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REVIEW

Resolute Integrity® drug-eluting stent: safety and efficacy for the treatment of coronary artery disease

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Abstract: The need to develop a local antirestenotic mechanism to prevent in-stent thrombosis has driven the development of new generation stents. The Resolute Integrity® stent is a zotarolimus-eluting system with a new BioLinx™ polymer that allows a slower drug elution. Recently available data has shown the clinical efficacy and safety of this stent in randomized and observational studies. The Resolute Integrity stent system has demonstrated noninferiority when compared with other stents and holds the promise to treat more complex coronary lesions.

Keywords: zotarolimus, BioLinx, coronary stenosis, stents, restensosis, stent thrombosis

Introduction

Angioplasty with stenting is recommended for patients who have a blockage in one or two coronary arteries. In the past, restenosis was the Achilles' heel for balloon angioplasty with bare metal stents, secondary to intimal hyperplasia and elastic recoil of the coronary artery.

The need to develop a local antirestenotic mechanism was raised after several unsuccessful trials of systemic antirestenosis therapies were tested in patients.[1,2]

The concept of a metallic stent covered with an antiproliferative drug started with the first generation, including sirolimus-eluting (CYPHER®; Cordis Corporation, Hialeah, FL, USA) and paclitaxel-eluting (Taxus™ Express²™; Boston Scientific, Natick, MA, USA) stents. Drug-eluting stent(s) (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.[3–5]

A concern with these first-generation stents has been the risk of late thrombosis, especially after discontinuation of dual antiplatelet therapy.[6] This problem may have been related to the permanent polymers coating the stent, that were used to help in the process of drug release; these polymers may also cause inflammation and hypersensitivity reactions, which can precipitate thrombosis.[7]

About 5% of DES patients require repeat procedures within a year, posing increasing risk among diabetic patients. The long-term safety of DES remains an important area of clinical investigation, particularly the avoidance of late stent thrombosis (ST).[8]

Second-generation DES include the zotarolimus-eluting stent (ZES) (Endeavor® [E-ZES]; Medtronic, Minneapolis, MN, USA) and everolimus-eluting stent (EES) (XIENCE V® [XV-EES]; Abbott Laboratories, Abbott Park, IL, USA), which are both coated with new polymers and drugs, and appear to have lower restenosis rates, better radial strength, and improved radioopacity.[9]

Video abstract

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A newer stent was recently released by Medtronic, with the name Resolute Integrity® zotarolimus-eluting coronary stent system (R-ZES). The R-ZES is a device/drug combination product, comprised of the following device components: the Integrity coronary stent and MicroTrac delivery systems and a formulation of zotarolimus in a polymer coating.[10]

In this review, we summarize the available basic and clinical evidence for this device.

Design and pharmacology of R-ZES and preclinical data

Platform

The R-ZES consists of a balloon-expandable intracoronary DES pre-mounted on the MicroTrac Over the Wire or rapid exchange stent delivery system. The stent is manufactured from a cobalt alloy and is formed from a single wire bent into a continuous sinusoid pattern and then laser fused back into it.[11]

Zotarolimus

Zotarolimus is a tetrazole-containing macrocyclic immunosuppressant. It is a semisynthetic derivative of rapamycin, and an analog of sirolimus (used in the first-generation DES); it, however, has a shorter in vivo half-life and a reduced potential for causing systemic immunosuppression.[12]

The molecular formula of zotarolimus is C52H79N5012, and its molecular weight is 966.2 Da.

The R-ZES contains 10 mcg of zotarolimus per millimeter of stent length, for all diameters, meaning that the total drug per stent is a function of stent length, irrespective of stent diameter.

The polymer system

BioLinx™ (Medtronic, Minneapolis, MN, USA) is a blend of three different polymers, ie, a hydrophobic C10 polymer, to control drug release; a biocompatible and hydrophilic C19 polymer; and polyvinyl pyrolidone, to allow an early burst of drug release.[13] The BioLinx polymer provides increased coating durability, improved biocompatibility, and extended drug elution, such that at least 85% of the zotarolimus is released within 60 days, with the remainder being released within 180 days.[14]

Preclinical data

The R-ZES has a cobalt–chromium stent backbone, BioLinx polymer, and the antirestenotic drug zotarolimus. The main difference between the R-ZES and its predecessor, the E-ZES, lies in this polymer, which has better drug-release kinetics. The E-ZES elutes the zotarolimus in 1 week, whereas the R-ZES takes 60 days to elute 85% of the zotarolimus and 180 days to elute it completely.

Therefore, one of the advantages of the BioLinx polymer is better control of the rate of drug elution, despite using a similar dose of zotarolimus to the E-ZES. Another advantage is its hydrophilic surface, which allows no adherence to activated monocytes, further supporting the noninflammatory nature of the tripolymer blend.[15,16] A study on inflammatory scores in swine showed equivalent biocompatibility between R-ZES compared with E-ZES.[17] Scanning electron microscope studies show endothelialization as early as 28 days and confluent endothelialization at 180 days after implantation.[18]

The R-ZES was found to be superior to the E-ZES and comparable with other limus-eluting stents in terms of antirestenotic efficacy.[19]

Clinical efficacy studies on the R-ZES

The safety and effectiveness of the R-ZES was established in the global RESOLUTE clinical trial program, which consisted of five clinical trials: RESOLUTE United States (US), RESOLUTE All-Comers, RESOLUTE International, RESOLUTE First in Man (FIM), and RESOLUTE Japan. The same product was used in all five trials – the R-ZES on rapid exchange sprint delivery system. Other independent trials have been completed in the past few months and have contributed more data to evaluate the efficacy and safety of this device. Detailed descriptions of each study can be found in Table 1.

RESOLUTE FIM

The RESOLUTE FIM trial[13] was a prospective, nonrandomized, multicenter study of the R-ZES in 139 patients with de novo coronary lesions and 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, and 6, 9, and 12 months; acute procedure success; and 9-month target vessel failure (TVF), target lesion revascularization (TLR), ST, neointimal hyperplastic (NIH) volume, and percent NIH volume obstruction. 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, and 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%,

ST was 0.0%, NIH volume was 6.55 ± 7.83 mm^3, and percent NIH volume obstruction was 3.73% ± 4.05%. Overall, in this feasibility study, the Resolute stent demonstrated low in-stent late lumen loss, minimal NIH in-growth, low TLR, no ST, and acceptable TVF and MACE.

