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ORIGINAL RESEARCH

Impact of Coronary Calcification on Clinical Outcomes After Implantation of Newer-Generation Drug-Eluting Stents

Rayyan Hemetsberger, MD; Mohammad Abdelghani, MD, PhD; Ralph Toelg, MD; Nader Mankerious, MD; Abdelhakim Allali, MD; Hector M. Garcia-Garcia, MD, PhD; Stephan Windecker, MD; Thierry Lefèvre, MD; Shigeru Saito, MD; Ton Slagboom, MD; David Kandzari, MD; Jacques Koolen, MD; Ron Waksman, MD; Gert Richardt, MD

BACKGROUND: Percutaneous coronary intervention of calcified lesions was associated with worse outcomes in the era of bare-metal and first-generation drug-eluting stents. Data on percutaneous coronary intervention of calcified lesions with newer-generation drug-eluting stents are scarce. Therefore, we investigated the impact of lesion calcification on clinical outcomes in patients undergoing percutaneous coronary intervention with a bioresorbable-polymer sirolimus-eluting stent or a durable-polymer everolimus-eluting stent.

METHODS AND RESULTS: Patients (n=2361) from BIOFLOW II, IV, and V trials were categorized into moderate/severe versus none/mild lesion calcification by a core laboratory. End points were target-lesion failure (TLF) (cardiac death, target-vessel myocardial infarction, or target-lesion revascularization) and probable/definite stent thrombosis at 2 years. The agreement in calcification assessment between the operator and the core laboratory was weak (weighted κ, 0.23). Patients with moderate/severe calcification (n=303; 16%) had higher TLF (13.5% versus 8.4%; *P*=0.003) and stent thrombosis rates (2.1% versus 0.2%; *P*<0.0001), whereas target-lesion revascularization was not different between the groups (5.0% versus 3.9%; *P*=0.302). After adjustment, calcification did not emerge as an independent predictor of TLF (adjusted hazard ratio [aHR], 1.37; 95% CI, 0.89–2.08; *P*=0.148) but did for target-vessel myocardial infarction (aHR, 1.66; 95% CI, 1.03–2.68; *P*=0.037). TLF rates were similar between bioresorbable-polymer sirolimus-eluting stent and durable-polymer everolimus-eluting stent (12.6% versus 15.4%, *P*=0.482) in moderate/severe calcification. In none/mild calcification, the bioresorbable-polymer sirolimus-eluting stent showed lower TLF (7.5% versus 10.3%, *P*=0.045).

CONCLUSIONS: With newer-generation drug-eluting stents, moderate/severe lesion calcification was not associated with more TLF after adjustment for the higher risk of patients with coronary calcification, whereas the rate of target-vessel myocardial infarction was higher. The bioresorbable-polymer sirolimus-eluting stent and durable-polymer everolimus-eluting stent were equally effective and safe in calcified lesions.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifiers: NCT01356888, NCT01939249, NCT02389946.

Key Words: BIOFLOW ■ calcified coronary lesion ■ newer-generation drug eluting stent ■ Orsiro ■ Xience

Percutaneous coronary intervention (PCI) in calcified coronary artery lesions is associated with impaired stent delivery, suboptimal stent expansion, increased periprocedural complications, and unfavorable long-term clinical outcomes.[1–3] Coronary calcification per se indicates higher morbidity of the patients with more advanced coronary artery disease.[2] Calcified coronary lesions are often longer and more

Correspondence to: Rayyan Hemetsberger, MD, Heart Center Bad Segeberg, Segeberger Kliniken GmbH, Am Kurpark 1, 23795 Bad Segeberg, Germany. E-mail: rayyan.hemetsberger@hotmail.com

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CLINICAL PERSPECTIVE

What Is New?

- With newer-generation drug-eluting stents, moderate/severe lesion calcification was not associated with a higher rate of target-lesion revascularization or target-lesion failure but with more stent thrombosis and target-vessel myocardial infarction at 2 years.
- Bioresorbable polymer sirolimus-eluting stents and durable polymer everolimus-eluting stents were equally effective and safe in calcified lesions.

What Are the Clinical Implications?

- Our findings suggest a smaller role of the stent platform and a possibly bigger role of antithrombotic management to improve the outcomes of these lesions, which should be evaluated in a well-powered randomized trial comparing different newer-generation drug-eluting stent platforms in moderate/severe calcified lesions after adequate lesion preparation.

Nonstandard Abbreviations and Acronyms

BP-SES	bioresorbable-polymer sirolimus-eluting stent
DES	drug-eluting stent
DP-EES	durable-polymer everolimus-eluting stent
ST	stent thrombosis
TLF	target-lesion failure
TLR	target-lesion revascularization
TV-MI	target-vessel myocardial infarction

tortuous than noncalcified lesions, and patients have more often triple-vessel disease.[2] With an increasing extent of coronary calcification, the likelihood of multivessel disease is higher.[2] In the setting of PCI of heavily calcified lesions, the stent polymer and drug coating may be damaged, which could result in subsequent stent failure such as thrombosis or restenosis.[1,2]

With first generation drug-eluting stents (DESs) the incidence of target-lesion revascularization (TLR) after PCI was higher in calcified lesions.[4] Similarly, after PCI with newer-generation permanent polymer-coated DESs, target-vessel failure was higher in calcified lesions, driven by higher rates of cardiac death and target-vessel–related myocardial infarction.[5] Notably, implantation of a newer generation, ultra-thin-strut bioresorbable-polymer sirolimus-eluting stent (BP-SES) after lesion preparation with modified balloons and/or rotational atherectomy resulted in low TLR rates at 9 months in one trial.[6]

In the randomized BIOFLOW II,[7] IV,[8] and V[9] trials, 2 newer-generation DESs were compared. The ultra-thin-strut BP-SES had a lower target-lesion failure (TLF) rate as compared with a thin-strut durable-polymer everolimus-eluting stent (DP-EES).

In this patient-level analysis of pooled data from the randomized BIOFLOW II, IV, and V trials, we sought to investigate the impact of coronary calcification on TLF after PCI with newer-generation DESs and whether a newer-generation, ultra-thin-strut BP-SES can improve the outcome as compared with a DP-EES. Furthermore, though most stent trials exclude calcification, ≈20% of included patients have severe calcification after core-laboratory assessment.[2] Thus, we evaluated the agreement between the operators with the core laboratory in assessment of lesion calcification severity.

