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REVIEW

The Resolute™ Integrity Zotarolimus-Eluting Stent in Coronary Artery Disease: A Review

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ABSTRACT

The introduction of first-generation drug-eluting stents (DES) was a major advance in the percutaneous treatment of coronary artery disease, with DES significantly reducing the incidence of restenosis and major adverse coronary events compared with bare metal stents. Next-generation DES now utilizes lower profiles, thinner struts, and other technological advances to help extend their safety and efficacy. Importantly, studies of next-generation devices have now gone beyond controlled clinical trials with selected populations to registries and studies with all-comer populations, where more diverse and complex sets of patients and lesions have been managed. Thus, a large body of evidence and comparative data about the safety and efficacy of these devices has accumulated. The Resolute™ zotarolimus-eluting stent (R-ZES; Medtronic Inc., Santa Rosa, CA, USA) is a next-generation DES that uses a novel biocompatible polymer on a cobalt alloy stent platform to extend the duration of drug elution and improve the stent's efficacy. The Integrity™ platform (Medtronic, Inc., Santa Rosa, CA, USA) used in the most recent iteration of the R-ZES stent further enhances the flexibility and deliverability of the stent in complex lesions by incorporation of a continuous sinusoidal design. In the following review, the clinical data is critically examined for the R-ZES and discuss its performance using comparative data currently available for next-generation DES. It is concluded that R-ZES use in complex patients and lesions is associated with durable efficacy and safety and represents another generational improvement in DES technology, which undoubtedly will enhance patient outcomes postpercutaneous coronary interventional.

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INTRODUCTION

Drug-eluting stents (DES) have not only improved clinical outcomes compared with bare metal stents (BMS), they have vastly enhanced our capability and confidence to tackle increasingly complex patients and lesions traditionally treated with coronary artery bypass graft surgery (CABG) [1–3]. This has in turn increased percutaneous coronary interventional (PCI) procedural volumes worldwide and DES use in clinical and angiographic scenarios not initially tested and approved by the U.S. Food and Drug Administration (FDA), otherwise referred to as off-label use. The result has been justifiable concerns regarding the efficacy and associated risk of DES in these situations. However, these concerns have been continually addressed by carefully collected outcomes analyses from large longitudinal registries, data from randomized controlled trials (RCTs), and translational research studies combined with advances in DES technology. Importantly, this effort has been a result of unprecedented collaboration between regulatory bodies, industry, and the interventional community. In this review, the clinical outcome data of the most recently FDA-approved DES are critically examined, the Resolute™ zotarolimus-eluting stent (R-ZES, Medtronic, Inc., Santa Rosa, CA, USA), and the unique features of the next iteration of the R-ZES built on the Integrity™ platform (Medtronic, Inc., Santa Rosa, CA, USA) to further enhance stent flexibility and deliverability, especially in complex lesions.

R-ZES

The Integrity BMS is a new iteration of the Driver™ BMS (Medtronic, Inc., Santa Rosa, CA, USA); the zotarolimus-eluting version is the Resolute Integrity stent where Integrity BMS replaces the Driver platform in the new stent. The Integrity stent platform uses a single cobalt chromium wire to form a continuous sinusoidal pattern of crowns and struts wrapped helically around a mandrel with a 0.09 mm strut thickness and a 1.12 mm crossing profile. This unique manufacturing technology enhances stent flexibility, deliverability, and conformability without sacrificing radial strength [4]. A study of stent longitudinal distortion tested seven stent platforms including the Endeavor™ Driver (Medtronic, Inc., Santa Rosa, CA, USA), Resolute Integrity (Medtronic, Inc., Santa Rosa, CA, USA), Liberte™ (Boston Scientific, Natick, MA, USA), Omega™ Promus Element™ (Boston Scientific, Natick, MA, USA), Multilink 8Xience Prime™ (Abbott Vascular, Santa Clara, CA, USA), and Vision™ Xience V™ (Abbott Vascular, Santa Clara, CA, USA) [5]. The Resolute Integrity DES was more resistant to longitudinal distortion in elongation tests than the Omega Element or Driver stents, and similar to the other stents tested. The authors note that ideally there must be a balance between stent flexibility and stiffness which has been shown to correlate with the number of connectors between hoops [6]. The Resolute Integrity and the Driver platform have two connections compared with three for Xience V and Xience Prime stents, but the unique helical single-wire design decreases the longitudinal distortion of the Resolute

Integrity stent thus maintaining a balance between flexibility and longitudinal integrity [5, 6].

