Zilver PTX Global Data Analysis Highlights DES Benefits in Challenging Patient Populations

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Disclosure

Speaker name: **Michael Dake**

I have the following potential conflicts of interest to report:

- [x] Consulting
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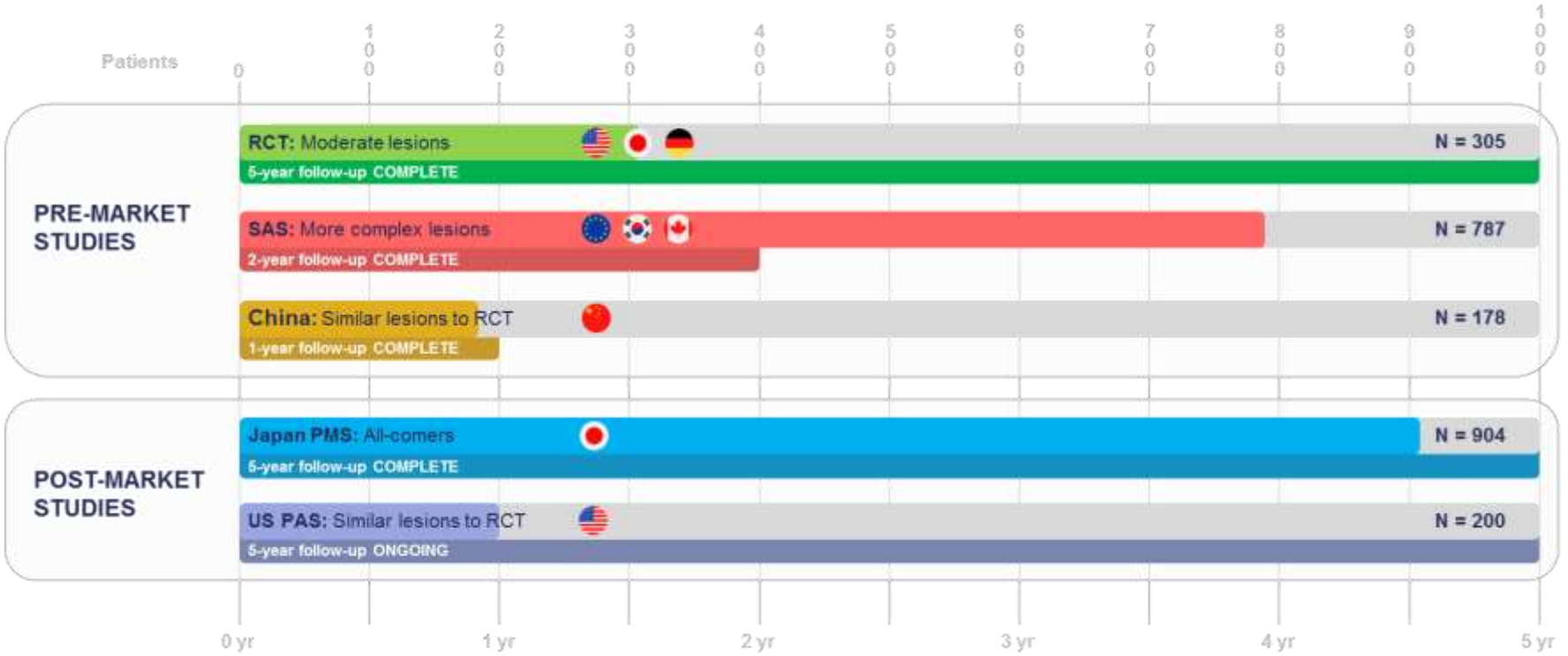
Global Clinical Program for Zilver PTX

