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ORIGINAL STUDIES

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Safety and efficacy of the next generation Resolute Onyx zotarolimus-eluting stent: Primary outcome of the RESOLUTE ONYX core trial

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Abstract

Objectives: To assess the safety and efficacy of the novel Resolute (R-) Onyx drug-eluting stent (DES).

Background: The R-Onyx DES consists of a composite wire with an outer shell of cobalt chromium alloy and a platinum-iridium inner core to enhance radiopacity, with thinner, swaged struts and modified stent geometry compared with the predicate Resolute DES, resulting in a slightly lower total drug load in most sizes.

Methods: This was a prospective, single-arm non-inferiority trial compared with a historical control. Patients with stable angina/ischemia and up to 2 *de novo* target lesions ≤35 mm long with reference vessel diameter (RVD) of 2.25–4.2 mm were enrolled. The primary endpoint was late lumen loss at 8-month follow-up. Propensity-score adjusted outcomes from the single-arm RESOLUTE-US trial served as the control.

Results: Seventy-five patients (85 lesions) were enrolled. Mean patient age was 66 ± 9 years, 73% were male, and 32% had diabetes. Mean lesion length was 14.28 ± 6.68 mm, mean RVD was 2.57 ± 0.48 mm, and 86% of lesions were class B2/C. In-stent late lumen loss at 8 months was 0.24 ± 0.39 mm with R-Onyx DES compared with 0.36 ± 0.52 mm with Resolute DES ($P < 0.001$ for noninferiority, $P = 0.029$ for superiority). At 8 months, clinically driven target lesion revascularization occurred in 3 patients (4.0%) and target lesion failure occurred in 5 patients (6.7%).

Conclusions: In-stent late lumen loss is non-inferior, and appears to be superior, with the thin-strut novel composite wire R-Onyx DES compared with Resolute DES. Continued evolution of stent design can improve angiographic outcomes in complex lesions, even in the current era of next-generation DES.

KEYWORDS
drug eluting stents, late lumen loss, percutaneous coronary intervention, zotarolimus

1 | INTRODUCTION

Drug-eluting stents (DES) continue to evolve with the aim to improve procedural success and further reduce the risk of adverse events. This has led to the use of DES in increasingly complex patient and lesion

Trial registration: ClinicalTrials.gov, NCT02419521

subsets, which may be associated with challenging stent delivery [1–4]. Although device success is around 97% with current-generation DES, improving device deliverability and conformability are important to ensure continued high procedural success, which also influences long-term patient outcomes. Moreover, enhanced radiopacity is important for accurate placement of stents within a lesion, especially for bifurcated or heavily calcified lesions and overweight patients. Stent implantation also alters local vascular geometry and may cause vascular injury, resulting in changes in wall shear stress dependent on stent design, and can mediate cellular proliferation and neointimal hyperplasia [5]. Furthermore, while target lesion revascularization (TLR) with current generation DES is uncommon, clinical success is still limited by the development of in-stent restenosis, particularly in patients with significant anatomic complexity [6]. Thinner stent struts might further reduce neointimal hyperplasia and enhance post-DES outcomes. In addition, reducing stent strut thickness may help address the need for improved deliverability.

Importantly, such design iteration could be unfavorable by reducing radiopacity and compromising radial strength. Reduced radiopacity may increase geographic miss, and lack of radial strength can lead to recoil and underexpansion, both of which may result in adverse patient outcomes, including increased late luminal loss, repeat revascularization, and stent thrombosis. The Resolute (R-) Onyx DES (Medtronic, Santa Rosa, CA), an iteration of the Resolute DES family [7], is composed of a composite wire material with a platinum-iridium inner core, and an outer shell of the same cobalt chromium alloy as the predecessor Resolute Integrity and Resolute DES, but with a swaged shape and thinner stent struts with sustained radial strength (Figure 1). Zotarolimus dose density and polymer are identical between the R-Onyx, Resolute Integrity, and Resolute DES; however, due to modified stent geometry, the overall drug load is 10–25% lower with R-Onyx DES compared with both Resolute and Resolute Integrity, with the exception of the 2.75 mm size, in which the drug load is on average 10% higher.

