Insights on paclitaxel safety from the femoral-popliteal RCTs

Peter Schneider, MD

Professor of Surgery

Division of Vascular & Endovascular Surgery
University of California San Francisco
San Francisco, CA, US

Disclosures

Consulted for:

Boston Scientific, Surmodics, Cagent, CSI, Philips, Medtronic, Intervene, Limflow, Silk Road, Cagent, Devoro

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Summary Level Meta-analysis of Paclitaxel in the Femoropopliteal Disease

4/5 Years

Paclitaxel-Femoropopliteal Arteries

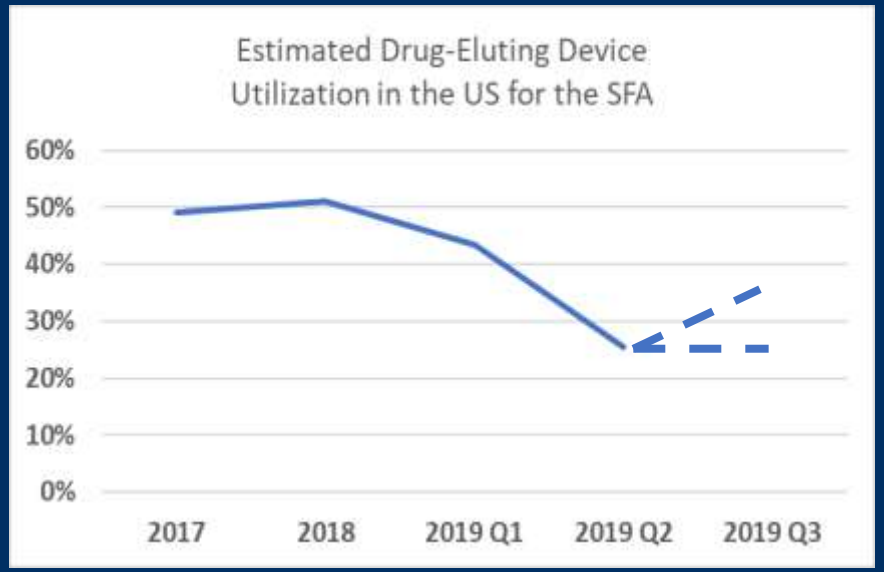
Study	Paclitaxel Events	Paclitaxel Total	Control Events	Control Total	Risk Ratio	RR	95%-CI	Weight (fixed)	Weight (random)
THUNDER [57]	12	48	8	54		1.69	[0.75; 3.78]	23.9%	26.9%
ZILVER-PTX [9,19]	42	297	12	177		2.09	[1.13; 3.85]	47.7%	46.3%
IN.PACT SFA [10,56]	24	184	7	103		1.92	[0.86; 4.30]	28.5%	26.8%
Fixed effect model		**529**		**334**		**1.94**	**[1.28; 2.96]**	**100.0%**	--
Random effects model						**1.93**	**[1.27; 2.93]**	--	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.92$

Figure 3. Random effects forest plot of all-cause death at 4 to 5 years. Pooled point estimate was expressed as risk ratio (RR).

$$\text{Exposure}_i = \text{Dose}_i \times (\pi \times D_i \times \text{Length}_i) \times \text{Time}_i$$

where, Dose_i is the nominal paclitaxel dose loaded on the balloon or stent ($\mu g/mm^2$), D_i is the reference vessel diameter (mm), Length_i is the treated lesion length (mm), and Time_i indicates the available follow-up time period (years). Random



Based on earnings reports, market research reports, physician & hospital inputs

Katsanos et al. JAHA 2018;7:e011245

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Characteristics of These Trials

- Powered for one-year patency, not long-term mortality.
- Small control groups (some RCTs 2:1)=unstable estimates.
- Was there bias in mortality assessment (ascertainment bias)?
- Were both groups treated the same after randomization (treatment bias?)
- Is there a dose response (biologic gradient)?
- Is there clustering of deaths as to cause (mechanism)?
- Is there a consistent danger signal?
- Is this a causal relationship or an association?

