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【 REVIEW ARTICLE 】

Recent Least Burdensome Approach for the Approval of Innovative Medical Devices in Japan -Regulatory Approval Review of an Everolimus-eluting Bioresorbable Scaffold-

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Abstract:

Although a domestic trial in Japan revealed that Absorb bioresorbable vascular scaffold (BVS) has no inferiority to everolimus-eluting stent (EES) cohort in the primary endpoint of the target lesion failure at 12 months, the scaffold/stent thrombosis (ST) rates with the BVS at 24 months were higher than those with the EES (Absorb BVS 3.1% vs. EES 1.5%), the ST rate of 3.1% with Absorb BVS is not an acceptable level in Japan. A cause-of-ST analysis revealed that cases in which diagnostic imaging and ensuing post-dilatation had been performed appropriately had lower ST rates than those without such management (within 1 year: 1.37% vs. 7.69%, from 1 to 2 years: 0.00% vs. 8.33%). Therefore, a further evaluation was needed to confirm that the ST rate with the Absorb BVS would be reduced by a proper implementation procedure. Regulatory approval was given conditionally to initiate rigorous post-marketing data collection in order to ensure the proper use of this device in limited facilities. The One-year Use-Result Survey in Japan for the Absorb BVS revealed no instances of ST. This approach to reducing the premarket regulatory burden of clinical trials and enhancing the post-marketing commitments of medical device regulation is useful for expediting patient access to innovative medical devices.

Key words: everolimus-eluting bioresorbable scaffold, Use-Result Survey, scaffold thrombosis

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Introduction

The Japanese Government has endeavored to expedite patient access to medical devices through several government policy initiatives. Examples of recent policies include the SAKIGAKE Designation System (1), corresponding to US medical devices' "breakthrough therapy designation" envisaged in "the 21st Century Cures Act of the US" (2, 3), and the Fast-Break Scheme for innovative medical devices (4), which are intended to expedite patient access for which a high medical need exists at an earlier stage of development in Japan based on clinical evidence not confined to rigorous prospective randomized control studies, but including other adequate clinical data considered reasonably likely to predict a clinical benefit and safety based on a limited patient population in certain clinical settings.

Specifically, the Fast-Break Scheme allows substitution of additional pre-marketing clinical trials with rigorous post-marketing real-world data collection using a Use-Result Survey under the Pharmaceuticals and Medical Devices Act (PMD Act), considering the pre- and post-marketing balance in collaboration with relevant academic medical societies (e.g., restricting sales to certified experts and institutions deemed capable of rescuing patients in the event of an emergency) (Fig. 1). The Use-Result Survey should be conducted under Good Post-marketing Surveillance Practice (GPSP), which is a Japanese system for ensuring the quality and reliability of a survey (5).

The everolimus-eluting bioresorbable vascular scaffold

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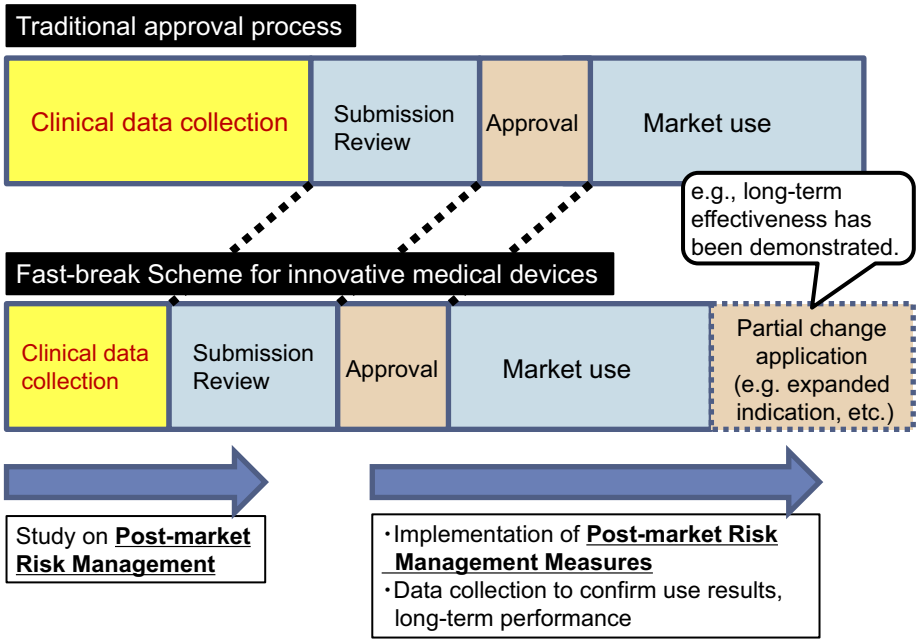

