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CLINICAL RESEARCH

Clinical Outcomes of the Resolute Zotarolimus-Eluting Stent in Patients With In-Stent Restenosis

2-Year Results From a Pooled Analysis

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Objectives This study sought to assess the clinical safety and effectiveness of the Resolute zotarolimus-eluting stent (R-ZES) in patients with in-stent restenosis (ISR) from 2 large trials.

Background ISR treatment is associated with higher rates of subsequent cardiac events compared with treatment of de novo lesions. Although drug-eluting stents (DES) are an option, second-generation DES are largely untested in the treatment of ISR.

Methods A total of 3,489 patients were pooled from the RAC (RESOLUTE All Comers) trial and the RESOLUTE International (RINT) registry. Two-year clinical endpoints included clinically driven target lesion revascularization (TLR), target lesion failure (TLF), cardiac death (CD), target vessel myocardial infarction (TVMI), combined CD or TVMI (CD/TVMI), and Academic Research Consortium definite and probable stent thrombosis (ST).

Results Overall, 281 patients (8.1%) received an R-ZES for ISR. Two-year TLR and TLF rates were significantly higher in ISR patients than in non-ISR patients (TLR: 12.7% vs. 4.3%, $p = 0.003$; TLF: 17.4% vs. 9.4%, $p = 0.007$); however, the CD/TVMI rate was not (6.9% vs. 6.1%, $p = 0.711$). Seven ISR patients had ST. Two-year outcomes by ISR stent type were similar: bare-metal stent (BMS)-ISR TLR was 12.5% and TLF was 17.2%; DES-ISR TLR was 13.0% and TLF was 18.8%. CD/TVMI was 7.3% and 7.2% for BMS-ISR and DES-ISR, respectively.

Conclusions Using R-ZES to treat ISR appears equally safe in BMS-ISR and DES-ISR, with CD/TVMI rates comparable to 2-year outcomes in other clinical trials. Although revascularization rates are still higher in ISR lesions, the R-ZES offers an effective alternative for treatment of BMS-ISR and DES-ISR. (Randomized, Two-Arm, Non-inferiority Study Comparing Endeavor-Resolute Stent With Abbot Xience-V Stent [RESOLUTE-AC]; NCT00617084; and RESOLUTE International Registry: Evaluation of the Resolute Zotarolimus-Eluting Stent System in a 'Real-World' Patient Population [RINT]; NCT00752128) (J Am Coll Cardiol Intv 2013;6:905–13) © 2013 by the American College of Cardiology Foundation

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Drug-eluting stents (DES) have substantially reduced revascularization rates in de novo lesions, and outcomes have further improved with the advent of second-generation DES. In-stent restenosis (ISR) is historically considered the Achilles heel of percutaneous coronary interventions (PCI) and has been associated with worse outcomes than treatment of de novo lesions. Previous studies have reported target lesion revascularization (TLR) rates around 15% and target vessel revascularization (TVR) rates as high as 22% at 1 year following retreatment of a restenotic lesion (1–5). Moreover, an ISR after DES implantation is regarded as an exceedingly challenging lesion with an even worse outcome than bare-metal stent (BMS)-ISR. Although there are promising observations with drug-eluting balloons (DEB) (5–11) and with certain first-generation DES for treatment of ISR (1), the optimal treatment modality of ISR has yet to be established. In particular, data about ISR treatment with new-generation DES are missing.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CD = cardiac death
DES = drug-eluting stent(s)
ISR = in-stent restenosis
MI = myocardial infarction
PCI = percutaneous coronary intervention
R-ZES = Resolute zotarolimus-eluting stent(s)
ST = stent thrombosis
TLF = target lesion failure
TLR = target lesion revascularization
TVMI = target vessel myocardial infarction
TVR = target vessel revascularization

The Resolute zotarolimus-eluting stent (R-ZES) (Medtronic Vascular, Santa Rosa, California) is a contemporary thin-strut cobalt-chromium, open-cell stent with a thin biocompatible coating (BioLinx, Medtronic Vascular). The R-ZES has been tested in a global clinical trial program of randomized and observational studies in well-defined patient subgroups using similar rigorous methodologies to provide a comprehensive assessment of DES performance in a wide variety of clinical and anatomic conditions. In aggregate, the studies revealed an excellent efficacy and safety of the R-ZES, which is at least noninferior to the everolimus-eluting stent (12–15).

