dfir Dansk Forening for Interventionel Radiologi / Danish Society of Interventional Radiology

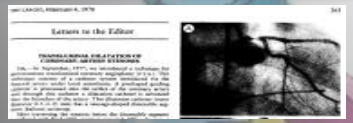
Drug-eluting technology (balloons and stents)

PD Dr. Christian Wissgott EBIR
Institute for Diagnostic and Interventional Radiology / Neuroradiology
– Academic Teaching Hospital of the University of Kiel

Evolution of endovascular therapy…

The search for...

Ballon Angioplasty 1977


Letters to the Editor

Neotinimal Hyperproliferation

NO Implant

Bare Metal Stent 1986


The New England Journal of Medicine

Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty

Reduction of Proliferation

Permanent Implantat

Drug Eluting Stent 2001

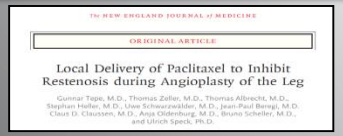

The New England Journal of Medicine

A RANDOMIZED COMPARISON OF A SIROLIMUS-ELUTING STENT WITH A STANDARD STENT FOR CORONARY REVASCULARIZATION

Limitation of Hyperproliferation

Permanent Implantat

Drug Eluting Balloon 2003


ORIGINAL ARTICLE

Local Delivery of Paclitaxel to Inhibit Restenosis during Angioplasty of the Leg

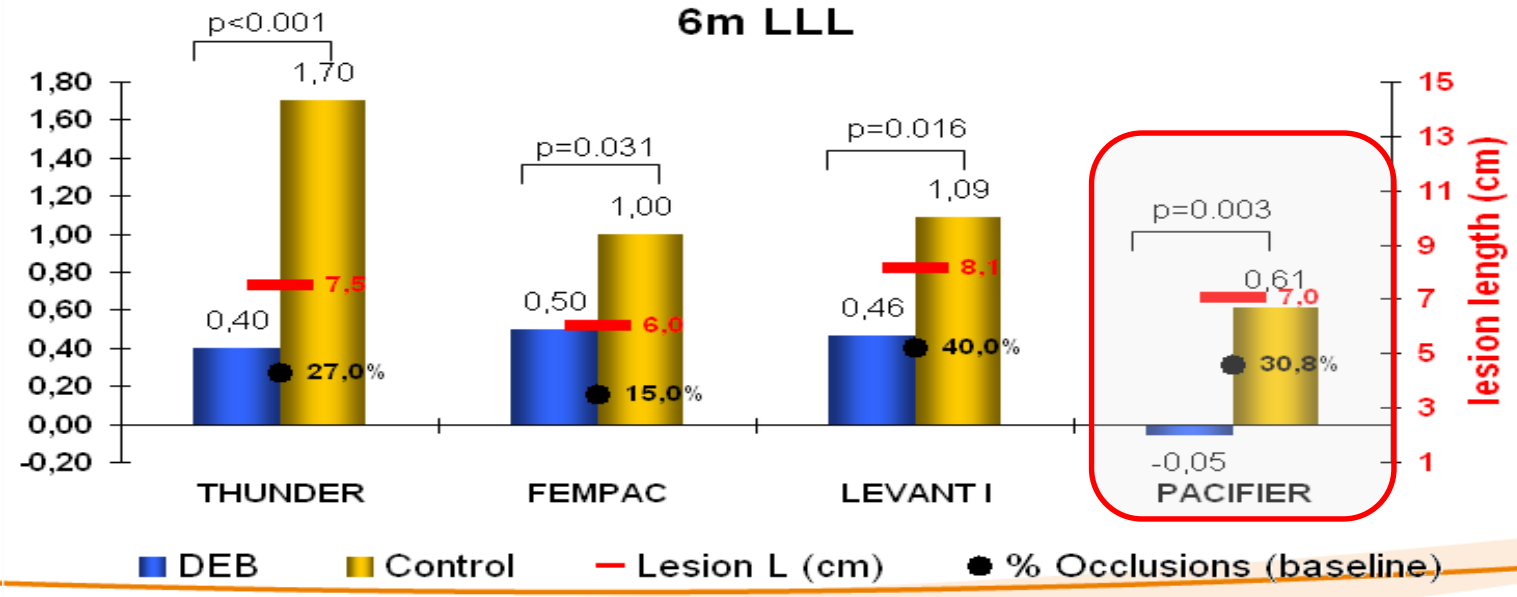
Limitation of Hyperproliferation

NO Implantat

… Egg-laying woolly milk sow

6-month Angio – FU PACIFIER

	DEB	Control	P value
Late Lumen Loss mm	**-0.05**	**0.61**	***0.003***



TLR after 12 months 7,1 % vs. 27,9%

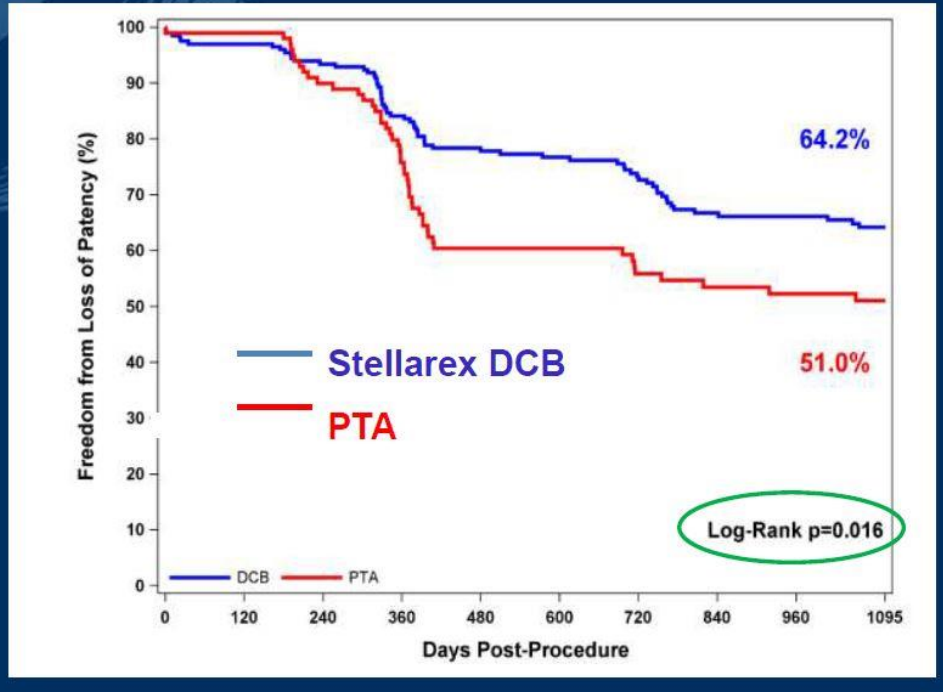
- ILLUMENATE PIVOTAL Trial

@LINC 2020

Primary Patency Through 3 Years

Significant difference in patency between Stellarex DCB and PTA

Primary patency defined as the absence of target lesion restenosis determined by DUS and freedom from CD-TLR during an office visit



Primary endpoint analysis at 12 months

Efficacy: Primary patency

DCB		Δ	
Low dose	High dose	(two-sided 90% lower bound)	$P_{non\text{-}inferiority}$
83% (156/188)	81.5% (141/173)	1.5% (-5.2%)	<0.01

Primary endpoint for non-inferiority met

Safety: Freedom from MAE

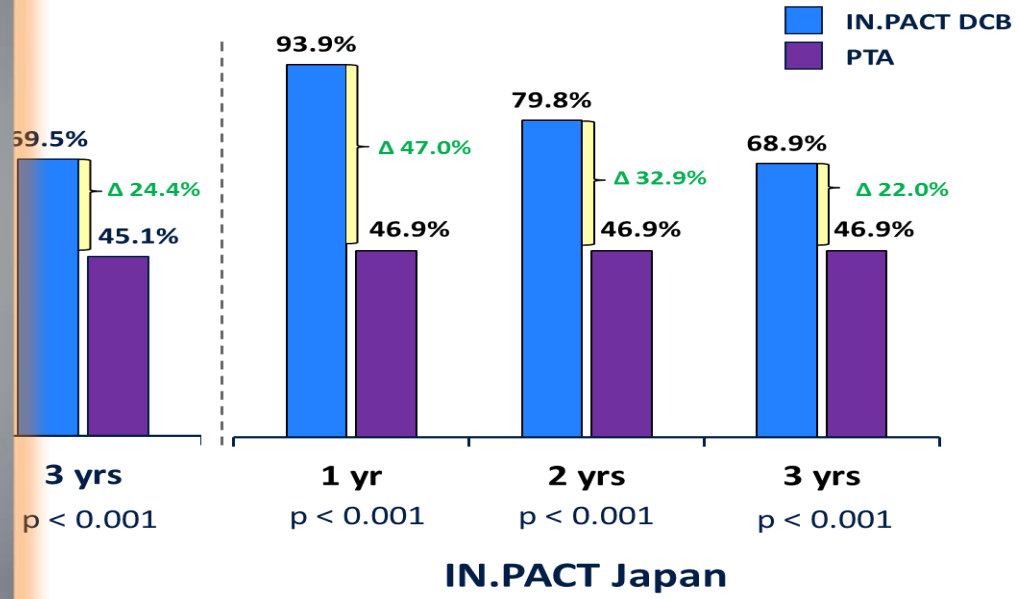
DCB		Δ	
Low dose	High dose	(two-sided 90% lower bound)	$P_{non\text{-}inferiority}$
91% (182/200)	92.6% (175/189)	-1.6% (-6.5%)	<0.01

Primary endpoint for non-inferiority met

Steiner S et al. Eur Heart J 2020; pre-published online

COMPARE RCT

als: Patency Through 3 Years



estenosis as determined by duplex ultrasound (DUS); Peak Systolic Velocity Ratio (PSVR) ≤ 2.4.
Gaithersburg, MD June 19, 2019.

Katsanos, et al. paclitax

SYSTEMATIC REVIEW AND META-ANALYSIS

American Heart Association | American Stroke Association

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

CONCLUSION #1
PTX ASSOCIATED WITH HIGHER MORTALITY

CONCLUSION #2
MORTALITY RELATED TO PTX dose

1. Katsanos K, et al., J Am Heart Assoc 2018;7:e011245. DOI: 10.1161/JAHA.118.011245.

Increased Mortality Risk of Paclitaxel?

Characteristics of these RCTs :

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 (treatment bias?)

Bradford-Hill-Criteria*

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?

*Austin Bradford-Hill. Criteria for causation, 1965

Dose Issue Is Readily Evaluated

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

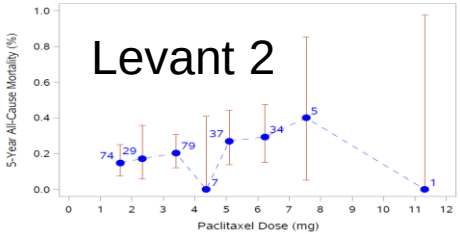
where, Dose_i is the nominal paclitaxel dose loaded on the balloon or stent ($\mu g/mm^2$), D_i is the reference vessel diameter (mm), Length_i is the treated lesion length (mm), and Time_i indicates the available follow-up time period (years). Random

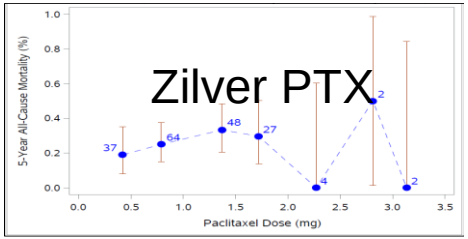
Assumption: continuous, linear and increasing exposure over time.

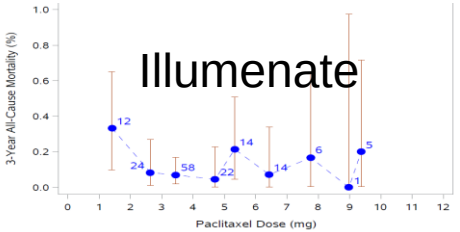
- Tissue paclitaxel in pre-clinical models decreases over 6 months to nearly non-detectable levels.
- Time is disproportionately available for studies with longer-term follow-up.
- The longer you follow someone and the older the patient, the higher likelihood of a mortality event.

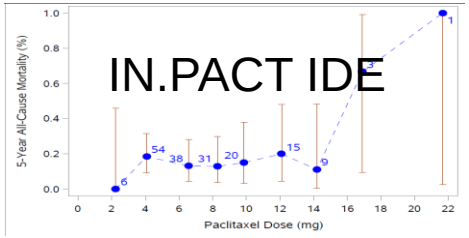
Katsanos et al. JAHA 2018;7:e011245

Dose effect and mortality

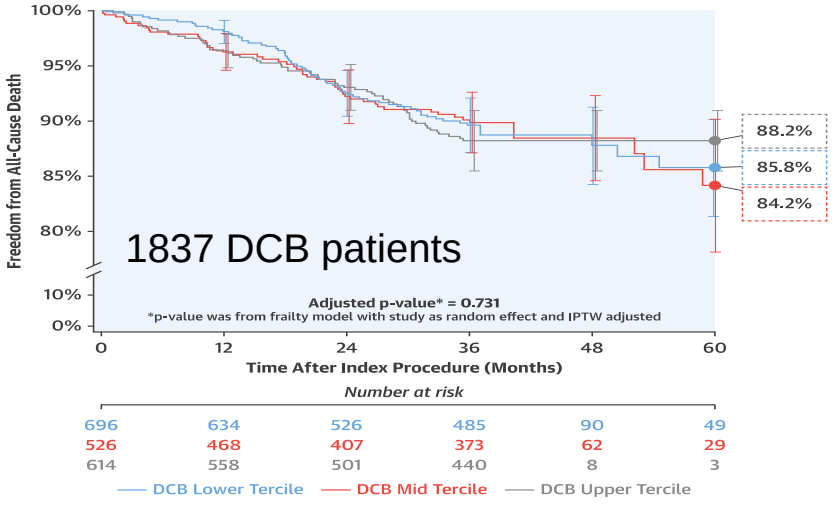








CENTRAL ILLUSTRATION Kaplan-Meier Freedom From All-Cause Death by Paclitaxel Dose in All DCB Patients



Distribution of Paclitaxel Dose in Each Paclitaxel Tercile in DCB

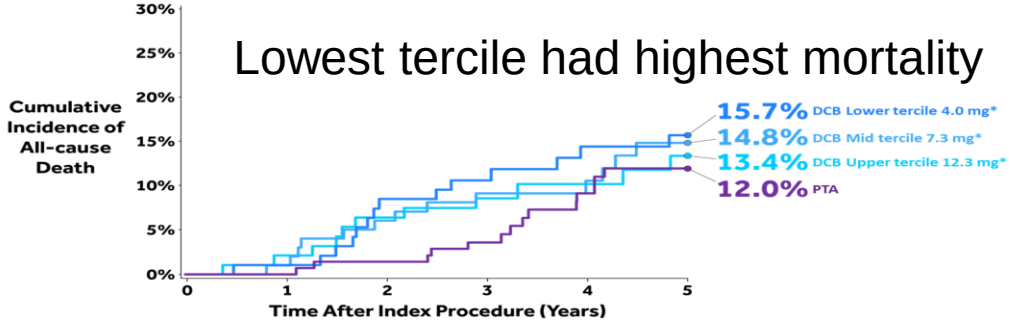
Paclitaxel Dose	N	Mean μg	Std μg	Median μg	Q1, Q3 μg	Range μg
DCB Lower Tercile	696	5019.0	1508.6	4752.0	3653, 6924	1850, 6951
DCB Mid Tercile	526	10007.5	1757.7	9504.0	8448, 11618	6989, 13822
DCB Upper Tercile	614	19978.2	6122.1	18654.0	15399, 22705	13902, 61949

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

Dose effect and 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	

FDA Letter August 7, 2019
"…no clear evidence of a paclitaxel dose effect on mortality, and no identified pathophysiologic mechanism for the late deaths."

