Bioresorbable Scaffolds vs. Metallic Drug-Eluting Stents: Are We Getting Any Closer to a Paradigm Shift?

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Editorial Viewpoint: Bioresorbable Scaffolds vs. Metallic Drug-Eluting Stents: Are We Getting Any Closer to a Paradigm Shift?

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Since the first catheter-based coronary treatment in 1977, interventional cardiology has witnessed several practice-changing paradigm shifts. The transition from balloon angioplasty to bare-metal stents (BMS) to drug-eluting stents (DES) substantially advanced the safety and efficacy of percutaneous coronary interventions (PCI) and improved patient outcomes (1). Bioresorbable vascular scaffolds (BVS) have emerged as a promising new link in this chain of major breakthroughs in intracoronary device technology. BVS provide temporary vessel support, retain the ability of anti-restenotic drug elution, and dissolve within a well-defined time frame. Due to this principle function, BVS may provide therapeutic features which could extend well beyond current metallic DES by enabling positive vessel remodeling and late lumen gain (2), enhancing the process of long-term arterial healing (3), entailing plaque shielding properties (4), and restoring physiological vasomotion (5). In aggregate, these properties bear the potential to further advance clinical outcomes including the ability to reduce angina symptoms compared with metallic stents (6).

The conformability and superior flexibility of BVS allows for minimal changes of vessel geometry and along with the eventual absorption of the lumen-protruding struts attenuate the unfavorable hemodynamic changes which are typically imposed by rigid stents (7). Elimination of late-acquired malapposition (an established trigger of stent thrombosis) or edge-related vascular responses in the long term are additional theoretical benefits of BVS. On the other hand, strut thickness is larger compared with new-generation DES, which leads to suboptimal crossing profiles, limits the ability to treat complex (e.g. excessively tortuous or calcified) lesions or implant overlapping BVS, and results in inferior immediate, post-procedural angiographic outcomes of device performance (6).

A variety of BVS is currently under investigation and both polymer-based as well as metal (magnesium)-based BVS with drug-eluting properties have entered clinical investigations (8). The everolimus-eluting Absorb BVS is the most widely used and

investigated device to date. The initial ABSORB cohort A and B studies demonstrated the feasibility of the BVS in highly selected patients with simple lesions (9). Real-world observations (10-13) and, more recently, randomized trials (3, 6, 14, 15) have gone a step further by comparing the performance of the BVS with new-generation DES. Against this background, 1-year angiographic and clinical results of the ABSORB China trial are reported in this issue of the *Journal* (16). The trial, designed to enable regulatory approval of the device in China, randomized 480 patients with up to 2 *de novo* lesions in a 1:1 fashion to Absorb BVS or the metallic everolimus-eluting Xience stent platform. The study was able to show non-inferiority of the BVS vs. Xience for the primary angiographic endpoint, in-segment late lumen loss at 12 months (0.19 ± 0.38 vs. 0.13 ± 0.37, Pnon-inferiority=0.01). Of note, minimal lumen diameter was smaller (2.27 ± 0.03 vs. 2.50±0.03 mm, p<0.001), and % diameter stenosis was greater (18.5±0.92% vs. 11.3±0.76% p<0.001) for the BVS within the device, whereas in-segment measures did not differ. Clinical outcomes including target-lesion failure and stent thrombosis were similarly low between the two groups, although the study was not powered for any individual or composite clinical endpoint (16). The open-label design in contrast to the single-blinded design of previous randomized trials of BVS vs. DES (3, 6, 14, 15) also needs to be taken into account.

ABSORB China is a valuable contribution to the growing body of evidence comparing the angiographic and clinical performance of BVS vs. the current standard-of-care for PCI, i.e. new-generation DES (17). The findings are in line with recent randomized trials (3, 6, 14, 15), indicating non-inferiority of angiographic efficacy and comparably low mid-term rates of device- as well as patient-oriented clinical events. The concordance of findings across different ethnicities corroborates their generalizability, and the consistency in a STEMI cohort (3) extends the disease-specific indications of the device to patients with higher-risk clinical presentation. Notably, however, the findings remain applicable to

relatively non-complex anatomies as bifurcation and calcified lesions were under-represented, and left main lesions or multi-vessel treatment were excluded from these trials.

