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DRUG ELUTING STENTS

Real-World Safety and Effectiveness Outcomes of a Zotarolimus-Eluting Stent: Final 3-Year Report of the RESOLUTE International Study

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Objectives: *We evaluated the safety and effectiveness of the Resolute™ zotarolimus-eluting stent (R-ZES) in real-world clinical practice through 3 years.*
Background: *A randomized comparison of the R-ZES and the XIENCE V™ everolimus-eluting stent showed no difference in any outcomes through 3-year follow-up in high-volume academic centers. RESOLUTE International is a confirmatory trial designed to evaluate the R-ZES in real-world clinical practice.*
Methods: *RESOLUTE International is a single arm, observational trial that enrolled 2,349 patients from 88 centers with only a few inclusion and exclusion criteria. The primary end-point was the composite of cardiac death and target vessel myocardial infarction (TV-MI) at 1 year. Secondary end-points include target lesion failure (TLF), target vessel revascularization (TVR), and their components, and stent thrombosis (ST).*
Results: *At 3 years 97.2% of patients completed clinical follow-up. The mean age was 63.4 ± 11.2 years, 77.8% were male, and 30.4% had diabetes. The average number of stents per patient was 1.6 ± 1.0; and mean stent length was 30.9 ± 20.5 mm. Dual antiplatelet therapy was used in 91.1% of patients at 1 year, 43.0% at 2 years, and 34.6% at 3 years. Cardiac death and TV-MI occurred in 161 patients (7.0%). There were 6 (0.3%) very late ST events for a total ST rate of 1.1% through 3 years. The rates of clinically driven target lesion revascularization (TLR), TVR, and TLF were 5.7%, 7.4%, and 11.4%, respectively.*
Conclusions: *The safety and effectiveness of the R-ZES through 3 years in this real-world all-comer study was consistent with previously reported all-comer trials.* (J Interven Cardiol 2013;26:515–523)

Introduction

First generation drug-eluting stents (DES) reduced revascularization rates compared with bare metal stents and became standard of care for the treatment of lesions in coronary arteries.[1–4] Late (30 days to 1 year) and very late (after 1 year) stent thrombosis (ST) was noted in several studies and meta-analyses, particularly when the inclusion criteria of these studies were broadened to include more high-risk patient and lesion characteristics, and more diverse study centers.[5–11] DES were redesigned to produce new generation devices with improved polymer behavior and an expected lower rate of ST.[12] Clinical trial results suggest that late and very late ST rates are indeed lower with second- and third-generation DES,[13–17] although the studies lacked power to reach definitive conclusions.[18] Data on patients undergoing percutaneous coronary intervention (PCI) and DES placement with clinical and lesion characteristics reflective of routine clinical practice have been limited. Recently, randomized trials evaluating new DES have included broader patient populations in order to better reflect routine clinical practice.[13,14,19] These studies also obtained long-term

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follow-up data, which enables assessment of clinical outcomes, including late and very late ST, in a patient population reflective of real-world settings. This report describes the 3-year clinical outcomes of patients enrolled in the RESOLUTE International study.

Methods

Study Design and Patient Population. RESOLUTE International is 1 of the 5 studies included in the RESOLUTE Global Clinical Trial Program. The overall program has enrolled and treated 5,130 patients with the Resolute™ zotarolimus-eluting stent (R-ZES; Medtronic, Inc., Santa Rosa, CA, USA). All studies have used similar data collection processes, end-point definitions, and evaluation and analytic methodologies.[14,15,20–24] The RESOLUTE International study is a prospective, multicenter, single-arm study that enrolled 2,349 patients from 88 sites in 17 countries worldwide, between August 28, 2008 and March 19, 2009. Detailed study methods and definitions have been previously reported[23] and are summarized here. Key inclusion criteria were age of at least 18 years, coronary lesion amenable to PCI with DES, and a signed informed patient consent. Exclusion criteria were limited to presence of pregnancy, inability to conform to study procedures or required medications, and participation in a concurrent trial. No restrictions were placed on the number, size, or location of lesions or vessels treated.

