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5-Year Safety and Efficacy of Resolute Zotarolimus-Eluting Stent

The RESOLUTE Global Clinical Trial Program

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ABSTRACT

OBJECTIVES The authors evaluated the 5-year cumulative incidence of cardiovascular events following Resolute zotarolimus-eluting stent (R-ZES) implantation.

BACKGROUND Individual trials are often underpowered to show differences for low-frequency adverse events. The R-ZES was studied in 10 prospective clinical trials, designed with identical adverse event definitions, ascertainment, and adjudication.

METHODS The RESOLUTE Global Clinical Trial Program includes 7,618 patients treated with R-ZES: RESOLUTE first-in-human study (N = 139), RESOLUTE All Comers (N = 1,140), RESOLUTE International (N = 2,349), RESOLUTE US (N = 1,402), RESOLUTE US 38 mm (N = 114), RESOLUTE Japan (N = 100), RESOLUTE Japan Small Vessel Study (N = 65), RESOLUTE Asia (N = 311), RESOLUTE China Randomized Controlled Trial (N = 198), and RESOLUTE China Registry (N = 1,800). The 5-year cumulative incidence of events was calculated.

RESULTS The 5-year cumulative incidence of cardiac events was 13.4% for target lesion failure and included 5.0% cardiac death, 4.4% target vessel myocardial infarction, and 6.3% clinically driven target lesion revascularization. Dual-antiplatelet therapy at 1, 3, and 5 years was 91%, 37%, and 32%, respectively. The 5-year cumulative incidence of definite or probable stent thrombosis was 1.2%, which comprised 0.7% at 1 year and an annualized rate of 0.1% thereafter. Five-year use of dual-antiplatelet therapy varied geographically from 63% in Japan to 11% in Europe.

CONCLUSIONS In the largest group of R-ZES patients examined to date, the majority of stent-related events, including target vessel myocardial infarction and stent thrombosis, occurred within the first year of implantation with much lower risks of these events out to 5 years. (J Am Coll Cardiol Intv 2017;10:247–54) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ARC = Academic Research Consortium

DAPT = dual-antiplatelet therapy

DES = drug-eluting stent(s)

MI = myocardial infarction

R-ZES = Resolute zotarolimus-eluting stent(s)

ST = stent thrombosis

TLF = target lesion failure

TLR = target lesion revascularization

TV-MI = target vessel myocardial infarction

Although bare-metal stents were associated with high rates of restenosis and repeat revascularization, after 1 year, once the stent healed, restenosis and stent thrombosis (ST) were rare (1). First-generation drug-eluting stents (DES) used antiproliferative drugs to reduce neointimal hyperplasia and restenosis, but were associated with higher rates of very late ST (after 1 year) as compared with bare-metal stents (2–4). The higher risk of late adverse events with first-generation DES has been attributed to chronic inflammation (5) and delayed and incomplete re-endothelialization (6,7). Furthermore, late neoatherosclerotic changes (8) have resulted in a "late catch-up" phenomenon with first-generation DES (9,10). Second-generation DES, including Resolute zotarolimus-eluting stent (R-ZES) (Medtronic, Santa Rosa, California) and Xience everolimus-eluting stent (Abbott Vascular, Santa Clara, California), have demonstrated improved safety profiles compared with first-generation DES (11,12). However, individual trials are often underpowered to evaluate low-frequency adverse events, in particular very late ST, and limited long-term data are available.

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The RESOLUTE Global Clinical Trial Program includes 10 prospective trials with common clinical definitions and adjudication procedures (13–20). These features allow outcomes from the program to be pooled to provide reliable estimates of the true risk of long-term cardiovascular events. We evaluated short- and long-term 5-year outcomes with R-ZES in the RESOLUTE Global Clinical Trial Program.

METHODS

STUDY DESIGN AND POPULATION. Subjects treated with R-ZES were pooled from 10 trials in the RESOLUTE Global Clinical Trial Program (**Table 1**). Study designs and results have been published previously (13,14,16–19,21,22). The majority of patients were enrolled in all-comers trials (RESOLUTE All Comers, RESOLUTE International, RESOLUTE China Randomized Controlled Trial, and RESOLUTE China Registry). All RESOLUTE trials used uniform endpoint definitions, adjudication processes, and follow-up procedures. Post-procedure in all 10 trials, patients were prescribed a minimum of 75 mg of aspirin daily indefinitely and a thienopyridine for a minimum of 6 months. Complete 5-year follow-up is available for the RESOLUTE first-in-human, RESOLUTE All Comers, RESOLUTE US, and RESOLUTE Japan trials. The RESOLUTE International trial has completed the final 3-year planned follow-up; follow-up of all other trials was ongoing at the time of this analysis.

