Paclitaxel safety in patients with CLTI

Marianne Brodmann, MD

Division of Angiology, Medical University Graz Austria

Disclosure

Speaker name:

Marianne Brodmann, MD

I have the following potential conflicts of interest to report:

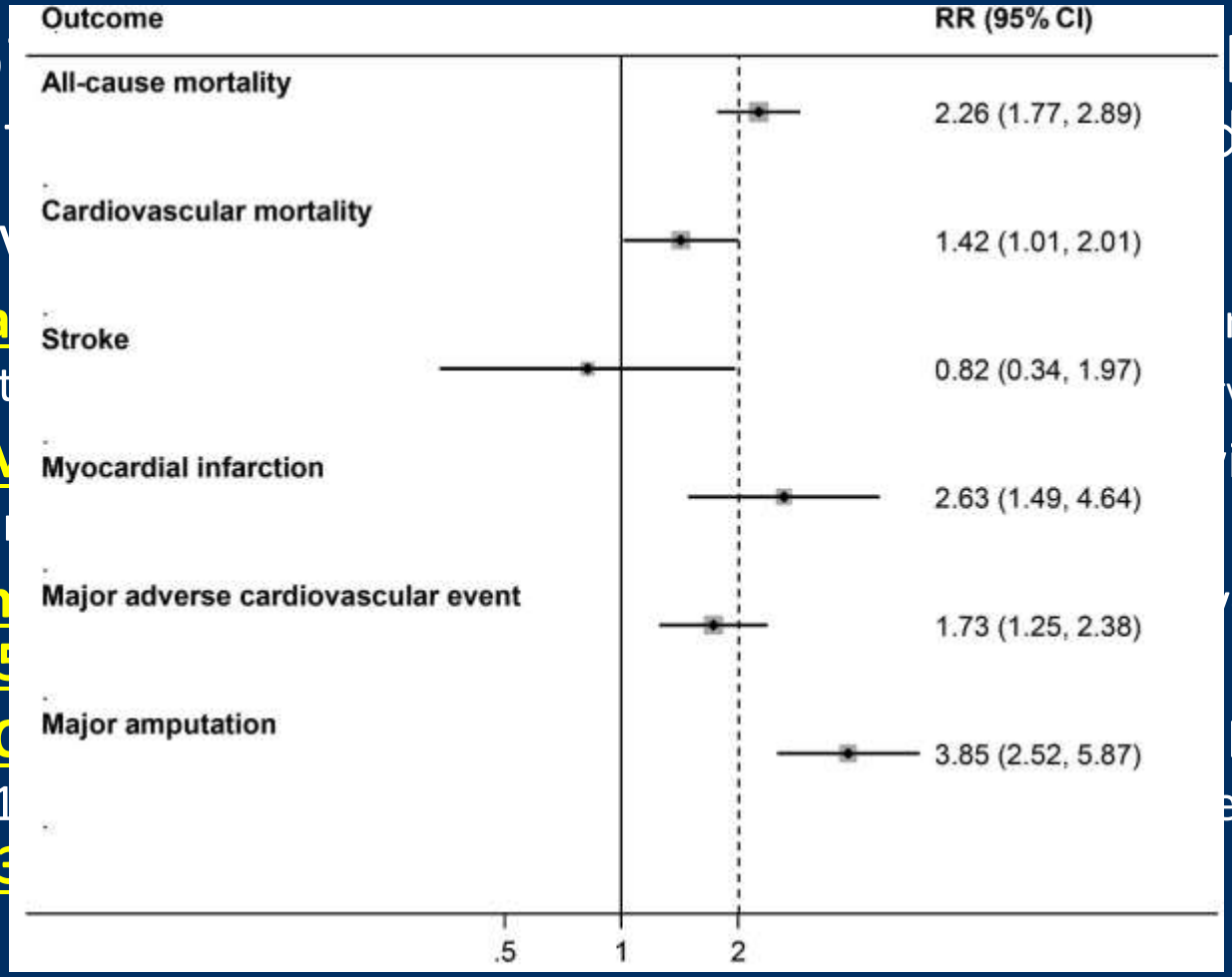
- ☒ Consulting
- ☐ Employment in industry
- ☐ Stockholder of a healthcare company
- ☐ Owner of a healthcare company
- ☐ Other(s)

- ☐ I do not have any potential conflict of interest

Risk of CLTI

Patients with CLTI are not healthy!

