Deciding whether to internationalize the registry: Japan's academic perspective

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Agenda

1. My experience of effectively utilizing RWD for daily practice.

- Zilver PTX (2012)
- Paclitaxel individual level meta-analysis(2018)

post-marketing surveillance

- ALLIANCE Registry (2023)
- ALLIANCE Ⅱ Registry (2025 on going)

RWD Registry to expand the indication or revising IFU

2. My expectation

Main areas of application for RWD

So called PMS
- Long-term safety and/or efficacy evaluation of high-risk implantable medical devices
- Full life cycle clinical evaluation of medical devices used to treat rare diseases
- Post-marketing surveillance studies
- Post-approval surveillance studies
- Post-approval device surveillance as a condition of approval.

Single arm study
- Use RWD as an external target for clinical trials
- Use RWD to set target values (OPG) for single-arm trials
- Support pre-market clinical evaluation of products as a supplement to existing evidence

Expansion indication
- Expand indications or contraindications
- Revise product IFU based on RWD

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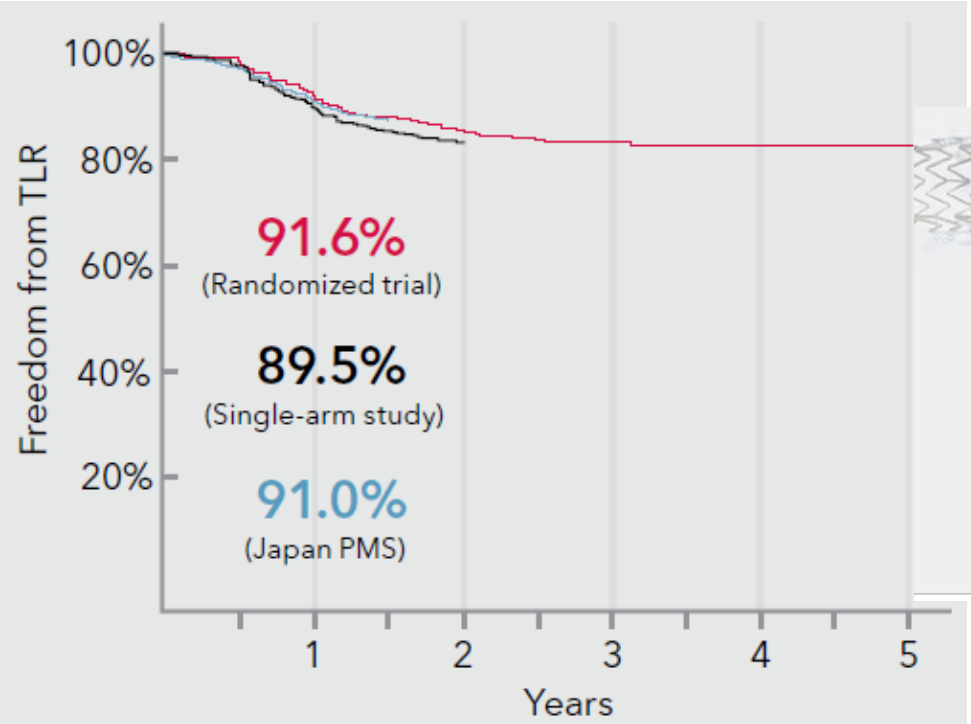
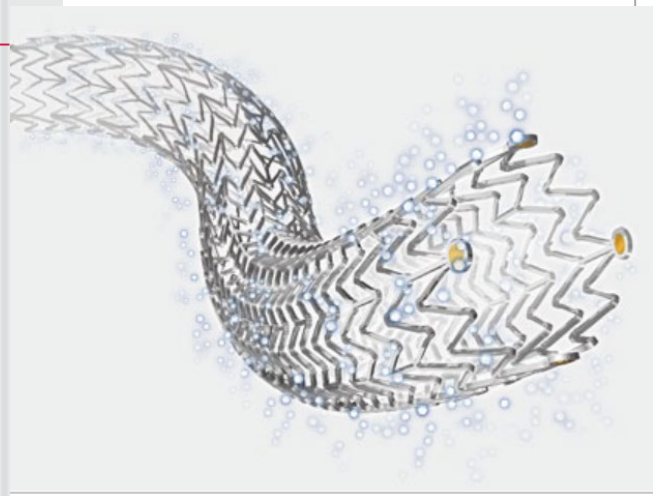
2012

