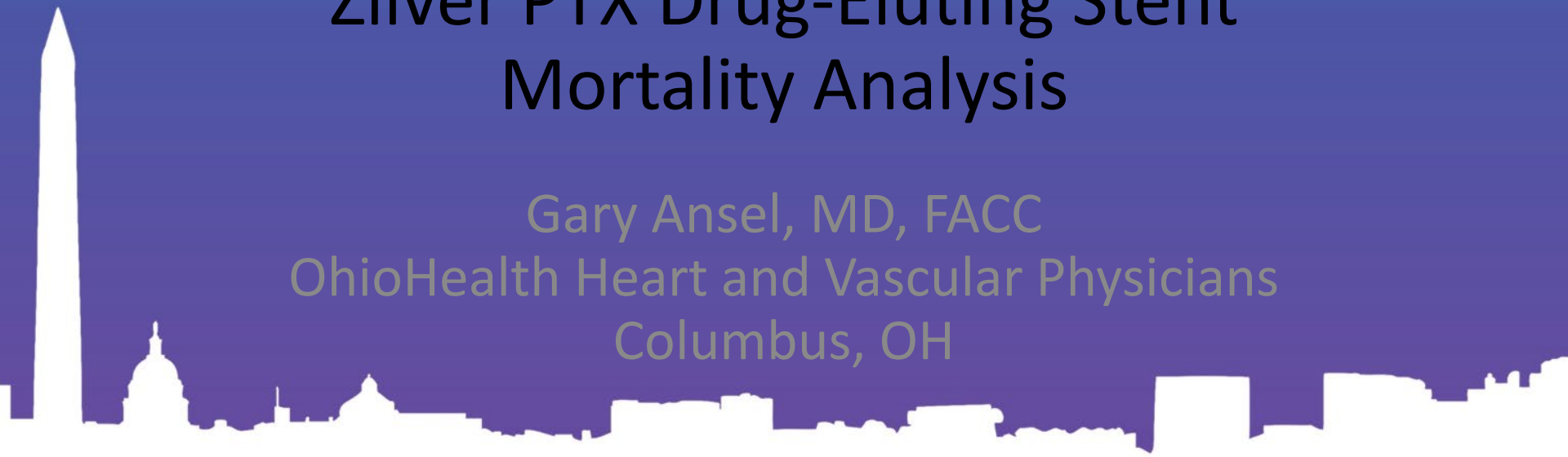
CRT 19 CARDIOVASCULAR RESEARCH TECHNOLOGIES

Zilver PTX Drug-Eluting Stent Mortality Analysis

Gary Ansel, MD, FACC
OhioHealth Heart and Vascular Physicians
Columbus, OH



iMPACT YOUR PRACTICE

CRT 19 CARDIOVASCULAR RESEARCH TECHNOLOGIES

Gary Ansel, MD, FACC

Disclosures:

Advisory and consultation services: Medtronic, CR Bard, Boston Scientific, Cook Medical, Philips Medical, WL Gore, Veryan Medical, Reflow Medical, Shockwave, Intact Vascular, Abbott Vascular, Alucent, Contego Medical, Cardiovascular Systems. Surmodics, Vascular Dynamics, Vatrix, and VIVA Physicians.

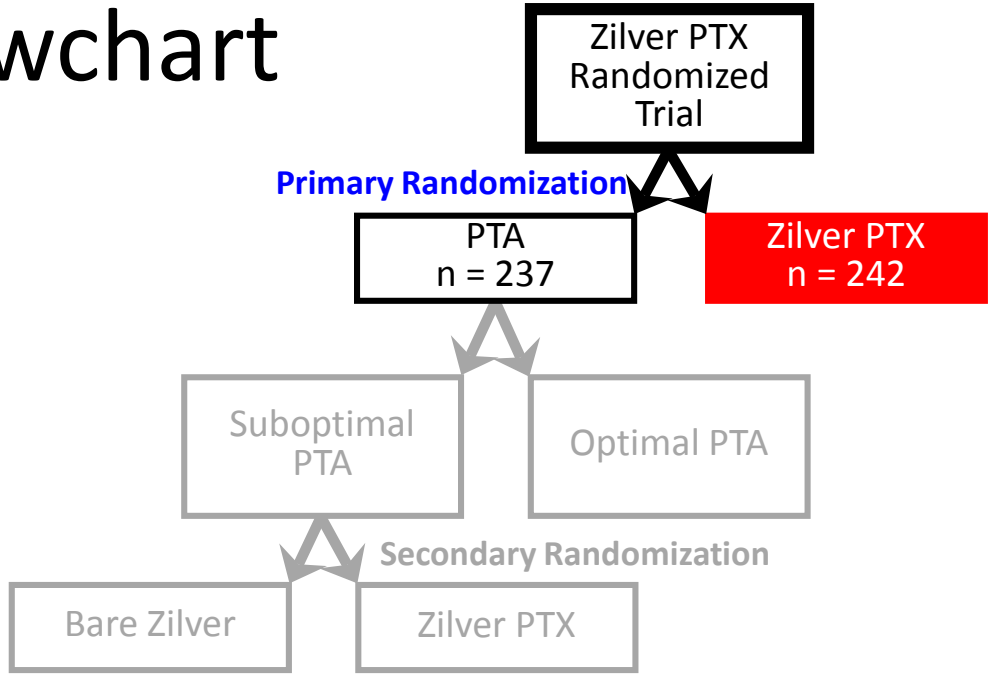
Recent Correction to 5-year Zilver PTX Publication

