AsiaIntervention 2015;1:18-25

Resolute zotarolimus-eluting coronary stent implantation in Asian patients with multivessel disease and long lesions: clinical outcomes in RESOLUTE Asia

Robaayah Zambahari[1]*, MD; Michael Lee[2], MD; Shirish Hiremath[3], MD; on behalf of the RESOLUTE Asia Investigators

1. Department of Cardiology, National Heart Institute, Kuala Lumpur, Malaysia; 2. Department of Cardiology, Queen Elizabeth Hospital, Hong Kong, China; 3. Department of Cardiology, Ruby Hall Clinic, Pune, India

KEYWORDS

- complex lesions
- coronary artery disease
- drug-eluting stent
- zotarolimus-eluting stent

Abstract

Aims: To examine two-year clinical outcomes after implantation of the Resolute zotarolimus-eluting stent (R-ZES) for the treatment of multivessel disease and long lesions in the RESOLUTE Asia (R-Asia) study.

Methods and results: The R-Asia study includes two cohorts: R-Asia Dual Vessel (≥2 vessels treated with R-ZES) and R-Asia 38 mm (at least one lesion stented with a 38 mm R-ZES). Patients were enrolled simultaneously at 25 centres across Asia from June 2010 to March 2012. A total of 311 patients were enrolled in R-Asia Dual Vessel (n=202) and R-Asia 38 mm (n=109). Device success was 99% in R-Asia Dual Vessel and 97% in R-Asia 38 mm. At two years, clinically driven target lesion revascularisation was 2.5% in R-Asia Dual Vessel and 1.9% in R-Asia 38 mm, and target lesion failure was 5.5% and 4.6%, respectively. There were no cases of ARC definite/probable stent thrombosis in R-Asia Dual Vessel, and a single case (0.9%) of early stent thrombosis in R-Asia 38 mm.

Conclusions: R-Asia demonstrates good long-term safety and efficacy of R-ZES when used for treatment of multivessel disease and for long lesions in an Asian population. Trial registration: ClinicalTrials.gov identifier: NCT01132456.

**Corresponding author: National Heart Institute, 145 Jalan Tun Razak, 50586 Kuala Lumpur, Malaysia.*
E-mail: robaayah@ijn.com.my

DOI: 10.4244/AsiaInterv_V1I1A6

Introduction

Two thirds of patients treated with drug-eluting stents (DES) for coronary artery disease in all-comers studies underwent percutaneous coronary intervention (PCI) of complex lesions[1-4]. Long lesions (>18 mm) and multivessel treatment accounted for 20% and 60% of patients in the RESOLUTE All Comers study, respectively[2]. Longer stent length is associated with higher risk for restenosis[5]. In a study comparing single-vessel and multivessel treatment with DES, the six-month incidence of major adverse cardiac events was more than double among patients undergoing multivessel stenting[6]. The objective of the RESOLUTE Asia (R-Asia) study is to assess outcomes in Asian patients treated with the Resolute™ zotarolimus-eluting stent (R-ZES; Medtronic Inc., Santa Rosa, CA, USA) for multivessel treatment (R-Asia Dual Vessel cohort) and in long lesions (R-Asia 38 mm cohort).

The pooled one-year outcomes of patients treated with the 38 mm R-ZES in the R-Asia 38 mm cohort and the RESOLUTE US (R-US) 38 mm cohort (n=269) have been previously published[7]. Target lesion failure (TLF) at one year was 5.4% and comprised 1.4% clinically driven target lesion revascularisation (TLR), 0.9% cardiac death, and 3.6% target vessel myocardial infarction (MI)[7]. Outcomes in the R-Asia Dual Vessel cohort have not been published.

This report provides the two-year outcomes in both R-Asia Dual Vessel and R-Asia 38 mm. The R-Asia study also extends the RESOLUTE Global Program to include more clinical outcome data in Asian patients. Differences in patient characteristics between Asian and Caucasian populations could affect clinical outcomes. As compared to Caucasian populations, Asian populations tend to have a smaller body habitus and therefore smaller coronary arteries[8,9], a lower body mass index, and different associations of body mass index and health risks[10-12]. R-Asia builds on the clinical results available in an Asian population, including RESOLUTE China (R-China) Randomised Controlled Trial (RCT)[13] and R-China Registry[14], conducted in China, and RESOLUTE Japan[15], conducted in Japan. This report also discusses differences in clinical outcomes from those observed in other studies, including in primarily Caucasian patients.

Methods

R-Asia was a closed-cohort, observational study which enrolled patients implanted with R-ZES from June 2010 to March 2012 at 25 centres in Bangladesh, Hong Kong, India, Indonesia, Korea, Malaysia, Singapore, Taiwan, and Thailand. The study was registered at ClinicalTrials.gov (NCT01132456).

