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Authors: Martin Jakl, Pavel Cervinka, Jan Kanovsky, Petr Kala, Martin Poloczek, Michaela Cervinkova, Hiram G. Bezerra, Zdenek Valenta, Marco Aurelio Costa

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Randomized comparison of 9-month stent strut coverage of biolimus and everolimus drug-eluting stents assessed by optical coherence tomography in patients with ST-segment elevation myocardial infarction. Long-term (5-years) clinical follow-up (ROBUST trial)

Martin Jakl[1, 2], Pavel Cervinka[3], Jan Kanovsky[4, 5], Petr Kala[4], Martin Poloczek[4], Michaela Cervinkova[1, 3], Hiram G. Bezerra[6], Zdenek Valenta[7], Marco Aurelio Costa[6]

[1]Department of Military Internal Medicine and Military Hygiene, Faculty of Military Health Sciences, University of Defense, Hradec Kralove, Czech Republic

[2]Department of Emergency Medicine, University Hospital in Hradec Kralove, Czech Republic

[3]Department of Cardiology, Krajska Zdravotni a.s., Masaryk Hospital and UJEP Usti nad Labem, Czech Republic

[4]Department of Cardiology and Internal Medicine, University Hospital Brno, Czech Republic

[5]Medical Faculty of Masaryk University, Brno, Czech Republic

[6]Harrington Heart and Vascular Institute, University Hospitals Case Medical Center, Cleveland, United States

[7]Department of Biostatistics, Czech Academy of Science, Prague, Czech Republic

Address for correspondence: Dr. Pavel Cervinka, Department of Cardiology, Krajska Zdravotni, a.s., Masaryk Hospital in Usti and Labem, Socialni pece 3316/12A, 40113 Usti nad Labem, Czech Republic, tel: +420477117886, fax: +420477112727, e-mail: pavel.cervinka@kzcr.eu

Abstract

Background: The aim of the study was to compare healing (assessed by optical coherence tomography [OCT]) of biolimus A9 (BES) and everolimus drug-eluting stents (EES) at 9-month follow-up in patients with ST-segment elevation myocardial infarction (STEMI) treated by primary percutaneous coronary intervention (pPCI). Nine-month clinical and angiographic data were also compared in both groups as well as clinical data at 5 years of follow-up.

Methods: A total of 201 patients with STEMI were enrolled in the study and randomized either to pPCI with BES or EES implantation. All patients were scheduled for 9 months of angiographic and OCT follow-up.

Results: The rate of major adverse cardiovascular events (MACE) was comparable at 9 months in both groups (5% in BES vs. 6% in the EES group; p = 0.87). Angiographic data were also comparable between both groups. The main finding at 9-month OCT analysis was the greatly reduced extent of mean neointimal area at the cost of a higher proportion of uncovered struts in the BES group (1.3 mm^2 vs. 0.9 mm^2; p = 0.0001 and 15.9% vs. 7.0%; p = 0.0001, respectively). At 5 years of clinical follow-up the rate of MACE was comparable between both groups (16.8% vs. 14.0%, p = 0.74).

Conclusions: The study demonstrates a very low rate of MACE and good 9-month stent strut coverage of second-generation BES and EES in patients with STEMI. BES showed greatly reduced extent of mean neointimal hyperplasia area at the cost of a higher proportion of uncovered struts when compared to EES. The rate of MACE was low and comparable in both groups at 5 years.

Key words: drug-eluting stent, primary percutaneous coronary intervention, stent strut coverage, optical coherence tomography, ST-segment elevation myocardial infarction, clinical trials

Introduction

Although drug-eluting stents (DES) represent breakthrough technology in interventional cardiology due to their reduction of re-stenosis, concerns still exist regarding a possible increase in late stent thrombosis in patients with ST-segment elevation myocardial infarction (STEMI) treated with DES, especially when a large thrombus burden is present [1, 2]. Second-generation DES have reduced either in-stent re-stenosis or stent thrombosis compared with bare metal stents or first-generation DES [3, 4]. These improvements may be explained by better biocompatibility of both drug-eluting polymer and the eluted drug. Furthermore, better healing with a low incidence of uncovered struts has been found after using second-generation DES when assessed by optical coherence tomography (OCT) [5, 6]. However, these data are coming mostly from observational studies, and data from randomized trials are scarce. The main objective of this randomized study was therefore to compare the 9-month healing

(assessed by OCT) of 2 second-generation DES: biolimus A9-eluting stents (BES) and everolimus-eluting stents (EES).

