Early Phase Arterial Reaction Following Drug-Eluting and Bare-Metal Stent Implantation in Patients With ST-Segment Elevation Myocardial Infarction

Optical Coherence Tomography Assessment at 2 Weeks

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SUMMARY

The early phase arterial reaction after implantation of second-generation drug-eluting stents (2nd DES) and bare-metal stents (BMS) in patients with ST-segment elevation myocardial infarction (STEMI) remains unclear.

The MECHANISM pilot study is a multi-center prospective registry that enrolled 24 STEMI patients (from 11 centers) who had undergone implantation of everolimus-eluting ($n = 6$), biolimus A9-eluting ($n = 6$) or zotarolimus-eluting stents ($n = 6$), or BMS ($n = 6$). Scheduled optical coherence tomography (OCT) was performed 2 weeks after implantation, and images were independently analyzed at a core laboratory in a blinded fashion. Intra-stent thrombus was quantitatively analyzed in terms of the maximal area and the percentage of cross-sections with thrombus (the numbers of cross-section with thrombus $\times 100$ divided by total number of cross-sections within the stented segment). More than 90% of struts were already covered 2 weeks after the index procedure, regardless of the stent type. There were no differences in stent diameter, minimal lumen diameter, minimal lumen area, neointimal thickness, or the frequencies of malapposed and uncovered struts among the 4 groups. The quantity of intra-stent thrombus also did not differ among the 4 groups.

The results of this pilot study suggest that the 2-week vascular responses seem to be similar among 2nd DES and BMS in STEMI patients. Considering the possible advantage of 2nd DES in the prevention of restenosis, 2nd DES are a feasible option for the treatment of patients with STEMI. (Int Heart J 2015; 56: 389-394)

Key words: Second generation DES, Arterial healing, Neointima, Intra-stent thrombus

The use of drug-eluting stents (DES) after percutaneous coronary intervention (PCI) has reduced the risk of restenosis compared to that with the use of bare metal stents (BMS).^{1,2} However, DES are associated with delayed arterial healing and persistent arterial inflammation that may increase the risk of stent thrombosis.³⁻⁵ In particular, implanting DES in patients with ST-segment elevation myocardial infarction (STEMI) has been a controversial issue, because the lesions have high thrombogenicity and are potentially high risk for early stent thrombosis.^{6,7} Recently, second-generation DES—everolimus-eluting stents (EES), biolimus-eluting stents (BES), and zotarolimus-eluting stents (ZES)—have been developed and used widely. The stent materials, designs, poly-

mers, and antiproliferative drugs have been improved compared with those used for first-generation DES, such as the sirolimus-eluting and paclitaxel-eluting stents. Previous studies have shown that the incidences of stent thrombosis and repeat revascularization in second-generation DES are equal to or less than those in BMS.^{8,9} The mechanism of this favorable effect is, however, still unknown.

Pathological studies have revealed that some local factors are associated with the incidence of stent thrombosis: namely, stent expansion, neointimal coverage of stent struts, malapposed struts, and restenosis.^{10,11} Although the evaluation of these microscopic features used to be impossible *in vivo*, optical coherence tomography (OCT) has made it possible because

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of its high resolution.¹²⁻¹⁴⁾

This study was designed to compare second-generation DES and BMS in patients with STEMI, using OCT to evaluate the short-term changes in vascular morphological characteristics during the high-thrombogenicity period following stent implantation. The secondary aim of this pilot study was to calculate the sample size required in the main trial (MECHANISM-AMI; ClinicalTrials.gov NCT02014753) based on the OCT measurements in this study.