The RAC (RESOLUTE All Comers) and RINT (RESOLUTE International) studies accrued a high proportion of patients with complex clinical and lesion characteristics, including ISR. Here, we present a pooled analysis of RAC and RINT patients with an ISR treated with the R-ZES to assess the clinical safety and effectiveness of the R-ZES in this population. Considering the possibility of a late catch-up following treatment of ISR, which was most striking after brachytherapy (16,17), our analysis comprised a follow-up period of 2 years. An additional analysis compared the performance of the R-ZES depending on the type of restenosis either following BMS or DES implantation.

Methods

Patients and protocol. The design of the RAC and RINT studies, which were both large, multicenter, open-label, prospective clinical trials with minimal exclusion criteria, have been previously described (14,18). Briefly, the RAC trial was a randomized, noninferiority study that compared the R-ZES to the Xience V everolimus-eluting stent (Abbott Vascular, Santa Clara, California) in patients with chronic, stable coronary artery disease or acute coronary syndromes. To be included in the study, patients had to have at least 1 coronary artery stenosis >50% with a reference diameter of 2.25 to 4.0 mm, and there were no restrictions regarding the total number of treated lesions, treated vessels, lesion length, or number of stents implanted. The RINT registry was an observational study of patients with symptomatic coronary artery disease, all of whom received at least 1 R-ZES. Like the RAC trial, the RINT registry had no restrictions on clinical indication (stable angina vs. acute coronary syndromes), number of treated vessels and lesions, lesion type, or lesion length. Both studies were also similar in their exclusion criteria, post-procedure dual antiplatelet therapy, and scheduled follow-up. Exclusion criteria included a known intolerance to a study drug, metal alloys, or contrast media; planned surgery within 6 months after the index procedure; childbearing potential; or concurrent participation in another trial that could affect the study procedures. Post-procedure dual antiplatelet therapy consisted of lifelong daily aspirin (≥75 mg) and daily clopidogrel (75 mg) for at least 6 months. Patient follow-up was performed by telephone or clinic visit at 1, 6, 12, and 24 months and is planned to continue annually for 5 years.

Clinical endpoints and definitions. Similar endpoint definitions were used in the RAC trial and the RINT registry and have been previously described (14,18). The same definitions were used for the endpoints assessed in the present pooled analysis. The principal endpoints for the pooled analysis were: 1) target lesion failure (TLF), defined as a composite of cardiac death (CD), target vessel myocardial infarction (TVMI), or clinically driven TLR; and 2) combined probable and definite stent thrombosis (ST), as defined by the Academic Research Consortium. Using the

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same endpoints, an additional analysis was performed to evaluate the outcomes of ISR patients by stent type (BMS vs. DES). Events as adjudicated in the RAC trial and RINT registry were utilized for the present pooled analysis, and endpoints were assessed at 1 and 2 years.

Statistical analysis. All data were analyzed according to the intention-to-treat principle. Descriptive statistics were determined for baseline patient and lesion characteristics, and data are presented as percentage or mean ± SD. The clinical outcomes were compared with propensity score–adjusted p values to adjust for differences in patient characteristics between groups (ISR vs. non-ISR, and BMS vs. DES-ISR). Propensity scores were calculated using logistic regression with treatment group (ISR vs. non-ISR) as the dependent variable and the following baseline characteristics as the independent variables: age, sex, current smoker, prior PCI, hyperlipidemia, diabetes, hypertension, prior myocardial infarction (MI), prior coronary artery bypass grafting (CABG), unstable angina or MI, target vessel=left anterior descending coronary artery (LAD), American College of Cardiology/American Heart Association lesion class B2 or C lesion, moderate/severe calcification, bend >45°, TIMI (Thrombolysis In Myocardial Infarction) flow grade 3, reference vessel diameter (RVD), lesion length, and pre-procedure percent diameter stenosis. Multivariate predictors were calculated using stepwise logistic regression. Variables selected for the multivariate analysis were those with a p value ≤0.2 in the simple logistic regression analysis. In the multiple logistic regression analysis, only those with a p value of ≤0.1 were kept in the analysis. A p value of <0.05 was considered statistically significant.

The cumulative incidence of events was analyzed using the Kaplan-Meier method and is shown with 2-sided 95% confidence intervals and log-rank p values. For each endpoint, treatment groups were compared on time to event using Cox proportional hazards regression. All statistical analyses were performed using SAS version 9.1 or higher (SAS Institute, Cary, North Carolina).

