Zilver PTX® Post-Market Surveillance Study of Paclitaxel-Eluting Stents for Treating Femoropopliteal Artery Disease in Japan: 12-Month Results

Hiroyoshi Yokoi, M.D.
Department of Cardiovascular Medicine
Fukuoka Sanno Hospital
Fukuoka, Japan

On behalf of the Investigators

Other Japan Zilver PTX PMS Committee (JPPC) Members:
Takao Ohki, MD, PhD,
Kimihiko Kichikawa, MD,
Masato Nakamura, MD, PhD,
Kimihiro Komori, MD,
Shinsuke Nanto, MD, PhD,
and Michael D. Dake, MD

Disclosure

Speaker name:

.....Hiroyoshi Yokoi.....

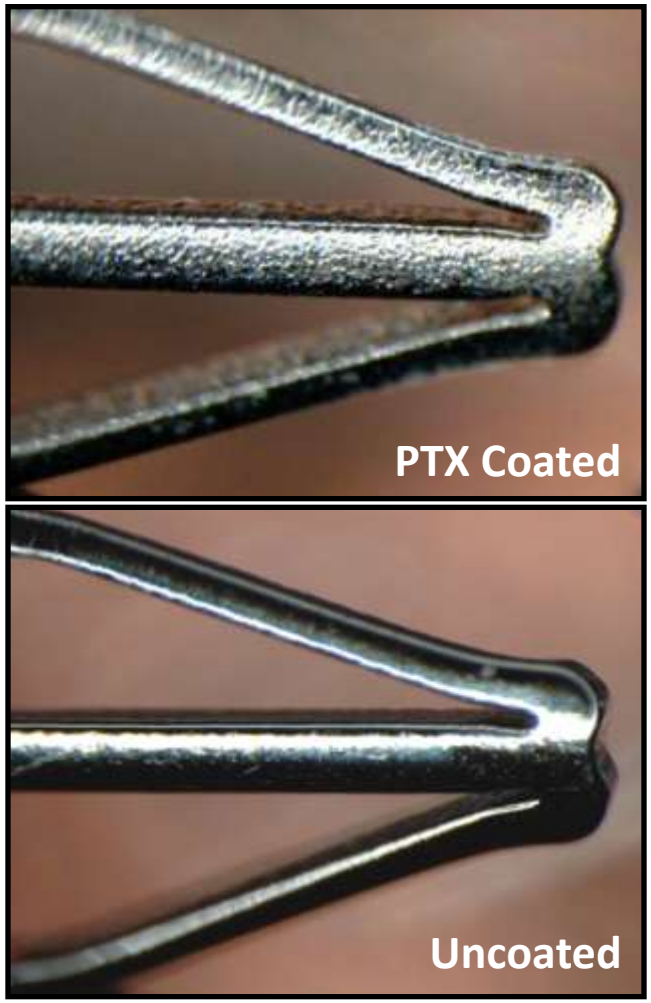
I have the following potential conflicts of interest to report:

- ☐ Consulting
- ☐ Employment in industry
- ☐ Stockholder of a healthcare company
- ☐ Owner of a healthcare company
- ☒ Other(s) Cook,

- ☐ I do not have any potential conflict of interest

Zilver PTX Drug-Eluting Stent

- Designed for the SFA
- Available in 50 countries including US, EU and Japan
- Dual therapy
  - **Mechanical scaffold:** Zilver Flex® stent platform
  - **Drug therapy:** Paclitaxel only
    - No polymer or binder
    - 3 µg/mm^2 dose density
- Sponsor: Cook Medical



Zilver PTX Clinical Program

Pre-market studies

- Randomized Controlled Trial (RCT)
  - 479 patients enrolled in United States, Japan, Germany
- Pre-market Single-Arm Study (SAS)
  - 787 patients enrolled in Europe, Korea, Canada

Multiple post-market studies, including

- Japan Post-market Surveillance (PMS)
  - 907 patients

Japan PMS Compared to RCT and SAS

<table>
<tr><th></th><th>Zilver PTX RCT</th><th>Zilver PTX SAS</th><th>Zilver PTX Japan PMS</th></tr>
<tr><td rowspan="7">Key Study Criteria</td><td colspan="2">No significant untreated inflow tract stenosis</td><td rowspan="7">ALL patients treated with Zilver PTX enrolled (up to enrollment limit), NO exclusion criteria</td></tr>
<tr><td colspan="2">At least one patent runoff vessel</td></tr>
<tr><td>Maximum 2 Zilver PTX stents per lesion</td><td>Maximum 4 Zilver PTX stents per patient</td></tr>
<tr><td>Lesion length ≤ 14 cm</td><td rowspan="2">No exclusions</td></tr>
<tr><td>One lesion per limb</td></tr>
<tr><td>No prior stent in SFA</td><td>In-stent restenosis included</td></tr>
<tr><td>Excluded if serum creatinine > 2.0, renal failure, or dialysis</td><td>No exclusions</td></tr>
<tr><td>Antiplatelets</td><td colspan="3">Clopidogrel or ticlopidine recommended for 60 days, aspirin indefinitely</td></tr>
<tr><td>Follow-up</td><td>5 years</td><td>2 years</td><td>5 years</td></tr>
<tr><td>Patency</td><td>Core laboratory analysis</td><td colspan="2">Site analysis</td></tr>
<tr><td>Stent Integrity</td><td colspan="3">X-ray core laboratory analysis</td></tr>
</table>

Increasingly complex patients and lesions

12-month Follow-up for Japan PMS

- 907 patients treated with Zilver PTX
- 838 patients eligible for 12-month follow-up
  - 69 patients reached study endpoint (death, withdrawal, loss to follow-up)
- 12-month follow-up available for 802 patients (96% follow-up compliance)
- Patency assessed by ultrasound when this was standard of care: 467 patients (58%)
  - No significant differences in demographics, comorbidities, or lesion characteristics compared to patients who did *not* undergo ultrasound

