Cook Medical Statement to the MEDCAC Panel on Lower Extremity Peripheral Artery Disease

MEDCAC Panel Meeting
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Disclosures

- Research/Research Grants, Clinical Trial Support
  - W. L. Gore (major)
  - Cook Medical (major)
- Consulting Fees/Honoraria
  - W. L. Gore
  - Cook Medical
  - Abbott Vascular (minor)
  - Medtronic (minor)
- Equity Interests/Stock Option
  - TriVascular (minor)
  - Intact Vascular (minor)
  - Arsenal (minor)
  - 480 Medical (minor)
  - PQ Bypass (minor)
  - AneuMed (minor)
- Officer, Director, Board Member or other Fiduciary Role
  - VIVA Physicians Group
- Speaker's Bureau
  - None

MEDCAC convened to answer the following questions

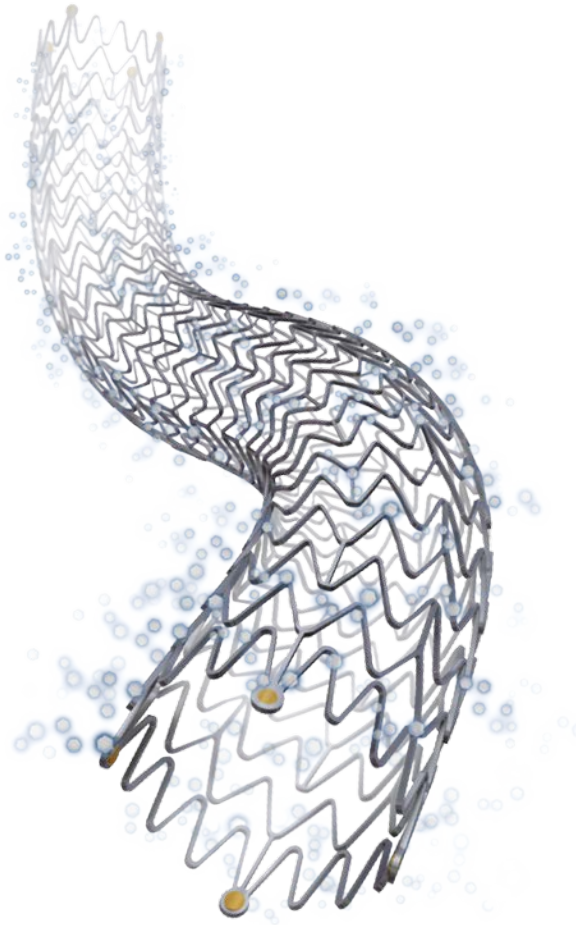
- For adults with:
    1. asymptomatic lower extremity PAD
    2. lower extremity intermittent claudication (IC)
    3. lower extremity critical limb ischemia (CLI)

  how confident are you that there is sufficient evidence for an intervention that improves:
    a. Immediate/near-term health outcomes?
    b. Long-term health outcomes?

Evidence from the Zilver PTX Drug-eluting Peripheral Stent clinical studies should provide confidence in this technology's ability to improve outcomes for patients with IC and CLI

Zilver PTX Drug-Eluting Peripheral Stent

- Scaffold plus drug
  - **Mechanical scaffold:** Zilver Flex® Stent Platform
  - **Drug therapy:** Paclitaxel only
    - 3 µg/mm^2 dose density
    - No polymer or binder
- Approved globally, including US, Japan, EU
- US Indication:
  - improving luminal diameter for the treatment of *de novo* or restenotic symptomatic lesions in native vascular disease of the above-the-knee femoropopliteal arteries having reference vessel diameter from 4 mm to 7 mm and total lesion lengths up to 140 mm per limb and 280 mm per patient.



Existing therapies have limitations

- Medical and/or exercise therapy
  - limited effectiveness, poor compliance
- PTA
  - acceptable for simple lesions, but limited effectiveness
- Drug-coated balloon
  - Successful pre-dilatation needed, limited long-term data
- Scoring/cutting balloon
  - limited data
- Atherectomy
  - possible increased complications, limited data
- Stent grafts
  - collateral coverage
- Bare metal stents
  - superior to PTA, still limited by restenosis
- Surgical bypass
  - attendant morbidity and mortality

