

Paclitaxel and Mortality in PAD; The Latest Update

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Faculty Disclosure

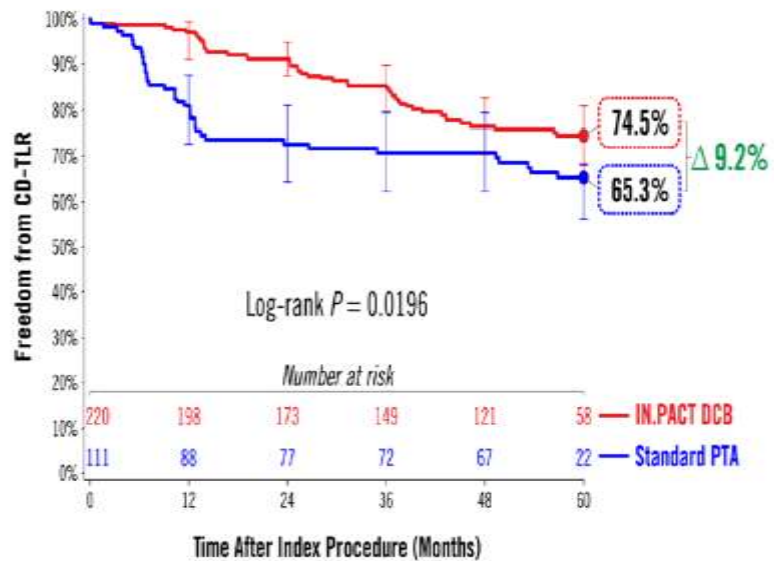
Thomas Zeller, MD

For the 12 months preceding this presentation, I disclose the following types of financial relationships:

- **Honoraria received from:** Abbott Vascular, BIBA Medical, Biotronik, Boston Scientific Corp., Cook Medical, Efemoral, Gore & Associates, Medtronic, Philips-Spectranetics, Shockwave, Veryan
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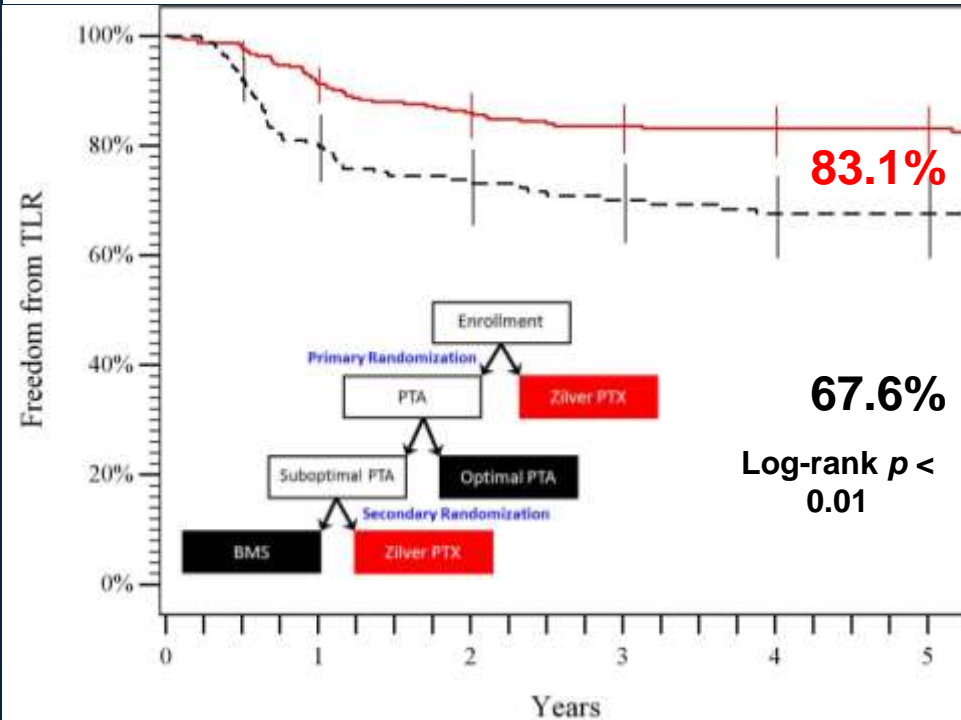
DCB vs DES 5-year Freedom from TLR

IN.PACT SFA Trial: Freedom from CD-TLR through 5 Years



Laird J. VIVA 2018.

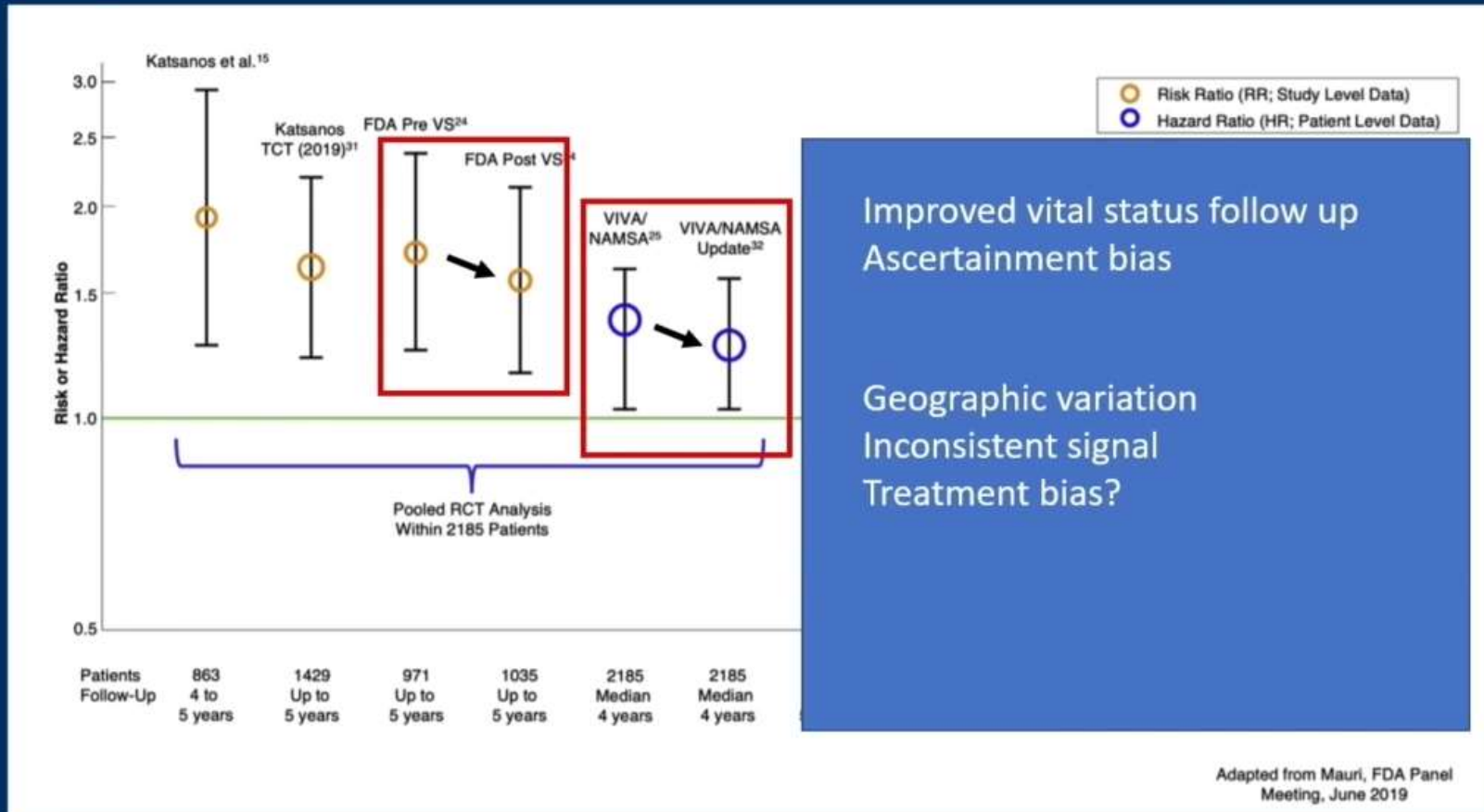
5-year Freedom from TLR Zilver[®] PTX[®] vs Standard Care



Dake M et al. Circulation 2016;133:1472-1483.