Patient Demographics and Comorbidities

	Zilver PTX RCT	Zilver PTX SAS	Zilver PTX Japan PMS
Patients	236	787	907
Age (years)	68 ± 10 *	67 ± 10 *	74 ± 9
Male	66%	73%	70%
Diabetes	50% *	36% *	59%
High cholesterol	76% *	58%	61%
Hypertension	89%	80% *	85%
Pulmonary disease	19% *	9%	8%
Renal disease	10% *	11% *	44%[1]

* $p < 0.01$ compared to Japan PMS

[1] Of patients with renal disease in the Japan PMS, 82% were in renal failure defined as eGFR< 60 and/or dialysis

Japan PMS patients are older and have a higher prevalence of diabetes and renal disease

Baseline Lesion Characteristics

		Zilver PTX RCT		Ziver PTX SAS		Zilver PTX Japan PMS
Lesions		247		900		1081
Lesion length (cm)		6.6 ± 3.9 *		10.0 ± 8.2 *		14.7 ± 9.7
Diameter stenosis (%)		80 ± 17 *		85 ± 16 *		92 ± 11
Total occlusions		30% *		38%		42%
In-stent restenosis (ISR)		0% *		15%*		19%
Patent runoff vessels	**0**	0%		0%		7%
	1	22%	*	19%	*	32%
	2	35%		35%		32%
	3	42%		45%		29%

* $p < 0.05$ compared to Japan PMS

Japan PMS lesions are more complex
(e.g., longer, more ISR, fewer patent runoff vessels)

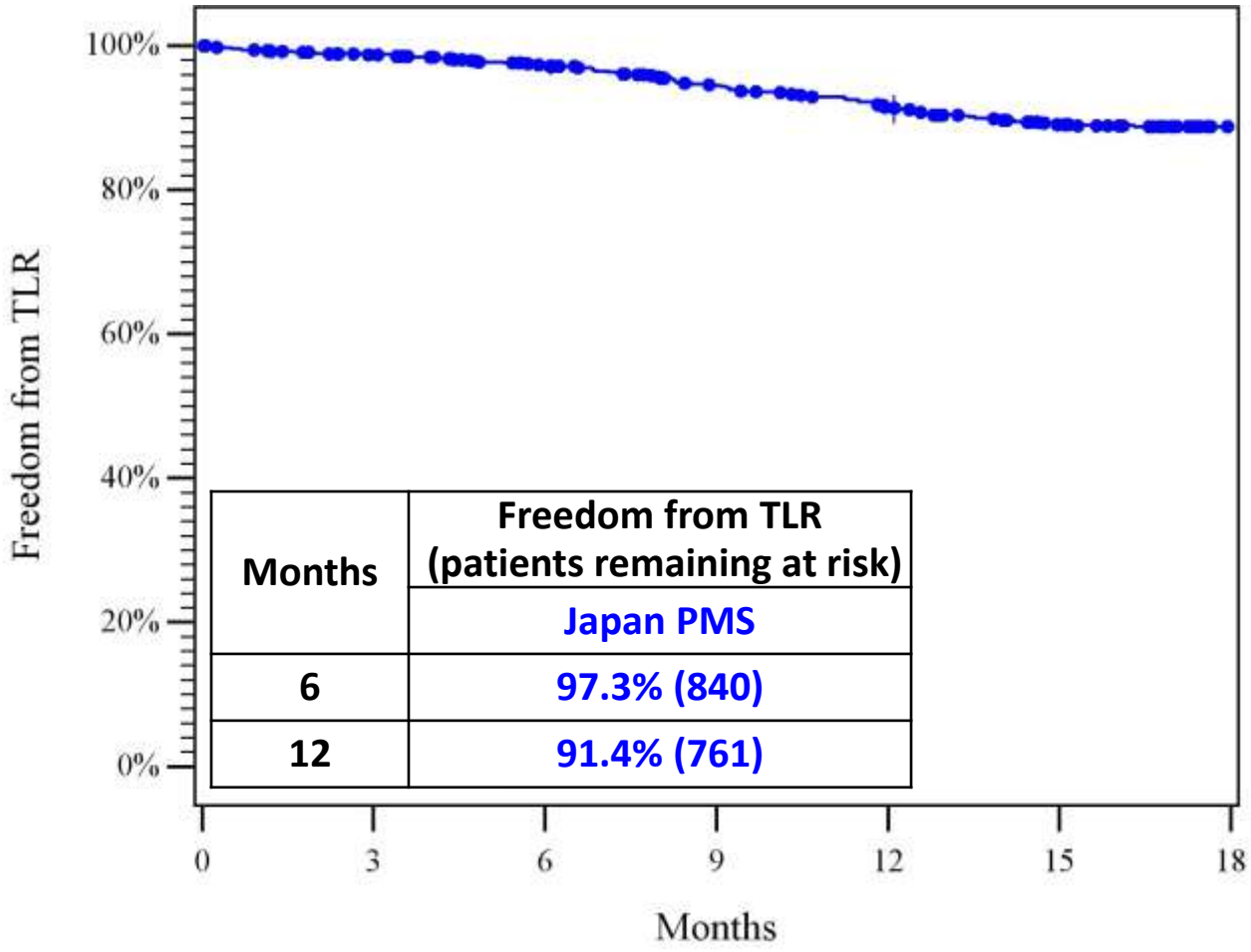
Baseline Clinical Assessment

Pre-procedure Clinical Assessment		Zilver PTX RCT		Zilver PTX SAS		Zilver PTX Japan PMS
Rutherford	1	0.8%		0.5%		7%
	2	53%		32%		26%
	3	38%		56%		41%
	4	6%	*	5%	*	10%
	5	3%		6%		9%
	6	0%		0.2%		1%
	Not reported	-		-		6%

