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Clinical and Angiographic Results With the Next-Generation Resolute Stent System

A Prospective, Multicenter, First-in-Human Trial

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Objectives The RESOLUTE trial examined the safety and efficacy of a next-generation zotarolimus-eluting coronary stent, Resolute (Medtronic CardioVascular Inc., Santa Rosa, California).

Background Revascularization benefits associated with current drug-eluting stents are often diminished in the presence of complex coronary lesions and in certain patient cohorts. Resolute uses a new proprietary polymer coating that extends the duration of drug delivery to match the longer healing duration often experienced in more complex cases.

Methods The RESOLUTE trial was a prospective, nonrandomized, multicenter study of the Resolute stent in 139 patients with de novo coronary lesions with reference vessel diameters ≥2.5 and ≤3.5 mm and lesion length ≥14 and ≤27 mm. The primary end point was 9-month in-stent late lumen loss by quantitative coronary angiography. Secondary end points included major adverse cardiac events (MACE) at 30 days, 6, 9, and 12 months; acute device, lesion, and procedure success; and 9-month target vessel failure (TVF), target lesion revascularization (TLR), stent thrombosis, neointimal hyperplastic (NIH) volume, and percent NIH volume obstruction.

Results The 9-month in-stent late lumen loss was 0.22 ± 0.27 mm. Cumulative MACE were 4.3%, 4.3%, 7.2%, and 8.7% at 30 days, 6, 9, and 12 months, respectively. Acute lesion, procedure, and device success rates were 100.0%, 95.7%, and 99.3%, respectively. At 9 months, TLR was 0.0%, TVF was 6.5%, stent thrombosis was 0.0%, NIH volume was 6.55 ± 7.83 mm^3, and percent NIH volume obstruction was 3.73 ± 4.05%.

Conclusions In this feasibility study, the Resolute stent demonstrated low in-stent late lumen loss, minimal neointimal hyperplastic ingrowth, low TLR, no stent thrombosis, and acceptable TVF and MACE. (The RESOLUTE Clinical Trial; NCT00248079) (J Am Coll Cardiol Intv 2009;2:977–85) © 2009 by the American College of Cardiology Foundation

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Drug-eluting stents (DES) have significantly reduced the rates of clinical and angiographic restenosis compared with bare-metal stents (BMS) in patients undergoing percutaneous coronary interventions for symptomatic coronary artery disease (1–3). However, the revascularization benefits with DES are often diminished in the presence of high-risk lesions and in certain patient cohorts, such as patients with diabetes (4), patients with diffuse or multivessel disease, patients with chronic renal failure (5), patients with left main disease or ostial disease, or patients who present with chronic total occlusions (6).

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Abbreviations and Acronyms

ARC = Academic Research Consortium
BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
IVUS = intravascular ultrasound
LIA = late incomplete apposition
MACE = major adverse cardiac events
MI = myocardial infarction
MLD = minimal lumen diameter
NIH = neointimal hyperplasia
QCA = quantitative coronary angiography
TLR = target lesion revascularization
TVF = target vessel failure
TVR = target vessel revascularization
ZES = zotarolimus-eluting stent(s)

The Resolute (Medtronic CardioVascular, Inc., Santa Rosa, California) is a next-generation zotarolimus-eluting stent (ZES) system designed to match the efficacy and safety of the Endeavor stent (Medtronic) while improving clinical outcomes in more complex lesion subsets. The Resolute stent consists of the antiproliferative agent zotarolimus and the low-profile, thin-strut Driver (Medtronic) BMS platform, like the Endeavor stent. However, instead of the phosphorylcholine coating of the Endeavor stent, the Resolute stent employs the BioLinx tri-polymer coating to extend drug elution to match the potentially delayed arterial healing times associated with treatment of more complex lesions and to combat the greater sustained stimulus to the proliferative response in these more difficult patients (7).

The objectives of this first-in-human, prospective, nonrandomized, multicenter study of the Resolute stent system were to: 1) assess the early feasibility and safety of implanting the Resolute stent system in human coronary arteries on the basis of acute success rates and incidence of major adverse cardiac events (MACE) at 30 days; and 2) assess the medium-term safety and efficacy of the Resolute stent system on the basis of in-segment late lumen loss at 9 months and the cumulative incidence of MACE at 6, 9, and 12 months.

