

4-Year Clinical Outcomes and Predictors of Repeat Revascularization in Patients Treated With New-Generation Drug-Eluting Stents



A Report From the RESOLUTE All-Comers Trial
(A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention)

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Objectives

The aim of the study was to investigate 4-year outcomes and predictors of repeat revascularization in patients treated with the Resolute zotarolimus-eluting stent (R-ZES) (Medtronic, Minneapolis, Minnesota) and XIENCE V everolimus-eluting stent (EES) (Abbott Vascular, Abbott Park, Illinois) in the RESOLUTE (A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention) All-Comers trial.

Background

Data on long-term outcomes of new-generation drug-eluting stents are limited, and predictors of repeat revascularization due to restenosis and/or progression of disease are largely unknown.

Methods

Patients were randomly assigned to treatment with the R-ZES (n = 1,140) or the EES (n = 1,152). We assessed pre-specified safety and efficacy outcomes at 4 years including target lesion failure and stent thrombosis. Predictors of revascularization at 4 years were identified by Cox regression analysis.

Results

At 4 years, the rates of target lesion failure (15.2% vs. 14.6%, p = 0.68), cardiac death (5.4% vs. 4.7%, p = 0.44), and target vessel myocardial infarction (5.3% vs. 5.4%, p = 1.00), clinically-indicated target lesion revascularization (TLR) (7.0% vs. 6.5%, p = 0.62), and definite/probable stent thrombosis (2.3% vs. 1.6%, p = 0.23) were similar with the R-ZES and EES. Independent predictors of TLR were age, insulin-treated diabetes, SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score, treatment of saphenous vein grafts, ostial lesions, and in-stent restenosis. Independent predictors of any revascularization were age, diabetes, previous percutaneous coronary intervention, absence of ST-segment elevation myocardial infarction, smaller reference vessel diameter, SYNTAX score, and treatment of left anterior descending, right coronary artery, saphenous vein grafts, ostial lesions, or in-stent restenosis.

Conclusions

R-ZES and EES demonstrated similar safety and efficacy throughout 4 years. TLR represented less than one-half of all repeat revascularization procedures. Patient- and lesion-related factors predicting the risk of TLR and any revascularization showed considerable overlap. (A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention [RESOLUTE-AC]; [NCT00617084](https://doi.org/10.1016/j.jacc.2013.12.036)) (J Am Coll Cardiol 2014;63:1617–25) © 2014 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

- CAD** = coronary artery disease
- CI** = confidence interval
- DAPT** = dual antiplatelet therapy
- DES** = drug-eluting stent(s)
- EES** = everolimus-eluting stent(s)
- MI** = myocardial infarction
- OR** = odds ratio
- POCE** = patient-oriented composite endpoint
- R-ZES** = RESOLUTE zotarolimus-eluting stent(s)
- ST** = stent thrombosis
- TLF** = target lesion failure
- TLR** = target lesion revascularization
- TV-MI** = target vessel-myocardial infarction

New-generation drug-eluting stents (DES) provide improved safety and efficacy compared with early-generation DES and bare-metal stents and represent the standard of care in current clinical practice (1). RESOLUTE zotarolimus-eluting stents (R-ZES) and everolimus-eluting stents (EES) have been the first new-generation DES approved by the U.S. Food and Drug Administration and have been directly compared in 2 large-scale randomized trials showing similar outcomes throughout 2 years of follow-up (2,3). However, target lesion revascularization (TLR) continues to occur in >5% of patients treated with new-generation DES at 2 years, suggesting that specific risk factors confer an increased risk

of restenosis. Moreover, progression of coronary artery disease (CAD) leading to revascularization of a segment not previously treated results in rates of repeat revascularization as high as 15% at 2 years. Identification of clinical and angiographic characteristics associated with restenosis and progression of CAD in patients treated with new-generation DES may help to address this clinical issue. We therefore assessed 4-year clinical outcomes in the RESOLUTE (A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention) All-Comers trial and identified predictors of repeat revascularization in patients treated with new-generation DES.

Methods

Full details on the RESOLUTE All-Comers randomized clinical trial have been described elsewhere (4). The study complied with the Declaration of Helsinki, all enrolled patients provided written informed consent, and ethics committees approved the protocol at all sites.

Study design. Overall, 2,292 patients with stable CAD or acute coronary syndromes requiring revascularization were randomized to the R-ZES (n = 1,140) or the EES (n = 1,152). There were no restrictions in terms of the number of

treated lesions, vessels, implanted stents, or lesion length. Follow-up was planned at 6 months, 1 year, and annually thereafter through 4 years. Dual antiplatelet therapy (DAPT) with daily aspirin (≥ 75 mg) and clopidogrel (75 mg) was prescribed for at least 6 months. Low-dose aspirin was continued indefinitely. Study data were managed and analyzed by an academic research organization (Cardialysis, Rotterdam, the Netherlands).