PMS of Zilver PTX

- First approved and covered by insurance in Japan. (in January 2012)
- Initially the use was limited to 95 facilities, **with all cases registered**.
- Data collected as part of the company's PMS with the cooperation of academic societies. Main focus was the risk of thrombotic event.
- The target lesion revascularization (TLR) rate is consistent with clinical trials)
- **US expanded the indication of Zilver PTX for ISR based on this sub-analysis of this PMS**





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Zilver PTX Post-Market Surveillance Study of Paclitaxel-Eluting Stents for Treating Femoropopliteal Artery Disease in Japan

12-Month Results

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ABSTRACT

OBJECTIVES This multicenter, prospective, post-market surveillance study in Japan evaluates the paclitaxel-coated Zilver PTX stent in real-world patients with complex lesions.

BACKGROUND The Zilver PTX stent is the first drug-eluting stent (DES) approved for the superficial femoral artery. Previously, results from a large randomized study and a complementary, large single-arm study supported the safety and effectiveness of the DES.

METHODS There were no exclusion criteria, and consecutive patients with symptomatic peripheral artery disease (PAD) treated with the DES were enrolled in the study. Clinically driven target lesion revascularization (TLR) was defined as reintervention performed for ≥50% diameter stenosis after recurrent clinical symptoms of PAD. Clinical benefit was defined as freedom from persistent or worsening symptoms of ischemia. Patency was evaluated by duplex ultrasound where physicians considered this standard of care.

RESULTS In this study, 907 patients were enrolled at 95 institutions in Japan. There were numerous comorbidities including high incidences of diabetes (58.8%), chronic kidney disease (43.8%), and critical limb ischemia (21.5%). Lesions were also complex, with an average length of 14.7 cm, 41.6% total occlusions, and 18.6% in-stent restenosis. In total, 1,861 DES were placed in 1,075 lesions. Twelve-month follow-up was obtained for >95% of eligible patients. Freedom from TLR was 91.0%, and clinical benefit was 87.7% through 12 months. The 12-month primary patency rate was 86.4%.

CONCLUSIONS Despite more challenging lesions, results from the current study are similar to outcomes from the previous Zilver PTX studies, confirming the benefit of the Zilver PTX DES in a real-world patient population. (Zilver PTX Post-Market Study in Japan; NCT02254837) (J Am Coll Cardiol Intv 2016;9:271–7) © 2016 by the American College of Cardiology Foundation. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Manuscript received [illegible], accepted September 22, 2015.

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In December 2018, JAHA. 7(24):e011245.doi: 10.1161/JAHA.118.011245.

Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Konstantinos Katsanos, MD, PhD, MSc, EBIR; Stavros Spiliopoulos, MD, PhD; Panagiotis Kitrou, MD, PhD; Miltiadis Krokidis, MD, PhD; Dimitrios Karnabatidis, MD, PhD

Background—Several randomized controlled trials (RCTs) have already shown that paclitaxel-coated balloons and stents significantly reduce the rates of vessel restenosis and target lesion revascularization after lower extremity interventions.