- The morb… known to be equal to or higher … disease (CHD)
- Recent rev…
  - Risk of a… ng patients with CLI (183 vs 81 event… val [CI], 1.77–2.89)
  - Risk of M… ith CLI (42 vs 16 events/ 1000 pe…
  - Risk of m… vents/1000 person- years; **RR, 3.85**
  - Risk of C… half-fold higher (74 vs 52 events/1… events/1000 person-years; **RR, 1.73**



[1] https://doi.org/10.1016/j.atherosclerosis.2019.09.012

Risk of CLTI _ How to overcome?

- Revascularization is key element of improvement of PAD outcomes
  - Limb salvage
    - Associated with reduced mortality
  - Possibility to walk pain free and exercise reduces CV mortality and morbidity

  - Revascularization in CLTI/mainly BTK has limited success rates with conventional angioplasty (POBA)
    - High rates of CDTLR

Drug coated devices raised hope for CLTI improvement !

Risk of Paclitaxel

- Meta-analysis 2018[1] challenged the use of paclitaxel coated devices in general with following statement

➡ Paclitaxel-coated devices for FP lesions increase the overall risk of death at 2 and 5 year FU

Faced significant criticism regarding its methodology including pooling study level data—patient level data was not available—not using a survival analysis method, and not accounting for patients who were lost to follow-up

- Several FU evaluations of RCT and real world patient data have revised the meta-analysis findings [2-4]

[1] Katsanos K, et al. J Am Heart Assoc 2018;7:e011245.
[2] Schneider PA et al. J Am Coll Cardiol 2019;73:2550-63.
[3] Secemsky EA, et al. JAMA Cardiol 2019;4:332-40.
[4] Gray WA et al. Circulation 2019;140:1145-55.

Risk of Paclitaxel_CLTI

- Several RCT´s have been conducted as well as real world data with regard to paclitaxel coated devices and treatment of CLTI patients

- Meta-analysis published 2020 is addressing the issue of Paclitaxel coated devices in CLTI
  - Mortality After Paclitaxel-Coated Device Use in Patients With Chronic Limb-Threatening Ischemia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials; Journal of Endovascular Therapy 2020, Vol. 27(2) 175–185

Risk of Paclitaxel_CLTI_metanalysis

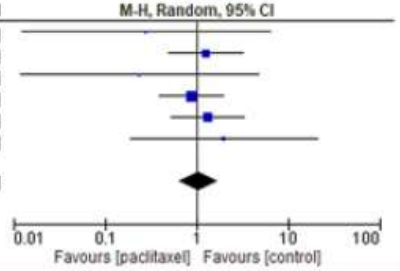
- 1450 patients were randomized to a paclitaxel- coated device (n=866) or an uncoated control (n=584)
- Six studies included below-the-knee lesions, and 5 studies included lesions above-the-knee
- There was no association between lesion location and mortality risk
- Eight studies used paclitaxel-coated balloons; 1 study used paclitaxel-eluting stents
- In 1 study the devices contained a paclitaxel dose of 2 µg/mm, all other devices delivered a paclitaxel dose of 3 or 3.5 µg/mm