RESOLUTE US

The RESOLUTE US trial[8] recruited patients with de novo native coronary lesions suitable for one- or two-vessel treatment with stents from 2.25 to 4.0 mm in diameter. In the main analysis cohort (2.5 to 3.5 mm stents and single-lesion treatment), the primary end point was 12-month target lesion failure (TLF), defined as the composite of cardiac death, myocardial infarction, and clinically driven TLR, compared with data from E-ZES trials, adjusting for baseline covariates through propensity scores. There were 1402 patients enrolled, with a mean reference vessel diameter of 2.59 ± 0.47 mm and diabetes prevalence of 34.4%. In the main analysis cohort, TLF was 3.7% at 12 months compared with historical E-ZES results (where TLF was 6.5%). The R-ZES met the 3.3% margin of noninferiority (rate difference = −2.8%, upper one-sided 95% confidence interval [CI]: −1.3%, $P < 0.001$). The overall TLF rate was 4.7%, and rates of cardiac death, myocardial infarction, and TLR were 0.7%, 1.4%, and 2.8%, respectively. The 12-month rate of ST was 0.1%. In this study, the R-ZES achieved a very low rate of clinical restenosis while maintaining low rates of important clinical safety events, such as death, myocardial infarction, and ST, at 1-year follow-up.

RESOLUTE International Registry

The primary objective of the Resolute International Registry[20] was to document the safety and overall clinical performance of the R-ZES in a "real-world" patient population of 2349 patients requiring stent implantation. The primary end point was the adjudicated cumulative 1-year incidence of cardiac death and target vessel myocardial infarction. The investigators recruited 2349 patients with 3147 lesions (1.6 ± 1.0 stents per patient); among the study patients, 46.0% had acute coronary syndrome, 30.5% were diabetic, and ≥1 complex criterion for stent placement was present in 67.5% of patients. One-year follow-up was completed for 97.9% of patients. The 1-year incidence of the primary end point was 4.3% (95% CI: 3.5% to 5.2%) and for Academic Research Consortium definite and probable ST,[21] 0.9% (95% CI: 0.5% to 1.3%). Clinically driven TLR and TLF were 3.4% (95% CI: 2.7% to 4.3%) and 7.0% (95% CI: 6.0% to 8.2%), respectively. In everyday practice, the R-ZES performed similarly well as in the Resolute All-Comers randomized trial.

RESOLUTE All-Comers

In the RESOLUTE All-Comers trial,[22] patients with at least one coronary lesion 2.25–4.0 mm in diameter, with greater than 50% stenosis, were randomly assigned to a R-ZES or a Xience V everolimus-eluting stent (XV-EES) at 17 centers in Europe and Israel. Randomization was completed by an interactive voice response system, and stratified by center. Study investigators were not masked to treatment allocation but those who did data management and analysis, and patients were masked. There were no restrictions as to the number of vessels or lesions treated, or the number of stents implanted. We assessed per specific safety and efficacy outcomes at 2 years, with specific focus on patient-related composite outcomes (all death, all myocardial infarction, and all revascularization) and stent-related composite outcomes. Analyses were by intention to treat. In total, 1140 patients were assigned to the zotarolimus-eluting stent and 1152 to the everolimus-eluting stent; of these, 1121 and 1128 patients, respectively, completed 2-year follow-up. The patient-related outcome (231 [20.6%] zotarolimus vs 231 [20.5%] everolimus; difference 0.1%, 95% CI: −3.2 to 3.5; $P = 0.958$) and stent-related outcome (126 [11.2%] vs 121 [10.7%]; difference 0.5%, 95% CI: −2.1 to 3.1; $P = 0.736$) did not differ between groups, although the rates of the stent-related outcome were substantially lower than were those for the patient-related outcome. Three patients in each group (0.3%) had very late (after 1 year) ST.[23] Overall, similar safety and efficacy outcomes were sustained between the two new-generation DES at 2-year follow-up.

RESOLUTE Japan

The objective of the RESOLUTE Japan study[24] was to verify the safety and efficacy of the R-ZES for the treatment of de novo lesions in native coronary arteries, in 100 subjects. The primary outcome measures were in-stent late lumen loss (time frame: postprocedure and 8 months) and the difference between the postprocedure immediate minimal lumen diameter and follow-up angiography minimal lumen diameter. The results were that the R-ZES in-stent late lumen loss at 8 months was 0.13 ± 0.22 mm, which met the primary noninferiority end point (and demonstrated superiority) compared with the historical Taxus stent 8-month in-stent late lumen loss of 0.42 ± 0.50 mm.

The TWENTE trial

The aim of the TWENTE study[25] was to compare the safety and efficacy of the R-ZES with the XV-EES at 1-year follow-up. This investigator-initiated, patient-blinded, randomized

