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Comparison of everolimus- and paclitaxel-eluting stents in dialysis patients☆

Masaya Otsuka *, Nobuo Shiode, Yoshiko Masaoka, Tomokazu Okimoto, Hiromichi Tamekiyo, Tomoharu Kawase, Kenichi Yamane, Yuzo Kagawa, Naoya Hironobe, Tasuku Higashihara, Yuto Fujii, Yasuhiko Hayashi

Division of Cardiology, Cardiovascular Center, Akane Foundation Tsuchiya General Hospital, Hiroshima, Japan

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ABSTRACT

Background: We previously reported that the incidence of 1-year major adverse cardiac events (MACE) in patients treated with paclitaxel-eluting stents (PES) was lower than that in the sirolimus-eluting stents in dialysis patients. However, it remains unclear whether there are differences in clinical outcomes between everolimus-eluting stents (EES) and PES.

Methods: Between February 2010 and September 2013, 102 maintenance dialysis patients with 135 lesions treated with EES were compared to 107 maintenance dialysis patients with 147 lesions treated with PES. One-year clinical outcomes were investigated.

Results: Diabetes mellitus was present in 64.7% in the EES group and 71.0% in the PES group ($p = 0.33$). Heavy calcification was in 27.4% vs. 34.0% ($p = 0.23$). Rotational atherectomy was undergone in 11.1% vs. 23.1% ($p < 0.01$). Total stented length was not significantly different (23.5 ± 14.6 mm vs. 24.4 ± 13.2 mm, $p = 0.60$). One patient in the EES group was lost to follow up. At 12 months, MACE occurred in 13.2% in the EES group and 17.4% in the PES group ($p = 0.25$). Target lesion revascularization (TLR) was observed in 9.5% vs. 10.4% respectively ($p = 0.77$). Mortality was 11.8% vs. 13.1% ($p = 0.35$). Cardiac death was 5.0% vs. 7.7% ($p = 0.09$). Definite stent thrombosis was observed in 2.0% vs. 0% ($p = 0.14$). Subgroup analysis in patients with diabetes mellitus revealed no significant differences in MACE (12.7% vs. 14.9%, $p = 0.36$), TLR (8.3% vs. 7.4%, $p = 0.42$), mortality (13.7% vs. 13.2%, $p = 0.28$), and cardiac death (6.3% vs. 8.0%, $p = 0.15$) between the two groups.

Conclusions: One-year clinical outcomes following EES and PES implantations are similar in dialysis patients.

1. Introduction

Patients with end-stage renal disease (ESRD), especially those on dialysis, have been shown to have higher mortality and major adverse cardiac event (MACE) rates compared with non-dialysis patients following first-generation sirolimus-eluting stent (SES) implantation [1]. Meanwhile, hemodialysis was found to be a predictor of MACE but not of target lesion revascularization (TLR) following paclitaxel-eluting stent (PES) implantation [2]. Some retrospective studies reported that the clinical restenosis in patients treated with PES was lower than that in patients with SES in dialysis patients [3,4]. On the other hand, a randomized study showed that angiographic data at 8-month follow-up after percutaneous coronary intervention (PCI) were similar between HD patients treated with SES and those treated with PES [5]. Second-generation everolimus-eluting stent (EES) was designed with the goal of improving safety, efficacy, and device performance. Randomized clinical trials showed that EES was better than PES in terms of safety and efficacy [6,7]. However, it is important to note that in COMPARE trial [6], patients with chronic renal failure were included only in 3%, and SPIRIT IV trial [7] excluded patients with serum creatinine level of >2.5 mg/dL or on dialysis. Therefore, no conclusions were made in terms of ESRD. RENAL-DES was the first randomized trial showing effectiveness in terms of clinical restenosis of second-generation EES in comparison with bare metal stent in patients with chronic kidney disease (CKD), and the efficacy of EES in preventing restenosis was independent of the severity of CKD, including severe CKD and kidney failure [8]. However, it remains unclear whether there are differences in clinical outcomes between EES and PES in patients with ESRD, especially those on dialysis. To address this issue, we compared clinical outcomes between EES and PES in patients on dialysis.