VIVA/Namsa Individual Patient Data Project

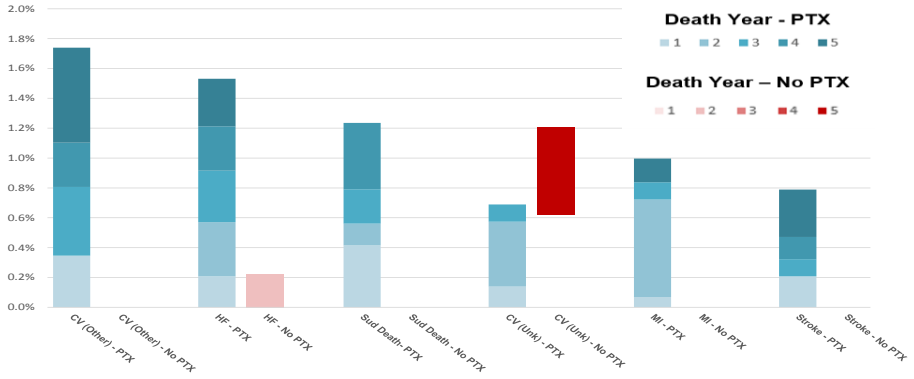
No dose effect:
Medium dose lower risk than low or high dose.

Model	Hazard Ratio (95% CI) 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)

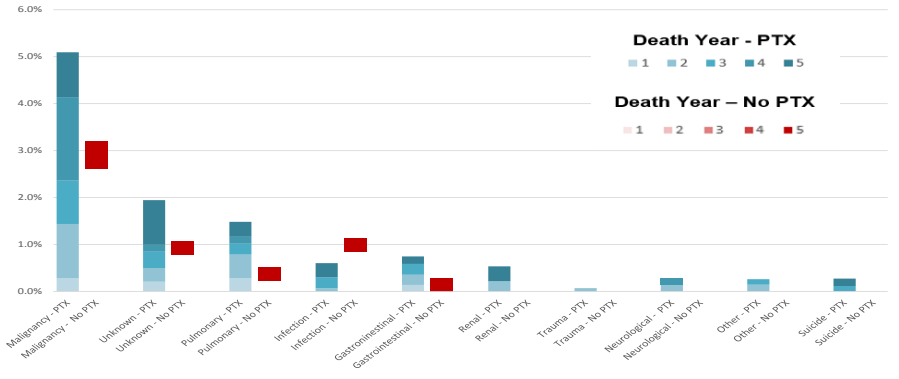
K Rocha-Singh, TCT 2019

No Clustering of Deaths: What is the mechanism?

CV Death Subtypes



Non-CV Death Subtypes



Biological mechanism?

E Whatley PhD. FDA Presentation. FDA Panel. June, 2019

Missing Data at 5 Years: Pivotal RCTs

Effort to Locate Withdrawn or Lost to Follow-up

Study	Device	N	Pre-FDA Panel	After Search
Zilver PTX	DES	300	38.3%	26.0%
	PTA	174	36.2%	25.9%
Levant 2	DCB	316	15.8%	12.7%
	PTA	186	14.4%	11.3%
IN.PACT SFA	DCB	220	19.1%	2.7%
	PTA	110	14.5%	2.7%

FDA Panel packet for June, 2019: Table 4
Whatley E. FDA presentation at Panel Meeting. June, 2019

Missing Data at 5 Years: Pivotal RCTs :
Withdrawn or Lost to Follow-up

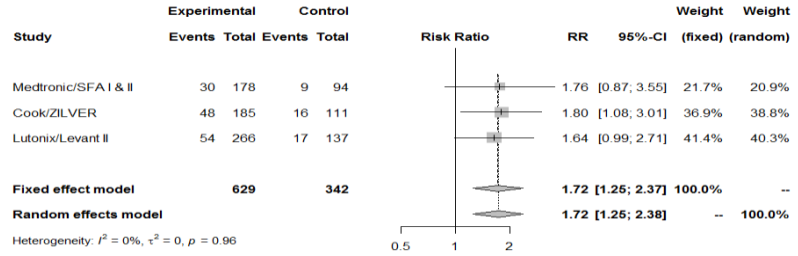
Study	Device	N	Pre-FDA Panel	After Search	% Missing Patients Located
Zilver PTX	DES	300	38.3%	26.0%	32%
	PTA	174	36.2%	25.9%	28%
Levant 2	DCB	316	15.8%	12.7%	20%
	PTA	186	14.4%	11.3%	22%
IN.PACT SFA	DCB	220	19.1%	2.7%	86%
	PTA	110	14.5%	2.7%	81%

20%-86% of missing patients

Impact on datas?

FDA Panel packet for June, 2019: Table 4
Whatley E. FDA presentation at Panel Meeting. June, 2019

5 Year Point Estimate from FDA: RR 1.72

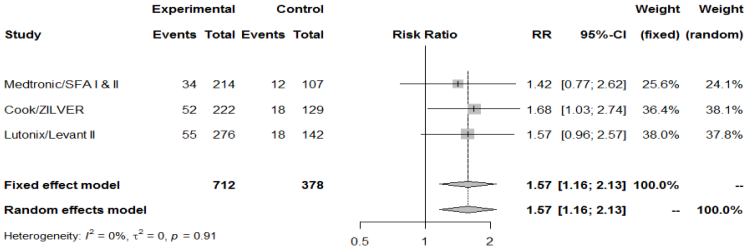


Study	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio	RR	95%-CI	Weight (fixed)	Weight (random)
Medtronic/SFA I & II	30	178	9	94		1.76	[0.87; 3.55]	21.7%	20.9%
Cook/ZILVER	48	185	16	111		1.80	[1.08; 3.01]	36.9%	38.8%
Lutonix/Levant II	54	266	17	137		1.64	[0.99; 2.71]	41.4%	40.3%
Fixed effect model		**629**		**342**		**1.72**	**[1.25; 2.37]**	**100.0%**	--
Random effects model						**1.72**	**[1.25; 2.38]**	--	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.96$

0.5 1 2

After Vital Status Ascertainment: 1.57



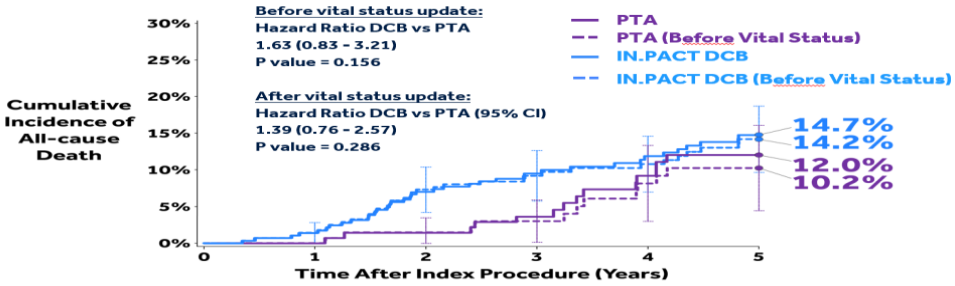
Study	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio	RR	95%-CI	Weight (fixed)	Weight (random)
Medtronic/SFA I & II	34	214	12	107		1.42	[0.77; 2.62]	25.6%	24.1%
Cook/ZILVER	52	222	18	129		1.68	[1.03; 2.74]	36.4%	38.1%
Lutonix/Levant II	55	276	18	142		1.57	[0.96; 2.57]	38.0%	37.8%
Fixed effect model		**712**		**378**		**1.57**	**[1.16; 2.13]**	**100.0%**	--
Random effects model						**1.57**	**[1.16; 2.13]**	--	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.91$

0.5 1 2

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)



# At Risk	0	365	730	1095	1460	1825
DCB Before Update	288 (0)	272 (4)	250 (20)	203 (25)	160 (28)	40 (34)
PTA Before Update	142 (0)	139 (0)	130 (2)	111 (4)	88 (9)	19 (11)
DCB After Update	288 (0)	282 (4)	265 (20)	225 (27)	186 (32)	72 (38)
PTA After Update	142 (0)	141 (0)	135 (2)	117 (5)	98 (11)	29 (14)

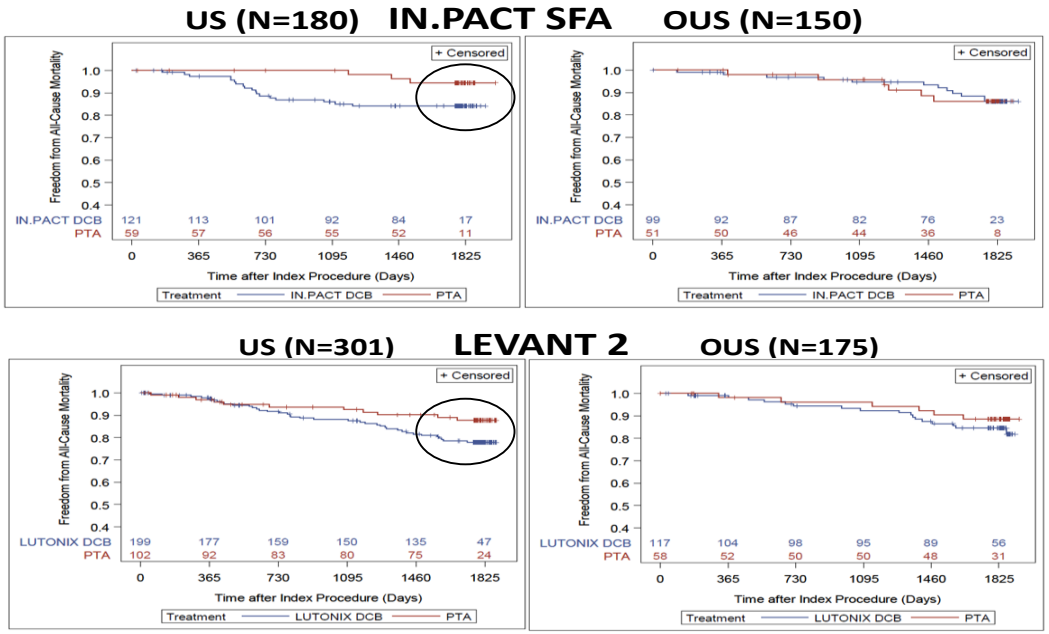
Hazard Ratio 1.63 1.39
Decrease 38%

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

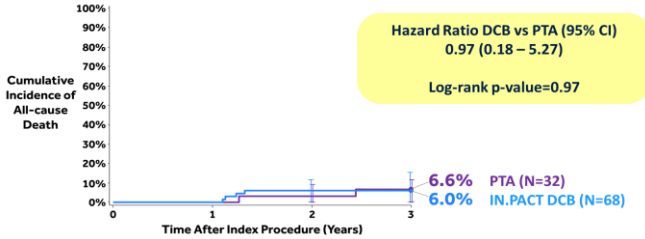
Mauri L. Presentation at FDA panel June 20, 2019

Geographic bias: signal of mortality not consistent

Why more dangerous in one geography than another?



IN.PACT Japan



N at Risk				
IN.PACT DCB	68	67	62	31
PTA	32	32	28	12
Cumulative Incidence (Cumulative Deaths)				
IN.PACT DCB	0.0% (0)	0.0% (0)	6.0% (4)	6.0% (4)
PTA	0.0% (0)	0.0% (0)	3.1% (1)	6.6% (2)

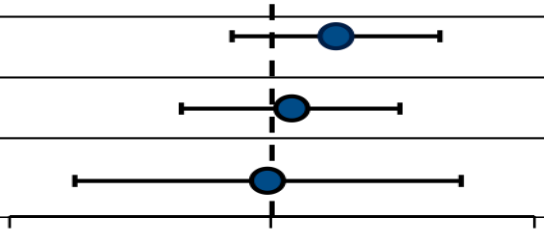
Major mortality difference in the US but not in other geographies

E Whatley PhD. FDA Presentation FDA Panel. June, 2019
L Mauri MD. Manufacturers Presentation. FDA Panel. June 2019

Pooled IN.PACT IDE and Japan Trials

Hazard Ratio for Mortality by Region DCB vs PTA (as treated)[1]

Subgroup (N_{DCB}/N_{PTA})	IN.PACT DCB (Mortality)	PTA (Mortality)	Hazard Ratio (95% CI)	p-value for interaction[2]
Region				
US (121/59)	16.7% (20)	10.3% (6)	**1.77** (0.71, 4.42)	
EU (99/51)	14.3% (14)	12.2% (6)	**1.18** (0.45, 3.07)	**0.74**
Japan (68/32)	6.0% (4)	6.6% (2)	**0.97** (0.18, 5.27)	

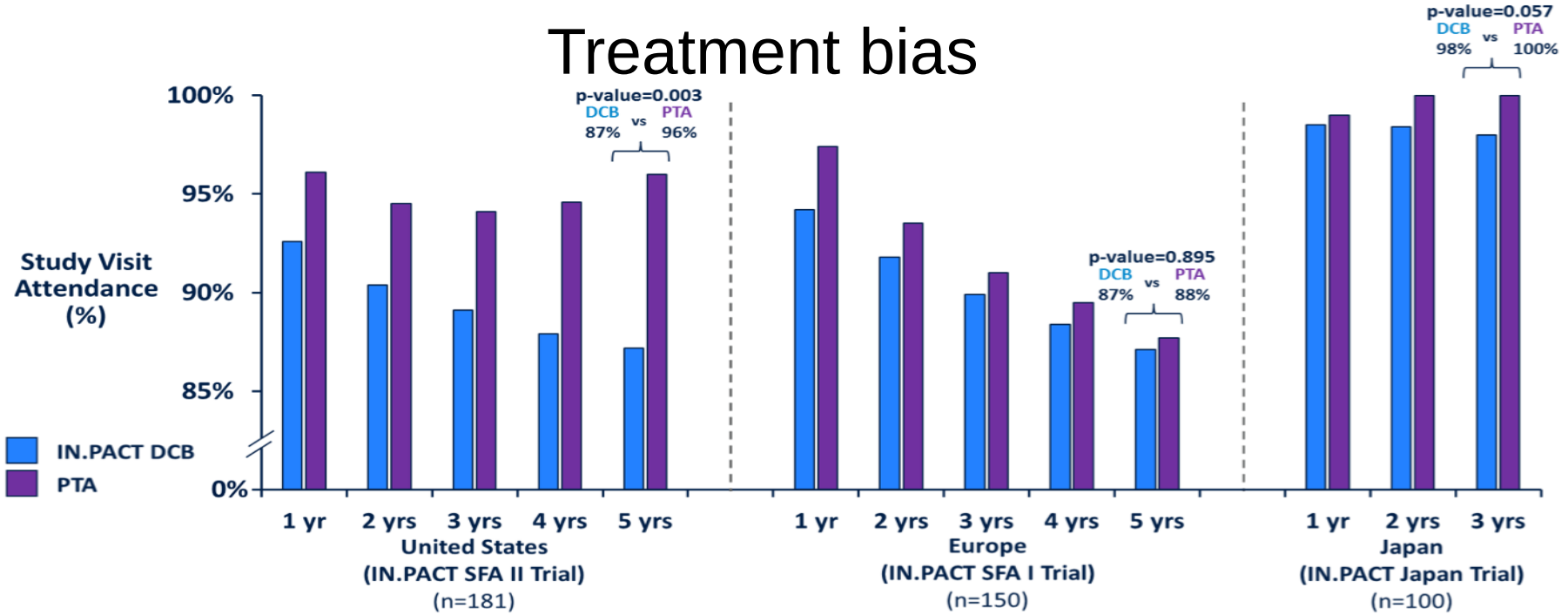


Favors DCB **Favors PTA**

1. Presented by Mauri L, Circulatory System Devices Panel Meeting, Gaithersburg, MD June 19, 2019.
2. p-value derived from Cox Proportional Hazard model by testing treatment-by-region-interaction term.

IN.PACT: SFA I and II and Japan RCTs

Follow-up Visit Attendance by Region



DCB and PTA patients treated differently

Difference in treatment greater in US than other geographies

Dual Antiplatelet Therapy After Treatment

"PTA patients: significantly more likely to continue dual antiplatelet therapy at every time interval."