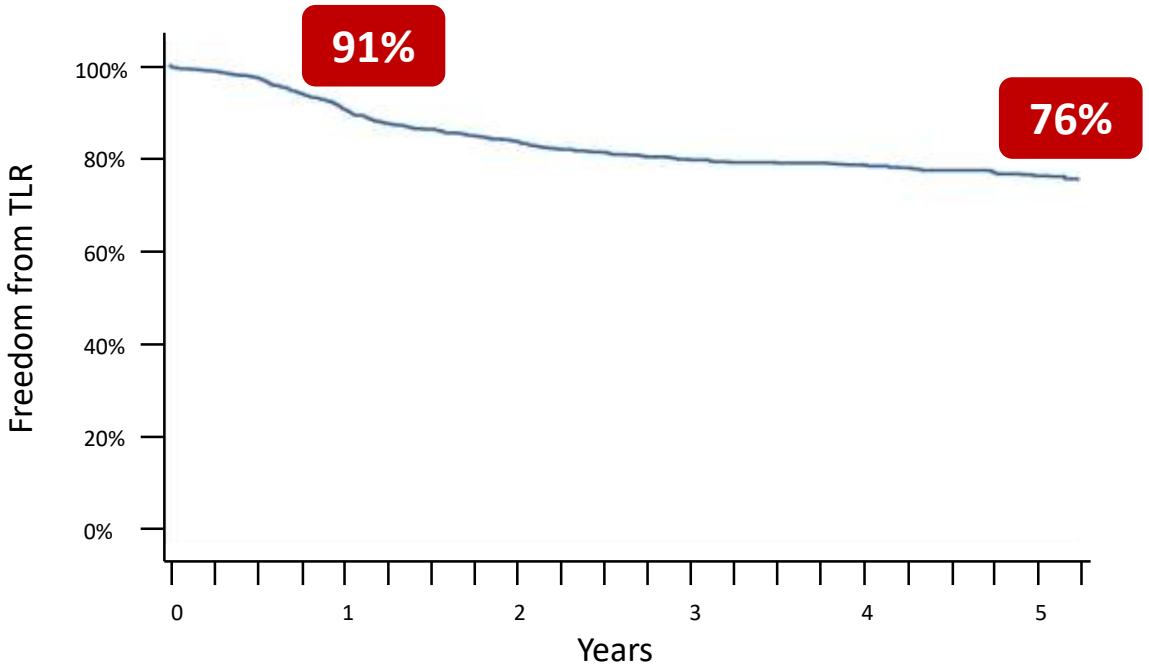


More than 2400 patients included in current Zilver PTX clinical program

Patient and Lesion Characteristics

Characteristic	Value
Patients / Lesions	2374 / 2686
Age (years)	69.5 ± 9.6
Male	71%
Diabetes	49%
Lesion length (cm)	11.1 ± 8.7
Total occlusions	36%
In-stent restenosis	13%
Severe calcification	17%
Rutherford 4-6 (CLI)	15%
No patent runoff vessels	2%

Freedom from TLR Based on Global Data Analysis



- High rate of freedom from TLR
- Nearly 2400 patients
- 5-year results

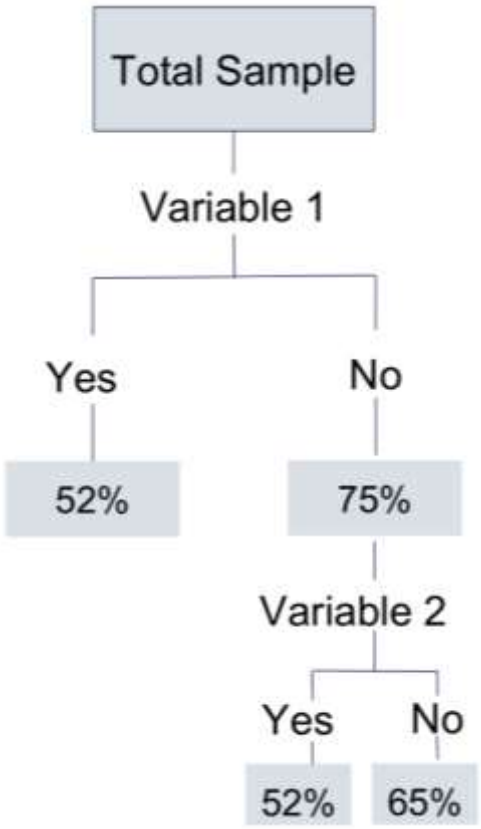
What patient and lesion factors impact TLR rates?

What Patient and Lesion Factors Impact TLR Rates?

