JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 6, NO. 10, 2013

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcin.2013.05.016

A Clinical and Angiographic Study of the XIENCE V Everolimus-Eluting Coronary Stent System in the Treatment of Patients With Multivessel Coronary Artery Disease

The EXECUTIVE Trial (EXecutive RCT: Evaluating XIENCE V in a Multi Vessel Disease)

Flavio Ribichini, MD,* Michele Romano, MD,† Renato Rosiello, MD,† Luigi La Vecchia, MD,‡ Ester Cabianca, MD,‡ Giuseppe Caramanno, MD,§ Diego Milazzo, MD,§ Paolo Loschiavo, MD,‖ Stefano Rigattieri, MD,‖ Salvatore Musarò, MD,¶ Bruno Pironi, MD,¶ Antonio Fiscella, MD,# Francesco Amico, MD,# Ciro Indolfi, MD,**†† Carmen Spaccarotella, MD,** Antonio Bartorelli, MD,†† Daniela Trabattoni, MD,†† Francesco Della Rovere, MD,‡‡ Andrea Rolandi, MD,‡‡ Federico Beqaraj, MD,§§ Riccardo Belli, MD,§§ Pietro Sangiorgio, MD,‖‖ Rosvaldo Villani, MD,¶¶ Andrea Berni, MD,## Imad Sheiban, MD,*** Maria Josè Lopera Quijada, MSC,††† Barbara Cappi, MSC,††† Licia Ribaldi, BS,††† Corrado Vassanelli, MD,* on behalf of the EXECUTIVE Trial Investigators

Verona, Mantova, Vicenza, Agrigento, Roma, Catania, Catanzaro, Milano, Genova, Torino, Bologna, and Vigevano, Italy

Objectives This study sought to investigate the efficacy and performance of the XIENCE V everolimus-eluting stent (EES) (Abbott Vascular, Santa Clara, California) in the treatment of de novo coronary lesions in patients with 2- to 3-vessel multivessel coronary artery disease (MV-CAD).

Background Drug-eluting stents (DES) have emerged as an alternative to conventional coronary artery bypass surgery in patients with MV-CAD although first-generation DES yielded inferior efficacy and safety compared with surgery.

Methods Prospective, randomized (1:1), multicenter feasibility trial was designed to assess angiographic efficacy of EES compared with the TAXUS paclitaxel-eluting stent (PES) in 200 patients, and a prospective, open-label, single-arm, controlled registry was designed to analyze the clinical outcome of EES at 1-year follow-up in 400 MV-CAD patients. For the randomized trial, the primary endpoint was in-stent late loss at 9 months. For the registry, the primary endpoint was a composite of all-cause death, myocardial infarction, and ischemia-driven target vessel revascularization at 12 months.

Results The primary endpoint per single lesion was significantly lower in the EES group compared with the PES group (-0.03 ± 0.49 mm vs. 0.23 ± 0.51 mm, $p = 0.001$). Similar results were observed when analyzing all lesions (0.05 ± 0.51 mm vs. 0.24 ± 0.50 mm, $p < 0.001$). Clinical outcome at 1 year yielded a composite of major adverse cardiac events of 9.2% in the single-arm registry, and 11.1% and 16.5% in the EES and PES randomized groups, respectively ($p = 0.30$).

Conclusions The EXECUTIVE trial was a randomized pilot trial dedicated to the comparison of the efficacy of 2 different DES among patients with 2- to 3-vessel MV-CAD. The study shows lower in-stent late loss at 9 months with the EES XIENCE V compared with the PES TAXUS Libertè, and a low major adverse cardiac event rate at 1 year in patients with 2-to 3-vessel MV-CAD. (EXECUTIVE [EXecutive RCT: Evaluating XIENCE V in a Multi Vessel Disease]; NCT00531011) (J Am Coll Cardiol Intv 2013;6:1012–22)

Progress in medical care and economic and social development result in a continuous increment of life expectancy, and elderly patients are frequently exposed to widespread forms of atherosclerosis. In most cases, patients with multivessel (MV) coronary artery disease (CAD) have diffuse atherosclerosis and complex lesions, are often diabetic, and present with impaired left ventricular function. Initial comparisons between percutaneous coronary intervention

See page 1023

(PCI) with bare-metal stents and coronary artery bypass graft surgery had shown a relative equivalence of the 2 treatments in terms of survival, but a clearly higher efficacy of surgery in preventing ischemic recurrences (1–4). Such studies, however, included patients with relatively low angiographic complexity and with 1- or 2-vessel disease in over 40% of cases, and excluded patients with left main lesions or impaired left ventricular function, a selection that clearly reduced the potential benefits of surgery (5). With the advent of drug-eluting stents (DES), results of PCI improved significantly (6,7), but unlike surgery, remained strongly influenced by the severity and extent of the MV-CAD. Such differences was clearly demonstrated in the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial, a real "all-comers study" that randomized patients with 3-vessel disease, including those with left main stenosis, to PCI with DES or to coronary surgery (8,9). Based on such observations, recent guidelines on myocardial revascularization confirm the superiority of coronary bypass surgery over PCI in patients with MV-CAD, in particular in those cases with diffuse disease as expressed by intermediate or high SYNTAX scores, whereas PCI is considered to be an appropriate alternative in patients with limited angiographic complexity (10–12). The recently developed SYNTAX score II (13) has demonstrated the ability to better guide decision making between surgery and PCI than the assessment provided by the anatomic SYNTAX score alone. Current recommendations, however, are based on the results obtained with sirolimus-eluting stents and paclitaxel-eluting stents (PES), both considered to belong to the "first generation" of DES.

More recent investigations have demonstrated significantly better clinical and angiographic outcomes of a new-generation everolimus-eluting stent (EES) compared with PES (14–16). The availability of safer and more effective DES generates the hypothesis that these may reduce the gap between PCI and surgery in patients with MV-CAD. However, despite the myriad of studies performed with DES, patients with advanced MV-CAD have been regularly excluded from comparative PCI trials, and despite the lack of dedicated studies, PCI in patients with MV-CAD has become current practice.

Aim of the study. The EXECUTIVE (EXecutive RCT: Evaluating XIENCE V in a Multi Vessel Disease) trial (NCT00531011) aims to assess the efficacy and performance of the XIENCE V EES (Abbott Vascular, Santa Clara, California) in the treatment of de novo coronary artery lesions in patients with MV-CAD (intended as 2- or 3-vessel disease). Its efficacy in preventing neointimal proliferation 9 months after stent placement as assessed by quantitative coronary angiography (QCA) was also compared with the TAXUS Libertè PES (Boston Scientific, Natick, Massachusetts).

