Zilver PTX Drug-Eluting Stent Mortality Analysis

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Recent Correction to 5-year Zilver PTX Publication

- Katsanos et al. meta-analysis published December 6, 2018 in JAHA
- Data reviewed and errors identified in 5-year Zilver PTX publication
  - Incorrect patient flow diagram submitted during final publication process
  - Mortality numbers transposed in overall primary randomization comparison
- Corrections submitted to Circulation on December 18, 2018 and published on February 19, 2019
- The incorrect numbers have only appeared in the 5-year Zilver PTX publication
  - All global regulatory submissions and presentations have used the correct numbers

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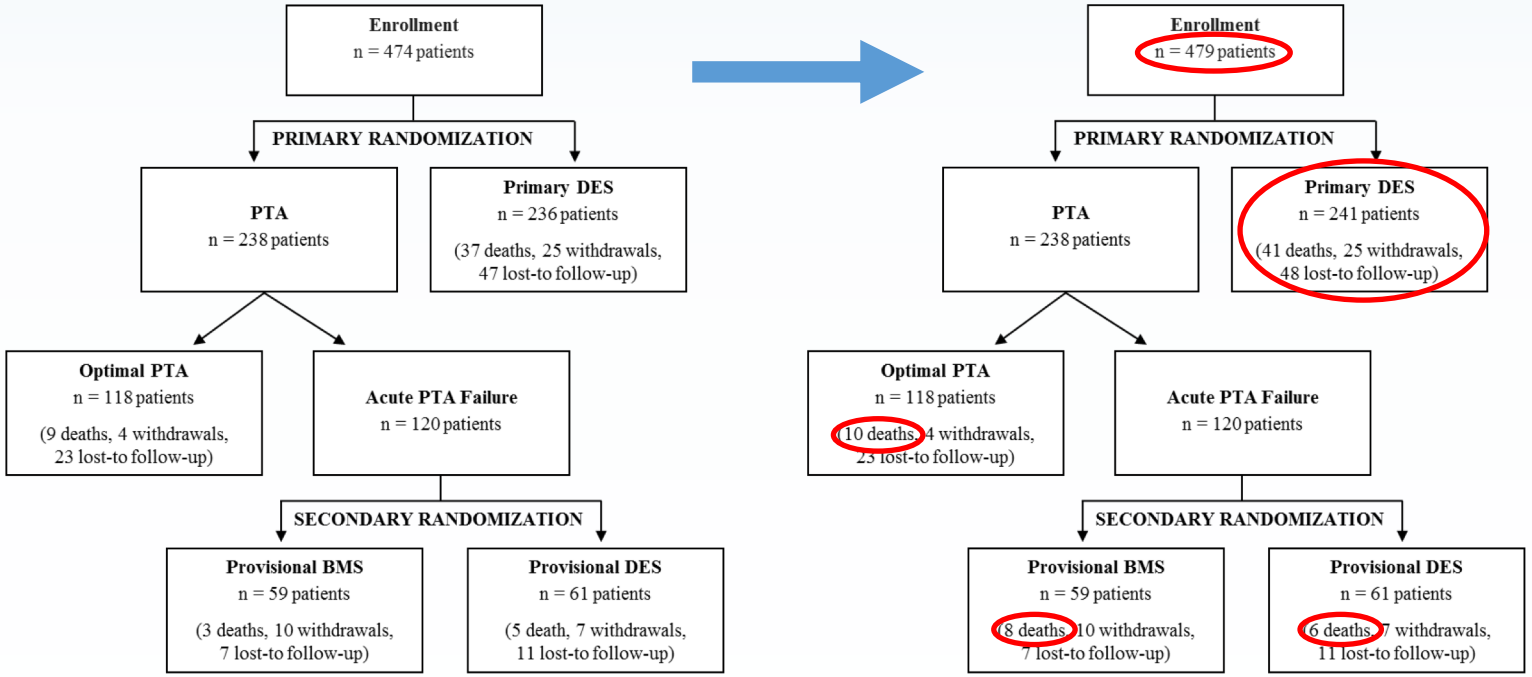
Recent Correction to 5-year Zilver RCT Publication

