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The End of the Paclitaxel Scare:

Review of the data and lessons learned

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Disclosure of Relevant Financial Relationships

Within the prior 24 months, I have had a relevant financial relationship(s) with an ineligible company(ies) listed below.

Unrestricted Grant Support	Becton Dickinson, Boston Scientific, Cook Medical, Medtronic, Philips, Surmodics, TriReme Medical
Consultant Fees/Honoraria	Philips, Medtronic, Boston Scientific, Surmodics, Encompass Medical, eFemoral, Cagent, Sonovascular, Conformal Medical, Contego Medical, ReValve, Alucent, Edwards LifeSciences
Individual Stock(s)/Stock Options	eFemoral, Encompass Medical, Xenter, and Reflow Medical

Background

- Paclitaxel-coated peripheral angioplasty devices have consistently shown improved patency versus uncoated devices in randomized trials.[1-6]
  - Reduces vessel restenosis and target vessel revascularization
  - Systemic absorption is negligible
- A 2018 study-level meta-analysis, and subsequent patient-level analyses, observed a late mortality risk in patients treated with paclitaxel-coated devices.[7,8]
- Following 2019 statements by FDA and global regulators,[9] use of paclitaxel devices for peripheral artery disease dropped by as much as 50% due to worldwide alterations in practice patterns.

1. Dake et al. Circulation. 2016;133:1472-83.
2. Tepe et al. JACC Cardiovasc Interv. 2015;8:102-8.
3. Rosenfield et al. N Engl J Med. 2015;373:145-53.
4. Laird et al. Circ Cardiovasc Interv. 2019;12:e007702.
5. Krishnan et al. Circulation. 2017;136:1102-13.
6. Sachar et al. JACC Cardiovasc Interv. 2021;14:1123-33
7. Katsanos K, et al. JAHA 2018;7:e011245.
8. Rocha-Singh et al. Circulation. 2020;141:1859-69.
9. U.S. Food & Drug Administration. Paclitaxel-Coated Balloons and Stents for Peripheral Arterial Disease, Resources. https://www.fda.gov/medical-devices/cardiovascular-devices/paclitaxel-coated-balloons-and-stents-peripheral-arterial-disease#resources. Updated July 11, 2023. Accessed September 12, 2023.

Final LIMR-NAMSA Patient-Level Meta-analysis on Paclitaxel Safety

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On behalf of Sahil A. Parikh MD, Peter A. Schneider MD,
Christopher M. Mullin MS, Tyson Rogers MS

Conducted by the Lankenau Institute for Medical Research

Analysis performed by North American Science Associates

Rationale for the 2023 LIMR-NAMSA Analysis

FDA and industry enlisted an independent physician steering committee to analyze the final updated patient-level data sets and address methodological limitations of prior paclitaxel meta-analyses

More complete vital status data

95% 5-year follow-up completeness

More patient-years of follow-up

Added 3355.5 patient-years

Added RCT studies

RANGER SFA
RANGER SFA II

More detailed analysis of treatment group crossovers

More detailed analyses of paclitaxel dose and covariates

LIMR-NAMSA 2023 Analysis

Included Studies

	Randomized Patients	Patient-Years of Follow-up	Total Deaths	Follow-up Completeness
ILLUMENATE RCT	300	1362.7	58	96.9%, 5 yrs
ILLUMENATE EU RCT	294	1324.0	55	95.0%, 5 yrs
IN.PACT SFA I/II	331	1608.1	53	97.5%, 5 yrs
IN.PACT SFA Japan	100	282.5	6	96.8%, 3 yrs
LEVANT I	101	181.2	9	93.3%, 2 yrs
LEVANT II	476	2198.6	91	96.0%, 5 yrs
LEVANT Japan	109	203.1	5	94.4%, 2 yrs
Zilver PTX	474	2277.8	84	97.3%, 5 yrs
RANGER SFA	105	258.8	12	87.3%, 3 yrs
RANGER II SFA	376	1496.2	61	87.3%, 5 yrs*
TOTAL	**2,666**	**11,193.2**	**434**	**95.0%, 5 yrs**

