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Efficacy of Everolimus Eluting Stent Implantation in Patients With Calcified Coronary Culprit Lesions: Two-Year Angiographic and Three-Year Clinical Results From the SPIRIT II Study

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Background: Little is known about the impact of treatment with drug-eluting stents (DES) on calcified coronary lesions. This analysis sought to assess the safety and efficacy of the XIENCE V everolimus-eluting stent (EES) in patients with calcified or noncalcified culprit lesions. Methods: The study population consisted of 212 patients with 247 lesions, who were treated with EES alone. Target lesions were angiographically classified as none/mild, moderate, or severe grades of calcification. The population was divided into two groups: those with at least one target lesion moderately or severely calcified (the calcified group: 68 patients with 75 calcified lesions) and those with all target lesions having mild or no calcification (the noncalcified group: 144 patients). Six-month and 2-year angiographic follow-up and clinical follow-up up to 3 years were completed. Results: The baseline characteristics were not significantly different between both groups. When compared with the noncalcified group, the calcified group had significantly higher rates of 6-month in-stent angiographic binary restenosis (ABR, 4.3% vs. 0%, $P = 0.03$) and ischemia-driven target lesion revascularization (ID-TLR, 5.9% vs. 0%, $P = 0.01$), resulting in numerically higher major cardiac adverse events (MACE, 5.9% vs. 1.4%, $P = 0.09$). At 2 years, when compared with the noncalcified group, the calcified group presented higher in-stent ABR (7.4% vs. 0%, $P = 0.08$) and ID-TLR (7.8% vs. 1.5%, $P = 0.03$), resulting in numerically higher MACE (10.9% vs. 4.4%, $P = 0.12$). At 3 years, ID-TLR tended to be higher in the calcified group than in the noncalcified group (8.6% vs. 2.4%, $P = 0.11$), resulting in numerically higher MACE (12.1% vs. 4.7%, $P = 0.12$). Conclusions: The MACE rates in patients treated with EES for calcified lesions were higher than in those for noncalcified lesions, but remained lower than the results of previously reported stent studies. EES implantation in patients with calcified culprit lesions was safe and associated with favorable reduction of restenosis and repeat revascularization. © 2010 Wiley-Liss, Inc.

Key words: calcification; everolimus; stents; coronary artery disease; revascularization

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INTRODUCTION

Various characteristics of coronary lesion morphology affect immediate and late clinical outcomes after percutaneous coronary intervention (PCI) in patients with coronary artery disease (CAD) [1]. Among them, coronary artery wall calcium is one of the predominant risk factors and is often found in advanced lesions [2]. Consequently, the treatment of calcified coronary stenosis is challenging for interventional cardiologists and associated with a high frequency of restenosis and target lesion revascularization (TLR) [3–5]. The advent of drug-eluting stents (DES) has impacted on the practice of interventional cardiology by inhibiting neointimal hyperplasia and thereby reducing the rates of restenosis and TLR in patients with relatively simple coronary artery lesions when compared with bare metal stents (BMS) [6], leading to treatment with DES for more difficult anatomies such as totally occluded lesions, saphenous vein lesions, small reference vessel diameter (RVD), and diffuse long lesions. Even in these complex lesions, DES was associated with favorable outcomes. So far, a subanalysis of the TAXUS IV trial was the only study comparing the effectiveness of DES and BMS in patients with calcified coronary stenoses, demonstrating that the TAXUS paclitaxel-eluting stents (PES: Boston Scientific, Natick, MA) reduced the degree of late lumen loss and the incidence of restenosis and TLR in this clinical subset when compared with BMS [7].