Bradford-Hill Criteria

Austin Bradford-Hill. Criteria for causation, 1965

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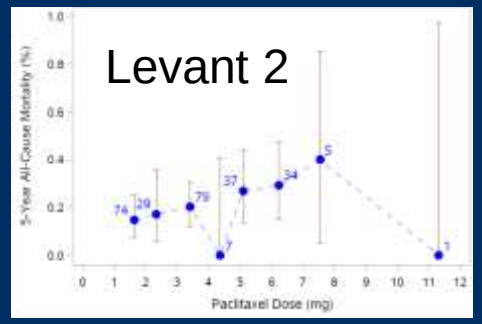
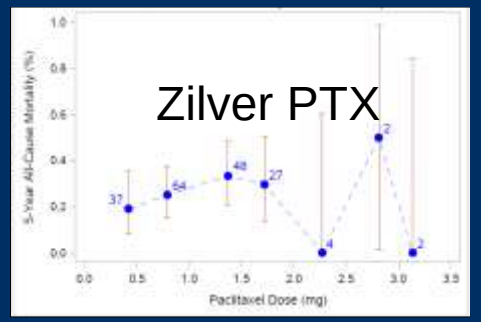
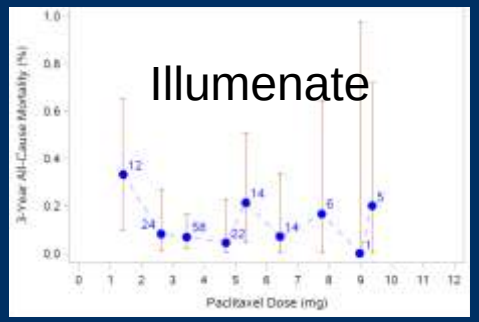
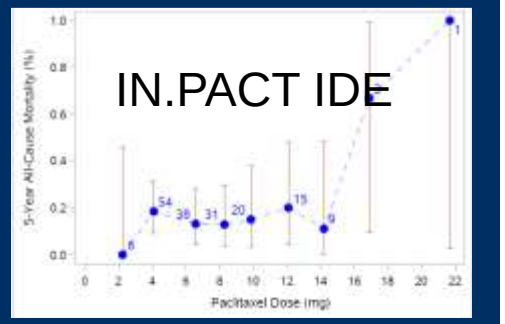
No Dose Effect On Mortality

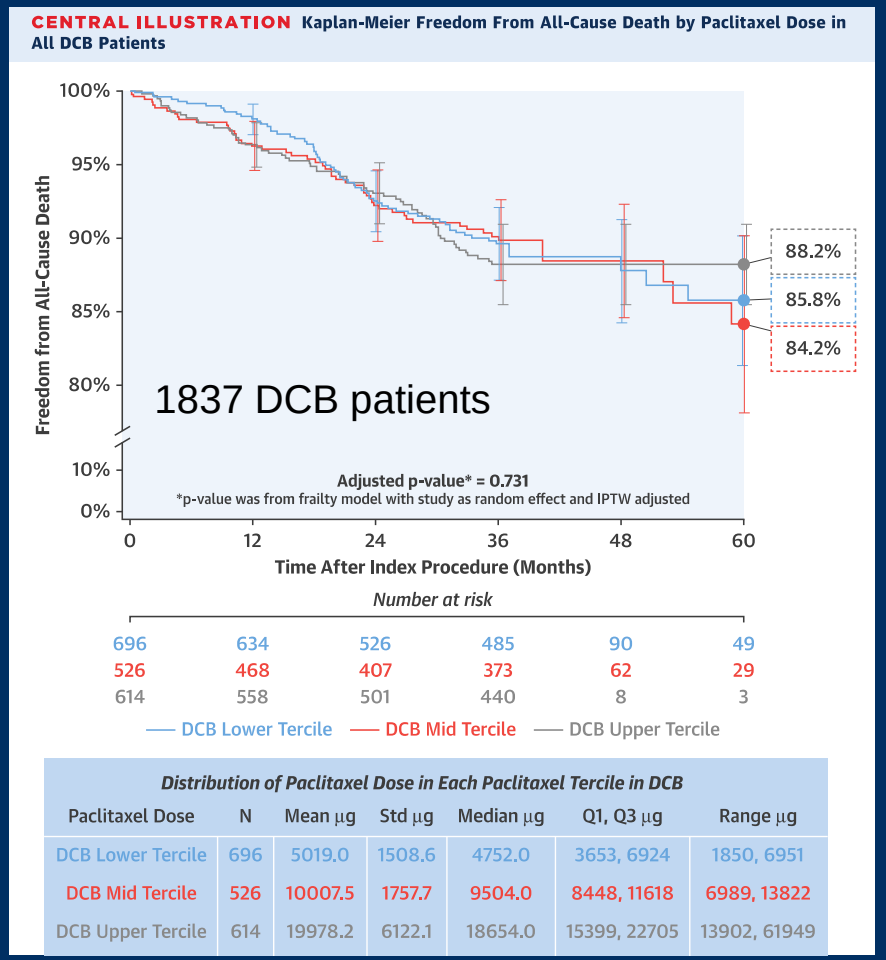








Dose administered vs All-cause mortality



Distribution of Paclitaxel Dose in Each Paclitaxel Tercile in DCB

Paclitaxel Dose	N	Mean µg	Std µg	Median µg	Q1, Q3 µg	Range µg
DCB Lower Tercile	696	5019.0	1508.6	4752.0	3653, 6924	1850, 6951
DCB Mid Tercile	526	10007.5	1757.7	9504.0	8448, 11618	6989, 13822
DCB Upper Tercile	614	19978.2	6122.1	18654.0	15399, 22705	13902, 61949

