Combined Manufacturer Presentation

FDA Panel Day 2

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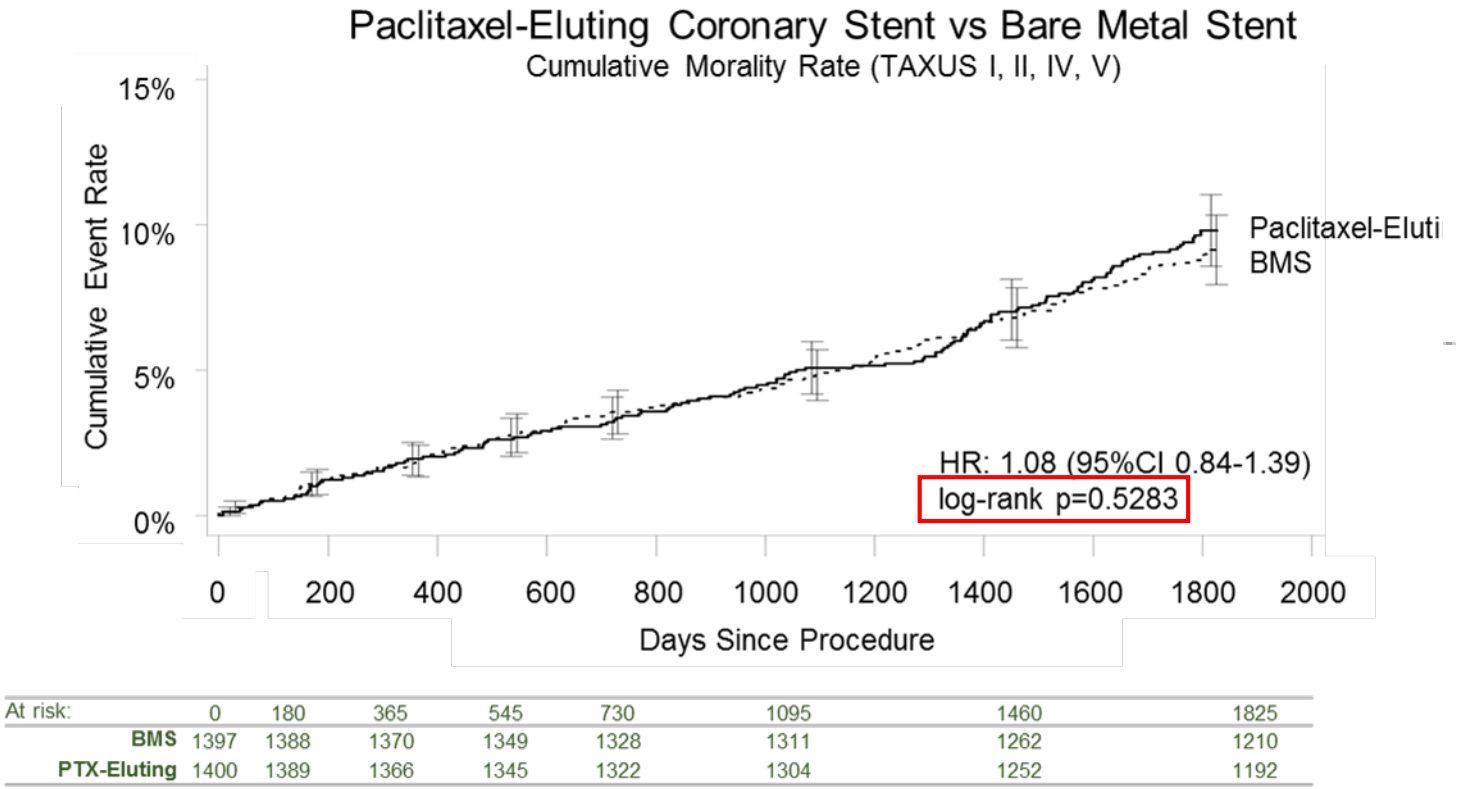
Agenda

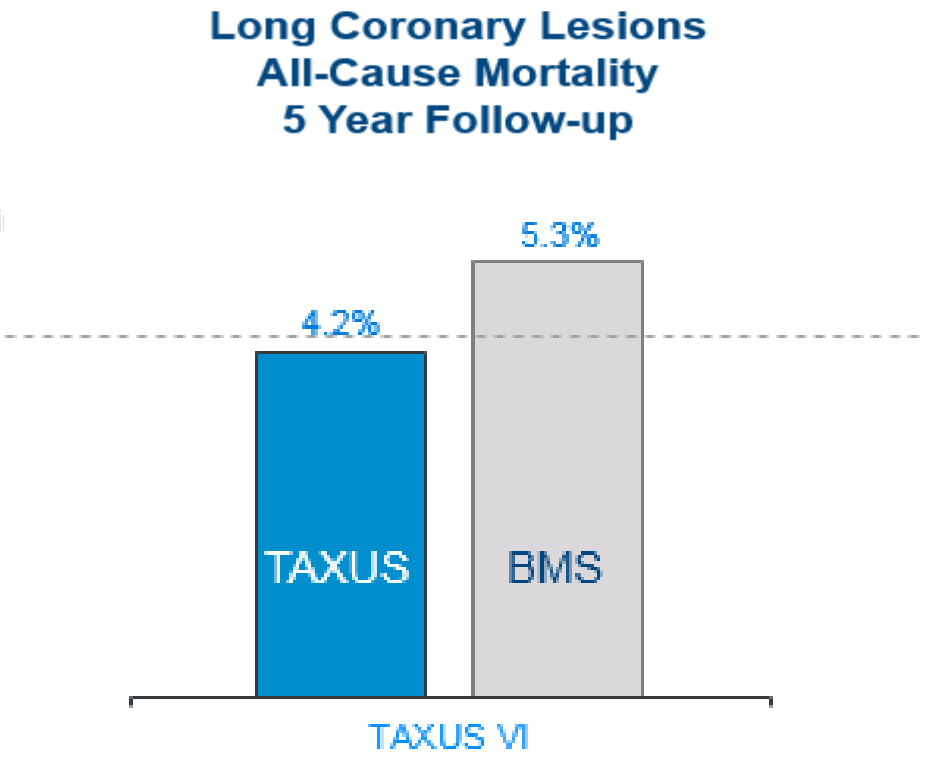
Dr. Daniel Clair	Ongoing Studies and Implications
Dr. Laura Mauri	Interpreting Multiple Sources of Safety Data
Dr. Eric Secemsky	Analysis of Medicare Beneficiary Data
Dr. Laura Mauri	Next Steps and Conclusion

