Azienda Ospedaliero Universitaria Careggi

Servizio Sanitario della Toscana

Long-term Results from the IN.PACT SFA DCB Clinical Trial: **Continued Efficacy, Continued Safety**

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UNIVERSITÀ DEGLI STUDI FIRENZE

Disclosures

- Consultant / Speaker / Proctor / Advisory Board
  - Bayer
  - Bolton
  - Boston Scientific
  - Cook
  - Medtronic
  - Penumbra
  - Shockwave Medical
  - Philips
  - Volcano Philips
  - W.L. Gore & Associates

Background

- Numerous randomized trials with drug-coated balloons (DCBs) have shown improved outcomes of DCB over PTA[2-10]

		1-Year	2-Year	3-Year	4-Year	5-Year
Primary Patency	IN.PACT SFA IN.PACT™ DCB	87.5%[1]	79.0%[1]	69.5%[2]	Not assessed after 3 years	
	Levant II Lutonix™ DCB	73.5%[3]	58.6%[4]	Not Reported	Not Reported	Not Reported
	ILLUMENATE US Stellarex™ DCB	82.3%[5]	72.1%[6]	Not Reported	Not Reported	Not Reported
		1-Year	2-Year	3-Year	4-Year	5-Year
CD-TLR	IN.PACT SFA IN.PACT™ DCB	2.4%[7]	9.1%[8]	15.2%[2]	23.4%[9]	25.5%[10]
	Levant II Lutonix™ DCB	12.3%[3]	18.0%[4]	Not Reported	Not Reported	Not Reported
	ILLUMENATE US Stellarex™ DCB	7.9%[5]	Not Reported	Not Reported	Not Reported	Not Reported

- Published results of the IN.PACT SFA Trial have demonstrated superiority of the IN.PACT™ Admiral™ DCB over percutaneous transluminal angioplasty (PTA)[2,7,8]
- Long-term data from randomized trials for DCBs available in the U.S. are limited