Treatment bias

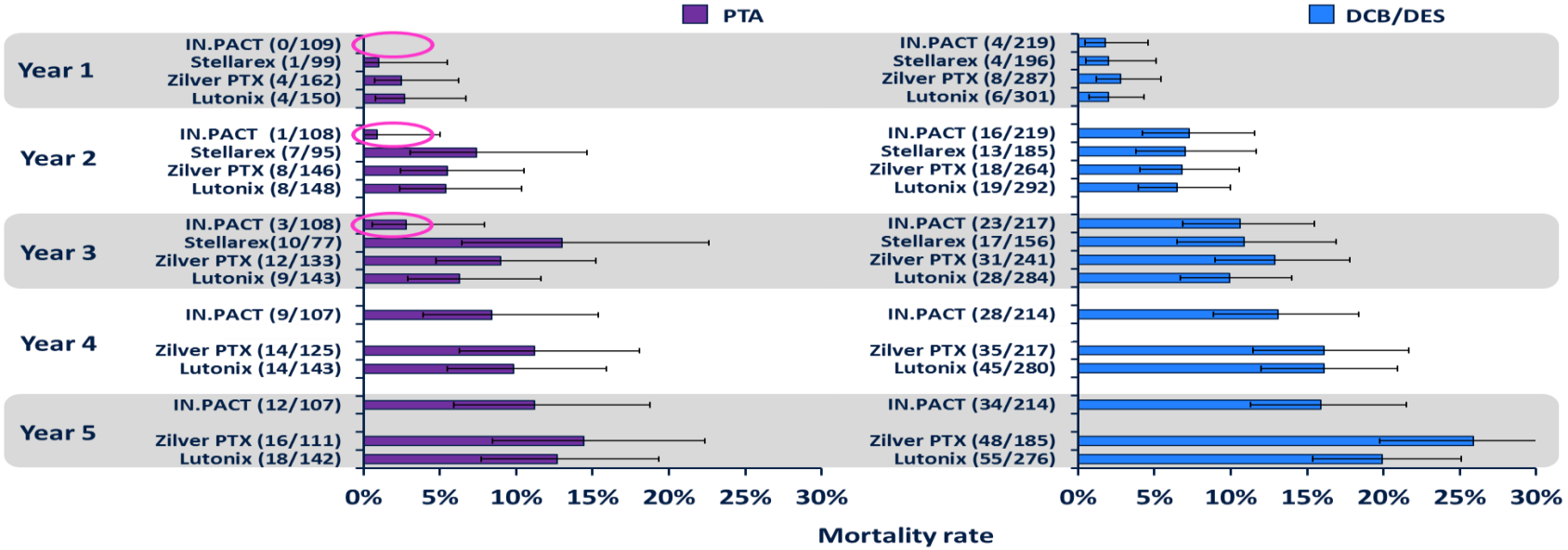
TABLE 4 Antiplatelet Regimens Through 36 Months

	IN.PACT DCB (n = 1,837)	PTA (n = 143)	Difference (95% CI)	p Value*
Discharge				
ASA	96.4 (1,766/1,832)	98.6 (141/143)	−2.2 (−10.7 to 6.3)	0.231
Clopidogrel	93.6 (1,715/1,832)	95.8 (137/143)	−2.2 (−10.7 to 6.3)	0.370
Cilastazol	4.6 (79/1,711)	3.6 (3/83)	1.0 (−10.0 to 12.0)	1.000
Prasugrel	0.5 (8/1,621)	0.0 (0/111)	0.5 (−9.1 to 10.1)	1.000
Ticlopidine	1.3 (24/1,832)	3.5 (5/143)	−2.2 (−10.7 to 6.3)	0.054
ASA + clopidogrel, ticlopidine, cilastazol, or prasugrel	92.6 (1,697/1,832)	97.2 (139/143)	−4.6 (−13.1 to 3.9)	0.040
30 days				
ASA	95.2 (1,684/1,768)	97.9 (138/141)	−2.6 (−11.2 to 6.0)	0.205
Clopidogrel	82.5 (1,458/1,768)	88.7 (125/141)	−6.2 (−14.7 to 2.4)	0.063
Cilastazol	4.2 (69/1,652)	3.7 (3/82)	0.5 (−10.6 to 11.6)	1.000
Prasugrel	0.8 (12/1,557)	0.0 (0/109)	0.8 (−8.9 to 10.5)	1.000
Ticlopidine	1.3 (23/1,768)	3.5 (5/141)	−2.2 (−10.8 to 6.3)	0.093
ASA + clopidogrel, ticlopidine, cilastazol, or prasugrel	81.7 (1,445/1,768)	90.1 (127/141)	−8.3 (−16.9 to 0.2)	0.011
6 months				
ASA	90.5 (1,479/1,634)	99.3 (139/140)	−8.8 (−17.4 to −0.1)	<0.001
Clopidogrel	52.1 (852/1,634)	68.6 (96/140)	−16.4 (−25.0 to −7.8)	<0.001
Cilastazol	5.1 (78/1,529)	3.7 (3/82)	1.4 (−9.7 to 12.6)	0.795
Prasugrel	0.6 (8/1,423)	1.9 (2/108)	−1.3 (−11.1 to 8.5)	0.153
Ticlopidine	1.3 (21/1,634)	3.6 (5/140)	−2.3 (−10.9 to 6.4)	0.048
ASA + clopidogrel, ticlopidine, cilastazol, or prasugrel	49.4 (807/1,634)	72.9 (102/140)	−23.5 (−32.0 to −14.9)	<0.001
12 months				
ASA	88.9 (1,403/1,578)	94.9 (129/136)	−5.9 (−14.7 to 2.8)	0.029
Clopidogrel	46.9 (740/1,578)	55.9 (76/136)	−9.0 (−17.7 to −0.2)	0.049
Cilastazol	5.4 (79/1,469)	3.7 (3/81)	1.7 (−9.5 to 12.9)	0.797
Prasugrel	0.5 (7/1,367)	1.9 (2/104)	−1.4 (−11.4 to 8.6)	0.129
Ticlopidine	0.8 (13/1,578)	3.7 (5/136)	−2.9 (−11.6 to 5.9)	0.031
ASA + clopidogrel, ticlopidine, cilastazol, or prasugrel	42.8 (676/1,578)	57.4 (78/136)	−14.5 (−23.2 to −5.8)	0.001
24 months				
ASA	86.6 (1,090/1,258)	93.7 (118/126)	−7.0 (−16.2 to 2.1)	0.024
Clopidogrel	35.6 (448/1,258)	54.8 (69/126)	−19.1 (−28.2 to −10.0)	<0.001
Cilastazol	5.9 (69/1,167)	4.1 (3/73)	1.8 (−10.0 to 13.6)	0.795
Prasugrel	0.7 (8/1,190)	2.1 (2/94)	−1.5 (−11.9 to 9.0)	0.163
Ticlopidine	0.9 (11/1,258)	2.4 (3/126)	−1.5 (−10.6 to 7.6)	0.126
ASA + clopidogrel, ticlopidine, cilastazol, or prasugrel	30.9 (389/1,258)	54.0 (68/126)	−23.0 (−32.0 to −13.9)	<0.001
36 months				
ASA	85.4 (988/1,157)	87.1 (108/124)	−1.7 (−11.0 to 7.6)	0.688
Clopidogrel	34.8 (403/1,157)	48.4 (60/124)	−13.6 (−22.7 to −4.3)	0.004
Cilastazol	6.9 (74/1,070)	5.6 (4/72)	1.4 (−10.6 to 13.3)	0.812
Prasugrel	0.6 (7/1,089)	2.2 (2/92)	−1.5 (−12.2 to 9.1)	0.151
Ticlopidine	0.6 (7/1,157)	2.4 (3/124)	−1.8 (−11.1 to 7.4)	0.094
ASA + clopidogrel, ticlopidine, cilastazol, or prasugrel	30.4 (352/1,157)	45.2 (56/124)	−14.7 (−23.9 to −5.5)	0.001

Schneider et al. J Am Coll Cardiol 2019;73:2550

Comparison of mortality rates

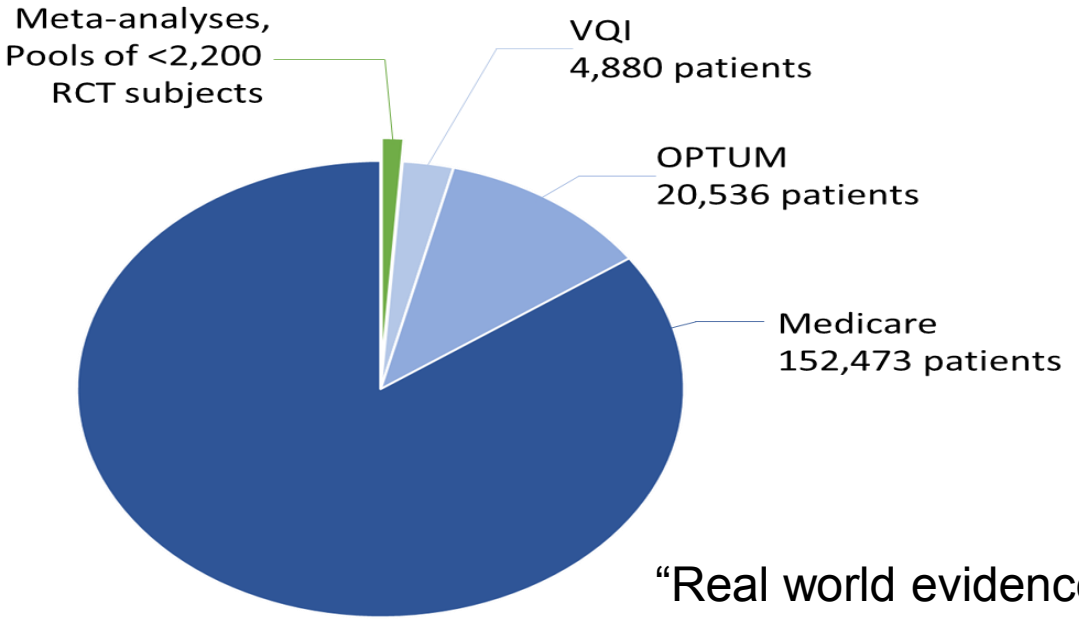
small sample sizes lead to inaccurate estimation



Presented by Mauri L, Circulatory System Devices Panel Meeting, Gaithersburg, MD June 19, 2019.
Source data from FDA Executive Summary Table 6 (Appendix P), June 2019. Proportion rate for each study are reported. Error bars are Exact Binomial 95% Confidence Intervals.

Evidence: Overview

Outside of RCT a lot of datas…

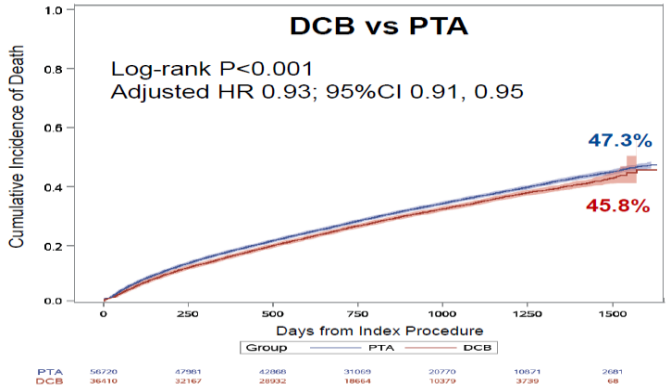


“Real world evidence”

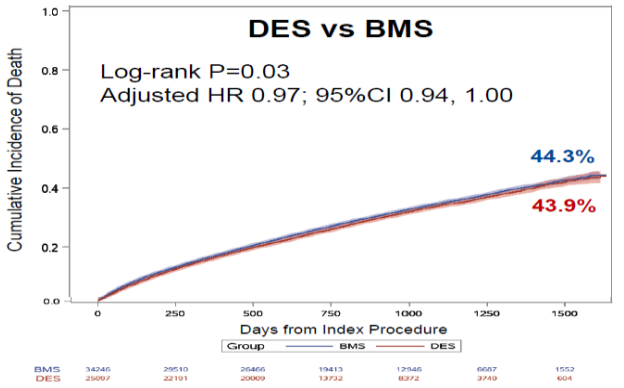
LARGE OBSERVATIONAL DATA CONFIRM SAFETY OF PTX DEVICES / CMS

UPDATED ANALYSIS OF MEDICARE BENEFICIARY DATA

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



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



- N= 152k pts
- Prespecified analysis protocol reviewed by the FDA
- Median 799 days followup

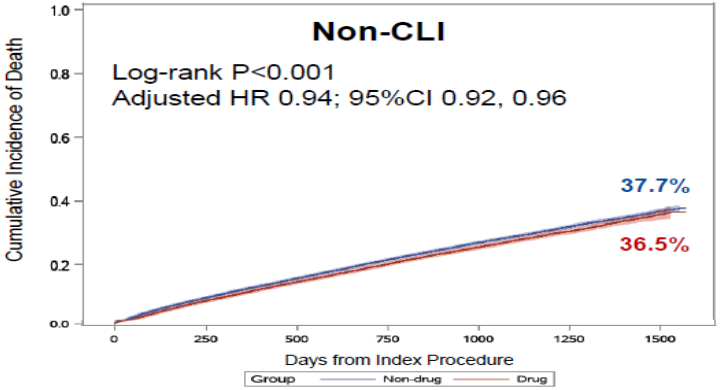
No difference in survival between drug coated vs non drug coated devices

CMS_Centers for Medicare & Medicaid Services

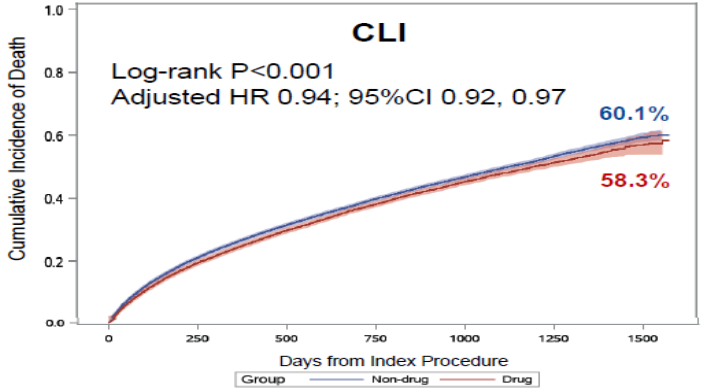
LARGE OBSERVATIONAL DATA CONFIRM SAFETY OF PTX DEVICES / CMS

UPDATED ANALYSIS OF MEDICARE BENEFICIARY DATA

Non-CLI: 61.3% (N=93,432)



CLI: 38.7% (N=59,041)



- N= 152k pts
- Prespecified analysis protocol reviewed by the FDA
- Median 799 days followup

No difference in survival between Non- CLI vs CLI patients

CMS_Centers for Medicare & Medicaid Services

LONG-TERM SAFETY OF DRUG-COATED DEVICES FOR PERIPHERAL ARTERY REVASCULARIZATION: AN UPDATED ANALYSIS OF MEDICARE BENEFICIARY DATA
TCT 2019 Eric A. Secemsky,

Cardiovasc Intervent Radiol
https://doi.org/10.1007/s00270-019-02329-z

CIRSE

CLINICAL INVESTIGATION ARTERIAL INTERVENTIONS

Long-Term Mortality of Matched Patients with Intermittent Claudication Treated by High-Dose Paclitaxel-Coated Balloon Versus Plain Balloon Angioplasty: A Real-World Study

Konstantinos P. Donas[1] · Anne Sohr[1] · Georgios A. Pitoulias[2] · Fernando Alfonso[3] · Giovanni Torsello[1]

5-y mortality from MUNSTER Real-World Study comparing IN.PACT DCB vs POBA

Univariate analysis of 77 pairs of propensity score-matched patients

Group	Group A	Group B
Device	**POBA**	**DCB**
Mortality rate	26%	20.80%

(median follow-up of 61.7 and 61.8 months, respectively)
p = 0.8

Comparison of the patients of group B who died versus those who survived showed no correlation between the dose of paclitaxel with increased mortality (p = 0.4).

