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TRANSLATIONAL

Bioresorption and Vessel Wall Integration of a Fully Bioresorbable Polymeric Everolimus-Eluting Scaffold

Optical Coherence Tomography, Intravascular Ultrasound, and Histological Study in a Porcine Model With 4-Year Follow-Up

Shimpei Nakatani, MD,[a] Yuki Ishibashi, MD, PhD,[a] Yohei Sotomi, MD,[b] Laura Perkins, DVM, PhD,[c] Jeroen Eggermont, PhD,[d] Maik J. Grundeken, MD,[b] Jouke Dijkstra, PhD,[d] Richard Rapoza, PhD,[c] Renu Virmani, MD,[e] Patrick W. Serruys, MD, PhD,[f] Yoshinobu Onuma, MD, PhD[a]

ABSTRACT

OBJECTIVES The aim of the present study was to investigate the relationship between the integration process and luminal enlargement with the support of light intensity (LI) analysis on optical coherence tomography (OCT), echogenicity analysis on intravascular ultrasound, and histology up to 4 years in a porcine model.

BACKGROUND In pre-clinical and clinical studies, late luminal enlargement has been demonstrated at long-term follow-up after everolimus-eluting poly-L-lactic acid coronary scaffold implantation. However, the time relationship and the mechanistic association with the integration process are still unclear.

METHODS Seventy-three nonatherosclerotic swine that received 112 Absorb scaffolds were evaluated in vivo by OCT, intravascular ultrasound, and post-mortem histomorphometry at 3, 6, 12, 18, 24, 30, 36, 42, and 48 months.

RESULTS The normalized LI, which is the signal densitometry on OCT of a polymeric strut core normalized by the vicinal neointima, was able to differentiate the degree of connective tissue infiltration inside the strut cores. Luminal enlargement was a biphasic process at 6 to 18 months and at 30 to 42 months. The latter phase occurred with vessel wall thinning and coincided with the advance integration process demonstrated by the steep change in normalized LI (0.26 [interquartile range (IQR): 0.20 to 0.32] at 30 months versus 0.68 [IQR: 0.58 to 0.83] at 42 months, $p < 0.001$).

CONCLUSIONS In this pre-clinical model, late luminal enlargement relates to strut integration into the arterial wall. Quantitative LI analysis on OCT could be used as a surrogate method for monitoring the integration process of poly-L-lactic acid scaffolds, which could provide insight and understanding on the imaging-related characteristics of the bioresorption process of polylactide scaffolds in human. (J Am Coll Cardiol Intv 2016;9:838–51)

From the [a]ThoraxCenter, Erasmus Medical Center, Rotterdam, the Netherlands; [b]Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; [c]Abbott Vascular, Santa Clara, California; [d]Leiden University Medical Center, Leiden, the Netherlands; [e]CVPath Institute, Gaithersburg, Maryland; and the [f]International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College London, London, United Kingdom. This study was funded by Abbott Vascular. Drs. Perkins and Rapoza are full-time employees of Abbott Vascular. Drs. Serruys and Onuma are members of the advisory board of Abbott Vascular. Dr Virmani receives research support from Abbott Vascular, BioSensors International, Biotronik, Boston Scientific, Medtronic, MicroPort Medical, OrbusNeich Medical, SINO Medical Technology, and Terumo Corporation; has speaking engagements with Merck; receives honoraria from Abbott Vascular, Boston Scientific, Lutonix, Medtronic, and Terumo Corporation; and is a consultant for 480 Biomedical, Abbott Vascular, Medtronic, and W.L. Gore. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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As an alternative approach to metal drug-eluting stents, fully bioresorbable polymeric drug-eluting scaffolds provide transient vessel support with drug-delivery capability. As the scaffold begins to resorb, the vessel is no longer caged, and therefore luminal area as well as vessel area could increase simultaneously without creating evagination (1-5). The everolimus-eluting scaffold (Absorb; Abbott Vascular, Santa Clara, California) consists of a semicrystalline poly-L-lactic acid (PLLA) backbone coated by a thin amorphous layer of poly-D,L-lactic acid containing the antiproliferative agent everolimus. After implantation, the polylactide strut progressively degrades by hydrolysis, and its molecular weight starts to decrease from its initial molecular weight of around 100 kDa (molecular weight loss) (6). The PLLA molecules remain at the implanted site until the polymeric chains become small enough to diffuse from the site into the surrounding tissue (mass loss). As small oligomers or monomers gradually leave the site, there is progressive replacement by a provisional matrix initially composed of a milieu of extracellular matrix components. This initially acellular provisional matrix is gradually cellularized with connective tissues, and the struts and footprints eventually become fully integrated into the surrounding neointimal tissue of the vessel wall (6,7).