No Signal Present in Randomized Trials of Paclitaxel Device Use in Other Vessel Beds – Coronary, Long Lesions

Boston Scientific TAXUS (PTX DES vs BMS) Patient-Level Meta-Analysis (~2800 Patients) 5Y All-Cause Mortality[1]



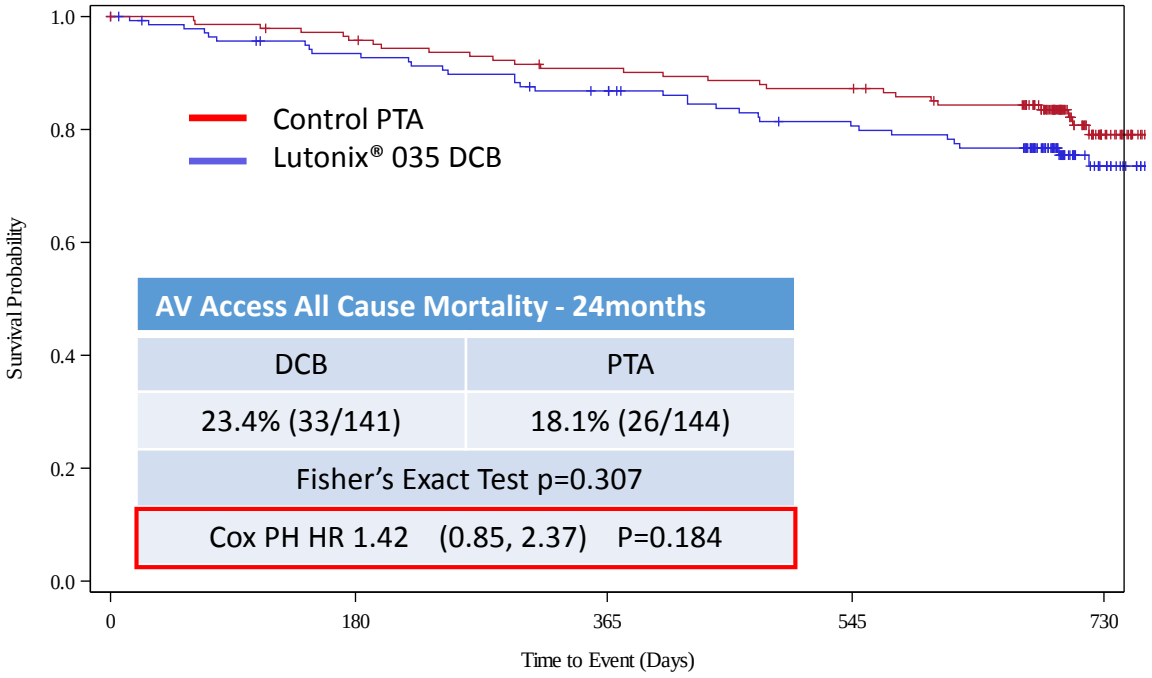
Boston Scientific TAXUS VI Randomized Trial (n=436)



1. Stone GW, et al. JACC Cardiovasc Interv. 2011;4(5):530-542.

No Signal Present in Randomized Trials of Paclitaxel Device Use in Other Vessel Beds – Arteriovenous Dialysis Access

Lutonix® 035 DCB AV Access Study: Survival through 24 months



AV Access All Cause Mortality - 24months	
DCB	PTA
23.4% (33/141)	18.1% (26/144)
Fisher's Exact Test p=0.307	
Cox PH HR 1.42 (0.85, 2.37) P=0.184	

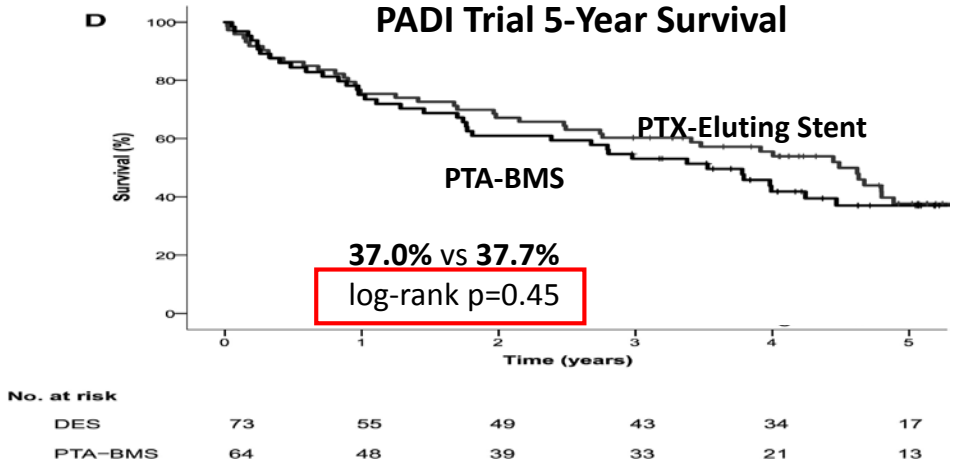
IN.PACT™ AV Access Study: All-Cause Mortality (Interim 12-mo Results[1])

All-cause Mortality	IN.PACT™ AV Access DCB (N=170)	PTA (N=160)	P-value[1]
Within cut-off of Apr 1, 2019[1]	**11.2% (19/170)**	**11.3% (18/160)**	**0.983**

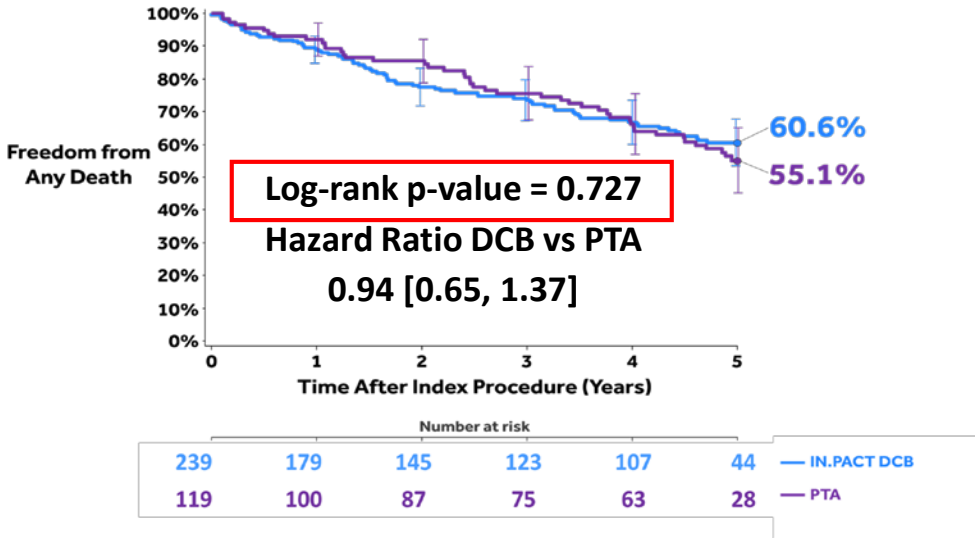
1. Interim results with 80% of patients completing 12-month follow-up.