Patients enrolled in R-Asia were adults eligible for PCI due to clinical evidence of ischaemic heart disease, stable/unstable angina, or silent ischaemia, or who had a positive functional study, and stenotic lesions (≥50% and <100%) in *de novo* native coronary arteries with a reference vessel diameter of 3.0 to 4.0 mm (assessed visually by the site) and lesion length ≤35 mm in the 38 mm length cohort, and reference vessel diameter of 2.25 mm to 4.0 mm and lesion length of ≤27 mm in the Dual Vessel cohort. Thrombolysis In Myocardial Infarction (TIMI) flow score ≥2 was required. The R-Asia 38 mm cohort enrolled patients with one or two lesions, in which at least one lesion met the reference vessel diameter and lesion length requirements and could be treated with the 38 mm length R-ZES. Dual target lesions required separate vessels in both cohorts.

Stent usage determined cohort assignment **(Figure 1)**. Exclusion criteria included hypersensitivity to study materials and drugs, serious cardiovascular or circulatory comorbidities, planned PCI of any vessel within 30 days post-index procedure and/or planned PCI of the target vessel(s) within 12 months post-procedure, inability to comply with the dual antiplatelet regimen, acute MI within 72 hours, severe calcification, and unprotected left main disease. Physicians implanted R-ZES according to the instructions for use. Patients in both cohorts with >1 target lesion underwent treatment of all lesions during the index procedure.

The hospital's routine standard of care was followed in line with applicable guidelines and the R-ZES instructions for use, in conjunction with dual antiplatelet therapy: 75 to 100 mg of aspirin for three days prior to the index procedure or a periprocedural loading dose of 250 to 500 mg; 75 mg of clopidogrel for three days prior to the procedure or a periprocedural loading dose between 300 and 600 mg. Following the index procedure, the following dual antiplatelet therapy (DAPT) was recommended: 75 to 100 mg of aspirin daily indefinitely and 75 mg of clopidogrel daily for six to 12 months or longer as per physician's decision.

Follow-up visits (telephone or in-clinic evaluation) were scheduled at 30 days, six months, nine months, and annually up to three years in the Dual Vessel cohort and through five years in the 38 mm length cohort. Monitoring (100%) of case report forms and informed consent documentation was conducted on all patients and will continue up to the end of follow-up.

The primary endpoint was one-year target vessel failure (TVF: cardiac death, target vessel MI, or clinically driven target vessel revascularisation [TVR]) for the Dual Vessel cohort, and one-year TLF (cardiac death, target vessel MI, or clinically driven TLR) for the 38 mm cohort. Secondary endpoints included TVF, TLF, and major adverse cardiac events (MACE: death, MI, emergent coronary bypass surgery, or clinically driven TLR), the components of the composite endpoints, death, cardiac death or target vessel MI, and Academic Research Consortium (ARC)[16] definite/probable stent thrombosis. All deaths were considered cardiac unless unequivocally documented otherwise. MI was adjudicated according to the extended historical definition[17]. Revascularisations could be performed either by PCI or by surgery.

Additional endpoints included the attainment of <50% residual stenosis of the target lesion using any percutaneous method (lesion success), using only the assigned device (device success), or with no in-hospital MACE (procedure success).

Event adjudication was performed by an independent clinical events committee composed of cardiologists not involved in the study. Clinical event definitions were harmonised across the RESOLUTE Global Clinical Trial Program, a process that was validated in a prior study[18]. A similarly independent data safety