Methods

Study overview and patient population. The RESOLUTE trial was a prospective, multicenter, nonrandomized, single-arm study of the use of the Resolute stent to treat 139 consecutive patients with symptomatic ischemic heart disease attributable to native coronary artery stenosis amenable to treatment by percutaneous stenting. Of the 139 consecutive patients enrolled, the first 30 consented to a 4-month follow-up evaluation by quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) measurements, and the next 100 consented to a 9-month follow-up evaluation by QCA and IVUS. Nine additional patients were enrolled as part of a pharmacokinetic substudy and were not required to undergo baseline IVUS or 4-month or 9-month angiographic and IVUS evaluation (Fig. 1). The results of the 4-month, 30-patient cohort were reported previously (8).

The study was conducted according to the Declaration of Helsinki, and local ethics committees approved the study protocol. All patients provided signed, written consent. Individuals eligible for enrollment were consecutive patients 18 years of age or older with symptomatic ischemic heart disease due to de novo stenotic lesions (>50% angiographic diameter stenosis by visual estimate) in native coronary arteries. The target lesion had to be a single de novo lesion in a native coronary artery with a reference vessel diameter ≥2.5 and ≤3.5 mm, a lesion length ≥14 and ≤27 mm, and a Thrombolysis In Myocardial Infarction flow grade ≥2. Patients were excluded if they experienced a recent (<72 h) myocardial infarction (MI), underwent prior stent placement within the target vessel or any other vessel within 30 days before the index procedure, or had any general contraindication to the revascularization procedure and routine dual antiplatelet therapies. Principal angiographic exclusion criteria were: left main or ostial target lesion; severe calcification by angiography; bifurcation lesion; location of the target lesion at a 45° bend; significant stenosis >50% proximal or distal to the target lesion that might require revascularization or impede runoff; involvement of a side branch >2.0 mm in diameter; or left ventricular ejection fraction <30%.

Device description. The Resolute stent is similar to the Endeavor stent except that the biomimetic phosphorylcholine drug carrier of the Endeavor stent is replaced with the BioLinx polymer system. The BioLinx polymer system (7) consists of a blend of 3 different polymers: 1) the hydrophobic C10 polymer, which aids in the control of drug release; 2) the hydrophilic C19 polymer, which supports biocompatibility; and 3) polyvinyl pyrrolidinone, which increases the initial drug burst and enhances the elution rate (9). Like the phosphorylcholine coating of the Endeavor stent, the new polymer coating of the Resolute is biocompatible. The hydrophilic surface mimics the body's biological chemistry, thereby reducing the risk of an inflammatory response.

Autopsy examinations have identified polymer hypersensitivity as 1 possible risk factor contributing to stent-thrombosis deaths associated with first-generation sirolimus- and paclitaxel-eluting