Methods

Study population, study design, and PCI procedures

The ROBUST trial (NCT 00888758) is a multicenter, randomized, interventional trial comparing BES and EES with OCT-guided stent implantation in STEMI patients, with 9 months of angiographic and OCT follow-up. Patients were randomly assigned 1:1 (sealed envelope) to either primary PCI with everolimus (n = 100; Promus™, Boston Scientific, Natick, MA, USA) or biolimus A9 DES (n = 101; BioMatrix®, Biosensors International, Biosensors Europe, Morges, Switzerland). The study design has been recently described in detail in a sub-analysis publication of the ROBUST study, and we refer to this original paper [7]. Briefly, 201 patients with STEMI treated by primary PCI in 2 tertiary hospitals were enrolled in this study between February 2011 and October 2012. National and institutional regulatory authorities approved the study, and all patients provided written informed consent. Inclusion criteria were as follows: chest pain with a duration of > 20 min and < 12 h and ST-segment elevation > 0.1 mV in ≥ 2 contiguous leads on a 12-lead electrocardiogram. Patients of age 18–85 years with a stenosis in a native coronary vessel and eligible for stenting were enrolled in the study. Exclusion criteria were as follows: 1) reference diameter > 4 mm, 2) left main coronary artery disease, 3) cardiogenic shock, and 4) ostial lesions. Procedures were performed by radial approach using a 6-French sheath and guiding catheters. Patients were pre-treated with 5000 IU of heparin together with 500 mg of acetylsalicylic acid (ASA) intravenously, and 600 mg clopidogrel orally. Unfortunately, the study was stopped prematurely because of budget restrictions and did not reach the originally calculated sample of 400 patients powered for the clinical comparison. However, the sample size was adequate for OCT and quantitative coronary angiography (QCA) analysis. Dual antiplatelet therapy (ASA plus clopidogrel) post-procedure was recommended for 12 months in both groups. Primary PCI was performed according to standard practice with stent implantation at low pressure (≤ 10 atm) with high pressure (≥ 15 atm) non-compliant balloon post-dilatation inside the stent. After stent implantation was considered optimal, final angiography was performed, using at least 2 orthogonal projections.

Patient follow-up, clinical outcomes, endpoints, and definitions, OCT image acquisition and analysis

All patients were scheduled for 9 months of detailed clinical, angiographic, and OCT follow-up. In addition to predefined endpoints, subsequent long-term clinical follow-up was also performed. The following features were captured in the QCA analysis at 9-month follow-up: binary re-stenosis, diameter stenosis, and minimal lumen diameter. OCT was performed employing a C7-XR™ intravascular imaging system (LightLab® Imaging, St. Jude Medical Company, St. Paul, Minnesota, USA) with a C7 Dragonfly™ intravascular imaging catheter, and succeeded the QCA. A non-occlusive technique was used in all patients, with continuous flushing of the artery with contrast dye (total quantity 15 mL) through the guiding catheter using an injector with a speed of 4 mL/s. Automated pullback was performed at a rate of 20 mm/s for a length of 54 mm.

Optical coherence tomography analysis provided the mean and minimal lumen diameter, mean and minimal lumen area, in-segment area of stenosis, and number of uncovered and malapposed stent struts. In every frame the center of the vessel lumen was calculated by automated software and confirmed by an analyst. The longest, shortest, and mean dimension passing through this center was recorded. The smallest of all such dimensions in the stented segment was referred to as the minimal lumen diameter. The mean of all such mean dimensions in the stented segment was referred as the mean lumen diameter. The minimal and mean luminal areas of the in-stent segment and reference segment were determined in an analogous way. The reference area was defined as the average of 5 mm (25 frames) proximal and distal to the stent edge, except for slices of bad quality, with image distorting side branches, or severe dissection. The inter-slice distance was 200 μm along the entire target segment. The cross-sectional OCT images were analyzed by 2 expert analysts at the Cardiovascular Imaging Core Lab in the Harrington Heart and Vascular Institute of the University Hospital (Cleveland Medical Center, OH, USA). The analysts were blinded to the clinical data. OCT analysis was performed in a strut-to-strut manner using OCTivat-Stent software [8, 9] followed by thorough editing by the analysts. The concordance-correlation coefficient of automatically measured stent and lumen areas were 0.97 and 0.99, respectively. The software analysis before editing had a 94% sensitivity and 90% specificity in the identification of uncovered struts. After editing, the inter-observer variability of measured values and identification of uncovered struts was reduced by 30% compared to fully manual analysis [10].