- Incorrect patient flow diagram submitted during final publication process
- Error does not impact conclusions drawn by Katsanos



Risk Ratio (95% CI) for All-cause death at 4 to 5 years	
Based on original figure	1.94 (1.28 – 2.96)*
Based on corrected figure	1.66 (1.14 – 2.44)

* Katsanos K, et al. 2018. JAHA

Original and corrected figures both represent intent-to-treat assignments

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Recent Correction to 5-year Zilver RCT Publication

- Mortality numbers transposed in overall primary randomization comparison
  - Mortality rates in the publication compare the primary randomization groups but did not account for all patients who received a Zilver PTX stent
- Data available to Katsanos et al. did not identify all patients that were treated with a Zilver PTX stent
  - Patient-level data were not used in the analysis
  - 40% of patients treated with a Zilver PTX stent were included in the control arm of the analysis

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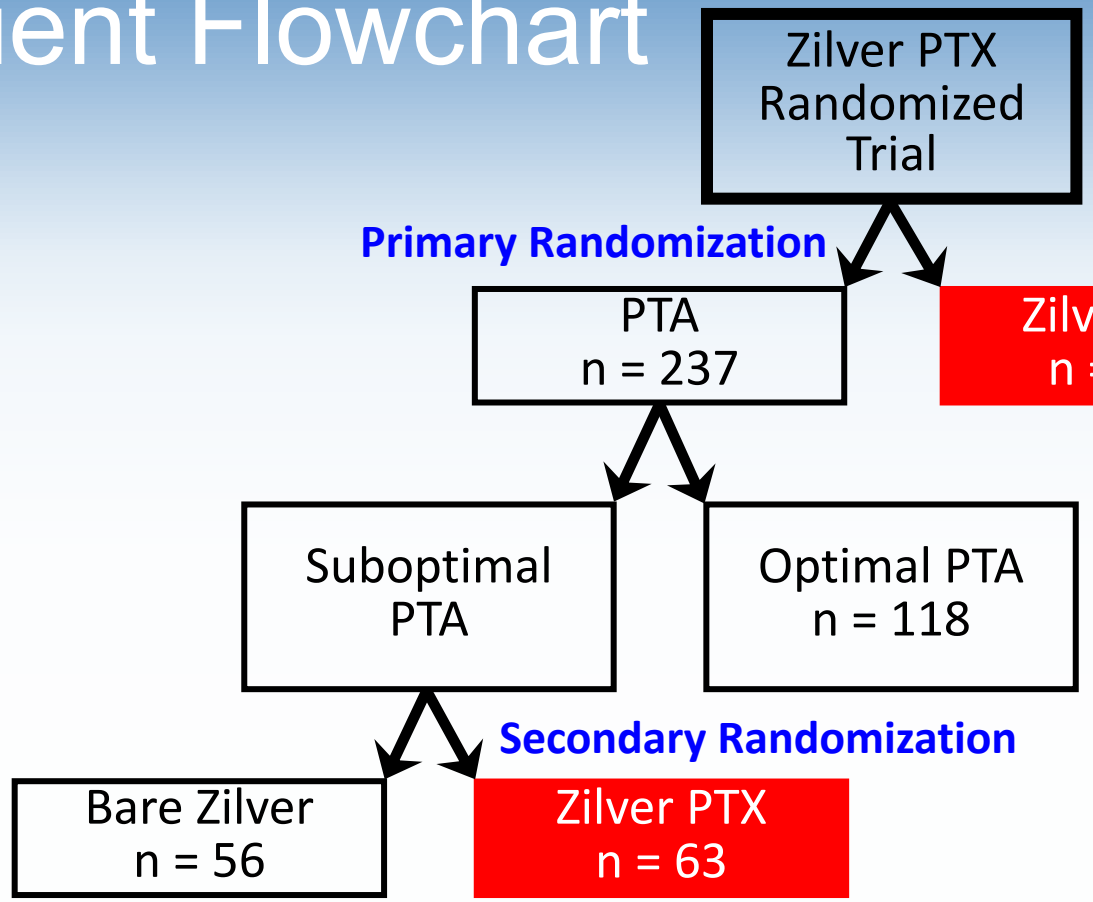
RCT Patient Flowchart