- Katsanos K, 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

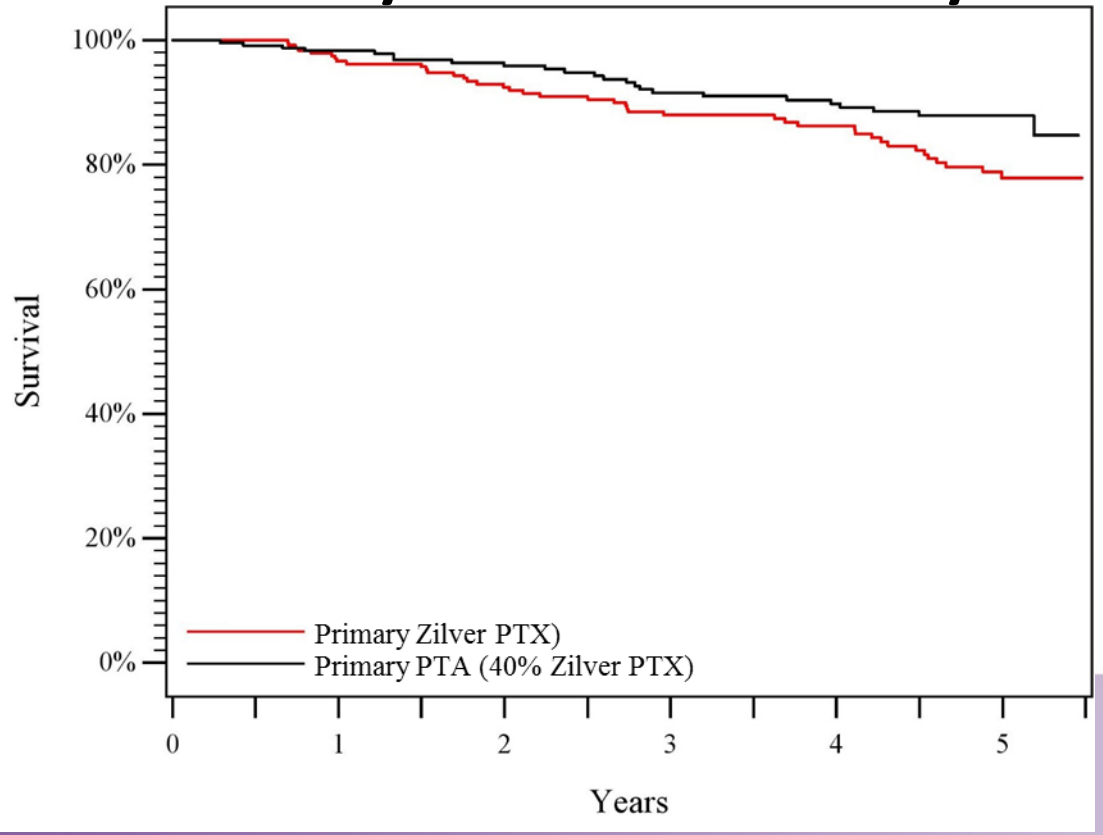
Risk Ratio (95% CI) for All-cause death at 4 to 5 years	
Based on original figure	1.94 (1.28 – 2.96)*
Based on corrected figure	1.66 (1.14 – 2.44)

