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EDITORIAL

Bioresorbable Scaffolds (BRS): A Ten-Year Saga Turned Sour

Antonis S. Manolis, MD

Third Department of Cardiology, Athens University School of Medicine, Athens, Greece; E-mail: asm@otenet.gr

Abstract

The first generation bioresorbable scaffolds (BRS) did not deliver their promise for reduced risk of late stent thrombosis and neoatherosclerosis forming inside the stent and restoration of endothelial vasomotion. To our chagrin, the incidence of early, late and very late scaffold thrombosis was higher than conventional metallic stents leading to increased rates of adverse cardiovascular events and outcomes. Unfortunately, it took a decade to fully appreciate these major drawbacks. The manufacturer of the first, apparently hastily approved BRS in both Europe and the USA discontinued its production in September 2017. Nevertheless, hope remains and newer generation BRS are already in the pipeline expecting that improved technology and implantation strategies may overcome these severe limitations and finally recredit and reinstate the BRS concept. ***Rhythmos 2018;13(2): 26-29.***

Key Words: bioresorbable vascular scaffolds; coronary artery disease; acute coronary syndromes; coronary stents; scaffold thrombosis; stent thrombosis; adverse cardiovascular events

Abbreviations: BRS = bioresorbable scaffold; BVS = bioresorbable vascular scaffold; EES = everolimus eluting stent; MI = myocardial infarction; RR = relative risk

Introduction

Despite more complications, including early and late thrombosis, reported with the first available drug-eluting bioresorbable scaffold / stent (BRS),[1, 2] the Absorb bioresorbable vascular scaffold (BVS) (Abbott Vascular, Santa Clara, CA, USA), an everolimus-eluting BRS, this stent received CE Mark approval in Europe in 2011 (www.medscape.com/viewarticle/735561) and was approved by the US Food and Drug Administration (FDA) in July 2016 (www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm509805.htm). Unlike metallic stents, bare or drug-eluting, the BRS is gradually absorbed in the body over 2-5 years. The undelivered promise of the BRS was the potential for reduced risk of late stent thrombosis and neoatherosclerosis forming inside the stent and restoration of endothelial vasomotion.

ABSORB Trials

The first human implants of the Absorb BVS took place in 2006.[3] After the publication of proof of concept and imaging studies, and early favorable reports in small number of patients,[4-6] the disappointing results of the

ABSORB II randomized controlled trial (RCT) in 501 patients were published in 2016.[7] The trial did not meet its endpoints of superior vasomotor reactivity and non-inferior late luminal loss for the Absorb BVS compared to the metallic stent, as there was no difference in vasomotor reactivity, while the BVS had significantly higher late luminal loss. In addition, a higher rate of target vessel myocardial infarction (MI), including peri-procedural MI, was observed in the Absorb group.

Furthermore, there followed the results of the ABSORB III trial which were also worrisome. The trial demonstrated noninferior rates of target lesion failure (cardiac death, target vessel MI, or ischemia-driven target lesion revascularization) at 1 year in 2,008 patients with coronary artery disease randomized to BVS versus cobalt-chromium everolimus-eluting stents (EES).[8] Through 3 years, the primary composite endpoint of target lesion failure occurred in 13.4% of BVS patients and 10.4% of EES patients (p = 0.06), and between 1 and 3 years in 7% vs 6% of patients, respectively (p=0.39). However, target vessel MI through 3 years was increased with BVS (8.6% vs. 5.9%; p=0.03), as was device thrombosis (2.3% vs. 0.7%; p=0.01). In BVS-assigned patients, treatment of very small vessels (<2.25 mm) was an independent predictor of 3-year target lesion failure and scaffold thrombosis.

BRS Thrombosis

The most worrisome of all problems associated with the first generation of BRS relates to their long-term safety with regards to increased risk of thrombosis;[1, 2] a recent RCT (AIDA) comprising 1845 patients receiving either a BRS (924 patients) or a metallic stent (921 patients), target-vessel failure was similar in the two groups (11.7% vs 10.7%, respectively; hazard ratio-HR, 1.12), however, device thrombosis was higher in the BRS group (2-year cumulative event rates, 3.5% vs. 0.9%; HR, 3.87; P<0.001) through 2 years of follow-up. [9]

A network meta-analysis including 91 trials confirmed that the Absorb BVS was associated with increased risk of long-term and very late scaffold thrombosis compared to current-generation metallic drug-eluting stents.[10] Another meta-analysis of 7 trials in which 5583 patients were randomly assigned to Absorb BVS (n=3261) or metallic EES (n=2322) and followed up for 2 years showed that the BVS had higher 2-year relative risks of the device-oriented composite endpoint than did EES (9.4% vs 7.4%; relative risk -RR 1.29, p=0·0059).[11] These differences were driven by increased rates of target vessel-related MI (5.8% vs 3.2%; RR 1.68, p=0·0003) and ischemia-driven target lesion revascularization (5.3% vs 3.9%; 1.40, p=0.0090) with BVS, with non-significant differences in cardiac mortality. The cumulative 2-year incidence of device thrombosis was higher with BRS than with EES (2.3% vs 0.7%; RR 3.35, p<0·0001). The authors concluded that BRS was associated with increased rates of adverse events and device thrombosis cumulatively at 2 years and between 1 and 2 years of follow-up compared with EES. Very similar results were reported by another review of these 7 trials including 5,583 patients randomized to receive either the study BVS (n = 3,261) or the EES (n = 2,322). [12] Over a median of 2 years, risk of target lesion failure (9.6% vs. 7.2%, p = 0.003) and stent thrombosis (2.4% vs. 0.7%, p< 0.0001) were both significantly higher with BRS.

