19JUN2019

FDA ADVISORY PANEL

Zilver® PTX® Drug-Eluting Peripheral Stent

Circulatory Systems
Device Panel Meeting

COOK® MEDICAL

Introduction

Aaron Lottes, PhD
Lead Scientist for Zilver PTX

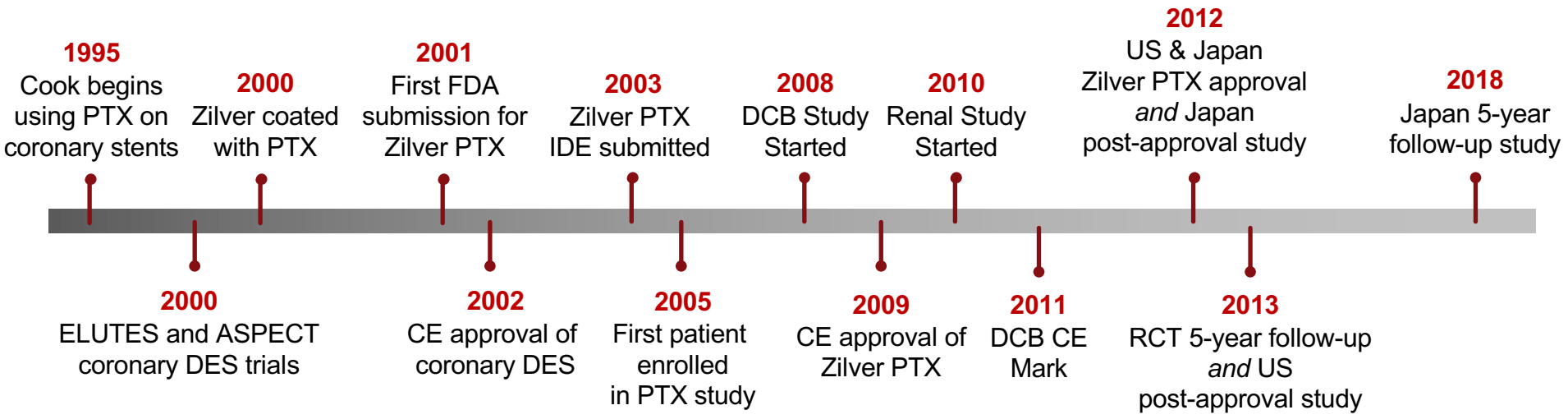
Director Regulatory Science
PAD Therapies
Cook Medical

Michael Dake, MD
Global Principal Investigator for Zilver PTX

Senior Vice President of Health Sciences, Professor of Medical Imaging, Medicine, and Surgery, University of Arizona, Tucson/Phoenix

Paid consultant of Cook Medical

Cook Medical's 25 Year History with Paclitaxel



- **No mortality signal in 25 years, across multiple studies and devices**

Overview

Purest Data on Paclitaxel

Because other paclitaxel devices were not yet approved, the Zilver PTX RCT and Japan PMS provide the best data available to look at paclitaxel treatment

Actual Treatment

Any analysis that does not consider known paclitaxel treatment is inappropriate for analyzing mortality and simply does not make sense

Patient Impact

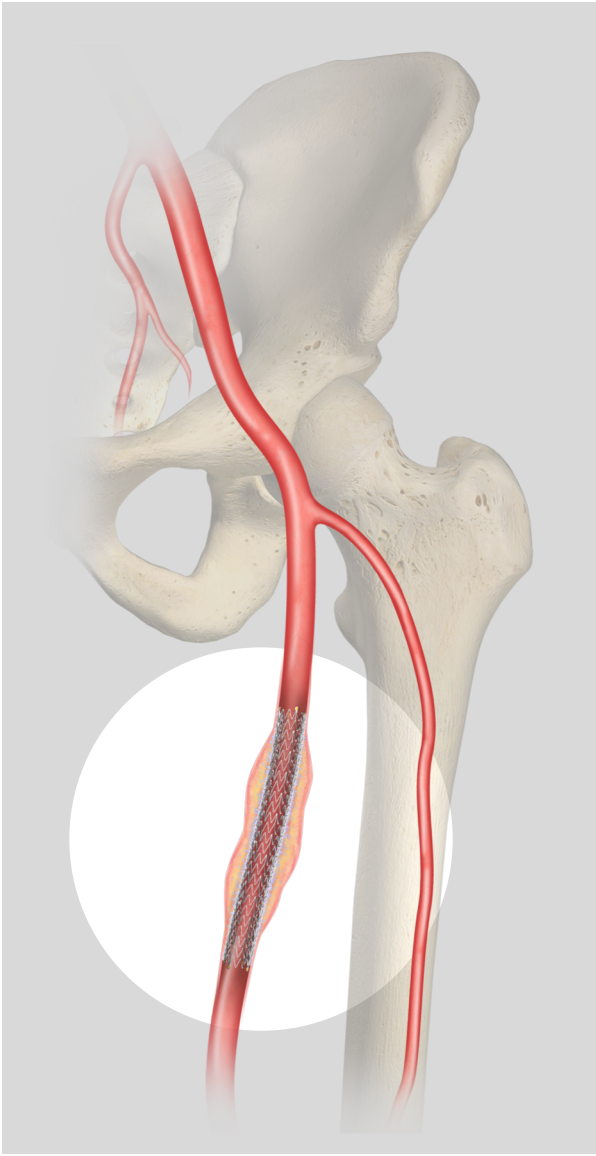
There is no mortality signal with Zilver PTX and the current situation is limiting patient access to the proven benefits of paclitaxel devices

ZILVER PTX

Patient Benefit

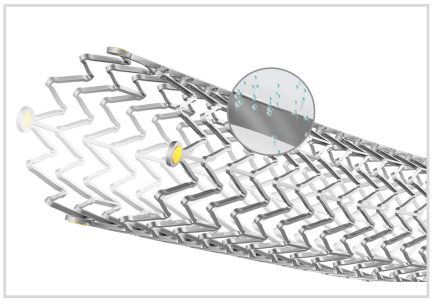
Durable results through 5 years

- Greater than 40% reduction in restenosis
- Greater than 40% reduction in reinterventions
- Proven clinical benefit in real-world patients



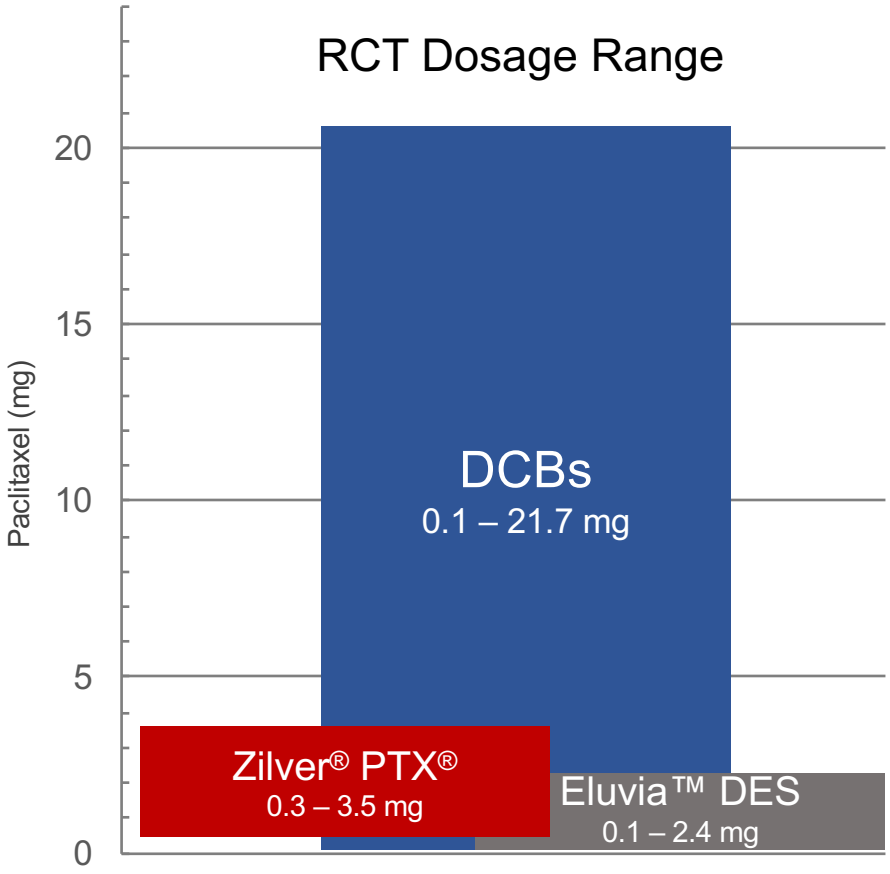
Dake MD, et al. Circulation. 2016;133:1472-1483
Yokoi H, et al. J Am Coll Cardiol Intv. 2016;9:271-277

Device Overview

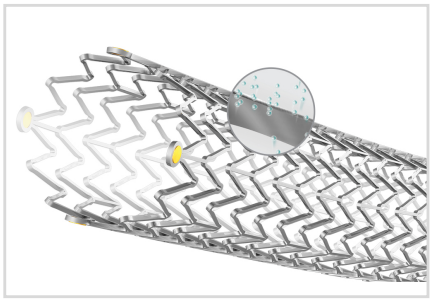


Coating

Low dose, amorphous coating with no polymer or excipient



Device Overview



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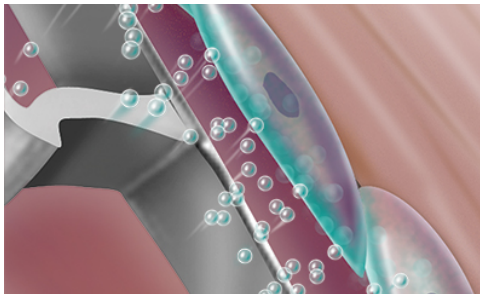
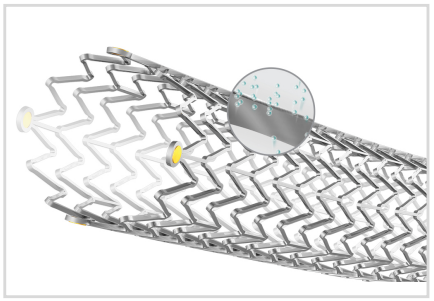