Additional 3355.5 patient-years and 163 new deaths since the 2020 VIVA meta-analysis

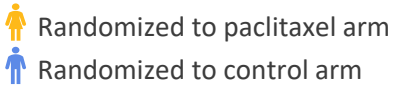
* † RANGER II SFA 5-year follow-up was ongoing at the time of the data snapshot

LIMR-NAMSA 2023 Analysis
Four Analysis Sets

Intent-to-Treat (ITT)

Paclitaxel Arm n=1731

Control Arm n=935



As-Treated (AT)

AT, Late Crossover Censored

AT, Crossover as Time-Varying Covariate

LIMR-NAMSA 2023 Analysis
Four Analysis Sets

Intent-to-Treat (ITT)

Paclitaxel Arm n=1731

Control Arm n=935

Randomized to paclitaxel arm

Randomized to control arm

As-Treated (AT)

Paclitaxel Arm n=1797

Control Arm n=870

Any patients exposed to paclitaxel at the index procedure were included in the paclitaxel analysis group

AT, Late Crossover Censored

AT, Crossover as Time-Varying Covariate

LIMR-NAMSA 2023 Analysis
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AT, Late Crossover Censored

Paclitaxel Arm n=1797

Control Arm n=870

Patients with known exposure to paclitaxel at any time during study follow-up were censored at the time of exposure

AT, Crossover as Time-Varying Covariate

Late Crossover

LIMR-NAMSA 2023 Analysis
Four Analysis Sets

Intent-to-Treat (ITT)

Paclitaxel Arm n=1731

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AT, Late Crossover Censored

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Control Arm n=870

Patients with known exposure to paclitaxel at any time during study follow-up were censored at the time of exposure

AT, Crossover as Time-Varying Covariate

Paclitaxel Arm n=1865

Control Arm n=802

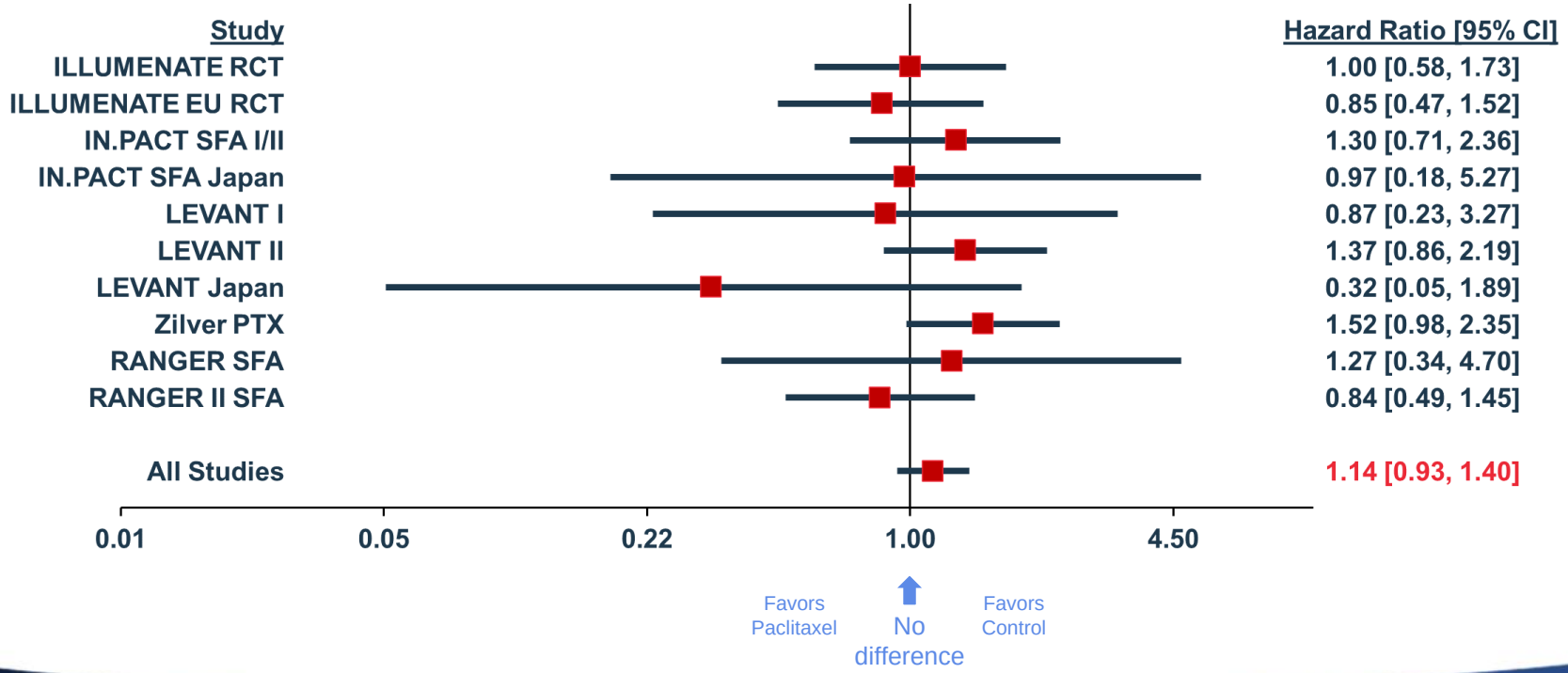
Patients with known exposure to paclitaxel crossed to the paclitaxel group from the date of their first exposure