End-points. The primary end-point was the composite of cardiac death or target vessel myocardial infarction (TV-MI) at 1 year. Secondary end-points included clinical safety and efficacy outcomes through 2 years. Safety end-points include cardiac death, MI (Q-wave and non-Q wave), and definite and probable ST as defined by the Academic Research Consortium (ARC).[11] Efficacy end-points included target lesion revascularization (TLR), target lesion failure (TLF; composite of cardiac death, TV-MI, or clinically driven TLR), and target vessel failure (TVF; cardiac death, TV-MI, or target vessel revascularization [TVR]). Major adverse cardiac events (any death, any MI, emergent coronary bypass grafting, or TLR by percutaneous or surgical methods) were also reported.

Definitions. End-point definitions are similar for all studies in the RESOLUTE Global Clinical Program.[14,15,21,24] Cardiac death included any death due to immediate cardiac cause (e.g., MI, low output failure, fatal arrhythmia), any unwitnessed death or death of unknown cause, and all procedure-related deaths including those related to concomitant treatment. MIs were reported using the extended historical definition for all-comer studies.[25] Clinically driven TLR or TVR included revascularization at the target lesion (or vessel) associated with positive functional ischemia study or ischemic symptoms and an angiographic minimal lumen diameter stenosis $\geq$50%, or revascularization of a target lesion (or vessel) with diameter stenosis $\geq$70% without either angina or a positive functional study. Patients were prospectively defined as being "complex" if they had at least 1 of the following clinical or lesion characteristics: renal insufficiency (serum creatinine $\geq$140 μmol/L), left ventricular ejection fraction $<$30%, acute MI ($\leq$72 hours), $>$1 lesion per vessel, $\geq$2 vessels stented, lesions $>$27 mm, bifurcations, bypass grafts, in-stent restenosis, unprotected left main, lesions with thrombus or total occlusion. All other patients were defined as "simple." Lesion characteristics were assessed by visual estimation only.

Study Procedures. The protocol encouraged all investigators to follow their site-specific procedures for the treatment of patients undergoing PCI. Follow-up in clinic or telephonically occurred at 30 days, 6 months, 12 months, 24 months, and 36 months following the index procedure. Pre- and postprocedural angiographic parameters were visually estimated. The R-ZES was available in the lengths of 8/9, 12, 14/15, 18, 24, 30, and 38 mm, and diameters of 2.25, 2.5, 2.75, 3.0, 3.5, and 4.0 mm. Recommended aspirin therapy included at least 75 mg beginning 3 days prior to the procedure or a preprocedure loading dose of at least 250 mg, and a daily dose of at least 75 mg continued indefinitely. Recommended clopidogrel therapy included 75 mg for 3 days prior to the procedure, or a loading dose of at least 300 mg, with continued treatment at a daily dose of 75 mg for at least 6 months following the procedure.

Event Adjudication. An independent Clinical Events Committee (CEC; Cardiovascular Research Foundation, New York, NY), comprising members not involved in study operation or management, reviewed all available documentation related to any serious adverse event. Our study encouraged real-world use of the R-ZES, and therefore did not use an angiographic core laboratory. All angiograms associated with any adverse event, along with any other supporting

documentation surrounding the event, were sent to the CEC for adjudication. In the case of any MI events, the measurement of cardiac enzymes was based on center-specific procedures. As part of the RESOLUTE Global Clinical Trial Program, the RESOLUTE International study CEC activities were harmonized with the RESOLUTE All Comers[14] and RESOLUTE US studies[24] in order to ensure consistency in clinical data review across the entire clinical program. A Global Oversight Committee evaluated the consistency of major cardiac adverse events (death, MI, TLR, TVR) adjudication across the individual committees, and provided recommendations; however, the RESOLUTE International CEC's decision was considered final for all events.

Study Management. Personnel trained to evaluate clinical documentation visited each center at least once to assess compliance and review all patient consent forms. Personnel verified all source data for a random sample of 25% of patients for 1-year follow-up and approximately 20% of the patients for the 2-year and 3-year follow-up. Patients were classified as fully monitored if all of their clinical source documentation (including the consent form) and available records associated with any adverse events were reviewed. These procedures were consistent with those performed in well-controlled, randomized trials. Patients were classified as partially monitored if their consent form and all available supporting records associated with any adverse events were reviewed. Procedures were also put in place to ensure data consistency and accuracy. An electronic data capture system was used to collect case report form data, which includes automatic edit checks to minimize missing or eligible data. The RESOLUTE International study was performed according to the Declaration of Helsinki. Each centers' ethics committee or equivalent, if required, approved the study protocol. Signed, informed consent was obtained from each patient.