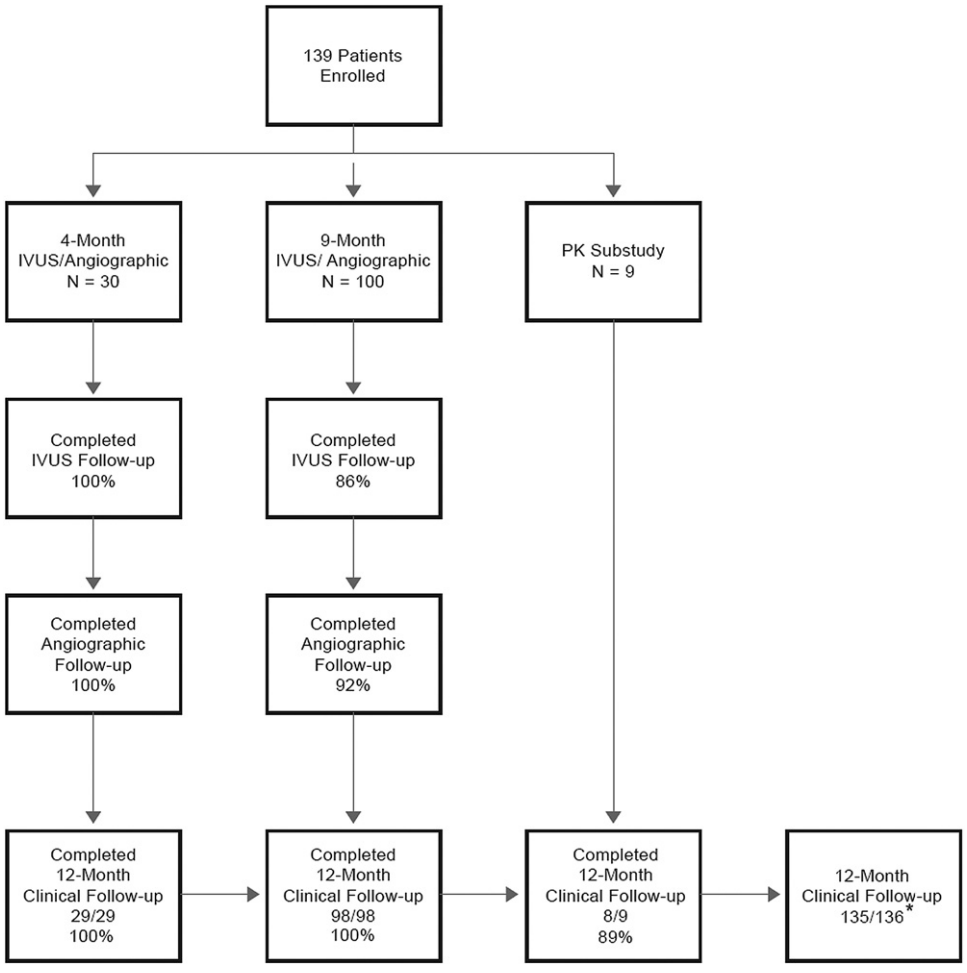

Figure 1. Patient Disposition

Of the 139 consecutive patients enrolled in the RESOLUTE trial, the first 30 consented to a 4-month follow-up with quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS), and the next 100 consented to a 9-month follow-up with QCA and IVUS. Nine additional patients were enrolled as part of a pharmacokinetic (PK) substudy and were not required to undergo baseline IVUS or 4- or 9-month angiographic and IVUS evaluation. A total of 135 patients completed 12-month clinical follow-up. *3 patients died, and 1 was lost to follow-up.

stents (10,11). In a study comparing the Resolute stent, including the new polymer coating, with the Driver BMS in porcine coronary arteries, there were no significant inflammatory differences between the cohorts at 28 days, and endothelialization in the presence of the BioLinx polymer was rapid and complete (12). In another study comparing the Endeavor stent and the Resolute stent in porcine coronary arteries, biocompatibility was similar out to 180 days (12).

The BioLinx coating of the Resolute stent enables finer control of the rate of drug elution. Although the zotarolimus dose is similar for the Endeavor stent and the Resolute stent, drug elution is slower with the Resolute stent, resulting in an extended duration of drug availability to the arterial tissue. In the porcine model, the Resolute stent elutes 85% of its zotarolimus content during the first 60 days after procedure, and the remainder of the drug is completely eluted by 180 days (Fig. 2) (12).

Interventional procedure and adjunctive drug therapies. Twelve sites in Australia and New Zealand participated in this study. Stents were deployed according to standard procedure. Heparin was administered to maintain an activated clotting time ≥250 s or between 200 and 250 s if a glycoprotein IIb/IIIa receptor inhibitor was administered. Patients received aspirin (at least 75 mg daily, within 24 h before the procedure and continued indefinitely after the procedure) and clopidogrel (≥300-mg loading dose within 24 h before the procedure and then 75 mg daily for a minimum of 6 months after the procedure). Pre-dilation was mandatory and undertaken with a balloon length

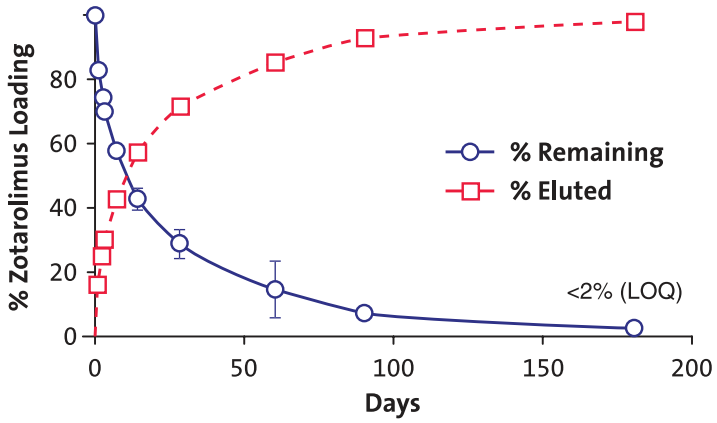

Figure 2. The In Vivo Elution of the Resolute Zotarolimus-Eluting Stent System

The Resolute stent elutes >85% of zotarolimus during the first 60 days after procedure, and the remainder of the drug is completely eluted at 180 days. Reprinted with permission from Meredith et al. (8). LOQ = level of quantification.

shorter than the stent. Post-dilation, if required, was also performed with a balloon length less than or equal that of the stent. Resolute stents were available in diameters ranging from 2.5 to 3.5 mm and in lengths from 8 to 30 mm.

