

Predictors of early and late outcomes after everolimus and paclitaxel-eluting coronary stents

Robert J. Applegate^{1*}, MD; James B. Hermiller², MD; Paul C. Gordon³, MD; Manejeh Yaqub⁴, MD; Poornima Sood⁴, MD, M Phil; Xiaolu Su⁴, MS; Sherry Cao⁴, MS; Krishnankutty Sudhir⁴, MD, PhD; Gregg W. Stone⁵, MD

1. Wake Forest School of Medicine, Winston-Salem, NC, USA; 2. The St. Vincent Heart Center of Indiana, Indianapolis, IN, USA; 3. The Miriam Hospital, Providence, RI, USA; 4. Abbott Vascular, Santa Clara, CA, USA; 5. Columbia University Medical Center and The Cardiovascular Research Foundation, New York, NY, USA

KEYWORDS

- coronary
- drug-eluting stents
- MACE
- TVF
- predictor

Abstract

Aims: To evaluate whether the improved outcomes with newer generation drug-eluting stents (DES) utilising thin-strut stents are consistent among different patient and angiographic subgroups.

Methods and results: Clinical outcomes over three years were collected in the SPIRIT III trial comparing the XIENCE V[®] everolimus-eluting stents (EES) (Abbott Vascular, Santa Clara, CA, USA) to the TAXUS[®] paclitaxel-eluting stents (PES) (Boston Scientific, Natick, MA, USA). Potential predictors of adverse clinical outcomes were assessed using demographic, clinical, and procedural variables by logistic and Cox regression analyses. For three-year target vessel failure, the independent predictors identified by Cox regression were number of vessels treated (HR=2.19 [1.50, 3.19], p<0.0001), HbA1c (%) (HR=1.17 [1.05, 1.29], p=0.004), total cholesterol (>200 mg/dl) (HR=1.63 [1.13, 2.36], p=0.009), and female gender (HR=1.42 [1.01, 2.01], p=0.05). Logistic regression analysis identified the same predictors except for the female gender. The clinical results with EES compared to PES were consistent among the multiple subgroups examined with the possible exception of patients with diabetes.

Conclusions: Clinical factors and stent type were the most important multivariable predictors of adverse clinical outcomes in this contemporary trial of first versus second generation DES. The benefit of the EES compared to the PES was consistent across a wide range of patient and angiographic subgroups with the possible exception of patients with diabetes.

*Corresponding author: Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1045, USA.
E-mail: bapplega@wfubmc.edu

Abbreviations

EES	everolimus-eluting stent
MACE	major adverse cardiac event
MI	myocardial infarction
PCI	percutaneous coronary intervention
PES	paclitaxel-eluting stent
TLR	target lesion revascularisation
TVF	target vessel failure
TVR	target vessel revascularisation
ZES	zotarolimus-eluting stent

Introduction

Drug-eluting stents (DES) have dramatically reduced the rates of restenosis and the need for repeat revascularisation in patients undergoing percutaneous coronary intervention (PCI) for symptomatic coronary artery disease^{1,2}. However, the rates of event-free survival after DES implantation vary among patient and lesion subgroups. Patient risk factors including older age, diabetes, hypertension and chronic kidney disease are associated with mortality and adverse cardiovascular events, and procedural factors such as small vessel size, longer lesions, and multiple and overlapping stents have been associated with higher rates of clinical restenosis^{3,4}. Whether differences in event-free survival exist between first generation sirolimus-eluting and paclitaxel-eluting stents has been the subject of debate and numerous studies.⁵

Current coronary DES systems consist of a metallic stent backbone, durable polymer and antiproliferative drug. Each of these components may affect device safety and efficacy, although isolating the effect of each component to outcomes is problematic. Newer generations of DES have incorporated stents with thinner struts, more biocompatible and less potentially inflammatory polymers, and lower drug dosages in an effort to minimise stent-associated late clinical events such as stent thrombosis, which may arise from delayed or poor vessel healing. The large-scale SPIRIT III randomised controlled clinical trial compared clinical and angiographic outcomes from use of a TAXUS® EXPRESS2® paclitaxel-eluting stent (PES) (Boston Scientific, Natick, MA, USA) to that of a thinner strut XIENCE V® everolimus-eluting stent (EES) (Abbott Vascular, Santa Clara, CA, USA).⁶ At nine months, and at two and three years, the EES resulted in lower major adverse event rates than the PES⁶⁻⁸. Whether this benefit extends to all subgroups of patients enrolled in the study, however, remains uncertain. Therefore, the current analysis was performed to identify the independent predictors of outcomes in the SPIRIT III trial.

Methods

The design of the SPIRIT III trial has been previously described⁶. In brief, SPIRIT III was a prospective, multicentre, randomised, single-blind, controlled clinical study in which 1,002 patients with up to two *de novo* lesions in native coronary arteries with a reference vessel diameter (RVD) of 2.5-3.75 mm and lesion length ≤ 28 mm were randomised in a 2:1 ratio to receive either the EES (XIENCE V®) or the PES (TAXUS® EXPRESS2®).

Inclusion criteria

Enrolment was restricted to patients ≥ 18 years of age with stable or unstable angina or inducible ischaemia. Patients who met the clinical eligibility criteria provided signed informed consent prior to enrolment. Eligibility of the patient to be enrolled in the study was confirmed based on the angiogram just before the intended procedure (the pre-procedure angiography). Key angiographic inclusion criteria included a maximum of two *de novo* native coronary artery lesions, each in a different epicardial vessel, RVD of ≥ 2.5 mm and ≤ 3.75 mm, lesion length ≤ 28 mm by visual estimation, % diameter stenosis (%DS) of $\geq 50\%$ and $< 100\%$, TIMI flow of ≥ 1 , non-target vessel percutaneous intervention in non-target vessel planned ≥ 90 days prior to or > 9 months after the index procedure.

Exclusion criteria

Major clinical exclusion criteria included PCI in the target vessel prior to or planned within nine months of the index procedure, or in a non-target vessel within nine months of index procedure; acute or recent myocardial infarction (MI); left ventricular ejection fraction $< 30\%$; use of chronic anticoagulation or immunosuppressive therapy; known autoimmune disease, renal insufficiency, recent major bleed, haemorrhagic diathesis or objection to blood transfusions; contraindications or allergy to any of the study medications, components of the study stents, or iodinated contrast that could not be pre-medicated; elective surgery planned within nine months after the procedure necessitating antiplatelet agent discontinuation; platelet count $< 100,000$ cells/mm³ or $> 700,000$ cells/mm³, white blood cell count $< 3,000$ cells/mm³, serum creatinine > 2.5 mg/dL or dialysis, or liver disease; stroke or transient ischaemic attack within six months; comorbid conditions limiting life expectancy to less than one year or that could affect protocol compliance; and participation in another investigational study that had not yet reached its primary endpoint.