Table 1 Completed trials on the R-ZES to date

	RESOLUTE First in Man[13]	RESOLUTE US[8]	RESOLUTE International[20]	RESOLUTE All-Comers[22]	LongOCT[45]
ClinicalTrials.gov identifier	NCT00248079	NCT00726453	NCT00752128	NCT00617084	NCT01133925
Purpose	Safety, efficacy, and PK on single de novo lesions in native coronaries with RVD 2.5 to 3.5 mm	Safety and effectiveness on de novo lesions with RVD 2.25 to 4.2 mm	Evaluation of R-ZES in real-world patients	Compare the R-ZES, XV-EES with respect to cardiac death, myocardial infarction, and TLR at 1 year in a real-world patient population	In vivo vascular response to the prolonged drug release R-ZES compared with the faster kinetic E-ZES by optical coherence tomography
Start date	November 2005	July 2008	August 2008	April 2008	May 2008
Primary completion date	June 2007	January 2011	October 2010	May 2010	August 2009
Estimated completion date	October 2011	June 2016	December 2012	December 2013	May 2011
Patients enrolled	139	1402	2349	2292	21
Allocation	Nonrandomized	Single group	Registry	Randomized	Nonrandomized
Masking	Open label	Open label	Open label	Open label	Open label
Devices	R-ZES	R-ZES	R-ZES	R-ZES/XV-EES	R-ZES/E-ZES
Lesion criteria	Single de novo in native coronary artery. Length: ≥14–≤27 mm RVD: 2.5–3.5 mm	One or two de novo lesions in native coronary arteries. RVD: 2.25–4.2 mm	At least one coronary artery suitable for stenting. RVD: 2.23–3.5 mm	At least one coronary lesion with ≥50% stenosis. RVD: 2.25–4.0 mm	One or two coronary arteries. Length: >20 mm
Primary outcome	In-stent LLL by QCA (9 months)	TLF (12 months)	Cardiac death and myocardial infarction (12 months)	TLF (12 months)	In-stent NIH at overlapping vs non-overlapping sites (6 months). Percent uncovered and malapposed struts in OCT (6 months)
Secondary outcome	MACE rate (30 days, 4, 6, 9, and 12 months) Acute success, TVF, TLR (9 months) Neointimal hyperplastic volume by IVUS Pharmacokinetic parameters (60 days) Angiographic parameters	TVF MACE Death Target vessel MI ST (12 months)	Overall stent thrombosis (12 months)	In-stent LLL by QCA (13 months)	MACE (1, 6, and 12 months) IVUS parameters (6 months) QCA parameters (6 months)
Status	Completed	Active, not recruiting	Active, not recruiting	Active, not recruiting	Unknown

Notes: Gray areas = no reported information. R-ZES and E-ZES, Medtronic (Minneapolis, MN, USA); XV-EES, Abbott Laboratories (Abbott Park, IL, USA); CYPHER®, Cordis Corporation (Hialeah, FL, USA).

Abbreviations: ACS, acute coronary syndrome; DES, drug-eluting stent(s); E-ZES, Endeavor® zotarolimus-eluting stent; IVUS, intravenous ultrasound; LLL, late luminal loss; MACE, major adverse cardiac events; MI, myocardial infarction; NA, not available; NIH, neointimal hyperplasia; OCT, optical coherence tomography; PK, pharmacokinetics; QCA, quantitative coronary angiography; RVD, reference vessel diameter; R-ZES, RESOLUTE Integrity® zotarolimus-eluting stent; ST, stent thrombosis; TLF, target lesion failure; TLR, target lesion revascularization; TVF, target vessel failure; XV-EES, XIENCE V® everolimus-eluting stent.

noninferiority study had limited exclusion criteria (acute ST-segment elevation myocardial infarctions not eligible). Patients (n = 1391, 81.4% of the eligible population) were randomly assigned to the R-ZES (n = 697) or the XV-EES (n = 694). Liberal use of stent postdilation was encouraged. Cardiac biomarkers were systematically assessed. The primary end point was TVF, a composite of cardiac death, myocardial infarction not clearly attributable to non-target vessels, and clinically indicated target-vessel revascularization. With the R-ZES and XV-EES, TVF occurred in 8.2% and 8.1%,

TWENTE[25]	RESOLUTE Japan[24]	Long-DES IV[27]	Talarico et al[28]	Resolute Italian[29]
NCT01066650	NCT00927940	NCT01186094	NA	NA
Investigate whether the clinical outcome following the randomized implantation of the R-ZES versus XV-EES is similar, as assessed in a noninferiority setting by comparing TVF of both stents	Safety and efficacy of the R-ZES for the treatment of de novo lesions in native coronary arteries	Compare the efficacy of a sirolimus-eluting stent (CYPHER®) and R-ZES implantation for long coronary lesions	Compare efficacy of R-ZES and E-ZES on real-world population	Evaluate the clinical outcome on unrestricted R-ZES use in patients receiving off-label lesion treatment and multiple DES implantations
June 2008	March 2009	May 2009	October 2008	January 2008
August 2010	December 2010	April 2011	NA	NA
September 2012	December 2014	June 2011	January 2010	April 2009
1380	100	502	467	820
Randomized Single blind R-ZES/XV-EES Chronic stable coronary artery disease or ACS. Length: no limit RVD: no limit	Single group Open label R-ZES One or two de novo lesions in native coronary arteries. RVD: 2.25–3.5 mm Length: <27 mm	Randomized Single blind R-ZES/CYPHER® Stable angina or ACS with at least one native "long" lesion with >50% stenosis. Length: >25 mm RVD: >2.5 mm	Randomized Open label R-ZES/E-ZES Chronic coronary disease or ACS with at least one lesion with >50% stenosis. Length: any RVD: >2.25 mm	Randomized Open label R-ZES Chronic stable coronary artery disease or ACS. Length: no limit RVD: no limit
TVF in both stents (1 year)	In-stent LLL (8 months)	In-stent LLL (9 months)	MACE (12 months)	TLF (12 months)
Efficacy, safety, long-term outcome, and the acute angiographic results of the implantation of both DES (1 year)	TLF (12 months) Success, MACE, TVF, ST (12 months) Rates of incomplete stent apposition, neointimal hyperplastic volume (8 months)	All deaths, ST, stent malapposition, TVF, TLR, TVR, volume of intimal hyperplasia (1 year)	Stent thrombosis	Stent thrombosis
Active, not recruiting	Active, not recruiting	Completed	Completed	Completed

respectively (absolute risk difference 0.1%; 95% CI: –2.8% to 3.0%, noninferiority = 0.001). There was no significant between-group difference in TVF components. The definite-or-probable ST rates were relatively low and similar for the R-ZES and XV-EES (0.9% and 1.2%, respectively, $P = 0.59$). Definite ST rates were also low (0.58% and 0%, respectively, $P = 0.12$). With the XV-EES, probable ST beyond day 8 was observed only in patients not adhering to dual antiplatelet therapy. In this study, the R-ZES was noninferior to the XV-EES in treating real-world patients with a vast majority

of complex lesions and off-label indications for DES, which were implanted with liberal use of postdilation.

