Paclitaxel Use In CLTI Patients: Is There Still Any Evidence Of An Increased Amputation Risk?

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Peter A. Schneider Disclosures

Consulting:

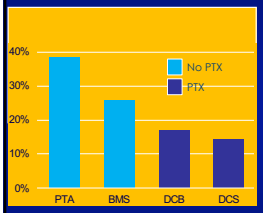
Surmodics, Medtronic, Boston Scientific, Phillips, Cagent, Acotec, Abbott, Endologix, Shockwave, Silk Road, Healthcare Inroads, Inari, BD

Under Development: Drug Eluting Technology for Lower Extremity Revascularization

	DCB	DES
Femoral-popliteal	Paclitaxel: Lutonix, IN.PACT Stellarex, Ranger, Surveil, Chocolate Touch Numerous CE mark approved devices. Limus: in development	Paclitaxel: Zilver, Eluvia DRS in development Limus: Sirocco, Strides, Stroll-failed trials
BTK	Paclitaxel: Lutonix, IN.PACT, Biolux- failed trials, Stellarex stopped, Ranger stopped Acotec in clinical trial, reformulated IN.PACT Limus: MedAlliance, Concept, Surmodics in clinical trials	Paclitaxel: SAVAL (SES) trial failed, PADI (DES) Limus: BE coronary DES (off label) DRS: LIFE-BTK (approved), Reva, R3 (in clinical trials)

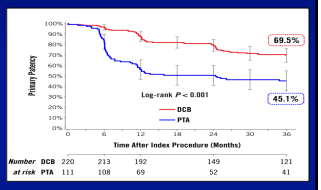
Efficacy of Paclitaxel for Femoral-popliteal Revascularization

2-Year Target Lesion Revascularization



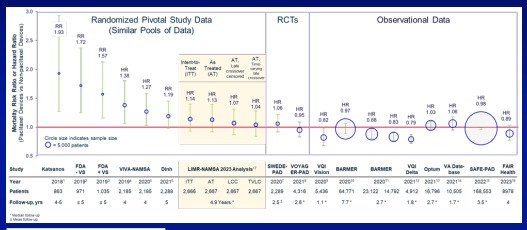
Sridharan et al. J Vasc Surg. 2018;67:343.

3-Year Primary Patency



Schneider et al. Circ: Cardiovasc Interv 2018;11:e005891

Paclitaxel Mortality Risk Studies (2018-present)



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

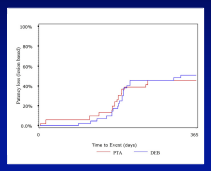
July 11, 2023

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).

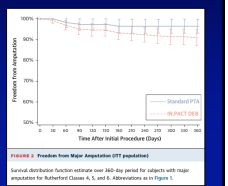
Based on the FDA's review of the totality of the available data and analyses, we have determined that the data does not support an excess mortality risk for paclitaxel-coated devices. The FDA previously communicated about this topic in 2019 and is now providing updated information.

July 11, 2023: FDA Update

Paclitaxel BTK DCB vs POBA: Three Failed Trials



BIOLUX P-II
Zeller et al. JACC: Cardiovasc Interv 2015;8:1614



IN.PACT DEEP
Zeller et al. JACC 2014;64:1568

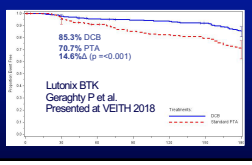


TABLE 5 Primary and Secondary Safety Endpoints

	IN-DEB	PTA	p Value
6-month primary safety endpoint	17.7 (41/232)	15.8 (18/114)	0.021*
12-month major amputation	8.8 (20/227)	3.6 (4/111)	0.080
12-month all-cause mortality	10.1 (23/227)	8.1 (9/111)	0.551
12-month death and amputations†	35.2 (80/227)	25.2 (28/111)	0.064
12-month death, major amputation or clinically driven TLR†	26.9 (61/227)	23.4 (26/111)	0.496
Amputation-free survival	81.1 (184/227)	89.2 (99/111)	0.057

