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ORIGINAL RESEARCH

Coronary Endothelium-Dependent Vasomotor Function After Drug-Eluting Stent and Bioresorbable Scaffold Implantation

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BACKGROUND: Early generation drug-eluting stents (DESs) showed a high grade of coronary endothelial dysfunction that was attributed to lack of stent reendothelialization. Endothelium-dependent vasomotor response of current DESs and bioresorbable scaffolds (BRSs) remains unknown. This study sought to assess the device-related endothelial function of current devices and to correlate neointima healing with endothelial function.

METHODS AND RESULTS: A total of 206 patients from 4 randomized trials treated with the durable-polymer everolimus-eluting Xience (n=44), bioresorbable-polymer sirolimus-eluting Orsiro (n=35), polymer-free biolimus-eluting Biofreedom (n=24), bioactive endothelial-progenitor cell-capturing sirolimus-eluting Combo DES (n=25), polymer-based everolimus-eluting Absorb (n=44), and Mg-based sirolimus-eluting Magmaris BRS (n=34) underwent endothelium-dependent vasomotor tests and optical coherence tomography imaging, as per protocol, at follow-up. Crude vasomotor responses of distal segments to low-dose acetylcholine (10^{-6} mol/L) were different between groups: bioresorbablepolymer DEShad the worst (–8.4%±12.6%) and durable-polymer DES had the most physiologic (–0.4%±11.8%; *P*=0.014). High-dose acetylcholine (10^{-4} mol/L) showed similar responses between groups (ranging from –10.8%±11.6% to –18.1%±15.4%; *P*=0.229). Device healing was different between devices. Uncovered struts ranged from 6.3%±7.1% (bioresorbable-polymer DES) to 2.5%±4.5% (bioactive DES; *P*=0.056). In multivariate models, endothelium-dependent vasomotor response was associated with age, bioresorbable-polymer DES, and angiographic lumen loss, but not with strut coverage nor plaque type. Endothelial dysfunction (defined as ≥4% vasoconstriction) was observed in 46.6% of patients with low-dose and 68.9% with high-dose acetylcholine, without differences between groups.

CONCLUSIONS: At follow-up, endothelial dysfunction was frequently observed in distal segments treated with current stents without remarkable differences between devices. Although neointima healing was different between devices, poor healing was not associated with endothelial dysfunction.

Key Words: drug-eluting stents ■ endothelial dysfunction ■ optical coherence tomography ■ ST-segment–elevation myocardial infarction

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CLINICAL PERSPECTIVE

What Is New?

- Stent-related endothelial dysfunction of distal coronary segments is one of the major causes of persistent angina after stent implantation. Previous studies have shown larger endothelial dysfunction with first-generation drug-eluting stents than with bare-metal stents.
- The worse endothelial function associated with first-generation drug-eluting stents was attributed to a lack of stent reendothelialization.
- The stent-related endothelial dysfunction of current stent technologies is mainly unknown.

What Are the Clinical Implications?

- Coronary arteries treated with current stents had similar or mildly different dysfunctional vasomotor responses to endothelial-dependent stimuli.
- Moreover, the healing pattern, irrespective of stent type, was not associated with the vasomotor response observed in distal coronary segments.

Nonstandard Abbreviations and Acronyms

BES	biolimus-eluting stent
BRS	bioresorbable scaffold
DES	drug-eluting stent
EES	everolimus-eluting stent
PLLA	poly-L-lactide
SES	sirolimus-eluting stent

The coronary endothelium is the natural mono-cell layer between blood and the artery wall. In normal conditions, the endothelial cells act as barrier, preventing lipid deposition and infiltration of the intima by inflammatory cells. Moreover, the coronary endothelium plays an important role controlling the epicardial vasomotor tone in response to flow-mediated local shear stress forces and vasoactive agents.[1] In healthy coronary arteries, intracoronary acetylcholine stimulates the release of nitric oxide. Nitric oxide is a potent coronary vasodilator agent and is the key regulator of the epicardial vasomotor tone. For this reason, experimental intracoronary infusion of acetylcholine in healthy coronary arteries normally induces vasodilation.[1]

Common cardiovascular risk factors damage the endothelial function and cell junctions by cellular oxidative stress and inactivation of the nitric oxide pathway. Dysfunctional endothelium promotes a vasoconstrictive, proinflammatory, and procoagulant milieu that has been described as the first stage of atherosclerosis. Moreover, the lack of cellular integrity allows the direct pass of acetylcholine, when used in experimental intracoronary infusion tests, into the vessel wall. For this reason, in dysfunctional endothelium, acetylcholine activates the muscarinic receptors of vascular smooth muscle cells (mainly located in the tunica media) and causes vasoconstriction.[1]

Percutaneous coronary intervention (PCI) denudates the endothelium. Therefore, intracoronary acetylcholine infusion immediately after stent implantation, regardless the stent type, causes vasoconstriction of peristent coronary segments.[2,3] According to pathologic studies, bare-metal stents present with complete healing (defined as complete strut coverage and reendothelialization) at 4 months.[2] In contrast, the healing process of first-generation durable-polymer drug-eluting stents (DESs) is often delayed and, in some cases, permanently incomplete at very long-term follow-up.[2] Lack of stent healing, stent-mediated coronary flow disturbances, polymer-related inflammatory response, and direct action of the antiproliferative drug have all been hypothesized to explain the worse peristent endothelial function observed with first-generation durable-polymer DESs compared with bare-metal stents.[3,4]

The current generation of DESs (second-generation durable-polymer, bioresorbable-polymer, and polymer-free DESs) aim to enhance stent healing by controlling the antiproliferative drug kinetics, reducing stent thrombogenicity and minimizing the inflammatory response. Bioactive DESs capture circulating endothelial progenitor cells aiming to accelerate and promote stent reendothelialization. Finally, different technologies of bioresorbable scaffolds (BRSs) have demonstrated endothelium-dependent vasomotor response within the scaffold segment once the scaffold has lost its radial force.[5,6] However, the endothelial function of distal coronary segments treated with current-generation DESs and BRSs remains largely unknown. In addition, it is uncertain if incomplete device healing, regardless device type, is related to the endothelial function observed in distal coronary segments.

The objectives of the present study are to compare the endothelial function of distal coronary segments treated with current DESs and BRSs and to determine the morphological factors, including device healing and distal plaque characteristics, associated with the endothelial dysfunction of distal coronary segments.

METHODS

Study Design and Population

The authors declare that all supporting data are available in the article (and its online supplementary files).

This is a pooled data analysis of 4 investigator-initiated, multicenter, controlled, randomized clinical trials comparing 6 types of DESs and BRSs.[5–8] All study protocols included prespecified assessment of the endothelial function and optical coherence tomography (OCT) imaging at follow-up. All studies were performed according to the provisions of the Declaration of Helsinki, and the ethics committee of all participating institutions approved the respective study protocols. Written, informed consent was obtained from all patients. Table S1 summarizes the main study design characteristics of the 4 trials included in the present study.

Stent Types

Table S2 summarizes the stent characteristics of the study devices. In brief, the following 6 different types of DESs were investigated: durable-polymer everolimus-eluting stent (EES; Xience, Abbott Vascular, Santa Clara, CA), bioresorbable-polymer sirolimus-eluting stent (SES; Orsiro, Biotronik, Baar, Switzerland), polymer-free biolimus-eluting stent (BES; Biofreedom, Biosensors, Morges, Switzerland), bioactive endothelial progenitor cell–capturing SES (Combo, OrbusNeich, Hoevelaken, the Netherlands), poly-L-lactide (PLLA)–based everolimus BRS (Absorb stents, Abbott Vascular, Santa Clara, CA), and Mg-based sirolimus BRS (Magmaris, Biotronik).

Vasomotor Function Assessment

All of the studies had identical vasomotor test protocols. A detailed description of the vasomotor test is shown in Data S1. In summary, patients were requested to stop all vasomotor drugs at least 24 hours before elective coronary angiography. Endothelium-dependent vasomotor function was examined by intracoronary infusion of acetylcholine. A total of 2 graded concentrations of acetylcholine 10^{-6} mol/L and 10^{-4} mol/L were infused via microcatheter for 2 minutes at 2 mL/min. Endothelium-independent vasomotor assessment was performed by 200 μg of nitroglycerin bolus injection via guiding catheter. Cine-fluoroscopy recordings were obtained for each phase at the same angiographic view as follow-up baseline images.

Angiographic Analysis

Angiographic analysis of all 4 randomized trials was performed by a central core laboratory (Barcelona Cardiac Imaging core-laboratory [BARCICORE-lab], Barcelona, Spain) following the same methodology. Quantitative coronary angiography (QCA) analysis was performed with dedicated offline software (CASS, Pie Medical, Maastricht, the Netherlands). A detailed description of the QCA analysis of the stent segment and distal coronary segment in the vasomotor test is described in Data S1.

Endothelium-dependent vasomotor change of distal segments was measured considering the core laboratory variability for repeated mean lumen diameter measures (3.9%).[9] Significant responses were defined by ≥4% mean lumen diameter change (vasodilation or vasoconstriction) with respect to the follow-up baseline image. Therefore, endothelial dysfunction was defined as ≥4% vasoconstriction to intracoronary acetylcholine.

OCT Analysis

OCT analysis was performed by a central core laboratory (BARCICORE-lab) using specific software for analysis (LightLab Imaging, Westford, MA).[10] A detailed description of the OCT analysis can be found in Data S1.

Statistical Analysis

Categorical variables are presented as counts and percentages, and quantitative variables are presented as mean±SD. Comparisons of categorical variables were estimated with the χ^2 test, and comparisons of quantitative values between groups were estimated with a 1-way ANOVA test. Comparisons of serial quantitative measurements (such as lumen diameter changes to low-dose and high-dose acetylcholine) were estimated with the Student *t* test for paired samples with Bonferroni correction for multiples comparisons (significant *P* values were considered ≤0.025). Unadjusted and adjusted comparisons of percentage vasomotor changes between study devices and predictors of endothelial dysfunction were estimated with generalized estimating equations. Multivariate models were performed including all covariates associated with endothelial dysfunction with a *P* value <0.15 in at least 1 of the 2 predictive models (endothelial dysfunction during low-dose and high-dose acetylcholine). A 2-sided *P* value ≤0.05 was considered statistically significant. Statistical analysis was performed with the SPSS software, version 20.0 (SPSS Inc., Armonk, NY).