With a handful of randomized comparisons of the BVS vs. metallic DES including >1,800 patients now available, our ability has grown to draw a more complete picture of this technology both in terms of mid-term angiographic efficacy as well as clinical performance. Because interpretation of findings is limited by the modest sample size of individual studies, a synthesis of the available evidence by performing a meta-analysis of five trials [ABSORB-II (6); ABSORB China (16); ABSORB-JAPAN (14); EVERBIO II (15); and ABSORB STEMI-TROFI II (3)] focusing on angiographic and clinical endpoints that are comparable across the trials provides further insights. When addressing angiographic efficacy by using the primary endpoint of in-segment late lumen loss, BVS is associated with significantly greater late lumen loss than metallic DES [0.05 mm, 95% confidence interval (CI): 0.01 to 0.09] (**Figure**). Risks of the device-oriented composite endpoint target lesion failure (OR 1.15; 95% CI: 0.71 to 1.85), the patient-oriented composite endpoint of death, myocardial infarction or any revascularization (OR 0.93, 95% CI: 0.67 to 1.30) and definite or probable stent thrombosis [Odds ratio (OR) 1.86; 95% CI: 0.55 to 6.27)] do not differ between BVS and metallic DES throughout the observed period of follow-up. Of note, there was no significant heterogeneity across trials for the analyzed outcomes.

Collectively, individual randomized trials have demonstrated non-inferior angiographic efficacy results for the BVS compared with metallic DES [i.e., the Xience stent in all but one trials (15)]; however, a significant difference of late lumen loss in favor of DES emerged in the present systematic review. This finding may need to be interpreted in light of the low reported rates of peri-procedural intracoronary imaging in some of the trials (15,16). Given the importance of accurate size estimation and the limitations in terms of aggressive post-dilatation techniques (due to the risk of polymeric stent disruption in case of excessive

overexpansion), intracoronary imaging – in particular optical coherence tomography – to guide and optimize BVS implantation may assume a prominent role for improving post-procedural and presumably longer-term angiographic outcomes (18), although this requires confirmation in appropriately designed studies.

While angiographic measures of device efficacy are essential, the clinical relevance of these differences needs to be placed in a broader perspective. The penetration of bioresorbable stents in routine interventional practice within the next years will be determined largely by their impact on patient outcomes. At present, both randomized and observational evidence (10-13) suggests comparable device efficacy and similarly low event rates, as confirmed also in the poled analysis presented here. Although it becomes increasingly challenging for new intracoronary devices to achieve meaningful improvements against the current standard-of-care, clinical studies with larger and more complex populations and longer follow-up durations (extending to the time frame prior to, as well as following complete stent resorption) are critical to definitively establish at least the non-inferiority of the BVS (and of other BVS currently under development) vs. the best available metallic DES. In this respect, long-term outcomes of ABSORB II, the ongoing ABSORB III (NCT01751906) and ABSORB IV trials (NCT02173379) with 5,000 patients, and the AIDA trial (NCT01858077) with 2,690 patients and 5-year follow-up will critically expand current evidence and inform our practice.

Rates of BVS vs. metallic DES thrombosis were similar in all individual trials during a 6- to 12-months follow-up (3, 6, 14-16) and did not differ when >1,500 patients were pooled (**Figure**); notably, point estimates indicate a 74% numerically higher risk of BVS vs. metal stent thrombosis. Along the same lines, observational studies that included relatively more complex patient and lesion subset have demonstrated 6-12 months definite/probable BVS thrombosis rates up to 3% in general populations (12) and up to 2.4% in STEMI

patients (11), with consistent numerical (albeit not statistically significant) preponderance over DES. These figures have raised some concerns and need to be viewed also in conjunction with evidence of very late (up to 44-month) thrombosis related to scaffold discontinuity or restenosis during advanced stages of the resorption process, which may be more delayed in man compared with experimental (porcine) models (19). Adequately powered randomized trial data with prolonged follow-up as those mentioned above will provide the answer whether these concerns can be alleviated to more definitely confirm the safety of the BVS vs. new-generation DES.

Summarizing the facts and fiction of the Absorb BVS, the theoretical advantages of "uncaging" the treated vessel are substantial, yet the BVS (and other emerging device technologies) somehow pay the price of current standards being extraordinarily high with new-generation DES. At present, evidence on the performance of the BVS vs. contemporary DES does indicate clinical non-inferiority – the Hippocratic analogue of *primum non nocere* ("first, do no harm") in the randomized trials world. This needs to be further corroborated and carefully weighed against concerns regarding thrombotic complications in larger, broadly inclusive, longer-term studies, also addressing issues of cost-effectiveness and optimal adjunctive antiplatelet regimens. Within the time frame needed for a BVS that is implanted today to be fully absorbed, we should be able to answer these questions.