Quantitative strut analysis was also performed using this dedicated software, which takes into account the characteristics of both types of stent (thickness of struts and polymer) used in this study. OCT endpoints were in-stent minimal lumen area, in-stent area of stenosis, the percentage of uncovered stent struts, the percentage of malapposed stent struts, and the mean area of neointimal hyperplasia.

An uncovered strut was defined as a strut with no detectable neointimal layer on any part of its luminal surface.

Struts were classified as malapposed if the distance between the superficial reflection and the vessel lumen contour was superior to the nominal thickness of the stent strut. The real position of the inner surface of the stent strut was anticipated to be in the center of the blooming, which is difficult to determine exactly. Thus, the distance was measured from the inner surface of the blooming to the vessel wall and then corrected for half of the thickness of the blooming (18 μm) [11, 12]. The final cut-off value for malapposition was 144 μm for BioMatrix® and 106 μm for Promus Element™. Neointimal hyperplasia cross-sectional area was calculated as the stent cross-sectional area minus the luminal cross-sectional area.

Clinical endpoints

Adverse events were classified as major adverse cardiac events (MACE) and were defined as a composite of death, myocardial infarction (MI), or target-lesion revascularization (TLR) after the index procedure. MI was defined as an increase in cardiac troponin values (> 5×99^{th} percentile upper reference limit [URL]) in patients who have normal baseline values ($\leq 99^{th}$ percentile URL) or an increase in cardiac troponin values > 20% when the baseline values are elevated and stable or declining. Pathological Q waves are defined as per amplitude, location, and depth if appeared in at least 2 contiguous leads [13]. All TLR required significant stenosis (≥ 50% of diameter stenosis in QCA) and objective evidence of ischemia related to the re-stenotic artery before treatment.

Statistical analysis

Categorical variables were described as group counts and relative frequencies (percentages), while continuous variables were described as group means, standard deviations (SDs), and totals (N). Tests of statistical hypotheses in contingency tables were performed using the Fisher Exact Test based on a hypergeometric distribution. Because most of the

continuous variables subject to statistical testing showed significant departures from normality (as expressed by, e.g., the Shapiro-Wilk normality test), the non-parametric Wilcoxon Rank-Sum Test was used to compare continuous outcomes across different groups defined by either of the treatment arms (BES vs. EES). Kaplan-Maier plots and Log-Rank Tests were used to compare survival distribution. Statistical significance was set to alpha = 0.05 for all tests. In the case of multiple test scenarios (e.g., a battery of tests performed on a batch of variables), a Bonferroni-Holm correction of the nominal level of statistical significance was applied in order to keep the family-wise type I error rate alpha at 0.05. The sample size was estimated to reach test power 1-beta = 0.8 for angio-guided vs. OCT-guided assessment (first primary endpoint), as published before [7]. Thus, for comparison of uncovered strut incidence and the extent of neointimal hyperplasia in EES vs. BES (second primary endpoint), the Marginal Test power was assessed retrospectively as 1-beta = 0.97 for both tests. The statistical analysis was conducted with R software (R version 3.5.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline demographic and procedural characteristics

Baseline demographic and procedural characteristics were well-balanced in both groups (Table 1). All procedures were carried out without complications. We did not observe any MACE immediately related to the initial PCI.

Angiographic and OCT analysis at 9 months of follow-up

Angiographic data were available for 89% (90/101) of patients in the BES group and 96% (96/100) in the EES group. The only significant difference was in minimal segment diameter; other findings were otherwise comparable in both groups (Table 3).