No Signal Present in Randomized Trials of Paclitaxel Device Use in Other Vessel Beds – Below-the-Knee Arteries

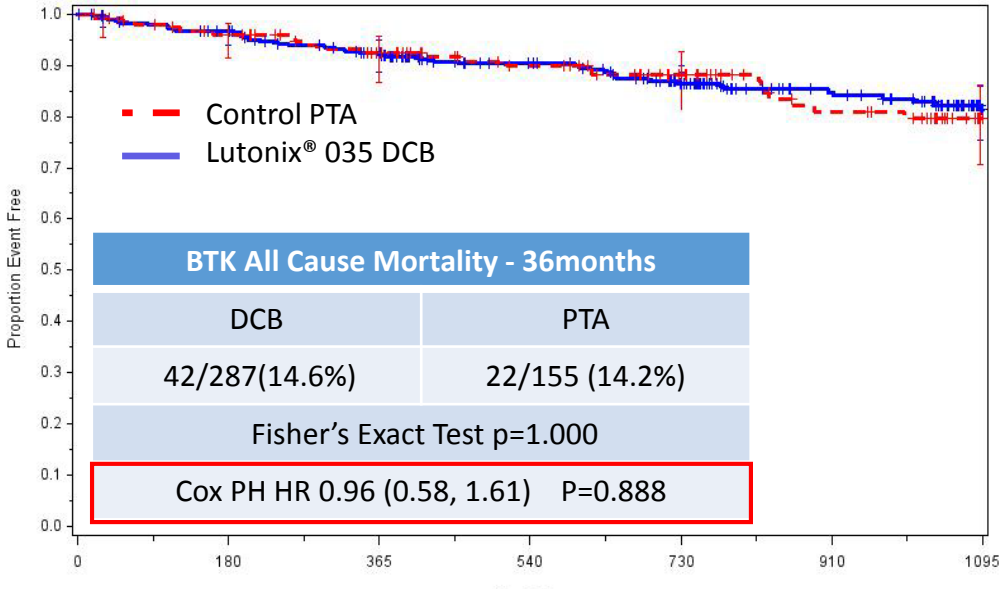
Boston Scientific



IN.PACT DEEP Study: Survival through 5 years

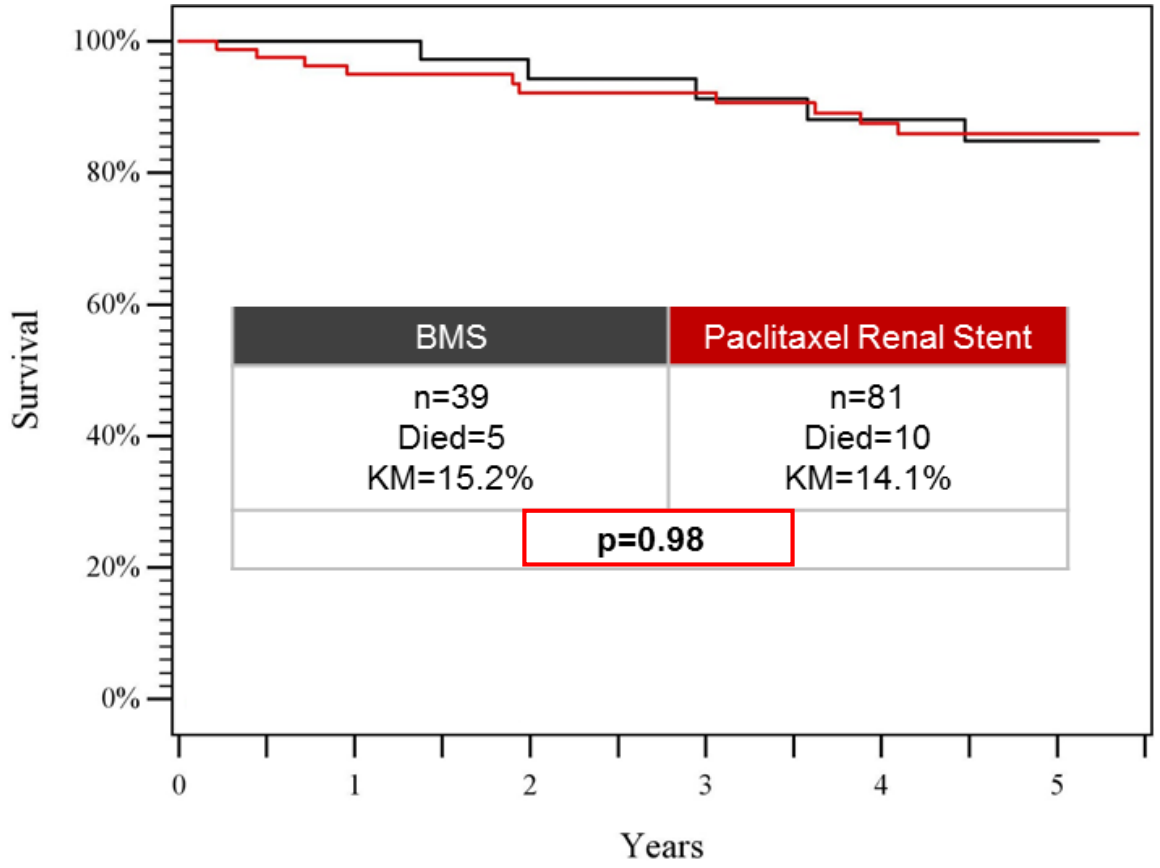


Lutonix® 014 DCB Below-The-Knee Study: Survival through 36 months (interim)



No Signal Present in Randomized Trials of Paclitaxel Device Use in Other Vessel Beds – Renal Arteries

Cook Medical Renal Paclitaxel-eluting Stent:
Survival Through 5 years



No Signal Present in Randomized Trials of Paclitaxel Device Use in Other Vessel Beds

- Coronary Arteries
- Arteriovenous Dialysis Access
- Below-the-Knee Arteries
- Renal arteries

- Paclitaxel devices have been commercially available for over 15 years.
- No mortality signal has been observed in randomized trials in multiple vessel beds.