* Katsanos K, et al. 2018. JAHA

RCT Patient Flowchart



Zilver PTX RCT
5-year Mortality Analysis



PTA*	Zilver PTX
n = 237	n = 242
Died = 24	Died = 41
KM = 15.3%	KM = 22.1%

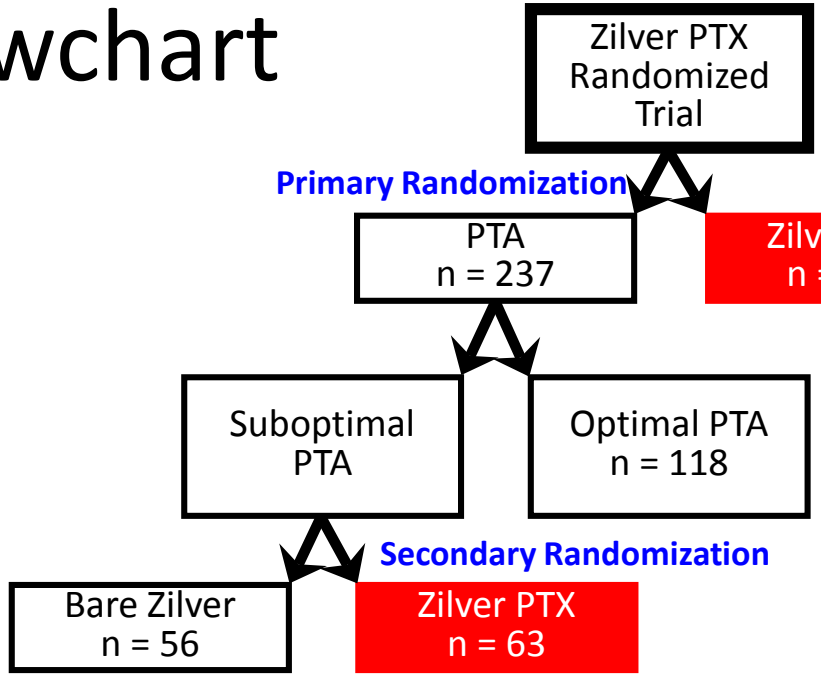
p=0.04

***40% of PTA group = Zilver PTX**

Zilver PTX Key Points

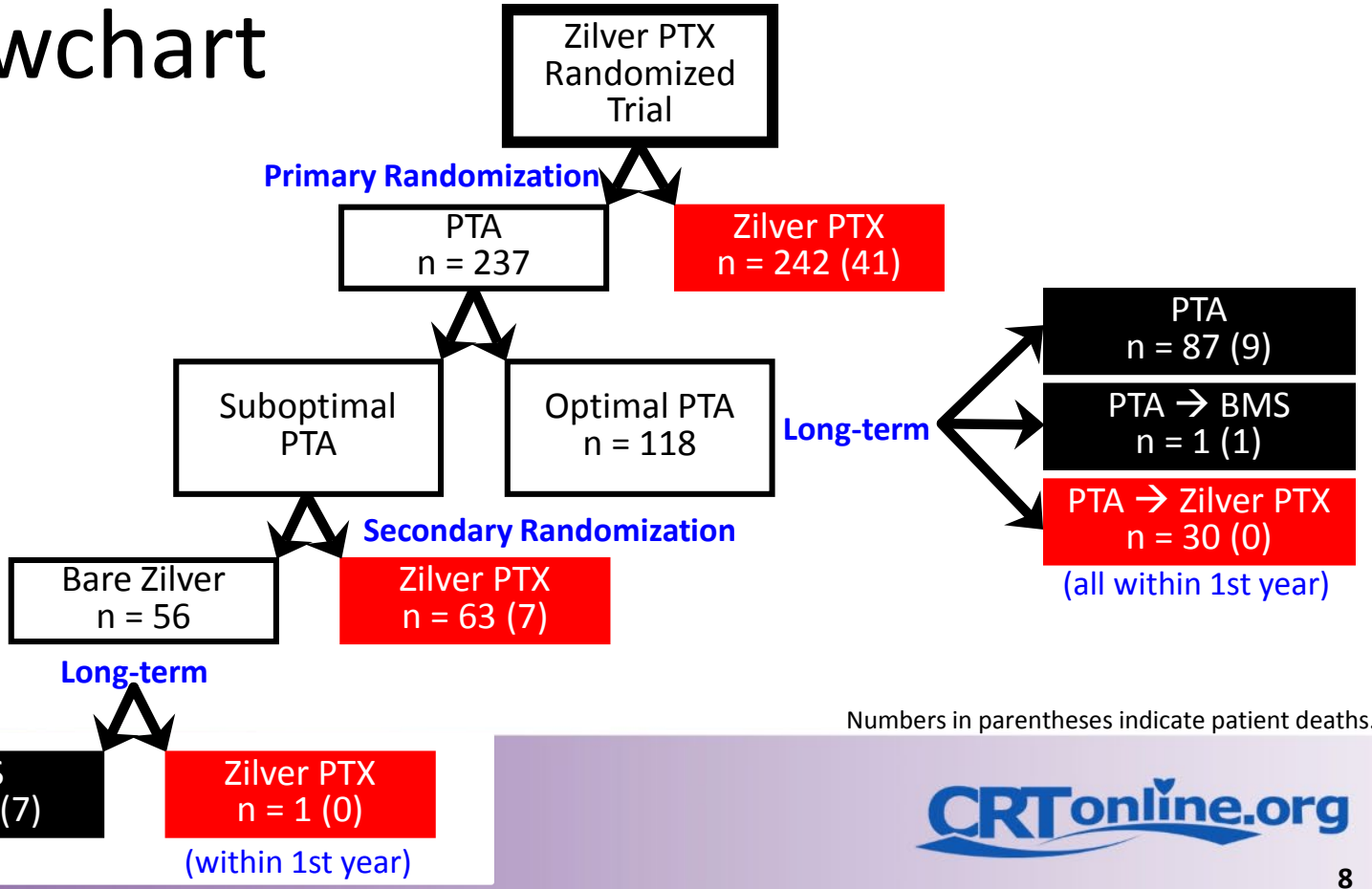
- Data available to Katsanos K, et al. did not identify all patients who were treated with a Zilver PTX stent
  - Patient-level data were not used in the analysis
  - 40% of patients in the PTA group were treated with a Zilver PTX stent
- Patient level analysis demonstrates no difference in mortality rate for Zilver PTX compared to PTA/BMS
  - Causes of death for Zilver PTX are similar to PTA/BMS

