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Impact of Optimized Procedure-Related Factors in Drug-Eluting Balloon Angioplasty for Treatment of In-Stent Restenosis

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ABSTRACT

OBJECTIVES The aim of this study was to investigate the impact of optimizing procedure-related factors during drug-eluting balloon (DEB) angioplasty on clinical outcomes of drug-eluting stent in-stent restenosis (ISR).

BACKGROUND Although DEB angioplasty is recommended as a reasonable option for ISR, recurrent target lesion failure (TLF) still occurs in many patients after DEB angioplasty.

METHODS Consecutive patients with drug-eluting stent ISR treated with DEB (SeQuent Please) were collected from 4 centers in Korea. The primary outcome was 2-year TLF. Procedure-related modifiable independent predictors for TLF and their best cutoff values were determined.

RESULTS In a total of 256 patients (309 lesions), TLF occurred in 52 patients (20.3%). Modifiable independent predictors of TLF among procedure-related factors were residual diameter stenosis after lesion preparation (residual percentage diameter stenosis [%DS]), DEB-to-stent ratio (BSR), and DEB inflation time ($T_{inflation}$), whose best cutoff values were 20%, 0.91, and 60 s, respectively. TLF rates were significantly higher in groups with residual %DS ≥20% (34.7% vs. 12.5%; adjusted hazard ratio: 2.15; 95% confidence interval: 1.86 to 2.48; $p < 0.001$), BSR ≤0.91 (46.4% vs. 21.9%; adjusted hazard ratio: 2.02; 95% confidence interval: 1.75 to 2.34; $p < 0.001$), and $T_{inflation}$ ≤60 s (26.2% vs. 14.0%; adjusted hazard ratio: 1.82; 95% confidence interval: 1.36 to 2.45; $p < 0.001$). When classifying ISR lesions by combination of procedure-related factors, TLF occurred in 8.3% in the fully optimized procedure group (residual %DS <20%, BSR >0.91, and $T_{inflation}$ >60 s) and 66.7% in the nonoptimized group (residual %DS ≥20%, BSR ≤0.91, and $T_{inflation}$ ≤60 s) ($p < 0.001$).

CONCLUSIONS Residual %DS after lesion preparation, BSR, and $T_{inflation}$ were the only modifiable procedure-related factors in DEB angioplasty. Fully optimized DEB angioplasty with optimal lesion preparation, prolonged inflation, and sufficient dilation may play an important role in reducing TLF after DEB angioplasty. (J Am Coll Cardiol Intv 2018;11:969–78)

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ABBREVIATIONS AND ACRONYMS

BSR = drug-eluting balloon-to-stent ratio

CI = confidence interval

DEB = drug-eluting balloon

DES = drug-eluting stent(s)

HR = hazard ratio

ISR = in-stent restenosis

MI = myocardial infarction

%DS = percentage diameter stenosis

$T_{inflation}$ = total inflation time of drug-eluting balloon

TLF = target lesion failure

TLR = target lesion revascularization

In-stent restenosis (ISR) is a major concern in coronary intervention, even in the era of newer generation drug-eluting stents (DES) with enhanced performance (1). ISR is still clinically important, because of its considerable incidence ranging from 3% to 20% of patients (1) and the high proportion of patients with ISR presenting with acute coronary syndrome (1), which may translate into increased rates of future adverse cardiovascular events (2).

To date, drug-eluting balloon (DEB) is 1 of the options for ISR treatment. The most recent European Society of Cardiology/European Association for Cardiothoracic Surgery guidelines recommend both DEBs and DES as class IA for the treatment of ISR (3,4). However, DEBs have been challenged by second-generation DES with superior angiographic and clinical efficacy compared with DEBs (2,4–6). Indeed, DEB angioplasty for ISR has shown a substantial rate of target lesion failure (TLF) of up to 20% (4,7), with even worse outcomes for DES ISR (5,8,9).

SEE PAGE 979

Given that the antiproliferative drug coating on the DEB is mainly responsible for preventing lesion failure, delivering a sufficient amount of drug into the wall of the target lesion is crucial. Thus, procedural modifications toward optimized lesion preparation, wider contact area, and longer contact time may maximize drug delivery and thereby enhance clinical outcomes after DEB angioplasty (10). Another important fact is that many cases of DES ISR are associated with insufficient expansion of DES at the index procedure. Thus, sufficient expansion with minimal residual stenosis after lesion preparation might be another important procedure-related component during DEB angioplasty. Nevertheless, it is unknown whether the optimization of procedure-related factors would affect the efficacy and safety of DEB angioplasty for ISR treatment.

Therefore, we sought to evaluate the impact of procedure-related factors during DEB angioplasty on the clinical outcomes of patients with DES ISR, using the unselected population from a dedicated multicenter ISR registry treated with DEB angioplasty.

METHODS

An extended description of study methods is presented in the Online Appendix.

STUDY POPULATION. The patient population was derived from the HOST-ISR-DEB (Harmonizing Optimal Strategy for Treatment of ISR With DEB) registry, which was a dedicated multicenter all-comers registry for ISR treated with DEBs. From 2009 through 2014, 269 consecutive patients who underwent DEB angioplasty for ISR were prospectively enrolled at 4 centers in South Korea, regardless of previous stent types. To select the exclusive DES ISR population, 13 patients with bare-metal stent ISR were excluded, leaving 256 patients with 309 lesions in the final population (**Figure 1**). Angiographic follow-up was not mandatory. The study protocol was approved by the ethics committee at each participating center and was conducted according to the principals of the Declaration of Helsinki. All patients provided written informed consent upon enrollment in the registry.

DEB PROCEDURES AND MEDICATIONS. Coronary interventions were performed according to current standard techniques. DEB angioplasty for ISR was performed using a commercialized paclitaxel-eluting balloon, coated with 3 μg paclitaxel/mm^2 (SeQuent Please, B. Braun, Melsungen, Germany). Pre-dilation of the ISR lesion was performed using a conventional balloon with multiple high-pressure inflations (11). The choice of diameter and length of pre-dilating balloon and DEB was left to the operator's discretion. The DEB was carefully prepared and delivered rapidly to the lesion within 1 min after insertion of the DEB into aqueous phase inside the guide catheter. Total inflation time of the DEB and maximum pressure were determined by the operator according to patient tolerance and reaction of treated lesions, and data were systematically collected. DEB angioplasty was considered successful if the DEB fully covered the entire segment of the ISR lesion, final residual stenosis was <30%, final target vessel flow was TIMI (Thrombolysis In Myocardial Infarction) grade 3, and absence of significant edge dissection or in-stent dissection was greater than type C. Unless there was an undisputed reason for discontinuing dual-antiplatelet therapy, all patients were advised to take aspirin (at least 100 mg/day) indefinitely and clopidogrel (75 mg/day) for at least 6 months after the index procedure.

QUANTITATIVE CORONARY ANGIOGRAPHY. Quantitative coronary analysis of angiographic images of index DEB procedures was performed at a central core laboratory (Seoul National University Hospital Cardiovascular Clinical Research Center) by specialized quantitative coronary angiography technicians who were blinded to the contents and purpose of this study. The Cardiovascular Angiography Analysis System 5.7 quantitative coronary angiographic system (Pie Medical Imaging, Maastricht, the Netherlands) was used for automated contour