Key angiographic exclusion criteria included aorto-ostial location, left main location, bifurcation involvement, excessive tortuosity, extreme angulation ($\geq 90^\circ$), heavy calcification, target vessel containing thrombus, other significant lesions ($> 40\%$ DS) in the target vessel or side branch for which intervention was required within nine months. If two target lesions were treated, each of these lesions had to meet all angiographic inclusion/exclusion criteria.

Randomisation and blinding

Randomisation could only take place after verification of the inclusion/exclusion criteria and successful predilatation of the first target lesion. Following confirmation of all general and angiographic eligibility, telephone randomisation to EES vs. PES was performed as previously described⁶. Although the operators were by necessity unblinded during the stent implant procedure, the patient and staff involved in follow-up assessments remained blinded until all patients completed the primary endpoint follow-up, with a standardised follow-up interview script used to reduce bias. A patient was considered enrolled in the study from the moment he or she had been randomised.

Interventional procedure

EES were available in 2.5, 3.0, and 3.5 mm diameters, and in 8, 18, and 28 mm lengths. The full range of US-manufactured PES was available, ranging from 2.5 to 3.5 mm in diameter and from 8 to 32 mm in length. The stent selected was of sufficient length to cover approximately 3 mm of non-diseased tissue on either side of the lesion. In patients receiving multiple stents for a single lesion, 1 mm to 4 mm of stent overlap was recommended. Post-dilatation was left to the discretion of the investigator; and if performed, it was only done with balloons sized to fit within the boundaries of the stent. If an additional stent was needed for bailout purposes, it was required to be from the same treatment arm as the first implanted stent.

Patients who were not on chronic antiplatelet or aspirin therapy were required to receive aspirin ≥ 300 mg pre-procedure and a loading dose of clopidogrel bisulfate ≥ 300 mg no later than one hour after the procedure. All patients were to be maintained on 75 mg clopidogrel bisulfate daily for a minimum of six months and ≥ 80 mg of aspirin daily throughout the length of the trial (five years) following the index procedure. Subjects who developed hypersensitivity to clopidogrel bisulfate were switched to ticlopidine hydrochloride at a dose in accordance with standard hospital practice.

Stent delivery system

The XIENCE V EES, evaluated in the SPIRIT trials, consisted of either the L-605 cobalt chromium (CoCr) alloy-coated MULTI-LINK VISION or MULTI-LINK MINI VISION stent mounted on a MULTI-LINK RX VISION or MULTI-LINK MINI VISION RX delivery system, respectively. All stent diameters were available in 8-28 mm lengths. The coating consisted of two layers: a primer layer and a drug matrix layer. The EES contains $100 \mu\text{g}/\text{cm}^2$ of everolimus, which is released from a thin ($7.8 \mu\text{m}$), non-adhesive, durable, biocompatible fluoropolymer coated onto a low profile ($0.0032''$ [0.0813 mm] strut thickness), flexible cobalt-chromium stent⁶.

Statistical methods for clinical results

For the intent-to-treat population, univariable and multivariable logistic and Cox regression analyses were used to identify significant predictors of nine-month and three-year target vessel failure (TVF: cardiac death, myocardial infarction [MI], or ischaemia-driven target vessel revascularisation [TVR]) and major adverse cardiac events (MACE: cardiac death, MI, or ischaemia-driven target lesion revascularisation [TLR]). These two pre-specified composite endpoints were used as the measures of interest for the present *post hoc* analysis as they occurred with the highest frequency of all clinically-assessed outcome measures, providing more power for multivariable and subgroup analyses. Univariable and multivariable logistic and Cox regression analyses were also used to identify predictors of nine-month and three-year cardiac death or MI and TLR, which were used as separate measures of safety and clinical efficacy. Demographic, clinical and procedural

variables were included in these analyses. Cox regression analyses were performed to identify significant predictors of nine-month and three-year outcomes (TVF, MACE, cardiac death or MI, and TLR) to adjust the follow-up duration through the time-to-event nature of the model.

For the univariable analyses, coefficients, Wald chi-square p-values, odds ratios (or hazard ratio from the Cox model), and 95% confidence intervals for the odds ratios (or hazard ratio) were displayed. For the multivariable analyses, models were built using a stepwise (forward/backward) elimination procedure, with independent variables entered into the model at the 0.20 significance level and removed at the 0.05 level. A final model was selected and presented with selection criteria based on both statistical significance and clinical consideration, with the exception of stent treatment type, which was forced into the final model of the multivariable regression analysis. Displayed for each variable in the final multivariable model were the final coefficient, the standard error for the coefficient, and the p-value from the Wald chi-square, the odds ratios (or hazard ratio from the Cox model), and 95% confidence intervals for the odds ratios (or hazard ratio). In addition, the adequacy of the fitted model was displayed in the multivariable logistic regression analysis and was evaluated by the Hosmer and Lemeshow goodness-of-fit test and c-statistic, which is the area under the receiver operating characteristic (ROC) curve. A score test for proportionality based on scaled Schoenfeld residuals was also performed to assess the proportional hazards assumption for the Cox proportional hazards model. All statistical analyses were performed in the intention to treat population by using SAS version 9.1.3 (SAS Institute Inc, Cary, NC, USA).

Results

The rates of TVF and MACE at nine months and three years are shown in **Figure 1**. At nine months, clinical follow-up was available in 980 patients (97.8%), including 658 EES patients and 322 PES patients. There was no significant difference in the rates of TVF between EES and PES (7.6% vs. 9.7%, respectively; $p=0.27$). MACE was significantly reduced by 43% in the EES cohort compared to the PES cohort (5.0% vs. 8.8%, respectively; $p=0.036$). Clinical follow-up at three years was available in 948 patients (94.6%), including 636 EES patients and 312 PES patients. At three years, TVF occurred significantly less frequently with EES as compared with the PES (14.3% vs. 20.0%, respectively; $p=0.03$), as did MACE (9.7% vs. 16.4%, respectively; $p=0.004$).

