JACC: CARDIOVASCULAR INTERVENTIONS VOL. 6, NO. 4, 2013

ISSN 1936-8798/$36.00

PUBLISHED BY ELSEVIER INC.

http://dx.doi.org/10.1016/j.jcin.2012.11.006

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

Sigmund Silber, MD, PHD,* Patrick W. Serruys, MD, PHD,† Martin B. Leon, MD,‡ Ian T. Meredith, MBBS, PHD,§ Stephan Windecker, MD,‖ Franz-Josef Neumann, MD, PHD,¶ Jorge Belardi, MD,# Petr Widimsky, MD, DRSC,** Joe Massaro, PHD,†† Victor Novack, MD, PHD,‡‡ Alan C. Yeung, MD,§§ Shigeru Saito, MD,‖‖ Laura Mauri, MD, MSC¶¶

Munich and Bad Krozingen, Germany; Rotterdam, the Netherlands; New York, New York; Melbourne, Australia; Bern, Switzerland; Buenos Aires, Argentina; Prague, Czech Republic; Boston, Massachusetts; Be'er-Sheva, Israel; Palo Alto, California; and Kamakura, Japan

Objectives The aim of this study was to describe the process to obtain Food and Drug Administration (FDA) approval for the expanded indication for treatment with the Resolute zotarolimus-eluting stent (R-ZES) (Medtronic, Inc., Santa Rosa, California) in patients with coronary artery disease and diabetes.

Background The R-ZES is the first drug-eluting stent specifically indicated in the United States for percutaneous coronary intervention in patients with diabetes.

Methods We pooled patient-level data for 5,130 patients from the RESOLUTE Global Clinical Program. A performance goal prospectively determined in conjunction with the FDA was established as a rate of target vessel failure at 12 months of 14.5%. In addition to the FDA pre-specified cohort of less complex patients with diabetes (n = 878), we evaluated outcomes of the R-ZES in all 1,535 patients with diabetes compared with all 3,595 patients without diabetes at 2 years.

Results The 12-month rate of target vessel failure in the pre-specified diabetic cohort was 7.8% (upper 95% confidence interval: 9.51%), significantly lower than the performance goal of 14.5% ($p < 0.001$). After 2 years, the cumulative incidence of target lesion failure in patients with noninsulin-treated diabetes was comparable to that of patients without diabetes (8.0% vs. 7.1%). The higher risk insulin-treated population demonstrated a significantly higher target lesion failure rate (13.7%). In the whole population, including complex patients, rates of stent thrombosis were not significantly different between patients with and without diabetes (1.2% vs. 0.8%).

Conclusions The R-ZES is safe and effective in patients with diabetes. Long-term clinical data of patients with noninsulin-treated diabetes are equivalent to patients without diabetes. Patients with insulin-treated diabetes remain a higher risk subset. (The Medtronic RESOLUTE Clinical Trial; NCT00248079; Randomized, Two-arm, Non-inferiority Study Comparing Endeavor-Resolute Stent With Abbot Xience-V Stent [RESOLUTE-AC]; NCT00617084; The Medtronic RESOLUTE US Clinical Trial (R-US); NCT00726453; RESOLUTE International Registry: Evaluation of the Resolute Zotarolimus-Eluting Stent System in a 'Real-World' Patient Population [R-Int]; NCT00752128; RESOLUTE Japan–The Clinical Evaluation of the MDT-4107 Drug-Eluting Coronary Stent [RJ]; NCT00927940). (J Am Coll Cardiol Intv 2013;6:357–68) © 2013 by the American College of Cardiology Foundation

From the *Heart Center at the Isar, Munich, Germany; †Thoraxcenter Erasmus Medical Center, Rotterdam, the Netherlands; ‡Columbia University Medical Center, New York-Presbyterian Hospital, New York, New York; §MonashHeart and Monash University, Melbourne, Australia; ‖University Hospital Foundation, Bern, Switzerland; ¶Heart Center Bad Krozingen, Bad

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 6, NO. 4, 2013
APRIL 2013:357–68

Abbreviations and Acronyms

ARC = Academic Research Consortium
BMS = bare-metal stent(s)
CAD = coronary artery disease
CEC = Clinical Events Committee
CK = creatinine kinase
DES = drug-eluting stent(s)
EES = everolimus-eluting stent(s)
FDA = Food and Drug Administration
ITDM = insulin-treated diabetes mellitus
LAD = left anterior descending artery
LCX = left circumflex artery
LMCA = left main coronary artery
MACE = major adverse cardiac events
MI = myocardial infarction
NITDM = noninsulin-treated diabetes mellitus
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent(s)
RCA = right coronary artery
R-ZES = Resolute zotarolimus-eluting stent(s)
SES = sirolimus-eluting stent(s)
TLF = target lesion failure
TLR = target lesion revascularization
TVF = target vessel failure
TV-MI = target vessel myocardial infarction
TVR = target vessel revascularization

Patients with diabetes mellitus are in general at greater risk of developing cardiovascular events (1–3), and those undergoing percutaneous coronary intervention (PCI) for obstructive coronary artery disease (CAD) have an increased risk of restenosis and stent thrombosis (4–6). Although several randomized studies (7–10), registries (11,12), and post hoc subgroup analyses from large randomized trials (7,13–15) have shown drug-eluting stents (DES) to be superior to bare-metal stents (BMS) in reducing neointimal hyperplasia and therefore restenosis rates in patients with diabetes, patients with diabetes continue to be a higher risk subset associated with worse clinical outcomes (16–18).

The Resolute zotarolimus-eluting stent (R-ZES) (Medtronic, Inc., Santa Rosa, California) is a new-generation DES comprising a thin-strut cobalt alloy BMS and a durable polymer that allows prolonged drug elution for treatment of patients with complex lesions and clinical characteristics (19). The safety and effectiveness of the R-ZES has been established in over 5,000 patients enrolled in 5 clinical trials, including 2 large international trials with minimal exclusion criteria (20–25). To obtain a specific indication for use in patients with diabetes, a prespecified analysis plan was developed in collaboration with the U.S. Food and Drug Administration (FDA) to test the performance of the R-ZES against a performance goal derived from the published data and pooled ENDEAVOR (Medtronic, Inc.) data (26). Patients enrolled in the RESOLUTE Global Clinical Trial Program (Table 1) served as the study population. This statistical plan was established before the reporting of the primary outcomes from the first large randomized all-comers RESOLUTE trial (RESOLUTE All-comers Trial: A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention) (21,22). The purpose of this paper is to describe the process used in obtaining FDA approval for the expanded indication for use in patients with diabetes for the R-ZES and to report the 2-year clinical outcomes in complex patients with and without diabetes.

Methods

Patient selection. For this analysis, we pooled patient-level data for 5,130 patients from 5 controlled studies, with 1 randomized (21,22) and 4 single-arm (20,23–25) designs of the RESOLUTE Global Clinical Trial Program (Table 1). In concordance with the FDA, the predefined subset of the pooled cohort was based on the inclusion and exclusion criteria of studies in patients with diabetes in the published data at the time the study was designed (Table 2). Because the enrollment criteria of the randomized RESOLUTE All Comers (21,22) and the observational RESOLUTE International (24) studies included more complex patients, the high-risk subsets from these 2 studies were excluded from the primary analysis. Patients with acute myocardial infarction (MI) within 72 h of the index procedure, lesion length >27 mm, >2 lesions/vessel, in-stent restenosis, unprotected left main lesions, bifurcation lesions, total occlusions, bypass grafts, thrombus, left ventricular ejection fraction <30%, or serum creatinine ≥1.6 mg/dl (≥140 μmol/l, according to Table 2) were excluded.

