Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Two-year vascular responses to drug-eluting stents with biodegradable polymer versus durable polymer: An optical coherence tomography sub-study of the NEXT

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ARTICLE INFO

Article history:
Received 9 January 2017
Received in revised form 29 March 2017
Accepted 25 April 2017
Available online xxx

Keywords:
Optical coherence tomography
Drug-eluting stents
Percutaneous coronary intervention

ABSTRACT

Background: This study aimed to compare very late vascular response after stent implantation between everolimus-eluting stent (EES) with a thin, non-adhesive, durable, biocompatible fluorinated polymer and biolimus-eluting stent (BES) with a biodegradable polymer by optical coherence tomography (OCT).
Methods and results: In the NOBORI-BES Versus XIENCE V/PROMUS-EES Trial (NEXT), a formal OCT substudy investigated 48 patients (27 EES-treated lesions in 23 patients and 28 BES-treated lesions in 25 patients) with 2-year (18–30 months) follow-up imaging at 18 centers. The percentage of uncovered strut by neointima was significantly lower in EES compared with BES ($2.1 \pm 4.7\%$ vs. $7.9 \pm 10.8\%$, $p = 0.013$). The percentage of malapposed strut was not different between EES and BES ($0.1 \pm 0.3\%$ vs. $0.5 \pm 1.3\%$, $p = 0.138$). The frequency of stent with evagination, which is identified as outward bulges in the luminal contour between struts, was significantly lower in EES compared with BES (22% vs. 86%, $p < 0.001$). The frequency of neoatherosclerosis was not different between EES and BES (11% vs. 11%, $p = 1.000$).
Conclusions: At 2 years after stent implantation, uncovered stent strut by neointima and evagination were less frequently observed in EES compared with BES. This OCT study suggests that the very late vascular response is different between EES and BES.

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http://dx.doi.org/10.1016/j.jjcc.2017.04.005
0914-5087/

Introduction

Drug eluting stents (DES) have reduced late (<1 year) in-stent restenosis as compared to drug-free bare metal stents. However, concerns have been raised about the very late (>1 year) prognosis of DES. Several studies in first-generation DESs have suggested that permanent polymers lead to persistent inflammation, which might be associated with vessel positive remodeling, late-acquired stent malapposition, neoatherosclerosis, and very late stent thrombosis [1]. To overcome this problem, second-generation DESs with improved polymers have been designed. The XIENCE V (Abbot Vascular, Santa Clara, CA, USA)/PROMUS (Boston Scientific, Natick, MA, USA) everolimus-eluting stent (EES) is coated with a thin, non-adhesive, durable, biocompatible fluorinated polymer releasing everolimus. The NOBORI biolimus-eluting stent (BES; Terumo, Tokyo, Japan) is coated with a biodegradable polymer (polylactic acid) eluting biolimus A9, a highly lipophilic analogue of sirolimus. The aim of the present study was to compare very late vascular response at 2 years (18–30 months) after stent implantation between EES with durable polymer and BES with biodegradable coating by using optical coherence tomography (OCT).

Methods

Study population

This is a pre-specified sub-study of the NOBORI Biolimus-Eluting Versus XIENCE V/PROMUS Everolimus-Eluting Stent Trial (NEXT). The NEXT is a prospective, multicenter, randomized, assessor-blind, non-inferiority trial comparing EES with BES in Japan [2]. Between May and October 2011, 3241 patients were enrolled in the NEXT without any exclusion criteria and randomly assigned to undergo percutaneous coronary intervention (PCI) with either EES or BES. Randomization was performed by a web-based allocation system and was stratified by center, diabetic status, and participation in the imaging sub-studies (angiography, intravascular ultrasound, OCT, and coronary endothelial function). The OCT sites ($n = 18$ centers) were preselected based on their willingness to participate in the present sub-study. The primary endpoint in the present OCT substudy was percentage of uncovered struts at 2 years (18–30 months) after stent implantation. At study initiation, we did not know the estimated percentage of uncovered struts necessary to determine the sample size. Therefore, all patients enrolled in the OCT sites were candidates for the present sub-study. The exclusion criteria for the follow-up OCT examination were as follows: (1) apparent congestive heart failure, (2) renal insufficiency (serum creatinine > 2.0 mg/dl), and (3) lesions unsuitable for OCT imaging (left main coronary artery lesions, ostial right coronary artery lesions, excessively tortuous vessel, and vessel size > 4.0 mm). Eventually, 121 patients were assigned to the OCT sub-study scheduling follow-up OCT examination at 2 years (18–30 months) after the index PCI procedure. The study was approved by the institutional review board or medical ethics committee at each participating center, and all patients gave written informed consent. The trial was registered with http://www.clinicaltrials.gov, unique identifier NCT01303640.