RESULTS

Baseline Clinical and Angiographic Characteristics

A total of 206 patients were included (44 durable-polymer EESs, 35 bioresorbable-polymer SESs, 24 polymer-free BESs, 25 bioactive SESs, 44 PLLA-based BRSs, and 34 Mg-based BRSs). Table 1 shows the baseline clinical and angiographic characteristics of the study population. There were statistically significant differences regarding the clinical indication of stent implantation. Stent implantation was performed in the context of ST-segment–elevation myocardial infarction

Table 1. Baseline Clinical, Angiographic, and Procedural Characteristics

	Durable-polymer EES, n=44	Bioresorbable-polymer SES, n=35	Polymer-free BES, n=24	Bioactive SES, n=25	PLLA-based BRS, n=44	Mg-based BRS, n=34	*P* value
Age, y	57.9±8.5	58.8±8.6	56.6±7.8	56.8±8.5	60.7±9.6	59.0±9.8	0.412
Male sex	41 (93.2)	33 (94.3)	23 (95.8)	19 (76.0)	38 (86.4)	30 (88.2)	0.170
Body mass index	28.6±4.2	28.5±3.6	28.3±4.5	28.2±4.0	28.5±5.5	28.2±4.4	0.999
Smoking status							0.002
No	22 (50.0)	10 (28.3)	4 (16.7)	3 (12.0)	23 (52.3)	13 (38.2)	
Current	14 (31.8)	20 (57.1)	17 (70.8)	19 (76.0)	12 (27.3)	16 (47.1)	
Former	8 (18.2)	5 (14.3)	3 (12.5)	3 (12.0)	9 (20.5)	5 (14.7)	
Hypertension	28 (63.6)	15 (42.9)	13 (54.2)	6 (24.0)	28 (63.6)	16 (47.1)	0.015
Hypercholesterolemia	29 (65.9)	22 (62.9)	15 (62.5)	15 (60.0)	30 (68.2)	24 (70.6)	0.193
Diabetes	5 (11.4)	9 (25.7)	4 (16.7)	2 (8.0)	5 (11.4)	4 (11.8)	0.358
Treated with insulin	1 (2.3)	2 (5.7)	2 (8.3)	0	3 (6.8)	1 (2.9)	0.630
Previous PCI	12 (27.3)	0	0	1 (4.0)	14 (31.8)	2 (5.9)	<0.001
Clinical indication							<0.001
Chronic coronary symptoms	21 (47.7)	0	0	0	17 (38.6)	0	
NSTEMI acute coronary syndrome	7 (15.9)	0	0	0	8 (18.2)	0	
STEMI	16 (36.4)	35 (100.0)	24 (100.0)	25 (100.0)	19 (43.2)	34 (100.0)	
Number of diseased vessels							0.058
1	28 (63.6)	26 (74.3)	16 (66.7)	17 (68.0)	28 (63.6)	27 (79.4)	
2	16 (36.4)	9 (25.7)	8 (33.3)	8 (32.0)	12 (27.3)	5 (14.7)	
3	0	0	0	0	4 (9.1)	0	
Culprit vessel							0.522
LAD	27 (61.4)	17 (48.6)	11 (45.8)	12 (48.0)	24 (54.5)	17 (50.0)	
LCX	8 (18.2)	4 (11.4)	5 (20.8)	4 (16.0)	12 (27.3)	6 (17.6)	
RCA	9 (20.5)	14 (40.0)	8 (33.3)	9 (36.0)	8 (18.2)	11 (32.4)	
Pretreatment TIMI flow							<0.001
0	11 (25.0)	25 (71.4)	13 (54.2)	15 (60.0)	13 (29.5)	26 (76.5)	
1	3 (6.8)	3 (8.6)	1 (4.2)	4 (16.0)	3 (6.8)	3 (8.8)	
2	1 (2.3)	2 (5.7)	6 (25.0)	4 (16.0)	1 (2.3)	4 (11.8)	
3	29 (65.9)	5 (14.3)	4 (16.7)	2 (8.0)	27 (61.4)	1 (2.9)	
Predilatation	30 (68.2)	27 (77.1)	5 (20.8)	7 (28.0)	28 (63.6)	31 (91.2)	<0.001
Thrombus aspiration	13 (29.5)	23 (65.7)	10 (41.7)	7 (28.0)	16 (36.4)	20 (58.8)	0.004
Number of devices							0.089
1	39 (88.6)	32 (91.4)	21 (87.5)	25 (100.0)	43 (97.7)	34 (100.0)	
2	5 (11.4)	3 (8.6)	3 (12.5)	0	1 (2.3)	0	
Device diameter, mm	3.2±0.3	3.3±0.3	3.3±0.4	3.3±0.4	3.3±0.3	3.2±0.3	0.427
Device length, mm	20.2±7.9	20.9±6.4	21.8±5.7	20.0±4.3	19.8±4.1	20.6±3.8	0.784
Postdilatation	6 (13.6)	6 (17.1)	1 (4.2)	4 (16.0)	9 (20.5)	31 (91.2)	<0.001
Posttreatment TIMI flow							0.660
2	0	2 (5.7)	2 (8.3)	1 (4.0)	2 (4.5)	2 (5.9)	
3	44 (100.0)	33 (94.3)	22 (91.7)	24 (96.0)	42 (95.5)	32 (94.1)	
Ejection fraction, %	55.4±9.7	54.5±7.0	51.7±7.2	51.4±10.2	56.1±9.8	49.9±9.4	0.028

Data are provided as mean±SD or number (percentage). *P* values indicate a 1-way ANOVA test for quantitative data and a χ^2 test for qualitative data. BES indicates biolimus-eluting stent; BRS, bioresorbable scaffold; EES, everolimus-eluting stent; LAD, left anterior descending artery; LCX, left circumflex; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; PLLA, poly-L-lactide; RCA, right coronary artery; SES, sirolimus-eluting stent; STEMI, ST-segment–elevation myocardial infarction; and TIMI, thrombolysis in myocardial infarction.

in 36.4% versus 100.0% versus 100.0% versus 100.0% versus 43.2% versus 100.0%, respectively (P<0.001). Time intervals between stent implantation and invasive follow-up were 6 months (24 polymer-free BESs and 25 bioactive SESs), 12 months (35 bioresorbable-polymer SESs and 34 Mg-based BRSs), 13 months (28 durable-polymer EESs and 25 PLLA-BRSs), and 36 months (16 durable-polymer EESs and 19 PLLA-BRSs) according to the different study protocols. Moreover, according to the respective study protocols, predilatation and post-dilatation were more frequently performed in patients treated with BRSs.

In-Device QCA Analysis

In-device QCA analysis is shown in Table 2. At follow-up, minimal lumen diameter and diameter stenosis were different between study groups. Durable-polymer EESs and bioresorbable-polymer SESs were associated with smaller lumen loss (0.10±0.19 mm and 0.05±0.26 mm, respectively) than polymer-free BESs and bioactive SESs (0.36±0.63 mm and 0.33±0.31 mm, respectively) and PLLA and Mg-based BRSs (0.36±0.46 and 0.47±0.41 mm, respectively; P<0.001).

Vasomotor Response of Distal Coronary Segments

Table 3 shows the unadjusted vasomotor responses to endothelium-dependent and independent vasomotor stimuli at follow-up. Vasomotor changes were measured on average 32.3±7.1 mm distal length to the device edge, without differences between study groups (P=0.288). Figure 1 shows the unadjusted comparisons of vasomotor changes in each phase of the test with respect to the follow-up baseline reference.

At low-dose acetylcholine, vessels treated with bioresorbable-polymer SESs (–8.4%±12.6%), polymer-free BESs (–7.6%±14.2%), and Mg-based BRSs (–5.8%±13.0%) showed statistically significant vasoconstriction. In contrast, durable-polymer EESs, bioactive SESs, and PLLA-based BRSs showed a nonstatistically significant trend toward vasoconstriction. These differences between devices were statistically significant in the unadjusted analysis (P=0.014).

At high-dose acetylcholine and nitroglycerin infusions, all current-generation DESs and BRSs had statistically significant vasoconstriction (ranging from –10.8%±11.6% to –18.1%±15.4%) and vasodilatation (ranging from 9.7%±9.5% to 13.5%±13.2%), respectively. There were no differences between devices in the unadjusted comparisons.

OCT Findings

Optimal OCT imaging of stent and distal coronary segments was obtained in 196 and 190 patients, respectively. Table 4 summarizes the OCT findings.

Stent healing was different between devices. Absent neointima was more frequently observed with bioresorbable-polymer SESs (36.4%) and durable-polymer EESs (23.3%) than with polymer-free BESs (16.7%), PLLA-based BRSs (14.0%), and bioactive SESs (13.0%; P=0.044). The healing pattern of Mg-based BRSs could not be evaluated because of the advanced bioresorption state of the scaffold at 1 year. Uncovered and malapposed struts were different between devices, and were more frequently observed

Table 2. Quantitative Coronary Angiography Analysis (in Stent)

	Durable-polymer EES, n=44	Bioresorbable-polymer SES, n=35	Polymer-free BES, n=24	Bioactive SES, n=25	PLLA-based BRS, n=44	Mg-based BRS, n=34	*P* value
Baseline (after PCI)							
Stent length, mm	17.17±5.98	18.28±5.82	20.60±4.70	18.37±4.52	17.83±4.60	18.96±4.34	0.163
Minimum lumen diameter, mm	2.66±0.35	2.74±0.39	2.71±0.37	2.69±0.39	2.64±0.40	2.54±0.33	0.320
Reference lumen diameter, mm	2.79±0.38	2.97±0.42	2.84±0.50	2.80±0.56	2.95±0.45	2.85±0.37	0.380
Diameter stenosis, %	4.34±7.01	7.70±4.68	3.33±13.25	2.24±13.54	10.23±6.59	10.71±5.50	<0.001
Mean lumen diameter, mm	2.96±0.34	3.06±0.38	3.10±0.38	3.04±0.39	2.98±0.36	2.89±0.31	0.216
Follow-up (after nitroglycerin)							
Stent length, mm	16.89±5.48	18.28±5.77	20.48±4.87	18.51±4.77	17.94±4.18	18.92±4.36	0.119
Minimum lumen diameter, mm	2.56±0.39	2.69±0.45	2.35±0.66	2.36±0.53	2.28±0.56	2.07±0.58	<0.001
Late lumen loss, mm	0.10±0.19	0.05±0.26	0.36±0.63	0.33±0.31	0.36±0.46	0.47±0.41	<0.001
Reference lumen diameter, mm	2.79±0.43	2.94±0.38	2.73±0.59	2.81±0.55	2.85±0.46	2.74±0.35	0.455
Diameter stenosis, %	7.95±6.89	8.87±7.07	10.27±27.93	14.06±20.01	19.88±14.85	25.07±15.88	<0.001
Binary restenosis	1 (2.3)	0	2 (8.3)	2 (8.0)	2 (4.5)	5 (14.7)	0.094
Mean lumen diameter, mm	2.90±0.38	3.03±0.41	2.86±0.38	2.77±0.44	2.78±0.50	2.65±0.47	0.010

Data are provided as mean±SD or number (percentage). *P* values indicate a 1-way ANOVA test. BES indicates biolimus-eluting stent; BRS, bioresorbable scaffold; EES, everolimus-eluting stent; PCI, percutaneous coronary intervention; PLLA, poly-L-lactide; and SES, sirolimus-eluting stent.