* $p < 0.01$ compared to Japan PMS

Japan PMS patients have significantly greater incidence of CLI (twice that of the pre-market studies)

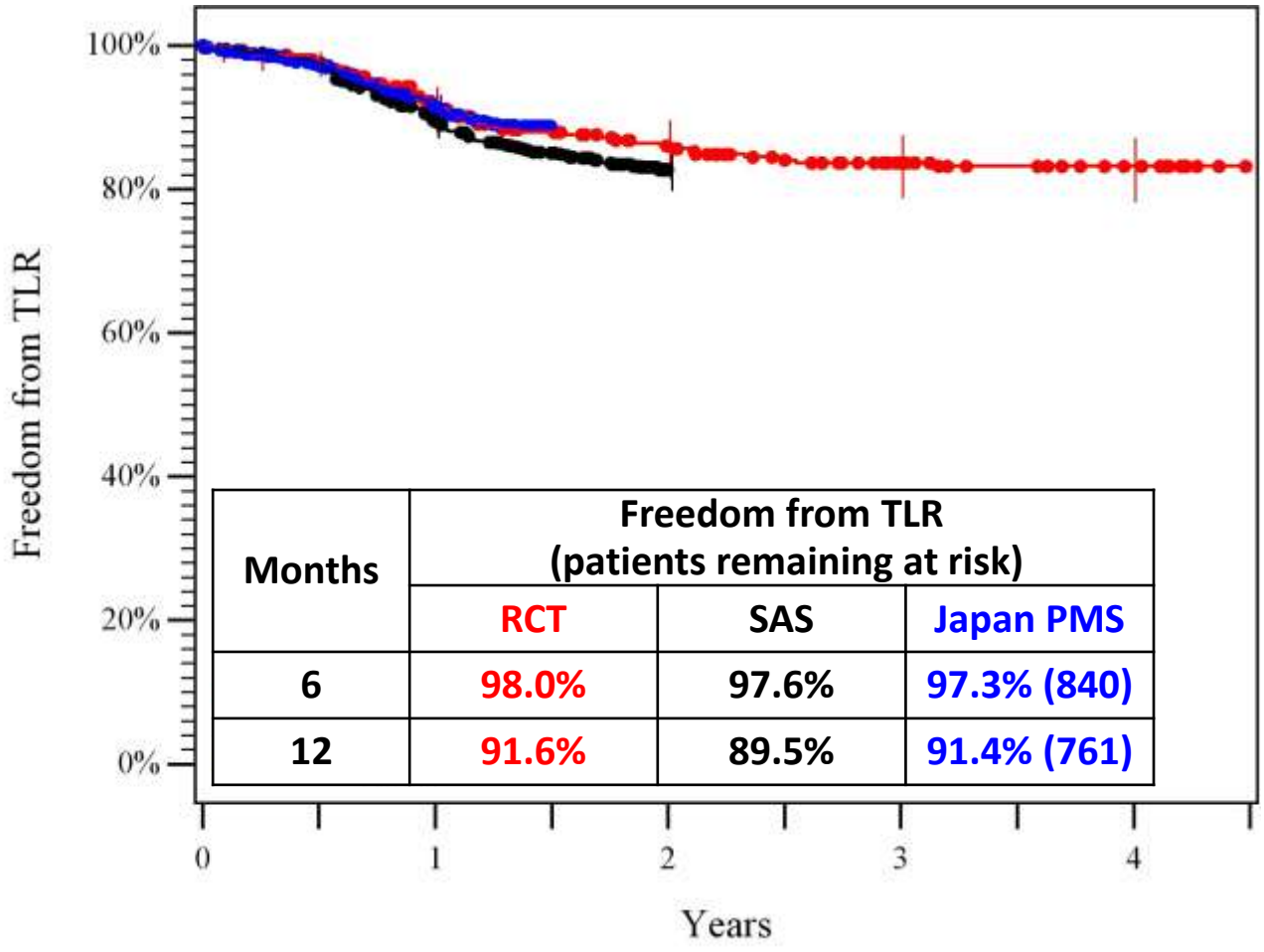
Freedom from TLR



Months	Freedom from TLR (patients remaining at risk)
	Japan PMS
6	97.3% (840)
12	91.4% (761)