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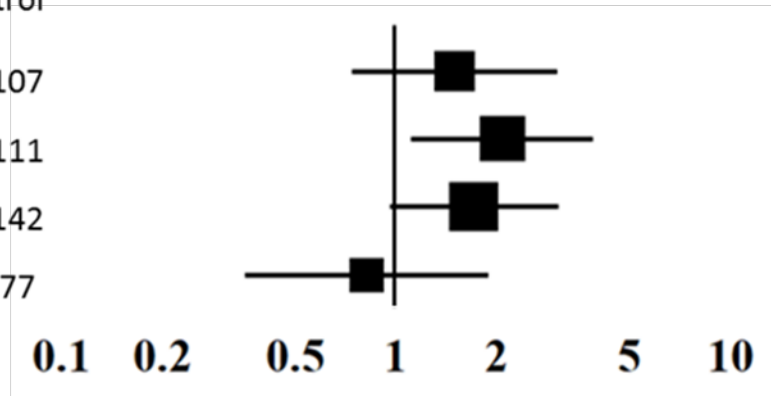
Interpreting Multiple Sources of Safety Data

	Avoidance of selection bias	Precision / Power	Generalizability	Requirements
Randomized Controlled Trial	+++	+	+	Unbiased ascertainment
Meta-Analysis of RCTs (trial-level or patient-level)	++	++	+	Quality and homogeneity of contributing RCTs
Large Real-World Comparative Analysis	+	+++	+++	Reliable adjustment to address selection bias

Available RCT Data are Limited in their Interpretation

	Risk ratio	Lower limit	Upper limit	Experiment	Control	Follow-up Time
Medtronic – SFA I/II	1.417	0.765	2.623	34/214	12/107	5y
Cook – Zilver	1.800	1.076	3.011	48/185	16/111	5y
BD – LEVANT 2	1.572	0.961	2.572	55/276	18/142	5y
Philips – ILLUMENATE	0.839	0.404	1.744	17/156	10/77	3y



Limitations

- Study design: designed to examine 1-year efficacy not long-term mortality
- Paclitaxel treatment: incompletely recorded before and after randomization with varied study designs
- Small sample sizes: unbalanced randomization with unstable estimates for mortality
- Missing data: high rates of withdrawal and lost to follow-up (initially 14-38% at 5 years)
- Variable adherence: risk factor modification, guideline medications, screening, medical care and visits
- Incomplete blinding: single blind, with unblinding after 1 year

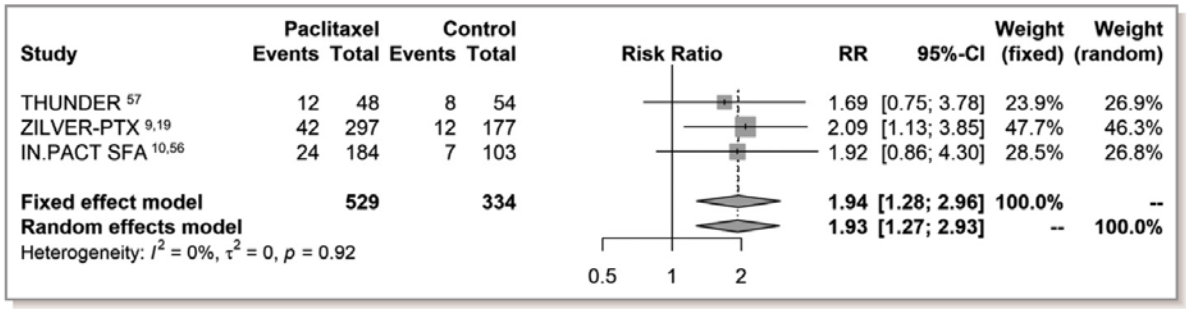
FDA Panel Packet "Paclitaxel-Coated Drug Coated Balloon and Drug-Eluting Stent Late Mortality Panel"; Appendix P Figures 13 (Philips – ILLUMENATE 3-yr data) and 14 (Medtronic – SFA I/II, Cook – Zilver, and BD – Levant 2 5-yr data).

Meta-Analyses are Limited by Heterogeneity and Quality of Data Collection

Examples of Study Heterogeneity

- Device types varied not just in dose, but also by excipient, presence of stent
- Trial variations
  - Definitions (e.g. patient and lesion characteristics, endpoints, adjudication)
  - Treatment cross-over varied (designed, allowed, prohibited)
  - Durations
  - Conduct and execution
- Removing one study or changing analysis population changes results
- Sensitive to large amount of missing data

JAHA Analysis[1]



VIVA/NAMSA Analysis[2]

VIVA-NAMSA Analysis Presented June 19, 2019	Hazard Ratio Paclitaxel vs. Control (95% CI)
Primary model	1.38 (1.06, 1.80)
As Treated, unadjusted	1.36 (1.04, 1.78)
As Treated, adjusted	1.37 (1.04, 1.80)
With additional long-term follow-up	1.30 (1.03, 1.63)
Censoring at control crossover to paclitaxel	1.31 (1.00, 1.72)
Missing data sensitivity / weighted analysis	1.36 (1.05, 1.77)
Fixed effects two-stage meta-analysis	1.36 (1.05, 1.77)
Random effects two-stage meta-analysis	1.34 (1.01, 1.78)
DCB devices only	1.25 (0.92, 1.69)
Using Zilver 2nd randomization instead of primary	1.19 (0.89, 1.60)

1. Katsanos K, et al. J Am Heart Assoc 2018;7:e011245. DOI: 10.1161/JAHA.118.011245.
2. Mullin C, presented at FDA Panel June 19, 2019.

Well-Conducted Large Observational Studies Increase Precision (~224k patients)

Data source/study population	Study Inclusion [Obs. period]	Follow-up	Methods	Sample Size	Hazard Ratio (P value)	95% CI
Vascular Quality Initiative (VQI)[1]	Sep '16 – Sep '17	Mean: 509 days	Propensity matching (1:1) analysis	4,880	**0.87 (0.12)**	0.73, 1.04
OPTUM (Medicare Advantage and commercial payors)[2]	Apr '15 – Dec '17 [Dec 31, 2018]	Median: 763 days	IPTW Cox model	20,536	**1.09 (0.11)**	0.98, 1.22
Medicare fee-for-service **inpatient** claims[3] Drug coated vs non-drug coated devices	Jan '16 – Dec '16 [Sep 30, 2017]	Median: 389 days	Multivariable Cox model	16,560	**0.97 (0.43)**	0.91, 1.04
Medicare fee-for-service **inpatient** claims[4] Drug-eluting vs bare metal stents	Dec '12 – Sep '15 [Dec 31, 2016]	Median: 2 years	Multivariable Cox model	51,456	**0.98 (0.53)**	0.93, 1.03
Medicare fee-for-service **inpatient and outpatient** claims[5] Drug coated vs non-drug coated devices	Jan '15 – Dec '17 [Apr 23, 2019]	Median: 799 days	IPTW Cox model	152,473	**0.94 (<0.001)**	0.93, 0.96

1. Bertges D, presented at SVS 2019.
2. Yeh RW, presented at FDA General Issues Panel June 20, 2019.
3. Secemsky E, et al., JAMA Cardiol. 2019. doi: 10.1001/jamacardio.2019.0325.
4. Secemsky E, et al., J Am Coll Cardiol. 2019;73:2636-2638.
5. Secemsky E, presented at FDA General Issues Panel June 19, 2019.