Table 3. Vasomotor Response of Distal Coronary Segment (Unadjusted)

Device type	Baseline	Low-dose acetylcholine	*P* value*	High-dose acetylcholine	*P* value†	Nitroglycerin	*P* value‡
Durable-polymer EES, n=44	1.98±0.38 NA	1.95±0.34 (–0.39±11.78)	0.428	1.75±0.36 (–10.84±11.63)	<0.001	2.16±0.41 (9.86±10.76)	<0.001
Bioresorbable-polymer SES, n=35	1.96±0.42 NA	1.80±0.48 (–8.38±12.63)	0.001	1.61±0.47 (–18.05±15.44)	<0.001	2.20±0.46 (13.48±13.18)	<0.001
Polymer-free BES, n=24	2.09±0.37 NA	1.94±0.46 (–7.64±14.22)	0.009	1.75±0.54 (–16.11±21.60)	0.001	2.31±0.36 (11.18±8.66)	<0.001
Bioactive SES, n=25	2.18±0.47 NA	2.00±0.65 (–8.33±20.11)	0.056	1.84±0.65 (–15.99±20.21)	0.001	2.38±0.52 (9.74±9.50)	<0.001
PLLA-based BRS, n=44	2.16±0.46 NA	2.11 ± 0.49 (–1.84±11.33)	0.192	1.91±0.54 (–11.57±15.84)	<0.001	2.38±0.44 (11.84±13.41)	<0.001
Mg-based BRS, n=34	2.00±0.45 NA	1.90±0.56 (–5.83±13.01)	0.017	1.73±0.54 (–13.85±15.69)	<0.001	2.21±0.43 (11.20±9.51)	<0.001

Data are provided as mean±SD. For acetylcholine comparisons, significant *P* values are considered when $P \leq 0.025$ after Bonferroni correction. BES indicates biolimus-eluting stent; BRS, bioresorbable scaffold; EES, everolimus-eluting stent; NA, not applicable; PLLA, poly-L-lactide; and SES, sirolimus-eluting stent.

*P values indicate the paired *t* test analyses comparing the crude mean lumen diameter changes between baseline and low-dose acetylcholine.

†P values indicate the paired *t* test analyses comparing the crude mean lumen diameter changes between baseline and high-dose acetylcholine.

‡P values indicate the paired *t* test analyses comparing the crude mean lumen diameter changes between baseline and nitroglycerin.

with bioresorbable-polymer SESs (6.3% uncovered and 2% malapposed struts) than with other device technologies (all had <3.6% uncovered struts and <1.1% malapposed struts; *P*=0.056 and *P*=0.037, respectively). In contrast, neointima thickness was larger with bioactive SESs (184 µm), polymer-free BESs (158 µm), and PLLA-based BRSs (143 µm) than with durable-polymer EESs (103 µm) and bioresorbable-polymer SESs (84 µm; *P*<0.001).

The most frequent plaque type observed in the distal coronary segments was similar between groups: normal (nonatherosclerotic) artery was observed in 37.4%, fibrous plaque was observed in 25.3%, lipid-rich plaque was observed in 27.4%, and calcific plaque was observed in 10.0% (*P*=0.841). Plaque burden was also similar in all groups (41.0%±9.5%; *P*=0.610).

Stent Healing and Endothelial Function

Crude correlations between vasomotor changes to low-dose and high-dose acetylcholine and percentage of uncovered and malapposed struts are shown in Figure 2. None of the correlations were statistically

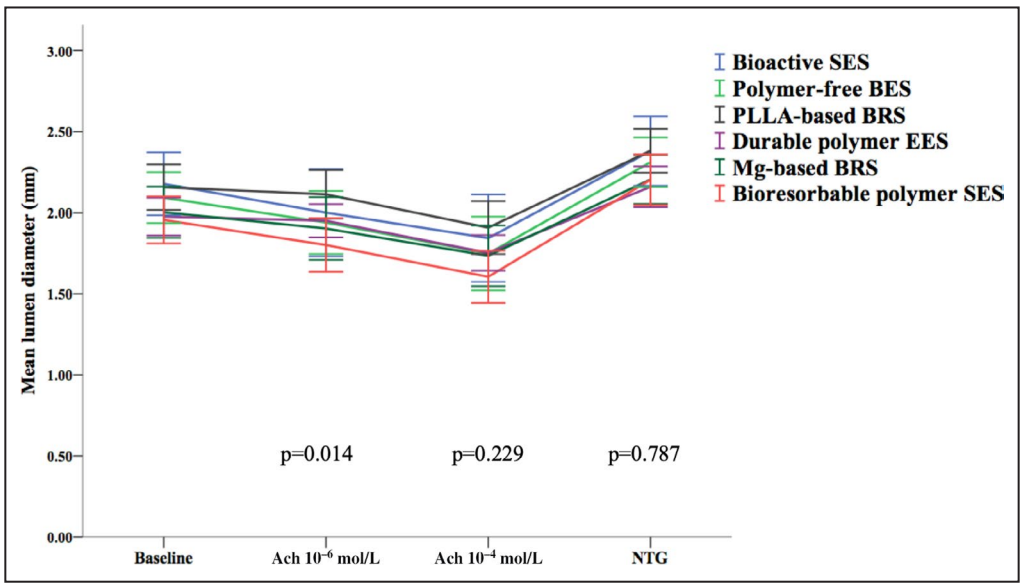

Figure 1. Vasomotor response to endothelium-dependent and independent stimuli.
P values were estimated with a 1-way ANOVA test and indicate the unadjusted difference between study groups of the percentage (mean lumen diameter) vasomotor change in each phase of the test, with respect to the follow-up baseline reference image. Ach indicates acetylcholine; BES, biolimus-eluting stent; BRS, bioresorbable scaffold; EES, everolimus-eluting stent; NTG, nitroglycerin; PLLA, poly-L-lactide; and SES, sirolimus-eluting stent.

Table 4. OCT Findings

	Durable-polymer EES, n=43	Bioresorbable-polymer SES, n=33	Polymer-free BES, n=24	Bioactive SES, n=23	PLLA-based BRS, n=43	Mg-based BRS, n=30	*P* Value
Device							
Device length, mm	20.0±6.9	20.6±5.8	22.7±5.8	20.3±4.3	19.8±4.0	20.0±3.9	0.352
Neointima pattern							0.044
Absent	10 (23.3)	12 (36.4)	4 (16.7)	3 (13.0)	6 (14.0)	NA	
Homogeneous	29 (67.4)	15 (45.5)	16 (66.7)	13 (56.5)	33 (76.7)	NA	
Heterogeneous	2 (4.7)	1 (3.0)	0	1 (4.3)	3 (7.0)	NA	
Layered	2 (4.7)	5 (15.2)	4 (16.7)	6 (26.1)	1 (2.3)	NA	
Major evaginations	7 (16.3)	13 (39.4)	3 (12.5)	3 (13.0)	1 (2.3)	NA	0.001
Neoatherosclerosis	3 (7.0)	2 (6.1)	4 (16.7)	2 (8.7)	3 (7.0)	NA	0.629
Lumen area, mm^2							
Reference	7.35±2.49	8.87±2.63	9.11±3.68	8.56±3.12	9.05±2.77	8.04±2.06	0.045
In-device minimal	5.42±1.59	6.54±1.63	5.44±2.06	5.08±2.51	5.04±2.22	4.15±1.93	<0.001
In-device mean	6.92±1.88	7.91±1.93	7.31±2.12	6.39±2.43	7.16±2.52	6.54±2.19	0.098
Area stenosis, %	24.3±14.9	24.3±24.7	35.4±22.1	39.7±22.8	44.3±18.5	49.6±17.3	<0.001
Device area, mm^2							
In-device minimal	6.32±1.64	7.28±1.53	7.37±2.11	6.94±2.09	6.26±1.90	NA	0.029
In-device mean	7.62±1.74	8.44±1.77	8.79±2.54	7.88±2.21	8.38±2.52	NA	0.202
Neointima area, mm^2	0.82±0.38	0.62±0.56	1.50±1.04	1.50±0.74	1.24±0.58	NA	<0.001
Malapposition area, mm^2	0.10±0.53	0.11±0.32	0.01±0.03	0.00±0.02	0.02±0.05	NA	0.450
Uncovered struts, %	3.57±4.78	6.29±7.06	3.56±4.62	2.51±4.54	3.28±4.60	NA	0.056
RUTTS ≥30%	10 (23.3)	14 (42.4)	7 (29.2)	3 (13.0)	10 (23.3)	NA	0.137
Uncovered struts ≥5%	10 (23.3)	14 (42.4)	5 (20.8)	3 (13.0)	11 (25.6)	NA	0.128
Malapposed struts, %	1.09±3.50	2.00±4.04	0.34±1.32	0.13±0.61	0.37±1.04	NA	0.037
Malapposed struts ≥5%	3 (7.0)	4 (12.1)	1 (4.2)	0	0	NA	0.106
Neointima thickness, µm	102.8±46.7	84.0±57.6	158.3±96.5	184.3±105.0	143.5±56.4	NA	<0.001
Distal							
Segment length	28.9±11.8	19.2±11.0	24.5±9.3	25.8±9.6	28.7±10.9	17.3±9.7	<0.001
Plaque type							0.841
Normal*	14 (33.3)	14 (46.7)	7 (29.2)	10 (43.5)	14 (33.3)	12 (41.4)	
Fibrous	14 (33.3)	6 (20.0)	4 (16.7)	6 (26.1)	12 (28.6)	6 (20.7)	
Lipid rich	11 (26.2)	7 (23.3)	10 (41.7)	6 (26.1)	12 (28.6)	6 (20.7)	
Calcified	3 (7.1)	3 (10.0)	3 (12.5)	1 (4.3)	4 (9.5)	5 (17.2)	
Lumen area, mm^2							
Minimal	3.01±1.47	4.59±1.71	3.87±1.53	3.57±1.55	3.89±1.89	4.10±1.54	0.003
Mean	5.07±2.04	6.28±1.82	6.31±2.56	5.64±2.52	6.36±2.58	5.66±1.76	0.083
Vessel area, mm^2							
Mean	8.87±3.41	10.32±2.56	11.07±4-34	9.53±4.16	10.65±3.92	10.25±2.99	0.140
At minimal lumen area	7.03±3.31	8.56±2.54	8.89±3.45	7.71±3.65	8.50±3.47	9.05±2.85	0.086
Plaque burden, %							
Mean	41.7±10.0	39.1±9.7	42.7±7.7	40.2±8.3	40.1±8.5	42.7±12.2	0.610
Maximal	59.9±11.8	50.8±12.7	59.0±8.5	56.2±10.1	57.6±11.3	54.8±15.3	0.032