The XIENCE V everolimus-eluting stent (EES; Abbott Vascular, Santa Clara, CA) has been designed to release the drug from a thin (7.8 μm), nonadhesive, durable, biocompatible fluorinated copolymer coated onto a low-profile (0.0032-in [0.0813-mm] strut thickness), flexible cobalt–chromium stent. Preclinical studies have shown more rapid endothelialization with this stent compared to sirolimus-eluting and PES [8]. Following favorable results with this device in the SPIRIT FIRST randomized study [9], the SPIRIT II study in Europe, India, and New Zealand [10] and the SPIRIT III study [11] in the United States were performed to evaluate the EES in comparison with a widely used PES (TAXUS EXPRESS2 or TAXUS LIBERTE; Boston Scientific, Natick, MA) in patients with CAD. The SPIRIT II and SPIRIT III trials revealed that EES was superior to PES in terms of late luminal loss, which implied that EES more efficiently suppressed neointimal hyperplasia than PES [8]. Therefore, EES implantation in calcified culprit lesions has the potential to achieve good outcomes. The aim of this analysis was to assess and compare the safety and efficacy of EES in patients with calcified or noncalcified coronary culprit lesions.

MATERIALS AND METHODS

Study Population

The SPIRIT II trial was a prospective, controlled, randomized (3:1), single-blinded, parallel two-arm, and multicenter clinical evaluation of EES versus PES in the treatment of patients with CAD. It was approved by the ethics committee at each participating institution, and all patients gave written informed consent. The design and methods of the SPIRIT II trial have been previously reported along with 6-month outcomes [8]. In brief, angiographic eligibility for inclusion required a maximum of two de novo native coronary artery lesions, which had to be located in different major epicardial vessels, with a RVD between 2.5 and 4.25 mm by visual estimation, a lesion length $\leq$28 mm, a visually estimated stenosis between 50 and 99% of the luminal diameter and a thrombosis in myocardial infarction (MI) flow grade of 1 or more. Patients having target lesions with an aorto-ostial or left main location, heavy calcification, or a visible thrombus within the target vessel were excluded from the trial. In addition, patients were not eligible for enrollment if they had a known diagnosis of acute MI 3 days prior to the baseline procedure, a left ventricular ejection fraction $<$30%, were awaiting a heart transplant, or had a known hypersensitivity or contraindication to drugs or materials, which could be used in the trial.

Stent Description

The EES has been previously described in detail [8]. The EES is composed of the MULTI-LINK VISION stent (Abbott Vascular), which is a balloon expandable stent made of medical grade L-605 cobalt chromium alloy, coated with a durable polymer-containing everolimus.

Procedures and Postinterventional Medication

All procedures were performed electively. Target lesions were treated using standard interventional techniques with mandatory predilatation and stent implantation at a pressure not exceeding the burst pressure rate and could be covered with a single stent or two overlapping stents. Postdilatation with a balloon shorter than the implanted stent was allowed at physician discretion if an optimal angiographic result was not obtained. Bailout stenting for edge dissection was permitted. Either unfractionated heparin or bivalirudin could be used for procedural anticoagulation according to local practice. The administration of glycoprotein IIb/IIIa inhibitors was left to the discretion of the physicians. Treatment aspirin was started at least 24 hr before the procedure and continued for at least 1 year.

A loading dose of 300 mg of clopidogrel was administered before the procedure, followed by 75 mg daily for a minimum of 6 months.

Clinical device success was defined as a successful delivery and deployment of the first inserted study stent (in an overlapping stent setting, a successful delivery and deployment of the first and second study stent) at the intended target lesions with attainment of final residual stenosis of less than 50% of the target lesion by quantitative coronary angiography (QCA). Bailout patients were included as clinical device success only if the above criteria for clinical device success were met. Clinical procedure success included the definition of clinical device success, but with the use of any adjunctive device and the absence of ischemia-driven major adverse cardiac events (MACE) during the hospital stay. In dual lesion setting, both lesions had to meet clinical procedure success.

Angiographic Analysis

QCA assessment of all baseline and follow-up angiograms was performed at an independent angiographic core laboratory (Cardialysis BV, Rotterdam, The Netherlands) using the CAAS II analysis system (Pie Medical BV, Maastricht, The Netherlands). Quantitative measures, including RVD, minimal luminal diameter (MLD), diameter stenosis (DS), were performed within the stent (in-stent analysis), within 5-mm proximal and distal to the stent edge and over the entire segment (in-segment analysis). Acute gain was defined as the difference between MLD after PCI minus MLD before PCI. Late loss was defined as the difference between MLD after PCI minus MLD at follow-up. Angiographic binary restenosis (ABR) was defined in every segment as DS $\geq$ 50% at follow-up.