The Optical Coherence Tomography in Long Lesions (LongOCT) trial

In the LongOCT study,[26] the vascular response to R-ZES, the ZES with prolonged drug release, was evaluated in vivo and compared with E-ZES, a ZES with faster kinetics, by means of OCT. The study had a pool of 43 patients, of which 21 were treated with "slow-release" ZES and 22 patients were treated with "fast-release" ZES. The primary end point was assessed after 6 months by the presence of in-stent NIH. The percentage of uncovered and malapposed struts were considered co-primary end points. The new generation slow-release ZES had better suppression of the neointimal response but had a higher proportion malapposed and uncovered struts, as assessed by OCT at 6-month follow-up.

Percutaneous treatment of long native coronary lesions with drug-eluting stent-IV (LONG-DES IV) trial

This randomized, multicenter, prospective trial, called the LONG-DES IV,[27] compared R-ZES and sirolimus-eluting stents (SES) in 500 patients with long (≥25 mm) native coronary lesions. The primary end point of the trial was in-segment late luminal loss at 9-month angiographic follow-up. The baseline characteristics were not different between the R-ZES and SES groups, including lesion lengths (32.4 ± 13.5 mm vs 31.0 ± 13.5 mm, $P = 0.27$). At 9-month angiographic follow-up, the R-ZES was noninferior to the SES with respect to in-segment late luminal loss, the primary study end point (0.14 ± 0.38 mm vs 0.12 ± 0.43 mm, P for noninferiority = 0.03, P for superiority = 0.68). In addition, in-stent late luminal loss (0.26 ± 0.36 mm vs 0.24 ± 0.42 mm, respectively; $P = 0.78$) and the rates of in-segment (5.2% vs 7.2%, respectively; $P = 0.44$) and in-stent (4.0% vs 6.0%, respectively; $P = 0.41$) binary restenosis were not significantly different between the two groups. There were no significant between-group differences in the rate of adverse clinical events (death, myocardial infarction, ST, TLR, and composite outcomes). Overall, in patients with de novo long coronary artery disease, R-ZES implantation showed noninferior angiographic outcomes as compared with SES implantation.

Talarico et al

Talarico et al (Rome, Italy)[28] conducted an independent study that compared the clinical outcome of patients treated with E-ZES and R-ZES in a total of 467 patients; of these, 233 were treated with E-ZES and 234 with R-ZES. At 12-month follow-up, MACE rate was significantly lower in the R-ZES group compared with E-ZES group (4.2% vs 14.6%; $P < 0.01$) and, this difference was secondary to nonsignificant lower MI and death rates, as well as significant lower TLR (3.4% vs 10.3%, $P < 0.01$).

Resolute Italian study in all comers

The Resolute Italian study[29] was a prospective trial conducted independently of any commercial funding (and was not part of the RESOLUTE clinical trials funded by Medtronics). The study was conducted to assess the clinical performance of R-ZES. The study patients comprised 820 high-risk patients, including patients with acute coronary syndrome (57%), diabetes mellitus (23%), and American College of Cardiology (ACC)/American Heart Association (AHA) type B2/C lesion[30] (74%). The primary end points were TLF (defined as myocardial infarction, cardiac death, or TLR) and ST as defined by the Academic Research Consortium,[21] evaluated immediately postprocedure and at 12-month follow-up. The overall in-hospital TLF was 4.0% (95% CI: 2.9%–5.6%) and comprised 0.9% (95% CI: 0.4%–1.8%) cardiac death, and 3.3% (95% CI: 2.3%–4.7%) periprocedural myocardial infarction – only two cases (0.2%, 95% CI: 0.1%–0.9%) of definite acute ST were observed during the hospital stay. At a median time of 12 months follow-up (interquartile range 10–18), the overall TLF rate was 7.1% (95% CI: 5.5%–9.0%), clinically detected revascularization was 4%, and ST (definite or probable) was 1.1%. As a conclusion, the use of E-ZES was safe, effective, and associated with favorable procedural and 12-month outcomes despite the treatment of unselected complex clinical and anatomical presentation.

Upcoming trials

At this point, some of the studies in the global RESOLUTE clinical trial program are still active: RESOLUTE US,[8] RESOLUTE International,[20] and RESOLUTE All-Comers.[22] RESOLUTE Japan's preliminary results were shown at the Japanese Association of Cardiovascular Intervention's 2011 annual meeting,[24] but formal publication of results is still pending. The RESOLUTE US trial is not only active but is still enrolling patients for a 38 mm stent-length substudy.[8]

Other active studies, which will continue to accrue follow-up results in the next few years, are the TWENTE[25] trial and the LONG-DES IV trial.[27] Several other independent trials are summarized in Table 2.

In the following years we will see the R-ZES being tested against other DES,[31,32] such as the Taxus® Liberté® stent (Boston Scientific),[33] the Promus™ Element (Boston Scientific),[10] the Synergy™ (Boston Scientific), the Orsiro™ (Biotronik SE & Co, KG, Berlin, Germany),[34] the Taxus Element™ (Boston Scientific), and Xience Prime™ (Abbott Laboratories),[25] and against non-stent devices such as the IN.PACT Falcon drug-eluting balloon (Invatec Roncadelle, Italy).[35]

It will be interesting to see the outcomes in more specific subtypes of lesions and patients. For example, in the Clinical Evaluation of the MDT-4107 Drug-Eluting Coronary Stent in the Treatment of De Novo Lesions in Small Diameter Native Coronary Arteries (RJ-SVS) trial,[36] the R-ZES's safety and efficacy will be tested in small vessels (2.25 mm). Other special populations, such as patients with long and complex lesions, will be studied in the RESOLUTE Asia trial.[37]

Clinical safety of the R-ZES

The United States Food and Drug Administration (FDA) approved the use of the R-ZES on February 17, 2012. The approved use has been limited so far to patients with coronary artery disease and diabetes, and is approved with a target length of ≤27 mm, and with reference vessel diameters of ≥2.25 mm to ≤4.2 mm.