Abbreviations and Acronyms

CAD = coronary artery disease
CI = confidence interval
DES = drug-eluting stent(s)
EES = everolimus-eluting stent(s)
MACE = major adverse cardiac event(s)
MLD = minimal lumen diameter
MV = multivessel
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent(s)
QCA = quantitative coronary angiography
TVR = target vessel revascularization

Methods

Detailed information regarding the study protocol has been published previously (17). In brief, the EXECUTIVE trial is a prospective, double-arm, randomized multicenter trial comparing the XIENCE V EES to the TAXUS Liberté PES in the treatment of patients with MV-CAD, performed in parallel to a nationwide, prospective, open-label, single-arm registry evaluating the performance of the EES in patients with 2- or 3-vessel MV-CAD treated in daily practice. MV-CAD was defined as in previous recent studies of coronary revascularization by PCI or coronary bypass surgery (1–4,6,7,18). The study was

From the *Department of Medicine, Università di Verona, Verona, Italy; †Azienda Ospedaliera Carlo Poma, Mantova, Italy; ‡Ospedale san Bortolo, Vicenza, Italy; §Azienda Ospedaliera San Giovanni di Dio, Agrigento, Italy; ‖Ospedale Sandro Pertini, Roma, Italy; ¶Ospedale Generale Madre Vannini, Roma, Italy; #Azienda Ospedaliera Cannizzaro, Catania, Italy; **Azienda Ospedaliera Mater Domini Università degli Studi Magna Graecia, Catanzaro, Italy; ††IRCCS Centro Cardiologico Monzino, Milano, Italy; ‡‡Ente Ospedaliero Ospedali Galliera, Genova, Italy; §§Ospedale Maria Vittoria, Torino, Italy; ‖‖Ospedale Maggiore, Bologna, Italy; ¶¶Azienda Ospedaliera di Pavia e provincia, Ospedale di Vigevano, Vigevano, Italy; ##Azienda Ospedaliera S. Andrea, Roma, Italy; ***Azienda Ospedaliera Universitaria Molinette San Giovanni Battista, Torino, Italy; and the †††Abbott Vascular Knoll-Ravizza S.p.A., Milano, Italy. This study was sponsored by Abbott Vascular Knoll-Ravizza S.p.A., Italy. Dr. Ribichini has received a fee from Abbott Vascular Knoll-Ravizza S.p.A. to design the study, develop the statistical analysis, and write the manuscript. Dr. Bartorelli is on the advisory board of Abbott Vascular. Drs. Lopera Quijada, Cappi, and Ribaldi are employees of Abbott Vascular Knoll-Ravizza S.p.A. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received August 2, 2012; revised manuscript received May 15, 2013, accepted May 24, 2013.

conducted in 30 centers in Italy that enrolled 600 patients in total.

The EXECUTIVE randomized trial enrolled 200 patients fulfilling the eligibility criteria. By randomization, treatment was assigned in a 1:1 ratio to receive EES or PES. In the EXECUTIVE registry, 400 patients with MV-CAD suitable to receive treatment of coronary lesions with multiple EES entered a prospective, controlled registry. The study was approved by the medical ethics committee at each participating center. All patients provided written informed consent before their participation in this study. All patients were screened for eligibility for recruitment according to the Instructions For Use of the XIENCE V EES, and the TAXUS Liberté PES.

The study flowchart is shown in Figure 1, and the inclusion/exclusion criteria are shown in Table 1.

Randomization and patient enrollment. After verifying the selection (inclusion/exclusion) criteria, candidates were randomized according to an automatic centralized allocation system to 1 of 2 study arms. Selected sites recruited patients with MV-CAD into either the randomized section or the single-arm registry section (see the Online Appendix). No site enrolled patients simultaneously in the randomized study and the single-arm registry. The 2 study groups ran in parallel from October 2008 to March 2010.

Revascularization technique and treatment strategy. The most complete degree of revascularization was pursued, considering as equivalent both "anatomic," which includes all vessels with a significant stenosis >70% irrespective of viable myocardium, or "functional," that is, only vessels with significant stenosis >70% supplying viable ischemic myocardium (19). Because the completeness of the revascularization refers to the vessels suitable for PCI, small, tortuous, or diffusely atheromatous vessels were not treated, but all patients included in the study must have had at least 2 suitable major vessels treated with PCI and stent implantation. All major epicardial coronary arteries could be treated, with the exception of the left main trunk, and with a planned maximum of 4 DES implanted. Staged procedures to complete revascularization were allowed within 1 month of the index PCI.

The clinical risk of all patients entering the trial was classified according to the EuroSCORE (20), and the angiographic complexity of the treated lesions was assessed by the SYNTAX score obtained at baseline angiograms (21).

Stent implantation technique. Treatment of the target lesion could be performed with either a single stent or planned overlapping stents. Stents could be deployed either directly or after pre-dilation. Post-dilation with noncompliant balloons could be performed if appropriate. Bailout procedures were performed in cases of major dissection; occlusive complication; chest pain or ischemic electrocardiographic changes that do not respond to repeat balloon inflations and medical therapy. In the randomized study, the stent added in bailout was of the same type of that designated by the treatment allocation. In the single-arm registry, only EES could be added.

Medication. Before PCI, all patients were pre-treated with a loading dose of either ticlopidine 500 mg day for at least 48 h before, or clopidogrel 300 mg, ideally at least 6 h before PCI, and conventional doses of aspirin (325 to 500 mg in patients with acute coronary syndromes and 100 to 160 mg in stable patients). During the procedure, patients received intravenous heparin to maintain an activated clotting time over 300 s. After successful stent implantation, all patients received standard medications, including aspirin 100 to 160 mg/day, ticlopidine 250 mg twice daily, or clopidogrel 75 mg/day for at least 6 months. A regimen of dual antiplatelet treatment was maintained for 12 months if well tolerated in patients without augmented risk for bleeding. Statins were recommended in all patients.

Patients participating in the randomized trial had planned follow-up imaging and QCA at 9 months. Angiograms were analyzed by an independent angiographic core laboratory (Euro Imaging S.r.l., Rome, Italy) blinded to the stent type.

EXECUTIVE randomized trial primary endpoint. The primary endpoint of the randomized trial was in-stent lumen loss at 270-day follow-up. To avoid interlesion clustering of restenosis, the protocol specified that a single lesion would be randomly selected by computer for analysis of late loss.

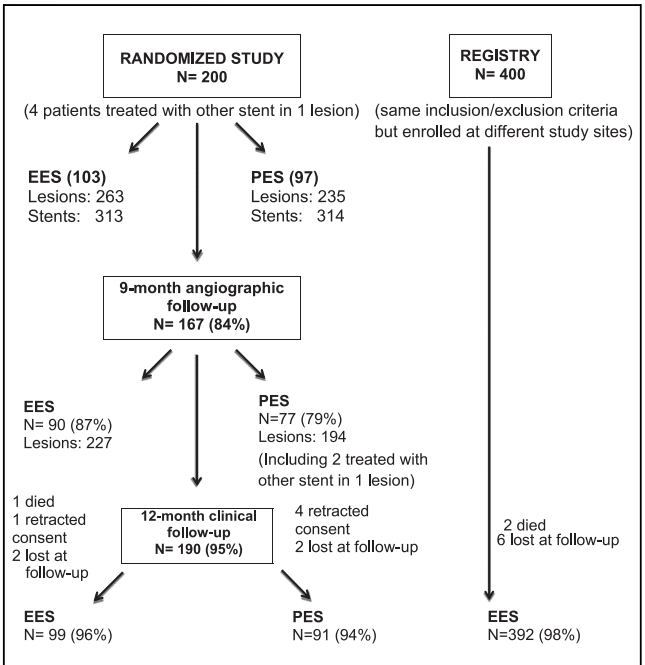

Figure 1. The CONSORT Diagram Showing Patients Study Flow

Study design and numbers of patients with follow up controls. EES = everolimus-eluting stent(s); PES = paclitaxel-eluting stent(s).

