Comparison of Zotarolimus-*E*luting *S*tent Versus *S*irolimus-*E*luting Stent for De *N*ovo *C*oronary Artery Dis*E*ase in Patients With *DIABETES* Mellitus from the ESSENCE-DIABETES II Trial

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Angiographic and clinical outcomes remain relatively unfavorable for diabetic patients even after the use of drug-eluting stent. This prospective, multicenter, randomized study compared the relative efficacy and safety of resolute zotarolimus-eluting stent (R-ZES) and sirolimus-eluting stent (SES) implantation in diabetic patients with coronary artery disease. The primary end point was noninferiority of angiographic in-segment late loss at 9 months. Clinical events were also monitored for at least 12 months. Patient recruitment was prematurely stopped after enrollment of 256 patients (127 in R-ZES group and 129 in SES) because of discontinuing production of SES. The R-ZES was noninferior to the SES for 9-month in-segment late loss (0.34 ± 0.30 vs 0.39 ± 0.43 mm; difference −0.048; 95% confidence interval −0.157 to 0.061; upper 1-sided 95% confidence interval 0.044; p <0.001 for noninferiority). In addition, in-stent late loss (0.22 ± 0.29 vs 0.21 ± 0.40 mm, p = 0.849) and the rates of in-segment (1.2% vs 6.7%, p = 0.119) and in-stent (1.2% vs 3.3%, p = 0.621) binary restenoses were similar between the 2 groups. At 12 months, there were no statistical differences between the 2 groups in the incidence of any clinical outcomes (death, myocardial infarction, stent thrombosis, ischemia-driven target lesion revascularization, ischemia-driven target vessel revascularization, and composite outcomes). In conclusion, despite having reduced power because of early study termination, our study suggests that the R-ZES has noninferior angiographic outcomes at 9 months to the SES in diabetic patients with coronary artery disease. **(Am J Cardiol 2013;112:1565−1570)**

Patients with diabetes mellitus (DM) have a greater burden of atherosclerosis, smaller coronary arteries, and a greater risk of repeat revascularization after implantation of a bare-metal stent compared with nondiabetic patients.[1] Although the use of drug-eluting stent (DES) has been shown to improve both angiographic and clinical outcomes compared with bare-metal stent,[2] DM has been known as a key predictor of worse prognostic outcome even after DES use.[3,4] Recently, the relative efficacies of various DES including sirolimus-eluting stents (SES) in patients with DM have been evaluated in several randomized studies, in which SES showed long-term favorable clinical outcomes with sustained efficacy.[5,6] However, the selection of a specific type of DES in patients with DM remains a controversial issue.[7] The recently introduced resolute zotarolimus-eluting stents (R-ZES) have shown promising clinical and angiographic outcomes in large registry and randomized trials.[8−15] However, there were also limited usable data for the R-ZES in patients with DM.[16] Furthermore, little has been known regarding whether there are differences in efficacy and safety between R-ZES and SES in diabetic patients. To address these issues, this prospective randomized study compared angiographic and clinical outcomes of R-ZES and SES in diabetic patients.

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Methods

This prospective randomized study included 256 patients aged 18 years and older with coronary artery disease. The study involved 8 cardiac centers in Korea from September 2008 to January 2012. Patients were considered eligible if they had DM with either stable angina or an acute coronary syndrome and who had at least 1 coronary lesion (defined as stenosis of >50% and visual reference diameter of ≥2.5 mm) suitable for stent implantation. The diagnosis of DM was confirmed in all patients receiving active treatment with an oral hypoglycemic agent or insulin. For patients with a diagnosis of DM who were on a dietary therapy alone, documentation of an abnormal blood glucose level after an overnight fast was required. Patients were excluded if they had contraindication to aspirin and clopidogrel, unprotected left main disease (diameter stenosis ≥50% by visual estimate), graft vessel disease, left ventricular ejection fraction <30%, recent history of hematologic disease or leukocyte count <3,000/mm^3 and/or platelet count <100,000/mm^3, hepatic dysfunction with aspartate aminotransferase or alanine aminotransferase ≥3× the upper normal reference limit, history of renal dysfunction or serum creatinine level of ≥2.0 mg/dl, serious noncardiac co-morbid disease with a life expectancy <1 year, primary angioplasty for acute myocardial infarction (MI) within 24 hours, or inability to follow the protocol. In patients with multiple lesions fulfilling the inclusion and exclusion criteria, the first stented lesion was considered as the target lesion. The institutional review board at each participating center approved the protocol. All patients provided written informed consent.