METHODS

Patients and study design: This pilot study was a multi-center prospective registry enrolling 24 STEMI patients (from 11 institutions) who had undergone EES ($n = 6$; Xience V or Xience Prime; Abbot Vascular, Santa Clara, CA, USA), BES ($n = 6$; Nobori; Terumo, Tokyo), ZES ($n = 6$; Resolute Integrity; Medtronic Vascular, Santa Rosa, CA, USA), or BMS ($n = 6$; Multi-Link 8; Abbot Vascular, Santa Clara, CA, USA) implantation between November 2012 and May 2013. STEMI was defined as a recent symptom of ischemia with electrocardiographic abnormalities, elevation of at least 0.1 mV in the ST segment, and troponin I level elevation.¹⁵⁾ The stent types, the use of thrombus aspiration devices, the use of distal protection devices, and the endpoint of the PCI procedure were left to the operators' discretion. The patients received dual antiplatelet therapy (100 mg/day aspirin and 75 mg/day clopidogrel after 300 mg loading) without other antiplatelet agents after the index PCI, and the scheduled OCT examination was performed 2 weeks after implantation and was independently analyzed at a core laboratory in a blinded fashion. Unfractionated heparin was administered during the coronary catheterization. Patients were excluded from this study if they 1) were younger than 20 years or older than 85 years, 2) had intolerance to aspirin, clopidogrel, heparin, or contrast, 3) demonstrated hemodynamic and respiratory instability, 4) had terminal stage cancer or dementia, or 5) refused consent for participation. The consecutive STEMI patients matching the inclusion criteria and not matching the exclusion criteria were enrolled this study. All centers submitted and received the approval of their Medical Ethics Committees, and the enrolled patients provided written informed consent.

OCT analysis: The scheduled OCT examination was performed 2 weeks after implantation. Briefly, a frequency-domain OCT catheter (Dragonfly™; St. Jude Medical, St. Paul, MN, USA) was advanced to the distal end of the stent over a 0.014-inch guide wire, followed by the infusion of contrast medium into the coronary artery from the guiding catheter at 3.5 mL/s, serving as a flush to clear the area of blood. The entire lesion was then imaged using an automatic pullback system moving at 18 or 36 mm/s. All images were digitally stored and submitted to a core laboratory for off-line evaluation (OCT Imaging Core Laboratory, Division of Cardiovascular Medicine, Kobe University Hospital, Kobe, Japan) and subsequent analysis using proprietary software (ILIMIEN™, St. Jude Medical, St. Paul, MN).

The stent diameters, lumen diameters, lumen areas, and neointimal thicknesses were measured, and the incidences of uncovered and malapposed struts were assessed at 1 mm intervals. Intra-stent thrombus was defined as a mass protruding be-

yond the stent strut into the lumen with attenuation behind the mass and assessed at every cross-section.¹⁶⁾ Quantitative assessment of intra-stent thrombus was performed by measuring the maximal area and the percentage of cross-sections with thrombus, calculated as cross-sections with thrombus $\times 100$ divided by all cross-sections. To differentiate intra-stent thrombus from plaque protrusion or neointimal hyperplasia, we defined thrombus as protruding masses showing both significant signal attenuation and surface irregularity.

Statistical analysis: All statistical analyses were performed using MedCalc (version 13.0; MedCalc Software, Mariakerke, Belgium). Continuous variables are presented as the mean $\pm$ SD. Differences between the continuous parameters in the 4 groups were calculated using one-way ANOVA. Categorical variables are presented as frequency counts. Between-group comparisons of categorical variables were performed using the chi-square test. Values were considered statistically significant at $P < 0.05$.

RESULTS

There were no differences in baseline characteristics among the 4 groups (Table I). Although no patients received antiplatelet therapy at baseline, one patient in the BMS group was prescribed warfarin for chronic atrial fibrillation.