Zilver PTX Clinical Program

<table>
<tr><th></th><th>Randomized Clinical Trial (RCT)</th><th>Single-Arm Study (SAS)[1]</th><th>Japan Post-Market Surveillance Study (PMS)[1]</th></tr>
<tr><td>Regions</td><td>US, Japan, Germany</td><td>EU, Korea, Canada</td><td>Japan</td></tr>
<tr><td>Patients (Age ≥ 65)</td><td>479
(US: 230
Japan + Germany: 63)</td><td>787
(504)</td><td>907
(771)</td></tr>
<tr><td rowspan="6">Key Study Criteria</td><td colspan="2">No significant untreated inflow tract stenosis</td><td rowspan="6">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>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</td></tr>
<tr><td>Excluded if serum creatinine > 2.0, renal failure, or dialysis</td><td>No exclusions</td></tr>
<tr><td>Follow-up</td><td>5 years (complete)</td><td>2 years (complete)</td><td>5 years (ongoing)</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>
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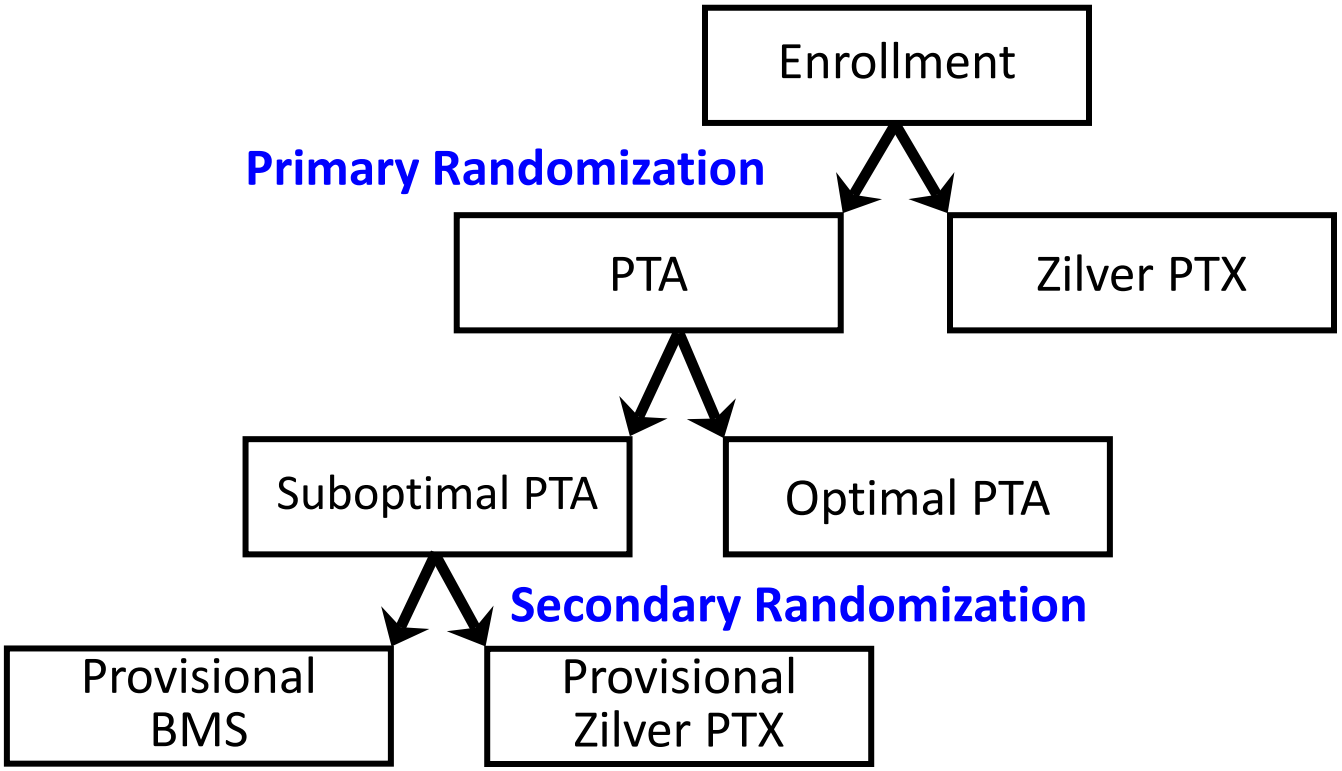
Increasingly complex patients and lesions

[1] These studies included patients with lesions > 140 mm in length and previously stented lesions that are outside of the approved indication for use in the US.

Zilver PTX RCT Study Design

- Pivotal study to obtain regulatory approval in the US and Japan
- 5-year follow-up complete



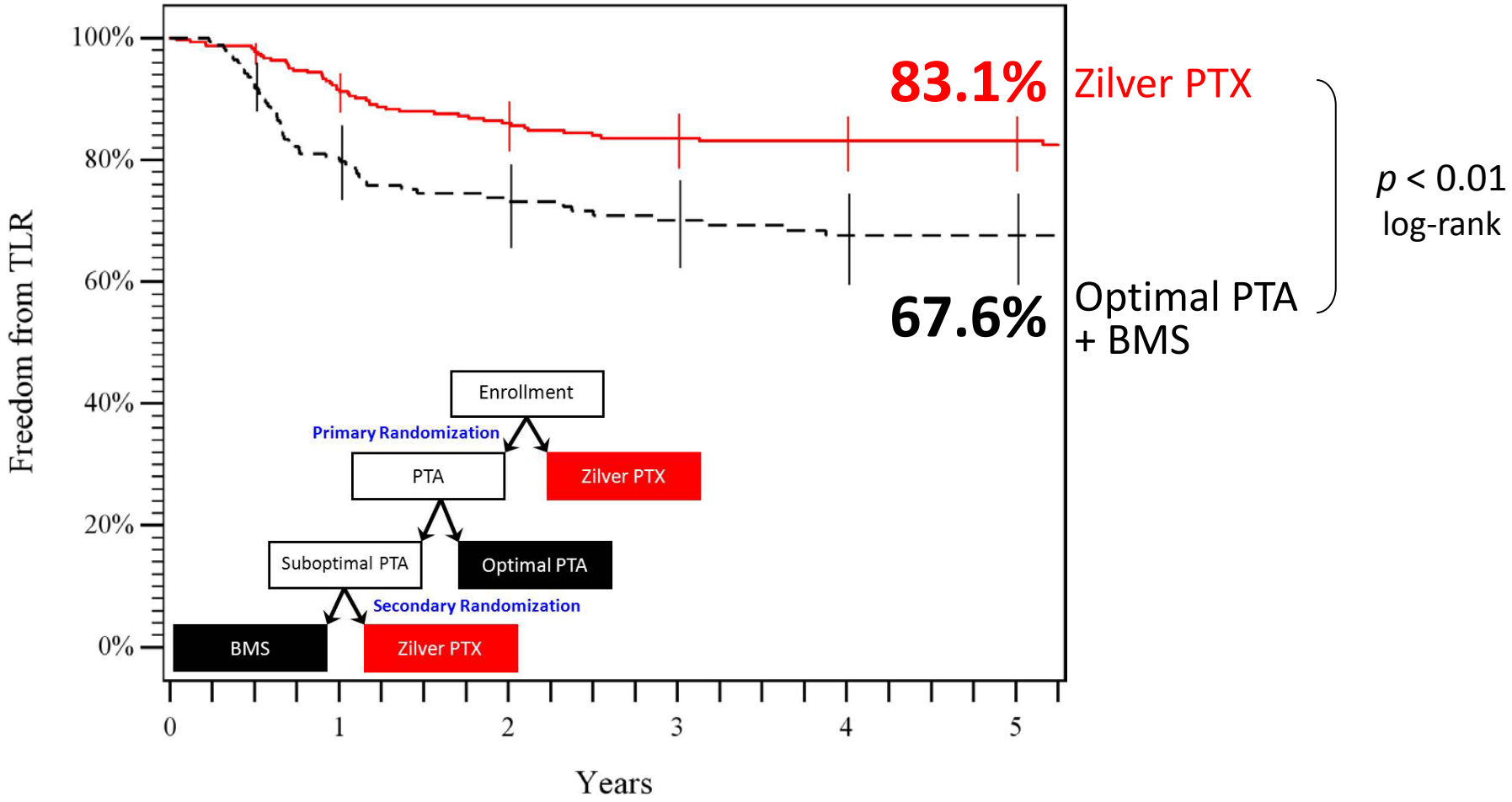
RCT: Demographics, Comorbidities, and Lesion Characteristics

