

Current Status of Trial Outcomes for the Absorb Stent

How does Absorb compare to everolimus-eluting metallic stents?

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Newer drug-eluting metallic stents (DES) have a first-line therapy recommendation as a revascularization option for patients with coronary artery disease due to superior angiographic and clinical outcomes in comparison with preceding stent platforms.¹ However, late adverse events related to the stented segment can continue to accrue, with accelerated in-stent atherosclerosis as an important underlying mechanism.²

In recent years, fully bioresorbable stents eluting antirestenotic drugs have attracted considerable interest as a technology alternative to metallic DES.³ Among bioresorbable stent platforms, the Absorb everolimus-eluting bioresorbable vascular scaffold (Abbott Vascular) has been the first of such devices approved for medical use in Europe.⁴ The Absorb is a balloon-expandable, bioresorbable scaffold that consists of a poly(L-lactide) backbone (150- μ m thickness) coated with poly(D, L-lactide) in a 1:1 ratio with everolimus (drug concentration 8.2 μ g/mm).⁴ As with other bioresorbable stent platforms, Absorb provides transient scaffolding of the target lesion during the elution of the antirestenotic drug everolimus, and then it degrades into inert component products after approximately 3 years.

RECENT TRIALS

Preliminary studies showed encouraging results with Absorb in preclinical models and simple coronary artery lesions in humans.⁵ In addition, six recent randomized trials enrolling approximately 4,000 patients with moderately complex coronary artery disease have investigated the outcomes of Absorb compared (mainly) to the everolimus-eluting metallic stent (EES) (Table 1).⁶⁻¹¹ The majority of these trials were small-scale, not adequately powered for clinical endpoints, included highly selected patient popula-

tions, and had only a short- to midterm follow-up. The primary endpoint consisted of angiographic measures of efficacy (namely, late lumen loss [LLL]) in three trials^{7,9,11} and imaging measures of efficacy (namely, healing score) in one trial,¹⁰ with the remaining trials powered for composite clinical outcomes.^{6,8} Angiographic follow-up was planned in four studies.⁷⁻¹⁰

All but one trial⁹ had a multicenter design, with two trials enrolling patients with acute myocardial infarction.^{9,10} Three trials⁶⁻⁸ were designed to support the postmarket approval of Absorb in the United States, China, and Japan, and included predominantly stable patients with single de novo noncomplex target lesions, thus excluding patients at higher risk for device failure. Overall, these studies documented that Absorb has comparable efficacy to EES. However, there were some instances of higher thrombotic risk in the first phase after Absorb implantation.⁶ These data were consistent with those from large registries in routine clinical practice, which documented a rate of adverse events with Absorb that was higher than the rate we routinely observe after stenting with contemporary metallic DES.¹²

RECENT META-ANALYSES

To summarize the available evidence and to shed more light on the possible advantages and shortcomings of this new technology, four meta-analyses have been recently published (Table 2).¹³⁻¹⁶ The first meta-analysis¹³ explored the aggregate data of completed randomized trials⁶⁻¹¹ in which 3,738 participants underwent percutaneous coronary intervention with either Absorb (n = 2,337) or EES (n = 1,401). In this study, patients treated with Absorb had a similar risk of target lesion revascularization, target lesion

