DCB current update

Lawrence A. Garcia, MD
Chief, Section Interventional Cardiology
and Vascular Interventions
Director, Vascular Medicine
Professor of Medicine
St. Elizabeth's Medical Center
Tufts University School of Medicine
Boston, MA

Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Abbott, Medtronic
• Consulting (non-compensated)	• Medtronic, Boston Scientific, Abbott, Phillips
• Major Stock Shareholder/Equity	• Primacea, TissueGen, CV Ingenuity, Orchestra, R3 Vascular, Transit Medical, Syntervention, Essential Medical
• Royalty Income	• None
• Ownership/Founder	• Innovation Vascular Partners
• Intellectual Property Rights	• None
• Other Financial Benefit	• None

Issues raised recently

Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Konstantinos Katsanos, MD, PhD, MSc, EBIR; Stavros Spiliopoulos, MD, PhD; Panagiotis Kitrou, MD, PhD; Miltiadis Krokidis, MD, PhD; Dimitrios Karnabatidis, MD, PhD

Background—Several randomized controlled trials (RCTs) have already shown that paclitaxel-coated balloons and stents significantly reduce the rates of vessel restenosis and target lesion revascularization after lower extremity interventions.

Methods and Results—A systematic review and meta-analysis of RCTs investigating paclitaxel-coated devices in the femoral and/or popliteal arteries was performed. The primary safety measure was all-cause patient death. Risk ratios and risk differences were pooled with a random effects model. In all, 28 RCTs with 4663 patients (89% intermittent claudication) were analyzed. All-cause patient death at 1 year (28 RCTs with 4432 cases) was similar between paclitaxel-coated devices and control arms (2.3% versus 2.3% crude risk of death; risk ratio, 1.08; 95% CI, 0.72–1.61). All-cause death at 2 years (12 RCTs with 2316 cases) was significantly increased in the case of paclitaxel versus control (7.2% versus 3.8% crude risk of death; risk ratio, 1.68; 95% CI, 1.15–2.47; —number-needed-to-harm, 29 patients [95% CI, 19–59]). All-cause death up to 5 years (3 RCTs with 863 cases) increased further in the case of paclitaxel (14.7% versus 8.1% crude risk of death; risk ratio, 1.93; 95% CI, 1.27–2.93; —number-needed-to-harm, 14 patients [95% CI, 9–32]). Meta-regression showed a significant relationship between exposure to paclitaxel (dose-time product) and absolute risk of death (0.4±0.1% excess risk of death per paclitaxel mg-year; $P<0.001$). Trial sequential analysis excluded false-positive findings with 99% certainty (2-sided α, 1.0%).

Conclusions—There is increased risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the lower limbs. Further investigations are urgently warranted.

Clinical Trial Registration—URL: www.crd.york.ac.uk/PROSPERO. Unique identifier: CRD42018099447. (***J Am Heart Assoc.* 2018;7:e011245. DOI: 10.1161/JAHA.118.011245.**)

Key Words: balloon angioplasty • paclitaxel • paclitaxel-coated balloon • paclitaxel-eluting stent