Local Drug Delivery

Short-term drug delivery, no long-term paclitaxel exposure, only BMS remains

Device Overview



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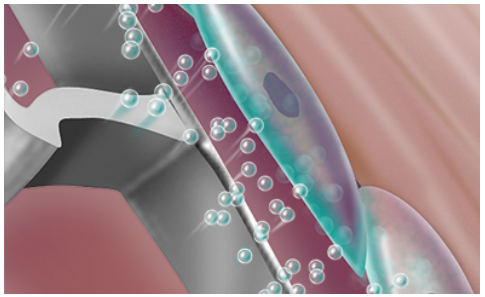

Local Drug Delivery

Short-term drug delivery, no long-term paclitaxel exposure, only BMS remains

Long-term data

Only peripheral DES with long-term safety data

Zilver PTX Clinical Program

Study	Device	Follow-up	# of Patients
RCT	Zilver PTX	5 years	336
	PTA/BMS		143
Japan PMS	Zilver PTX	5 years	904
	BMS	3 years	190
EU BMS	BMS	5 years	110
US PAS	Zilver PTX	5 years[1]	200
Single-arm Study	Zilver PTX	2 years	787
French Reimbursement	Zilver PTX	2 years	119
China	Zilver PTX	1 year	178
REAL PTX	Zilver PTX	3 years	75
	DCB[2]	3 years	75

[1] Ongoing [2] 77.3% INPact, 21.3% Lutonix, 1.4% Other.

- >1,000 patients to support US approval
- >2,500 patients in global pre- and post-market studies
- >300,000 stents to treat patients globally

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[1] Ongoing [2] 77.3% INPact, 21.3% Lutonix, 1.4% Other.

- Large studies
- Long-term follow-up
- Concurrent comparator groups

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[1] Ongoing [2] 77.3% INPact, 21.3% Lutonix, 1.4% Other.

- No exclusion criteria
- All treated patients enrolled
- Pure treatment comparison

Zilver PTX Clinical Program

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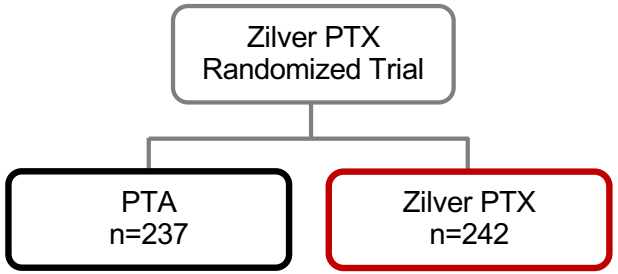
[1] Ongoing [2] 77.3% INPact, 21.3% Lutonix, 1.4% Other.

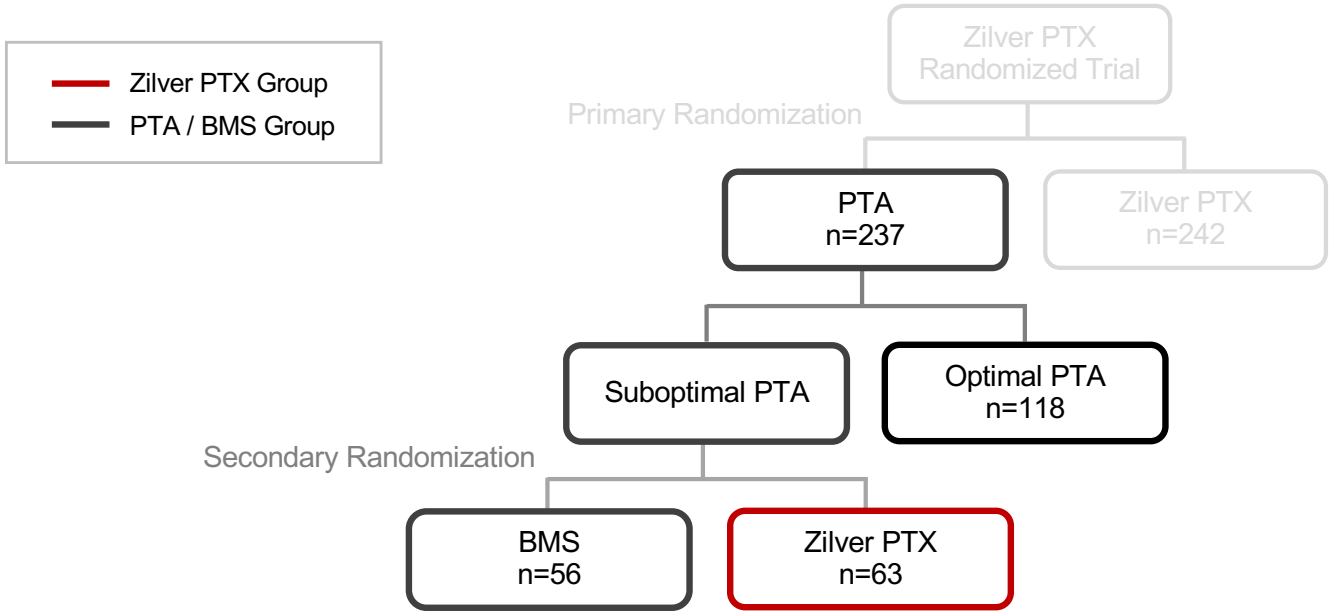
- Trial designed with multidisciplinary physician input and approval from FDA, PMDA, and BfArM

Primary Randomization

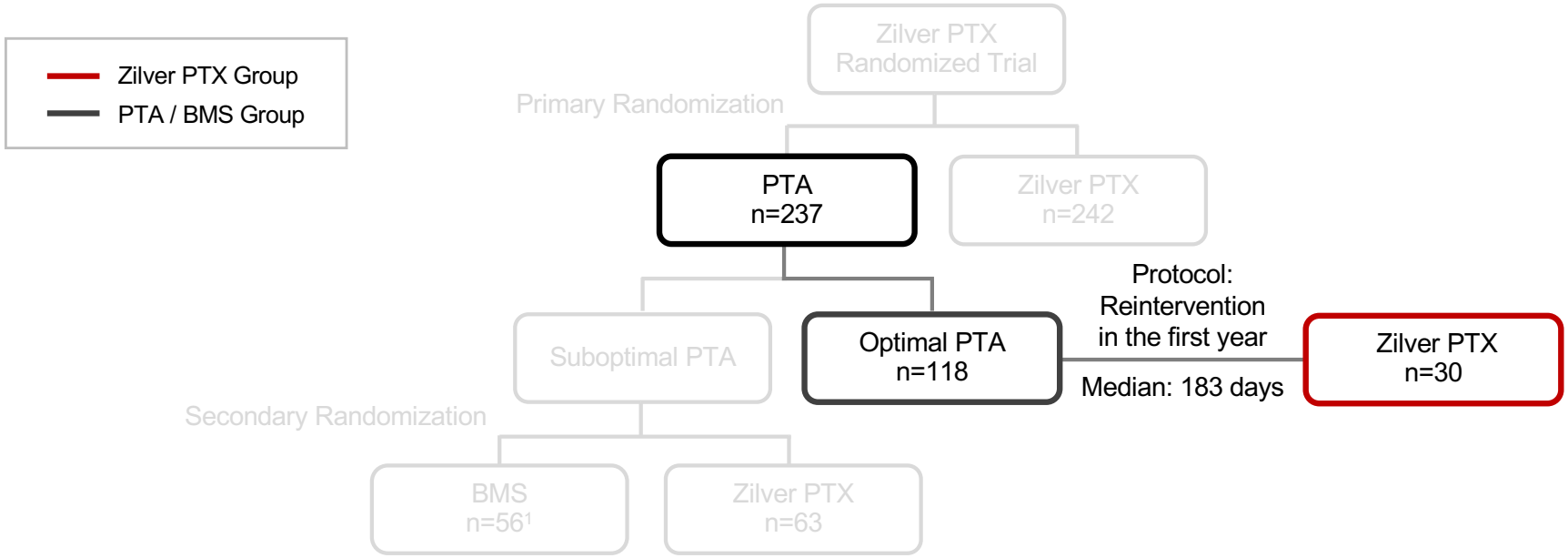
Zilver PTX Group
PTA / BMS Group



Secondary Randomization

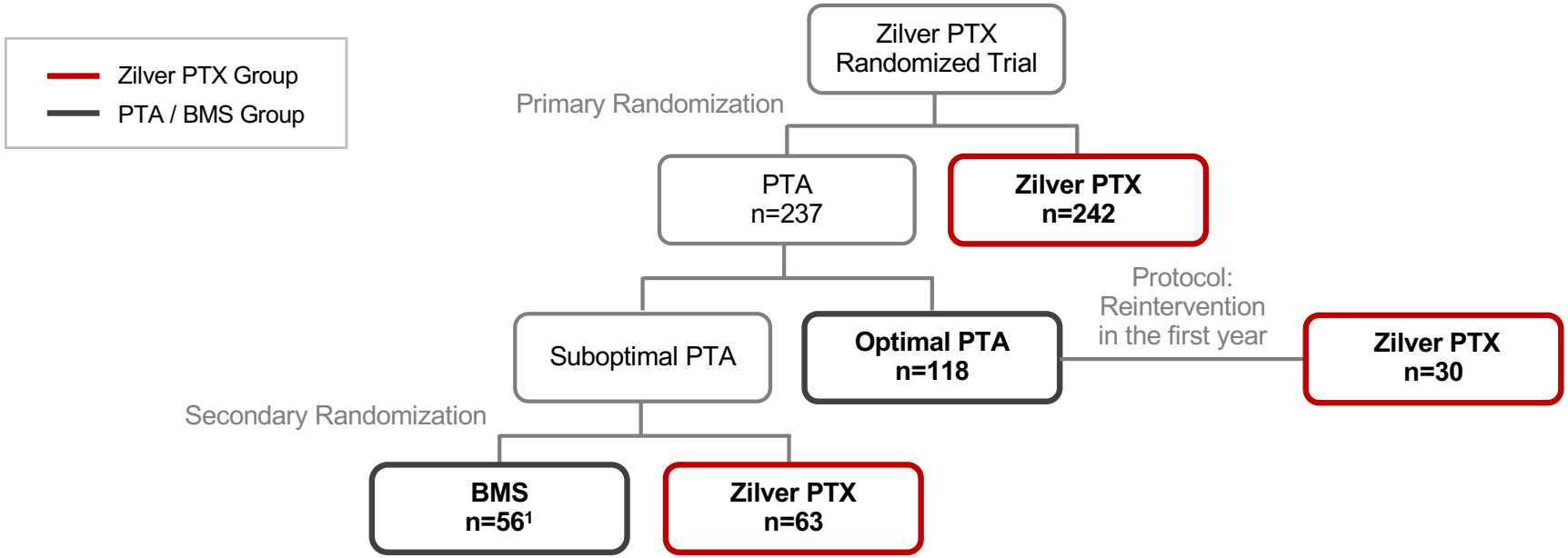


Early Crossover



[1] *One BMS patient received Zilver PTX during reintervention within the first year.*