Because the RESOLUTE First-in-Man (20), RESOLUTE US (23), and RESOLUTE Japan studies (25) used the same criteria, all patients from these 3 studies were included in the pre-specified analysis.

Krozingen, Germany; #Cardiovascular Institute of Buenos Aires, Buenos Aires, Argentina; **Cardiocenter Kralovske Vinohrady, Charles University, Prague, Czech Republic; ††Harvard Clinical Research Institute, Boston Massachusetts; ‡‡Soroka Clinical Research Center, Be'er-Sheva, Israel; §§Stanford University School of Medicine, Palo Alto, California; ||||Shonan Kamakura General Hospital, Kamakura, Japan; and the ¶¶Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. This work was supported by Medtronic. Dr. Silber has received grant, travel, and analysis support from Medtronic. Drs. Leon, Belardi, and Yeung serve as advisors to Medtronic. Dr. Meredith serves as a consultant to Boston Scientific and Medtronic. Dr. Widimsky has received speaker's honoraria from Medtronic. Dr. Windecker has received research grant support via institutional grants from Abbott, Biotronik, Biosensors, Boston Scientific, and Cordis. Dr. Belardi has received support from Eli Lilly and Medtronic. Dr. Massaro is a paid consultant for Harvard Clinical Research Institute, which was funded by the sponsor. Dr. Novack has served as consultant to Harvard Clinical Research Institute, which received payment from Medtronic for data management and analysis. Dr. Mauri has served as consultant to Medtronic; and has received support from institutional grants from Abbott, Boston Scientific, Cordis, Medtronic, Eli Lilly, Daiichi Sankyo, Bristol-Myers Squibb, and Sanofi aventis. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Michael A. Kutcher, MD, served as Guest Editor for this paper.

Manuscript received September 26, 2012; accepted November 13, 2012.

Table 1. The 5 Studies From the RESOLUTE Clinical Trial Program as the Source for the FDA Pre-Specified Analysis

	RESOLUTE FIM (22)	RESOLUTE All Comers (20,21)	RESOLUTE International (23)	RESOLUTE US (24)	RESOLUTE Japan (25)
Enrollment dates	Dec 2005–Oct 2006	Apr 2008–Oct 2008	Aug 2008–Mar 2009	Aug 2008–Dec 2009	Mar 2009–Oct 2009
Primary endpoint	In-stent late loss at 4 months	TLF at 1 yr	CD/TV-MI at 1 yr	TLF at 1 yr	In-stent late loss at 8 months
Percent external monitoring	100%	100%	25%	100%	100%
Patients with the R-ZES (n = 5,130)	139	1,140	2,349	1402	100
All patients with DM (n = 1,535, 29.9%)	24 (17.3%)	268 (23.5%)	716 (30.5%)	482 (34.4%)	45 (45%)
Patients with DM for the pre-specified analysis (n = 878, 17.2%)	24 (17.3%)	85 (7.5%)	242 (10.3%)	482 (34.4%)	45 (45%)

For definition of these parameters, please see text.
CD = cardiac death; DM = diabetes mellitus; FDA = Food and Drug Administration; FIM = first in man; R-ZES = Resolute zotarolimus-eluting stent; TLF = target lesion failure; TV-MI = target vessel myocardial infarction.

Thus, our pre-specified analysis population for the FDA comprised 878 patients with diabetes (Tables 1 to 4). We also compared these results with the 1,903 patients without diabetes but having the same inclusion/exclusion criteria. In addition to this pre-specified diabetic cohort, we evaluated the safety and efficacy of the R-ZES in all 1,535 patients with diabetes, including the 657 complex patients, compared with all 3,595 (also, including complex) patients without diabetes (Table 1).

Diabetic status. Patients were classified as having diabetes if they were on a regimen of insulin and/or taking oral antidiabetic agents or on a modified diet to control diabetes. Patients were considered insulin-treated if they were taking insulin. Patients were considered noninsulin-treated if they were taking only oral antidiabetic agents or on a modified diabetes diet only or both oral agents and a modified diet. The same criteria were used for all trials in the global RESOLUTE Clinical Program.

All RESOLUTE trials required the same dual antiplatelet therapy. A daily dose of at least 75 mg aspirin was prescribed indefinitely, and 75 mg of clopidogrel was prescribed daily for at least 6 months.

Study management. Each patient consent form was externally verified for all studies. Source files were reviewed for all patients in the RESOLUTE First-In-Man (20), All Comers (21,22), US (23), and Japan (25) studies. For the RESOLUTE International study, although 25% of patient charts were externally monitored, there were no differences in clinical outcomes between fully monitored and partially monitored patients through 1 year (24). Independent Clinical Events Committees (CEC) reviewed all serious adverse events. All studies were conducted according to the Declaration of Helsinki; all study protocols were approved by local ethics committees.

In addition to the CEC event adjudication process specific for each study, a CEC Global Oversight Committee was organized to ensure consistency in clinical data review and to harmonize the interpretation of event definitions across the CECs from the 3 largest trials, the RESOLUTE All Comers, RESOLUTE International, and RESOLUTE US trials. The Global Oversight Committee evaluated the consistency of event adjudication on the basis of interpretation of event guidelines and provided recommendations to the respective primary CEC. The cross-adjudication process included a minimum of 10% of the events from each of the 3 trials (maximum of 100 events/trial) to be cross-adjudicated by an alternate participating CEC. The selection of cross-adjudicated events was based on event type: death, MI, stent thrombosis, target lesion, or vessel revascularization.

Choice and definitions of the clinical outcome parameters. The primary objective for the pre-specified FDA analysis population was to compare the rate of target vessel failure (TVF), defined as a composite of cardiac death, target vessel

Table 2. Inclusion and Exclusion Criteria for Patients in the FDA Pre-Specified Analysis Cohort