Table 1. Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
General	
1. Patient must be at least 18 years of age. 2. Written informed consent prior to any study-related procedure. 3. MVD, as documented by coronary angiography, i.e., presenting a severe stenosis (>50%) amenable to PCI in at least 2 major epicardial vessels (15). 4. Patient must have evidence of myocardial ischemia (e.g., stable or unstable angina, silent ischemia, positive functional study or a reversible change in the ECG consistent with ischemia). 5. Patient must be an acceptable candidate for CABG surgery. 6. Patient must agree to undergo all protocol-required follow-up examinations.	1. Patient has had a known diagnosis of AMI within 72 h preceding the index procedure (nonprocedural/spontaneous MI, CK-MB ≥2 times upper limit of normal) and CK and CK-MB have not returned within normal limits at the time of procedure. 2. Patient has a known LVEF <30%. 3. Patient is receiving chronic anticoagulation therapy. 4. Patient has a known hypersensitivity or contraindication to aspirin, paclitaxel, either heparin or bivalirudin, clopidogrel or ticlopidine, everolimus, cobalt, chromium, nickel, tungsten, acrylic and fluoro polymers or contrast sensitivity that cannot be adequately pre-medicated. 5. Elective surgery is planned within the first 9 months (±14 days) after the procedure that will require discontinuing either aspirin or clopidogrel. 6. Patient has a platelet count <100,000 cells/mm^3 or >700,000 cells/mm^3, a WBC of <3,000 cells/mm^3, or documented or suspected liver disease (including laboratory evidence of hepatitis). 7. Patient has known renal insufficiency (e.g., serum creatinine level of more than 2.5 mg/dl, patient on dialysis). 8. Patient has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions. 9. Patient has had a CVA or TIA within the past 6 months. 10. Patient has other medical illness (e.g., cancer or congestive heart failure) or known history of substance abuse (alcohol, cocaine, heroin, etc.) that may cause noncompliance with the protocol, confound the data interpretation, or is associated with a limited life expectancy (i.e., <1 year). 11. Patient is already participating in another investigational-use device or drug study or has completed the follow-up phase of another study within the last 30 days.
Angiographic	
7. Patients may receive up to 4 planned XIENCE V EES stents, depending on the number of vessels treated and their respective lesion length. When multiple lesions are present in 1 or more main coronary branches, complete revascularization should be attempted with the implantation of a maximum of 4 planned stents. 8. Target lesions must be de novo lesions (no prior stent implant, no prior brachytherapy). 9. Target vessel reference diameter must be between 2.5 mm and 4.0 mm by visual estimate. 10. Target lesion <28 mm by visual estimation.	12. Target lesion meets any of the following criteria: • Left main location. • Located within an arterial or saphenous vein graft or distal to a diseased arterial or saphenous vein graft (defined as vessel irregularity per angiogram and >20% stenosed lesion by visual estimation). • Heavy calcification. 13. The patient may need more than 4 planned stents.

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CK = creatine kinase; CK-MB = creatine kinase–myocardial band; CVA = cerebrovascular accident; ECG = electrocardiogram; EES = everolimus-eluting stent; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MVD = minimal vessel diameter; PCI = percutaneous coronary intervention; TIA = transient ischemic attack; WBC = white blood cell count.

All randomized lesions were instead included in the analysis for other angiographic data.

EXECUTIVE randomized trial secondary endpoints. The secondary endpoints are as follows:

- Stent thrombosis at 30 days and 1 year adjudicated as per protocol and the Academic Research Consortium definitions (22).
- Angiographic in-segment minimal lumen diameter (MLD) and in-segment late loss at 270 days post-procedure.
- Revascularizations: target lesion, target vessel (TVR), or any revascularization at 30 days, and 1 year.
- Composite endpoint of cardiac death, myocardial infarction, Q-wave and non–Q-wave, and ischemia-driven target lesion revascularization at 30 days and 1 year.
- Composite endpoint of all-cause death, myocardial infarction (Q-wave and non–Q-wave), and TVR at 30 days and 1 year.

EXECUTIVE single-arm registry primary endpoint. The primary endpoint is a composite endpoint of all-cause death, myocardial infarction (Q-wave and non–Q-wave), and ischemia-driven TVR at 1 year.

EXECUTIVE registry secondary endpoints. The secondary endpoints of the registry are the same as the randomized study, except for the angiographic assessment at 270 days.

Data management and statistical methods. Independent study monitors verified all case report form data onsite. All

major adverse cardiac events (MACE) were adjudicated by an independent clinical events committee blinded to treatment assignment with review of original source documentation (see the Online Appendix).

Sample size calculation of the EXECUTIVE randomized trial. The EXECUTIVE randomized trial aimed primarily to demonstrate noninferiority of the XIENCE V with respect to the TAXUS Libertè stent. If noninferiority was shown and the in-stent late loss was found to be lower in the XIENCE V arm, then superiority could be tested 2-sided at the 5% level. The sample size for the randomized part of the study was based on the primary endpoint of in-stent late loss at 270 days and on the following assumptions: 1-tailed noninferiority test; alpha = 0.05; randomization ratio 1:1; noninferiority margin delta 0.12; true mean in-stent late loss and standard deviation are assumed to be equal to 0.20 ± 0.41 mm in the XIENCE V EES arm: 0.16 ± 0.41 mm, 95% confidence interval (CI): 0.11 to 0.20; and true mean in-stent late loss and standard deviation are assumed to be equal to 0.30 ± 0.53 mm in the TAXUS Liberté stent arm. These assumptions are based on SPIRIT III (A Clinical Evaluation of the Investigational Device XIENCE V Everolimus Eluting Coronary Stent System [EECSS] in the Treatment of Subjects With De Novo Native Coronary Artery Lesions) trial results at 8 months (14).

Given the aforementioned assumptions, analyzing 81 lesions per arm provides more than 90% power. In order to account for dropouts and to ensure enough angiographic data, 200 patients were enrolled (approximately 100 EES and 100 PES). Sample size calculations were performed using NCSS-PASS 2002 (NCSS, Version 15 Statistical Software, Kaysville, Utah).