A calcified coronary culprit lesion was defined as "readily apparent densities noted within the apparent vascular wall at the site of the stenosis." By qualitative assessment of the angiograms at the core laboratory, target lesions were classified as severe ("radioopacities noted without cardiac motion prior to contrast injection generally involving both sides of the arterial wall"), moderate ("densities noted only during the cardiac cycle prior to contrast injection"), or none/mild (lesions other than severe and moderate calcified lesions). The reliability of the qualitative categorization of coronary calcium on coronary angiography has been previously established [9].

Follow-Up and Definition

The principal clinical end points for the SPIRIT II trial have been previously defined and reported [10]. Enrolled patients were followed to assess the incidence of MACE, including cardiac death, MI, and ischemia-driven target lesion revascularization (ID-TLR) either by PCI or coronary artery bypass surgery. ID-TLR was defined as revascularization at the target lesion associated with any of the following: noninvasive positive functional ischemic study (e.g., exercise testing or equivalent tests) or invasive positive functional ischemia study (e.g., fractional flow reserve or coronary flow reserve); ischemic symptoms and an angiographic DS $\geq$ 50% by on-line QCA; DS $\geq$ 70% by on-line QCA without either ischemic symptoms or a positive functional study. MACE and stent thrombosis events were adjudicated by an independent Clinical Events Committee and a Data Safety Monitoring Board oversaw the safety of the trial. Definite or probable stent thrombosis was also adjudicated in a post hoc analysis using the Academic Research Consortium definitions [12].

Clinical follow-up was scheduled at 30, 180, and 270 days and yearly thereafter for 5 years. Angiographic follow-up for all patients was performed at 180 days and at 2 years for a subset of patients. The 6 months, 2, and 3 years follow-up formed the basis of the present analysis.

Data Management and Statistical Analysis

In this analysis, we focused on patients treated with EES alone. The study population was divided into two groups: On a patient level, those with at least one target lesion moderately or severely calcified (the calcified group) and those with all lesions having mild or no calcification (the noncalcified group). On a per-lesion basis, moderately or severely calcified lesions were compared to non- or mildly calcified lesions. Categorical variables were compared using Fisher's exact test. Continuous variables were presented as means $\pm$ SD and compared using the Wilcoxon two-sample test. The time to event estimates were evaluated using Kaplan–Meier methods and compared by the log rank test. A value of $P < 0.05$ was considered statistically significant. Statistical analysis was performed with SAS software 9.1.3 for Windows (SAS Institute, Cary, NC).

RESULTS

Patient and Lesion Characteristics

In the SPIRIT II trial, 220 patients were actually treated with EES alone. Eight patients were excluded, because the films of these patients were not assessable to qualify the extent of lesion calcification due to poor-imaging quality. Finally, the study population consisted of 212 patients with 247 lesions. At least one moderate

TABLE I. Baseline Patient Demographic and Clinical Characteristics of the Calcified and the Noncalcified Groups

	Calcified group	Noncalcified group	*P* value
Number of patients (*n*)	68	144	
Age in years (mean ± SD)	63.6 ± 10.0	61.3 ± 10.4	0.13
Male (%)	75.0	70.1	0.52
Diabetes mellitus (%)	19.1	22.2	0.72
Insulin used (%)	4.4	4.9	1.0
Oral drug used (%)	13.2	13.9	1.0
Hypertension requiring medication (%)	67.6	66.0	0.88
Hypercholesterolemia requiring medication (%)	72.3	66.7	0.52
Previous myocardial infarction (%)	34.8	34.0	1.0
Current smoking (%)	38.1	28.1	0.19
Clinical presentation			
Stable angina (%)	67.6	59.0	0.29
Unstable angina (%)	25.0	28.5	0.63

or severe lesion calcification was present in 68 patients with 75 calcified lesions (30.4%), including 71 moderately calcified (28.7%) and 4 severely calcified lesions (1.6%). These 68 patients were classified as the calcified group. The remaining 144 patients were classified as the noncalcified group. At the lesion level, noncalcified lesions from all patients were merged in the noncalcified group (172 lesions). Baseline clinical characteristics were not significantly different between both groups (Table I).

