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Comparison between zotarolimus-eluting stents and first generation drug-eluting stents in the treatment of patients with acute ST-segment elevation myocardial infarction

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ABSTRACT

Background: The purpose of this study was to compare the two year efficacy and safety of zotarolimus-eluting stents (ZES) and first-generation DES, sirolimus- (SES) and paclitaxel-eluting stents (PES), in an all-comer registry receiving primary percutaneous coronary intervention (PCI) for acute ST-segment elevation myocardial infarction (STEMI).

Methods: A total of 711 consecutive STEMI patients (ZES: 135, SES: 427, and PES: 149), who underwent primary PCI between January 2005 and June 2008 were enrolled from three centers. In our study, the efficacy analysis endpoint was target vessel failure (cardiac death, target vessel related myocardial infarction, and ischemia-driven target vessel revascularization) at 2 years. The safety analysis endpoint was a composite of all cause death, non-fatal myocardial infarction, and stent thrombosis within 2 years.

Results: At 2 years, the rates of target vessel failure in the ZES, SES, and PES groups were 14.8%, 12.9%, and 19.5%, respectively ($p = 0.141$). The rates of composite safety endpoints at 2 years were not different among the three groups (ZES 8.1% vs. SES 13.1% vs. PES 16.8%, $p = 0.102$). However, when comparing the two groups, ZES was safer than PES (adjusted HR 0.48, 95% CI 0.24–0.98, $p = 0.046$). There was also a non-significant trend in favor of ZES in the rate of stent thrombosis (ZES 1.5% vs. SES 2.3% vs. PES 4.7%, $p = 0.186$).

Conclusion: In the treatment of STEMI patients, ZES showed similar and acceptable efficacy compared to first-generation DES (SES and PES) up to 2 years. In addition, ZES seems to be more favorable than PES in terms of safety.

1. Introduction

Due to the excellent efficacy of drug-eluting stents (DES) [1,2], the use of DES increased remarkably even for off-label indications including acute ST-segment elevation myocardial infarction (STEMI) [3]. However, concerns regarding safety exist due to the increased risk of very late stent thrombosis in patients implanted with DES [4–6]. In addition, patients with acute STEMI have a greater thrombotic milieu, and lesions causing acute STEMI are known to contain greater necrotic core and ruptured fibrous cap, which are prone to thrombosis [7,8]. Moreover, delayed healing in stented acute MI culprit sites and exposure of uncovered stent struts for extended periods of time have been documented for the first-generation DES, namely the sirolimus- (SES) and paclitaxel-eluting stents (PES) [7,8].

The zotarolimus-eluting stent (ZES) is a second-generation DES, using zotarolimus, a synthetic analog of sirolimus, and a biocompatible hydrophilic phosphorylcholine polymer, coated on a low-profile cobalt-alloy Driver stent [9]. Due to these profiles, ZES showed more rapid endothelial coverage than first-generation DES in an animal stenting model [10]. Therefore, there is anticipation that ZES could be less thrombotic and might result in improved safety compared with SES or PES. However, data comparing the long-term outcomes between ZES and first-generation DES are limited. The aim of this study was to compare the long-term outcomes between ZES, SES and PES in consecutive patients receiving primary percutaneous coronary intervention (PCI) for acute STEMI.

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2. Method

2.1. Study population

This study was a retrospective analysis of consecutive patients with acute STEMI who were enrolled in the 3*S*-Registry and treated with one of three types of DES (ZES, SES, or PES). The 3*S*-Registry is a three-center registry that collects patients with acute STEMI who received DES since Jan 1, 2005. The three centers composing the registry are large-volume hospitals; *S*eoul National University Hospital, *S*eoul National University Bundang Hospital, and *S*amsung Medical Center. We analyzed all-comers regardless of the clinical or anatomical presentation, including patients with cardiogenic shock (defined as persistent systolic blood pressure < 90 mm Hg, or the need of vasopressors or intra-aortic balloon pump required to maintain blood pressure > 90 mm Hg), survivors from resuscitation, and those whose culprit lesions were associated with previously implanted stents. In this study, patients enrolled from Jan 1, 2005 to June 31, 2008 were analyzed. Exclusion criteria were ages below 18 years, expected survival less than 1 year due to other medical conditions, and more than two kinds of DES inserted.