Data are provided as mean±SD or number (percentage). *P* values indicate a 1-way ANOVA test for quantitative data and a χ^2 test for qualitative data. BES indicates biolimus-eluting stent; BRS, bioresorbable scaffold; EES, everolimus-eluting stent; NA, not applicable; OCT, optical coherence tomography; PLLA, poly-L-lactide; RUTTS, ratio of uncovered to total stent struts and SES, sirolimus-eluting stent.

*Normal artery includes adaptive intima thickening.

significant. Of note, the slope direction of the Pearson correlation coefficient was different among stent types. Only polymer-free BESs showed a mild association (R=0.169) between percentage of uncovered struts and mean lumen diameter change to low-dose acetylcholine.

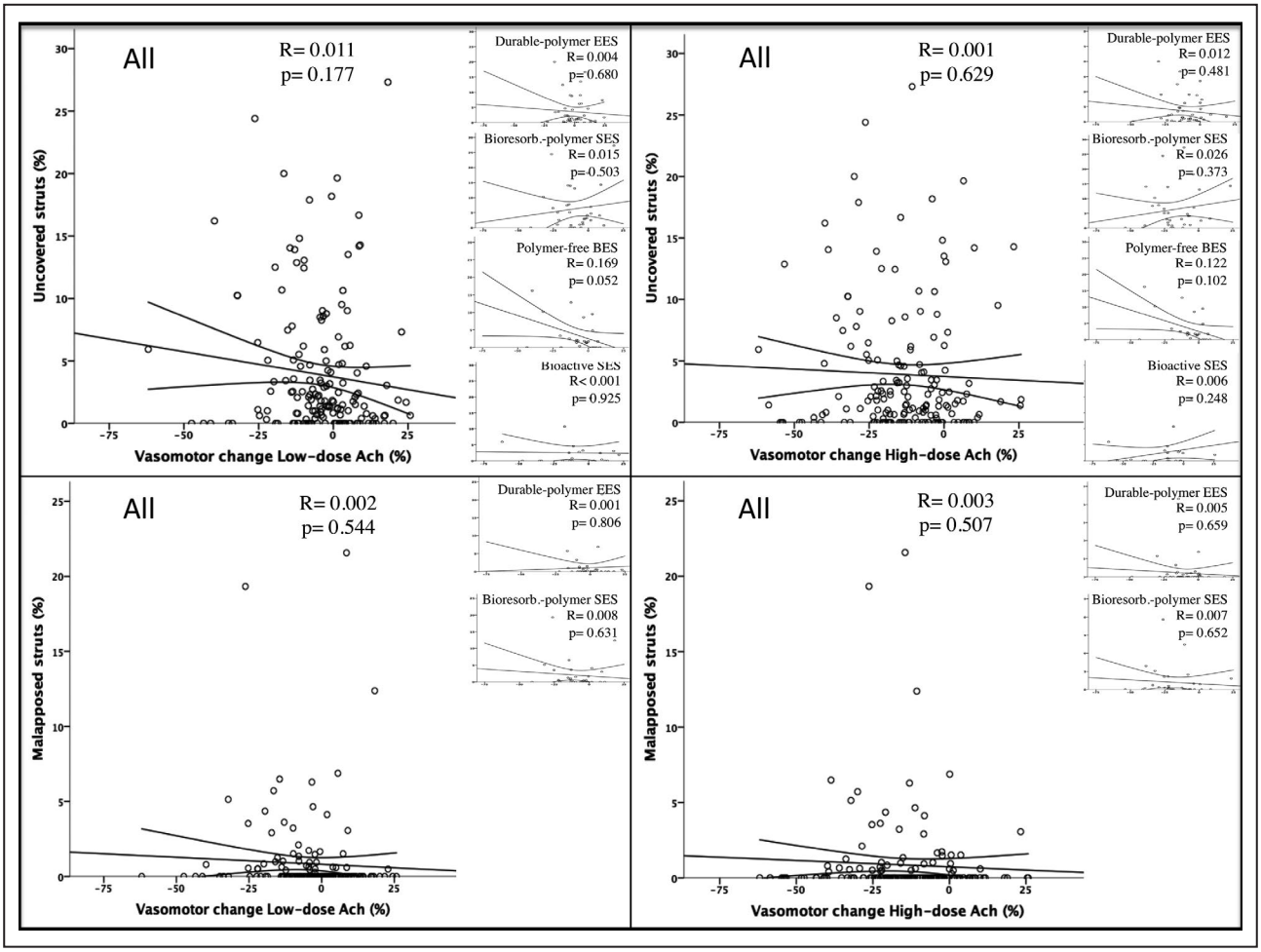

Figure 2. Correlation between strut coverage and incomplete apposition and the vasomotor response to acetylcholine. Vasomotor changes are defined as mean lumen diameter changes of distal stent segment to low-dose acetylcholine (10^{-6} mol/L) and high-dose acetylcholine (10^{-4} mol/L) with respect to the baseline follow-up. Ach indicates acetylcholine; BES, biolimus-eluting stent; EES, everolimus-eluting stent; and SES, sirolimus-eluting stent.

Predictors of Endothelium-Dependent Vasomotor Response

Predictive univariate and multivariate (linear) models of vasomotor changes to low-dose and high-dose intracoronary acetylcholine are shown in Tables S3 and S4. Age, sex, smoking, dyslipidemia, previous acute coronary syndrome, stent length, device type, and angiographic lumen loss were associated in the univariate analyses. Multivariate models of the vasomotor response to low-dose acetylcholine showed bioresorbable-polymer SESs and angiographic lumen loss as independent factors. Patient's age and bioresorbable-polymer SESs were independent predictive factors of the vasomotor response to high-dose acetylcholine infusion.

Figure 3 shows the histogram frequency distribution of the vasomotor changes at low-dose and high-dose acetylcholine infusions. Endothelial dysfunction (defined as ≥4% vasoconstriction) was observed in 46.6% of patients (at low-dose acetylcholine infusion) and 68.9% of patients (at high-dose acetylcholine infusion). Predictive univariate and multivariate (binary logistic) models of endothelial dysfunction to low-dose and high-dose acetylcholine are shown in Tables 5 and 6. Hypertension, left anterior descending stent implantation, stent type, total stent length, distal reference lumen diameter, and stent malapposition were associated with endothelial dysfunction in the univariate analyses. However, multivariate models failed to identify any statistically significant association with any of those covariates. The low-dose acetylcholine endothelial dysfunction multivariate model showed a trend toward larger dysfunction in patients with hypertension (P=0.070) and patients treated with bioresorbable-polymer SESs (P=0.083).

DISCUSSION

The main findings of the study are (1) at follow-up, event-free patients treated with current iterations of DESs and BRSs often showed endothelial dysfunction of distal coronary segments, regardless of the

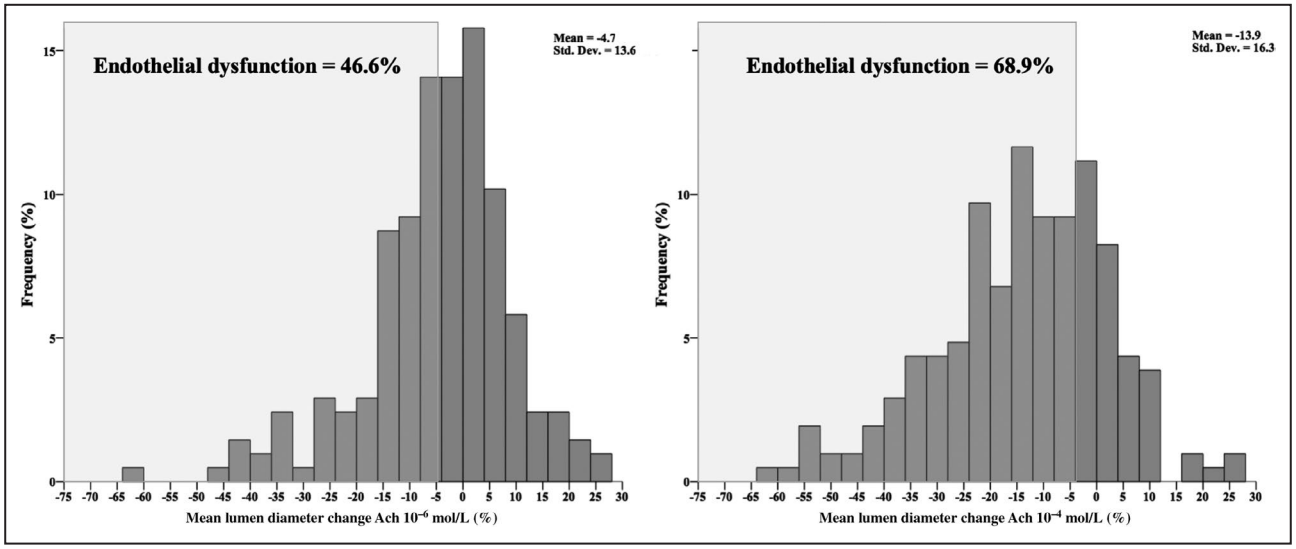

Figure 3. Frequency distribution of endothelium-dependent vasomotor change.
Frequency histogram of mean lumen diameter changes (percentage) to incremental doses of acetylcholine. Endothelial dysfunction was defined as ≥4% vasoconstriction according to the core laboratory variability. Ach indicates acetylcholine; and Std. Dev., standard deviation.

device type; (2) although all DESs and BRSs had different healing patterns, as assessed by OCT, strut coverage and apposition did not modify the vasomotor response to acetylcholine; and (3) plaque-type characteristics of distal segments were not associated with the endothelium-dependent vasomotor response to acetylcholine.