	PTA	Zilver PTX	*p*-value
Patients	238	236	ns
Age (years) **Age ≥ 65 years**	68 ± 11 61%	68 ± 10 63%	
Male	64%	66%	
Diabetes	42%	50%	
High cholesterol	70%	76%	
Hypertension	82%	89%	0.02*
Past/current smoker	84%	86%	ns
Normal-to-normal lesion length (mm)	63 ± 41	66 ± 39	
Total occlusions	27%	33%	
Lesion Calcification: Little **Moderate** **Severe**	38% 22% 35%	26% 35% 37%	<0.01*
Rutherford class ≤ 3 (IC) **Rutherford class 4-6 (CLI)**	91.5% 8.5%	91.3% 8.7%	ns

* Statistically significant

5-year Freedom from TLR

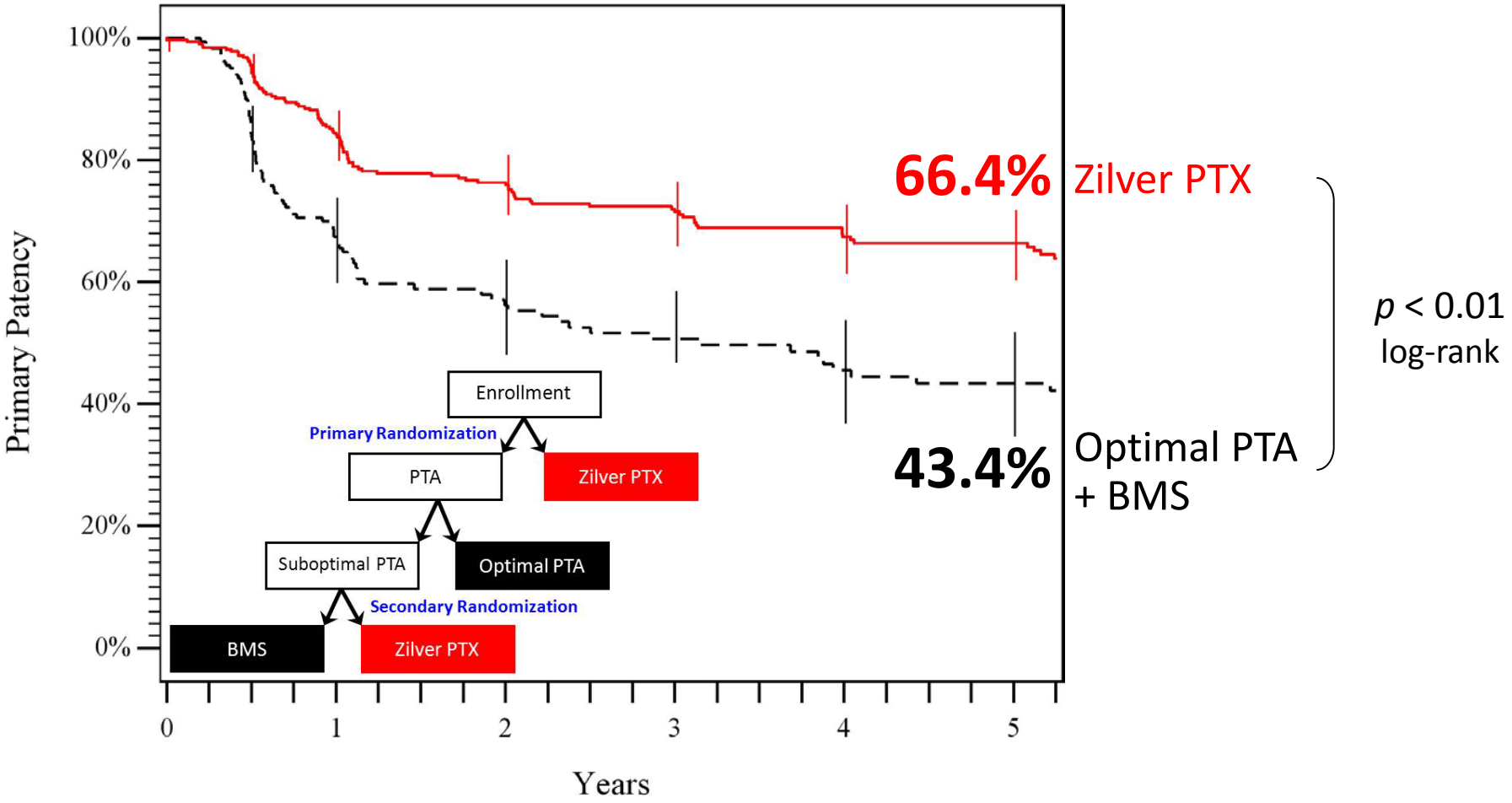
Zilver PTX vs. Standard Care



At 5 years, Zilver PTX demonstrates a 48% reduction in reintervention compared to standard care (optimal PTA + BMS)

5-year Primary Patency (PSVR < 2.0)

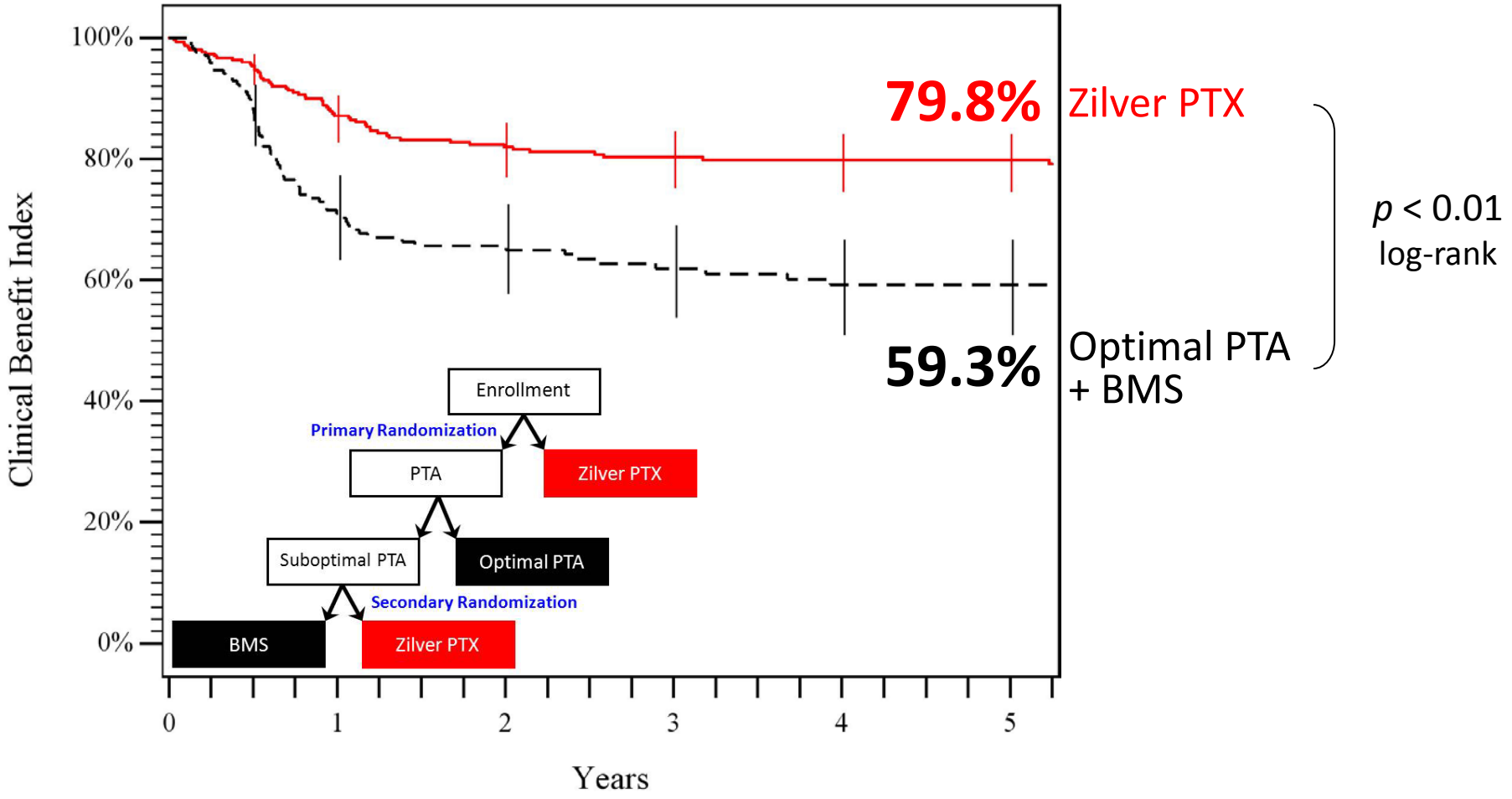
Zilver PTX vs. Standard Care



At 5 years, Zilver PTX demonstrates a 41% reduction in restenosis compared to standard care (optimal PTA + BMS)