The Baseline lesion characteristics are shown in Table II. The calcified group had numerically more left anterior descending lesions than the noncalcified group (49.3% vs. 36.6%, $P = 0.07$) and significantly less left circumflex artery lesions than in the noncalcified group (17.3% vs. 34.9%, $P = 0.006$). Lesion complexity was greater in the calcified group than in the noncalcified group according to ACC/AHA lesion type classification (Type B2/C lesion was 100% vs. 69%, $P < 0.001$). Preprocedural QCA revealed no statistically significant differences between the two groups.

Procedural Outcomes

The procedural characteristics are shown in Table II. According to the study protocol, all lesions were to be treated with predilatation. Devices for plaque modification before stent implantation, such as rotational atherectomy, were not used. Bailout stenting was performed in 6.7% of the calcified group and 5.2% of the noncalcified group ($P = 0.77$). The calcified group had a numerically higher glycoprotein IIb/IIIa inhibitor usage (11.8% vs. 6.9%, $P = 0.29$). Target lesions were treated with 1.2 EES stents on average in both groups. When compared with noncalcified lesions, calcified lesions were treated with longer stents (23.2 ± 8.8 mm vs. 22.0 ± 7.4 mm, $P = 0.28$), a relatively larger diameter of the stent (3.18 ± 0.35 mm vs. 3.10 ± 0.36 mm, $P = 0.10$) and a larger maximum stent deployment pressure (14.1 ± 2.1 vs. 13.8 ± 2.6 atmospheres, $P = 0.16$). Both groups had a high-clinical device success rate of 98.7% for the calcified group and 99.4% for the noncalcified group ($P = 0.52$). There was also a high-clinical procedure success of 100% in the calcified group and 98.6% in the noncalcified group ($P = 1.0$). QCA results at postprocedure indicated no significant difference between the two groups (Table III).

Angiographic Results at 6 Months and 2 Years

Six-month follow-up angiography was available in 70 of 75 (93%) lesions in the calcified group and in 156 of 172 (91%) in the noncalcified group (Table III). In-stent late loss was similar in both groups (0.13 ± 0.37 mm in the calcified group vs. 0.12 ± 0.25 mm, $P = 0.73$). As shown in Table III and Fig. 1, in-stent ABR was observed in three lesions (4.3%) in the calcified group, whereas no in-stent ABR was observed in the noncalcified group ($P = 0.03$). These three in-stent ABR lesions included two focal in-stent restenoses and one diffuse proliferative in-stent restenosis. Likewise, the calcified group had a higher rate of in-segment ABR than the noncalcified group; however, the difference did not reach statistical significance (7.1% vs. 1.9%, $P = 0.11$).

Two-year follow-up angiography was available in 27 of 75 (36%) lesions in the calcified group and in 66 of 172 (38%) in the noncalcified group (Table III). In-stent late loss was similar in both groups (0.40 ± 0.47 mm in the calcified group vs. 0.31 ± 0.28 mm, $P = 0.54$). As shown in Table III and Fig 1, in-stent ABR was observed in two lesions (7.4%) in the calcified group, whereas no in-stent ABR was observed in the noncalcified group ($P = 0.08$). These two in-stent

TABLE II. Baseline Lesion and Procedural Characteristics of the Calcified Group and Noncalcified Group