Late Crossover

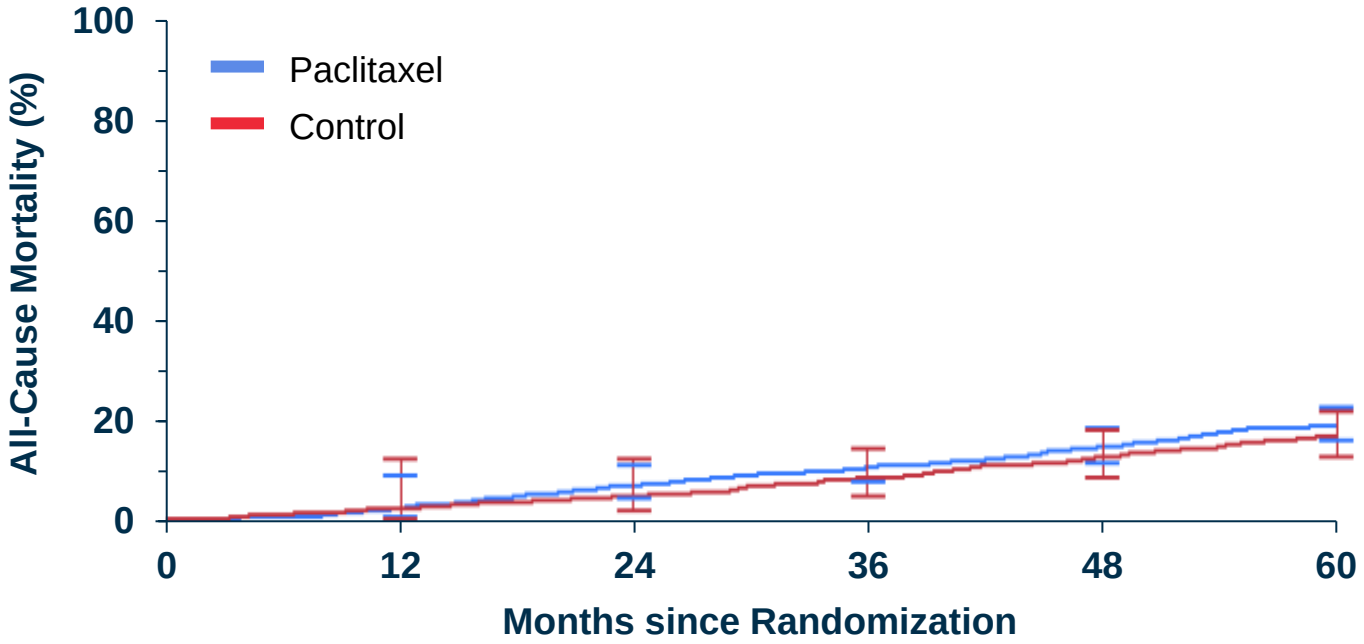
LIMR-NAMSA 2023 Analysis

Intent-to-Treat Mortality Analysis

No statistically significant mortality signal

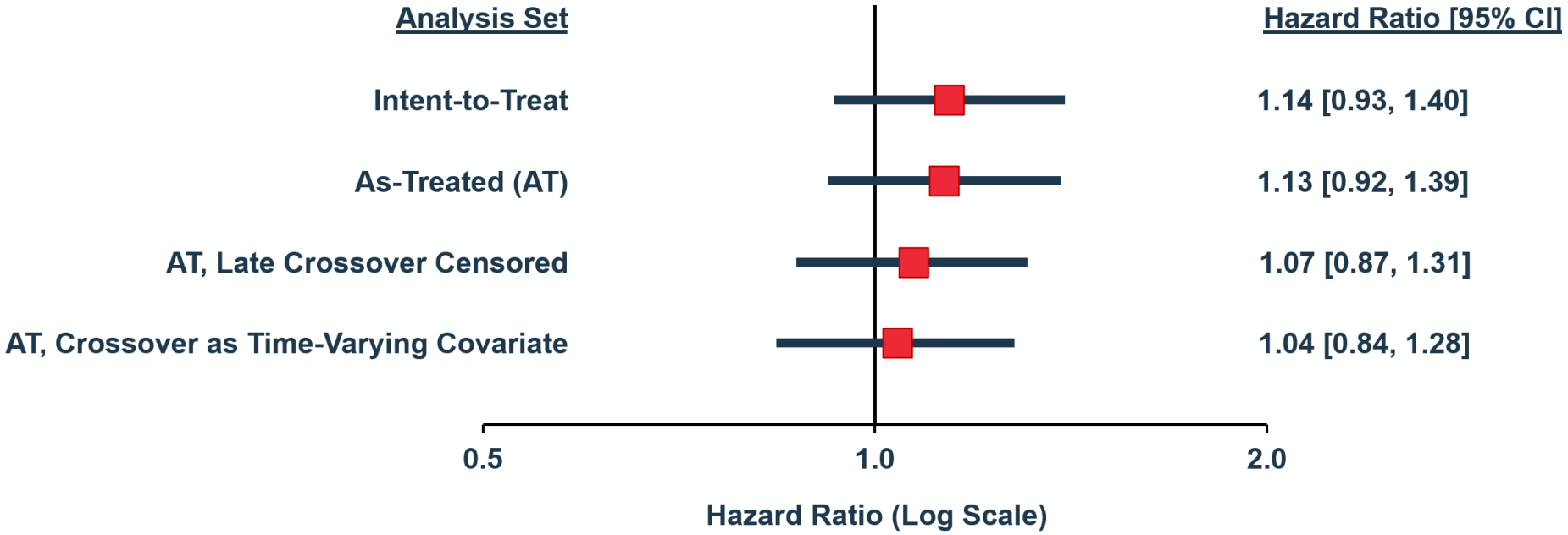


LIMR-NAMSA 2023 Analysis
Kaplan-Meier Estimate of Mortality through 5 Years (ITT)



Number at Risk						
1731	1662	1509	1338	1144	584	Paclitaxel
935	893	821	716	638	355	Control

LIMR-NAMSA 2023 Analysis
ITT, As-Treated, and Crossover Mortality Analyses



- **Lack of a Mortality Signal Across All Analyses**
- **Accounting for Crossover Further Reduced HR**

