Clinical and Angiographic Evaluation of the Resolute Zotarolimus-Eluting Coronary Stent in Japanese Patients

– Long-Term Outcome in the RESOLUTE Japan and RESOLUTE Japan Small Vessel Study –

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Background: This study evaluated the safety and efficacy of the RESOLUTE™ zotarolimus-eluting stent (R-ZES; Medtronic, Inc, Santa Rosa, CA, USA) in Japanese patients for the treatment of de novo native coronary lesions.

Methods and Results: Both RESOLUTE Japan (R-Japan) and RESOLUTE Japan Small Vessel Study (R-Japan SVS) were prospective, multicenter, single-arm observational studies. R-Japan enrolled 100 patients (reference vessel diameter, 2.5–3.5 mm) and R-Japan SVS enrolled 65 patients (at least 1 lesion suitable for 2.25-mm stent) treated with R-ZES. In R-Japan, in-stent late lumen loss (LLL; the primary endpoint) at 8 months was 0.12 ± 0.22 mm and volume obstruction on intravascular ultrasound was $2.33 \pm 3.51\%$. At 4 years, there were no cases of clinically driven target lesion revascularization (TLR); the target lesion failure (TLF; composite of cardiac death, target vessel myocardial infarction, and clinically driven TLR) was 5.6% (5/90). In R-Japan SVS, in-stent LLL at 9 months was 0.27 ± 0.33 mm, TLF (primary endpoint) was 4.6% (3/65), without incidence of TLR. At 3 years, TLF was 7.9% (5/63) and clinically driven TLR, 3.2% (2/63).

Conclusions: R-Japan and R-Japan SVS demonstrate substantial suppression of neointimal hyperplasia, low LLL, and excellent and sustained long-term clinical outcome with R-ZES in Japanese patients. (*Circ J* 2015; **79**: 96–103)

Key Words: Coronary restenosis; Drug-eluting stent; Interventional ultrasonography; Percutaneous coronary intervention; Zotarolimus

Use of the Resolute zotarolimus-eluting stent (R-ZES; Medtronic, Inc, Santa Rosa, CA, USA) for percutaneous coronary intervention (PCI) has been associated with excellent long-term outcomes throughout the Global RESOLUTE Clinical Trial Program. There are limited data, however, on Japanese patients. The Resolute Asia (R-Asia) study was recently conducted throughout Asia, but it included few Japanese patients and focused on complex subgroups (currently data are available only for the 38-mm length cohort).¹

Genetic and ethnicity variations might influence the safety and effectiveness of the R-ZES in Japanese patients. Kohsaka et al compared the clinical characteristics of >8,000 patients who underwent elective coronary revascularization in Japan (Coronary Revascularization Demonstrating Outcome registry

[CREDO-Kyoto]) with >7,000 similar US patients (Texas Heart Research database) and found that Japanese patients were older, more likely to be smokers and have diabetes mellitus or prior stroke, but less likely to be obese, have prior myocardial infarction (MI), renal insufficiency, history of peripheral vascular disease, or hypertension.² Furthermore, there may be procedural differences. Japanese operators are more likely to use intravascular ultrasound (IVUS) guidance, to post-dilate stents, and to use higher inflation pressures.^{3–6}

RESOLUTE Japan (R-Japan) and the RESOLUTE Japan Small Vessel Study (R-Japan SVS) were designed to evaluate the safety and efficacy of R-ZES in Japanese patients. Clinical outcomes from these 2 studies have not previously been published.

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Methods

Study Overview and Patients

The R-Japan and R-Japan SVS were prospective, multicenter, single-arm, open-label trials that enrolled patients with ischemic heart disease attributable to stenotic native coronary artery lesions that were amenable to treatment by percutaneous stenting with R-ZES.