Statistical Analyses. Patients in whom the implantation of at least 1 R-ZES was attempted or achieved comprise the intention-to-treat analyses cohort. We prospectively planned to evaluate baseline and event data for several subgroups, including patients with complex clinical and lesion characteristics and by the extent of monitoring. Categorical variables are presented as frequencies and percentages and continuous variables are presented as means and standard deviations. The Kaplan–Meier method was used to calculate the cumulative incidence figures.

Table 1. Patient Characteristics at Baseline

	Total (n = 2,349)
Age, years	63.4 ± 11.2
Men	77.8 (1,828)
Current smoker	24.3 (570)
Hyperlipidemia	63.9 (1,500)
Hypertension	68.0 (1,598)
Diabetes mellitus	30.4 (715)
Insulin treated	8.9 (210)
Prior myocardial infarction	27.0 (635)
Prior PCI	29.6 (696)
Prior coronary artery bypass grafting	8.4 (197)
Acute coronary syndrome	
Stable angina	37.4 (878)
Unstable angina	26.1 (612)
Acute myocardial infarction (<72 hours)	20.0 (469)
STEMI (<72 hours)	10.7 (252)
Left ventricular ejection fraction <30%	3.2 (50/1,545)
Serum creatinine (μmol/L)	90.07 ± 38.45 (1,857)
Moderate/severe renal impairment (creatinine clearance* <60 mL/min)	18.9 (351/1,857)

All data presented as percentages (n) or mean ± standard deviation (n). PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction. *Estimated using the Cockcroft-Gault formula.[31]

Results

Patient Data and Follow-Up. At 3 years, 97.2% of patients completed clinical follow-up. The patient baseline demographics have been previously reported[23] and are shown in Table 1. The mean age was 63.4 ± 11.2 years, 77.8% of patients were male, and 30.4% had diabetes mellitus. Prior PCI had been performed in 29.6% of patients, and 8.4% underwent prior coronary artery bypass grafting. A history of any MI was reported in 27.0% of patients, and an acute MI (AMI; <72 hours) was present in 20%. Baseline lesion and procedure characteristics are summarized in Table 2. Most lesions were de novo (92.4%) with 57.1% in American College of Cardiology/American Heart Association (ACC/AHA) class B2/C and 18.2% bifurcated lesions. Multivessel treatment occurred in 14% of patients. Overall 67.5% of patients met the definition for complex. The average number of stents per patient was 1.6 ± 1.0 with an average stent length of 30.9 ± 20.5 mm. Treated coronary arteries were left

Table 2. Lesion and Procedural Characteristics

	Total (n = 2,349 patients, 3,148 lesions)
De novo lesions	92.4 (2,908)
ACC/AHA class B2/C lesions	57.1 (1,799)
Chronic total occlusion lesions	6.3 (199)
Bifurcation lesions	18.2 (573)
Preprocedure thrombus* lesions	12.0 (378)
Patients with multiple vessels treated	14.0 (330)
Target vessel location, patients	
Left main artery	2.6 (62)
Left anterior descending artery	51.0 (1,199)
Left circumflex artery	27.5 (646)
Right coronary artery	32.5 (764)
Bypass graft (SVG + arterial graft)	1.8 (42)
Reference vessel diameter, mm*	2.9 ± 0.5
Minimum lumen diameter, mm*	0.5 ± 0.4
Lesion length, mm*	18.8 ± 10.8
≥1 Small vessel (RVD ≤ 2.75 mm)	45.4 (1,067)
Preoperative percent diameter stenosis	84.48 ± 12.14
Lesions treated per patient	1.3 ± 0.7
Stents per patient	1.6 ± 1.0
Stent length per patient	30.9 ± 20.5
Patients with ≥3 stents	14.3 (337)

All data presented as percentages (n) or mean ± standard deviation (n). ACC/AHA, American College of Cardiology/American Heart Association; RVD, reference vessel diameter; SVG, saphenous vein graft. *By visual estimation.

anterior descending (51.0%), right (32.5%), and the left circumflex (27.5%).