Radial strength is primarily responsible for creating and maintaining vessel patency and studies have shown it to be an important predictor of clinical performance [7–9]. In-house testing at Medtronic has shown equivalence in radial strength between the Driver and Integrity stents. Performance of the Resolute Integrity stent platform was compared with five other contemporary stents deployed in an idealized vessel using finite element simulations [7]. Percent malposition of stent struts, defined as the strut distance from the wall >10 μm was least with the Resolute Integrity platform at 9% and maximal with the Promus Element stent at 43% [10]. Furthermore, these investigators used finite element analysis correlated with bench testing of radial strength and demonstrated similar radial strength to the Promus Element stent (~0.012 mm/N diameter reduction at given force) and greater radial strength than the Multilink Vision (~0.16 mm/N) or Xience Prime stents (~0.018 mm/N diameter reduction) (Personal Communication).

The R-ZES is covered with a proprietary BioLinx™ (Medtronic, Inc., Santa Rosa, CA, USA) tripolymer, a blend of the hydrophilic C19 polymer, polyvinyl pyrrolidinone (PVP) and the hydrophobic C10 polymer. The PVP component results in an overall hydrophilic polymer which enhances the biocompatibility of the stent [11]. There is an initial release of zotarolimus from the surface of the stent followed by extended drug elution. Nearly 85% of the zotarolimus (dose density ~1.6 μg/mm^2) is released by 60 days, and completely by 180 days [11].

The thin strut, low profile, and continuous sinusoidal design combined with the biocompatible polymer and extended drug release is designed to maximize deliverability and efficacy of this new generation R-ZES. However, the evidence regarding its long-term safety for complex patient subsets also needs to be critically examined. This review will summarize the clinical data for the R-ZES and discuss results in the context of complex "real-world" PCI.

METHODS

The PubMed database was used to identify all prospective clinical trials for the R-ZES and the everolimus-eluting stent (EES) for the past 5 years. Related presentations for the past 2 years were obtained from the Transcatheter Cardiovascular Therapeutics, American College of Cardiology, and PCRonline websites. The PubMed database was also searched for preclinical data using a zotarolimus-eluting stent, Biolinx polymer, coronary stent design, and coronary stent performance search terms. Additional data related to stent design and performance was requested from Medtronic, Inc.

R-ZES CLINICAL STUDIES

The first-in-man R-ZES experience (RESOLUTE study) was a 139 patient, multicenter, prospective study examining 9-month in-stent late loss and target lesion revascularization (TLR) in stenotic de novo lesions in coronary vessels with reference vessel diameter between 2.5 and 3.5 mm in diameter and 14 mm to 27 mm in length [12]. The study required a 4-month angiographic and intra-vascular ultrasound (IVUS) follow-up in the first 30 patients and a 9-month follow-up in the remainder. Complex patients with recent

myocardial infarction, left ventricular ejection fraction (LVEF) <30% and ostial, bifurcation, heavily calcified, or left main lesions were excluded. Dual anti-platelet therapy (DAPT) with aspirin and clopidogrel was prescribed for 6 months post-PCI, and aspirin continued indefinitely thereafter. The 9-month in-stent late lumen loss was 0.22 ± 0.27 mm. TLR rates at 9 months, 1, 2, and 4 years were 0.0%, 0.8%, 1.5%, and 2.3%, respectively. The Academic Research Consortium (ARC)-defined definite and probable stent thrombosis (ST) events at 4 years remained at 0.0% [12, 13]. Though this experience was restrictive and may not reflect "real-world" DES use, it certainly set the best-case reference of R-ZES performance.

The results from the single-arm RESOLUTE US trial (R-US), which included 1,402 patients with 1- or 2-vessel coronary artery disease from 116 US centers with lesions suitable for 2.25–4.0 mm R-ZES was reported in April 2011 [14]. Though the main analysis was performed on a prespecified group of single-lesion patients treated with 2.5–3.5 mm R-ZES, a 241 patient cohort received the 2.25 mm R-ZES or had two lesions treated. The study enrolled 1,242 patients in the clinical cohort. The overall (2.25–4.0 mm) target lesion failure (TLF) rate was 4.7%, and rates of cardiac death, myocardial infarction (MI), and TLR were 0.7%, 1.4%, and 2.8%, respectively. The 12-month rate of ST was 0.1% [15].