TABLE 1. MAIN CHARACTERISTICS OF COMPLETED RANDOMIZED TRIALS INVESTIGATING THE ABSORB STENT

Trial	Main Inclusion Criteria	Patients Enrolled (n =)	Diabetes (%)	ACS at Admission (%)	Lesions Enrolled (n =)	B2/C Type (%)	Primary Endpoints	Registration Number
ABSORB China ⁷	Age $\geq$ 18 years, evidence of myocardial ischemia, $\leq$ 2 de novo coronary lesions, reference vessel diameter $\geq$ 2.5 and $\leq$ 3.75 mm, lesion length $\leq$ 24 mm	480	24	64*	503	73	12-month in-segment LLL	NCT01923740
ABSORB II ¹¹	Age $\geq$ 18 and $\leq$ 85 years, evidence of myocardial ischemia, $\leq$ 2 de novo coronary lesions	501	24	21*	546	47	36-month coronary vasomotion and MLD	NCT01425281
ABSORB III ⁶	Age $\geq$ 18 years, evidence of myocardial ischemia, $\leq$ 2 de novo coronary lesions, reference vessel diameter $\geq$ 2.5 and $\leq$ 3.75 mm, lesion length $\leq$ 24 mm	2,008	32	26*	2,098	71	12-month TLF	NCT01751906
ABSORB Japan ⁸	Age $\geq$ 20 years, evidence of myocardial ischemia, $\leq$ 2 de novo coronary lesions, reference vessel diameter $\geq$ 2.5 and $\leq$ 3.75 mm, lesion length $\leq$ 24 mm	400	36	13*	412	76	12-month TLF	NCT01844284
EVERBIO II ⁹	Age $\geq$ 18 years, stable or unstable ischemic heart disease	158 (240) [†]	19	35	208 (325) [†]	37	9-month in-device LLL	NCT01711931
TROFI II ¹⁰	Age $\geq$ 18 years, STEMI $\leq$ 24 h after symptom onset requiring emergent PCI, reference vessel diameter $\geq$ 2.25 and $\leq$ 3.8 mm	191	17	100	193	100	6-month healing score	NCT01986803

Abbreviations: ACS, acute coronary syndrome; LLL, late lumen loss; MLD, minimal lumen diameter; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TLF, target lesion failure.

*Unstable angina only.

[†]Without (with) patients/lesions included in the biolimus-eluting stent arm.

failure, and death as those treated with EES after a median follow-up of 12 months. There was a nonsignificant increase in the risk of myocardial infarction associated with Absorb versus EES. Most importantly, patients treated with Absorb had a twofold higher risk of definite or probable stent thrombosis than those treated with EES, with the highest

risk (threefold) between 1 and 30 days after implantation. Furthermore, this report provided the only available meta-analytic insight of the angiographic performance of Absorb as compared to that of a metallic DES. Lesions treated with Absorb displayed greater in-device LLL than those treated with a metallic stent. In particular, significantly worse angio-

TABLE 2. MAIN CHARACTERISTICS OF PUBLISHED META-ANALYSES INVESTIGATING THE ABSORB STENT

Investigators	Studies Included (Analysis Level)	Patients Available for Analyses (n =)	Main Endpoints	Summary Statistics	Sensitivity Analyses (Main Covariates Explored)	Follow-up (mo)
Cassese et al ¹³	Randomized controlled trials of Absorb vs EES (six trials; study-level analysis)	3,738	TLR, definite or probable stent (scaffold) thrombosis, LLL	Peto OR and WMD (fixed- and random-effects model), mid-p exact method	Diabetes; ACS, vessel size, complex lesions (type B2/C), post-dilation after Absorb	12 (median)
Bangalore et al ¹⁶	Randomized controlled trials of Absorb vs EES (six trials; study-level analysis)	3,738	MI, definite or probable stent (scaffold) thrombosis	OR (fixed- and random-effects model), RR (fixed- and random-effects model), Peto OR	ACS, postdilation after Absorb	12 (median)
Lipinski et al ¹⁴	Randomized controlled trials, retrospective and prospective registries of Absorb vs DES (26 studies; study-level analysis)	10,510	MI, definite or probable stent (scaffold) thrombosis	OR (random-effects model)	ACS or STEMI	6.4 (mean)
Stone et al ¹⁵	Randomized controlled trials of Absorb vs EES (four trials; patient-level analysis)	3,389	POCE, TLF	RR (fixed-effects model)	Diabetes; ACS, vessel size, complex lesions (type B2/C)	12 (median)

Abbreviations: ACS, acute coronary syndrome; DES, drug-eluting metallic stents; EES, everolimus-eluting metallic stents; LLL, late lumen loss; MI, myocardial infarction; OR, odds ratio; POCE, patient-oriented composite endpoints; RR, relative risk; STEMI, ST-elevation myocardial infarction; TLF, target lesion failure; TLR, target lesion revascularization; WMD, weighted mean difference.

graphic outcomes for Absorb relative to EES were observed in those trials,^{9,10} which performed angiographic surveillance at 6 to 9 months per protocol. However, Absorb showed a comparable angiographic efficacy to EES at ≥ 12 months,^{7,8} likely due to an adaptive response of coronary vessel walls after Absorb implantation.