Institutional review boards at all sites approved the study protocol. Written informed consent was obtained from all patients. The trial complies with the Declaration of Helsinki. All clinical outcomes were adjudicated by an independent clinical events committee. Definitions for complex patients, clinically driven target lesion revascularization (TLR), target lesion failure (TLF), and ST are defined as previously described for the RESOLUTE Global Clinical Trial Program (23–25).

STATISTICAL ANALYSIS. All analyses were conducted on an intention-to-treat basis. Continuous parameters were presented as mean ± SD and compared using the Student *t* test or Wilcoxon rank sum test. Nominal parameters were presented as percentages and compared using the Fisher exact test. Kaplan-Meier estimates of the 5-year cumulative incidence of outcomes are presented with 2-sided 95% confidence intervals. Patients who did not experience an endpoint, who prematurely withdrew from the study, or who had not yet reached the 5-year visit at the time of this analysis were censored at the time of last known follow-up. A value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed by the Baim Institute for Clinical Research (Boston, Massachusetts) using PC SAS for Windows version 9.1 (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE AND PROCEDURE CHARACTERISTICS. **Table 2** provides baseline patient and lesion characteristics. The RESOLUTE Global Clinical Trial Program includes 7,618 patients treated with R-ZES. Mean age was 63 ± 11 years, 75% were men, and 30% had diabetes mellitus. One-quarter of patients were revascularized for myocardial infarction (MI) and 38% for unstable angina. One-half of the patients underwent stenting of a small vessel (reference vessel diameter ≤2.75 mm), 15% of a long lesion (lesion length >27 mm), 15% at a bifurcation, and 6% for total occlusion. Although the complexity of patients varied by study, approximately one-half of all patients had 1 or more complex characteristics. A mean of 1.3 ± 0.6 lesions (1.6 ± 1.0 stents) were treated per patient.

CUMULATIVE INCIDENCE OF EVENTS. The 5-year cumulative incidence of adverse cardiac events was 13.4% for TLF, 5.0% for cardiac death, 4.4% for target vessel myocardial infarction (TV-MI), and 6.3% for

clinically driven TLR (Table 3, Figure 1). At 1 year, the cumulative incidence of TV-MI was 2.8%, whereas non-TV-MI was 0.3%. However, the cumulative incidence of TV-MI and of non-TV-MI between 1 and 5 years were 1.8% (or annualized at 0.45%) and 1.0% (or annualized at 0.25%), respectively. The majority of Academic Research Consortium (ARC) definite or probable ST occurred during the first year after the index procedure: the 5-year cumulative incidence of ARC definite or probable ST was 1.2% and comprised 0.5% early ST (<30 days), 0.2% late ST (30 days to 1 year), and 0.5% very late stent thrombosis (1 to 5 years), or an annualized very late ST rate of 0.1%. Adjusted hazard ratios and 95% confidence intervals were calculated for TLF at 5 years stratified by the following baseline covariates: diabetes mellitus, acute coronary syndrome, lesion length, bifurcation, and reference vessel diameter (Table 4).

DUAL-ANTIPLATELET THERAPY. Figure 2 shows patient-reported dual-antiplatelet therapy (DAPT) use for each study and in the pooled analysis. The majority of patients were on DAPT at 30 days, 6 months, and 1 year, and the use was relatively consistent across studies. DAPT at 3 and 5 years in the pooled analysis was 37% and 32%, respectively, and varied considerably by geography: 63% at 5 years in a Japanese population (RESOLUTE Japan) and 11% at 5 years in a European population (RESOLUTE All Comers).