Methods and Results—A systematic review and meta-analysis of RCTs investigating paclitaxel-coated devices in the femoral and/or popliteal arteries was performed. The primary safety measure was all-cause patient death. Risk ratios and risk differences were pooled with a random effects model. In all, 28 RCTs with 4663 patients (89% intermittent claudication) were analyzed. All-cause patient death at 1 year (28 RCTs with 4432 cases) was similar between paclitaxel-coated devices and control arms (2.3% versus 2.3% crude risk of death; risk ratio, 1.08; 95% CI, 0.72–1.61). All-cause death at 2 years (12 RCTs with 2316 cases) was significantly increased in the case of paclitaxel versus control (7.2% versus 3.8% crude risk of death; risk ratio, 1.68; 95% CI, 1.15–2.47; —number-needed-to-harm, 29 patients [95% CI, 19–59]). All-cause death up to 5 years (3 RCTs with 863 cases) increased further in the case of paclitaxel (14.7% versus 8.1% crude risk of death; risk ratio, 1.93; 95% CI, 1.27–2.93; —number-needed-to-harm, 14 patients [95% CI, 9–32]). Meta-regression showed a significant relationship between exposure to paclitaxel (dose-time product) and absolute risk of death (0.4±0.1% excess risk of death per paclitaxel mg-year; $P<0.001$). Trial sequential analysis

2018

Inclusion criteria

Eligible clinical trial
1. Approved device for SFA
2. Conducted for Japanese
3. Trial under GCP or GPSP
4. F/U >1year

Identification

15 studies of 8 companies were identified by study principle investigators

Excluded
1 study due to not available in market
2 studies: cooperation was not available