Patient Factors	Lesion Factors
Male vs. Female	Lesion length (≤15cm vs. >15cm)
Diabetes	Total occlusion
Smoking status	In-stent restenosis
Rutherford (0-4 vs. 5-6)	Calcification (none-moderate vs. severe)
Patent runoff vessels (0-1 vs. 2+)	Reference vessel diameter (<5mm vs. ≥5mm)
	Stent diameter
	Stent oversizing (≤30% vs. >30%)

Step 1:
Classification Tree Analysis

- Ranks variables based on impact on TLR
  - Most impactful variable selected at each bifurcation
  - Identifies overall most and least impactful variables
- Provides input to other predictive models



Step 1:
Classification Tree Analysis

- Ranked factors based on impact on TLR and identified most and least impactful factors

Most Impact on TLR	Moderate Impact on TLR	Minimal Impact on TLR
In-stent restenosis	Stent diameter	Rutherford
Lesion length	Smoking status	Male vs. Female
Reference vessel diameter	Patent runoff vessels	Calcification
Total occlusion	Stent oversizing	Diabetes

Breiman, L. Machine Learning. 2001. 45:5-32. http://doi.org/10.1023/A:1010933404324

Step 2:
Cox Proportional Hazards Model

- Classification Tree ranked factors for impact on TLR
  - Most impact
  - Moderate impact
  - Minimal impact
- All factors from Classification Tree were included in Cox Proportional Hazards model
  - 2-, 3-, and 4-way interactions were tested for factors with the most impact
- Cox model confirmed the impact of the various patient and lesion factors on TLR
  - Identified significant interactions between some factors

Factors with Most Impact on TLR

Factors with Most Impact on TLR from Classification Tree	p-value[1]	Interpretation
In-stent restenosis	< 0.001	• ISR is significant • Lesion length is significant in non-ISR lesions
Lesion length	0.34	
ISR and lesion length	**0.013**	
Total occlusion	< 0.001	• Occlusion is significant • RVD is significant in non-CTO • Larger vessels (≥5 mm) more likely to be free from TLR
Reference vessel diameter	0.33	
Occlusion and RVD	**0.037**	

[1] joint p-value; not univariate

Factors with Moderate Impact on TLR

Factors with Moderate Impact on TLR from Classification Tree	p-value[1]	Interpretation
Stent oversizing	0.043	• Oversizing (>30%) may impact TLR
Smoking status	0.64	• No significant impact on TLR
Patent runoff vessels	0.91	
Stent diameter	0.12	

[1] joint p-value; not univariate

Factors with Minimal Impact on TLR

Factors with Minimal Impact on TLR from Classification Tree	p-value[1]	Interpretation
Rutherford	0.065	• No significant impact on TLR
Male vs. Female	0.68	
Calcification	0.98	
Diabetes	0.22	

[1] joint p-value; not univariate

For Zilver PTX patients, Rutherford, sex, calcification, and diabetes did NOT have significant impact on TLR

Conclusions from Zilver PTX Global Data Analysis

- Nearly 2400 patients from 5 studies across 16 countries
  - Including ISR, long lesions, no patent runoff vessels
- High freedom from TLR sustained through 5 years
- Consistency between Classification Tree and Cox model results
- ISR and total occlusions identified as significant factors for TLR
  - Lesion length is significant in non-ISR lesions
  - RVD is significant in non-CTO lesions
- For Zilver PTX patients, sex, calcification, and diabetes did NOT have significant impact on TLR

Long-term Safety Information on Paclitaxel Eluting Stents: Insights from the Zilver PTX Programme

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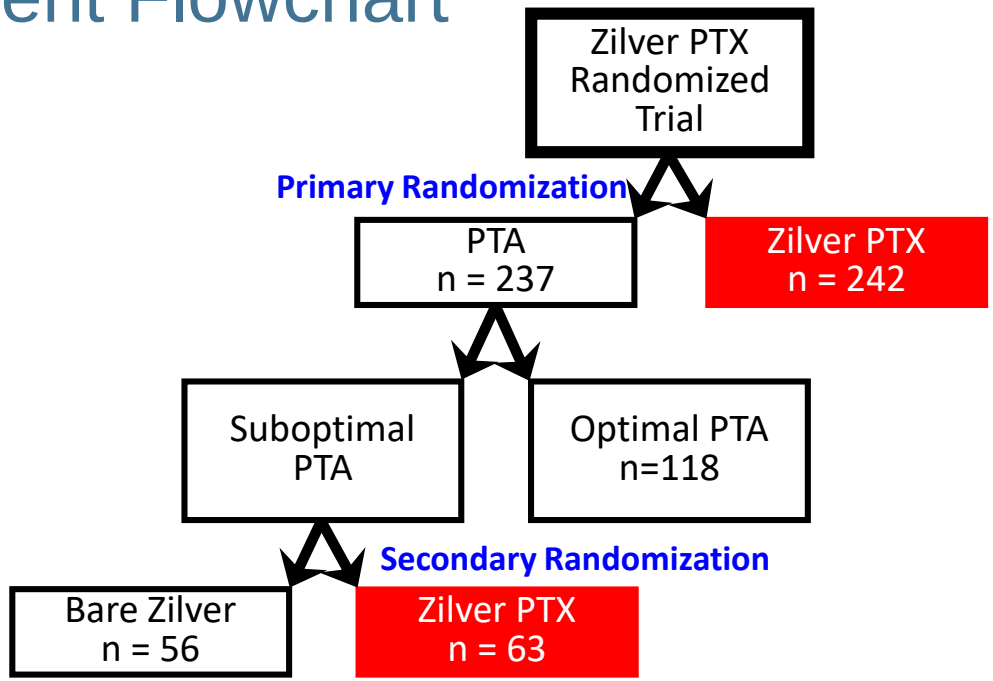
Zilver PTX Key Points