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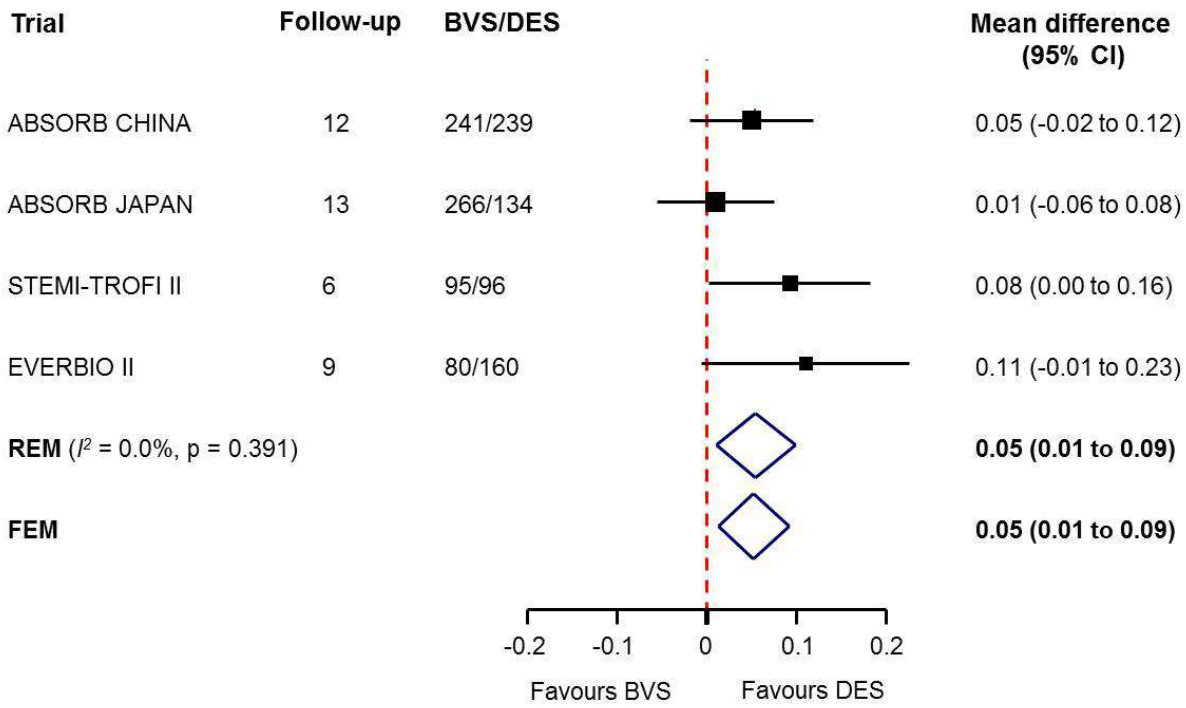
Figure Legend

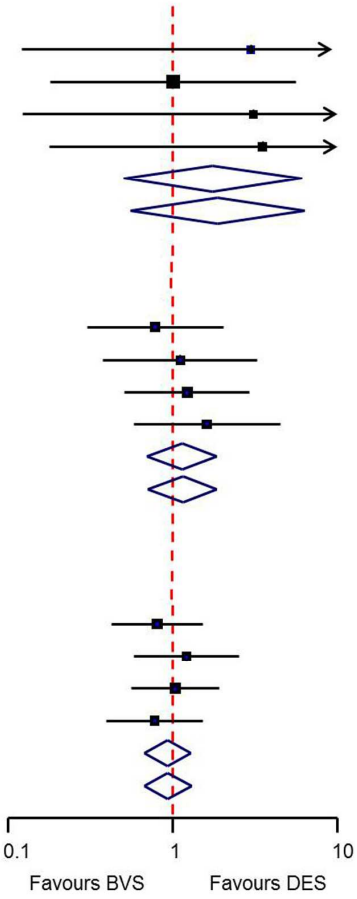
Figure. (**A**) Characteristics of randomized trials comparing BVS vs. metallic DES. (**B**) Meta-analysis of BVS vs. metallic DES for in-segment late lumen loss in randomized trials with reported angiographic follow-up. Each study is presented by name with point estimate of mean difference and respective 95% confidence intervals (CI). (**C**) Meta-analysis of BVS vs. metallic DES for stent thrombosis (definite or probable); the device-oriented composite endpoint target-lesion failure [cardiac death, target-vessel myocardial infarction (MI), or ischemia-driven target lesion revascularization]; and the patient-oriented composite endpoint of death, MI, or any revascularization at follow-up. Each study is presented by name with point estimate of odds ratio (OR) and respective 95% CIs. The overall mean difference (**B**) and overall OR (**C**) and the respective 95% CIs are shown according to random effects model (REM) and fixed effects model (FEM) with studies weighted by the inverse of their variance. Follow-up is shown in months. The EVERBIO trial is not included in analysis of stent thrombosis due to zero events in both intervention arms.