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

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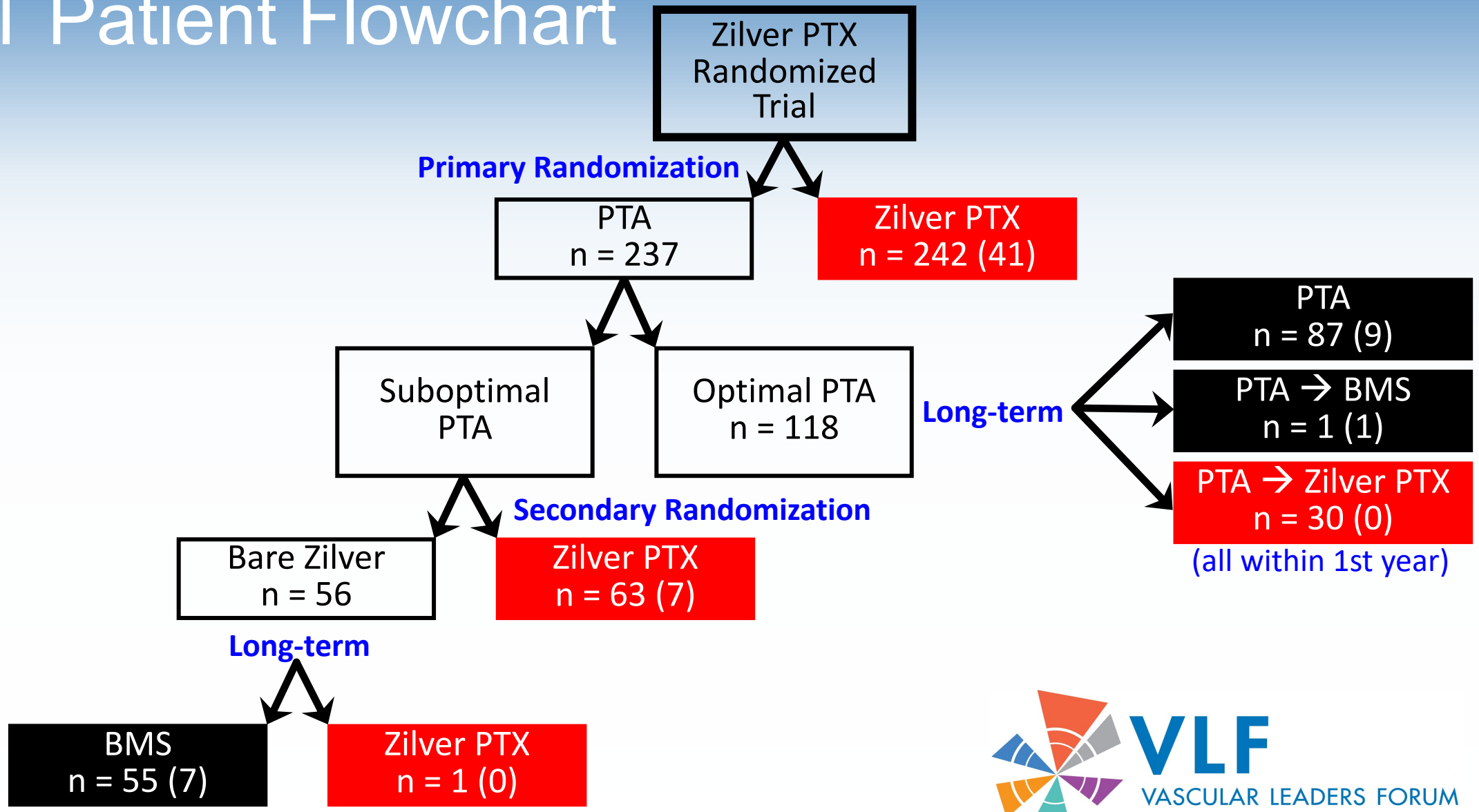
RCT Patient Flowchart