Mechanisms and Risk Factors for BRS Thrombosis

When the results of all the major ABSORB trials were analyzed, it was indicated that vessel sizing and operator technique were strongly associated with BVS-related outcomes during 3-year follow-up; the optimal approach that was recommended comprised the concept of the so-called "PSP" (optimal predilation, vessel and device sizing, and post-dilation) to optimize BVS outcomes.[13] Thus, incomplete strut apposition appears to be the most important reason for BRS thrombosis with a detrimental outcome; improving the implantation technique may be able to overcome this horrendous BRS complication.[14] Furthermore, some studies have indicated that patient characteristics (e.g. ST-elevation MI, small vessel-diameter, etc.) may adversely impact BRS thrombosis.[15] Other studies have proposed BRS design with scaffold discontinuity suggesting an unfavorable resorption-related process as the most common mechanism underlying very late BRS thrombosis, (42%), followed by strut malapposition (18%) and neoatherosclerosis (18%).[16] Finally, recommendations from an Expert Panel are provided for the optimal approach to use of the current generation BRS to minimize complications and risks associated with this early technology, including longer (2- to 3-year) duration of dual antiplatelet therapy if the bleeding risk is low.[17]

Due to all these dismal results with the first-generation BRS, Abbott stopped selling and discontinued the production of the Absorb BVS in September 2017 (www.vascular.abbott/us/products/coronary-intervention/absorb-bioresorbable-scaffold-dissolving-stent.html), while Boston Scientific scrapped the development of their BRS (https://www.massdevice.com/boston-scientific-end-renuvia-bioresorbable-coronary-stent-program/).

Newer Generation BRS

Although all these results have been disappointing and a setback for this novel technology, newer generation BRS

with improved technologies are being developed (Table 1) and tested in newer trials.[18-20] Whether these newer BRS may overcome the limitations of the first generation BRS remains to be seen in future RCTs. Recently, one such trial tested NeoVas, a new poly-l-lactic acid BRS that elutes sirolimus from a poly-D, l-lactide coating, in 560 patients randomized to NeoVas BRS (n=278) and cobalt-chromium everolimus-eluting stents (CoCr-EES) (n=282).[21] It showed that the NeoVas BRS was noninferior to CoCr-EES for the primary endpoint of 1-year angiographic in-segment late loss, and resulted in comparable 1-year clinical outcomes, including recurrent angina. However, the ABSORB trials had similarly favorable results initially, and it was only after longer-term follow up that all turned sour and dreaded adverse effects, particularly late thrombosis, became apparent. Nevertheless, the dream of a "vanishing stent" remains alive in an attempt to restore vasomotion and achieve regression of underlying plaque, and vessel remodelling leading to an increased vessel lumen size. Only time will tell whether this technology will remain a dream or become a reality. A recent study from the Massachusetts Institute of Technology identified structural irregularities and asymmetric material degradation as the main design flaw in the first-generation BRS, generating hope for future technological improvements in this field.[22]

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Table 1. Bioresorbable Vascular Scaffolds / Bioresorbable Stents

BRS Model	Manufacturer	Scaffold / Eluted drug	Strut / Coat thickness	Full absorption	CE mark	FDA approval
ABSORB BVS	Abbott *	PLLA / everolimus	150 / 3 μm	~3 years	1/2011	7/2016
DESolve CX	Elixir Medical	PLLA / novolimus	120/<3 μm	~1 year	5/2014	-
ART PURE	ART & Terumo	PDLLA / sirolimus	170 / - μm	~1 year	5/2015	-
MAGMARIS	Biotronik	Mg / sirolimus	150/8 μm	~1 year	6/2016	-
FANTOM	Reva Medical	TP / sirolimus	125 / - μm	~1 year	4/2017	-
NeoVas	Lepu Medical	PLLA / sirolimus	180 μm	NA	-	-
MAGNITUDE	Amaranth Medical	PLLA / sirolimus	98 /- μm	~ 1 year	-	-
IDEAL BIOSTENT	Xenogenics	poly-anhydride ester (SA & AAA) / sirolimus +SA	175 μm	~ 1 year	-	-
MIRAGE	Manli Cardiology Ltd	PLLA / sirolimus	170 μm	~ 1 year	-	-
Xinsorb	Huaan Biotechnology	PLLA / sirolimus	160 μm	2-3 years	-	-
MeRes100	Meril R&D	PLLA / sirolimus	100 μm	2-3 years	-	-
Firesorb	MicroPort	PLLA/ sirolimus	100-125 μm	~ 1 year	-	-
Unity	QualiMed	Mg+PLLA/ sirolimus	160 μm	~ 1 year	-	-
On-ABS	OrbusNeich Medical	PLLA/EPC+sirolimus	150 /- μm	NA	-	-

AAA = adipic acid anhydride; BRS = bioresorbable scaffolds; EPC = endothelial progenitor cell (capture technology); Mg = magnesium; PDLLA = poly-d,l-lactic acid; PLLA = poly-l-lactic acid; SA = salicylic acid; TP = tyrosine polycarbonate

* discontinued production in September 2017