1. Medtronic IFU M052624T0001_rev1H.
2. Schneider P et al. Circ-CI 2018;11:1-15.
3. Rosenfield K et al. NEJM 2015;373:145-53.
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5. Krishnan P et al. Circulation 2017;136:1102-1113.
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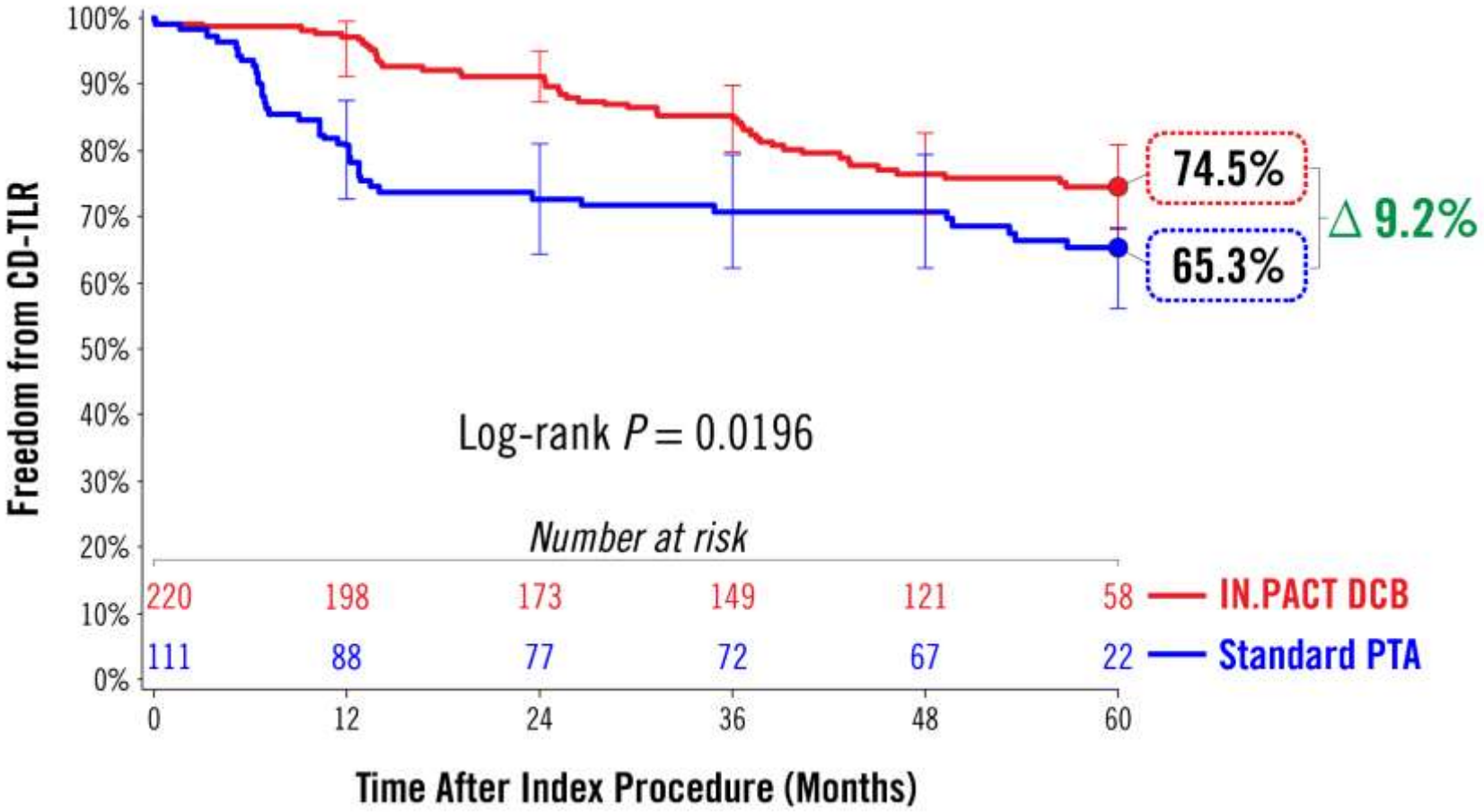
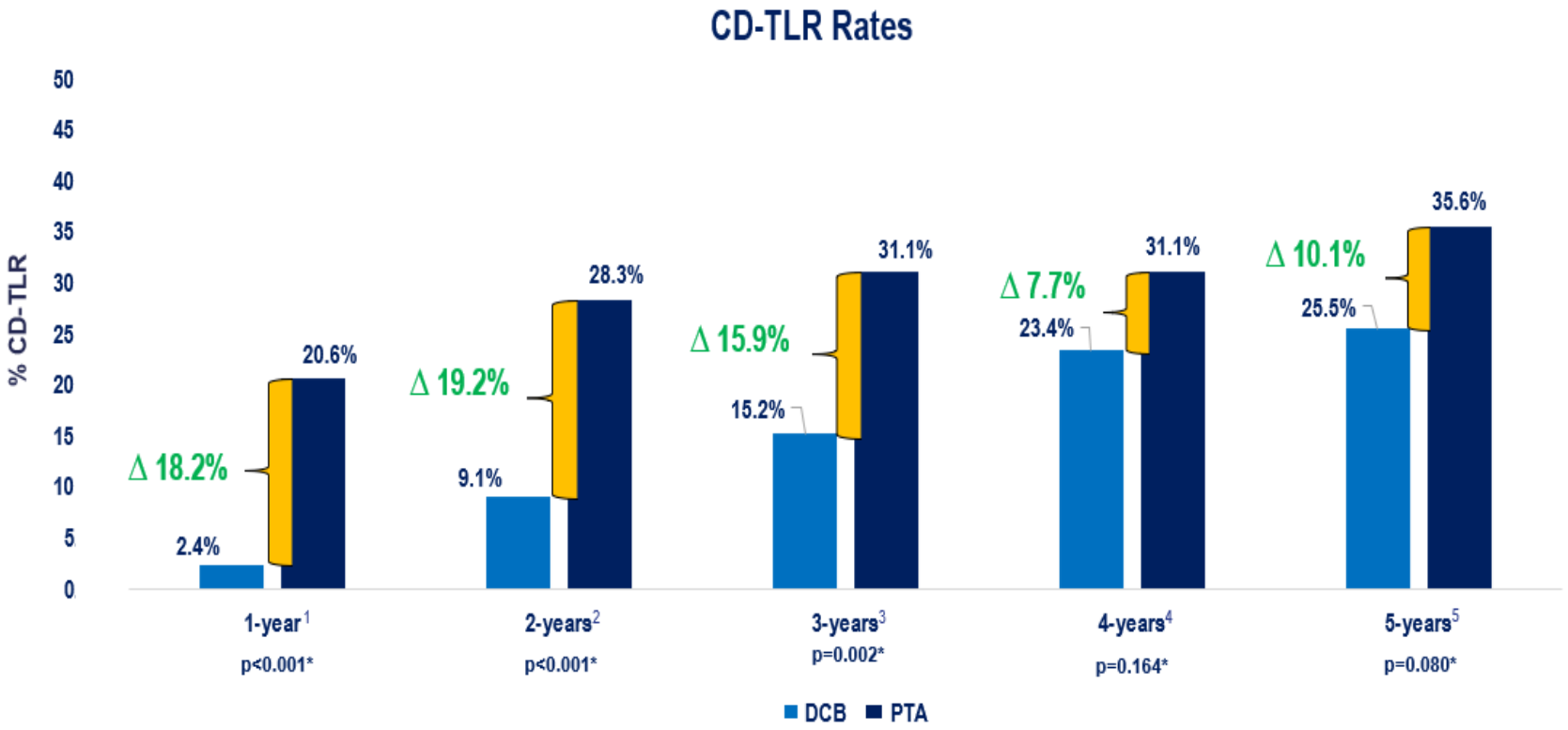
7. Tepe G et al. Circ 2015;131:495-502.
8. Laird JR et al. JACC 2015;66:2329-2338.
9. Schneider P. IN.PACT SFA Four-Year Results. VIVA 2017.
10. Laird JR. IN.PACT SFA Five-Year Results. VIVA 2018.