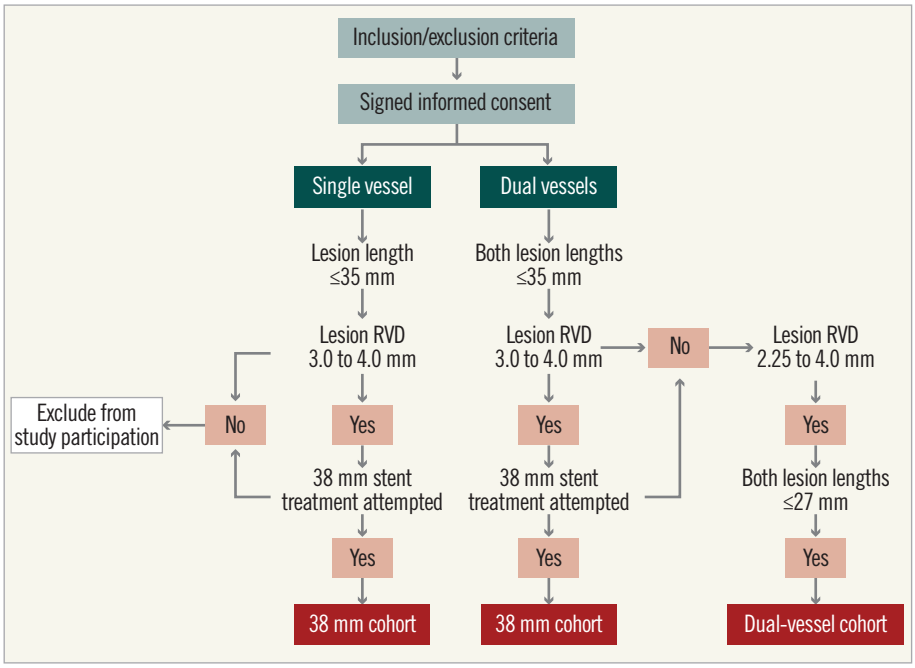

Figure 1. *Enrolment process for the RESOLUTE Asia study. Stent usage determined cohort assignment to either RESOLUTE Asia Dual Vessel cohort or RESOLUTE Asia 38 mm cohort. If the lesion length was ≤35 mm it was at the physician's discretion to consider the patient for 38 mm length RESOLUTE zotarolimus-eluting stent treatment. If no 38 mm length stent treatment was attempted, the patient was considered for enrolment to the Dual Vessel cohort if each vessel had a lesion with length ≤27 mm. RVD: reference vessel diameter*

monitoring board of cardiologists and at least one biostatistician reviewed the study throughout follow-up and could recommend early termination to the sponsor. Angiograms were analysed by an angiographic core laboratory (Cardiovascular Research Foundation, New York, NY, USA).

All patients provided written informed consent. Ethics committee approval was obtained at all sites where it was required, and the protocol complied with the Declaration of Helsinki and local regulations. An independent data safety monitoring board provided guidance on the progress of the trial.

STATISTICAL ANALYSIS

All analyses were conducted based on the intention-to-treat principle. Baseline and outcome data are provided descriptively: categorical variables are reported using counts and percentages, and continuous variables are reported using means and standard deviations. The Kaplan-Meier method was used to calculate time-to-event within each cohort. All analyses were performed using SAS software version 9.1 or later (SAS Institute, Cary, NC, USA).

Results

The R-Asia study enrolled 311 patients (544 lesions): 202 patients (408 lesions) in the Dual Vessel cohort and 109 patients (136 lesions) in the 38 mm cohort. Baseline characteristics are shown in **Table 1**. Mean age was 60±10 and 57±10 years in the R-Asia Dual Vessel and 38 mm cohorts, respectively. In both cohorts, 84% of the patients were men; history of diabetes was present in 46% of the Dual Vessel cohort and 31% of the 38 mm cohort patients. In the 38 mm cohort, only 28% of patients presented with stable angina. Multivessel treatment with R-ZES was performed in 24% of the 38 mm length cohort. **Table 2** provides lesion characteristics and success rates. One third of the lesions in the Dual Vessel cohort

Table 1. Baseline patient characteristics.

	Dual Vessel cohort (N=202 patients)	38 mm cohort (N=109 patients)
Age (yrs)	60.1±9.8	56.9±10.1
Male sex	84.7% (171/202)	84.4% (92/109)
Prior MI	29.4% (58/197)	35.2% (38/108)
Prior PCI	9.4% (19/202)	11.9% (13/109)
Diabetes mellitus	46.0% (93/202)	31.2% (34/109)
Insulin-dependent	6.4% (13/202)	5.5% (6/109)
Hyperlipidaemia	41.1% (83/202)	30.3% (33/109)
Hypertension	69.3% (140/202)	61.5% (67/109)
History of stroke or TIA	3.0% (6/202)	2.8% (3/109)
Current smoker	15.3% (31/202)	18.3% (20/109)
Revascularisation for angina or MI		
Stable angina	41.2% (82/199)	27.5% (30/109)
Unstable angina	47.2% (94/199)	54.1% (59/109)
Myocardial infarction	11.6% (23/199)	18.3% (20/109)

Values are reported as mean±SD or percent of patients (no. of patients/total patients). MI: myocardial infarction; PCI: percutaneous coronary intervention; TIA: transient ischaemic attack

Table 2. Baseline lesion characteristics.

Lesion characteristics	Dual Vessel cohort (n=408 lesions)	38 mm cohort (n=136 lesions)
Vessel location (per lesion)		
LAD	37.6% (142/378)	51.1% (68/133)
LCX	31.2% (118/378)	19.5% (26/133)
RCA	31.2% (118/378)	29.3% (39/133)
RVD, mm	2.69±0.52	2.80±0.34
MLD, mm	0.84±0.39	0.77±0.34
Diameter stenosis, %	68.97±12.71	72.78±11.15
Lesion length, mm	15.26±6.59	26.25±8.50
Total stent length per lesion, mm	21.0±7.1	35.1±10.5
Number of stents per lesion	1.0±0.2	1.0±0.3
Thrombus	4.2% (16/378)	3.8% (5/133)
Calcification		
None/mild	86.8% (328/378)	78.9% (105/133)
Moderate	11.4% (43/378)	19.5% (26/133)
Severe*	1.9% (7/378)	1.5% (2/133)
Pre-procedure TIMI score 0 or 1	2.9% (11/378)	7.5% (10/133)
ACC/AHA modified lesion class B2/C	61.1% (231/378)	87.2% (116/133)
Bifurcation lesion (any)	33.1% (125/378)	45.1% (60/133)
	Dual Vessel cohort (n=202 patients)	**38 mm cohort (n=109 patients)**
Number of lesions treated per patient	2.0±0.2	1.3±0.5
Total stent length per patient, mm	42.5±11.8	44.7±13.7
Number of stents per patient	2.1±0.3	1.3±0.6
Success rates	**Dual Vessel cohort (n=378 lesions)**	**38 mm cohort (n=133 lesions)**
Lesion success, %	100% (377/377)	100% (132/132)
Device success, %	99% (376/378)	97% (129/133)
Procedure success, %	97% (183/188)	97% (103/106)