Patients eligible for enrollment were ≥ 20 years with clinical evidence of ischemic heart disease, stable or unstable angina, silent ischemia, and/or a positive functional study. To be considered for inclusion, patients had to have native coronary artery de novo lesions consisting of either a single target lesion or 2 target lesions in separate vessels. Target lesions had to be ≤ 27 mm in length (and therefore amenable to single stent implantation) and have $\geq 50\%$ and $< 100\%$ stenosis. For R-Japan, target vessel(s) had to have a reference vessel diameter (RVD) of 2.5–3.5 mm (and implanted stents, 2.5–3.5 mm in diameter) and a thrombolysis in MI flow ≥ 2 . The R-Japan SVS required that 1 lesion would be amenable to treatment with a 2.25-mm stent, while a second vessel could be treated with a 2.25–3.5-mm stent.

Patients were excluded if there was evidence of acute MI within 72 h of index procedure, previous PCI of the target vessel within 9 months of index procedure, planned PCI of any vessel within 30 days after the index procedure, or planned PCI of the target vessel(s) within 12 months after the procedure. Additionally, patients were excluded if there were any general contraindications to the revascularization procedure, device, routine antiplatelet therapy, or if the patient had severely impaired left ventricular systolic function (documented left ventricular ejection fraction $< 30\%$). The main angiographic exclusion criteria were: left main or ostial lesions, target lesion involving a side branch > 2.0 mm, severe calcification, 45° bend proximal to the target lesion, target vessel having other lesions $> 40\%$ diameter stenosis, evidence of thrombus or excessive tortuosity (2 bends $> 90^\circ$ to reach the target lesion).

The studies were conducted according to the Declaration of Helsinki. The study protocol was approved by the institutional review board at each site and all patients provided written informed consent.

Procedure

R-Japan enrolled 100 patients between 23 March 2009 and 30 October 2009 at 14 study sites in Japan, and the R-Japan SVS enrolled an additional 65 patients between 17 June 2010 and 5 January 2011 at 11 study sites in Japan. Clinical and demographic data were collected on all patients along with baseline angiographic recordings at stent implantation. Additionally, IVUS data at stent implantation were recorded in all patients enrolled in R-Japan. Stents were deployed according to the standard procedure at each site. Heparin was used to maintain activated clotting time ≥ 250 s. Patients received aspirin (≥ 81 mg daily within 24 h prior to the procedure) and ticlopidine or clopidogrel prior to the procedure, with loading and maintenance dosing according to the manufacturer's instructions for use.

Pre-dilation was mandatory and undertaken with a balloon diameter of at least 0.5 mm smaller than the diameter of the planned stent, and balloon length matching or shorter than the lesion length to be dilated and shorter than the stent to be implanted. Post-dilation was at the discretion of the operator.

Follow-up

All R-Japan trial patients were requested to undergo follow-up angiography and IVUS at 8 months after the procedure while

all R-Japan SVS patients were requested to undergo angiographic follow-up at 9 months. Clinical follow-up was conducted for both study cohorts at 30 days, 6, 9 and 12 months after the procedure, and yearly thereafter, and was completed either by phone or outpatient clinic visit. All R-Japan trial centers reported 12-month outcomes. Patients were required to consent again after 1 year. One center (8 subjects) elected to stop participation after 12 months, but patients are still followed for safety information as required by the local regulatory agency.

Endpoints

Device success was defined as the attainment of $< 50\%$ residual stenosis on quantitative coronary angiography (QCA). Lesion success was defined as device success using the study device only. Procedure success was defined as device success and without the occurrence of major adverse cardiac event (MACE) during the hospital stay.

The R-Japan trial's primary endpoint was in-stent late lumen loss (LLL) assessed at 8 months after the procedure on QCA. Other QCA endpoints in both studies included in-stent and in-segment percent stenosis, rate of binary restenosis, and minimal lumen diameter.