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Medicare Beneficiary Data Analysis: Characteristics Pre-Weighting

Characteristic (%)	Drug-Coated Device (N=61,507)	Non-Drug-Coated Device (N=90,966)	Standardized difference (%)
Age, mean ± SD	76.5 ± 7.4	77.0 ± 7.7	6.6%
Female	44.4%	45.1%	1.4%
Caucasian	83.3%	81.5%	4.8%
Critical limb ischemia	36.8%	40.0%	6.5%
Prior amputation	6.1%	7.4%	5.3%
Tobacco use	41.5%	44.1%	5.1%
Diabetes mellitus	34.8%	37.7%	6.0%
Heart failure	14.3%	16.0%	4.8%
Chronic lung disease	19.0%	21.0%	5.2%
Renal failure	18.1%	20.3%	5.5%
Liver disease	1.2%	1.4%	1.9%
Obesity	6.4%	7.2%	3.1%
Malignancy	1.9%	2.3%	2.7%
Stent	40.8%	37.6%	6.5%
Atherectomy use	42.7%	31.2%	24.1%
Inpatient	31.8%	39.9%	16.9%
Procedural volume	217.9 ± 181.5	188.8 ± 159.0	17.1%

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Critical limb ischemia	36.8%	40.0%	6.5%
Prior amputation	6.1%	7.4%	5.3%
Tobacco use	41.5%	44.1%	5.1%
Diabetes mellitus	34.8%	37.7%	6.0%
Heart failure	14.3%	16.0%	4.8%
Chronic lung disease	19.0%	21.0%	5.2%
Renal failure	18.1%	20.3%	5.5%
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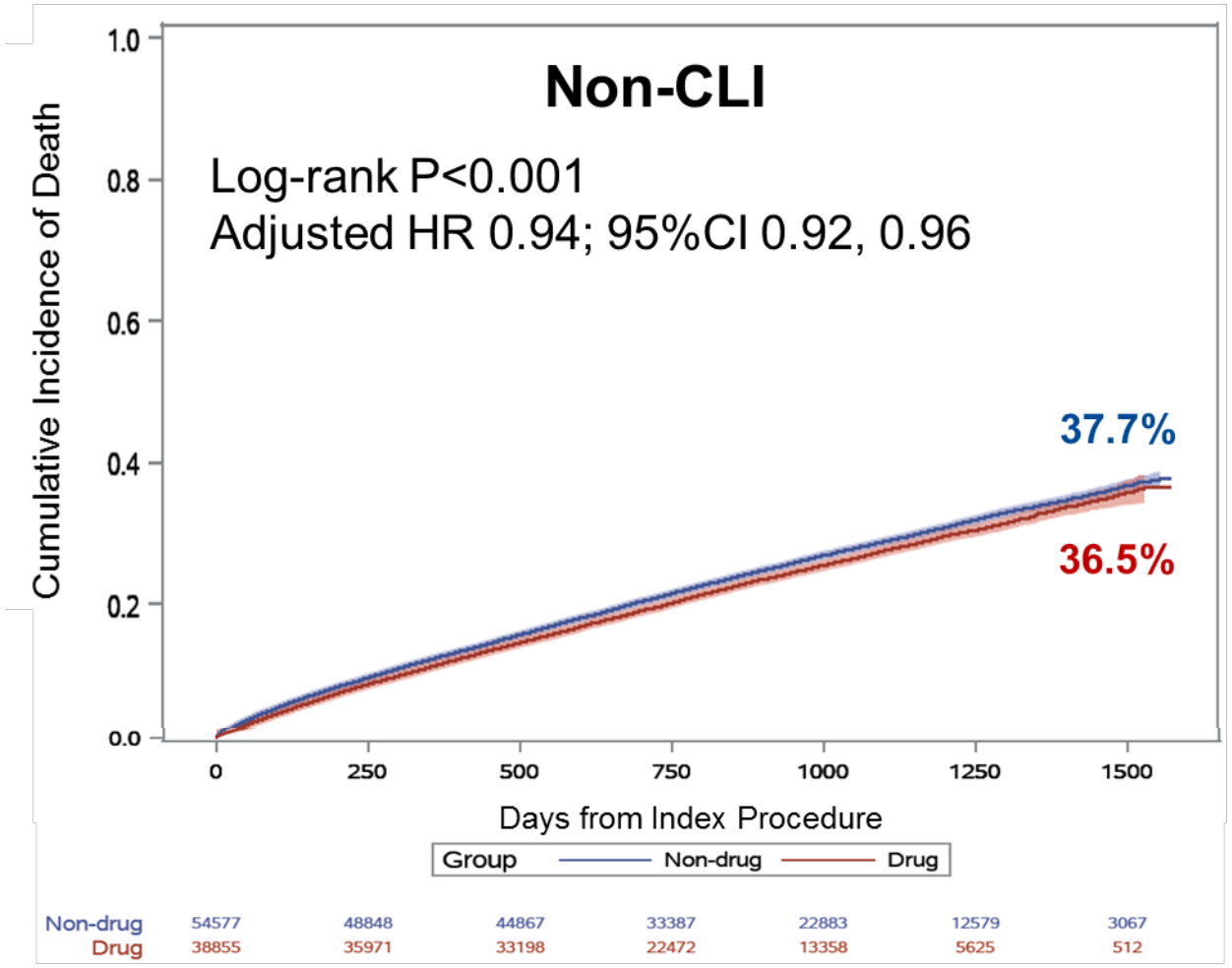
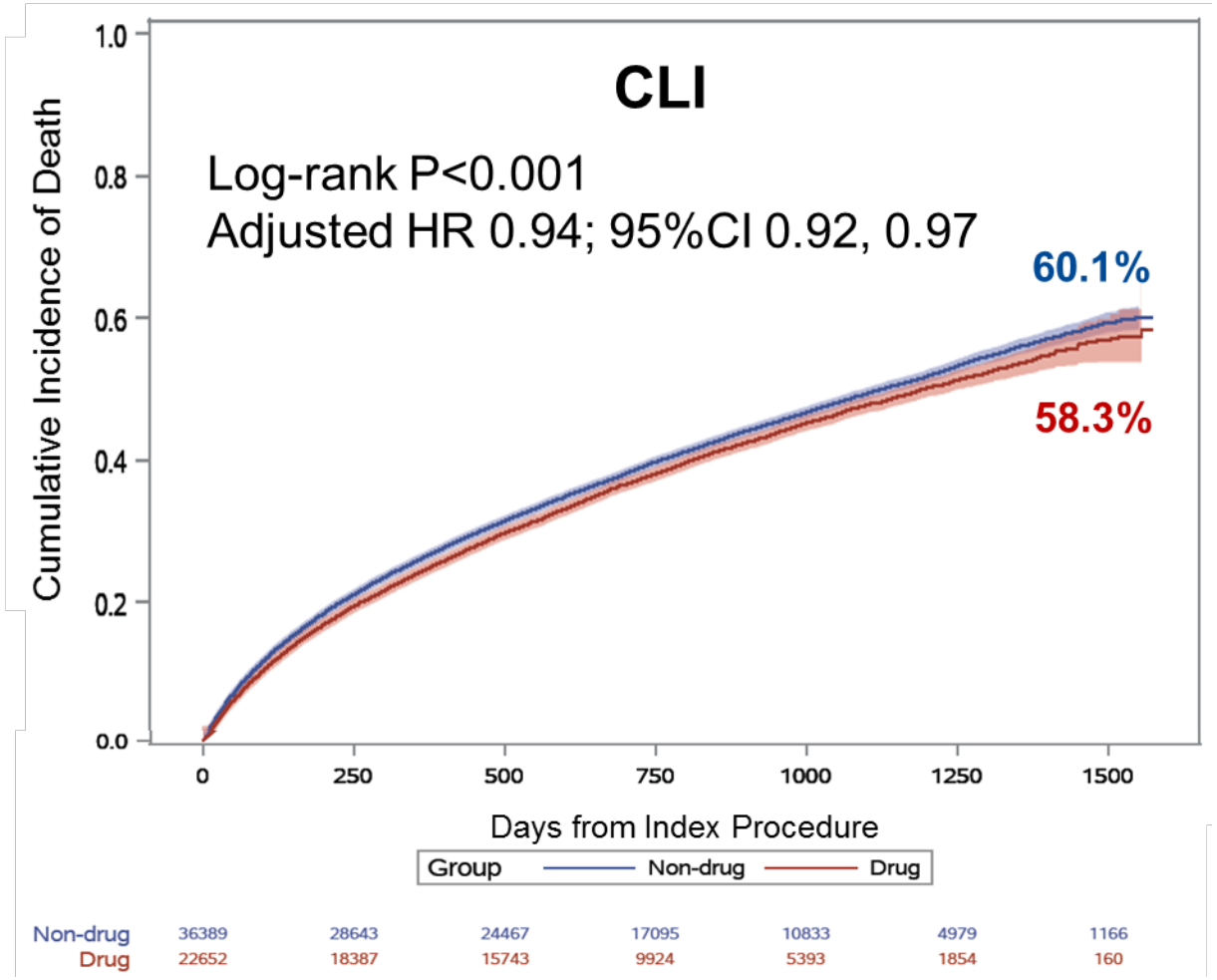
Medicare Beneficiary Data Analysis: PAD Severity - Weighted Results