5-year Clinical Benefit Index

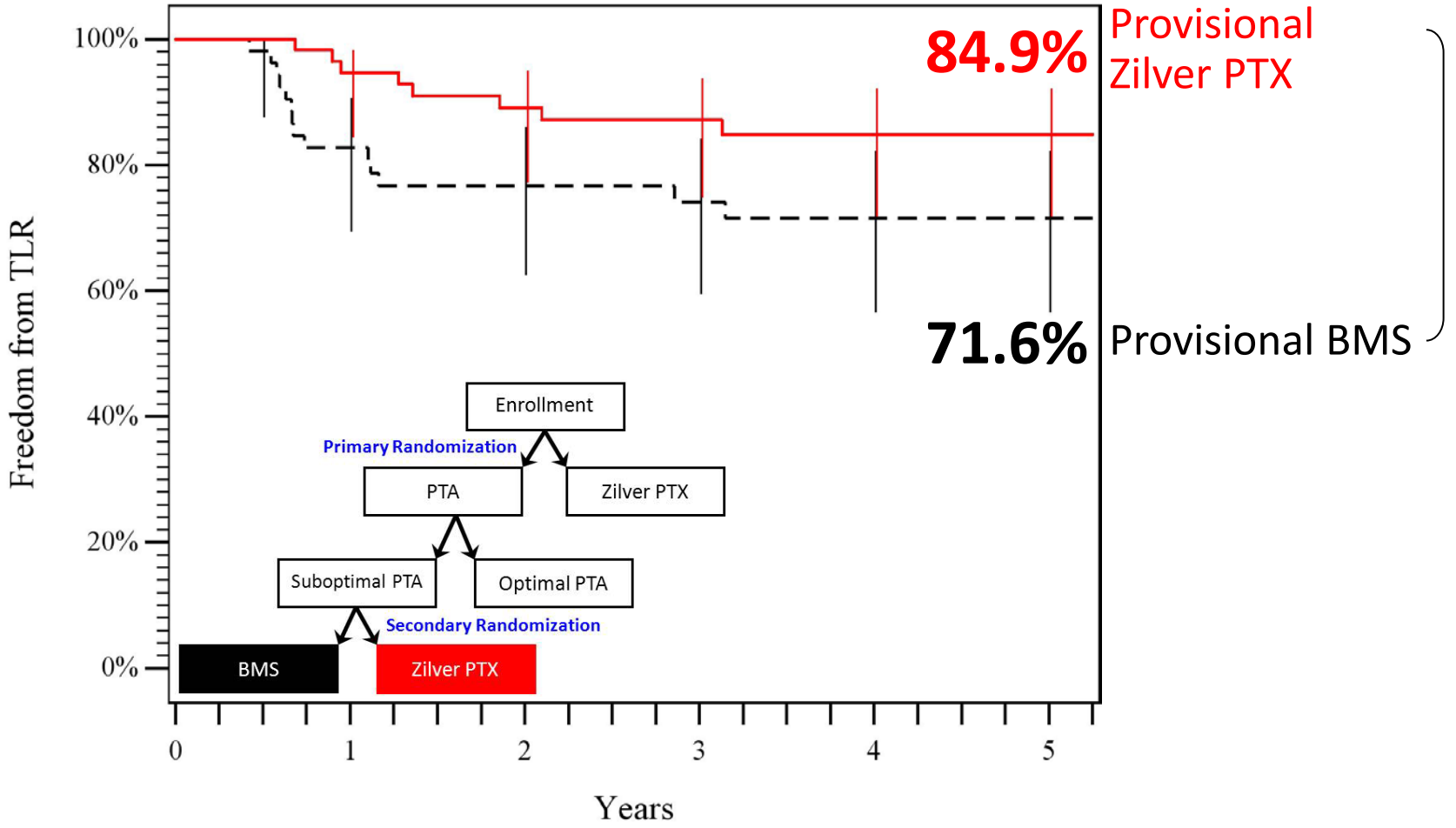
Zilver PTX vs. Standard Care



At 5 years, Zilver PTX has a superior clinical benefit index (rate of freedom from persistent or worsening claudication, rest pain, ulcer, or tissue loss)