Results

A total of 3,489 patients were included in the pooled analysis. Of these patients, complete data were available for 3,475. Overall, 3,194 patients received an R-ZES to treat a non-ISR lesion, whereas 281 patients (8.1%) received an R-ZES to treat an ISR lesion (91 patients from the RAC trial and 190 patients from the RINT registry). At 1 year, clinical follow-up data were available in 281 ISR patients and 3,169 non-ISR patients; at 2 years, clinical follow-up data were available in 276 ISR patients and 3,127 non-ISR patients. Table 1 compares the baseline demographics of the ISR patients and non-ISR patients. In summary, ISR patients were older, not current smokers, and had more hypertension, hyperlipidemia, insulin-dependent diabetes mellitus, previous MI, and prior CABG. Patients with ISR more often underwent coronary intervention for stable angina than non-ISR patients; nonetheless, nearly half of the ISR cohort presented with an acute coronary syndrome.

Pre- and post-procedure lesion characteristics for the ISR and non-ISR patients are presented in Table 2. For both groups, the most frequent lesion location was the LAD, followed by the right coronary artery (RCA) and left circumflex artery; however, ISR patients had more RCA

Table 1. Baseline Patient Demographic Characteristics

Baseline Characteristics	Resolute ISR (n = 281)	Resolute Non-ISR (n = 3,194)	p Value
Age, yrs	65.3 ± 10.5 (281)	63.6 ± 11.1 (3,194)	0.015
Male	77.6 (218/281)	77.4 (2,472/3,194)	0.943
Diabetes mellitus	31.0 (87/281)	27.9 (890/3,194)	0.268
Insulin dependent	12.1 (34/281)	8.4 (268/3,194)	0.034
Current smoker	14.6 (41/281)	25.8 (825/3,194)	<0.001
Hyperlipidemia	81.1 (228/281)	62.4 (1,993/3,194)	<0.001
History of hypertension	79.0 (222/281)	68.0 (2,173/3,194)	<0.001
Family history of CAD	36.2 (79/218)	32.0 (809/2,530)	0.197
Prior myocardial infarction	53.9 (151/280)	25.3 (803/3,178)	<0.001
Prior PCI	100.0 (281/281)	24.4 (778/3,194)	<0.001
Prior CABG	12.5 (35/281)	8.5 (272/3,194)	0.026
Cardiac status			<0.001
Stable angina	42.7 (120/281)	35.4 (1,132/3,194)	
Unstable angina	30.6 (86/281)	23.4 (746/3,194)	
Myocardial infarction	16.7 (47/281)	32.6 (1,042/3,194)	

Values are mean ± SD (N) or % (n/N).
CABG = coronary artery bypass graft; CAD = coronary artery disease; ISR = in-stent restenosis; PCI = percutaneous coronary intervention.

Table 2. Pre- and Post-Procedure Lesion Characteristics

Characteristics	Resolute ISR (n = 281 Patients, 410 Lesions)	Resolute Non-ISR (n = 3,194 Patients, 4,614 Lesions)	p Value
Vessel location			<0.001
LAD	36.7 (141/384)	43.9 (1,939/4,412)	
LCX	22.9 (88/384)	24.0 (1,058/4,412)	
RCA	34.6 (133/384)	28.7 (1,267/4,412)	
LMCA	1.6 (6/384)	1.9 (82/4,412)	
SVG	3.6 (14/384)	1.4 (60/4,412)	
LIMA	0.5 (2/384)	0.1 (6/4,412)	
ISR after BMS*	70.8 (199/281)	0.0 (0/3,194)	NA
ISR after DES*	26.0 (73/281)	0.0 (0/3,194)	NA
Pre-procedure thrombus	5.1 (19/370)	10.2 (438/4,286)	0.002
Lesion class B2/C	59.7 (227/380)	64.4 (2,829/4,392)	0.068
RVD, mm†	2.92 ± 0.56 (362)	2.84 ± 0.51 (4,137)	0.005
MLD, mm†	0.69 ± 0.50 (380)	0.62 ± 0.49 (4,365)	0.005
Lesion length, mm†	18.0 ± 12.9 (361)	16.6 ± 10.1 (4,113)	0.040
Stent diameter, mm	3.2 ± 0.5 (281)	3.1 ± 0.5 (3,194)	0.002
Stent length, mm	22.1 ± 6.4 (281)	20.9 ± 6.6 (3,194)	0.005
Pre-procedure % diameter stenosis†	75.5 ± 17.8 (380)	77.6 ± 17.6 (4,365)	0.022
Post-procedure % diameter stenosis†	10.7 ± 14.2 (383)	9.9 ± 13.9 (4,397)	0.220

Values are % (n/N) or mean ± SD (N). *The original stent type was unknown in 9 ISR patients. †For RESOLUTE International, angiographic measurements are site reported.