The 5-year findings of the present real-world study showed **no increased mortality for the matched patients who underwent PCBA versus POBA**.

In addition, there **was no correlation between mortality and the dose of paclitaxel used**.

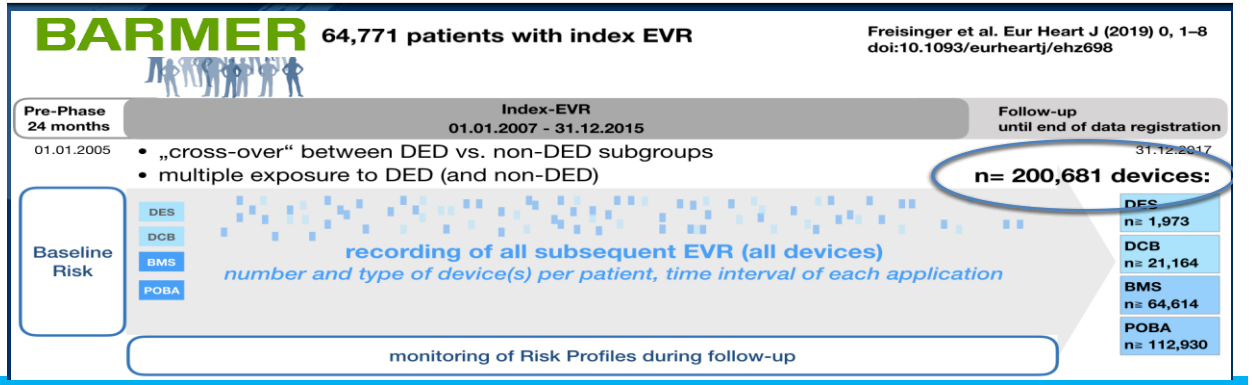
ESC European Society of Cardiology
European Heart Journal (2019) 0, 1–8
doi:10.1093/eurheartj/ehz698

Mortality after use of paclitaxel-based devices in peripheral arteries: a real-world safety analysis

Eva Freisinger [1]*, Jeanette Koeppe [2], Joachim Gerss [2], Dennis Goerlich [2], Nasser M. Malyar[1], Ursula Marschall[3], Andreas Faldum [2], and Holger Reinecke[1]

- Retrospective study of **~ 9.2 million participant of the** German BARMER Health Insurance

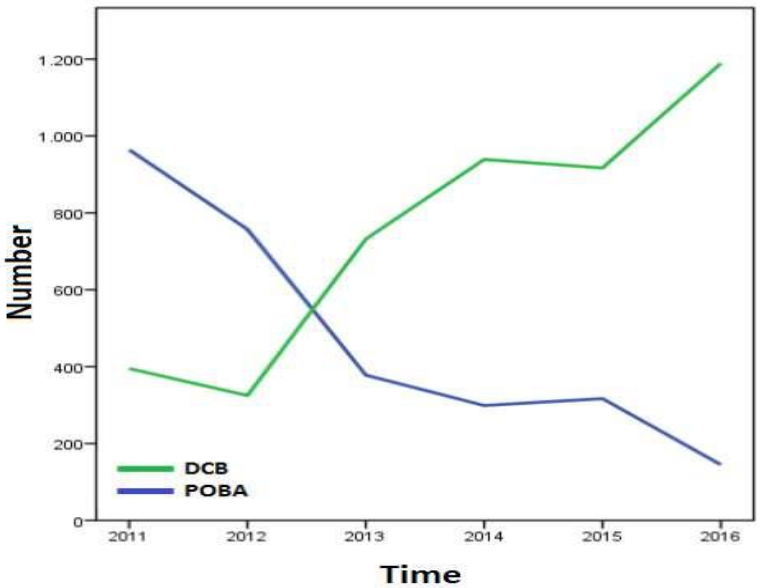
- **Index = 64,771 patients** with first endovascular intervention between 2007 - 2015
- recording **each single device** (DES, DCB, BMS, POBA) that applied **over the entire study period**
- **200,681 devices; median FU 7.6 years; 98% completeness**



This real-world analysis showed no evidence for increased mortality associated with paclitaxel-based devices for **over 11 years.**

Freisinger E, et al "Mortality after use of paclitaxel-based devices in peripheral arteries: a rea world safety analysis" Eur Heart J 2019; DOI: 10.1093/eurheartj/ehz698.

POBA vs. DCB Use Femoropopliteal Lesions Bad Krozingen 2011 - 2016



01/2011 -06/2016

POBA

n = 2860

DCB

n=4497

UNIVERSITÄTS FREIBURG · BAD KROZINGEN HERZZENTRUM

POBA vs. DCB Mortality Bad Krozingen

DCB	POBA
01/2013 -03/2016 n = 1178	01/2011 -06/2016 n = 580
FU < 36 months n = 111 (9.4%)	FU < 36 months n = 65 (11.2%)
□	□
n = 1067	**n = 515**

UNIVERSITÄTS HERZZENTRUM FREIBURG · BAD KROZINGEN

POBA vs. DCB Mortality Bad Krozingen

360 patients died
22.8%

DCB	POBA
n = 184	n = 176
17.2%	34.2%

UNIVERSITÄTS HERZZENTRUM FREIBURG · BAD KROZINGEN

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: www.elsevier.com/locate/eclinm

Benefit and risk from paclitaxel-coated balloon angioplasty for the treatment of femoropopliteal artery disease: A systematic review and meta-analysis of randomised controlled trials

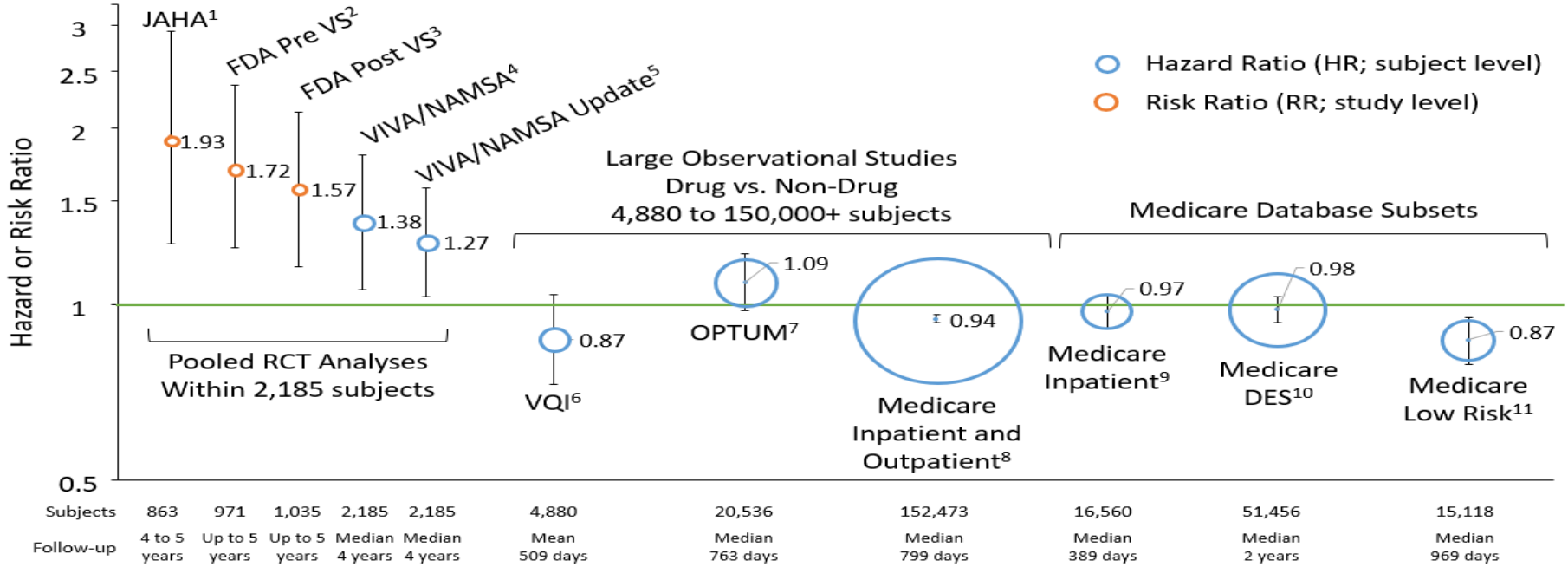
Christof Klumb[a], Thomas Lehmann[b], René Aschenbach[a], Niklas Eckardt[a], Ulf Teichgräber[a,*]

BENEFIT AND RISK FROM PTX COATED BALLOON SYSTEMATIC REVIEW

Key takeaways:

- The authors conclude: "The risk of 2-year all-cause mortality at 2 years was increased, but without evidence of causation"

Increased Mortality Risk of Paclitaxel? Shrinking Hazard Ratio

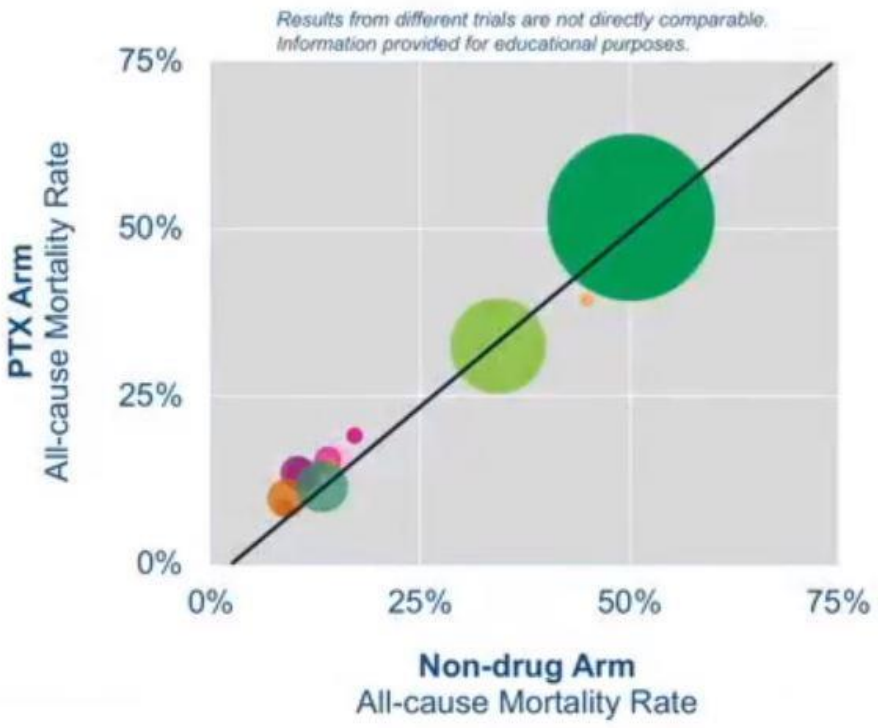


1. Katsanos, K, et al. JAHA 2018; 7:e011245.
2. FDA Executive Summary Figure 14; pre vital status.
3. Whatley E, FDA presentation, Circulatory System Devices Panel Meeting, Gaithersburg, MD June 19, 2019; post vital status.
4. Rocha-Singh KJ, et al. VIVA-NAMSA presentation, Circulatory System Devices Panel Meeting, Gaithersburg, MD June 19, 2019.
5. Rocha-Singh, K. VIVA-NAMSA Analysis, TCT, San Francisco, CA 2019.
6. Bertges DJ, SVS Abstract 2019.
7. Yeh RW, OPTUM Presentation, Circulatory System Devices Panel Meeting, Gaithersburg, MD, June 19-20, 2019.
8. Secemsky EA, Medicare Presentation, Circulatory System Devices Panel Meeting, Gaithersburg, MD, June 19-20, 2019.
9. Secemsky EA, et al. JAMA Cardiol 2019;4:332-40.
10. Secemsky EA, et al. J Am Coll Cardiol 2019;73:2636-38.
11. Secemsky EA, Medicare low-risk presentation, TCT, San Francisco, CA 2019.

Note: For specific adjustments and methodologies, see the cited publications and presentations.

Modified from L. Mauri, MD: Combined Industry Presentation. FDA Panel June, 2019

Control Mortality vs PTX Mortality Weighted for Sample Size



- Zilver PTX RCT, 5y
- Zilver PTX Japan, 3y
- IN.PACT meta-analysis, standard cohort, 5y
- Stellarex meta-analysis, RCTs, 3y
- Lutonix meta-analysis, 5y
- VIVA- Primary model May 2019, 5y

Patient-level, device-specific

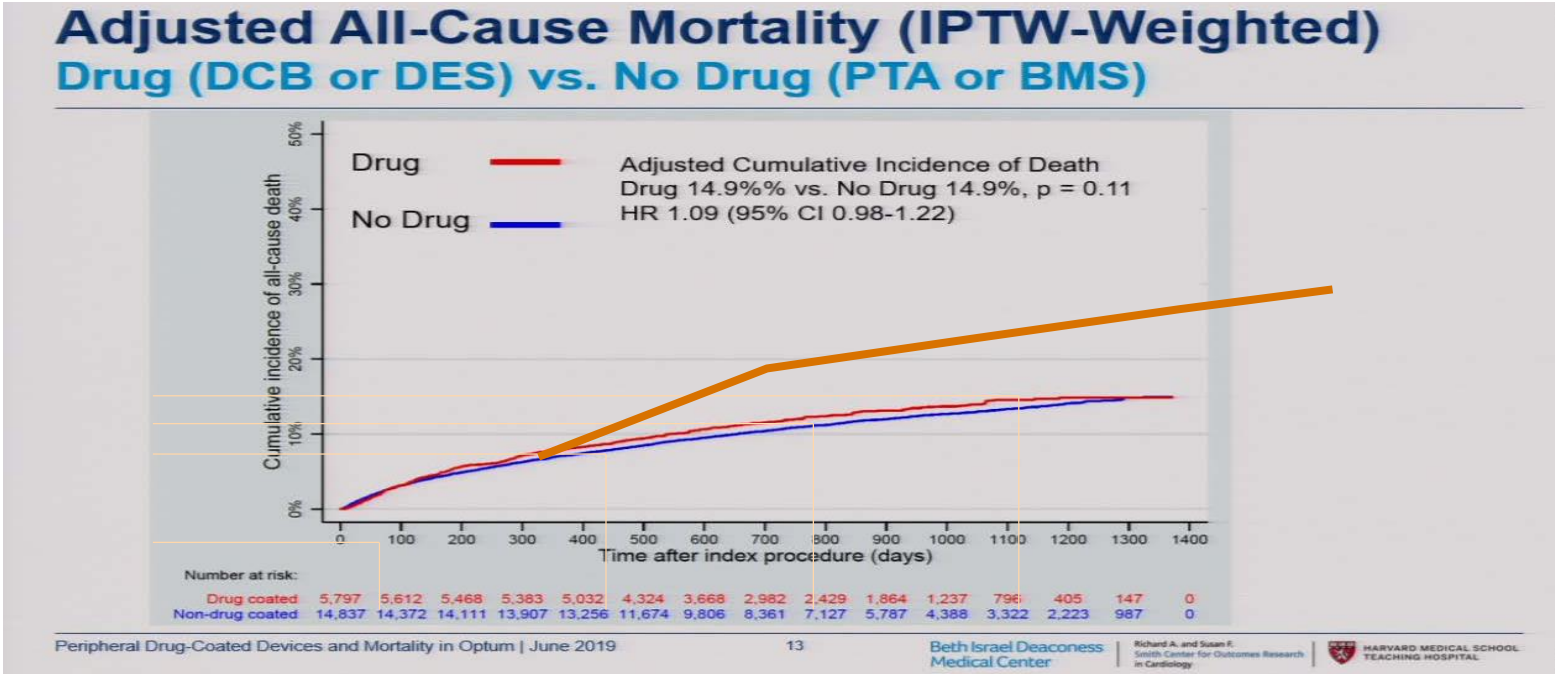
- Lutonix BTK, 3y
- PADI (BTK), 5y
- IN.PACT DEEP (BTK), 5y
- TAXUS meta-analysis (coronary), 5y

Other vessel beds

- Medicare Inpatient, ~2y
- VQI- propensity matched, ~2y
- Medicare DCS vs BMS, ~2y

Large observational studies

Zilver PTX RCT & Japan- Dake MD, et al. Cardiovasc Intervent Radiol. 2019. doi: 10.1007/s00270-019-02324-4.
Stellarex- Gray WA, et al. Circulation. 2019;140(14):1145-1155.
IN.PACT- Schneider PA, et al. J Am Coll Cardiol. 2019;73(20):2550-2563.
Lutonix- Ouriel K, et al. JACC Cardiovasc Interv. 2019. pii: S1936-8798(19)31836-9
VIVA- Rocha-Singh K, Mullins C; June 19, 2019 Circulatory System Devices Panel.
PADI- Spreen MI, et al. J Am Heart Assoc. 2017 Apr 14;6(4). pii: e004877.
IN.PACT DEEP & Lutonix BTK- Combined Industry Presentation June 20, 2019 Circulatory System Devices Panel. Slide 5
Medicare Inpatient- Secemsky EA, et al. JAMA Cardiol. 2019;4(4):332-340.
Medicare DCS vs BMS- et al. J Am Coll Cardiol. 2019;73(20):2636-2638.
VQI- Bertges DJ, et al. RS01. June 2019 SVS Abstract.