5-year Freedom from TLR

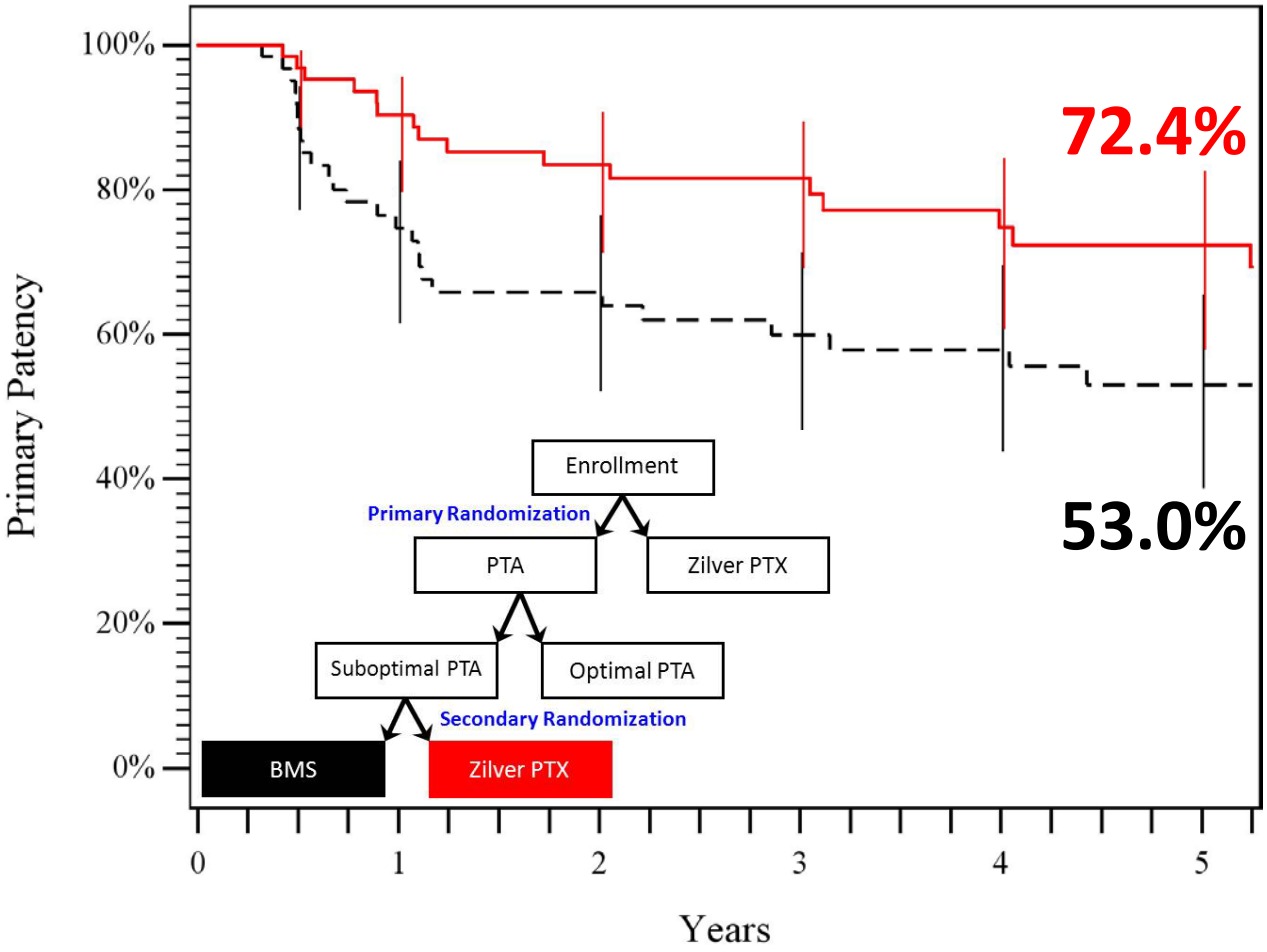
Provisional Zilver PTX vs. BMS



At 5 years, Zilver PTX demonstrates a 47% reduction in reintervention compared to BMS

5-year Primary Patency (PSVR < 2.0)