Values are reported as mean±SD (no. of lesions) or percent of lesions (no. of lesions/total lesions). *Patients enrolled in the study with severe calcification were protocol deviations. ACC/AHA: American College of Cardiology/American Heart Association; LAD: left anterior descending; LCX: left circumflex; MLD: minimum lumen diameter; RCA: right coronary artery; RVD: reference vessel diameter; TIMI: Thrombolysis In Myocardial Infarction

and nearly half in the 38 mm length cohort had bifurcations, and lesion length was 15.26±6.59 and 26.25±8.50 mm, respectively. The lesion length and reference vessel diameter among lesions treated in the R-Asia 38 mm cohort with R-ZES 38 mm (i.e., after excluding any secondary lesions treated with a differently sized stent) were 29.06±6.50 mm and 2.82±0.32 mm, respectively. Both studies attained 100% lesion success, and similarly high rates of device success (99% and 97%) and procedure success (97% and 97%) in the R-Asia Dual Vessel and 38 mm cohorts, respectively.

Table 3 presents clinical outcomes at one and two years in both the Dual Vessel and 38 mm cohorts. In the Dual Vessel cohort, the one-year incidence of TVF was 4.5% (the primary endpoint), TLF 4.0%, clinically driven TLR 1.0%, and target vessel MI 2.5% (all of which occurred in-hospital and were non-Q-wave MI). At two years, the incidence of TVF was 6.5% **(Figure 2A)**, TLF was 5.5% **(Figure 2B)** and clinically driven TLR 2.5%. There were no additional MI events from one to two years, and ARC definite/probable ST remained 0%.

In the 38 mm cohort, the one-year incidence of TLF was 3.7% (primary endpoint) and comprised four target vessel MI events (three of which occurred in-hospital and were non-Q-wave MI, and one of which was a clinically driven TLR in a patient who also had a target vessel MI) in the first 30 days. Between one and two years, there was one additional clinically indicated TLR but no additional target vessel MI events. At two years, the incidence of TLF was 4.6% **(Figure 3A)**, and TVF 5.6% **(Figure 3B)**.

ARC definite/probable stent thrombosis was low in both studies. There were no events in the Dual Vessel cohort and one early stent thrombosis in the 38 mm cohort. DAPT use in the Dual Vessel and 38 mm cohorts was 91% and 94%, respectively, at one year, and 66% and 78%, respectively, at two years.

Discussion

The main findings of our study are the good procedure success and the long-term clinical outcomes in both the R-Asia Dual Vessel and the R-Asia 38 mm study cohorts. Procedure success was 97% in both cohorts. Clinical events remained low. In the Dual Vessel

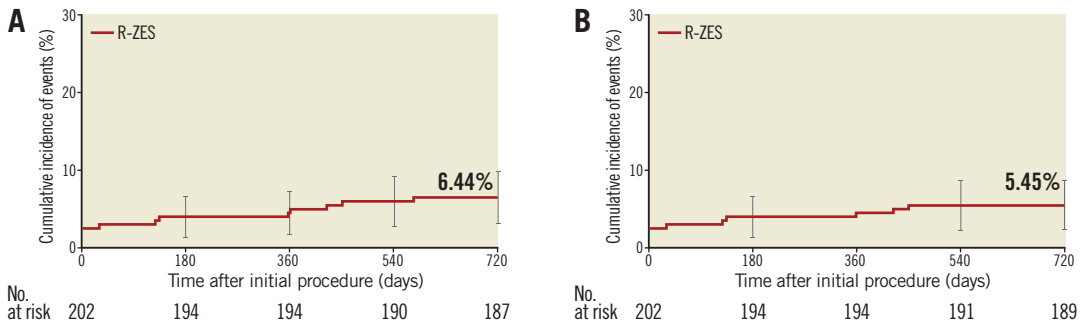

Figure 2. *Cumulative incidence of TVF and TLF at two years in RESOLUTE Asia Dual Vessel cohort. Cumulative incidence of TVF (A) and TLF (B) for all patients assigned to the Dual Vessel cohort. The cumulative incidence of clinical events was calculated using the Kaplan-Meier method and compared using the log-rank test. R-ZES: Resolute zotarolimus-eluting stent; TLF: target vessel failure, a composite of cardiac death, target vessel myocardial infarction, and clinically driven target vessel revascularisation; TVF: target vessel failure, a composite of cardiac death, target vessel myocardial infarction, and clinically driven target vessel revascularisation*

Table 3. One- and two-year clinical outcomes in the RESOLUTE Asia Dual Vessel and 38 mm cohorts.