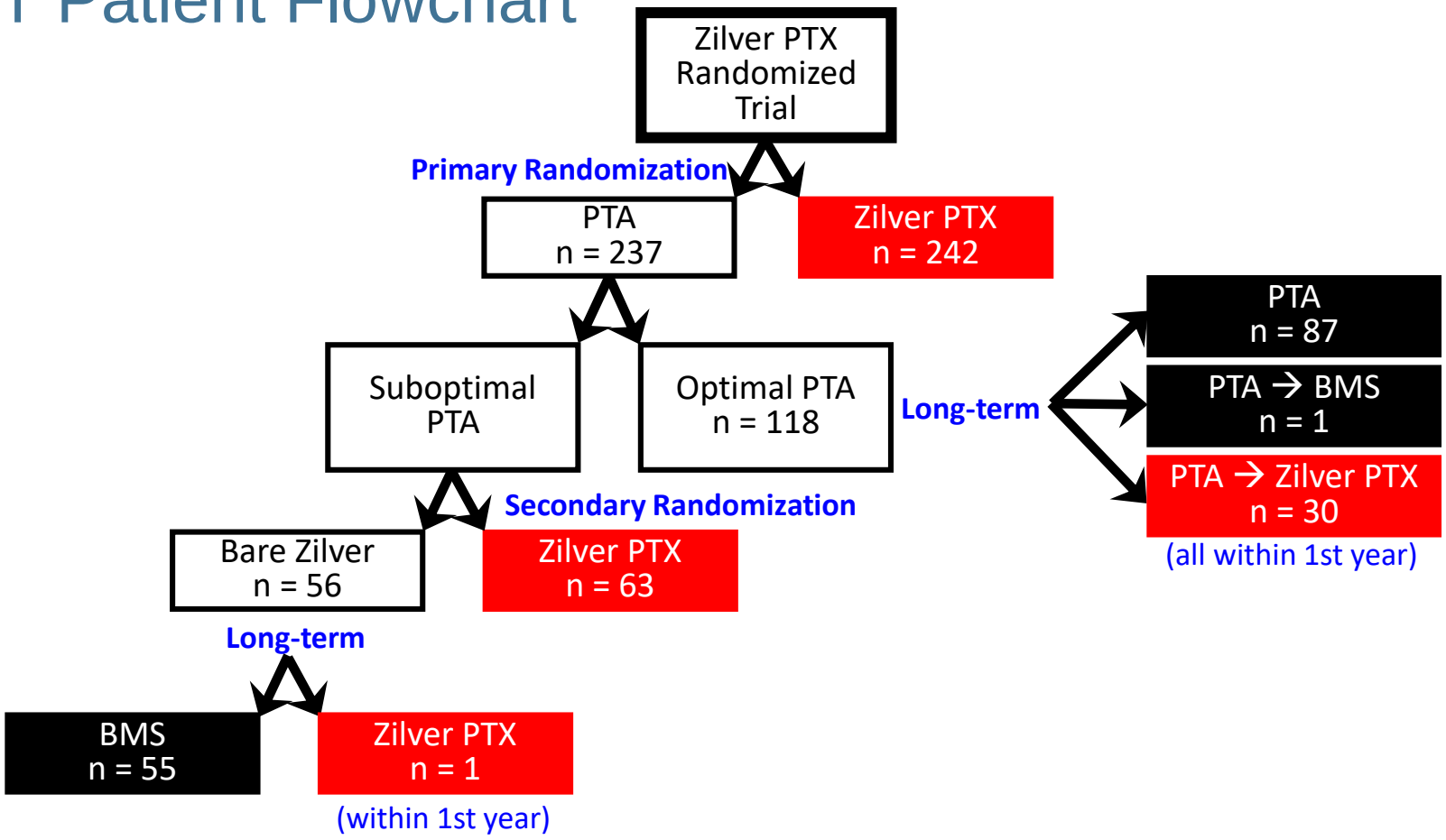
- Data used by Katsanos, et al. did not identify all patients that were treated with Zilver PTX
  - Patient-level data were not used in the analysis
  - Some patients treated with Zilver PTX were included in the control arm of the analysis
- Patient level analysis demonstrates no difference in mortality rate for Zilver PTX compared to PTA/BMS
  - Causes of death for Zilver PTX are similar to PTA/BMS