Risk of Paclitaxel_CLTI_metanalsis

A. 6-Month All Cause Mortality

Study or Subgroup	Paclitaxel Events	Paclitaxel Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Gouëffic 2019	0	18	1	15	2.4%	0.28 [0.01, 6.43]
Mustapha 2019	14	287	6	155	26.8%	1.26 [0.49, 3.21]
Scheinert 2015	0	6	1	4	2.6%	0.24 [0.01, 4.72]
Spreen 2017	10	73	10	64	35.8%	0.88 [0.39, 1.97]
Zeller 2014	16	239	6	119	28.2%	1.33 [0.53, 3.31]
Zeller 2015	2	28	1	28	4.3%	2.00 [0.19, 20.82]
Total (95% CI)		651		385	100.0%	1.06 [0.65, 1.72]
Total events	42		25			

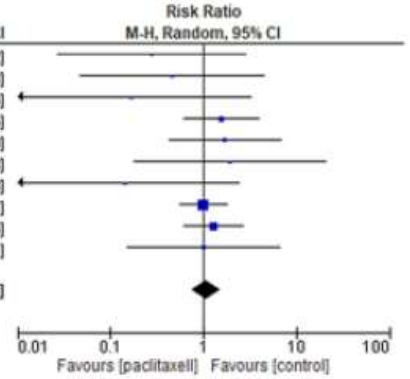
Heterogeneity: Tau² = 0.00; Chi² = 2.51, df = 5 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)



B. 12-Month All Cause Mortality

Study or Subgroup	Paclitaxel Events	Paclitaxel Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Dake 2016	1	27	2	15	2.5%	0.28 [0.03, 2.82]
DeBoer 2017	1	14	2	13	2.6%	0.46 [0.05, 4.53]
Gouëffic 2019	0	18	2	15	1.5%	0.17 [0.01, 3.26]
Haddad 2017	10	48	6	45	15.5%	1.56 [0.62, 3.95]
Liistro (BTK) 2013	5	65	3	67	6.9%	1.72 [0.43, 6.90]
Liistro (SFA) 2013	2	53	1	51	2.4%	1.92 [0.18, 20.58]
Scheinert 2015	0	6	2	4	1.7%	0.14 [0.01, 2.38]
Spreen 2017	18	73	16	64	39.0%	0.99 [0.55, 1.77]
Zeller 2014	23	239	9	119	24.4%	1.27 [0.61, 2.66]
Zeller 2015	2	28	2	28	3.7%	1.00 [0.15, 6.61]
Total (95% CI)		571		421	100.0%	1.07 [0.74, 1.53]
Total events	62		45			

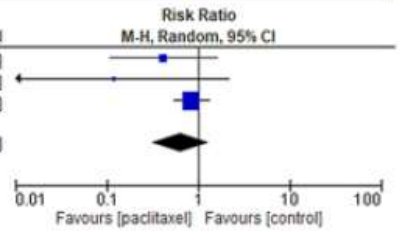
Heterogeneity: Tau² = 0.00; Chi² = 6.92, df = 9 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.34 (P = 0.73)



C. 24-Month All Cause Mortality

Study or Subgroup	Paclitaxel Events	Paclitaxel Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Dake 2016	3	27	4	15	22.1%	0.42 [0.11, 1.62]
Gouëffic 2019	0	18	3	15	5.9%	0.12 [0.01, 2.16]
Spreen 2017	24	73	25	64	72.0%	0.84 [0.54, 1.32]
Total (95% CI)		118		94	100.0%	0.64 [0.31, 1.32]
Total events	27		32			

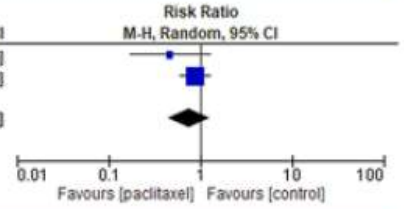
Heterogeneity: Tau² = 0.14; Chi² = 2.62, df = 2 (P = 0.27); I² = 24%
Test for overall effect: Z = 1.20 (P = 0.23)