Clinical Outcomes. Clinical outcomes through 3 years are shown in Table 3 and Figure 1. One-year outcomes are included for comparison. Cardiac death or TV-MI occurred in 161 patients (7.0%), and cardiac death occurred in 82 (3.6%) patients through 3 years. For the 89 (3.9%) patients who experienced a TV-MI event through 3 years, 69 were non-Q wave. The rates of clinically driven TLR and TVR were 5.7% and 7.4%, respectively. The composite end-point of TLF occurred in 261 (11.4%) patients through 3 years. There were 6 (0.3%) very late ST events for a total ST rate of 1.1% through 3 years (Fig. 2). The incremental event rates from years 1 to 3 are shown in Table 3. Between 1- and 3-year follow-up there were 62 (2.8%) cardiac death or TV-MI events, 49 (2.2%) TLR events, and 6 (0.3%) ARC definite or probable ST events.

Clinical Outcomes by Select Subgroups. The rates of cardiac death and TV-MI and TLR at 3 years for select subgroups are shown in Figure 3. Except for patient groups known to be at higher risk, such as those with diabetes mellitus, the rates of cardiac death and TV-MI in this all-comer patient population were generally consistent across the subgroups. The rates of TLR across the subgroups were consistent across all subgroups. Figure 4 shows the consistency in safety and effectiveness outcomes at 3 years for all-comer

Table 3. Clinical Outcomes Through 3 Years Follow-Up

	1 Year (n = 2,337)	3 Year (n = 2,284)	Difference (%) Between Year 1 and Year 3 and 95% CI
Cardiac death or TV-MI*	4.2 (99)	7.0 (161)	−2.8 (−4.1, −1.5)
Death	2.4 (57)	6.1 (139)	−3.6 (−4.8, −2.5)
Cardiac death	1.5 (34)	3.6 (82)	−2.1 (−3.0, −1.2)
TV-MI*	3.0 (71)	3.9 (89)	−0.9 (−1.9, 0.2)
Q-wave	0.5 (12)	0.9 (20)	−0.4 (−0.8, 0.1)
Non-Q wave	2.5 (59)	3.0 (69)	−0.5 (−1.4, 0.5)
Clinically driven TLR	3.5 (81)	5.7 (130)	−2.2 (−3.4, −1.0)
Clinically driven TVR	4.2 (99)	7.4 (168)	−3.1 (−4.5, −1.8)
TLF	7.1 (165)	11.4 (261)	−4.4 (−6.0, −2.7)
TVF	7.7 (180)	12.9 (294)	−5.2 (−6.9, −3.4)
ARC definite/probable stent thrombosis (all)	0.9 (20)	1.1 (26)	−0.3 (−0.9, 0.3)
Early (<30 days)	0.7 (17)	0.7 (17)	NA
Late (31–360 days)	0.1 (3)	0.1 (3)	NA
Very late (361–1,080 days)	NA	0.3 (6)	NA

All data presented as percentages (number of events) unless otherwise noted. ARC, Academic Research Consortium; NA, not applicable; TLF, target lesion failure; TLR, target lesion revascularization; TVF, target vessel failure; TVR, target vessel revascularization. *Target vessel myocardial infarction: any myocardial infarction that occurs in a territory of a coronary artery that cannot be attributed with certainty to any other vessel than the target vessel.