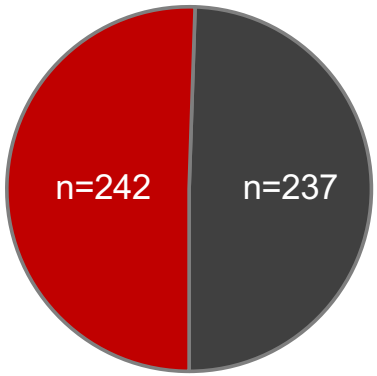
Actual Treatment



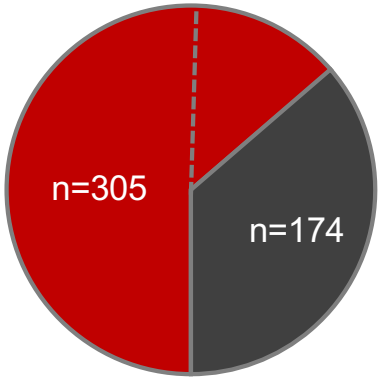
[1] One BMS patient received Zilver PTX during reintervention within the first year.

Treatment Results

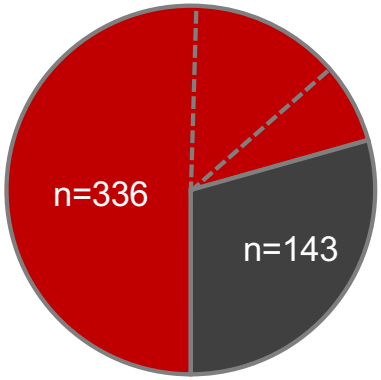
Primary Randomization



Primary + Secondary Randomization



Actual Treatment = Primary + Secondary + Crossover



Treatment Results

- Zilver PTX
- PTA / BMS

Primary Randomization

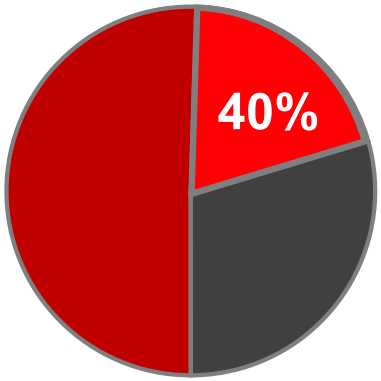
Primary + Secondary Randomization

n=242

n=174

- 40% of patients initially randomized to PTA were actually treated with Zilver PTX

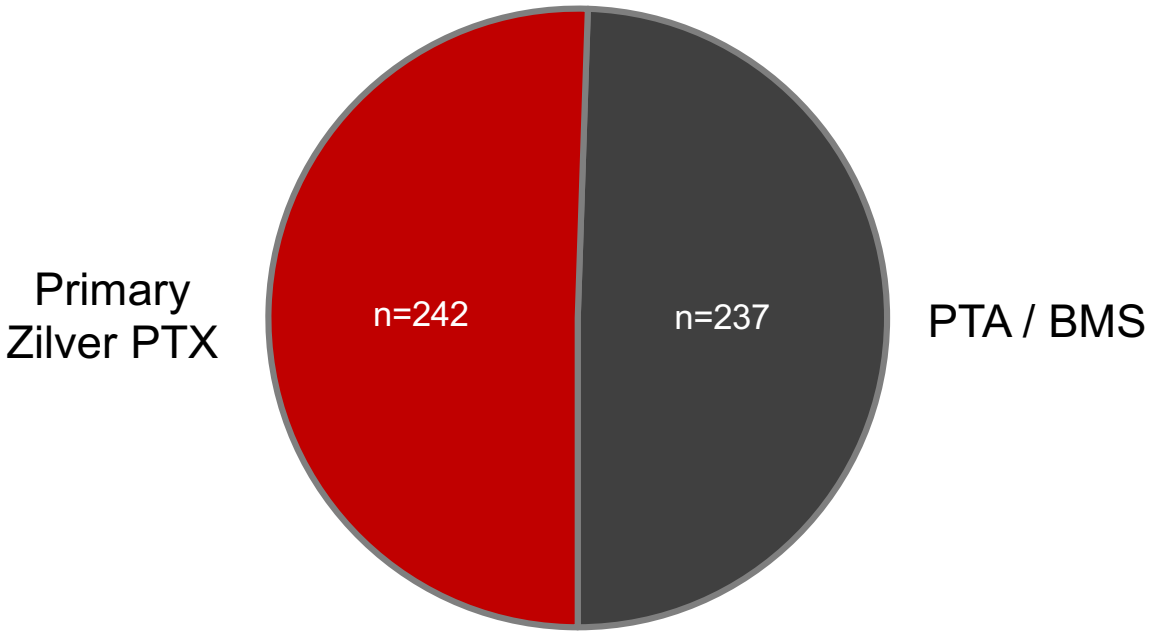
Actual Treatment = Primary + Secondary + Crossover