Definitions and adjudication. The primary endpoint was target lesion failure (TLF), defined as the composite of cardiac death, target vessel myocardial infarction (TV-MI), or clinically-indicated TLR. Secondary endpoints were the individual components of the primary endpoint, a patient-oriented composite endpoint (POCE) (all-cause death, any myocardial infarction [MI], any revascularization), major adverse cardiac event (death, MI, emergent bypass graft, or clinically-indicated TLR), target vessel failure (cardiac death, TV-MI, or clinically-indicated target vessel revascularization), their components, and stent thrombosis (ST). The extended historical definition of MI was used (5). TLR was defined as any revascularization for a stenosis within the stent or within a 5-mm border proximal and distal to the stent. Any revascularization included all TLR, all target vessel revascularization, and any non-target vessel revascularization. ST was adjudicated according to the Academic Research Consortium criteria (6). An independent clinical events committee blinded to treatment allocation adjudicated endpoints according to pre-specified definitions. **Statistical analysis.** All analyses were conducted using the intention-to-treat population. Comparisons between groups were based on the Fisher exact test for categorical outcomes and a 2-sample *t* test for continuous outcomes. The time-sensitive nature of any response variable was analyzed using the Kaplan-Meier method. Baseline clinical, lesion, procedure, and angiographic characteristics in the overall trial population were analyzed for associations with TLR and any revascularization throughout 4 years (univariate analysis). A multiple logistic regression analysis was then conducted with an entry criterion of 0.2 and a stay criterion of 0.1 (multivariate analysis). Statistical analyses were conducted using SAS software version 9.1 or later (SAS Institute, Cary, North Carolina).

Results

Follow-up data at 4 years were available for 1,122 (98.4%) R-ZES patients and 1,124 (97.6%) EES patients (Online Fig. 1). As previously reported, baseline clinical and angiographic characteristics were well balanced (4) (Online Table 1).

Clinical outcomes at 4 years. Clinical outcomes at 4-year follow-up are shown in Table 1. TLF (15.2% vs. 14.6%, $p = 0.68$) and POCE (30.4% vs. 28.6%, $p = 0.36$) occurred with similar frequency in R-ZES- and EES-treated patients. Figure 1 shows cumulative event rates of TLF and POCE through 4 years for all patients. Rates

and OrbusNeich. Dr. Stefanini has received speaker fees from Abbott Vascular, Biosensors and Biotronik. Dr. Silber has received research grants and lecture fees from Abbott Vascular, Boston Scientific, and Medtronic. Dr. Windecker has received research grants and speaker fees from Abbott Vascular, Biotronik, Boston Scientific, Biosensors, Cordis, Medtronic, St. Jude Medical, and Edwards Lifesciences; and has received speaker fees from AstraZeneca and Eli Lilly. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received October 24, 2013; revised manuscript received November 29, 2013, accepted December 24, 2013.

Table 1 Clinical Outcome at 4 Years

	R-ZES (n = 1,122)	EES (n = 1,124)	Difference (95% CI), %	p Value
TLF	15.2 (171)	14.6 (164)	0.6 (−2.3 to 3.6)	0.679
TVF	17.6 (198)	17.1 (192)	0.6 (−2.6 to 3.7)	0.738
MACE	18.7 (210)	18.9 (212)	−0.1 (−3.4 to 3.1)	0.957
POCE	30.4 (341)	28.6 (321)	1.8 (−1.9 to 5.6)	0.355
Death or TV-MI	12.9 (145)	13.1 (147)	−0.2 (−2.9 to 2.6)	0.950
Cardiac death or TV-MI	10.1 (113)	9.3 (105)	0.7 (−1.7 to 3.2)	0.569
Death	8.5 (95)	8.6 (97)	−0.2 (−2.5 to 2.1)	0.940
Cardiac death	5.4 (61)	4.7 (53)	0.7 (−1.1 to 2.5)	0.444
TV-MI	5.3 (60)	5.4 (61)	−0.1 (−1.9 to 1.8)	1.000
Q-wave	1.2 (13)	0.8 (9)	0.4 (−0.5 to 1.2)	0.402
Non-Q-wave	4.4 (49)	4.6 (52)	−0.3 (−2.0 to 1.5)	0.839
Any revascularization	21.1 (237)	18.6 (209)	2.5 (−0.8 to 5.8)	0.139
CABG	3.1 (35)	2.5 (28)	0.6 (−0.7 to 2.0)	0.375
PCI	19.0 (213)	16.6 (187)	2.3 (−0.8 to 5.5)	0.152
Any TLR	9.2 (103)	8.0 (90)	1.2 (−1.1 to 3.5)	0.329
CABG	1.7 (19)	1.3 (15)	0.4 (−0.7 to 1.4)	0.496
PCI	8.0 (90)	6.9 (78)	1.1 (−1.1 to 3.3)	0.337
Any TVR	13.3 (149)	11.9 (134)	1.4 (−1.4 to 4.1)	0.341
CABG	2.1 (24)	1.9 (21)	0.3 (−0.9 to 1.4)	0.655
PCI	11.7 (131)	10.6 (119)	1.1 (−1.5 to 3.7)	0.421
Clinically-driven TLR	7.0 (79)	6.5 (73)	0.5 (−1.5 to 2.6)	0.615
CABG	1.2 (14)	1.2 (14)	0.0 (−0.9 to 0.9)	1.000
PCI	6.2 (70)	5.5 (62)	0.7 (−1.2 to 2.7)	0.474
Clinically-driven TVR	9.9 (111)	9.5 (107)	0.4 (−2.1 to 2.8)	0.776
CABG	1.6 (18)	1.6 (18)	0.0 (−1.0 to 1.0)	1.000
PCI	8.7 (98)	8.4 (94)	0.4 (−1.9 to 2.7)	0.763
Definite or probable ST	2.3 (26)	1.6 (18)	0.7 (−0.4 to 1.9)	0.228
Early (0–30 days)	1.1 (12)	0.5 (6)	0.5 (−0.2 to 1.3)	0.165
Late (31–360 days)	0.6 (7)	0.2 (2)	0.4 (−0.1 to 1.0)	0.108
Very late (361–1,440 days)	0.7 (8)	0.9 (10)	−0.2 (−0.9 to 0.6)	0.814
Definite ST	1.5 (17)	0.7 (8)	0.8 (−0.1 to 1.7)	0.074
Early (0–30 days)	0.8 (9)	0.1 (1)	0.7 (0.2 to 1.3)	0.011
Late (31–360 days)	0.4 (5)	0.2 (2)	0.3 (−0.2 to 0.7)	0.288
Very late (361–1,440 days)	0.4 (4)	0.4 (5)	−0.1 (−0.6 to 0.4)	1.000