OCT analysis revealed that $> 90\%$ of struts were already covered 2 weeks after the index PCI in all stent groups (Figure 1; EES $95.06 \pm 5.59\%$, BES $98.05 \pm 1.45\%$, ZES $92.24 \pm 8.45\%$, BMS $95.33 \pm 5.05\%$, $P = 0.40$). There were no differences in the stent diameters, minimal lumen diameters, minimal lumen areas, neointimal thicknesses, or the frequencies of malapposed and uncovered struts among the 4 groups (Table II). The maximal area of thrombus did not differ among the 4 groups (Figure 2; EES $0.64 \pm 0.68 \text{ mm}^2$, BES $0.86 \pm 0.63 \text{ mm}^2$, ZES $0.17 \pm 0.12 \text{ mm}^2$, BMS $0.32 \pm 0.26 \text{ mm}^2$, $P = 0.09$). There were no differences in the number of cross-sections (EES 166.2 ± 88.3 , BES 179.2 ± 49.5 , ZES 177.3 ± 41.7 , BMS 154.3 ± 51.5 , $P = 0.88$) or number of cross-sections with thrombus (EES 29.5 ± 25.8 , BES 58.2 ± 57.2 , ZES 18.3 ± 15.7 , BMS 43.2 ± 39.0 , $P = 0.32$). Nor were there any differences in the percentage of cross-sections with thrombus (Figure 2; EES $17.0 \pm 15.5\%$, BES $30.3 \pm 23.9\%$, ZES $9.8 \pm 7.0\%$, BMS $28.1 \pm 20.3\%$, $P = 0.19$).

In a limited number of patients ($n = 19$) who had undergone OCT examinations immediately and 2 weeks after index PCI, various serial changes in thrombus appearance were observed, including resolving or worsening (Figure 3).

DISCUSSION

This is the first report to show that second-generation DES struts are covered with tissue within 2 weeks after implantation, as demonstrated by OCT. In addition, the quantity of intra-stent thrombus did not vary with the type of stent implanted in this sample size. Although we could not accept all the results on faith because of the small sample size, the results of this pilot study should help the sample size calculation for subsequent studies to elucidate the difference in vascular responses among stent types. The superiority of DES implanta-

Table I. Baseline Characteristics

	EES (n = 6)	BES (n = 6)	ZES (n = 6)	BMS (n = 6)	P
Patient characteristics					
Age (years)	61.8 ± 11.1	65.2 ± 10.4	68.3 ± 10.5	59.7 ± 12.1	0.56
Male, n (%)	5 (83.3)	5 (83.3)	3 (50.0)	4 (66.7)	0.53
Hypertension, n (%)	3 (50.0)	5 (83.3)	4 (66.7)	4 (66.7)	0.68
Dyslipidemia, n (%)	4 (66.7)	6 (100.0)	3 (50.0)	5 (83.3)	0.22
Diabetes mellitus, n (%)	5 (83.3)	3 (50.0)	3 (50.0)	3 (50.0)	0.56
Smoking, n (%)	6 (100)	5 (83.3)	3 (50.0)	4 (66.7)	0.22
Family history, n (%)	1 (16.7)	1 (16.7)	0	0	0.54
Lesion characteristics					
LAD/LCX/RCA	3/2/1	4/1/1	3/0/3	3/1/1	0.62
Peak CPK (mg/dL)	2087.8 ± 1886.0	2550.8 ± 2057.1	2296.6 ± 1674.3	3471.2 ± 1894.8	0.61
Peak CPK-MB (mg/dL)	202.2 ± 223.4	206.0 ± 175.9	242.0 ± 174.8	299.5 ± 145.2	0.79
Procedural characteristics					
Stent diameter (mm)	3.17 ± 0.52	3.33 ± 0.26	3.04 ± 0.25	3.46 ± 0.51	0.32
Total stent length (mm)	23.5 ± 9.2	26.7 ± 9.8	24.0 ± 4.2	15.8 ± 4.2	0.10
Aspiration device, n (%)	4 (66.7)	6 (100.0)	4 (66.7)	5 (83.3)	0.43
Distal protection, n (%)	0	1 (16.7)	0	2 (33.3)	0.24
Post dilation, n (%)	4 (66.7)	3 (50.0)	4 (66.7)	2 (33.3)	0.60

Differences among the 4 groups were calculated using one-way ANOVA or chi-square test. LAD indicates left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; CPK, creatine phosphokinase; EES, everolimus-eluting stent; BES, biolimus-eluting stent; ZES, zotarolimus-eluting stent; and BMS, bare-metal stent.