Once the guidewire had crossed the target lesion, patients who met the inclusion and exclusion criteria were randomly assigned in a 1:1 ratio to R-ZES (Endeavor Resolute, Medtronic Cardiovascular, Santa Rosa, California) or SES (Cypher Select Plus, Cordis, Johnson & Johnson, Warren, New Jersey) implantation using interactive Web response system. The allocation sequence was computer generated, stratified according to participating, center and blocked with block sizes of 4 and 6 varying randomly. Random assignments were stratified according to participation sites. The procedure was performed according to standard techniques. Administration of glycoprotein IIb/IIIa inhibitors was at the discretion of the operator. After the procedure, all patients received 100 mg/day of aspirin indefinitely and 75 mg/day of clopidogrel for at least 12 months. A 12-lead electrocardiogram was obtained after the procedure and before discharge. Serum levels of creatine kinase, its MB isoenzyme, were assessed 8, 12, and 24 hours after the procedure, and thereafter if considered necessary.

The primary end point of this trial was in-segment late loss at 9-month angiographic follow-up. The secondary end points included 9-month angiographic outcomes of in-stent late loss, in-stent and in-segment binary restenoses at 9 months (diameter stenosis of ≥50%). At 12 months, stent thrombosis, ischemia-driven target lesion revascularization, ischemia-driven target vessel revascularization, and major adverse cardiac events including death from any cause, MI, or ischemia-driven target lesion revascularization were also assessed.

Table 1
Baseline clinical characteristics

Variable	R-ZES (n = 127)	SES (n = 129)
Age (yrs)	63.4 ± 8.6	62.7 ± 8.9
Men	70 (55.1)	88 (68.2)
Hypertension	88 (69.3)	93 (72.1)
Treatment of diabetes mellitus		
Oral hypoglycemic agent	102 (80.3)	101 (78.3)
Insulin	17 (13.4)	19 (14.7)
Dietary therapy alone	8 (6.3)	9 (7.0)
Glycosylated hemoglobin (%)	7.6 ± 1.4	7.8 ± 1.5
Total cholesterol ≥200 mg/dl	75 (59.1)	65 (50.4)
Current smoker	35 (27.6)	47 (36.4)
Previous percutaneous coronary intervention	7 (5.5)	7 (5.4)
Previous MI	6 (4.7)	3 (2.3)
Clinical diagnosis		
Stable angina	71 (55.9)	77 (59.7)
Unstable angina	46 (36.2)	39 (30.2)
Acute MI	10 (7.9)	13 (10.1)
Left ventricular ejection fraction (%)	62.3 ± 7.2	61.2 ± 7.7
Multivessel disease	62 (48.8)	60 (46.5)

Data are expressed as mean ± SD or number (percentage).

Angiographic success was defined as in-segment diameter stenosis of <30% by quantitative coronary angiographic analysis. MI was defined as creatine kinase-MB elevation of >3× or creatine kinase elevation of >2× the upper normal limit with at least 1 of the following: ischemic symptoms, development of pathologic Q waves, and ischemic electrocardiographic changes. Revascularization was defined as ischemia driven if there was stenosis of ≥50% of the diameter, as documented by a positive functional study, ischemic changes on an electrocardiogram, or ischemic symptoms, or in the absence of documented ischemia, if there was stenosis of ≥70% as assessed by quantitative coronary analysis. Stent thrombosis was assessed according to the Academic Research Consortium definitions[17] and was classified by the timing of the event (acute, 0 to 24 hours; subacute, 1 to 30 days; and late, >31 days).