Non-CLI: 61.3% (N=93,432)



CLI: 38.7% (N=59,041)



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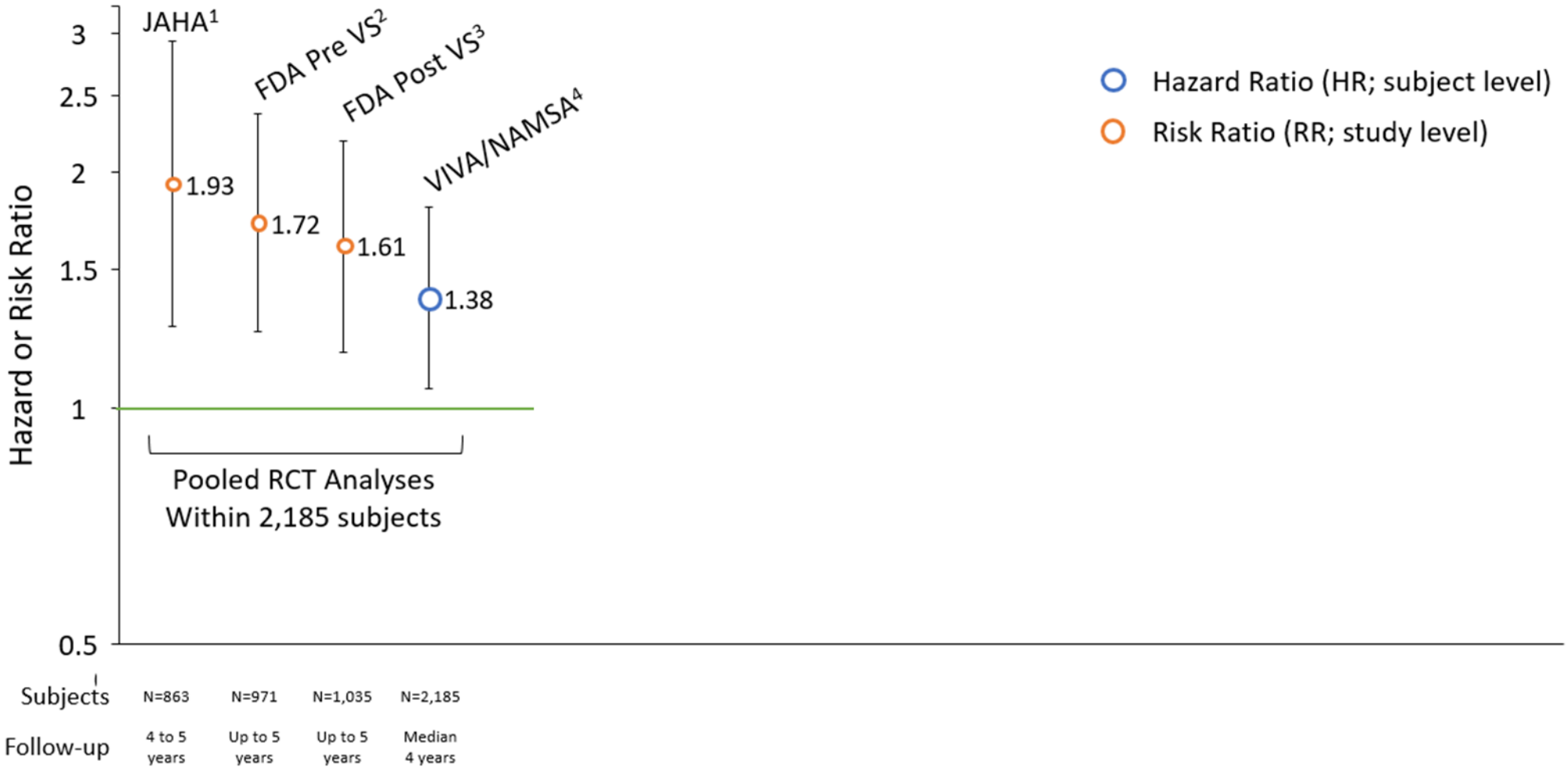
Large Well-Conducted Observational Studies Demonstrate No Mortality Signal