Baseline clinical characteristics associated with TVF are shown in **Table 1**. At nine-month follow-up, female gender, total cholesterol $>200 \text{ mg/dL}$, and triglycerides $>150 \text{ mg/dL}$ were associated with TVF. At three-year follow-up, haemoglobin A1c (HbA1c) (%) was associated with TVF in addition to female gender and total cholesterol $>200 \text{ mg/dL}$. As shown in **Table 2**, female gender and total cholesterol $>200 \text{ mg/dL}$ were also associated with an increased risk of MACE at both nine months and three years. HbA1c (%) and current smoking were associated with MACE at three-year follow-up. Procedural characteristics associated with TVF (**Table 3**) and

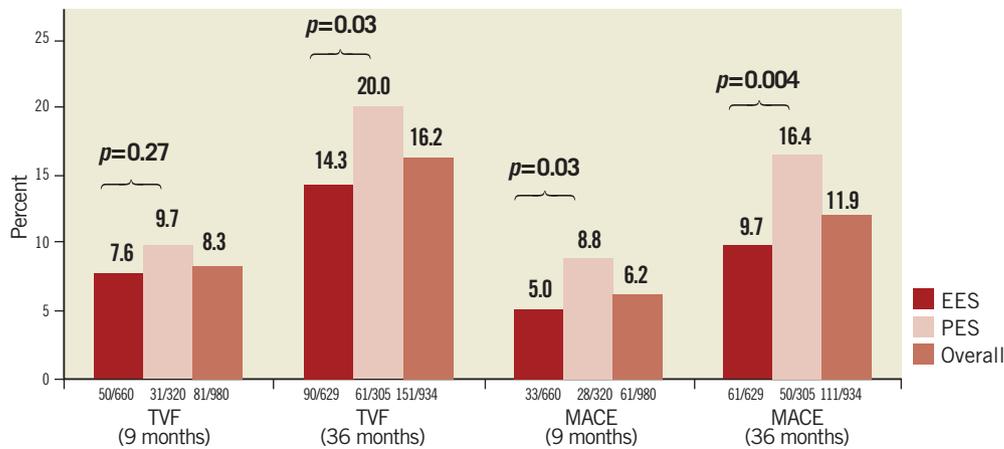


Figure 1. Bar graph of percent incidence of target vessel failure (TVF) and major adverse cardiac events (MACE) at nine months and three years for everolimus-eluting stents (EES) and paclitaxel-eluting stents (PES).

Table 1. Clinical characteristics according to target vessel failure.

	With target vessel failure	Without target vessel failure	p-value
According to target vessel failure at 9 months	(n=81)	(n=920)	
Age (years)	62.76±11.31 (81)	63.11±10.36 (920)	0.79
Female	46.9% (38/81)	30.0% (276/920)	0.003
Hypertension requiring medication	75.3% (61/81)	75.5% (694/919)	1.00
Hypercholesterolaemia requiring medication	67.9% (53/78)	73.9% (670/907)	0.29
Total cholesterol >200 mg/dL	34.6% (27/78)	18.1% (163/901)	0.0009
High density lipoprotein <60 mg/dL	89.6% (69/77)	92.9% (836/900)	0.26
Triglycerides >150 mg/dL	44.2% (34/77)	32.7% (294/899)	0.04
Diabetes mellitus	28.4% (23/81)	29.1% (267/918)	1.00
Requiring insulin	6.2% (5/81)	7.1% (65/918)	1.00
HbA1c (%)	6.47±1.36 (79)	6.25±1.25 (884)	0.17
Current smoker	25.6% (20/78)	22.8% (207/906)	0.58
Prior myocardial infarction	16.7% (13/78)	19.5% (176/901)	0.65
Unstable angina	25.0% (20/80)	20.5% (185/904)	0.39
According to target vessel failure at 3 years	(n=151)	(n=850)	
Age (years)	62.01±10.46 (151)	63.27±10.42 (850)	0.17
Female	38.4% (58/151)	30.1% (256/850)	0.05
Hypertension requiring medication	78.7% (118/150)	74.9% (637/850)	0.36
Hypercholesterolaemia requiring medication	70.7% (104/147)	73.9% (619/838)	0.42
Total cholesterol >200 mg/dL	28.6% (42/147)	17.8% (148/832)	0.003
High density lipoprotein <60 mg/dL	91.8% (134/146)	92.8% (771/831)	0.61
Triglycerides >150 mg/dL	37.7% (55/146)	32.9% (273/830)	0.26
Diabetes mellitus	26.5% (40/151)	29.5% (250/848)	0.50
Requiring insulin	6.0% (9/151)	7.2% (61/848)	0.73
HbA1c (%)	6.57±1.74 (146)	6.22±1.14 (817)	0.02
Current smoker	29.3% (43/147)	22.0% (184/837)	0.06
Prior myocardial infarction	22.6% (33/146)	18.7% (156/833)	0.31
Unstable angina	24.2% (36/149)	20.2% (169/835)	0.28

Table 2. Clinical characteristics according to major adverse cardiac events.

	With major adverse cardiac events	Without major adverse cardiac events	p-value
According to major adverse cardiac events at 9 months	(n=61)	(n=940)	
Age (years)	64.35±11.22 (61)	63.00±10.38 (940)	0.37
Female	49.2% (30/61)	30.2% (284/940)	0.003
Hypertension requiring medication	77.0% (47/61)	75.4% (708/939)	0.88
Hypercholesterolaemia requiring medication	70.7% (41/58)	73.6% (682/927)	0.65
Total cholesterol >200 mg/dL	37.9% (22/58)	18.2% (168/921)	0.0008
High density lipoprotein <60 mg/dL	87.7% (50/57)	92.9% (855/920)	0.18
Triglycerides >150 mg/dL	45.6% (26/57)	32.9% (302/919)	0.06
Diabetes mellitus	26.2% (16/61)	29.2% (274/938)	0.67
Requiring insulin	6.6% (4/61)	7.0% (66/938)	1.00
HbA1c (%)	6.45±1.23 (59)	6.26±1.26 (904)	0.24
Current smoker	28.8% (17/59)	22.7% (210/925)	0.27
Prior myocardial infarction	15.3% (9/59)	19.6% (180/920)	0.50
Unstable angina	28.3% (17/60)	20.3% (188/924)	0.14
According to major adverse cardiac events at 3 years	(n=111)	(n=890)	
Age (years)	62.74±10.66 (111)	63.13±10.41 (890)	0.72
Female	42.3% (47/111)	30.0% (267/890)	0.01
Hypertension requiring medication	80.0% (88/110)	74.9% (667/890)	0.29
Hypercholesterolaemia requiring medication	71.3% (77/108)	73.7% (646/877)	0.64
Total cholesterol >200 mg/dL	31.5% (34/108)	17.9% (156/871)	0.002
High density lipoprotein <60 mg/dL	90.7% (97/107)	92.9% (808/870)	0.43
Triglycerides >150 mg/dL	39.3% (42/107)	32.9% (286/869)	0.19
Diabetes mellitus	26.1% (29/111)	29.4% (261/888)	0.51
Requiring insulin	6.3% (7/111)	7.1% (63/888)	1.00
HbA1c (%)	6.55±1.65 (108)	6.24±1.19 (855)	0.05
Current smoker	31.5% (34/108)	22.0% (193/876)	0.04
Prior myocardial infarction	23.1% (25/108)	18.8% (164/871)	0.30
Unstable angina	26.6% (29/109)	20.1% (176/875)	0.13

MACE (**Table 4**) included the presence of multivessel disease at both nine months and three years and smaller pre-procedure RVD at three years.