Numbers in parentheses indicate patient deaths.

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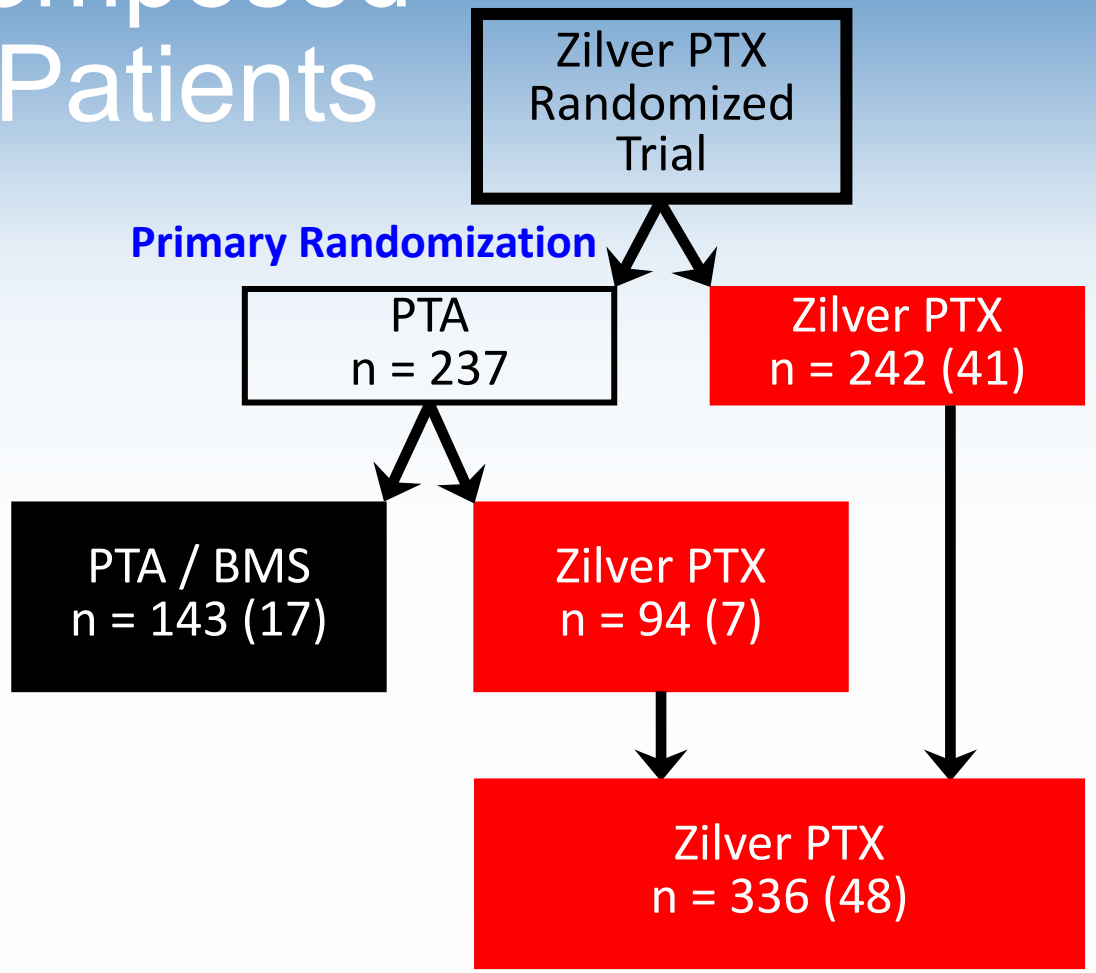
PTA Group Composed of Zilver PTX Patients