Data management and core laboratories. Conduct of the trial was monitored by a contract research organization (Pacific Clinical Research Group, New South Wales, Australia). All data were submitted to a central data coordinating facility (Cardiovascular Data Analysis Center, Harvard Clinical Research Institute, Boston, Massachusetts). All events were adjudicated by an independent clinical events committee managed by the Harvard Clinical Research Institute.

Coronary angiograms performed at baseline and at 4- and 9-month follow-up were reviewed by an independent angiographic core laboratory (Brigham and Women's Angiographic Core Laboratory, Boston, Massachusetts). Standard image acquisition was performed with 2 or more angiographic projections of the stenosis before and after stent placement. Qualitative analysis was performed on the basis of the modified American College of Cardiology/American Heart Association classification (13). Quantitative angiographic analysis was performed on the basis of a validated automated edge detection algorithm (Medis CMS, Leiden, the Netherlands) (14). Frames were selected for analysis in the 2 "sharpest and tightest" views that minimized foreshortening and vessel overlap. The contrast-filled injection catheter was used as the calibration source. The IVUS images were also examined by an independent core laboratory (Cardiovascular Core Analysis Laboratory, Stanford University, Palo Alto, California) (15,16). For both coronary angiograms and IVUS images, quantitative analysis was performed to evaluate the in-stent region (bordered by the stent margins) as well as the in-segment region (in-stent region plus 5-mm margins proximal and distal to the stent).

Study end points and definitions. The primary efficacy end point, in-stent late lumen loss, was examined by QCA at the 9-month follow-up. Secondary angiographic and IVUS efficacy end points included in-segment late lumen loss at 9 months, angiographic binary restenosis (both in-stent and in-segment) at 9 months, and percent volume obstruction assessed by IVUS at 9 months. A tertiary analysis was also performed comparing the 9-month in-stent late lumen loss in the RESOLUTE trial with the historical ENDEAVOR II trial matched patient subset (patients who received the Endeavor ZES).

Late lumen loss was defined as the difference between the minimal lumen diameter (MLD) at the completion of the stenting procedure and the MLD measured at angiographic follow-up. Angiographic binary restenosis was defined as a stenosis ≥50% of the lumen diameter of the target lesion (determined by the angiographic core laboratory). Reference vessel diameter was defined as the average of the normal segments within 10 mm proximal and distal to the target lesion from 2 orthogonal views with QCA. Percent diameter stenosis was defined as: (1 − [MLD/reference vessel diameter] × 100), and acute gain was defined as the MLD immediately after the procedure minus the MLD before the procedure. Neointimal hyperplastic (NIH) area was computed as stent minus lumen area. Volumetric analysis was performed by means of Simpson's method for the entire stented segment. In detailed analysis, NIH growth was analyzed as NIH area/volume divided by the corresponding stent area/volume to adjust for the different stent sizes. The entire in-stent NIH growth was evaluated as percent NIH volume (i.e., NIH volume × 100/stent volume). The most severe luminal obstruction by NIH growth within the stent

segment was determined as the maximum of percent NIH area (i.e., NIH area × 100/stent area).

Secondary clinical safety and efficacy end points included MACE (defined as the composite of all-cause death, MI, and clinically driven target lesion revascularization [TLR]); the individual components of the composite end point in-hospital, at 30 days and at 6, 9, and 12 months; stent thrombosis (acute, <1 day; subacute, 1 to 30 days; and late, >30 days); clinically driven target vessel revascularization (TVR) at 9 months; and target vessel failure (TVF) (composite of cardiovascular death, MI, and clinically driven TVR) at 9 months.