Bradford-Hill Criteria: Association vs. Causation

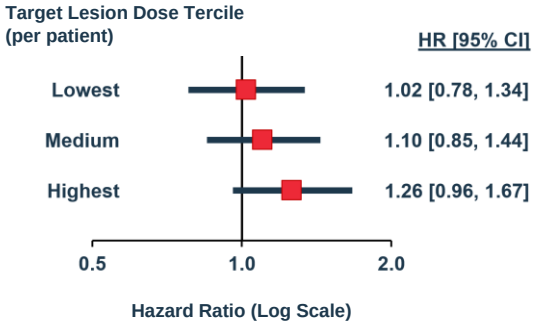
Criterion for Plausible Causality	Description
Temporality	The cause must precede the outcome
Strength	Strong relationship between variables (high relative risk)
Biological Gradient	Dose-response: more exposure leads to more outcome
Consistency	The relationship is consistent in different studies and populations
Specificity	Single cause for a single effect
Plausibility	There is biological rationale for the relationship
Coherence	Relationship is consistent with previous knowledge
Analogy	The relationship is synonymous with other, similar relationships
Experiment	**Strong criterion. Randomly assigned treatment changes the clinical outcome. Change in cause = change in effect

LIMR-NAMSA 2023 Analysis
Paclitaxel Dose Analysis Methods

- Total paclitaxel dose was calculated by each sponsor for the device(s) used to treat patients at the index procedure (as-treated approach).
- Index procedure nominal load data (μg/mm^2) was standardized within each study, based on the number and length of devices used in each target lesion.
- Analysis was based on a Cox proportional hazards model, stratified by study.
- An analysis of dose terciles by study was performed to compare low-, medium-, and high-dose patients, versus patients that did not receive paclitaxel. Cut points for terciles were calculated separately for each study.
- Given the confounding effect of lesion length on dose and mortality, both unadjusted and adjusted dose analyses were performed.

LIMR-NAMSA 2023 Analysis
As-Treated Dose Analysis Results

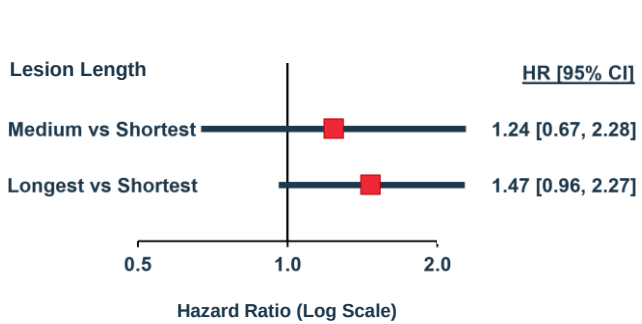
Unadjusted dose analysis for paclitaxel patients



No statistically significant dose effect.

Dose was calculated per patient based on the number and length of paclitaxel devices used during the index procedure and standardized within each study.

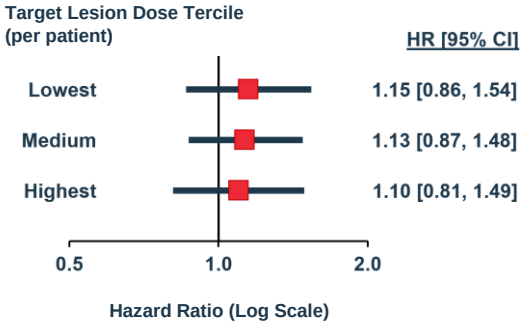
Unadjusted lesion length analysis for non-paclitaxel patients



Lesion length confounding observed in non-paclitaxel patients.

Dose analyses not protected by randomization.

Dose analysis adjusted for lesion length in paclitaxel patients



No statistically significant dose effect.