2.2. Treatment and follow up

All patients were premedicated with loading dose of aspirin (300 mg) and clopidogrel (300 to 600 mg). Unfractionated heparin was administered either before or during the intervention to achieve adequate anticoagulation. Coronary angiography and angioplasty were performed following the current standard techniques. The use of glycoprotein IIb/IIIa inhibitor and intravascular ultrasound guidance was left to the operator's discretion. The type of stent to be implanted was decided by the operator during the procedure. Dual antiplatelet therapy (DAT) was recommended for at least 12 months. Clinical follow-up after PCI was recommended at 1 month, 3 months, 6 months, and then every 3 to 4 months thereafter. The decision for routine angiographic follow-up was left up to the discretion of the treating physician.

Clinical, angiographic, procedural and outcome data were collected by independent nurses and researchers who had not participated in the treatment of the study patients. Patient data were retrospectively reviewed through electrical medical records and the subjects who were lost to out-patient follow-up were contacted by telephone at regular 6 month intervals. For validation of complete follow-up data, information about vital status was obtained from the Korea National Statistical Office using a unique personal identification number.

2.3. Study endpoints and definitions

Clinical outcomes were assessed at 24 months for all-cause death, cardiac death, non-fatal myocardial infarction (MI), ischemia-driven target-lesion revascularization (TLR), ischemia-driven target-vessel revascularization (TVR), and stent thrombosis. All deaths were considered to have been from cardiac cause unless a non-cardiac origin was definitely documented. Myocardial infarction was defined according to the recommendations of the ESC/ACCF/AHA/WHF task force [11]. Since cardiac enzymes routinely increase after PCI for STEMI due to early washout, we did not incorporate the periprocedural MI criteria into our working definition of MI. TLR was defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis of the target lesion. TVR was defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. Revascularization of the target lesion or vessel was defined as ischemia-driven if diameter stenosis was more than 75% on visual estimation or if diameter stenosis was more than 50% with symptom or sign of ischemia (angina, positive stress test or imaging). The presence of stent thrombosis was assessed by the Academic Research Consortium (ARC) definitions and "definite or probable" categories were used to define stent thrombosis [12].

We established two study endpoints; efficacy analysis endpoint and safety analysis endpoint. Efficacy analysis endpoint was target vessel failure (TVF), the composite of cardiac death, target vessel related MI, and ischemia-driven TVR. Safety analysis endpoint was composed of all-cause death, nonfatal MI and stent thrombosis.

2.4. Statistical analysis

Baseline and angiographic characteristics among the patients treated with ZES, SES, or PES were compared using one-way ANOVA for continuous variables and chi-square test for categorical variables. Cumulative event curves were plotted by means of the Kaplan–Meier method, and the differences among the three stent groups were assessed with the log-rank test. To adjust for differences in baseline characteristics, a Cox proportional hazards model was used and the adjusted hazard ratios were calculated. The variables used in multivariate analyses were selected if they are significantly different among the 3 groups or if they have predictive values. The adjusted variables were as follows: age (continuous), sex (male or female), hypertension (yes or no), diabetes mellitus (yes or no), smoking (current or non-current), dyslipidemia (yes or no), shock (yes or no), culprit lesion (4 categories), number of disease vessel (continuous), previous coronary angioplasty (yes or no), previous bypass surgery (yes or no), previous myocardial infarction (yes or no), stent diameter (continuous), and stent length (continuous).