DISCUSSION

In a pooled analysis of 7,618 patients treated with R-ZES in the RESOLUTE Global Clinical Trial Program comprising 10 prospective clinical trials, the 5-year cumulative incidence of TLF was 13.4%, clinically driven TLR 6.3%, and ARC definite/probable ST 1.2%. The majority of stent-related events, including TV-MI and ST, occurred within the first year of implantation, with much lower risks of these events out to 5 years. These findings demonstrate a favorable long-term safety profile of the R-ZES among patients of the type enrolled in the RESOLUTE Global Clinical Trial Program and due to the sustained outcomes after 1 year, annualized at 0.9% for clinically driven TLR and 0.1% for ST.

Relatively large cohorts with 5-year data are needed to analyze late or rare adverse events, including MI and ST. One method to do so is with large randomized controlled trials. The PROTECT (Patient Related OuTcomes with Endeavor versus Cypher Stenting) trial, a randomized trial of 8,709 patients, showed a lower incidence of very late ST

TABLE 1 RESOLUTE Trial Characteristics

	RESOLUTE First-in-Human	RESOLUTE All Comers	RESOLUTE International	RESOLUTE Japan	RESOLUTE US	RESOLUTE Japan SVS	RESOLUTE China RCT	RESOLUTE China Registry	RESOLUTE Asia, Dual Vessel Cohort	R-ZES 38 mm (RESOLUTE US 38 mm and RESOLUTE Asia 38 mm)
Study type	Multicenter, prospective, observational	Multicenter, prospective, randomized	Multicenter, prospective, observational	Multicenter, prospective, observational	Multicenter, prospective, observational	Multicenter, prospective, observational	Multicenter, prospective, randomized	Multicenter, prospective, observational	Multicenter, prospective, observational	Multicenter, prospective, observational
Total number of R-ZES patients	139	1,140	2,349	100	1,402	65	198	1,800	202	223
Lesion criteria	Single de novo lesions	All comers population	All comers population	Up to 2 lesions in 2 separate vessels	Up to 2 lesions in 2 separate vessels	Up to 2 lesions in 2 separate vessels	All comers population	All comers population	2 lesions in 2 separate vessels	At least 1 lesion amenable to 38 mm DES
Planned duration of DAPT*	≥6 months	≥6 months	≥6 months	≥6 months	≥6 months	≥6 months	≥6 months	≥6 months	≥6 months	≥6 months
Planned duration of follow-up	5 yrs	5 yrs	3 yrs	5 yrs	5 yrs	5 yrs	5 yrs	5 yrs	5 yrs	5 yrs
Follow-up completed	5 yrs	5 yrs	3 yrs	5 yrs	5 yrs	3 yrs	3 yrs	2 yrs	2 yrs	3 yrs

*All trials recommended daily aspirin indefinitely.
DAPT = dual-antiplatelet therapy; DES = drug-eluting stent; R-ZES = Resolute zotarolimus-eluting stent.

TABLE 2 Baseline Patient and Lesion Characteristics

	Resolute (N = 7,618 Patients; N = 10,186 Lesions)
Patients	
Age, yrs	63 ± 11
Male	75 (5,747/7,618)
Diabetes mellitus	30.4 (2,317/7,618)
Insulin-dependent diabetes	6.7 (514/7,618)
History of hypertension	71 (5,406/7,618)
History of hyperlipidemia	62 (4,747/7,618)
History of smoking	57 (4,376/7,618)
Prior PCI	26 (1,966/7,618)
Prior coronary artery bypass surgery	6 (480/7,618)
Prior MI	29 (2,204/7,548)
Reason for revascularization	
Stable	33 (2,327/7,042)
Unstable	38 (2,683/7,042)
MI	26 (1,825/7,042)
Lesions	
Pre-procedure RVD, mm	2.8 ± 0.5 (9,619)
Lesion length, mm	18.2 ± 11.3 (9,518)
Pre-procedure percent diameter stenosis	77.5 ± 16.2 (9,868)
Moderate/severe calcification*	30.0 (2,269/7,567)
LAD vessel location	53.2 (4,049/7,618)
AHA/ACC lesion class B2/C*	72.0 (5,462/7,586)
Pre-procedure TIMI flow grade 3*	78.8 (5,979/7,586)
Small vessel (RVD ≤2.75 mm)	49.0 (4,715/9,619)
Long lesions (lesion length >27 mm)	14.7 (1,397/9,518)
Bifurcation lesion	14.5 (1,103/7,603)
Total occlusion	6.1 (603/9,894)
In-stent restenosis	4.2 (321/7,603)
Multivessel treatment	20.5 (1,562/7,618)
Complex patient	46.7 (3,561/7,618)
Number of lesions treated per patient	1.3 ± 0.6
Number of stents per patient	1.6 ± 1.0
Total stent length per patient, mm	33.1 ± 22.6

Values are mean ± SD or % (n/N). *For patients with multiple lesions, worst case is used.