Multivariable analysis

The predictors of composite endpoints of TVF and MACE at nine months and three years are shown in **Table 5** from both logistic (**Table 5a**) and Cox (**Table 5b**) regression analyses. These two statistical methods produced very similar results. At nine months (logistic regression analysis), the number of diseased vessels, female gender, and total cholesterol >200 mg/dL were identified as predictors of TVF. At three years (Cox regression analysis), the predictors of TVF included the number of vessels treated, HbA1c (%), total cholesterol >200 mg/dL, and female gender. At nine months (logistic regression analysis), the predictors of MACE were total cholesterol >200 mg/dL, female gender, and number of vessels treated. At three years (Cox regression analysis), the predictors of MACE were the number of vessels treated, total cholesterol

>200 mg/dL, female gender, and HbA1c (%). Stent type (use of EES rather than PES) was a significant predictor of lower MACE at three years ($p=0.03$; HR=0.64 [95% CI, 0.44-0.95]).

The predictors of cardiac death or MI (safety) and ischaemia-driven TLR (clinical efficacy) at nine months and three years are shown in **Table 6** from both logistic (**Table 6a**) and Cox (**Table 6b**) regression analyses. The predictors of cardiac death or MI at nine months (logistic regression analysis) included the number of diseased vessels and prior cardiac intervention, and at three years (Cox regression analysis) were the number of vessels treated, current tobacco use, and HbA1c (%). The predictors of TLR were female gender and total cholesterol >200 mg/dL at nine months (logistic regression analysis), and female gender, number of stents implanted and age at three years (Cox regression analysis).

Subgroup interaction analysis

Implantation of EES as compared with PES reduced the rate of TVF at three years, and MACE at both nine months and three years.

Table 3. Procedural characteristics according to target vessel failure.

	With target vessel failure (n=81)	Without target vessel failure (n=920)	p-value
According to target vessel failure at 9 months			
Subject level analyses			
No. of target vessels			
Single	48.1% (39/81)	66.8% (615/920)	0.001
Multiple	51.9% (42/81)	33.0% (304/920)	0.0009
No. of treated vessels			
Single	72.8% (59/81)	85.7% (788/920)	0.006
Multiple	27.2% (22/81)	14.3% (132/920)	0.006
Lesion level analyses			
Target coronary artery			
Left anterior descending	49.2% (29/59)	42.4% (334/787)	0.34
Left circumflex	18.6% (11/59)	26.9% (212/787)	0.22
Right coronary	32.2% (19/59)	30.4% (239/787)	0.77
Left main protected	0.0% (0/59)	0.3% (2/787)	1.00
Target lesion			
Pre-procedure reference vessel diameter (mm)	2.70±0.48 (59)	2.78±0.44 (787)	0.20
Pre-procedure minimal luminal diameter (mm)	0.87±0.40 (59)	0.80±0.41 (787)	0.22
Diameter stenosis (%)	67.2±13.4 (59)	70.8±13.4 (787)	0.05
Lesion length (mm)	15.5±5.9 (59)	14.7±5.5 (785)	0.28
According to target vessel failure at 3 years			
Subject level analyses			
No. of target vessels			
Single	51.0% (77/151)	67.9% (577/850)	<0.0001
Multiple	49.0% (74/151)	32.0% (272/850)	<0.0001
No. of treated vessels			
Single	72.2% (109/151)	86.8% (738/850)	<0.0001
Multiple	27.8% (42/151)	13.2% (112/850)	<0.0001
Lesion level analyses			
Target coronary artery			
Left anterior descending	45.9% (50/109)	42.5% (313/737)	0.53
Left circumflex	20.2% (22/109)	27.3% (201/737)	0.13
Right coronary	33.9% (37/109)	30.0% (221/737)	0.44
Left main protected	0.0% (0/109)	0.3% (2/737)	1.00
Target lesion			
Pre-procedure reference vessel diameter (mm)	2.70±0.44 (109)	2.79±0.45 (737)	0.04
Pre-procedure minimal luminal diameter (mm)	0.81±0.40 (109)	0.81±0.41 (737)	0.96
Diameter stenosis (%)	69.5±13.7 (109)	70.7±13.4 (737)	0.42
Lesion length (mm)	15.1±5.8 (108)	14.7±5.5 (736)	0.45

To determine if there was an interaction between DES type and clinical and procedural factors, we evaluated the relative risk of selected clinical and procedural characteristics, as well as angiographic results stratified by EES vs. PES, for TVF and for MACE at three years. There were no significant interactions between the subgroups and stent randomisation for the occurrence of TVF or MACE at three years.

Discussion

The present study evaluated the independent predictors of TVF and MACE at nine months and three years after DES placement in a contemporary group of patients. Results from logistic and Cox regression analyses were similar due to the relatively high three-year follow-up rates in the SPIRIT III (94.6%) trial. Clinical variables including female gender, total cholesterol >200 mg/dL, and

Table 4. Procedural characteristics according to major adverse cardiac events.