The characteristics of the patients involved in the reviewed studies were homogeneous among the trials, and the conclusions are based on a total studied population of 7152 people (Table 3). The addition of more complex coronary lesions and patients was seen in results of the RESOLUTE US,[8] RESOLUTE All-Comers,[22] TWENTE,[25] and RESOLUTE Italian[29] trials. Among these complex patient populations were patients with acute coronary syndromes, multiple lesions, multivessel disease, and, in some, the presence of at least one off-label criterion, meaning renal insufficiency, ejection fraction of less than 30%, the occurrence of an acute myocardial infarction within the previous 72 hours, more than one lesion per vessel, lesions of more than 27 mm, bifurcations, bypass grafts, unprotected left main artery, lesions with thrombus, or total occlusions. Smaller lesions (<2.25 mm) were rarely intervened in any of these trials (Table 4).

The clinical safety profile of the R-ZES suggests that its antirestenotic efficacy is superior to that of the E-ZES and similar to other limus-eluting stents.[19]

Primary and secondary end point results are shown in Table 5 for the RESOLUTE trials; similar data for all other studies on R-ZES are also presented in Table 6.

The RESOLUTE FIM trial[13] was the first to report the safety and efficacy of this stent. The safety was comparable to the E-ZES;[8] RESOLUTE FIM also showed promising efficacy, with significantly less in-stent late lumen loss at nine months: 0.22 ± 0.27 mm, which was significantly less than seen in the ENDEAVOR II study.[38] It also demonstrated that there was no overt positive remodeling of the vessels and little or no recoil of the stent. Also, the presence of low NIH volume and percent NIH volume obstruction was consistent with the antiproliferative effect of zotarolimus. Six cases of late incomplete apposition were noted at 9-month follow-up with intravascular ultrasound, but only one required a TLR at 280 days. Guagliumi et al[26] have also described the presence of a higher rate of late incomplete apposition with R-ZES stents, through the use of OCT. Late incomplete apposition is a phenomenon potentially associated with late ST, but this has not been conclusively demonstrated.[39]

Lesion length and complexity

Along with angiography and intravascular ultrasound, OCT has been used in vivo to evaluate the vascular response to stents, and, according to Guagliumi et al,[26] the differences found between the R-ZES and E-ZES were based on different release kinetics, with the R-ZES showing slow release and the E-ZES a fast-release kinetic. The OCT showed more suppression of NIH with the R-ZES arm versus the E-ZES but a higher proportion of patients with uncovered and malapposed struts at 6-month follow-up. It has been demonstrated in the past that overlapping sites of DES have greater NIH compared with non-overlapping segments.[26] Interestingly, the degree of NIH response in the R-ZES group was similar between overlapping and nonoverlapping segments, allowing interventionists to treat longer and more complex lesions.

Lesion complexity is another factor that was described in some studies,[8,20,22,23,25] including the one by Talarico et al[28] that described that patients treated with the R-ZES had longer and more complex lesions, with higher rate of ACC/AHA B2/C,[30] and higher SYNTAX™ score[40,41] and bifurcated lesions.

The outcome in bifurcation lesions was evaluated in the multicenter Italian registry that evaluated lesions with more than 70% stenosis at a major bifurcation point and a main vessel diameter of more than 2.5 mm. Here, 180 patients were enrolled and showed a procedural success rate of 98.3% and no reported MACE or ST in the first 9 months.[34]

Small vessel disease

During the 2012 meeting of the ACC,[42] the RESOLUTE group presented updated data on the safety and effectiveness

Table 2 Ongoing trials with the R-ZES

Trial	RESOLUTE Japan SVS[36]	RESOLUTE China RCT[33]	RESOLUTE Asia[37]	RESOLUTE China registry[33]	DUTCH-PEERS[46]
ClinicalTrials.gov identifier	NCT01150500	NCT01334268	NCT01132456	NCT01243749	NCT01331707
Purpose	Verify the safety and efficacy of the R-ZES in the treatment of de novo lesions in native coronary arteries with an RVD that allows the use of 2.25 mm diameter stents	Evaluate the in-stent LLL and the follow-up angiography minimal lumen diameter of the R-ZES compared to Taxus Liberté paclitaxel-eluting coronary stent system in a real-world all-comer patient population requiring stent implantation	Document the safety and overall clinical performance of the E-ZES in a patient population with long lesion(s) and/or dual vessels requiring stent implantation	Document the safety and overall clinical performance of the R-ZES in a real-world patient population requiring stent implantation	Evaluate clinical efficacy of Promus Element versus the R-ZES
Start date	June 2012	September 2011	June 2010	December 2010	November 2010
Primary completion date	October 2011	September 2012	March 2013	December 2013	December 2012
Estimated completion date	June 2016	December 2017	April 2016	July 2017	December 2013
Patients enrolled (n)	63	400	312	1800	1788
Allocation	Nonrandomized	Randomized	Nonrandomized	Registry	Randomized
Masking	Open label	Open label	Open label	Open label	Single blind
Devices	R-ZES	R-ZES/Taxus Liberté	R-ZES	R-ZES	R-ZES/Promus Element
Lesion criteria	De novo lesions in native coronary arteries. RVD: 2.25 mm	Not specified	Patients with at least one lesion amenable to treatment with a 38 mm length. Patients with dual vessel treatment where each vessel has a lesion with length ≤ 27 mm and RVD between 2.25–4.0 mm	Not specified	Per operator's judgment
Primary outcome	TLF (9 months)	In-stent LLL (9 months)	TLF for the 38 mm cohort. TVF for dual vessel cohort	TLF (12 months)	TVF (1 year)
Secondary outcome	Success MACE TVF LLL (9 months)	Device success Death TVF TLF ST (30 days; 6 and 12 months; 2, 3, 4, and 5 years)	Death, MI, MACE, TLF (30 days; 6, 9, 12, and 18 months; 2 and 3 years)	Overall ST (12 months)	NA
Status	Active, not recruiting	Active, not recruiting	Active, not recruiting	Active, not recruiting	Active, not recruiting

Notes: Gray areas = no reported information. R-ZES and E-ZES, Medtronic (Minneapolis, MN, USA); Taxus Liberté, Promus Element, and Synergy, Boston Scientific (Natick, MA, USA); IN.PACT Falcon, Invatec (Roncadelle, Italy); Orsiro, Biotronik (Biotronik SE & Co, KG, Berlin, Germany); Xience Prime, Abbott Laboratories (Abbott Park, IL, USA).
Abbreviations: CT, computerized tomography; DAP, dual antiplatelet therapy; DES, drug-eluting stent(s); EES, everolimus-eluting stent; E-ZES, Endeavor® zotarolimus-eluting stent; IVUS, intravenous ultrasound; LLL, late luminal loss; MACE, major adverse cardiac events; MI, myocardial infaction; NA, not available; QCA, quantitative coronary angiography; RVD, reference vessel diameter; R-ZES, RESOLUTE Integrity® zotarolimus-eluting stent; ST, stent thrombosis; TLF, target lesion failure; TLR, target lesion revascularization; TVF, target vessel failure; TVR, target vessel revascularization.