Insights on paclitaxel safety from the femoral-popliteal RCTs

Efficacy Has Been Consistent But the Mortality Risk Has Not

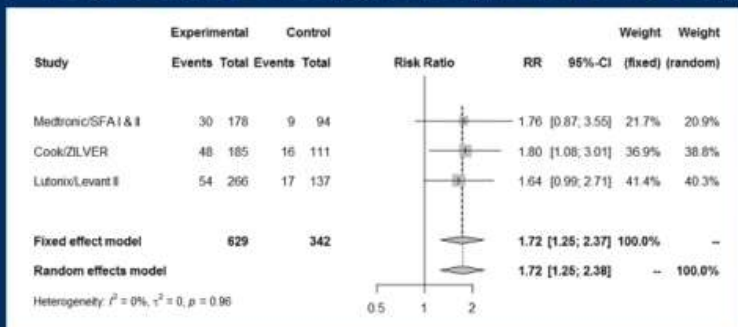


Schneider et al. J Vasc Surg 2021;73:311

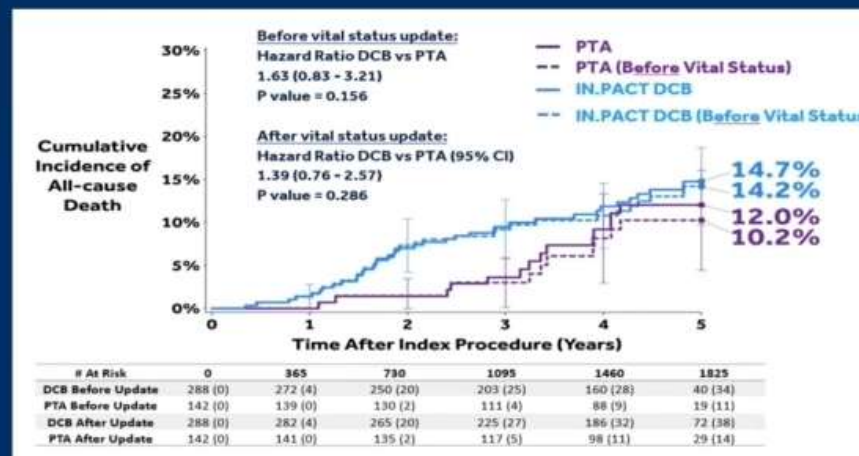
Insights on paclitaxel safety from the femoral-popliteal RCTs

Ascertainment Bias: When Missing Patients Were Identified the Risk Decreased

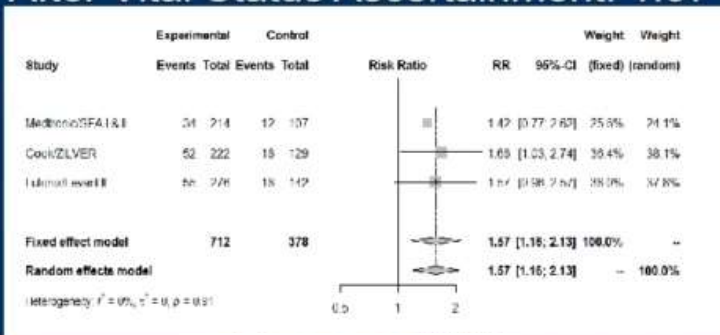
5 Year Point Estimate from FDA: RR 1.72



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)



After Vital Status Ascertainment: 1.57



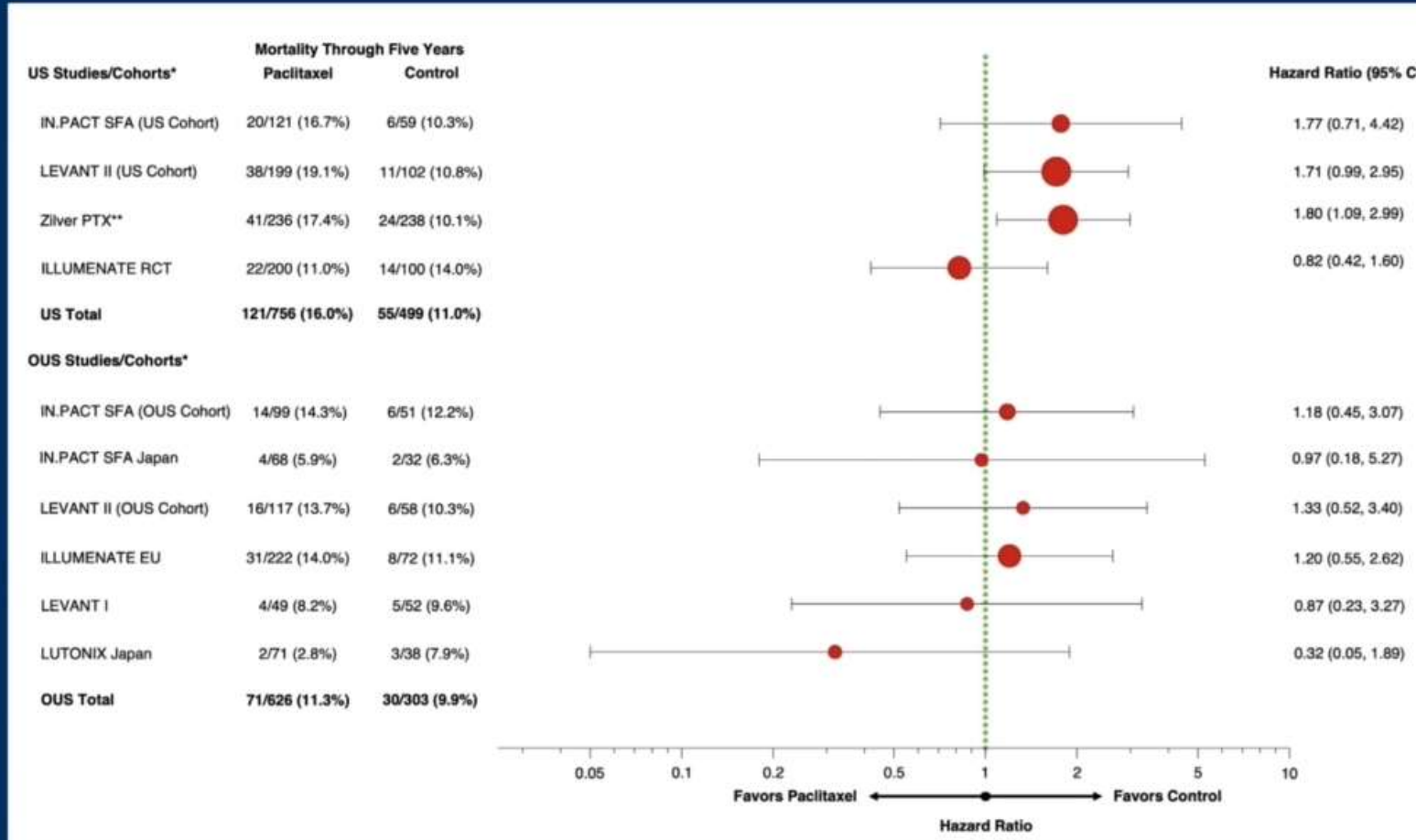
Hazard Ratio 1.63 → 1.39
Decrease 38%

Decrease 21%

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

Insights on paclitaxel safety from the femoral-popliteal RCTs

Geographic Factors Play a Role



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

Insight from AcoArt I- 5 Year Follow Up

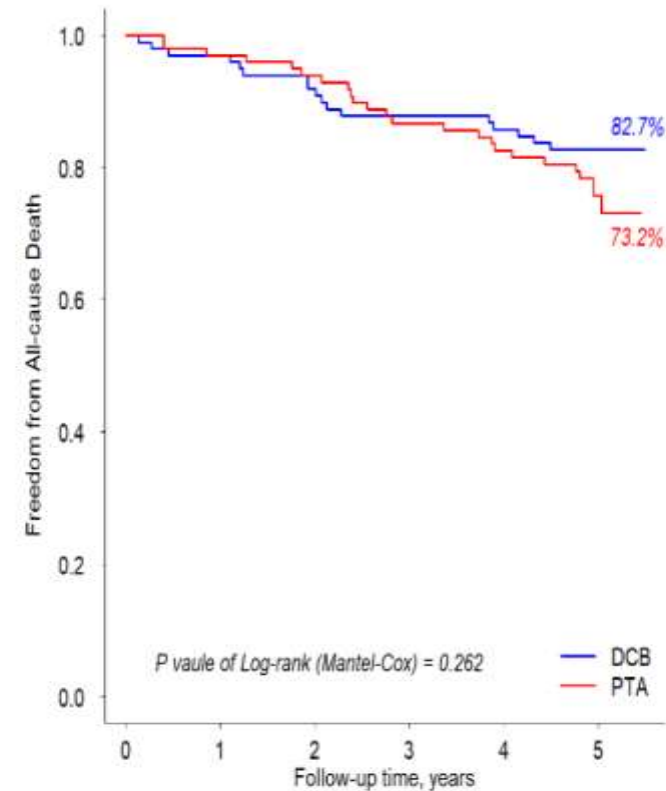
Dierk Scheinert, MD on behalf of
Guo Wei , MD