Results

Michael Dake, MD
Global Principal Investigator for Zilver PTX

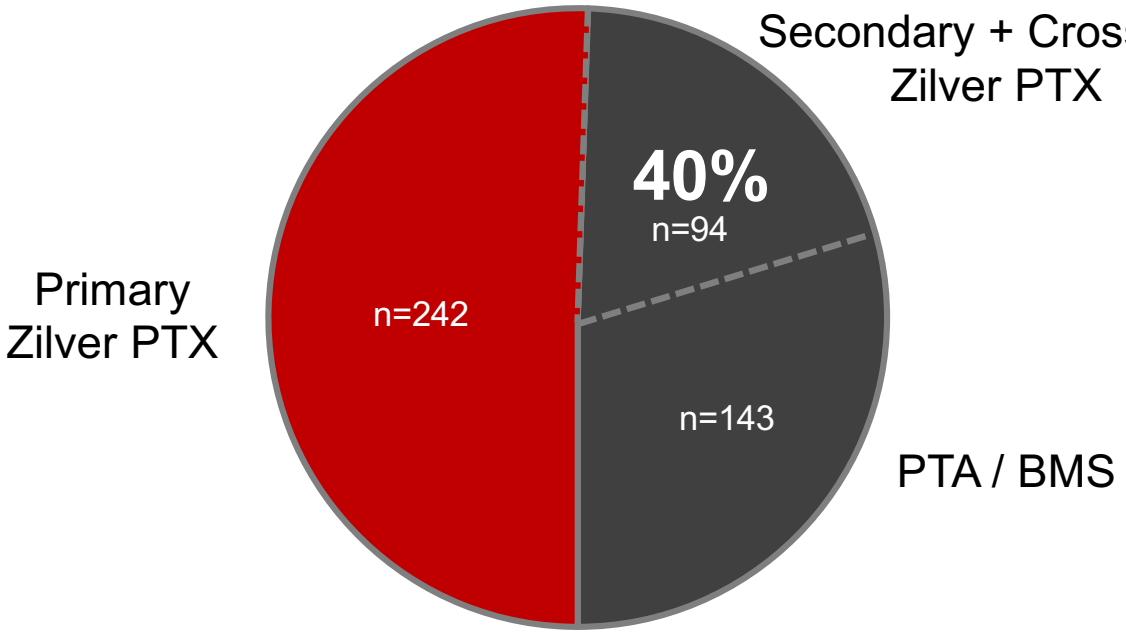
Primary Randomization



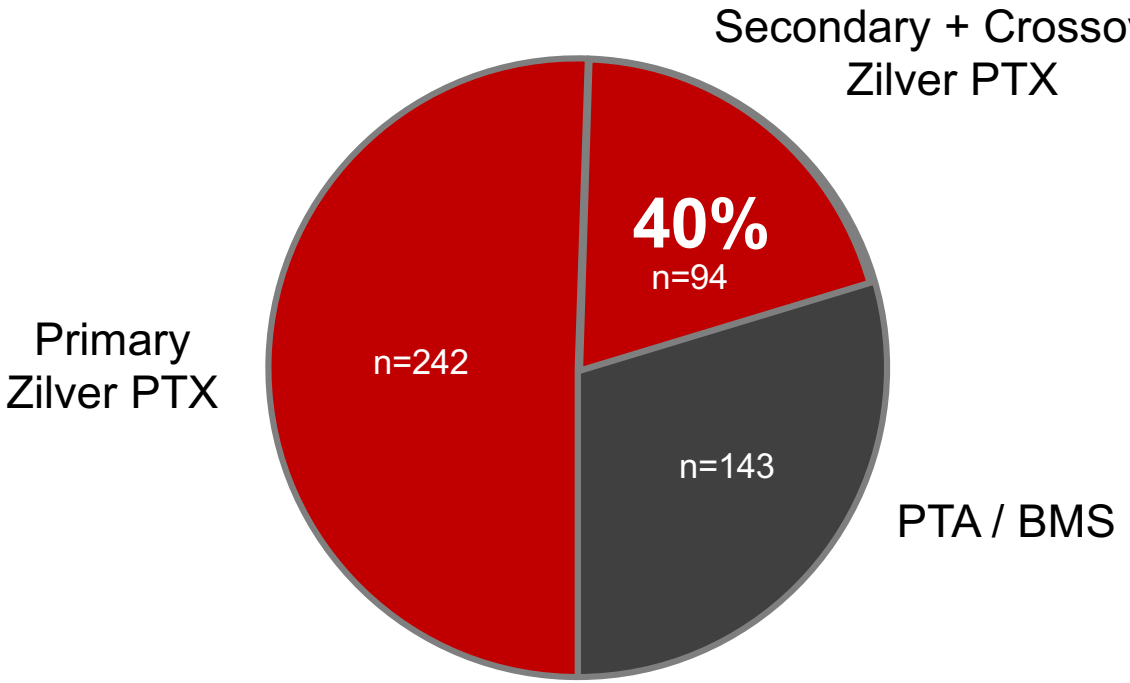
- Intent to treat is considered the standard for effectiveness
- Based on international standards, to evaluate safety we must analyze how patients were treated[1], not how they were randomized

[1] ICH E9: statistical principles for clinical trials, Section 6.3

Zilver PTX Patients in PTA/BMS Group

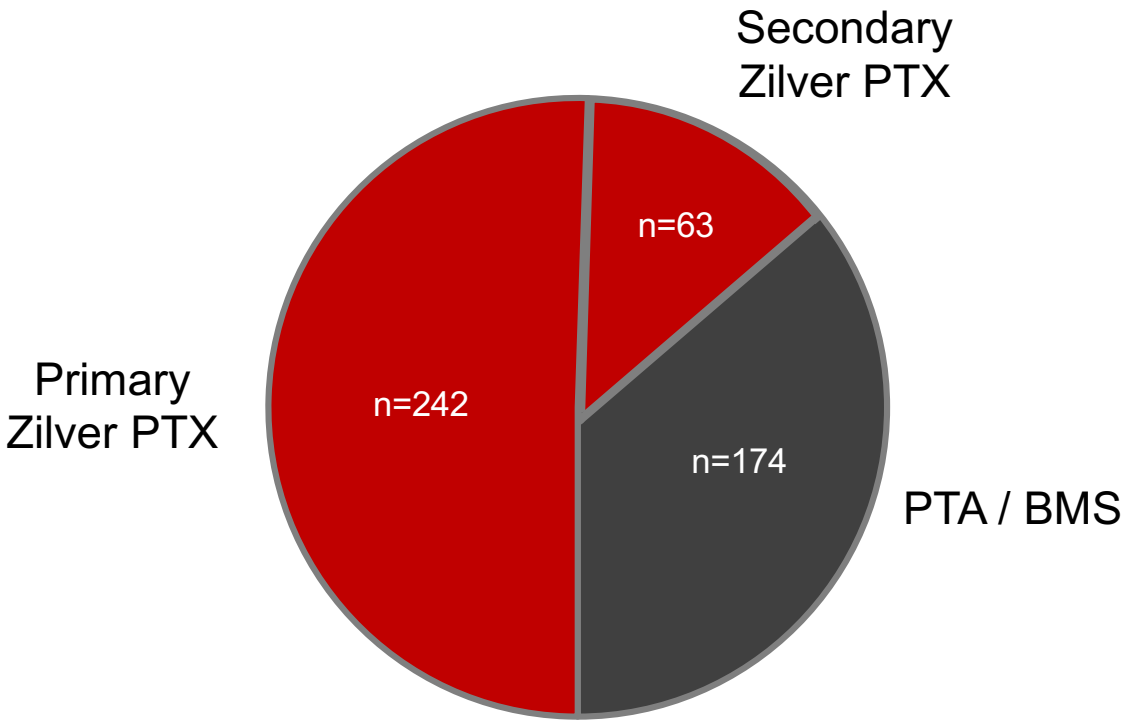


Zilver PTX Results Attributed to PTA/BMS

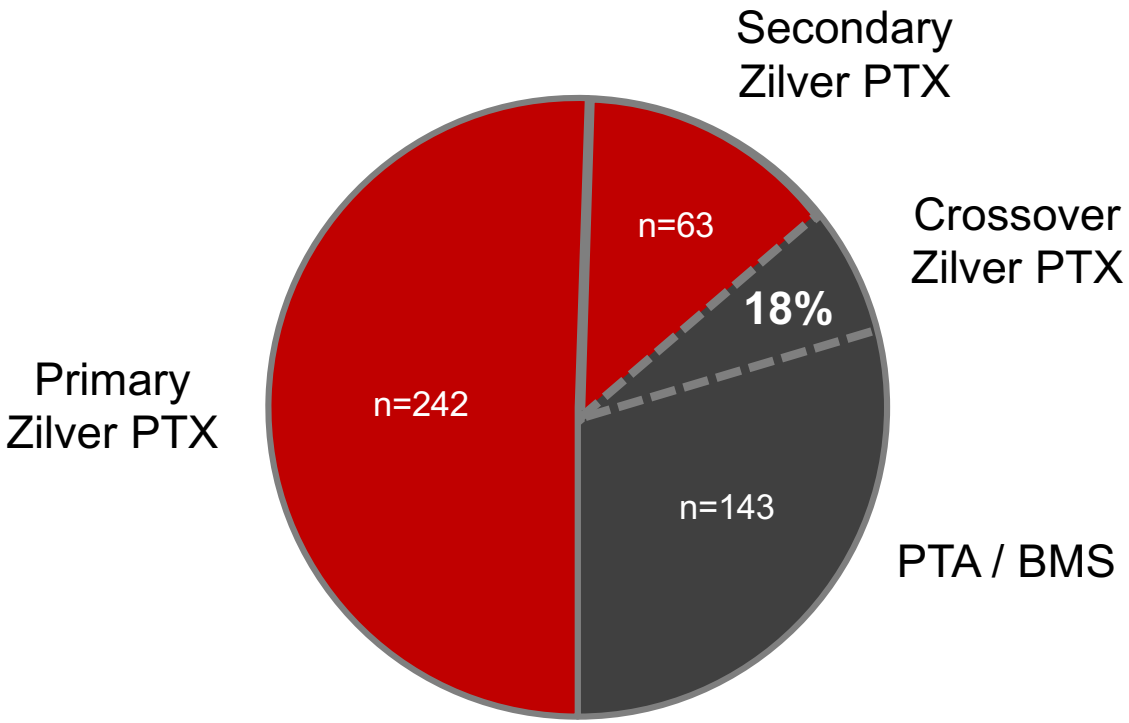


- 40% of the PTA/BMS group was treated with Zilver PTX
- Any analysis based on intent to treat is inappropriate for assessing paclitaxel mortality

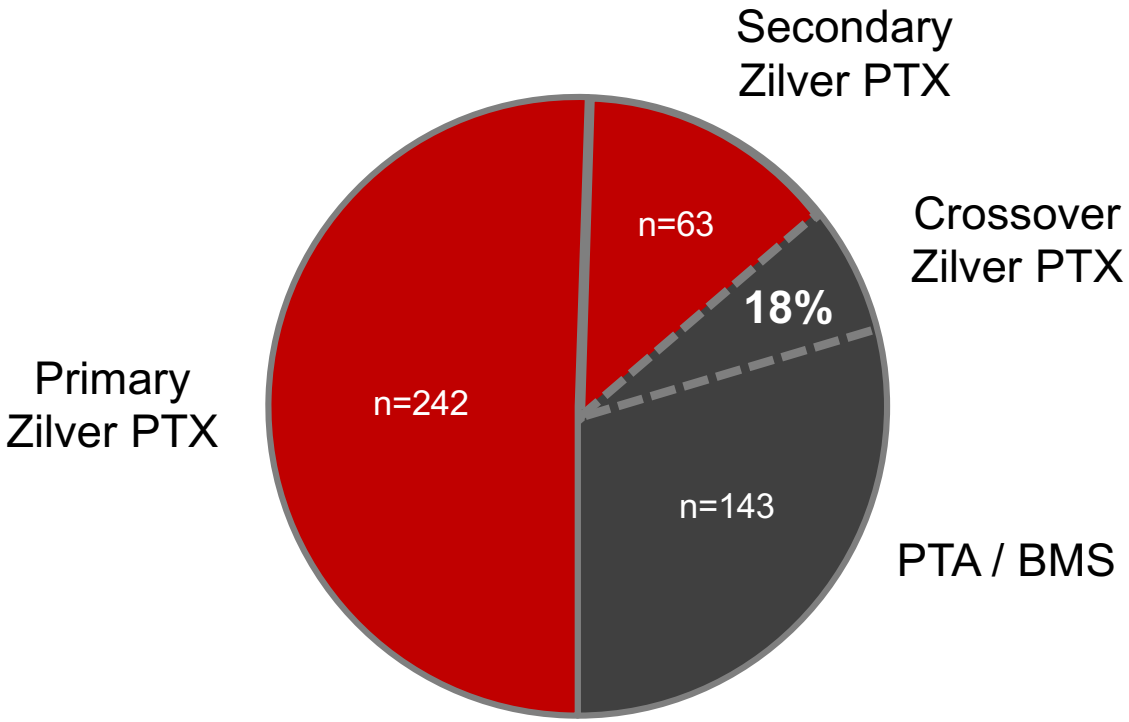
Secondary Randomization



Early Crossover



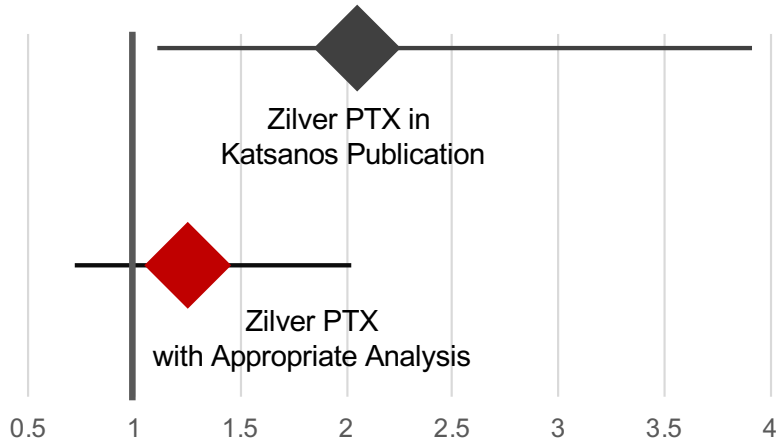
Zilver PTX Results Attributed to PTA/BMS