IN.PACT SFA Trial

Freedom from CD-TLR through 5 Years



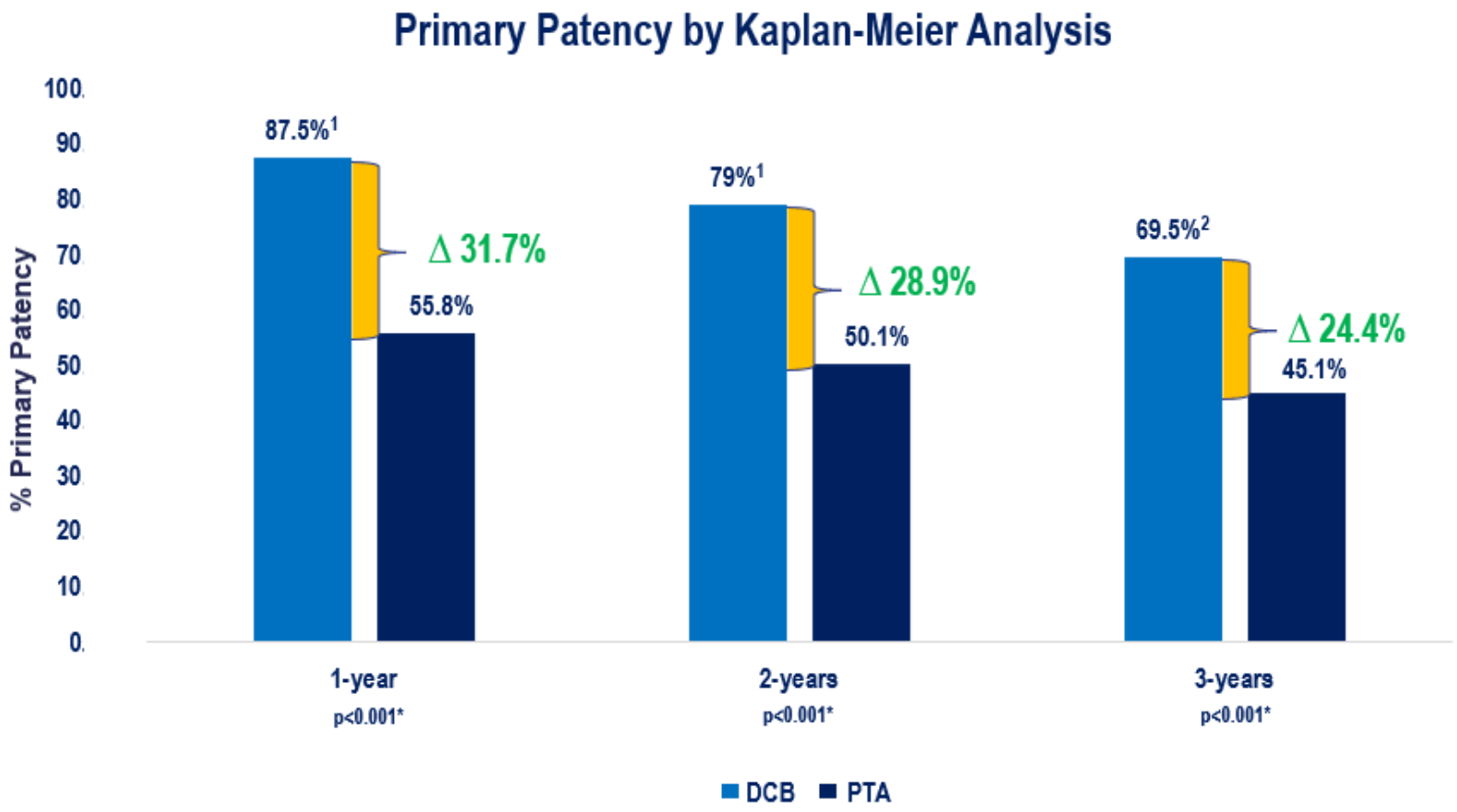
IN.PACT SFA Trial through the Years



1. Tepe G. et al. Circ 2015;131:495-502.
2. Laird J.R. et al. JACC 2015;66:2329-2338.
3. Schneider P. et al. Circ-CI 2018;11:1-8.
4. Schneider P. VIVA 2017.
5. Laird J.R. VIVA 2018.

* p-value compares DCB to PTA.

IN.PACT SFA Trial through the Years



1. Medtronic IFU M052624T001_Rev1H.
2. Schneider P. et al. Circ-CI 2018;11:1-8.

* p-value compares DCB to PTA.

IN.PACT SFA Trial
Safety Outcomes through 5 Years

	IN.PACT DCB (N=220)	PTA (N=111)	P-value†
Primary Safety Composite[1]	70.7% (130/184)	59.6% (62/104)	0.068
Major Adverse Events[2]	42.9% (79/184)	48.1% (50/104)	0.459
All-cause Death	15.8% (29/184)	9.6% (10/104)	0.156
Device- or Procedure- related Death through 5 Years[3]	0 (0/184)	0 (0/104)	--
CD-TVR	29.3% (54/184)	40.4% (42/104)	0.068
Major Target Limb Amputation	0.5% (1/184)	0.0% (0/104)	1.000
Thrombosis	2.2% (4/184)	4.8% (5/104)	0.292

1. Safety Composite Endpoint consists of: freedom from device/procedure related death to 30 days; freedom from target limb amputation within 60 months; and freedom from clinically-driven TVR within 60 months.
2. Composite of death, clinically-driven TVR, target limb major amputation, and thrombosis.
3. All deaths adjudicated by the CEC.

† P-values are based on Fisher's exact test for superiority with significance level of 0.05.

IN.PACT SFA Trial

No Device or Procedure-related Deaths

All-cause Death Through 5 Years			CEC-Adjudicated	
	DCB (N=184)	PTA (N=104)	Device-related	Procedure-Related
Cardiac-related	3.3% (6)	1.0% (1)	No	No
Malignancy-related	2.7% (5)	3.9% (4)	No	No
Respiratory-related	1.6% (3)	0.0% (0)	No	No
Neurological-related	2.2% (4)	0.0% (0)	No	No
Hepatobiliary-related	0.5% (1)	0.0% (0)	No	No
Gastrointestinal-related	1.6% (3)	1.9% (2)	No	No
Renal-related	0.5% (1)	0.0% (0)	No	No
Infection-related	1.1% (2)	0.0% (0)	No	No
Other	0.5% (1)	1.9% (2)	No	No
Unknown	1.6% (3)	1.0% (1)	No	No

Categorized by system-class

Dec 6th 2018…
DCB increase risk of death!

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 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.

Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. 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. J Am Heart Assoc. 2018 Dec 18;7(24):e011245

Background

- Recent JAHA meta-analysis of summary-level published and presented studies raised concerns about paclitaxel devices for the treatment of femoropopliteal disease.[1]

- JAHA meta-analysis demonstrated higher risk of mortality at 2 years and 5 years in the paclitaxel arms of RCTs, attributed to paclitaxel exposure.[1]