Death was defined as the occurrence of death from any cause during the study period. Myocardial infarction was defined as a creatine kinase elevation ≥2 times above the upper limit of normal with any associated elevation in the myocardial band or the development of new pathologic Q waves in 2 contiguous electrocardiographic leads. Target lesion revascularization was defined as any percutaneous intervention or bypass surgery performed on the index target lesion at any time after the index procedure. Target vessel revascularization was defined as any percutaneous intervention or bypass surgery performed on the index target vessel at any time after the index procedure. Stent thrombosis was defined as an acute coronary syndrome with angiographic documentation of vessel occlusion or thrombus within or adjacent to a previously stented segment, consistent with the ENDEAVOR I to IV clinical studies (17–21); in the absence of angiography, stent thrombosis could be confirmed by acute MI in the distribution of the treated vessel or death resulting from cardiac causes within 30 days. All stent thrombosis events were also adjudicated according to Academic Research Consortium (ARC) criteria (22).

Acute lesion success was defined as achievement of a target lesion percent diameter stenosis <50% by any method; device success was defined as acute lesion success with only the Resolute stent; and procedure success was defined as device success without in-hospital MACE.

Statistical methods. The main objective of the RESOLUTE trial was to demonstrate the acute safety of the Resolute ZES and gather information on the mid- and long-term safety and efficacy of the device. Therefore the trial was designed to minimize the number of subjects exposed to the device while still providing enough information on safety and efficacy. A sample size of 139 subjects was deemed sufficient to provide reasonable confidence in the estimates of safety and efficacy generated by this study. All analyses were made on an intention-to-treat basis, defined as the set of 139 patients with qualifying stenosis in which treatment with the Resolute stent system was intended (i.e., all patients in whom a guidewire was used to initiate the procedure). Angiographic and IVUS data, collected at baseline and at 4- or 9-month follow-up, were analyzed on all RESOLUTE patients with technically successful paired data for the pairwise comparisons. Categorical variables were tested with contingency tables analyses (exact or chi-square approximations), and continuous variables were tested with unpaired Student *t* test or Wilcoxon rank sum test, depending on variable distribution. Comparisons between matched cohorts of the RESOLUTE and ENDEAVOR II studies were presented with differences (with 95% confidence intervals) and p values. All statistical tests were 2-sided, and a p value <0.05 was considered statistically significant.

Results

Patient characteristics. Baseline clinical characteristics for all 139 patients are reported in Table 1. The age, sex-distribution, and risk-factor profiles of the study patients were consistent with those of a population of patients presenting with ischemic symptoms due to a discrete de novo lesion in a single native coronary artery (23).

Procedural outcomes. Procedural and lesion characteristics are summarized in Table 2. Of the 139 patients enrolled, there were 140 lesions (in 1 patient, the treated lesion was later adjudicated by the angiographic core laboratory as being 2 lesions in the same vessel.). The mean lesion length was 15.61 ± 6.13 mm. The acute lesion success rate was 100.0% (140 of 140), the procedure success rate was 95.7% (133 of 139), and the device success rate was 99.3% (139 of 140).

Angiographic and IVUS outcomes. The 4- and 9-month QCA results are presented in Table 3. At 4 months, the in-stent late lumen loss was 0.12 ± 0.26 mm, the in-segment late lumen loss was 0.05 ± 0.20 mm, and both the in-stent and -segment binary angiographic restenosis were 0.0%.

At 9 months, the in-stent late lumen loss was 0.22 ± 0.27 mm, and in-segment late lumen loss was 0.12 ± 0.27 mm. There were no significant edge effects. At 9 months, in-stent binary restenosis was 1.0%, and in-segment binary restenosis was 2.1%. Compared with the matched cohort from the ENDEAVOR II study (18), the 9-month in-stent late lumen loss with the Resolute stent was significantly less than that seen with the Endeavor stent (0.62 ± 0.46 mm) (difference = −0.39 mm [95% confidence interval: −0.49 to −0.29], p < 0.001).

Table 1. Patient Characteristics (n = 139)

Age (yrs)	60.7 ± 10.0
Male	76.3
Diabetes mellitus	17.3
Hyperlipidemia	94.2
History of smoking	70.5
Prior myocardial infarction	46.4
Prior percutaneous coronary intervention	18.7

Values are mean ± SD or %.