Optical coherence tomography data in sufficient quality were available for 85% (86/101) of patients in the BES group and 91% (91/100) in the EES group. No persistent thrombi were found in the target segment in either group. The main finding was the greatly reduced extent of mean neointimal area, accompanied by a higher proportion of uncovered struts in the BES group (Table 4).

Adverse event analysis

The clinical endpoint was MACE incidence at 9-month follow-up. During the first 9 months MACE occurred in 5 patients in the BES group (one patient died of possible stent thrombosis, 2 underwent TLR, and 3 underwent another myocardial revascularization) and in 6 patients in the EES group (1 patient suffered MI with TLR, 1 underwent scheduled TLR, and 3 underwent another myocardial revascularization), not fulfilling criteria of statistically significant difference (4.9% vs. 6.0%, p = 0.84). Two of the adverse events were considered as early (i.e., occurring within 30 days after initial PCI): a definite stent thrombosis occurring in the EES group, and a death due to possible stent thrombosis occurred in the BES group.

In addition to this predefined endpoint, long-term clinical follow-up was also performed. No patient was lost to the follow-up, and all study patients completed the follow-up of 5 years. MACE distribution was similar in the BES and EES groups (16.8% vs. 14.0%, p = 0.74). During the long-term follow-up MACE occurred in 17 patients in the BES group (6 patients died, 2 suffered MI, and 9 underwent TLR) and in 14 patients in the EES group (3 patients died, 2 suffered MI, and 8 underwent TLR). All MIs were located on the baseline target lesion. In the case of multiple MACE in a single patient, only the first MACE was included in the analysis.

Discussion

To our knowledge, this is the first randomized trial evaluating 9-month strut coverage of second-generation DES (biolimus A9 and everolimus) assessed by OCT in a cohort of patients with STEMI. The 5-year clinical follow-up is also unique.

The main finding of this study was the highly reduced extent of mean neointimal area accompanied by a higher proportion of uncovered struts in the BES vs. the EES group (0.9 mm^2 vs. 1.3 mm^2; p = 0.0001 and 16 % vs. 7%; p = 0.0001, respectively). Furthermore, there was also a statistically insignificant trend of higher mean and minimal lumen diameter (3.4 mm vs. 3.2 mm; p = 0.06 and 2.9 mm vs. 2.8 mm; p = 0.09) and mean and minimal area (8.9 mm^2 vs. 8.0 mm^2; p = 0.06 and 6.6 vs. 6.1 mm^2; p = 0.08) in favor of the biolimus A9 stent. A possible underlying mechanism for the higher number of uncovered struts in the biolimus A9 group may be the different stent/polymer/antiproliferative-drug platform of the stents. The BioMatrix DES uses a biodegradable PDLLA poly-(D3L-lactide) polymer, which is degraded over 6–9 months into carbon dioxide and water after implantation, and the coating is confined to the abluminal stent surface. However, it has been shown that both the parent polymer

compound as well as its degradation products may cause inflammation [14]. Furthermore, the abluminal PLA polymer appears to be more susceptible to delamination and cracks during implantation and stent expansion [15]. Moreover, thicker struts may delay full neointimal coverage. Research has shown that the thinner the struts, the better the stent healing [16]. On the other hand, biolimus A9 is the limus analog with the highest lipophilicity, which can improve uptake by the vessel wall [17]. Compared to everolimus, biolimus is also a strong activator of the major autophagy regulator ULK1 in vascular smooth muscle cells [18]. In the porcine model of the stent healing process this correlates with reduction of the inflammatory reaction and neointimal hyperplasia [19]. A higher local tissue drug concentration along with the specific biological activity of biolimus A9 may explain the numerically lower mean neointimal area/late lumen loss and higher minimal lumen diameters reported in previous trials as well as in the presented study [20, 21].