Current evidence of endothelial dysfunction after PCI is still controversial and not fully understood for several reasons. First, preexisting endothelial dysfunction is probably the most important contributing factor of the vasomotor response observed in distal coronary segments. In patients with stable angina and healthy or nonobstructive coronary arteries, the prevalence of epicardial endothelial dysfunction has been noted to be between 40% and 70%.[11–13] This prevalence is similar to that noted in distal coronary segments treated with the current generations of DESs and BRSs. Second, most of the evidence regarding the endothelial function after PCI comes from nonrandomized studies including few patients. Moreover, several of those studies included patients with persistent symptoms or with multivessel disease scheduled for staged PCI. In our opinion, randomized trials aiming to recruit patients for scheduled, per protocol, dedicated vasomotor test at follow-up is of paramount importance to assess the device-related vasomotor response. Finally, endothelial function assessment has been performed following different methods such as supine exercise, atrial pacing, and intracoronary acetylcholine infusion, and this hampers the interpretation of the vasomotor changes observed with different devices. In addition, the intracoronary acetylcholine vasomotor test has been performed using different infusion doses, flow rates, and selective infusions.

Endothelial function assessment with intracoronary acetylcholine infusion is often associated with cardiac rhythm disorders (such as bradycardia and transient atrioventricular blocks) and in few cases with flow-limiting coronary spasms. For these reasons, it is advisable to start with low acetylcholine doses and, in the case of no complications, follow with larger doses. Most of the protocols show significant differences among low acetylcholine doses but share the same distal intracoronary dilution at the highest dose (estimated around 10^{-6} mol/L considering a coronary flow of 80 mL/min in selected arteries). Table S5 summarizes some of those endothelial function protocols with the estimated distal coronary acetylcholine dilutions. It is well known that the vasomotor response to acetylcholine has a dose-dependent correlation, especially in men.[11] A careful revision of the literature shows this dose-dependent relationship using low-dose (10^{-6} mol/L) and high-dose (10^{-4} mol/L) acetylcholine infusion or equivalents (Figure 4).

In the present study, bioresorbable-polymer SESs had the statistically significant largest vasoconstriction and a trend toward larger endothelial dysfunction than other stent technologies. It is noteworthy that bioresorbable-polymer SESs had the largest percentage of uncovered struts (6.3%), malapposed struts (2.0%), major coronary evaginations (39.4%), and absent neointima (36.4%). However, the durable-polymer EES showed several OCT findings indicative of poor stent healing as well (3.6% uncovered struts, 1.1% malapposed struts, 16.3% major coronary evaginations, and

Table 5. Predictors of Distal Coronary Endothelial Dysfunction With Low-Dose Acetylcholine

Parameter	No endothelial dysfunction (n=110), mean±SD or n (%)	Endothelial dysfunction (n=96), mean±SD or n (%)	Odds ratio (95% CI)	*P* value*	Adjusted odds ratio (95% CI)	*P* value†
Age, y	59.1±8.4	57.9±9.5	0.984 (0.955–1.015)	0.315	…	…
Male sex	98 (89.1)	86 (89.6)	1.053 (0.433–2.590)	0.909	…	…
Current smoker	50 (45.5)	49 (51.0)	1.251 (0.721–2.172)	0.426	…	…
Hypertension	52 (47.3)	54 (56.2)	1.434 (0.830–2.478)	0.197	1.721 (0.957–3.092)	0.070
Hypercholesterolemia	77 (70.0)	58 (60.4)	0.654 (0.368–1.162)	0.152	…	…
Diabetes	14 (12.7)	15 (15.6)	1.270 (0.578–2.789)	0.552	…	…
Body mass index	28.0±4.7	28.9±4.1	1.050 (0.982–1.122)	0.151	…	…
Left ventricle EF, %	53.3±9.3	53.7±9.3	1.005 (0.974–1.036)	0.768	…	…
Acute coronary syndrome	97 (88.2)	88 (91.7)	1.474 (0.583–3.726)	0.412	…	…
Left anterior descending	51 (46.4)	57 (59.4)	1.691 (0.975–2.932)	0.061	1.597 (0.878–2.908)	0.125
Number of diseased vessels >1	33 (30.0)	31 (32.3)	1.113 (0.615–2.013)	0.724	…	…
Stent type						
Durable polymer EES	26 (59.1)	18 (40.9)	Reference	NA	Reference	NA
Bioresorbable polymer SES	15 (42.9)	20 (57.1)	1.926 (0.775–4.786)	0.148	2.313 (0.896–5.972)	0.083
Polymer-free BES	12 (50.0)	12 (50.0)	1.565 (0.582–4.204)	0.375	1.677 (0.606–4.641)	0.320
Bioactive SES	12 (48.0)	13 (52.0)	1.444 (0.531–3.929)	0.411	2.378 (0.790–7.156)	0.123
PLLA-based BRS	25 (56.8)	19 (43.2)	1.098 (0.471–2.560)	0.829	1.318 (0.543–3.199)	0.542
Mg-based BRS	20 (58.8)	14 (41.2)	1.011 (0.407–2.511)	0.981	1.163 (0.449–3.013)	0.756
Total stent length, mm	20.0±4.8	21.1±6.5	1.037 (0.990–1.086)	0.129	1.041 (0.992–1.094)	0.105
Stent size, mm	3.2±0.4	3.3±0.3	1.642 (0.713–3.782)	0.244	…	…
QCA: poststent RVD, mm	2.85±0.46	2.89±0.42	1.217 (0.651–2.274)	0.538	…	…
QCA: FU in-stent MinLD, mm	2.37±0.57	2.42±0.54	1.143 (0.699–1.872)	0.594	…	…
QCA: late lumen loss, mm	0.25±0.46	0.29±0.35	0.796 (0.395–1.601)	0.522	…	…
QCA: distal RVD, mm	2.21±0.60	2.10±0.41	0.641 (0.381–1.076)	0.093	0.684 (0.388–1.208)	0.191
OCT: absent neointima pattern	18 (20.7)	17 (21.5)	1.051 (0.498–2.217)	0.896	…	…
OCT: uncovered struts, %	3.5±5.2	4.3±5.5	1.028 (0.968–1.091)	0.372	…	…
OCT: malapposed struts, %	0.7±2.8	1.0±2.6	1.040 (0.911–1.188)	0.562	1.029 (0.921–1.150)	0.614
OCT: neointima thickness, μm	128.6±76.8	128.8±77.9	1.000 (0.996–1.004)	0.986	…	…
OCT: distal plaque type					…	…
Normal	37 (36.3)	34 (38.4)	Reference	NA		
Fibrous	27 (26.5)	21 (23.9)	0.846 (0.405–1.767)	0.657		
Lipid rich	29 (28.4)	23 (26.1)	0.863 (0.421–1.771)	0.688		
Calcific	9 (8.8)	10 (11.4)	1.209 (0.439–3.332)	0.713		
OCT: distal plaque burden, %	40.3±9.5	41.9±9.5	1.018 (0.987–1.050)	0.263	…	…

Endothelial dysfunction was defined as mean lumen diameter vasoconstriction ≥4.0% at low-dose acetylcholine (10^{-6} mol/L). BES indicates biolimus-eluting stent; BRS, bioresorbable scaffold; EES, everolimus-eluting stent; EF, ejection fraction; MinLD, minimal lumen diameter; NA, not applicable; OCT, optical coherence tomography; PLLA, poly-L-lactide; QCA, quantitative coronary angiography; RVD, reference vessel diameter; and SES, sirolimus-eluting stent.

**P* values indicate the results of the univariate analyses obtained with generalized estimating equations (binary logistic).

†*P* values indicate the results of the multivariate analyses obtained with generalized estimating equations (binary logistic).

23.3% absent neointima), but was associated with the best endothelial function. These results are in line with previous publications in which poor strut coverage, as assessed by OCT, was not associated with endothelial dysfunction.[14–16] Therefore, other unknown factors, different than strut coverage, might also explain the apparent mild differences among bare-metal stents, DESs, and BRSs shown in the Figure 4.[9,17] It is possible that the direct antiproliferative drug action, biocompatibility of different stent polymers and materials, and the quality of the reendothelialization may play important roles in the appearance of endothelial dysfunction after device implantation.[18,19] Unfortunately, OCT is unable to assess the mono-cell layer of endothelial cells (<1 μm thickness) because of the axial resolution of the imaging technique (15–20 μm).