IVUS measurements at 8 months in R-Japan included neointimal hyperplasia, computed as stent minus lumen area, rate of persistent or late incomplete stent apposition (ISA), neointimal hyperplasia volume, and percent volume obstruction. ISA was identified as ≥ 1 struts clearly separated from the vessel wall with evidence of blood speckles behind the strut, and categorized as persistent (visible both at baseline and follow-up), resolved (visible only at baseline), and late acquired (only visible at follow up).⁷

The R-Japan SVS primary endpoint was 9-month target lesion failure (TLF), defined as a composite of cardiac death, target vessel MI or clinically driven target lesion revascularization (TLR) by percutaneous or surgical methods. Secondary clinical endpoints in both studies included the composite endpoint MACE as well as the individual endpoints that comprised MACE: all-cause death, MI, emergency coronary artery bypass graft surgery, and clinically driven TLR on percutaneous or surgical methods. Additionally, target vessel failure was defined as a composite of cardiac death, target vessel MI, and clinically driven target vessel revascularization on percutaneous or surgical methods. Stent thrombosis was defined according to the Academic Research Consortium (ARC) criteria.⁸ Acute device success was defined as achievement of target lesion percent diameter stenosis $< 50\%$ using only the R-ZES; lesion success was defined as acute lesion success by any method, and procedural success was defined as lesion success without in-hospital MACE.

All deaths were considered cardiac unless an unequivocal non-cardiac cause could be established. Any MI that could not clearly be attributed to a vessel other than the target vessel was considered a target-vessel MI. Non-Q-wave MI was defined as elevated creatinine kinase ≥ 2 -fold the laboratory upper limit of normal in the absence of new pathological Q-waves.

Data Management and Core Laboratories

All data were submitted to a central data coordinating facility (Cardiovascular Research Foundation [CRF], New York, NY, USA). Independent Data Safety Monitoring Board, clinical events committee, and core laboratories (CRF) reviewed all primary data. Angiography and IVUS were evaluated by an independent core laboratory at CRF.

Table 1. Baseline and Procedure Characteristics

	RESOLUTE Japan (n=100)	RESOLUTE Japan SVS (n=65)
Baseline characteristics		
Age (years)	67.7±10.4	69.4±9.5 (65)
Male	77.0 (77)	67.7 (44)
BMI (kg/m ²)	24.3±3.1	24.3±3.6
Diabetes mellitus	45.0 (45)	41.5 (27)
Insulin-dependent	10.0 (10)	10.8 (7)
Hypertension	81.0 (81)	87.7 (57)
Hyperlipidemia	78.0 (78)	80.0 (52)
History of smoking	62.0 (62)	56.9 (37)
Current smoker	22.0 (22)	9.2 (6)
Prior PCI	42.0 (42)	67.7 (44)
Prior MI	25.0 (25)	32.3 (21)
Positive stress test	64.3 (27/42)	85.7 (12/14)
History of stroke or TIA	11.0 (11)	13.8 (9)
LVEF >40%	97.0 (96/99)	95.3 (61/64)
Target lesion vessel location (patients)		
Left anterior descending	46.0 (46)	35.4 (23)
Left circumflex	27.0 (27)	35.4 (23)
Right coronary artery	35.0 (35)	38.5 (25)
Lesion characteristics		
	n=108 lesions	n=71 lesions
AHA/ACC lesion class B2/C	52.8 (57)	45.1 (32)
Lesion length (mm)	15.52±5.37	12.75±5.42
Pre-procedure		
RVD (mm)	2.85±0.44	2.12±0.31
MLD (mm)	0.87±0.25	0.67±0.25
% Diameter stenosis	69.17±7.80	68.32±10.73
Procedure characteristics		
	n=108 lesions	n=71 lesions
Post-dilation	78 (84)	73 (52)
Maximum post-dilation pressure (kPa) (n)	1,805±401 (84)	1,712±326 (52)
Final stent length (mm)	20.86±6.34	19.25±5.98
Acute gain in-segment (mm)	1.57±0.41	1.10±0.35
Device success	100	100
Procedure success	98 (98/100)	96.9 (63)
Lesion success	100	100 (71)
Stent fracture type I†	0.9 (1)	0.0 (0)

Data given as mean±SD or % (n). †Single stent fracture. ACC, American College of Cardiology; AHA, American Heart Association; BMI, body mass index; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MLD, minimum lumen diameter; PCI, percutaneous coronary intervention; RVD, reference vessel diameter; TIA, transient ischemic attack.