The RESOLUTE all-comers (R-AC) trial was an international, multicenter RCT including 2,292 patients with an open-label random assignment of a wide variety of unrestricted coronary lesions in a 1:1 fashion to either R-ZES or EES [16]. There were no restrictions on the number of lesions, vessels, or number of implanted stents. Most importantly, 1,520 patients were defined as complex based on prespecified definition, with a well-balanced allocation to R-ZES (764 patients and 1,227 lesions) and EES (756 patients and 1,242 lesions) groups. The definition of complex patients is shown in Table 1.

Table 1 Prespecified definition of complex patients in RESOLUTE all-comers trial [16]

Complex patients criteria *(presence of at least one of the following)*
Acute myocardial infarction within 72 h
Left ventricular ejection fraction <30%
Renal insufficiency or failure (serum creatinine ≥140 μmol/L)
Treatment of bifurcation coronary lesions
Treatment of saphenous vein graft lesions
Treatment of arterial graft lesions
Treatment of in-stent restenosis lesions
Treatment of unprotected left main coronary lesions
Treatment of ≥2 coronary vessels
Treatment of coronary lesions ≥27 mm in length
Treatment of >1 lesion per coronary vessel
Treatment of coronary vessels with presence of thrombus
Treatment of coronary total occlusions

The primary 12-month noninferiority endpoint of TLF, defined as a composite of cardiac death, target vessel MI, and clinically indicated TLR, was met (R-ZES 8.2% vs. EES 8.3%, noninferiority $P < 0.001$) [16]. The mean SYNTAX^{TM} (Boston Scientific, Natick, MA, USA) score was 16.6 ± 9.4 in the complex R-ZES patients, compared with 11.2 ± 7.9 in the simple R-ZES patients [17]. Patients with recent acute MI, diabetes mellitus (DM), and LVEF <35% constituted 43.5%, 23.1%, and 3.8% of the complex patient cohort, respectively. Bifurcation, left main, saphenous vein graft, and chronic total occlusion PCI were performed in 26%, 3.1%, 3.5%, and 25% of

complex patients. Overall, TLF was 6.3% and 9.3% ($P = 0.015$) at 1 year for simple and complex patients, respectively. Similarly, target vessel failure (TVF) in the entire study, defined as a composite of cardiac death, target-vessel MI, and clinically indicated target vessel revascularization (TVR) was 7.1% and 10.4% ($P = 0.009$) at 1 year for simple and complex patients, respectively. A patient oriented 1-year composite endpoint including all cause death, MI, and any repeat revascularization was identified as a secondary clinical endpoint and was also higher for complex patients compared with simple (16.1% vs. 11.6%, $P = 0.004$). Definite or probable ST occurred in 2.2% of complex patients and in 1.35% of simple patients, with no difference between the R-ZES and EES groups (P value for interaction = 0.14) [17].

Prespecified 2-year clinical outcomes of the R-AC trial demonstrated sustained safety and efficacy for the R-ZES and EES [18]. The rates of TLF at 3 years were 13.1% for R-ZES and 12.4% for EES ($P = 0.614$). Additionally, the rates of definite or probable ST at 3 years were also low [19]. Rates of definite or probable very late stent thrombosis (VLST) were 0.5% for both stents. DAPT use was 84.4 and 83.5% at 1 year for the R-ZES and EES groups, respectively ($P = 0.60$).

The RESOLUTE International Trial (R-Int) trial enrolled an unrestricted cohort of 2,349 patients, two-thirds of which were complex with at least one R-ZES (2.25–4.0 mm stent diameter). Nearly 30% of patients were diabetic and 46% presented with an acute coronary syndrome (ACS). The composite primary endpoint of cardiac death and target vessel MI at 1 year was 4.3% [20].

The pooled RESOLUTE clinical program derived from five R-ZES studies (RESOLUTE, R-US, R-AC, R-Int and RESOLUTE Japan) includes 5,130 patients [21]. Nearly 30% of patients had DM and 46% were complex. The diabetic cohort was older with expectedly more patients with hypertension, hyperlipidemia, or prior PCI. At 2 years, clinically-driven TLR was 4.7% and definite or probable ST was 0.9%. In a prespecified analysis of less complex patients with DM, 2-year rates of clinically-driven TLR and definite or probable ST for patients with DM ($n = 861$) was 4.8% and 0.3%, respectively (Fig. 1) [21]. In the nondiabetic cohort ($n = 1{,}903$) these 2-year endpoints were reached in 3.4% and 0.4% patients, respectively. These data indicate consistently low event rates and durable clinical outcomes in the higher-risk patients with DM. Based on these data the R-ZES is the first DES approved by the FDA for use in patients with DM.