Several studies, including patients with angina and no obstructive coronary arteries, have associated

Table 6. Predictors of Distal Coronary Endothelial Dysfunction With High-Dose Acetylcholine

Parameter	No endothelial dysfunction (n=64), mean±SD or n (%)	Endothelial dysfunction (n=142), mean±SD or n (%)	Odds ratio (95% CI)	*P* value*	Adjusted odds ratio (95% CI)	*P* value†
Age, y	59.0±8.6	58.3±9.1	1.016 (0.970–1.064)	0.506	…	…
Male sex	58 (90.6)	126 (88.7)	0.815 (0.303–2.190)	0.684	…	…
Current smoker	32 (50.0)	67 (47.2)	0.893 (0.494–1.614)	0.709	…	…
Hypertension	28 (43.8)	78 (54.9)	1.567 (0.866–2.835)	0.138	1.701 (0.878–3.297)	0.116
Hypercholesterolemia	43 (67.2)	92 (64.8)	0.899 (0.482–1.677)	0.737	…	…
Diabetes	9 (14.1)	20 (14.1)	1.002 (0.429–2.341)	0.997	…	…
Body mass index	27.8±4.3	28.7±4.5	1.023 (0.926–1.130)	0.656	…	…
Left ventricle EF, %	53.0±8.0	53.7±9.8	1.008 (0.963–1.055)	0.730	…	…
Acute coronary syndrome	55 (85.9)	117 (82.7)	0.667 (0.233–1.909)	0.451	…	…
Left anterior descending	30 (46.9)	78 (54.9)	1.381 (0.765–2.493)	0.284	1.278 (0.671–2.434)	0.455
Number of diseased vessels >1	19 (29.7)	45 (31.7)	1.099 (0.578–2.090)	0.779	…	…
Stent type						
Permanent polymer EES	13 (29.5)	31 (70.5)	Reference	NA	Reference	NA
Bioresorbable polymer SES	6 (17.1)	29 (82.9)	2.027 (0.677–6.065)	0.206	2.396 (0.734–7.822)	0.148
Polymer-free BES	9 (37.5)	15 (62.5)	0.699 (0.245–1.997)	0.504	0.798 (0.284–2.244)	0.669
Bioactive SES	9 (36.0)	16 (64.0)	0.746 (0.263–2.114)	0.581	1.012 (0.320–3.197)	0.984
PLLA-based BRS	15 (34.1)	29 (65.9)	0.811 (0.330–1.992)	0.647	0.886 (0.355–2.211)	0.796
Mg-based BRS	12 (35.3)	22 (64.7)	0.769 (0.296–2.000)	0.590	0.868 (0.332–2.269)	0.773
Total stent length, mm	20.6±5.6	20.4±5.7	0.995 (0.945–1.048)	0.845	0.997 (0.943–1.055)	0.919
Stent size, mm	3.3±0.4	3.2±0.3	0.776 (0.251–2.395)	0.659	…	…
QCA: poststent RVD, mm	2.90±0.45	2.86±0.44	1.103 (0.481–2.527)	0.817	…	…
QCA: FU in-stent MinLD, mm	2.43±0.57	2.38±0.55	0.840 (0.479–1.473)	0.543	…	…
QCA: late lumen loss, mm	0.21±0.48	0.29±0.37	1.668 (0.629–4.423)	0.304	…	…
QCA: distal vessel RVD, mm	2.23±0.54	2.13±0.51	0.694 (0.391–1.233)	0.213	0.774 (0.408–1.469)	0.433
OCT: absent neointima pattern	10 (19.6)	25 (21.7)	1.139 (0.501–2.589)	0.756	…	…
OCT: uncovered struts, %	4.0±5.4	3.9±5.3	0.995 (0.935–1.059)	0.874	…	…
OCT: malapposed struts, %	0.4±1.1	1.0±3.1	1.160 (0.951–1.413)	0.143	1.119 (0.950–1.319)	0.177
OCT: neointima thickness, μm	140.2±89.1	123.8±71.1	0.997 (0.993–1.002)	0.227	…	…
OCT: distal plaque type					…	…
Normal	23 (39.0)	48 (36.6)	Reference	NA		
Fibrous	14 (23.7)	34 (26.0)	1.164 (0.525–2.581)	0.709		
Lipid rich	16 (27.1)	36 (27.5)	1.078 (0.499–2.330)	0.848		
Calcific	6 (10.2)	13 (9.9)	1.038 (0.350–3.080)	0.946		
OCT: distal plaque burden, %	40.0±9.9	41.5±9.3	1.017 (0.983–1.052)	0.332	…	…

Endothelial dysfunction was defined as mean lumen diameter vasoconstriction ≥4.0% at high-dose acetylcholine (10^{-4} mol/L). BES indicates biolimus-eluting stent; BRS, bioresorbable scaffold; EES, everolimus-eluting stent; MinLD, minimal lumen diameter; NA, not applicable; OCT, optical coherence tomography; PLLA, poly-L-lactide; QCA, quantitative coronary angiography; RVD, reference vessel diameter; and SES, sirolimus-eluting stent.

**P* values indicate the results of the univariate analyses obtained with generalized estimating equations (binary logistic).

†*P* values indicate the results of the multivariate analyses obtained with generalized estimating equations (binary logistic).

the observation of epicardial coronary endothelial dysfunction with adverse cardiovascular outcomes at long-term follow-up.[20] In a meta-analysis, patients with endothelial dysfunction showed larger risks of a composite end point of cardiac death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, and stroke than patients without endothelial dysfunction.[20] The clinical relevance of distal peridevice endothelial dysfunction remains unknown. One study that included 104 patients with persistent symptoms after stent implantation undergoing to vasomotor examination showed that 49% of the patients had epicardial vasoconstriction to acetylcholine infusion (73% located in the stented vessel—alone or together with other vessels—and 27% merely in nonstented vessels) at 18 months.[21] Similar to the present

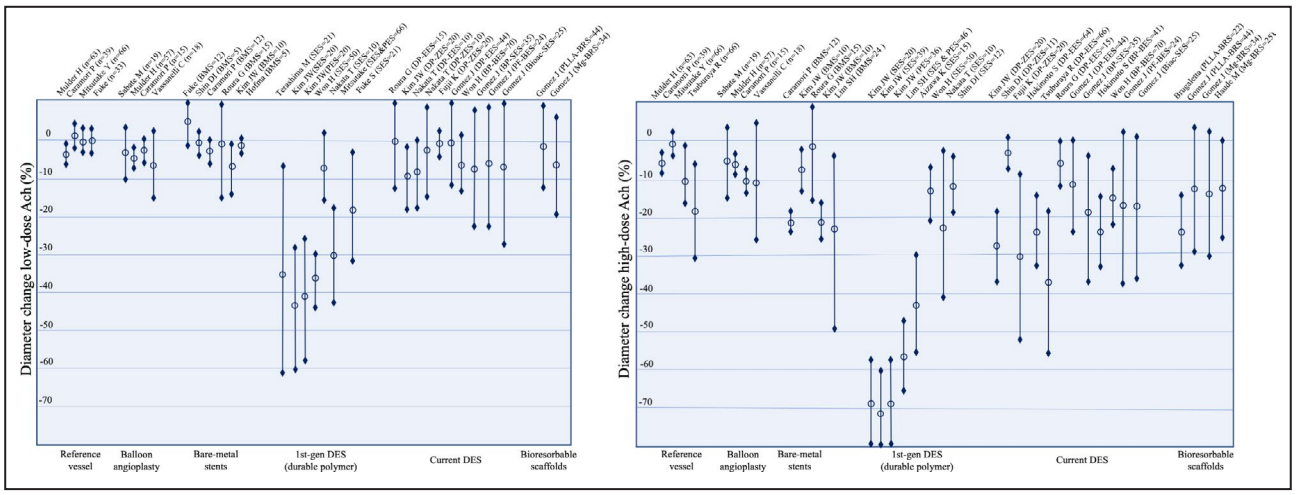

Figure 4. Vasomotor responses to low-dose and high-dose acetylcholine.
Main mean diameter vasomotor changes (percentage±SD) to intracoronary low-dose acetylcholine (estimated intracoronary dilution of 10^{-8} mol/L) and to high-dose acetylcholine (10^{-6} mol/L) reported in previous studies according to stent type. Ach indicates acetylcholine; DES, drug-eluting stent; and gen, generation.

study, the population included in this study were more frequently men and had more severe risk factor profiles than patients undergoing an acetylcholine vasomotor test because of angina and no obstructive coronary arteries.[12,21]

This study has several limitations. First, according to the study protocols, the vasomotor test was performed at different months of follow-up for each device type. For this reason, follow-up time cannot be added as covariate in the multivariate models and therefore has not been considered in the present study. However, it is remarkable that 83% of patients underwent vasomotor test between 6 and 13 months follow-up. Moreover, vasomotor tests were performed selectively for each device when the healing process had theoretically achieved a steady state after complete release of the antiproliferative drug and coating (if applicable) had been resorbed. Second, the study groups had a limited number of patients and were not based on sample size calculations for the assessment of the study end points. Moreover, baseline clinical and procedural characteristics were significantly different between groups. Third, the vasomotor test was performed with intracoronary infusion of acetylcholine via microcatheter located 5-mm proximal to the stent edge. This was performed to avoid complications associated with the infusion of acetylcholine via guiding catheter but limits the assessment of the stent-related proximal endothelium-dependent vasomotor response. Finally, ECG changes and angina symptom assessment were not obtained during the vasomotor test. Therefore, the endothelial vasomotor function of the coronary microcirculation is unknown in the present study.

CONCLUSIONS

Endothelial dysfunction of distal coronary segments treated with several generations of DESs and BRSs is often observed in event-free patients at follow-up. Although all generations of DESs and BRSs clearly show different healing patterns, this seems to have no significant effect, or a minimal effect, on the vasomotor response to acetylcholine infusion. Further randomized trials powered to assess the differences between stent technologies are needed to investigate the role of endothelial dysfunction after stent implantation.

ARTICLE INFORMATION

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Disclosures

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Vasomotor test

Patients were requested to stop all vasomotor drugs at least 24 hours before coronary angiography. Non-study vasomotor drugs were not allowed before acetylcholine (Ach) infusion (i.e., in case of radial access). Operators were requested to repeat the same angiographic views as in the index procedure, and those recordings were used as reference follow-up images.

Then, endothelium-dependent vasomotor function was examined by the intracoronary infusion of two incremental doses of Ach for 2 minutes at 2 ml/min: low-dose Ach (10^{-6} mol/L) and high-dose (10^{-4} mol/L). Ach doses were infused via workhorse micro-catheter located >5 mm proximal to the stent. Assuming 80 ml/min of resting coronary flow, the final blood concentrations were estimated as 10^{-8} mol/L and 10^{-6} mol/L, respectively. In case of severe spasm, angina symptoms, atrial fibrillation or AV block during low-dose Ach infusion, the vasomotor test was stopped immediately and high-dose Ach infusion was not given. Endothelium-independent vasomotor test was performed by 200 μg of nitro-glycerine (NTG) bolus injection via the guiding catheter. All vasomotor drug concentrations were infused with 2 minutes of washout period in between. Cine-fluoroscopic recordings were obtained for each phase at the same angiographic view as the reference follow-up image.

Angiographic analysis

Angiographic analysis was performed by a core-laboratory (BARCICORE-lab, Barcelona, Spain) using specific software for quantitative coronary angiography analysis (CASS 5.9; Pie Medical BV, Maastricht, the Netherlands). Analysts were blinded to the study groups.