AHA/ACC = American Heart Association/American College of Cardiology; LAD = left anterior descending; MI = myocardial infarction; PCI = percutaneous coronary intervention; RVD = reference vessel diameter; TIMI = Thrombolysis In Myocardial Infarction.

TABLE 3 Cumulative Incidence of Cardiovascular Events Up to 5 Years*

Event	Incidence
MACE	18.6
Target lesion failure	13.4
Target vessel failure	16.6
Death	9.9
Cardiac death	5.0
All MI	5.6
TV-MI	4.4
Cardiac death or TV-MI	8.7
Clinically driven TLR	6.3
Clinically driven TVR	10.0
ARC definite or probable ST	1.2
Definite	0.8
Probable	0.4

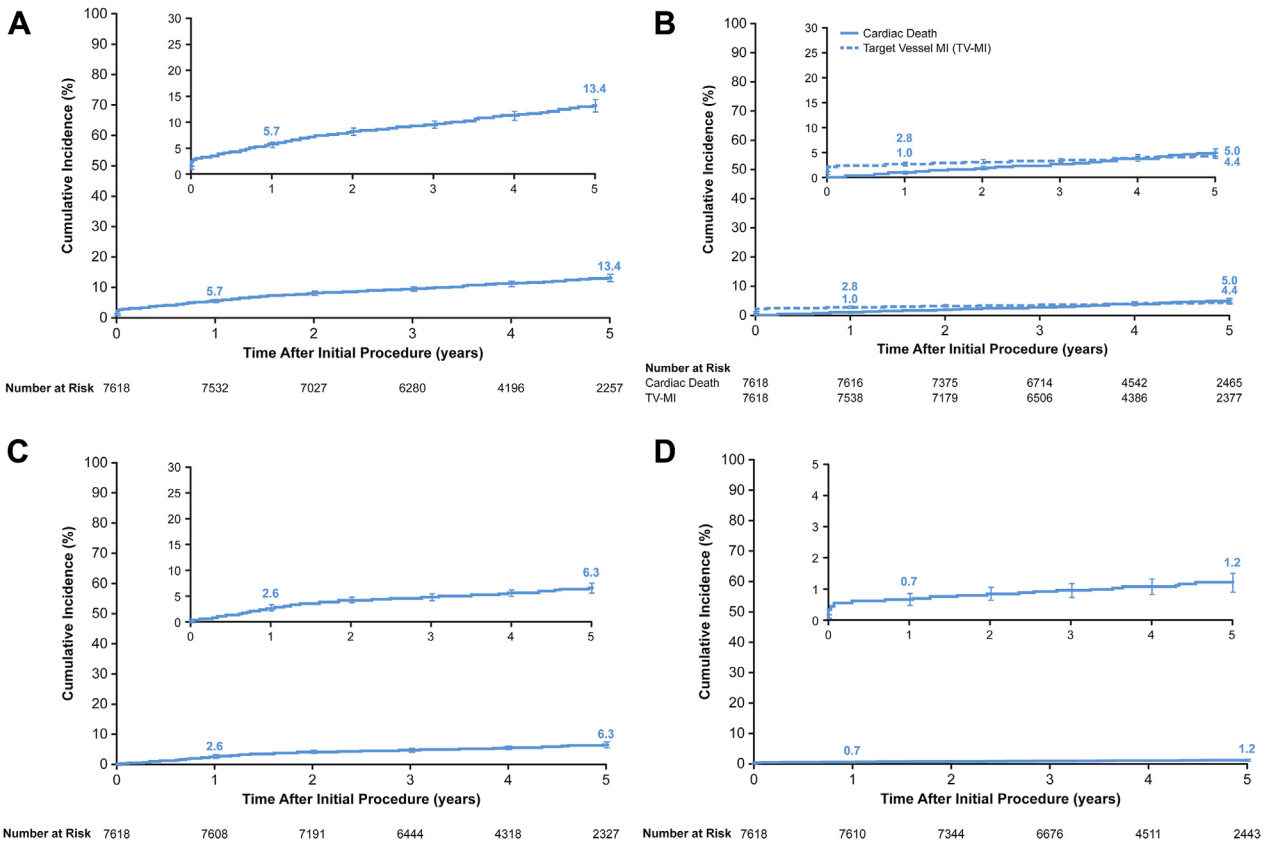
*Kaplan-Meier estimates (%). N = 7,618 at baseline.