Dose tercile vs
Freedom from All-cause mortality

FDA Panel June 19-20, 2019 Figures 37-40
Schneider et al. J Am Coll Cardiol 2019;73:2550

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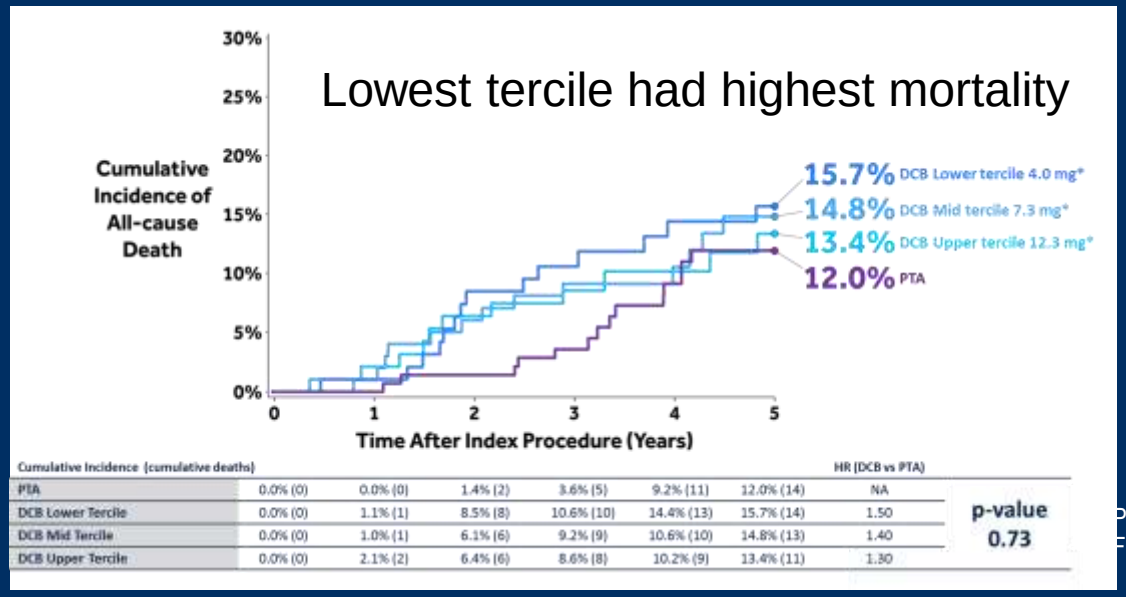
No Dose Effect on Mortality

Pooled IN.PACT IDE and Japan Trials
5-Year Mortality by Dose Tercile (As Treated)



Cumulative Incidence (cumulative deaths)							HR (DCB vs PTA)	
PTA	0.0% (0)	0.0% (0)	1.4% (2)	3.6% (5)	9.2% (11)	12.0% (14)	NA	p-value 0.73
DCB Lower Tercile	0.0% (0)	1.1% (1)	8.5% (8)	10.6% (10)	14.4% (13)	15.7% (14)	1.50	
DCB Mid Tercile	0.0% (0)	1.0% (1)	6.1% (6)	9.2% (9)	10.6% (10)	14.8% (13)	1.40	
DCB Upper Tercile	0.0% (0)	2.1% (2)	6.4% (6)	8.6% (8)	10.2% (9)	13.4% (11)	1.30	

Presented by L. Mauri, MD
FDA Panel , June 19, 2019.

VIVA/Namsa Individual Patient Data Project

No dose effect: Medium dose lower risk than low or high dose.

