One View On The Final Result Of The Scare And Concern That Paclitaxel Coated Devices For Lower Extremity Treatments- Increased Mortality And Amputation Rates: The Case Is Closed: What Were Its Costs?

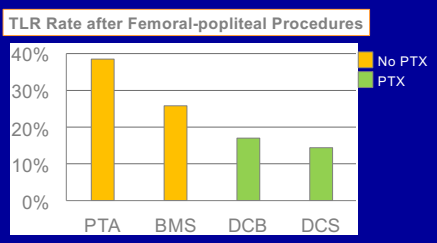
Peter A. Schneider, MD
University of California San Francisco

Peter A. Schneider Disclosures

Consulting:

Surmodics, Medtronic, Boston Scientific, Phillips, Cagent, Acotec, Abbott, Endologix, Shockwave, Silk Road, Healthcare Inroads, Inari, BD

Paclitaxel Therapies Reduce Repeat Procedures at 2 Years



Sridharan ND, et al. J Vasc Surg. 2018;67(1):343-352. doi: 10.1016/j.jvs.2017.06.112.
BMS, bare metal stent; DCB, drug-coated balloon; DCS, drug-coated stent; PTA, percutaneous transluminal angioplasty

Final Patient Level Updated Meta-Analysis

2,666 RCT patients
95% 5-year F/U
3,355 More years of patient F/U

Some Crossover data
ITT, but also As Treated

Baseline Characteristics	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**

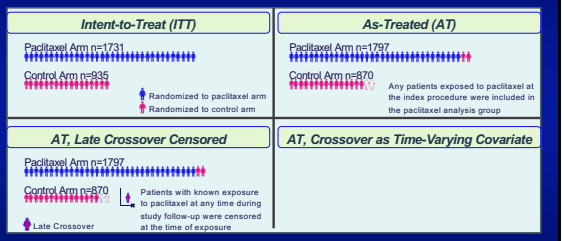
Final Patient Level Updated Meta-Analysis

Intent-to-Treat (ITT)	*As-Treated (AT)*
Paclitaxel Arm n=1731 Control Arm n=935 Randomized to paclitaxel arm Randomized to control arm	
AT, Late Crossover Censored	*AT, Crossover as Time-Varying Covariate*

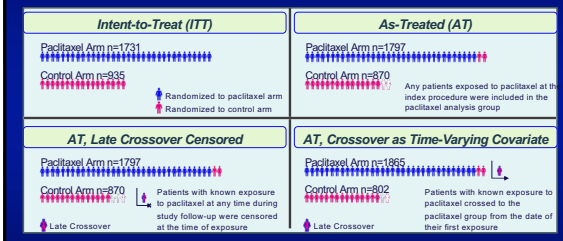
Final Patient Level Updated Meta-Analysis

Intent-to-Treat (ITT)	*As-Treated (AT)*
Paclitaxel Arm n=1731 Control Arm n=935 Randomized to paclitaxel arm Randomized to control arm	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*

Final Patient Level Updated Meta-Analysis

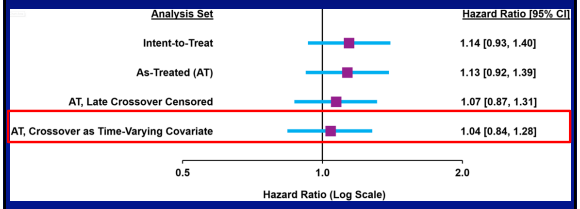


Final Patient Level Updated Meta-Analysis



Final Patient Level Updated Meta-Analysis

ITT, As-Treated, and Crossover Analyses of Mortality Risk

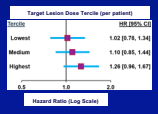


- Lack of a Mortality Signal Across All Analyses
- Accounting for Crossover Further Reduced HR

Dose Analysis and Lesion Length

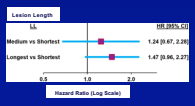
2023 Patient Level Updated Meta-Analysis

Unadjusted dose analysis for paclitaxel patients



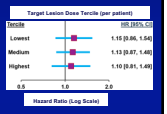
No statistically significant dose effect.

Lesion length analysis for non-paclitaxel patients



Lesion length confounding in non-paclitaxel patients.

Dose analysis adjusted for lesion length in paclitaxel patients



Lesion Length is an Unexpected Confounding Variable

Covariate Analysis

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)	1.26 (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 (0.19, 3.95)	0.96 (0.56, 1.64)
Randomization year	0.93 (0.87, 1.00)	0.99 (0.75, 1.31)

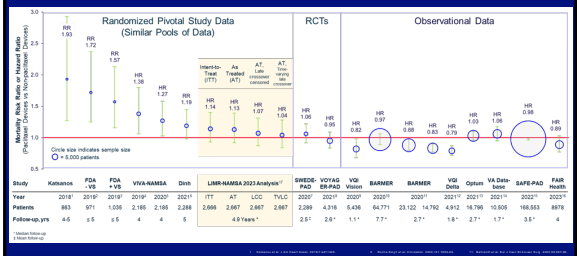
No notable covariate effects

Two significant effects among 38 hazard ratios expected by chance alone.

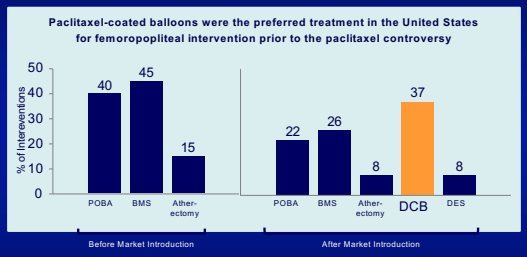
No significant effect in primary mortality analysis.

Paclitaxel Mortality Risk Studies

(2018-present)



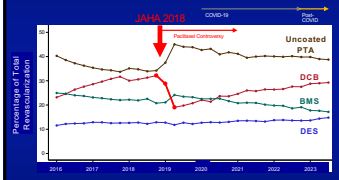
What was the Patient Impact of the Paclitaxel Controversy?



Mohapatra et al. J Vasc Surg. 2020;71:560-6.
Adapted from the work of E Secemsky, Charing Cross Symposium 2024

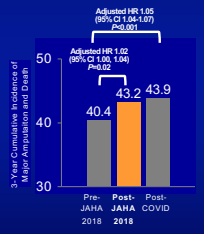
What was the Patient Impact of the Paclitaxel Controversy?

Paclitaxel controversy: significant decline in DCB use, primarily replaced by PTA and BMS



602,222 femoropopliteal artery revascularization procedures performed between 1/1/2016 through 9/30/2023 among patients insured by Medicare

Increased risk of major amputation and death, not driven by COVID alone.



E Secemsky, Charing Cross Symposium 2024

One View On The Paclitaxel Scare: The Case Is Closed

Conclusions

- Final and updated patient-level analysis of pivotal RCTs, conducted with input from the FDA, provides the most complete follow-up data on paclitaxel-coated devices.
- Five-year vital status available in 95% of patients and a comprehensive examination of the impact of treatment-group crossovers.
- Consistent lack of paclitaxel mortality signal across multiple analyses.
- Accounting for crossover further reduced the hazard ratio.
- No dose effect.
- Consequences of paclitaxel controversy still being felt.

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*

Lancet 2023; 2023;402:1848-56

One View On The Final Result Of The Scare And Concern That Paclitaxel Coated Devices For Lower Extremity Treatments-Increased Mortality And Amputation Rates: The Case Is Closed: What Were Its Costs?

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.