	Dual Vessel cohort 1 year (N=202 patients)	Dual Vessel cohort 2 years (N=200 patients)	38 mm cohort 1 year (N=109 patients)	38 mm cohort 2 years (N=108 patients)
TLF	4.0% (8)	5.5% (11)	3.7% (4)	4.6% (5)
Death	0.5% (1)	0.5% (1)	0.0% (0)	0.0% (0)
Cardiac death	0.5% (1)	0.5% (1)	0.0% (0)	0.0% (0)
Target vessel MI	2.5% (5)	2.5% (5)	3.7% (4)	3.7% (4)
Clinically driven TLR	1.0% (2)	2.5% (5)	0.9% (1)	1.9% (2)
Clinically driven TVR	1.5% (3)	3.5% (7)	0.9% (1)	2.8% (3)
Cardiac death or target vessel MI	3.0% (6)	3.0% (6)	3.7% (4)	3.7% (4)
MACE	4.0% (8)	5.5% (11)	3.7% (4)	3.7% (4)
TVF	4.5% (9)	6.5% (13)	3.7% (4)	5.6% (6)
ARC definite/probable stent thrombosis	0.0% (0)	0.0% (0)	0.9% (1)	0.9% (1)
Early (≤30 days)	0.0% (0)	0.0% (0)	0.9% (1)	0.9% (1)
Late (31-360 days)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Very late (>360 days)	NA	0.0% (0)	0.0% (0)	0.0% (0)

Values are reported as percent of patients (no. of patients). MACE: major adverse cardiac events (a composite of death, MI, emergent coronary artery bypass surgery, or clinically driven TLR); MI: myocardial infarction; TLF: target lesion failure (a composite of cardiac death, target vessel MI, or clinically driven TLR); TLR: target lesion revascularisation; TVF: target lesion failure (composite of cardiac death, target vessel MI, or clinically driven TVR); TVR: target vessel revascularisation

and 38 mm cohorts, the two-year incidence of TLF was 5.5% and 4.6%, and of TVF was 6.5% and 5.6%, respectively. ARC definite/probable ST was 0% in the Dual Vessel and 0.9% (n=1 early) in the 38 mm cohort. These low adverse event rates were achieved in spite of a complex patient population. In the Dual Vessel and 38 mm cohorts, 59% and close to 72% presented with acute coronary syndrome, and treatment of a bifurcation lesion was 33% and 45%, respectively. Additionally, in the R-Asia 38 mm cohort, lesion length was 26.25±8.50 mm.

Multivessel PCI is associated with a higher risk for repeat revascularisation, target vessel MI and other lesion-specific clinical outcomes. Nevertheless, the R-Asia Dual Vessel cohort showed low adverse events, and compared favourably to everolimus-eluting stent (EES) patients at two years **(Table 4)**[19-21]. In an analysis of the SPIRIT III clinical trial of the XIENCE V everolimus-eluting coronary stent system in patients undergoing multivessel PCI with EES, at two years TLR was 6.1%[19] as compared to 2.5% in the R-Asia Dual Vessel cohort.

Additionally, the R-ZES 38 mm allows for long lesions to be treated with a single stent, thereby reducing the need for stent overlap, which can result in higher neointimal hyperplasia and restenosis rates, even with DES[22]. However, even with a single stent, longer lesions have a greater likelihood of covering a bifurcation, which can lead to side branch jailing and increase the risk of periprocedural myocardial infarction[23]. The design of the R-ZES, with thin, round struts[24] may have decreased emboli dislodgement and might help explain the low rate of target vessel MI (3.7% at 30 days and no events thereafter). Additionally, a concern with long