BMS = bare-metal stent(s); DES = drug-eluting stent(s); ISR = in-stent restenosis; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LIMA = left internal mammary artery; LMCA = left main coronary artery; MLD = minimum luminal diameter; RCA = right coronary artery; RVD = reference vessel diameter; SVG = saphenous vein graft.

lesions and fewer LAD lesions than did non-ISR patients. Both groups had similarly complex, class B2/C lesions, although lesions were longer in ISR patients. Pre-procedure thrombus was present twice as often in non-ISR patients. The RVD and minimum lumen diameter were larger and the percent diameter stenosis was smaller in ISR patients

Table 3. Clinical Outcomes at 1 and 2 Years

	1 Year			2 Years		
Endpoints	Resolute ISR (RAC and RINT) (n = 281)	Resolute Non-ISR (RAC and RINT) (n = 3,169)	p Value*	Resolute ISR (RAC and RINT) (n = 276)	Resolute Non-ISR (RAC and RINT) (n = 3,127)	p Value*
TVF	11.4 (32/281)	7.6 (240/3,169)	0.155	18.8 (52/276)	10.6 (331/3,127)	0.017
TLF	10.7 (30/281)	6.9 (219/3,169)	0.096	17.4 (48/276)	9.4 (294/3,127)	0.007
Death	2.8 (8/281)	2.1 (66/3,169)	0.410	5.4 (15/276)	3.9 (122/3,127)	0.456
Cardiac death	1.8 (5/281)	1.4 (43/3,169)	0.304	2.9 (8/276)	2.6 (81/3,127)	0.565
TVMI	2.8 (8/281)	3.5 (110/3,169)	0.507	4.7 (13/276)	3.8 (120/3,127)	0.905
Cardiac death or TVMI	3.9 (11/281)	4.6 (146/3,169)	0.820	6.9 (19/276)	6.1 (192/3,127)	0.711
Clinically driven TLR	7.5 (21/281)	3.1 (97/3,169)	0.054	12.7 (35/276)	4.3 (135/3,127)	0.003
Clinically driven TVR	8.5 (24/281)	3.8 (122/3,169)	0.097	14.5 (40/276)	5.7 (179/3,127)	0.011
MACE†	12.1 (34/281)	7.8 (248/3,169)	0.107	19.9 (55/276)	11.1 (347/3,127)	0.011
Stent thrombosis, ARC def/prob	2.1 (6/281)	1.0 (32/3,169)	0.269	2.5 (7/276)	1.2 (37/3,127)	0.332
Early (≤30 days)	0.7 (2/281)	0.9 (27/3,169)	0.974	0.7 (2/276)	0.9 (27/3,127)	0.980
Late (>30 and ≤360 days)	1.4 (4/281)	0.2 (6/3,169)	0.185	1.4 (4/276)	0.2 (6/3,127)	0.183
Very late (>360 days)	NA	NA	NA	0.4 (1/276)	0.2 (5/3,127)	0.889

Values are % (n/N). *p value is adjusted to propensity score with the following baseline variables as independent variables: age, sex, current smoker, prior percutaneous coronary intervention, hyperlipidemia, diabetes, hypertension, prior myocardial infarction, prior bypass surgery, unstable angina or myocardial infarction, left anterior descending artery, B2/C lesion, moderate/severe calcification, bend >45°, Thrombolysis In Myocardial Infarction flow grade 3, reference vessel diameter, lesion length, and percent diameter stenosis. †MACE is a composite of death, myocardial infarction (Q-wave and non–Q-wave), emergent coronary artery bypass surgery, or repeat clinically indicated target-lesion percutaneous or surgical revascularization.

ARC = Academic Research Consortium; MACE = major adverse cardiac events; RAC = RESOLUTE All Comers trial; RINT = RESOLUTE International registry; TLR = target lesion revascularization; TVF = target vessel failure; TVMI = target vessel myocardial infarction; TVR = target vessel revascularization; other abbreviations as in Table 2.

compared with non-ISR patients. There was no statistically significant difference in the post-procedure percent diameter stenosis between the 2 groups. Within the ISR group, ISR occurred almost 3 times more often in lesions treated with a BMS than in those treated with a DES.