Sample size calculation of the executive registry. A sample size of 500 patients (400 included in the registry and 100 treated with the EES in the randomized study) produces a 2-sided 95% CI around clinical endpoint estimates. Assuming from previous studies a true 1-year incidence of the composite endpoint of all-cause death, myocardial infarction (Q-wave and non–Q-wave), and ischemia-driven TVR at 12 months rate comprised between 10% and 14%, the expected CIs, assuming 10% lost to follow-up, were estimated to comprise between 7.4% and 17.6% (16). Half the width of the CI would vary between 2.9 and 3.4; 95% CIs have been calculated using Clopper-Pearson.

Analysis population. The intention-to-treat population for the EXECUTIVE randomized trial consisted of all patients randomized to the study, regardless of the treatment actually received.

Statistical analyses. The primary outcome had to be tested using an analysis of covariance on 1 single randomized lesion by patient: the model included the treatment effect and post-procedure MLD value as quantitative covariate. Additionally, a supportive analysis was carried out by means of a repeated measures analysis model, using recorded data for all lesions and taking into account the interdependency of lesions within patients, by using a mixed model method with patient as random effect. Subgroup analysis was carried out on primary outcome using separate mixed models, including treatment, the subgroup factor and its interaction with treatment, baseline (post-procedure MLD) as covariate, and patient as random effect. A significant treatment by factor interaction indicates a significantly different treatment effect in 1 of the 2 categories. Patients and lesions baseline and characteristics were checked for homogeneity between XIENCE V and TAXUS Libertè groups using the Student *t* test for continuous variables, the Fisher exact test for binomial categorical variables, and the chi-square test for multinomial qualitative ones. The same methods were used to check homogeneity of characteristics between patients included in the randomized trial and in the registry.

Results

Between October 2008 and March 2010, 600 patients were enrolled in 30 Italian sites. In the randomized study, 103 patients received 313 XIENCE V stents on 263 lesions, and 97 patients received 314 TAXUS Liberté stents on 235 lesions. In the single-arm registry, 400 patients were treated with 1,127 stents on 983 lesions (Fig. 1).

Baseline and procedural characteristics. Baseline characteristics of the patients were well matched between the 2 randomized groups, and were not substantially different from those of patients entered in the registry except for a higher number of patients with elevated troponin in the registry (Table 2). An additive EuroSCORE ≥6 was calculated in 32% of the randomized patients (34% in the EES arm, and 29.9% in the PES arm). The mean number of lesions treated was 2.5 ± 1.3 in each of the 3 groups. In the PES arm of the randomized study, the baseline lesion length was slightly longer (13.38 ± 6.56 vs. 12.17 ± 5.72, p = 0.03), there were some more bifurcation lesions (14.9% vs. 9.1%, p = 0.05), and distal dissections after stenting were reported more frequently in this group, which may explain the need for more stents per lesion (1.34 ± 0.64 vs. 1.21 ± 0.49, p = 0.01) (23) (Table 3).

The angiographic characteristics at baseline of the 2 randomized groups and a comparison between the patients enrolled in the registry and the randomized study are shown in Table 3. The baseline angiographic complexity as assessed by the SYNTAX score was low (12.7 ± 5.24), whereas the clinical risk was intermediate (mean logistic EuroSCORE = 4.79 ± 5.6), and these were almost identical among groups. A complete revascularization according to the PCI strategy planned at enrollment was obtained in all randomized cases and in 396 (99%) of the 400 patients entered in the

Table 2. Patients Baseline Characteristics

	XIENCE RCT (n = 103)	TAXUS RCT (n = 97)	p Value	All RCT (n = 200)	Registry (n = 400)	p Value
Age, yrs	64.7 ± 10	64.0 ± 10	0.62	64.3 ± 10.2	64.3 ± 9.5	1.00
Male	76 (73.8)	69 (74.2)	0.75	149 (74.5)	317 (79.3)	0.21
Arterial hypertension	76 (73.8)	71 (76.3)	1.00	150 (75.0)	277 (69.3)	0.15
Current smokers	31 (30.1)	21 (22.6)	0.20	52 (26.0)	125 (31.3)	0.22
Dyslipidemia	72 (70.0)	63 (67.7)	0.55	137 (68.5)	242 (60.5)	0.06
Diabetes	24 (23.3)	30 (32.2)	0.27	55 (27.5)	136 (34)	0.11
Cerebrovascular disease	3 (2.9)	6 (6.5)	0.32	9 (4.5)	16 (4.0)	0.83
Previous myocardial infarction						
NSTEMI >72 h	26 (25.2)	20 (21.5)	0.50	46 (23.0)	85 (21.3)	0.68
STEMI >72 h	20 (19.4)	16 (17.2)	0.71	36 (18.0)	70 (17.5)	0.91
Previous CABG	1 (1.0)	1 (1.0)	1.00	2 (1)	6 (1.5)	0.73
Previous PCI	15 (14.6)	19 (20.4)	0.35	34 (17.0)	74 (18.5)	0.74
LVEF, %	56.2 ± 7.7	55.90 ± 8.2	0.79	56.1 ± 7.9	54.8 ± 8.2	0.061
≥50	63 (61)	59 (61)	1.0	122 (61)	250 (62.5)	0.91
<50 >30	40 (39)	38 (39)	1.0	78 (39)	150 (37.5)	0.91
Unstable angina	41 (39.8)	40 (43.0)	0.89	81 (41)	171 (42.8)	0.66
Stable angina/silent ischemia	41 (39.8)	47 (50.5)	0.25	88 (44)	179 (44.8)	0.93
Positive TnI pre-PCI, %*	10 (9.1)	16 (15.8)	0.21	26 (13.0)	91 (22.8)	0.004
2-Vessel disease	72 (70)	57 (58.8)	0.11	129 (64.5)	282 (70.5)	0.14
3-Vessel disease	31 (30)	40 (41.2)	0.11	71 (35.5)	118 (29.5)	0.14
Syntax score, per patient	12.9 ± 5.18	12.48 ± 5.33	0.57	12.7 ± 5.24	12.59 ± 5.60	0.81
Syntax score, >22	6 (5.8)	5 (5.2)	1.00	11 (5.5)	22 (5.5)	1.00
EuroSCORE, logistic	4.3 ± 3.8	5.3 ± 6.9	0.22	4.79 ± 5.57	4.36 ± 5.35	0.36
EuroSCORE ≥6	23 (22.3)	22 (22.7)	1.00	45 (22.5)	70 (17.5)	0.15
Biochemical data						
Total cholesterol, mg/dl	185.04 ± 42.9	183.4 ± 44.29	0.81	184.23 ± 43.46	186.89 ± 47.98	0.55
LDL cholesterol, mg/dl	110.8 ± 34.44	108.81 ± 37.45	0.74	109.77 ± 35.92	115.3 ± 42.36	0.18
HDL cholesterol, mg/dl	42.92 ± 10.68	44.11 ± 13.97	0.56	43.51 ± 12.39	42.59 ± 13.4	0.48
Triglycerides, mg/dl	150.23 ± 81.27	151.87 ± 72.07	0.89	151.04 ± 76.66	145.38 ± 78.53	0.45
Creatinine, mg/dl	0.95 ± 0.23	1.02 ± 0.3	0.07	0.98 ± 0.26	0.99 ± 0.26	0.72
Hemoglobin, g/dl	13.76 ± 1.44	13.84 ± 1.55	0.71	13.79 ± 1.49	13.87 ± 1.53	0.58
hs-CRP, mg/l	3.19 ± 3.59	5.32 ± 7.91	0.08	4.27 ± 6.24	2.94 ± 7.03	0.09
Data per treated lesions	263	235		498	983	
Stents implanted, total	313	314		627	1127	
Stents per patient	2.40 ± 0.75	2.27 ± 0.69	0.20	3.15 ± 1.20	2.83 ± 0.98	<0.001
Stents per lesion	1.21 ± 0.49	1.34 ± 0.64	0.012	1.27 ± 0.56	1.16 ± 0.42	<0.001
Stent length, mm	17.7 ± 5.3	18.1 ± 5.8	0.42	17.8 ± 5.5	18.8 ± 5.3	<0.001
Stent diameter, mm	2.88 ± 0.41	3.03 ± 1.81	0.22	2.95 ± 1.29	2.93 ± 0.66	0.75
Direct stenting	94 (35.9)	90 (38.1)	0.58	184 (36.9)	383 (39)	0.46