Abbreviations: ESRD, end-stage renal disease; MACE, major adverse cardiac event; SES, sirolimus-eluting stent; TLR, target lesion revascularization; PES, paclitaxel-eluting stent; PCI, percutaneous coronary intervention; EES, everolimus-eluting stent; CKD, chronic kidney disease; IVUS, intravascular ultrasound; OCT, optical coherence tomography; MLD, minimum lumen diameter; RVD, reference vessel diameter; %DS, percent diameter stenosis; ARC, Academic Research Consortium; MI, Myocardial infarction; GUSTO, global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries.

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* Corresponding author at: Division of Cardiology, Cardiovascular Center, Akane Foundation Tsuchiya General Hospital, 3-30 Nakajima-cho, Naka-ku, Hiroshima, 730-8655, Japan. Tel.: +81 82 243 9191; fax: +81 82 241 1865.
E-mail address: Masaya.Otsuka@ma7.seikyou.ne.jp (M. Otsuka).

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2. Methods

2.1. Patient population

From February 2010, EES (Xience V, Abbott Vascular, Santa Clara, CA, USA) (Promus, Boston Scientific, Natick, MA, USA) was introduced in Tsuchiya General Hospital (Hiroshima, Japan). Until the end of September 2013, 248 maintenance dialysis patients were treated with coronary stents for the treatment of coronary artery disease. Maintenance dialysis was defined as regular hemodialysis or peritoneal dialysis for at least 1 month. The details of 248 patients were that 102 patients were treated with EES, 107 patients were treated with PES (Taxus Liberté, Taxus Element, Boston Scientific, Natick, MA, USA), and 39 patients were treated with other stents. In this study, 102 maintenance dialysis patients with 135 lesions treated with EES were compared to 107 maintenance dialysis patients with 147 lesions treated with PES. Of these, from March 2011 to September 2013, 60 patients were prospectively randomized to either EES (32 patients) or PES (28 patients). In the randomized arm, maintenance dialysis patients aged ≥20 years with native coronary artery disease were eligible. Angiographic inclusion criteria required vessel diameters 2.5 mm to 4 mm. Exclusion criteria were contraindications to dual antiplatelet drugs, inability to provide informed consent, in-stent restenosis, stent thrombosis, and coronary artery bypass graft lesions. In patients who were not included in the randomized arm, stent selection was left to operator discretion. The EES platforms used in this study were Xience V, Xience Prime, Xience Xpedition, Promus, and Promus Element. The PES platforms were Taxus Liberté and Taxus Element. Written, informed consent was obtained from all patients, and the protocol had the approval of the local hospital Research Ethics Committee.

2.2. Procedure

All interventions were done according to standard techniques, and all decisions concerning the PCI strategy were made by experienced interventional cardiologists (NS or YH) based on the morphology of the target lesions. If a patient had a highly calcified lesion detected by angiography, intravascular ultrasound (IVUS), and/or optical coherence tomography (OCT), rotational atherectomy (Rotablator, Boston Scientific, Natick, MA, USA) was performed prior to stent implantation. Procedural success was defined as an immediate percent diameter stenosis <50% without an associated in-hospital MACE. Dual antiplatelet therapy (aspirin ≥81 mg, 75 mg clopidogrel or 200 mg ticlopidine/day) was recommended for at least 6 months post-procedure and up to 12 months in patients with no risk of high bleeding. Aspirin therapy was recommended indefinitely.