Clinical outcomes. Table 3 summarizes the clinical outcomes at 1 and 2 years of ISR and non-ISR patients treated with an R-ZES. At 1 year, there were no statistically significant differences in the clinical outcomes between the 2 groups, although a numerical difference was observed in the rate of overall ST (2.1% vs. 1.0%, p = 0.269) and late ST (1.4% vs. 0.2%, p = 0.185) in the ISR and non-ISR cohorts, respectively. At 2 years, however, ISR patients experienced significantly more TVF (18.8% vs. 10.6%, p = 0.017), TLF (17.4% vs. 9.4%, p = 0.007), clinically driven TLR (12.7% vs. 4.3%, p = 0.003), clinically driven TVR (14.5% vs. 5.7%, p = 0.011), and major adverse cardiac events (19.9% vs. 11.1%, p = 0.011). The ST rate was numerically higher in the ISR group (2.5% vs. 1.2%, respectively, p = 0.332), with a marginally significant log-rank p value of 0.058 in the Kaplan-Meier analysis. Nonetheless, rates of death, CD, and TVMI remained similar between the 2 groups. Kaplan-Meier curves illustrating the time to event occurrence for the study's principal endpoints are presented in Figures 1A to 1D.

The proportion of patients on dual antiplatelet therapy at 6 months and 1 year in both the ISR and non-ISR groups was similar (95.3% vs. 95% and 89.4% vs. 89%, respectively). At 2 years, only 41% vs. 35.1% were on dual antiplatelet therapy, but the vast majority of patients (97.3% vs. 95.1%) were receiving aspirin.

Multivariate predictors of TLF. Multivariate analysis identified several independent predictors of TLF in R-ZES–treated patients at 2 years (Table 4). In the total pooled population, predictors of TLF included ISR, prior CABG, vessel bend $\geq 45°$, previous MI, unstable angina, and pre-procedure RVD. In the ISR subgroup, predictors of TLF included prior CABG, unstable angina, and patient age.

Performance of the R-ZES for treatment of a BMS or DES restenosis. Baseline characteristics were similar between patients with a BMS-ISR or DES-ISR treated with an R-ZES (Table 5). Clinical outcomes at 2 years according to ISR stent type were similar (Table 6): for the BMS-ISR subgroup, the rate of TLR was 12.5%, and the rate of TLF was 17.2%; for the DES-ISR subgroup, the rate of TLR was 13.0%, and TLF was 18.8%. Combined CD or MI rates were 7.3% and 7.2% for BMS-ISR and DES-ISR, respectively. Six ST events occurred in the BMS-ISR subgroup, and 1 event occurred in the DES-ISR subgroup.

Discussion

The occurrence of ISR remains a significant limitation of coronary stent implantation in daily practice. Although DES can effectively reduce the incidence of ISR in a given lesion and patient, the global burden of ISR is not reduced by DES due to the increasing use of coronary stents and the higher complexity of treated coronary anatomies.

We assessed one of the largest datasets on patients with ISR from 2 prospective all-comer trials that were designed with consistent definitions, adjudication methods, and data collection. About 8% of the patients in the pooled analysis presented with an ISR. The rate of ISR patients was lower than in previous DES registries (19–22). The numbers of ISR patients were disproportionally high in the alluded registries, probably because restenotic lesions were regarded as a preferable indication for DES implantation as long as DES were not used in all patients without particular contraindications, which was the case in our cohort. Therefore, our ISR ratio presumably represents a more adequate picture of the contemporary ISR burden, of which approximately one-quarter of the ISR patients had a restenosis after former DES implantation.

Although patients with ISR more often underwent coronary intervention for stable angina than did the non-ISR patients, nearly half of the ISR cohort presented with an acute coronary syndrome. The recognition that a considerable proportion of patients with ISR presented with an acute coronary syndrome is in line with several previous reports, which have disproved the original perception of ISR as a benign clinical issue (3,23,24).