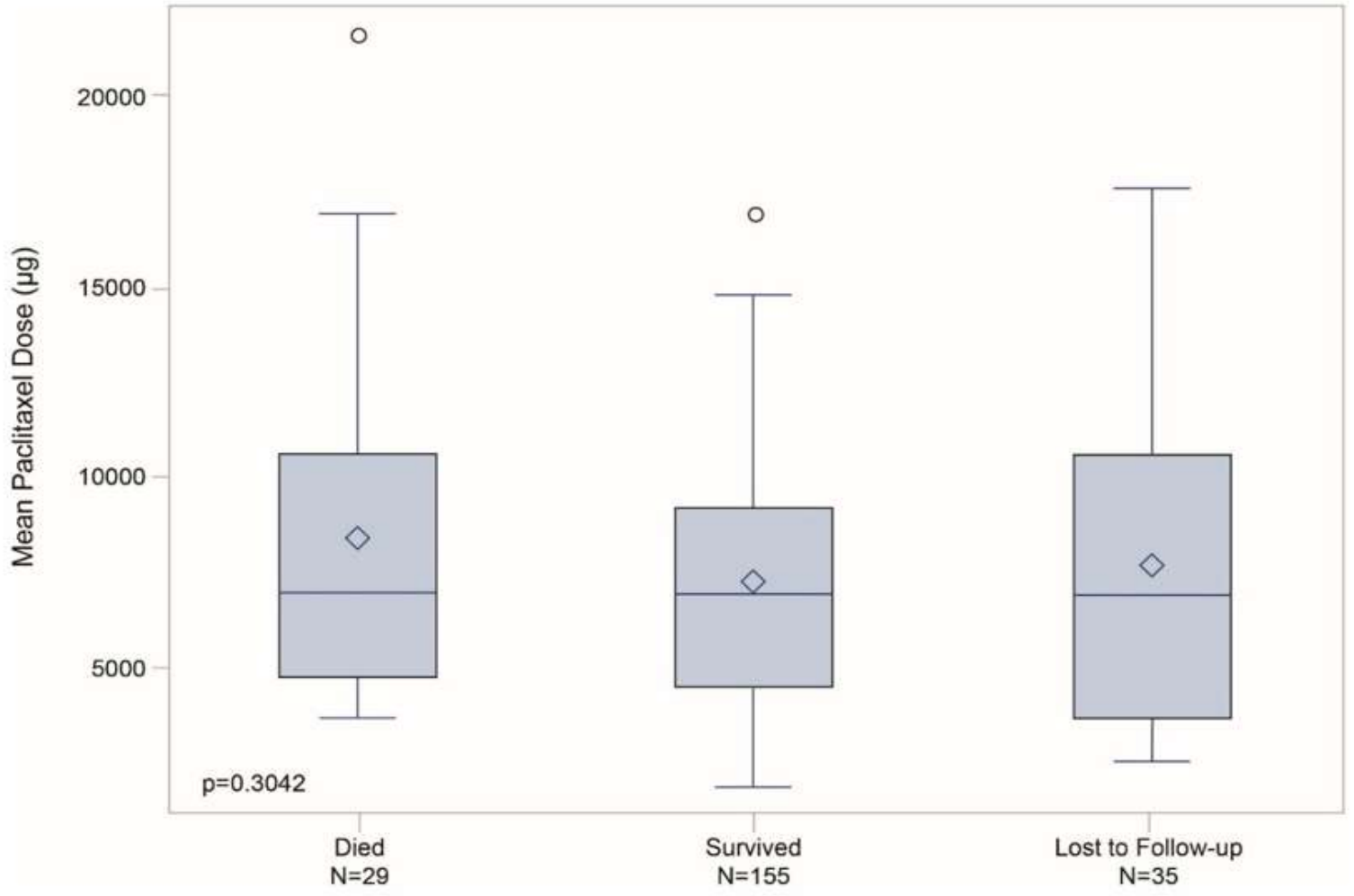
- Evidence from individual DCB and DES RCTs demonstrates safety of these devices with mortality that is comparable to rates in epidemiology studies of similar patient populations and other vascular device trials.[2-7]

- Individual patient-level analysis on 1980 patients from IN.PACT Clinical program was conducted to investigate any potential connection between paclitaxel and mortality.

1. Katsanos K, et al. Journal of the American Heart Association 2018; 7: e011245.
2. Dake M. et al. Circulation. 2016;133:1472-83.
3. Kruse R, et al.. J Endovasc Ther. 2015;22:855-61.
4. Shammas NW, et al. J Invasive Cardiol. 2017;29:207-208.
5. Stavroulakis K,et al.. J Endovasc Ther. 2015;22:31-7.
6. Caro J, et al. BMC Cardiovasc Disord. 2005;5:14.
7. Mueller T, et al. J Vasc Surg. 2014;59:1291-9.

IN.PACT SFA Trial through 5 Years

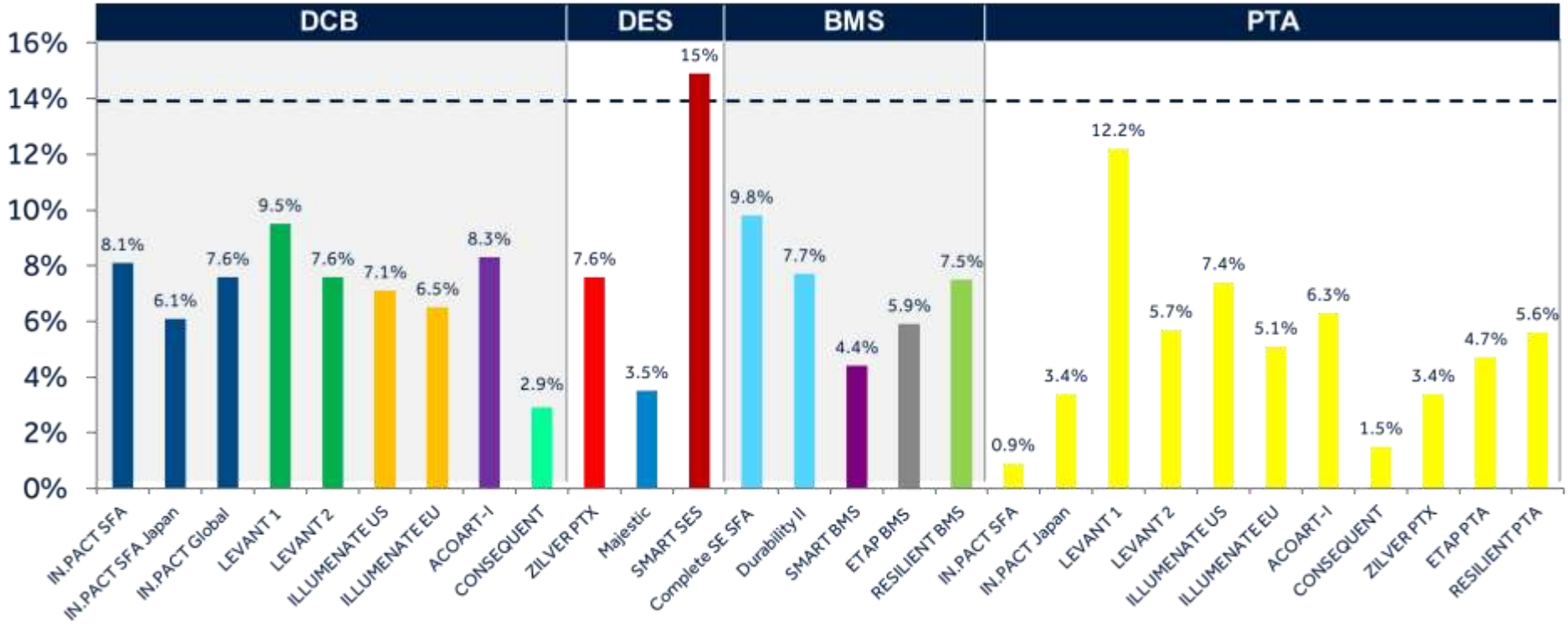
No Relationship between Paclitaxel Dose and Mortality Rate



