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Overtime evaluation of the vascular HEALing process after everolimus-eluting stent implantation by optical coherence tomography. The HEAL-EES study☆

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ABSTRACT

Purpose: Second-generation drug-eluting stent (DES) have shown a better safety and efficacy as compared to first generation DES due to an improved vascular healing process. This process has not been so far evaluated in vivo in an overtime fashion by optical coherent tomography (OCT). We sought to evaluate the vascular healing process after everolimus-eluting stent (EES) implantation at 6, 9 and 12 months, by OCT.

Methods: Consecutive 36 patients undergoing percutaneous coronary intervention with EES were randomized 1:1:1 to receive OCT imaging at 6 (group A), 9 (group B) or 12-month follow-up (group C). One patient from group C was excluded because of target lesion revascularization at 1-month, whereas 5 patients withdraw the informed consent. Finally, 30 patients were analyzed.

Results: Neointimal thickness was not different between 3 groups (group A: 99.50 [94.06–127.79] μm, group B: 107.26 [83.48–133.59] μm, group C: 127.67 [102.51–138.49] μm; $p = 0.736$). Although the percentage of "uncovered struts" was significantly higher in group A as compared to the other groups (8.0% vs. 4.4% vs. 2.9%, respectively; $p = 0.180$), the ratio of uncovered to total struts per section <30% was similar between 3 groups (0.3% vs. 0.3% vs. 0%, respectively; $p = 1.000$).

Conclusion: Healing process following EES implantation seems almost completed at 6-month follow-up. These data, which need to be confirmed in a larger study, may support the decision to shorten dual antiplatelet therapy.

1. Introduction

First generation drug-eluting stents (DES) reduced in-stent restenosis, as compared to bare metal stents, conversely exhibiting an increased rate of stent thrombosis [1–6]. Second generation DES, especially everolimus-eluting stent (EES), have reduced either in-stent restenosis or stent thrombosis compared with first generation DES [7–12]. These improvements may be explained by the increase in biocompatibility of drug-eluting polymer and of the eluted drug and are supported by low incidence of uncovered struts by optical coherence tomography (OCT) analysis [13,14].

Based on these technological improvements, recent studies with second generation DES have reported the non-inferiority of short-term (3–6 months) dual antiplatelet therapy (DAT) as compared with long-term (12 months) DAT in terms of major adverse cardiac events rate [15–19]. Nevertheless, all these data are not supported by OCT or pathological data on the serial vascular healing process at those time points.

The aim of this study was therefore to evaluate in vivo the overtime vascular healing process after EES implantation at 6, 9 and 12 months, by OCT.

2. Methods

2.1. Study Design and Population

This was a prospective, randomized, controlled trial comparing 6, 9 and 12-month OCT findings after EES (Xience™, Abbott vascular, Santa Clara, California, USA) implantation. All the patients who met all the inclusion/exclusion criteria were randomized 1:1:1 to receive an OCT imaging study at 6-month (group A), 9-month (group B) or 12-month (group C). Inclusion criteria were presence of one or two de novo lesions in a native coronary artery including lesions with a diameter stenosis of at least 75% (visual estimate) or a functional study documenting the hemodynamic relevance of the target lesion with

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reference vessel diameters (RVD) ranging from 2.5 to 3.5 mm. Exclusion criteria were left main disease, ST-elevation myocardial infarction, ostial, severely calcified or thrombotic lesions, severe angulation or tortuosity of the vessel, allergy or contraindication to prolonged treatment with aspirin or clopidogrel, anticoagulation therapy, comorbidity with short expectancy of life, chronic renal disease (serum creatinine more than 2 mg/dl) and impossibility to perform follow-up. The study was approved by the local Ethical committee and all patients provided written informed consent.

2.2. Study Procedures

Device implantation was performed according to standard technique. Pre-dilatation, post-dilatation, and bailout stenting were left to operator's discretion. All the patients received loading dose of aspirin (300 mg) and clopidogrel (600 mg) before the procedure and 100 IU/kg of intra-venous unfractionated heparin during the procedure. After stent implantation, dual antiplatelet therapy (aspirin 100 mg and 75 mg of clopidogrel daily) was prescribed to all the patients for 12 months.

2.3. Angiographic Analysis

Quantitative coronary angiographic (QCA) analysis was performed offline by an expert analyst in the independent core laboratory of the Hospital Clinic, blinded to follow-up time, using automated edge-detection algorithms (CMS version 6.0, Medis Medical Imaging Systems, Leiden, The Netherlands). Lesion complexity was analyzed according to the AHA/ACC lesion classification [20]. In each lesion, the coronary segment including the stent and 5-mm proximal and distal to the stent edges were analyzed at baseline and at follow-up. Reference vessel diameter (RVD), the minimal lumen diameter (MLD) and the percent diameter stenosis (%DS) were analyzed. Late loss was estimated as the difference between the MLD at post-implantation and at follow-up using matched angiographic views. Binary restenosis was defined as stenosis >50% of the luminal diameter in the target lesion. To evaluate intraobserver variability, the analyst repeated the analysis 3 months later.