We hypothesized that the characteristics of the R-Onyx DES would safely provide similar angiographic outcomes as predicate Resolute DES. Therefore, the RESOLUTE ONYX Core trial was a multicenter, prospective study designed to compare the novel R-Onyx DES to historical control data for the Resolute DES.

2 | MATERIALS AND METHODS

2.1 | Device description

The R-Onyx DES uses 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 the R-Onyx DES is the same cobalt chromium alloy as the Resolute DES. The dense inner core of R-Onyx DES is an alloy of 90% platinum and 10% iridium used to enhance radiopacity (Figure 1). The strut thickness of Resolute DES and R-Onyx DES are 91 and 81 μm, respectively, for the 2.25–4.0 mm diameter sizes. R-Onyx has a swaged shape and a larger strut width-to-thickness ratio than Resolute DES to maintain radial strength despite thinner struts. Specifically, the width of R-Onyx remains 91 μm but the thickness was reduced to 81 μm. Zotarolimus dose density and polymer are identical to the Resolute DES; however, due to modified stent geometry, the overall drug load is slightly reduced in most sizes of the R-Onyx DES.

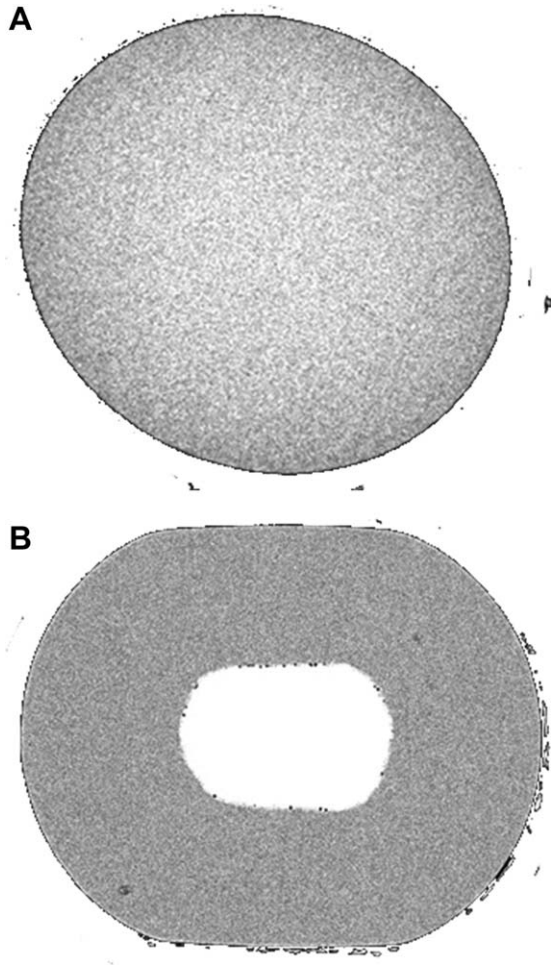


FIGURE 1 Cross-sectional view of (**A**) strut of Resolute DES (91 μm thickness) and (**B**) swaged strut of R-Onyx DES (81 μm thickness), not shown to scale. Both stents are manufactured using a continuous sinusoid wire. The Resolute DES consists of a solid cobalt alloy (shown in gray). The R-Onyx DES is manufactured from a composite wire, which has an outer shell and an inner core. The outer shell, which is in contact with the vessel, is of the identical cobalt chromium alloy used for the Resolute DES. The inner core wire material is a platinum-iridium alloy (shown in white) intended to enhance radiopacity. R, Resolute; DES, drug-eluting stent