Katsanos et al JAHA Dec 2018

Issues raised recently

Study	Paclitaxel Events	Paclitaxel Total	Control Events	Control Total	RR	95%-CI	Weight (fixed)	Weight (random)
THUNDER [28]	2	48	1	54	2.25	[0.21; 24.04]	1.9%	2.9%
ZILVER-PTX [23]	9	297	4	177	1.34	[0.42; 4.29]	10.0%	12.1%
IN.PACT SFA [11]	4	207	0	107	4.66	[0.25; 85.80]	1.3%	1.9%
FEMPAC [29]	1	45	0	42	2.80	[0.12; 66.93]	1.0%	1.6%
LEVANT I [27]	2	49	4	52	0.53	[0.10; 2.77]	7.8%	6.0%
LEVANT II [26]	7	290	4	144	0.87	[0.26; 2.92]	10.7%	11.1%
CONSEQUENT [36]	2	70	1	65	1.86	[0.17; 20.00]	2.1%	2.9%
ILLUMENATE EU [35]	3	199	1	61	0.92	[0.10; 8.68]	3.1%	3.2%
ISAR-STATH [51]	1	48	0	107	6.65	[0.28; 160.31]	0.6%	1.6%
ISAR-PEBIS [55]	1	33	0	33	3.00	[0.13; 71.04]	1.0%	1.6%
ACOART I [42]	2	100	2	100	1.00	[0.14; 6.96]	4.0%	4.3%
IN.PACT SFA JAPAN [34]	0	68	0	32			0.0%	0.0%
FINN-PTX [18]	0	23	0	18			0.0%	0.0%
EFFPAC [47]	1	85	2	86	0.51	[0.05; 5.48]	4.0%	2.9%
LUTONIX JAPAN [48]	1	71	1	38	0.54	[0.03; 8.32]	2.6%	2.2%
PACIFIER [45]	0	42	3	43	0.15	[0.01; 2.75]	6.9%	1.9%
RANGER SFA [37]	2	71	1	34	0.96	[0.09; 10.20]	2.7%	2.9%
ILLUMENATE pivotal [43]	4	200	1	100	2.00	[0.23; 17.66]	2.7%	3.4%
BIOLUX P-1 [44]	0	30	2	30	0.20	[0.01; 4.00]	5.0%	1.8%
DEBATE-SFA [50]	2	53	1	51	1.92	[0.18; 20.58]	2.0%	2.9%
DEBELLUM [39]	0	25	0	25			0.0%	0.0%
FAIR [54]	2	47	3	44	0.62	[0.11; 3.56]	6.2%	5.4%
RAPID [49]	1	80	2	80	0.50	[0.05; 5.40]	4.0%	2.9%
BATTLE [21]	1	86	2	85	0.49	[0.05; 5.35]	4.0%	2.9%
DEBATE-in-SFA [22]	5	85	6	170	1.67	[0.52; 5.31]	8.0%	12.2%
DRECOREST [46]	4	29	2	28	1.93	[0.38; 9.72]	4.1%	6.3%
PACUBA [53]	0	35	0	39			0.0%	0.0%
FREEWAY [52]	1	90	2	81	0.45	[0.04; 4.87]	4.2%	2.9%
Fixed effect model		**2506**		**1926**	**1.06**	**[0.73; 1.55]**	**100.0%**	--
Random effects model					**1.08**	**[0.72; 1.61]**	--	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.98$

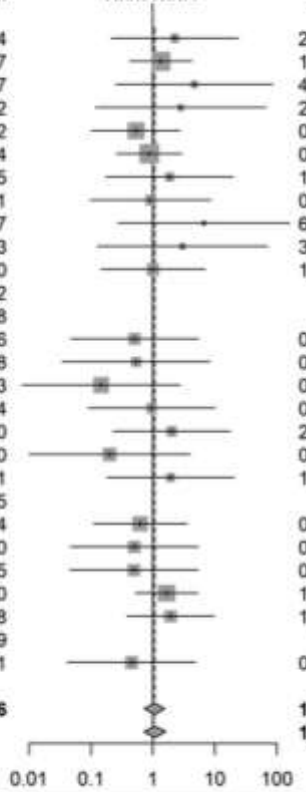

Figure 1. Random effects forest plot of all-cause patient death at 1 year. Pooled point estimate was expressed as risk ratio (RR).