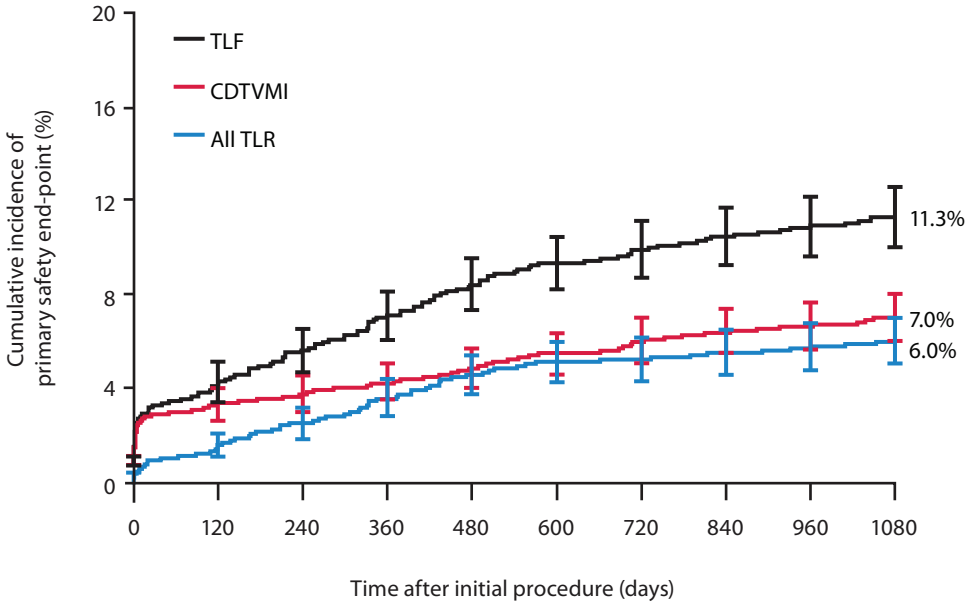

Figure 1. Cumulative incidence of target lesion failure, cardiac death and myocardial infarction, and target lesion revascularization. Cumulative events through 3-year follow-up for cardiac death and target vessel myocardial infarction (CDTVMI), target lesion failure (TLF; cardiac death, target vessel myocardial infarction or clinically driven target lesion revascularization [TLR]), and TLR.

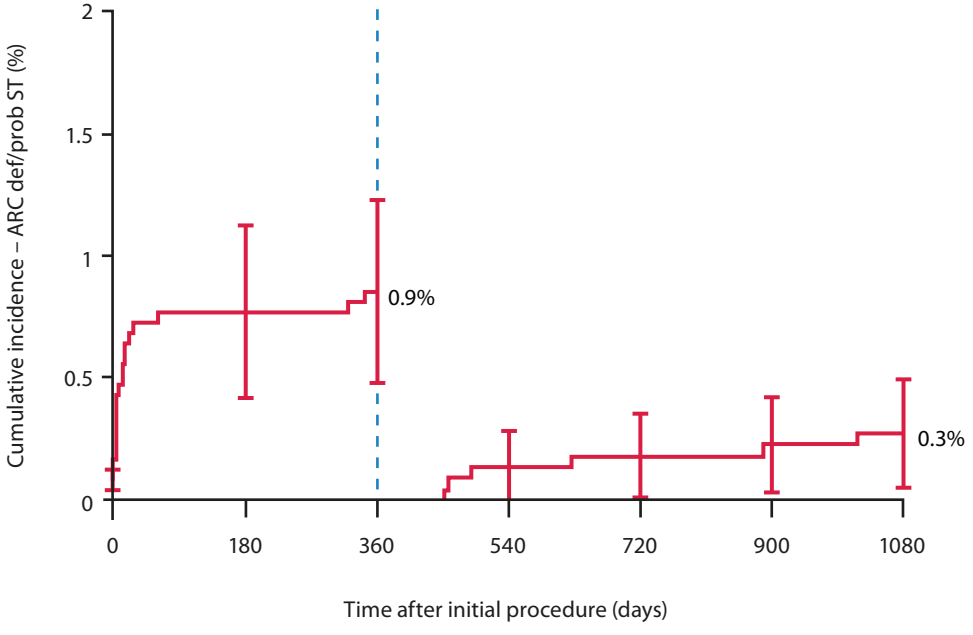

Figure 2. Cumulative incidence of definite and probable stent thrombosis. Stent thrombosis (ST) adjudicated according to Academic Research Consortium (ARC) criteria.

