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Relative dose and vascular response after drug-eluting stent implantation: A dosimetric 3D-intravascular ultrasound study

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ABSTRACT

Background: In drug-eluting stents (DESs), the theoretical drug dose exposed to the vessel wall per stent surface area may vary due to the fixed loading dose and differences in the stent surface area once expanded in varying vessel sizes. The aim of this study was to evaluate the potential effects of different dose intensities, as estimated by 3D-IVUS dosimetry, on vascular response after DES implantation.

Methods: Follow-up (6–9 months) 3D-IVUS was performed in 840 coronary lesions treated with a single DES of the following types: sirolimus (SES, n = 148), paclitaxel (PES, n = 162), Endeavor zotarolimus (E-ZES, n = 233), Resolute zotarolimus (R-ZES, n = 147), and everolimus (EES, n = 150). Volume index (volume/length, mm^3/mm) was obtained for vessel, lumen, plaque, stent, and neointima. In each lesion, exposed dose intensity was calculated as known loading dose divided by measured luminal surface area of the stented segment. Lesions were divided into tertiles based on the exposed dose intensity: high, medium, and low dose groups.

Results: The exposed dose intensity ranged 0.74–1.76 $\mu g/mm^2$ for SES, 0.41–1.18 $\mu g/mm^2$ for PES, 0.71–1.57 $\mu g/mm^2$ for E-ZES, 0.72–1.63 $\mu g/mm^2$ for R-ZES, and 0.40–0.99 $\mu g/mm^2$ for EES. All types of DES showed no significant difference in neointimal hyperplasia among the 3 groups, except that E-ZES showed significantly less neointimal hyperplasia in the high dose group.

Conclusions: Detailed 3D-IVUS revealed significant lesion-to-lesion variability in dose intensity exposed to the vessel wall following DES implantation. However, the major types of DES appear to yield equally effective neointimal suppression, despite the varying dose intensity, except for E-ZES.

1. Introduction

Many types of drug-eluting stents (DESs) have been developed and tested in human clinical trials and have demonstrated significant reduction of clinical and angiographic restenosis as well as target lesion revascularization (TLR) compared with bare-metal stents. Each component of the DES, including platform, drug, or polymer, is associated with acute to long-term results. To date, every DES has been approved with only one or two types of stent design with a stent diameter of 2.25 to 4.0 mm. The theoretical drug dose exposed to the vessel wall per stent surface area may vary due to the fixed loading dose and differences in the stent surface area once expanded in varying vessel sizes. Generally, when the same stent design and drug dose are used for different vessel diameters, smaller target vessel dimensions may result in relatively higher dose exposure. For example, when 2.5 mm and 4.0 mm Endeavor zotarolimus-eluting stents (E-ZES) are expanded nominally, the theoretical exposed drug dose per stent surface area of the 2.5 mm E-ZES is 1.6 times as much as that of the 4.0 mm E-ZES because of the same loading dose (Fig. 1). On the other hand, smaller target vessel dimensions have been reported as an independent predictor of restenosis and repeat revascularization after DES implantation [1–3]. Although there have been many clinical studies investigating the impact of different loading doses on neointimal hyperplasia in DES [4–9], there are few reports focused on the relationship between local drug dose intensity and vascular response after DES implantation. Thus, the aim of this study was to evaluate the potential effects of different theoretical dose intensities, as estimated by three-dimensional intravascular ultrasound (3D-IVUS) dosimetry, on vascular response after DES implantation.

2. Methods

2.1. Study population

The original study data were pooled at both patient and lesion levels from 11 DES trials: SIRIUS [10], SVELTE [11], SIRIUS 2.25 [12], Zomaxx I

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Stent Diameter		SES	PES	E-ZES /R-ZES	EES
	2.25 mm	8.4 ± 0.3 μg/mm			
	2.5 mm		6.5 ± 0.2 μg/mm	10 μg/mm	4.7 ± 0.1 μg/mm
	2.75 mm				
	3.0 mm				
	3.5 mm	9.8 ± 0.3 μg/mm			6.5 ± 0.2 μg/mm
	4.0 mm				

Fig. 1. The varieties of stent diameter and loading drug dose on each stent type. Drug dose is represented as a dose-per-length, calculated as an amount of loading drug dose divided by its stent length. Because the dose-per-length has a slight variety in the same diameter of the stent according to various stent lengths, the values are expressed as mean ± SD, except that E- and R-ZES have uniform dose-per-length despite various stent lengths. The fields of unused stent sizes in the present study are shaded.