Trial	Pts	Primary endpoint	Secondary endpoints
ABSORB CHINA (Ref. 16)	480	In-segment late lumen loss	•Target lesion failure •Death, MI, any revascularization
ABSORB JAPAN (Ref. 14)	400	In-segment late lumen loss	•Target lesion failure •Death, MI, any revascularization
STEMI TROFI II (Ref. 3)	191	"Healing score" by OCT	•Device-oriented composite endpoint
EVERBIO II (Ref. 15)	160	In-stent late lumen loss	•In-segment late lumen loss •Device-oriented MACE •Death, MI, any revascularization
ABSORB II (Ref. 6)	501	Vasomotion at 3y	•Target lesion failure •Death, MI, any revascularization

Late lumen loss



Trial	Follow-up	BVS	DES	OR (95% CI)
Stent thrombosis (Definite/Probable)				
ABSORB CHINA	12	1/241	0/239	2.99 (0.12 to 73.70)
ABSORB JAPAN	12	4/266	2/134	1.01 (0.18 to 5.57)
STEMI-TROFI II	6	1/95	0/96	3.06 (0.12 to 76.15)
ABSORB II	12	3/335	0/166	3.51 (0.18 to 68.26)
REM (I^2 = 0.0%, p = 0.839)				**1.74 (0.50 to 6.02)**
FEM				**1.86 (0.55 to 6.27)**
Device-oriented composite endpoint				
Target lesion failure				
ABSORB CHINA	12	8/241	10/239	0.79 (0.30 to 2.03)
ABSORB JAPAN	12	11/266	5/134	1.11 (0.38 to 3.27)
EVERBIO II	9	9/80	15/160	1.23 (0.51 to 2.94)
ABSORB II	12	16/335	5/166	1.62 (0.58 to 4.49)
REM (I^2 = 0.0%, p = 0.785)				**1.14 (0.70 to 1.85)**
FEM				**1.15 (0.71 to 1.85)**
Patient-oriented composite endpoint				
Death, MI, or any revascularization				
ABSORB CHINA	12	19/241	23/239	0.80 (0.43 to 1.52)
ABSORB JAPAN	12	26/266	11/134	1.21 (0.58 to 2.53)
EVERBIO II	9	21/80	41/160	1.03 (0.56 to 1.90)
ABSORB II	12	24/335	15/166	0.78 (0.40 to 1.52)
REM (I^2 = 0.0%, p = 0.781)				**0.93 (0.67 to 1.29)**
FEM				**0.93 (0.67 to 1.30)**



Online Appendix

Statistical Methods

For meta-analyses, the mean difference and odds ratio were used as the metrics of choice for continuous and categorical outcomes respectively. In-segment late lumen loss was chosen as the primary outcome of interest, and the mean (accompanied by the respective standard error) values at angiographic follow-up for each intervention were extracted. We also considered stent thrombosis (definite/probable), target-lesion failure, and the composite outcome of death, myocardial infarction, or any revascularization, which were summarized and presented as frequencies. Between-study heterogeneity was evaluated with the $\chi 2$ test-based Q-statistic and was considered statistically significant at a level of <0.10. We further quantified the effect of the heterogeneity across studies using the I2 statistic, which is independent of the number of studies (1, 2) and obtained its 95% confidence intervals (3). I2 takes values between 0% and 100%, with values of 25% typically suggesting low, 50% moderate, and 75% large heterogeneity. Fixed effects models with studies weighted by the inverse of their variance and random effects models using the Der Simonian and Laird method were used to combine the data across studies (4). When there is no detectable between-study heterogeneity, the two models give identical results. In the presence of detectable between-study heterogeneity, random effects give wider confidence intervals. We performed meta-analysis in Stata version 13.0.

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