Table 2. Procedural and Lesion Characteristics

Characteristic	139 Patients 140 Lesions
Target artery	
Left anterior descending	34.3
Left circumflex	25.7
Right coronary artery	40.0
ACC/AHA class	
A	1.4
B1	17.1
B2	49.3
C	32.1
Length of lesion (mm)	15.61 ± 6.13
Pre-procedure reference vessel diameter (mm)	2.81 ± 0.40
Minimal lumen diameter (mm)	0.83 ± 0.34
Acute gain (mm) [in-stent]	1.93 ± 0.45
Acute gain (mm) [in-segment]	1.53 ± 0.51
Diameter stenosis [pre]	70.30 ± 11.37
Diameter stenosis [post]	3.36 ± 8.54
Device- success*	99.3
Procedure success†	95.7
Lesion success‡	100.0

Values are % or mean ± SD. *Device success was defined as <50% residual in-segment final stenosis with only the Resolute stent. †Procedure success was defined as <50% residual in-segment final stenosis with the Resolute stent without a major adverse cardiac event in-hospital. ‡Lesion success was defined as <50% residual in-segment final stenosis.
ACC = American College of Cardiology; AHA = American Heart Association.

The 4- and 9-month IVUS results are presented in Table 4. The mean external elastic membrane volume after procedure at 4 and 9 months were similar, indicating that there was no significant positive or negative remodeling overall. Moreover, the stent volume was similar, indicating no stent recoil. The NIH volume was 0.55 ± 1.38 mm^3 after procedure, 3.72 ± 4.21 mm^3 at 4 months, and 6.55 ± 7.83 mm^3 at 9 months. The percent NIH volume obstruction was 2.23 ± 2.43% at 4 months and 3.73 ± 4.05% at 9 months. Six late incomplete appositions (LIA) (involving 1 or more stent struts) were identified, with 2 involving the edge of the stent and 4 involving the body of the stent. One LIA was associated with positive vessel remodeling (external elastic membrane volume: after procedure = 231.7 mm^3; at follow-up = 258.9 mm^3; percent difference = 11.7%), whereas the other 5 were modest.

Clinical outcomes. Table 5 summarizes the cumulative composite and component MACE at 30 days, 6, 9, and 12 months. Figure 3 presents the cumulative incidence of TLR and cardiac death and MI through 12 months and dual antiplatelet therapy at 30 days, 6, 9, and 12 months. The 30-day incidence of MACE was 4.3%, which consisted entirely of 6 cases of periprocedural non–Q-wave MI. Of these 6 events, 5 occurred at the time of the index procedure and were due to factors that occurred before study stent implantation. All 6 cases of periprocedural non–Q-wave MI resolved uneventfully.

From 30 days to 9 months, 4 additional events occurred—1 cardiac death, 1 noncardiac death, and 2 iatrogenic non–Q wave MIs precipitated by protocol mandated follow-up—resulting in a 9-month cumulative MACE of 7.2% (10 of 139).

From 9 months to 12 months there was 1 additional noncardiac death due to cancer and 1 TLR, resulting in a 12-month cumulative incidence of MACE of 8.7% (12 of 138). The cumulative incidence of TVF at 9 months was 6.5%; at 12 months it was 7.2%. According to protocol-specified definitions, there were no cases of stent thrombosis through 12 months; however, there was 1 case of possible stent thrombosis with ARC criteria (22).

Discussion

In this first-in-human feasibility study, RESOLUTE, we report the safety and efficacy of the Resolute stent, which consists of the low-profile, thin-strut Driver BMS platform, the antiproliferative agent zotarolimus, and the new proprietary biomimetic BioLinx polymer system. Overall, the Resolute stent demonstrated a safety profile comparable to that of the Endeavor stent (17–20). In the RESOLUTE trial, patient, vessel, and lesion characteristics were similar to previous first-in-human DES studies (17,24–27), although the average lesion length was longer (15.61 ± 6.13 mm) and there were more B2/C lesions (81%) in the present study. Despite the longer lesion length and complexity, the Res-

Table 3. Angiographic Results at 4 and 9 Months

Variable	In-Stent	In-Segment
Minimal lumen diameter (mm)		
After procedure (n = 140)	2.76 ± 0.39	2.36 ± 0.43
At 4 months (n = 30)	2.68 ± 0.39	2.38 ± 0.40
At 9 months (n = 96)	2.51 ± 0.48	2.21 ± 0.45
Diameter stenosis (% of lumen diameter)		
After procedure (n = 140)	3.36 ± 8.54	17.80 ± 8.24
At 4 months (n = 30)	7.18 ± 7.86	17.74 ± 7.57
At 9 months (n = 96)	10.13 ± 12.63	21.08 ± 10.62
Late lumen loss (mm)		
At 4 months (n = 30)	0.12 ± 0.26	0.05 ± 0.20
At 9 months (n = 96)	0.22 ± 0.27	0.12 ± 0.27
Late loss index*		
At 4 months (n = 30)	0.06 ± 0.17	0.01 ± 0.18
At 9 months (n = 96)	0.12 ± 0.16	0.08 ± 0.21
Binary restenosis (%)†		
At 4 months (n = 30)	0.0	0.0
At 9 months (n = 96)	1.0	2.1

Values are mean ± SD or n (number of lesions for each measure). *Late loss index was defined as the ratio of late loss to acute gain. †Binary restenosis was defined as >50% diameter stenosis.