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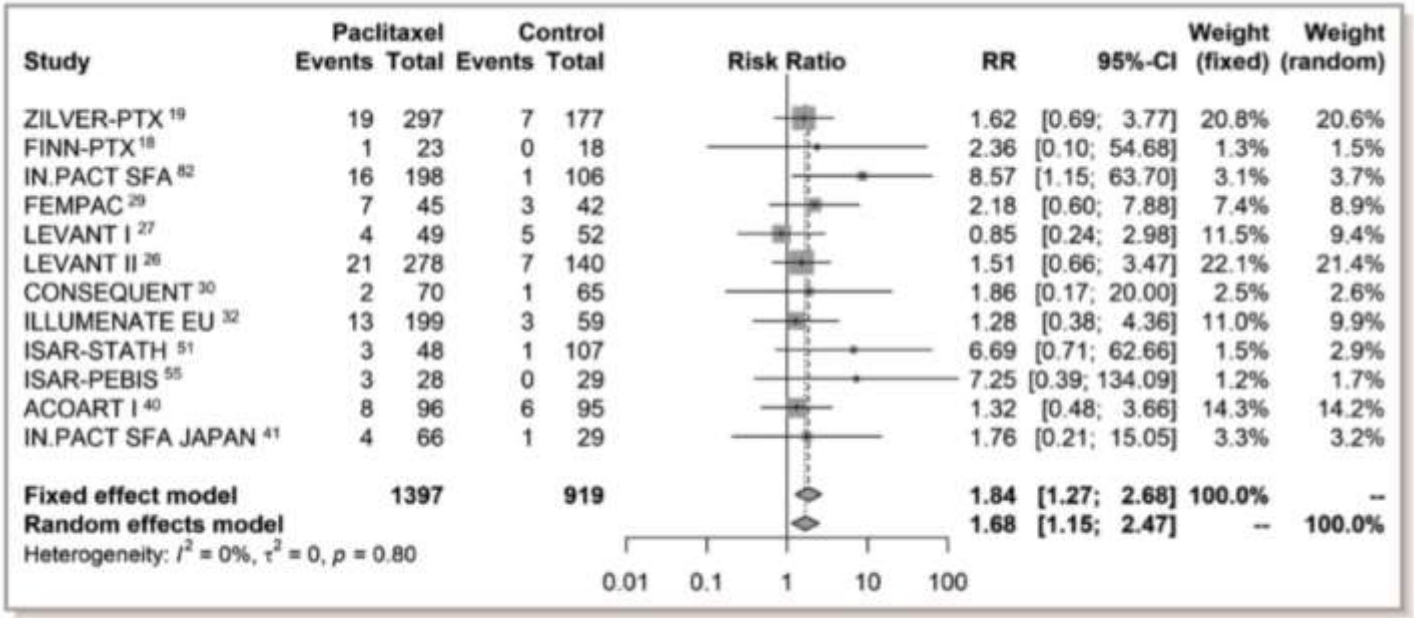

Figure 2. Random effects forest plot of all-cause death at 2 years. Pooled point estimate was expressed as risk ratio (RR).

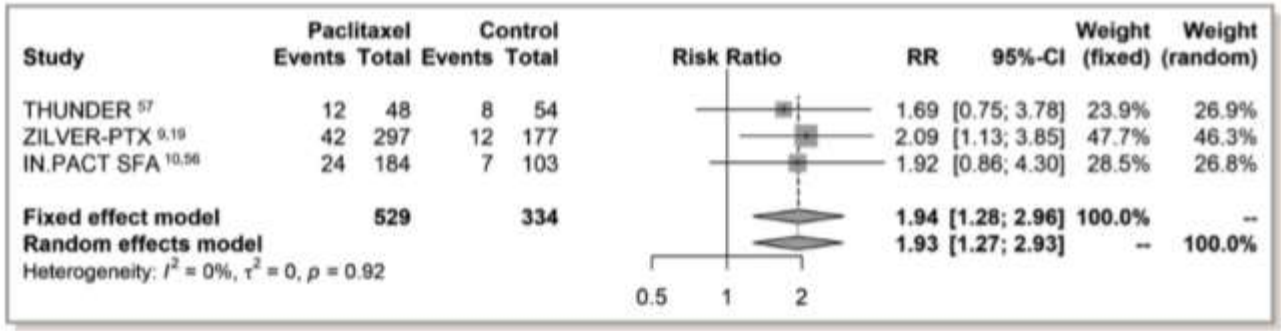

Figure 3. Random effects forest plot of all-cause death at 4 to 5 years. Pooled point estimate was expressed as risk ratio (RR).

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Safety questions in the US

- FDA has issued a warning letter regarding DCB/DES use in the US
  - Meta-analysis based risk
  - Analysis is ITT not ATA
- Initial caution while falling short of calling for banning the devices has then turned to *moratorium*
- Suggest current data requires high level review as to potential basis of mortality risk
- Patient level data released at LINC/TLF/CRT suggest no mortality interaction
- FDA panel to met June 2019—no changes in recommendation

August 7, 2019 UPDATE: Treatment of Peripheral Arterial Disease with Paclitaxel-Coated Balloons and Paclitaxel-Eluting Stents Potentially Associated with Increased Mortality

August 7, 2019

Earlier this year, we notified health care providers about a late mortality signal in patients treated for peripheral artery disease (PAD) in the femoropopliteal artery with paclitaxel-coated balloons and paclitaxel-eluting stents. We are issuing this update to provide the latest information on our analysis of long-term follow-up data from premarket trials and to provide summary information from our June 2019 advisory panel meeting. In addition, we are including recommendations to health care providers for assessing and treating patients with PAD using paclitaxel-coated devices.