Values are % (n).
 CABG = coronary artery bypass graft; CI = confidence interval; EES = everolimus-eluting stent(s); MACE = major adverse cardiac event(s); PCI = percutaneous coronary intervention; POCE = patient-oriented cardiac event(s); R-ZES = Resolute zotarolimus-eluting stent(s); ST = stent thrombosis; TLF = target lesion failure; TLR = target lesion revascularization; TVF = target vessel failure; TV-MI = target vessel-myocardial infarction; TVR = target vessel revascularization.

of cardiac death (5.4% vs. 4.7%, $p = 0.44$) and TV-MI (5.3% vs. 5.4%, $p = 1.00$) were comparable between R-ZES- and EES-treated patients (Table 1). Repeat revascularization occurred with similar frequency among R-ZES- and EES-treated patients in terms of TLR (9.2% vs. 8.0%, $p = 0.33$) and any revascularization (21.1% vs. 18.6%, $p = 0.14$). Figure 2 shows cumulative event rates of TLR and any revascularization through 4 years of follow-up for all patients. Rates of ST were similar with the R-ZES and the EES at 4 years (definite or probable: 2.3% vs. 1.6%, $p = 0.23$; definite: 1.5% vs. 0.7%, $p = 0.07$) as well as very late ST (definite or probable: 0.7% vs. 0.9%, $p = 0.81$; definite: 0.4% vs. 0.4%, $p = 1.00$) (Table 1). Cumulative event rates of definite or probable ST through 4 years, overall as well as according to a landmark analysis at 1 year, are presented in Figure 3.

Of note, no differences were observed with respect to DAPT adherence between the 2 groups through 4 years of follow-up (Table 2).

Predictors of TLR. At 4 years, TLR occurred in 193 patients (8.6%). As summarized in Table 3 and Figure 4, the following clinical and angiographic characteristics were identified as independent predictors of TLR: younger age (odds ratio [OR]: 0.98, 95% confidence interval [CI]: 0.96 to 0.99, $p = 0.003$), insulin-treated diabetes (OR: 1.97, 95% CI: 1.25 to 3.11, $p = 0.004$), higher SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score (OR: 1.03, 95% CI: 1.02 to 1.05, $p < 0.001$), and treatment of saphenous vein grafts (OR: 2.28, 95% CI: 1.12 to 4.68, $p = 0.024$), ostial lesions (OR: 2.17, 95% CI: 1.30 to 3.62, $p = 0.003$), or in-stent restenosis (OR: 2.44, 95% CI: 1.53 to 3.90, $p < 0.001$).

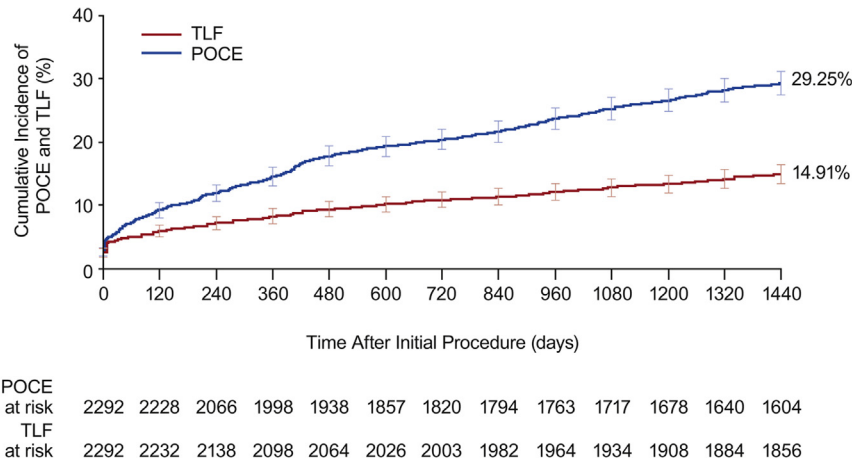


Figure 1 Cumulative Incidence of TLF and POCE

Target lesion failure (TLF) includes cardiac death, target vessel myocardial infarction, or clinically indicated target-lesion revascularization. Patient-oriented composite endpoint (POCE) includes all-cause death, any myocardial infarction, or any revascularization.