DELIVER study[47]	RESOLUTE Integrity US[48]	RAMSES[49]	IRIS-Integrity[31]	BIO-RESORT[35]	OCELOT[32]
NCT01297257	NCT01638507	NCT01722799	NCT01392846	NCT01674803	NCT01293773
Assess the deliverability of the R-ZES as a primary stent or as a secondary crossover stent following delivery failure of another stent type in real-world patients	Conduct a prospective, multicenter evaluation of the procedural and clinical outcomes of subjects that are treated with the commercially available R-ZES	Evaluate the clinical efficacy of the drug-eluting balloon IN.PACT Falcon and the effectiveness and cost-effectiveness incremental analysis of R-ZES in patients with de novo lesions in small vessels	Prospective, observational, cohort study to evaluate the relative efficacy and safety of R-ZES compared to other DES	Head-to-head comparisons between biodegradable and contemporary third-generation durable polymer DES	Safety and efficacy in the prevention of TLF of second-generation paclitaxel-eluting stents versus R-ZES versus Xience Prime EES in diabetic patients.
February 2011 October 2012	July 2012 February 2014	December 2012 December 2013	July 2011 July 2013	November 2012 November 2016	October 2010 October 2012
May 2012	February 2015	December 2014	July 2017	November 2016	December 2012
8900	230	290	1000	3540	750
Observational Open label	Observational Open label	Randomized Single blind	Observational Open label	Randomized Single blind	Randomized Open label
R-ZES	R-ZES	R-ZES/IN.PACT Falcon paclitaxel DES	R-ZES/other DES	R-ZES/Synergy/ Orsiro	R-ZES/ Taxus Element/ Xience Prime
Symptomatic ischemic heart disease or bypass graft stenosis amenable for percutaneous treatment	De novo lesions in native coronary arteries with an RVD of 2.2–4.2 mm	De novo lesions in native coronary arteries. >50% stenosis by CT and >70% by angiography. RVD: 2.25–2.75 mm Length: <25 mm	Not specified	Significant coronary disease amenable to treatment	One or more de novo stenosis ≥ 70% in a native coronary artery
Delivery success (1–3 days)	Composite rate of cardiac death and target vessel myocardial infarction (12 months)	TVF (1 year)	Composite death (12 months)	TVF (1 year)	TLF (1 year)
In-hospital MACE (1–3 days)	MACE TLF TVF TLR TVR Compliance with dual antiplatelet therapy (30 days, 6, 12, and 24 months)	Cost-effectiveness and drug utility (6 months and 1 year)	Death all causes, TVR, TLR, ST (6 months and 1 year)	TLF (1 year)	Effect of glucose levels on repeat revascularization (1 year) TLR (12, 24, and 36 months) Effect of DAP on outcome (3 years)
Recruiting	Recruiting	Not open yet	Recruiting	Not open yet	Recruiting

Table 3 Summary of baseline characteristics in patients

	R-FIM[13]	R-US[8]	R-Int[20]	R-AC[22]	LongOCT[45]	TWENTE[25]	R-J[24]	Long-DES IV[27]	Talarico et al[28]	R-Ita[29]	Total
Patients (n)	139	1402	2349	1140	21	697	100	250	234	820	7152
Age (mean ± SD)	60.7 ± 10	64.1 ± 0.7	63.5 ± 11.2	64.4 ± 10.9	68.7 ± 10.5	63.9 ± 10.9	64.1 ± 10.7	62.8 ± 9.7	65.6 ± 10.9	65.9 ± 11	65.1 ± 10.8
Male (%)	76.3	68.3	77.8	76.7	71	72.5	77	73.6	76	79.6	75.1
Diabetes mellitus (%)	17.3	34.4	30.5	23.4	14	22.7	45	27.2	30.7	23.5	28.3
Hypertension (%)		84.2	68	71.1	48	55.4	81	60	74.8	68.8	69.2
Hyperlipidemia (%)	94.2	87.7	63.9	63.9	57	57	78	56.4	59.4	57.8	46.7
History of smoking (%)	70.5	20.9	24.2	26.5		25.3	22	27.2	17.6	45.7	27.1
Prior MI (%)	46.4	21.6	27	28.9	38	30.6	25	1.2	9.4	28.4	25.6
Prior PCI (%)	18.7	32.7	29.6	31.8	38	19.9	42	6.2	28.2	24.6	29.3
Prior CABG (%)	0	8.8	8.4	10	0	9.8	0	1.6	4.3	12.3	8.4

Note: Gray areas = no reported information.
Abbreviations: CABG, coronary artery bypass graft; Long-DES IV, Percutaneous Treatment of Long Native Coronary Lesions With Drug-Eluting Stent-IV; LongOCT, Optical Coherence Tomography in Long Lesions; MI, myocardial infarction; PCI, percutaneous coronary intervention; R-AC, RESOLUTE All-Comers; R-FIM, RESOLUTE First in Man; R-Int, RESOLUTE International; R-Ita, Resolute Italian; R-J, RESOLUTE Japan; R-US, RESOLUTE United States.

of the R-ZES on vessels of ≤2.5 mm diameter. From the pooled results of the five RESOLUTE studies, there were a total of 1956 patients (38.1%) with vessel diameter ≤ 2.5 mm and 3174 patients (61.9%) with vessel diameter > 2.5 mm. The data from all five RESOLUTE studies were adjusted for differences in patients' baseline characteristics, and the RESOLUTE group concluded that, after 2 years of follow-up, there were no significant differences in the safety and effectiveness outcomes between patients with large- and small-vessel disease. Interestingly, patients with small-vessel disease were older and had a higher proportion of females and a high rate of diabetes, hypertension, hyperlipidemia, and multivessel disease.[42]

Off-label use/complex patients

Some of the reviewed trials have expanded patient eligibility to include more complex patients and lesions,[8,22,25] with the idea of expanding the treatment options for these patients. It is known that diabetes, recent myocardial infarction, chronic kidney disease, ostial lesions, and total occlusions represent a higher risk for restenosis and ST. The results demonstrated higher event rates in complex versus noncomplex patients but no differences between the R-ZES and other DES currently being used in clinical practice. Overall, there is encouraging safety data in higher-risk populations.