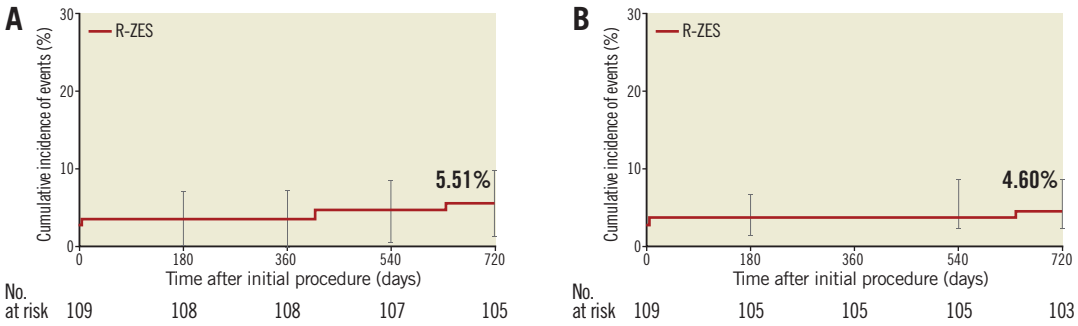

Figure 3. *Cumulative incidence of TVF and TLF at two years in the RESOLUTE Asia 38 mm vessel cohort. Cumulative incidence of TVF (A) and TLF (B) for all patients assigned to the 38 mm cohort. The cumulative incidence of clinical events was calculated using the Kaplan-Meier method and compared using the log-rank test. R-ZES: Resolute zotarolimus-eluting stent; TLF: target lesion failure, a composite of cardiac death, target vessel MI, or clinically driven target lesion revascularisation; TVF: target vessel failure, a composite of cardiac death, target vessel myocardial infarction, and clinically driven target vessel revascularisation*

Table 4. Clinical outcomes for treatment of multivessel disease and long lesions.

		Multivessel PCI		Coronary revascularisation of long lesions		
		R-Asia Dual Vessel cohort (R-ZES)	SPIRIT III analysis on 2-vessel treatment (XIENCE V EES arm)	R-Asia 38 mm cohort (R-ZES)	P38 (XIENCE PRIME EES)	PLATINUM Long Lesion (PROMUS Element EES)
No. at baseline		202	103	109	203	102
One-year outcomes	TLF	4.0 (8)		3.7 (4)		3.1 (3)
	Cardiac death	0.5 (1)	0.0 (0)	0.0 (0)	3.0 (6)	0.0 (0)
	MI		5.0 (5)		3.4 (7)	0.0 (0)
	Target vessel MI	2.5 (5)		3.7 (4)		0.0 (0)
	TLR	1.0 (2)	4.0 (4)	0.9 (1)		3.1 (3)
	TVR	1.5 (3)		0.9 (1)	3.9 (8)	4.1 (4)
	MACE*	4.0 (8)	8.0 (8)	3.7 (4)	10.3 (21)	
	ST	0.0 (0)	~2%	0.9 (1)	1.0 (2)	0.0 (0)
Two-year outcomes	TLF	5.5 (11)		4.6% (5)		8.8 (8)
	Cardiac death	0.5 (1)	1.0 (1)	0.0 (0)		3.6 (3)
	MI		7.1 (7)			0.0 (0)
	Target vessel MI	2.5 (5)		3.7 (4)		0.0 (0)
	TLR	2.5 (5)	6.1 (6)	1.9 (2)		5.2 (5)
	TVR	3.5 (7)		2.8 (3)		7.2 (7)
	MACE*	5.5 (11)	12.2 (12)	3.7 (4)		
	ST	0.0 (0)	~4%	0.9 (1)		0.0 (0)

Values are reported as percent of patients (no. of patients). * MACE was defined in the RESOLUTE Clinical Trial Program, including R-Asia, as the composite of death, myocardial infarction, emergent coronary bypass surgery, or clinically driven TLR; in SPIRIT III as the composite of cardiac death, MI, or TLR. MACE was defined in P38 as the composite of cardiac death, MI, and TVR. MACE: major adverse cardiac events; MI: myocardial infarction; ST: ARC definite/probable stent thrombosis; TLF: target vessel failure; TLR: clinically driven target lesion revascularisation; TVR: clinically driven target vessel revascularisation

stents is tractability in tortuous coronary anatomy; however, the 38 mm R-ZES was delivered successfully in 97% of patients in the R-Asia 38 mm cohort.

The clinical outcomes in R-Asia 38 mm also compared favourably to those observed in other studies **(Table 4)**. In the P38 global study (which had different inclusion and exclusion criteria, including a required lesion length of ≥35 mm), in which XIENCE PRIME™ (Abbott Vascular, Santa Clara, CA, USA) EES was implanted, at one year TVR was 3.9%[20] (as compared with 0.9% TVR in R-Asia 38 mm). Additionally, two-year TLF in the PLATINUM Clinical Trial to Assess the PROMUS Element Stent System for Treatment of Long *De Novo* Coronary Artery Lesions (PLATINUM LL) study (32 mm and 38 mm PROMUS Element™ EES; Boston Scientific, Marlborough, MA, USA) was 8.8%[21], as compared with 4.6% in R-Asia 38 mm.

A RESOLUTE 38 mm substudy of R-Asia 38 mm and R-US 38 mm was prospectively designed to analyse one-year TLF using one vessel per patient and compared with a performance goal (19%) derived from historical data[7]. Even at two years, TLF in R-Asia 38 mm (including patients treated for dual vessel that included R-ZES 38 mm) was 4.6% and well below the one-year historical performance goal of 19%.