o = outlier ◊ = mean

Mortality Rates From Trials of SFA Therapy

All-Cause Death at 2 Years



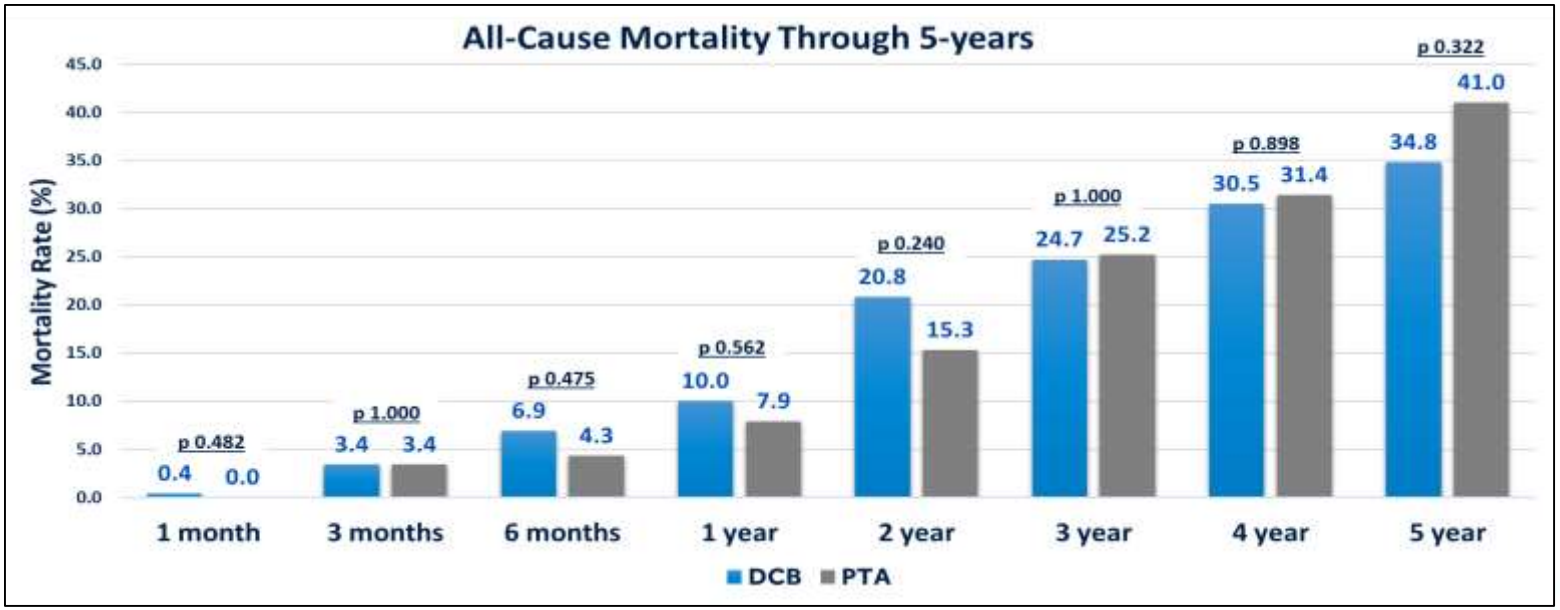
IN.PACT SFA	Laird J, et al., J Am Coll Cardiol 2015: 66; 2329-38.
IN.PACT Japan	Presented by Iida, O. LINC 2018, Leipzig Germany.
IN.PACT Global	Micari A, et al., J Am Coll Cardiol –Cardiovasc Interv 2018: 11; 945-53.
LEVANT 1	Scheinert D, et al., J Am Coll Cardiol - Cardiovasc Interv 2014: 7; 10-19.
LEVANT 2	Lutonix IFU.
ILLUMENATE US	Presented by Mathews S, NCVH 2018, New Orleans, USA.
ILLUMENATE EU	Presented by Schroder H, CIRSE 2017, Copenhagen, Denmark.
ACOART-I	Presented by Guo W, LINC 2017, Leipzig, Germany.
CONSEQUENT	Albrecht T, et al., Cardiovasc Intervent Radiol 2018: 41; 1008-14.
ZILVER PTX	Dake M, et al., J Am Coll Cardiol 2013: 61; 2417-27.
Majestic	Muller-Hulsbeck S, et al., Cardiovasc Interv Radiol 2017:40;1832-1838.
SMART SES	Duda et al., J Endovasc Ther 2006: 14; 701-710.
SMART BMS	Duda et al., J Endovasc Ther 2006: 14; 701-710.
Complete SE SFA	Data on file. Medtronic, Inc.
Durability II	Rocha-Singh K, et al., Cather Cardiovasc Interv 2015 : 86; 164-170.
ETAP BMS	Rastan A, et al., J Endovasc Ther 2015: 22; 22-27.
RESILIENT BMS	LifeStent IFU. Revised 2/04-16.
Dashed Line:	Caro J, et al., BMC Cardiovasc Disord. 2005;5:14.