To reduce the bias of treatment selection and any other potential confounders in this observational study, we used inverse probability weighting (IPW). In brief, propensity scores were calculated based on the 12 covariates, which were the same as the ones described for multivariate analyses except post-treatment variables; stent diameter and stent length. After creating the inverse probability of treatment weight (propensity score weight), 3 groups were balanced by IPW and Cox proportional hazard model was fitted to compare the outcomes of the stent groups. All statistical analysis was performed with SPSS (version 17.0, SPSS Inc.) and SAS (version 9.2, SAS Institute Inc.).

3. Results

3.1. Baseline characteristics

The study profile is shown in Fig. 1. Between January 2005 and June 2008, a total of 984 consecutive patients received treatment for STEMI. Among these patients, 728 patients underwent primary PCI. Seventeen patients were excluded for the following reasons; 5 received mixed DES stents, 10 underwent emergent bypass surgery, 1 received an unidentifiable stent, and 1 refused further treatment, thus leaving 711 all-comer acute STEMI patients for final analysis (ZES: 135, SES: 427, and PES: 149).

Baseline clinical characteristics of the three groups are shown in Table 1. There were no significant differences in baseline clinical characteristics among the 3 groups. The patients were 62.6 ± 12.4 years of age, 74.0% of them were men, and 28.8% had diabetes mellitus. The angiographic and procedural characteristics of the 3 groups (Table 2) were also comparable except for the stent diameter, which was slightly but significantly larger in the ZES group (mean stent diameter: 3.17 ± 0.51 vs. 3.03 ± 0.36 vs. 3.09 ± 0.39 mm for ZES vs. SES vs. PES respectively, $p = 0.002$ by ANOVA).

There were 7 patients (5.2%) in the ZES group, 26 (6.1%) in the SES group, and 10 (6.7%) in the PES group who had died during the initial procedure and hospitalization period ($p = 0.863$). For patients who had been successfully discharged, the use of beta-blockers and statins were significantly different among the 3 groups (Table 3). Beta-blocker use was significantly lower in the SES group compared with the ZES and PES groups, and statins were significantly more often prescribed in the ZES group compared with the SES and PES groups. Although all patients were maintained on DAT for at least 12 months, the mean duration of clopidogrel use was significantly longer in the ZES group compared with the SES and PES groups (16.9 vs. 13.8 vs. 14.5 months for the ZES, SES, and PES groups respectively, $p = 0.001$).

3.2. Clinical outcomes up to 2 years

The cumulative outcomes of the crude study population at 1 month, 1 year, and 2 years are presented in Table 4. When comparing all the three groups, there were no statistically significant differences amongst the groups regarding all-cause death, cardiac death, nonfatal myocardial infarction, target vessel related myocardial infarction, ischemia-driven target-lesion revascularization, or ischemia-driven target-vessel revascularization. However, when comparing two of the three groups by pair-wise comparison, the cumulative rate of the efficacy analysis endpoint (TVF rate) at 2 years was marginally higher in the PES group (19.5%) compared with the SES (12.9%) group ($p = 0.049$, Fig. 2A, Table S1). In addition, the cumulative rate of the composite safety analysis endpoint at 2 years (death, nonfatal MI, and stent thrombosis) was significantly lower in the ZES group compared with the PES group (8.1% vs. 16.8%, $p = 0.032$, Fig. 3A, Table S1).

In multivariate analysis using Cox proportional hazard models, the SES group showed a significantly lower rate of TVF compared with PES group (adjusted HR 0.46, 95%CI 0.25–0.84, $p = 0.011$) and the ZES group was associated with a lower rate of safety analysis endpoint compared with the PES group (adjusted HR 0.11, 95%CI 0.01–0.93, $p = 0.043$). This result was driven mainly by high incidence of all-cause death in the PES group (13.4%) compared with the ZES group (6.7%) (Fig. 3B). Because there is no close connection between early deaths (especially in-hospital deaths) and different types of stents, we analyzed composite safety endpoints after exclusion of in-hospital deaths and confirmed the consistent results (ZES 3.1%