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.