	With major adverse cardiac events	Without major adverse cardiac events	p-value
According to major adverse cardiac events at 9 months	(n=61)	(n=940)	
Subject level analyses			
No. of target vessels			
Single	50.8% (31/61)	66.3% (623/940)	0.02
Multiple	49.2% (30/61)	33.6% (316/940)	0.02
No. of treated vessels			
Single	72.1% (44/61)	85.4% (803/940)	0.009
Multiple	27.9% (17/61)	14.6% (137/940)	0.009
Lesion level analyses			
Target coronary artery			
Left anterior descending	56.8% (25/44)	42.1% (338/802)	0.06
Left circumflex	20.5% (9/44)	26.7% (214/802)	0.48
Right coronary	22.7% (10/44)	30.9% (248/802)	0.31
Left main protected	0.0% (0/44)	0.2% (2/802)	1.00
Target lesion			
Pre-procedure reference vessel diameter (mm)	2.69±0.46 (44)	2.78±0.45 (802)	0.20
Pre-procedure minimal luminal diameter (mm)	0.84±0.36 (44)	0.81±0.41 (802)	0.60
Diameter stenosis (%)	68.2±13.5 (44)	70.6±13.4 (802)	0.26
Lesion length (mm)	15.1±5.0 (44)	14.7±5.6 (800)	0.59
According to major adverse cardiac events at 3 years	(n=111)	(n=890)	
Subject level analyses			
No. of target vessels			
Single	55.0% (61/111)	66.6% (593/890)	0.02
Multiple	45.0% (50/111)	33.3% (296/890)	0.02
No. of treated vessels			
Single	72.1% (80/111)	86.2% (767/890)	0.0004
Multiple	27.9% (31/111)	13.8% (123/890)	0.0004
Lesion level analyses			
Target coronary artery			
Left anterior descending	51.3% (41/80)	42.0% (322/766)	0.12
Left circumflex	22.5% (18/80)	26.8% (205/766)	0.50
Right coronary	26.3% (21/80)	30.9% (237/766)	0.44
Left main protected	0.0% (0/80)	0.3% (2/766)	1.00
Target lesion			
Pre-procedure reference vessel diameter (mm)	2.67±0.41 (80)	2.79±0.45 (766)	0.01
Pre-procedure minimal luminal diameter (mm)	0.79±0.37 (80)	0.81±0.41 (766)	0.59
Diameter stenosis (%)	70.4±13.2 (80)	70.5±13.4 (766)	0.94
Lesion length (mm)	15.1±5.4 (79)	14.7±5.6 (765)	0.47

HbA1c were independent predictors of both TVF and MACE. Procedural factor treatment of dual vessels were predictors of clinical outcomes at two years⁹ and remained an independent predictor of TVF and MACE. Finally, stent type (use of EES rather than PES) was also a multivariable predictor of lower MACE at three years. These observations provide evidence that demographic, clinical, and procedural characteristics remain important factors in deter-

mining clinical outcomes in the contemporary DES era. The benefits of EES compared to PES were present across a broad range of clinical and angiographic subgroups including those identified as predictors of higher adverse outcomes at three years in multivariable regression analysis, with the possible exception of patients with diabetes mellitus in whom the outcomes of EES and PES were not significantly different. These data should provide reassurance that

Table 5a. Multivariable predictors of target vessel failure and major adverse cardiac events at nine months and three years (logistic regression analysis).

Variable	Coding for binary variables	p-value	Odds ratio [95% CI]
Predictors of 9-month target vessel failure			
Drug-eluting stent type	EES vs. PES	0.78	0.93 [0.56, 1.54]
No. of diseased vessels	Multiple vs. single	0.0003	2.48 [1.52, 4.03]
Gender	Female vs. male	0.001	2.24 [1.37, 3.66]
Total cholesterol (>200 mg/dL)	Yes vs. no	0.005	2.10 [1.25, 3.52]
Model checking statistics Hosmer and Lemeshow goodness-of-fit test C-statistic (the area under the ROC curve): 0.67			0.95
Predictors of 3-year target vessel failure			
Drug-eluting stent type	EES vs. PES	0.18	0.77 [0.53, 1.13]
No. of treated vessels	Dual vs. single	<0.0001	2.36 [1.53, 3.63]
Total cholesterol (>200 mg/dL)	Yes vs. no	0.004	1.83 [1.21, 2.77]
HbA1c (%)		0.007	1.19 [1.05, 1.35]
Model checking statistics Hosmer and Lemeshow goodness-of-fit test C-statistic (the area under the ROC curve): 0.61		0.31	
Predictors of 9-month major adverse cardiac events			
Drug-eluting stent type	EES vs. PES	0.24	0.72 [0.41, 1.25]
Total cholesterol (>200 mg/dL)	Yes vs. no	0.007	2.22 [1.24, 3.96]
Gender	Female vs. male	0.008	2.12 [1.22, 3.67]
No. of treated vessels	Dual vs. single	0.02	2.11 [1.12, 3.98]
Model checking statistics Hosmer and Lemeshow goodness-of-fit test C-statistic (the area under the ROC curve): 0.66			0.94
Predictors of 3-year major adverse cardiac events			
Drug-eluting stent type	EES vs. PES	0.04	0.65 [0.42, 0.99]
No. of treated vessels	Dual vs. single	0.002	2.23 [1.36, 3.66]
Total cholesterol (>200 mg/dL)	Yes vs. no	0.01	1.83 [1.15, 2.92]
HbA1c (%)		0.02	1.17 [1.02, 1.35]
Gender	Female vs. male	0.02	1.64 [1.06, 2.53]
Model checking statistics Hosmer and Lemeshow goodness-of-fit test C-statistic (the area under the ROC curve): 0.64		0.50	

EES, one of the newest generations of DES, provides consistent and durable benefits for up to three years across a broad range of clinical and procedural subgroups.

A baseline total cholesterol of >200 mg/dL emerged as a multivariable clinical predictor of TVF and MACE at both nine months and three years, despite the observation that almost three-fourths of all patients were receiving therapy for hypercholesterolaemia. Given the contemporary clinical emphasis on the aggressive management of hypercholesterolaemia, the observation that total cholesterol >200 mg/dL was associated with adverse events may identify patients who are relatively resistant to statins, or have more severe forms of hyperlipidaemia. Also, female gender emerged as another multivariable predictor of TVF and MACE at both nine months and three years. Female gender has been variably identified as an adverse clinical characteristic following percutaneous coronary revascularisation procedures¹⁰⁻¹⁴. More recent studies evaluating outcomes after DES

use have not identified female gender as an adverse factor affecting clinical or angiographic restenosis¹³. Our observation that EES use vs. PES use was associated with a substantially lower risk of TVF or MACE at three years in women (with no gender-specific interactions present) is supported by observations from the SPIRIT II and III trials^{15,16}, as well as the one year outcomes of the larger SPIRIT IV trial, which demonstrated a 47% reduction in target lesion failure in women with EES compared to PES¹⁷. These observations together suggest that the type of stent used may be an important determinant of clinical outcomes in women.

Considerable debate has arisen over the relative benefit between different DES in patients with diabetes¹⁸⁻²⁰. In the SPIRIT III randomised trial, no difference was observed in the overall rates of TVF or MACE between EES or PES in the subgroup of patients with diabetes⁶⁻⁸, consistent with the results of the recent meta-analyses^{19,20}. Despite the similarity of clinical outcomes in this trial

Table 5b. Multivariable predictors of target vessel failure and major adverse cardiac events at nine months and three years (Cox regression analysis).