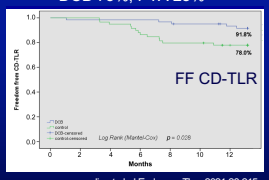
Trend toward increased amputation risk

Paclitaxel-Coated BTK DCB

Medtronic
- 3.5 ug per mm2
- 50 subjects: RCT vs PTA
- LLL at 9 months
- Subsegmental LLL: 0.59mm vs 0.94mm
- Classic LLL: 0.89 vs 1.31mm

Micari TCT 2020

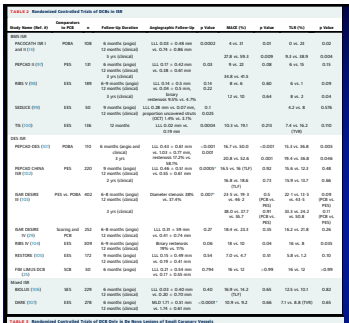
Acotec
- Acoart II BTK Study
- 120 subjects: RCT vs PTA
- Target lesion 17cm
- Occlusion 75-80%
- Primary patency at 6months:
  - DCB 75%, PTA 28%



Jia et al. J Endovasc Ther 2021;28:215

RCTs of Coronary DCB

Jeger et al. JACC: CI 2020



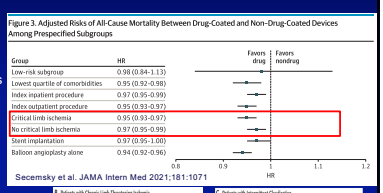
ISR

Small vessel

Paclitaxel in CLTI Patients: No increase in mortality risk

SAFE PAD

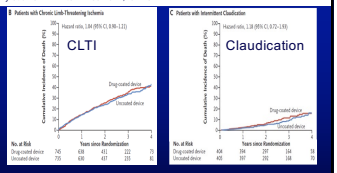
Mortality assessment 168,553 Medicare recipients underwent endovascular therapy
41.9% received paclitaxel coated devices



Secemsky et al. JAMA Intern Med 2021;181:1071

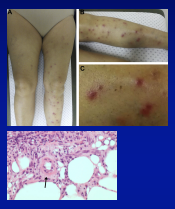
SWEDEPAD

RCT: paclitaxel versus non-paclitaxel devices in lower extremity PAD
2,289 subjects; mean follow-up time 2.49 years
100% vital status follow-up HR 1.06, 95% CI (0.92-1.22)

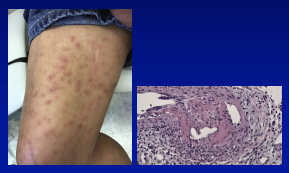


Nordanstig et al. New Engl J Med 2020; doi: 10.1056/NEJMoa2005206.

Particulate Embolization After DCB



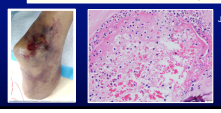
Thomas et al. J Vasc Surg 2014;59:520



Hawkins et al. J Am Acad Derm 2022;23:1

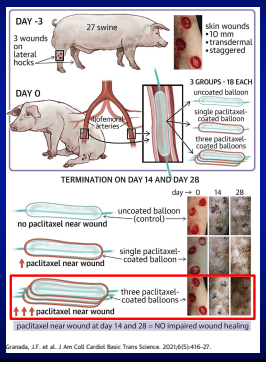
The no-flow phenomenon following drug-coated balloon angioplasty in a patient with chronic limb-threatening ischemia and a history of below-knee amputation

Mitsuo Sobajima (MD, PhD) *, Tetsuhiko Imamura (MD, PhD, FJCC), Atsuko Fukuo (MD), Yohei Ueno (MD, PhD), Hiroshi Onoda (MD, PhD), Hiroshi Ueno (MD, PhD), Koichiro Kinugawa (MD, PhD, FJCC)



J Cardiol Cases 2023;27:132

FDA-Mandated Pre-clinical Protocol



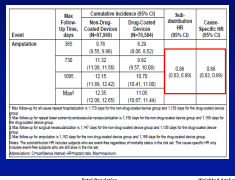
Granada, J.F. et al. J Am Coll Cardiol Basic Trans Science. 2021;6(5):416-27.

Healing not impaired
in distal extremity wounds in presence of intentional paclitaxel overdose.