D. 36-Month All Cause Mortality

Study or Subgroup	Paclitaxel Events	Paclitaxel Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Dake 2016	5	27	6	15	22.5%	0.46 [0.17, 1.26]
Spreen 2017	30	73	30	64	77.5%	0.88 [0.60, 1.28]
Total (95% CI)		100		79	100.0%	0.76 [0.45, 1.28]
Total events	35		36			

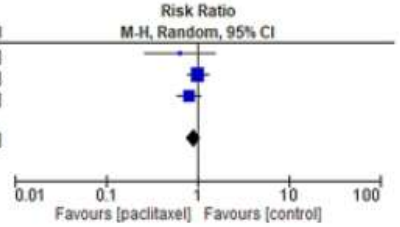
Heterogeneity: Tau² = 0.06; Chi² = 1.37, df = 1 (P = 0.24); I² = 27%
Test for overall effect: Z = 1.03 (P = 0.30)



E. 60-Month All Cause Mortality

Study or Subgroup	Paclitaxel Events	Paclitaxel Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Dake 2016	7	27	6	15	4.6%	0.65 [0.27, 1.58]
Spreen 2017	46	73	40	64	54.4%	1.01 [0.78, 1.31]
Zeller 2014	74	239	45	119	41.0%	0.82 [0.61, 1.10]
Total (95% CI)		339		198	100.0%	0.91 [0.75, 1.10]
Total events	127		91			

Heterogeneity: Tau² = 0.00; Chi² = 1.74, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 1.00 (P = 0.32)



Risk of Paclitaxel_CLTI_metanalysis

Subgroup and Sensitivity Analyses for All-Cause Mortality

Paclitaxel dose, μg/mm^2	
<2.0	1.01 (0.78 to 1.31)
2.0–3.0	0.90 (0.54 to 1.49)
3.5	0.86 (0.64 to 1.14)
Device type	
Drug-coated balloon	0.91 (0.70 to 1.17)
Drug-coated stent	0.82 (0.45 to 1.48)
Lower limb	
Above the knee	0.61 (0.31 to 1.20)
Below the knee	0.96 (0.80 to 1.16)
Lesion length, cm	
<10	0.80 (0.45 to 1.41)
≥10	0.87 (0.66 to 1.14)

[a]Data are given as the risk ratio (95% confidence interval).

Risk of Paclitaxel_CLTI_metanalysis

- Mean follow-up was 25.6 months (range 6–60)
- 10 of 11 studies reported a minimum 12-month follow-up
- There were **18.6%** (161) deaths among 866 subjects in the paclitaxel device group and **19.9%** (116) deaths among 584 subjects in the non-coated control group (RR 0.93, 95% CI 0.78 to 1.12, p=0.45)