2.2 | Clinical study design

The RESOLUTE ONYX Core (2.25–4.0 mm) Clinical Study was a single-arm, open-label, multicenter, noninferiority study involving 12 centers in the United States using propensity-adjusted results of the angiographic cohort of the RESOLUTE-US clinical trial as a historical control (Supporting Information Table S1) [8]. Eligible patients had evidence of ischemic heart disease, stable or unstable angina, and/or a positive

functional study demonstrating a need for treatment of up to 2 target lesions in separate vessels. Key exclusion criteria included evidence of an acute myocardial infarction (MI) within 72 hr before the intended procedure, planned percutaneous coronary intervention (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, patients received aspirin 75–325 mg daily indefinitely and a thienopyridine daily for at least 6 months and up to 12 months in patients who were not at high risk of bleeding [9]. All enrolled patients were required to undergo angiography at 8 months at the center where the index procedure was performed. Clinical follow-up was performed at 30 days, 6 months, and 8 months postintervention.

The institutional review board at each center approved the study protocol, and all patients provided written informed consent. A Data Monitoring Committee continuously monitored the ongoing safety and scientific validity of the study, and an independent Clinical Events Committee adjudicated clinical endpoints.

2.3 | Quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS)

QCA was performed after bolus infusion of intracoronary nitrates during the index procedure and at 8-month follow-up. A cohort of patients was enrolled in an IVUS sub-study, in which IVUS was performed at the end of the index procedure and at the time of the 8-month angiogram. An independent core laboratory performed the QCA and IVUS analyses (Beth Israel Deaconess Medical Center - Cardiovascular Imaging Core Laboratory, Boston, MA and Cardiovascular Research Foundation, NY, respectively).

2.4 | Study endpoints

The primary endpoint was in-stent late lumen loss at 8 months post-procedure. Secondary angiographic endpoints included binary angiographic restenosis, defined as $\geq$50% diameter stenosis (DS). Secondary clinical endpoints included acute device, lesion, and procedure success; cardiac death; target vessel MI; cardiac death and target vessel MI combined; TLR; target lesion failure (TLF); stent thrombosis; and major adverse cardiac events (MACE; defined as death, Q-wave and non-Q-wave MI, emergency coronary bypass surgery, or clinically driven repeat TLR). Additional endpoints in the IVUS subgroup included the rate of incomplete stent apposition (categorized as persistent or late), neointimal hyperplastic volume, and percent volume obstruction.

2.5 | Statistical analyses

The primary endpoint of in-stent late lumen loss at 8 months post-procedure was compared to the angiographic cohort of the single-arm RESOLUTE US Clinical Trial using a non-inferiority margin of 0.20 mm adjusting for propensity score quintile. A total sample size of 75 patients (60 evaluable patients assuming an 80% angiographic follow-up rate) was calculated to yield >80% power to detect noninferiority using a 2-sample *t* test with a 1-sided significance level of 0.05, assuming a true equivalence of the means between the 2 groups and a relatively smaller standard deviation of 0.45 mm for R-Onyx DES. The propensity score method was used to adjust for differences in baseline characteristics between the cohorts since patients in the two cohorts were not directly randomized. Propensity scores were calculated using the following covariates: lesion length, baseline reference vessel diameter (RVD), age, sex, diabetes, history of MI, and Canadian Cardiovascular Society angina class. If non-inferiority of in-stent late lumen loss was demonstrated and a numerically smaller in-stent late lumen loss with R-Onyx DES was observed, then a superiority analysis was performed using propensity score adjustment. An independent statistician who was blinded to the study outcomes performed the propensity score analysis and submitted propensity score calculations to the Food and Drug Administration for review and approval prior to any data analysis.

Categorical variables are expressed as counts and percentages and continuous variables are presented as mean $\pm$ standard deviation. All analyses were performed using SAS for Windows, version 9.1 or higher (SAS, Cary, NC).