Statistical Analysis

The aim of this study was to report the long-term outcomes of the R-Japan and R-Japan SVS trials. All analysis was performed on an intention-to-treat basis, defined as the set of 100 patients in the R-Japan and 65 patients in the R-Japan SVS who met the entry criteria in which treatment with the Resolute stent system was intended. Categorical variables are presented as number and percentage and were compared using the chi-squared or the Fisher's exact test. Continuous variable are presented as the number of known values, mean, standard deviation, and were compared using the t-test or Wilcoxon rank-sum test, as appropriate. Cumulative incidence of clinical events was calculated using the Kaplan-Meier method. All statistical analysis was done using SAS (Cary, NC, USA; version 8.1 or higher).

Results

Baseline and Lesion Characteristics

The R-Japan trial enrolled 100 patients (108 lesions) and R-Japan SVS enrolled 65 patients (71 lesions). A total of 90 patients in R-Japan were available at 4 years (2 patients were lost to follow-up and 8 patients were not consented for publication of data beyond 1 year) and 63 patients in R-Japan SVS were available at 3 years due to loss of 2 patients to follow-up. **Table 1** lists the baseline clinical, angiographic, and procedural characteristics for both studies. Among R-Japan and R-Japan SVS patients, mean age was 67.7±10.4 and 69.4±9.5 years, respectively, and 77.0% and 67.7% were men, respectively. There was a high prevalence of diabetes mellitus, history of smoking, history of stroke or transient ischemic attack, and hypertension. As compared with R-Japan SVS, patients in

Table 2. Quantitative Measurements at Baseline and Follow-up

Variable	RESOLUTE Japan		RESOLUTE Japan SVS	
	After procedure (n=100 patients, n=108 lesions)	Follow-up (n=99 patients, n=107 lesions)	After procedure (n=65 patients, n=71 lesions)	Follow-up (n=62 patients, n=67 lesions)
RVD (mm)	2.89±0.44 (108)	2.85±0.42 (107)	2.18±0.35 (71)	2.14±0.32 (67)
In-segment				
MLD (mm)	2.45±0.43 (108)	2.35±0.47 (107)	1.77±0.33 (71)	1.65±0.36 (67)
% diameter stenosis	15.23±7.39 (108)	17.71±8.72 (107)	18.93±9.09 (71)	23.10±12.12 (67)
In-stent				
MLD (mm)	2.79±0.40 (108)	2.66±0.46 (107)	2.11±0.31 (71)	1.86±0.39 (67)
% diameter stenosis	3.28±7.19 (108)	6.52±9.20 (107)	2.93±8.92 (71)	12.92±14.63 (67)
Proximal edge				
MLD (mm)	2.86±0.44 (104)	2.76±0.53 (101)	2.23±0.41 (67)	2.08±0.40 (63)
% diameter stenosis	0.90±8.21 (104)	3.86±11.31 (101)	-2.33±10.94 (67)	2.48±12.68 (63)
Distal edge				
MLD (mm)	2.51±0.49 (104)	2.48±0.48 (105)	1.83±0.33 (68)	1.75±0.37 (65)
% diameter stenosis	12.96±8.99 (104)	13.00±8.36 (105)	16.33±7.52 (68)	18.58±10.44 (65)
Binary restenosis	—			
In-segment	—	0.0 (0/107)	—	3.0 (2/67)
In-stent	—	0.0 (0/107)	—	1.5 (1/67)
Late loss (mm)				
In-segment	—	0.10±0.25 (107)		0.13±0.36 (67)
In-stent	—	0.12±0.22 (107)		0.27±0.33 (67)
Proximal edge	—	0.10±0.27 (100)		0.16±0.38 (62)
Distal edge	—	0.03±0.24 (103)		0.09±0.35 (63)
Loss index				
In-segment	—	0.05±0.17 (107)		0.06±0.48 (67)
In-stent	—	0.07±0.12 (107)		0.18±0.22 (67)

Data given as mean±SD (n) or % (n/N). Abbreviations as in Table 1.