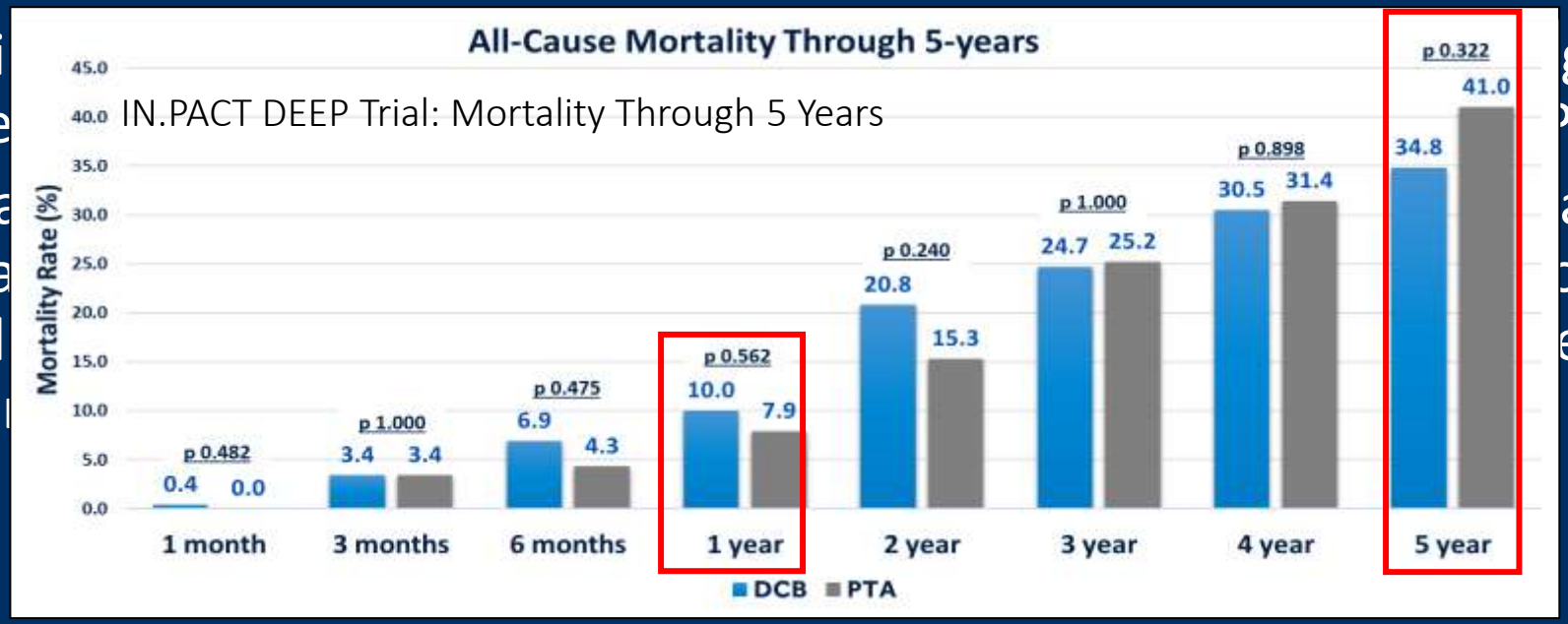
The authors conclude: There was no observed difference in short- to midterm mortality among a pooled patient population of predominately CLTI patients treated with paclitaxel-coated balloons or stents compared with uncoated controls.

Risk of Paclitaxel_CLTI_BTK_RCT data

- The IN.PACT DEEP Clinical Drug-Coated Balloon Trial 5-Year Outcomes; Zeller T et al; J Am Coll Cardiol Intv 2020;13:431–43