Variable	Coding for binary variables	p-value	Hazard ratio [95% CI]
Predictors of 9-month target vessel failure			
Drug-eluting stent type	EES vs. PES	0.67	0.90 [0.56, 1.45]
Total cholesterol (>200 mg/dL)	Yes vs. no	0.005	1.99 [1.23, 3.21]
No. of diseased vessels	Multiple vs. single	0.0002	2.39 [1.51, 3.76]
Gender	Female vs. male	0.001	2.17 [1.37, 3.44]
Proportionality checking statistics (Score test based on scaled Schoenfeld residuals)		0.21	
Predictors of 3-year target vessel failure			
Drug-eluting stent type	EES vs. PES	0.12	0.76 [0.54, 1.07]
No. of treated vessels	Dual vs. single	<0.0001	2.19 [1.50, 3.19]
HbA1c (%)		0.004	1.17 [1.05, 1.29]
Total cholesterol (>200 mg/dL)	Yes vs. no	0.009	1.63 [1.13, 2.36]
Gender	Female vs. male	0.05	1.42 [1.01, 2.01]
Proportionality checking statistics (Score test based on scaled Schoenfeld residuals)		0.29	
Predictors of 9-month major adverse cardiac events			
Drug-eluting stent type	EES vs. PES	0.21	0.71 [0.42, 1.21]
Total cholesterol (>200 mg/dL)	Yes vs. no	0.008	2.10 [1.21, 3.63]
Gender	Female vs. male	0.007	2.07 [1.22, 3.51]
No. of treated vessels	Dual vs. single	0.02	2.04 [1.13, 3.70]
Proportionality checking statistics (Score test based on scaled Schoenfeld residuals)		0.26	
Predictors of 3-year major adverse cardiac events			
Drug-eluting stent type	EES vs. PES	0.03	0.64 [0.44, 0.95]
No. of treated vessels	Dual vs. single	0.001	2.07 [1.33, 3.23]
Total cholesterol (>200 mg/dL)	Yes vs. no	0.02	1.69 [1.10, 2.57]
Gender	Female vs. male	0.02	1.60 [1.07, 2.38]
HbA1c (%)		0.02	1.15 [1.02, 1.30]
Proportionality checking statistics (Score test based on scaled Schoenfeld residuals)		0.40	

between EES and PES in the diabetic subgroup, HbA1c emerged as an important multivariable predictor of both TVF and MACE at three years in the overall study population. This observation is at odds with recent evaluations that did not find that diabetes was a multivariable predictor of clinical restenosis in all patients⁴. Several factors may be important in explaining potential reasons for this apparent dichotomy. First, we examined HbA1c as a continuous variable, and in all study patients, not just diabetics, which had not been previously done. It is possible that HbA1c is a more sensitive measure of the effect of diabetes on clinical outcomes than is obtained by simple assessment of the presence or absence of the disease itself. Second, previous studies used restenosis as an endpoint, whereas we evaluated broader clinical outcomes that included MI and death. These two different endpoints represent the consequences of different pathophysiologic processes, restenosis vs. the clinical expression of atherosclerosis, which are likely affected dif-

ferently by diabetes. In support of this, HbA1c was a multivariable predictor of cardiac death or MI (safety) but not a multivariable predictor of TLR (clinical efficacy) at three years in the SPIRIT III trial. Our observations support the inclusion of HbA1c as a clinical endpoint in future trials of stent therapy.

The observation that EES use was a significant predictor of lower event rates is consistent with prior animal and clinical studies that have evaluated rates of restenosis following the use of thinner strut BMS compared to thicker strut BMS²¹⁻²³. However, no difference in rates of clinical restenosis or clinical outcomes between a thin-strut zotarolimus-eluting stent (ZES) and PES was noted in a large randomised trial^{24,25}. Both the EES and the ZES system are based on thin-strut cobalt chromium stent platforms, however the drug delivery kinetics of the two stent systems are substantially different, with the majority of zotarolimus released within 14 days from the ZES compared to 30 days observed with the release of everolimus from

Table 6a. Multivariable predictors of cardiac death or myocardial infarction and ischaemia-driven target lesion revascularisation at nine months and three years (logistic regression analysis).

Variable	Coding for binary variables	p-value	Odds ratio [95% CI]
Predictors of 9-month cardiac death or myocardial infarction			
Drug-eluting stent type	EES vs. PES	0.77	0.89 [0.41, 1.95]
No. of diseased vessels	Multiple vs. single	0.0008	3.80 [1.74, 8.27]
Model checking statistics Hosmer and Lemeshow goodness-of-fit test C-statistic (the area under the ROC curve): 0.66		0.38	
Predictors of 3-year cardiac death or myocardial infarction			
Drug-eluting stent type	EES vs. PES	0.13	0.64 [0.36, 1.15]
No. of treated vessels	Dual vs. single	0.005	2.51 [1.33, 4.72]
HbA1c (%)		0.006	1.27 [1.07, 1.50]
Current smoker	Yes vs. no	0.03	1.96 [1.08, 3.59]
Model checking statistics Hosmer and Lemeshow goodness-of-fit test C-statistic (the area under the ROC curve): 0.65		0.14	
Predictors of 9-month target lesion revascularisation			
Drug-eluting stent type	EES vs. PES	0.24	0.65 [0.32, 1.33]
Total cholesterol (>200 mg/dL)	Yes vs. no	0.006	2.77 [1.34, 5.69]
Gender	Female vs. male	0.005	2.76 [1.35, 5.63]
Model checking statistics Hosmer and Lemeshow goodness-of-fit test C-statistic (the area under the ROC curve): 0.70		0.98	
Predictors of 3-year target lesion revascularisation			
Drug-eluting stent type	EES vs. PES	0.11	0.65 [0.39, 1.10]
Gender	Female vs. male	0.001	2.37 [1.40, 4.03]
No. of stents implanted	Multiple vs. single	0.01	2.00 [1.17, 3.42]
Age (years)		0.03	0.97 [0.95, 1.00]
Model checking statistics Hosmer and Lemeshow goodness-of-fit test C-statistic (the area under the ROC curve): 0.65		0.45	

the EES platform²⁶⁻²⁸. Differences in vascular responses to the varying polymers may also explain the disparate outcomes between stent types.