ISR may not only cause MIs, but it also has a higher recurrence rate than de novo lesions, and treatment strategies for ISR are by far less established than in other coronary anatomies. Current guidelines recommend the use of cutting or scoring balloons for lesion preparation followed by DEB treatment or DES implantation (25,26). DES of the first generation were effective in the treatment of a restenosis following BMS or DES (1,4,27–29). We present the first large cohort of patients undergoing ISR treatment with a new-generation cobalt-chromium, thin strut, limus-eluting stent, namely the Resolute stent, which releases zotarolimus from a biocompatible polymer.

The principal finding of our investigation was that the TLF rate nearly doubled in patients with ISR, compared with non-ISR patients, and was mainly driven by a higher TLR rate. The Kaplan-Meier curves of TLR rates divided after 6 months and continuously separated thereafter. Nonetheless, TLR rates of 7.5% after 12 months and 12.7% after 2 years are still in a very reasonable range compared with other studies (3,5,19,24,30). Moreover, PCI of ISR with R-ZES was safe, with no excess of CD or TVMI observed out to 2 years. Notably, the ST events were numerically higher in ISR patients at 1 and 2 years, but the difference did not reach statistical significance. This was also noted among the BMS-ISR compared with the DES-ISR subgroup, with inadequate power to allow meaningful comparison.

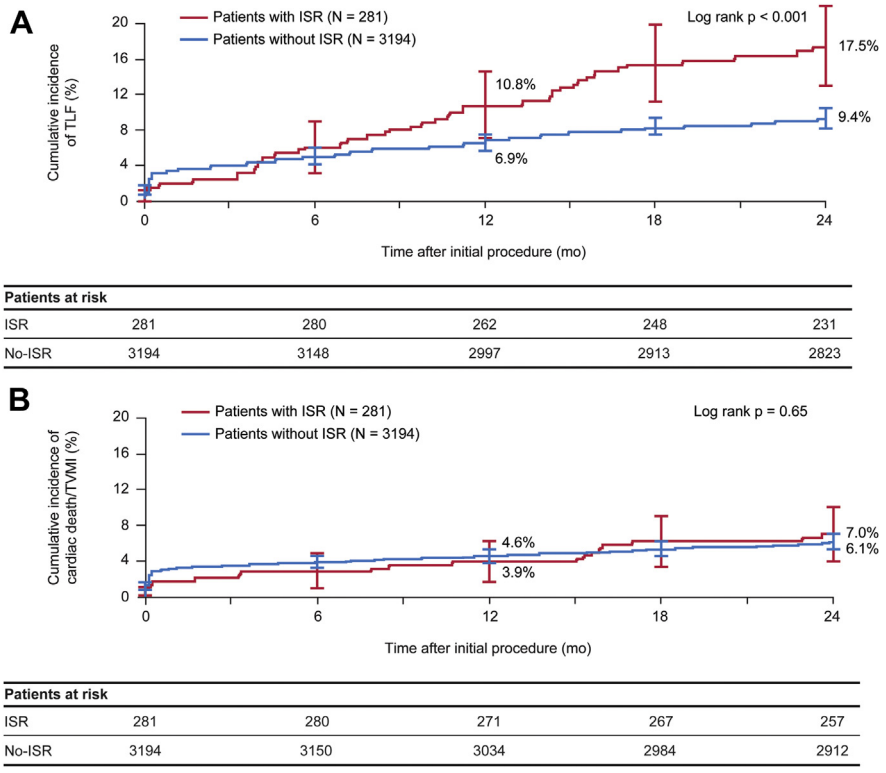
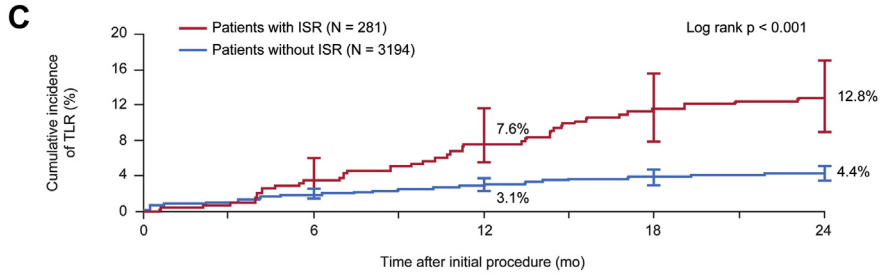