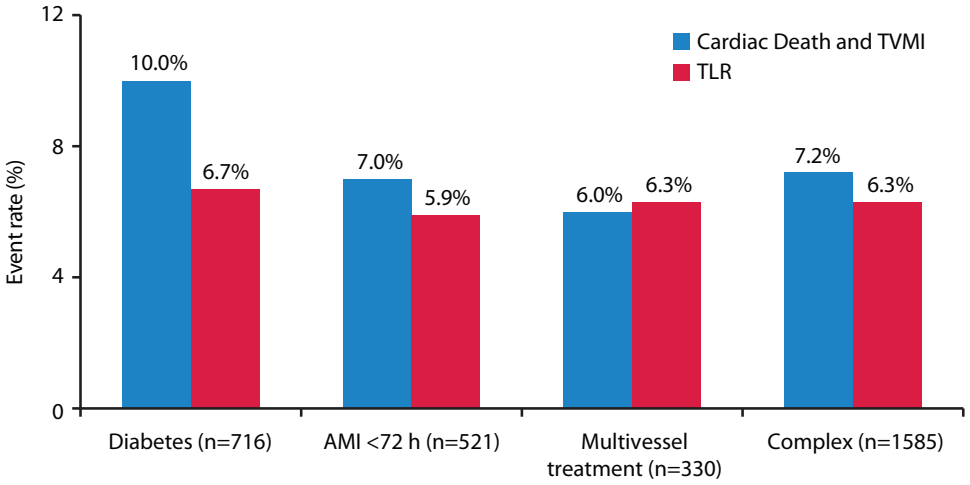

Figure 3. Three-year rates of cardiac death and myocardial infarction and clinically driven target lesion revascularization for select subgroups. Complex patients were defined as having any of the following: bifurcation, bypass graft, in-stent restenosis, acute MI (AMI) <72 hours, left ventricular ejection fraction <30%, >2 vessels stented, renal insufficiency or failure (serum creatinine ≥140 μmol/L), lesion length >27 mm, >1 lesion per vessel, or lesion with thrombus or total occlusion (thrombolysis in MI [TIMI] = 0). TLR = target lesion revascularization; TVMI = target vessel myocardial infarction.

patients from the RESOLUTE All Comers trial and the RESOLUTE International trial. Overall DAPT usage remained high through 1 year postprocedure and dropped to 43% in year 2 and 34.6% in year 3. DAPT adherence remained high through 3 years in India but decreased in Western Europe and the remaining countries (Table 4).

Discussion

Extended 3-year follow-up of this large cohort of patients from the RESOLUTE International study further establishes the long-term safety and efficacy of the R-ZES and contributes to the growing body of clinical evidence from the RESOLUTE Global Clinical

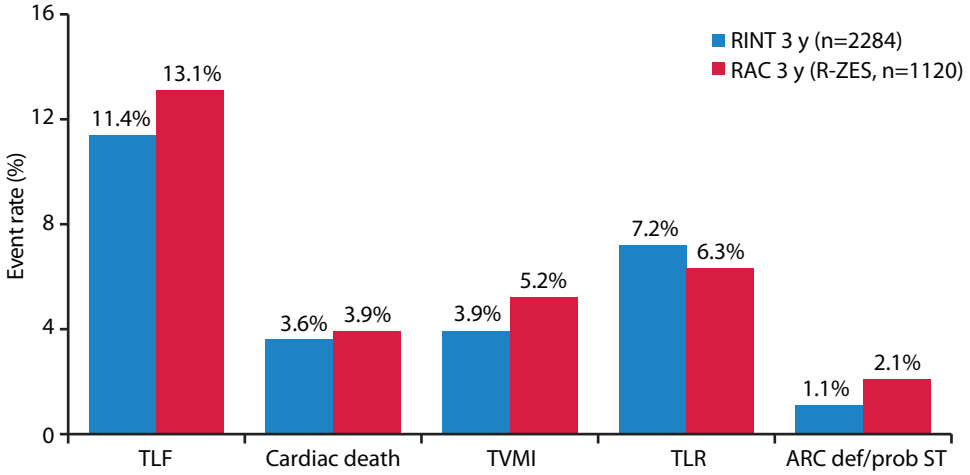

Figure 4. Comparison of 3-Year Clinical Outcomes for the RESOLUTE International Study and the RESOLUTE All Comers Trial. ARC def/prob ST = Academic Research Consortium definite/probable stent thrombosis, RAC = RESOLUTE All Comers; RINT = RESOLUTE International; TLF = target lesion failure (cardiac death, TVMI, or clinically-driven TLR), TLR = target lesion revascularization, TVMI = target vessel myocardial infarction.

Table 4. Dual Antiplatelet Therapy* Adherence by Geographic Region

	30-Day (%)	6 Months (%)	1 Year (%)	2 Years (%)	3 Years (%)
Western Europe† (n = 1,929)	97.4	95.7	90.5	39.5	28.7
India (n = 174)	97.7	97.7	98.8	97.6	98.2
Rest of world‡ (n = 248)	96.4	95.5	90.5	39.2	31.7
Overall	97.5	95.9	91.1	43.0	34.6

*Aspirin and clopidogrel or ticlopidine. †Austria, Belgium, Finland, Germany, the Netherlands, Norway, Portugal, Spain, Switzerland, United Kingdom. ‡Argentina, Czech Republic, Estonia, Greece, Slovak Republic, South Africa.