Table 4. Intravascular Ultrasound Results at 4 and 9 Months

Variable	After Procedure (n = 130)	4 Months (n = 30)	9 Months (n = 100)
EEM volume, mm^3	334.58 ± 111.34 (94)	337.46 ± 88.12 (22)	332.50 ± 114.28 (68)
Stent volume, mm^3	169.21 ± 57.44 (116)	167.74 ± 44.76 (24)	169.22 ± 57.43 (88)
Neointimal hyperplastic volume, mm^3	N/A	3.72 ± 4.21 (24)	6.55 ± 7.83 (88)
Volume obstruction, %	N/A	2.23 ± 2.43 (24)	3.73 ± 4.05 (88)

Values are mean ± SD (n [patients with available data for each parameter]).
EEM = external elastic membrane.

olute achieved high acute lesion, procedure, and device success rates. Cumulative MACE rates were low and largely driven by an unexpectedly high number of procedural events unrelated to the study stent, including 1 protocol violation (elevated cardiac enzymes at enrollment), 4 sidebranch occlusion events at the time of balloon pre-dilation, and 2 iatrogenic events related to the IVUS 9-month follow-up. There was a low rate of TVF, no protocol-defined or ARC definite or probable early or late stent thromboses, and only 1 patient required a TLR through 12 months.

On the basis of the study's QCA and IVUS results, the Resolute stent also showed promising efficacy. The primary end point of this trial, the in-stent late lumen loss at 9 months, was 0.22 ± 0.27 mm, which was significantly less than that seen in the matched Endeavor stent cohort of the ENDEAVOR II study (18). The low level of late loss with the Resolute stent translated into a modest level of binary in-stent restenosis (1.0%) and binary in-segment restenosis (2.1%). Mauri et al (28) previously described the curvilinear relationship between late lumen loss and angiographic binary restenosis and predicted a restenosis rate in a population with a mean reference vessel diameter of 2.79 mm and a mean post-procedure MLD of 2.68 mm. In our study, the mean pre-procedure reference vessel diameter was 2.81 mm and the mean post-procedure MLD was 2.76 mm. Extrapolating from this relationship, a late lumen loss of 0.22 mm would correlate with approximately 1.0% to 2.0% in-stent binary restenosis, which is indeed what we observed in this study. These data support the BioLinx design hypothesis that extending the duration of zotarolimus release results in lower late loss.

The 9-month IVUS results confirmed that the mean external elastic membrane volume was well-preserved, indicating there was no overt positive remodeling of the vessels overall. The stent volume was also well-conserved, indicating that there was little or no recoil of the stent. In addition, the NIH volume and percent NIH volume obstruction were quite low, consistent with the potent antiproliferative effect of zotarolimus. There were, however, 6 LIA noted at the

Table 5. Cumulative Composite of MACE at 30 Days, 6, 9, and 12 Months

Variable	30 Days n = 139 Patients n = 140 Lesions	6 Months n = 139 Patients n = 140 Lesions	9 Months n = 139 Patients n = 140 Lesions	12 Months n = 138 Patients* n = 139 Lesions
Any MACE	4.3 (6/139)	4.3 (6/139)	7.2 (10/139)	8.7 (12/138)
Death	0.0 (0/139)	0.0 (0/139)	1.4 (2/139)	2.2 (3/138)
Cardiac-related	0.0 (0/139)	0.0 (0/139)	0.7 (1/139)	0.7 (1/138)
Myocardial infarction	4.3 (6/139)	4.3 (6/139)	5.8 (8/139)	5.8 (8/138)
Q-wave	0.0 (0/139)	0.0 (0/139)	0.0 (0/139)	0.0 (0/138)
Non–Q-wave	4.3 (6/139)	4.3 (6/139)	5.8 (8/139)	5.8 (8/138)
Target lesion revascularization (lesion level)	0.0 (0/140)	0.0 (0/140)	0.0 (0/140)	0.7 (1/139)
CABG	0.0 (0/140)	0.0 (0/140)	0.0 (0/140)	0.0 (0/139)
PTCA	0.0 (0/140)	0.0 (0/140)	0.0 (0/140)	0.7 (1/139)
Target vessel revascularization	0.0 (0/139)	0.0 (0/139)	0.0 (0/139)	0.7 (1/138)
Target vessel failure	4.3 (6/139)	4.3 (6/139)	6.5 (9/139)	7.2 (10/138)
Stent thrombosis				
Protocol defined (lesion level)	0.0 (0/140)	0.0 (0/140)	0.0 (0/140)	0.0 (0/138)
ARC definite/probable	0.0 (0/140)	0.0 (0/140)	0.0 (0/140)	0.0 (0/138)
ARC all	0.0 (0/140)	0.0 (0/140)	0.7 (1/140)	0.7 (1/138)