Values are mean ± SD, n (%), or n. *Positive TnI levels are considered as >0.5 ng/l.

HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; NSTEMI; non–ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; RCT = randomized controlled trial; TnI = troponin I; other abbreviations as in Table 1.

registry. There were no differences regarding balloon pressure for stent deployment and direct stent implantation.

Follow-up. All patients entered in the study had 1-month follow-up. In the randomized study, the pre-specified angiographic follow-up at 9 months was obtained in 167 (84%) patients: 90 (87%) in the XIENCE V arm and 77 (79%) in the TAXUS Libertè arm. Clinical follow-up at 1 year was obtained in 99 and 91 patients in the XIENCE V and TAXUS Libertè groups, respectively. Follow-up of the registry study at 1 year was obtained in 392 patients (98%) (Fig. 1).

Angiographic outcomes. Table 4 shows the quantitative angiographic measurements of all lesions of the randomized arms and the results of the QCA at follow up observed in all patients with an angiographic follow up (419 lesions). Figure 2 shows in detail the late loss at 9 months of the randomized study as a single lesion per patient analysis: primary endpoint 90 XIENCE V and 77 TAXUS Libertè

Table 3. Baseline Characteristics and Procedural Details

	XIENCE (n = 263)	TAXUS (n = 235)	p Value*	All RCT (n = 498)	Registry (n = 983)	p Value
ACC/AHA lesion classification†						
A	33 (12.5)	28 (11.9)	0.98	61 (12.2)	77 (7.8)	<0.001
B1	82 (31.2)	77 (32.8)		159 (31.9)	471 (47.9)	
B2	77 (29.3)	67 (28.5)		144 (28.9)	275 (28.0)	
C	71 (27.0)	63 (26.8)		134 (26.9)	160 (16.3)	
Type of lesion						
Single	239 (90.9)	200 (85.1)	0.052	439 (88.2)	881 (89.6)	0.43
Bifurcation	24 (9.1)	35 (14.9)		59 (11.8)	102 (10.4)	
Calcification†						
Moderate	47 (17.9)	51 (21.7)	0.087	97 (19.5)	343 (34.9)	<0.001
Severe	2 (0.8)	7 (2.9)		8 (1.6)	21 (2.1)	
Thrombus†						
Moderate	19 (7.2)	18 (7.7)	0.60	37 (7.4)	49 (5.0)	0.017
Severe	5 (1.9)	2 (0.9)		7 (1.4)	4 (0.4)	
Diffuse	64 (24.3)	68 (28.9)	0.26	132 (26.5)	257 (26.1)	0.90
Ostial	14 (5.3)	14 (6.0)	0.85	28 (5.6)	54 (5.5)	0.90
TIMI flow pre-PCI						
3	206 (78.3)	200 (85.1)	0.059	406 (81.5)	808 (82.2)	0.96
2	41 (15.6)	21 (8.9)		62 (12.4)	122 (12.4)	
1	7 (2.7)	10 (4.3)		17 (3.4)	31 (3.1)	
0	9 (3.4)	4 (1.7)		13 (2.6)	22 (2.2)	
Vessel treated						
LAD	108 (41.1)	104 (44.3)	0.74	212 (42.6)	394 (40)	0.24
Circumflex	83 (31.6)	68 (28.9)		151 (30.3)	281 (28.6)	
RCA	72 (27.4)	63 (26.8)		135 (27.1)	308 (31.3)	
Noncompliant BD	79 (30.0)	81 (34.5)	0.29	160 (32.1)	411 (41.8)	<0.001
Reference vessel						
Diameter	2.60 ± 0.59	2.62 ± 0.61	0.71	2.61 ± 0.60	2.61 ± 0.64	1.00
Diameter stenosis	72.15 ± 13.88	71.59 ± 11.93	0.63	71.88 ± 12.98	70.22 ± 11.54	0.014
Lesion length	12.17 ± 5.72	13.38 ± 6.56	0.030	16.31 ± 6.73	15.52 ± 5.76	0.019

Values are n (%) or mean ± SD. *Student *t* test for continuous variables, Fisher exact test for type of lesion, diffuse, ostial, culprit, complete revascularization, and noncompliant BD post-dilation, and chi-square test for other qualitative ones. †As defined by American College of Cardiology (ACC)/American Heart Association (AHA) (23).

BD = balloon dilation; LAD = left anterior descending coronary artery; NC = noncompliant balloon; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Tables 1 and 2.

(Fig. 2A) and 225 XIENCE V and 194 TAXUS Libertè all lesions analysis (Fig. 2B). The primary endpoint of in-stent late loss in the analysis per single lesion was significantly less in the EES group compared with the PES group (−0.03 ± 0.49 mm vs. 0.23 ± 0.51 mm, p = 0.001). Similar results were observed in the analysis of all lesions (0.05 ± 0.51 mm vs. 0.24 ± 0.50 mm, p < 0.001).