K Rocha-Singh, TCT 2019

	Hazard Ratio (95% CI)		
Model	**Low Dose Vs. None**	**Medium Dose Vs. None**	**High Dose Vs. None**
Propensity score adjusted, stratified by study, fixed effect	1.30 (0.92, 1.82)	1.23 (0.87, 1.73)	1.50 (1.08, 2.08)
Propensity score adjusted, stratified by study, random effect	1.30 (0.92, 1.82)	1.23 (0.87, 1.73)	1.41 (0.96, 2.07)

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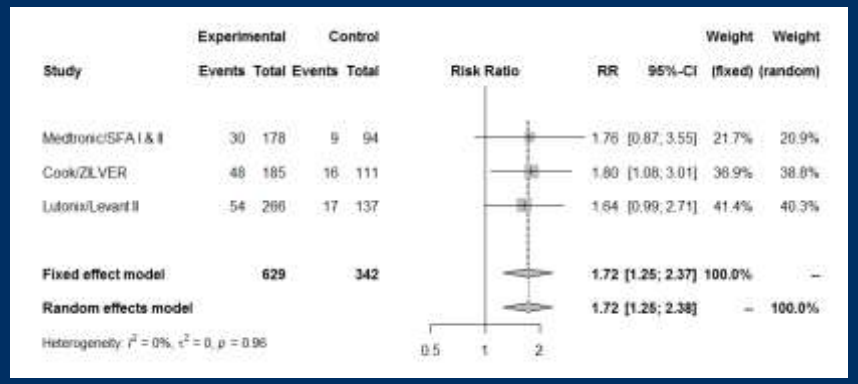
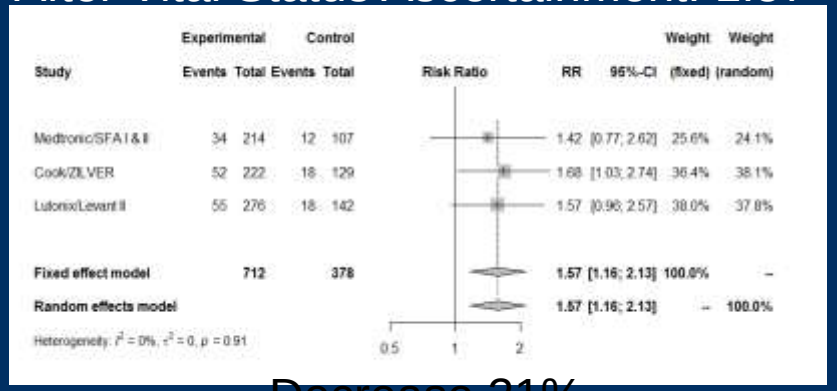
Ascertainment Bias: When Missing Patients Were Identified the Risk Decreased

5 Year Point Estimate from FDA: RR 1.72

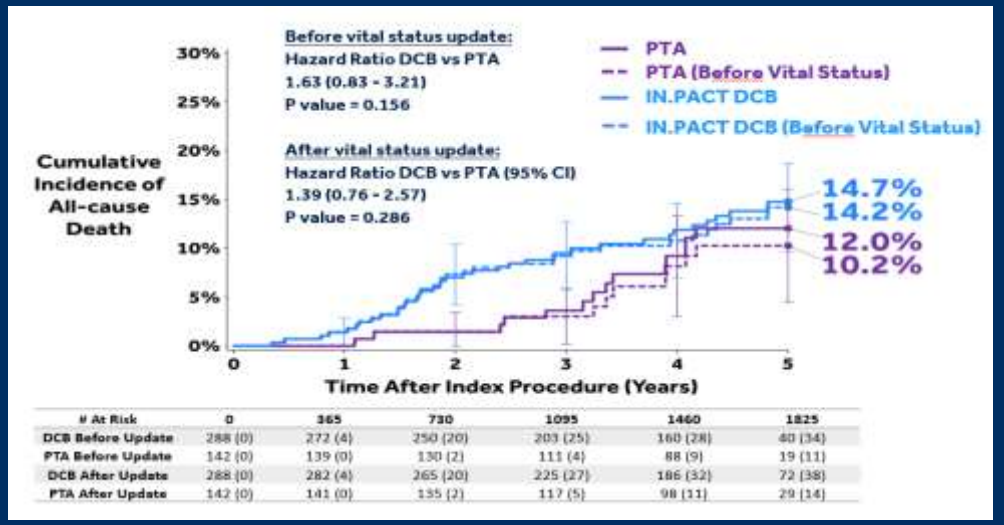


After Vital Status Ascertainment: 1.57



Decrease 21%

Pooled IN.PACT IDE and Japan: Mortality difference between DCB and PTA through 5 years Before (4%) and after (2.7%) updated vital status data (As Treated)



Hazard Ratio 1.63→1.39
Decrease 38%

FDA panel packet June 19-20, 2019 Whatley E. Presentation at FDA panel: June 19, 2019
Mauri L. Presentation at FDA panel June 20, 2019