	Calcified group	Noncalcified group	*P* value
Number of patients (*n*)	68[a]	144[a]	
Number of lesions (*n*)	75[a]	172[a]	
Angiographic characteristics			
Degree of calcification			
None/mild (%)	0	100	<0.001
Moderate (%)	94.7	0	<0.001
Severe (%)	5.3	0	0.008
Lesion location			
Right coronary artery (%)	33.3	28.5	0.45
Left anterior descending (%)	49.3	36.6	0.07
Left circumflex artery (%)	17.3	34.9	0.006
ACC/AHA lesion type			
A (%)	0	1.2	1.0
B1 (%)	0	29.8	<0.001
B2 (%)	88.0	56.1	<0.001
C (%)	12.0	12.9	1.0
QCA measurements			
Reference vessel diameter (mm)	2.81 ± 0.63	2.65 ± 0.46	0.13
Minimal lumen diameter (mm)	1.19 ± 0.48	1.07 ± 0.30	0.10
Diameter stenosis (%)	58 ± 10	60 ± 9	0.27
Lesion length (mm)	13.3 ± 5.6	12.8 ± 5.7	0.41
Procedural characteristics			
Number of stent implanted per lesion	1.2 ± 0.5	1.2 ± 0.4	0.98
Total stent length per lesion (mm)	23.2 ± 8.8	22.0 ± 7.4	0.28
Average stent diameter per lesion (mm)	3.18 ± 0.35	3.10 ± 0.36	0.10
Balloon/artery ratio	1.19 ± 0.17	1.21 ± 0.16	0.43
Maximum stent deployment pressure (atm)	14.1 ± 2.1	13.8 ± 2.6	0.16
Post dilatation performed (%)	42.7	35.5	0.32
Bailout stenting performed (%)	6.7	5.2	0.77
Glycoprotein IIb/IIIa inhibitor use(%)	11.8	6.9	0.29
Clinical device success (per lesion) (%)	98.7	99.4	0.52
Clinical procedure success (per patient) (%)	100	98.6	1.0

Values are % or mean ± standard deviation.
ACC/AHA, American College of Cardiology/American Heart Association; QCA, quantitative coronary angiography.
[a]Total number of patients and lesions. These numbers may change throughout the table below due to missing values.

ABR lesions included two focal in-stent restenoses. Likewise, the calcified group had a higher rate of in-segment ABR than the noncalcified group; however, the difference did not reach statistical significance (11.1% vs. 3.1%, $P = 0.15$).

Clinical Outcomes up to 3 Years

The clinical outcomes up to 3 years are shown in Table IV. Within 30 days after the procedure, no adverse events occurred in the calcified group, although non-Q-wave MI was observed in two patients (1.4%) of the noncalcified group. Between 30 days and 6 months after the procedure, one patient in the noncalcified group underwent a non-ID-TLR, which was performed 175 days after PCI due to in-segment distal restenosis with no ischemic symptoms. During the same period, four patients (5.9%) in the calcified group, each of whom had moderate calcified lesion, received ID-TLR for the following reasons: one in-stent focal restenosis, one in-segment distal restenosis, one diffuse proliferative in-stent restenosis, and one stent thrombosis. The rate of all TLR, including ID- and non-ID-TLR, was significantly higher in the calcified group than in the noncalcified group (5.9% vs. 0.7%, $P = 0.04$, Table IV). The total hierarchical MACE rate at 6 months was 5.9% in the calcified group and 1.4% in the noncalcified group ($P = 0.09$).

Between 6 months and 2 years after the procedure, in the noncalcified group, one patient died unexpectedly 600 days after PCI following an hospitalization due to mucuous congestion in the trachea cannula; this event was adjudicated as a cardiac death; two additional patients developed a non-Q-wave MI (one of which was treated for ID-TLR) and one additional patient developed an ID-TLR, which was performed

TABLE III. Six-Month and 2-Year Angiographic Analysis of the Calcified Group and Noncalcified Group

	In stent			In segment		
	Calcified group	Noncalcified group	*P* value	Calcified group	Noncalcified group	*P* value
Number of lesions	75	172		75	172	
Postprocedure						
MLD (mm, mean ± SD)	2.55 ± 0.41	2.47 ± 0.39	0.17	2.18 ± 0.49	2.14 ± 0.41	0.87
DS (%, mean ± SD)	14 ± 5	13 ± 6	0.22	24 ± 10	22 ± 9	0.08
Acute gain (mm, mean ± SD)	1.37 ± 0.38	1.40 ± 0.38	0.88	NA	NA	
6-month follow-up						
Number of lesions	70	156		70	156	
MLD (mm, mean ± SD)	2.42 ± 0.62	2.36 ± 0.46	0.22	2.15 ± 0.65	2.09 ± 0.45	0.37
DS (%, mean ± SD)	18± 14	15 ± 7	0.18	26 ± 15	22 ± 9	0.40
Late loss (mm, mean ± SD)	0.13 ± 0.37	0.12 ± 0.25	0.73	0.04 ± 0.37	0.08 ± 0.31	0.15
ABR (%)	4.3	0	0.03	7.1	1.9	0.11
2-year follow-up						
Number of lesions	27	66		27	65	
MLD (mm, mean ± SD)	2.06 ± 0.57	2.22 ± 0.42	0.28	1.82 ± 0.58	2.03 ± 0.41	0.10
DS (%, mean ± SD)	22 ± 21	18 ± 10	0.80	31 ± 19	25 ± 11	0.20
Late loss (mm, mean ± SD)	0.40 ± 0.47	0.31 ± 0.28	0.54	0.23 ±0.49	0.20 ± 0.30	0.80
ABR (%)	7.4	0	0.08	11.1	3.1	0.15