Repeat coronary angiography was mandatory at 9 months after stenting, or earlier if indicated by clinical symptoms or evidence of myocardial ischemia. Clinical follow-up visits were scheduled at 30, 120, and 240 days and 1 year. At each participating center, patient data were recorded prospectively on standard case report forms and gathered in the central data management center (Asan Medical Center, Seoul, Korea). All adverse clinical events were adjudicated by an independent events committee blinded to the treatment groups.

Coronary angiograms were obtained after intracoronary nitroglycerin administration. Procedural (baseline), post-procedural, and follow-up angiograms were submitted to the angiographic core analysis center (Asan Medical Center, Seoul, Korea). Digital angiograms were analyzed using an automated edge detection system (CASS II; Pie Medical, Maastricht, The Netherlands). Angiographic variables included absolute lesion length, stent length, reference vessel diameter, minimum lumen diameter, percent diameter stenosis, binary restenosis rate, acute

Table 2
Angiographic and procedural characteristics

Variable	R-ZES (n = 127)	SES (n = 129)
Target coronary artery		
Left anterior descending	80 (63.0)	70 (54.3)
Left circumflex	20 (15.7)	28 (21.7)
Right	27 (21.3)	31 (24.0)
TIMI flow grade 0 or 1	5 (3.9)	3 (2.3)
Bifurcation lesions	17 (13.4)	16 (12.4)
Thrombus	2 (1.6)	3 (2.3)
Moderate to severe tortuosity	3 (2.4)	4 (3.1)
Moderate to severe calcification	16 (12.6)	12 (9.3)
Number of used stents at the target lesion	1.1 ± 0.3	1.2 ± 0.4
Maximal inflation pressure (atm)	11.7 ± 3.3	13.5 ± 3.5
Use of intravascular ultrasound	95 (74.8)	90 (69.8)
Use of glycoprotein IIb/IIIa inhibitor	0 (0)	1 (0.8)
Predilation before stenting	123 (96.9)	121 (93.8)
Poststenting adjunctive balloon dilatation	84 (66.1)	92 (71.9)
Largest balloon size for adjunctive dilatation (mm)	3.56 ± 0.42	3.55 ± 0.48
Multivessel stenting	44 (34.6)	33 (25.6)
Number of angiographic follow-up patients	85 (66.9)	90 (69.8)

Data are expressed as mean ± SD or number (percentage).
TIMI = thrombolysis in myocardial infarction.

Table 3
Quantitative angiographic measurements

Variable	R-ZES (n = 127)	SES (n = 129)	p
Reference diameter (mm)	3.06 ± 0.50	3.02 ± 0.45	0.436
Lesion length (mm)	21.1 ± 12.2	21.8 ± 11.3	0.673
Stented length at the target lesion (mm)	27.2 ± 11.6	26.7 ± 11.0	0.724
Minimum lumen diameter (mm)			
In segment			
Before procedure	1.06 ± 0.41	1.08 ± 0.43	0.742
After procedure	2.31 ± 0.56	2.29 ± 0.44	0.843
At follow-up	2.25 ± 0.56	2.14 ± 0.57	0.192
In stent			
After procedure	2.71 ± 0.48	2.67 ± 0.42	0.502
At follow-up	2.54 ± 0.57	2.45 ± 0.58	0.302
Diameter stenosis (%)			
In segment			
Before procedure	65.5 ± 12.2	64.4 ± 12.5	0.506
After procedure	18.4 ± 11.2	17.0 ± 9.9	0.305
At follow-up	21.9 ± 12.0	25.0 ± 21.0	0.232
In stent			
After procedure	7.5 ± 9.0	7.5 ± 7.2	0.966
At follow-up	15.2 ± 11.0	16.7 ± 15.5	0.474
Acute gain (mm)			
In segment	1.25 ± 0.59	1.21 ± 0.47	0.613
In stent	1.65 ± 0.52	1.59 ± 0.45	0.359
Late loss (mm)			
In segment	0.34 ± 0.30	0.39 ± 0.43	0.391
In stent	0.22 ± 0.29	0.21 ± 0.40	0.849
Binary angiographic restenosis			
In segment	1/85 (1.2)	6/90 (6.7)	0.119
In stent	1/85 (1.2)	3/90 (3.3)	0.621

Data are expressed as mean ± SD or as number (percentage).