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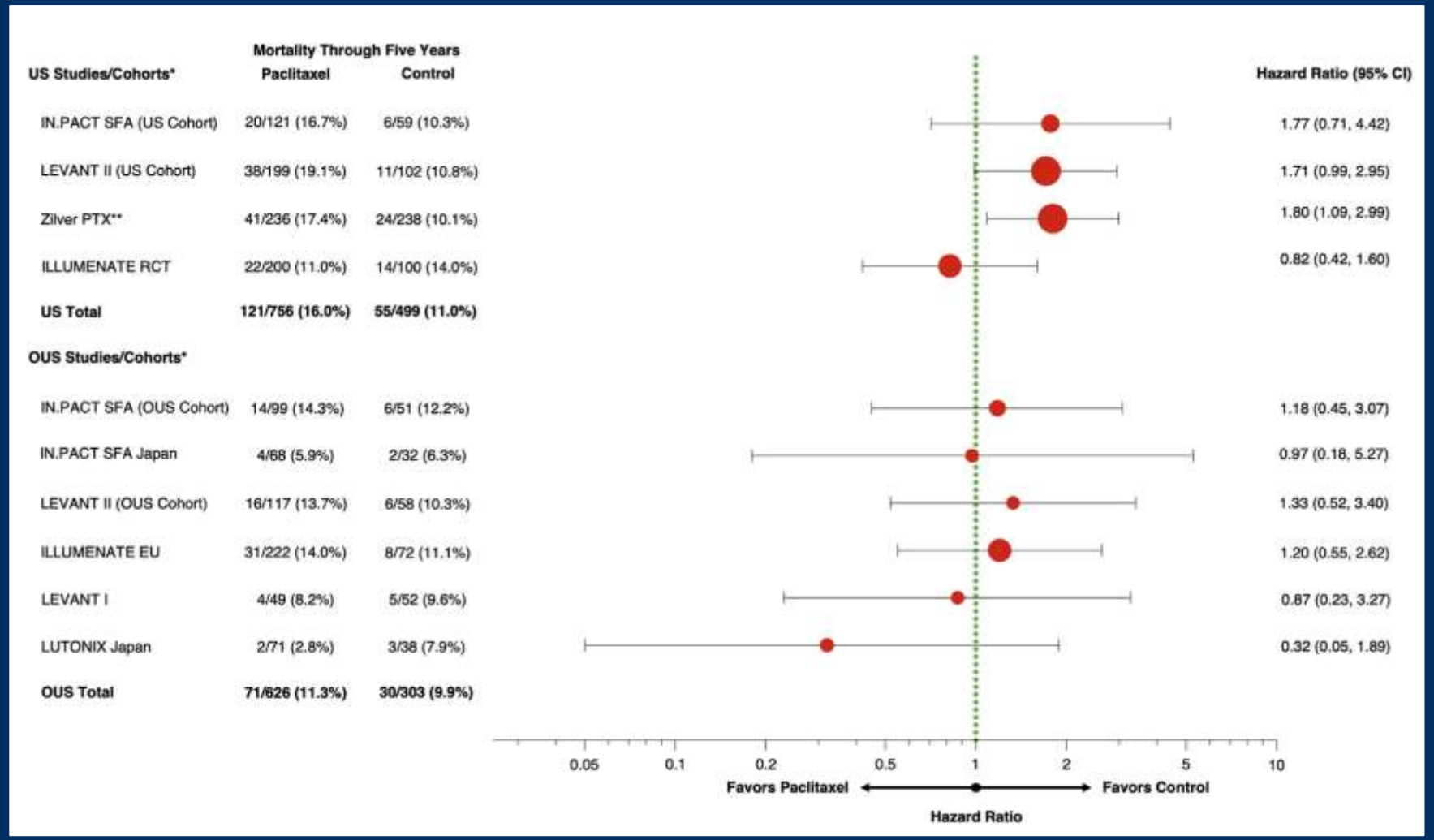
Geographic Factors Play a Role