- Analyses by Katsanos, et al and FDA do not account for 18% of patients treated with Zilver PTX
- Zilver PTX mortality results were attributed to PTA/BMS group

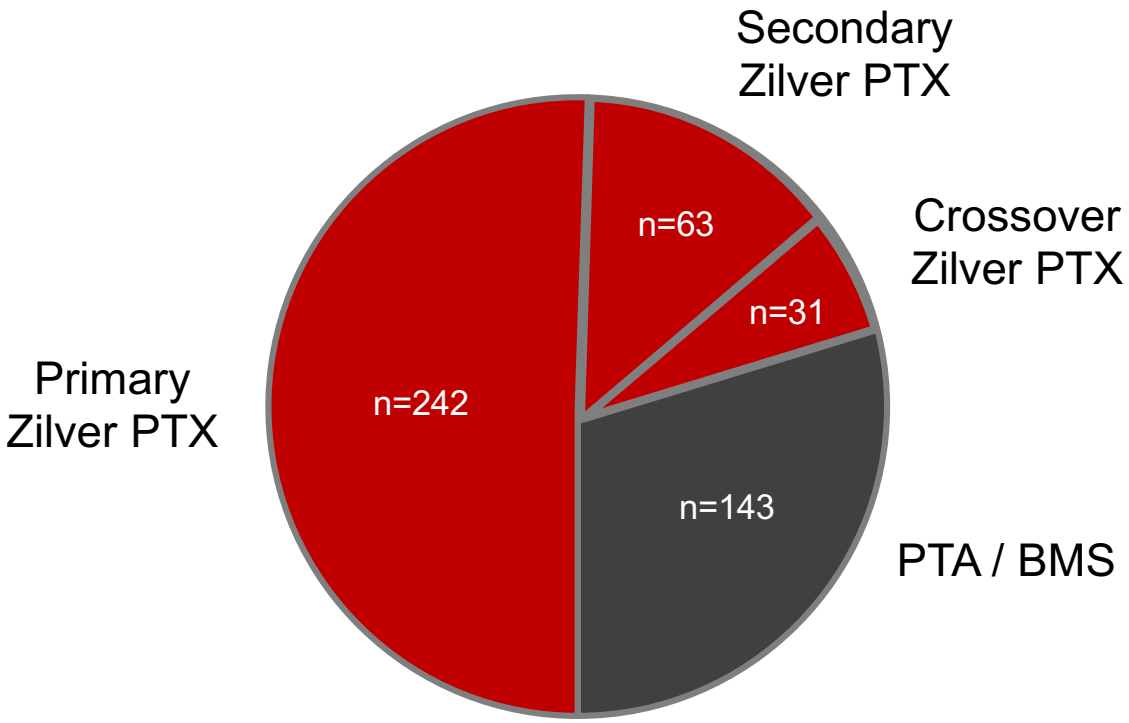
Paclitaxel Mortality Meta-Analysis

- Original analysis including 18% Zilver PTX in Control Group[1]
- Analysis including actual Zilver PTX treatment



- Evaluating all patients treated with Zilver PTX changes the conclusion
- In addition, the result of the meta-analysis becomes non-significant

Actual Treatment

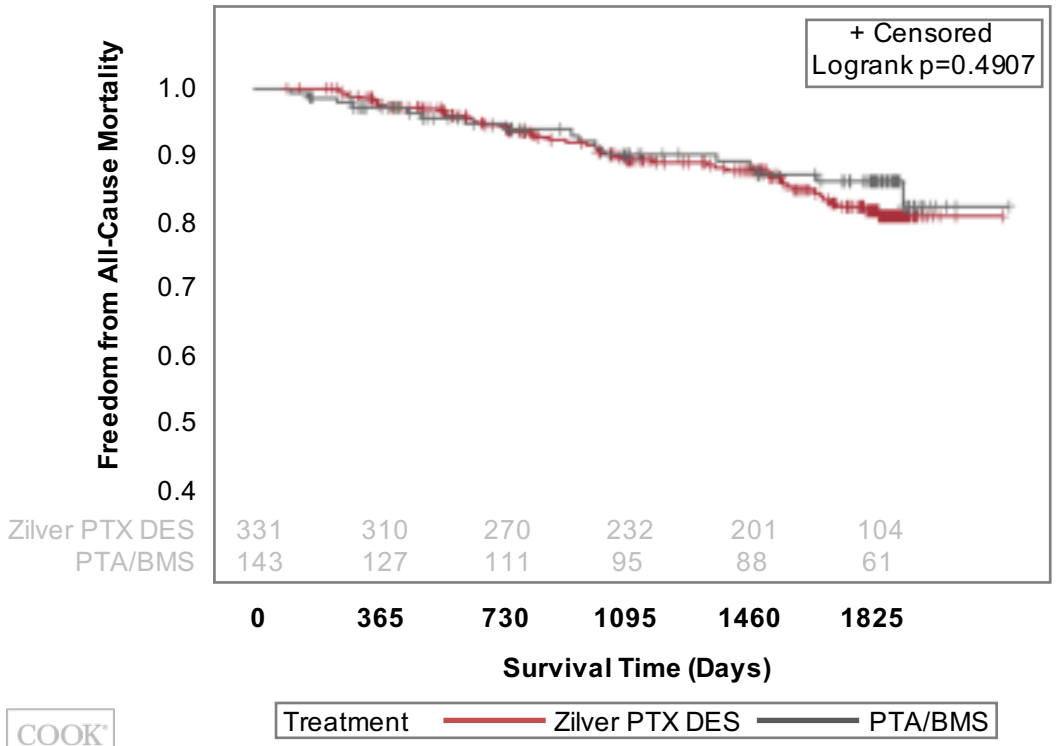


- Actual treatment is an appropriate assessment of paclitaxel-related mortality
- FDA modified as-treated analysis and Cook analysis include actual treatment

ZILVER PTX RCT

FDA Analysis of Actual Treatment

FDA Panel Pack (Appendix E)

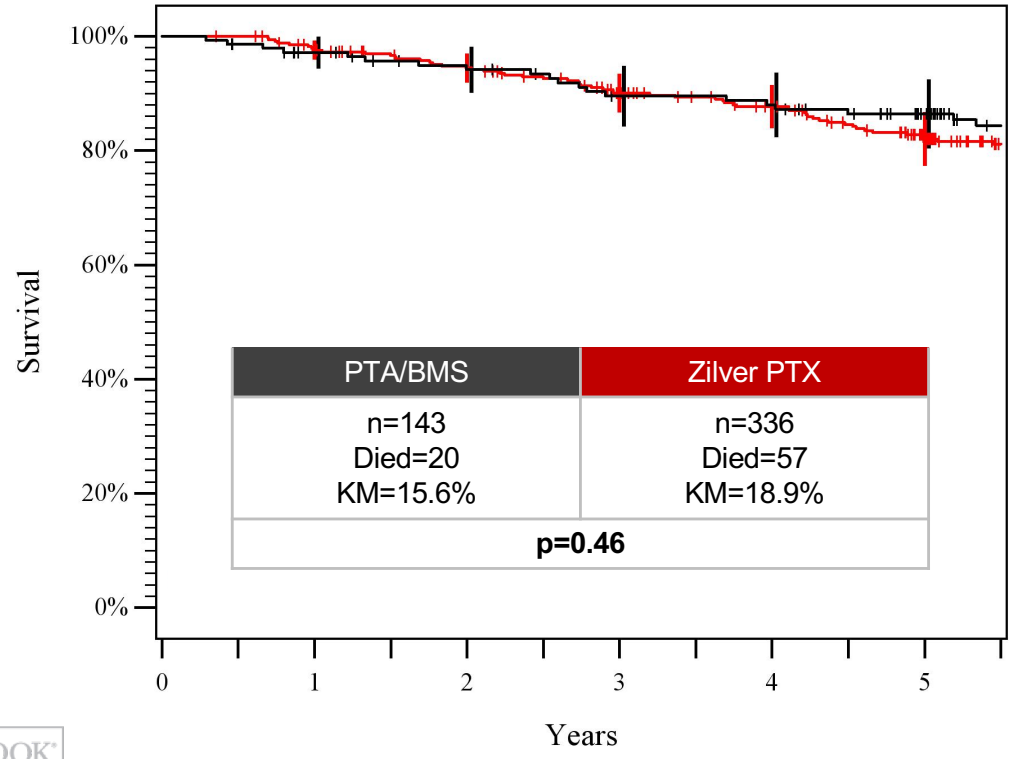


Note: The colors of the above graph were adjusted to be consistent with this presentation. No other changes were applied.