Provisional Zilver PTX vs. BMS

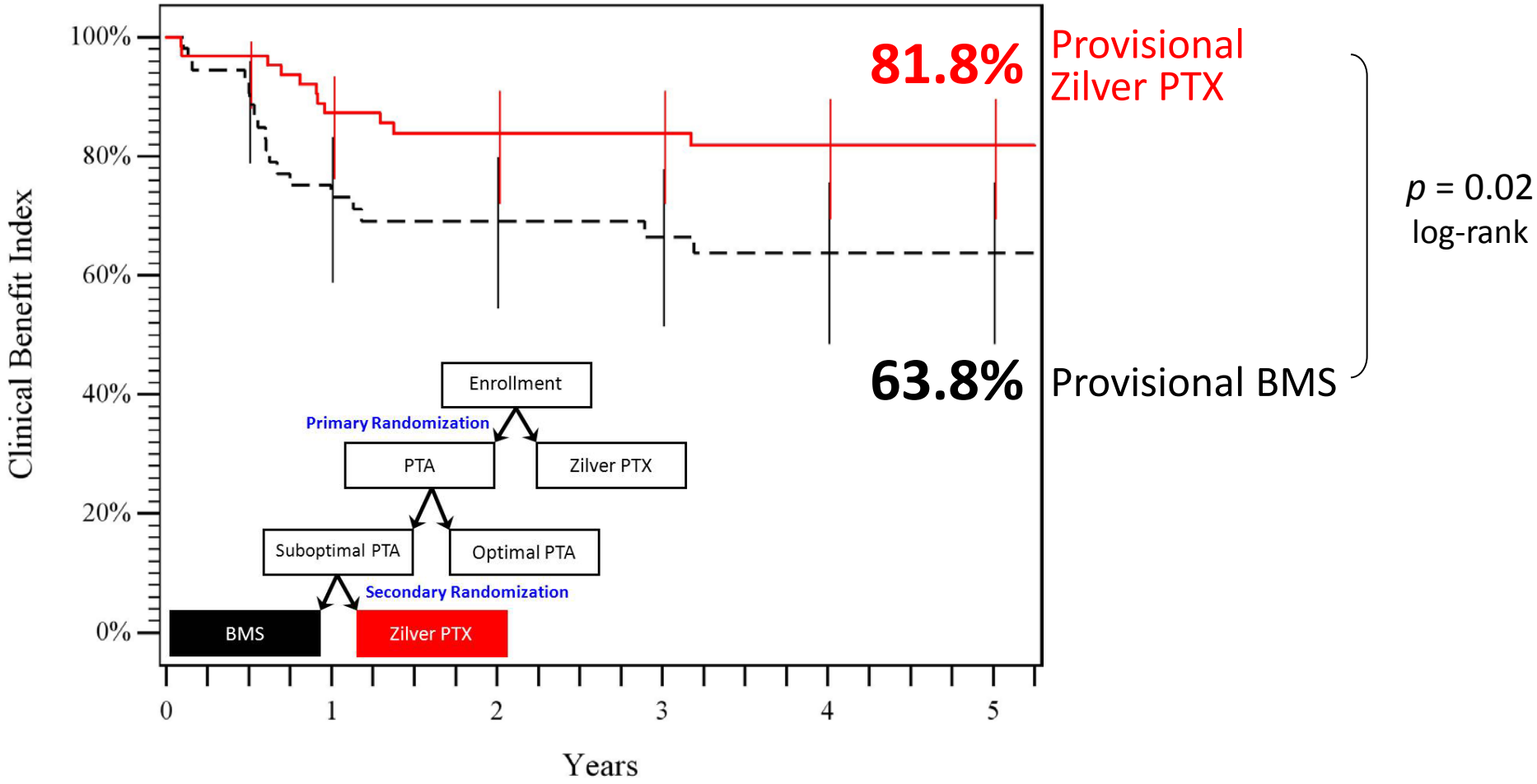


$p = 0.03$ log-rank

At 5 years, Zilver PTX demonstrates a 41% reduction in restenosis compared to BMS

5-year Clinical Benefit Index

Provisional Zilver PTX vs. BMS



At 5 years, Zilver PTX has a superior clinical benefit index (rate of freedom from persistent or worsening claudication, rest pain, ulcer, or tissue loss)

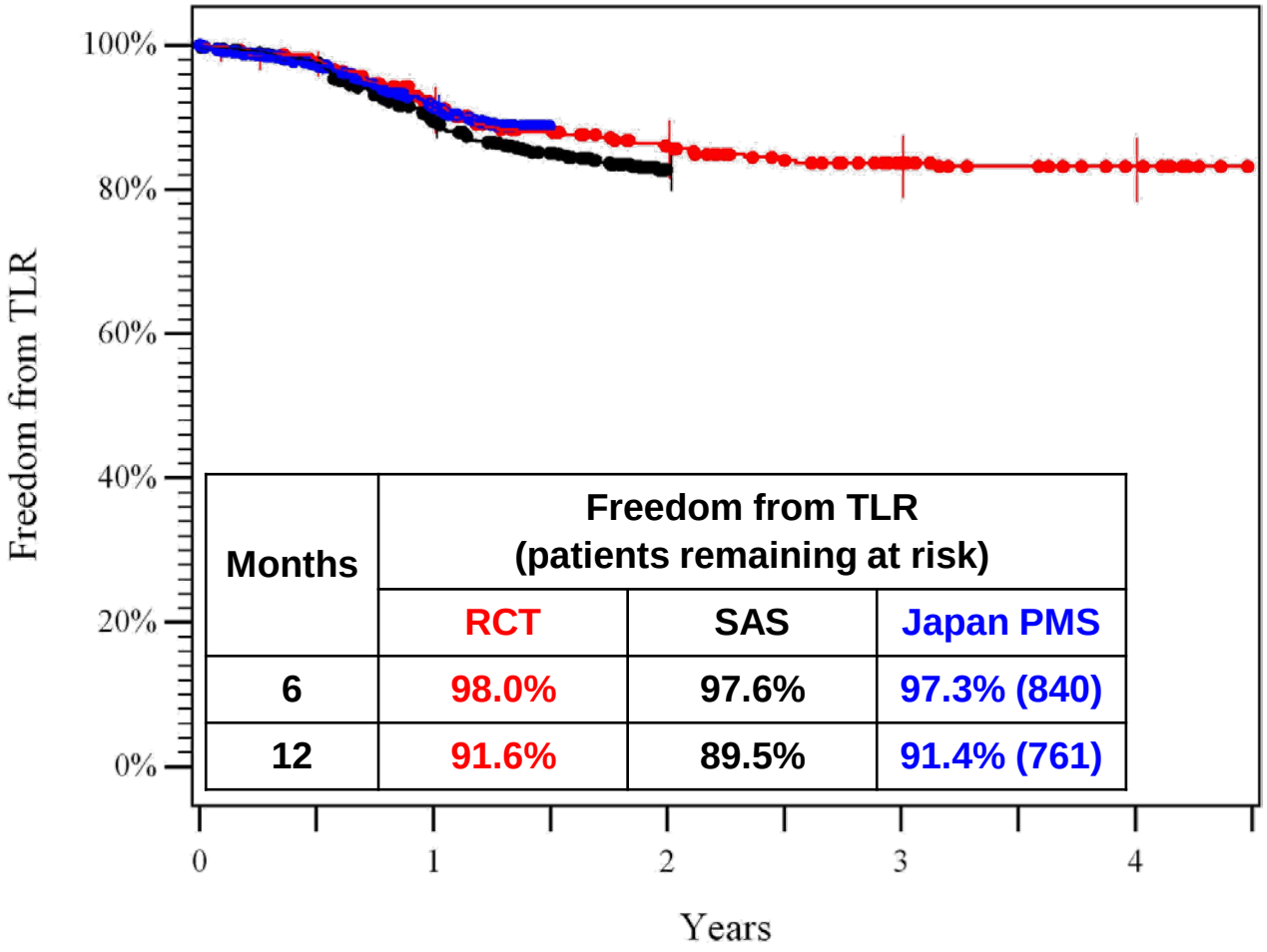
Overall Patient Demographics and Comorbidities