This communication updates our January 17 (/medical-devices/letters-health-care-providers/treatment-peripheral-arterial-disease-paclitaxel-coated-balloons-and-paclitaxel-eluting-stents) and March 15, 2019 (/medical-devices/letters-health-care-providers/update-

paclitaxel-coated devices used to treat PAD was presented at the panel. Our meta-analysis of these trials identified a late mortality signal in study subjects treated with paclitaxel-coated

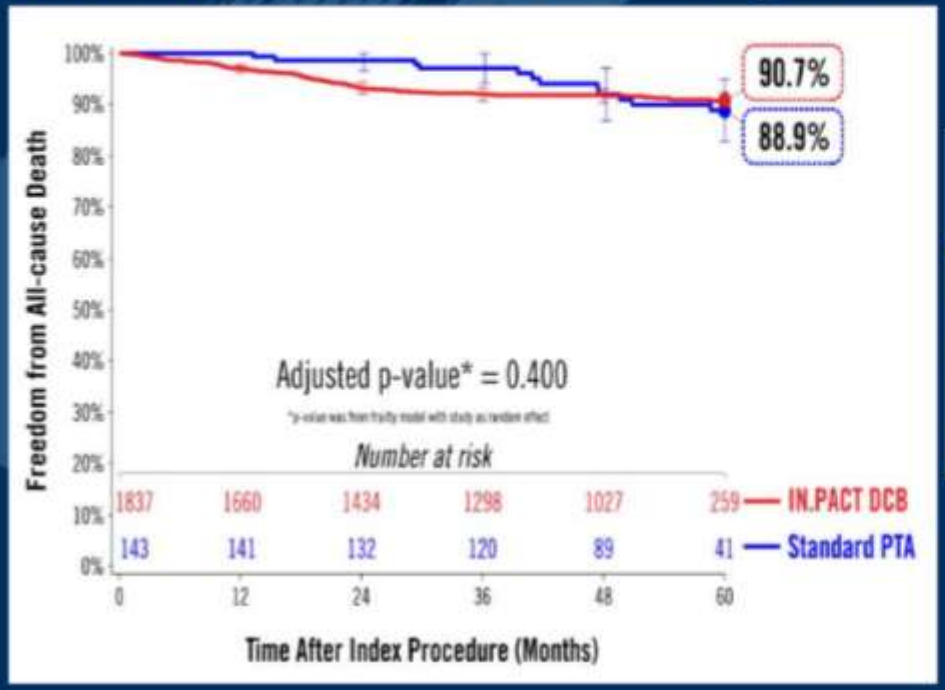
devices compared to patients treated with uncoated devices. Specifically, in the three randomized trials which enrolled a total of 1090 patients, the crude mortality rate at 5 years was 19.8% (range 15.9% - 23.4%) in patients treated with paclitaxel-coated devices compared to 12.7% (range 11.2% - 14.0%) in subjects treated with uncoated devices. The relative risk for increased mortality at 5 years was 1.57 (95% confidence interval 1.16 – 2.13), which corresponds to a 57% relative increase in mortality in patients treated with paclitaxel-coated devices. A meta-analysis performed by VIVA (Vascular InterVentional Advances) Physicians of patient-level data provided by manufacturers reported similar findings with a hazard ratio of 1.38 (95% confidence interval 1.06 - 1.80).

The Panel concluded that a late mortality signal associated with the use of paclitaxel-coated devices to treat femoropopliteal PAD was present. The Panel and the FDA agreed that the magnitude of the signal should be interpreted with caution because of multiple limitations in the available data including wide confidence intervals due to a small sample size, pooling of studies of different paclitaxel-coated devices that were not intended to be combined, substantial

IN.PACT Clinical Program: Patient-Level Meta-Analysis

Mortality Through 5 Years

Freedom From All-Cause Mortality Through 5 Years



5-years	DCB (n=1837)	PTA (n=143)	P-value*
All-cause Mortality	9.3% (140)	11.2% (12)	0.399