gain, late loss, and the patterns of restenosis. Quantitative coronary angiographic measurements of target lesions were obtained for the stented segment (in stent) and the margins 5 mm proximal and distal to the stent (in segment). In-segment late loss was calculated within the analysis segment itself, but separately considering stented segment, proximal and distal edges and taking the maximum change in minimum lumen diameter within those 3 segments and applying it to this segment as a whole (maximal regional late loss method).[18] Patterns of angiographic restenosis were assessed using the Mehran classification.[19]

On the basis of results from previous trial,[20] we assumed an in-segment angiographic late loss of 0.43 ± 0.45 mm in both arms. Calculation of the sample size was based on a margin of noninferiority for in-segment late loss of 0.129 mm, which is equal to 30% of an assumed mean late loss after the implantation of SES. Using a 1-sided 5% significance level, we estimated that 152 patients per group were needed to demonstrate noninferiority of R-ZES with a statistical power of 80%. Expecting that approximately 20% of the patients would not return for follow-up angiography, total sample size was estimated to be 380 patients. Analyses of the 2 groups were performed according to the intention-to-treat principle. Continuous variables are presented as mean ± SD or median (interquartile range) and were compared using Student unpaired *t* or Mann-Whitney *U* test. Categorical variables are presented as numbers or percentages and were compared using chi-square or Fisher's exact test. The noninferiority hypothesis was assessed statistically using a Z-test, by which 1-sided p values for noninferiority were calculated to compare differences between groups with margins of noninferiority, according the method of Chow and Liu.[21] All p values are 2-sided, except those from noninferiority testing of the primary end point. A p value <0.05 was considered to indicate a significant difference. All statistical analyses were performed using SAS, version 9.1 (SAS Institute, Cary, North Carolina).

Results

Patient recruitment was prematurely halted on January 2012, owing to discontinuing production of SES. From September 2009 to January 2012, 256 patients were enrolled (127 in R-ZES group and 129 in SES). Table 1 lists similar baseline clinical characteristics between 2 groups, except more men in the SES group (p = 0.031). The similar angiographic and procedural characteristics are also listed in Table 2, except the more maximal inflation pressure in the SES group (p <0.001). The angiographic success rate was 100% in both groups.

The 2 groups had similar baseline and postprocedural quantitative coronary angiographic characteristics (Table 3). Follow-up angiography was performed in 175 patients (68.4%), with 85 (66.9%) of R-ZES and 90 (69.8%) of SES patients. The median duration of angiographic follow-up was similar in 2 groups (290 days [interquartile range 263 to 310] and 293 days [interquartile range 259 to 339] for the R-ZES and SES groups, respectively, p = 0.931). Patients

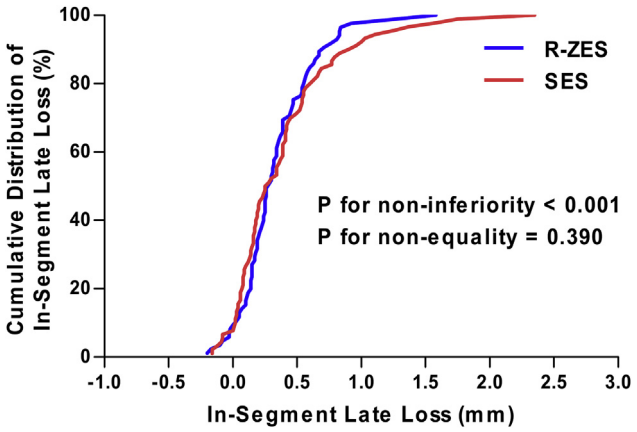

Figure 1. Cumulative rates of in-segment late loss at follow-up angiography.