3 | RESULTS

3.1 | Patient characteristics

A total of 75 patients with 85 lesions were enrolled and underwent stent placement in 1 or more lesions. Patient flow is illustrated in Figure 2, and baseline demographics and clinical characteristics are shown in Table 1 and Supporting Information Table S2. The average patient age was 66.1 $\pm$ 9.4 years, 73.3% of patients were male, and 32.0% had diabetes mellitus. Furthermore, 40% of patients had undergone prior PCI. Procedural and lesion characteristics are presented in Table 2. The mean lesion length was 14.28 $\pm$ 6.68 mm, the mean RVD was 2.57 $\pm$ 0.48 mm, and 85.9% of the lesions were American College of Cardiology/American Heart Association class B2 or C. Vascular access was performed by the radial approach in the majority of cases (61.3%). Per-protocol, pre-dilatation was performed on all lesions; post-dilatation was performed in 51.1% of cases. Device and lesion success rates were both 100%.

3.2 | Angiographic outcomes

The primary endpoint, in-stent late lumen loss at 8 months, was 0.24 $\pm$ 0.39 mm for R-Onyx DES compared with 0.36 $\pm$ 0.52 mm for the historical Resolute DES control (upper limit of the propensity score adjusted one-sided 95% confidence interval of the mean difference = $-$0.02 mm, $P < 0.001$ for noninferiority and $P = 0.029$ for superiority; Figure 3). Late luminal loss stratified by propensity score quintile is shown in Supporting Information Table S3. Angiographic in-stent binary restenosis occurred in 4 patients (5.5%) and in-segment binary restenosis occurred in 6 patients (8.2%). Other angiographic endpoints are shown in Table 3. In-stent late lumen loss was 0.29 $\pm$ 0.48 among diabetics compared with 0.21 $\pm$ 0.34 among nondiabetics ($P = 0.48$).

3.3 | IVUS cohort

At 8 months, incomplete stent apposition was present in 2 of the 20 evaluable lesions in the IVUS cohort (10%). In both of these lesions,

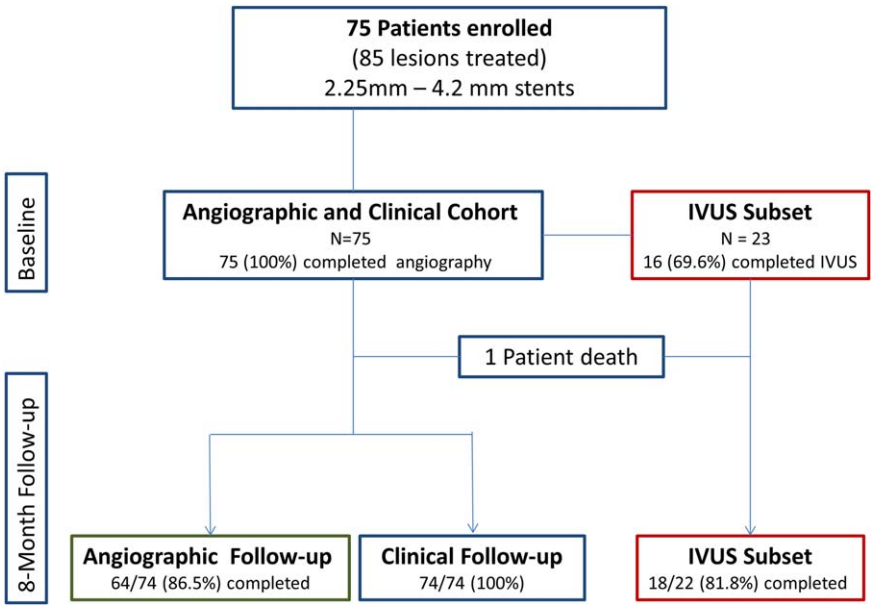


FIGURE 2 **Patient disposition.** Baseline enrollment and evaluable patients at 8 months for all patients, the angiographic cohort, and the IVUS subset [Color figure can be viewed at wileyonlinelibrary.com]

the incomplete apposition was present acutely (i.e., both were cases of persistent incomplete stent apposition). There were no cases of late acquired incomplete stent apposition. Neointimal hyperplastic volume was 9.88 ± 9.38 mm^3 and percent volume obstruction was $6.88 \pm 8.00\%$ (Table 3).