Inclusion criteria	Clinical inclusion: Clinical evidence of ischemic heart disease, stable or unstable angina, silent ischemia, and/or a positive functional test Angiographic inclusion: (measurements may be made by careful visual estimate) Total stent length ≤100 mm Target lesion stenosis ≥50% and <100% with a reference diameter ≤4.0 mm
Exclusion criteria	Clinical exclusion: Acute myocardial infarction ≤72 h Cardiogenic shock or in Killip class IV History of stroke or transient ischemic attack within 6 months preceding the index procedure History of bleeding diathesis or coagulopathy or will refuse blood transfusions Severe hepatic disease Documented left ventricular ejection fraction <30% at the most recent evaluation Platelet count <100,000 or >700,000 cells/mm^3 or a WBC count <3,000 cells/mm^3 Serum creatinine level ≥140 μmol/l within 7 days before index procedure Procedural exclusion: PCI of a nontarget vessel within 24 h before the index procedure 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 Implantation of a DES in any nontarget vessel within 30 days before the index procedure PCI of a nontarget vessel with a BMS within 30 days before index procedure that results in any MACE. If the BMS is implanted within 72 h before the index procedure, a post-procedural serial CK or CK-MB measurement above the ULN of the investigational site, within 2 SD below ULN required for enrollment Target lesion requires treatment with a device other than standard PCI before stent placement, including, but not limited to, cutting balloon, atherectomy, laser, or thrombus aspiration during the index procedure Any previous or planned treatment of the target vessel with other than DES anti-restenotic therapies, including, but not limited, to brachytherapy Angiographic exclusion: Target lesion located in arterial or venous vessels Target vessel is excessively tortuous (2 bends >90° to reach the target lesion) Significant stenosis (>50%) proximal or distal to the target lesion with any of the following characteristics: aorto-ostial location or within 5 mm of the origin of the left LAD, LCX, or RCA; bifurcation involving a side branch >2.0 mm in diameter; unprotected left main lesion with an obstruction >50%, lesion is at or distal to a >45° bend in the vessel; is severely calcified; total lesion length/vessel >27 mm; more than 2 lesions/vessel or more than 3 vessels treated; visible thrombus In-stent restenosis

BMS = bare-metal stent(s); CK = creatine kinase; CK-MB = creatine kinase-myocardial band; DES = drug-eluting stent(s); FDA = Food and Drug Administration; LAD = left anterior descending; LCX = left circumflex; MACE = major adverse cardiac events; PCI = percutaneous coronary intervention; ULN = upper limit of normal; WBC = white blood cell.

myocardial infarction (TV-MI), and ischemia-driven target vessel revascularization (TVR) in patients with diabetes at 12 months against a pre-defined performance goal (see the following text).

Pre-specified secondary objectives included major adverse cardiac events (MACE), defined as a composite of any death, any MI, emergent coronary artery bypass, and ischemia-driven revascularization by any method and target lesion failure (TLF), defined as a composite of cardiac death, TV-MI, and ischemia-driven target lesion revascularization (TLR). Any death was considered cardiac unless a noncardiac cause could be confirmed. Any MI for which a clear ascription to a target vessel could not be determined was counted as a TV-MI. All endpoint definitions have been previously described in detail and are consistent among the 5 studies (20–25,27). Definite and probable stent thrombosis was adjudicated according to the Academic Research Consortium (ARC) criteria (28).

Pre-defined hypothesis and statistical methods. All studies in the RESOLUTE Global Clinical program were prospectively designed with similar inclusion and exclusion criteria, clinical documentation forms, endpoint definitions, adjudication procedures, and statistical methodologies. To evaluate the performance of the R-ZES in patients with diabetes against previously published evidence, the following pre-specified analysis was designed in conjunction with the FDA to support the approval of an expanded indication for treatment of patients with diabetes with the R-ZES in the United States.

All data were analyzed according to the intention-to-treat principle. To develop the pre-specified performance goal, we performed a meta-analysis of studies reporting outcomes of patients with diabetes, treated with sirolimus- (SES) and paclitaxel-eluting stents (PES) (7,8,13,15,29), and used data from the ENDEAVOR pooled studies (30) to define an expected rate of TVF in a diabetic patient population after treatment with various DES. Thus, the weighted meta-analytic rate for the 12-month TVF rate was calculated to be 11.08%. The performance goal was established at 14.5%, which includes a clinically acceptable margin. The hypothesis for this analysis accounted for the differences in the protocols of the individual studies in the published data. Rejection of the null hypothesis at a 1-sided 0.05 level of significance would signify that the upper 95% limit around the TVF rate would be <14.5%. With 80% power, this resulted in a sample size requirement of 604 evaluable patients. This performance

Table 3. Baseline Characteristics of the FDA Pre-Specified Analysis Cohort

Baseline Characteristics	R-ZES, Non-DM (n = 1,903)*	R-ZES DM (n = 878)*	p Value†	R-ZES NITDM (n = 628)‡	R-ZES ITDM (n = 250)‡	p Value§
Age (yrs)	63.5 ± 10.8	65.2 ± 10.2	<0.001	65.5 ± 10.3	64.6 ± 10.0	0.255
Male	74.4 (1,415)	66.4 (583)	<0.001	70.4 (442)	56.4 (141)	<0.001
History of smoking	59.3 (1,128)	58.1 (510)	0.562	60.2 (378)	52.8 (132)	0.049
Current smoker	22.1 (421)	18.2 (160)	0.018	18.6 (117)	17.2 (43)	0.699
Hyperlipidemia	76.0 (1,446)	86.2 (757)	<0.001	86.0 (540)	86.8 (217)	0.828
History of hypertension	73.1 (1,392)	87.6 (769)	<0.001	86.0 (540)	91.6 (229)	0.023
Prior myocardial infarction	25.5 (481/1,883)	24.9 (216/716)	0.741	25.7 (160/622)	22.9 (56/245)	0.433
History of premature CAD in first-degree relative	42.2 (663/1,571)	37.8 (369/711)	0.053	37.6 (191/508)	38.4 (78/203)	0.864
Prior percutaneous coronary revascularization	29.5 (562)	34.6 (304)	0.008	33.9 (213)	36.4 (91)	0.530
Prior CABG	7.4 (140)	10.5 (92)	0.006	11.1 (70)	8.8 (22)	0.331
Reason for revascularization			0.211			0.105
Stable angina	45.5 (865)	46.2 (406)		46.8 (294)	44.8 (112)	
Unstable angina	31.3 (596)	28.9 (254)		28.5 (179)	30.0 (75)	
Myocardial infarction	6.6 (125)	5.4 (47)		4.3 (27)	8.0 (20)	
Silent ischemia	2.1 (40)	2.1 (18)		1.8 (11)	2.8 (7)	
Vessel location (patient level)						
LAD	47.7 (907)	44.8 (393)	0.164	45.4 (285)	43.2 (108)	0.599
LCX	30.1 (573)	30.8 (270)	0.723	30.9 (194)	30.4 (76)	0.935
RCA	31.1 (591)	34.7 (305)	0.055	32.8 (206)	39.6 (99)	0.060
LMCA	0.5 (9)	1.1 (10)	0.079	1.3 (8)	0.8 (2)	0.733
Serum creatinine (μmol/l)	84.9 ± 19.4 (1,756)	87.1 ± 24.9 (816)	0.033	86.3 ± 24.2 (586)	89.0 ± 26.7 (230)	0.162

Values are mean ± SD, % (n), % (n/N), or mean ± SD (N). *All denominators are 1,903 patients and 878, respectively, unless reported otherwise. †p values represent the comparisons at baseline between patients with diabetes and patients without diabetes. ‡All denominators are 628 patients and 250, respectively, unless reported otherwise. §p values represent the comparison at baseline between patients with diabetes taking insulin and patients with diabetes not taking insulin.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; ITDM = insulin-treated diabetes mellitus; LMCA = left main coronary artery; NITDM = noninsulin-treated diabetes mellitus; other abbreviations as in Tables 1 and 2.

goal was developed and agreed in collaboration with the U.S. FDA and the Harvard Clinical Research Institute (Boston, Massachusetts).