Schneider et al. J Vasc Surg 2021;73:311

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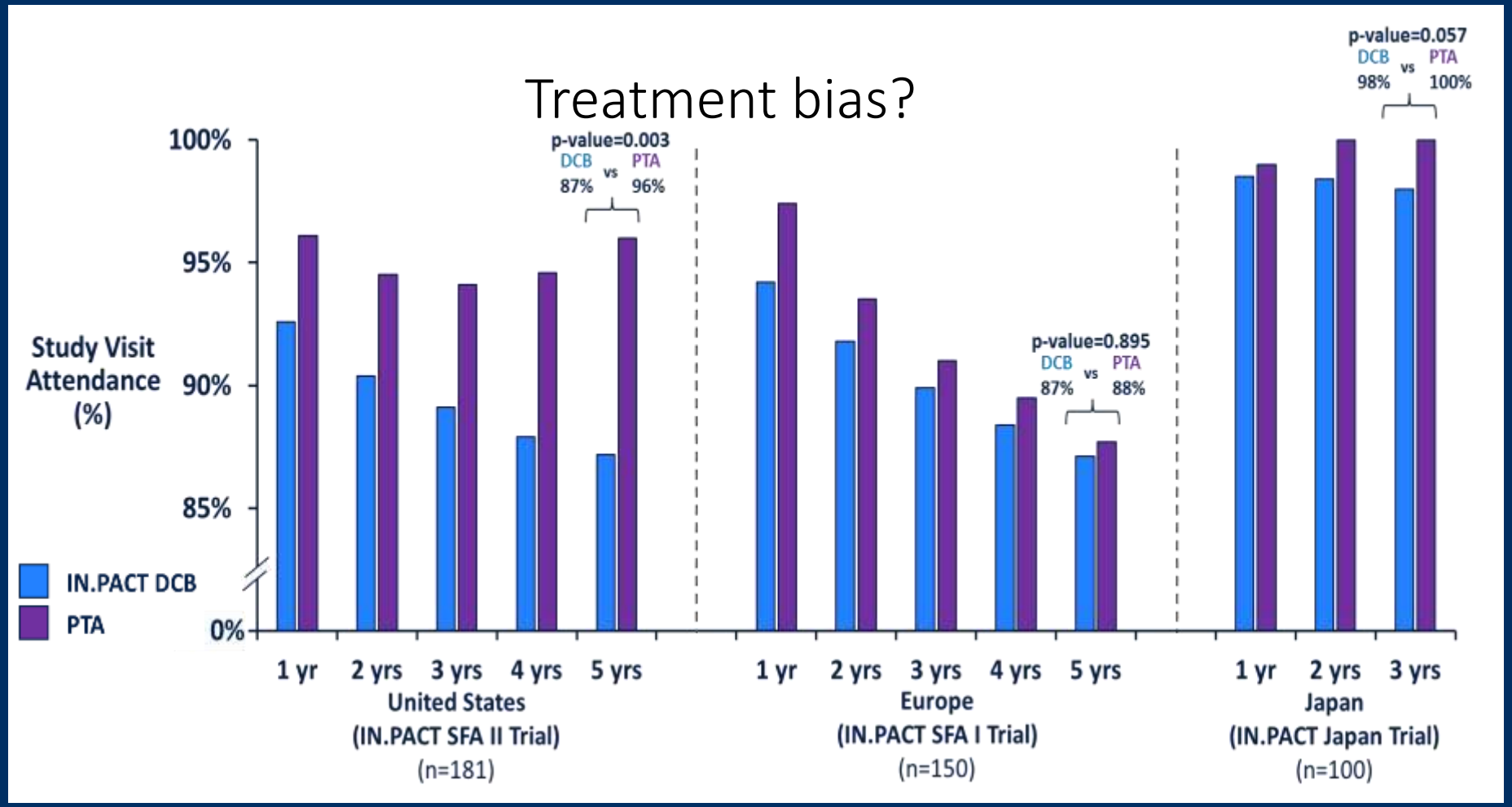
Follow-up Visit Attendance by Region



DCB and PTA patients treated differently

Difference in treatment is greater in US than other geographies

Presented by L Mauri MD. FDA Panel. June 19, 2019.