The rate of uncovered struts in both groups in the present study may seem high (16% in the BES group and 7% in the EES group) when compared to the healing pattern in the studies published recently. Hamshere et al. [22] found a lower number of uncovered struts in both everolimus vs. zotarolimus-eluting stents (2.4% vs. 1.2%, p = 0.31) at 6 months in patients with diabetes. Furthermore, Iannaccone et al. [23], in their systematic review and meta-analysis, reported the rate of uncovered struts in biolimus and everolimus stents of 7.7% vs. 2.8%. In the STACCATO trial, the average percentage of uncovered struts was 4.3% in the everolimus group and 8.7% in the biolimus A9 group (p = 0.019) [20]. However, it must be acknowledged that the aforementioned studies did not include any, or very few, patients in the setting of STEMI. For example, in the STACCATO study, which enrolled patients with STEMI/non-STEMI/SAP, only 9 patients in both groups underwent a 9-month OCT study. On the contrary, in the present study a 9-month OCT analysis was eligible in 91 patients in the BES group and 87 patients in the EES group. The higher frequency of uncovered struts after DES in STEMI patients was first reported in the literature by Gonzalo et al. [24]. A possible explanation is that the thrombus, which is present in 100% of cases of STEMI, causes delay in the healing process, resulting in a numerically higher rate of uncovered struts. Although we did observe a substantial difference between the stents in the proportion of uncovered struts, this did not translate into a difference in MACE. Moreover, the rate of MACE was low and comparable in both groups at 9-month as well as at 5-year follow-up in the present study (5% in the biolimus A9 group and 6% in the everolimus group; p = 0.84 and 16.8% vs. 14.0%; p = 0.74, respectively). Stent thrombosis occurred only in 1 patient in both groups.

This is in concordance with data from observational studies and registries suggesting that biolimus-eluting stents are safe [25–27]. However, in a large meta-analysis by Kang et al. [28] biodegradable polymer biolimus-eluting stents were inferior to cobalt-chromium everolimus-eluting stents in terms of the increased risk of stent thrombosis. The presented study was underpowered to confirm such a finding, but evidence of increased incidence of uncovered struts might explain the underlying mechanism.

Limitations of the study

There are limitations to our study. First, this study was underpowered for the clinical endpoints. This is partly due to a lower-than-expected incidence of adverse events and budget restrictions. Secondly, the study population did not include high-risk patients, such as those with ostial disease, graft intervention, cardiogenic shock, or renal insufficiency. It is possible that stent performance is different in specific populations not included in the study.

Conclusions

In conclusion, at 9-month follow-up in the setting of STEMI, the biolimus A9 drug-eluting stent was associated with a higher proportion of uncovered struts and lower extent of mean neointimal area detected with OCT when compared to the EES. However, this difference did not translate into a higher rate of MACE in the biolimus A9 group. On the contrary, the rate of MACE was very low in both groups at 9 months and 5 years.

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Conflict of interest: None declared

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Table 1. Baseline demographic and procedural characteristics.

	BioMatrix®	**Promus™**	**P**
N	101	100	
Age [years]	58.4 ± 9.6	59.2 ± 10.0	0.474
Male [%]	89	82	0.241
Smoking [%]	61	61	1.0
Diabetes mellitus [%]	25	21	0.721
Hypertension [%]	49	53	0.574
History of CAD:			
Previous MI [%]	5	7	0.568
Previous PCI [%]	3	5	0.498
Previous CABG [%]	0	0	1.0
Infarct-related artery:			
LAD [%]	39	33	0.743
RCA [%]	46	54	0.213
LCx [%]	15	13	0.821
TIMI flow before PCI:			
0–I [%]	78	82	0.22
MLD before PCI [mm]	0.38 ± 0.49	0.43 ± 0.51	0.705
GPIIb/IIIa inhibitors [%]	36	29	0.288
Diameter stenosis [%]	88 ± 17	91 ± 14	0.183
Aspiration [%]	40	39	0.823
DAPT before PCI [%]	99	98	0.919
OCT guided [%]	51	53	0.814
Number of stents per patient	1.3	1.4	0.123

Total stent length [%]	25.2 ± 10.6	26.8 ± 15.8	0.728
Max balloon diameter [mm]	3.6 [3.5–3.8]	4.0 [3.5–4.0]	0.81
Max implant pressure [atm]	17.8 ± 2.4	17.4 ± 2.6	0.233
Fluoroscopy time [min]	9.6 ± 5.2	9.9 ± 5.3	0.574
Staged procedure			
Single vessel PCI [%]	13	10	0.951
CABG [%]	1	1	1.0

CAD — coronary artery disease; CABG — coronary artery bypass graft; DAPT — dual antiplatelet treatment; GPIIb/IIIa — glycoprotein IIb/IIIa; LAD — left anterior descending; LCx — left circumflex; MI — myocardial infarction; MLD — minimal lumen diameter; OCT — optical coherence tomography; PCI — percutaneous coronary intervention; RCA — right coronary artery; TIMI — Thrombolysis in Myocardial Infarction

Table 2. Post-procedural angiographic, optical coherence tomography (OCT), and biomarker characteristics.