Predictors of any revascularization. At 4 years, any revascularization occurred in 446 patients (19.9%). As summarized in Table 3 and Figure 4, the following clinical and angiographic characteristics were identified as independent predictors of any revascularization: younger age (OR: 0.98, 95% CI: 0.97 to 0.99, $p = 0.004$), diabetes (OR: 1.38, 95% CI: 1.08 to 1.76, $p = 0.011$), previous PCI (OR: 1.64, 95% CI: 1.28 to 2.11, $p < 0.001$), ST-segment elevation MI (OR: 0.73, 95% CI: 0.56 to 0.91, $p = 0.005$), smaller reference vessel diameter (OR: 0.76, 95% CI: 0.62 to 0.93, $p = 0.008$), higher SYNTAX score (OR: 1.04, 95% CI: 1.03 to 1.05, $p < 0.001$), and treatment of left anterior descending (OR: 0.74, 95% CI: 0.58 to 0.94, $p = 0.013$), right coronary artery (OR: 1.30, 95% CI: 1.01 to 1.67,

$p = 0.044$), saphenous vein grafts (OR: 2.54, 95% CI: 1.38 to 4.68, $p = 0.003$), ostial lesions (OR: 1.62, 95% CI: 1.06 to 2.48, $p = 0.026$), or in-stent restenosis (OR: 1.60, 95% CI: 1.10 to 2.32, $p = 0.014$).

Discussion

The long-term 4-year clinical follow-up of this large-scale contemporary all-comer trial can be summarized as follows: 1) the new-generation R-ZES and EES have a similar safety and efficacy profile; 2) very late ST occurred infrequently with no difference between the R-ZES and the EES; 3) TLR represents less than one-half of all repeat revascularization procedures; 4) independent

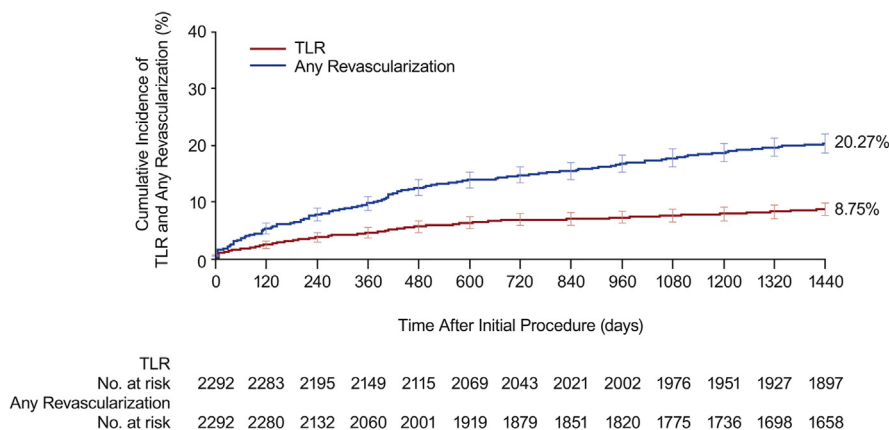


Figure 2 Cumulative Incidence of TLR and Any Revascularization

TLR = target lesion revascularization.