Table 4
Clinical outcomes at 12 months

Variable	R-ZES (n = 127)	SES (n = 129)	p
Death	0	1 (0.8)	0.999
Cardiac	0	0	
Noncardiac	0	1 (0.8)	
MI	1 (0.8)	1 (0.8)	0.999
Q wave	0	1 (0.8)	
Non−Q wave	1 (0.8)	0	
Ischemia-driven TLR	2 (1.6)	1 (0.8)	0.621
Drug-eluting stent	1 (0.8)	0	
Cutting balloon	1 (0.8)	1 (0.8)	
Stent thrombosis	0	1 (0.8)	0.999
Acute	0	0	
Subacute	0	1 (0.8)	
Late	0	0	
Procedure-related non−Q-wave MI	12 (9.4)	4 (3.1)	0.036
Ischemia-driven TVR	4 (3.1)	2 (1.6)	0.445
Death/MI/ischemia-driven TVR	5 (3.9)	3 (2.3)	0.498
MACE (death/MI/ischemia-driven TLR)	3 (2.4)	2 (1.6)	0.683

Data are expressed as number (percentage).

MACE = major adverse cardiac event; TLR = target lesion revascularization; TVR = target vessel revascularization.

undergoing angiographic follow-up were more likely to have stable angina ($p = 0.033$) than those who did not return for angiographic follow-up. Those with angiographic follow-up have similar anatomical and procedural characteristics, except the more maximal inflation pressure ($p = 0.037$). Quantitative coronary angiographic measurements at follow-up are listed in Table 3. In-segment late loss of R-ZES using maximal regional late loss method, the prespecified primary end point, was noninferior to that of SES group (0.34 ± 0.30 vs 0.39 ± 0.43 mm; difference, −0.048; 95% confidence interval, −0.157 to 0.061; upper 1-sided 95% confidence interval, 0.044; $p < 0.001$ for noninferiority; Figure 1). In-segment late loss using analysis segment late loss method was similar between the R-ZES and SES groups (0.11 ± 0.30 vs 0.17 ± 0.37 mm; difference, −0.052; 95% confidence interval, −0.153 to 0.050; $p = 0.317$). In-stent late loss and the rates of in-segment and in-stent binary restenosis were not statistically different between the 2 groups. There was no significant difference for the patterns of restenosis between the 2 groups. In the R-ZES group, 1 was focal (class IC). In the SES group, 4 were focal (3 in class 1B and 1 in class 1C) and 2 were diffuse (1 in class II and 1 in class IV).

Clinical outcomes during follow-up are listed in Table 4. Although there were no significant differences in lesion characteristics, more procedure-related non−Q-wave MI occurred in R-ZES group. However, in-hospital events, including Q-wave MI, emergency bypass surgery, or death, did not occur in either group. At 12 months, the incidence of individual and composite clinical outcomes did not significantly differ between the 2 groups. During 12 months, 1 definite stent thrombosis occurred in the SES group, which was a subacute stent thrombosis.

Discussion

In this randomized trial involving patients with DM and coronary artery disease, R-ZES was noninferior to SES as assessed by 9-month angiographic in-segment late luminal loss. Moreover, both R-ZES and SES showed comparable low rates of clinical outcomes for 12 months, suggesting that both stents appear to be effective in the treatment of coronary artery disease in diabetic patients.

The use of DES significantly improved both angiographic and clinical outcomes compared with bare-metal stent in patients with DM.[2] However, DM still remains a major determinant of worse prognostic outcome even after DES use.[3,4] Therefore, an investigation to identify the relative efficacies of particular DES is clinically important to the physician's choice of devices in the management of these high-risk patients. The previous comparison of everolimus-eluting stent versus sirolimus-eluting Stent implantation for de novo coronary artery disease in patients with diabetes mellitus (ESSENCE-DIABETES) randomized trial showed that everolimus-eluting stents were noninferior to SES in angiographic outcomes and comparable in clinical outcomes.[22] The present study further investigated relative efficacies between R-ZES and SES in diabetic patients using a randomized controlled study design.

In this trial, R-ZES was noninferior to SES for in-segment late loss using maximal regional late loss method, the prespecified primary end point. In-segment late loss using analysis segment late loss method and in-stent late loss were not statistically different between the 2 groups. In earlier nonselective population studies, R-ZES was associated with low in-stent and in-segment late losses (in-stent: 0.22 to 0.29 mm, in-segment: 0.12 to 0.15 mm) and was comparable with that observed in our study.[10,12,15,23] In previous studies with diabetic population, the late loss of SES (in-stent: 0.09 to 0.26 mm, in-segment: 0.06 to 0.43 mm) was also comparable with that observed in this study.[5,6] Angiographic measurements such as in-stent and in-segment late losses have been used as suitable surrogate markers for clinical stent efficacy and primary end points in DES trials.[24] Therefore, in diabetic patients with coronary

artery disease, R-ZES may have a comparable efficacy to SES.