ABR, angiographic binary restenosis; DS, diameter stenosis; MLD, minimal luminal diameter; NA, not applicable; RVD, reference vessel diameter.

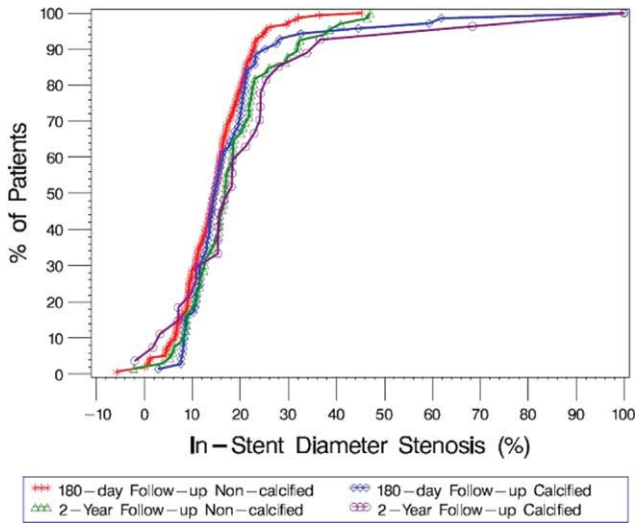

Fig. 1. Cumulative frequency of in-stent diameter stenosis at 6 months and 2 years. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

488 days after PCI due to ischemia. During the same period, in the calcified group, two patients developed a non-Q-wave MI and one additional patient developed an ID-TLR, which was performed 701 days after PCI due to acute coronary syndrome. The rate of all TLR, including ID- and non-ID-TLR, was significantly higher in the calcified group than in the noncalcified group (9.0% vs. 2.1%, $P = 0.03$, Table IV). The total hierarchical MACE rate at 2 years was 10.9% in the calcified group and 4.4% in the noncalcified group ($P = 0.12$).

At 3 years, higher hierarchical ID-TLR were maintained in the calcified group when compared with the noncalcified group (6.9% vs. 0.8%, $P = 0.03$), resulting in numerically higher MACE (12.1% vs. 4.7%, $P = 0.12$).

There were no occurrences of acute (≤1 day), subacute (>1 day and ≤30 days), or late (>30 days and ≤1 year) definite/probable stent thrombosis in the entire population. Two patients with very late (>1 year) definite/probable stent thrombosis were identified in the noncalcified group, which occurred 521 and 721 days, respectively, after PCI.

DISCUSSION

The principal findings of this study are the following: (1) angiographically, the calcified lesion was associated with a similar late loss at 2 years with noncalcified lesion (0.40 mm vs. 0.31 mm, $P = 0.54$), but was associated with a trend of higher in-stent binary restenosis rate (7.4% vs. 0%, $P = 0.08$); (2) at 3 years, MACE rate was nonsignificantly, but nearly three times higher in patients treated calcified lesions than in those for noncalcified culprit lesions (12.1% vs. 4.7%, $P = 0.12$), which was mainly driven by higher ID-TLR-PCI (6.9% vs. 0.8%, $P = 0.03$).