For baseline comparisons, the 2-sample *t* test was used for continuous variables, and data are presented as mean ± SD. The Fisher exact test was used for binary variables. Time to event analyses is reported with the Kaplan-Meier method. A p value of <0.05 was considered statistically significant. The Harvard Clinical Research Institute, an independent clinical research organization, performed all statistical analyses with SAS (version 9.1 or higher; SAS Institute, Inc., Cary, North Carolina).

Results

Baseline clinical characteristics for patients in the pre-specified analysis population by diabetes status are presented in Table 3. In general, as compared with patients without diabetes, patients with diabetes were older, more often female, more often hyperlipidemic or hypertensive, more often presented with prior PCI or prior coronary artery bypass surgery but less often were current smokers. Of the 878 patients with diabetes, 250 (28.5%) required insulin treatment. Baseline characteristics by insulin requirements were more similar between groups; however, there were more women and more hypertensive patients in the insulin-treated group (Table 3).

Primary endpoint at 1 year for FDA approval. The 12-month rate of the primary endpoint of TVF in the 878 R-ZES patients in the pre-specified diabetic cohort was 7.8% (upper 95% confidence interval: 9.51%) and significantly lower than the performance goal of 14.5% (p = 0.001). Therefore, the pre-set performance goal for the FDA was met. Additional safety and efficacy outcomes at 12 months for the pre-specified diabetic cohort were as follows: TLF was 6.6%, all death was 2.8%, the combination of cardiac death and TV-MI was 3.6%, MACE was 7.5%, and ARC definite and probable stent thrombosis was 0.3%.

Clinical outcomes at 2 years. Clinical outcomes at 2 years for the pre-specified patient population are shown in Tables 4 and 5. The rates of MACE, all death, TVF, and TLF were significantly higher in the pre-specified diabetic cohort than in the nondiabetic cohort (Table 4). These outcomes were also significantly higher in patients with diabetes taking insulin as compared with the noninsulin-treated cohort (Table 5). The incidence of ARC definite and probable stent thrombosis through 2 years was very low, regardless of the presence or severity of diabetes: in the pre-specified cohort, the rates of stent thrombosis were 0.4% for the

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 6, NO. 4, 2013
APRIL 2013:357–68

Table 4. 2-Year Clinical Outcomes for Patients in the Pre-Specified Analysis Cohort by Diabetes Status

	R-ZES, Non-DM (n = 1,903)*	R-ZES DM (n = 878)*	p Value
TVF	8.9 (164)	12.1 (104)	0.01
TLF	7.2 (132)	9.5 (82)	0.04
TVR	5.3 (98)	7.9 (68)	0.01
TLR	3.4 (63)	4.8 (41)	0.11
TV-MI	3.1 (58)	2.3 (20)	0.27
Death	2.4 (44)	4.9 (42)	<0.001
Cardiac death	1.1 (20)	3.4 (29)	<0.001
Noncardiac death	1.3 (24)	1.5 (13)	0.72
Cardiac death or TV-MI	4.1 (76)	5.2 (45)	0.20
Major adverse cardiac events	8.8 (162)	11.3 (97)	0.04
Stent thrombosis (ARC definite/probable)	0.4 (8)	0.3 (3)	>0.99
Early (≤30 days)	0.2 (3)	0.2 (2)	0.66
Late (>30 and ≤360 days)	0.2 (3)	0.1 (1)	>0.99
Very late (>360–720 days)	0.1 (2)	0.0	>0.99

Values are % (n). *All denominators at 2-year follow-up are 1,846 and 861 DM and non-DM cohorts, respectively. For definition of the clinical outcome parameters, please see text.
ARC = Academic Research Consortium; other abbreviations as in Table 1.

nondiabetic patients and 0.3% in the diabetic group (p > 0.99) (Table 4). Of the 250 patients taking insulin, there were 2 patients with stent thrombosis, and of the 628 diabetic patients not treated with insulin, only 1 patient had stent thrombosis throughout the 2 years (Table 5). In the entire pre-specified diabetic cohort of 878 patients, not a single patient had a very late stent thrombosis (Tables 4 and 5). The 30-day, 6-month, and 1- and 2-year rate of dual antiplatelet therapy usage was 96.1%, 94.8%, 90.3%, and 59.1%, respectively, for the pre-specified diabetic population.

As in the pre-specified cohort (Tables 4 and 5), in the whole population, including the complex patients, the rates of stent thrombosis were not significantly different between patients with and without diabetes (1.2% vs. 0.8%) as well as between insulin-treated and noninsulin-taking patients with diabetes (1.8% vs. 0.9%) (Table 6). Dual antiplatelet therapy usage in the overall diabetic and nondiabetic groups at 1 year was 89.9% and 89.2% and at 2 years was 52.8% and 42.5%, respectively.

Figure 1 shows the cumulative incidence of TLF and its components for patients with diabetes according to insulin treatment and for patients without diabetes at 1- and 2-year follow-up for the pre-specified analysis population. Time-to-event analyses show that the incidence of TLF (Fig. 1A) and its components of cardiac death and TV-MI (Fig. 1B) and TLR (Fig. 1C) in patients with noninsulin-treated diabetes are comparable to that of patients without diabetes. The clinical events are significantly higher in the insulin-treated patients than in the noninsulin-treated diabetic and nondiabetic patients. The analysis of all R-ZES patients, including the nondiabetic and diabetic complex patients, shows the same pattern with significantly higher event rates in the insulin-treated patients but no difference between the noninsulin-treated diabetic and the nondiabetic patients (Fig. 2).

Discussion

The present publication describes the effect of the R-ZES on clinical outcomes in 2 important analyses populations: a pre-specified cohort of patients from 5 prospectively planned and harmonized studies (Table 1)—on the basis of which the FDA approved the specific indication for PCI in patients with diabetes in the United States; and the full cohort of patients treated with the R-ZES, including the more complex patients.

The concept of a pre-specified prospective cohort analysis relative to a historical control. In general, randomized trials are more rigorous than observational studies, yet they are often limited in power to address many individual clinical questions, due to the sample size of individual populations. Therefore, an acceptable compromise of a prospectively planned analysis compared with a performance goal was derived from historical data. This acceptability of a performance goal study on the basis of historical data was used for U.S. approval of the first-generation Taxus Liberté PES (Boston Scientific, Natick, Massachusetts) (31). The TAXUS ATLAS trial (TAXUS ATLAS: A Multi-center, Single-arm Study of the TAXUS Liberté-SR Stent for the Treatment of Patients With de Novo Coronary Artery Lesions)—a prospective, single-arm study in de novo coro-

Table 5. 2-Year Clinical Outcomes for Patients With Diabetes in the Pre-Specified Analysis Cohort by Insulin Requirements

	R-ZES NITDM (n = 628)*	R-ZES ITDM (n = 250)*	p Value
TVF	10.4 (64/617)	16.4 (40/244)	0.02
TLF	7.9 (49)	13.5 (33)	0.01
TVR	7.3 (45)	9.4 (23)	0.33
TLR	4.2 (26)	6.1 (15)	0.29
TV-MI	1.3 (8)	4.9 (12)	0.004
Death	3.9 (24)	7.4 (18)	0.04
Cardiac death	2.8 (17)	4.9 (12)	0.14
Noncardiac death	1.1 (7)	2.5 (6)	0.21
Cardiac death or TV-MI	3.9 (24)	8.6 (21)	0.01
Major adverse cardiac events	9.4 (58)	16.0 (39)	0.008
Stent thrombosis (ARC definite/probable)	0.2 (1)	0.8 (2)	0.20
Early (≤30 days)	0.2 (1)	0.4 (1)	0.49
Late (>30 and ≤360 days)	0.0	0.4 (1)	0.28
Very late (>360–720 days)	0.0	0.0	—

Values are % (n/N) or % (n). *All denominators at 2-year follow-up are 617 and 244 for NITDM and ITDM cohorts, respectively. For definition of the clinical outcome parameters, please see text.
Abbreviations as in Tables 1, 3, and 4.