ARC = Academic Research Consortium; MACE = major adverse cardiac event(s); MI = myocardial infarction; ST = stent thrombosis; TLR = target lesion revascularization; TV-MI = target vessel myocardial infarction; TVR = target vessel revascularization.

with Endeavor compared with Cypher DES at 5 years (0.6% vs. 2.1%; $p < 0.001$) and a similar incidence to that with R-ZES in our analysis (0.5%) (26). Additionally, COMPARE (A Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice) randomized 1,800 patients to Xience or Taxus and showed a lower incidence of very late ST (1 to 5 years) with Xience (2.6% vs. 4.0%; $p = 0.03$) (27). The Resolute All Comers trial, which randomized 2 second-generation DES, showed no difference in long-term cardiovascular event rates between R-ZES and Xience everolimus-eluting stent, including very late ST (1.2% vs. 1.1%; $p = 0.84$) (28). These low adverse event rates with current-generation Resolute and Xience are likely due to design improvements as compared with first-generation DES, including thinner stent struts and use of a more biocompatible polymer (29–31). Despite the fact that in the RESOLUTE Global Clinical Trial program, three-quarters of patients were enrolled in all-comers trials, the 3.7% cumulative incidence of TLR between 1 and 5 years with R-ZES is similar to or numerically lower than that observed in other clinical programs and studies (**Table 5**), as is the 0.5% rate of very late ST (1 to 5 years).

The component studies in the RESOLUTE Global Clinical Trial Program were conducted concurrently in diverse geographies (Asia, Australia, Europe, and North and South America) with the large majority of patients enrolled outside the United States, and geographic differences in long-term use of DAPT were evident. The 5-year use of DAPT was higher in Japan and lower in Europe despite the fact that the European trial was in an all-comers population, 35% of whom were revascularized for acute MI (<72 h from onset of symptoms), whereas the Japanese study included only patients with simple lesions. This difference in DAPT use may reflect not only geographic differences, but also temporal differences. The RESOLUTE All Comers trial enrolled patients in 2008, whereas RESOLUTE Japan did not enroll patients until late 2009 (3,32). Thus, patients had reached 6-month follow-up in RESOLUTE All Comers (the recommended duration of DAPT at the time) before the growing concerns of increased very late ST with

FIGURE 1 5-Year Cumulative Incidence of Events



Five-year cumulative incidence of target lesion failure **(A)**, cardiac death and target vessel myocardial infarction (TV-MI) **(B)**, clinically driven target lesion revascularization **(C)**, and Academic Research Consortium definite or probable stent thrombosis **(D)**.

(first-generation) DES in 2009 (3,33,34). Although the recommended duration of DAPT was 6 months in all studies that comprise the RESOLUTE Global Clinical Trial Program, patients enrolled in studies after 2009 may have been encouraged to extend the duration of DAPT. Furthermore, long-term studies of DES in European countries suggest shorter use of DAPT (27,28,35) than in the United States (36).