40% of PTA group = Zilver PTX

70% of patients in study = Zilver PTX

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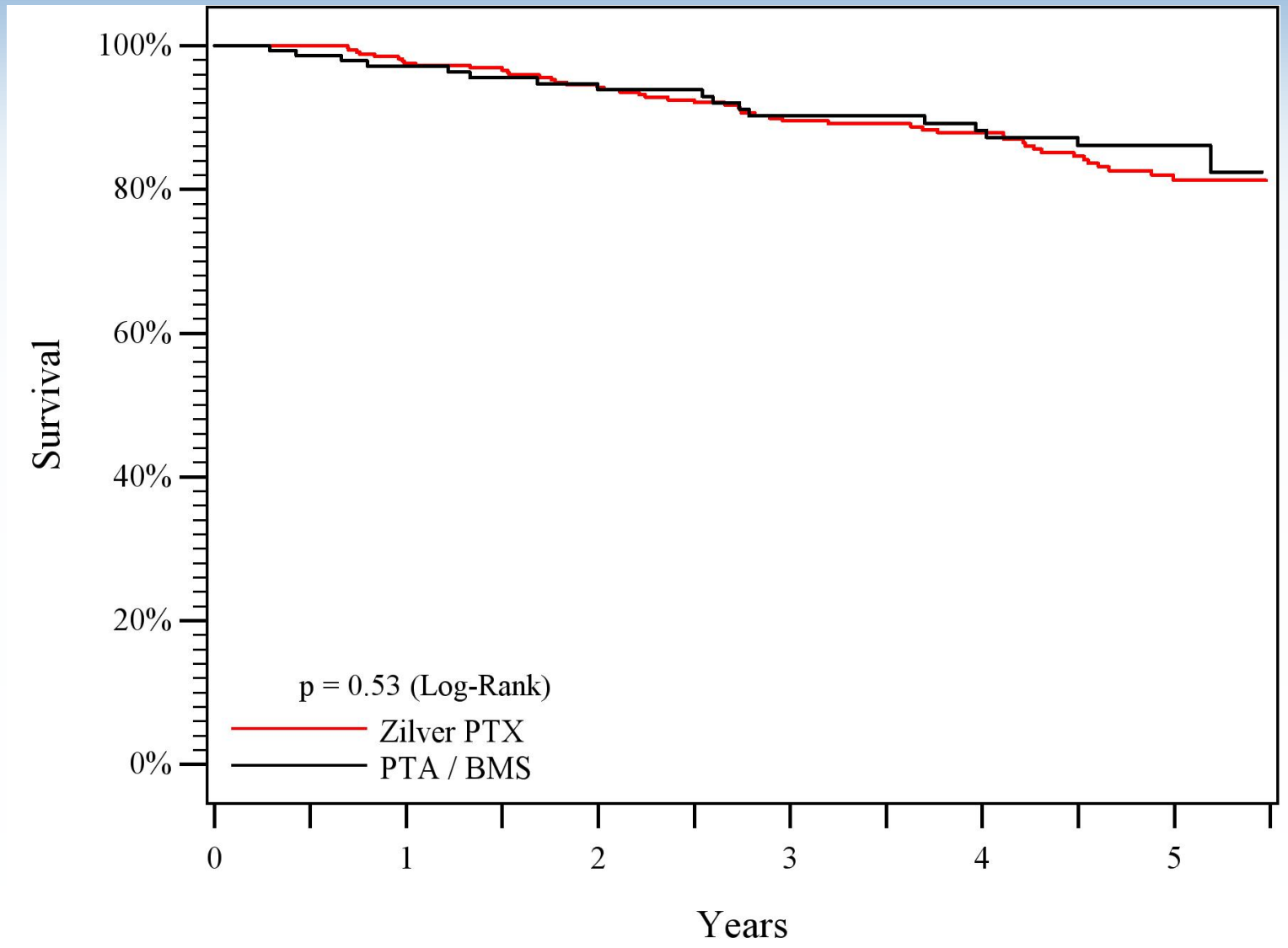
Zilver PTX RCT Final 5-year Mortality Analysis