RCT Patient Flowchart

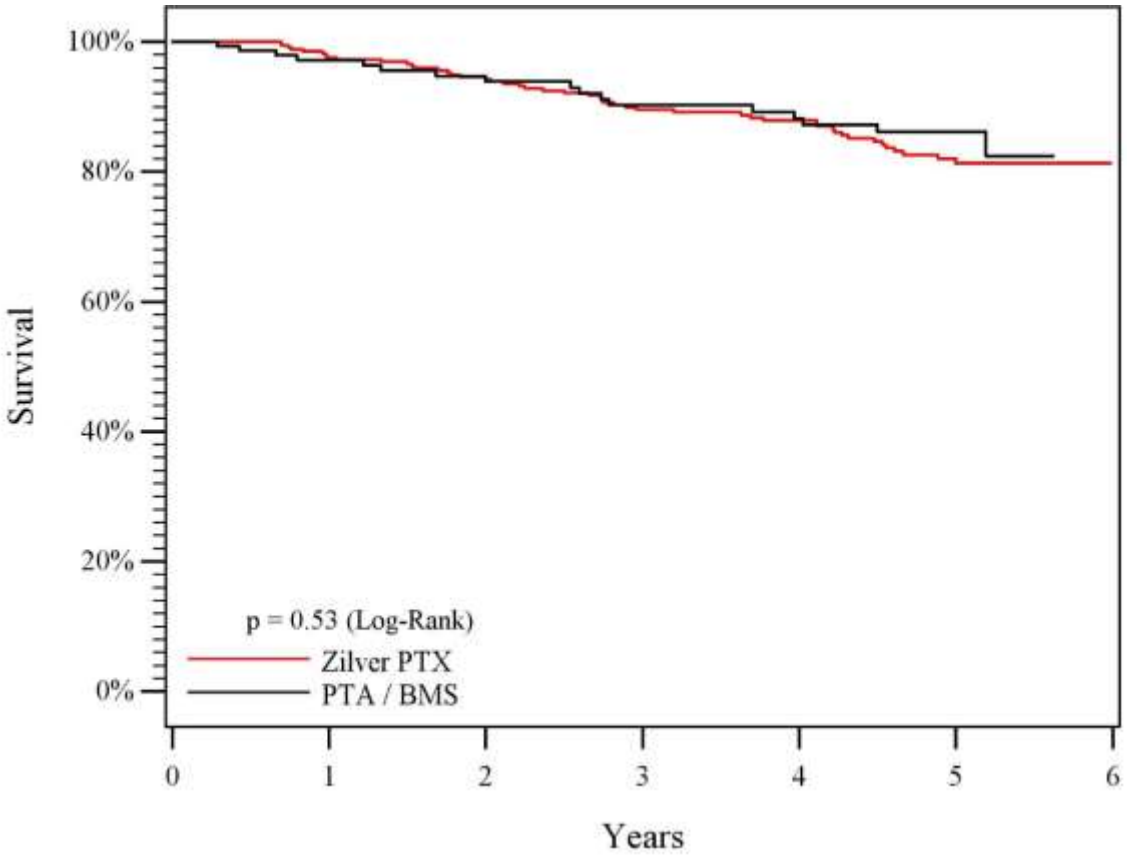


The RCT study design allowed optimal PTA patients requiring reintervention within the first year post-procedure to cross over to treatment with the Zilver PTX stent