3.4 | Clinical outcomes

Clinical outcomes are presented in Table 4. At 8-month follow-up, the rate of TLF was 6.7% (5 patients; Figure 4). Clinically driven TLR occurred in 3 patients (4%), target vessel MI in 2 patients (2.7%; both attributed to peri-procedural MIs that occurred at the index procedure), and there were no cardiac deaths. There was one episode of stent thrombosis, which occurred on the day of index procedure.

TABLE 1 Baseline demographics and clinical characteristics of the study population

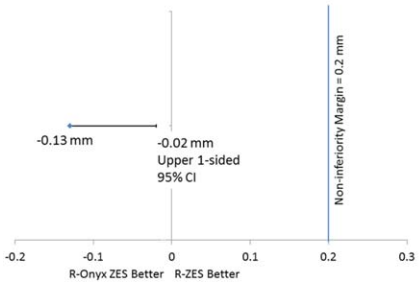
	N = 75
Age (years), mean ± SD	66.1 ± 9.4
Male sex	73.3% (55/75)
BMI (kg/m^2)	31.3 ± 5.4
Diabetes mellitus	32.0% (24/75)
Hyperlipidemia	85.3% (64/75)
Hypertension	73.3% (55/75)
Previous MI	23.0% (17/74)
Previous PCI	40.0% (30/75)
Stable angina	46.7% (35/75)
Unstable angina	37.3% (28/75)
History of stroke or TIA	14.9% (11/74)
Current smoker	16.0% (12/75)

Values are mean ± SD or (%).
Abbreviations: BMI, body mass index; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

TABLE 2 Procedural and lesion characteristics of the study population

	N = 75 patients (*N* = 85 lesions)
Vessel location (per patient)	
Left anterior descending	49.3% (37/75)
Left circumflex artery	22.7% (17/75)
Right coronary artery	38.7% (29/75)
Left main artery	1.3% (1/75)
Modified ACC/AHA lesion class	
A	1.2% (1/85)
B1	12.9% (11/85)
B2	42.4% (36/85)
C	43.5% (37/85)
Lesion length	14.28 ± 6.68
RVD	2.57 ± 0.48
Minimum lumen diameter	0.95 ± 0.32
Mean % stenosis preprocedure	62.98 ± 10.75
Lesion success[a]	100.0% (85/85)
Device success[b]	100.0% (85/85)
Procedure success[c]	96.0% (72/75)

Values are mean ± SD or % (m/n).
Abbreviation: ACC/AHA, American College of Cardiology/American Heart Association.
[a]<50% residual stenosis of the target lesion using any percutaneous method.
[b]<50% residual stenosis of the target lesion using only the assigned device.
[c]<50% residual stenosis of the target lesion and no in-hospital major adverse cardiovascular events.



R-Onyx ZES (N=75 Patients N=85 Lesions)	Historical Control R-ZES (N=100 Patients N=104 Lesions)	Difference [Upper 1-sided 95%CI]	P-value (non inferiority) (superiority)
0.24±0.39 mm	0.36±0.52 mm	-0.13 [-0.02]	<0.001 0.029

FIGURE 3 **Primary endpoint of propensity score adjusted in-stent late lumen loss at 8 months.** The R-Onyx DES met the criteria for non-inferiority and superiority compared with the Resolute DES. R, Resolute; DES, drug-eluting stent [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

In this prospective clinical study of the R-Onyx DES, the R-Onyx DES demonstrated noninferiority and superiority for 8-month in-stent late lumen loss compared with the historical control Resolute DES. This low late loss was reflected clinically in low rates of TLF and clinically driven TLR. These findings support the hypothesis that specific characteristics of the R-Onyx DES stent, including thinner struts, greater radiopacity, modified strut shape, and identical drug density but generally lower overall drug load compared with the predicate Resolute DES, may have contributed to superior angiographic outcomes with 100% device and lesion success rates in this cohort of patients with complex lesion anatomy according to ACC/AHA lesion scores.