*P-value was from frailty model with study as random effect

Schneider LINC 2019, JACC 2019

IN.PACT Clinical Program: Patient Level Meta-Analysis

Key Baseline Characteristics

DCB mortality group: older with more comorbidities

DCB Cohort			
	Death (N=140 patients)	Survival (N=1697 patients)	P value
Age (yrs)	72.7±9.4 (137)	68.1±9.8 (1690)	**<0.001**
Carotid Artery Disease	32.8% (38/116)	21.5% (318/1481)	**0.007**
Coronary Heart Disease	52.3% (69/132)	42.0% (682/1623)	**0.028**
Diabetes Mellitus	53.2% (74/139)	40.2% (681/1694)	**0.003**
Renal Insufficiency*	23.8% (30/126)	9.1% (138/1518)	**<0.001**
Below-the-knee Vascular Disease of Target Leg (Stenotic/Occluded)	55.0% (72/131)	45.7% (736/1610)	**0.045**
Rutherford Category			
1	0.0% (0/140)	0.1% (1/1694)	**<0.001**
2	24.3% (34/140)	34.9% (591/1694)	
3	55.0% (77/140)	55.6% (942/1694)	
4	16.4% (23/140)	7.7% (130/1694)	
5	4.3% (6/140)	1.8% (30/1694)	

*baseline serum creatinine ≥ 1.5 ng/dl

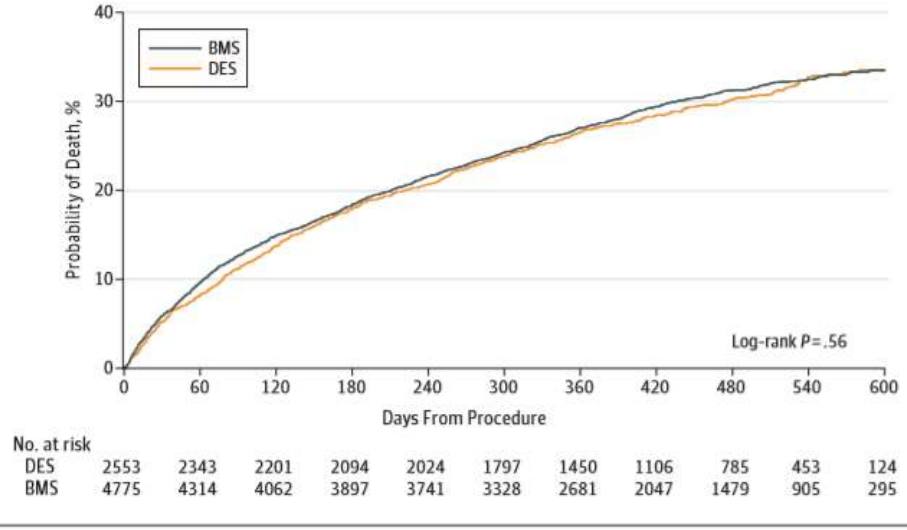
Schneider LINC 2019, JACC 2019

JAMA Cardiology | Original Investigation

Association of Survival With Femoropopliteal Artery Revascularization With Drug-Coated Devices

Eric A. Secemsky, MD, MSc; Harun Kundi, MD; Ido Weinberg, MD; Michael R. Jaff, DO; Anna Krawisz, MD; Sahil A. Parikh, MD; Joshua A. Beckman, MD; Jihad Mustapha, MD; Kenneth Rosenfield, MD; Robert W. Yeh, MD

C DES vs BMS



No. at risk

DES	2553	2343	2201	2094	2024	1797	1450	1106	785	453	124
BMS	4775	4314	4062	3897	3741	3328	2681	2047	1479	905	295

Displayed are the cumulative incidence curves for all-cause mortality after femoropopliteal artery revascularization, stratified by treatment with drug-coated devices (drug) vs non–drug-coated devices (nondrug) (A), drug-coated balloons (DCB) vs uncoated balloons (PTA) (B), and drug-eluting stents (DES) vs bare metal stents (BMS) (C).