RCT Patient Flowchart



Zilver PTX RCT Final 5-year Mortality Analysis



PTA / BMS	ZILVER PTX
n = 143	n = 336
Died = 17	Died = 48
KM = 17.6%	KM = 18.7%

p = 0.53

No significant difference between Zilver PTX and PTA / BMS

Zilver PTX Covariate Analysis

- Cox proportional hazards model
- Included comorbidities that may be related to mortality as well as other factors of interest
- No significant difference between Zilver PTX and PTA / BMS

Covariate	Multivariate p-value
Age	**0.0002**
PTX vs. PTA/BMS	**0.54**
Hypertension	0.46
Hypercholesterolemia	0.63
Pulmonary disease	0.58
Previous MI	0.94
Diabetes	0.11
Gender	0.47
Carotid disease	0.14
Congestive heart failure	0.08
Cardiac arrhythmia	0.21
Claudication/CLI	0.15
Country	0.56
Smoking	0.17
Lesion length	0.12

Zilver PTX Dose Analysis

5-year Mortality Rate				
Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
11.5%	13.6%	13.4%	20.0%	13.2%
p=0.72				

~0.3 mg **Increasing Total Paclitaxel Dose** **~3 mg**

No impact of Zilver PTX paclitaxel dose on mortality rate

The amount of paclitaxel on a Zilver PTX stent is approximately 10% to 20% of the amount on a DCB for the same device size and dose density

Causes of Death Through 5 Years – RCT

Cause	RCT – PTX (n=336)	RCT – PTA / BMS (n=143)
Cardiovascular	4.8%	5.6%
Cancer	4.8%	1.4%
Pulmonary	1.8%	1.4%
Stroke	0.6%	0.7%
Trauma	0.0%	1.4%
GI	0.3%	0.0%
Multiple/Unknown	2.1%	1.4%

No significant difference in cause of death, p=0.56

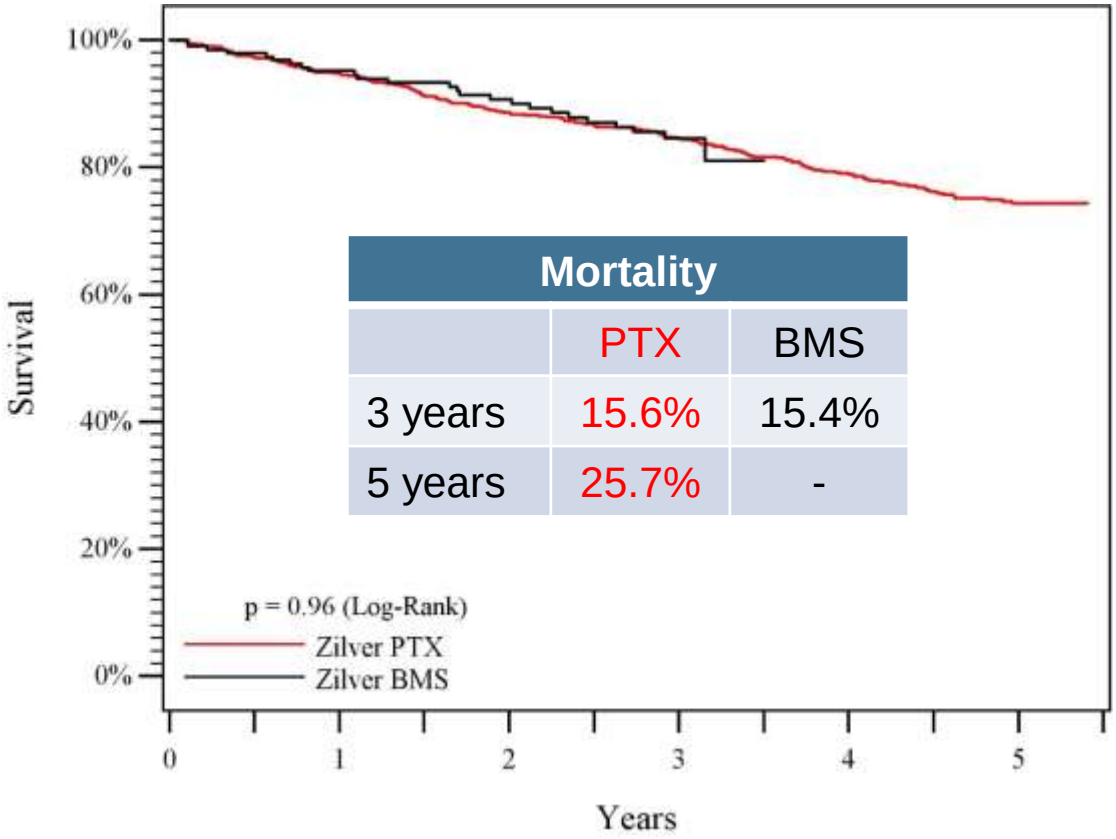
Causes of Death Through 5 Years – RCT and BMS