TABLE 3 Angiographic and IVUS measurements at 8 months follow-up

Angiographic measurements	*N* = 75
RVD (mm)	2.53 ± 0.44
Minimum lumen diameter (mm)	
In-stent	2.13 ± 0.44
In-segment	1.89 ± 0.49
DS, % of lumen diameter	
In-stent	15.70 ± 16.65
In-segment	25.50 ± 14.26
Binary restenosis	
In-stent	5.5% (4/73)
In-segment	8.2% (6/73)
Late loss (mm)	
In-stent	0.24 ± 0.39
In-segment	0.15 ± 0.38
IVUS measurements	***N* = 20 lesions**
Late acquired incomplete apposition	0 (0/20)
Neointimal hyperplastic volume (mm^3)	9.88 ± 9.38 (*n* = 17)
Percent volume obstruction	6.88 ± 8.00 (*n* = 17)

Values are mean±SD or % (m/n).
Abbreviation: IVUS, intravascular ultrasound.

Several factors may have resulted in the superior in-stent late lumen loss with the R-Onyx DES. Randomized trials of bare metal stents have demonstrated that for stents with similar design, the risk for restenosis is dependent on strut thickness [10]. The R-Onyx DES has identical drug dose density and polymer coating composition as the Resolute DES and Resolute Integrity, but with slightly less total drug load in most sizes. The results of the current study support the hypothesis that continued reduction in strut thickness can improve late lumen loss when radial strength is preserved, even when compared with current generation DES. Furthermore, the results confirm that any differences in total drug load with R-Onyx DES did not negatively affect angiographic outcomes. Strut shape may also affect endothelialization, neointimal hyperplasia, and possibly stent thrombosis by influencing endothelial shear stress (**6**). The R-Onyx stent has a "swaged" shape compared with Resolute DES (Figure 1). Further study is required to determine whether the swaged shape of the R-Onyx strut favorably influences outcomes beyond acute deliverability.

The rates of TLF and clinically driven TLR at 8-month follow-up for R-Onyx DES were 6.7% (5 events) and 4% (3 events), respectively.

TABLE 4 Clinical outcomes at 8-month follow-up

Endpoint	*N* = 75
TLF	6.7% (5)
Target vessel failure	12.0% (9)
MACEs	9.3% (7)
Cardiac death or target vessel MI	2.7% (2)
Cardiac death	0.0% (0)
Noncardiac death	1.3% (1)
Clinically driven TLR	4.0% (3)
Acute stent thrombosis (0–24 hr)	1.3% (1)
Subacute or late stent thrombosis	0.0% (0)

Values are % (*n*).
Abbreviation: MI, myocardial infarction.