Department of Vascular and Endovascular Surgery,
Chinese PLA General Hospital, Beijing, China
On behalf of AcoArt I Trial investigators



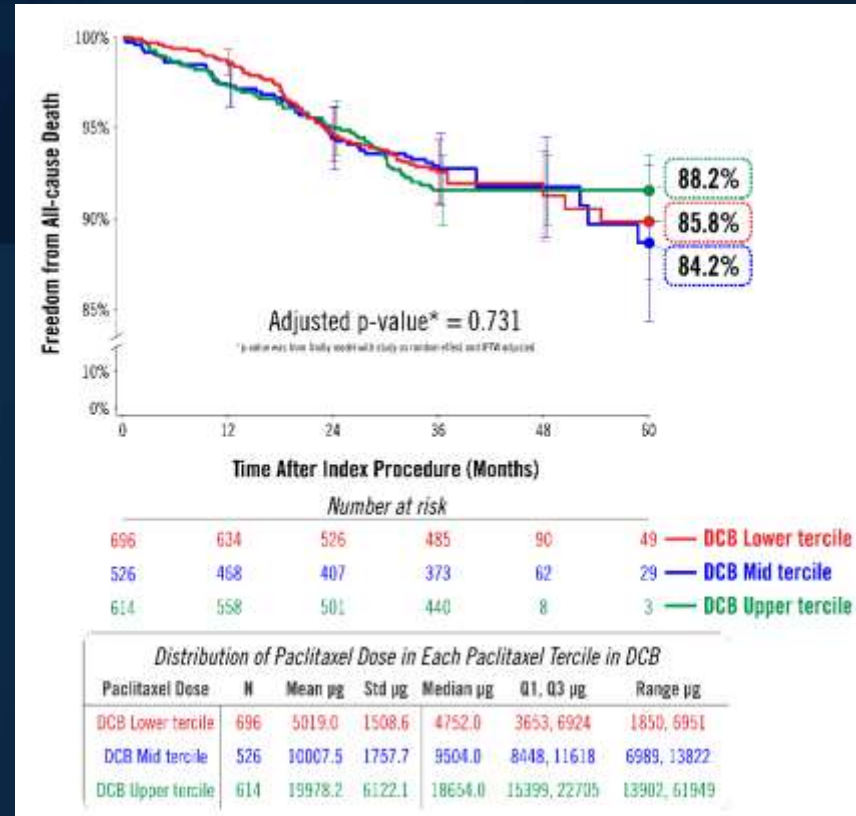
Freedom from All-cause Death through 5 years

No significant statistical difference on mortality between DCB and PTA over 5-years follow up, even more patients died in PTA group Vs. DCB group (24 vs.17)



Kaplan-Meier Curves of Freedom From All-cause Death Between the DCB Group and PTA Group

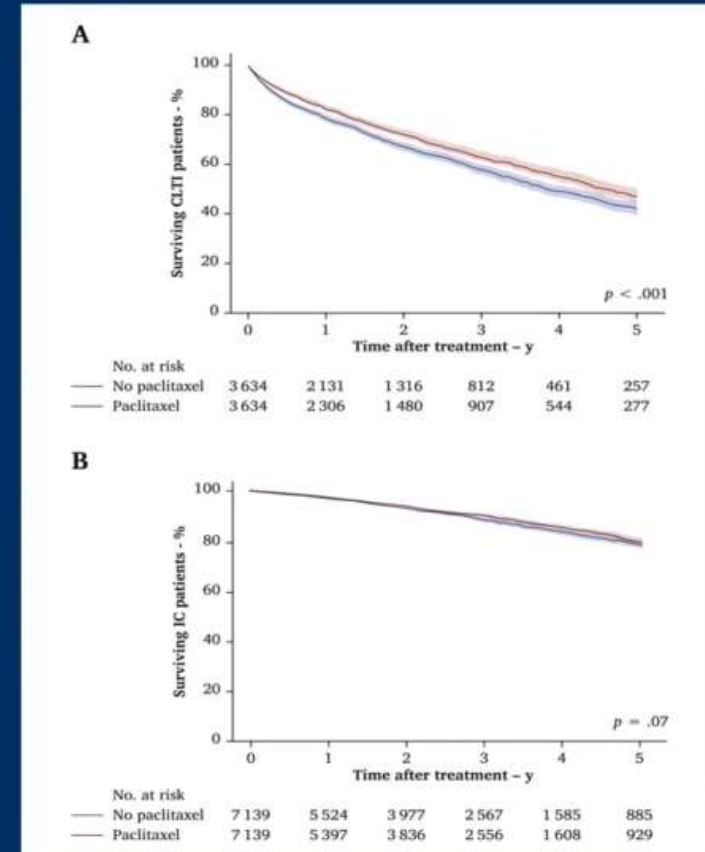
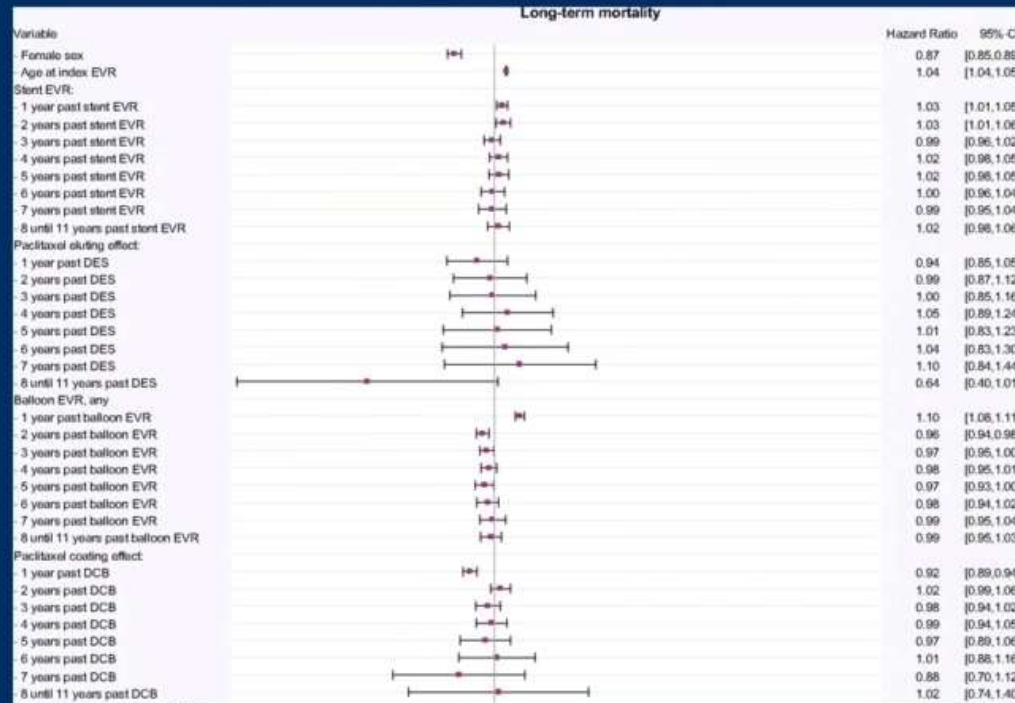
Kaplan-Meier Freedom from All-Cause Death by Paclitaxel Dose in All DCB Patients



Peter A. Schneider, MD; John R. Laird, MD; Gheorghe Doros, PhD; Qi Gao, MS; Gary Ansel, MD; Marianne Brodmann, MD; Antonio Micari, MD, PhD; Mehdi H. Shishehbor, DO, MPH, PhD; Gunnar Tepe, MD; Thomas Zeller, MD. Mortality not correlated with paclitaxel exposure: an independent patient-level meta-analysis of IN.PACT Admiral drug-coated balloon. JACC 2019

BARMER Health Insurance Data

- 64,771 patients treated between 2007-2015; DCB = 2,648, DES = 676
- 21,546 matched patients treated between 2010-2018; DCB = 6,871, DES = 3,902



Freisinger E, et al. *EHJ* 2019; Bherendt CA, et al. *Eur J Vasc Endovasc Surg* 2020.

