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Comparisons of detailed arterial healing response at seven months following implantation of an everolimus- or sirolimus-eluting stent in patients with ST-segment elevation myocardial infarction

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ABSTRACT

Background: The difference of arterial healing response following everolimus-eluting stent (EES) or sirolimus-eluting stent (SES) implantation in patients with ST-segment elevated myocardial infarction (STEMI) has not been compared in detail.
Methods: Thirty-five patients with STEMI were randomly implanted with an EES or SES (23 EES, 12 SES). At seven months, neointimal thickness (NIT) and strut malapposition were evaluated by optical coherence tomography (OCT) and the grade and heterogeneity of neointimal coverage (NIC) and development of intra-stent thrombi were evaluated by angioscopy.
Results: No significant differences were noted in clinical events experienced by the two groups, although one patient with an EES died following a papillary muscle rupture and one patient with a SES experienced sub-acute stent thrombosis. On OCT, although the EES implants showed a greater NIT than the SES implants (94.8 ± 88.8 μm vs 65.6 ± 63.3 μm, $P<0.0001$), both the EES and SES showed an excellent suppression of neointimal proliferation in the culprit lesion of STEMI. The frequency of uncovered and malapposed struts of EES was significantly lower than that of SES (2.7% vs. 15.7%, $P<0.0001$, 0.7% vs. 2.3%, $P<0.0001$, respectively). The ratio of stents fully covered with neointima of EES group was significantly higher than that of SES group ($P=0.04$). Angioscopic analysis also showed greater dominant NIC grade with homogenous NIC in EES than in SES ($P=0.03$, $P=0.0002$, respectively). The incidence of massive intra-stent thrombus of EES was lower than that of SES ($P=0.05$).
Conclusion: For patients with STEMI, EES may promote better arterial healing response than SES.

1. Introduction

The preferred treatment of patients with ST-segment elevation myocardial infarction (STEMI) is primary percutaneous coronary intervention (PCI) with stent implantation [1,2]. However, drug-eluting stent (DES) implantation in patients with STEMI is controversial as several studies have demonstrated that vessel healing at the culprit site is substantially delayed after DES implantation compared with that in patients with stable angina [3–8]. Further, exposed and malapposed stent struts, which may be associated with late stent thrombosis, were more common after DES than bare metal stent implantation, especially in patients with STEMI [9].

The everolimus-eluting stent (EES) is a second-generation DES, in which everolimus, an anti-proliferative agent, is released from thin, non-adhesive, durable, biocompatible fluoropolymer coated onto a low-profile, flexible cobalt–chromium stent [10,11]. In non-STEMI patients, EES implants are reported to induce more favorable vascular responses, such as a lower incidence of uncovered struts and intracoronary thrombus, than sirolimus-eluting stents (SES) despite similar neointimal thickness [11,12]. Although EES treatment is a possible option for the treatment of patients with STEMI, the detailed vessel healing response after EES implantations in patients with STEMI has not been fully clarified.

The aim of this study was to evaluate the detailed arterial healing response following implantation of second-generation EES in patients with STEMI using optical coherence tomography (OCT) and angioscopy, and to compare the healing response with that of first-generation SES.

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2. Methods

2.1. Study design

This study was a single-center, randomized controlled trial designed to compare EES (PROMUS, Boston Scientific Corp, Xience V, Abbott Vascular) and SES (Cypher Select, Cordis Corp) in patients with STEMI.

Ninety-eight consecutive patients with STEMI who visited Hyogo Prefectural Awaji Hospital between February 2010 and July 2011 and who met the following inclusion criteria were considered as candidates for the study: 1) patients presenting with symptoms of acute myocardial infarction <24 h before arrival at the catheterization laboratory; 2) total creatinine kinase (CK) or CK-MB greater than twice the upper limit of our hospital's laboratory normal; 3) the ECG revealed a ST segment elevation >0.1 mV in 2 continuous leads [13]. Candidates who met the following criteria were excluded: 1) patients with multiple vessel disease or chronic total occlusion requiring coronary artery bypass grafting surgery (n=8); 2) patients presenting with a culprit lesion where the reference external elastic membrane diameter was >4.0 mm (n=32); 3) patients presenting with a culprit lesion where the reference external elastic membrane diameter was <2.5 mm, measured by intravascular ultrasound (IVUS) (n=6); 4) patients whose culprit lesion was judged unsuitable for OCT and angioscopy procedure, because of conditions such as left main trunk disease (n=5) or shock vital (n=6); 5) patients with severe dementia that increased risk of difficulty in follow-up angiography (n=4). Of the 37 patients, two patients moved away from the study area, and 35 patients were enrolled in the study protocol. The remaining 35 patients were randomly assigned to either the EES (n=23) or SES (n=12) group (Fig. 1). We conducted 2:1 assignment of EES and SES, because several authors have reported that first generation DES implants may have a negative result for STEMI patients [14,15].

We hypothesized that the favorable performance of EES implants, despite similar neointimal proliferation compared with SES implants, is mainly due to the reduction of exposed and malapposed stent struts [8,11,12]. The required sample size was calculated from assumptions derived from previous data: A type I error of 0.05 (two-sided); power of 80%; and differences in the frequency of uncovered and malapposed struts, and in the ratio of stents fully covered with neointima between EES and SES implants of 8%, 1.5%, and 40%, respectively [12,16–18]. These calculations show that the minimum sample size of struts was 858 and that the minimum required sample size was 12 in each group.