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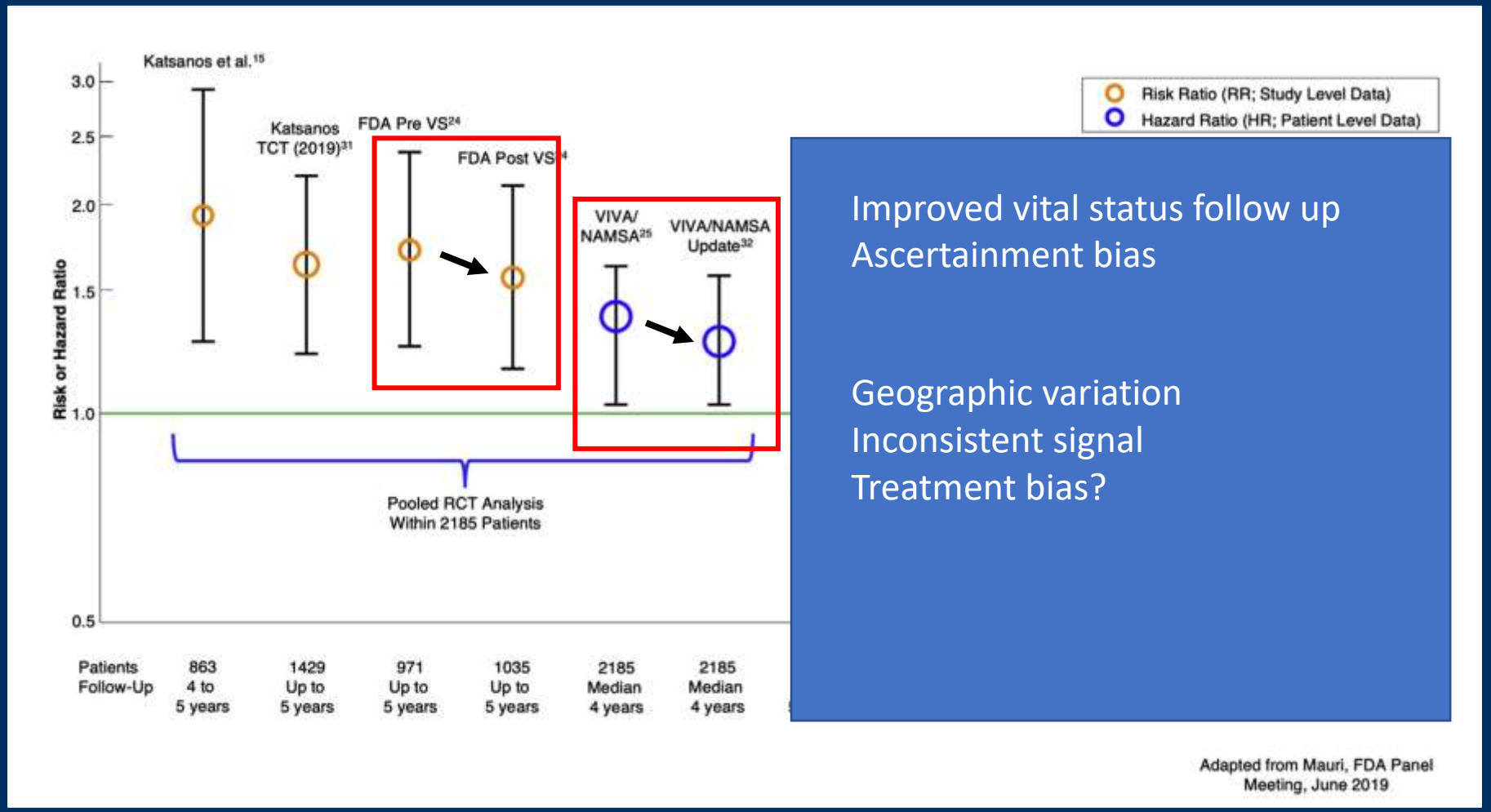
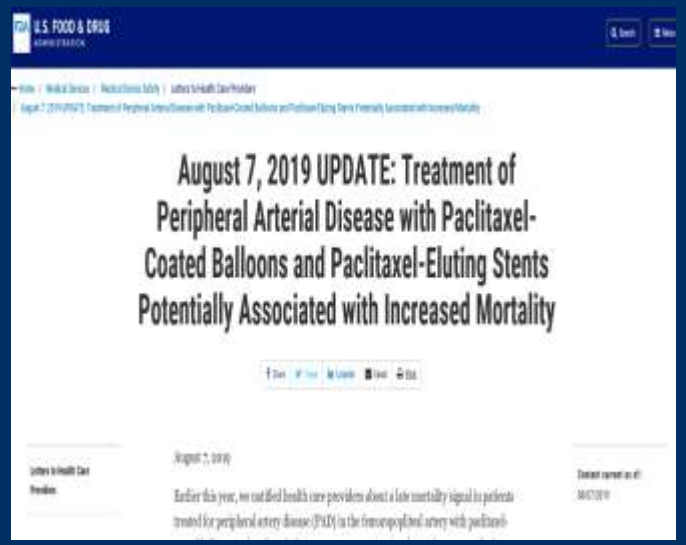
Efficacy Has Been Consistent But the Mortality Risk Has Not



Schneider et al. J Vasc Surg 2021;73:311

Aug.7 2019: FDA Update



"The Panel concluded that a late mortality signal associated with the use of paclitaxel-coated devices to treat femoropopliteal PAD was present.

…the **magnitude of the signal should be interpreted with caution because of multiple limitations in the available data** including… small sample size, pooling of studies of different paclitaxel-coated devices that were not intended to be combined, substantial amounts of missing study data…

No clear evidence of a paclitaxel dose effect on mortality, and no identified pathophysiologic mechanism for the late deaths."