We also observed that in-segment and in-stent restenosis rates were not significantly different between R-ZES and SES in diabetic patients. In our R-ZES group, the restenosis rates were comparable with those of previous nonselective population studies (in-stent restenosis rate: 1.0% to 4.2%, in-segment restenosis rate: 2.1% to 13.4%).[10,12,15,23] In previous studies with diabetic population, restenosis rates of SES group (in-stent restenosis: 3.4% to 6.7%, in-segment restenosis: 3.5% to 8.5%) were also comparable with those observed in our study.[5,6] The major advance of R-ZES compared with the earlier version of ZES is its polymer coatings, enabling sustained release of zotarolimus to control neointimal hyperplasia in more difficult patient subsets.[23] Consistent with previous studies comparing 2 ZES generations,[25−27] in our diabetic population, these improved biocompatible polymer coatings of R-ZES may favorably affect to control neointimal hyperplasia.

All clinical events were not statistically different, in line with previous studies demonstrating similar efficacy and safety for R-ZES and SES.[6,12,27] Recently, in diabetic patients with R-ZES implantation, a pooled analysis described that the R-ZES was safe and effective in patients with DM and obtained Food and Drug Administration approval for the expanded indication for the use in diabetic patients.[28] Consistent with these previous findings, the present study also showed that clinical outcomes of R-ZES were excellent and were comparable with those of SES, which had been known as more effective first-generation DES in high-risk patients with DM.[16]

The present study has several limitations. First, in this study, patient enrollment was prematurely stopped after enrollment of 256 patients because of discontinuing production of SES. Furthermore, angiographic follow-up rate was 68.4%, which was lower than the protocol-based estimated rate. Second, our study was to evaluate angiographic outcomes not powered for clinical outcomes. Furthermore, in-segment late loss using maximal regional late loss method, the prespecified primary end point, was similar to that of analysis segment late loss method in clinical relevance.[18] Third, the SES group included significantly more men. There was an imbalance of the maximal pressure in procedural characteristics. Nevertheless, considering these potential effects, our overall findings would not change. Fourth, diabetic patients taking insulin has consistently been shown to be an independent predictor of adverse outcomes after stent implantation. The overall results in studies of patients with diabetes could depend on the percentage of patients with diabetes taking insulin.[29] However, in our study, the proportion of patients taking insulin was fewer than previous studies,[28] which would affect favorable results. Finally, in the R-ZES group, the more procedure-related non-Q MI occurred. However, there were no differences in the 9-month angiographic and 12-month clinical outcomes. These differences may be a chance factor because of the small sample size.

Disclosures

The authors have no conflicts of interest to disclose.