Table 3. IVUS: Change at 8 Months in RESOLUTE Japan

Variable	Baseline (n=105)	Eight-month follow-up (n=103)
Minimal lumen area (mm ²)	5.83±1.83 (105)	5.70±1.92 (103)
Mean lumen area (mm ²)	6.85±2.02 (99)	6.81±2.05 (99)
EEM volume (mm ³)	300.32±149.02 (99)	299.90±128.60 (98)
Plaque volume (mm ³)	150.89±89.06 (99)	151.22±75.58 (98)
Stent volume (mm ³)	149.43±66.34 (99)	148.60±59.57 (99)
Lumen volume (mm ³)	149.28±66.01 (99)	145.70±58.54 (99)
NH volume (mm ³)	NA	3.19±4.53 (99)
Percent volume obstruction	NA	2.33±3.51 (99)
ISA		
After procedure	9.5 (10/105)	NA
Resolved	NA	3.9 (4/103)
Persistent	NA	4.9 (5/103)
Late acquired	NA	2.9 (3/103)
At 8 months	NA	7.8 (8/103)

Data given as mean±SD (n), or % (n). EEM, external elastic membrane; ISA, incomplete stent apposition; IVUS, intravascular ultrasound; NH, neointimal hyperplasia.

R-Japan were less likely to have prior PCI (42.0% vs. 67.7%) or prior MI (25.0% vs. 32.3%).

Lesions characteristics in R-Japan and R-Japan SVS were similar (lesion length 15.5±5.4 mm and 12.8±5.4 mm, class B2/C 53% and 45%, LAD location 43% and 32%, respectively). RVD, however, was 2.85±0.44 mm in R-Japan vs. 2.12±0.31 mm in R-Japan SVS.

Procedural Outcomes

High rates of lesion (100% for both), device (100% for both) and procedure success (98% for R-Japan and 96.9% for R-Japan SVS) were achieved. Physicians in R-Japan chose to use post-dilation 78% of the time. The maximum pressure used for post-dilation was 1,805±401 kPa. Physicians in R-Japan SVS chose to use post-dilation 73% of the time, and maximum

Variable	1 year (n=100)	2 years (n=92)	3 years (n=92)	4 years (n=90)
Target lesion failure	4.0 (4)	4.3 (4)	4.3 (4)	5.6 (5)
Death				
From any cause	1.0 (1)	1.1 (1)	4.3 (4)	5.6 (5)
Cardiac death	0.0 (0)	0.0 (0)	0.0 (0)	1.1 (1)
Target-vessel MI				
Any	4.0 (4)	4.3 (4)	4.3 (4)	4.4 (4)
Q-wave MI	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Non-Q-wave MI	4.0 (4)	4.3 (4)	4.3 (4)	4.4 (4)
Clinically driven TLR	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Clinically driven TVR	1.0 (1)	2.2 (2)	4.3 (4)	4.4 (4)
MACE	5.0 (5)	5.4 (5)	9.8 (9)	12.2 (11)
Target vessel failure	5.0 (5)	6.5 (6)	8.7 (8)	10.0 (9)
Stent thrombosis				
Definite stent thrombosis	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Probable stent thrombosis	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)

Data given as % (n). MACE, major adverse cardiac events; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

Figure 1. Four-year cumulative incidence of target lesion failure in RESOLUTE Japan. R-ZES, Resolute zotarolimus-eluting stent. Target lesion failure is a composite of cardiac death, target vessel myocardial infarction, or clinically driven target lesion revascularization. Event rates were derived using the Kaplan-Meier method.

post-dilation pressure was $1,712 \pm 326$ kPa. Post-procedure acute in-segment gain was 1.57 ± 0.41 mm in R-Japan and 1.10 ± 0.35 mm in R-Japan SVS.

QCA

QCA was available at 8 months in R-Japan and at 9 months in R-Japan SVS (Table 2). The primary endpoint in R-Japan of in-stent LLL at 8 months after the procedure was 0.12 ± 0.22 mm without any occurrence of binary stenosis. R-Japan met its study objective of non-inferiority of 8-month in-stent LLL, and subsequently showed superiority compared to the ENDEAVOR IV Taxus PES arm (0.42 ± 0.50 mm; difference, -0.29 mm; 95% CI: -0.41 to -0.16 , $P < 0.0001$). In R-Japan SVS, 9-month in-stent LLL was 0.27 ± 0.33 mm; there were 2 cases of in-segment (3.0%) and 1 case of in-stent

(1.5%) binary restenosis.