- All patients analyzed by actual treatment
- No mortality signal

ZILVER PTX RCT

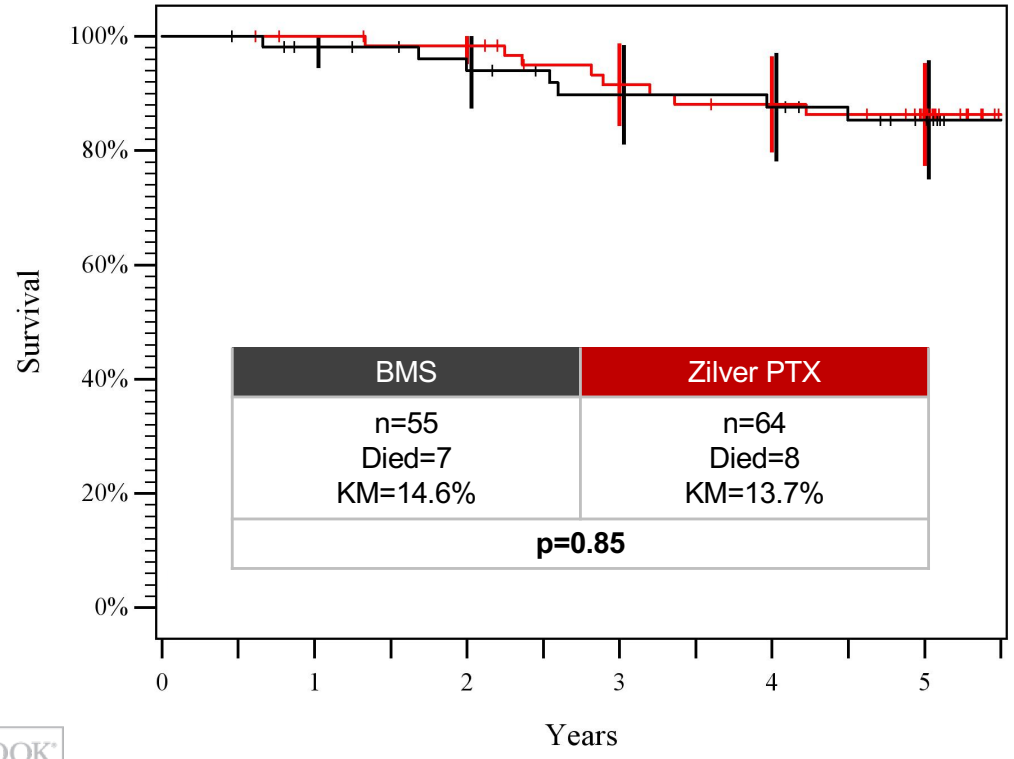
Cook Analysis of Actual Treatment



- Includes new patient status for 92% of patients previously lost-to follow-up
- Added data confirmed no mortality signal

ZILVER PTX RCT

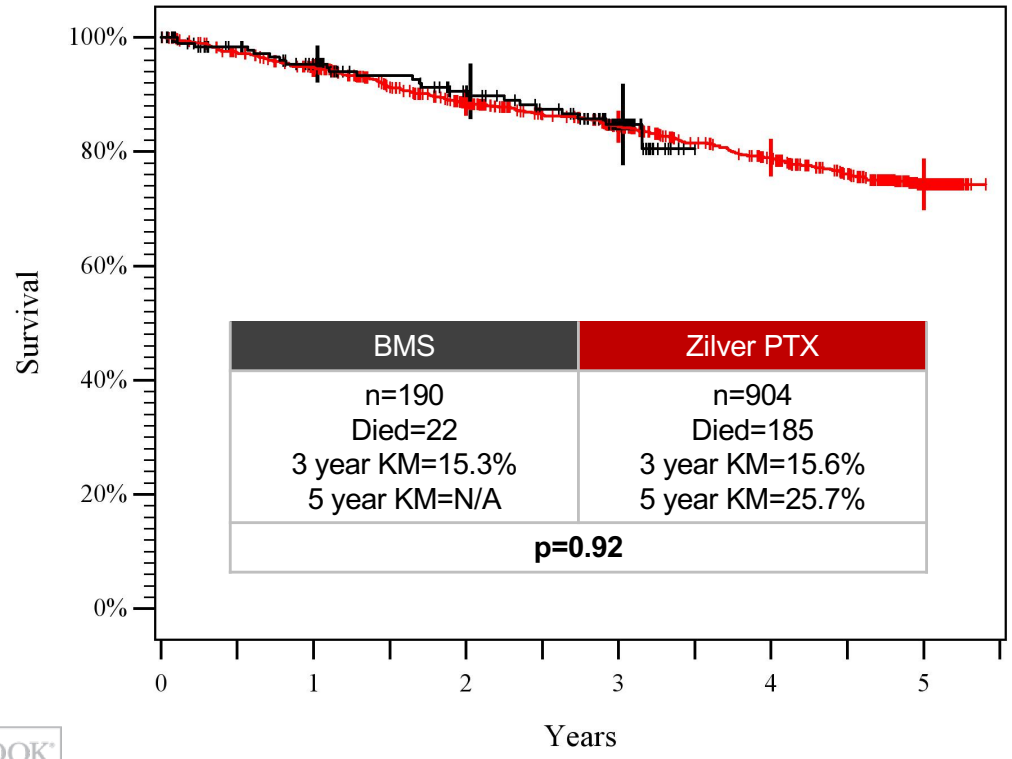
Randomized Comparison to BMS



- Head-to-head comparison of Zilver PTX to BMS
- No mortality signal

JAPAN POST-MARKET STUDIES

Japan PMS: No Mortality Signal

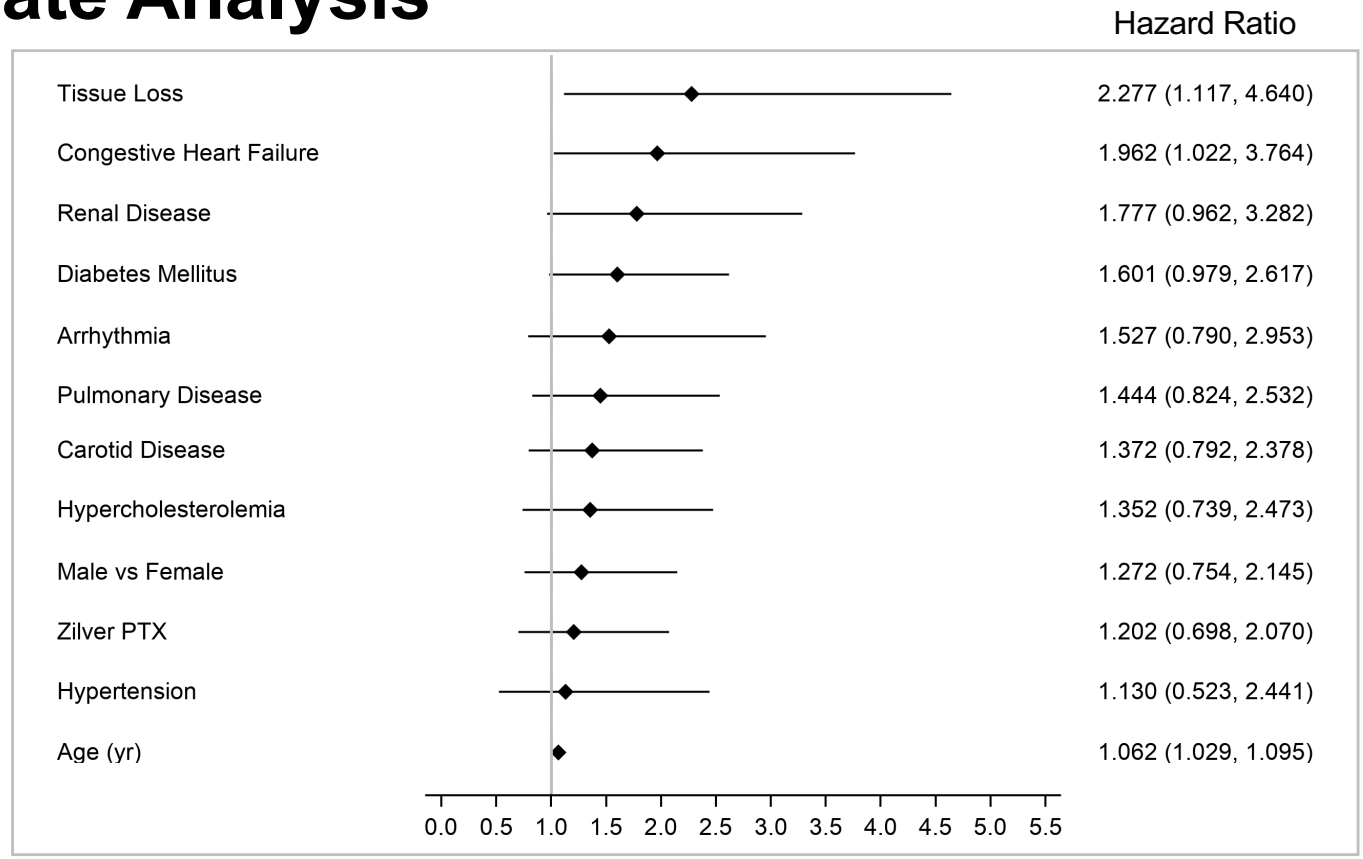


- Large, real-world, post-market studies
- No increase in rate of mortality after 3 years
- No mortality signal