METHODS

Study Population and Design

Patient-level data were pooled from the BIOFLOW II, IV, and V trials. The study designs have been published previously and are available on ClinicalTrials.gov (Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifiers: NCT01356888, NCT01939249, NCT02389946). Briefly, the trials were prospective, 2:1 randomized, multicenter comparing a BP-SES (Orsiro; Biotronik, Bülach, Switzerland) and a DP-EES (Xience; Abbott, Santa Clara, CA) in de novo native coronary artery lesions. Patient inclusion and exclusion criteria varied slightly among the trials and are summarized in Table S1.

The trials complied with the provisions of the Declaration of Helsinki and were approved by the institutional review board or ethics committee at each enrolling site. Eligible patients signed written informed consent. An independent clinical events committee adjudicated all clinical end points. An independent core laboratory (MedStar Cardiovascular Research Network, Angiographic Core Laboratory, Washington, DC) analyzed all angiographic data. The trials were funded by Biotronik. The authors (R.H., R.T., G.R.) had unrestricted access to the data and are responsible for the analyses and drafting of the article. The data that support the findings of this study are available from the corresponding author upon reasonable request after obtaining the approval of the study sponsor.

For the current analysis, we included patients with core laboratory–assessed coronary lesion calcification. Patients with >1 lesion with different degrees of coronary calcifications (mixed lesion calcifications) were excluded

from the analysis. Lesion calcification was assessed angiographically and classified according to a modified scheme of the American College of Cardiology and American Heart Association[10] into: none or mild, moderate (visible on moving images during the heart cycle without contrast injection generally involving only 1 side of the arterial wall), and severe calcification (visible on still frame before contrast injection generally involving both sides of the arterial wall).

Study End Points

The main end points were TLF at 2 years; a composite of cardiac death, target-vessel myocardial infarction (TV-MI), or ischemia-driven TLR; and definite or probable stent thrombosis (ST) according to the Academic Research Consortium criteria.[11]

Periprocedural myocardial infarction was defined according to the modified Academic Research Consortium criteria as a troponin or creatine kinase myocardial band measured within 48 hours of the interventional procedure elevated >3 times above the upper limit of normal. Spontaneous myocardial infarction was defined as any troponin or creatine kinase myocardial band elevation above the upper limit of normal with associated ischemic symptoms, new electrocardiographic abnormalities suggestive of ischemia, or new development of imaging evidence of infarction. Ischemia-driven revascularization was defined as any repeat revascularization of the target lesion or vessel because of either ischemic symptoms or abnormal coronary physiologic study and ≥50% coronary stenosis by quantitative angiography, or any revascularization of a ≥70% diameter stenosis. Cardiac death was any death attributable to any proximate cardiac cause, unwitnessed death, or death of unknown cause. All clinical outcomes are reported on a patient-level.

Operator–Core Laboratory Agreement on Calcification Severity

The agreement between operator and core-laboratory assessment of lesion calcification grade was evaluated. For this purpose, only patients with a single lesion were included in this analysis. Calcification was classified in none/mild, moderate, and severe. The frequency of the operator assessment relative to each calcification class as assessed by the core laboratory was calculated.

Statistical Analysis

Patient-level data were combined as a single data set. Baseline, lesion, and procedural characteristics were summarized as mean±SD or as medians with lower and upper quartile for continuous variables, and as frequencies and percentages for categorical variables. Continuous variables were compared using 2-sided *t* test or the nonparametric Wilcoxon rank sum test, and categorical variables were compared using the χ^2 test. The clinical end points were compared using Kaplan-Meier time-to-event estimates and Cox regression. For selection of predictors of TLF and TV-MI, a Cox regression analysis was performed using a *P* value of <0.05 as an entry criterion. The following variables were included: calcification, age, sex, hyperlipidemia, prior PCI/coronary artery bypass graft, multivessel treatment, type B2/C lesion, predilatation, and postdilatation. Additionally, the stent (DP-EES versus BP-SES) was forced into the analysis. To avoid multicollinearity, the components of type B2/C lesion were not included in the model. The degree of agreement between the interventionalist and core-laboratory assessment of coronary calcification (none/mild, moderate, severe) was assessed using the weighted κ statistics[12] in patients with single lesions only. According to Landris and Koch,[13] the strength of agreement for κ values <0 was considered "none," for 0 to 0.2 "slight," for 0.21 to 0.4 "fair," for 0.41 to 0.6 "moderate," for 0.61 to 0.8 "substantial," and for 0.81 to 1.0 "almost perfect."

All analysis were performed using SAS version 9.4 (SAS Institute, Cary, NC). A *P*<0.05 was considered to indicate statistical significance.

RESULTS

The study flowchart is illustrated in Figure S1. Out of 2361 patients, 76 (3%) had mixed lesion calcifications and were excluded from the current analysis. Three hundred forty patients did not have a complete 2-years of follow-up and were also excluded. Of the remaining patients, 303 (16%) had moderate/severe calcification, 1642 (84%) had none/mild calcification. Patients with moderate/severe calcification were older; more often women; more often had hypercholesterolemia, prior PCI, or coronary artery bypass graft surgery; and were less often smokers as compared with patients with none/mild calcification (Table 1). Clinical presentation did not differ between the groups. However, patients with more calcification more often underwent multivessel treatment. Calcified lesions were more frequently type B2/C, required more pre- and postdilatations, and resulted in a higher residual stenosis (8.9% versus 6.9%, *P*<0.0001) (Table 2).