Freedom from TLR rate is 91.4% through 12 months in the Japan PMS

Freedom from TLR



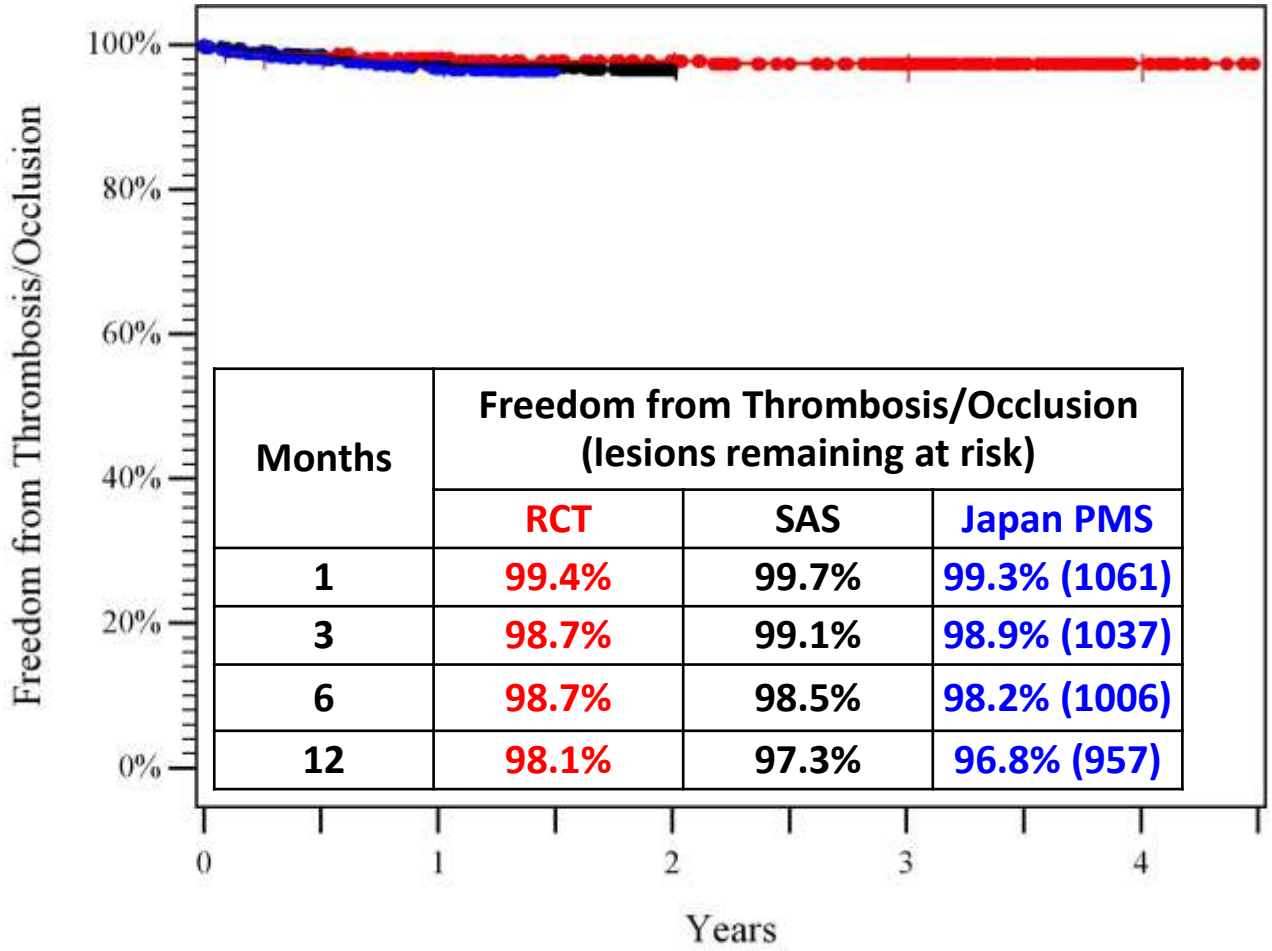
Months	Freedom from TLR (patients remaining at risk)		
	RCT	SAS	Japan PMS
6	98.0%	97.6%	97.3% (840)
12	91.6%	89.5%	91.4% (761)

TLR rate in the Japan PMS is similar to both pre-market studies

Thrombosis/Occlusion

- The clinical impact of peripheral stent thrombosis is substantially less than that of coronary stent thrombosis
- SFA stent thrombosis can be difficult to distinguish from total occlusion caused by restenosis
- Unlike the ARC classification for coronary stent thrombosis, there is not yet a standardized classification for stent thrombosis in the SFA
- The following results are site reported total occlusion of suspected thrombotic origin
  - Easier to distinguish from restenosis at earlier timepoints (e.g., < 30 days)
  - More difficult to distinguish from restenosis at later timepoints (e.g., > 90 days)