Figure 1. Kaplan-Meier Curves for the Study's Principal Endpoints

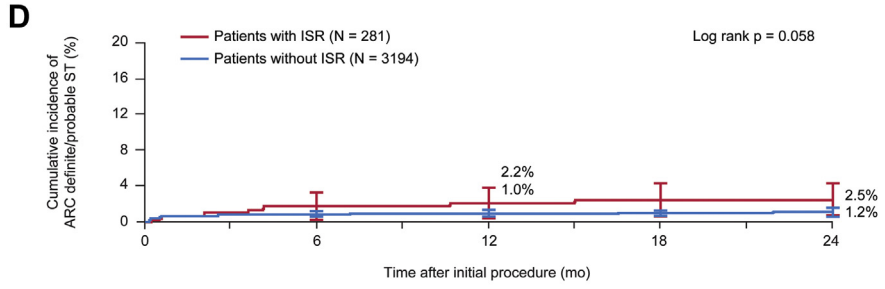
Kaplan-Meier curves illustrating time to event occurrence for **(A)** target lesion failure (TLF); **(B)** composite occurrence of cardiac death and target vessel myocardial infarction (TVMI). **(C)** clinically driven target lesion revascularization; and **(D)** stent thrombosis (probable/definite as defined by the Academic Research Consortium). ARC = Academic Research Consortium; ISR = in-stent restenosis; ST = stent thrombosis; TLR = target lesion revascularization.

The treatment of ISR patients and non-ISR patients with R-ZES resulted in a similar acute angiographic success as documented in a post-procedural diameter stenosis of some 10% in both cohorts. Thus, the higher TLF rate in the ISR cohort was probably not the consequence of an under-expansion of the R-ZES. There was also no obvious major imbalance in risk factors for restenosis in the patient and lesion characteristics of both groups. It rather appears that the ISR per se carries a higher disposition for a TLF, possibly due to the unique biology of an ISR. Consequently, ISR was the strongest independent predictor for TLF in our total study population.

Nevertheless, revascularization rates with R-ZES compare favorably with other contemporary ISR trials (3–5,15,19,21,24). Because longer observation periods are missing in most ISR studies, a comparison of the RESOLUTE pooled data has been confined to 9- and 12-month revascularization rates. Regarding BMS-ISR, our TLR and TVR rates are in line with the sirolimus-eluting stent group in the ISAR-DESIRE (Intracoronary Stenting or Angioplasty for Restenosis Reduction: Drug-Eluting Stents for In-Stent Restenosis) trial (8% TVR), the DEB group in the PEPCAD II (Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease II) study (6% TLR), and the findings in TAXUS V-ISR (Randomized Trial Evaluating Slow-Release Formulation TAXUS Paclitaxel-Eluting Coronary Stent in the Treatment of In-Stent Restenosis) (10.5% TVR at 9 months) (1,5,29). Remarkably, the R-ZES appears to be equally effective in patients with BMS-ISR and with DES-ISR. Treatment of DES-ISR with DEB or another DES was by far less successful in previous studies. In PEPCAD-DES (6), treatment of DES-ISR with DEB resulted in a TLR rate of 15.3% at 6 months. Similar rates were observed in ISAR-DESIRE–II (TLR 16.6% after treatment of DES-ISR with sirolimus-eluting stents and 14.5% after treatment with paclitaxel-eluting stents) (4) and in the study done by Steinberg et al. (3) (TVR 22.2% after DES treatment of DES-ISR vs. 10.3% for BMS-ISR). These previous observations supported the notion that DES-ISR is a particularly resistant lesion with high cardiac event rates after percutaneous retreatment. The excellent outcome in our small DES-ISR subgroup has to be



Patients at risk					
ISR	281	281	267	253	237
No-ISR	3194	3188	3072	2994	2903



Patients at risk					
ISR	281	281	274	270	264
No-ISR	3194	3186	3109	3065	2995

Figure 1. Continued

interpreted cautiously. It is, however, conceivable that the R-ZES is more effective than first-generation DES or DEB in the therapy of DES-ISR because a very effective anti-proliferative compound was applied without apposition of another thick metal/polymer layer but with preserved stent scaffolding.

Regarding the Kaplan-Meier curves of the cumulative incidence in TLR, there was a continuous rise of events during the entire observation period in the ISR cohort. Nevertheless, this increase did not seem to be overproportional compared with the non-ISR cohort, though a late catch-up phenomenon cannot be entirely excluded (16,17).