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

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Covariate Analysis – RCT

- 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 (p=0.54)

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

Dose Analysis

- Meta-analysis from Katsanos incorrectly identified Zilver PTX as a high dose device
  - Total amount of paclitaxel on a Zilver PTX stent is approximately 10% to 20% of the amount on a DCB
- Zilver PTX has similar total amount of paclitaxel compared to Eluvia with no polymer and a shorter paclitaxel exposure

Device	Paclitaxel Density	Total Paclitaxel Load (7 x 80 mm)		Paclitaxel Exposure
Boston Scientific Eluvia	0.167 µg/mm^2 total area	**0.3 mg**		≥1 year permanent polymer
Cook Zilver PTX	3 µg/mm^2 abluminal area	**0.7 mg**		2 months polymer free
Bard Lutonix DCB	2 µg/mm^2 abluminal area	**3.0 mg**		< 2 months
Medtronic In.Pact DCB	3.5 µg/mm^2 abluminal area	**6.9 mg**		< 2 months

References: Device SSEDs/IFUs; Müller-Hülsbeck, Expert Opinion on Drug Delivery 2016, Dake, et al. JVIR 2011; Gongora, et al. JACC Cardio Interv, 2015; http://www.bostonscientific.com/en-US/products/stents--vascular/eluvia-drug-eluting-stent-system/sustained-drug-release.html (23Feb2019)

Dose Analysis – RCT

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

~0.3 mg
~30 mm

Increasing Total Paclitaxel Dose
Increasing Lesion Length

~3 mg
~300 mm

No impact of Zilver PTX paclitaxel dose on mortality rate

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Causes of Death Through 5 Years – RCT and BMS

Cause	RCT – PTX (n=336)	RCT – PTA / BMS (n=143)	p-value	Zilver BMS Study* (n=110)
Cardiovascular	4.8%	5.6%	0.66	4.5%
Cancer	4.8%	1.4%	0.11	6.4%
Pulmonary	1.8%	1.4%	> 0.99	1.8%
Stroke	0.6%	0.7%	> 0.99	0.0%
Trauma	0.0%	1.4%	0.09	0.0%
GI	0.3%	0.0%	> 0.99	0.9%
Multiple/Unknown	2.1%	1.4%	> 0.99	0.9%