RCT Patient Flowchart



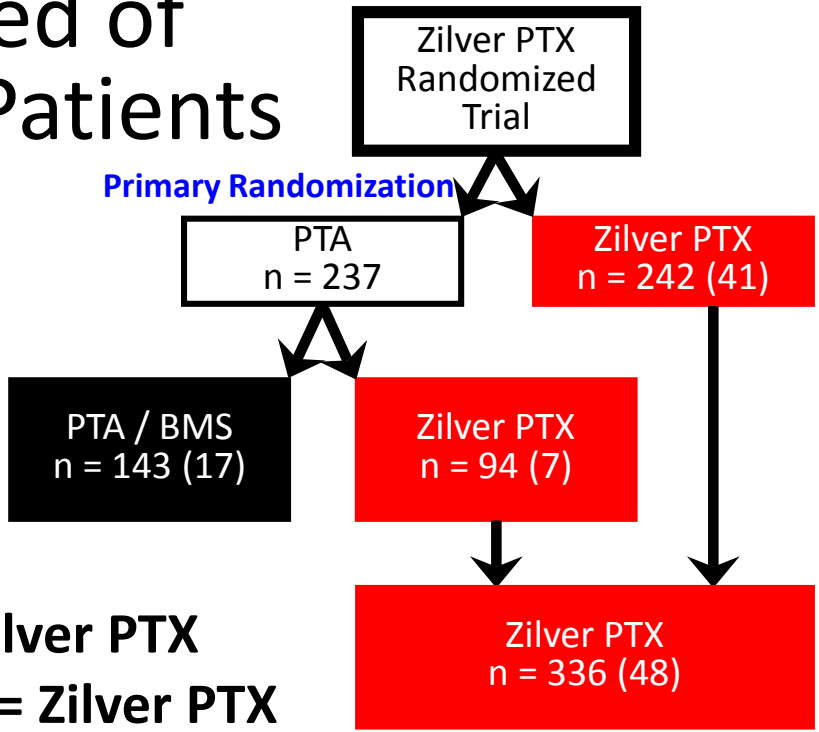
The RCT study design allowed optimal PTA patients requiring reintervention within the first year post-procedure to cross over to treatment with the Zilver PTX stent

RCT Patient Flowchart



Numbers in parentheses indicate patient deaths.

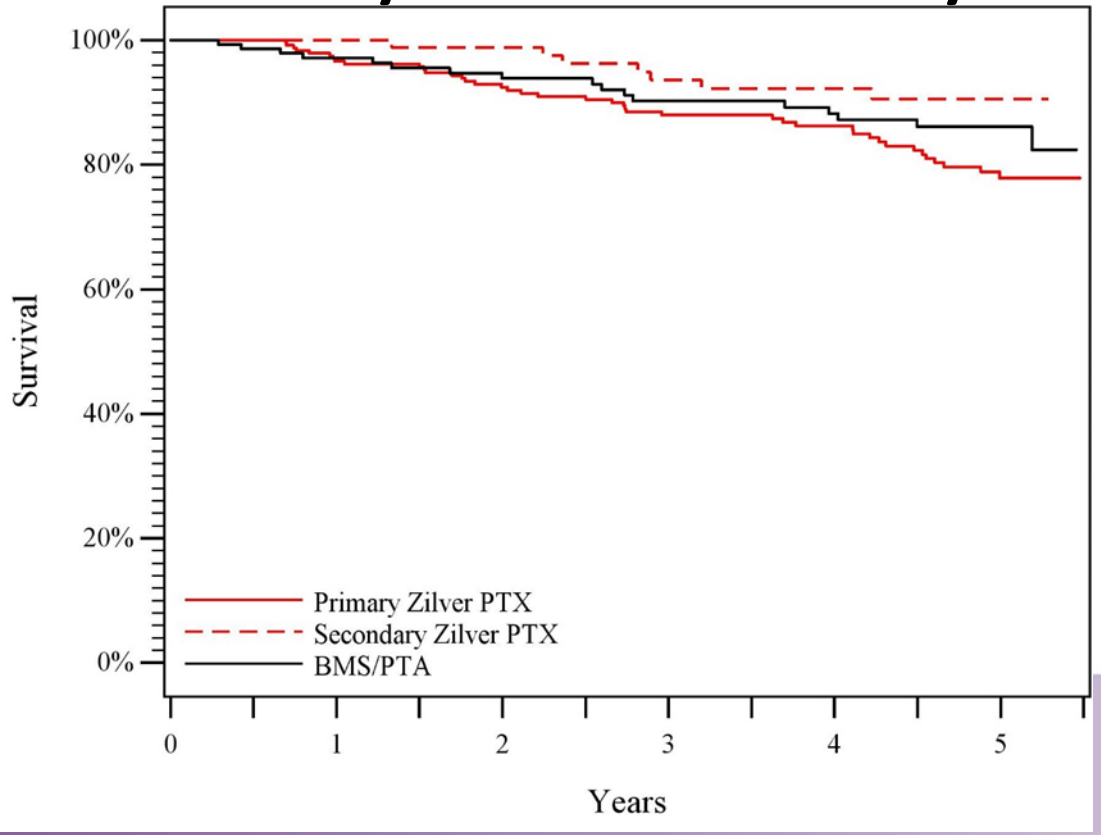
PTA Group Composed of Zilver PTX Patients