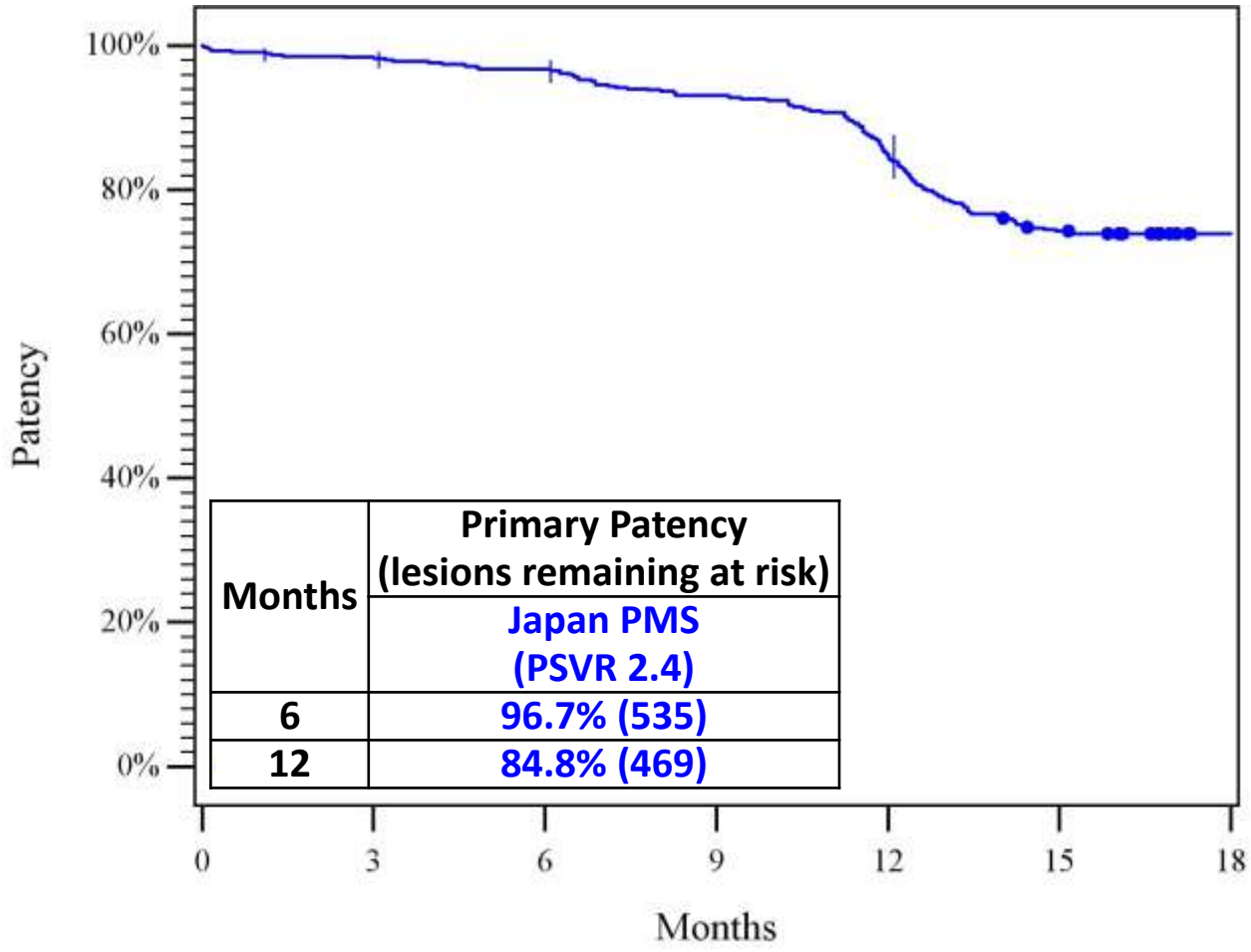
Freedom from Thrombosis/Occlusion



Months	Freedom from Thrombosis/Occlusion (lesions remaining at risk)		
	RCT	SAS	Japan PMS
1	99.4%	99.7%	99.3% (1061)
3	98.7%	99.1%	98.9% (1037)
6	98.7%	98.5%	98.2% (1006)
12	98.1%	97.3%	96.8% (957)

The 12 month thrombosis/occlusion rate of 3.2% from the Japan PMS is low and similar to Zilver PTX in RCT (1.9%) and SAS (2.7%), bare Zilver in RCT (3.6%), and BMS peri-procedural rates in literature (2-5%)

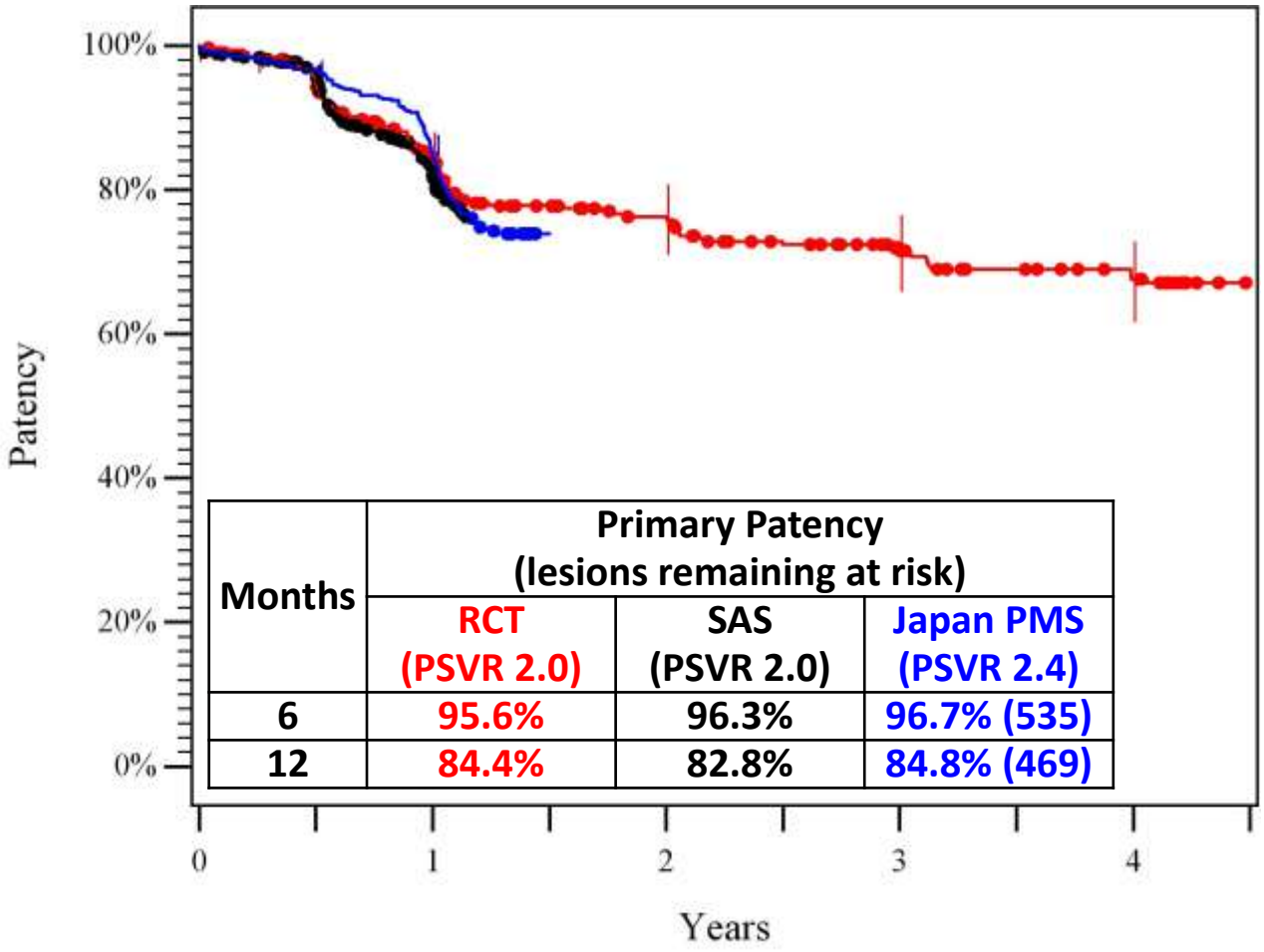
Primary Patency by Duplex Ultrasonography