Clinical outcomes at 2 years are presented in Figure 1. TLF at 2 years occurred in 13.5% of patients with moderate/severe calcification and in 8.4% of patients with none/mild calcification (log rank *P*=0.003). The difference was driven by TV-MI (11.2% versus 4.8%, log rank *P*<0.0001). TLR did not differ between the 2 groups (5.0% versus

Table 1. Clinical Characteristics at Baseline

	Moderate or Severe Calcification, n=303 Patients	None or Mild Calcification, n=1642 Patients	*P* Value
Age, y	65.9±9.2	63.9±10.2	0.0019
BMI	24.2±13.4	26.1±10.5	0.0741
Women	29.4 (89/303)	23.9 (392/1642)	0.0415
Hypertension	80.9 (245/303)	76.8 (1247/1623)	0.1237
Hyperlipidemia	80.5 (244/303)	73.4 (1202/1637)	0.0092
Diabetes mellitus	32.8 (99/302)	31.8 (522/1641)	0.7393
Smoking status			0.0735
Current smoker	19.8 (60/303)	24.9 (408/1641)	
Former smoker	35.3 (107/303)	36.4 (597/1641)	
Never smoked	44.9 (136/303)	38.8 (636/1641)	
Prior myocardial infarction	27.6 (82/297)	27.9 (456/1633)	0.9114
Prior PCI/CABG	46.4 (140/302)	39.7 (648/1633)	0.0301
Prior stroke or TIA	4.6 (14/302)	6.9 (113/1641)	0.1459
Renal disease	5.6 (17/303)	8.0 (132/1641)	0.1435
Cancer	9.9 (30/303)	8.1 (133/1640)	0.3015
Clinical presentation			0.7125
Stable angina	54.1 (164/303)	54.2 (889/1641)	
Documented silent ischemia	13.9 (42/303)	16.3 (267/1641)	
Acute coronary syndrome*	32.0 (97/303)	29.6 (485/1641)	0.3907

Data are mean±SD or percent (n/N). BMI indicates body mass index; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; and TIA, transient ischemic attack.

* Non–ST-segment–elevation myocardial infarction and unstable angina.

3.9%, *P*=0.304). Cardiac death was 2.0% in moderate/severe calcification and 0.7% in none/mild calcification (log rank *P*=0.077). Definite or probable stent thrombosis occurred in 8 cases (2.1%) in moderate/severe calcification and in 4 cases (0.2%) in none/mild calcification (log rank *P*<0.0001) (Figure 2, Table S2).

After accounting for confounders (on multivariable Cox regression analysis) calcification was a significant predictor of TV-MI (adjusted hazard ratio [aHR], 1.66 [95% CI, 1.03–2.68]; *P*=0.037) but did not emerge as an independent predictor of TLF (aHR, 1.37 [95% CI, 0.89–2.08]; *P*=0.148) (Table 3).

No significant difference in TLF was observed between the BP-SES and DP-EES in moderate/severe calcification (TLF: 15.4% versus 12.6%, log rank *P*=0.482; for BP-SES versus DP-EES, respectively). On the other hand, in none/mild calcification, BP-SES showed a lower rate of TLF at 2 years as compared with DP-EES (TLF: 10.3% versus 7.5%, *P*=0.045, respectively) Figure 3. However, there was no interaction between the stent platform and the calcification degree (*P* for interaction=0.756). The rate of ST was numerically different between BP-SES and DP-EES in moderate/severe calcification (3.0% versus 2.0% for BP-SES versus DP-EES, respectively, log-rank *P*=0.572) and in none/mild calcification (0.1% versus 0.6% for BP-SES versus DP-EES, respectively, log-rank *P*=0.072). The crude rate of ST is presented in Table S2.

Operator–Core Laboratory Agreement on Calcification Severity

Patients with a single culprit lesion (n=1889) were included in this analysis. Core-laboratory adjudication was conducted by a team of trained observers who followed a predefined analysis protocol aimed at minimizing interobserver variability. To further secure a precise and reproducible analysis, inter- and intraobserver variability was tested in a random sample of 50 cases. This analysis showed a 94% interobserver agreement (k statistic, 0.72), and a 96% intraobserver agreement (k statistic, 0.92).

The strength of agreement on lesion calcification severity between the operator and the core laboratory was weak (weighted κ, 0.23 [95% CI, 0.18–0.28]; *P*<0.0001) (Table 4). Severe and moderate calcification were frequently underestimated by the operator. Severe calcification was estimated by the operator as moderate calcification in 34.3% of the cases and as none/mild calcification in 44.8% of the cases. Moderate calcification was assessed by the operator as none/mild in 71.0% of the cases. The operator–core laboratory agreement was 20.9% in

Table 2. Lesion Characteristics and Procedural Parameters (Core Laboratory)

	Moderate or Severe Calcification, n=337 Lesions	None or Mild Calcification, n=1915 Lesions	*P* Value
Multivessel treatment*	16.6 (50/302)	10.2 (167/1641)	0.0012
Complex lesion (B2/C)	90.5 (305/337)	46.3 (877/1896)	<0.0001
Bifurcation lesion	10.7 (36/337)	10.1 (193/1915)	0.7351
Thrombus	2.1 (7/337)	0.8 (16/1915)	0.0366
Vessel tortuosity			<0.0001
None	41.2 (139/337)	70.6 (1352/1915)	
Moderate	38.6 (130/337)	16.3 (313/1915)	
Severe	20.2 (68/337)	13.1 (250/1915)	
Calcification			<0.0001
None/mild	…	100 (1915/1915)	
Moderate	76.0 (256/337)	…	
Severe	24.0 (81/337)	…	
Lesion length, mm	14.94±9.22	13.09±6.49	0.0212
Long lesion, >20 mm	24.6 (83/337)	14.3 (272/1903)	<0.0001
RVD, mm	2.69±0.55	2.68±0.52	0.9530
RVD ≤2.75 mm	56.1 (189/337)	58.5 (1120/1915)	0.4097
Procedural characteristics			
Stent			0.3385
BP-SES	63.8 (215/337)	66.5 (1273/1915)	
DP-EES	36.2 (122/337)	33.5 (642/1915)	
Maximum stent implantation pressure, atm	14.23±2.91	14.00±3.04	0.2311
Stent length, mm	22.46±7.44	20.35±6.85	<0.0001
Overlapping stents	3.6 (12/337)	2.2 (43/1915)	0.1491
Predilatation	96.4 (324/336)	86.1 (1619/1881)	<0.0001
Postdilatation	59.1 (189/320)	47.8 (854/1786)	0.0002
Diameter stenosis at baseline	56.0 (46.7–65.5)	61.4 (51.9–71.9)	<0.0001
Diameter stenosis after procedure	8.9 (3.0–15.2)	6.9 (1.7–12.1)	<0.0001

Data are meanŁ}SD or percent (n/N). BP-SES indicates bioresorbable-polymer sirolimus-eluting stent; DP-EES, durable-polymer everolimus-eluting stent; and RVD, reference-vessel diameter.

* Patient level.

severe calcification, 26.1% in moderate calcification, and 87.6% in none/mild calcification, as defined by the core laboratory (Figure 4).