Diabetic patients

A total of 2024 diabetic patients, including insulin- and noninsulin-dependent diabetics, participated in all the ten studies reviewed by us, representing 28.3% of the sample. As we already know, diabetes is a factor for poor prognosis in patients with coronary disease as well as for higher rate of periprocedural complications, such as in-stent stenosis, ST, and death.[43] The rate of TLF in this group after 1 year was similar to that of the overall trial population, which demonstrates efficacy and safety in this particular group of patients.[11]

In-stent thrombosis

The data on ST seems to be conflicting at this point. In the RESOLUTE All-Comers trial, the rate of definite ST was significantly higher in the R-ZES group (1.2%) than in the XV-EES group (0.3%, $P = 0.01$) at 12 months, which was primarily related to a higher rate of definite ST at 30 days in the zotarolimus-stent group than in the everolimus-stent group.[23] Talarico et al,[28] reported a significantly higher number of definite, probable, and possible cases of ST in the E-ZES group (with one case of definite ST), while no definite or probable

Table 4 Baseline procedural and lesion characteristics

	R-FIM[13]	R-US[8]	R-Int[20]	R-AC[22]	LongOCT[45]	TWENTE[25]	R-J[24]	Long-DES IV[27]	Talarico et al[28]	R-Ita[29]
Patients/lesions (n)	139/140	1402		1140/3366	21	697	100	250	234	820/1352
Target artery										
LAD	34.3	45.9	51	52.6	57	40.9	42.6	62.4		39.1
LCx	25.7	32.2	27.5	33	14	22.5		12.4		30.6
RCA	40	31.2	32.5	37.3	29	32.3		24.8		24.3
Left main	0	0.6	2.6	2.2	0	26		0		3.2
Bypass graft	0	0	1.8	2.5	0	2.3		0		2.7
ACC/AHA class[30]										
A	1.4					7.1				
B1	17.1					22.3				
B2	49.3	37.6				31.7	30.5			53.8
C	32.1	37.6				38.9	22.3			20
SYNTAX score[40]				14.8 ± 9.3				14.0 ± 7.5		
Multi-vessel treatment	0	10.4	67.5	58.4		25		49.6		71
Length of lesion (mm)	15.61 ± 6.13	13.06 ± 5.88	18.8 ± 10.8	11.89 ± 7.50		9.85–22.54	15.52 ± 5.37	32.4 ± 13.5		19.19 ± 10.78
RVD (mm)	2.81 ± 0.40	2.59 ± 0.47	2.9 ± 0.5	2.63 ± 0.57		2.30–3.05	2.85 ± 0.44	3.25 ± 0.47		2.86 ± 0.54
Bifurcated lesions	0	0	21.8	16.9		23.9	18.5	91		21.2
Thrombus present	0	0	0	5.3		3.1		2		7.8
Minimal lumen diameter (mm)	0.83 ± 0.34	0.77 ± 0.35	0.5 ± 0.4	0.95 ± 0.54		0.72–1.29		0.92 ± 0.46		0.48 ± 0.42

Note: Gray areas = no reported information.

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; LAD, left anterior descendent; LCx, left circumflex; Long-DES IV, Percutaneous Treatment of Long Native Coronary Lesions with Drug-Eluting Stent-IV; LongOCT, Optical Coherence Tomography in Long Lesions; R-AC, RESOLUTE All-Comers; RCA, right coronary artery; R-FIM, RESOLUTE First in Man; R-Int, RESOLUTE International; R-Ita, Resolute Italian; R-J, RESOLUTE Japan; R-US, RESOLUTE United States; RVD, reference vessel diameter.

Table 5 Global data on safety and effectiveness in the RESOLUTE trials

Composite safety and effectiveness	Resolute First in Man[13]			RESOLUTE US[8]			RESOLUTE International[20]	RESOLUTE All-Comers[22]		RESOLUTE Japan[24]
	9 months	12 months	48 months	2.25 mm	2.5–3.5 mm	4 mm	12 months	12 months	24 months	12 months
Patients (n)	139	139	139	150	1112	60	2349	1140	1140	100
TLF				5.5%	3.8%	6.8%	7.0%	8.1%	11.2%	4.0%
TVF	6.5%	7.2%	10.1%	8.2%	5.3%	6.8%	7.7%	8.9%	12.6%	5.0%
MACE	7.2%	8.6%	13.8%	6.8%	4.6%	8.5%	8.2%	8.6%	12.5%	5.0%
Effectiveness										
Clinically driven TVR	0%	0.7%	3.6%	6.8%	3.8%	3.4%	4.2%	4.9%	7.3%	1.0%
TLR	0%	0.7%	2.2%	4.1%	2.2%	3.4%	3.4%	3.9%	5.7%	0%
TLR, PCI	0%	0.7%	2.2%	4.1%	1.9%	3.4%	3.2%	3.4%	5.0%	0%
TLR, CABG	0%	0%	0%	0%	0.3%	0%	0.3%	0.5%	1.1%	0%
Non-TL TVR	0%	0%	1.4%	2.7%	1.9%	1.7%	1.1%	1.9%	3.1%	1.0%
Non-TL TVR, PCI	0%	0%	1.4%	2.7%	1.6%	1.7%	1.1%	1.5%	2.6%	1.0%
Non-TL TVR, CABG	0%	0%	0%	0%	0.4%	0%	0%	0.4%	0.5%	0%
Safety										
Total deaths	1.4%	2.2%	5.8%	2.7%	0.9%	1.7%	2.4%	1.6%	3.2%	1.0%
Cardiac death	0.7%	0.7%	0.7%	1.4%	0.4%	0%	1.4%	1.3%	2.6%	0%
Non-cardiac death	0.7%	1.4%	5.1%	1.4%	0.5%	1.7%	1.0%	0.3%	0.6%	1.0%
Cardiac death/TVMI	6.5%	6.5%	6.5%	2.1%	1.7%	3.4%	4.3%	5.3%	7.0%	4.0%
TVMI	5.8%	5.8%	5.8%	0.7%	1.4%	3.4%	3.1%	4.2%	4.7%	4.0%
ST ARC[21]										
Definite/probable	0%	0%	0%	1.4%	0%	0%	0.9%	1.6%	0.7%	0%
Definite	0%	0%	0%	0.7%	0%	0%	0.7%	1.2%	0.3%	0%
Probable	0%	0%	0%	0.7%	0%	0%	0.3%	0.5%	0.4%	0%