Treatment-Covariate Interaction Hazard Ratios

Baseline Variable	Between Study	Within Study
Age	0.87 (0.74, 1.02)	0.99 (0.97, 1.01)
Sex	0.42 (<0.01, >100.00)	1.08 (0.70, 1.65)
Race	3.53 (0.07, >100.00)	1.07 (0.44, 2.62)
Obesity	10.50 (0.34, >100.00)	1.09 (0.68, 1.75)
Smoking (active vs never)	0.22 (<0.01, 22.29)	0.85 (0.47, 1.51)
Smoking (previous vs never)	0.97 (0.04, 25.05)	0.71 (0.41, 1.23)
Diabetes	1.87 (0.01, >100.00)	1.21 (0.80, 1.83)
Insulin-dependent diabetes	0.04 (<0.01, 11.64)	1.28 (0.59, 2.78)
Coronary heart disease	2.55 (0.24, 26.91)	0.91 (0.52, 1.59)
Carotid artery disease	1.65 (0.26, 10.35)	1.10 (0.67, 1.81)
Hypertension	1.35 (<0.01, >100.00)	1.03 (0.51, 2.10)
Hyperlipidemia	2.79 (0.28, 27.41)	1.20 (0.73, 1.96)
Renal insufficiency	71.62 (0.09, >100.00)	1.05 (0.56, 1.97)
Prior myocardial infarction	>100.00 (0.02, >100.00)	0.59 (0.35, 0.99)
Rutherford class	<0.01 (<0.01, 7.11)	1.37 (0.64, 2.94)
Lesion count	23.75 (0.05, >100.00)	0.70 (0.17, 2.90)
Lesion length	0.88 (0.75, 1.04)	1.00 (0.96, 1.04)
Geography	0.83 (0.18, 3.95)	0.96 (0.56, 1.64)
Randomization year	0.93 (0.87, 1.00)	0.99 (0.75, 1.31)

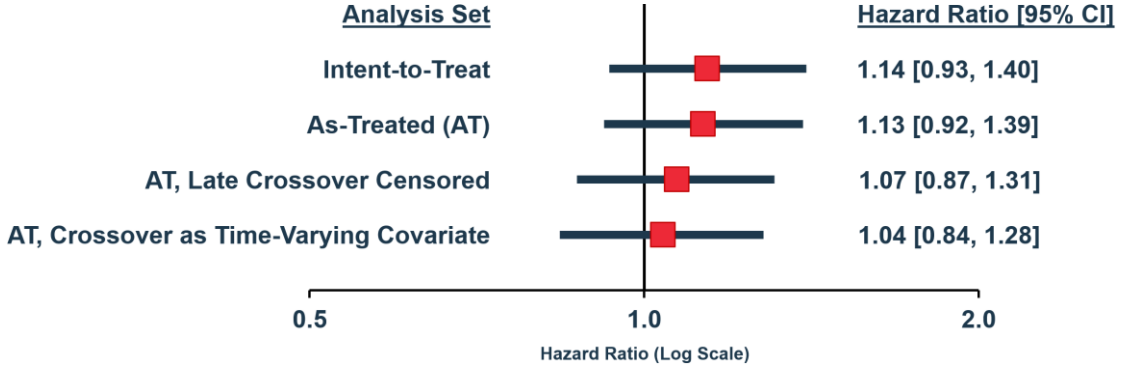
No notable covariate effects

- Two significant effects among 38 hazard ratios expected by chance alone
- No significant effect in primary mortality analysis