Finally, these comparisons are based on the use of the older generation TAXUS EXPRESS platform, which has been replaced by the thin-strut TAXUS® Liberté® (Boston Scientific). It could be argued, therefore, that the comparisons to TAXUS EXPRESS are of historical interest. However, the clinical outcomes of the XIENCE and TAXUS Liberté DES have been compared in the single centre randomised COMPARE trial²⁹. In this “all comers” trial, EES use was associated with a relative risk of the primary endpoint MACE of 0.69 (95% CI, 0.50-0.95; p=0.02) compared to PES. This magnitude of benefit of EES compared to PES is comparable to that observed in the SPIRIT IV trial at one year¹⁷. Thus use of EES appears to be superior to that of PES independent of the stent platform. Ultimately, further studies will be needed to confirm the results of the COMPARE trial.

There are limitations of this study that merit discussion. This is a *post hoc* evaluation of the clinical outcomes from the SPIRIT III study, and thus may be subject to bias. However, there were no sig-

nificant differences in the clinical and angiographic variables of either stent group so it is unlikely that selection bias significantly affected the study results. Likewise, rates of angiographic and clinical follow-up were excellent and similar in both groups so it is unlikely that ascertainment bias affected the study outcomes. Additionally, while it was interesting to look at the multivariable predictors of cardiac death or MI and TLR, SPIRIT III was not powered for these relatively low frequency events when considered separately. Similar analyses of the larger DES trials such as SPIRIT IV might be able to provide more insights. Finally, patients in this randomised clinical trial were carefully selected with explicit criteria that excluded several high-risk groups of patients and lesions. Thus, these observations may not be generalised beyond the current study population.

Conflict of interest statement

R. Applegate reports having received research support from Cordis and Abbott Vascular and serving on the scientific advisory board for Abbott Vascular; J. Hermiller reports serving as a consultant for

Table 6b. Multivariable predictors of cardiac death or myocardial infarction and ischaemia-driven target lesion revascularisation at nine months and three years (Cox regression analysis).

Variable	Coding for binary variables	p-value	Hazard ratio [95% CI]
Predictors of 9-month cardiac death or myocardial infarction			
Drug-eluting stent type	EES vs. PES	0.83	0.92 [0.43, 1.98]
No. of diseased vessels	Multiple vs. single	0.0003	4.07 [1.89, 8.79]
Prior cardiac interventions	Yes vs. no	0.05	0.38 [0.14, 1.01]
Proportionality checking statistics (Score test based on scaled Schoenfeld residuals)		0.01	
Predictors of 3-year cardiac death or myocardial infarction			
Drug-eluting stent type	EES vs. PES	0.11	0.63 [0.36, 1.10]
No. of treated vessels	Dual vs. single	0.006	2.31 [1.27, 4.20]
Current smoker	Yes vs. no	0.03	1.91 [1.08, 3.38]
HbA1c (%)		0.003	1.25 [1.08, 1.45]
Proportionality checking statistics (Score test based on scaled Schoenfeld residuals)		0.56	
Predictors of 9-month target lesion revascularisation			
Drug-eluting stent type	EES vs. PES	0.23	0.65 [0.33, 1.30]
Total cholesterol (>200 mg/dL)	Yes vs. no	0.007	2.63 [1.31, 5.29]
Gender	Female vs. male	0.005	2.69 [1.34, 5.40]
Proportionality checking statistics (Score test based on scaled Schoenfeld residuals)		0.44	
Predictors of 3-year target lesion revascularisation			
Drug-eluting stent type	EES vs. PES	0.12	0.67 [0.41, 1.10]
Gender	Female vs. male	0.0009	2.34 [1.41, 3.86]
No. of stents implanted	Multiple vs. single	0.01	1.92 [1.16, 3.20]
Age (years)		0.03	0.97 [0.95, 1.00]
Proportionality checking statistics (Score test based on scaled Schoenfeld residuals)		0.13	

Abbott Vascular and Boston Scientific Corp.; P. Gordon reports having received research support from Abbott Vascular; G. Stone reports serving on the scientific advisory board for Abbott Vascular and Boston Scientific Corp.; K. Sudhir, M. Yaqub, P. Sood, X. Su and S. Cao are full-time employees of Abbott Vascular and own stock and/or options of Abbott Vascular.

References

- Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE, The SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med.* 2003;349:1315-23.
- Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME, 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.
- Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA.* 2005;293:2126-30.
- Kastrati A, Dibra A, Mehilli J, Mayer S, Pinieck S, Pache J, Dirschinger J, Schomig A. Predictive factors of restenosis after coronary implantation of sirolimus- or paclitaxel-eluting stents. *Circ.* 2006;113:2293-300.
- Stettler C, Wandel S, Allemann S, Kastrati A, Morice MC, Schomig A, Pfisterer ME, Stone GW, Leon MB, de Lezo JS, Goy JJ, Park SJ, Sabate M, Suttorp MJ, Kelbaek H, Spaulding C, Menichelli M, Vermeersch P, Dirksen MT, Cervinka P, Petronio AS, Nordmann AJ, Diem P, Meier B, Zwahlen M, Reichenbach S, Trelle S, Windecker S, Juni P. Outcomes associated with drug-eluting and bare-metal stents: A collaborative network meta-analysis. *Lancet.* 2007;370:937-48.
- Stone GW, Midei M, Newman W, Sanz M, Hermiller JB, Williams J, Farhat N, Mahaffey KW, Cutlip DE, Fitzgerald PJ, Sood P, Su X, Lansky AJ, 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.