Clinical outcomes. At 30 days, the incidence of clinical events was similar in the 2 randomized groups (1.0% and 2.2% in the EES and PES groups, respectively), and slightly higher in the registry (4.7%) (Table 5). At 1 year, 74% and 67% of patients were still under dual antiplatelet therapy in the EES and PES randomized groups, respectively, 20% and 28% were on aspirin alone, and 6% and 5% had stopped both drugs (p = 0.3). In the registry, 70% were still on dual antiplatelet therapy, 26% on aspirin, and 4% had stopped both drugs. In the XIENCE V group, 1 patient died 3 days after the procedure because of heart failure, and 1 patient died in the TAXUS Libertè group at 1 year likely because of a possible stent thrombosis. For the analysis of the clinical performance in the registry study, the 400 patients included in the registry were pooled with the 103 enrolled in the XIENCE V arm of the randomized study, for a total of 503 patients, 491 of whom had 1-year follow-up. The occurrence of clinical events was similar between patients entered in the registry and those included in the randomized study. Of note, most of the events classified as myocardial infarctions occurred within 1 month and were periprocedural, whereas very few cases occurred spontaneously during follow-up. The clinical outcome of the whole study population is detailed in Table 5.

Table 4. Angiographic Quantitative Assessment (Descriptive Statistics for All Lesions)

	XIENCE (n = 263)	TAXUS (n = 235)	p Value
Pre-procedural QCA			
D-Ref, mm	2.59 ± 0.57	2.66 ± 0.62	0.24
MLD, mm	0.74 ± 0.43	0.75 ± 0.38	0.88
Stenosis, %	71.97 ± 14.11	71.90 ± 12.09	0.95
Post-procedural, QCA			
D-Ref, mm	2.72 ± 0.47	2.77 ± 0.46	0.24
In-stent MLD, mm	2.34 ± 0.48	2.412 ± 0.47	0.15
In-segment MLD, mm	2.00 ± 0.49	2.08 ± 0.48	0.10
In-stent stenosis, %	13.97 ± 9.36	13.28 ± 8.49	0.43
In-segment stenosis, %	26.77 ± 11.35	25.39 ± 10.78	0.20
Acute gain, mm	1.60 ± 0.56	1.66 ± 0.44	0.22
9-Month angiographic follow-up	225 lesions	194 lesions	
D-Ref, mm	2.86 ± 0.54	2.74 ± 0.54	0.042
In-stent MLD, mm	2.29 ± 0.64	2.17 ± 0.61	0.055
In-segment MLD, mm	2.1 ± 0.57	2.042 ± 0.52	0.28
In-stent stenosis, %	20.15 ± 14.99	21.66 ± 15.78	0.31
In-segment stenosis, %	26.87 ± 12.59	22.3 ± 60	0.27
In-stent LL, mm	0.05 ± 0.51	0.24 ± 0.50	<0.001
In-segment LL, mm	−0.10 ± 0.48	0.037 ± 0.42	0.002

Values are mean ± SD or n.
D-ref = reference diameter; LL = late loss; MLD = minimum lumen diameter; QCA = quantitative coronary analysis.

Subgroup analysis for the randomized study. The results for the primary endpoint in subgroups of patients according to diabetic status, lesion length, multiple stenting, SYNTAX score, EuroSCORE, and the degree of vessel disease are shown in Figure 3. The analysis shows an overall significant superiority of the EES (p = 0.0026) and a consistent trend in favor of the EES in all subgroups. Significantly better angiographic outcomes with EES were observed in patients treated with a single stent per lesion (p = 0.001), patients with shorter lesions (p = 0.001), nondiabetic patients (p = 0.039), patients with 2-vessel disease (p = 0.019), and in patients with a higher EuroSCORE (p = 0.003).

Discussion

Although implantation of DES in patients with MVD has become common practice, data about efficacy and safety of DES in this specific setting are scarce. Indeed, most of the available data derive from the analysis of subgroups of patients treated with multiple stenting in trials that allowed the inclusion of patients with maximum 2-vessel disease or with nonspecified MV-CAD (24,25), whereas in most of the seminal DES studies, this characteristic was a pre-specified exclusion criterion (26–30). Therefore, the study of the efficacy and safety of new-generation DES in this context deserves further study.

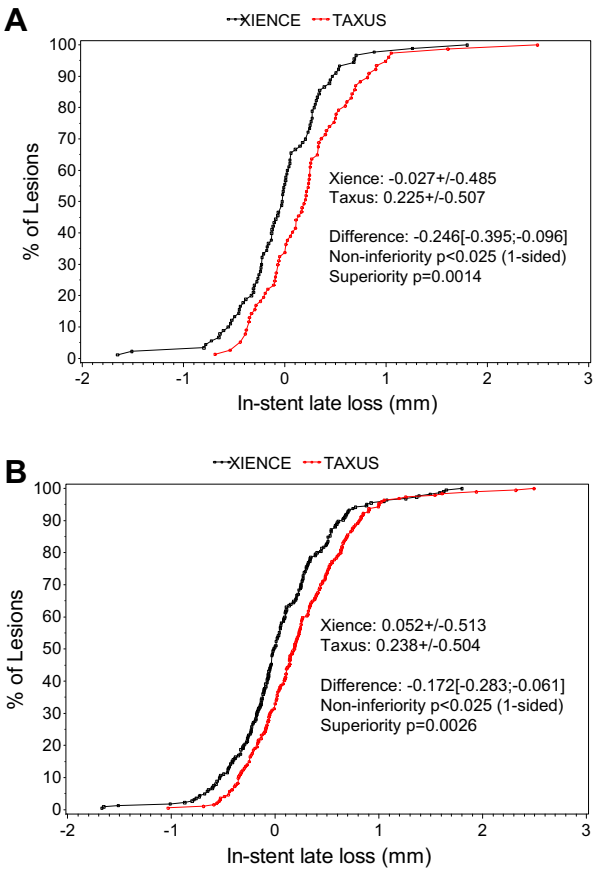

Figure 2. Primary Endpoint

(A) Late lumen loss at 9 months from 1 lesion per patient. **(B)** Late lumen loss at 9 months from all lesions treated.

Our trial shows the angiographic superiority of EES over PES in the specific setting of patients with 2- and 3-vessel disease. Indeed, the late luminal loss observed in this study is very low, even lower than that reported in previous studies that assessed the same stents with a lower number of observations. This is true in all the treated lesions (0.05 ± 0.51 mm vs. 0.24 ± 0.50 mm, p < 0.001), as well as in the pre-specified analysis of 1 lesion per patient (−0.03 ± 0.49 mm vs. 0.23 ± 0.51 mm, p = 0.001).