1. Katsanos. K. JAHA 2018; 7:e011245.
2. FDA Analysis, pre vital status.
3. FDA Analysis, post vital status.
4. VIVA-NAMSA Analysis. June 3, 2019.

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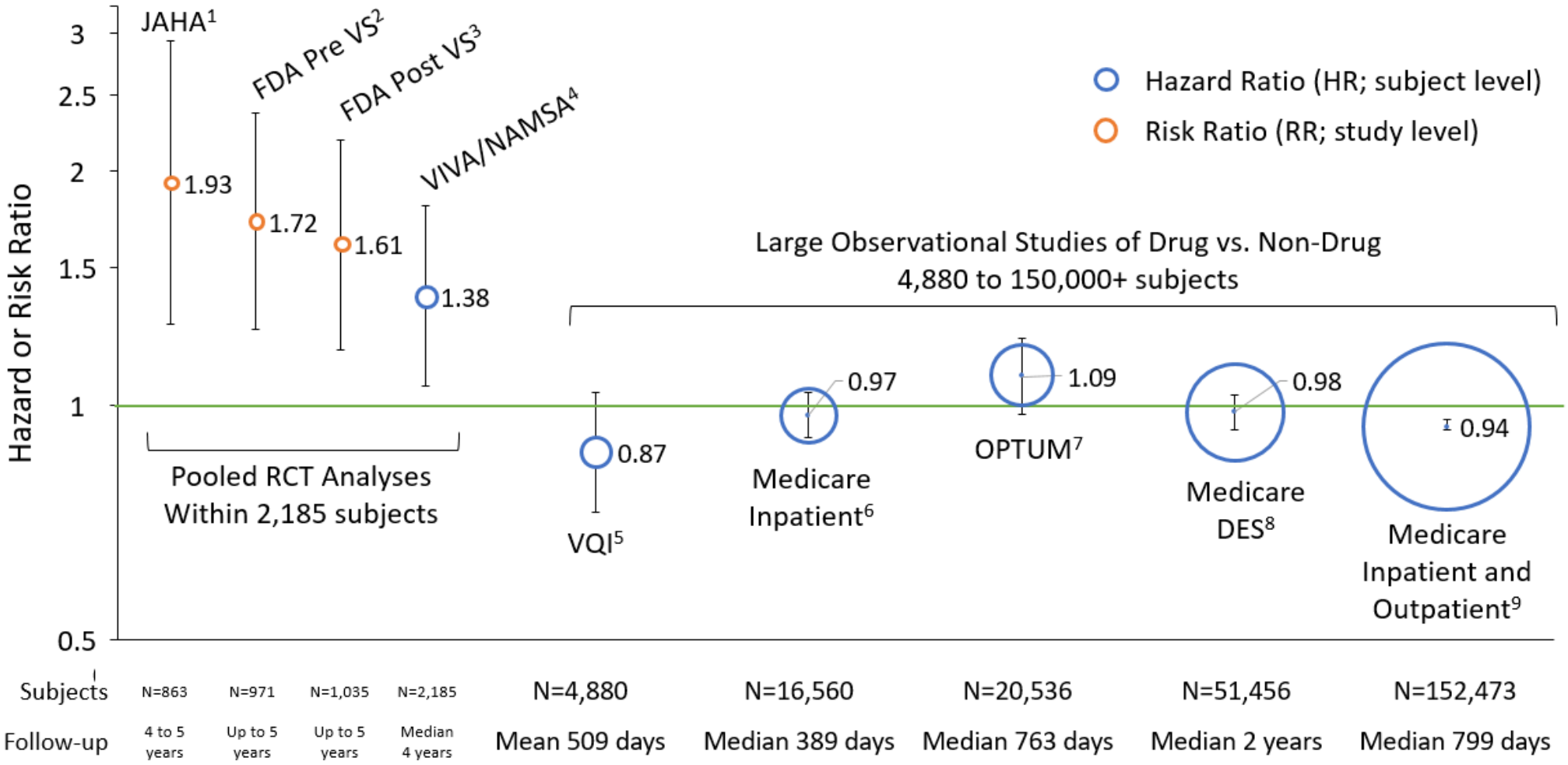

1. Katsanos. K. JAHA 2018; 7:e011245.
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5. Bertges DJ, SVS Abstract 2019.
6. Secemsky EA et al. JAMA Cardiol 2019.
7. Yeh RW, FDA Presentation, June 19-20, 2019.
8. Secemsky EA et al. J Am Coll Cardiol 2019;73:2636-2638.
9. Secemsky EA, FDA Presentation, June 19-20, 2019.

