diameters ≥2.5 mm (3). However, implantation of a 2.25-mm diameter stent in very small vessels may risk perforation, distal dissection, and vessel closure; if the stent is implanted below nominal pressure, this may lead to malapposition and underexpansion with subsequent complications in recrossing the stent with a post-dilation balloon or an increased risk for stent thrombosis. A thin-strutted DES with optimized deployment might overcome these therapeutic limitations.

In the present study, we studied the safety and efficacy of the R-Onyx 2.0 mm ZES, which is mounted on a balloon with a nominal pressure of 12 atm and is therefore sized appropriately for implantation within vessels with extremely small diameters. The study met its primary endpoint with a 5.0% rate of TLF at 12 months compared with the pre-specified performance goal of 19.0%, a criterion that is lower than the performance goal of 20.4% used to assess the 2.25-mm everolimus-eluting stent (11) and less than the 21.1% performance goal to assess the 2.25-mm platinum-chromium everolimus-eluting stent (10). Although we did not have a direct comparator arm, the efficacy of the R-Onyx 2.0-mm ZES appears consistent with that previously observed for DES in slightly larger vessels. A post hoc, pooled quantitative coronary angiographic analysis of the RESOLUTE Global Clinical Trial experience, which enrolled subjects with target vessels ≥2.25 mm by visual estimation, reported 1-year TLF rate of 5.9% in those with

small vessels (2.25 mm ≤ RVD <2.75 mm) and 7.9% for patients who happened to be enrolled with extremely small vessels (RVD <2.25 mm) (22). The SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions) Small Vessel trial enrolled subjects with lesions involving coronary vessels with RVD ≥2.25 and <2.50 mm by visual inspection; TLF at 1 year was 8.1% (11). A post hoc analysis of that study that compared TLF rates between patients with RVD above and below the median demonstrated that the rate of TLF was much higher for patients with extremely small vessels (13.9% for RVD ≤2.12 mm vs. 1.6% for RVD >2.12 mm), suggesting a higher risk inherent in treating patients with increasingly smaller vessel size (11). In the present study, the low rates of TLF and MACE were observed despite a required RVD <2.25 mm by visual estimation and a mean RVD among the study population of only 1.91 ± 0.26 mm by QCA.

Angiographic follow-up in a subset of subjects demonstrated that in-stent late lumen loss with the R-Onyx 2.0-mm stent also appears comparable with that observed in prior trials of ZES in larger vessel diameters. The in-stent late loss for R-Onyx 2.0 mm at 13 months was 0.26 ± 0.48 mm, similar to that observed in the RESOLUTE All Comers (A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention) trial (0.27 ± 0.43 mm), despite a substantially larger pre-procedural RVD in the latter (2.63 ± 0.57 mm) (23). However, in-segment percentage diameter stenosis and the rate of in-stent binary restenosis were relatively high in the present study (37.92 ± 21.54% and 12.0%, respectively). The former may reflect the presence of diffuse disease around target lesions located in the distal coronary tree, and the latter may reflect the absence of "headroom" for even small amounts of late loss when implanting a stent within a vessel of such narrow caliber. Although this did not appear to have a clinical impact at 1-year post-procedure, a greater duration of follow-up is required to determine whether progression of inflow and/or outflow disease, or continued in-stent late loss, may influence longer term outcomes.

STUDY LIMITATIONS. The study was limited by its relatively small sample size, particularly for the angiographic subset, but the overall population was similar in size to other small vessel studies. There was no separate comparator arm, but randomization to a bare-metal stent was believed to be unethical, and there is no other commercially available DES approved for use in lesions with extremely small RVD in the countries of the participating sites.

CONCLUSIONS

In this first report of a DES with a dedicated size to treat lesions with RVD <2.25 mm, the R-Onyx 2.0-mm ZES was associated with a low rate of TLF and in-stent late loss consistent with that of prior-generation ZES in lesions with larger RVD, without a signal for stent thrombosis. The use of this novel-sized DES appears to be a feasible approach for the treatment of coronary lesions in extremely small vessels.

ACKNOWLEDGMENTS Yun Peng, MS, provided statistical support; Lisa Bousquette, MS, Hiroko Ookubo, and Michelle Dauler provided expert study management; and Beth Ferri, PhD, provided editorial assistance, including preparation of figures and tables (all employees from Medtronic).

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PERSPECTIVES

WHAT IS KNOWN? Smaller RVD is associated with an increased risk for restenosis and TLF after stent implantation. There is no commercially available DES in the United States dedicated to treat lesions within extremely small vessels (RVD ≥2.0 and <2.25 mm).

WHAT IS NEW? To date, whether a DES can successfully treat lesions within such small vessels has never been evaluated. In this prospective, multicenter study of subjects undergoing PCI for the treatment of coronary lesions in extremely small vessels, the R-Onyx 2.0-mm ZES was associated with minimal late lumen loss and a low rate of TLF at 1 year (5%) without a signal for stent thrombosis. Therefore, the use of this novel-sized DES appears to be a feasible approach for the treatment of coronary lesions in extremely small vessels.

WHAT IS NEXT? Studies with a greater duration of follow-up are required to determine whether disease progression around the stent, or accrual of further late loss within the stent, may influence long-term event rates after stent implantation for lesions within such small-diameter vessels.

REFERENCES

1. Garg S, Serruys PW. Coronary stents: current status. J Am Coll Cardiol 2010;56:S1–42.

2. Schunkert H, Harrell L, Palacios IF. Implications of small reference vessel diameter in patients undergoing percutaneous coronary revascularization. J Am Coll Cardiol 1999;34:40–8.