Figure 1. Representative OCT images 2 weeks after stenting. **A:** everolimus-eluting stent, **B:** biolimus-eluting stent, **C:** zotarolimus-eluting stent, **D:** bare-metal stent.**Table II.** OCT Measurements 2 Weeks After Stenting

	EES (n = 6)	BES (n = 6)	ZES (n = 6)	BMS (n = 6)	P
Mean stent diameter (mm)	3.08 ± 0.42	3.17 ± 0.34	2.96 ± 0.12	3.26 ± 0.45	0.51
Minimal stent diameter (mm)	2.51 ± 0.46	2.53 ± 0.36	2.49 ± 0.15	2.85 ± 0.45	0.31
Minimal lumen diameter (mm)	2.39 ± 0.39	2.36 ± 0.31	2.41 ± 0.14	2.65 ± 0.36	0.39
Minimal lumen area (mm ²)	5.67 ± 2.10	5.71 ± 1.81	5.61 ± 0.70	7.00 ± 2.07	0.47
Neointimal thickness (mm)	0.046 ± 0.032	0.048 ± 0.016	0.030 ± 0.009	0.040 ± 0.009	0.36
Malapposed struts (%)	7.16 ± 15.9	0.44 ± 0.34	2.41 ± 2.38	1.38 ± 1.16	0.50
Uncovered struts (%)	4.94 ± 5.59	1.95 ± 1.46	7.76 ± 8.45	4.67 ± 5.05	0.40
Incidence of intra-stent thrombus, n (%)	5 (83.3)	6 (100)	6 (100)	6 (100)	0.37

Data are presented as mean ± SD. Differences among the 4 groups were calculated using one-way ANOVA. OCT indicates optical coherence tomography; EES, everolimus-eluting stent; BES, biolimus-eluting stent; ZES, zotarolimus-eluting stent; and BMS, bare-metal stent.

tion compared with BMS has been shown in previous pathological and intravascular imaging studies.^{1,2)} However, there is a concern that the arterial inflammation promoted by polymers and over-suppression of neointimal proliferation might increase the incidence of stent thrombosis, especially in STEMI patients.¹⁷⁻¹⁹⁾ Newly designed second-generation DES have become primary devices in daily PCI practice, and the safety of second-generation DES in STEMI patients was demonstrated in recent studies.^{8,9)} The present study showed that the rate of tissue coverage in second-generation DES was comparable with that in BMS. This adequate coverage might lead to a favorable result in patients who are treated with second-generation

DES, considering their advantage of an accelerated healing process compared to 1st generation DESs.

The implantation of second-generation DES in STEMI patients decreases the incidence of restenosis compared with that in patients implanted with BMS. However, the effect on suppression of stent thrombosis is still controversial. Previous studies have shown that the incidence of stent thrombosis did not differ between second-generation DES and BMS.⁸⁾ On the other hand, the EXAMINATION trial showed that EES implantation decreased the incidence of thrombosis, and the authors speculated that this could have been due to the thromboresistant ability of EES polymer coating.⁹⁾ The current study

Figure 2. Quantitative analysis of intra-stent thrombus. **A:** Maximal thrombus area, **B:** percentage of cross-sections with thrombus. Data are presented as mean ± SD. Differences among the 4 groups were calculated using one-way ANOVA. EES indicates everolimus-eluting stent; BES, biolimus-eluting stent; ZES, zotarolimus-eluting stent; and BMS, bare-metal stent.

Figure 3. Representative intra-stent thrombus cases (white arrow). Case **A:** Intra-stent thrombus immediately after index PCI (**A-1:** axial view, **A-2:** longitudinal view) that decreased 2 weeks after stenting (**A-3:** axial view, **A-4:** longitudinal view). Case **B:** Intra-stent thrombus immediately after index PCI (**B-1:** axial view, **B-2:** longitudinal view) that increased 2 weeks after stenting (**B-3:** axial view, **B-4:** longitudinal view). PCI indicates percutaneous coronary intervention.