The vasomotor responses of the distal coronary segment, to endothelium-dependent and independent stimuli, were assessed taking into account the core-laboratory variability for mean lumen diameter repeated measures. The 2-standard deviation (SD) difference between quantitative angiographic measures of matched coronary segments is 3.9%. Therefore, a vasoconstrictive response to low-dose or high-dose Ach infusion (meaning endothelial dysfunction) was defined when ≥4% vasoconstriction was observed with respect to reference mean lumen diameter. Distal coronary segment was defined as the segment between the stent edge and up to 20-40 mm according to natural landmarks (such as bifurcations).

Quantitative optical coherence tomography analysis

Quantitative optical coherence tomography (OCT) analysis was performed each 1-mm according to standard core-laboratory procedures using specific off-line software (LightLab Imaging, US). In summary, the software drew the lumen contour automatically of all proximal, stent and distal segments. Stent contour was performed semi-automatically by pointing the inner strut surface of the stent struts. Scaffold contour of polymer-based bioresorbable scaffolds (BRS) was drawn from the endoluminal border of the black box. Scaffold contours of magnesium-based BRS was not feasible due to the advanced bioresorption state observed at 1 year.

Taking into account the axial resolution of OCT (20 μm) and the different strut thickness of the study devices (Table S2); strut malapposition was defined as distances between the inner strut surface and the lumen contour >110 μm for durable-polymer everolimus-eluting stents (EES), >80 μm (≤ 3 mm nominal diameter stents) and >100 μm (>3 mm nominal diameter stents) for bioresorbable-polymer sirolimus-eluting stents (SES), >130 μm for polymer-free

biolimus-eluting stents (BES) and >120 μm for bioactive SES. Strut malapposition of BRS were assessed qualitatively when the abluminal border of the strut was separated from the vessel wall.

In case of permanent DES, neointima thickness (NIT) was automatically estimated from the endoluminal border of the stent struts to the lumen contour. In case of negative (or zero) values, stent struts were classified as uncovered. NIT of polymeric BRS was estimated from the endoluminal border of the strut cores (black boxes). Since the mean ± SD thickness of the endoluminal frame of polymeric struts at post-implantation (without tissue coverage) is 34±6 μm; NIT of polymer based BRS was estimated resting 30 μm to the crude distance obtained from the endoluminal border of the black box. Uncovered struts were defined when NIT was ≤ 30 μm.

Distal native coronary segment was analysed > 5 mm distal to the stent edge up to the last cross-section of the OCT recording. The software automatically drew the lumen contour and dedicated analysts manually drew the external elastic membrane (EEM) at 1-mm cross-sections. Plaque burden was estimated for each cross-section as (lumen-EEM/EEM x 100) and the mean value of all analysed cross-section has been estimated for lesion level analysis.

Qualitative optical coherence findings of the device segment

Two blinded analysts were requested to assess the following in-stent qualitative OCT findings: the neointima pattern, the observation of cross-sections with a ratio of uncovered to total stent struts (RUTSS) ≥30%, major coronary evaginations and neoatherosclerotic plaques.

Neointima pattern was classified into 4 types according to the neointima tissue observed at cross-sections with largest neointima tissue: absent, homogeneous,

heterogeneous and layered patterns. Homogeneous, heterogeneous and layered neointima were assessed in case the cross-section with largest neointima tissue had neointima thickness >100 μm in >50% of the stent perimeter. Absent neointima was defined in case any OCT cross-section presented with such amount of neointima tissue. Coronary evaginations were defined as the presence of an outward bulge in the luminal vessel contour between apposed struts with a maximal depth of the bulge exceeding that of the actual strut thickness. Major evaginations were defined as the occurrence of cross-sectional evagination in ≥ 3 mm of length with a minimal evagination depth of 10% of the nominal stent diameter. Neoatherosclerotic plaques were defined as the presence of a fibroatheroma or fibrocalcific plaques within the neointima of a stented segment with a longitudinal extension of ≥ 1 mm. Fibroatheroma plaques were characterized as signal-poor regions with high signal-attenuation and diffuse borders. Fibrocalcific plaques were defined as signal-poor regions with low signal attenuation and clear plaque borders.

Qualitative optical coherence findings of native arteries (distal to device edge)

Plaque type of distal coronary segment was assessed in case of >5 mm native coronary artery imaged distal to the stent edge. Operators were requested to classify the most frequent plaque type in the entire distal segment as follows: normal or adaptive intima thickening, fibrous plaque, lipid-rich plaque and calcific plaque. Plaque types were classified according to the following definitions:

1. Normal coronary artery wall with a three-layered architecture and a thin intima (< 300 μm), without intimal thickening, fibrotic, lipid or calcific plaque.

2. Intimal thickening. Preserved layered architecture, but thickened initima (300-600 μm).
3. Fibrotic plaques. The endothelial layer is a homogeneous, high backscattering tissue > 600 μm depth.
4. Lipid-rich (fibrolipidic) plaques. The endothelial layer contains a low-signal pool with diffuse border and has high attenuation of the OCT signal. A lipid-rich plaque was defined as presence of a lipid pool in 2 or more quadrants in any of the cross-sectional images. Thin-cap fibroatheroma was defined as a lipid-rich plaque with the thinnest fibrous cap thickness < 65 μm.
5. Calcific (fibrocalcific) plaques. The endothelial layer contains a low-signal pool with clear border and has low attenuation of the OCT signal.

Table S1. Study design characteristics of the 4 studies included in the present investigation.

	BVS-FLOW	RE-TROFI2	MAGSTEMI	FUNCOMBO
Randomization	Xience (Abbott, United States) *vs.* Absorb (Abbott, United States)	Xience (Abbott, United States) *vs.* Absorb (Abbott, United States)	Orsiro (Biotronik, Switzerland) *vs.* Magmaris (Biotronik, Switzerland)	Combo (OrbusNeich, Netherlands) *vs.* Biofreedom (Biosensors; Switzerland)
Eligible patients	70	63	108 out of 150*	60
Number of Institutions	3	2	4	3
Study stents	Xience (Abbott, United States) *vs.* Absorb (Abbott, United States)	Xience (Abbott, United States) *vs.* Absorb (Abbott, United States)	Orsiro (Biotronik, Switzerland) *vs.* Magmaris (Biotronik, Switzerland)	Combo (OrbusNeich, Netherlands) *vs.* Biofreedom (Biosensors; Switzerland)
Main inclusion criteria	Stable or stabilized coronary syndromes. DM excluded	STEMI	STEMI	STEMI
Primary endpoint	Endothelial-dependent vasomotion within the scaffold segment	Endothelial-dependent vasomotion within the scaffold segment	Endothelial-independent vasomotion within the scaffold segment	Endothelial-dependent vasomotion of distal coronary segment
Power calculation for primary endpoint	A total of 35 patients per group were requested to assess a difference in Doppler-ultrasound average peak velocity (APV) larger than 12.0 cm/sc. at maximal hyperemia.	No sample size calculation	A total of 148 patients to detect in-stent/scaffold vasodilatory response ≥3% in ~15% in the Orsiro group and 40% in the Magmaris group.	No sample size calculation
Follow-up (months)	13	36	12	6
Patients with Ach vasomotor test	54	35	68	49
Causes for NO vasomotor test:				
- Refused FU angiography	9	16	8	8
- Clinical event before angio FU	1	3	5	0
- Target vessel stenosis at FU	4	3	10	1
- Coronary spasms before Ach	1	0	3	1
- Other	1	6	14	1

* Acetylcholine test was performed, as per protocol, in consecutive patients of 4 selected Institutions participating in the MAGSTEMI trial. There were 108 patients included in those Institutions.
DM= diabetes mellitus; FU= follow-up; STEMI= ST-segment elevation myocardial infarction.

Table S2. Stent design characteristics of study devices.

	Durable-polymer EES	Bioresorbable-polymer SES	Polymer-free BES	Bioactive SES	Polymer-based BRS	Mg-based BRS
Brand	Xience (Abbott, United States)	Orsiro (Biotronik, Switzerland)	Biofreedom (Biosensors; Switzerland)	Combo (OrbusNeich, Netherlands)	Absorb (Abbott, United states)	Magmaris (Biotronik, Switzerland)
Platform						
Type	Permanent	Permanent	Permanent	Permanent	Bioresorbable	Bioresorbable
Material	CoCr	CoCr	Stainless steel	Stainless steel	Polymer (PLLA)	Magnesium
Strut thickness (µm)	87	60-80	119	100	157	150
Coating						
Type	Durable	Bioresorbable	No polymer	Bioresorbable	Bioresorbable	Bioresorbable
Material	Polyvinylcrylate	PLLA	-	PDLLA	PDLLA	PLLA
Absorption time	-	15 months	-	90 days	90 days	15 months
Polymer thickness (µm)	7-8	7	-	5	2-4	1
Distribution	Conformal	Conformal/Asym	-	Abluminal	Conformal	Conformal
Additional coating	-	Silicon carbide	-	Anti-CD34 Ab.	-	-
Antiproliferative drug						
m-TOR inhibitor	Everolimus	Sirolimus	Biolimus A9	Sirolimus	Everolimus	Sirolimus
Dose	100 µg/cm2	140 µg/cm2	15.6 µg/mm	5 µg/mm	100 µg/cm2	140 µg/cm2
Distribution	Conformal	Conformal	Abluminal	Abluminal	Conformal	Conformal
Release (80%)	1 month	3 months	48 hours	14 days	1 month	3 months
Complete release	4 months	12 months	30 days	45 days	3 months	Unknown
Loss of mechanical force	Never	Never	Never	Never	6-12 months	<3 months
Complete bioresorption	Never	Never	Never	Never	4 years	9 months

CoCr = Cobalt-chromium; PLLA= poly-L-lactide; PDLLA= Poly-D,L-lactide

Table S3. Predictors of low dose Ach vasomotor change of distal coronary segment.