From a clinical standpoint, the results observed at 1 year in the 503 patients treated with EES in the EXECUTIVE trial yielded a very low rate of MACE, with a composite of death, myocardial infarction, and ischemia-driven TVR of 9.2%, a reassuring finding considering that most myocardial infarctions were peri-procedural and not spontaneous during follow-up. Such results closely replicate the observations derived from lower-risk populations of MV patients such as those analyzed in the SPIRIT III and IV (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of

Table 5. Clinical Results

	XIENCE (n = 103)	TAXUS (n = 97)	All RCT (n = 200)	Registry All (n = 503)
0–1 Month				
Cardiac death	1 (1.0)	—	1 (0.5)	2 (0.4)
Noncardiac death	—	—	—	—
Target vessel QMI	—	—	—	3 (0.6)
Target vessel NQMI	—	2 (2.2)	2 (1.1)	17 (3.5)
TLR–TVR–non-TVR	—	—	—	1 (0.2)
Subacute stent thrombosis	—	—	—	1 (0.2)
All MACE (all-cause death, MI, and TVR)	1 (1.0)	2 (2.2)	3 (1.6)	23 (4.7)
0–12 Months	99	91	190	491
Cardiac death	1 (1.0)	1 (1.1)	2 (1.1)	2 (0.4)
Noncardiac death	—	—	—	1 (0.2)
Target vessel QWMI	—	—	—	3 (0.6)
Target vessel NQWMI	1 (1.0)	3 (3.3)	4 (2.1)	20 (4.1)
ID-TLR	6 (6.1)	7 (7.7)	13 (6.8)	16 (3.3)
NID-TLR	1 (1.0)	2 (2.2)	3 (1.6)	2 (0.4)
ID-TVR	2 (2.0)	2 (2.2)	4 (2.1)	4 (0.8)
NID-TVR	1 (1.0)	3 (3.3)	4 (2.1)	1 (0.2)
No TVR revascularization	5 (5.1)	1 (1.1)	6 (3.2)	8 (1.6)
Definite stent thrombosis (ARC)	—	—	—	—
Probable stent thrombosis (ARC)	—	—	—	1 (0.2)
Possible stent thrombosis (ARC)	—	1 (1.1)	1 (0.5)	—
All MACE (all-cause death, MI, and TVR)	11/99 (11.1)*	15/91 (16.5)*	26/190 (13.7)	45/491 (9.2)

Values are % n, n, or n/N (%). *p value: Fisher exact test to compare XIENCE and TAXUS; p = 0.30.

ARC = Academic Research Consortium; ID = ischemia-driven; MACE = major adverse clinical event; MI = myocardial infarction; NID = non-ischemia driven; NQMI = non–Q-wave myocardial infarction; QMI = Q-wave myocardial infarction; RCT = randomized controlled trial; TLR = target lesion revascularization; TVR = target vessel revascularization.

Subjects With De Novo Native Coronary Artery Lesions) studies (6.2%), as well as in the most recent Resolute All-Comers study that showed a 9.7% of all MACE at 1 year in the EES-treated arm (31,32).

The EES XIENCE V is a second-generation DES in which the drug is released from a thin (7.8 μm) nonadhesive, durable, biocompatible fluorinated copolymer onto a low-profile (0.0813-mm) strut thickness, flexible cobalt–chromium stent. Everolimus is an effective antiproliferative agent through the inhibition of growth factor–stimulated cell proliferation by causing cell cycle arrest in the late G1 stage in the cell cycle. Pre-clinical studies have shown more rapid and more complete endothelialization with this stent compared with sirolimus-eluting and paclitaxel-eluting stents (33), and clinical studies with the EES have demonstrated its superiority over the PES TAXUS Express (14–16).

The SPIRIT III randomized study enrolled 1,002 patients with mainly single coronary disease. Angiographic follow-up was planned for a subset of 564 patients at 240 days and showed that the EES was superior to the PES (in-segment late loss 0.14 ± 0.4 mm vs. 0.28 ±0.48 mm, p < 0.004). Moreover, at 2-year follow-up, treatment with EES compared with PES resulted in a significant 32% reduction in target vessel failure (10.7% vs. 15.4%; hazard ratio, 0.68; 95% CI: 0.48 to 0.98; p = 0.04) and a 45% reduction in MACE (7.3% vs. 12.8%; hazard ratio, 0.55; 95% CI: 0.36 to 0.83; p = 0.004) (14).

EXECUTIVE represents a unique population with MV-CAD patients treated with DES at an intermediate clinical risk (additive EuroSCORE ≥6 in 32% of the randomized patients), and with low angiographic complexity (SYNTAX score ≤22 in 95% of patients, mean 12.7 ± 5.24). The calculation of risk, taking into account both the angiographic severity of CAD and the clinical risk, has been proposed as a "global risk score," a new classification that may better define the subgroups of patients with MV-CAD requiring myocardial revascularization (34). Patients enrolled in the EXECUTIVE trial represent a less complex cohort under an angiographic standpoint compared with the population assessed in the SYNTAX (28.4 ± 11.5) and the ARTS II (Arterial Revascularization Therapies Study II) studies (20.8 ± 9.5), with a logistic EuroSCORE 4.79 ± 5.6, compared with 3.8 ± 2.6 in the SYNTAX trial, and 2.12 ± 15.2 in the ARTS II trial (7,8).

Study limitations. The trial was not powered to test clinical differences. Furthermore, due to some protocol restrictions, few patients in the EXECUTIVE trial had intermediate

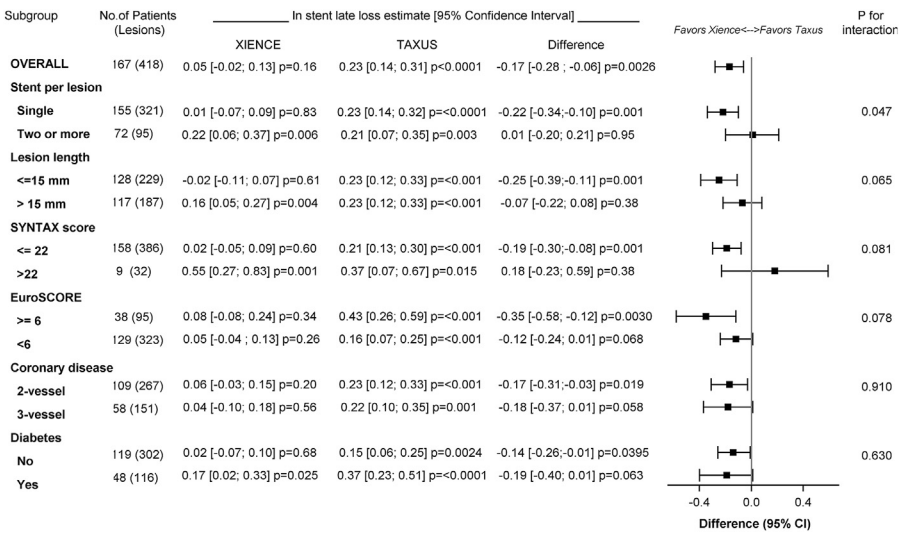

Figure 3. Landmark Analysis of the Primary Endpoint in Different Subgroups

The p value is from the test statistic for testing the interaction between the treatment and any subgroup variable. CI = confidence interval.

SYNTAX scores; none was in the highest range >32, and none had left ventricular ejection fraction <30%. These exclusion criteria were introduced to allow patients with severe and diffuse forms of CAD the possibility of surgical revascularization, a treatment that was shown to offer better clinical results and that had proved more appropriate in patients with high angiographic complexity, as recommended in the most recent international documents (10–12). For the same reason, the criteria used in the SYNTAX trial to evaluate the completeness of revascularization could not be applied. Due to the limited sample size, some minor angiographic and procedural baseline characteristics were observed. For the same reason, the statistical analysis of subgroups yields nonsignificant results among subgroups with the lower number of observations.