ADVISORY COMMITTEE MEETING

June 19-20, 2019: Circulatory System Devices Panel of the Medical Devices Advisory Committee Meeting Announcement

JUNE 19-20, 2019

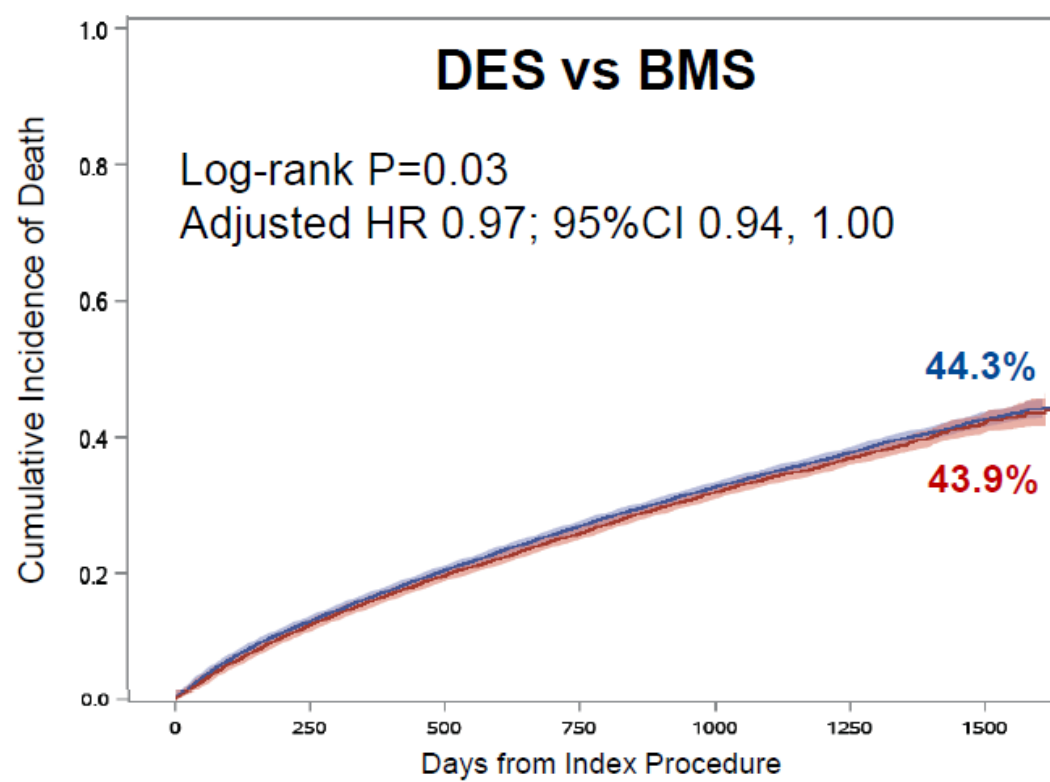
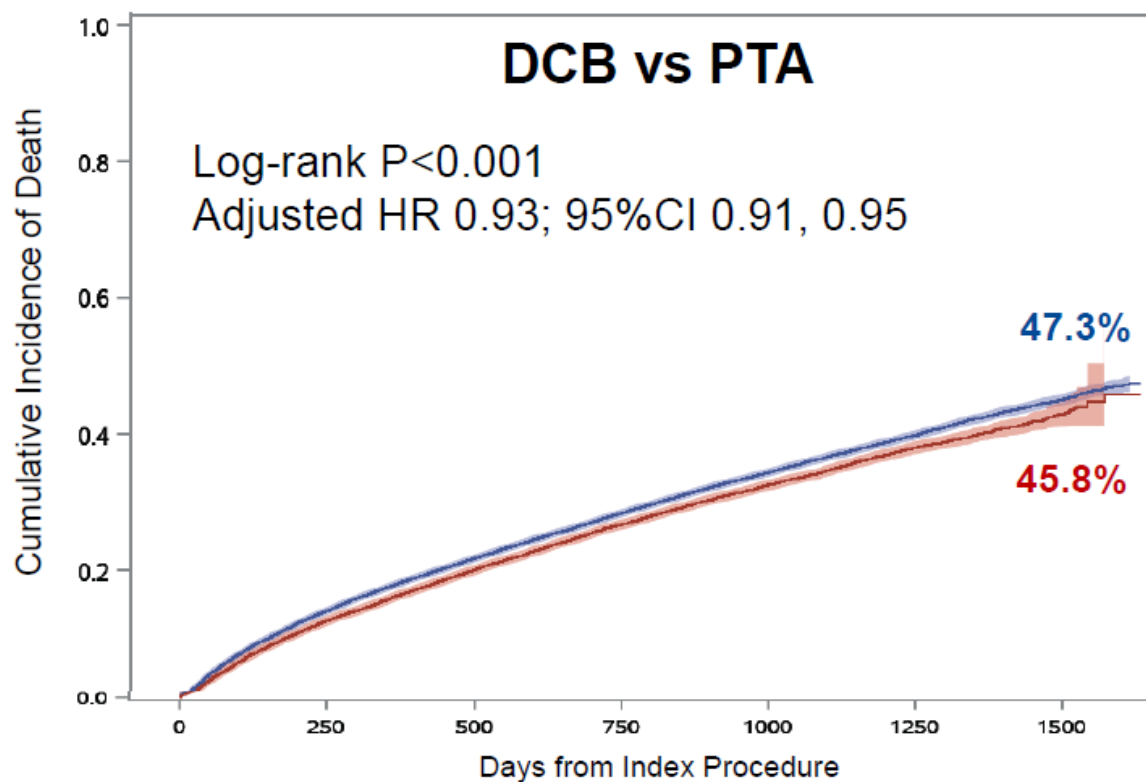
Analysis #3

- **152,473 Medicare beneficiaries** who underwent femoropopliteal artery revascularization from **01/1/2015 to 12/31/2017** at 3,042 U.S. institutions
 - Both inpatient and outpatient procedures
- **Drug-coated devices (DES/DCB)** compared with **non-drug-coated devices (BMS/PTA)**
- All-cause mortality was analyzed through **04/30/2019**
 - Median follow-up 799 days, longest 1,573 days

Device Type: Weighted Results

DCB: 23.9% (N=36,410); PTA: 37.2% (N=56,720)

DES: 16.5% (N=25,097); BMS: 22.5% (N=34,246)