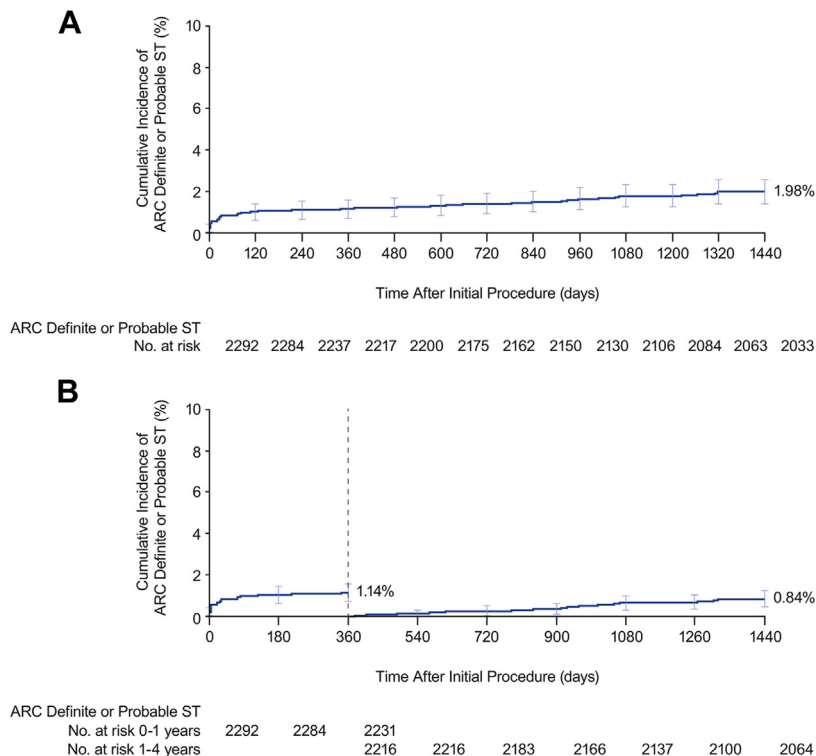


Figure 3 Cumulative Incidence of Definite or Probable Stent Thrombosis

Cumulative incidence of definite or probable stent thrombosis (ST) through 4 years overall (A) and according to a landmark analysis at 1 year (B). ARC = Academic Research Consortium.

Table 2 Adherence to DAPT

	R-ZES (n = 1,140)	EES (n = 1,152)	p Value
At 30 days			
Aspirin	95.6 (1,082/1,132)	95.2 (1,083/1,138)	0.69
Clopidogrel	98.2 (1,112/1,132)	98.7 (1,123/1,138)	0.40
DAPT	93.9 (1,063/1,132)	94.4 (1,074/1,138)	0.66
At 1 yr			
Aspirin	95.0 (1,056/1,111)	94.2 (1,048/1,112)	0.45
Clopidogrel	87.9 (977/1,111)	87.1 (968/1,112)	0.56
DAPT	84.2 (935/1,111)	83.5 (928/1,112)	0.69
At 2 yrs			
Aspirin	93.9 (1,023/1,089)	93.1 (1,013/1,088)	0.44
Clopidogrel	20.1 (219/1,089)	20.9 (227/1,088)	0.67
DAPT	18.1 (197/1,089)	18.2 (198/1,088)	0.96
At 3 yrs			
Aspirin	92.5 (981/1,061)	92.3 (977/1,058)	0.94
Clopidogrel	15.1 (160/1,062)	16.2 (171/1,058)	0.51
DAPT	12.8 (136/1,061)	12.9 (136/1,058)	1.00
At 4 yrs			
Aspirin	91.1 (931/1,022)	90.8 (931/1,025)	0.88
Clopidogrel	15.0 (153/1,022)	15.3 (157/1,025)	0.76
DAPT	12.1 (124/1,022)	11.8 (121/1,025)	0.84

Values are % (n/N).

DAPT = dual antiplatelet therapy; other abbreviations as in Table 1.

Table 3 Baseline Characteristics of Patients With and Without TLR or Any Revascularization at 4 Years