40% of PTA group = Zilver PTX

70% of patients in study = Zilver PTX

Zilver PTX RCT
5-year Mortality Analysis

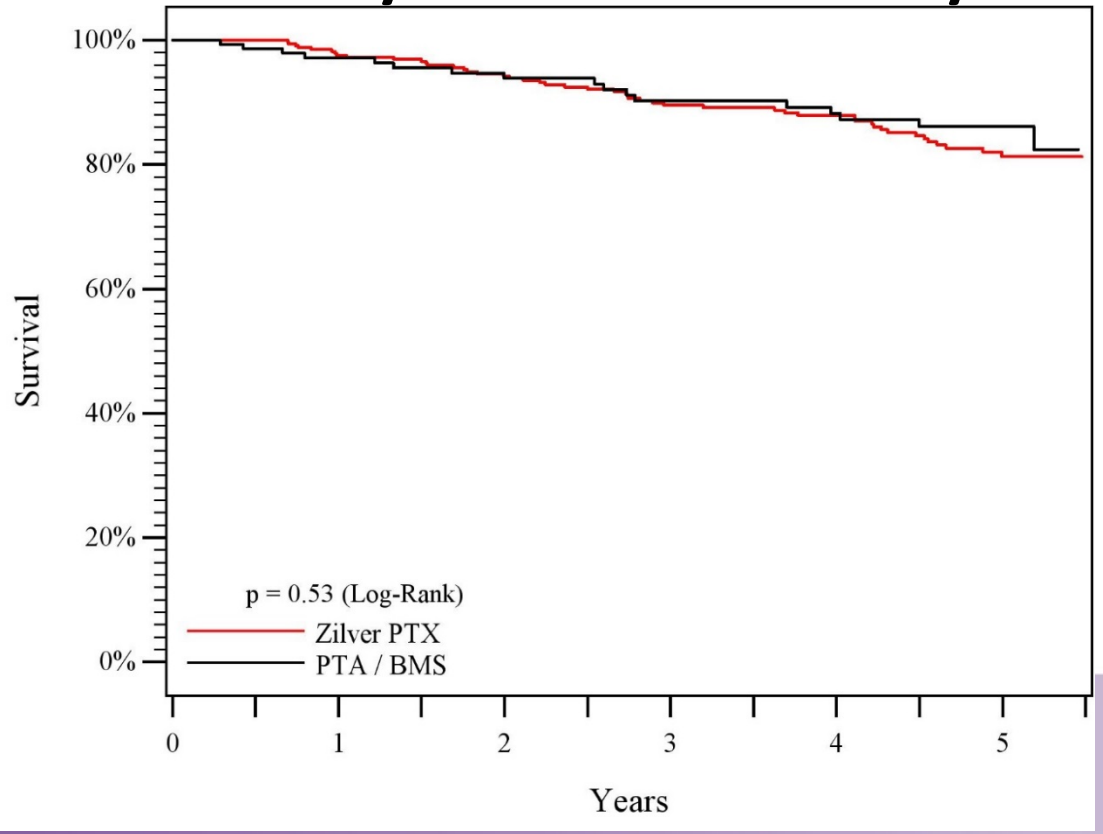


PTA / BMS	Zilver PTX
n = 143	n = 242
Died = 17	Died = 41
KM = 17.6%	KM = 22.1%

?

Zilver PTX
n = 94
Died = 7
KM = 9.4%

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

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=0.51)

Covariate	Multivariate p-value
Age	**0.0002**
Congestive heart failure	0.09
Diabetes	0.11
Lesion length	0.12
Carotid disease	0.13
Claudication/CLI	0.14
Smoking	0.17
Cardiac arrhythmia	0.21
Hypertension	0.46
Gender	0.50
PTX vs. PTA/BMS	0.51
Country (US, JP, Germany)	0.59
Pulmonary disease	0.61
Hypercholesterolemia	0.63
Previous MI	0.99

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

Dose Analysis

Device	Paclitaxel Density	Total Paclitaxel Load (7 x 80 mm)		Paclitaxel Exposure
Boston Scientific Eluvia	0.167 µg/mm² total area	**0.3 mg**		≥ 1 year permanent polymer
Cook Zilver PTX	3 µg/mm² abluminal area	**0.7 mg**		2 months polymer free
Bard Lutonix DCB	2 µg/mm² abluminal area	**3.5 mg**		< 2 months
Medtronic In.Pact DCB	3.5 µg/mm² 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

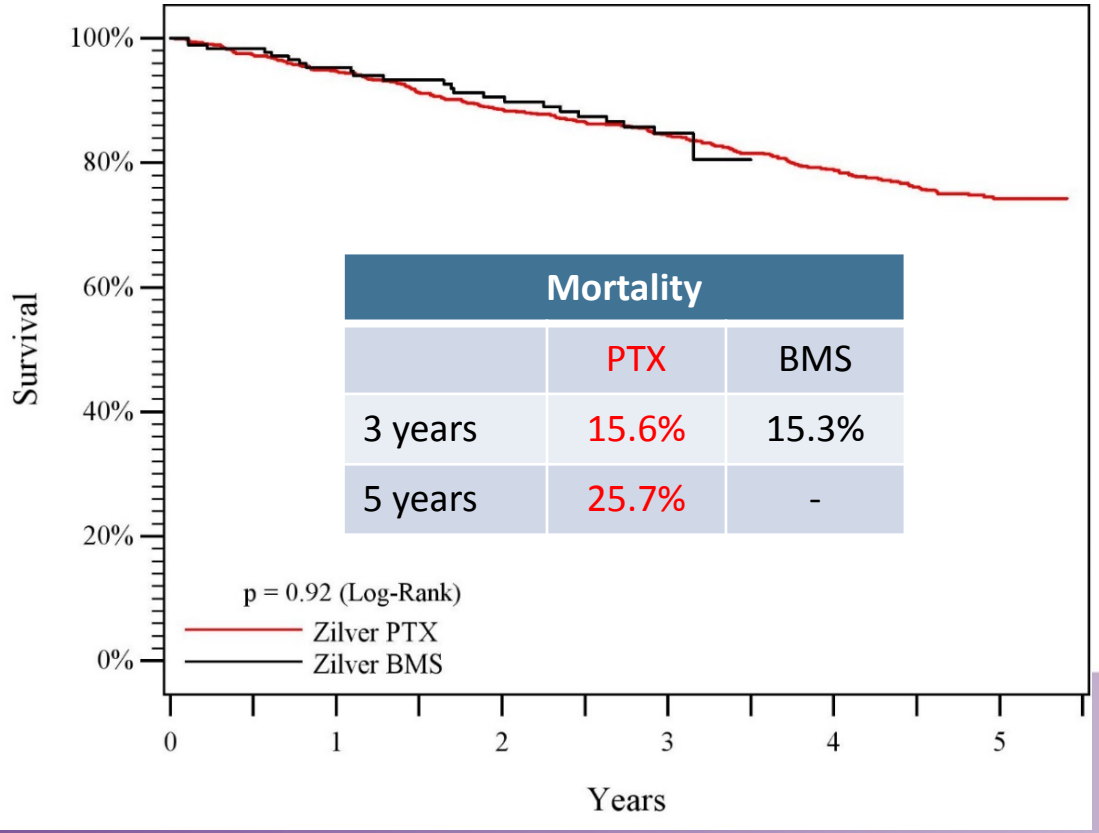
Causes of Death Through 5 Years – RCT and BMS