RW Yeh, MD. Peripheral drug coated devices and mortality in a national claims database. FDA Panel June, 2019

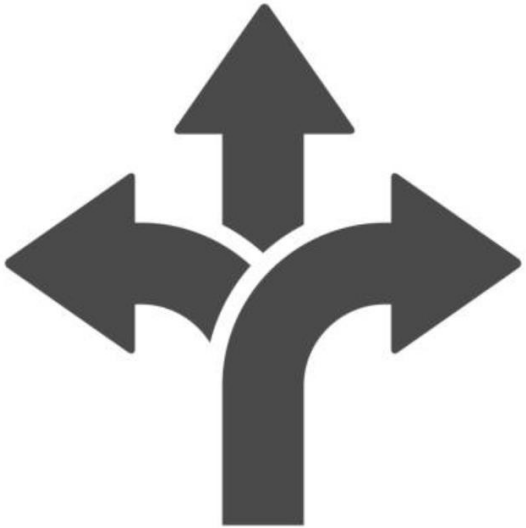
Where are the missing death?

Outlook: in the next 5 years were 5Y FU available of 29 studies with over 10.000 patients

N=10,118	Vessel Bed	Name of Study	N	Status	Estimated Completion	NCT
Independent N=7,350	Femoropopliteal	ZILVERPASS	220	Enrollment complete	December 2019: 2-year follow-up	NCT01952457
		HEROES-DCB	250	Currently enrolling	April 2019: 1-year follow-up	NCT02812966
		DCB-SFA	1080	Currently enrolling	June 2021: 2-year follow-up	NCT02648334
		BEST-SFA	120	Currently enrolling	September 2021: 2-year follow-up	NCT03776799
		Pittsburgh CLI DCB	50	Currently enrolling	December 2020: 1-year follow-up	NCT02758847
		Compare I	414	Enrollment complete	October 2020: 2-year follow-up	NCT02701543
		TRANSCEND	446	Currently enrolling	April 2024: 5-year follow-up	NCT03241459
		BASIL-3	861	Currently enrolling	December 2024: 5-year follow-up	ISRCTN14469736
	Infrainguinal	SWEDEPAD	3800	Currently enrolling	June 2021: 5-year follow-up	NCT02051088
		BEST-CLI	2100	Currently enrolling	December 2019: 5-year follow-up	NCT02060630
	Below-the-knee	DCB vs PTA in CLI and Crural arteries	70	Currently enrolling	June 2019: 1-year follow-up	NCT02750605
	AV Access	DEB in AVG	33	Enrollment complete	December 2018: 1-year follow-up	NCT03388892
		DCB for AVG Restenosis	40	Currently enrolling	December 2019: 3-mon. follow-up	NCT03360279
Industry-Sponsored N=2,768	Femoropopliteal	RANGER II SFA	388	Enrollment complete	August 2023: 5-year follow-up	NCT03064126
		IMPERIAL	524	Enrollment complete	March 2022: 5-year follow-up	NCT02574481
		The Chocolate Touch Study	585	Currently enrolling	December 2026: 2-year follow-up	NCT02924857
		EMINENT	750	Currently enrolling	December 2022: 3-year follow-up	NCT02921230
		BIOPACT-RCT	302	Not yet enrolling	June 2021: 1-year follow-up	NCT03884257
		Italy DEB vs Nitinol stents	84	Enrollment complete	December 2018: 1-year follow-up	NCT02212470
		ILLUMENATE US	300	Enrollment complete	July 2020: 5-year follow-up	NCT01858428
		ILLUMENATE EU	501	Enrollment complete	November 2018: 3-year follow-up	NCT01927068
		DISRUPT PAD III	400	Currently enrolling	December 2021: 2-year follow-up	NCT02923193
	Below-the-knee	DES BTK SAVAL	201	Currently enrolling	May 2024: 3-year follow-up	NCT03551496
		RANGER-BTK	30	Enrollment complete	November 2018: 1-year follow-up	NCT02856230
		Lutonix BTK	442	Enrollment complete	June 2020: 3-year follow-up	NCT01870401
		ILLUMENATE BTK	354	Currently enrolling	April 2024: 3-year follow-up	NCT03175744
		IN.PACT BTK	60	Enrollment complete	December 2020: 3-year follow-up	NCT02963649
	AV Access	ABISS AV DCB	150	Currently enrolling	December 2019: 1.5-year follow-up	NCT02753998
		IN.PACT AV Access	330	Enrollment complete	June 2023: 5-year follow-up	NCT03041467

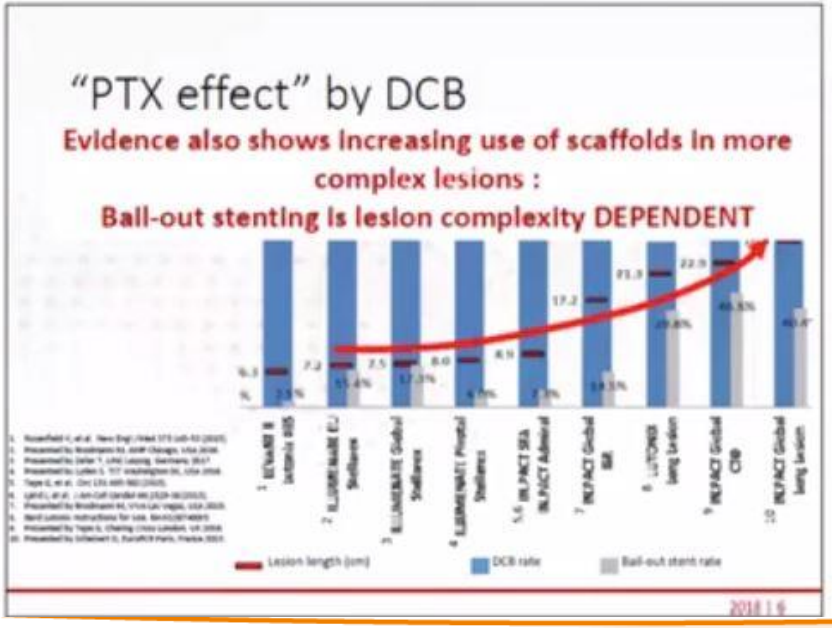
???

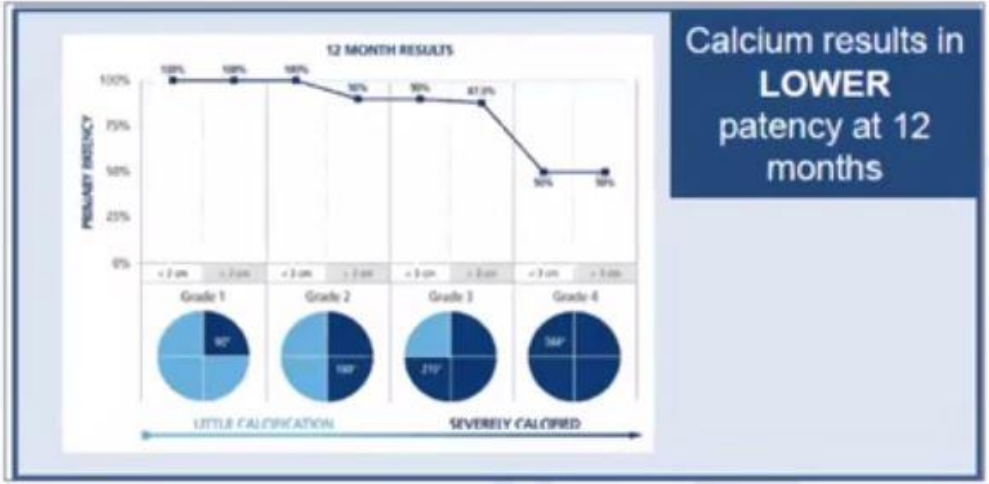
DCB



DES

Despite the benefit of improved clinical outcome, also DCBs (as it is for standard PTA) cannot be considered a "standalone" strategy due to the high rate of bail-out stenting linked to the complexity of the lesions and the poor efficacy in presence of calcium:

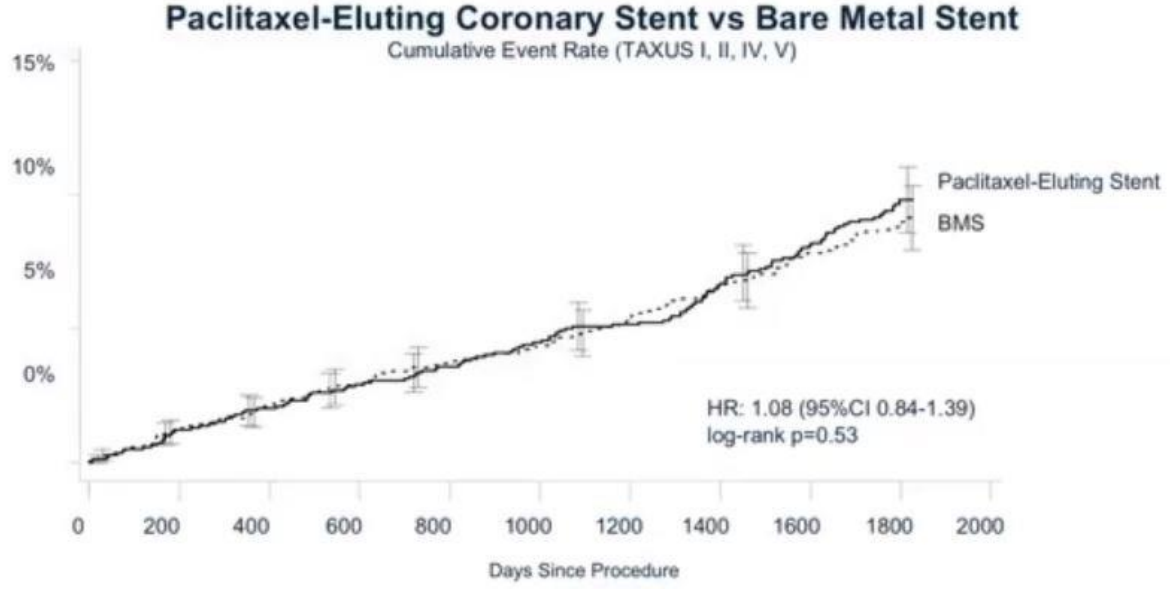




Cardiovasc. Intervent. Radiol. 2014;37(4):898-907

No All-cause Mortality Signal in Meta-analysis of Paclitaxel-eluting Stent vs BMS

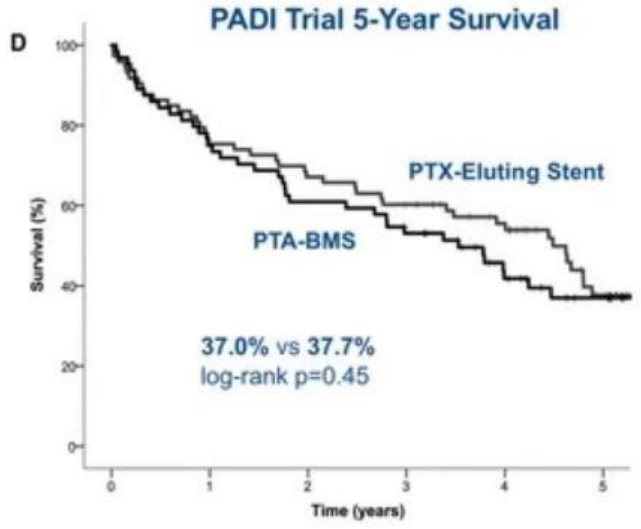
5-year patient-level meta-analysis of mortality in ~2800 patients with coronary artery disease treated with paclitaxel-eluting or bare metal stent



Stone GW, et al. JACC Cardiovasc Interv. 2011;4(5):530-542.
Cumulative event rate data on file. Abbreviations: BMS, bare metal stent; PTx, paclitaxel.

No Difference in All-cause Mortality between Paclitaxel-eluting Stent and Bare Therapy in CLI

- RCT of infrapopliteal paclitaxel-eluting stent placement to treat CLI (N=73)
- Similar survival rates for paclitaxel-eluting vs bare control through 5 years
- Paclitaxel-eluting stent treatment reduced major amputation rate by 57% at 5 years (19.3% vs 34.0%)



No. at risk						
DES	73	55	49	43	34	17
PTA-BMS	64	48	39	33	21	13

Abbreviations: BMS, bare metal stent; CLI, critical limb ischemia; PTA, percutaneous transluminal angioplasty.

Spreen MI, et al. J Am Heart Assoc. 2017;6(4). pii: e004877. doi: 10.1161/JAHA.116.004877.

Femoropopliteal atherosclerosis: do drug-eluting stents improve outcome?

Antonio Micari, Roberto Nerla and Alberto Cremonesi

J Cardiovasc Med 2018, 19 (suppl 1):e91–e92

In addition to these efficacy outcomes, some functional measures have been evaluated, such as patients walking distance and Rutherford class. Functional analyses outlined that, to achieve the same functional results provided by DEB and DES, the standard noneluting technology would require 45% more repeated revascularization procedures.

Key Factors for Restenosis Risk

Patient

- Diabetes[1-3]
- Smoking[2]
- Female sex[1,3]
- Renal failure/Dialysis[1-3]

Lesion/vascular

- Lesion length[1,2]
- Calcification[4]
- Occlusion[2,3]
- Critical limb ischemia[1,2]
- Poor runoff (0-1 below-the-knee vessels) [1-3]

*"In general, the **outcomes of revascularization** depend upon the extent of the disease in the subjacent arterial tree (**inflow, outflow and the size and length of the diseased segment**), the **degree of systemic disease** (co-morbid conditions that may affect life expectancy and influence graft patency) and the **type of procedure performed**."*[2]

1. Soga Y, et al. J Vasc Surg. 2011;54(4):1058-66.
2. TASC II- Norgren L, et al. Eur J Vasc Endovasc Surg. 2007;33 Suppl 1:S1-75.
3. Iida O, et al. JACC Cardiovasc Interv. 2014l;7(7):792-8.
4. Fujihara M, et al. J Endovasc Ther. 2019;26(3):322-330.