Months	Primary Patency (lesions remaining at risk)
	Japan PMS (PSVR 2.4)
6	96.7% (535)
12	84.8% (469)

Primary patency rate is 84.8% through 12 months in the Japan PMS

Primary Patency by Duplex Ultrasonography



Months	Primary Patency (lesions remaining at risk)		
	RCT (PSVR 2.0)	SAS (PSVR 2.0)	Japan PMS (PSVR 2.4)
6	95.6%	96.3%	96.7% (535)
12	84.4%	82.8%	84.8% (469)

Primary patency rate in the Japan PMS is similar to both pre-market studies

Additional Analyses of PMS Study (and other) Data

- PMS Study
  - Stent Integrity

Stent Integrity through 12 months

- 1066 stents were evaluated by sites in Japan PMS
  - 17 total fractures (1.6%)

	RCT	SAS	Japan PMS
Fracture Rate	**0.9%**	**1.5%**	**1.6%**
Number of Stents Evaluated	**457**	**1889**	**1066**

<u>Low fracture rate</u>, not significantly greater than in pre-market studies despite more complex lesions (e.g., longer, more ISR, fewer patent runoff vessels)

Additional Analyses of PMS Study (and other) Data

- PMS Study
  - Stent Integrity

- Zilver PTX in complex lesions
  - PMS Study: More complex vs. less complex lesions

Patient Demographics and Comorbidities

	Zilver PTX RCT	JPMS RCT-like	JPMS non-RCT-like	*p*-value
Patients	236	324	583	-
Age (years)	68 ± 10	73 ± 9	74 ± 8	NS
Male	66%	73%	69%	NS
Diabetes	50%	58%	59%	NS
High cholesterol	76%	59%	62%	NS
Hypertension	89%	86%	85%	NS
Pulmonary disease	19%	8%	8%	NS
Renal disease[1]	10%	42%	45%	NS

[1] Of patients with renal disease in the Japan PMS, 82% were in renal failure defined as eGFR< 60 and/or dialysis

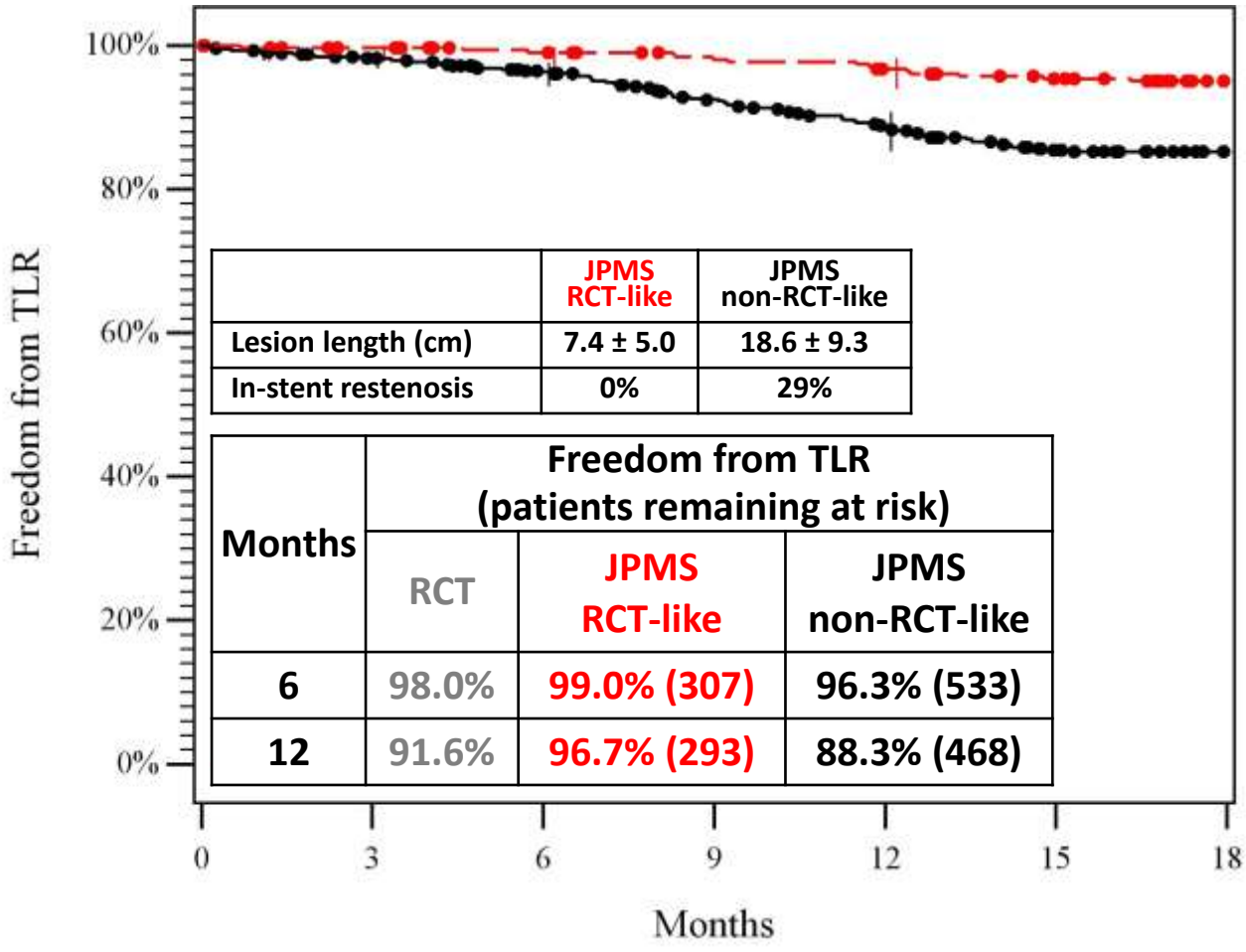
No significant differences between RCT-like and non-RCT-like patients