Laser

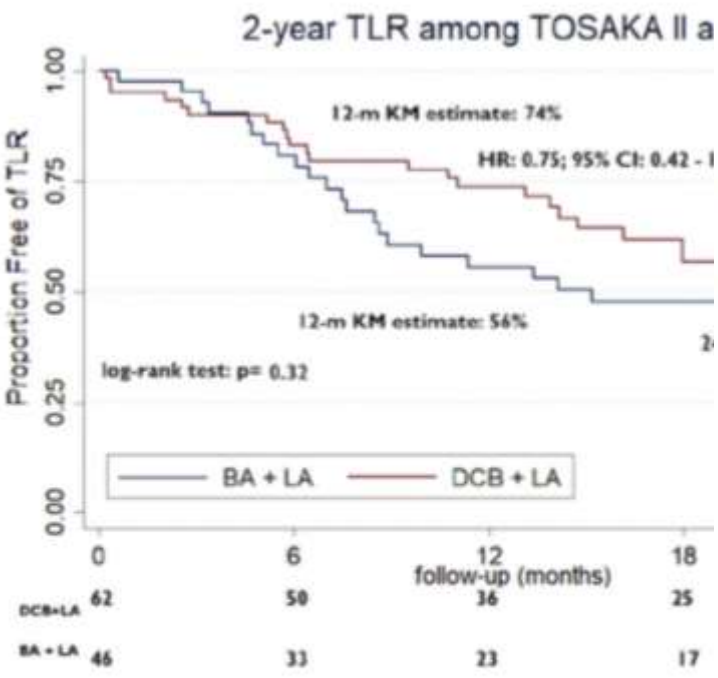


FIGURE 2 Kaplan–Meier survival curves for 24-
from target lesion revascularization among Tosaka II
[Color figure can be viewed at wileyonlinelibrary.com

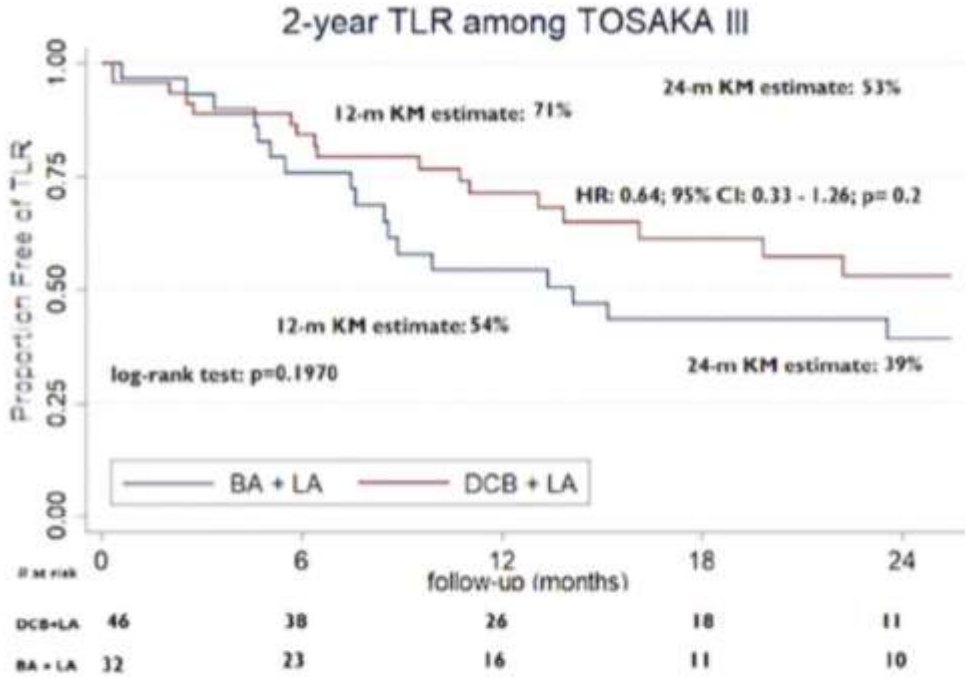


FIGURE 4 Kaplan–Meier survival curves for 24-month freedom from target lesion revascularization among Tosaka III lesions [Color figure can be viewed at wileyonlinelibrary.com]

Kokkinidis DG et al CCI 95, 3: Feb 15 2020

Original Research

Drug-coated Balloon Angioplasty of Femoropopliteal Lesions Maintained Superior Efficacy over Conventional Balloon: 2-year Results of the Randomized EffPac Trial