1. Berry C, Tardif JC, Bourassa MG. Coronary heart disease in patients with diabetes: part II: recent advances in coronary revascularization. *J Am Coll Cardiol* 2007;49:643−656.
2. Babapulle MN, Joseph L, Belisle P, Brophy JM, Eisenberg MJ. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. *Lancet* 2004;364:583−591.
3. Stone GW, Parise H, Witzenbichler B, Kirtane A, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Mockel M, Lansky AJ, Mehran R. Selection criteria for drug-eluting versus bare-metal stents and the impact of routine angiographic follow-up: 2-year insights from the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial. *J Am Coll Cardiol* 2010;56:1597−1604.
4. Tu JV, Bowen J, Chiu M, Ko DT, Austin PC, He Y, Hopkins R, Tarride JE, Blackhouse G, Lazzam C, Cohen EA, Goeree R. Effectiveness and safety of drug-eluting stents in Ontario. *N Engl J Med* 2007;357:1393−1402.
5. Stefanini GG, Holmes DR Jr. Drug-eluting coronary-artery stents. *N Engl J Med* 2013;368:254−265.
6. Bangalore S, Kumar S, Fusaro M, Amoroso N, Kirtane AJ, Byrne RA, Williams DO, Slater J, Cutlip DE, Feit F. Outcomes with various drug eluting or bare metal stents in patients with diabetes mellitus: mixed treatment comparison analysis of 22,844 patient years of follow-up from randomised trials. *BMJ* 2012;345:e5170.
7. Stone GW, Kedhi E, Kereiakes DJ, Parise H, Fahy M, Serruys PW, Smits PC. Differential clinical responses to everolimus-eluting and Paclitaxel-eluting coronary stents in patients with and without diabetes mellitus. *Circulation* 2011;124:893−900.
8. 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;377:1241−1247.
9. von Birgelen C, Basalus MW, Tandjung K, van Houwelingen KG, Stoel MG, Louwerenburg JH, Linssen GC, Said SA, Kleijne MA, Sen H, Lowik MM, van der Palen J, Verhorst PM, de Man FH. A randomized controlled trial in second-generation zotarolimus-eluting Resolute stents versus everolimus-eluting Xience V stents in real-world patients: the TWENTE trial. *J Am Coll Cardiol* 2012;59:1350−1361.
10. Massberg S, Byrne RA, Kastrati A, Schulz S, Pache J, Hausleiter J, Ibrahim T, Fusaro M, Ott I, Schomig A, Laugwitz KL, Mehilli J. Polymer-free sirolimus- and probucol-eluting versus new generation zotarolimus-eluting stents in coronary artery disease: the Intracoronary Stenting and Angiographic Results: test efficacy of Sirolimus- and Probucol-Eluting versus Zotarolimus-eluting Stents (ISAR-TEST 5) trial. *Circulation* 2011;124:624−632.
11. Park KW, Lee JM, Kang SH, Ahn HS, Yang HM, Lee HY, Kang HJ, Koo BK, Cho J, Gwon HC, Lee SY, Chae IH, Youn TJ, Chae JK, Han KR, Yu CW, Kim HS. Safety and efficacy of second-generation everolimus-eluting Xience V stents versus zotarolimus-eluting resolute stents in real-world practice: patient-related and stent-related outcomes from the multicenter prospective EXCELLENT and RESOLUTE-Korea registries. *J Am Coll Cardiol* 2013;61:536−544.
12. Ahn JM, Park DW, Kim YH, Song H, Cho YR, Kim WJ, Lee JY, Kang SJ, Lee SW, Lee CW, Park SW, Yun SC, Han S, Lee SY, Lee BK, Cho JH, Yang TH, Lee NH, Yang JY, Park JS, Shin WY, Kim MH, Bae JH, Kim MK, Yoon J, Park SJ. Comparison of resolute zotarolimus-eluting stents and sirolimus-eluting stents in patients with de novo long coronary artery lesions: a randomized LONG-DES IV trial. *Circ Cardiovasc Interv* 2012;5:633−640.
13. Yeung AC, Leon MB, Jain A, Tolleson TR, Spriggs DJ, Mc Laurin BT, Popma JJ, Fitzgerald PJ, Cutlip DE, Massaro JM, Mauri L. Clinical evaluation of the Resolute zotarolimus-eluting coronary stent system in the treatment of de novo lesions in native coronary arteries: the RESOLUTE US clinical trial. *J Am Coll Cardiol* 2011;57:1778−1783.
14. Neumann FJ, Widimsky P, Belardi JA. One-year outcomes of patients with the zotarolimus-eluting coronary stent: RESOLUTE International Registry. *EuroIntervention* 2012;7:1181−1188.