Complex type B2/C lesions (69.9% versus 49.0%, *P*<0.0001), tortuous lesions (46.3% versus 31.4%, *P*<0.0001), long lesions (18.8% versus 13.1%, *P*=0.0040), as well as the presence of thrombus (2.5% versus 0.7%, *P*=0.0034) were more common when operators disagreed with the core laboratory as when they agreed. More calcification led to more disagreement (*P*<0.0001) (Table S3).

DISCUSSION

In this patient-level pooled analysis from the randomized BIOFLOW trials investigating the impact of core laboratory–assessed lesion calcification on 2-year outcomes after PCI with newer-generation DESs, we found that:

1. Patients with moderate/severely calcified lesions had more comorbidities and more complex lesions.
2. After accounting for confounders, moderate/severe calcification was not associated with more TLF at 2 years as compared with none/mild calcification.
3. Moderate/severe calcification was associated with more ST and TV-MI, the main driver for TLF.
4. The operator–core laboratory agreement on the severity of coronary lesion calcification was weak.

This analysis addresses an important aspect in interventional cardiology, because patients become older and coronary lesion calcification increases with age.[1] The treatment of calcified lesions has become frequent. While

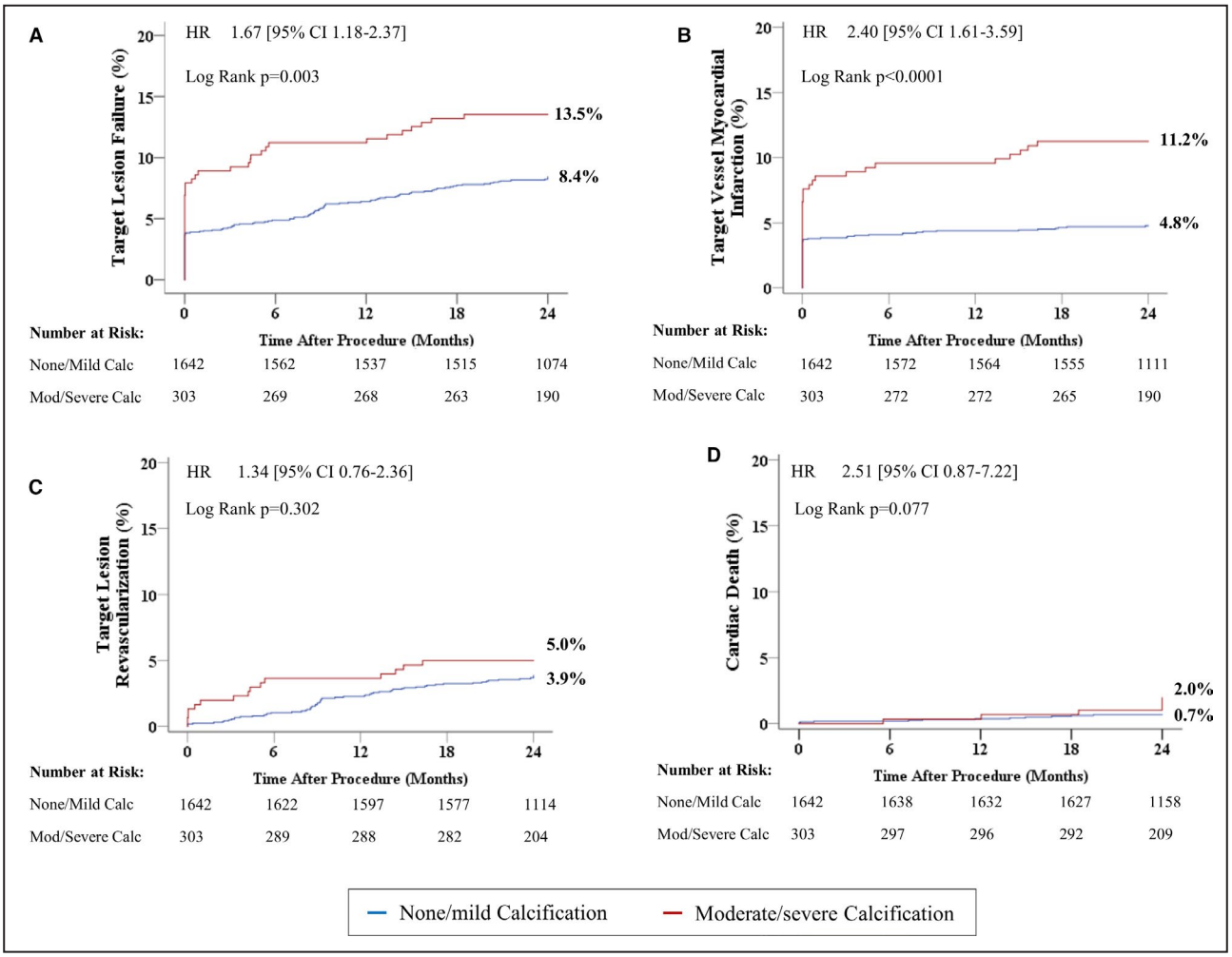

Figure 1. Kaplan-Meier curves of the clinical outcomes at 2 years for moderate (Mod)/severe calcification and none/mild calcification.

We evaluated the prognostic impact of calcified coronary lesions in patients who underwent percutaneous coronary intervention with newer-generation drug-eluting stents. Core laboratory–adjudicated moderate/severe calcification was not associated with target lesion failure (**A**) after adjustment for confounders but was associated with target-vessel myocardial infarction (**B**). Ischemia-driven target-lesion failure (**C**) and cardiac death (**D**) were not significantly associated with moderate/severe calcification. Calc indicates calcification; and HR, hazard ratio.