Table 6. Stent Thrombosis Through 2 Years for All Patients

	R-ZES Non-DM (n = 3,595)*	R-ZES DM (n = 1,535)*	R-ZES NITDM (n = 1,080)†	R-ZES ITDM (n = 455)†
Stent thrombosis (ARC definite/probable)	0.8 (29)	1.2 (18)	0.9 (10)	1.8 (8)
Early (≤30 days)	0.5 (18)	0.8 (12)	0.8 (8)	0.9 (4)
Late (>30–360 days)	0.2 (7)	0.3 (4)	0.1 (1)	0.7 (3)
Very late (>360–720 days)	0.1 (5)	0.1 (2)	0.1 (1)	0.2 (1)

Values are % (n). Stent thrombosis through 2 years for all (including the complex) patients. *All denominators at 2-year follow-up are 3,504 and 1,510 for the non-DM and DM cohorts, respectively. †All denominators at 2-year follow-up are 1,064 and 446 for the NITDM and ITDM cohorts, respectively. P values are not reported, because the study was not powered to detect differences between groups for this low-frequency event.

Abbreviations as in Tables 1, 3, and 4.

nary lesions—compared treatment with the Taxus Liberté PES versus a matched historical control group of patients from the TAXUS-IV and -V trials treated with the Taxus Express PES (31). The Taxus Liberté PES met its performance goal as compared with the Taxus Express PES for the primary clinical endpoint of TVR at 9 months. Subsequently, the Promus Element everolimus-eluting stent (EES) (Boston Scientific) gained U.S. approval by meeting a performance goal for the primary surrogate endpoint of late loss at 9 months (32).

For the first time, for the purpose of obtaining this specific indication with the U.S. FDA, a pre-specified performance goal was prospectively established to determine the safety and effectiveness of a DES for patients with diabetes. Inclusion and exclusion criteria (Table 2) for the pre-specified analysis cohort were aligned across the 5 RESOLUTE trials to support appropriate comparisons with patients in the studies used to derive the performance goal. Therefore, all 5 RESOLUTE trials used consistent endpoint definitions, and a Global Oversight Committee cross-adjudicated a subset of events, to ensure consistency in clinical endpoint review. Patient-level data were then pooled from the 5,130 patients from the RESOLUTE Global Clinical Program (Table 1). The rate of TVF in the pre-specified analysis cohort for the R-ZES–treated patients with diabetes at 12 months was 7.8%, considerably less than the predefined DES performance goal of 14.5% ($p = 0.001$). Thus, the primary endpoint of 1-year TVF met the performance goal, and the R-ZES achieved the first FDA approval of the specific expanded indication for PCI in patients with diabetes. The R-ZES is the only stent in the United States approved for use in patients with diabetes.

As shown in Figure 1, the 2-year clinical outcomes with the R-ZES in patients with diabetes not taking insulin overlap the outcome in patients without diabetes, even though the patients with diabetes not taking insulin had significantly more cardiovascular risk factors (Table 3). The same observation was also made when including the more-complex patients (Fig. 2). Therefore, the presence of noninsulin-requiring diabetes does not seem to affect clinical outcomes after treatment with the R-ZES.

Superiority of DES versus BMS in patients with diabetes. The DIABETES (Randomized comparison of sirolimus-eluting stent versus standard stent for percutaneous coronary revascularization in diabetic patients: the diabetes and sirolimus-eluting stent) trial (7) was the first prospective randomized trial comparing a DES versus BMS in patients with diabetes as an inclusion criterion (33). In 160 patients, the primary surrogate endpoint of in-segment late lumen loss at 9 months was significantly reduced with the Cypher SES (Cordis Corporation, Miami Lakes, Florida) compared with a BMS (0.06 ± 0.4 mm vs. 0.47 ± 0.5 mm). In the SCORPIUS trial (A German Multicenter, Randomized, Controlled, Open-Label Study of the Cypher Sirolimus-Eluting Stent in the Treatment of Diabetic Patients With De Novo Native Coronary Artery Lesions) (8), the same primary surrogate endpoint for the same DES was reached after 8 months in 200 patients with a significant reduction from 0.75 ± 0.59 mm to 0.17 ± 0.45 mm. In the DESSERT (An Italian Multicenter, Randomized, Single Blind Study of the Sirolimus Eluting Stent in the Treatment Of Diabetic Patients With De Novo Coronary Artery Lesions) study (9), the primary surrogate endpoint of in-stent late lumen loss was significantly reduced from 0.96 ± 0.61 mm to 0.14 ± 0.33 mm after treatment with the same DES after 8 months in 150 patients treated with oral anti diabetic medication and/or insulin.

Drug-eluting stents are preferred over BMS for PCI in patients with diabetes according to European and U.S. guidelines (34–36). However, although patients with diabetes are an everyday challenge in clinical practice and are regularly treated with DES, there is no randomized trial of DES versus BMS with a primary clinical endpoint based on an adequately calculated sample size for the clinical outcome in patients with diabetes as an inclusion criterion.

Are there differences between first-generation DES in patients with diabetes? The ISAR-DIABETES trial (Intracoronary Stenting and Antithrombotic Regimen: Diabetes Mellitus) (37), was the first randomized study directly comparing 2 DES in patients with diabetes. The primary endpoint was the surrogate parameter of in-segment late luminal loss after a mean follow-up of 196 days. In 205 patients, the primary

