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Lumen Gain and Restoration of Pulsatility After Implantation of a Bioresorbable Vascular Scaffold in Porcine Coronary Arteries

Jennifer P. Lane, BS,* Laura E. L. Perkins, DVM, PHD, DACVP,* Alexander J. Sheehy, MS,* Erica J. Pacheco, BS,† Michael P. Frie, BS,‡ Byron J. Lambert, PHD,* Richard J. Rapoza, PHD,* Renu Virmani, MD†

Santa Clara, California; Gaithersburg, Maryland; and Minneapolis, Minnesota

Objectives Using intravascular ultrasound (IVUS) and histomorphometry, this study sought to evaluate the potential of nonatherosclerotic porcine coronary arteries to undergo progressive lumen gain and a return of pulsatility after implantation with an everolimus-eluting bioresorbable vascular scaffold (BVS).

Background Unique benefits such as lumen gain and restored vasomotion have been demonstrated clinically after treatment with BVS; however, a more rigorous demonstration of these benefits with a randomized clinical trial has not yet been conducted.

Methods Seventy nonatherosclerotic swine received 109 everolimus-eluting BVS and 70 everolimus-eluting metal stents randomized among the main coronary arteries. Arteries were evaluated in vivo by angiography and IVUS and post-mortem by histomorphometry at time points from 1 to 42 months.

Results From 1 to 6 months, both BVS- and everolimus-eluting metal stent–implanted arteries demonstrated stable lumen areas (LAs). From 12 months to 42 months, there was a progressive increase in the LA of arteries implanted with a BVS as assessed by histomorphometry and IVUS. This lumen gain in the implanted segment corresponded to an increase in the reference vessel LA. Normalization in the in-segment LA (LA:reference vessel LA) was observed qualitatively by angiography and quantitatively by IVUS. Additionally, BVS-implanted arteries demonstrated restored in-segment pulsatility on the basis of IVUS assessment of the differences in the mid-scaffold area between end-diastole to end-systole.

Conclusions Starting at 12 months, BVS-implanted porcine coronary arteries underwent progressive lumen gain and showed restored pulsatility. These benefits demonstrated preclinically may translate into improvements in long-term clinical outcomes for patients treated with BVS compared with conventional drug-eluting stents. (J Am Coll Cardiol Intv 2014;7:688–95) © 2014 by the American College of Cardiology Foundation

From *Abbott Vascular, Santa Clara, California; †CVPath, Inc., Gaithersburg, Maryland; and the ‡American Preclinical Services, Minneapolis, Minnesota. This study was funded by Abbott Vascular. Dr. Virmani has received research support from 480 BioMedical, Abbott Vascular, Medtronic, W. L. Gore, OrbusNeich, Terumo Corporation, Biosensors International, Biotronik, SINOMedical Technology, MicroPort Medical, Boston Scientific, Cordis J&J, and Atrium; honoraria for serving on the Advisory Boards of 480 BioMedical, Abbott Vascular, Medtronic, and W. L. Gore; and honoraria from Terumo Corporation, Boston Scientific, Lutonix, Merck & Co., and Cordis J&J. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Drug-eluting stents (DES) currently serve as the standard of care for the interventional treatment of occlusive coronary artery disease; however, the success of DES has met with challenges, including delayed healing, endothelial dysfunction, stent thrombosis, and neoatherosclerosis (1–4). These challenges to the clinical safety and efficacy of DES have spurred the development of the latest advancement in percutaneous coronary intervention: bioresorbable vascular scaffolds (BVS). Beyond the approach of DES to prevent acute recoil, subchronic remodeling, and chronic restenosis, BVS aim to not only achieve success similar to that with DES, but also to allow for restoration of more normal vascular physiology, which may ultimately result in improved late clinical outcomes (5). As BVS offer the potential for novel therapeutic benefits over conventional DES, the term *vascular reparative therapy* (VRT) has been coined to describe the novel therapy delivered by these devices.