PCI in calcified coronary lesions with bare metal stent were linked to worse clinical outcomes, and data were inconsistent for first-generation DES,[1] data for newer-generation DES are scarce Promising clinical results with the Orsiro BP-SES were observed in the PREPARE-CALC (The Comparison of Strategies to Prepare Severely Calcified Coronary Lesions Trial) trial.[6] Two hundred patients underwent lesion preparation with either scoring/cutting balloons or up-front rotational atherectomy before implantation of the ultra-thin-strut BP-SES. After 9 months, the target-vessel failure rate was 8% versus 6%, respectively (*P*=not significant). In the TWENTE II study,[5] 1423 patients with stable angina treated with newer-generation durable-polymer zotarolimus-eluting stents (Resolute Integrity; Medtronic Vascular, Santa Rosa, CA) or 2 different DP-EESs (Promus Element; Boston Scientific, Natick, MA; or Xience V; Abbott) were analyzed on their clinical outcomes at 2 years. In patients with severe coronary calcification, target-vessel failure rates were higher than in nonsevere calcification (16.4% versus 9.8%, *P*=0.001). Cardiac death, TV-MI, and ST rates were higher, whereas target-vessel revascularization was not different. Calcification was an independent predictor of target-vessel failure at 2 years (hazard ratio [HR], 1.42 [95% CI, 1.02–1.99], *P*=0.04). Although TWENTE II analyzed severe versus nonsevere lesion calcification, our study compared moderate/severe versus none/mild calcification. About TLR, neither TWENTE II nor our analysis detected a difference between calcification severity groups at 2 years. On the other hand, in

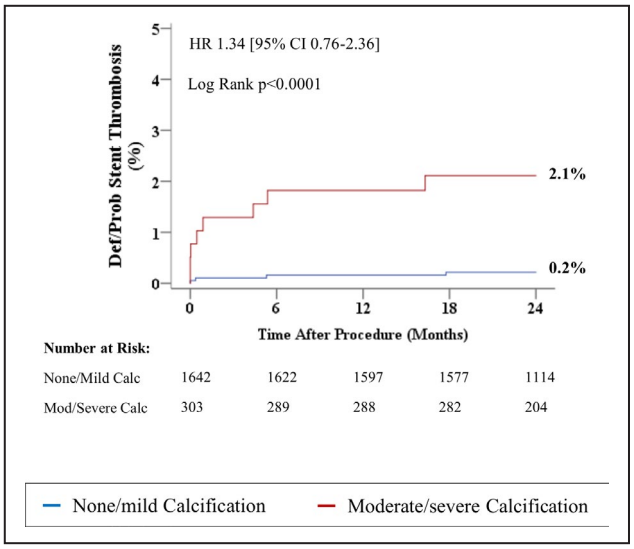

Figure 2. Kaplan-Meier curves of definite (Def)/probable (Prob) stent thrombosis at 2 years for moderate (Mod)/severe calcification and none/mild calcification.
The rate of stent thrombosis at 2 years was higher in moderate/severe calcification as compared with none/mild calcification. Calc indicates calcification; and HR, hazard ratio.

Table 3. Multivariable Analysis for the Predictors of TLF and TV-MI at 2 Years

	HR	95% CI	*P* Value
TLF			
Orsiro vs Xience	0.748	0.531–1.053	0.096
Calcification	1.366	0.895–2.084	0.148
Age, per y	1.017	0.999–1.035	0.060
Men	0.799	0.547–1.165	0.243
Hyperlipidemia	0.763	0.517–1.126	0.174
Prior PCI/CABG	1.341	0.944–1.905	0.101
Type B2/C lesion	1.007	0.698–1.469	0.973
Multivessel treatment	1.705	1.092–2.662	0.019
Predilatation	1.553	0.802–3.009	0.192
Postdilatation	2.454	1.689–3.566	<0.0001
TV-MI			
Orsiro vs Xience	0.757	0.501–1.142	0.184
Calcification	1.665	1.031–2.688	0.037
Age, per y	1.009	0.988–1.030	0.410
Men	0.675	0.434–1.047	0.079
Hyperlipidemia	0.737	0.462–1.177	0.202
Prior PCI/CABG	1.327	0.868–2.029	0.191
Type B2/C lesion	1.161	0.725–1.859	0.533
Multivessel treatment	1.756	1.045–2.950	0.034
Predilatation	2.042	0.814–5.124	0.128
Postdilatation	2.349	1.498–3.684	<0.0001

CABG indicates coronary artery bypass graft; HR, hazard ratio; PCI, percutaneous coronary intervention; TLF, target-lesion failure; and TV-MI, target-vessel myocardial infarction.

the Xience V/Promus postmarketing surveillance study in Japan,[14] TLR rate at 3 years was higher in calcified lesions as compared with noncalcified lesions (5.8% versus 3.1%, *P*=0.025). In that multicenter analysis, calcification was core-laboratory adjudicated. In another large single center registry[15] of 12 445 patients with documented operator-adjudicated calcification, optical coherence tomography was higher in moderate/severe calcification as compared with none/mild calcification. However, in that registry, >80% of patients with severe calcification underwent rotational atherectomy, which makes interstudy comparisons inappropriate.

In none/mild calcification, the rate of TLF was significantly lower when the ultra-thin-strut BP-SES was used as compared with the thin-strut DP-EES (7.5% versus 10.3%, log-rank *P*=0.045). This benefit could not be observed in moderate/severe calcification where BP-SESs and DP-EESs showed similar TLF rates (12.6% versus 15.4%, log-rank *P*=0.482). Of note, this comparison was performed with a small number of patients, because 199 patients with a BP-SES and 104 patients with a DP-EES were analyzed.

Newer-generation DESs exhibit lower rates of ST as compared with the first generation DES, which is explained by a faster endothelial coverage of the thinner struts.[16,17] The rate of ST is highest within the first year.[18] Thus, we observed in our population 10 cases of ST in the first year and an additional 2 cases in the second year. In the ultra-thin-strut BP-SES arm, all cases occurred in the first year; whereas in the thin-strut DP-EES arm, ST presented equally in the first and second years. In this context, an optical coherence tomography analysis of a prospective registry revealed uncovered struts and stent underexpansion to be common in acute/subacute ST, whereas neoatherosclerosis and uncovered struts were observed in late/very late ST.[19] Those observations are in line with our findings, because we observed a significantly higher rate of ST at 2 years in moderate/severe calcification as compared with none/mild calcification (2.1% versus 0.2%, log-rank *P*<0.0001). This high rate of ST in severely calcified lesions was also described in the TWENTE II study[5] (2.3% versus 0.9% for definite/probable ST in severe calcified lesions versus no severe calcified lesions, *P*=0.04). Most recently, a large-scale patient level analysis of 18 randomized controlled trials reporting 5-year outcomes of patients with coronary calcification[20] showed in moderate/severe calcified lesions treated with a second-generation DES an ST rate of 2.1%, and in none/mild lesion calcification a rate of 1.2%. These rates are remarkable, because they are similar to the 2-year ST rates observed in our analysis and in the TWENTE II study. The Kaplan-Meier curves further diverge beyond the period of 2 years. However, this comparison seems difficult, because