Available data

6 companies contracted and provided individual patient data of 12 studies

COOK, BIRD, Terumo, Boston scientific Medtronic, Cordis

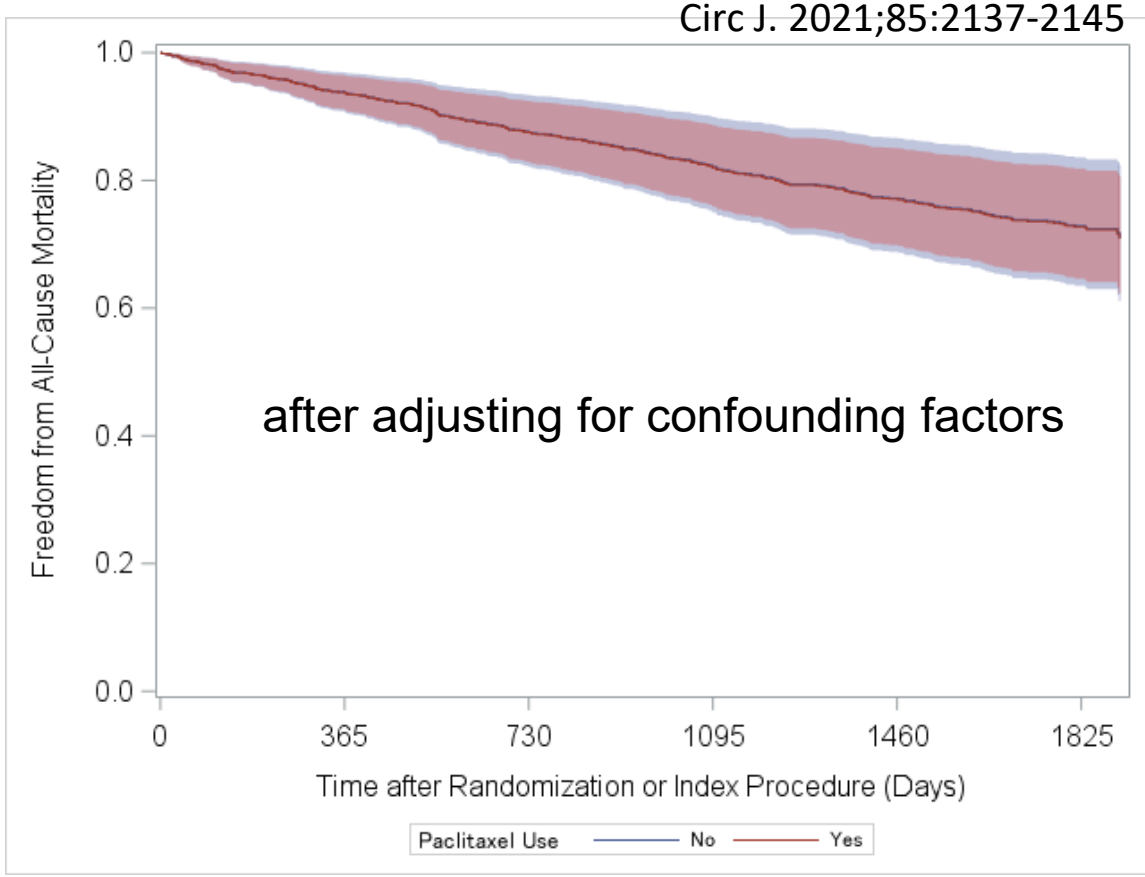
Analyzed data

A total of 2581 patients was analyzed independently

An Individual-Level Meta-Analysis Using Real-World and Pivotal Studies on Mortality From the Use of Paclitaxel-Containing Devices in Japanese Femoropopliteal Disease Patients

Masato Nakamura, MD, PhD; Munenori Takata, MD, PhD; Hiroyoshi Yokoi, MD; Takafumi Ueno, MD, PhD; Yuka Suzuki, PhD; Koji Ikeda, PhD; Takuhiro Yamaguchi, PhD

Circ J. 2021;85:2137-2145



after adjusting for confounding factors

Death is an indisputable hard endpoint, no difference in definitions among trials

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Protocoal of ALLIANCE Registry: Prospective multicenter all comer registry

Hypothesis：OPG 7.5% of TLF、3.0% non-inferiority margin、power of 95%

Exclusion criteria
- **ISR**
- **Enrollment to the other study**
- **Cases not ideal for DCB**
- **IC can not be obtained**

ALL COMER　PCI with DCB　1817 cases

Stand alone

Hybrid Strategy*

*Cases in which DES and DCB were overlapped for coronary artery lesions or bifurcation lesions