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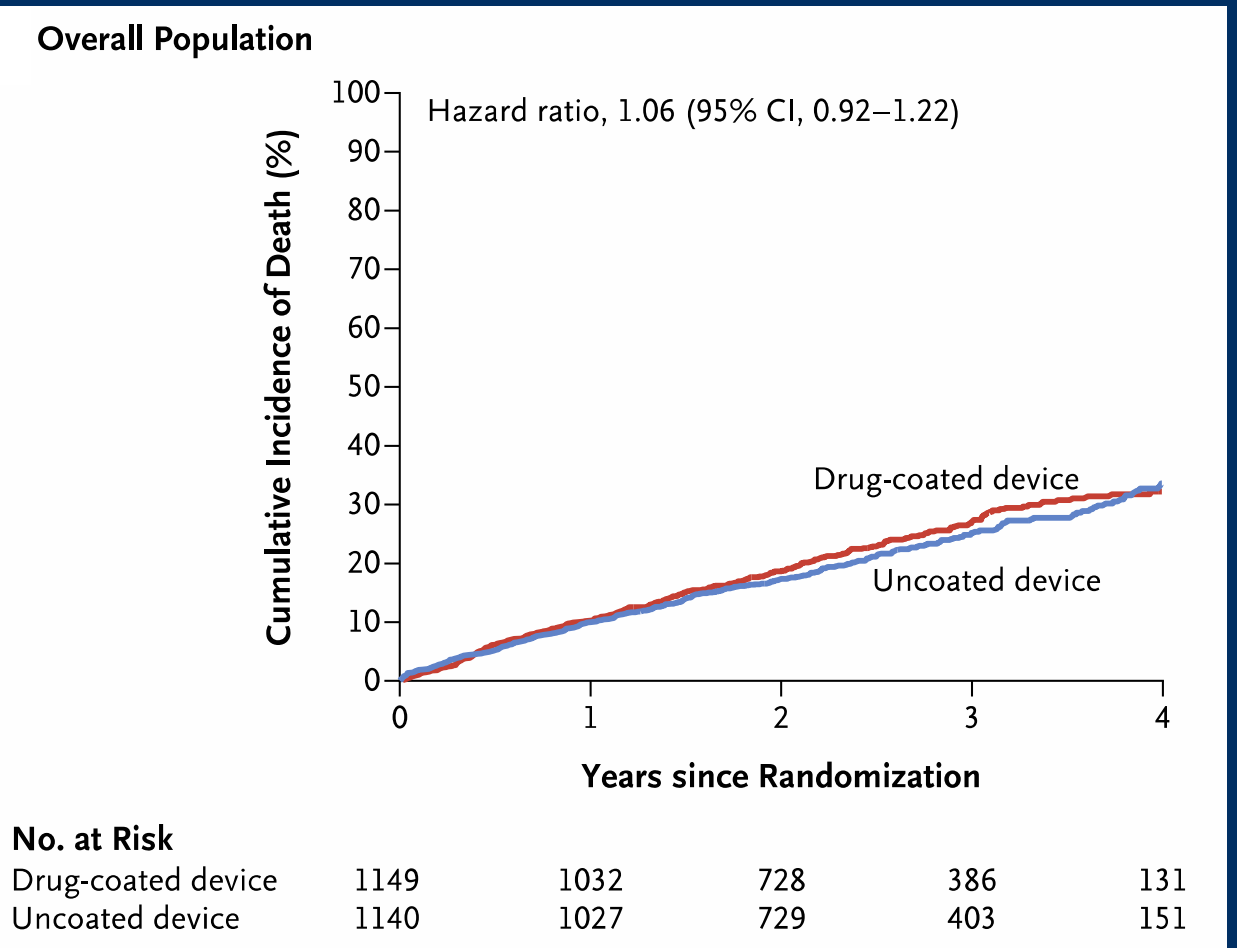
SWEDEPAD RCT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mortality with Paclitaxel-Coated Devices in Peripheral Artery Disease



2289 patients up to 4 years F/U
Paclitaxel vs plain device
CLTI 1480, claudication 809
Femoral-popliteal target lesion >80%
Lost to follow up 0
Overall mortality:
drug-10.2% vs non-drug-9.9% (HR 1.06)

Nordanstig et al N Engl J Med 2020, Dec 9, DOI: 10.1056

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Conclusion

- New data with more to follow.
- Working together: problem-solving across specialties, countries, manufacturers, regulatory agencies.
- Paclitaxel consistently efficacious but mortality signal not consistent.
  - No dose response and no mechanism.
  - Signal diminished with vital status ascertainment.
  - Signal primarily observed in the US.
  - Possibility of treatment bias associated with trial design or practice patterns may help explain inconsistency of signal.
- Trial design improvements: size, quality of follow-up, veracity of medical management and vital status ascertainment.