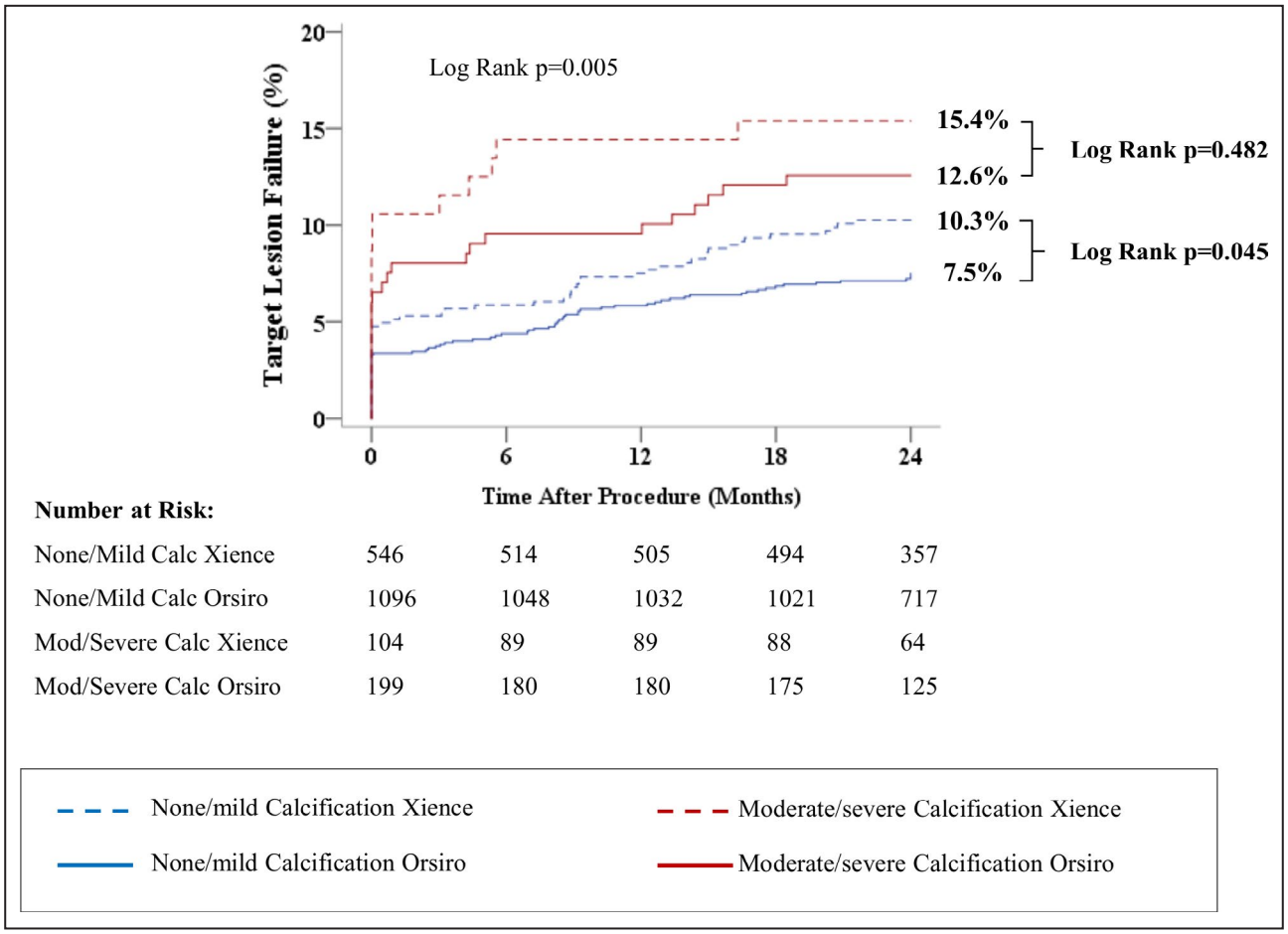

Figure 3. Kaplan-Meier curves of target-lesion failure at 2 years according to the stent and calcification severity.
In moderate (Mod)/severe calcification, target-lesion failure was not significantly different between both stent platforms, whereas in none/mild calcification, the bioresorbable-polymer sirolimus-eluting stent (Orsiro) showed lower rates as compared with the durable-polymer everolimus-eluting stent (Xience). Calc indicates calcification.

this large-scale analysis of 18 trials did not include the TWENTE studies or a study using the Orsiro stent.

Stent underexpansion is a strong predictor for stent failure such as ST, in-stent restenosis, and consequently TLR.[18,21] To prevent stent underexpansion, adequate preparation of calcified lesions is crucial. Calcified lesions may require dedicated preparation tools like cutting/scoring balloons, rotational or orbital atherectomy, or recently available intravascular lithotripsy. In the BIOFLOW V trial, calcified lesions requiring atherectomy were not excluded as long as adequate balloon predilatation was achieved. Unfortunately, data on those dedicated lesion preparation techniques were not available for further analysis. However, predilatation was frequent in moderate/severe calcified lesions (96.4% versus 86.1%, *P*<0.0001). In general, if stent underexpansion happens, postdilatation is required to prevent stent failure. In our population, 59.1% of moderate/severe calcified lesions and 47.8% of none/mild calcified lesions were postdilated (*P*=0.0002). Against our expectations, in multivariable analysis, postdilatation was a strong predictor of TLF at 2 years (HR, 2.45 [95% CI 1.69–3.57]; *P*<0.0001). We hypothesize that postdilatation was more often required in heavily calcified lesions with more stent underexpansion, because residual diameter stenosis was 8.9% versus 6.9% in moderate/severe versus none/mild

Table 4. Weighted κ Statistic for the Agreement of Assessment of the Calcification Classification Between the Core Laboratory and the Operator

	Core-Laboratory Assessment			
	None/Mild	Moderate	Severe	Total
Operator assessment				
None/mild	1415	147	30	1592
Moderate	187	54	23	264
Severe	13	6	14	33
Total	1615	207	67	1889

Weighted κ, 0.2292 (SE, 0.0279); 95% CI, 0.1746–0.2838; *P*<0.0001.