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

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

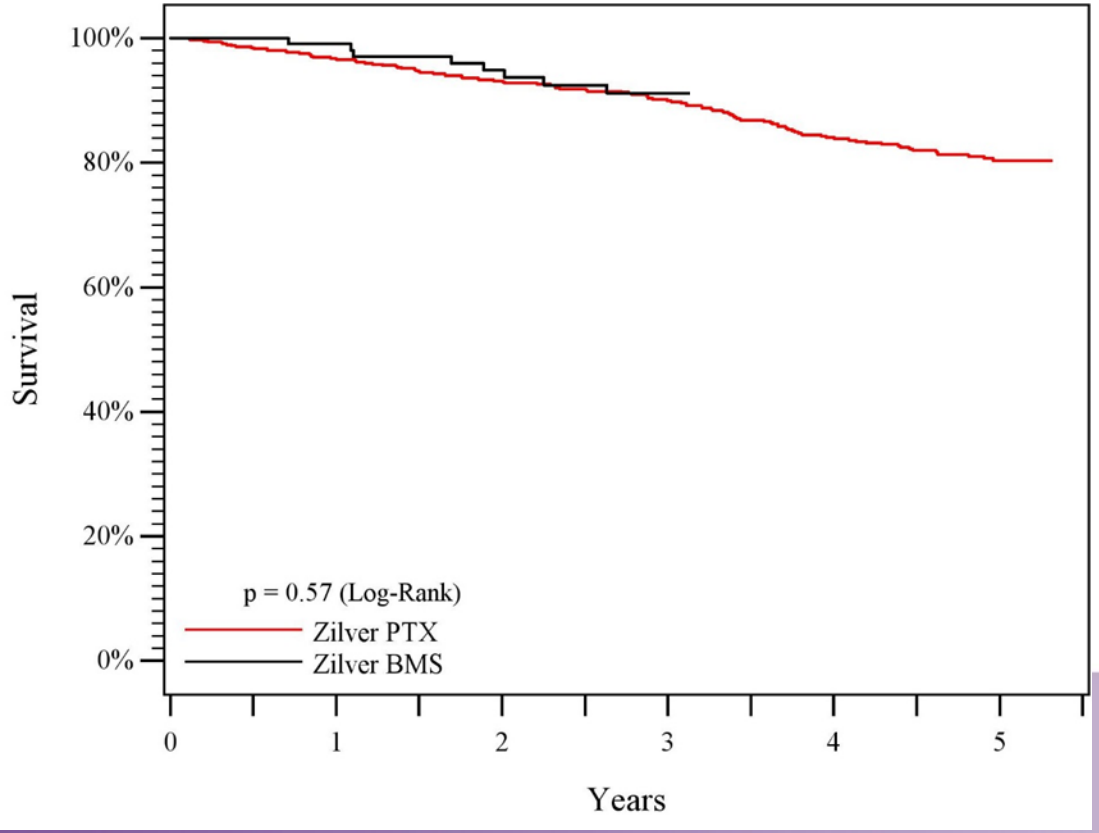
Japan Post-Market Studies – Zilver PTX and BMS