Parameter	Exponential B (95% CI)	p value	Adjusted exponential B (95% CI)	p value
Age (years)	0.92 (0.78 to 1.09)	0.319	0.96 (0.82 to 1.14)	0.660
Male	17.76 (0.23 to 1373.52)	0.195	22.39 (0.25 to 2036.91)	0.177
Current smoker	84.47 (2.10 to 3393.65)	0.019	4.62 (0.11 to 200.97)	0.426
Hypertension	2.24 (0.05 to 94.42)	0.673	-	-
Hypercholesterolemia	0.043 (<0.01 to 1.87)	0.102	0.07 (<0.01 to 2.89)	0.162
Diabetes mellitus	6.30 (0.06 to 643.88)	0.435	-	-
Body mass index	1.25 (0.85 to 1.83)	0.254	-	-
Left ventricle ejection fraction (%)	1.08 (0.89 to 1.31)	0.443	-	-
Acute coronary syndrome	21.74 (0.20 to 2372.73)	0.198	0.12 (<0.01 to 18.03)	0.404
Left anterior descending (culprit)	2.02 (0.05 to 82.59)	0.711	-	-
Number of vessel disease > 1	13.63 (0.18 to 1010.09)	0.234	-	-
Stent type:				
Permanent polymer EES	Reference	NA	Reference	NA
Bioresorbable polymer SES	2649.48 (14.84 to 472929.06)	0.003	3211.53 (26.86 to 383966.39)	0.001
Polymer-free BES	1398.15(0.2.34 to 837317.84)	0.026	182.67 (0.20 to 170788.18)	0.136
Bioactive SES	2791.49 (0.67 to 111688162.60)	0.062	1099.45 (0.21 to 5740609.32)	0.109
PLLA-based BRS	4.25 (0.0.04 to 408.03)	0.534	1.29 (0.16 to 113.37)	0.912
Mg-based BRS	229.07 (1.11 to 47384.01)	0.046	55.63 (0.32 to 9732.03)	0.127
Total stent length (mm)	1.33 (0.97 to 1.83)	0.077	1.26 (0.93 to 1.72)	0.137
Stent size (mm)	0.91 (<0.01 to 269.19)	0.975	-	-
QCA – Poststent RVD	0.22 (<0.01 to 31.96)	0.548	-	-
QCA – FU in-stent MinLD (mm)	0.15 (0.01 to 4.93)	0.290	-	-
QCA – Late lumen loss (mm)	161.32 (1.651 to 15763.53)	0.030	240.15 (1.76 to 32733.76)	0.029
QCA – Distal vessel RVD (mm)	0.27 (0.01 to 6.37)	0.420	-	-
OCT – Absent neointima pattern	0.89 (0.01 to 76.49)	0.960	-	-
OCT – Uncovered struts	1.32 (0.82 to 2.12)	0.255	-	-
OCT – Malapposed struts	1.28 (0.47 to 3.47)	0.634	-	-
OCT – Neointima thickness (µm)	1.01 (0.98 to 1.04)	0.437	-	-
OCT – Distal plaque type:				
Normal	Reference	NA	-	-
Fibrous	1.92 (0.01 to 326.73)	0.803	-	-
Lipid-rich	1.89 (0.02 to 168.63)	0.782	-	-
Calcific	3.96 (<0.01 to 9130.33)	0.727	-	-
OCT – Distal plaque burden (%)	1.15 (0.94 to 1.39)	0.172	-	-

Generalized estimating equations linear model. Mean lumen diameter changes have been inverted (vasoconstrictive response have positive values) to facilitate the results interpretation.

MinLD= minimal lumen diameter; OCT= optical coherence tomography; QCA= quantitative coronary angiography; RVD= reference vessel diameter

Table S4. Predictors of high dose Ach vasomotor change of distal coronary segment.

Parameter	Exponential B (95% CI)	p value	Adjusted exponential B (95% CI)	p value
Age (years)	0.75 (0.59 to 0.95)	0.018	0.77 (0.60 to 0.97)	0.039
Male	75.24 (0.49 to 11511.92)	0.092	75.66 (0.49 to 11595.59)	0.092
Current smoker	56.51 (0.64 to 4965.76)	0.077	1.25 (0.01 to 166.24)	0.929
Hypertension	3.17 (0.04 to 280.58)	0.614	-	-
Hypercholesterolemia	0.03 (<0.01 to 2.85)	0.127	0.05 (<0.01 to 5.32)	0.211
Diabetes mellitus	0.76 (<0.01 to 198.59)	0.922	-	-
Body mass index	1.32 (0.81 to 2.13)	0.262	-	-
Left ventricle ejection fraction (%)	1.08 (0.88 to 1.32)	0.464	-	-
Acute coronary syndrome	98.40 (0.27 to 35593.43)	0.127	0.86 (<0.01 to 650.89)	0.963
Left anterior descending (culprit)	11.05 (0.13 to 979.54)	0.294	-	-
Number of vessel disease > 1	11.20 (0.07 to 1685.42)	0.345	-	-
Stent type:				
Permanent polymer EES	Reference	NA	Reference	NA
Bioresorbable polymer SES	1352.54 (3.09 to 591775.18)	0.020	1901.98 (3.64 to 993412.40)	0.018
Polymer-free BES	194.78 (0.02 to 1771687.83)	0.257	27.01 (<0.01 to 558834.80)	0.516
Bioactive SES	171.718 (0.04 to 820772.69)	0.234	64.72 (0.01 to 704096.36)	0.379
PLLA-based BRS	2.06 (0.01 to 642.15)	0.805	1.04 (<0.01 to 402.52)	0.990
Mg-based BRS	20.28 (0.04 to 10079.03)	0.342	5.73 (0.01 to 4655.19)	0.610
Total stent length (mm)	1.06 (0.73 to 1.55)	0.755	0.99 (0.69 to 1.44)	0.966
Stent size (mm)	2.57 (<0.01 to 5932.32)	0.811	-	-
QCA – Poststent RVD	0.03 (<0.01 to 6.26)	0.202	-	-
QCA – FU in-stent MinLD (mm)	0.17 (<0.01 to 8.10)	0.364	-	-
QCA – Late lumen loss (mm)	47.75 (0.16 to 14706.85)	0.186	191.27 (0.35 to 103846.89)	0.102
QCA – Distal vessel RVD (mm)	0.10 (<0.01 to 6.49)	0.276	-	-
OCT – Absent neointima pattern	5.08 (0.01 to 2520.99)	0.608	-	-
OCT – Uncovered struts	1.13 (0.69 to 1.83)	0.630	-	-
OCT – Malapposed struts	1.38 (0.80 to 2.36)	0.245	-	-
OCT – Neointima thickness (µm)	1.00 (0.97 to 1.04)	0.982	-	-
OCT – Distal plaque type:				
Normal	Reference	NA	-	-
Fibrous	15.42 (0.03 to 9056.58)	0.400	-	-
Lipid-rich	0.40 (0.02 to 74.73)	0.730	-	-
Calcific	0.16 (<0.01 to 603.34)	0.659	-	-
OCT – Distal plaque burden (%)	1.07 (0.85 to 1.34)	0.589	-	-

Generalized estimating equations linear model. Mean lumen diameter changes have been inverted (vasoconstrictive response have positive values) to facilitate the results interpretation.

MinLD= minimal lumen diameter; OCT= optical coherence tomography; QCA= quantitative coronary angiography; RVD= reference vessel diameter

Table S5. Available endothelial function protocols.

Group	Infusion mode	Infusion Ach Doses	Infusion time	Comments
Harvard group [22]	Via microcatheter and infusion pump.	4 dilutions of 0.02, 0.2, 2 and 20 μg/ml at 0.8 ml/min.	Each dilution infused for 2 min.	- Final dilutions in selected segments ranging from 10^{-9} to 10^{-6} mol/L. * - Total selective doses of 0.03, 0.3, 3 and 30 μg.
Mayo Clinic group [23]	Via microcatheter and infusion pump.	3 dilutions of 0.18 (10^{-6}), 1.80 (10^{-5}) and 18 μg/ml (10^{-4} mol/L) at 1 ml/min; followed by a final bolus of 100 μg for vasospasm provocation test.	Each dilution infused for 3 min. Final bolus for 20 sc.	- Final dilutions in selected segments ranging from 10^{-8} to 10^{-6} mol/L for. * - Total selective doses of 0.5, 5, 50 and 100 μg. - Performed together with Doppler intracoronary wire.
WISE group [24]	Via guiding catheter and infusion pump	2 dilutions of 0.182 (10^{-6}) and 18.2 μg/ml (10^{-4} mol/L) at 2ml/min	Each dilution infused for 3min.	- Final dilutions in selected arteries of 10^{-8} and 10^{-6} mol/L. - Total selective doses of 0.5 and 50 μg.
Standford group [11]	Manual infusion via guiding catheter.	4 doses of 20, 50, 100 and 200 μg.	Each dilution infused for 1 min.	- Final dilutions in selected arteries ranging from 10^{-7} to 10^{-6} mol/L.*
Korean group [25]	Manual infusion via guiding catheter.	3 doses of 20, 50 and 100 μg.	Each dilution infused for 1 min.	- Final dilutions in selected arteries ranging from 10^{-7} to 10^{-6} mol/L.
Stuttgard group [21]	Manual infusion via guiding catheter.	4 doses of 2, 20, 100 and 200 μg.	Each dilution infused for 3 min.	- Final dilutions in selected arteries ranging from 10^{-8} to 10^{-6} mol/L.*
CorMicA trial and COVADIS group [13,26]	Mixed infusion by infusion pump and manual bolus via guiding catheter.	3 dilutions of 0.182 (10^{-6}), 1.82 (10^{-5}) and 18.2 μg/ml (10^{-4} mol/L) at 1 ml/min. Then, manual bolus of 100 μg for vasospasm provocation test.	Each dilution infused for 2 min. Manual bolus for 20 sc.	- Final dilutions in selected arteries ranging from 10^{-8} to 10^{-6} mol/L. *#
Spanish Society of Cardiology [27]	Manual infusion via guiding catheter.	3 doses of 2, 20 and 100 μg.	Each dilution infused for 3 min.	- Final dilutions in selected arteries of 10^{-8} to 10^{-6} mol/L. *
Present study	Via microcatheter and infusion pump.	2 dilutions of 10^{-6} and 10^{-4} mol/L at 2 ml/min.	Each dilution infused for 2 min.	- Final dilutions in selected segments of 10^{-8} and 10^{-6} mol/L. * - Total selective doses of 0.72 and 72 μg.

* Ach dilutions have been calculated with the molecular weight of acetylcholine chloride (182 gr/mol). Final concentrations have been estimated for a coronary flow of 80 ml/min in the proximal segment of the 3 main coronary arteries (i.e., 160 ml/min blood flow for left main coronary artery).
# Despite Ach dilutions are close to the referred mol/L, they are 50% inferior with respect to other protocols.