  – Ti … gioplasty re … PTA

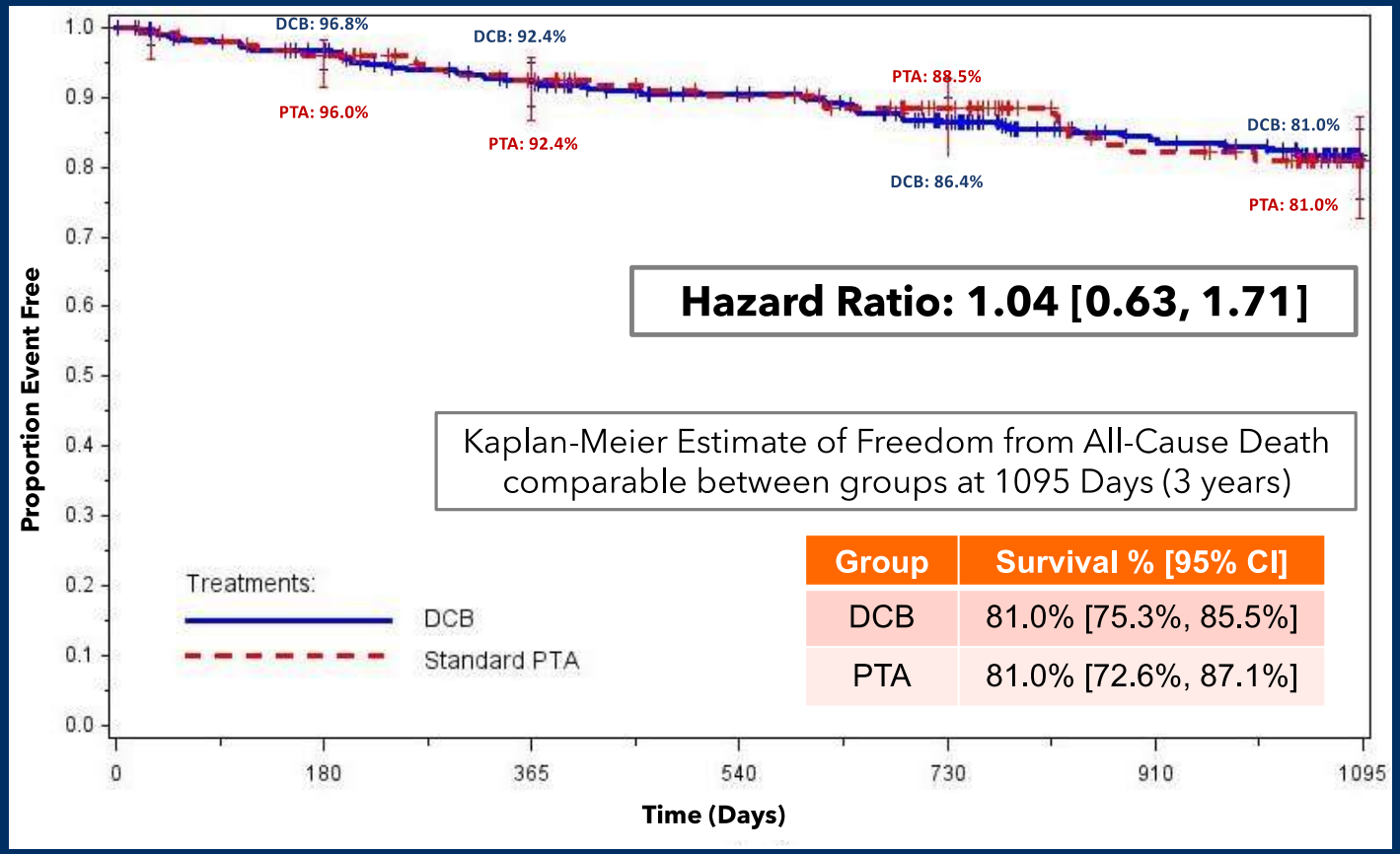
  – Pa … ation or all-ca … on" Drug El … e Knee Critical Li …