3. van der Heijden LC, Kok MM, Danse PW, et al. Small-vessel treatment with contemporary newer-generation drug-eluting coronary stents in all-comers: insights from 2-year DUTCH PEERS (TWENTE II) randomized trial. Am Heart J 2016;176:28–35.

4. Koning R, Eltchaninoff H, Commeau P, et al. Stent placement compared with balloon angioplasty for small coronary arteries: in-hospital and 6-month clinical and angiographic results. Circulation 2001;104:1604–8.

5. Mehilli J, Dibra A, Kastrati A, et al. Randomized trial of paclitaxel- and sirolimus-eluting stents in small coronary vessels. Eur Heart J 2006;27:260–6.

6. Lansky AJ, Yaqub M, Hermiller JB, et al. Side branch occlusion with everolimus-eluting and paclitaxel-eluting stents: three-year results from the SPIRIT III randomised trial. EuroIntervention 2010;6 Suppl J:J44–52.

7. Prasad A, Singh M, Lerman A, Lennon RJ, Holmes DR Jr., Rihal CS. Isolated elevation in troponin T after percutaneous coronary intervention is associated with higher long-term mortality. J Am Coll Cardiol 2006;48:1765–70.

8. Ramstrom J, Lund O, Cadavid E, Thuren J, Oxelbark S, Henze A. Multiarterial coronary artery bypass grafting with special reference to small vessel disease and results in women. Eur Heart J 1993;14:634–9.

9. Moses JW, Nikolsky E, Mehran R, et al. Safety and efficacy of the 2.25-mm sirolimus-eluting Bx Velocity stent in the treatment of patients with de novo native coronary artery lesions: the SIRIUS 2.25 trial. Am J Cardiol 2006;98:1455–60.

10. Teirstein PS, Meredith IT, Feldman RL, et al. Two-year safety and effectiveness of the platinum chromium everolimus-eluting stent for the treatment of small vessels and longer lesions. Catheter Cardiovasc Interv 2015;85:207–15.

11. Cannon LA, Simon DI, Kereiakes D, et al. The XIENCE nano everolimus eluting coronary stent system for the treatment of small coronary arteries: the SPIRIT Small Vessel trial. Catheter Cardiovasc Interv 2012;80:546–53.

12. Saito S, Maehara A, Vlachojannis GJ, Parise H, Mehran R, Investigators RJ. Clinical and angiographic evaluation of the resolute zotarolimus-eluting coronary stent in Japanese patients - long-term outcome in the RESOLUTE Japan and RESOLUTE Japan small vessel study. Circ J 2015;79:96–103.

13. Tanimoto S, Daemen J, Tsuchida K, et al. Two-year clinical outcome after coronary stenting of small vessels using 2.25-mm sirolimus- and paclitaxel-eluting stents: insight into the RESEARCH and T-SEARCH registries. Catheter Cardiovasc Interv 2007;69:94–103.

14. Turco MA, Ormiston JA, Popma JJ, et al. Reduced risk of restenosis in small vessels and reduced risk of myocardial infarction in long lesions with the new thin-strut TAXUS Liberte stent: 1-year results from the TAXUS ATLAS program. J Am Coll Cardiol Intv 2008;1:699–709.

15. Yeung AC, Leon MB, Jain A, et al. Clinical evaluation of the Resolute zotarolimus-eluting coronary stent system in the treatment of de novo lesions in native coronary arteries: the RESOLUTE US clinical trial. J Am Coll Cardiol 2011;57:1778–83.

16. Elezi S, Kastrati A, Neumann FJ, Hadamitzky M, Dirschinger J, Schomig A. Vessel size and long-term outcome after coronary stent placement. Circulation 1998;98:1875–80.

17. Rathore S, Terashima M, Katoh O, et al. Predictors of angiographic restenosis after drug eluting stents in the coronary arteries: contemporary practice in real world patients. EuroIntervention 2009;5:349–54.

18. Ardissino D, Cavallini C, Bramucci E, et al. Sirolimus-eluting vs uncoated stents for prevention of restenosis in small coronary arteries: a randomized trial. JAMA 2004;292:2727–34.

19. Moreno R, Fernandez C, Alfonso F, et al. Coronary stenting versus balloon angioplasty in small vessels: a meta-analysis from 11 randomized studies. J Am Coll Cardiol 2004;43:1964–72.

20. Siontis GC, Piccolo R, Praz F, et al. Percutaneous coronary interventions for the treatment of stenoses in small coronary arteries: a network meta-analysis. J Am Coll Cardiol Intv 2016;9:1324–34.

21. Latib A, Colombo A, Castriota F, et al. A randomized multicenter study comparing a paclitaxel drug-eluting balloon with a paclitaxel-eluting stent in small coronary vessels: the BELLO (Balloon Elution and Late Loss Optimization) study. J Am Coll Cardiol 2012;60:2473–80.

22. Parikh MA, Soverow J, Leon MB, et al. Outcomes of stenting extra-small (≤2.25 mm) vessels using the Resolute zotarolimus-eluting stent (R-ZES). EuroIntervention 2016;12:1215–21.

23. Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. N Engl J Med 2010;363:136–46.

KEY WORDS drug-eluting stent(s), percutaneous coronary intervention, reference vessel diameter, Resolute Onyx, restenosis, stent(s), zotarolimus

APPENDIX For a supplemental table, please see the online version of this article.