Program. This article details the final 3-year clinical outcomes for 2,349 patients, with only a few inclusion and exclusion criteria, from 88 study centers, which provided a broad patient cohort for evaluating R-ZES performance. Three-year clinical follow-up was completed for 97.2% of patients. The composite of cardiac death and TV-MI at 3 years was 7.0% and is comparable to rates reported from other new generation DES all-comer trials.[14,26,27] The CEC adjudicated deaths using the ARC criteria[11] (i.e., the total number of cardiac deaths) includes those that were classified as unknown. Of the 48 cardiac deaths that occurred during the 2nd and 3rd years of follow-up, 27 were due to unknown causes. Three-year cardiac mortality (3.6%) in the RESOLUTE International Study was nevertheless similar to that reported by the RESOLUTE All Comers and LEADERS trials.[15,28] Safety end-points occurred at low rates. The overall rate of TV-MI in RESOLUTE International was lower than the 3-year rates from the RESOLUTE All Comers trial (5.2%) and LEADERS trial (7.0% for the biolimus-eluting stent [BES]).[14,28] The 3-year TLR rate and modest accrual of events between years 1 and 3 was consistent with that observed in the RESOLUTE All Comers trial (6% with R-ZES and 5.8% with EES at 3 years)[14] and other new generation DES.[28] TLR rates were also consistent across various subgroups (Fig. 3), including high-risk complex patients and those with diabetes mellitus. Among the 3-year RESOLUTE International cohort, there were only 6 (4 definite and 2 probable) very late (361–1,080 days) ARC definite or probable ST events for a rate of 0.3%. These low rates are consistent with data reported from the RESOLUTE All Comers trial (late: R-ZES 0.6% and EES 0.2%; very late: R-ZES 0.5% and EES 0.5%),[14,15] and other new generation DES such as the BES (late, 0.6%; very late, 0.2%).[26]

There was a higher adherence to DAPT at 2- and 3-year follow-up (43.0% and 34.6%, respectively) compared with other all-comer trials (18% at 2 years in the RESOLUTE All Comers trial) but it is unclear whether there is any impact on very late ST rates in the present study. Analysis of DAPT adherence by geographic region (Table 4) suggests that prolonged use of DAPT varies regionally, use is most likely affected by numerous clinical and socioeconomic confounders, and there is uncertainty regarding the balance of risk and benefit of longer versus shorter DAPT use.

These results should be interpreted in the context of the following limitations. The overall, mean accrual rate per site was low in our study (3–4 patients per month). At the time of study initiation, R-ZES was a new device. There may, therefore, have been a bias against use of the stent, particularly because there were other DES available at that time. Although it has been suggested that underreporting of adverse events could occur more often in observational studies, we believe that the consistency of outcomes with previous R-ZES trials and numerous trial procedures confirm the validity of our results. These procedures included database self-checks and an independent CEC. We did, however, observe an apparently lower rate of TV-MI events in RESOLUTE International than in RESOLUTE All Comers (Fig. 4). This apparent difference may have been driven by underreporting of non-Q-wave events, which are more likely to be missed in long-term follow-up than Q-wave MIs.

In order to perform studies that mimic real-world practice as much as possible, treatment should be based on institution-specific procedures, typically based on expert-driven guidelines[29,30] as was recommended in the RESOLUTE International study. Each investigational site was encouraged to treat patients presenting for PCI using the same standard procedures applied to patients not treated within a clinical trial. Therefore, we believe that the event rates following treatment with the R-ZES in our study closely represent real-world use of

the stent. The post hoc analyses evaluating DAPT interruption and ST were exploratory and limited by the small number of observed events.

Conclusion

The 3-year clinical outcomes in this unrestrictive, diverse, real-world patient trial confirm the long-term safety and effectiveness of the R-ZES for the treatment of single or multivessel obstructive coronary artery disease. Safety and effectiveness outcomes were similar to rates observed with other new generation DES studies, including findings from the RESOLUTE Global Clinical Program.

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