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

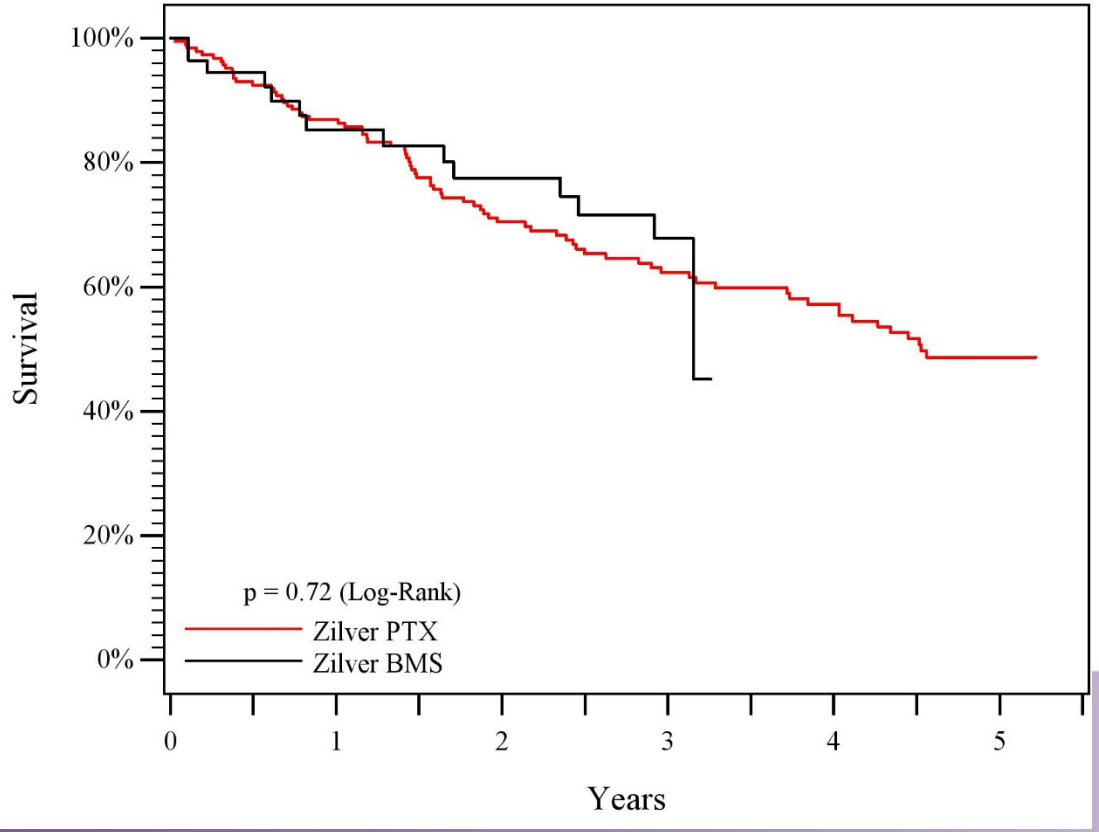
Japan Post-Market Studies – Zilver PTX and BMS Claudicants



Mortality		
	PTX	BMS
3 years	10.0%	8.8%
5 years	19.7%	-

No significant difference in mortality (p=0.57)

Japan Post-Market Studies – Zilver PTX and BMS CLI Patients



Mortality		
	PTX	BMS
3 years	37.7%	32.2%
5 years	51.3%	-

No significant difference in mortality (p=0.72)

Covariate Analysis – Japan

- Cox proportional hazards model to evaluate covariates
  - No significant difference between Zilver PTX and BMS (p=0.39)

Cox Model Results	
Covariate	**Multivariate p-value**
Age	**<0.0001**
Claudication/CLI	**<0.0001**
Hypercholesterolemia	**0.0005**
Gender	**0.003**
Diabetes	**0.04**
Carotid disease	0.06
PTX vs. BMS	0.39
Smoking	0.45
Hypertension	0.46
Lesion length	0.80
Pulmonary disease	0.90

Dose Analysis – Japan

5-year Mortality Rate				
Dose Group 1	Dose Group 2	Dose Group 3	Dose Group 4	Dose Group 5
17.4%	23.9%	16.1%	21.3%	21.5%
p=0.41				