	TLR			Any Revascularization		
	Yes (n = 193)	No (n = 2,053)	p Value	Yes (n = 446)	No (n = 1,800)	p Value
Age, yrs	63.5 ± 10.7	64.4 ± 10.8	0.255	64.1 ± 10.7	64.4 ± 10.8	0.603
Male	73.6 (142/193)	77.0 (1,580/2,053)	0.288	76.9 (343/446)	76.6 (1,379/1,800)	0.895
BMI, kg/m ²	28.1 ± 4.9 (193)	27.8 ± 4.3 (2,045)	0.275	28.2 ± 4.9 (446)	27.7 ± 4.2 (1,792)	0.048
Cardiac risk factors						
Diabetes mellitus	33.2 (64/193)	22.6 (464/2,053)	0.001	30.7 (137/446)	21.7 (391/1,800)	<0.001
Insulin treated	15.0 (29/193)	7.1 (145/2,053)	<0.001	12.3 (55/446)	6.6 (119/1,800)	<0.001
Hypertension	79.8 (154/193)	70.8 (1,454/2,053)	0.009	77.6 (346/446)	70.1 (1,262/1,800)	0.002
Hyperlipidemia	72.5 (140/193)	65.6 (1,346/2,053)	0.051	73.1 (326/446)	64.4 (1,160/1,800)	<0.001
Current smoker	24.4 (47/193)	26.1 (536/2,053)	0.595	25.8 (115/446)	26.0 (468/1,800)	0.926
Previous MI	35.3 (66/187)	29.2 (587/2,010)	0.092	35.9 (156/434)	28.2 (497/1,763)	0.003
Previous PCI	47.7 (92/193)	30.3 (623/2,053)	<0.001	46.2 (206/446)	28.3 (509/1,800)	<0.001
Previous CABG	17.1 (33/193)	9.1 (187/2,053)	<0.001	15.7 (70/446)	8.3 (150/1,800)	<0.001
Clinical characteristics						
Stable CAD	41.5 (80/193)	34.2 (702/2,053)	0.044	39.7 (177/446)	33.6 (605/1,800)	0.016
Unstable angina	19.2 (37/193)	19.2 (394/2,053)	0.995	19.5 (87/446)	19.1 (344/1,800)	0.849
AMI within 72 h	24.4 (47/193)	29.1 (597/2,053)	0.166	26.0 (116/446)	29.3 (528/1,800)	0.165
STEMI	33.3 (18/54)	48.4 (342/706)	0.689	37.7 (52/138)	49.5 (308/622)	0.025
NSTEMI	18.7 (36/193)	17.7 (364/2,053)	0.749	19.3 (86/446)	17.4 (314/1,800)	0.364
LVEF <30%	1.0 (1/101)	2.6 (29/1,098)	0.880	2.2 (5/232)	2.6 (25/967)	0.387
Target vessel						
Left main	4.7 (9/193)	2.2 (45/2,053)	0.036	2.5 (11/446)	2.4 (43/1,800)	0.923
LAD	47.7 (92/193)	51.0 (1,047/2,053)	0.377	43.3 (193/446)	52.6 (946/1,800)	<0.001
LCX	34.2 (66/193)	32.7 (671/2,053)	0.669	34.1 (152/446)	32.5 (585/1,800)	0.525
RCA	40.9 (79/193)	39.1 (802/2,053)	0.611	43.0 (192/446)	38.3 (689/1,800)	0.065
SVG	6.2 (12/193)	2.0% (41/2,053)	<0.001	5.4 (24/446)	1.6 (29/1,800)	<0.001
Arterial graft	0.5 (1/193)	0.1 (3/2,053)	0.272	0.4 (2/446)	0.1 (2/1,800)	0.163
Complexity of CAD						
SYNTAX score	17.6 ± 9.4 (156)	14.3 ± 9.1 (1,834)	<0.001	16.9 ± 9.5 (367)	14.1 ± 9.0 (1,623)	<0.001
Type B2/C lesions	81.4 (341/419)	78.6 (3,189/4,057)	0.749	80.3 (730/909)	78.5 (2,800/3,567)	0.888
Lesions with thrombus	3.4 (13/381)	4.9 (183/3,729)	0.397	3.0 (25/834)	5.2 (171/3,276)	0.063
Ostial lesions	8.7 (36/412)	3.4 (138/4,016)	<0.001	5.9 (53/899)	3.4 (121/3,529)	<0.001
Total occlusion	13.9 (58/416)	13.7 (557/4,056)	0.958	13.6 (123/906)	13.8 (492/3,566)	0.606
Calcified lesion	74.2 (299/403)	78.3 (3,098/3,958)	0.502	75.8 (666/879)	78.4 (2731/3,482)	0.434
Bifurcation lesion	31.4 (123/392)	29.6 (1,115/3,769)	0.330	29.5 (251/850)	29.8 (987/3,311)	0.891
In-stent restenotic lesion	20.7 (37/179)	7.0 (143/2,041)	<0.001	15.0 (64/428)	6.5 (116/1,792)	<0.001
TIMI flow grade 0–2	20.7 (86/416)	23.2 (940/4,056)	0.668	20.6 (187/906)	23.5 (839/3,566)	0.236
Allocated DES						
ZES	54.6 (238/436)	47.0 (1,936/4,118)	0.512	50.9 (474/932)	46.9 (1,700/3,622)	0.245
EES	42.9 (187/436)	52.0 (2,143/4,118)	0.713	46.9 (437/932)	52.3 (1,893/3,622)	0.281

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Table 3 Continued

Angiographic characteristics	TLR		Any Revascularization		p Value
	Yes (n = 193)	No (n = 2,053)	Yes (n = 446)	No (n = 1,800)	
Lesion length, mm	12.7 ± 9.0 (338)	12.9 ± 8.9 (3,278)	12.7 ± 8.8 (746)	12.9 ± 8.9 (2,870)	0.726
RVD, mm	2.5 ± 0.5 (338)	2.6 ± 0.6 (3,278)	2.5 ± 0.6 (746)	2.6 ± 0.6 (2,870)	0.029
MLD, mm	0.9 ± 0.5 (408)	0.9 ± 0.5 (3,981)	0.9 ± 0.5 (896)	0.9 ± 0.5 (3,493)	0.908
Percent diameter stenosis	64.9 ± 18.3 (408)	65.0 ± 18.6 (3,981)	64.3 ± 18.2 (896)	65.2 ± 18.7 (3,493)	0.211

Values are mean ± SD (n) or % (n/N).
 AMI = acute myocardial infarction; BMI = body mass index; CAD = coronary artery disease; DES = drug-eluting stent(s); LAD = left descending artery; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MLD = minimal lumen diameter; NSTEMI = non-ST-segment elevation myocardial infarction; RCA = right coronary artery; RVD = reference vessel diameter; STEMI = ST-segment elevation myocardial infarction; SVG = saphenous vein graft; SYNTAX = Synergy between PCI with Taxus and Cardiac Surgery; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

predictors of TLR and any revascularization are overlapping and include clinical and angiographic characteristics.

With regard to safety, R-ZES and EES are associated with comparable risks of cardiac death, MI, and ST through 4 years. Noteworthy, the rates of very late (≥ 1 year) ST were exceedingly low (0.4% with both devices). These findings are in line with recent evidence indicating that risks of ST no longer represent a limitation to the use of DES (7–10).