15. Meredith IT, Worthley S, Whitbourn R, Walters DL, McClean D, Horrigan M, Popma JJ, Cutlip DE, DePaoli A, Negoita M, Fitzgerald PJ. Clinical and angiographic results with the next-generation resolute stent system: a prospective, multicenter, first-in-human trial. *JACC Cardiovasc Interv* 2009;2:977−985.
16. Bangalore S, Kumar S, Fusaro M, Amoroso N, Attubato MJ, Feit F, Bhatt DL, Slater J. 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;125:2873−2891.
17. Laskey WK, Yancy CW, Maisel WH. Thrombosis in coronary drug-eluting stents: report from the meeting of the Circulatory System Medical Devices Advisory Panel of the Food and Drug Administration Center for Devices and Radiologic Health, December 7-8, 2006. *Circulation* 2007;115:2352−2357.
18. Ellis SG, Popma JJ, Lasala JM, Koglin JJ, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Stone GW. Relationship between angiographic late loss and target lesion revascularization after coronary stent implantation: analysis from the TAXUS-IV trial. *J Am Coll Cardiol* 2005;45:1193−1200.
19. Mehran R, Dangas G, Abizaid AS, Mintz GS, Lansky AJ, Satler LF, Pichard AD, Kent KM, Stone GW, Leon MB. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. *Circulation* 1999;100:1872−1878.
20. Dibra A, Kastrati A, Mehilli J, Pache J, Schuhlen H, von Beckerath N, Ulm K, Wessely R, Dirschinger J, Schomig A. Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. *N Engl J Med* 2005;353:663−670.
21. Chow SC, Liu JP. Design and Analysis of Clinical Trials. New York, NY: John Wiley and Son, 2004.
22. Kim WJ, Lee SW, Park SW, Kim YH, Yun SC, Lee JY, Park DW, Kang SJ, Lee CW, Lee JH, Choi SW, Seong IW, Lee BK, Lee NH, Cho YH, Shin WY, Lee SJ, Hyon MS, Bang DW, Park WJ, Kim HS, Chae JK, Lee K, Park HK, Park CB, Lee SG, Kim MK, Park KH, Choi YJ, Cheong SS, Yang TH, Jang JS, Her SH, Park SJ. Randomized comparison of everolimus-eluting stent versus sirolimus-eluting stent implantation for de novo coronary artery disease in patients with diabetes mellitus (ESSENCE-DIABETES): results from the ESSENCE-DIABETES trial. *Circulation* 2011;124:886−892.
23. 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;363:136−146.
24. Pocock SJ, Lansky AJ, Mehran R, Popma JJ, Fahy MP, Na Y, Dangas G, Moses JW, Pucelikova T, Kandzari DE, Ellis SG, Leon MB, Stone GW. Angiographic surrogate end points in drug-eluting stent trials: a systematic evaluation based on individual patient data from 11 randomized, controlled trials. *J Am Coll Cardiol* 2008;51:23−32.
25. Tada T, Byrne RA, Cassese S, King L, Schulz S, Mehilli J, Schomig A, Kastrati A. Comparative efficacy of 2 zotarolimus-eluting stent generations: resolute versus endeavor stents in patients with coronary artery disease. *Am Heart J* 2013;165:80−86.
26. Talarico GP, Burzotta F, Trani C, Tommasino A, Niccoli G, Porto I, Leone AM, Mongiardo R, Schiavoni G, Crea F. One-year outcomes of consecutive patients treated by endeavor zotarolimus and resolute zotarolimus stents: the impact of polymer coating in drug-eluting stent technology. *Catheter Cardiovasc Interv* 2013;81:268−273.
27. Cassese S, Ndrepepa G, King LA, Tada T, Fusaro M, Kastrati A. Two zotarolimus-eluting stent generations: a meta-analysis of 12 randomised trials versus other limus-eluting stents and an adjusted indirect comparison. *Heart* 2012;98:1632−1640.
28. Silber S, Serruys PW, Leon MB, Meredith IT, Windecker S, Neumann FJ, Belardi J, Widimsky P, Massaro J, Novack V, Yeung AC, Saito S, Mauri L. Clinical outcome of patients with and without diabetes mellitus after percutaneous coronary intervention with the resolute zotarolimus-eluting stent: 2-year results from the prospectively pooled analysis of the international global RESOLUTE program. *JACC Cardiovasc Interv* 2013;6:357−368.
29. Yang TH, Park SW, Hong MK, Park DW, Park KM, Kim YH, Han KH, Lee CW, Cheong SS, Kim JJ, Park SJ. Impact of diabetes mellitus on angiographic and clinical outcomes in the drug-eluting stents era. *Am J Cardiol* 2005;96:1389−1392.