7. Stone GW, Midei M, Newman W, Sanz M, Hermiller JB, Williams J, Farhat N, Caputo R, Xenopoulos N, Applegate R, Gordon P, White RM, Sudhir K, Cutlip DE, Petersen JL, for the SPIRIT III Investigators. Randomized comparison of everolimus-eluting and paclitaxel-eluting stents: Two-year clinical follow-up from the clinical evaluation of the Xience V everolimus eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions (SPIRIT) III trial. *Circulation*. 2009;119:680-6.
8. Applegate RJ, Yaqub M, Hermiller JB, Sood P, Yu S, Doostzadeh J, Williams JE, Farhat N, Caputo R, Lansky AJ, Cutlip DE, Sudhir K, Stone GW. Long-term (three-year) safety and efficacy of everolimus-eluting stents compared to paclitaxel-eluting stents (from the SPIRIT III trial). *Am J Cardiol*. 2011;107:833-40.
9. Applegate RJ, Hermiller JB, Sanz M, Doostzadeh J, Pierson W, Su X, Lansky AJ, Sudhir K, Stone GW. Comparison of everolimus-eluting and paclitaxel-eluting coronary stents in patients with two treated vessels: 2-year results from the SPIRIT III randomised trial. *EuroIntervention*. 2010;6:437-46.
10. Argulian E, Patel AD, Abramson JL, Kulkarni A, Champney K, Palmer S, Weintraub W, Wenger NK, Vaccarino V. Gender differences in short-term cardiovascular outcomes after percutaneous coronary interventions. *Am J Cardiol*. 2006;98:48-53.
11. Cutlip DE, Chauhan MS, Baim DS, Ho KK, Popma JJ, Carozza JP, Cohen DJ, Kuntz RE. Clinical restenosis after coronary stenting: Perspectives from multicenter clinical trials. *J Am Coll Cardiol*. 2002;40:2082-9.
12. Jacobs AK. Women, ischemic heart disease, revascularization, and the gender gap: What are we missing? *J Am Coll Cardiol*. 2006;47:63S-5S.
13. Solinas E, Nikolsky E, Lansky AJ, Kirtane AJ, Morice MC, Popma JJ, Schofer J, Schampaert E, Pucelikova T, Aoki J, Fahy M, Dangas GD, Moses JW, Cutlip DE, Leon MB, Mehran R. Gender-specific outcomes after sirolimus-eluting stent implantation. *J Am Coll Cardiol*. 2007;50:2111-6.
14. Thompson CA, Kaplan AV, Friedman BJ, Jayne JE, Gerling BR, Niles NW, Hettleman BD, Robb JF. Gender-based differences of percutaneous coronary intervention in the drug-eluting stent era. *Catheter Cardiovasc Interv*. 2006;67:25-31.
15. Lansky AJ, Ng VG, Mutlu H, Cristea E, Guiran JB, Midei M, Newman W, Sanz M, Sood P, Doostzadeh J, Su X, White R, Cao S, Sudhir K, Stone GW. Gender-based evaluation of the XIENCE V everolimus-eluting coronary stent system: Clinical and angiographic results from the SPIRIT III randomized trial. *Catheter Cardiovasc Interv*. 2009;74:719-27.
16. Seth A, Serruys PW, Lansky A, Hermiller J, Onuma Y, Miquel-Hebert K, Yu S, Veldhof S, Sood P, Sudhir K, Stone GW. A pooled gender based analysis comparing the XIENCE V[®] everolimus-eluting stent and the TAXUS paclitaxel-eluting stent in male and female patients with coronary artery disease, results of the SPIRIT II and SPIRIT III studies: Two-year analysis. *EuroIntervention*. 2010;5:788-94.
17. Stone GW, Rizvi A, Newman W, Mastali K, Wang JC, Caputo R, Doostzadeh J, Cao S, Simonton CA, Sudhir K, Lansky AJ, Cutlip DE, Kereiakes DJ, for the SPIRIT IV Investigators. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. *N Engl J Med*. 2010;362:1663-74.
18. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med*. 2007;356:989-97.
19. Kastrati A, Mehilli J, Pache J, Kaiser C, Valgimigli M, Kelbaek H, Menichelli M, Sabate M, Suttorp MJ, Baumgart D, Seyfarth M, Pfisterer ME, Schomig A. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med*. 2007;356:1030-9.
20. Stettler C, Allemann S, Wandel S, Kastrati A, Morice MC, Schomig A, Pfisterer ME, Stone GW, Leon MB, de Lezo JS, Goy JJ, Park SJ, Sabate M, Suttorp MJ, Kelbaek H, Spaulding C, Menichelli M, Vermeersch P, Dirksen MT, Cervinka P, De Carlo M, Erglis A, Chechi T, Ortolani P, Schalij MJ, Diem P, Meier B, Windecker S, Juni P. Drug eluting and bare metal stents in people with and without diabetes: Collaborative network meta-analysis. *BMJ*. 2008;337:a1331.
21. Kastrati A, Mehilli J, Dirschinger J, Dotzer F, Schuhlen H, Neumann F-J, Fleckenstein M, Pfafferoth C, Seyfarth M, Schomig A. Intracoronary stenting and angiographic results: Strut thickness effect on restenosis outcome (ISAR-STEREO) trial. *Circ*. 2001;103:2816-21.
22. Pache J, Kastrati A, Mehilli J, Schuhlen H, Dotzer F, Hausleiter J, Fleckenstein M, Neumann FJ, Sattelberger U, Schmitt C, Muller M, Dirschinger J, Schomig A. Intracoronary stenting and angiographic results: Strut Thickness Effect on Restenosis Outcome (ISAR-STEREO-2) Trial. *J Am Coll Cardiol*. 2003;41:1283-8.
23. Rogers C, Edelman ER. Endovascular stent design dictates experimental restenosis and thrombosis. *Circ*. 1995;91:2995-3001.
24. Leon MB, Kandzari DE, Eisenstein EL, Anstrom KJ, Mauri L, Cutlip DE, Nikolsky E, O'Shaughnessy C, Overlie PA, Kirtane AJ, McLaurin BT, Solomon SL, Douglas JS, Jr., Popma JJ, for the ENDEAVOR IV Investigators. Late safety, efficacy, and cost-effectiveness of a zotarolimus-eluting stent compared with a paclitaxel-eluting stent in patients with de novo coronary lesions: 2-year follow-up from the ENDEAVOR IV trial (randomized, controlled trial of the Medtronic Endeavor drug [ABT-578] eluting coronary stent system versus the Taxus paclitaxel-eluting coronary stent system in de novo native coronary artery lesions). *J Am Coll Cardiol Interv*. 2009;2:1208-18.
25. Leon MB, Mauri L, Popma JJ, Cutlip DE, Nikolsky E, O'Shaughnessy C, Overlie PA, McLaurin BT, Solomon SL, Douglas JS, Jr., Ball MW, Caputo RP, Jain A, Tolleson TR, Reen BM, III, Kirtane AJ, Fitzgerald PJ, Thompson K, Kandzari DE. 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.

26. Beijk MA, Piek JJ. XIENCE V everolimus-eluting coronary stent system: A novel second generation drug-eluting stent. *Expert Rev Med Devices*. 2007;4:11-21.
27. Kukreja N, Onuma Y, Serruys PW. Xience V everolimus-eluting coronary stent. *Expert Rev Med Devices*. 2009;6:219-29.
28. Wiemer M, Seth A, Chandra P, Neuzner J, Richardt G, Piek JJ, Desaga M, Macaya C, Bol CJ, Miquel-Hebert K, De Roeck K, Serruys PW. Systemic exposure of everolimus after stent implantation: A pharmacokinetic study. *Am Heart J*. 2008;156:751.e1-7.
29. Kedhi E, Joesoef KS, McFadden E, Wassing J, van Mieghem C, Goedhart D, Smits PC. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): A randomised trial. *Lancet*. 2010;375:201-9.