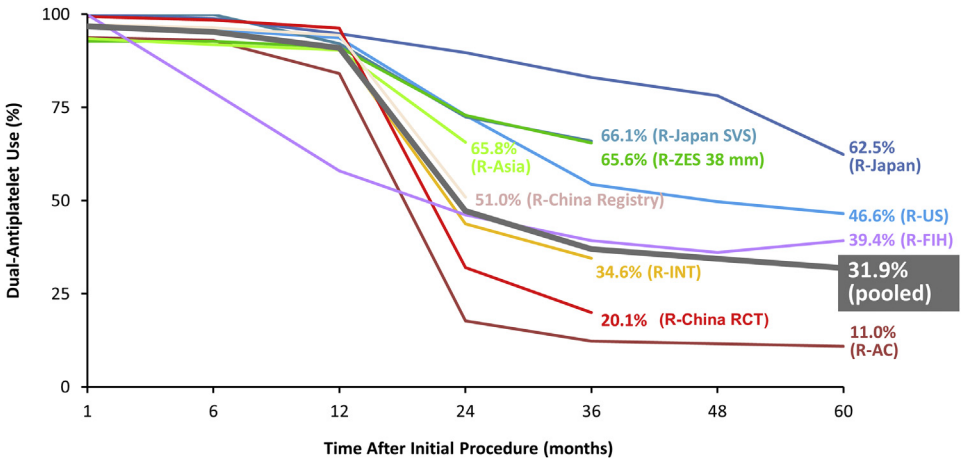
However, despite the variation in long-term DAPT durations used in the included trials, rates of stent-related events such as ST and TV-MI occurred primarily in the first year and were infrequent thereafter. The annualized risk of ST from years 1 to 5 was 0.6% lower than that observed in the first year. Similarly, the annualized risk of TV-MI from years 1 to 5 was 1.7% lower than that observed in the first year. By contrast, the risk of non-stent-related events was constant throughout follow-up. Although the low annualized risk of all MI and very late ST at 1 year may

TABLE 4 Cumulative Incidence of TLF at 5 Years*, Stratified by Various Baseline Covariates

	5 Yrs	Hazard Ratio (95% Confidence Interval)
All patients	13.4 (7,618)	
Diabetes mellitus	18.0 (2,317)	1.408 (1.217–1.630)
No diabetes mellitus	11.5 (5,301)	
Acute coronary syndrome	12.2 (3,693)	0.996 (0.859–1.154)
No acute coronary syndrome	14.5 (3,493)	
Lesion length ≥30 mm	13.7 (955)	1.249 (1.009–1.546)
Lesion length <30 mm	13.1 (6,402)	
Bifurcation	16.2 (1,103)	1.339 (1.106–1.620)
No bifurcation	12.8 (6500)	
RVD ≤2.5 mm	15.0 (2,722)	1.154 (0.992–1.342)
RVD >2.5 mm	12.3 (4,699)	

*Kaplan-Meier estimates are % (N).
RVD = reference vessel diameter; TLF = target lesion failure.

FIGURE 2 5-Year Dual-Antiplatelet Usage in the RESOLUTE Global Clinical Trial Program



Five-year dual-antiplatelet usage in the RESOLUTE Global Clinical Trial Program and across its 10 trials. Pooled **line in gray** represents the pooled outcomes with R-ZES in the RESOLUTE Global Clinical Trial Program. R-AC = RESOLUTE All Comers Trial; R-Asia = RESOLUTE Asia Trial, Dual Vessel cohort; R-China RCT = RESOLUTE China Randomized Controlled Trial; R-China Registry = RESOLUTE China Registry; R-FIH = RESOLUTE First-in-Human Trial; R-INT = RESOLUTE International Registry; R-Japan = RESOLUTE Japan Trial; R-Japan SVS = RESOLUTE Japan Small Vessel Study; R-US = RESOLUTE US Trial; R-ZES 38 mm = RESOLUTE US 38 mm substudy and R-Asia 38 mm substudy.

indicate that discontinuation of DAPT at 1 year is justified in this patient population, there has been a growing emphasis on individualizing DAPT duration and continuing long-term therapy in those at greater risk for ischemia and lowest risk of bleeding (37,38). Although the patient populations were distinct, the rate of very late ST observed in our analysis of RESOLUTE over years 1 through 5 (0.5%) was comparable to the 0.4% rate of ST observed over 12 to 30 months in the DAPT Study group randomized to

TABLE 5 Baseline Demographics and Key Clinical Outcomes Across Clinical Studies and Clinical Study Programs