IVUS

R-Japan included IVUS at baseline and at 8 months (Table 3). ISA on IVUS immediately after stenting was present in 9.6% ($n=10$) of implanted stents. ISA resolved at the 8-month IVUS follow-up in 4 of the 10 cases, but there were 3 cases (2.9%) of late acquired ISA. Neointimal hyperplasia volume at 8 months was 3.19 ± 4.53 mm³ (99 lesions) and percent volume obstruction was 2.33 ± 3.51 % (99 lesions).

Clinical Outcome

In R-Japan the incidence of adverse clinical events remained low and the 4-year incidence of TLF was 5.6% (Table 4; Figure 1). No patient required clinically driven TLR. Four

	9 months (n=65)	1 year (n=65)	2 years (n=65)	3 years (n=63)
Target lesion failure	4.6 (3)	6.2 (4)	7.7 (5)	7.9 (5)
Death				
For any cause	1.5 (1)	1.5 (1)	4.6 (3)	6.3 (4)
Cardiac death	1.5 (1)	1.5 (1)	1.5 (1)	1.6 (1)
Target vessel MI				
Any	3.1 (2)	3.1 (2)	3.1 (2)	3.2 (2)
Q-wave MI	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Non-Q-wave MI	3.1 (2)	3.1 (2)	3.1 (2)	3.1 (2)
Clinically driven TLR	0.0 (0)	1.5 (1)	3.1 (2)	3.2 (2)
Clinically driven TVR	0.0 (0)	3.1 (2)	6.2 (4)	6.3 (4)
MACE	6.2 (4)	7.7 (5)	12.3 (8)	14.3 (9)
Target vessel failure	4.6 (3)	7.7 (5)	10.8 (7)	11.1 (7)
Stent thrombosis				
Definite stent thrombosis	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Probable stent thrombosis	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)

Data given as % (n). Abbreviations as in Table 4.

Figure 2. Three-year cumulative incidence of target lesion failure in RESOLUTE Japan Small Vessel Study. R-ZES, Resolute zo-tarolimus-eluting stent. Target lesion failure is a composite of cardiac death, target vessel myocardial infarction, or clinically driven target lesion revascularization. Event rates were derived using the Kaplan-Meier method.

patients experienced non-Q-wave MI: 2 patients had periprocedural MI that were angiographically related to the target vessel, and 2 MI (1 acute and 1 late) could not be clearly attributed to a non-target vessel and were therefore as per protocol attributed as target vessel MI. There was 1 cardiac death that occurred between 3 and 4 years of follow-up.

Outcomes were numerically similar in R-Japan SVS out to 3 years (Table 5). TLF at 9 months occurred in 4.6% (3/65) of patients. The incidence of TLF was below the predicted TLF rate for 2.25-mm patients (9.7% with drug eluting stent, DES) and significantly lower than the pre-specified performance goal of 22.4% with bare metal stent (1-sided 95% CI: 11.5%, $P=0.0003$). One patient died 1 year after stenting due to cardiopulmonary arrest after urgent non-cardiac surgery complicated by disseminated-intravascular coagulation and multi-organ failure. Two patients developed periprocedural MI and

1 had clinically driven TLR 329 days after the index procedure. TLF at 3 years was 7.9% (5/63; Figure 2) due to 1 additional clinically driven TLR that occurred between 1 and 3 years.

Similar to R-Japan, no ARC definite or probable stent thrombosis was reported in R-Japan SVS. Notably, adherence to dual antiplatelet therapy was high, with 100% of patients receiving dual antiplatelet therapy at 30 days, 94.9% (94/99) at 1 year, and 73.2% at 4 years in the R-Japan. In R-Japan SVS, 98.4% (63/64) were on dual antiplatelet therapy at 9 months, and 66.1% (39/59) at 3 years.