Cause	RCT – PTX (n=336)	RCT – PTA / BMS (n=143)	Zilver BMS Study* (n=110)
Cardiovascular	4.8%	5.6%	4.5%
Cancer	4.8%	1.4%	6.4%
Pulmonary	1.8%	1.4%	1.8%
Stroke	0.6%	0.7%	0
Trauma	0.0%	1.4%	0
GI	0.3%	0.0%	0.9%
Multiple/Unknown	2.1%	1.4%	0.9%

No increased rate of cardiovascular, cancer, or other cause of death for Zilver PTX compared to PTA or BMS

*The Zilver BMS study enrolled 110 patients with femoropopliteal artery disease for 5-year follow-up

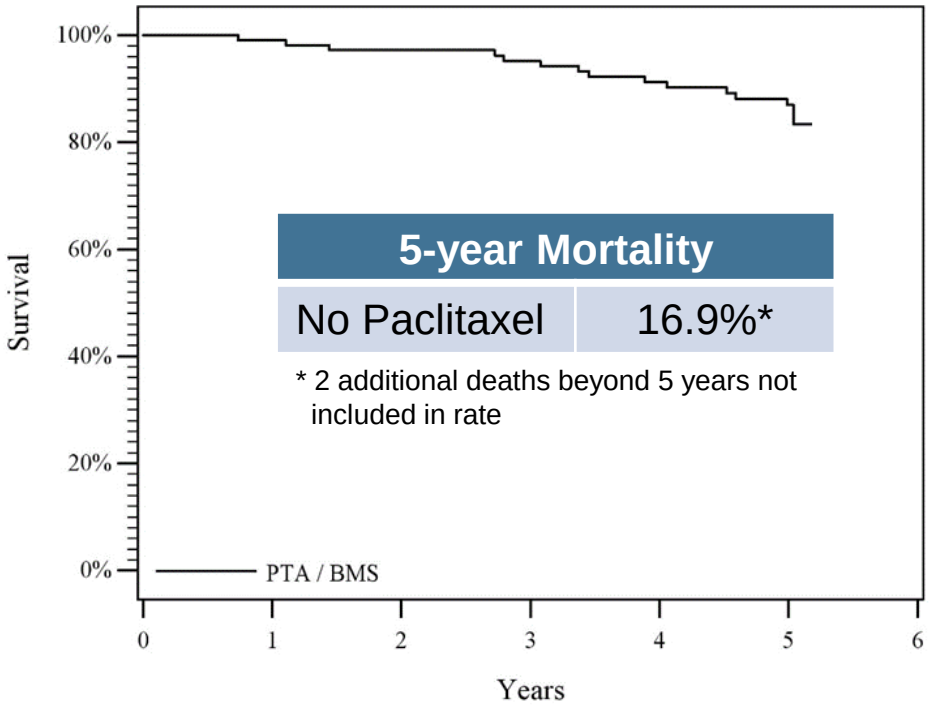
Additional Zilver PTX Studies – Japan PMS



Mortality		
	PTX	BMS
3 years	15.6%	15.4%
5 years	25.7%	-

- 904 Zilver PTX patients
  - 5-year follow-up
  - No exclusion criteria; challenging patient population (21% CLI)
- 208 BMS patients
  - 3-year follow-up
- No significant difference in mortality (p=0.96)