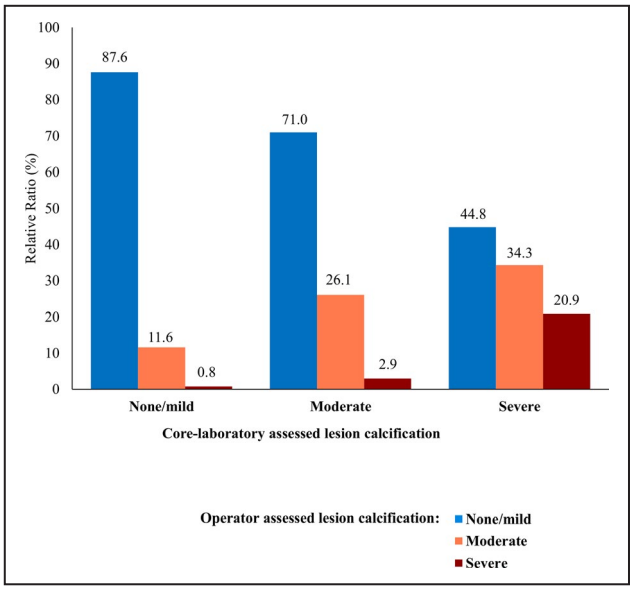

Figure 4. Coronary lesion calcification estimation by the interventionalist as compared with the core laboratory.
The *y* axis represents the coronary calcification stratified by the core laboratory. The columns represent the frequency of the different calcification degrees as estimated by the interventionalists. The strength of agreement in estimating lesion calcification between the operator and the core laboratory was weak (weighted κ, 0.23 [95% CI, 0.18–0.28]; *P*<0.0001).

calcification (*P*<0.0001), respectively. Thus, postdilatation might be a surrogate for stent underexpansion, a well-established risk factor for TLF. Another explanation might be that postdilatation probably cause more vessel injury, especially media laceration. Media injury was shown to be linked to in-stent restenosis,[16] which in turn also leads to TLF. Postdilatation in bifurcations may also induce side-branch compromise, resulting in periprocedural myocardial infarction and in turn to TLF. Nevertheless, in clinical practice, postdilatation is frequently required for optimal stenting results to prevent TLF. Therefore, this result should be interpreted with caution.

It is well known that visual estimates of lesion characteristics are less reliable than quantitative parameters.[12,22] As demonstrated in our analysis, the agreement between the operator and the core laboratory in severe calcified lesions was only 20.9% and in moderately calcified lesions 26.1%. The operator and the core laboratory best agreed in none/mild calcification in 87.6% of cases. A previous analysis on interobserver variability in the qualitative categorization of American College of Cardiology/American Heart Association lesion-type classification demonstrated total agreement in 67.8% of cases and a κ value of 0.33, which the authors classified as a poor agreement. However, when only analyzing calcification, the strength of agreement was κ=0.53.[23] On exploring the causes of disagreement in calcification categorization, type B2/C lesions, moderate/severe vessel tortuosity, lesion length, presence of thrombus and moderate calcification as well as severe calcification were more frequent in disagreement as in agreement cases.

Limitations

First, in the BIOFLOW II and IV trials, calcified lesions were an exclusion criterion, which leads to comparison of moderate/severe calcification from BIOFLOW V with none/mild calcification from BIOFLOW II, IV, and V. Second, although calcified lesions requiring atherectomy were not excluded as long as adequate balloon predilatation was achieved, we do not have the data of these dedicated lesion preparation techniques, which prevents us from further analysis on this topic. Third, no information on intravascular imaging was collected. As imaging is beneficial to guide PCI, especially in complex lesions, this information would have been of value. Fourth, cardiac death included unwitnessed death and death of unknown cause. Fifth, only patients with a single lesion were included in the operator–core laboratory agreement analysis. Sixth, as per the trial protocol, no distinction between none versus mild calcification was routinely recorded. Thus, comparison of outcomes of patients with none versus mild calcification was not possible.

CONCLUSIONS

With newer-generation DESs, moderate/severe lesion calcification was not associated with a higher TLR or TLF but with more TV-MI and stent thrombosis at 2 years. BP-SESs and DP-EESs were equally effective and safe in calcified lesions.

ARTICLE INFORMATION

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Affiliations

Heart Center Bad Segeberg, Segeberger Kliniken GmbH, Bad Segeberg, Germany (R.H., R.T., N.M., A.A., G.R.); Cardiology Department, Al-Azhar University, Cairo, Egypt (M.A.); Cardiology Department, Amsterdam University Medical Center, University of Amsterdam, the Netherlands (M.A.); Medstar Washington Hospital Center, Washington, DC (H.M.G., R.W.); Inselspital (University Hospital), Bern, Switzerland (S.W.); Hospital Privé Jaques Cartier, Massy, France (T.L.); Okinawa Tokushukai Shonan Kamakura General Hospital, Kamakura, Japan (S.S.); Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands (T.S.); Piedmont Heart Institute, Atlanta, GA (D.K.); and Catharina Hospital, Eindhoven, the Netherlands (J.K.).

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Supplementary Material

Tables S1–S3
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Major inclusion and exclusion criteria in the BIOFLOW-II, -IV, and -V trials.

	BIOFLOW-II	**BIOFLOW-IV**	**BIOFLOW-V**
Calcified lesions	Heavy calcification excluded	Heavy calcification excluded	Calcification not excluded*
Clinical presentation	Stable angina Unstable angina NSTEMI excluded STEMI excluded	Stable angina Unstable angina NSTEMI excluded STEMI excluded	Stable angina Unstable angina NSTEMI (hemodynamically stable) STEMI excluded
Lesions	1 or 2 de-novo Length ≤26 mm RVD 2.5-3.75 mm LM excluded Bifurcation excluded Thrombus excluded CABG excluded	1 or 2 de-novo Length ≤26 mm RVD 2.25-4.0 mm LM excluded Bifurcation excluded Thrombus excluded CABG excluded	Up to 3 de-novo Length ≤36 mm RVD 2.25-4.0 mm LM excluded Bifurcation excluded Thrombus excluded CABG excluded
LV function	<30% excluded	<30% excluded	<30% excluded

CABG = coronary artery bypass graft, LM = left main coronary artery, LV function = left ventricular function, NSTEMI = non-ST segment elevation myocardial infarction, STEMI = ST segment elevation myocardial infarction, RVD = reference vessel diameter.

*Atherectomy was allowed as long as adequate balloon pre-dilatation was achieved.