Many imaging modalities have been used to detect calcification at the site of a target lesion. Fluoroscopy can assess the presence or absence of culprit lesion calcium although it has limited sensitivity for the detection of small amounts of calcium [10]. However, the reliability in qualitative categorization of coronary calcium using fluoroscopy has been established [9]. Therefore, in this study, we classified the enrolled patients into the calcified (moderate or severe calcification) and noncalcified (none/mild calcification) groups

TABLE IV. Clinical End Points and Stent Thrombosis at 30 Days, 6 Months, 2, and 3 Years after the Procedure

	30 days			6 months			2 years			3 years		
	Calcified group ($n = 68$ patients)	Noncalcified group ($n = 144$ patients)	P value	Calcified group ($n = 68$ patients)	Noncalcified group ($n = 143$ patients)	P value	Calcified group ($n = 64$ patients)	Noncalcified group ($n = 137$ patients)	P value	Calcified group ($n = 58$ patients)	Noncalcified group ($n = 127$ patients)	P value
Hierarchical events												
Cardiac death (%)	0	0	NA	0	0	NA	0	0.7	1.0	0	0.8	1.0
MI (%)												
Q-wave (%)	0	0	NA	0	0	NA	0	0	NA	0	0	NA
Non-Q wave (%)	0	1.4	1.0	0	1.4	1.0	3.1	2.9	1.0	5.2	3.1	0.68
Revascularization (%)												
ID-TLR-CABG (%)	0	0	NA	0	0	NA	0	0	NA	0	0	NA
ID-TLR-PCI (%)	0	0	NA	5.9	0	0.01	7.8	0.7	0.01	6.9	0.8	0.03
MACE (%)	0	1.4	1.0	5.9	1.4	0.09	10.9	4.4	0.12	12.1	4.7	0.12
Nonhierarchical events												
All TLR (%)	0	0	NA	5.9	0.7	0.04	9.0[a]	2.1[b]	0.03	9.8[c]	3.0[d]	0.08
ID-TLR (%)	0	0	NA	5.9	0	0.01	7.8	1.5	0.03	8.6	2.4	0.11
Non-ID-TLR (%)	0	0	NA	0	0.7	1.0	1.5[a]	0.7[b]	0.54	1.6[c]	0.8[d]	0.53
ARC stent thrombosis, Definite + probable (%)	0	0	NA	0	0	NA	0	1.5	1.0	0	1.6	1.0
Acute (<1 day) (%)	0	0	NA	0	0	NA	0	0	NA	0	0	NA
Subacute (1–30 days) (%)	0	0	NA	0	0	NA	0	0	NA	0	0	NA
Late (>30 days–1 year) (%)	–	–	–	0	0	NA	0	0	NA	0	0	NA
Very late (>1 year) (%)	–	–	–	–	–	–	0	1.5	1.0	0	1.6	1.0

CABG, coronary artery bypass grafting; ID-TLR, ischemic-driven target lesion revascularization; MI, myocardial infarction; NA, not applicable; PCI, percutaneous coronary intervention.

[a] $n = 67$ patients.

[b] $n = 141$ patients.

[c] $n = 61$ patients.

[d] $n = 132$ patients.

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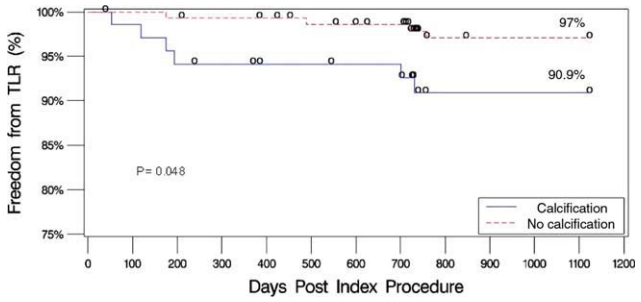

Fig. 2. Freedom from all TLR (including ID- and non-ID-TLR) during 3-year follow-up after EES implantation. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

according to angiographic assessments by a core laboratory.

The geometry and rigidity of calcified culprit lesions often prevent optimal device delivery, deployment, and conformability. Consequently, the treatment of this lesion subset with PCI is associated with a high frequency of acute complications and a low-success rate. This study showed high-clinical device success (98.7%), excellent clinical procedural success (100%), and the absence of MACE during the acute phase (up to 30 days after stent implantation) in the calcified group.