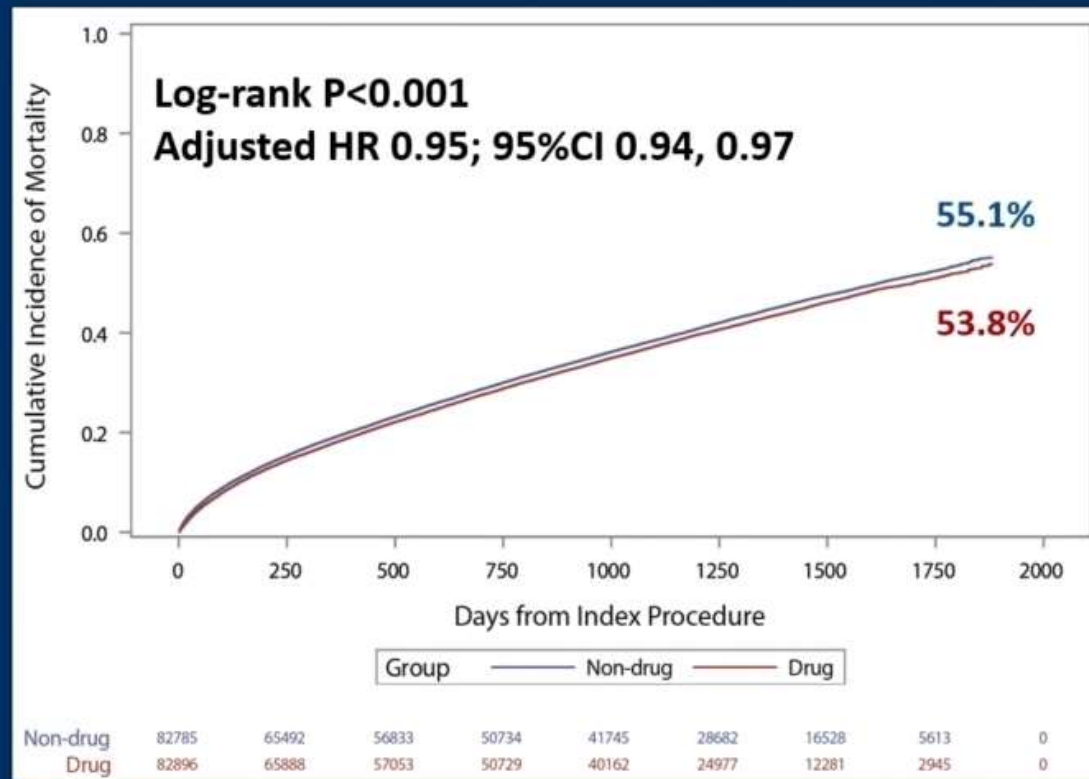


PTA	56720	47981	42868	31069	20770	10871	2681
DCB	36410	32167	28932	18664	10379	3739	68

BMS	34246	29510	26466	19413	12946	6687	1552
DES	25097	22191	20009	13732	8372	3740	604

SAFE-PAD Primary Results

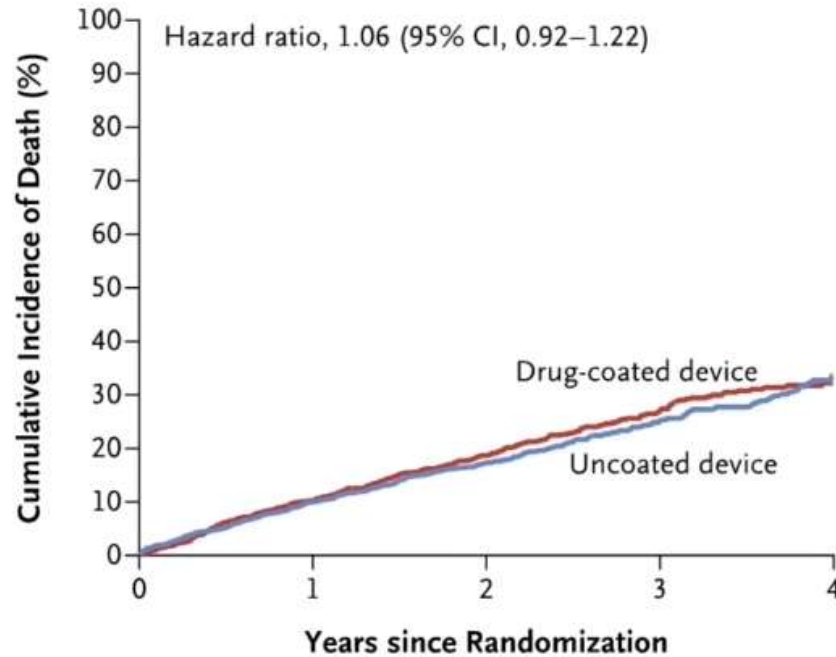
- 168,553 inpatients & outpatients treated between 2015-2018 at 2,978 U.S. institutions
- Median follow-up 2.72 years (IQR 0.87 - 3.77 years); longest follow-up 5.16 years



Insights on paclitaxel safety from the femoral-popliteal RCTs SWEDEPAD RCT

Mortality with Paclitaxel-Coated Devices in Peripheral Artery Disease

Overall Population



No. at Risk

Drug-coated device	1149	1032	728	386	131
Uncoated device	1140	1027	729	403	151

2289 patients up to 4 years F/U

Paclitaxel vs plain device

CLTI 1480, claudication 809

Femoral-popliteal target lesion >80%

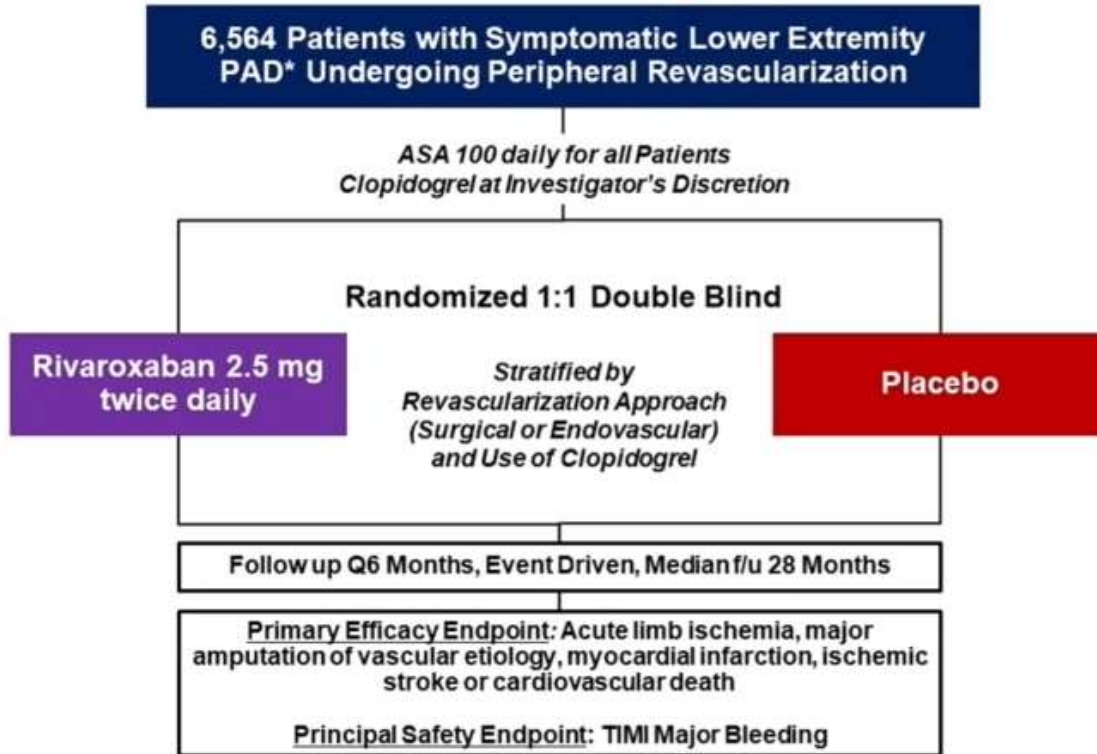
Lost to follow up 0

Overall mortality:

drug-10.2% vs non-drug-9.9% (HR 1.06)

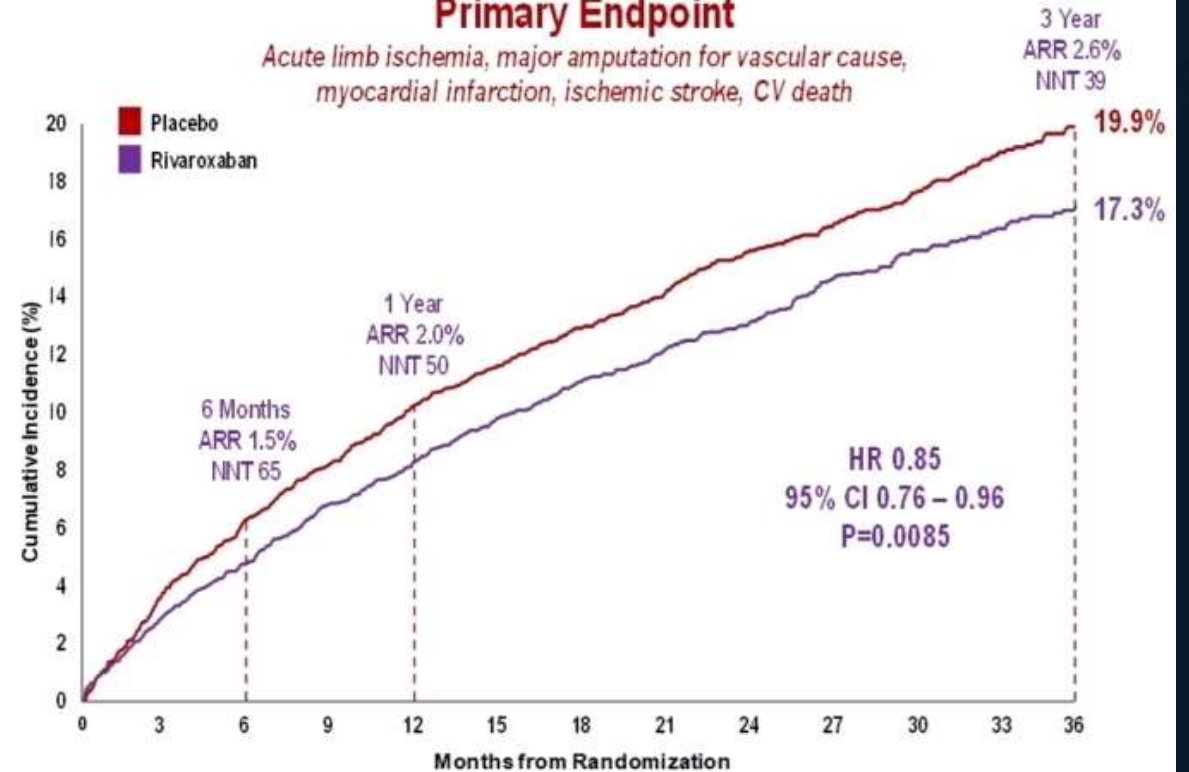
VOYAGER PAD

Trial Design



Primary Endpoint

Acute limb ischemia, major amputation for vascular cause, myocardial infarction, ischemic stroke, CV death