[13], Zomaxx II [13], ENDEAVOR III [14], ENDEAVOR IV [15], SPIRIT III [16], SPIRIT III Japan [16], RESOLUTE FIM [17], and RESOLUTE US [18]. The study design and 6- to 9-month results have been previously reported. From these studies, the results of 3D-IVUS analysis from patients meeting the following criteria were pooled: 1) patients with stable or unstable angina who had undergone successful treatment with a single sirolimus- (Cypher®, Cordis, Miami, FL: [SES]), paclitaxel- (Taxus® Express^{2}™, Boston Scientific, Natick, MA: [PES]), zotarolimus- (Endeavor®, Medtronic, Santa Rosa, CA: [E-ZES], Resolute®, Medtronic: [R-ZES]), or everolimus- (XIENCE V®, Abbott Vascular, Santa Clara, CA: [EES]) eluting stent with a stent diameter between 2.25 to 4.0 mm using standard stent implantation techniques;

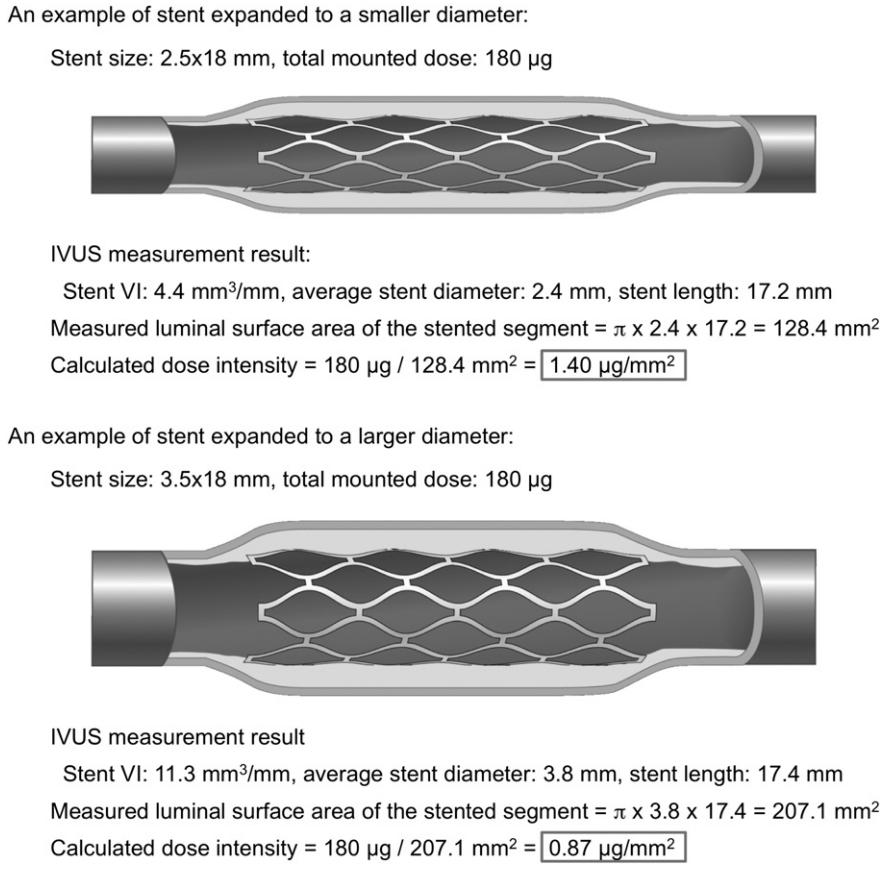

Fig. 2. Examples of differences in exposed dose intensity The exposed dose intensity can differ considerably from lesion to lesion.