Do We Have a Safety Problem With Paclitaxel?

IN.PACT DEEP Trial: Key Safety Outcomes Through 5 Years

IN.PACT Amphirion BTK DCB was recalled because of a lack of effectiveness and a trend of higher amputations in the DCB group. The fully enrolled trial included patient follow-up through 5 years.

	IN.PACT DEB (n = 239 Subjects)	Standard PTA (n = 119 Subjects)	P-value
Primary Composite Endpoint	57.1% (120/210)	55.2% (58/105)	0.810
Major Adverse Event[1]	62.4% (131/210)	58.1% (61/105)	0.465
Death, any	34.8% (73/210)	41.0% (43/105)	0.322

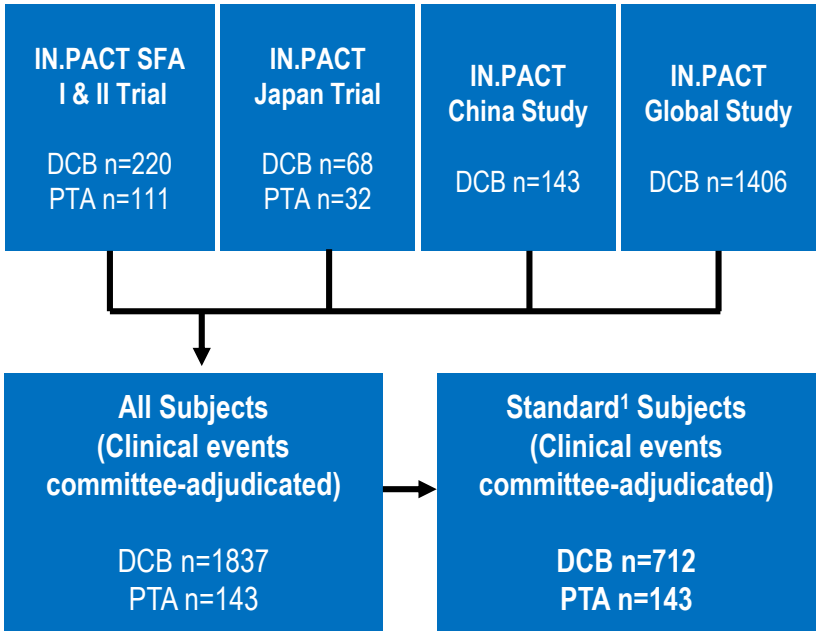


1. Death of any Cause, Major and Minor Amputation of target limb.

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

Independently conducted by the Baim Institute (formerly Harvard Clinical Research Institute)

Objective: Determine if there is a correlation between paclitaxel exposure and mortality by conducting an independent patient-level meta-analysis of 1,980 patients with up to five-year follow-up.



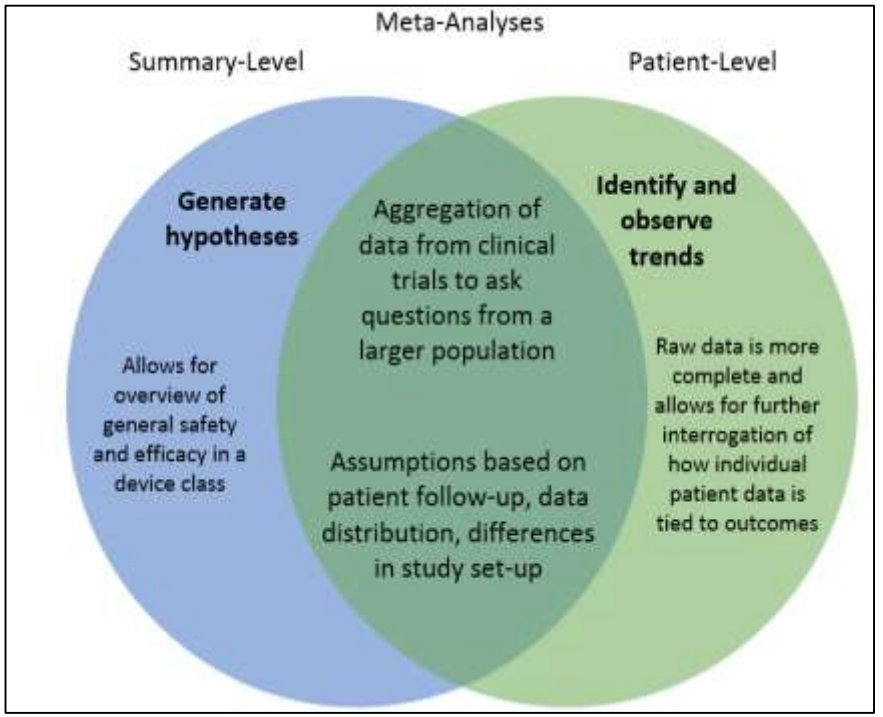
Analysis Conducted

1. Review of baseline, procedure, and follow-up data of individual patients.
2. Comparison of Survival vs. Mortality between treatment group.
3. Nominal dosage (mg) between Survival and Mortality (DCB n=1837).
4. Testing for alternative hypothesis.

1. The Standard criteria was established using similar definition as the IN.PACT SFA, IN.PACT Japan, and IN.PACT China studies which included simple, single de novo lesion ≤ 20 cm, Ca+ (none to mild) and excluded ISR.