As a part of the research protocol, all patients were prospectively scheduled to undergo follow-up coronary angiography with OCT and angioscopy regardless of symptoms. All patients provided written informed consent, and the study was approved by the Ethics Committee of Hyogo Prefectural Awaji Hospital.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

2.2. Percutaneous coronary intervention (PCI) procedure and anti-platelet therapy

Patients were given 200 mg of aspirin on arrival at the hospital, and a bolus of 5000 IU of heparin was administered before the percutaneous coronary intervention (PCI) procedure. Thrombectomy was performed after successful positioning of the guide-wire distal to the culprit lesion with thrombi-extraction catheter (Thrombuster GR™, KANEKA, Osaka, Japan). All PCI procedures were performed under intravascular ultrasound (IVUS) guidance (Volcano Corporation, Rancho Cordova, CA, USA). All patients received dual anti-platelet therapy with aspirin and clopidogrel. A loading dose of clopidogrel (300 mg) was administered immediately after the PCI procedure, followed by a maintenance dose of clopidogrel (75 mg/day) and aspirin (100 mg/day) until the follow-up date.

Several studies have shown that neointimal coverage occurred sooner with EES implants than with SES implants [8,11,12,17,18], and we previously demonstrated that the delayed neointimalization was observed in SES [16]. We scheduled follow-up examinations earlier than previous OCT studies, seven months after PCI, to facilitate the identification of differences in the vascular healing response between EES and SES implants.

2.3. Clinical events

Clinical events (death, cardiac death, myocardial infarction, stent thrombosis and target lesion revascularization) that occurred during the study period were evaluated. Target lesion revascularization was defined as any re-intervention (surgical or percutaneous) required to treat a luminal stenosis in the same stent as that treated at the index procedure.

2.4. OCT examination

At the beginning of the study, frequency-domain OCT had not been approved for clinical use in Japan at the beginning of the study, so time-domain OCT with coronary artery occlusion was used instead. Briefly, an over-the-wire type occlusion balloon catheter (Helios™, LightLab Imaging Inc., Westford, MA) and an OCT imaging probe (ImageWire™, LightLab Imaging Inc.) were inserted into the distal end of the stent implanted lesion. The occlusion balloon was then withdrawn until it was proximal to the DES. Blood was cleared from the imaging site by inflating the occlusion balloon to 0.5 to 0.8 atm and infusing low molecular weight dextran at 0.5 ml/s into the coronary artery from the distal tip of the occlusion balloon [11]. The entire length of the stent was imaged using an automatic pullback device at 1.5 mm/s and OCT data were recorded for off-line analysis. The OCT examination was performed before the angioscopy to avoid injury to the culprit lesions by the angioscope catheter. Images of cross sections at 10 frame intervals were analyzed. Bifurcation lesions with major side branches were excluded from the analysis.

Neointimal thickness (NIT) on the inside of each stent strut was measured at each cross-section. The maximum and minimum stent diameter, and area were measured. An uncovered strut stent was defined as one with a measured NIT of 0 μm. A malapposed strut was defined as one where the distance between the strut center reflection and the vessel wall was more than 108 μm for an EES and 170 μm for a SES. The criteria were determined by adding the strut and polymer thickness to the OCT resolution limit (EES, 81 μm + 7 μm + 20 μm; SES, 140 μm + 10 μm + 20 μm) [11].

Uncovered and malapposed struts were counted and the frequency calculated (number of uncovered or malapposed struts divided by the total number of struts). A stent eccentricity index (minimum stent diameter divided by maximum stent diameter in each cross-section) and a neointimal unevenness score (the maximum neointimal thickness

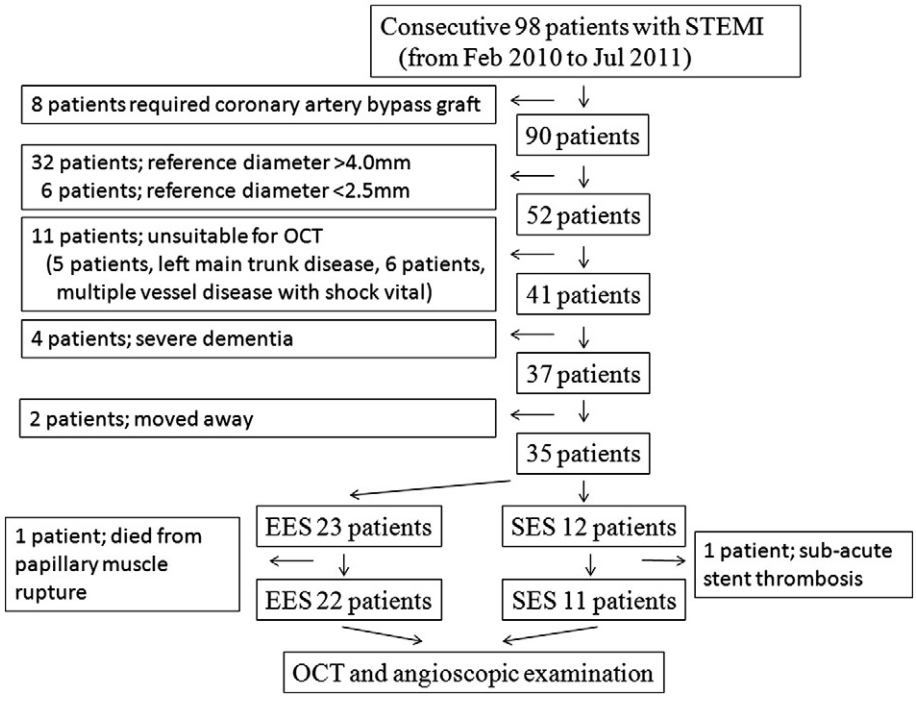

Fig. 1. Study population.