Discussion

The key finding of the present study is that use of R-ZES in a Japanese patient group was associated with substantial sup-

pression of neointimal hyperplasia and low rates of repeat revascularization and cardiovascular adverse events. In-stent LLL at 8 months was 0.12 ± 0.22 mm in R-Japan (2.5–3.5 mm RVD) and 0.27 ± 0.33 mm in R-Japan SVS (2.25 mm RVD). At 12 months, the incidence of TLR was 0% in R-Japan and 1.5% in R-Japan SVS, and remained low out to 4 years in R-Japan (0%) and 3 years in R-Japan SVS (3.2%). There were no cases of definite or probable stent thrombosis in either study. Both studies met their primary endpoints.

In comparison to the RESOLUTE US [R-US] study (2.25–4.0-mm stents), a prospective single-arm study conducted in the USA,⁹ R-Japan trial patients were older (67.7 ± 10.4 vs. 64.1 ± 10.7 years), and more likely to have diabetes mellitus (45.0% vs. 34.4%), prior MI (25.0% vs. 21.6%), and a history of smoking (62.0% vs. 20.9%). Moreover, their target lesions tended to be longer (15.52 ± 5.37 mm vs. 13.06 ± 5.88 mm). These differences in patient characteristics are similar to those observed in other analyses comparing Japanese and US patients treated with PCI.^{2,5,10}

In the R-Japan trial stent post-dilation was performed more frequently as compared with the R-US study (78% vs. 49%, respectively; data not shown), and the maximum pressure used for post-dilation was higher (1,805 kPa in R-Japan vs. 1,615 kPa in R-US; data on file at Medtronic, Inc). This higher rate is in line with other comparisons of Japanese vs. US procedural techniques with DES.^{3–6} In a comparison of Japanese and non-Japanese patient outcomes in the PLATINUM (Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of Up to Two de Novo Coronary Artery Lesions) trial, post-dilatation usage was 77.5% vs. 43.7%, and maximum balloon pressure was $1,733 \pm 324$ vs. $1,621 \pm 314$ kPa, respectively.¹⁰ The R-Japan trial achieved as a result a higher post-procedure luminal gain (1.91 mm in-stent and 1.57 mm in-segment) as compared with the R-US study (net gain of 1.72 mm in-stent and 1.34 mm in-segment; data not shown).

The LLL results are in line with those observed with R-ZES in other studies in the RESOLUTE Global Program, including the Resolute China Randomized Controlled Trial (R-China RCT), and RESOLUTE All Comers (R-AC), both conducted in all-comers populations, in addition to R-US. The RESOLUTE China Registry (R-China Registry) and RESOLUTE International (R-INT) studies (both real-world studies), did not include angiographic follow-up. The in-stent LLL in the R-Japan trial at 8 months (0.12 ± 0.22 mm) was numerically lower than that in the R-US angiographic cohort (2.25–4.0 mm, $n=153$ lesions; 0.30 ± 0.54 mm)⁹ and similar to that in R-China RCT at 9 months (0.16 ± 0.38 mm).¹¹ The R-US study included 20 patients in the 2.25-mm stent who underwent 8-month angiographic follow-up. In-segment LLL at 8 months was 0.18 ± 0.36 mm (data not shown), which is similar to that of the R-Japan SVS (2.25-mm stent) at 9 months (0.13 ± 0.36 mm).

The low percent volume obstruction at 8 months on IVUS in R-Japan ($2.33 \pm 3.51\%$) was numerically lower than that in the R-US trial 2.25–4.0-mm cohort with angiographic and IVUS cohort ($5.34 \pm 5.97\%$, $n=63$).⁹ An IVUS analysis conducted with xience everolimus-eluting stent (EES) in SPIRIT II (U.S.) vs. SPIRIT III (Japan) found comparatively similar outcomes: 8-month percent neointimal obstruction was $6.8 \pm 6.4\%$ vs. $3.5 \pm 4.2\%$ ($P=0.0004$).⁵

In the R-Japan trial, IVUS follow-up at 8 months revealed 3 cases (2.9%) of late acquired incomplete apposition, as compared to 1 case (1.7%) of late acquired ISA in R-US.¹² We did not find any correlations between the presence of post-procedure ISA at 8 months and clinical outcome at 1 year.