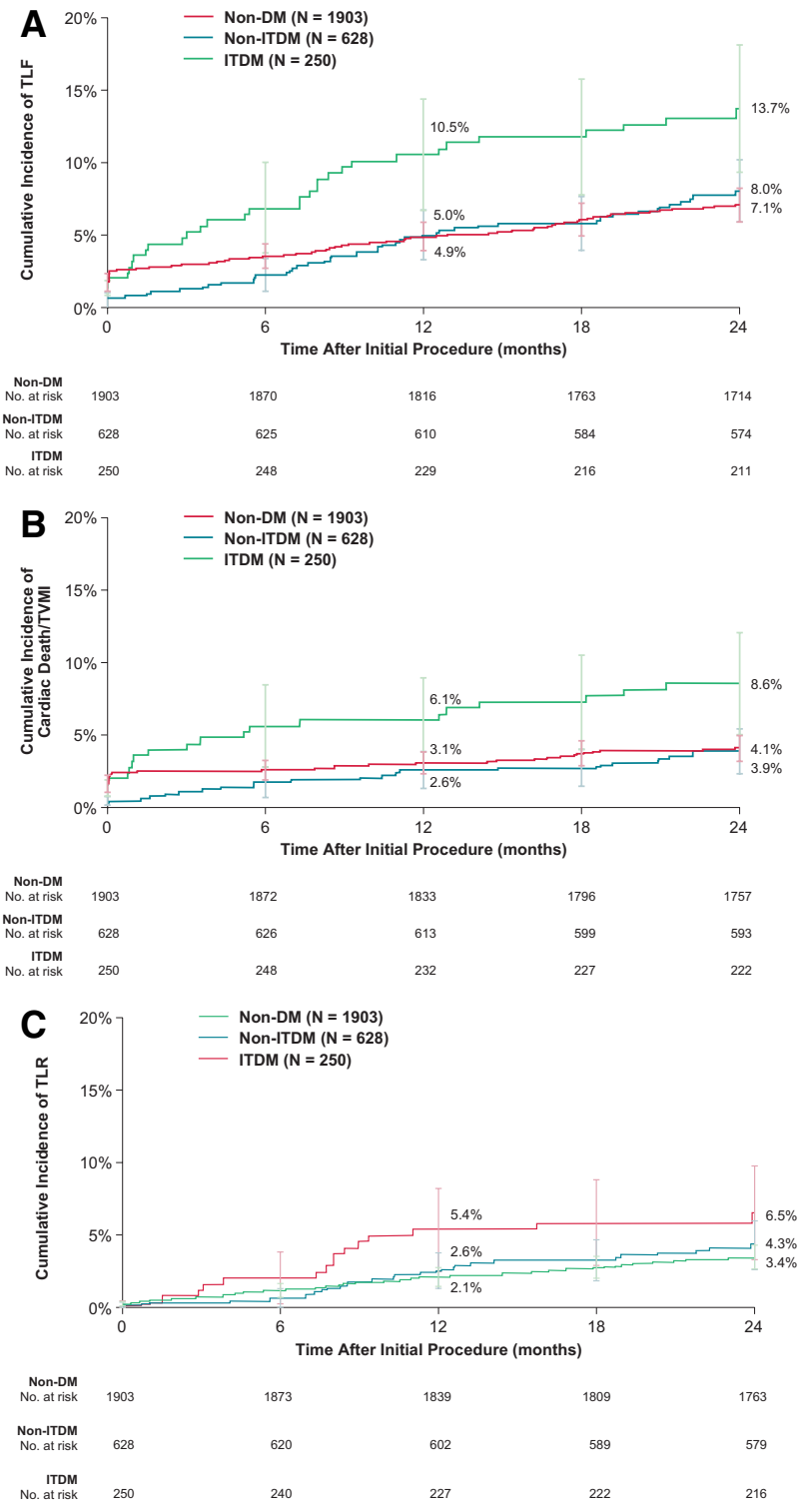

Figure 1. Cumulative Incidence of TLF and its Components for Patients in Pre-Specified Analysis

Cumulative incidence of target lesion failure (TLF) **(A)** and its components cardiac death or target vessel myocardial infarction (TVMI) **(B)** and ischemia-driven target lesion revascularization (TLR) **(C)** by diabetic status for patients in the pre-specified analysis population. DM = diabetes mellitus; ITDM = insulin-treated diabetes mellitus.

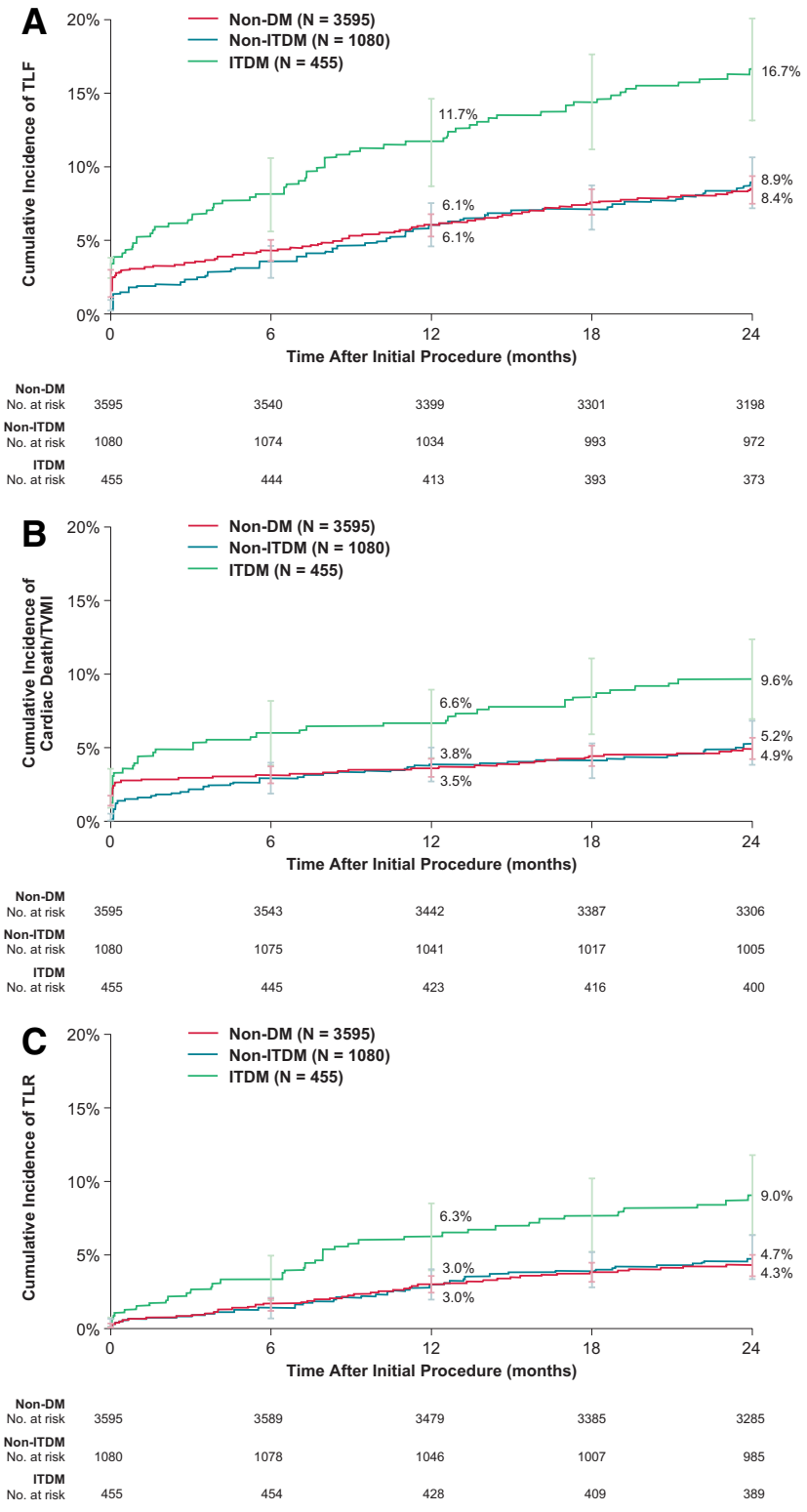

Figure 2. Cumulative Incidence of TLF and its Components for All Patients

Cumulative incidence of TLF **(A)** and its components, cardiac death or TVMI **(B)**, and ischemia-driven TLR **(C)** by diabetic status for all patients from the RESOLUTE Clinical Trial Program, including the complex patients. Abbreviations as in Figure 1.

angiographic endpoint was significantly higher for the Taxus PES (0.67 ± 0.62 mm) than for the Cypher SES (0.43 ± 0.45 mm). Although this study was underpowered for the clinical outcome, the reported TLR rate was 12.0% in the PES group and 6.4% in the SES group with a wide confidence interval of 0.82 to 4.27 (p = 0.13). The discussion of the comparison of the 2 first-generation DES in patients with diabetes has been controversial over the last years with pros and cons for either PES or SES (38–40). With the fading use of these 2 first-generation DES, however, this discussion today is of less practical importance.