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

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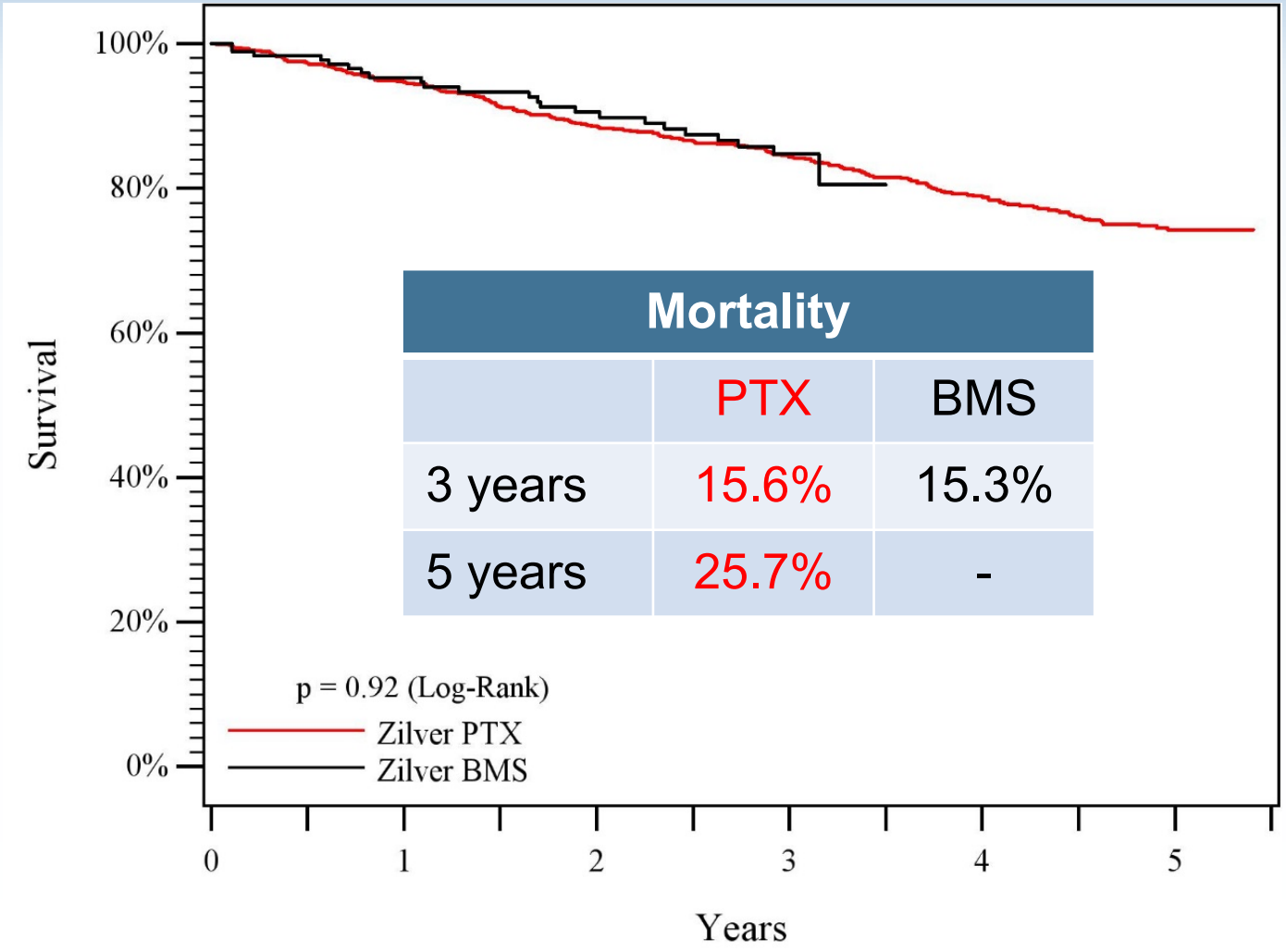
* The Zilver BMS study enrolled 110 patients with femoropopliteal artery disease for 5-year follow-up, ClinicalTrials.gov Identifier: NCT00827619

Japan Post-Market Studies – Zilver PTX and BMS



Mortality		
	PTX	BMS
3 years	15.6%	15.3%
5 years	25.7%	-

- No exclusion criteria
  - Challenging patient population, including CLI patients
- 904 Zilver PTX patients
  - 5-year follow-up
- 190 BMS patients
  - 3-year follow-up
  - Separate study, not randomized
- No significant difference in mortality (p=0.92)
- Same mortality rate of 5.1% per year for PTX & BMS
  - Linear from 0-3 and 3-5 years