The diabetic population included 29.6% of patients with insulin-dependent DM. At 1 year, event rates were significantly higher in patients with insulin-dependent diabetes mellitus IDDM compared with those without DM (TLR 6.3% vs. 2.9% [$P < 0.001$]; cardiac death or MI 6.6% vs. 3.6% [$P = 0.003$]; ST 1.5% vs. 0.7% [$P = 0.02$]) [22]. The cumulative incidence of TLF, cardiac

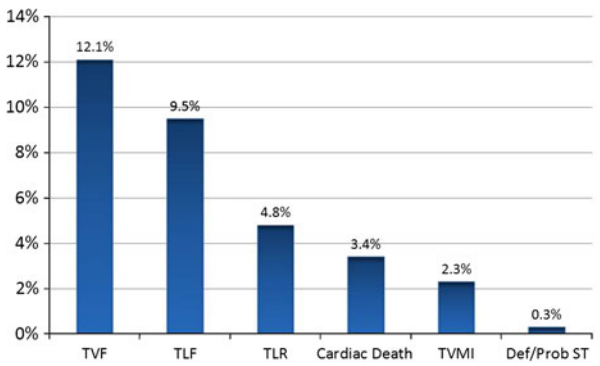

Fig. 1 Two-year event rates for standard-risk patients with diabetes mellitus ($n = 861$) in the pooled RESOLUTE global clinical program [21] *ST* stent thrombosis, *TLF* target lesion failure, *TLR* target lesion revascularization, *TVF* target vessel failure, *TVMI* target vessel myocardial infarction

death, target vessel MI, and TLR was similar for DM patients receiving the R-ZES (7.8%) and the EES (9.0%) at 1 year ($P = 0.96$); there was a trend to lower TLF in the non-DM patients (R-ZES 6.1%; EES 8.3%; [$P = 0.09$]). One year outcomes for R-ZES and EES DM patients were also similar for rates of TLR, cardiac death or MI, and ST [22]. These data also indicate to the strength of the RESOLUTE pooled clinical program which was conceptualized using similar event definitions, adjudication, and data management methodology across a myriad of R-ZES trials. It is imperative that data from this large and diverse cohort of patients representing a "real-world" patient population will continue to be the source of important data and guide contemporary PCI practice worldwide.

R-ZES RESULTS IN PERSPECTIVE

Stefanini et al. [17] compared the R-ZES results from the R-AC RCT to other RCTs with "all comer" patients. In the Sirolimus-Eluting and Paclitaxel-Eluting Stents for Coronary Revascularization (SIRTAX) trial, 12-month clinically-driven TLR and definite ST rate were 8.9% and 1.9%, respectively [23]. In the Limus Eluted From A Durable Versus ERodable Stent Coating (LEADERS) trial, though only a fifth of the patients had angiographic follow-up, clinically-driven TLR and definite ST rates were 5.5% and 2.0% at 12 months, respectively [24]. The Randomized Controlled Trial of Everolimus-eluting Stents and Paclitaxel-eluting Stents for Coronary Revascularization in Daily Practice (COMPARE) trial reported a 1-year clinically driven TLR of 2% and a definite ST rate of 0.4% [25]. There was no angiographic follow-up in the COMPARE trial. The results from the R-ZES trials, especially R-AC, compared very favorably with other all-comer studies, while including a much more complex patient population and lesion categories. A meta-analysis of 76 RCTs with 117,762 patient-years of follow-up found considerable variations in the magnitude of long-term TVR rates (39–61%) by DES type (ZES-R = EES > paclitaxel-eluting stent > ZES > BMS). Overall, there was no long-term increase in death with any of the DES [26]. In the R-AC trial, R-ZES was associated with a higher definite stent thrombosis at 1 year than EES (1.2% vs. 0.3%; [$P = 0.01$]), while definite or probable stent thrombosis at 2 years were 1.9% and 1.0% ($P = 0.08$) for R-ZES and EES, respectively [16, 18] However, in the TWENTE trial, definite or probable ST rates for R-ZES and EES were 0.9% and 1.2%, respectively ($P = 0.59$). Definite ST rates were also low (0.58% and 0%, respectively [$P = 0.12$]) [27]. Comparative data of ST across R-ZES and EES studies is shown in Fig. 2 [16, 20, 25, 27–34]. It is important to note that these data are not based on direct comparisons and on studies not powered for the low frequency ST event. These data suggest a very low risk of ST with R-ZES and EES stents and the observed differences are caused by chance.