Table 4. Multivariate Predictors of TLF to 2 Years

Population	Odds Ratio	p Value
Total		
ISR	1.856	<0.001
Prior CABG	1.758	<0.001
Bend ≥45°	1.382	0.010
Previous myocardial infarction	1.293	0.040
Unstable angina	1.273	0.040
Pre-procedure RVD, mm	0.801	0.050
ISR		
Prior CABG	4.195	<0.001
Unstable angina	2.516	0.009
Age, yrs	0.963	0.021

Abbreviations as in Tables 1 to 3.

Table 5. Baseline Characteristics of Pooled BMS-ISR and DES-ISR Patients*

Baseline Measures	BMS-ISR Subjects (n = 196)	DES-ISR Subjects (n = 70)	p Value
Age, yrs	65.5 ± 10.4 (196)	65.6 ± 10.6 (70)	0.878
Male	75.0 (147/196)	82.9 (58/70)	0.180
Prior MI	52.6 (103/196)	51.4 (36/70)	0.872
Prior PCI	98.5 (193/196)	98.6 (69/70)	0.952
Diabetes mellitus	29.1 (57/196)	32.9 (23/70)	0.554
Insulin-dependent	10.2 (20/196)	12.9 (9/70)	0.541
ACS, %	45.4 (89/196)	45.7 (32/70)	1.000
Vessel location			0.921
LAD	36.6 (97/265)	35.6 (32/90)	
LCX	23.4 (62/265)	23.3 (21/90)	
RCA	34.0 (90/265)	35.6 (32/90)	
Left main	1.1 (3/265)	2.2 (2/90)	
SVG	4.2 (11/265)	3.3 (3/90)	
Arterial graft	0.8 (2/265)	0.0 (0/90)	

Values are mean ± SD (N) or % (n/N). *3 patients with both BMS-ISR and DES-ISR are excluded.
ACS = acute coronary syndrome; MI = myocardial infarction; other abbreviations as in Tables 1 to 3.

Table 6. Clinical Outcomes at 2 Years of Pooled BMS-ISR and DES-ISR Patients

Safety Measures	BMS-ISR (n = 192)	DES-ISR (n = 69)	p Value*
TVF	19.3 (37)	18.8 (13)	0.995
TLF	17.2 (33)	18.8 (13)	0.761
Death	5.7 (11)	5.8 (4)	0.939
Cardiac death	3.1 (6)	2.9 (2)	0.975
Cardiac death or TVMI	7.3 (14)	7.2 (5)	0.985
TVMI	5.2 (10)	4.3 (3)	0.664
Clinically driven TLR	12.5 (24)	13.0 (9)	0.990
Clinically driven TVR	14.6 (28)	14.5 (10)	0.939
MACE	19.8 (38)	21.7 (15)	0.813
Stent thrombosis, ARC def/prob	3.1 (6)	1.4 (1)	0.452
Early, ≤30 days	1.0 (2)	0.0 (0)	0.231
Late, >30 and ≤360 days	1.6 (3)	1.4 (1)	0.948
Very late, >360 days	0.5 (1)	0.0 (0)	0.434

Values are % (n). Three patients with both BMS-ISR and DES-ISR are excluded. *p Value is adjusted to propensity score with the following baseline variables as independent variables: age, sex, current smoker, prior percutaneous coronary intervention, hyperlipidemia, diabetes, hypertension, prior myocardial infarction, prior bypass surgery, unstable angina or myocardial infarction, left anterior descending artery, B2/C lesion, moderate/severe calcification, bend >45°, Thrombolysis In Myocardial Infarction flow grade 3, reference vessel diameter, lesion length, and percent diameter stenosis.

Abbreviations as in Tables 2 and 3.

Study limitations. Although our study is based on high-quality data, the investigation has all the limitations of a non–pre-specified, post hoc analysis. For instance, no classification of ISR morphology was done, which could have been important for the comparison of ISR in BMS and DES patients, and the number of DES-ISR patients remains low. Furthermore, the present patient-based analysis limits the ability to evaluate outcomes related strictly to ISR lesions. It is unusual to pool the results of a randomized trial with that of a registry. Nevertheless, this variable has been included in the multivariate analyses, and no significant interactions have been observed.

Conclusions

The use of an R-ZES for treatment of ISR was safe, with rates of CD, MI, and ST in line with the overall 2-year events of both clinical trials. Rates of revascularization were higher in ISR compared with non-ISR patients. TVR and TLR rates of the R-ZES, however, are very persuasive in the perspective of other ISR trials. Thus, R-ZES offers an effective alternative for treatment of both BMS-ISR and DES-ISR in this challenging subset of patients.

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