Covariate Analysis

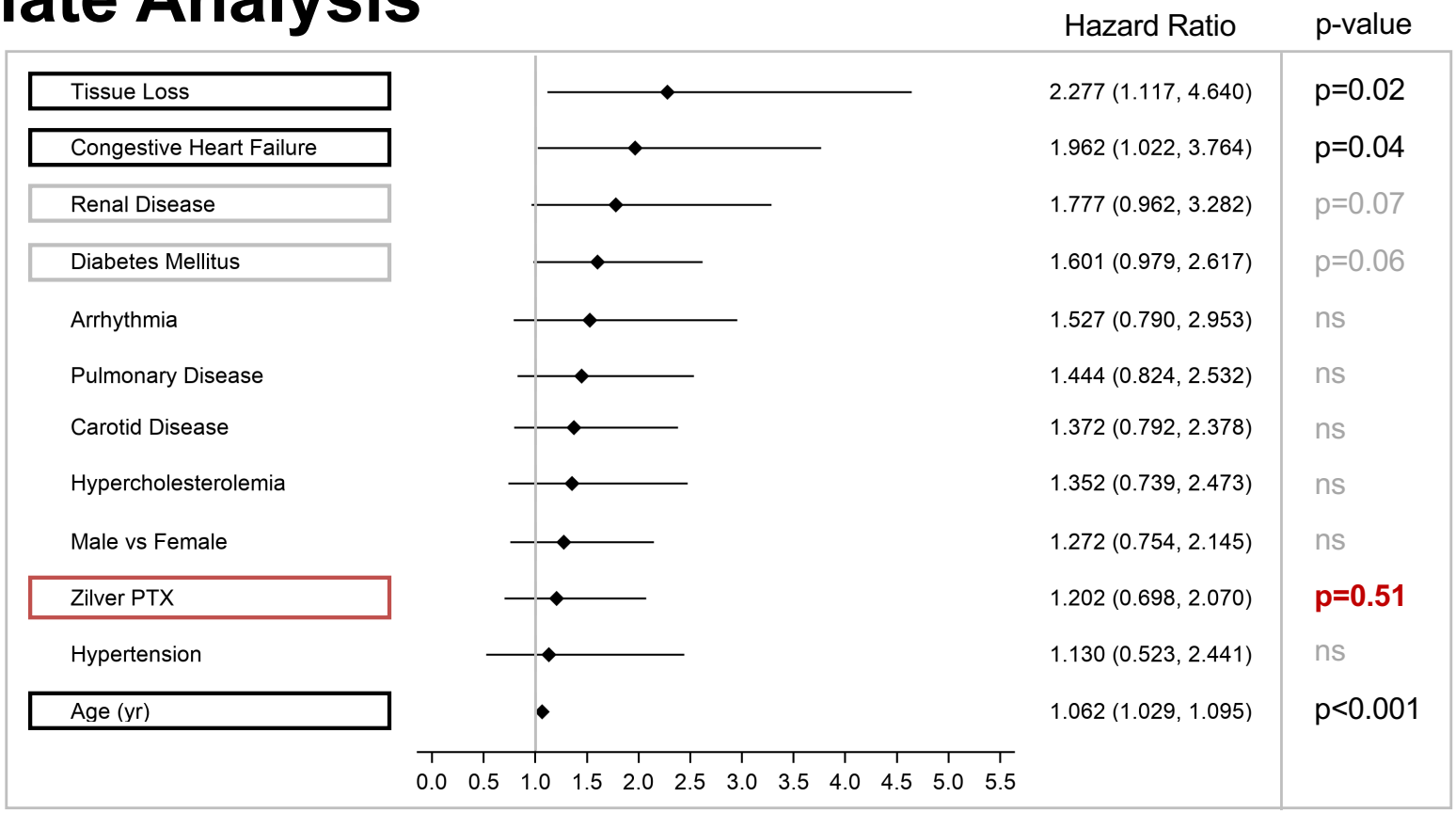
- No mortality signal for Zilver PTX when evaluating actual treatment
- What factors were associated with mortality?

Covariate Analysis



Additional non-significant factors included: smoking status, country, CLI/claudication, lesion length, previous MI, BMI

Covariate Analysis



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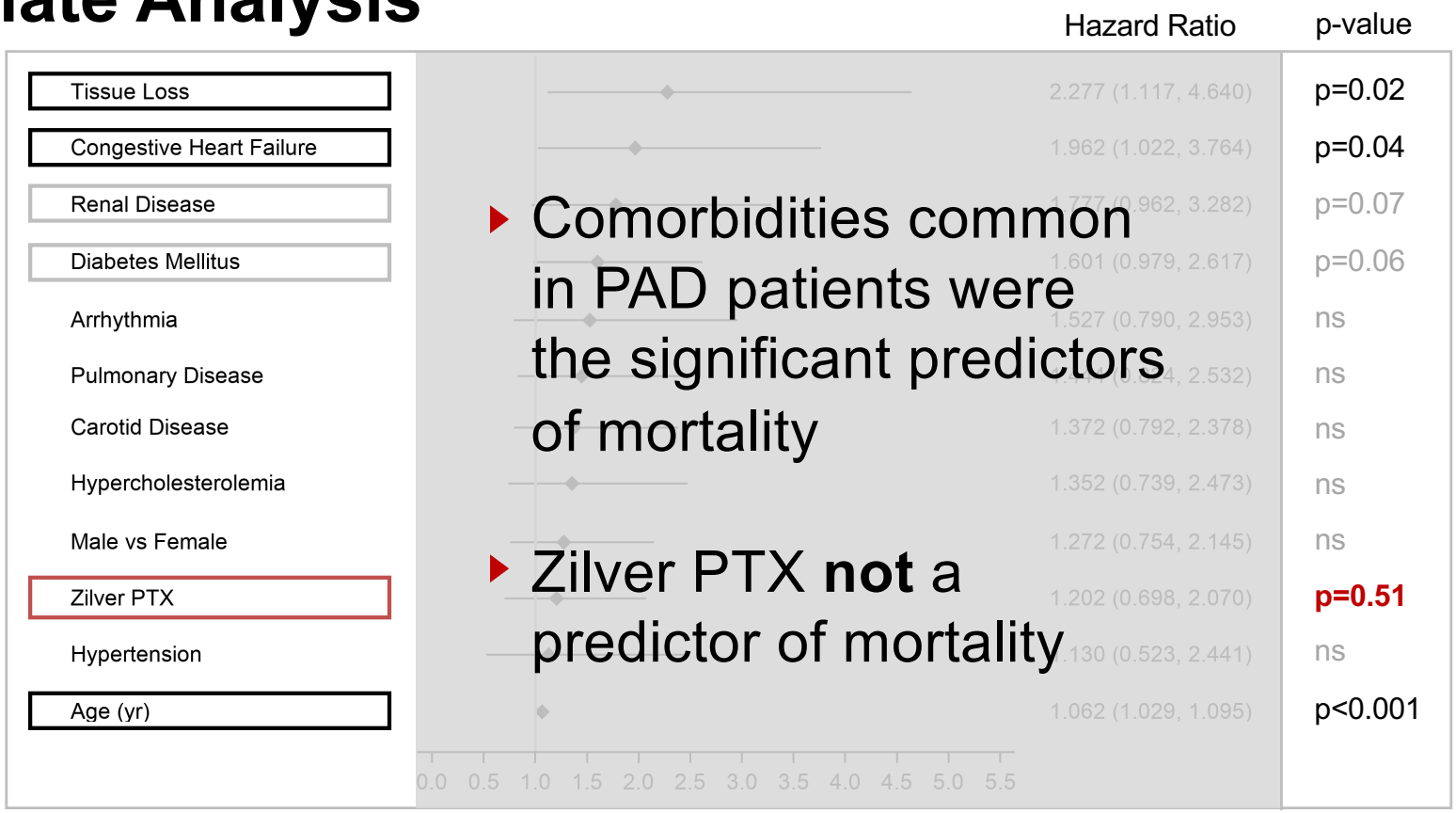
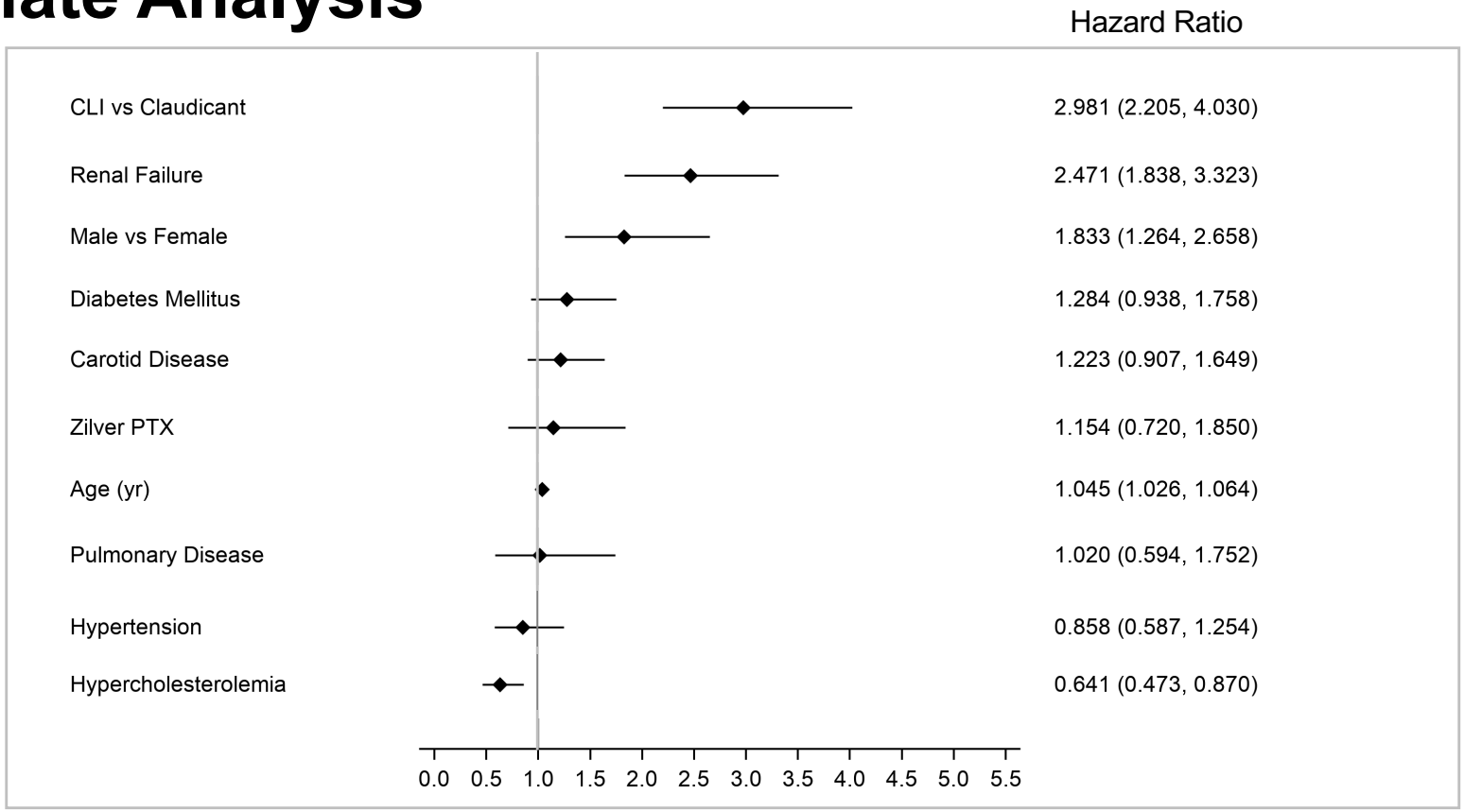
Covariate Analysis