Figure 1. **Fast-break Scheme for innovative medical devices. Under the traditional approval process, long-term data collection is needed. However, under the fast-break scheme, innovative medical devices satisfying all of the prescribed criteria are approved based on the existing data, conditional upon a Use-Results Survey. This leads to shorter data collection times than in the traditional approval process. However, this approach is to be applied only to brand-new medical devices satisfying the following criteria: (1) no appropriate alternative medical devices are available, or there is a reasonable likelihood of the new device having a higher efficacy and safety than existing products; (2) the target patient population is affected by life-threatening disease or a serious disability in daily life; (3) some supporting clinical evidence is available; (4) post-marketing commitment to an appropriate risk management plan in collaboration with relevant academic medical societies (e.g. restriction of sales to certified experts and institutions) and rigorous real-world evidence collection and evaluation has been made; and (5) the difficulty of conducting a new prospective clinical trial is considered justified.**

(BVS) Absorb GT1 (Abbott Vascular, Santa Clara, USA) was not actually developed under the Fast-Break Scheme, but its introduction does involve the pre- and post-marketing balance championed under this approach in order to expand the number of user facilities according to the results of Use-Result Survey.

We herein report our efforts to have the Absorb GT1 approved under the PMD Act in Japan.

Regulatory approval review of the absorbable scaffold in Japan

The Absorb GT1 is made of bio-absorbable polylactate, coated with a everolimus, which inhibits neointimal hyperplasia, as well as with a bio-absorbable polymer (6). In order to evaluate the effectiveness and safety of this scaffold, clinical trials using an Absorb BVS were conducted in the United State (ABSORB III trial) (7) and Japan (AVJ-301 trial) (8), both of which were designed to verify the non-inferiority of the Absorb BVS to the cobalt-chromium everolimus-eluting stent (CoCr-EES) (Abbott Vascular) with a primary endpoint of target lesion failure at 12 months. In both trials, it was confirmed that the Absorb BVS was not inferior to the CoCr-EES at 12 months [ABSORB III trial: Absorb BVS 7.8% (102/1313) vs. CoCr-EES 6.1% (41/677), p (non-inferiority) = 0.0070; AVJ-301 trial: Absorb BVS 4.2% (11/265) vs. CoCr-EES 3.8% (5/133), p (non-inferiority) <0.0001] (9). Although the scaffold/stent thrombosis (ST) rates at 12 months in the AVJ-301 trial were comparable between the 2 cohorts [Absorb BVS 1.5% (4/262) vs. CoCr-EES 1.5% (2/133)], an additional 4 instances of ST occurred during the 12 to 24 months follow-up only in the Absorb BVS group, suggesting the possibility of different behaviors between these 2 devices over the long term [Absorb BVS 3.1% (8/257) vs. CoCr-EES 1.5% (2/130)] (9). The ST rate of 3.1% with Absorb BVS is not an acceptable level in Japan in comparison to the real world data with EES (10).

In order to understand what this difference in ST rates at 24 months means, a cause-of-ST analysis was conducted. The greatest concern with the Absorb BVS at the initiation of the clinical trial was scaffold fracture due to over-expansion, so post-dilatation was not recommended at the time. The cause analysis revealed that cases in which diagnostic intracoronary imaging and ensuing post-dilatation had been performed appropriately had lower ST rates than those without such management [ST rate within 1 year with both

Table 1. The Scaffold Thrombosis Rate with the Absorb BVS Due to the Use of Intra-coronary Imaging Devices and Post Dilatation in the Japan Domestic Trial.

The use of diagnostic intra-coronary imaging device	Yes		No	
Post dilatation	Yes	No	Yes	No
Scaffold thrombosis with Absorb BVS (within 1 year)	1.37% (2/146)	3.13% (1/32)	0.00% (0/68)	7.69% (1/13)
Scaffold thrombosis with Absorb BVS (1-2 years)	0.00% (0/143)	3.13% (1/32)	2.99% (2/67)	8.33% (1/12)

BVS: bioresorbable vascular scaffold

Table 2. The Scaffold Thrombosis Rate and Target Lesion Failure Due to the Reference Vessel Diameter in the ABSORB III Trial.