Note: Gray areas = no reported information.

Abbreviations: CABG, coronary artery bypass graft; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; ST ARC, stent thrombosis as defined by Academic Research Consortium; TL, target lesion; TLF, target lesion failure; TLR, target lesion revascularization; TVF, target vessel failure; TVMI, target vessel myocardial infarction; TVR, target vessel revascularization.

Table 6 Global data on safety and effectiveness in other R-ZES studies (12-month outcomes)

Composite safety and effectiveness	TWENTE[25]	Long-DES IV[27]	Resolute Italian[29]		Talarico et al[28]
			12 months	24 months	
Patients (n)	695	250	820	820	234
TLF	7.9%	14%	4.0%	5.5%	
TVF	8.2%				
MACE	10.1				4.2%
Effectiveness					
Clinically driven TVR	3.3%	2.0%	0.5%	5.6%	
TLR	7.9%	1.6%			
TLR, PCI	2.2%				10.3%
TLR, CABG	0.6%				0%
Safety					
Total death		0.8%			
Cardiac death	1.0%	0.4%	0.9%	1.8%	0.4%
Non-cardiac death	2.2%	0.4%			
Cardiac death/TVMI	4.9%	12.4%			
TVMI	4.6%	11.6%	3.3%	2.2%	1.7%
ST ARC[21]					
Definite/probable	0.6%	0%	0.2%	0.7%	0%
Definite	0.9%	0%	0%	0.1%	0%
Probable	1.4%	0%	0%	0.7%	0.8%

Note: Gray areas = no reported information.

Abbreviations: CABG, coronary artery bypass graft; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; ST ARC, stent thrombosis as defined by Academic Research Consortium; TLF, target lesion failure; TLR, target lesion revascularization; TVF, target vessel failure; TVMI, target vessel myocardial infarction; TVR, target vessel revascularization.

ST was detected in the R-ZES group. The TWENTE trial[25] showed a lower incidence of definite in-stent thrombosis than was seen in the RESOLUTE All-Comers trial.

Patient-focused perspective

One of the most fearsome complications for a DES is in-stent thrombosis, which is often due to improper stent implantation.[6] Dual antiplatelet agents are indicated for at least 12 months in order to prevent this risk. For this reason, patients that are candidates for DES should be screened for contraindications to prolonged antiplatelet therapy. In all of the studies reviewed, a loading dose of clopidogrel 300 mg was given to the patients within 24 hours before the procedure, then 75 mg daily for at least 6 months to 1 year. Aspirin was used to complete the dual antiplatelet therapy, at a dose ranging from 75 to 100 mg daily indefinitely, unless the patient had indication for anticoagulation, in which case it was continued for at least 1 month after the procedure without changes in the dose or duration of clopidogrel. Procedural anticoagulation was achieved with heparin, maintaining an activated clotting time > 250 seconds, or between 200 and 250 seconds if a glycoprotein IIb/IIIa receptor inhibitor was administered. The use of glycoprotein IIb/IIIa receptor inhibitors was left to operator's discretion.

The studies on R-ZES, have suggested a variety of possible advantages in special population, such as diabetic patients,[8,24] and patients with more complex coronary lesions, such as multivessel disease, small-vessel disease, long lesions, bifurcations, or trifurcations.[8,13,23,24]

Technically, this new technology may offer superior scaffolding and a reduced profile exchange joint, without compromising on radial strength. The R-ZES has excellent radial strength and measures 1146 mmHg radial pressure – superior to the Promus Element and XV-EES, which measure 1000 mmHg and 850 mmHg radial pressure, respectively. The R-ZES also offers greater pushability, requiring a push force of 20 g/f, for more accurate delivery to the lesion site compared with the XV-EES, which requires an average push force of 86 g/f.

The dosage and duration of dual antiplatelet therapy remains as per guidelines[44] and should be continued for a year, and there is not enough data at this point to support any changes. Long-term studies are indicated to prospectively assess whether a shorter duration of dual antiplatelet therapy is safe and effective.

Conclusion and future perspectives

The R-ZES has shown promising results and introduced a new possible mechanism to prevent ST with its addition of the new polymer coating and delivery system. It also uses one continuous sinusoidal metallic strand to enhance range of motion, which may result in an easier and safer delivery,

and add to the technical advantage for the Interventionist by reducing the profile and improved pushability.

The data on clinical efficacy is promising and the safety, so far, is acceptable (at the same level as other widely used DES). Longer-term follow-up will further bolster knowledge about efficacy and safety issues.

As the use of the device extends across the US and the world, we need to continue to monitor the real-world use and results, to determine whether these results will remain generalizable to longer-term follow-up beyond 2 years and specifically, to higher risk subgroups. There is no doubt that this stent will have a major role in the treatment of coronary artery disease in the near future. Of note, the R-ZES is the first DES approved by the FDA for use in patients with diabetes, who account for about 30% of the nearly one million percutaneous cardiac interventions performed in the US each year. Overall, the R-ZES offers several notable benefits, including outstanding deliverability, which means it's easy to deliver to the stenosis site, and efficacy in complex patients and diabetics, but additional longer term safety and efficacy data are needed to cement its place in the DES armamentarium.

Disclosure

The authors report no conflicts of interest in this work.

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