Factors that Affect Restenosis Risk

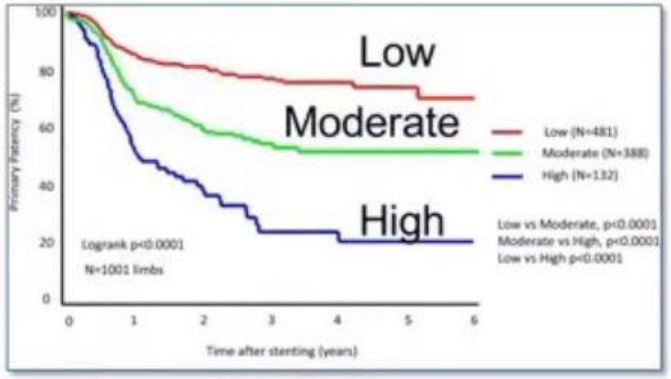
- Based on 807 patients (1001 limbs) with nitinol stents in the SFA
- Multicenter, retrospective

FeDCLIP Score

Risk Factor	Points
Lesion length >150 mm	2
Female	1
Diabetes	1
Dialysis	1
CLI	1
Poor runoff (0-1 BTK vessel)	1
Total	**7**

More points, greater risk

Primary Patency by Risk Group

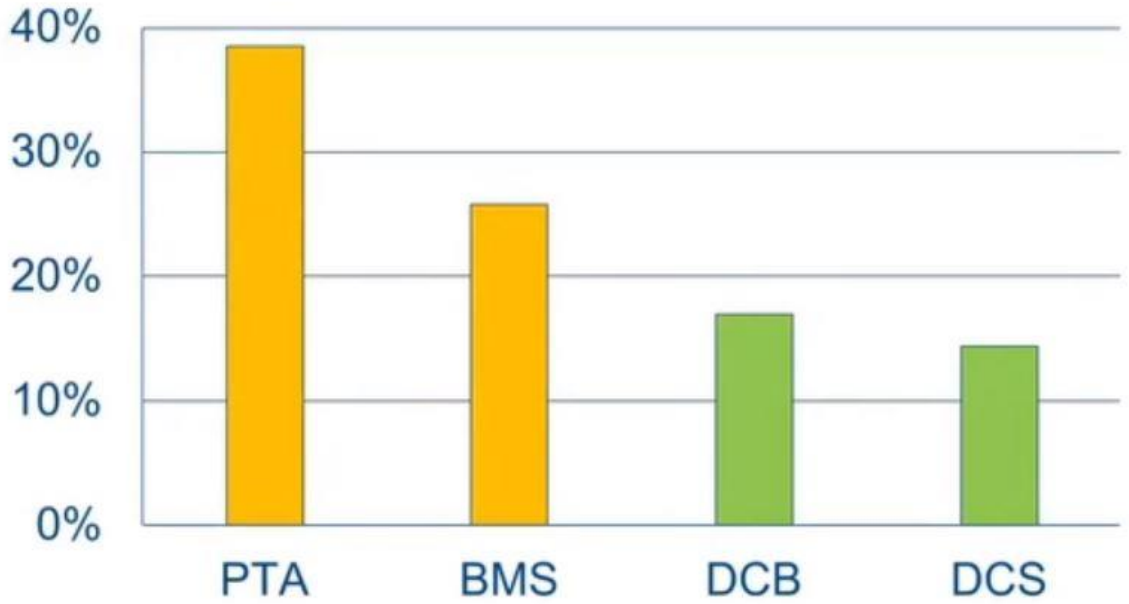


Score	Risk Category	1-Year Primary Patency
0-2	Low	85.7%
3-4	Moderate	71.5%
5-7	Severe	53.0%

Soga Y, et al. J Vasc Surg. 2011;54(4):1058-66.

Paclitaxel Therapies Reduce Repeat Procedures Through 2 Years

2-Year Target Lesion Revascularization Rate

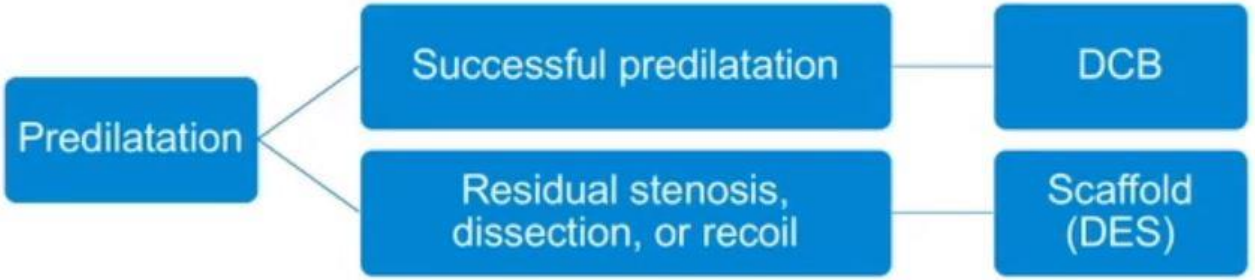


Sridharan ND, et al. J Vasc Surg. 2018;67(1):343-352. doi: 10.1016/j.jvs.2017.06.112.

BMS, bare metal stent; DCB, drug-coated balloon; DCS, drug-coated stent; PTA, percutaneous transluminal angioplasty

Considerations for DCB vs DES in PAD

- Severe calcium → Consider adjunctive atherectomy
- Long lesion → Consider a scaffold
- Predilate to assess vessel response (uncoated balloon angioplasty)

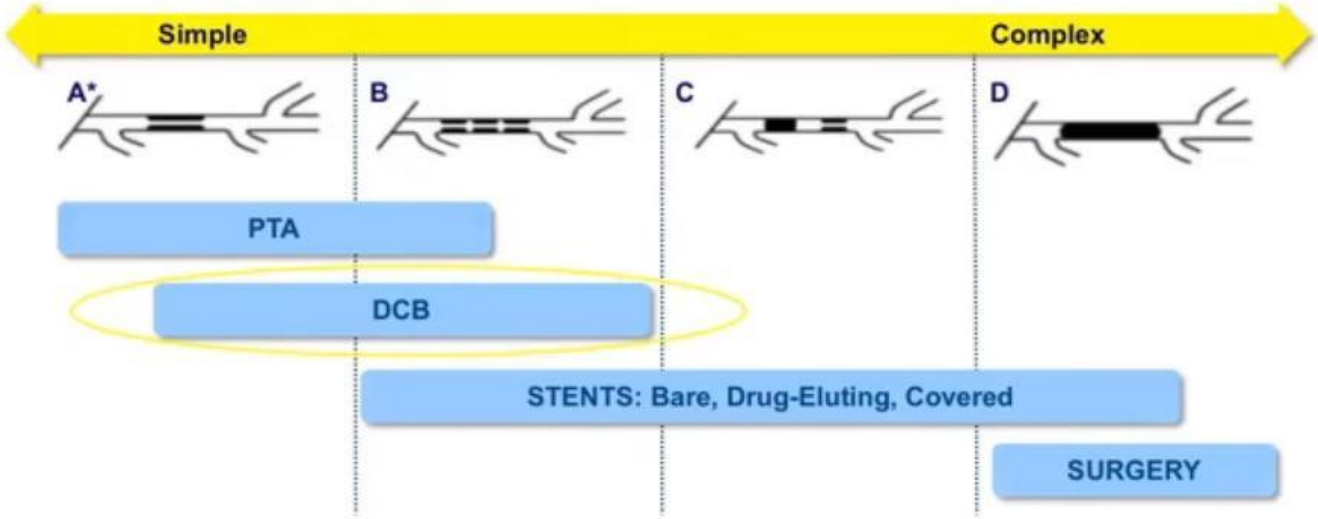


DCB, drug-coated balloon; DES drug-eluting stent.

Ansel G, Phillips JA. Drug elution, data, and decisions. Supplement to Endovascular Today. Nov 2014.
Rundback JH, et al. Curr Treat Options Cardiovasc Med. 2015 ;17(9):400.

Historical patient population for DCB studies

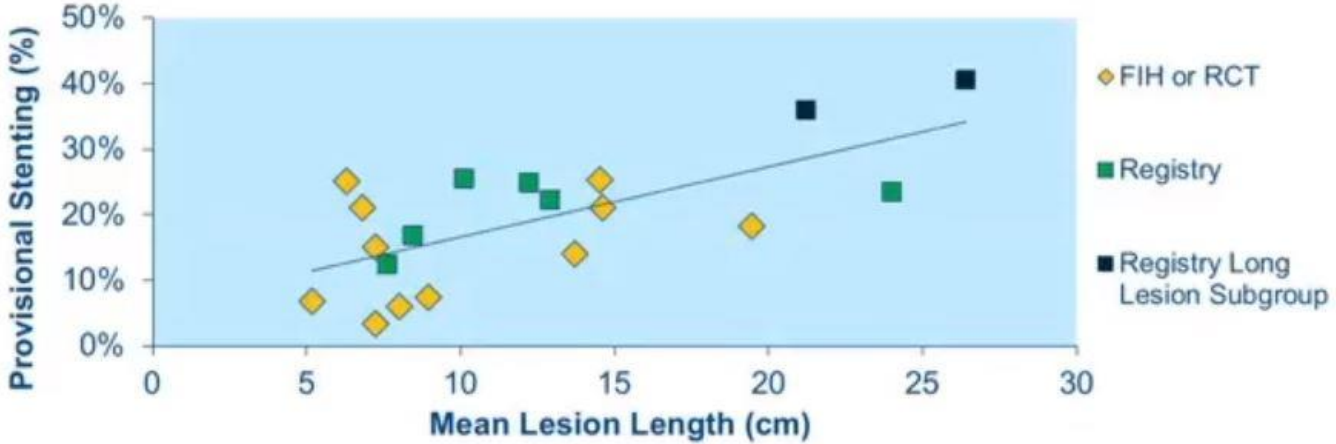
- DCB trial/registry patients represent population with less complex lesions
  - Primarily TASC A/B, lesion length <10 cm
  - Less calcification
  - Fewer occlusions



* TransAtlantic Inter-Society Consensus (TASC) II Lesion Classification (Type A, B, C, D) for peripheral arterial disease

Stents used in DCB studies

- Stents are utilized in studies intended to evaluate DCB efficacy
- Longer mean lesion length correlates with higher provisional stenting rate



Provisional Stenting in Randomized Controlled Trials may not be representative of actual stenting in studies due to study design

Results from different clinical investigations are not directly comparable. Information provided for educational purposes only.

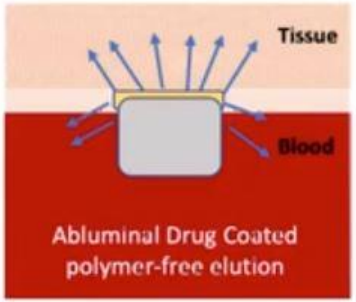
Zeller T. et al. J Endovasc Ther. 2014;21(3):359-68.
BIOLUX P-I- Scheinert D, et al. J Endovasc Ther. 2015;22(1):14-21.
REAL PTX- Scheinert D. LINC 2018.
DRASTICO- Liistro F, et al. J Am Coll Cardiol. 2019;74(2):205-215.
BIOLUX PIII Registry- Tepe G. LINC 2018.
RANGER SFA Registry- Lichtenberg M, et al. J Cardiovasc Surg (Torino). 2018;59(1):45-50
Micari A Et al. J Am Coll Cardiol Intv 2012
Schmidt A, et al. JACC Cardiovasc Interv. 2016;9(7):715-24.
Lutonix Registry- Thieme M, et al. JACC Cardiovasc Interv. 2017;10(16):1682-1690.
In.Pact Global Registry- Ansel G. TCT 2015.
ILLUMENATE FIH Schroeder H, et al. Catheter Cardiovasc Interv. 2015;86(2):278-86.
ILLUMENATE EU RCT - Schroeder H, et al. Circulation. 2017. pii: CIRCULATIONAHA.116.026493.
RANGER SFA- Bausback Y, et al. J Endovasc Ther. 2017;24(4):459-467.
IN.PACT SFA - Tepe G, et al. Circulation. 2014 pii: CIRCULATIONAHA.114.011004.
ILLUMENATE US RCT- Krishnan P, et al. Circulation. 2017 Jul 20. pii: CIRCULATIONAHA.117.028893.
LEVANT 2- Rosenfield K, et al. N Engl J Med. 2015;373(2):145-53.
CONSEQUENT- Tepe G, et al. Cardiovasc Intervent Radiol. 2017 Oct;40(10):1535-1544.

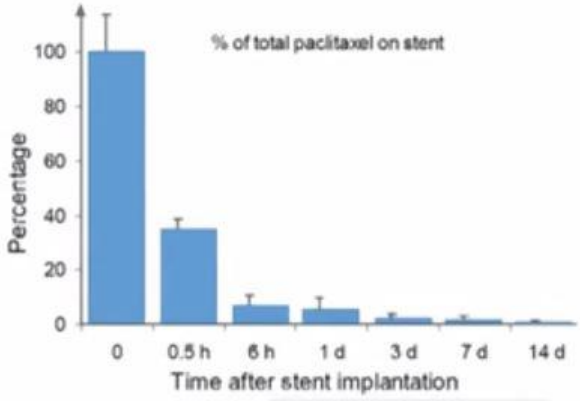
DES

Zilver PTX (Cook) provides a "**polymer-free fast elution approach**" to deliver the drug from a Self-Expanding nitinol platform.

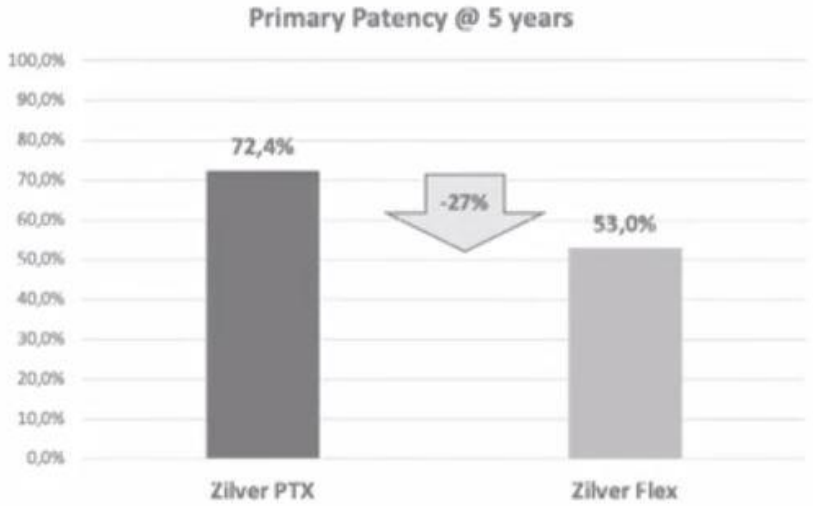
Crystals of pure drug are deposited on the bare Nitinol stent surface and quickly released:

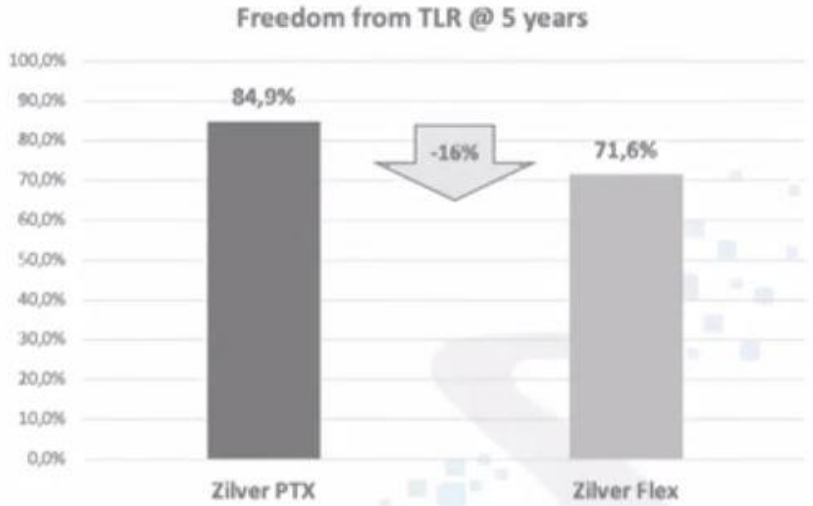
- Drug = **PACLITAXEL** (cytotoxic)
- Release = Polymer-free fast drug elution (days)





Cook Zilver PTX studies have shown that the impact of the drug from a bare metal stent has a visible and sustained benefit over time:





Zilver PTX RCT Trial – secondary randomization Zilver PTX vs Zilver Flex*

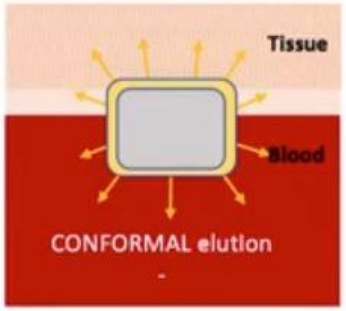
*Circulation DOI: 10.1161/CIRCULATIONAHA.115.016900

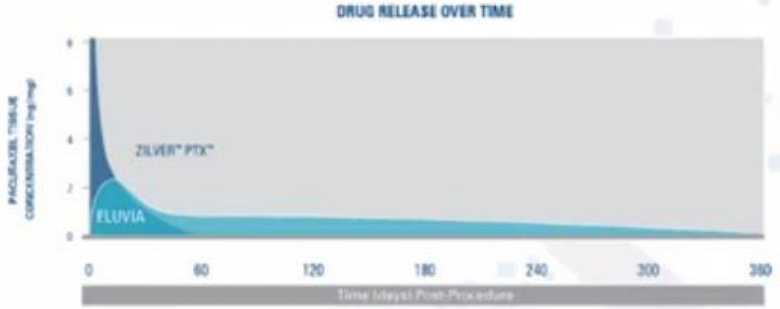
DES

Eluvia (Boston Scientific) provides a "**slow release approach**" utilizing a **durable polymer** to deliver drug from a Self-Exp nitinol platform.