Ulf Teichgräber, Thomas Lehmann, René Aschenbach, Dierk Scheinert, Thomas Zeller, Klaus Brechtel, Erwin Blessing, Michael Lichtenberg, Peter von Flotow, Britta Heilmeier, Sebastian Sixt, Steffen Brucks, Christian Erbel, Ulrich Beschorner, Michael Werk, Vicenç Riambau, Andreas Wienke, Christof Tobias Klumb, Markus Thieme See fewer authors

- 171 patients
- Randomized trial DCB compared with POBA
- KM difference 90.2% vs 67.2% ($p<0.001$)
- At 2 years no difference in clinical outcome
- No difference in mortality

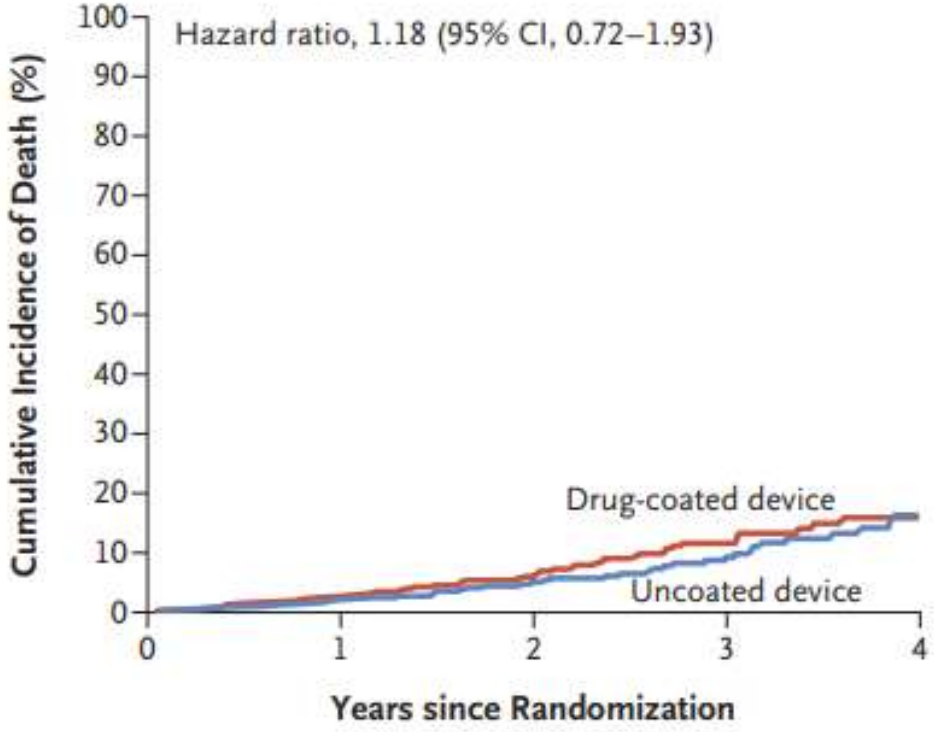
Teichgraber U et al. Radiology Mar 2020

ORIGINAL ARTICLE

Mortality with Paclitaxel-Coated Devices in Peripheral Artery Disease

Joakim Nordanstig, M.D., Ph.D., Stefan James, M.D., Ph.D., Manne Andersson, M.D., Ph.D., Mattias Andersson, M.D., Peter Danielsson, M.D., Ph.D., Peter Gillgren, M.D., Ph.D., Martin Delle, M.D., Ph.D., Jan Engström, M.D., Torbjörn Fransson, M.D., Maher Hamoud, M.D., Ph.D., Anna Hilbertson, M.D., Patrik Johansson, M.D., et al.

C Patients with Intermittent Claudication



No. at Risk

Drug-coated device	404	394	297	164	58
Uncoated device	405	397	292	168	70

Nordanstig et al NEJM Dec 2020 383:2538-46

FDA panel

- Panel did not endorse BTK DCB
- Lack of endorsement due to lack of data supportive compared to POBA
- Overall data mitigated no difference to POBA BTK

DCB update

- DCB's have dramatically changed the SFA landscape
  - Durability at 5 years in favor of DCB
  - ***Health care costs in favor of DCB***
- DCB data and combination therapy appear successful and low risk for best results
  - ***Econmics would suggest continued benefit***
- FDA has not updated their guidance from July 2019 ATK
- BTK guidance is no benefit for DCB
- Further registry data suggests no risk for ATK