Moreover, ZES has been found to have a positive impact on vessel remodeling and plaque change beneath the stent on integrated backscatter-IVUS.^{13,14}

Furthermore, the excellent clinical outcomes in R-Japan and R-Japan SVS were similar to those of other studies in the RESOLUTE Global Program. At 1 year, TLF in R-Japan was 4.0% and similar to the 3.7% in the R-US main study (2.5–3.5 mm),⁹ and clinically driven TLR was 0.0% in R-Japan vs. 2.2% in the R-US main study. As expected, 1-year TLF in R-Japan was numerically lower than that in the all comers groups, such as R-AC (8.2%)¹⁵ and R-INT (7.0%),¹⁶ R-China RCT (5.6%)¹¹ and R-China Registry (3.5%).¹⁷

One-year TLF in R-Japan SVS (4.6%) was similar to the RESOLUTE US 2.25 mm (4.8%).⁹ Additionally, in a pooled small vessel analysis (≤ 2.5 mm RVD in R-AC, R-INT, R-US, R-Japan trial) TLF at 2 years was 10.1%¹⁸ as compared with 7.7% in R-Japan SVS at 2 years. The incidence of 12-month TLF in R-Japan SVS (6.2%) was also similar, although numerically lower, to that with EES in the SPIRIT small vessel study (2.25-mm stent; 8.1%, $n=150$).¹⁹

In both R-Japan and R-Japan SVS, the need for repeat revascularization of the target vessel remained low. At 4 years, the rate of clinically driven TLR in R-Japan remained 0%. In R-US (2.5–3.5 mm), the incidence of clinically driven TLR was 2.0% at 1 year⁹ and 4.5% at 4 years (data on file at Medtronic, Inc). Also in small vessels, the incidence of clinically driven TLR in R-Japan SVS was similarly low at 1.5% at 1 year and 3.2% at 3 years.

R-Japan and R-Japan SVS showed no definite or probable stent thrombosis out to 4 years (R-Japan) or 3 years (R-Japan SVS). This exceptional performance of R-ZES is similar to that observed in other studies in the RESOLUTE Global Program, and may also reflect the frequent post-dilation and high maximum deployment pressures. Several studies have suggested that inadequate stent expansion is associated with acute stent thrombosis and restenosis,^{20–22} and adjuvant high-pressure non-compliant balloon post-dilation with IVUS guidance could improve stent expansion^{23,24} and lower restenosis rates.²⁵ The low stent thrombosis rate could be due to the early arterial repair that has been observed on angiography after ZES implantation.²⁶

Study Limitations

The main limitation of this study was that the 2 registries were single-arm non-randomized studies performed on a small number of patients and therefore no conclusion can be drawn on the performance of the R-ZES as compared with other DES in Japanese patients. Additionally, both studies had specific inclusion and exclusion criteria and therefore outcomes cannot be extrapolated to all patient groups. Clinical outcomes in R-Japan and R-Japan SVS, however, appear similar to those seen across the Global RESOLUTE Clinical Trial Program.

Conclusions

R-Japan and R-Japan SVS have demonstrated the safety and efficacy of R-ZES in Japanese patients. R-Japan and R-Japan SVS also represent one of the largest patient cohorts treated with R-ZES with angiographic follow-up mandated on all patients (and IVUS follow-up on all R-Japan patients). Additionally, R-Japan SVS provided valuable clinical outcomes on treatment of small vessels with the 2.25-mm R-ZES. This study, in conjunction with the comprehensive Global RESOLUTE Clinical Trial Program, provides further evidence to support the excellent safety and efficacy of R-ZES in Japanese patients.

treated for native coronary lesions with RVD between 2.25 and 3.5 mm.

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Supplementary Files

Supplementary File 1

Appendix

Please find supplementary file(s);
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