Values are %. *One patient did not complete the 12-month follow-up visit.
ARC = Academic Research Consortium; CABG = coronary artery bypass grafting; MACE = major adverse cardiac events (defined as death, myocardial infarction, emergent cardiac surgery, or repeat revascularization of the target lesion); PTCA = percutaneous transluminal coronary angioplasty.

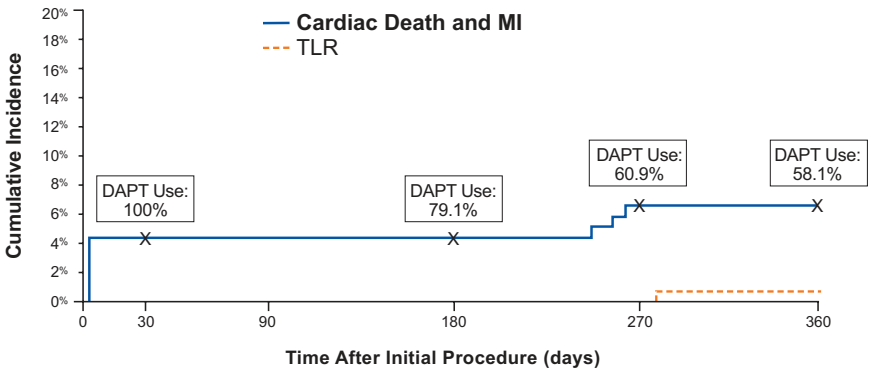

Figure 3. Cumulative Incidence of TLR and Cardiac Death and MI Through 12 Months and DAPT at 30 Days, 6, 9, and 12 Months

Kaplan-Meier graph depicting the cumulative incidence of cardiac death and myocardial infarction (MI) **(solid blue line)** and target lesion revascularization (TLR) **(dashed orange line)** to 12 months. Also presented is the percentage of patients receiving dual antiplatelet therapy (DAPT) (aspirin + clopidogrel or ticlopidine) at discrete time points (30, 180, 270, and 360 days).

9-month IVUS follow-up. Two were edge-related, and 4 were in the body of the stent. This is in contrast to the Endeavor I, II, and III trials (which included IVUS follow-up) where, in total, only 1 LIA was observed. This shows that the mean late loss and mean and SD of the late loss distribution seem to shift to the left. In doing so, one would expect to observe some degree of negative late loss and positive remodeling resulting in additional LIA by IVUS. Of the 6 observed LIA in the RESOLUTE trial, only 1 required a TLR (at 280 days). Although there have been several small studies that show a relationship between LIA and late stent thrombosis, it has not been conclusively demonstrated (29).

Conclusions

The results of the RESOLUTE feasibility study found the Resolute stent safe and effective, with high acute lesion, procedure, and device deployment success rates. Treatment of patients with symptomatic ischemic heart disease and single-vessel de novo lesions by means of the Resolute stent system resulted in sustained clinical effectiveness and very modest changes in vessel lumen dimensions up to 9 months and minimal late lumen loss. This translated into very low TLR, acceptable TVF and MACE rates, and no cases of protocol-defined or ARC definite or probable stent thrombosis. Three controlled studies (RESOLUTE US, RESOLUTE ALL COMERS, and RESOLUTE INTERNATIONAL) are currently underway to confirm the RESOLUTE study's results in more complex lesion cohorts.

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Key Words: coronary artery disease ■ drug-eluting stents ■ zotarolimus.

APPENDIX

For a list of the RESOLUTE stent trial investigators, please see the online version of this article.