IN.PACT Clinical Program: Patient-Level Meta-Analysis
Key Differences from JAHA Meta-analysis

- Inclusion of complete IN.PACT Clinical Program
  - 2 Single-arm Trials, IN.PACT Global & IN.PACT China and 2 RCTs (IN.PACT SFA and Japan), larger data set
  - JAHA used only RCTs (IN.PACT SFA, IN.PACT Japan)
- Inclusion of raw patient-level data across studies
  - Access to patient narratives, time to events, comorbidities, DCB usage, mortality adjudication
  - Paclitaxel dose calculated per patient, rather than per study
- Inclusion of complete data set with additional available longer-term data from IN.PACT RCT
  - IN.PACT SFA 5-year data, IN.PACT JAPAN 3-year data
  - JAHA utilized unpublished 4-year IN.PACT SFA, and 2-year IN.PACT Japan data



IN.PACT Clinical Program: Patient-Level Meta-Analysis
Key Baseline Characteristics

Overall Cohort[1]			
	IN.PACT™ Admiral™ DCB (n = 1837 patients)	PTA (n = 143 patients)	P-value
Age (yrs)	68.5±9.8 (1827)	69.4±9.0 (143)	0.279
Male	68.2% (1253/1837)	70.6% (101/143)	0.577
Carotid Artery Disease	22.3% (356/1597)	28.0% (37/132)	0.131
Coronary Heart Disease	42.8% (751/1755)	53.9% (76/141)	0.013
Diabetes Mellitus	41.2% (755/1833)	50.3% (72/143)	0.035
Renal Insufficiency[2]	10.2% (168/1645)	7.8% (11/141)	0.464
Rutherford Category			0.016
1	0.1% (1/1834)	0.0% (0/143)	
2	34.1% (625/1834)	42.7% (61/143)	
3	55.6% (1019/1834)	51.7% (74/143)	
4	8.3% (153/1834)	4.9% (7/143)	
5	2.0% (36/1834)	0.7% (1/143)	

1. Shishehbor M. Total IN.PACT All-Subjects Pooled 1-Year Analysis. VIVA, Las Vegas, USA 2018.
2. Baseline serum creatinine ≥ 1.5.

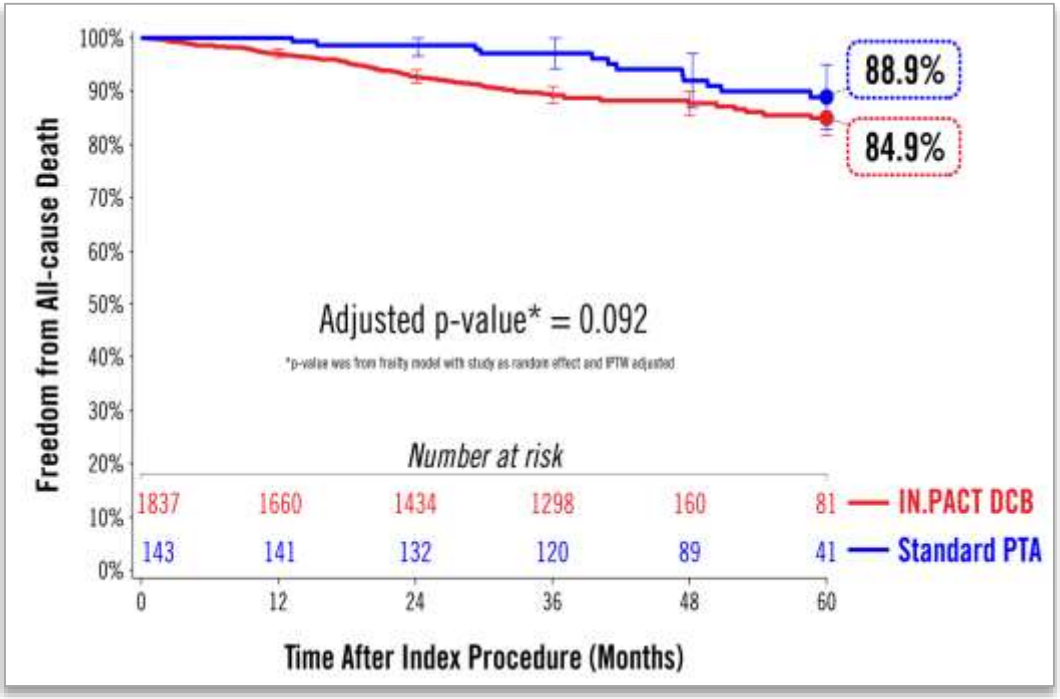
IN.PACT Clinical Program: Patient-Level Meta-Analysis
Key Baseline Lesion & Procedural Characteristics

Overall Cohort[1]			
Lesion/Procedural Characteristics[2]	**IN.PACT™ Admiral™ DCB (n = 1837 Subjects) (n = 2204 Lesions)**	**PTA (n = 143 Subjects) (n = 143 Lesions)**	**P-value**
Lesion Characteristics			
Lesion Type			
De Novo	78.5% (1730/2204)	95.8% (137/143)	<.001
Restenotic (non-stented)	7.0% (154/2204)	4.2% (6/143)	0.233
In-stent restenosis	18.0% (320/1773)	0%	
Lesion Length (cm)	11.53 ± 8.91	9.55 ± 4.86	<.001
Calcification	67.4% (1445/2145)	56.6% (82/145)[3]	0.011
Occluded Lesion (CTO)	35.3% (778/2204)	16.1% (23/143)	<.001
Procedural Characteristics			
Provisional Stent	20.7% (378/1828)	10.5% (15/143)	0.002

1. Shishehbor M. Total IN.PACT All-Subjects Pooled 1-Year Analysis. VIVA, Las Vegas, USA 2018.
2. Site reported.
3. Two subjects/lesions were assessed by sites as having tandem lesions but angiographic core lab considered as two different lesions.