Coronary angiography

Angiograms before the procedure, immediately after the procedure, and at 2 years (18–30 months) follow-up were evaluated at a single angiographic core laboratory (Cardiocore, Tokyo, Japan) with use of CAAS 5.9 (Pie Medical Imaging, Maastricht, The Netherlands). The reference lumen diameter, minimum lumen diameter, percent diameter stenosis [(1 − minimum lumen diameter/reference lumen diameter) × 100], acute gain (minimum lumen diameter immediately after the index procedure − minimum lumen diameter before the index procedure), and in-stent late lumen loss (minimum lumen diameter immediately after the index procedure − minimum lumen diameter at follow-up) were calculated. In-stent binary restenosis was defined as a diameter stenosis >50% at follow-up angiography.

OCT image acquisition

Frequency-domain OCT imaging system (ILUMINE OPTIS™, St. Jude Medical, St. Paul, MN, USA) was used in the present study. The procedure of the OCT image acquisition was as follows. After a Z-offset adjustment, a Dragonfly JP™ imaging catheter (St. Jude Medical) was advanced distally to the stent-treated lesion over a 0.014-inch conventional angioplasty guidewire. After the catheter placement, preheated contrast media at 37 °C was flushed through the guiding catheter at a rate of 2–4 ml/s for approximately 3–6 s using an injector pump. When a blood-free image was observed, the OCT imaging core was withdrawn across the entire stent-treated lesion at a rate of 20 mm/s using automatic pullback device. The OCT images were digitally stored and submitted to the core laboratory (Wakayama Medical University, Wakayama, Japan) for offline analysis.

OCT image analysis

OCT image analysis was performed using a dedicated off-line review system with semi-automated contour-detection software (St. Jude Medical). All cross-sectional images (frames) were initially screened for quality assessment. Frames with inadequate images including residual blood, sew-up artifacts, reverberation, and out-of-the-screen of any portion of the stent caused by imaging catheter bias were excluded from analysis. Frames with bifurcations of side branches and stent overlapping segments were also excluded because of difficulty with assessing lumen border and stent strut conditions [3]. After calibration adjustment, qualitative OCT analysis was performed at every frame to identify neoatherosclerosis, intra-stent thrombus, and evagination. Neoatherosclerosis is characterized by atherosclerotic findings in neointima including lipid (defined as a signal-poor, poorly delineated region), thin-cap fibroatheroma (TCFA: defined as a fibrous-cap of <65 μm thick over the lipid), calcification (defined as a signal-poor, well-delineated region), and microvessel (defined as a signal-poor, well-delineated void within neointima) [4]. Intra-stent thrombus was identified as a mass protruding into the lumen with significant attenuation behind the mass [5]. Evagination is identified as outward bulges in the luminal contour between struts, with the depth of the bulge exceeding the actual strut thickness [6,7] (Fig. 1). Quantitative OCT analysis was performed at intervals of 1 mm in the stent-treated lesion. Neointimal coverage was assessed on each individual strut. If neointimal coverage was observed, its thickness was measured from the lumen border to the center of the strut blooming. A malapposed strut was defined as a strut with a distance between the center of the strut blooming and the adjacent lumen border ≥110 μm in EES and ≥160 μm in BES. This criterion was determined by adding the actual strut thickness and polymer thickness to the OCT resolution limit (EES: 81 μm + 7.8 μm + 20 μm = 108.8 μm; and BES: 125 μm + 5 μm [non-absorbable polymer: Parylene C] + 20 μm = 150 μm). Intraobserver and interobserver reproducibility for strut apposition were excellent ($\kappa = 0.93$ and $\kappa = 0.86$, respectively) in the core laboratory [3]. Each stent strut condition was classified into one of four categories: (1) well-apposed to the vessel wall with neointimal coverage over the strut, (2) well-apposed to the vessel

Please cite this article in press as: Katayama Y, et al. Two-year vascular responses to drug-eluting stents with biodegradable polymer versus durable polymer: An optical coherence tomography sub-study of the NEXT. J Cardiol (2017), http://dx.doi.org/10.1016/j.jjcc.2017.04.005