	RCT	SAS	Japan PMS
Patients	236	787	907
Age (years) Age ≥ 65	68 ± 10 63%	67 ± 10 64%	74 ± 9 85%
Diabetes	50%	36%	59%
High cholesterol	76%	58%	61%
Hypertension	89%	80%	85%
Renal disease	10%	11%	44%[1]
Lesion length (cm)	6.6 ± 3.9	10.0 ± 8.2	14.7 ± 9.7
Total occlusions	33%	38%	42%
In-stent restenosis (ISR)	0%	15%	19%
Rutherford 4-6 (CLI)[1]	9%	11%	20%

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

Although SAS and Japan PMS did not include Medicare enrollees, these studies represent a broad, real-world, patient population, with a large majority of patients ≥ 65 years of age

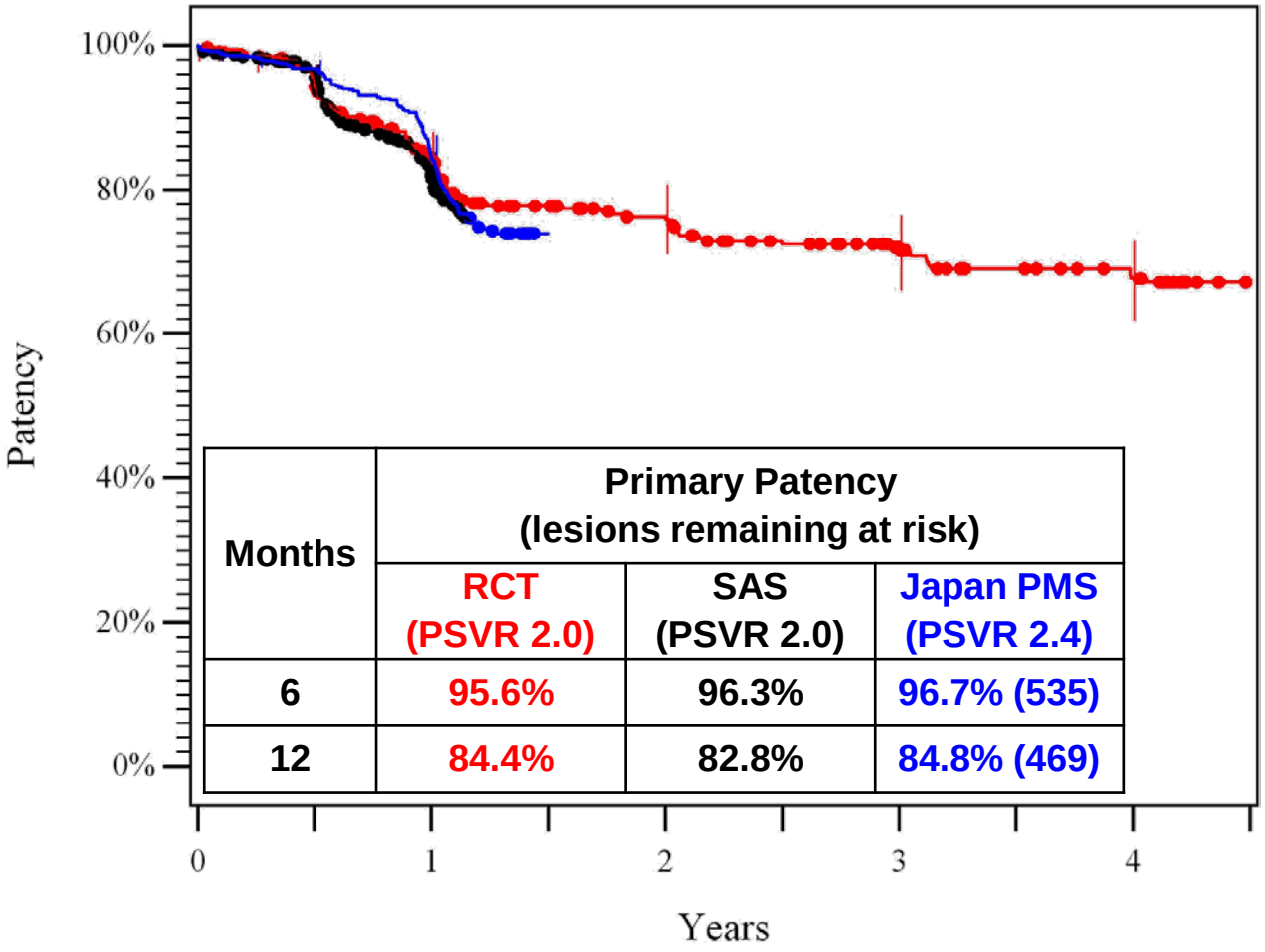
Overall Freedom from TLR



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)

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

Overall Primary Patency by Duplex Ultrasound



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

Conclusions

- Zilver PTX is the single most rigorously studied device for treatment of PAD of the SFA
  - Seven completed or ongoing clinical studies for regulatory submissions with >2400 patients
- 5-year data for Zilver PTX demonstrate superior clinical benefit and >40% reduction in reintervention and restenosis versus both standard care and bare metal stents through 5 years
- Consistently positive clinical results in the U.S. Medicare population and similar populations around the world, both in claudicants and CLI
- Acknowledged by CMS as resulting in “Substantial Clinical Improvement” when granted New Tech DRG Add-on status