2.3. Angiographic analysis

Coronary arteriograms were obtained in a routine manner. Patients received intracoronary isosorbide dinitrate before initial, post-procedural and follow-up angiograms to achieve maximal vasodilatation. The results from the single most severe view were recorded. Lesion length, minimum lumen diameter (MLD), reference vessel diameter (RVD) and percent diameter stenosis (%DS) were analyzed using a computerized, automated, edge-detection algorithm (Philips Medical System, Best, The Netherlands), as previously described [9]. The analyses were performed by experienced cardiologists who were unaware of the patients' clinical outcomes. Lesions were classified according to the modified American College of Cardiology/American Heart Association (ACC/AHA) criteria [10]. Eight-month angiographic follow-up was a part of predefined strategy based on whether patients had ischemic symptoms and/or positive functional ischemia studies. The definition of significant restenosis was %DS of ≥50% in the stented lesion at follow-up. In-segment analysis (including the stented segment as well as the margins 5 mm proximal and distal to the stent) was assessed. Acute gain was calculated as the difference between MLD at the end of intervention and MLD before intervention. Late loss was calculated as the difference between MLD at the end of intervention and MLD at the time of follow-up angiography.

2.4. Clinical follow-up and endpoints

Clinical follow-up information was obtained from medical records, by questionnaires sent to local physicians or by telephone contact. The Academic Research Consortium (ARC) definition of definite stent thrombosis was used as the endpoint for stent thrombosis [11]. Myocardial infarction (MI) during follow-up was diagnosed as serum creatinine kinase levels >3-fold the upper limit of the normal range or the presence of new Q waves on the electrocardiogram. TLR was defined as any repeat PCI or surgical bypass of the original target lesion. The target lesion was considered to be the area covered by the stent plus 5-mm margins proximal and distal to the edges of the implanted stent. The primary endpoint was 1-year MACE including cardiac death, MI, stent thrombosis and TLR. The secondary endpoint was 1-year TLR. When >1 clinical endpoint occurred in a patient, only the first event was counted for the event free survival analysis. Bleeding events occurring during follow-up were assessed according to global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries (GUSTO) [12].

2.5. Statistical analysis

Statistical analyses in the randomized arm were performed on an intention-to-treat principle. Continuous variables are expressed as mean ± standard deviation and they were evaluated by means of a Student's t -test. Categorical variables are expressed as frequencies and were evaluated by means of chi-square test or Fisher's exact test as appropriate. MACE was compared by Kaplan–Meier survival curves, and the corresponding p value was obtained from the log-rank test. Differences between event rates were compared using Cox proportional hazards regression analyses to estimate the hazard ratio (HR) and 95% CI. Values of $p < 0.05$ were considered statistically significant. Statistical analysis was performed using JMP, version 5.1 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patient characteristics, procedure and angiographic outcomes

Baseline characteristics of the study population are listed in Table 1. There were no significant differences between the EES and PES groups.

Table 1
Patient characteristics.

Variables	EES (N = 102)	PES (N = 107)	p value
Age, years	69.0 ± 10.1	68.1 ± 9.0	0.51
Male (%)	73 (71.6)	77 (72.0)	0.95
Hypertension (%)	93 (91.2)	100 (93.5)	0.54
Hyperlipidemia (%)	35 (34.3)	46 (43.0)	0.20
Diabetes mellitus (%)	66 (64.7)	76 (71.0)	0.33
Insulin treatment (%)	22 (21.6)	24 (22.4)	0.88
Current smoker (%)	11 (10.8)	14 (13.1)	0.61
Dialysis period, years	6.4 ± 6.3	6.2 ± 5.9	0.77
Ejection fraction, %	53.2 ± 14.5	52.1 ± 15.1	0.60
Previous MI (%)	25 (24.5)	27 (25.2)	0.90
Previous CABG (%)	12 (11.8)	8 (7.5)	0.29
Acute MI (%)	4 (3.9)	4 (3.7)	0.95
Extent of CAD			0.30
Single-vessel disease (%)	47 (46.1)	45 (42.1)	
Two-vessel disease (%)	43 (42.2)	41 (38.3)	
Three-vessel disease (%)	12 (11.8)	21 (19.6)	

Data are expressed as numbers (%) or mean ± SD. EES: everolimus-eluting stent; PES: paclitaxel-eluting stent; MI: myocardial infarction; CABG: coronary artery bypass graft surgery; CAD: coronary artery disease.