	Reference vessel diameter ≥2.25 mm (median=2.74 mm)		Reference vessel diameter<2.25 mm (median=2.09 mm)	
	Absorb BVS	CoCr-EES	Absorb BVS	CoCr-EES
Target lesion failure	6.7% (71/1,067)	5.5% (30/542)	12.9% (31/241)	8.3% (11/133)
Scaffold thrombosis	0.85% (9/1,058)	0.56% (3/540)	4.62% (11/238)	1.50% (2/133)

BVS: bioresorbable vascular scaffold, CoCr-EES: Cobalt-chromium everolimus-eluting stent

post-dilatation and diagnostic intracoronary imaging 1.37% (2/146) vs. without post-dilatation or diagnostic intracoronary imaging 7.69% (1/13); ST rate from 1 to 2 years with both post-dilatation and diagnostic intracoronary imaging 0.00% (0/143) vs. without either post-dilatation or diagnostic intracoronary imaging 8.33% (1/12)] (9) (Table 1). Furthermore, the frequency of ST with an Absorb BVS with a reference vessel diameter (RVD) <2.25 mm was higher than that with a CoCr-EES in the ABSORB III trial (Table 2). Therefore, it was considered that appropriate diagnostic intracoronary imaging (including measurement of the RVD) and proper size selection as well as proper implementation of post-dilatation were important factors for avoiding ST.

To confirm that the ST rate can actually be reduced through proper implementation of a series of procedures, including size selection and post-dilatation, a further evaluation was required. We conducted intense discussions with academics and industry professionals concerning whether to perform an additional clinical trial or receive approval. The decision was ultimately made to approve the device with some stipulations, as this device was considered to provide potential benefits to patients following the complete resorption of the BVS over the next several years. Indeed, a recent report revealed that although device thrombosis occurred in 2.4% of BVS-treated patients vs. 0.6% of EES-treated patients between 0 and 3 years [hazard ratio (HR), 3.86; 95% confidence interval (CI), 1.75-8.50], it occurred in 0.1% of BVS-treated patients vs. 0.3% of EES-treated patients between 3 and 5 years (HR, 0.44; 95% CI, 0.07-2.70) (p for interaction = 0.03) (11). In addition, under this decision, rigorous post-marketing data collection with the proper use of the device ensured in limited facilities under the guidance of certified experts (mainly AVJ-301 trial sites) was required.

In the Use-Result Survey, all cases up to 2,000 had to be registered at select user facilities with 3 months of follow-up. Provided the ST rate of these 2,000 cases did not exceed 0.9% in the Use-Result Survey for up to 3 months, then the number of user facilities would be expanded gradually, according to the chart (Fig. 2). Despite the lack of statistical evidence supporting the threshold for the 3-month thrombosis rate at 0.9%, better outcomes in the Use-Result Survey with the proper use of the Absorb BVS were required than were observed in the AVJ-301 trials. The threshold of 0.9% for the 3-month thrombosis rate is based on the results of the ABSORB III with RVD ≥2.25 (9).

One-year results of the use-result survey of absorbable scaffold in Japan

Although Absorb GT1 was approved in November 2016 in Japan, Abbott Vascular decided to stop selling the Absorb GT1 system globally in September 2017 due to lower-than-expected commercial sales. A total of 135 patients were enrolled in the Use-Result Survey.

Regarding patient characteristics, the average age was 64.0 years old, and the frequencies of male gender, stable angina pectoris, current smoking habit, diabetes mellitus, dyslipidemia, hypertension and history of percutaneous coronary intervention were 84%, 85%, 24%, 39%, 69%, 76% and 26%, respectively (12) (Table 3).

In lesion characteristics, the frequencies of lesions with left anterior descending coronary artery, left circumflex coronary artery, right coronary artery, moderate/severe calcification, bifurcation and American College of Cardiology-American Heart Association type B2 and type C were 48%, 22%, 30%, 12%, 12% and 52%, respectively (12).