- Comorbidities common in PAD patients were the significant predictors of mortality
- Zilver PTX **not** a predictor of mortality

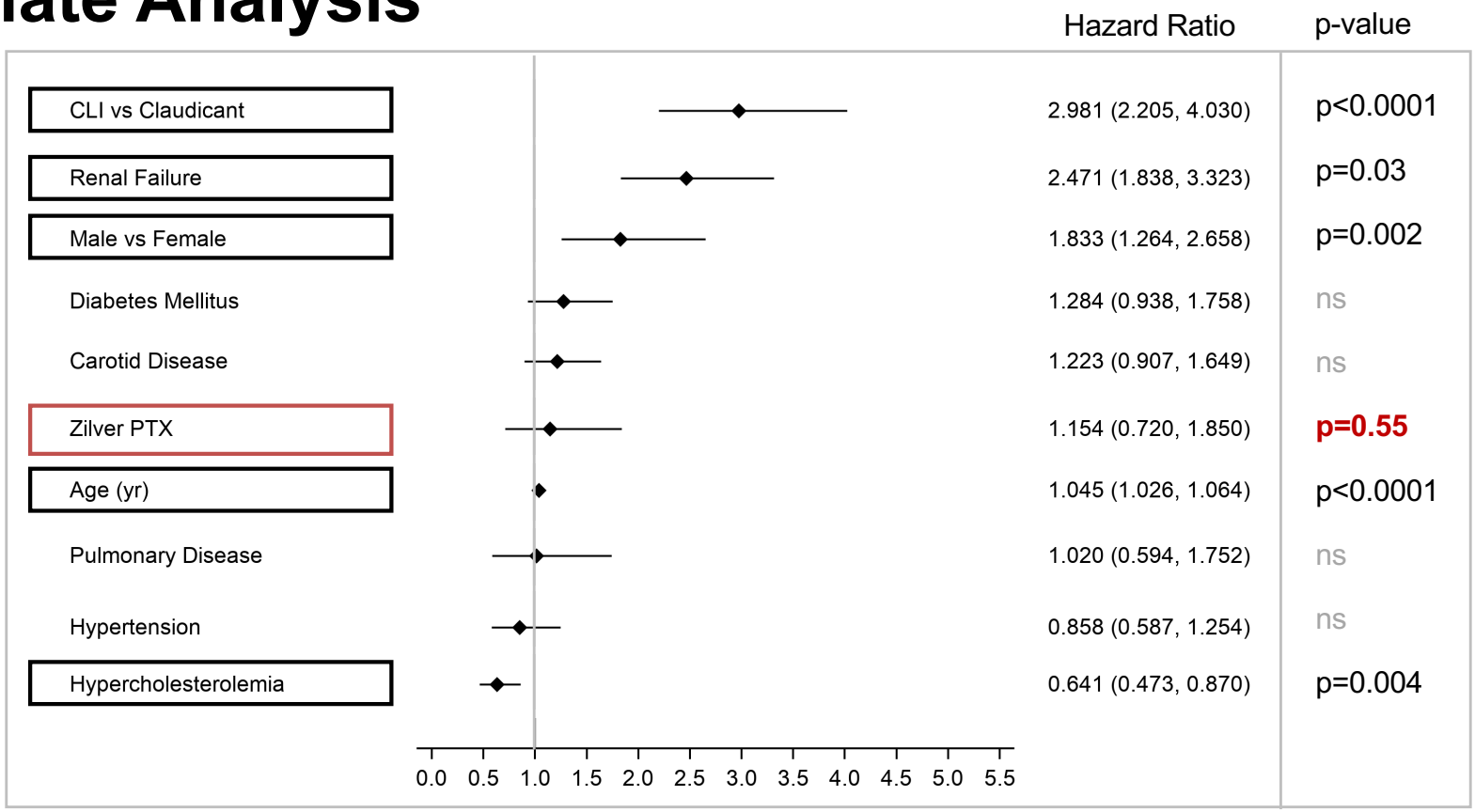
Additional non-significant factors included: smoking status, country, CLI/claudication, lesion length, previous MI, BMI

Covariate Analysis



Additional non-significant factors included: smoking status, lesion length

Covariate Analysis



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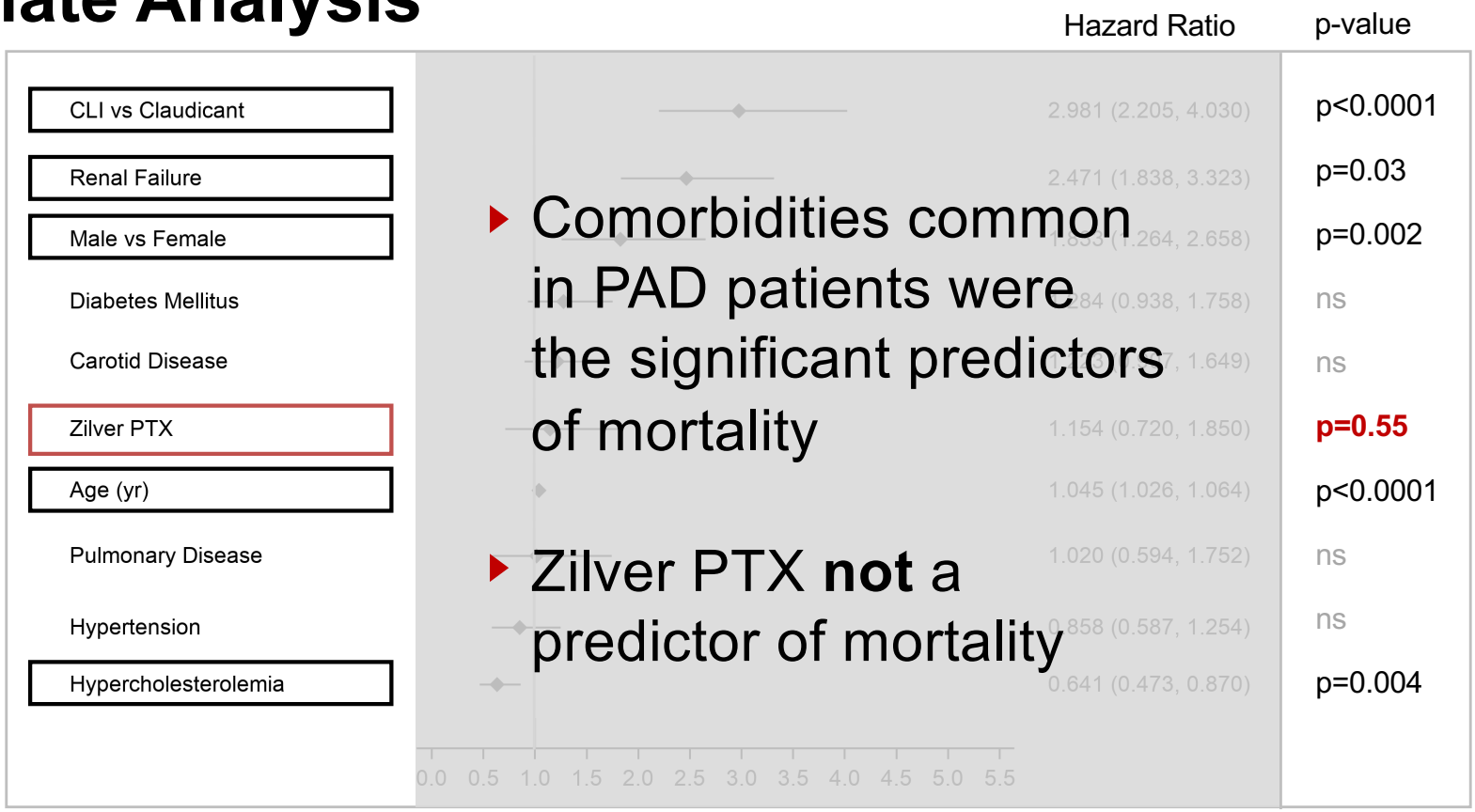
Covariate Analysis



- Comorbidities common in PAD patients were the significant predictors of mortality
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Additional non-significant factors included: smoking status, lesion length

Covariate Analysis: Dose

- Paclitaxel analyzed by dose (mg) per patient
- Significant predictors same as treatment arm analysis
  - RCT: Age, tissue loss, CHF
  - Japan: CLI, age, gender, renal, hypercholesterolemia

Study	Hazard Ratio	p-value
RCT	0.968 (0.659, 1.422)	**0.87**
Japan	1.162 (0.961, 1.404)	**0.13**

Covariate Analysis: Dose

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Study	Hazard Ratio	p-value
RCT	0.968 (0.[illegible], 1.22)	0.87
Japan	1.162 (0.961, 1.404)	0.13

Conclusion

- **Analysis must be based on actual treatment**

  Protocol defined secondary randomization and crossover must not be ignored

- **No mortality signal with Zilver PTX**

  When data are appropriately analyzed

- **Patient care is being negatively impacted**