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It is well-established that the scaffolding efficacy of the device is related to the timing of molecular weight reduction and the loss of mechanical integrity (8). However, at a late phase, it is still unclear whether the integration of strut footprints is associated with the late luminal enlargement. In the pre-clinical assessment of fully bioresorbable scaffolds, it is therefore important to assess the processes of molecular weight loss and integration in vivo. In humans, intravascular imaging has been used in vivo as a surrogate marker to understand the bioresorption and integration process, but the correlation between the surrogate assessment and the true bioresorption process needs to be established.

On intravascular ultrasound (IVUS), quantitative echogenicity has been demonstrated to correlate with the molecular weight of PLLA (9). On optical coherence tomography (OCT), the visual categorizations of strut appearance have previously been demonstrated to correlate with the integration process (10). However, this visual categorization was limited by its moderate reproducibility (k = 0.58). Recently, log-transformed optical coherence tomographic signal measurement (light intensity analysis) of strut cores was introduced as a feasible and reproducible method to assess the degree of strut integration after scaffold implantation (11). In humans, the median intensity value of strut cores increased significantly at 24 months and kept increasing up to 36 months, and most of pre-existing struts were indiscernible at 60 months on OCT (**Figure 1**). It was hypothesized

ABBREVIATIONS AND ACRONYMS

IQR = interquartile range

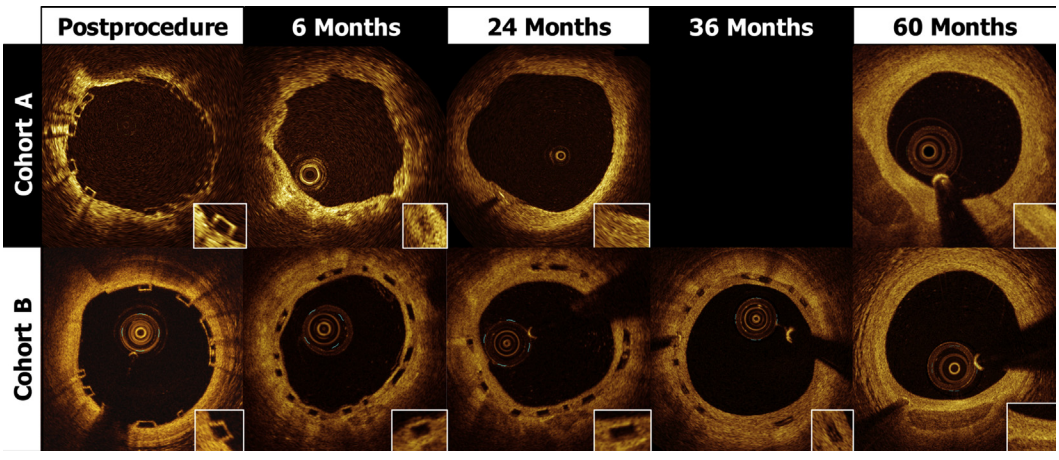
IVUS = intravascular ultrasound

OCT = optical coherence tomography

PLLA = poly-L-lactic-acid

TD = time-domain

FIGURE 1 Strut Appearance on Optical Coherence Tomography of Revision 1.0 (Used in the ABSORB Cohort A Study) and Revision 1.1 (Used in the ABSORB Cohort B Study) of the Absorb Device



The time to complete degradation of the Absorb A device was approximately 2 years, whereas that for the Absorb B device was approximately 3 years, resulting in the different appearance of strut cores on optical coherence tomography over time in Absorb B devices compared with that of Absorb A devices in humans (5,26).