Furthermore, regarding procedural characteristics, the

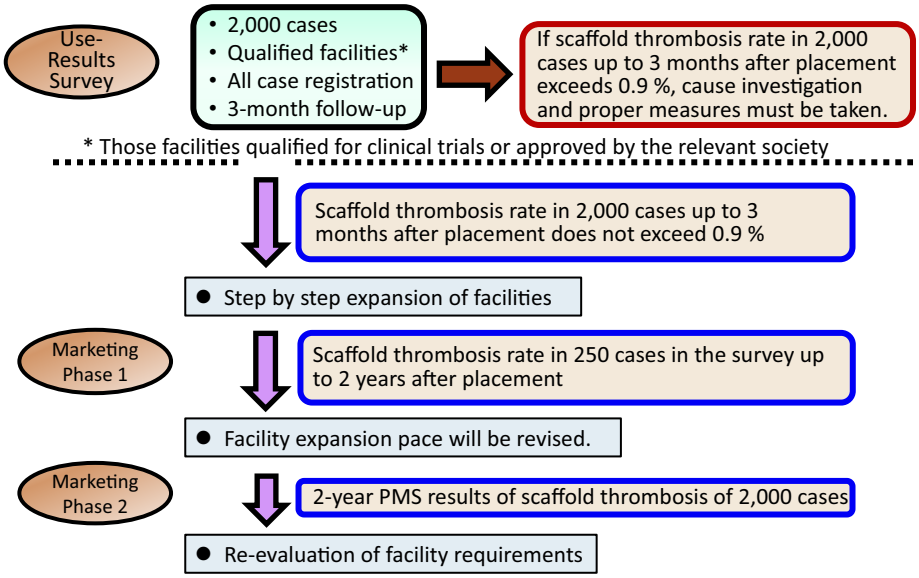

Figure 2. Overview of the Use-Results Survey and post-marketing safety measures. In the Use-Result Survey, all cases up to 2,000 had to be registered at select user facilities with 3 months of follow-up. Provided the ST rate of these 2,000 cases did not exceed 0.9% in the Use-Result Survey for up to 3 months, then the number of user facilities would be expanded gradually.

rates of single target lesion, pre-dilatation and post-dilatation were 97%, 100% and 99%, respectively (19) (Table 3). In the post-procedural optical coherence tomography measurement (Core Lab Assessment), the mean and minimal lumen areas were both higher in the Use-Result Survey than in the AVJ-301 trial (mean lumen area: 8.18±1.85 vs. 7.38±2.02 mm^2, minimal lumen area: 6.86±1.77 vs. 6.09±1.82 mm^2), and the percentage of malapposed struts was lower in the Use-Result Survey than in the AVJ-301 trial (1.89%±3.63% vs. 4.70%±6.68%) (12).

Regarding the clinical outcomes up to 1 year, the incidences of cardiac death, target vessel myocardial infarction, ischemia driven target lesion revascularization and any target lesion revascularization were 0%, 0%, 0% and 0.7%, respectively, in the Use-Result Survey (13) (Table 3).

Discussion

The major findings from the domestic pre- and post-marketing trials with the Absorb BVS were as follows: (1) The pre-marketing AVJ-301 trial showed that the ST rate with the Absorb BVS at 24 months was higher than that with the CoCr-EES [Absorb BVS 3.1% (8/257) vs. CoCr-EES 1.5% (2/130)], the ST rate of 3.1% with Absorb BVS is not an acceptable level in Japan. ; in this trial, the cases with diagnostic intracoronary imaging and ensuing post-dilatation had lower ST rates than those without this management. (2) The ongoing Use-Result Survey of the Absorb BVS being conducted in the limited facilities revealed favorable results, with no incidence of cardiac death, target vessel myocardial infarction or ischemic driven target lesion failure within one year.

The ABSORB III trial revealed higher three-year adverse event rates with the Absorb BVS than with the CoCr-EES, particularly target vessel myocardial infarction and ST (14). Furthermore, the pooled meta-analysis of the ABSORB trials revealed that the Absorb BVS was associated with increased rates of target lesion failure (mainly caused by ST) between one and three years and cumulatively through three years of follow-up compared with the CoCr-EES (15). In addition, the Japan AVJ-301 trial showed that the rate of target lesion failure at 24 months was non-significant but numerically higher in the BVS arm than in the CoCr-EES arm (8).

Although the mechanisms underlying scaffold failure were poorly understood, Yamaji et al. reported that the main mechanisms involved in ST were scaffold discontinuity (42%), malapposition (18%), underexpansion (10%) and an uncovered strut (5%). As whether or not optimized implantation can mitigate the risk of ST remains to be clarified (16), imaging devices will be essential for monitoring the long-term performance of the Absorb BVS (14). At the start of the AVJ-301 trial, additional balloon dilatation after scaffold implantation was not recommended due to concerns of scaffold fracture due to overexpansion. However, through the regulatory approval of Absorb GT1 and recent reports, it was suggested that proper implementation of a series of procedures, including post-dilatation, could help reduce the risk of scaffold failure (17), which was reflected in the post-marketing safety measures.