The clinical outcomes in R-Asia are also similar to those observed in "non-complex" populations treated with R-ZES. In the R-US main cohort (stent lengths 8-30 mm implanted), two-year TLF was 7.3% and clinically driven TLR was 4.3% (data on file at Medtronic, Inc.) (as compared to 5.5% and 2.5%, respectively, in R-Asia Dual Vessel, and 4.6% and 1.9%, respectively, in R-Asia 38 mm).

The outcomes in R-Asia were similar to those observed with R-ZES in other Asian populations. R-China RCT and R-China Registry both enrolled "all-comer" populations that included multivessel treatment. At one year, in patients treated with R-ZES, TLF was 5.6% in R-China RCT[13], and 3.5% in R-China Registry[14], and by comparison was similar to that in R-Asia: 4.0% TLF in R-Asia Dual Vessel and 3.7% TLF in R-Asia 38 mm.

Given the low adverse event rates in multivessel disease, R-ZES will be used in the "A Comparison of fractional flow reserve-guided percutaneous coronary intervention and coronary artery bypass graft surgery in patients with multivessel coronary artery disease" (FAME 3) trial. FAME 3 (NCT02100722) will randomise patients with multivessel coronary artery disease to PCI with R-ZES implantation assessed using fractional flow reserve vs. coronary artery bypass graft surgery (CABG), and is currently enrolling patients.

Limitations

Our study has important limitations. The R-Asia Dual Vessel and R-Asia 38 mm cohorts were observational studies. However, 100% monitoring was performed in the entire patient population at all clinical follow-up time points. Also, there was no minimum lesion length required in the R-Asia 38 mm cohort. However, the

lesion length was 29.06±6.50 mm in lesions treated with R-ZES 38 mm, and appropriate for treatment with a 38 mm stent length. Furthermore, the R-Asia 38 mm cohort did not exclude dual vessel treatment, and could therefore have created a bias in the R-Asia Dual Vessel cohort, which did not include lesions amenable to a 38 mm stent, as these patients were enrolled in the R-Asia 38 mm cohort. Additionally, SYNTAX score was not common practice at all study sites and was not calculated for all patients as part of the screening process. Lastly, both studies were relatively small, and both studies were specific to an Asian population. However, the clinical outcomes were consistent with those observed across the RESOLUTE Global Clinical Trial Program.

Conclusion

R-Asia Dual Vessel and R-Asia 38 mm demonstrate low two-year repeat revascularisation rates and good long-term safety and efficacy with R-ZES for treatment of multivessel disease and long lesions. R-Asia also extends the evidence supporting the safety and efficacy of R-ZES in the RESOLUTE Global Clinical Trial Program, specifically in an Asian population.

Impact on daily practice

Most patients undergoing percutaneous coronary intervention have complex disease, including multivessel disease or diffuse atherosclerosis. Treating these lesions can be technically challenging and is often associated with higher rates of major adverse cardiac events. There are limited long-term data in multivessel disease and long lesion treatment, in particular among Asian patients. RESOLUTE Asia (R-Asia), comprising R-Asia Dual Vessel (≥2 vessels treated with the Resolute zotarolimus-eluting stent [R-ZES]) and R-Asia 38 mm (at least one lesion stented with a 38 mm R-ZES), demonstrates good procedural outcomes and long-term safety and efficacy of R-ZES for the treatment of both multivessel disease and long lesions.

Acknowledgements

We thank Paul Christensen for study management, Nicole Brilakis and Colleen Gilbert for editorial assistance, and Minglei Liu and Yun Pen for statistical analysis oversight (all from Medtronic, Inc.).

Funding

This study was sponsored by Medtronic, Inc.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Neumann FJ, Widimsky P, Belardi JA. One-year outcomes of patients with the zotarolimus-eluting coronary stent: RESOLUTE International Registry. *EuroIntervention.* 2012;7:1181-8.

2. Serruys PW, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE, Kelbaek H, van Boven AJ, Hofma SH, Linke A, Klauss V, Wijns W, Macaya C, Garot P, DiMario C, Manoharan G, Kornowski R, Ischinger T, Bartorelli A, Ronden J, Bressers M, Gobbens P, Negoita M, van Leeuwen F, Windecker S. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Engl J Med.* 2010;363:136-46.

3. Kedhi E, Joesoef KS, McFadden E, Wassing J, van Mieghem C, Goedhart D, Smits PC. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. *Lancet.* 2010;375:201-9.

4. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Juni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet.* 2008;372:1163-73.

5. Mauri L, O'Malley AJ, Popma JJ, Moses JW, Leon MB, Holmes DR Jr, Teirstein PS, Cutlip DE, Donahoe D, Kuntz RE. Comparison of thrombosis and restenosis risk from stent length of sirolimus-eluting stents versus bare metal stents. *Am J Cardiol.* 2005;95:1140-5.