Table S2. Crude rates of stent thrombosis at 1 year and 2 years in moderate/severe vs none/mild calcification and in BP-SES and DP-EES.

	Mod/severe Calc	None/mild Calc	p-value
Definite/probable ST at 1 yr	7/370 (1.9%)	3/1812 (0.2%)	**<0.0001**
Definite/probable ST at 2yrs	8/303 (2.6%)	4/1642 (0.2%)	**<0.0001**
	Mod/severe Calc BP-SES	**Mod/severe Calc DP-EES**	**p-value**
Definite/probable ST at 1 yr	6/236 (2.5%)	1/134 (0.7%)	0.2229
Definite/probable ST at 2yrs	6/199 (3.0%)	2/104 (1.9%)	0.5735
	None/mild Calc BP-SES	**None/mild Calc DP-EES**	**p-value**
Definite/probable ST at 1 yr	1/1212 (0.1%)	2/600 (0.3%)	0.2165
Definite/probable ST at 2 yrs	1/1096 (0.1%)	3/546 (0.5%)	0.0760

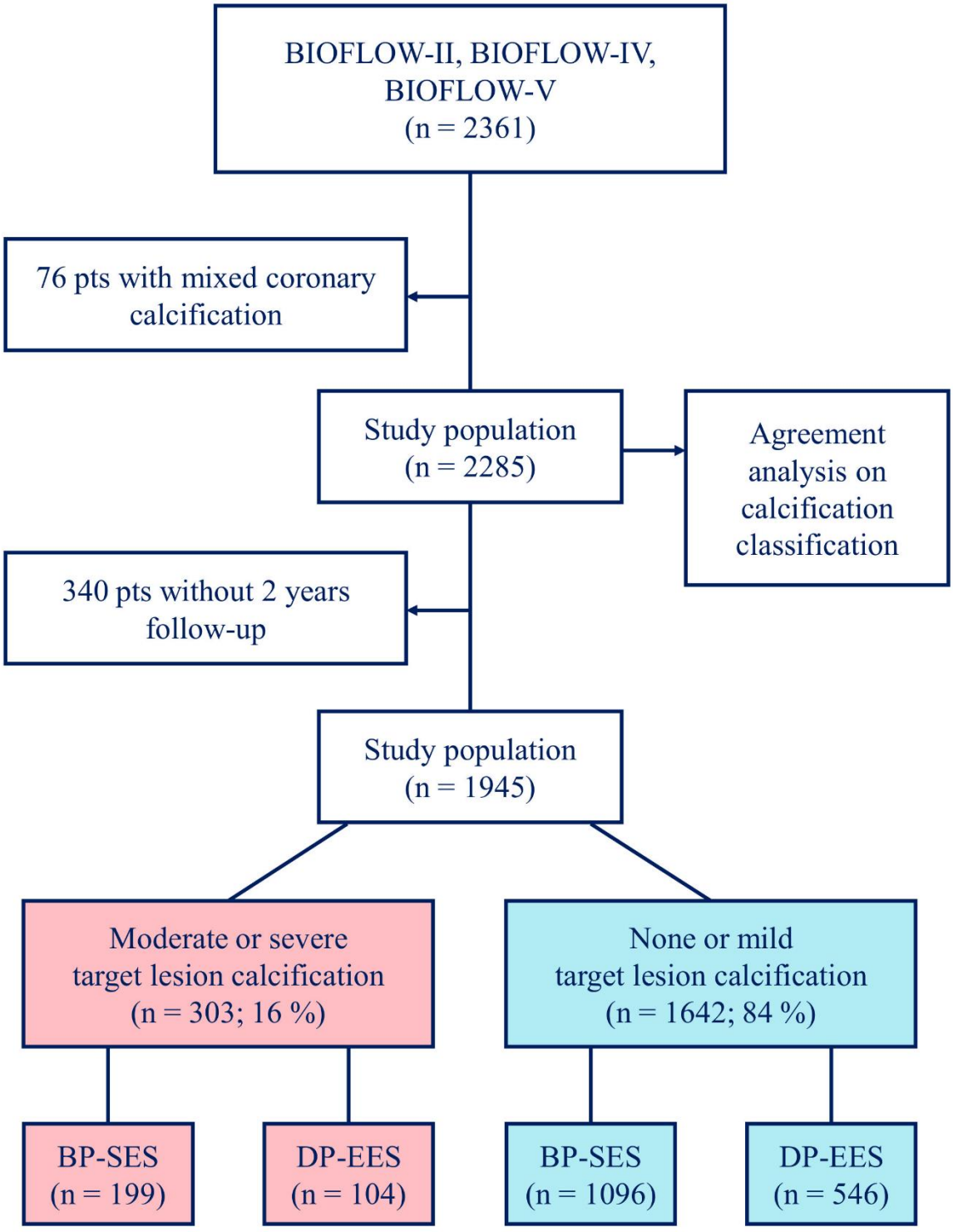
Table S3. Univariable Analysis of Disagreement of Coronary Lesion Calcification Degree Estimation between the Operator and Core-Laboratory.

	Disagreement n = 406	Agreement n = 1483	p-value
Complex lesion (B2/C)	69.9 (281/402)	49.0 (720/1470)	**<0.0001**
Bifurcation lesion	9.6 (39/406)	10.6 (157/1483)	0.5658
Thrombus	2.5 (10/406)	0.7 (11/1483)	**0.0034**
Moderate/severe tortuosity	46.3 (188/406)	31.4 (466/1483)	**<0.0001**
Calcification			**<0.0001**
None/mild	49.3 (200/406)	95.4 (1415/1483)	
Moderate	37.7 (153/406)	3.6 (54/1483)	
Severe	13.1 (53/406)	0.9 (14/1483)	
Lesion length, mm	12.5 (8.4 - 17.7)	11.5 (8.1 - 16.0)	**0.0090**
Long lesion (> 20 mm)	18.8 (70/375)	13.1 (194/1476)	**0.0040**
RVD, mm	2.70 ± 0.54	2.71 ± 0.53	0.9215
RVD ≤ 2.75 mm	55.4 (225/406)	56.7 (841/1483)	0.6421

Data are mean ± SD or median (Q1-Q3) or percent % (n/N)

*Acute MI (STEMI and NSTEMI) and unstable angina

Figure S1. Study flow chart.



Pts = patients, BP-SES = bioresorbable polymer sirolimus eluting stent, DP-EES = durable polymer everolimus eluting stent