In terms of risk of thrombotic complications, no patient in the calcified group suffered from stent thrombosis up to 3 years after PCI, whilst two thrombotic complications occurred in the noncalcified group. Although large population studies with long-term follow-up are mandatory, EES implantation for calcified culprit lesions appears to be safe up to 3 years.

This study also demonstrated that the rates of in-stent ABR (4.3%) and ID-TLR (5.9%) at 6 months for calcified culprit lesions are remarkably lower than that in previous BMS studies, in which these rates ranged from 12 to 23% and from 18 to 23%, respectively [3,4,7], suggesting that EES implantation is more effective for calcified culprit lesions than BMS implantation.

The rates of in-stent ABR and ID-TLR at 6 months and 2 years follow-up in this study were numerically higher in the calcified group. However, other DES trials have shown that the efficacy of DES was similar in patients with and without calcified culprit lesions [7]. A subanalysis of the TAXUS IV trial, in which enrolled patients ($n = 1310$) were divided into calcified and noncalcified groups employing to the same definition as this study, revealed that the rates of ABR and ID-TLR at 9 months follow-up after PES implantation were comparable in both groups (ABR rate is 7.5% in the calcified group and 8.0% in the noncalcified group, and ID-TLR rate is 5.1% in the calcified group and 4.3% in the noncalcified group). The variance in the results may be related to the different characteristics between PES and EES. In terms of stent design, the strut thickness of the EES (0.081 mm) is remarkably thinner than that of the PES (0.132 mm). Thin-strut stents cause less arterial injury at both the deployment site and its surrounding tissues than thick-strut stents and thus reduce the growth of neointimal hyperplasia [11]. The drug release kinetic and mechanisms of each DES also differ. As the plaque composition would affect the activity and diffusion of antiproliferative agents, each drug distribution or penetration into the calcified vessel wall may be different. These may also account for the observed difference in both trials. Randomized head-to-head (EES vs. PES) trials with large sample size are mandatory to identify which DES is more effective than the other in this particular lesion subset.

The results of angiographic follow up in EES patients at 2 years demonstrated a sizeable increase in the mean in-stent late loss amongst EES between 6 months and 2 years both in the calcified group (0.13 ± 0.37 mm vs. 0.40 ± 0.47 mm, $\Delta 0.27$ mm) and in the noncalcified group 0.12 ± 0.25 mm vs. 0.31 ± 0.28 mm, $\Delta 0.19$ mm). On the other hand, there is a certain increase in TLR rate between 6 months and 2 years in the calcified group (6M 5.9% vs. 2Y 9.0%, $\Delta 3.1\%$) but only a small increase in the noncalcified group (0.7% vs. 2.1%, $\Delta 1.4\%$). This might suggest that in the calcified lesion, a late decrease in MLD might be associated with a late increase in TLR. This phenomenon should be further investigated in a larger population with calcified lesions.

Limitations

This study had several limitations. First, we performed a post hoc analysis of the patient population that was not prespecified for this analysis. Second, the study population and the event rates are small, and thus this study has no power to allow a robust statistical analysis of potential differences in the effectiveness of EES for calcified and noncalcified lesions, even if some significant differences were identified. Third, our results should not be extrapolated to patients with severely calcified coronary lesions, because patients with severe calcification were supposed to be excluded from enrollment in the SPIRIT II trial according to the protocol, and thus the prevalence of severely calcified lesions was very low (1.6%) in our study population. Last, no preinterventional IVUS was performed to assess the location and severity of the calcification, although plaque composition of target lesions affects both angiographic and clinical outcomes after PCI with stents. Although larger randomized population trials

with longer follow-up period (more than 1 year) are warranted, our observations have provided a unique insight into the potential effectiveness of EES for calcified stenoses, considering that little is known so far about the impact of treatment with DES on calcified coronary lesions.

CONCLUSIONS

The MACE rates in patients treated with EES for calcified lesions tend to be higher than in those for noncalcified lesions driven by higher ID-TLR rates in calcified lesions. A relatively high-late loss and TLR rates between 6 months and 2 years in the calcified lesion group warrants further investigation.

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