Revision of proper use of DCB

SV

Balloon>=3mm
Agent DCB
450 cases

7.5% of TLF、6.0% of non-inferiority margin

Lesion length of 26 mm or more, and two or more AGENT DCB devices used

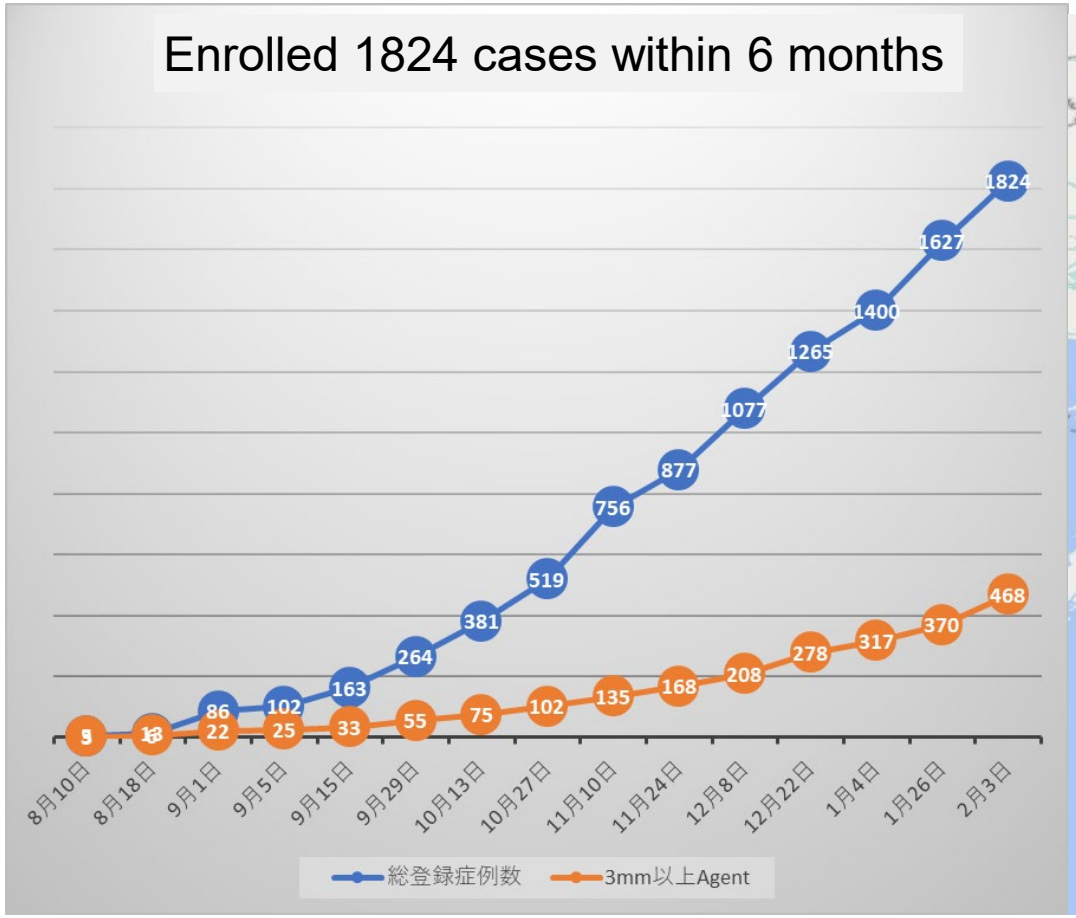
DCB of 40mm length

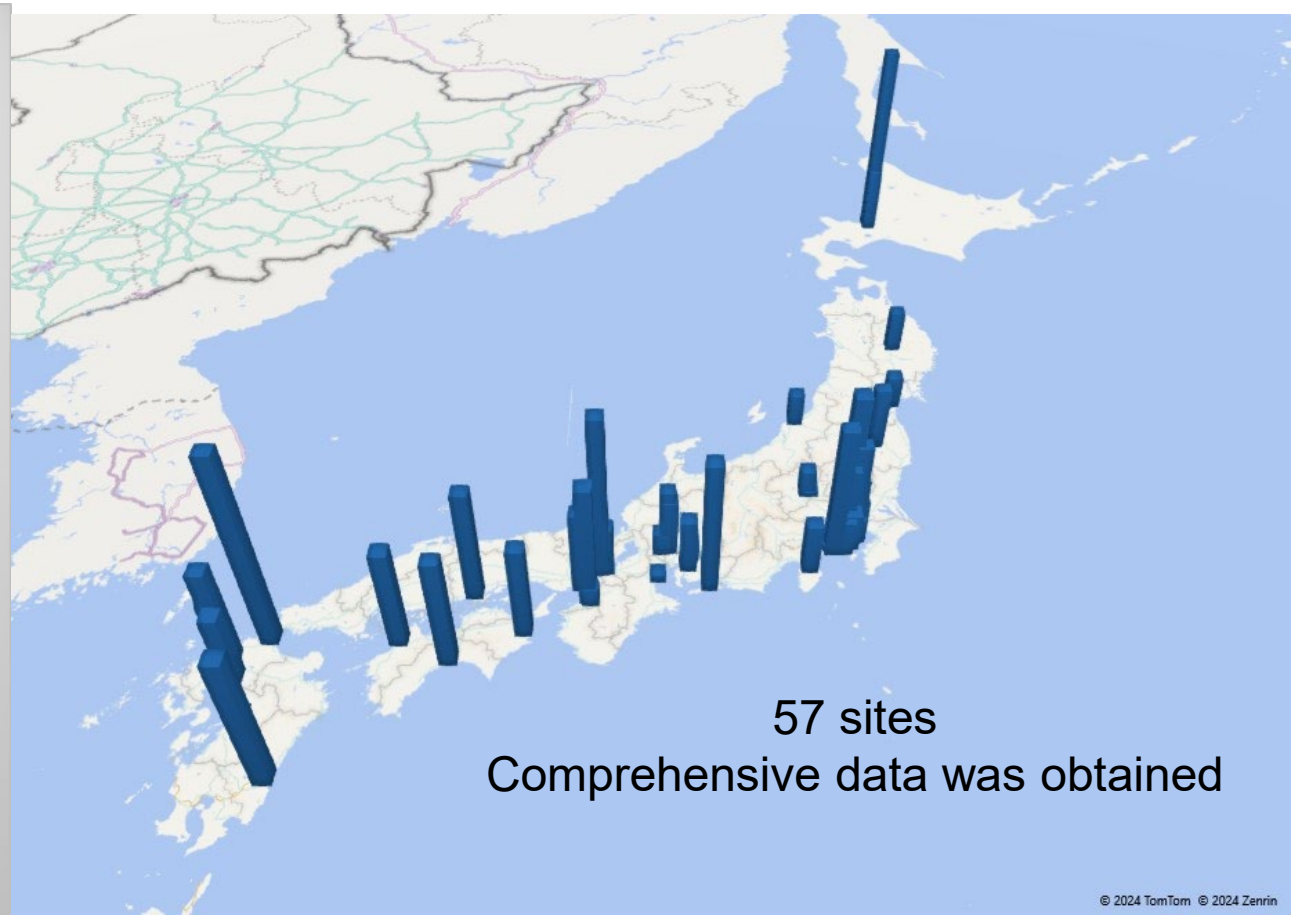
ALLIANCE Registry

Consultation prior to the ALLIANCE registry

- Research Plan: PMDA Medical Device Review Division I Consultation on the Necessity of Clinical Trials for Medical Devices (October 11, 2022)
- PMDA Medical Device Investigation and Standards Division, Reliability Assurance Section Registry Utilization Consultation (March 29, 2023)
- AMED: Selection of clinical research and physician-initiated clinical trials aiming to commercialize medical devices utilizing existing disease registration systems (patient registries) (November 2023)

Enrollment was completed in about 6 months.





Detailed full analysis has been completed, deliverables have been provided to Boston Scientific Inc., and an application for expanded use was submitted to the PMDA on August 8.

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Same institute as ALLIANCE registry.
Events are adjudicated by the same independent CEC as the Alliance registry.

Alliance registry (56%of HBR ; DAPT duration≒ 6 M)

DCB 1794 cases

- Stand alone
  - SV
  - DCB>=3mm → Expansion of DCB for non small vessel
- Hybrid strategy → Revision regarding proper use of DCB

Alliance short DAPT registry

HBR patients treated by DCB
900例

DAPT duration less than 1 month

1 year TLF+BARC 2,3,5

Investigate the safety and efficacy of short-term DAPT in matched subjects.