For specific adjustments and methodologies, see the cited publications

Industry Responses to FDA Panel Questions 1 – 5

FDA Question	Response
1. Presence of Signal	• Presence of a signal in meta-analysis, not in well-designed observational comparisons

2. Class Effect	• Cannot conclude a common class effect for late mortality
	  • Inconsistent observations across studies and sponsors
	  • Differences in device platforms

3. Impact of Missing Data	• Previously missing vital status data introduced uncertainty • Updated vital status information reduces observed mortality difference • RCTs did not uniformly collect treatment before and after randomization (e.g. additional paclitaxel, medical therapy)
4. Subgroup Analysis	• Predictors of mortality are those expected from PAD patient population, not paclitaxel • No clear treatment interactions by subgroups
5. Cause of Death	• No clustering of adverse events or mortality patterns to support a causal mechanism

Industry Responses to FDA Panel Questions 6 – 12

FDA Question	Response
6. Paclitaxel Dose/Mortality Relationship	• No paclitaxel dose-mortality relationship observed
7. Pre-clinical Studies	• Pre-clinical studies in paclitaxel devices do not demonstrate a plausible mechanism for late mortality • New pre-clinical studies are unlikely to yield additional insight
8. Benefit-risk Profile	• Totality of evidence exhibits consistent effectiveness and improvement in quality of life with paclitaxel devices • Updated data & analyses (RCTs, large high-quality observational studies) show long-term safety • Benefit-risk profile supports paclitaxel devices as first-line therapies for treatment of PAD
9. Post-market Studies / Surveillance	• Extend follow-up in large comparative studies (e.g. Medicare, OPTUM, VQI) through 5 years • Adhere to FDA guidance regarding Real World Evidence
10. Labeling	• Work with FDA to review and update consistent data sets and analyses for labeling • Subgroup analyses do not support indication changes
11. Changes to Study Design	Ongoing trials should continue with focused attention to completeness of data (e.g. vital status, medication, additional paclitaxel exposure) and long-term follow-up
12. Implications for Current Trials and other indications	• No mortality difference in four other vascular beds • All ongoing studies should continue to enroll (e.g. SWEDE-PAD, BASIL-3, VOYAGER-PAD, BEST-CLI) • Each device and indication should be evaluated on safety and effectiveness per normal FDA process

Over the Next 5+ years, 29 Studies will Yield Randomized Data on over 10,000 Patients

N=10,118	Vessel Bed	Name of Study	N	Status	Estimated Completion	NCT
Independent N=7,350	Femoropopliteal	ZILVERPASS	220	Enrollment complete	December 2019: 2-year follow-up	NCT01952457
		HEROES-DCB	250	Currently enrolling	April 2019: 1-year follow-up	NCT02812966
		DCB-SFA	1080	Currently enrolling	June 2021: 2-year follow-up	NCT02648334
		BEST-SFA	120	Currently enrolling	September 2021: 2-year follow-up	NCT03776799
		Pittsburgh CLI DCB	50	Currently enrolling	December 2020: 1-year follow-up	NCT02758847
		Compare I	414	Enrollment complete	October 2020: 2-year follow-up	NCT02701543
		TRANSCEND	446	Currently enrolling	April 2024: 5-year follow-up	NCT03241459
		BASIL-3	861	Currently enrolling	December 2024: 5-year follow-up	ISRCTN14469736
	Infrainguinal	SWEDEPAD	3800	Currently enrolling	June 2021: 5-year follow-up	NCT02051088
		BEST-CLI	2100	Currently enrolling	December 2019: 5-year follow-up	NCT02060630
	Below-the-knee	DCB vs PTA in CLI and Crural arteries	70	Currently enrolling	June 2019: 1-year follow-up	NCT02750605
	AV Access	DEB in AVG	33	Enrollment complete	December 2018: 1-year follow-up	NCT03388892
		DCB for AVG Restenosis	40	Currently enrolling	December 2019: 3-mon. follow-up	NCT03360279
Industry-Sponsored N=2,768	Femoropopliteal	RANGER II SFA	388	Enrollment complete	August 2023: 5-year follow-up	NCT03064126
		IMPERIAL	524	Enrollment complete	March 2022: 5-year follow-up	NCT02574481
		The Chocolate Touch Study	585	Currently enrolling	December 2026: 2-year follow-up	NCT02924857
		EMINENT	750	Currently enrolling	December 2022: 3-year follow-up	NCT02921230
		BIOPACT-RCT	302	Not yet enrolling	June 2021: 1-year follow-up	NCT03884257
		Italy DEB vs Nitinol stents	84	Enrollment complete	December 2018: 1-year follow-up	NCT02212470
		ILLUMENATE US	300	Enrollment complete	July 2020: 5-year follow-up	NCT01858428
		ILLUMENATE EU	501	Enrollment complete	November 2018: 3-year follow-up	NCT01927068
		DISRUPT PAD III	400	Currently enrolling	December 2021: 2-year follow-up	NCT02923193
	Below-the-knee	DES BTK SAVAL	201	Currently enrolling	May 2024: 3-year follow-up	NCT03551496
		RANGER-BTK	30	Enrollment complete	November 2018: 1-year follow-up	NCT02856230
		Lutonix BTK	442	Enrollment complete	June 2020: 3-year follow-up	NCT01870401
		ILLUMENATE BTK	354	Currently enrolling	April 2024: 3-year follow-up	NCT03175744
		IN.PACT BTK	60	Enrollment complete	December 2020: 3-year follow-up	NCT02963649
	AV Access	ABISS AV DCB	150	Currently enrolling	December 2019: 1.5-year follow-up	NCT02753998
		IN.PACT AV Access	330	Enrollment complete	June 2023: 5-year follow-up	NCT03041467

Next Steps and Recommendations

Collaboration across professional societies, investigators, patients, regulators and industry to improve investigation and patient care in PAD

1. Ongoing and Future PAD Studies
   - Emphasize complete follow-up through site education and consent for vital status ascertainment
   - Record prior and additional revascularizations, including treatment type, throughout follow-up
   - Ascertain adherence to optimal medical therapy, throughout follow-up
   - Implement structured minimum core data set and definitions for future PAD device evaluation
2. Real World Data
   - Extend follow-up in large comparative studies (e.g. Medicare, OPTUM, VQI) through 5 years
   - Adhere to FDA guidance regarding Real World Evidence
3. Labeling Recommendations
   - Work with FDA to review and update consistent data sets and analyses for labeling
   - Maintain current indications

Next Steps and Recommendations

4. Patient and Physician Guidance
   - Assess gaps in treatment, medical care, and risk factor modification for patients undergoing revascularization for PAD
   - Convene consortium of PAD stakeholders to create clinical guidelines for patients undergoing peripheral revascularization
   - Timely publication of updated data and results to inform patient and physician decision-making
5. Ensure patient access to treatment by reassuring healthcare providers regarding the benefit and safety of these devices

Next Steps and Recommendations

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   - Assess gaps in treatment, medical care, and risk factor modification for patients undergoing revascularization for PAD
   - Convene consortium of PAD stakeholders to create clinical guidelines for patients undergoing peripheral revascularization
   - Timely publication of updated data and results to inform patient and physician decision-making
5. Ensure patient access to treatment by reassuring healthcare providers regarding the benefit and safety of these devices

Request FDA update March 15th Letter to Healthcare Providers to convey the totality of evidence available in support of the benefit-risk profile of these devices for their indicated use.