Additional Bare Metal Stent Study



5-year Mortality	
No Paclitaxel	16.9%*

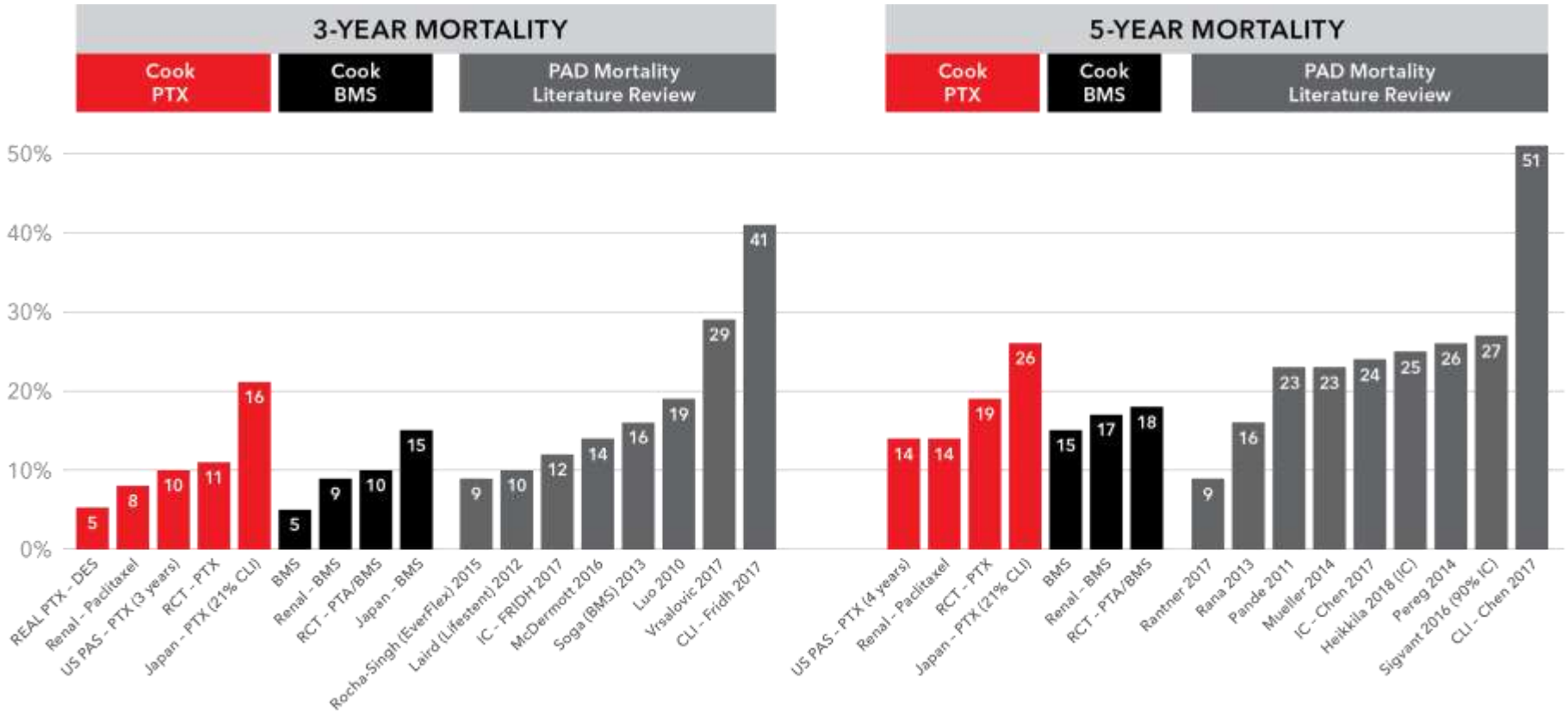
* 2 additional deaths beyond 5 years not included in rate

- 110 Zilver BMS patients
- 5-year follow-up
- Comparable mortality to Zilver PTX studies

Mortality Rates from Literature

- A literature review of mortality rates for PAD patients indicates:
  - 3-year mortality rates range from 9% to 29% (up to 41% for CLI patients)
  - 5-year mortality rates range from 9% to 27% (up to 51% for CLI patients)

Summary of Mortality Rates



Conclusions

- Conclusion of Katsanos, et al. was not based on patient-level data
- Patient-level analysis of RCT data shows no increased long-term mortality risk with Zilver PTX compared to PTA and BMS
  - Covariate analysis supports no significant difference
  - No impact of Zilver PTX paclitaxel dose on mortality rate
- Analysis of all global Zilver PTX data confirms RCT findings
- Mortality rates for the Zilver PTX stent are consistent with rates reported in literature for PAD patients

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