Patti et al. [35] reported in a 2008 meta-analysis of nine studies comparing DES with BMS in DM patients, including 1,141 patients, an in-stent restenosis (ISR) and TLR rates with BMS of 41% and 27%, significantly higher than first generation DES ISR and TLR rates of 8% and 8%, respectively ($P < 0.0001$ for both comparisons). In a pooled analysis of EES versus paclitaxel-eluting stent from the SPIRIT and COMPARE trials, ischemia-driven TLR rates were 6.1% and 5.5% for diabetics in the paclitaxel-eluting and EES recipients, respectively ($P = 0.60$); it was 6.9% and 3.6%, respectively in nondiabetics ($P < 0.0001$) [36]. In a more recent all-comer DES study presented by Jensen et al., TVR rates in patients with DM with sirolimus-eluting stent and EES were 10.7% and

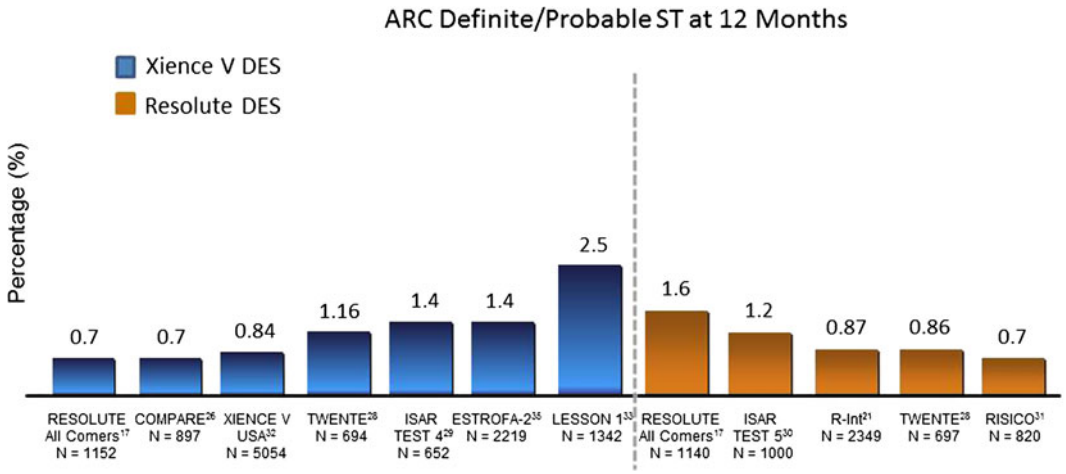

Fig. 2 Stent thrombosis across RESOLUTE and everolimus-eluting stent trials. ARC definite and probable ST at 12 months from 10 "real-world" clinical trials. It is important to note that these data are not based on direct comparisons and on studies not powered for the low frequency ST event. *ARC* Academic Research Consortium, *COMPARE* Second-Generation Everolimus-Eluting and Paclitaxel-Eluting Stents in Real-Life Practice, *ESTROFA-2* Estudio Espanol Sobre Trombosis de Stents Farmacoactivos de Segunda Generacion-2, *ISAR* Individualizable Drug-Eluting Stent System to Abrogate Restenosis, *LESSON 1* Long-term Comparison of Everolimus-Eluting and Sirolimus-Eluting Stents for Coronary Revascularization, *R-Int* RESOLUTE International, *RISICO* Resolute Italian Study in All Comers, *ST* stent thrombosis

6.7% at 18 months, respectively [37]. While this subgroup analysis was not powered to assess these endpoints, these data support the observation that significant strides have been made with respect to PCI outcomes in diabetics with complex coronary artery disease revascularized percutaneously with R-ZES.

CONCLUSION

R-ZES use in complex patients and lesions is associated with durable efficacy and safety and represents another generational improvement in DES technology, which will undoubtedly enhance patient outcomes post-PCI.

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