~0.3 mg
~3 cm

Increasing Total Paclitaxel Dose
Increasing Lesion Length

~8 mg
~40 cm x 2

No impact of Zilver PTX paclitaxel dose on mortality rate

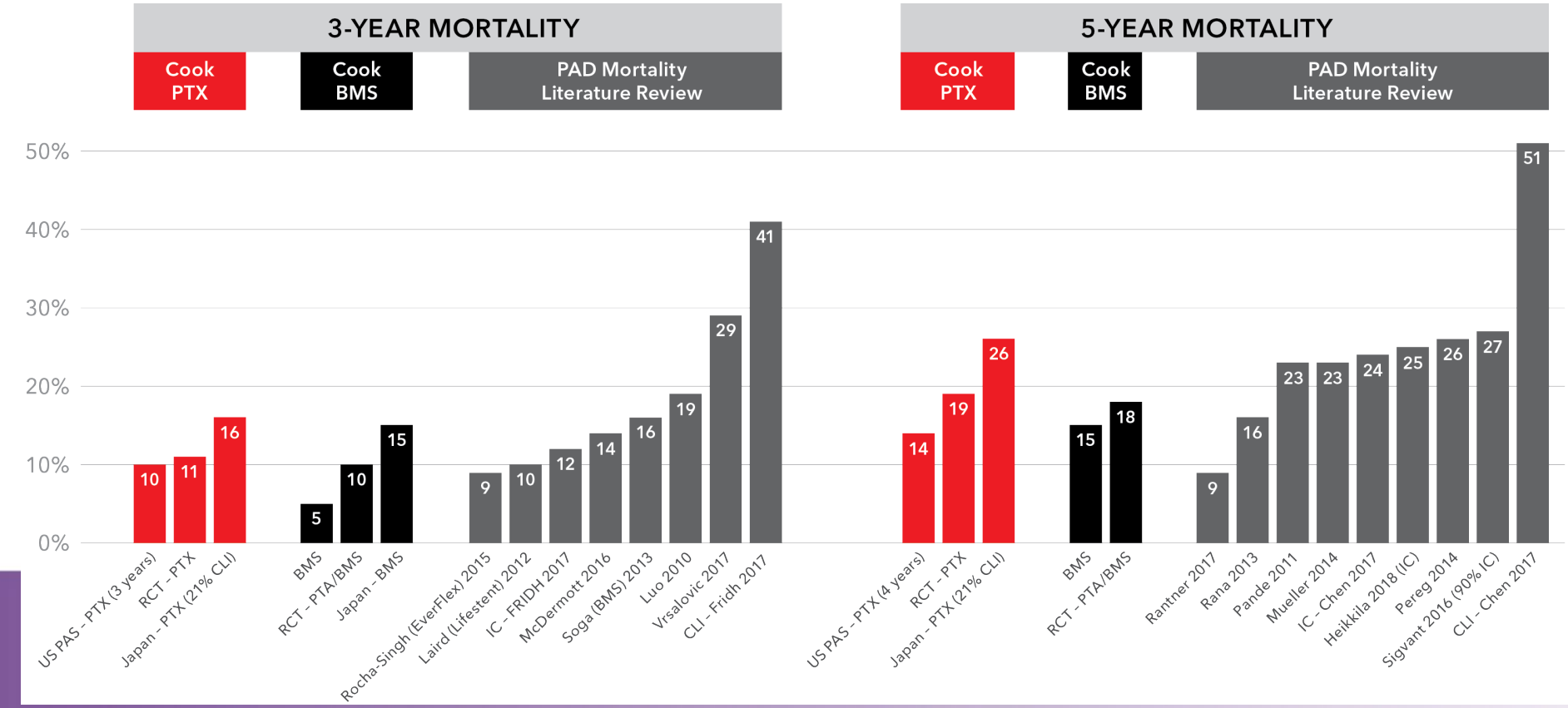
Causes of Death Through 5 Years – RCT & Japan

Cause	RCT – PTX (n=336)	RCT – PTA / BMS (n=143)	Japan – PTX (n=904)*
Cardiovascular	4.8%	5.6%	6.1%
Cancer	4.8%	1.4%	2.9%
Pulmonary	1.8%	1.4%	2.7%
Stroke	0.6%	0.7%	1.5%
Trauma/Accident	0.0%	1.4%	0.2%
GI	0.3%	0%	0.2%
Infection	0%	0%	0.2%
Renal	0%	0%	0.8%
Multiple/Unknown	2.1%	1.4%	5.9%

* Preliminary analysis

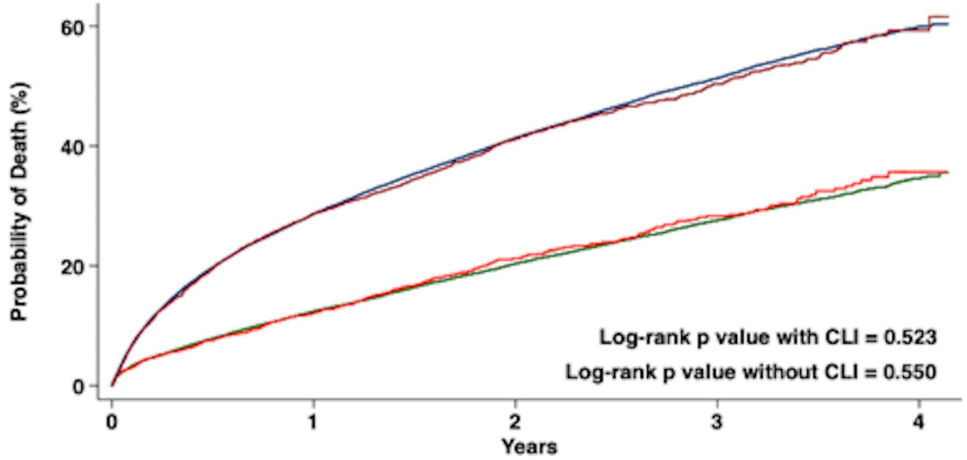
Similar causes of death as RCT

Mortality Rates from Literature



No Increased Long-term Mortality with DES

- 51,456 patients
  - 47,351 BMS
  - 4,105 DES (Zilver PTX)
- Similar mortality for BMS and DES through 4.1 years
  - Overall adjusted p=0.53
  - Without CLI adjusted p=0.95
  - With CLI adjusted p=0.32



No. at risk					
BMS without CLI	19305	16878	11923	6443	666
DES without CLI	1443	1267	800	378	35
BMS with CLI	28046	19996	12280	5570	534
DES with CLI	2662	1896	1020	418	33

Secemsky E, et al. J Am Coll Cardiol. E-pub ahead of print 01March2019. doi https://doi.org/10.1016/j.jacc.2019.02.020

Conclusions

- Conclusion of Katsanos K, 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
  - No significant differences in causes of death
- Mortality rates for the Zilver PTX stent are consistent with rates reported in literature for PAD patients
- Japan data confirm RCT findings showing no increased long-term mortality risk with Zilver PTX compared to BMS
- Cook will continue to work with global regulatory authorities and independent physician led groups to evaluate safety using patient-level data