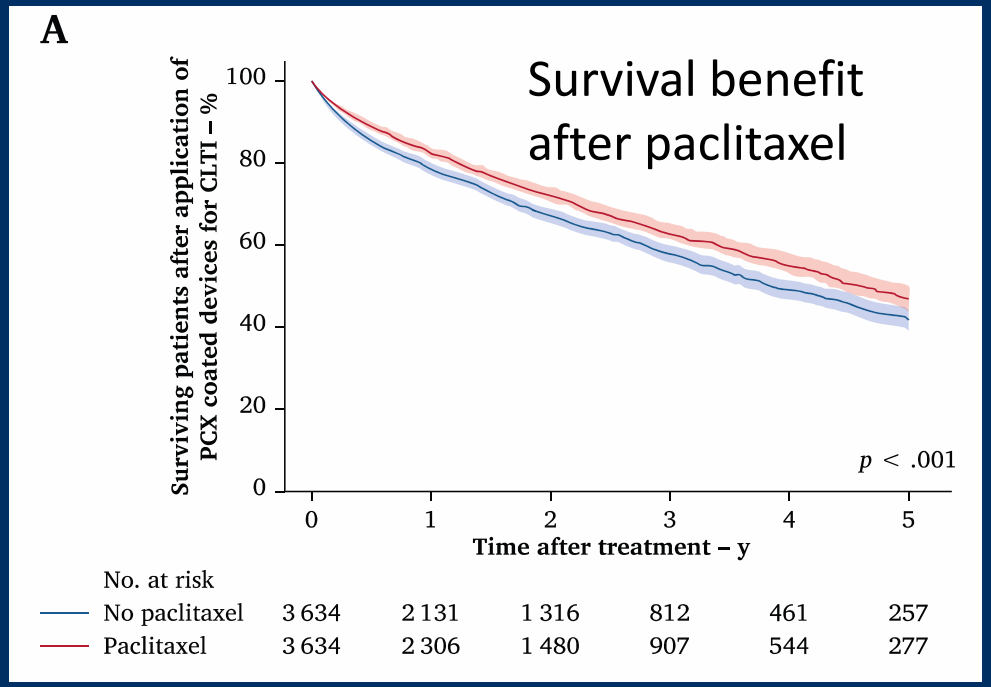
Risk of Paclitaxel_CLTI_BTK_RCT data

Lutonix BTK IDE Study: 12-Month Results & Interim Safety Analyses at Three Years

Freedom from all Cause Death at 3 years



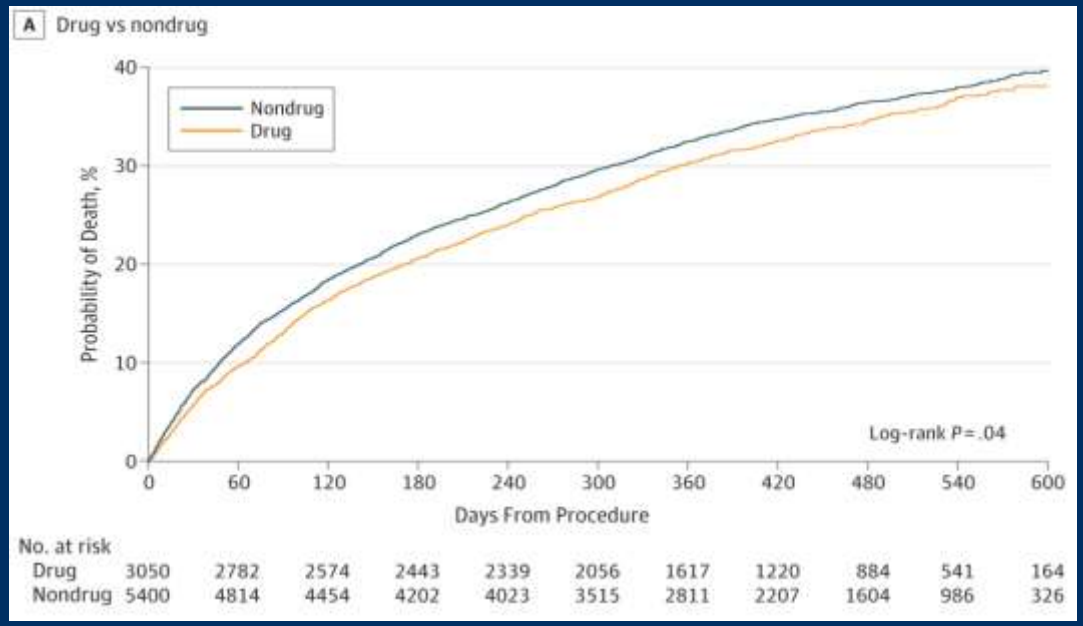
Risk of Paclitaxel_CLTI_Real worlddata



Propensity matched. CLTI patients treated with PTX for Fem-pop disease

Barmer Insurance-Germany

Behrendt et al. Eur J Vasc Endovasc Surg 2020 in press



Adjusted HR 0.93
95% CI, 0.85-1.01
Trend toward better survival with paclitaxel

Secemsky et al. JAMA Cardiology 2019

Risk of Paclitaxel_CLTI

Data so far do not show increased mortality with regard to the usage of paclitaxel coated devices in CLTI patients