Pure drug is deposited within a permanent polymeric matrix:

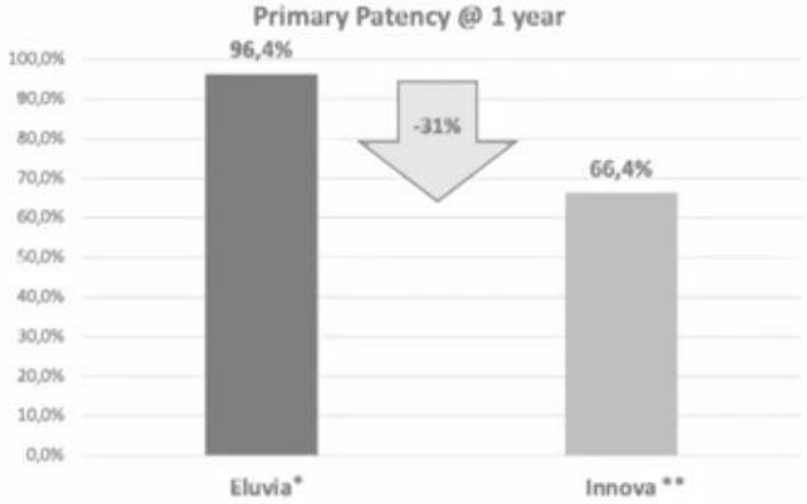
- Drug = **PACLITAXEL** (cytotoxic)
- Release = Durable polymeric slow drug elution (1 year)

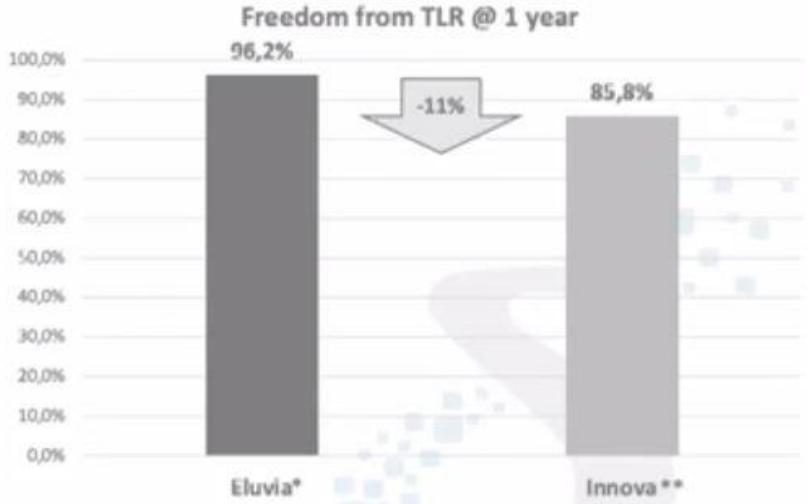




- Drug release from the Eluvia system is sustained over time
  - >90% of drug is released at 1 year
  - Drug release coincides with the restenotic cascade

Prolonging and sustaining the drug release from a bare metal stent even further (up to 1year), as seen in the clinical studies from the **Boston Scientific Eluvia DES**, has also shown better performances vs a bare metal stent platform:



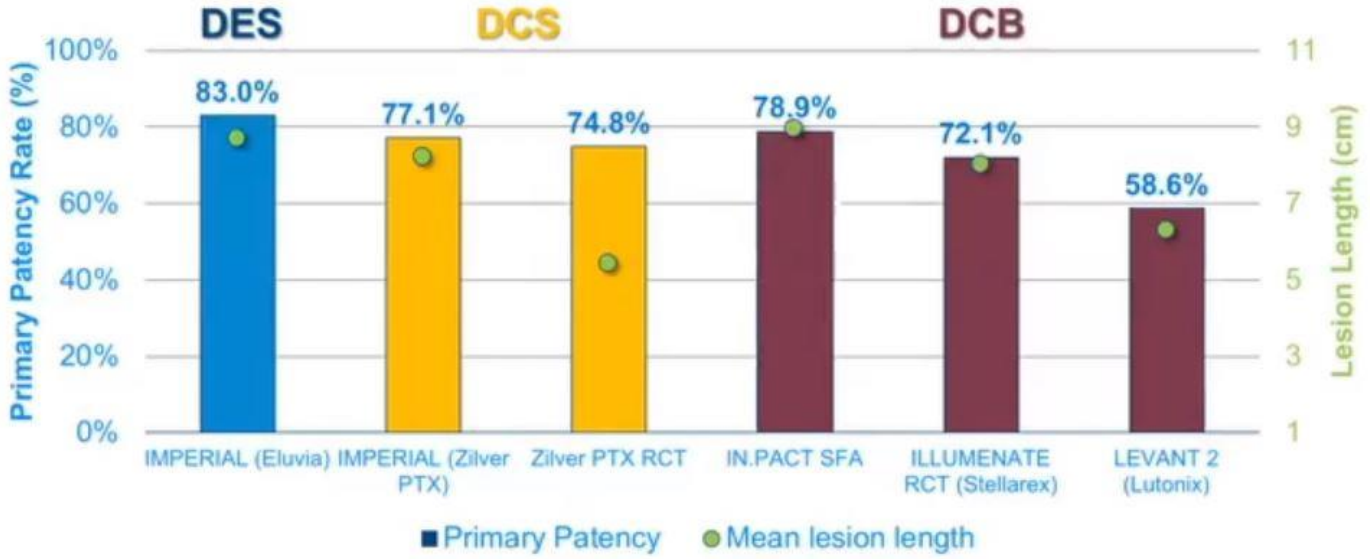


* MAJESTIC: Twelve-Month Results From the MAJESTIC Trial of the Eluvia Paclitaxel-Eluting Stent for Treatment of Obstructive Femoropopliteal Disease.Müller-Hülsbeck S, Keirse K, Zeller T, Schroë H, Diaz-Cartelle J.J Endovasc Ther. 2016 Oct;23(5):701-7. doi: 10.1177/1526602816660206. Epub 2016 May 18.

**SUPERNOVA: Clinical Trial - Catheter Cardiovasc Interv 2017 May;89(6):1069-1077. doi: 10.1002/ccd.26976. Epub 2017 Mar 15. Stent placement in the superficial femoral and proximal popliteal arteries with the innova self-expanding bare metal stent system. Richard J Powell , Michael R Jaff, Herman Schroë, Andrew Benko, Juan Diaz-Cartelle, Stefan Müller-Hülsbeck

2-Year Primary Patency for Paclitaxel-containing Devices

US Pivotal RCTs



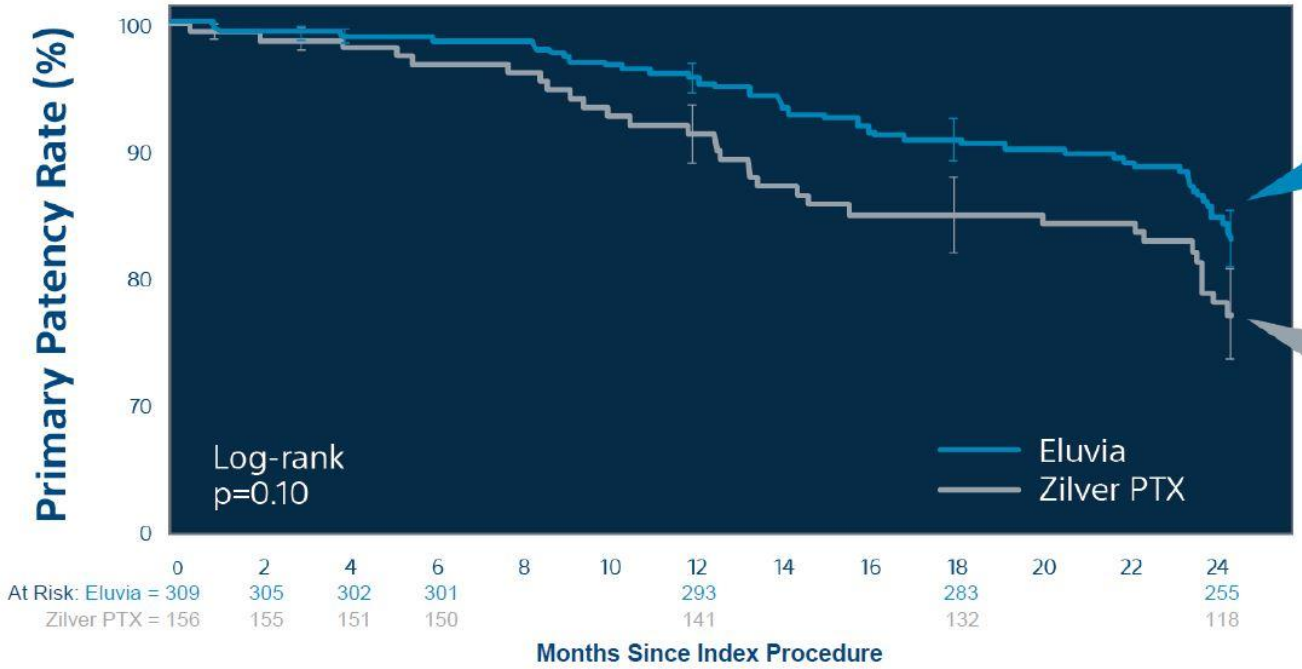
Results from different clinical investigations are not directly comparable. Information provided for educational purposes only.

Kaplan-Meier estimates at 24 months.
IMPERIAL (Eluvia)- Iida O, VIVA 2019, Nov 4-7 2019, Las Vegas.
Zilver PTX RCT- Dake, MD, et al. (2013). J Am Coll Cardiol 61(24): 2417-2427.
ILLUMENATE RCT (Stellarex)- Mathews S. NCVH, 2018. May 30, 2018. New Orleans, LA.
IN.PACT SFA- Laird, JR, et al. (2015). J Am Coll Cardiol 66(21): 2329-2338.
LEVANT 2 (Lutonix)- Laurich C, SVS Chicago 2015.

DCB, drug-coated balloon; DCS, drug-coated stent; DES, drug-eluting stent; RCT, randomized controlled trial.

Imperial

	Eluvia (N=309)	Zilver PTX (N=156)
Arterial Segments		
Ostial	1.6%	0.6%
Proximal SFA	12.9%	10.3%
Mid SFA	65.0%	66.7%
Distal	66.3%	65.4%
Proximal Popliteal Artery	18.0%	12.7%
Lesion length (mm)	86.5 ± 36.9	81.8 ± 37.3
Calcification		
None/Mild	36.5%	32.3%
Moderate	22.8%	34.8%
Severe	40.1%	32.3%
Reference Vessel Diameter (mm)	5.0 ± 0.8	5.1 ± 0.8
% Diameter Stenosis	80.7% ± 16.5%	80.8% ±16.4%
<50%	1.6%	1.9%
50%-<100%	67.2%	67.7%
100% (Occlusion)	31.2%	30.3%



Eluvia
83.0%

Zilver PTX
77.1%

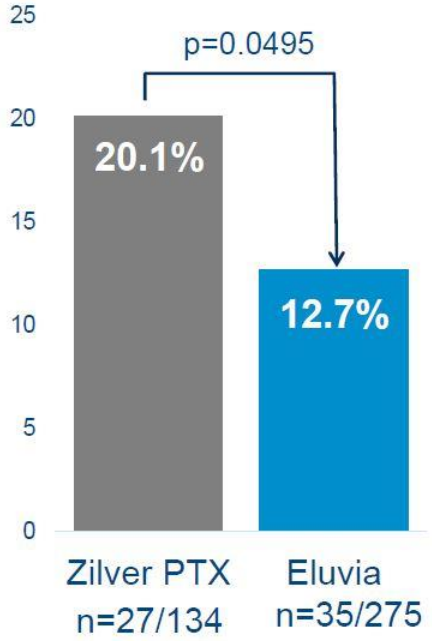
*Intention to treat. Kaplan-Meier estimate with standard errors. Primary patency defined as duplex ultrasound PSVR ≤2.4, in the absence of clinically-driven target lesion revascularization or bypass of the target lesion as assessed by the DUS core lab.

At Risk denotes the number of subjects entered in the calculation at the time interval

Eluvia Demonstrated the Highest Primary Patency Reported in an SFA US Pivotal Trial for DES or DCB**

Adapted from Iida, O, VIVA 2019 Presentation

7 **Highest-two year primary patency based on 24-month Kaplan-Meier estimates reported for IMPERIAL, IN.PACT SFA, ILLUMENATE, LEVANT II and Primary Randomization for Zilver PTX RCT.