6. Mikhail GW, Airoldi F, Tavano D, Chieffo A, Rogacka R, Carlino M, Montorfano M, Sangiorgi G, Corvaja N, Michev I, Orlic D, Di Mario C, Colombo A. The use of drug eluting stents in single and multivessel disease: results from a single centre experience. *Heart.* 2004;90:990-4.

7. Lee M, Hiremath S, Zambahari R, Leon M, Mauri L, Yeung A; RESOLUTE US and RESOLUTE Asia Investigators. One-year outcomes of percutaneous coronary intervention with the 38-mm Resolute zotarolimus-eluting stent. *Am J Cardiol.* 2013;112:1335-41.

8. Dhawan J, Bray CL. Are Asian coronary arteries smaller than Caucasian? A study on angiographic coronary artery size estimation during life. *Int J Cardiol.* 1995;49:267-9.

9. Lip GY, Rathore VS, Katira R, Watson RD, Singh SP. Do Indo-Asians have smaller coronary arteries? *Postgrad Med J.* 1999;75:463-6.

10. Choo V. WHO reassesses appropriate body-mass index for Asian populations. *Lancet.* 2002;360:235.

11. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet.* 2004;363:157-63.

12. Wang J, Thornton JC, Russell M, Burastero S, Heymsfield S, Pierson RN Jr. Asians have lower body mass index (BMI) but higher percent body fat than do whites: comparisons of anthropometric measurements. *Am J Clin Nutr.* 1994;60:23-8.

13. Xu B, Yang Y, Yuan Z, Du Z, Wong SC, Genereux P, Lu S; RESOLUTE China RCT Investigators. Zotarolimus- and paclitaxel-eluting stents in an all-comer population in China: the RESOLUTE China randomized controlled trial. *JACC Cardiovasc Interv.* 2013;6:664-70.

14. Qiao S, Chen L, Chen S, Wang W, Zhu G. One-year outcomes from an all-comers Chinese population of patients implanted with the resolute zotarolimus-eluting stent. *Am J Cardiol.* 2014;113:613-20.

15. Saito S, Prpic R, Popma JJ, Alexander J, Krucoff MW; ENDEAVOR Japan Investigators. The clinical evaluation of the Endeavor zotarolimus-eluting coronary stent in Japanese patients with de novo native coronary artery lesions: primary results and 3-year follow-up of the Endeavor Japan study. *Cardiovasc Revasc Med.* 2011;12:273-9.

16. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115: 2344-51.

17. Vranckx P, Cutlip DE, Mehran R, Kint PP, Silber S, Windecker S, Serruys PW. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies. *EuroIntervention.* 2010;5:871-4.

18. Vranckx P, McFadden E, Cutlip DE, Mehran R, Swart M, Kint PP, Zijlstra F, Silber S, Windecker S, Serruys PW. Clinical endpoint adjudication in a contemporary all-comers coronary stent investigation: methodology and external validation. *Contemp Clin Trials.* 2013;34:53-9.

19. Applegate RJ, Hermiller JJ, Sanz M, Doostzadeh J, Pierson W, Su X, Lansky AJ, Sudhir K, Stone GW. Comparison of everolimus-eluting and paclitaxel-eluting coronary stents in patients with two treated vessels: 2-year results from the SPIRIT III randomised trial. *EuroIntervention.* 2010;6:437-46.

20. Sgueglia GA, Belloni F, Summaria F, Conte M, Cortese B, Silva PL, Ricci R, Lioy E, Pucci E, Gaspardone A. One-year follow-up of patients treated with new-generation polymer-based 38 mm everolimus-eluting stent: The P38 study. *Catheter Cardiovasc Interv.* 2014 May 14. [Epub ahead of print].

21. Teirstein PS, Meredith IT, Feldman RL, Rabinowitz AC, Cannon LA, Lee TC, Dens J, Dubois CL, Mooney MR, Pompili VJ, Saito S, Allocco DJ, Dawkins KD, Stone GW. Two-year safety and effectiveness of the platinum chromium everolimus-eluting stent for the treatment of small vessels and longer lesions. *Catheter Cardiovasc Interv.* 2014 Jun 6. [Epub ahead of print].

22. Kereiakes DJ, Wang H, Popma JJ, Kuntz RE, Donohoe DJ, Schofer J, Schampaert E, Meier B, Leon MB, Moses JW. Periprocedural and late consequences of overlapping Cypher sirolimus-eluting stents: pooled analysis of five clinical trials. *J Am Coll Cardiol.* 2006;48:21-31.

23. Popma JJ, Mauri L, O'Shaughnessy C, Overlie P, McLaurin B, Almonacid A, Kirtane A, Leon MB. Frequency and clinical consequences associated with sidebranch occlusion during stent implantation using zotarolimus-eluting and paclitaxel-eluting coronary stents. *Circ Cardiovasc Interv.* 2009;2:133-9.

24. Turco MA. The Integrity bare-metal stent made by continuous sinusoid technology. *Expert Rev Med Devices.* 2011;8:303-6.