failed to show a difference in the quantity of intra-stent thrombus among EES, BES, and ZES, perhaps because of the small sample size. However, we were able to observe various serial changes in the appearance of the thrombus. The incidence of acute and subacute stent thrombosis is still approximately 1.4% in ACS patients while new devices and antiplatelet therapy may have a potential to improve the outcomes after PCI.²⁰⁾ A number of possible factors should influence a change in thrombus appearance, including lesion severity, procedural differences, the effect of antiplatelet therapy, and stent design. A recent pathological study showed that necrotic core prolapse and medial tear were more frequently observed in patients with early stent thrombosis than in those without stent thrombosis at 30 days after stent implantation to ACS lesions.²¹⁾ An ongoing large-scale clinical study (MECHANISM-AMI; ClinicalTrials.gov NCT02014753) aims to compare the early response of lesions in acute coronary syndrome within 1 month after treatment with EES to that with BMS. The MECHANISM main trial will attempt to reveal the factors determining the changes in thrombus appearance.

This study had several limitations. First, this pilot study was designed to evaluate the arterial reaction 2 weeks after stenting and the sample size was insufficient to demonstrate a statistically significant difference among stent types. Some of the OCT parameters had large standard deviations probably due to the heterogeneous vascular response at this early time point. Thus, there is the potential that the differences in any parameters among stent types will be clarified in the MECHANISM main trial. Second, there was selection bias. The number of patients who were excluded from this study is unclear because consecutive STEMI patients matching the inclusion criteria and not matching the exclusion criteria were enrolled. Furthermore, the selection of devices depended on the decision of the operator, including the type of stent. However, the characteristics of the patients, lesions, and stent size were similar with those in the J-AMI registry.²²⁾ Thus, this study

might reflect the characteristics of real-world STEMI patients in Japan. Third, patients who potentially had a high risk for stent thrombosis might have been excluded from this study, because they suffered from cardiorespiratory instability and/or severe renal dysfunction. Fourth, the tissue identified by OCT on the stent struts 2 weeks after stenting was not validated by histological findings. In particular, it is difficult to distinguish an intra-stent thrombus from plaque protruding into the stent lumen. However, no reports have presented histological data from tissue on stent struts a few weeks after stenting in humans. Further investigation is warranted. Fifth, only one patient in the BES group was implanted with 2 BESs with overlap. Stent overlap is associated with unfavorable arterial healing and stent thrombosis. However, the OCT measurements in this case, including neointimal thickness, frequency of uncovered struts, and thrombus size, were not far from the mean value. Sixth, the impact of anticoagulation therapy, including warfarin, unfractionated heparin, and other anticoagulants, was not clear in this study. The maximal area of thrombus and the percentage of cross-sections with thrombus were 0.35 mm² and 29.6% in the patient with BMS who received warfarin therapy. These values did not deviate from the range of the 95% confidence interval. Finally, the long-term favorable effects of second-generation DES were not clarified because this study was designed to evaluate only short-term changes in culprit lesions. Further study is warranted to evaluate the serial changes of second-generation DES implanted in culprit lesions.

In conclusion, the findings of this pilot study suggest that the 2-week vascular response appears to be similar with second-generation DES and BMS in STEMI patients. Considering the possible advantage of second-generation DES in the prevention of restenosis, these stents are a feasible option for the treatment of patients with STEMI.

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DISCLOSURE

Conflict of interest: Dr. Shinke and Dr. Otake are consultants for St. Jude Medical Co., Ltd. Dr. Morino is a consultant for Abbott Vascular Co., Ltd. and Terumo Co., Ltd. and receives a speaking honorarium from Boston Corp. Dr. Tanabe is a consultant for Abbott Vascular Co., Ltd. and Terumo Co., Ltd. Dr. Ako is a consultant for Abbott Vascular Co., Ltd. and receives speaking honoraria from Abbott Vascular Co., Ltd., Medtronic Co., Ltd., Terumo Co., Ltd. and Sanofi Co., Ltd. Dr. Hibi is a consultant for St. Jude Medical Co., Ltd. and Terumo. Dr. Ishii receives speaking honoraria from Astellas Pharma Inc. and Otsuka Pharma Inc. Dr. Otsuka is a consultant for Abbott Vascular Co., Ltd. Dr. Nishio, Dr. Hirohata, Dr. Furuya, Dr. Takaya, Dr. Takizawa, Dr. Kozuma, and Dr. Hirata have no conflicts of interest.

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