	Cypher (41) (N = 878)	Taxus (42) (N = 1,400)	Endeavor (43) (N = 2,132)	Xience (36,44) (N = 669)	Resolute (N = 7,618)	Synergy (45) (N = 846)	Absorb (46) (N = 2,164)
Age, yrs	62 ± 11	63 ± 11	63 ± 11	63 ± 11	63 ± 11	64 ± 10	63 (56–71)
Male	71.6 (629/878)	71.5 (1,001/1,400)	71.5 (1,524/2,132)	70.1 (469/669)	75.4 (5,747/7,618)	70.6	72.6 (1,568/2,161)
Diabetes mellitus	22.2 (195/878)	25.4 (355/1,400)	26.1 (555/2,129)	29.6 (198/669)	30.4 (2,317/7,618)	31.1	30.2 (652/2,159)
Prior MI	33.2 (287/865)	31.4 (430/1,369)	28.5 (604/2,117)	19.9 (130/652)	29.2 (2,204/7,548)	25.9	21.3 (457/2,143)
Reference vessel diameter, mm	2.7 ± 0.5	2.7 ± 0.5	2.7 ± 0.5 (2,124)	2.8 ± 0.5 (772)		2.6 ± 0.5	2.7 ± 0.4
AHA/ACC class B2/C lesions	59.1 (517/875)	64.0 (788/1,231)	71.4 (1,516/2,124)		72.0 (5,462/7,586)	76.8	66.6 (1,511/2,270)
TLR (0–5 yrs)	9.6 (80)	12.3 (162)	7.4 (151)	8.6 (54)	6.3		
0–1 yr	4.3 (37)	7.2	4.7 (99)	3.5	2.6	2.8	2.7 (57/2,147)
1–5 yrs	5.3 (43)	6.3	2.7 (52)	5.0	3.7		
MI (0–5 yrs)	7.9 (67)	7.7 (102)	3.3 (67)	4.4 (28)	5.6		
0–1 yr	3.8 (33)	3.8	2.2 (46)	2.8 (18/653)	3.0	5.3	5.7 (123/2,147)
1–5 yrs	4.2 (34)	3.9	1.1 (21)	1.6	2.6		
ARC definite/probable ST (0–5 yrs)	2.1 (17)	2.3	0.9 (19)	1.4 (9)	1.2		
0–1 yr	0.7 (6)	0.9	0.6 (12)	1.1	0.7	0.4 (3/832)	1.3 (28/2,130)
1–5 yrs	1.4 (11)	1.4	0.3 (6)	0.5	0.5		

Values are mean ± SD, median (interquartile range), % (n/N), or % (n).
Abbreviations as in Tables 2 and 3.

extended therapy (39). However, as more than one-half of the reduction in MI from long-term DAPT is related to the prevention of non-stent-related events (40), the low rates of ST observed here do not preclude the importance of prolonged DAPT in patients with high ischemic and low bleeding risk, for whom continuation of DAPT beyond 1 year may be important.

STUDY LIMITATIONS. Although the 10 prospective trials in the RESOLUTE Global Clinical Trial Program used the same endpoint definitions, adjudication processes, and follow-up procedures, patient populations varied, and patients enrolled may be of lower risk than those treated in the general population. Additionally, DAPT therapy beyond 1 year was not specified by any of the individual study protocols. Finally, although we tabulated clinical outcomes across multiple clinical programs, and baseline characteristics in these programs were similar, differences in trial designs exist and direct comparisons should be applied with caution.

CONCLUSIONS

Individual trials are often underpowered to evaluate low-frequency adverse events. Analysis of 7,618 patients treated with R-ZES in the RESOLUTE Global Clinical Trial Program, which comprised 10 prospective clinical trials with identical adverse event definitions, ascertainment, and adjudication, demonstrated a low rate of cardiac events as well as ST, particularly after the first year, that remained stable at 5 years.

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PERSPECTIVES

WHAT IS KNOWN? The concern of ST and neoatherosclerotic changes with first-generation DES compared with bare-metal stents were driven by late cardiovascular events (1 to 5 years). Second-generation DES have demonstrated an improved safety profile compared with first-generation DES; however, limited 5-year data in a large patient population are available with second-generation DES.

WHAT IS NEW? This analysis of 7,618 patients treated with R-ZES in the RESOLUTE Global Clinical Trial Program demonstrated a low cumulative incidence of cardiac events as well as definite or probable ST at 1 year that remained low and stable between 1 and 5 years. Stent-related events were rare after the first year.

WHAT IS NEXT? Future studies may help confirm the safety and efficacy of R-ZES in understudied or higher risk populations.

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