Conclusions

The results obtained in EXECUTIVE trial show that patients with 2- and 3-vessel disease having low-to-intermediate SYNTAX scores, with intermediate clinical risk, and belonging to a low-to-intermediate "global risk score" classification, have significantly better angiographic results of multiple PCI with the use of EES rather than with PES. These data, supported by the low incidence of clinical events, may help to further improve the currently known outcomes of PCI in patients with MVD. The ongoing EXCEL study (Evaluation of XIENCE PRIME or XIENCE V versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) will investigate the performance of EES XIENCE V compared with coronary surgery in patients with left main stenosis eventually associated with MV-CAD, and will provide additional knowledge about myocardial revascularization strategies in patients with MV-CAD.

Reprint requests and correspondence: Dr. Flavio Ribichini, University of Verona, Piazzale A. Stefani 1, 37126 Verona, Italy. E-mail: flavio.ribichini@univr.it.

REFERENCES

1. Rodriguez A, Bernardi V, Navia J, et al. Argentine Randomized Study: Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in patients with Multiple-Vessel Disease (ERACI II): 30-day and one-year follow-up results. ERACI II Investigators. J Am Coll Cardiol 2001;37:51–8.
2. Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001;344:1117–24.
3. The SoS Investigators. Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery Trial): a randomised controlled trial. Lancet 2002;360:965–9.
4. Daemen J, Boersma E, Flather M, et al. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. Circulation 2008;118:1146–54.
5. Taggart DP. Thomas B. Ferguson Lecture. Coronary artery bypass grafting is still the best treatment for multivessel and left main disease, but patients need to know. Ann Thorac Surg 2006;82:1966–75.
6. Serruys PW, Ong AT, Morice MC, et al. Arterial Revascularisation Therapies Study Part II: sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. EuroIntervention 2005;1:147–56.

7. Serruys PW, Onuma Y, Garg S, et al. 5-year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. J Am Coll Cardiol 2010;55:1093–101.
8. Serruys PW, Morice MC, Kappetein AP, et al., for the SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009; 360:961–72.
9. Mohr FW, Morice MC, Kappetein AP, et al. Coronary artery bypass surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013;381:629–38.
10. Wijns W, Kolh P, Danchin N, et al., Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPCI). Guidelines on myocardial revascularization. Eur Heart J 2010;31:2501–55.
11. Levine GN, Bates ER, Blankenship GC, et al. 2011 ACCF/AHA/ SCAI guideline for percutaneous coronary intervention: executive summary: 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.
12. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/ SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 appropriate use criteria for coronary revascularization focused update: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol 2012;59:857–81.
13. Farooq V, van Klaveren D, Steyerberg EW, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. Lancet 2013;381:639–50.
14. Stone GW, Midei M, Newman W, et al., SPIRIT III Investigators. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. JAMA 2008;299:1903–13.
15. Stone GW, Rizvi A, Newman W, et al., SPIRIT IV Investigators. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med 2010;362:1663–74.
16. Kedhi E, Joesoef KS, McFadden E, et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet 2010;375:201–9.
17. Ribichini F, Ansalone G, Bartorelli A, et al., EXECUTIVE Trial Investigators. A clinical and angiographic study of the XIENCE V everolimus-eluting coronary stent system in the treatment of patients with multivessel coronary artery disease. Study design and rationale of the EXECUTIVE trial. J Cardiovasc Med 2010;11:299–309.
18. Farkouh ME, Domanski M, Sleeper LA, et al., the FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012;367:2375–84.
19. van den Brand MJ, Rensing BJ, Morel MA, et al. The effect of completeness of revascularization on event-free survival at one year in the ARTS trial. J Am Coll Cardiol 2002;39:559–64.
20. Nashef SAM, Roques F, Gauducheau E, Lemeshow S, Salamon Rthe EuroSCORE study group. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999;16:9–13.
21. Sianos G, Morel M-A, Kappetein AP, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;2:219–27.
22. Cutlip DE, Windeker S, Merhan R, et al., Academic Research Consortium. Clinical end points in coronary stent trials. A case for standardized definitions. Circulation 2007;115:2344–51.
23. Ellis SG, Vandormael MG, Cowley MJ, et al. Coronary morphologic and clinical determinants of procedural outcome with angioplasty for multivessel coronary disease: implications for patient selection. Circulation 1990;82:1193–202.
24. Kereiakes DJ, Sudhir K, Hermiller JB, et al. Comparison of everolimus-eluting and paclitaxel-eluting coronary stents in patients undergoing multilesion and multivessel intervention: the SPIRIT III (A Clinical Evaluation of the Investigational Device XIENCE V Everolimus Eluting Coronary Stent System [EECSS] in the Treatment of Subjects With De Novo Native Coronary Artery Lesions) and SPIRIT IV (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Subjects With De Novo Native Coronary Artery Lesions) randomized trials. J Am Coll Cardiol Intv 2010;12:1229–39.
25. Caixeta A, Lansky AJ, Serruys PW, et al., SPIRIT II and III Investigators. Clinical follow-up 3 years after everolimus- and paclitaxel-eluting stents: a pooled analysis from the SPIRIT II (A Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions) and SPIRIT III (A Clinical Evaluation of the Investigational Device XIENCE V Everolimus Eluting Coronary Stent System [EECSS] in the Treatment of Subjects With De Novo Native Coronary Artery Lesions) randomized trials. J Am Coll Cardiol Intv 2010;3:1220–8.
26. Morice MC, Colombo A, Meier B, et al. Sirolimus vs paclitaxel-eluting stents in de novo coronary artery lesions. The Reality trial: a randomized controlled trial. JAMA 2006;295:895–904.
27. Windecker S, Remondino A, Eberli FR, et al. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. N Engl J Med 2005;353:653–62.
28. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773–80.
29. Moses JW, Leon MB, Popma JJ, et al., for the SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in native coronary arteries. N Engl J Med 2003;349:1315–23.
30. Stone GW, Ellis SG, Cox DA, et al., for the TAXUS-IV Investigators. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221–31.
31. 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.
32. Silber S, Windecker S, Vranckx P, Serruys PWRESOLUTE 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.
33. Nakazawa G, Finn AV, Ladich E, et al. Drug eluting stent safety: findings from preclinical studies. Expert Rev Cardiovasc Ther 2008;6: 1379–91.
34. Serruys PW, Farooq V, Vranckx P, et al. A global risk approach to identify patients with left main or 3-vessel disease who could safely and efficaciously be treated with percutaneous coronary intervention: the SYNTAX trial at 3 years. J Am Coll Cardiol Intv 2012;6:606–17.

Key Words: coronary artery disease ■ drug-eluting stent(s) ■ multivessel disease ■ randomized clinical trial.

APPENDIX

For an expanded list of the study investigators and the site locations, please see the online version of this paper.