While the COMPARE-ABSORB trial (18) showed higher risks of target vessel myocardial infarction (4.0% vs. 2.1%, p=0.02) and stent/scaffold thrombosis (2.0% vs. 0.6%, p=0.01) at 1 year than the XIENCE trial, in which pre- and post-dilatation were mandatory and intracoronary imaging was recommended for the treatment of target vessels <2.75 mm in diameter, these higher frequencies of post-dilatation

Table 3. Patient, Lesion and Procedural Characteristics as Well as the Post-procedural OCT Measurements and One-year Clinical Outcomes in Patients according to the Use-Result Survey of the Absorb BVS Vs. the Japan Domestic Trial.

	Use-result Survey	Japan domestic trial
Patient characteristics	(n=135)	(n=266)
Age, year	64.0±10.9	67.1±9.4
Male gender, %	84	79
Prior PCI, %	26	35
Prior MI, %	10	16
Stable angina, %	85	90
Diabetes mellitus, %	39	36
Hyperlipidemia, %	69	82
Hypertension, %	76	78
Current Smoker, %	24	20
Lesion characteristics	(n=139)	(n=275)
Target vessel, %		
LAD	48	46
LCX	22	23
RCA	30	31
Lesion type		
Moderate/severe calcification lesion, %	12	28
Moderate/severe tortuosity lesion, %	10	8
Eccentric lesion, %	27	82
ACC-AHA class (B2/C), %	52	76
Bifurcation lesion, %	12	37
Procedural characteristics	(n=139)	(n=275)
Single target lesion, %	97	97
Pre-dilatation, %	100	100
Post dilatation, %	99	82
By non-compliant balloon, %	88	64
Post-dilatation pressure ≥ 16 atm, %	87	42
Post-dilatation pressure ≥ 18 atm, %	69	31
Total scaffold length, mm	20.0±5.1	20.2±5.8
Post-procedural OCT measurement (Core Lab Assessment)	(n=139)	(n=86)
Mean lumen area, scaffold, mm^2	8.18±1.85 (127)	7.38±2.02 (80)
Minimal lumen area, scaffold, mm^2	6.86±1.77 (127)	6.09±1.82 (80)
Percentage of malapposed struts, %	1.89±3.63 (127)	4.70±6.68 (80)
1-year clinical outcome	(n=135)	(n=266)
Death, %	0.0	0.8
Cardiac death, %	0.0	0.0
MI, %	0.0	3.1
Target vessel MI, %	0.0	3.1
Any TLR, %	0.7	1.9
ID-TLR, %	0.0	1.9
Any revascularization, %	2.2	2.7

ACC-AHA: American College of Cardiology-American Heart Association, RCA: right coronary artery, LCX: left circumflex coronary artery, LAD: left anterior descending coronary artery, BVS: bioresorbable vascular scaffold, PCI: percutaneous coronary intervention, MI: myocardial infraction, OCT: optical coherence tomography, ID: ischemic-driven, TLR: target lesion revascularization

and adequate post-dilatation pressure led to favorable results, with no cases of cardiac death, target vessel myocardial infarction or ischemic-driven target lesion revascularization, although there were only 135 patients enrolled in the Use-Result Survey due to sales of the Absorb GT1 being stopped.

Taken together, these findings suggest that proper implementation procedures, including post-dilatation and adequate size selection using intravascular imaging, are extremely important when using an Absorb GT1. These findings will fa-

cilitate the improvement of implantation techniques and the development of the next-generation Absorb GT1. Long-term follow-up data of recommended antiplatelet therapy and its duration after Absorb GT1 implantation with proper implementation procedures are warranted.

Expanding the number of user facilities gradually after standardizing procedures based on real-world data obtained from limited facilities is very useful for expediting patient access to innovative medical devices with high medical needs in cases when there are concerns not about the effectiveness and safety of the device itself but about the device implantation procedure.

The Use-Result Survey System is part of a strategy to expedite patients' access to innovative medical devices and to accelerate the development of new medical devices while reducing the premarket regulatory burden of clinical trials and enhancing post-marketing commitments of medical device regulations over a product's life cycle (19, 20).

The authors state that they have no Conflict of Interest (COI).

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