Verify the non-inferiority of short-term DAPT (within one month)

We realized that RWD is useful and effective in promoting the appropriate use of medical device.

The basic effectiveness of medical devices does not vary from country to country. Indeed, we have a good experience

- FDA : Japanese Zilver PTX PMS to expand the indications for ISR use.
- PMDA : the US TAVI registry to expand the indications for TAV in TAV.

Further utilization of RWD promotes the appropriate use of medical devices and enhances their value.

- RWD, which is highly reliable, has minimal bias and provides clear results, can be applied to other countries and may be particularly useful for expanding the indication.

Enrollment completed in about 6 months, comprehensive data was collection
This data will be presented at TCT

Enrollment has just begun.

JAPAN-US HBD East 2025 Think Tank Meeting

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Investigate the safety and efficacy of short-term DAPT in matched subjects.
Verify the non-inferiority of short-term DAPT (within one month)

Support pre-market clinical evaluation of products as a supplement to existing evidence in every country.

We will cooperate with PMDA to promote the use of RWD

Further utilization of overseas RWD.

1. Expansion of indications or OPG of single-arm study
2. Implementation and integration of registries using the same protocol
3. Simultaneous implementation using the same protocol
4. Other

A step-by-step approach may be a realistic and practical method.

This may be a new type of HBD activity.

Thank you/Questions