LIMR-NAMSA 2023 Analysis

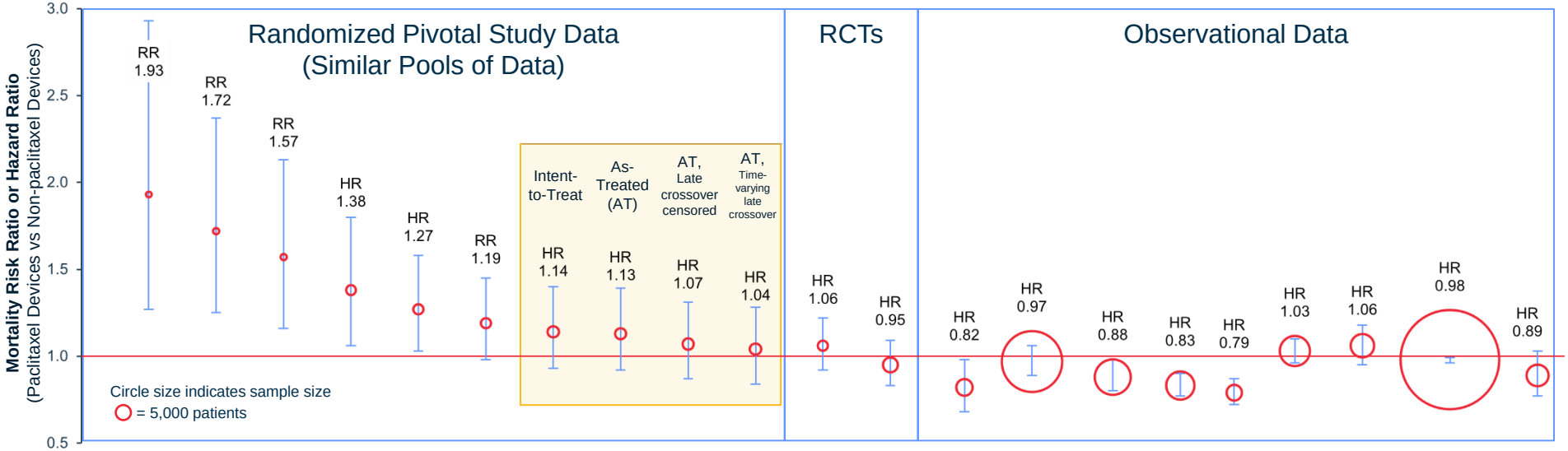
Summary

- Consistent lack of a significant paclitaxel mortality signal across 4 analysis sets:



- Accounting for crossover further reduced the hazard ratio
- No dose effect in the unadjusted analysis or when adjusted for lesion length
- No notable covariate interactions

Paclitaxel Mortality Risk In Perspective (2018-2023)



Study	Katsanos	FDA - VS	FDA + VS	VIVA-NAMSA		Dinh	LIMR-NAMSA 2023 Analysis				SWEDE-PAD	VOYAGER-PAD	VQI Vision	BARMER	BARMER		VQI Delta	Optum	VA Data-base	SAFE-PAD	FAIR Health
Year	2018[1]	2019[2]	2019[3]	2019[4]	2020[5]	2021[6]	ITT	AT	LCC	TVLC	20207	2021[8]	2020[9]	2020[10]	2020[11]		2021[12]	2021[13]	2021[14]	2022[15]	2023[16]
Patients	863	971	1,035	2,185	2,185	2,288	2,666	2,667	2,667	2,667	2,289	4,316	5,436	64,771	23,122	14,792	4,912	16,796	10,505	168,553	8978
Follow-Up, yrs	4-5	≤ 5	≤ 5	4	4	5	4.9 Years *				2.5 ‡	2.6 *	1.1 *	7.7 *	2.7 *		1.8 *	2.7 *	1.7 *	3.5 *	4

* Median follow-up
‡ Mean follow-up

1. Katsanos et al. J Am Heart Assoc. 2018;7:e011245.
2. Circulatory System Devices Panel, Docket No. FDA-2019-N-1677, Figure 14, June 19-20, 2019. Before vital status update.
3. Whatley E., FDA Executive Summary, Circulatory System Devices Panel Meeting, June 19, 2019. After vital status update.
4. Rocha-Singh et al., TCT 2019, San Francisco, CA.
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8. Hess et al. J Am Coll Cardiol. 2021;78:1768-78.
9. Bertges et al. Circ Cardiovasc Interv. 2020;13:e008528.
10. Freisinger et al. Eur Heart J. 2020;41:3732-9.
11. Behrendt et al. Eur J Vasc Endovasc Surg. 2020;59:587-96.
12. Bertges et al. JACC Cardiovasc Interv. 2021;14:2598-609.
13. Secemsky et al. EuroIntervention. 2021;17:590-8.
14. Gutierrez et al. J Am Heart Assoc. 2021;10:e018149.
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16. Dani et al. J Vasc Interv Radiol. 2023;34:1157-65 e8.