Baseline Lesion Characteristics

		Zilver PTX RCT	JPMS RCT-like	JPMS non-RCT-like	*p*-value
Lesions		247	378	703	-
Lesion length (cm)		6.6 ± 3.9	7.4 ± 5.0	18.6 ± 9.3	< 0.001
Diameter stenosis (%)		80 ± 17	89 ± 12	93 ± 9	< 0.001
Total occlusions		30%	28%	49%	< 0.001
In-stent restenosis		0%	0%	29%	< 0.001
Patent runoff vessels	**0**	0%	0%	10%	< 0.001
	1	22%	29%	33%	
	2	35%	36%	30%	
	3	42%	34%	27%	

Non-RCT-like lesions are significantly more complex than RCT-like lesions

Freedom from TLR



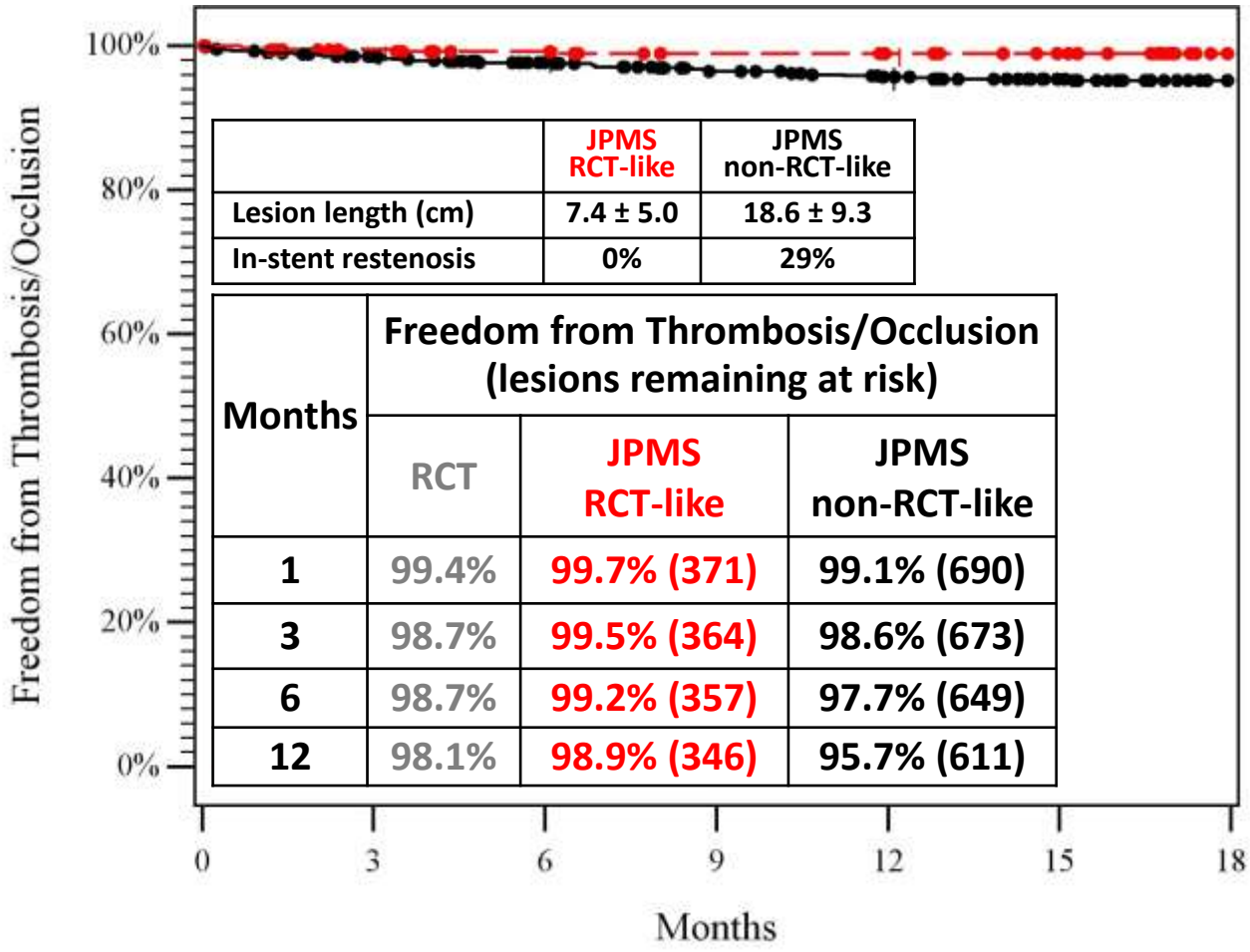
$p < 0.01$
log-rank

	JPMS RCT-like	JPMS non-RCT-like
Lesion length (cm)	7.4 ± 5.0	18.6 ± 9.3
In-stent restenosis	0%	29%

Months	Freedom from TLR (patients remaining at risk)		
	RCT	JPMS RCT-like	JPMS non-RCT-like
6	98.0%	99.0% (307)	96.3% (533)
12	91.6%	96.7% (293)	88.3% (468)

Freedom from TLR is excellent in complex lesions and slightly lower than in RCT-like lesions