ARR, absolute risk reduction; NNT, number needed to treat

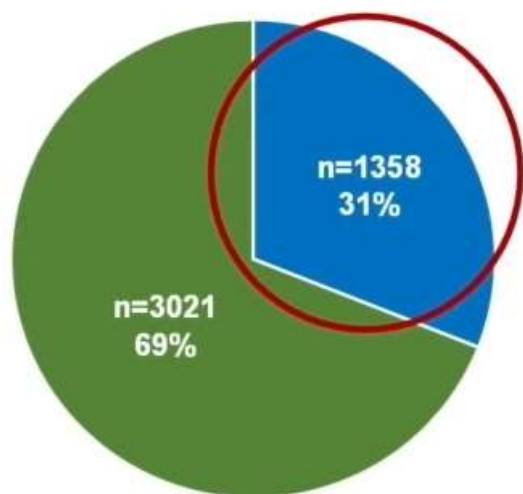


Bonaca MP, et al. NEJM 2020

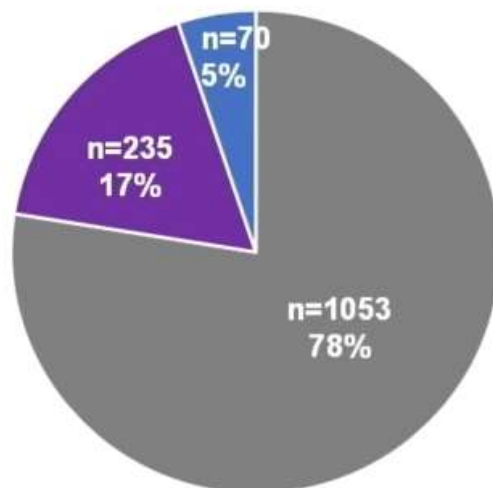
7 VOYAGER PAD

Results

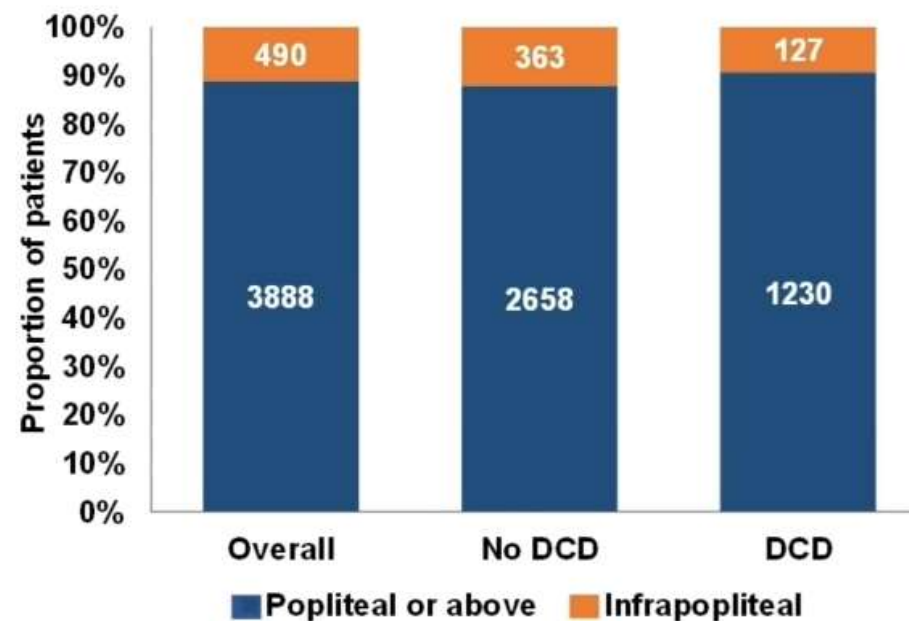
- Median follow-up of 31 months (IQR 25, 37 months)
- Complete ascertainment of vital status in 99.6% of patients