2.4. OCT Imaging and Analysis

OCT imaging was performed at follow-up and performed after intracoronary nitroglycerin injection, using the C7XR Fourier-Domain System (LightLab Imaging, Westford, Massachusetts) [21]. OCT data were analyzed at the independent core laboratory of the Hospital Clinic by an expert analyst, blinded to time of follow-up, using proprietary offline software. (LightLab Imaging, Westford, Massachusetts).

Quantitative analysis was performed at 1 mm intervals within the stent segment and 5 mm proximal and distal to the stent edges. The OCT software drew the lumen area automatically. Stent area was drawn at the adluminal site of the metallic struts. The neointima area was calculated as the difference between the stent and luminal areas. The coverage thickness of >0 μm on the top of each strut (tissue can be identified above the struts) has been used to classify struts as covered or uncovered [22]. The neointima thickness was automatically calculated from the center of the adluminal side of the strut to the lumen contour with the thickness ruler tool. According to the strut thickness of the used metallic stent (81 μm) and the resolution of the OCT images, a negative value larger than 100 μm was considered as non-covered and non-apposed. Values from 0 to −100 μm were considered as non-covered and apposed. In case of non-apposed struts with clear neointima tissue above the adluminal side of the strut an extra mark was drawn in order to consider this strut as covered and non-apposed [23–25]. Stent strut at the bifurcated lesion were excluded in this calculation for NIT. The number of uncovered struts per cross-section was

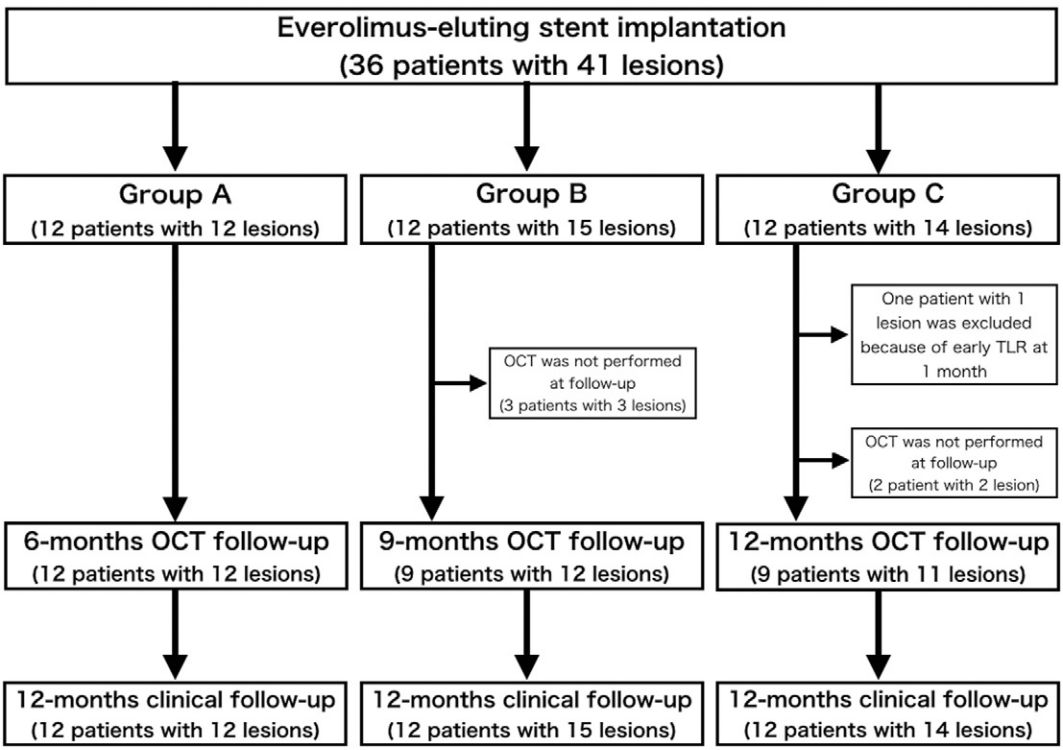

Fig. 1. Flow Diagram of Study Population Thirty-five patients with 41 lesions were enrolled and were randomized 1:1:1 to group A (12 patients with 12 lesions), group B (11 patients with 14 lesions) or group C (12 patients with 14 lesions). One patient with 1 lesion in group C was excluded because of early target lesion revascularization (TLR) at 1 month after index the procedure due to a remaining stent distal dissection. Two patients with 2 lesions in group B and 2 patients with 2 lesions in group C decided to prematurely discontinue the study. Finally, 30 patients with 35 lesions were analyzed by optical coherence tomography (OCT).