We observed a substantial difference between patient- and stent-related outcomes at 4 years. The former resulted in a 2-fold higher event rate, indicating that at least 50% of adverse events occurring after DES implantation are not related to the implanted device but rather to progression of CAD at nontreated sites. Similar findings were observed in terms of repeat revascularization procedures, among which TLR events represent less than one-half of overall repeat revascularization events. Therefore, optimization of secondary prevention and medical management appear as important as the initial choice between the different types of new-generation DES.

Predictors of TLR identified in this analysis are comparable to predictors identified in previous studies with early-generation DES and bare-metal stents (11–15). Features of angiographic complexity of CAD, including SYNTAX score, were strong predictors of TLR. With respect to clinical characteristics, age and diabetes continue to represent significant predictors of TLR (11,15). Overall, it is noteworthy that patients treated with new-generation DES feature the same predictors of TLR as patients treated with early-generation DES. This indicates that efficacy of new-generation DES remains limited by the same clinical and angiographic characteristics that affected early-generation DES efficacy.

Little evidence is available of the predictors of progression of disease beyond the target lesion among patients treated with coronary stent implantation. Our results are consistent with those of the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study findings with respect to the impact of diabetes and previous PCI on any revascularization (16). Moreover, we identified absence of ST-segment elevation MI, target lesion location, reference vessel diameter, and SYNTAX score as additional predictors of disease progression. Therefore, in addition to baseline clinical conditions, angiographic complexity of CAD appears to play a prominent role in disease progression. Although TLR represents less than one-half of repeat revascularization procedures, predictors of TLR and any revascularization are largely overlapping. This suggests that restenosis and progression of CAD at nontreated sites are influenced by similar clinical and angiographic factors.

Study limitations. First, this is a post-hoc analysis of a trial not primarily intended to investigate CAD progression. However, both TLR and any revascularization were