	Eluvia	Zilver PTX	P-Value
24-Month MAE	14.2% (39/275)	20.1% (27/134)	0.1236
Any death at 1 month	0%	0%	Undef
Target limb major amputation	1.5% (4/275)	0.7% (1/134)	>0.99
Target lesion revascularization	13.5% (37/275)	20.1% (27/134)	0.0803
Clinically-driven TLR	12.7% (35/275)	20.1% (27/134)	0.0495
Non-clinically-driven TLR	0.7% (2/275)	0.0% (0/134)	>0.99
Stent thrombosis	3.1% (9/295)	4.1% (6/145)	0.5818

Statistically significant reduction in CD-TLR with Eluvia at 24 months vs. Zilver PTX

Intention to treat.
Adapted from Iida, O, VIVA 2019 Presentation

Cardiovasc Intervent Radiol (2021) 44:1367–1374
https://doi.org/10.1007/s00270-021-02901-6

CIRSE

Check for updates

CLINICAL INVESTIGATION ARTERIAL INTERVENTIONS

24-Month Efficacy and Safety Results from Japanese Patients in the IMPERIAL Randomized Study of the Eluvia Drug-Eluting Stent and the Zilver PTX Drug-Coated Stent

Osamu Iida[1] · Masahiko Fujihara[2] · Daizo Kawasaki[3] · Shinsuke Mori[4] · Hiroyoshi Yokoi[5] · Akira Miyamoto[6] · Kimihiko Kichikawa[7] · Masato Nakamura[8] · Takao Ohki[9] · Juan Diaz-Cartelle[10] · Stefan Müller-Hülsbeck[11] · William A. Gray[12] · Yoshimitsu Soga[13]

Received: 2 April 2021 / Accepted: 15 June 2021 / Published online: 7 July 2021

Table 2 Events adjudicated by the Clinical Events Committee through 24 months[a]

	Eluvia ($n = 56$)	Zilver PTX ($n = 28$)	Difference [95% CI]	p^b
All deaths	5.6% (3/54)	11.1% (3/27)	− 5.6% [− 18.9%, 7.8%]	0.39
Target lesion revascularization[c]	5.6% (3/54)	18.5% (5/27)	− 13.0% [− 28.8%, 2.9%]	0.11
Target limb amputation	0.0% (0/54)	3.7% (1/27)	− 3.7% [− 10.8%, 3.4%]	0.33
Stent thrombosis	1.9% (1/54)	0.0% (0/27)	1.9% [− 1.7%, 5.4%]	1.00

[a]The CEC-adjudicated denominator is based on 1) subjects with CEC-adjudicated events (i.e., any death, target lesion/vessel revascularization, target limb amputation, stent thrombosis) through 24 months and 2) subjects with no events but their follow-up time reach on (or beyond) the earliest visit window

[b]P values from 2-sided Fisher's exact test

[c]All target lesion revascularizations met the criteria for "clinically driven;" i.e., a reintervention within 5 mm proximal or distal to the original treatment segment for angiographic diameter stenosis ≥ 50% in the presence of recurrent symptoms (i.e., increase in Rutherford class by 1 or more) or ABI decrease of at least 0.15 or 20% in the treated segment

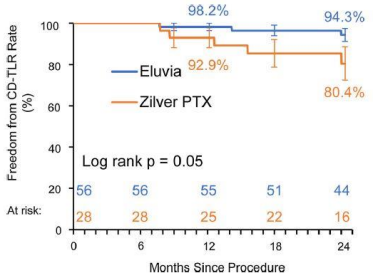


Fig. 1 Kaplan–Meier estimate of freedom from CD-TLR and standard errors

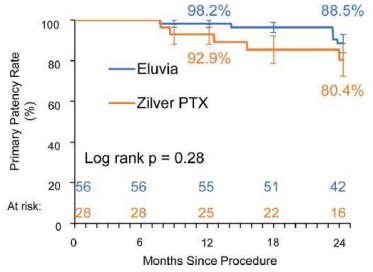


Fig. 2 Kaplan–Meier estimate of primary patency and standard errors

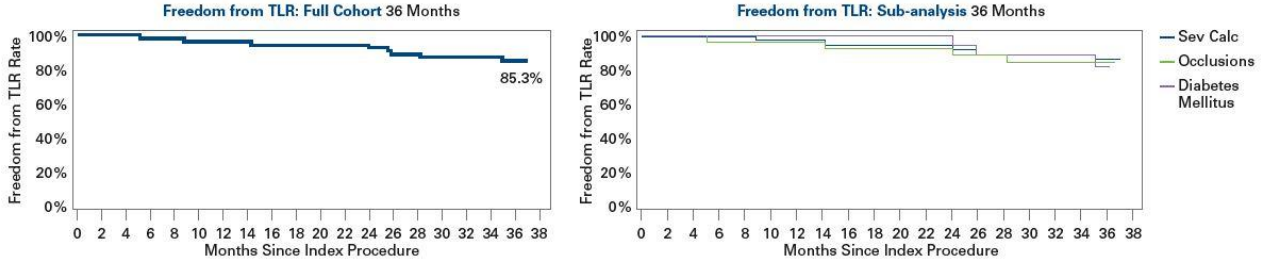
Majestic

BASELINE CHARACTERISTICS:

Patient Demographics	n = 57 subjects	Lesion Characteristics (Core Lab)	n = 57 lesions
Age (Years)	69.3 ± 9.3	Reference Vessel Diameter	5.2 ± 0.8
Male Gender	82.5%	Target Lesion Length	70.8 ± 28.1
Diabetes Mellitus	35.1%	Severely Calcified	64.9%
History of Smoking	87.7%	Percent Diameter Stenosis	86.3% ± 16.2%
Hypertension	73.7%	Total Occlusions	46.2%
Hyperlipidemia	63.2%	% Extending into Distal SFA	77.2%
Coronary Artery Disease	38.6%	% Extending into PPA	8.8%

3-YEAR RESULTS:

The Eluvia Stent continues to demonstrate unprecedented clinical outcomes with an 85.3% freedom from TLR at 3 years, one of the highest reported in comparable SFA clinical trials.



	12 Months	24 Months
Primary Patency[a]	96.4%	83.5%
Assisted Primary Patency[b]	98.2%	88.9%

Note: Kaplan-Meier Estimates. Per study protocol, primary patency was not evaluated at 36 months.

[a] Duplex ultrasound peak systolic velocity ratio ≤2.5 and absence of TLR or bypass.

[b] No TLR and those with TLR not for complete occlusion or bypass who were free of restenosis at 24 months.

[1] Müller-Hülsbeck S, et al. Long-Term Results from the MAJESTIC Trial of the Eluvia Paclitaxel-Eluting Stent for Femoropopliteal Treatment: 3 Year Follow up. Cardiovasc Interv Radiol. 2017, in press.

ZILVER PTX vs DCB (2-YEAR)

2-year result of the REAL PTX - randomized clinical trial comparing Zilver PTX vs. DCB treatment in femoropoliteal lesions

LINC 2017 – Dr. Scheinert

Click to view

METHODS

- Zilver PTX vs DCB (1:1 RCT)
- N=150 patients, 75 in each group
- Multicenter (5 centers in Eruope)
- Native femoropopliteal disease
- Independend core-lab assessment for angio and duplex
- Stratification for lesion length (1:1:1) – short(≤10cm) , middle (>10 & ≤20cm) and long (> 20 & ≤30cm)

CHARACTERISTIC

(Pts and Lesion)

	DCB n=75	Zilver PTX n=75
Lesion Length, cm	14.5 ± 9.2	16.0 ± 9.7
CTOs	53%	52%
Severe Calcification	23%	35%
SFA Lesion %	80%	84%
CLI (RC4-5) %	10%	16%

RESULTS

Primary Patency	DCB	Zilver PTX
1 yr	76%	76%
2 yr	49%	58%

1 yr Primary Patency by Lesion Length	DCB	Zilver PTX
≤10cm	76%	78%
>10 & ≤20cm	40%	57%
> 20 & ≤30cm	33%	43%

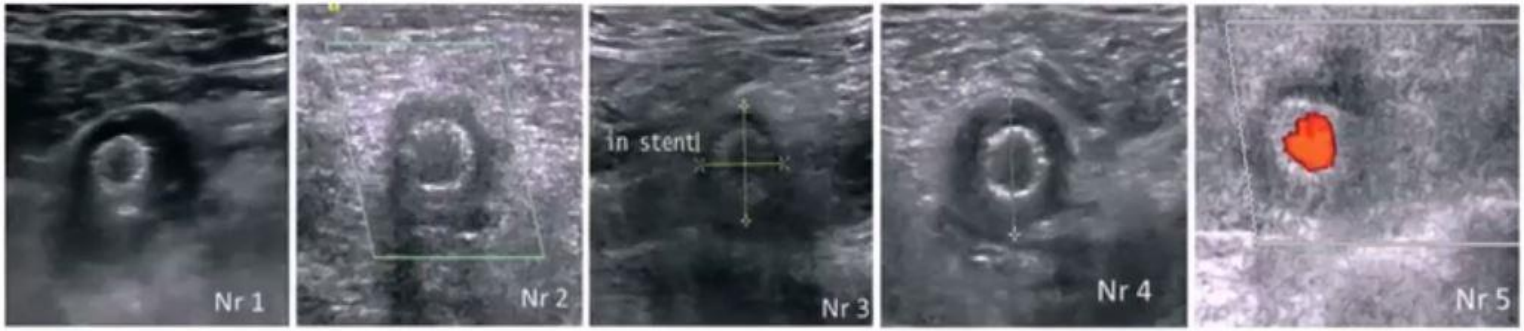
- 25% bailout stenting in DCB arm

KEY TAKEAWAYS

Risk of DES

The presence of the permanent polymer can represent a limit for the safety: the Munster Registry (an independent real word study conducted in Germany on the Eluvia stent) highlighted the risk of degeneration of the vessel wall (HALO) reporting the percentage of affected population:

- **8% at 1 years***
- **20% at 2 years****



* JACC vol 11, NO. 10, 2018 May 28, 2018:957-66
**. JACC Cadiovascular Intervention 2021 Mar 22;14(6):692-701. doi: 10.1016/j.jcin.2021.01.026

…other options ?

Tack Endovascular System

Multi-implant, minimal-metal focal dissection repair for tapering vessels from SFA to ankle

Tack® implants

Multiple pre-loaded nitinol implants

- ATK: 6 implants
- BTK: 4 implants

6mm or 8mm deployed length

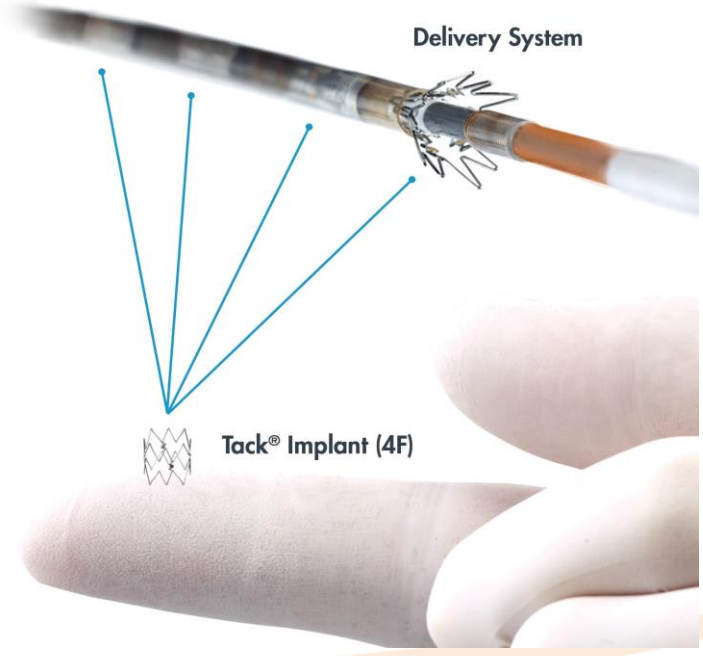
Each implant self-sizes to tapering anatomy

- ATK: 2.5 – 6.0mm and 4.0 – 8.0mm RVD
- BTK: 1.5 – 4.5mm RVD

OTW Delivery System

Accurate (≤1mm) deployment

- ATK: 6F/.035
- BTK: 4F/.014



INTENDED USE: The Tack Endovascular System is intended for use for the repair of post percutaneous transluminal balloon angioplasty (PTA) dissection(s).

CONTRAINDICATIONS: The Tack Endovascular System is contraindicated for the following: 1. Patients with residual stenosis in the treated segment equal to or greater than 30% after PTA. 2. Tortuous vascular anatomy significant enough to prevent safe introduction and passage of the device. 3. Patients with a known hypersensitivity to nickel-titanium alloy (Nitinol). 4. Patients unable to receive standard medication used for interventional procedures such as anticoagulants, contrast agents and antiplatelet therapy.

TOBA III Study Design

TOBA III
TACK OPTIMIZED BALLOON ANGIOPLASTY

Femoropopliteal dissection repair with Tack Endovascular System (6F)

Prospective, single-arm, non-blinded pivotal IDE study in US, Europe

201 subjects with post-PTA dissection following IN.PACT™ Admiral™ DCB

169 patients with standard lesions ≤150mm and 32 patients with long lesions >150mm - ≤250mm

Primary Safety Endpoint	Freedom from the occurrence of any new-onset MAE* at 30 days
Primary Efficacy Endpoint	Primary patency at 12 months: • Freedom from CEC adjudicated CD-TLR *and* • Freedom from core lab adjudicated DUS-derived binary restenosis

Brodmann M, Wissgott C, Brechtel K et al. Optimized drug-coated balloon angioplasty of the superficial and proximal popliteal arteries using the Tack Endovascular System: TOBA III 12-month results. *J Vasc Surg* 2020. Nov;72(5):1636-1647.e1.

Key baseline patient/lesion characteristics
(ITT population, core lab adjudicated)

TOBA III
TACK OPTIMIZED BALLOON ANGIOPLASTY

	Mean ± SD (N) or n/N (%)	
	Standard Lesion	Long Lesion
Age (y)	66.7 ± 9.4 (169)	63.7 ± 8.8 (32)
Male gender	58.6% (99/169)	59.4% (19/32)
Diabetes mellitus	29.3% (49/167)	40.6% (13/32)
Hypertension	79.6% (133/167)	93.3% (28/30)
Hyperlipidemia	73.5% (122/166)	90.0% (27/30)
ABI in treated leg	0.68 ± 0.18 (168)	0.62 ± 0.23 (29)
Rutherford 2	22.5% (38/169)	37.5% (12/32)
3	72.2% (122/169)	62.5% (20/32)
4	5.3% (9/169)	0.0% (0/32)

		Mean ± SD (N) or n/N (%)	
		Standard Lesion	Long Lesion
Target vessel:	SFA	90.0% (153/170)	96.9% (31/32)
	P1	2.9% (5/170)	0.0% (0/32)
	SFA and P1	6.5% (11/170)	3.1% (1/32)
Target lesion length (mm)		68 ± 42 (170)	154 ± 56 (32)
PTA treated length (mm)		99 ± 43 (164)	215 ± 53 (30)
RVD (mm):	Proximal	5.2 ± 0.8 (170)	5.3 ± 0.9 (32)
	Distal	5.2 ± 0.8 (170)	4.9 ± 0.8 (32)
Total Occlusion		34.7% (59/170)	50.0% (16/32)
Calcification:	Moderate	15.9% (27/170)	21.9% (7/32)
	Severe	20.0% (34/170)	9.4% (3/32)

Brodmann M, Wissgott C, Brechtel K et al. Optimized drug-coated balloon angioplasty of the superficial and proximal popliteal arteries using the Tack Endovascular System: TOBA III 12-month results. *J Vasc Surg* 2020. Nov;72(5):1636-1647.e1.

Post-PTA dissection severity and resolution
(ITT population, core lab adjudicated)

TOBA III
TACK OPTIMIZED BALLOON ANGIOPLASTY

Post-PTA Dissection (NHLBI)

	Standard Lesion	Long Lesion
A	14.0%	0.0%
B	40.9%	56.3%
C	33.5%	28.1%
D	11.6%	15.6%

	Mean ± SD (N) or %	
	Standard Lesion	Long Lesion
Dissections per patient	1.8 ± 1.1 (167)	2.6 ± 1.0 (32)
Tack implants per patient	4.1 ± 2.5 (169)	7.0 ± 3.6 (31)
Dissection resolution	**97.7%**	**98.8%**
Bail out stent rate	**0.6%**	**0.0%**

Brodmann M, Wissgott C, Brechtel K et al. Optimized drug-coated balloon angioplasty of the superficial and proximal popliteal arteries using the Tack Endovascular System: TOBA III 12-month results. *J Vasc Surg* 2020. Nov;72(5):1636-1647.e1.

Patency and freedom from CD-TLR

TOBA III
TACK OPTIMIZED BALLOON ANGIOPLASTY

(ITT population, core lab adjudicated)

Freedom from MAE at 30d	12m K-M Primary Patency	12m K-M Freedom from CD-TLR
Standard Lesion		
100%	95.0%	92.3% at 24 months
Long Lesion		
100%	89.3%	82.6% at 24 months

**Observational data; not powered for statistical significance*

Brodmann M, Wissgott C, Brechtel K et al. Optimized drug-coated balloon angioplasty of the superficial and proximal popliteal arteries using the Tack Endovascular System: TOBA III 12-month results. *J Vasc Surg* 2020. Nov;72(5):1636-1647.e1.

Conclusions

- The „PTX mortality gate“ is less alarming in view of the latest clinical studies
- Adding a drug to a device (both balloon or stent) improves its clinical performance
- Compared with PTA and/or BMS paclitaxel therapies reduce repeat procedures through 2 years
- DES, in the most complex lesions settings, resulted providing better performance vs. DCB
- Ad today there are 2 Paclitaxel coated Stents dedicated to SFA on the market, both of them presenting some strengths but also some technological intrinsic limitations
- DCB combined with Tack Implants provide some of the highest reported patency rates (95%)

Thank you very much for your attention