Paclitaxel: No Increase in Amputation Risk

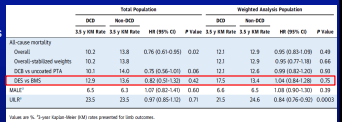
- Risk of amputation in over 160,000 patients in SAFE-PAD

  Risk of amputation in patients treated with paclitaxel devices was similar:
  HR 0.86 (95% CI 0.83-0.89)



- 4316 VOYAGER PAD patients

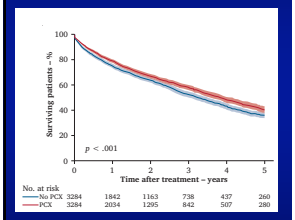
  Risk of MALE in patients treated with paclitaxel devices was similar:
  HR 1.08 (95% CI 0.90-1.30)



Secemsky et al. AMA Intern Med. 2021 Aug 1;181:1071-1080.
Hess et al. J Am Coll Cardiol 2021;78:1768-78.

CLTI: Barmer Insurance Study

BTK Paclitaxel treatment
14,738 patients with 5 years follow up
6,568 propensity matched pairs
DES or DCB vs plain



Heidemann et al. Eur J Vasc Endovasc Surg 2020

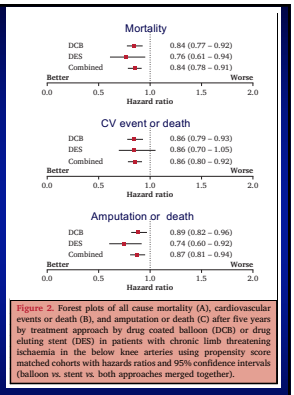
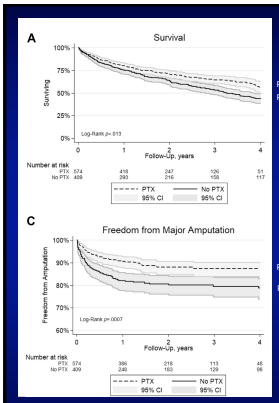


Figure 2. Forest plots of all cause mortality (A), cardiovascular events or death (B), and amputation or death (C) after five years by treatment approach by drug coated balloon (DCB) or drug eluting stent (DES) in patients with chronic limb threatening ischaemia in the below knee arteries using propensity score matched cohorts with hazards ratios and 95% confidence intervals (balloon vs. stent vs. both approaches merged together).

Better survival and fewer amputations among those who received paclitaxel



Kummins J Vasc Surg 2021;74:1682

Better Survival and Lower Amputation Risk with Paclitaxel in CLTI Patients

PTX
Plain

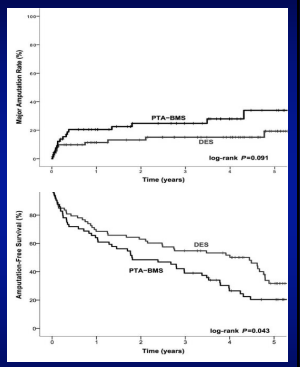
983 patients
58% received paclitaxel devices

Paclitaxel DES

PADI Trial:

PTA and Drug Eluting Stents for Infrapopliteal Lesions in Critical Limb Ischemia

- Multi-center randomized 2-arm study
- Limbs randomized to PTA ± BMS or paclitaxel-balloon expandable DES (Taxus Liberté)
  - 73 patients, 74 limbs-DES
  - 64 patients, 66 limbs-PTA ± BMS
- CLI, Rutherford 4-6
- de novo stenoses or occlusions BTK
- Vessel diameter 2-6 mm, length ≤ 90 mm



Spreen MI, et al. J Am Heart Assoc. 2017;6(4). pii: e004877.

Paclitaxel Use In CLTI Patients: Is There Still Any Evidence Of An Increased Amputation Risk?
Conclusion

- Amputation risk with paclitaxel is theoretical.
- Rigorous pre-clinical testing mandated by FDA.
- Rare clinical observation of cutaneous lesions from particulate embolization.
- Clinical studies, both RCTs and real-world, do not show increased risk of mortality or amputation in CLTI patients.

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