Are newer generation DES better for patients with diabetes? The ESSENCE-DIABETES trial (Randomized Comparison of Everolimus-Eluting Stent Versus Sirolimus-Eluting Stent Implantation for De Novo Coronary Artery DisEase in Patients With DIABETES Mellitus) (10) is the first randomized study directly comparing a newer generation DES (Xience V EES, Abbott Vascular) with a first-generation DES (Cypher Select and Select Plus SES, Cordis Corporation) in 300 patients with diabetes. The EES was shown to be noninferior to the SES for the primary surrogate endpoint of in-segment late loss at 8 months (0.23 ± 0.27 mm vs. 0.37 ± 0.52 mm, $p_{noninferiority}$ <0.001). Although underpowered for clinical outcomes, death, MI, and ischemia-driven TLR were not statistically different between these 2 DES. A recently published post hoc subgroup analysis from 4 pooled randomized trials with 27.6% diabetic patients compared the Xience V EES with a first-generation DES, Taxus PES (Express and Liberté, Boston Scientific) (41). In these 1,869 patients with diabetes, there were no differences in clinical outcomes after 2 years between the first- and newer generation DES.

A comparison of our pooled R-ZES 2-year outcomes with 2-year outcomes from a recently published pooled EES analysis (41) requires caution, because our pre-specified cohort of patients with diabetes excluded the complex cases (Table 2). By contrast, 3 of the 4 studies in the pooled EES data cohort also excluded complex patients with diabetes, and only 1 study enrolled complex patients with diabetes (17.2% of all pooled patients). With this caution in mind, the corresponding 2-year data for the 878 R-ZES (Table 4) and the 1,188 EES (41) patients with diabetes are as follows: ischemia-driven TLR, 4.8% versus 5.5%; ischemia-driven TVR, 7.9% versus 8.3%; and definite or probable stent thrombosis, 0.3% versus 1.6%. Including even the complex patients in our analysis, the 2-year rates for definite or probable stent thrombosis are 1.2% for the 1,335 diabetic patients treated with the R-ZES (Table 6) versus 1.6% for the 1,188 patients treated with the EES (41).

The problem of insulin-treated patients. Diabetes, particularly in patients taking insulin, has consistently been shown to be an independent predictor of adverse outcomes after stent implantation (42). The results in patients with diabetes treated with the R-ZES parallels results of other DES in that the rates for patients taking insulin have progressively worse clinical outcomes than the rates for patients not taking insulin (Figs. 1 and 2). Thus, the overall results in studies of patients with diabetes strongly depend on the percentage of patients with diabetes taking insulin (43). The proportion of patients taking insulin in the studies used to construct the performance goal ranged from 25.2% to 32.3% (7,14,30,44–46), consistent with the 28.5% from our analysis cohort.

In other randomized studies with diabetes as an inclusion criterion, the proportion of insulin-treated patients was 43% in the SCORPIUS (8), 25% in the DESSERT (9), and 15% in the ESSENCE-DIABETES (10) trials. In the post hoc pooled analysis of the EES and PES (41), 26.4% of patients taking insulin were included, which is comparable to 28.5% in our pre-specified cohort. Although these studies were not used to develop our performance goal, because these data were only recently published, the clinical results from the pooled Xience and Taxus studies are consistent with the rates of the studies used to construct our performance goal.

In accordance with our results for the R-ZES (Figs. 1 and 2), the EES also showed, as compared with patients with diabetes not taking insulin, considerably worse 2-year outcomes for insulin-treated patients with diabetes with significantly higher ischemia-driven TLR (10.8% vs. 3.7%) and higher MACE rates (14.8% vs. 8.4%) (41). Although both of the newer generation DES (i.e., the Resolute ZES and the Xience V) have improved outcomes compared with first-generation DES, there is still an opportunity to improve the treatment of CAD in patients taking insulin, and coronary artery bypass surgery should be strongly considered as an alternative revascularization strategy in these patients—especially with multivessel disease—as recommended by European and U.S. guidelines (35,36). The results of the FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial, an international study designed to define the optimal revascularization strategy for patients with diabetes and multivessel coronary disease, has provided more data with regard to this unresolved topic (47).

Conclusions

The R-ZES is now indicated for use in the United States for patients with diabetes and obstructive CAD. Patients with diabetes not taking insulin had similar clinical outcomes as patients without diabetes in all patient groups. Continued attention to improving outcomes for patients with obstructive CAD and diabetes who are taking insulin is needed.

Acknowledgments

Jane Moore, MS, and Colleen J. Gilbert, PharmD, CMPP, both employees of the sponsor provided editorial support; and David Snead, PhD, Minglei Liu, PhD, Yun Peng, PhD, and Manuela Negoita, MD, employees of the sponsor, participated in the design and development of the analysis plan.

Reprint requests and correspondence: Prof. Dr. Sigmund Silber, Heart Center at the Isar, Department of Cardiology, Am Isarkanal 36, 81379 Munich, Germany. E-mail: sigmund@silber.com.