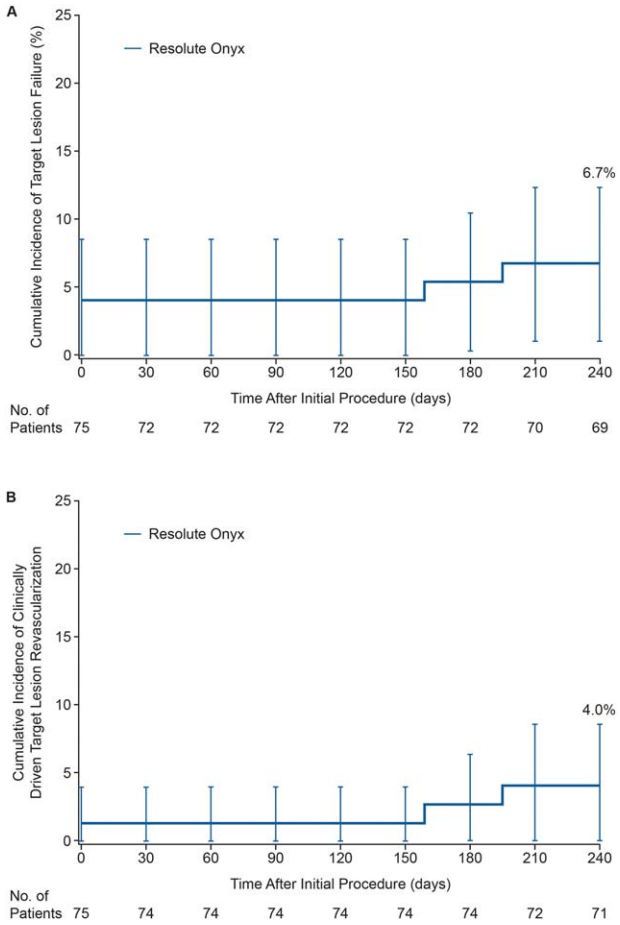


FIGURE 4 Kaplan-Meier curves for (A) TLF, and (B) clinically driven TLR [Color figure can be viewed at wileyonlinelibrary.com]

These rates compare favorably with those observed at 9-month follow-up in the angiographic sub-study of the RESOLUTE-US clinical trial (11.2% and 8.2% for TLF and clinically driven TLR, respectively). This is despite the greater anatomic complexity enrolled in the current study, in which 86% of the target lesions were classified as ACC/AHA type B2/C, compared with 75% of the target lesions in the RESOLUTE-US clinical trial. While such comparisons are underpowered and unadjusted, the relative rates of the clinical outcomes are qualitatively consistent with the angiographic outcomes demonstrated in the current study. The enhanced radiopacity of the R-Onyx stent might have also contributed to the low clinical event rates that were observed, since geographic miss has been associated with increased MACEs, including target vessel revascularization [11], although this is speculative. Moreover, TLF rates for R-Onyx were also similar to that of other DES with similar radiopacity [12]. Given the acute performance characteristics and the observed late loss of the R-Onyx DES, the findings of the current study indirectly support the incremental clinical utility of the R-Onyx over the predicate Resolute DES, particularly in the setting of complex lesion anatomy. Further, larger studies are required to confirm that the angiographic outcomes associated with R-Onyx DES translate into improved longer-term, stent-oriented clinical outcomes, and to compare the clinical outcomes with the various newest generations of thin-strutted, visible DES.

4.1 | Limitations

The RESOLUTE ONYX Core trial was not randomized. However, baseline differences between R-Onyx DES and the historical control were adjusted using the propensity score method, incorporating the known predictors of late lumen loss. Resolute DES was chosen as the historical control for this trial instead of R-Integrity DES, as late lumen loss measurements were available for Resolute DES through the Resolute-US trial. R-Integrity DES and Resolute DES have the same drug density and there are no significant differences in stent geometry or drug distribution. Superiority testing was a secondary analysis only if noninferiority was achieved. The study had a small sample size and was not powered for individual clinical outcomes.

5 | CONCLUSIONS

In-stent late lumen loss is non-inferior, and appears to be superior, with the thin-strut novel composite wire Resolute Onyx DES compared with Resolute DES. Continued evolution of stent design can improve angiographic outcomes, even in the current era of next-generation DES.

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CONFLICT OF INTEREST

Dr. Price reports consulting honoraria from AstraZeneca, ACIST Medical, Boston Scientific, Medtronic, St. Jude Medical, and The Medicines Company; and Speaker's fees from AstraZeneca, Abbott Vascular, Medtronic, St. Jude Medical and The Medicines Company. Dr. Haldis is a speaker for Astra Zeneca. Dr. Popma Almonacid receives institutional grants from Medtronic, Boston Scientific, and Abbott Vascular. Dr. Maehara is a consultant for Boston Scientific and receives institutional research grants from Boston Scientific and St Jude Medical. Dr. Mehran receives research grants to her institution from AstraZeneca, The Medicines Company, Bristol Myer Squibb, Bayer/Janssen J+J, Abbott Vascular, and Claret. Ms. Dauler and Mr. Peng are employees of Medtronic.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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