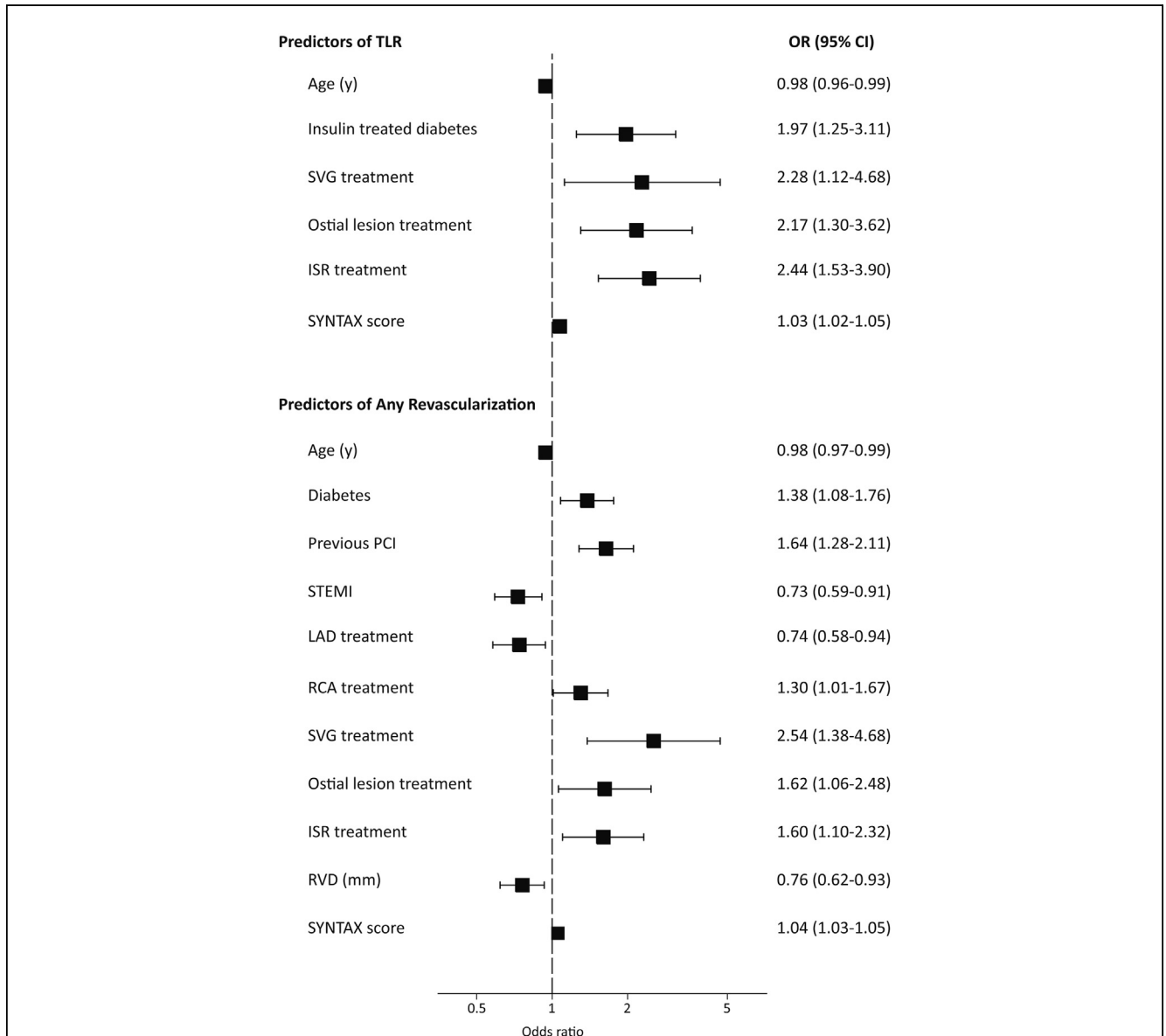


Figure 4 Independent Predictors of Target Lesion Revascularization and Any Revascularization

Independent predictors of target-lesion revascularization (**top**) and any revascularization (**bottom**). CI = confidence interval; ISR = in-stent restenosis; LAD = left descending artery; OR = odds ratio; PCI = percutaneous coronary intervention; RCA = right coronary artery; RVD = reference vessel diameter; STEMI = ST-segment elevation myocardial infarction; SVG = saphenous vein graft; SYNTAX = Synergy between PCI with Taxus and Cardiac Surgery.

pre-specified secondary endpoints adjudicated by a blinded clinical event committee. Second, the analysis of stent- and patient-related outcomes was not pre-specified and needs to be considered as hypothesis generating. Third, data on compliance with medications, apart from DAPT, were not available, and therefore it was not possible to evaluate the impact of compliance on restenosis and progression of CAD. Finally, we analyzed predictors in the overall population irrespective of stent allocation. However, stent type did not emerge as a predictor of TLR or of any revascularization.

Conclusions

At 4 years of follow-up, R-ZES and EES demonstrated similar safety and efficacy outcomes. TLR represented less than one-half of all repeat revascularization procedures. Patient- and lesion-related factors predicting the risk of TLR and any revascularization were largely overlapping.

Acknowledgments

The authors thank Minglei Liu, PhD, Yun Peng, PhD, Frank van Leeuwen, MD, and Miraida Weldam, MSc, of Medtronic for statistical analyses and overall trial management.

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REFERENCES

1. Stefanini GG, Holmes DR Jr. Drug-eluting coronary-artery stents. *N Engl J Med* 2013;368:254-65.
2. Silber S, Windecker S, Vranckx P, Serruys PW. Unrestricted randomised use of two new generation drug-eluting coronary stents: 2-year patient-related versus stent-related outcomes from the RESOLUTE All Comers trial. *Lancet* 2011;377:1241-7.
3. Tandjung K, Sen H, Lam MK, et al. Clinical outcome following stringent discontinuation of dual antiplatelet therapy after 12 months in real-world patients treated with second-generation zotarolimus-eluting resolute and everolimus-eluting Xience V stents: 2-year follow-up of the randomized TWENTE Trial. *J Am Coll Cardiol* 2013;61:2406-16.
4. Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Engl J Med* 2010;363:136-46.
5. Vranckx P, Cutlip DE, Mehran R, et al. 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.
6. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;115:2344-51.
7. Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet* 2012;379:1393-402.
8. Raber L, Magro M, Stefanini GG, et al. Very late coronary stent thrombosis of a newer-generation everolimus-eluting stent compared with early-generation drug-eluting stents: a prospective cohort study. *Circulation* 2012;125:1110-21.
9. Stefanini GG, Baber U, Windecker S, et al. Safety and efficacy of drug-eluting stents in women: a patient-level pooled analysis of randomised trials. *Lancet* 2013;382:1879-88.
10. Bangalore S, Kumar S, Fusaro M, et al. Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. *Circulation* 2012;125:2873-91.
11. Kastrati A, Schomig A, Elezi S, et al. Predictive factors of restenosis after coronary stent placement. *J Am Coll Cardiol* 1997;30:1428-36.
12. Lemos PA, Hoye A, Goedhart D, et al. Clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients: an evaluation from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) study. *Circulation* 2004;109:1366-70.
13. Mercado N, Boersma E, Wijns W, et al. Clinical and quantitative coronary angiographic predictors of coronary restenosis: a comparative analysis from the balloon-to-stent era. *J Am Coll Cardiol* 2001;38:645-52.
14. Kastrati A, Dibra A, Mehilli J, et al. Predictive factors of restenosis after coronary implantation of sirolimus- or paclitaxel-eluting stents. *Circulation* 2006;113:2293-300.
15. Kimura T, Morimoto T, Nakagawa Y, et al. Very late stent thrombosis and late target lesion revascularization after sirolimus-eluting stent implantation: five-year outcome of the j-Cypher Registry. *Circulation* 2012;126:1225-36.
16. Stone GW, Machara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011;364:226-35.

Key Words: all-comers population ■ drug-eluting stent(s) ■ everolimus-eluting stent(s) ■ long-term outcomes ■ Resolute zotarolimus-eluting stent(s).

▶ APPENDIX

For a supplemental table and figure, please see the online version of this article.