REFERENCES

1. Grundy SM, D'Agostino RB Sr, Mosca L, et al. Cardiovascular risk assessment based on US cohort studies: findings from a National Heart, Lung, and Blood Institute workshop. Circulation 2001;104:491–6.
2. Schramm TK, Gislason GH, Køber L, et al. Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people. Circulation 2008;117:1945–54.
3. Rydén L, Standl E, Bartnik M, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J 2007;28:88–136.
4. Kip KE, Faxon DP, Detre KM, Yeh W, Kelsey SF, Currier JW. Coronary angioplasty in diabetic patients. The National Heart, Lung, and Blood Institute percutaneous transluminal coronary angioplasty registry. Circulation 1996;94:1818–25.
5. Kornowski R, Mintz GS, Kent KM, et al. Increased restenosis in diabetes mellitus after coronary interventions is due to exaggerated intimal hyperplasia. A serial intravascular ultrasound study. Circulation 1997;95:1366–9.
6. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293:2126–30.
7. Sabaté M, Jiménez-Quevedo P, Angiolillo DJ, et al. Randomized comparison of sirolimus-eluting stent versus standard stent for percutaneous coronary revascularization in diabetic patients: the diabetes and sirolimus-eluting stent (DIABETES) trial. Circulation 2005;112: 2175–83.
8. Baumgart D, Klauss V, Baer F, et al. One-year results of the SCORPIUS study: a German multicenter investigation on the effectiveness of sirolimus-eluting stents in diabetic patients. J Am Coll Cardiol 2007;50:1627–34.
9. Maresta A, Varani E, Balducelli M, et al. Comparison of effectiveness and safety of sirolimus-eluting stents versus bare-metal stents in patients with diabetes mellitus (from the Italian multicenter randomized DESSERT study). Am J Cardiol 2008;101:1560–6.
10. Kim WJ, Lee SW, Park SW, et al. 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. Circ Cardiovasc Interv 2011;124:886–92.
11. Mulukutla SR, Vlachos HA, Marroquin OC, et al. Impact of drug-eluting stents among insulin-treated diabetic patients: a report from the National Heart, Lung, and Blood Institute dynamic registry. J Am Coll Cardiol Intv 2008;1:139–47.
12. Minha S, Bental T, Assali A, et al. A comparative analysis of major clinical outcomes using drug-eluting stents versus bare metal stents in diabetic versus nondiabetic patients. Catheter Cardiovasc Interv 2011; 78:710–7.
13. Abizaid A, Costa MA, Blanchard D, et al. Sirolimus-eluting stents inhibit neointimal hyperplasia in diabetic patients. Insights from the RAVEL trial. Eur Heart J 2004;25:107–12.
14. Moussa I, Leon MB, Baim DS, et al. Impact of sirolimus-eluting stents on outcome in diabetic patients: a SIRIUS (SIRolImUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions) substudy. Circ Cardiovasc Interv 2004; 109:2273–8.
15. Hermiller JB, Raizner A, Cannon L, et al. Outcomes with the polymer-based paclitaxel-eluting TAXUS stent in patients with diabetes mellitus: the TAXUS-IV trial. J Am Coll Cardiol 2005;45:1172–9.
16. Hong SJ, Kim MH, Ahn TH, et al. Multiple predictors of coronary restenosis after drug-eluting stent implantation in patients with diabetes. Heart 2006;92:1119–24.
17. Kumar R, Lee TT, Jeremias A, et al. Comparison of outcomes using sirolimus-eluting stenting in diabetic versus nondiabetic patients with comparison of insulin versus non-insulin therapy in the diabetic patients. Am J Cardiol 2007;100:1187–91.
18. Bauer T, Möllmann H, Weidinger F, et al. Impact of diabetes mellitus status on coronary pathoanatomy and interventional treatment: insights from the Euro Heart Survey PCI Registry. Catheter Cardiovasc Interv 2011;78:702–9.
19. Udipi K, Chen M, Cheng P, et al. Development of a novel biocompatible polymer system for extended drug release in a next-generation drug-eluting stent. J Biomed Mater Res A 2008;85A:1064–71.
20. Meredith IT, Worthley S, Whitbourn R, et al. Clinical and angiographic results with the next-generation resolute stent system: a prospective, multicenter, first-in-human trial. J Am Coll Cardiol Intv 2009;2:977–85.
21. 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.
22. Silber S, Windecker S, Vranckx P, Serruys PW, RESOLUTE All Comers Investigators. 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.
23. Yeung AC, Leon MB, Jain A, et al. 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;57:1778–83.
24. 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.
25. Saito S. RESOLUTE Japan 12 month results. Presented at the 20th Annual Meeting of the Japanese Association of Cardiovascular Intervention and Therapeutics in Osaka: Japan, 2011.
26. Mauri L, Massaro JM, Jiang S, et al. Long-term clinical outcomes with zotarolimus-eluting versus bare-metal coronary stents. J Am Coll Cardiol Intv 2010;3:1240–9.
27. Mauri L, Leon MB, Yeung AC, Negoita M, Keyes MJ, Massaro JM. Rationale and design of the 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). Am Heart J 2011;161:807–14.
28. 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.
29. Moussa I, Leon MB, Baim DS, et al. Impact of sirolimus-eluting stents on outcome in diabetic patients: a SIRIUS (sirolimus-coated Bx velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions) substudy. Circulation 2004;109:2273–8.
30. Mauri L, Massaro JM, Jiang S, et al. Long-term clinical outcomes with zotarolimus-eluting versus bare-metal coronary stents. J Am Coll Cardiol 2010;3:1240–9.
31. Turco MA, Ormiston JA, Popma JJ, et al. Polymer-based, paclitaxel-eluting TAXUS liberte stent in de novo lesions: the pivotal TAXUS ATLAS trial. J Am Coll Cardiol 2007;49:1676–83.
32. Meredith IT, Whitbourn R, Scott D, et al. Platinum QCA: a prospective, multicentre study assessing clinical, angiographic, and intravascular ultrasound outcomes with the novel platinum chromium thin-strut PROMUS Element everolimus-eluting stent in de novo coronary stenoses. EuroIntervention 2011;7:84–90.

33. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539–53.
34. Silber S, Albertsson P, Avilés FF, et al. Guidelines for percutaneous coronary interventions: the Task Force for percutaneous coronary interventions of the European Society of Cardiology. Eur Heart J 2005;26:804–47.
35. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. Eur Heart J 2010;31:2501–55.
36. Levine GN, Bates ER, Blankenship JC, et al. ACCF/AHA/SCAI guideline for percutaneous coronary intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol 2011;58:e44–122.
37. Dibra A, Kastrati A, Mehilli J, et al. Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. N Engl J Med 2005;353:663–70.
38. Lee SW, Park SW, Kim YH, et al. A randomized comparison of sirolimus- versus paclitaxel-eluting stent implantation in patients with diabetes mellitus 2-year clinical outcomes of the DES-DIABETES trial. J Am Coll Cardiol 2009;53:812–3.
39. Zhang F, Dong L, Ge J. Meta-analysis of five randomized clinical trials comparing sirolimus- versus paclitaxel-eluting stents in patients with diabetes mellitus. Am J Cardiol 2010;105:64–8.
40. Patterson C, Mapera S, Li HH, et al. Comparative effects of paclitaxel and rapamycin on smooth muscle migration and survival: role of AKT-dependent signaling. Arterioscler Thromb Vasc Biol 2006;26:1473–80.
41. Stone GW, Kedhi E, Kereiakes DJ, et al. Differential clinical responses to everolimus-eluting and paclitaxel-eluting coronary stents in patients with and without diabetes mellitus. Circulation 2011;124:893–900.
42. Abizaid A, Kornowski R, Mintz GS, et al. The influence of diabetes mellitus on acute and late clinical outcomes following coronary stent implantation. J Am Coll Cardiol 1998;32:584–9.
43. Yang TH, Park SW, Hong MK, et al. Impact of diabetes mellitus on angiographic and clinical outcomes in the drug-eluting stents era. Am J Cardiol 2005;96:1389–92.
44. Fajadet J, Wijns W, Laarman GJ, et al. Randomized, double-blind, multicenter study of the endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. Circ Cardiovasc Interv 2006;114:798–806.
45. Kandzari DE, Leon MB, Popma JJ, et al. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: a randomized controlled trial. J Am Coll Cardiol 2006;48:2440–7.
46. Leon MB, Mauri L, Popma JJ, et al. A randomized comparison of the ENDEAVOR zotarolimus-eluting stent versus the TAXUS paclitaxel-eluting stent in de novo native coronary lesions 12-month outcomes from the ENDEAVOR IV trial. J Am Coll Cardiol 2010;55:543–54.
47. Farkouh ME, Domanski M, Sleeper LA for the FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012;367:2375–84.

Key Words: clinical outcome ■ diabetes mellitus ■ percutaneous coronary intervention (PCI) ■ zotarolimus-eluting stent.