The Absorb BVS (Abbott Vascular, Santa Clara, California) is one such bioresorbable scaffold for which clinical results to date have provided insight into the benefits that these bioresorbable devices may offer over conventional DES. Specifically of interest are plaque regression and late lumen gain observed serially from 6 months to ≥3 years in the ABSORB family of trials (6–8). Of additional interest is the restoration of vasomotion in the treated region demonstrated at 12 and 36 months in Cohort B_2 (8,9) and at 24 months for cohort A of the ABSORB trial (10). These observations provide preliminary clinical evidence that the Absorb BVS can be distinguished from metal platforms (bare-metal stents, DES) that constrain coronary arteries through permanent caging. Despite the evidence to date, we as yet await the first reports of long-term randomized trials comparing these benefits of Absorb BVS directly with those of DES.

In this study conducted in porcine coronary arteries, we sought to provide insight into the clinical observations related to the Absorb BVS. This is achieved by using histological means for the direct morphometric comparison of arteries implanted with the Absorb BVS with those implanted with a metal DES with the inclusion of frequent follow-up time points. Through this comparison of the BVS with a metal DES at multiple time points from 1 to 42 months, the performance of these devices and the chronology at which the divergence in their performance occurs are illustrated in vivo. In addition, we provide a novel approach for assessing the potential benefits of a BVS over a DES through the examination of pulsatility over time.

Methods

Study devices. The Absorb BVS (Abbott Vascular) is a balloon-expandable, fully bioresorbable scaffold that consists of a poly(L-lactide) backbone with a poly(D, L-lactide) coating in a 1:1 ratio with everolimus. The BVS investigated in this study is the same construct as that used in Cohort B of the ABSORB clinical trial (11). The BVS is projected to retain radial strength through ~12 months (9,12,13). The XIENCE V Everolimus Eluting Coronary Stent System (EES) (Abbott Vascular), which served as a metal DES control for the study, is a balloon-expandable stent consisting of a cobalt-chromium alloy that is coated with a biocompatible fluorinated copolymer. BVS and EES share the same everolimus dose density (100 μg/cm^2) and comparable release kinetics (14).

Animals. This study received protocol approval from the Institutional Animal Care and Use Committee and was conducted in accordance with American Heart Association guidelines for preclinical research and the Guide for the Care and Use of Laboratory Animals (15) at an Association for Assessment and Accreditation of Laboratory Animal Care accredited institution. Sixteen nonatherosclerotic juvenile domestic cross-breed farm swine (ages 1 and 3 months) and 54 Yucatan mini-swine (ages 6, 12, 18, 24, 30, 36, and 42 months) were implanted via carotid access with a BVS and an EES. One day before the implantation procedure, the pigs received a loading dose of 325 mg aspirin and 150 mg clopidogrel. Thereafter, pigs were maintained to the respective follow-up time point on daily 81 mg aspirin and 75 mg clopidogrel per os through 24 months. Devices were implanted under angiographic guidance at a targeted balloon-to-artery ratio of 1.1:1.0 (10% overstretch) according to a predetermined randomized matrix. Each animal received 1 or 2 BVS (3.0 × 18 mm at 1, 3, and 6 months and 3.0 × 12 mm at 12, 18, 24, 30, 36, and 42 months) and 1 comparable-length EES in the main coronary artery. Each coronary artery was implanted with a single device as the anatomy allowed. Devices were inflated at a steady rate to be expanded to the appropriate diameter, with typical times for complete expansion generally being 5 to 10 s for both BVS and EES. This pressure at maximal expansion was then maintained for up to 30 s. Devices were deployed within a range of 5 to 20 atm. Due to the taper of the arteries, select arteries implanted with 3.0 × 18-mm (1 to 6 months) devices had a second comparable inflation in the proximal region to ensure proper device apposition proximally. For each time point, 7 to 9 animals were implanted with 12 to 13 BVS and 7 to 9 EES (Online Table 1). After device implantation and fluoroscopic assessment, animals recovered and were maintained for the designated study period.

In vivo imaging. At the designated endpoints, pigs were anesthetized, and implanted arteries were assessed

Abbreviations and Acronyms

BVS = bioresorbable vascular scaffold(s)
DES = drug-eluting stent(s)
EES = everolimus-eluting stent(s)
IVUS = intravascular ultrasound
LA = lumen area
MLD = mean lumen diameter
RLA = reference vessel lumen area
VRT = vascular reparative therapy