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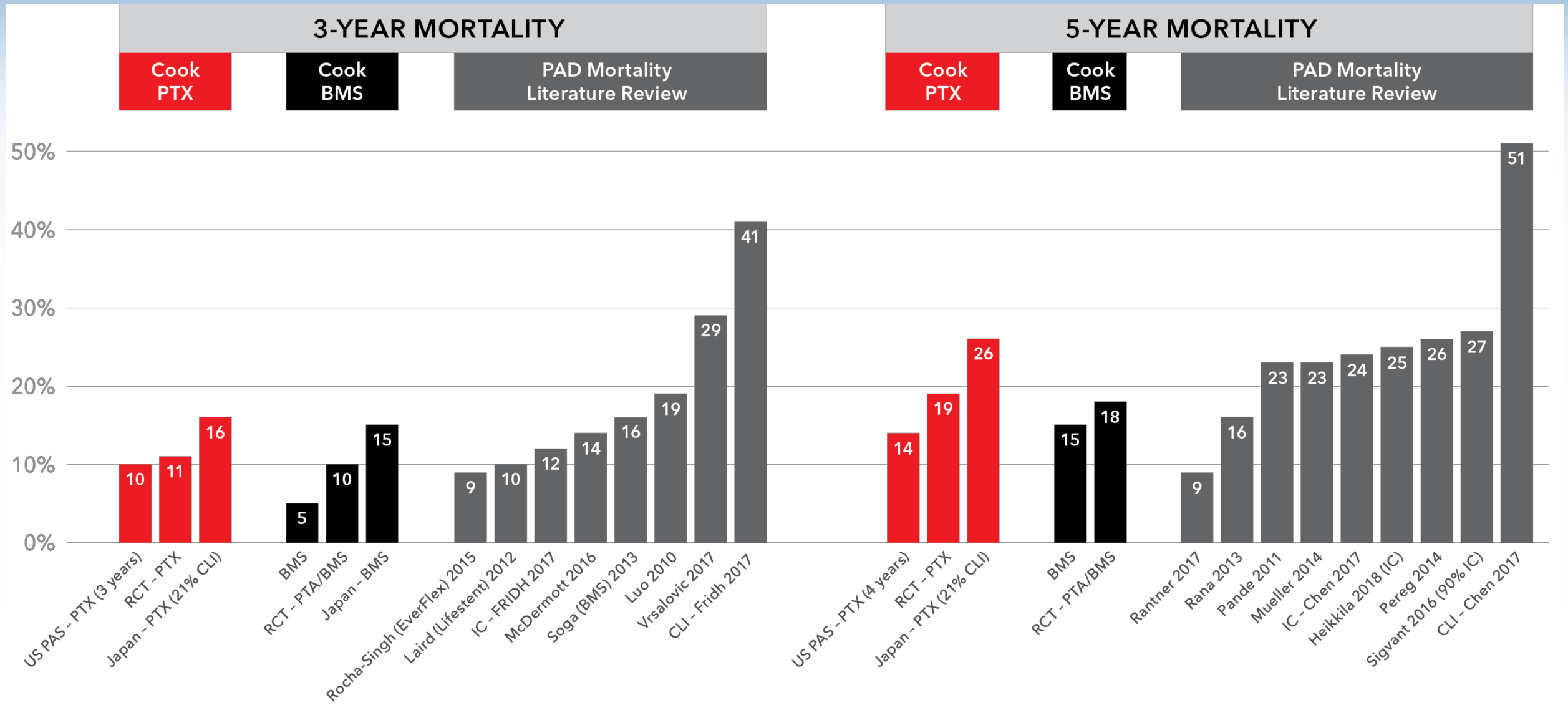
Mortality Rates from Literature



Conclusions

- Conclusion of Katsanos et al. was not based on patient-level data
- Patient-level analysis of RCT and Japan 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
  - No significant differences in causes of death
- Mortality rates for the Zilver PTX stent are consistent with rates reported in literature for PAD patients
- Cook will continue to work with global regulatory authorities and independent physician-led groups to evaluate safety using patient-level data