■ DCD ■ No DCD



■ Drug-coated balloon
 ■ Drug-eluting stent
 ■ Both

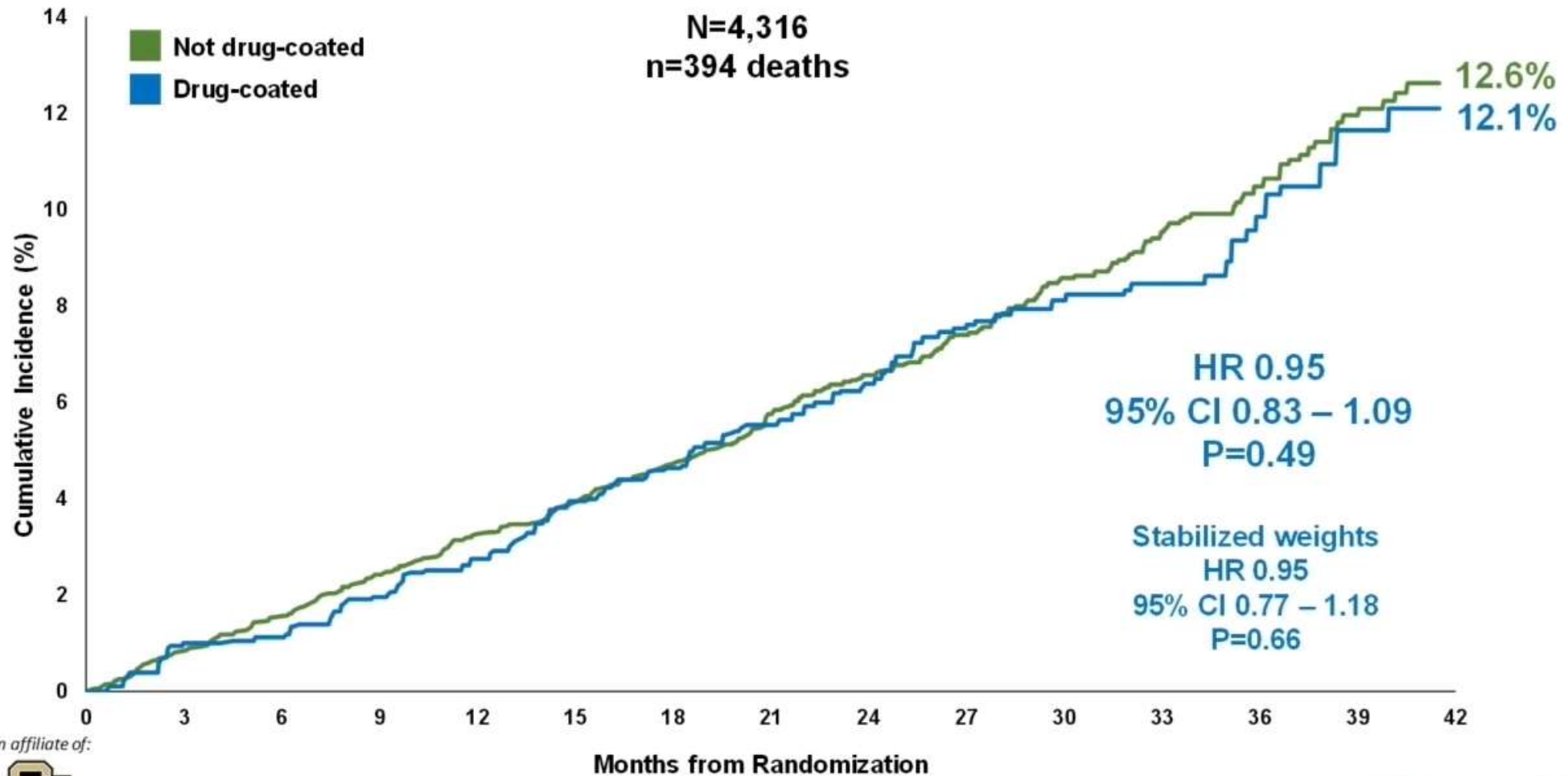


*1 patient missing lesion location

All-cause Mortality

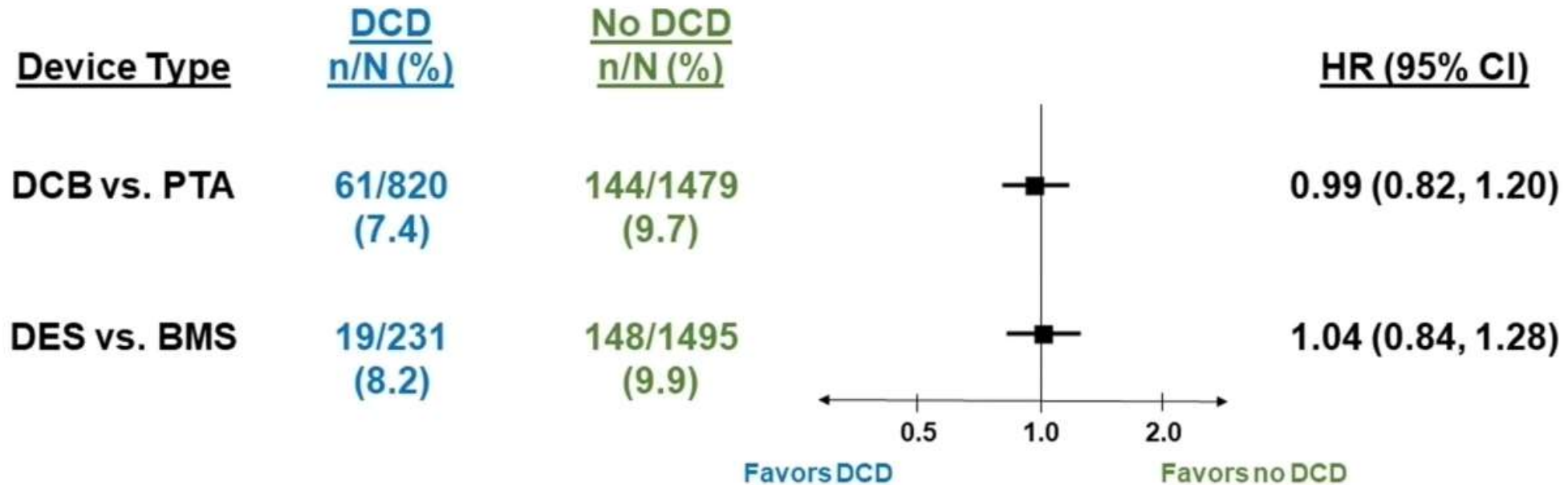
Weighted

N=4,316
n=394 deaths



Mortality and DCD Use by Device Type

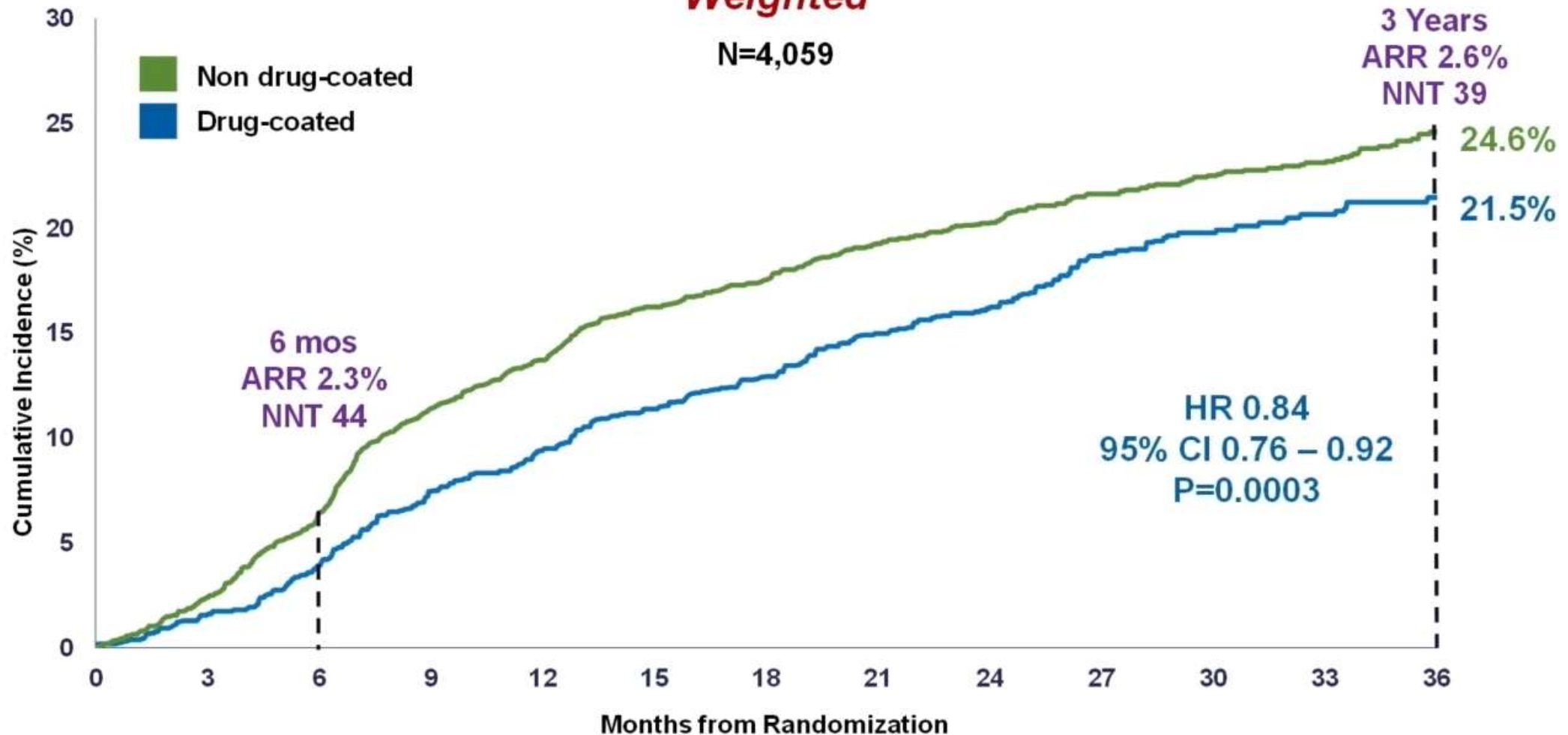
Weighted Hazard



DCB = drug-coated balloon
PTA = percutaneous transluminal angioplasty

DES = drug-eluting stent
BMS = bare metal stent

Unplanned Index Limb Revascularization *Weighted*



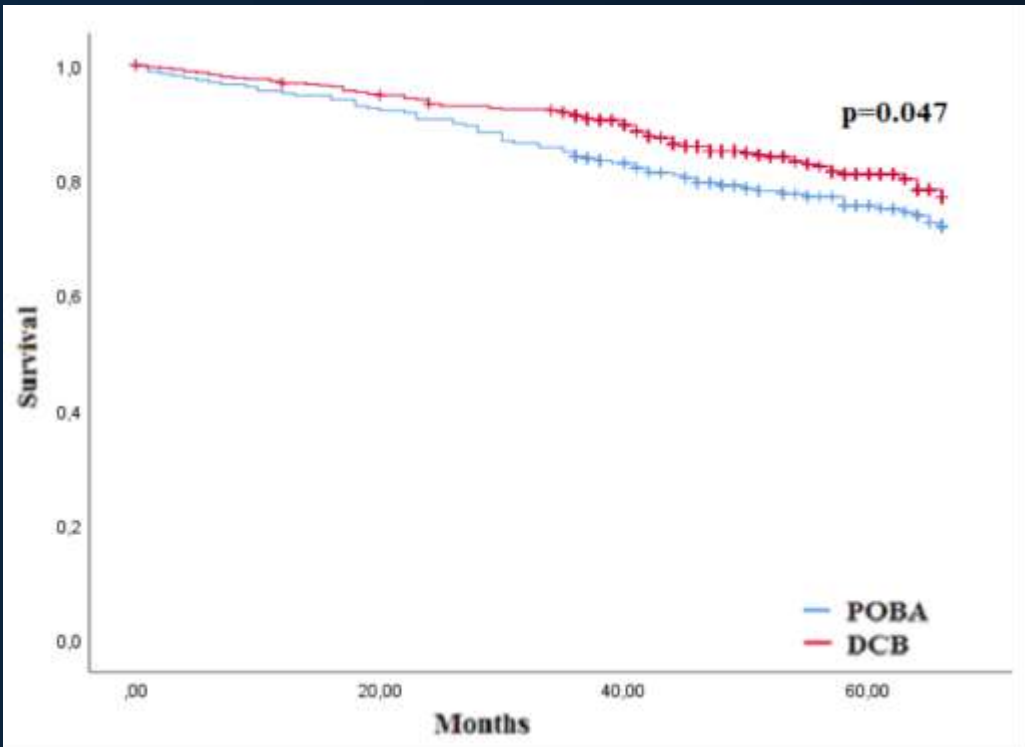
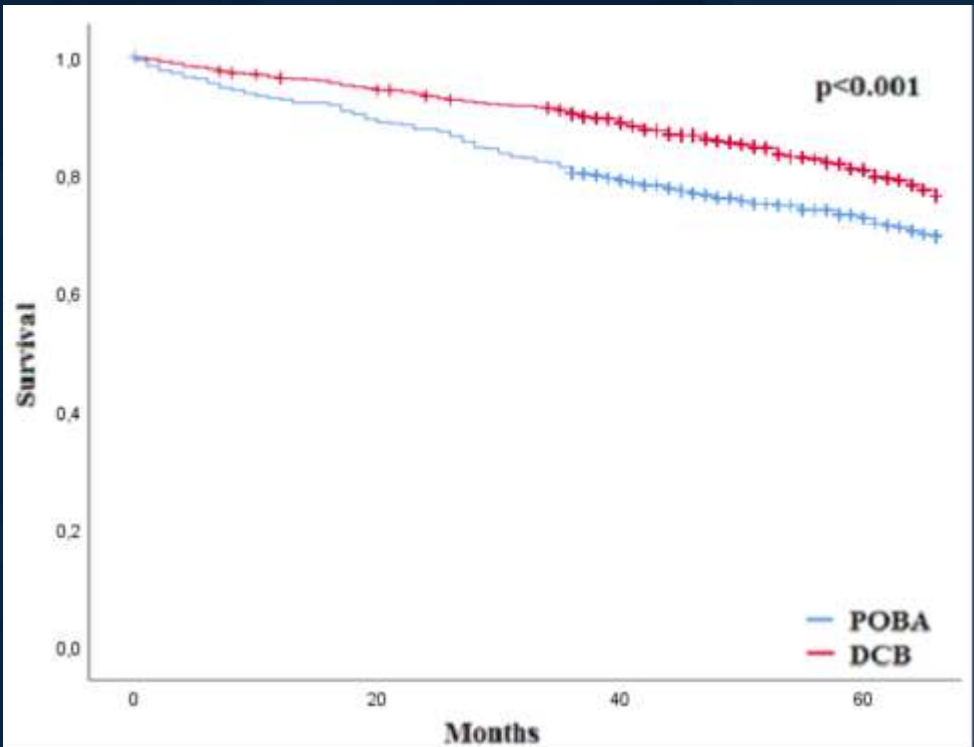
Hess CN...Bonaca MP et al. VIVA 2020

Paclitaxel Coated DCB in Femoro-popliteal Lesions

Kaplan-Mayer-Analysis Bad Krozingen

Survival of the entire cohort for POBA (n=514) and DCB-group (n=1065)

Survival of matched patients for POBA and DCB-group

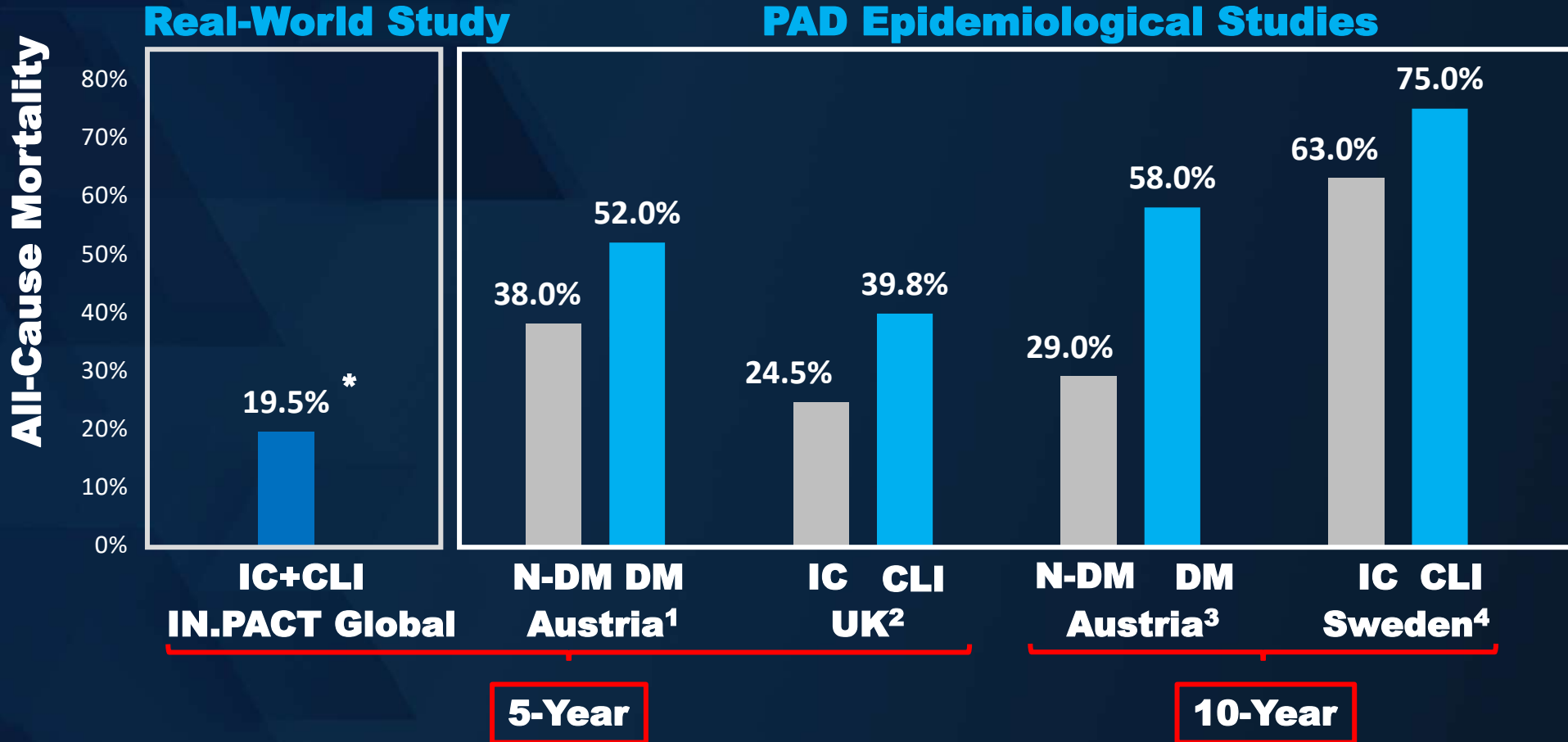


Kaplan-Meier analysis with the use of the Mantel-cox log-rank test.



IN.PACT Global Study

Long-term All-Cause Mortality in Context



*cumulative incidence K-M estimate
 IC = Intermittent Claudication
 CLI = Critical Limb Ischemia
 N-DM = Non-Diabetes Mellitus
 DM = Diabetes Mellitus

1. Mueller T. et al 2014 J Vasc Surg 2014;59:1291-9
2. Heikkila, K et al BJS 2018; 105: 1145-1154
3. Mueller T, et al 2016 Vasc Med 21:445-452 (<75 yrs age)
4. Sartipy, F. et al Eur J Vasc Endovasc Surg (2018) 55, 529e536

Paclitaxel – The Benefit Outweighs a Hypothetical Risk Summary

- The meta-analyses by Katsanos et al. with a suggested excess mortality following paclitaxel coated device treatment for femoro-popliteal artery disease was a single finding without confirmation in large real world studies
 - No dose response and no mechanism
 - Signal diminished with vital status ascertainment
 - Signal primarily observed in the U.S.
- Paclitaxel coated DCB and DES are to date the most clinically and cost-effective interventional tools for the treatment of even complex femoro-popliteal artery disease
- Withholding such devices to patients with severe PAOD may even harm them and results in increased global health care costs
- When will the agencies recall their warning?