	BioMatrix®	**Promus™**	**p**
Angiography eligible for analysis (n)	101	100	
TIMI flow [%]			
0–II	4	6	0.413
III	97	94	0.876
MLD in-stent [mm]	2.8 ± 0.41	2.9 ± 0.51	0.234
MLD in-segment [mm]	2.5 ± 0.49	2.5 ± 0.56	0.453
Diameter stenosis in-stent [%]	12.1 ± 4.96	12.5 ± 5.97	0.765
OCT eligible for analysis (n)	48	51	
Minimal lumen area [mm^2]	7.4 ± 2.0	6.7 ± 1.9	0.083
Mean lumen area [mm^2]	9.4 ± 2.3	8.6 ± 1.9	0.056
Area stenosis in-stent [%]	1.0 ± 24.9	9.2 ± 21.7	0.119
Malapposed struts [%]	0.16 [0–0.71]	0.36 [0–0.97]	0.862
CK max [μkat/L]	34 [11–47]	28 [11–35]	0.096

Troponin T max [μg/L]	50.4 [3.6–78.1]	40.9 [3.5–91.6]	0.571

CK max — creatine kinase peak; MLD — minimal lumen diameter; TIMI — Thrombolysis in Myocardial Infarction

Table 3. Angiographic data at 9-month follow-up.

	BioMatrix® (n = 90)	**Promus™ (n = 96)**	**P**
Reference segment diameter [mm]	3.2 ± 0.6	3.1 ± 0.7	0.13
Reference stent diameter [mm]	3.1 ± 0.7	3.1 ± 0.5	0.94
MLD in-segment [mm]	2.4 ± 0.5	2.1 ± 0.6	0.03
MLD in-stent [mm]	2.6 ± 0.5	2.6 ± 0.6	0.74
Mean segment diameter [mm]	3.0 ± 0.5	2.9 ± 0.5	0.45
Mean stent diameter [mm]	3.1 ± 0.6	3.1 ± 0.6	0.74
Late lumen loss [mm]	0.26 ± 0.56	0.26 ± 0.59	0.94
Area stenosis in-segment [%]	26 ± 12	29 ± 12	0.12
Area stenosis in-stent [%]	18 ± 13	17 ± 13	0.35
Binary re-stenosis [%]	2	3	0.32

MLD — minimal lumen diameter

Table 4. Optical coherence tomography data at 9-month follow-up.

	BioMatrix® (n = 86)	**Promus™ (n = 91)**	**P**
Mean stent lumen diameter [mm]	3.4 [2.9–3.8]	3.2 [2.9–3.5]	0.06
Minimal stent lumen diameter [mm]	2.9 [2.5–3.3]	2.8 [2.4–3.0]	0.09
Mean stent lumen area [mm^2]	8.9 [6.7–11.1]	8.0 [6.7–9.5]	0.06
Minimal stent lumen area [mm^2]	6.6 [5.0–8.8]	6.1 [4.8–8.1]	0.08
Mean reference lumen diameter [mm]	3.0 [2.7–3.4]	3.0 [2.7–3.4]	0.51
Mean reference lumen area [mm^2]	7.3 [5.6–9.2]	7.1 [5.8–9.0]	0.65
Area stenosis [%]	11 [–1–21]	15 [–4–28]	0.26

Uncovered struts [%]	15.9 [5.5–27.7]	7.0 [3.5–14.5]	0.0001
Malapposed struts [%]	0.1 [0–1.0]	0.1 [0–0.5]	0.4
Mean neointimal area [mm^2]	0.9 [0.6–1.4]	1.3 [0.9–1.9]	0.0001