The second study was an expanded pooled analysis¹⁴ of aggregate data from 26 studies (including prospective and retrospective registries) totaling 10,510 patients treated with either Absorb (n = 8,351) or DES (n = 2,159). Only two randomized controlled trials^{9,11} entered this analysis. After a mean follow-up of 6.4 months, patients treated with Absorb had a significantly higher risk of myocardial infarction and definite or probable thrombosis as compared to those patients treated with metallic DES, a finding consistent with the previous report. The higher risk of myocardial infarction

and definite or probable stent thrombosis remained significant when the analyses were limited to those studies with 12-month follow-up. No difference in the other safety and efficacy outcomes considered was observed.

The third study consisted of a patient-level, pooled meta-analysis of four randomized trials^{6-9,11} in which 3,389 patients were studied.¹⁵ Of these patients, 2,164 individuals received Absorb and 1,225 individuals received EES. The main results of this analysis were that target vessel-related myocardial infarction at 1-year follow-up was increased with Absorb, compared with EES, due in part to nonsignificant increases in periprocedural myocardial infarction and definite or probable stent thrombosis with Absorb. The analysis of independent predictors of adverse outcomes (the main advantage of such a kind of analysis) revealed consistent findings. No difference in the other safety and

efficacy outcomes was reported. Interestingly, although individual patient data were made available to the investigators, there was no specific evaluation of the relation between routine lesion preparation and postdilation during Absorb implantation. In line with these arguments, although there is still no firm evidence in favor or against this claim, many experts believe that postdilation helps improve outcomes after Absorb implantation.¹⁷ Indeed, recent registry data seem to support the clinical proficiency of implementing Absorb-specific implantation protocols.¹⁸

Finally, a fourth meta-analysis has recently been published.¹⁶ Similar to the first meta-analysis,¹³ all available randomized trials were included. Beyond calculations of risk estimates for main clinical outcomes, which remained consistent with those previously published, the investigators have explored two important areas of interest: (1) the possible relationship between device deployment characteristics (percent of patients who underwent postdilation), clinical characteristics (proportion of patients presenting with acute coronary syndrome at admission), and Absorb performance; and (2) the robustness of available data regarding the risk of definite or probable stent thrombosis with Absorb versus EES by means of a trial sequential analysis (a statistical analysis in which meta-analysis sample size calculations are combined with the threshold of statistical significance).

The numerical increase in myocardial infarction and definite or probable thrombosis observed with Absorb in this analysis was not evident in patients without acute coronary syndrome at admission or in those receiving postdilation, suggesting that patient selection and proper device deployment are instrumental to reduce this risk. Despite this, the investigators could demonstrate that available trials are underpowered to detect a difference in rare events, such as device thrombosis, because the aggregate sample size accounts for < 10% of what is required to address a measurable effect of Absorb for this endpoint. Larger randomized trials in this setting remain of paramount importance to determine whether the safety and efficacy of Absorb is comparable to or better than currently available metallic DES, particularly in those cases with high-risk clinical or angiographic features.

CONCLUSION

The available body of evidence regarding Absorb supports the necessity of prudent behavior with respect to this technology, avoiding extrapolating what we know from metallic stents and using that for implanting bioresorbable stents. The treatment effect of the Absorb when compared to metallic DES suggests a two- to threefold higher risk of definite or probable thrombosis, a finding that is consistent across the randomized trials and the registries. The future of Absorb technology

relies on the awareness of intrinsic limitations of this early generation platform and would benefit from the expected continuous iterations (a process similar to that observed in the case of earlier-generation metallic DES platforms).¹⁹ Meanwhile, the use of these devices should follow procedural protocols specific to this technology. In particular, a more liberal use of intravascular imaging remains of paramount importance to guide the meticulous implantation technique for current bioresorbable devices. The expected late advantages of Absorb will come from long-term follow-up data, and only a judicious selection of appropriate patients and vessels in the present phase will allow Absorb to revolutionize the field of interventional cardiology. ■

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