Freedom from Thrombosis/Occlusion



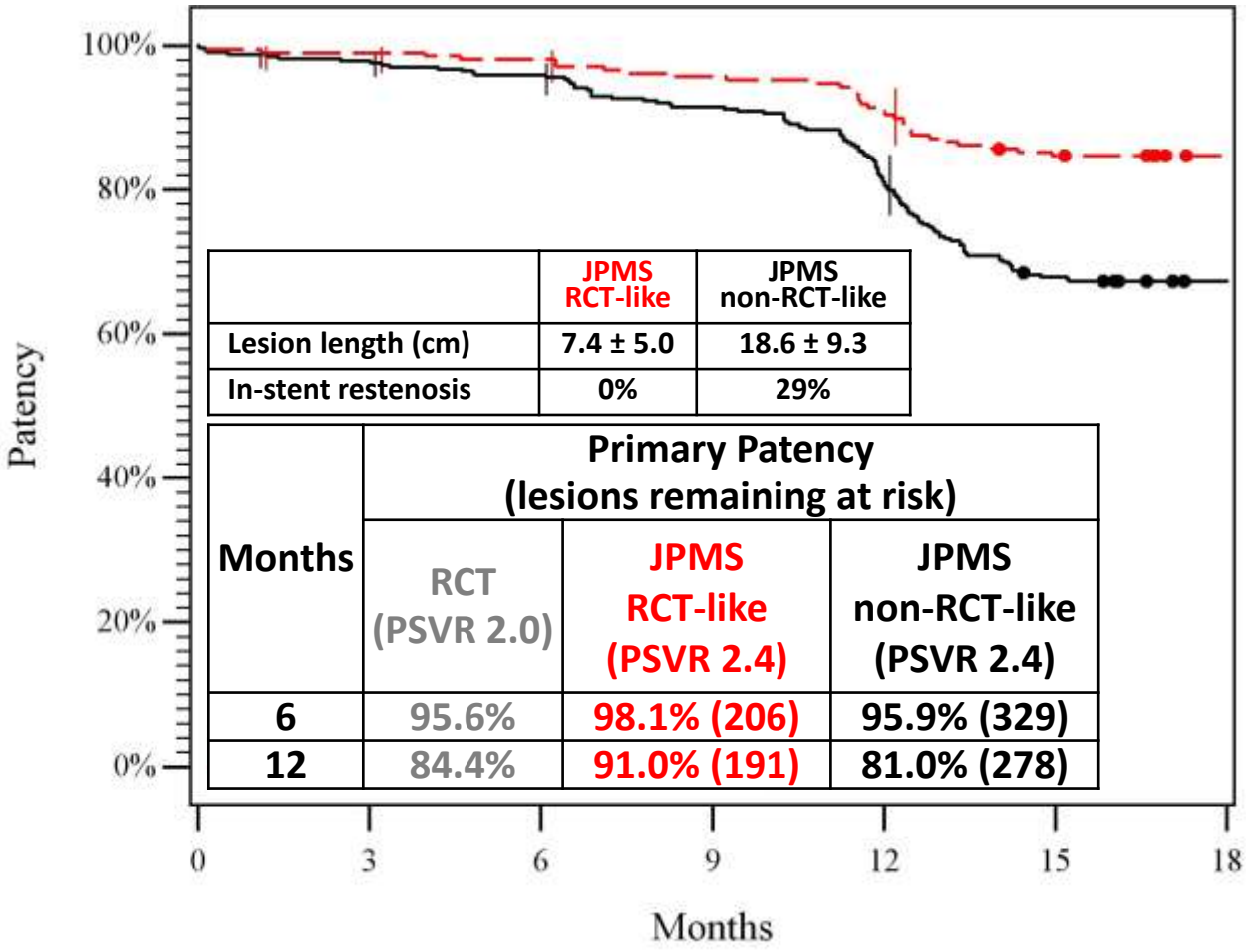
	JPMS RCT-like	JPMS non-RCT-like
Lesion length (cm)	7.4 ± 5.0	18.6 ± 9.3
In-stent restenosis	0%	29%

Months	Freedom from Thrombosis/Occlusion (lesions remaining at risk)		
	RCT	JPMS RCT-like	JPMS non-RCT-like
1	99.4%	99.7% (371)	99.1% (690)
3	98.7%	99.5% (364)	98.6% (673)
6	98.7%	99.2% (357)	97.7% (649)
12	98.1%	98.9% (346)	95.7% (611)

$p < 0.01$ log-rank

Thrombosis/occlusion rate in RCT-like subset is low and similar to that in RCT; the rate in complex lesions is similar to BMS peri-procedural rates in literature (2-5%)

Primary Patency by Duplex Ultrasonography



	JPMS RCT-like	JPMS non-RCT-like
Lesion length (cm)	7.4 ± 5.0	18.6 ± 9.3
In-stent restenosis	0%	29%

Months	Primary Patency (lesions remaining at risk)		
	RCT (PSVR 2.0)	JPMS RCT-like (PSVR 2.4)	JPMS non-RCT-like (PSVR 2.4)
6	95.6%	98.1% (206)	95.9% (329)
12	84.4%	91.0% (191)	81.0% (278)

$p < 0.01$
log-rank

Primary patency is excellent in complex lesions and slightly lower than in RCT-like lesions

Overall Conclusions from Japan PMS Study

- The PMS Study had a broad range of patient and lesion complexity, from straightforward to quite challenging
- Despite a high proportion of challenging cases, the 1-year PMS Study results were very good
  - No evidence of increased rates of thrombosis/occlusion or stent fracture in Japan vs. ROW
  - Low rate of TLR
  - Excellent patency at 12 months
- The PMS Study results are consistent with previous clinical studies of Zilver PTX
- Lessons learned in the PMS Study can further improve the great outcomes in treatment of SFA disease with the Zilver PTX drug-eluting stent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横井 良明
井上 直人
大木 隆生
ヒルトン福岡シーホーク
〒810-8650 福岡県福岡市 中央区地行浜2-2-3 TEL:092-844-8111
横井 宏佳
一般社団法人 Japan Endovascular Treatment Conference(JET)
中村 正人
南都 伸介
横井 宏佳
吉川 公彦
坂井 信幸