Conclusions

- This patient-level, pooled analysis of pivotal randomized controlled trials, conducted with input from the FDA, provides the most complete and current follow-up data of pivotal studies associated with FDA-approved paclitaxel-coated devices
- With five-year vital status available in 95% of evaluable patients and a comprehensive examination of the impact of treatment-group crossovers, this initiative represents the most complete patient-level analysis to date, or likely to be available in the future
- **No association between mortality risk and paclitaxel-coated device exposure or dose was observed in any of the pre-specified analytic approaches**

UPDATE: Paclitaxel-Coated Devices to Treat Peripheral Arterial Disease Unlikely to Increase Risk of Mortality - Letter to Health Care Providers

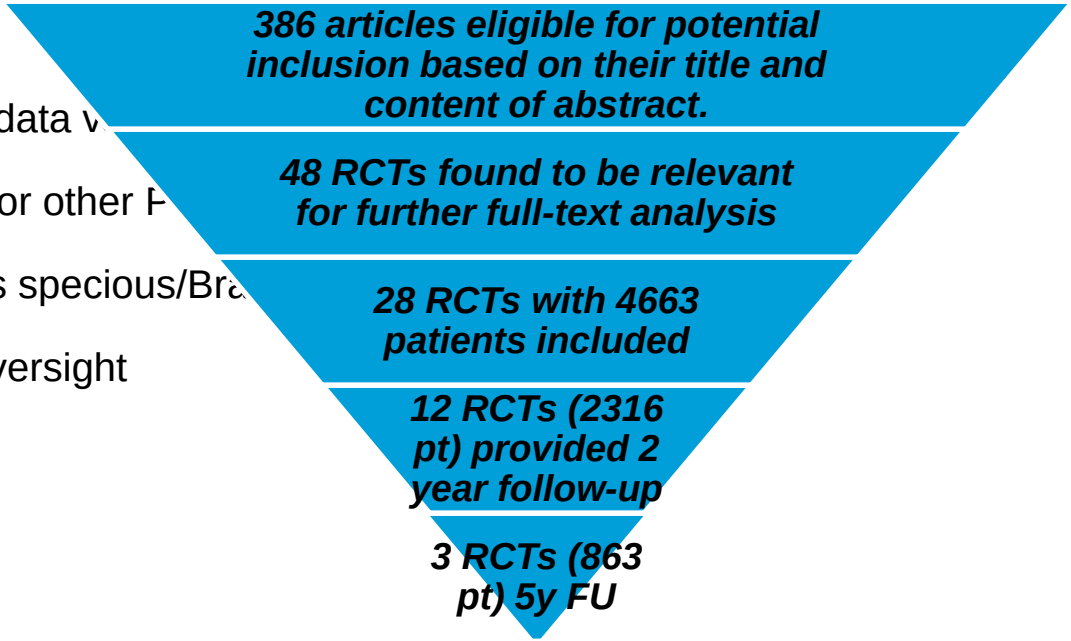
July 11, 2023

The U.S. Food and Drug Administration (FDA) is informing health care providers about updated information associated with paclitaxel-coated devices used to treat peripheral arterial disease (PAD).

Based on the FDA's review of the totality of the available data and analyses, we have determined that the data does not support an excess mortality risk for paclitaxel-coated devices. The FDA previously communicated about this topic in 2019 and is now providing updated information.

What happened?

- Incomplete data: more missing subjects than deaths at 5 years
- Selection bias
- Summary level data v
- No accounting for other F
- Dose analysis is specious/Bra
- Poor editorial oversight



Lancet, Published Online, October 24, 2023

Articles

Mortality in randomised controlled trials using paclitaxel-coated devices for femoropopliteal interventional procedures: an updated patient-level meta-analysis

Sahil A. Parikh, Peter A. Schneider, Christopher M. Mullin, Tyson Rogers, William A. Gray

Summary

Background Numerous randomised clinical trials and real-world studies have supported the safety of paclitaxel-coated devices for the treatment of femoropopliteal occlusive disease. However, a 2018 summary-level meta-analysis suggested an increased mortality risk for paclitaxel-coated devices compared with uncoated control devices. This study presents an updated analysis of deaths using the most complete and current data available from pivotal trials of paclitaxel-coated versus control devices.

Methods Ten trials comparing paclitaxel-coated versus control devices were included in a patient-level pooled analysis. Cox regression models were used to evaluate the effect of paclitaxel exposure on risk of death in both intention-to-treat (ITT; primary analysis) and three as-treated analysis sets accounting for treatment group crossover at the index procedure and over time. The effect of paclitaxel dose and baseline covariates were also evaluated…