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

Mortality Through 5 Years for All DCB vs PTA



5-Years	IN.PACT™ Admiral™ DCB (n = 1837)	PTA (n = 143)	P-value[1]
All-cause Mortality	15.1% (181)	11.2% (12)	0.092

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

IN.PACT Clinical Program: Patient-Level Meta-Analysis
Nominal Paclitaxel Dosage at Index Procedure

No difference in mean nominal dose of paclitaxel between DCB patients who died vs survived.

Subject Characteristics	Death (n = 181 Subjects)	Survival (n = 1656 Subjects)	P-value
Nominal Delivered Paclitaxel Dose[1]			
n	181	1655	
Mean ± SD (ug) (mg)	12202.06 ± 7721.66 12.2 ± 7.7	11368.72 ± 7371.19 11.4 ± 7.4	0.186
Lesion Length (cm), per lesion			
n	231	1973	
Mean ± SD	11.8 ± 9.3	11.5 ± 8.9	0.584

1. Nominal paclitaxel dosage calculated by taking into account the number of devices used on each individual patient at the index procedure.

IN.PACT Clinical Program: Patient-Level Meta-Analysis
Key Baseline Characteristics

DCB mortality group: older with more comorbidities

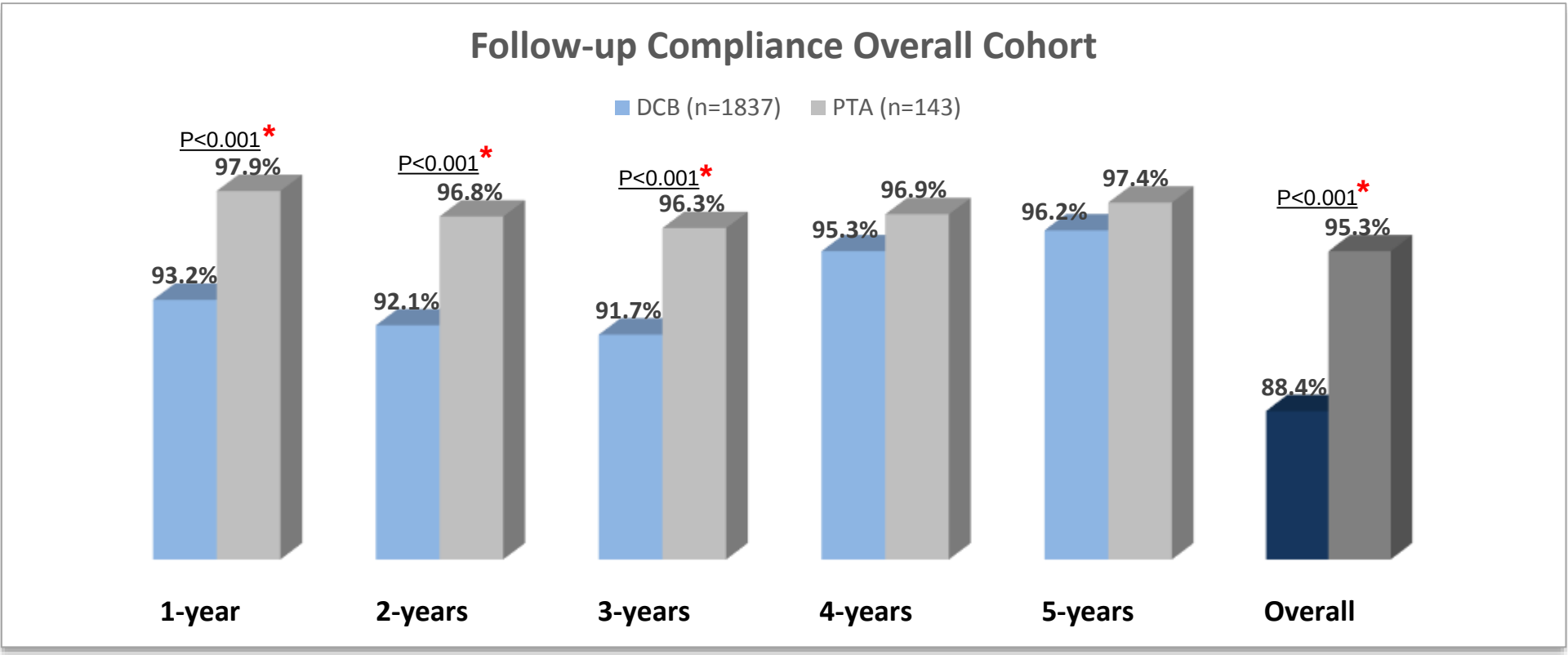
DCB Cohort			
	Death (n = 181 patients)	**Survival (n = 1656 patients)**	**P-value**
Age ± SD (yrs)	72.7±9.4 (178)	68.0±9.8 (1649)	<0.001
Carotid Artery Disease	31.5% (47/149)	21.3% (309/1448)	0.007
Coronary Heart Disease	53.5% (91/170)	41.6% (660/1585)	0.003
Diabetes Mellitus	55.0% (99/180)	39.7% (656/1653)	<0.001
Renal Insufficiency[1]	24.2% (39/161)	8.7% (129/1483)	<0.001
Below-the-knee Vascular Disease of Target Leg (Stenotic/Occluded)	57.6% (98/170)	45.2% (710/1571)	0.002
Rutherford Category			<0.001
1	0.0% (0/181)	0.1% (1/1653)	
2	24.9% (45/181)	35.1% (580/1653)	
3	57.5% (104/181)	55.4% (915/1653)	
4	13.8% (25/181)	7.7% (128/1653)	
5	3.9% (7/181)	1.8% (29/1653)	

1. Baseline serum creatinine ≥ 1.5 ng/dl.

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

Preliminary Analysis Adherence to Schedule Follow-up Visit Compliance and Mortality Risk

PTA showed significantly better compliance at the 1-, 2-, and 3-year follow-up time points compared to DCB.



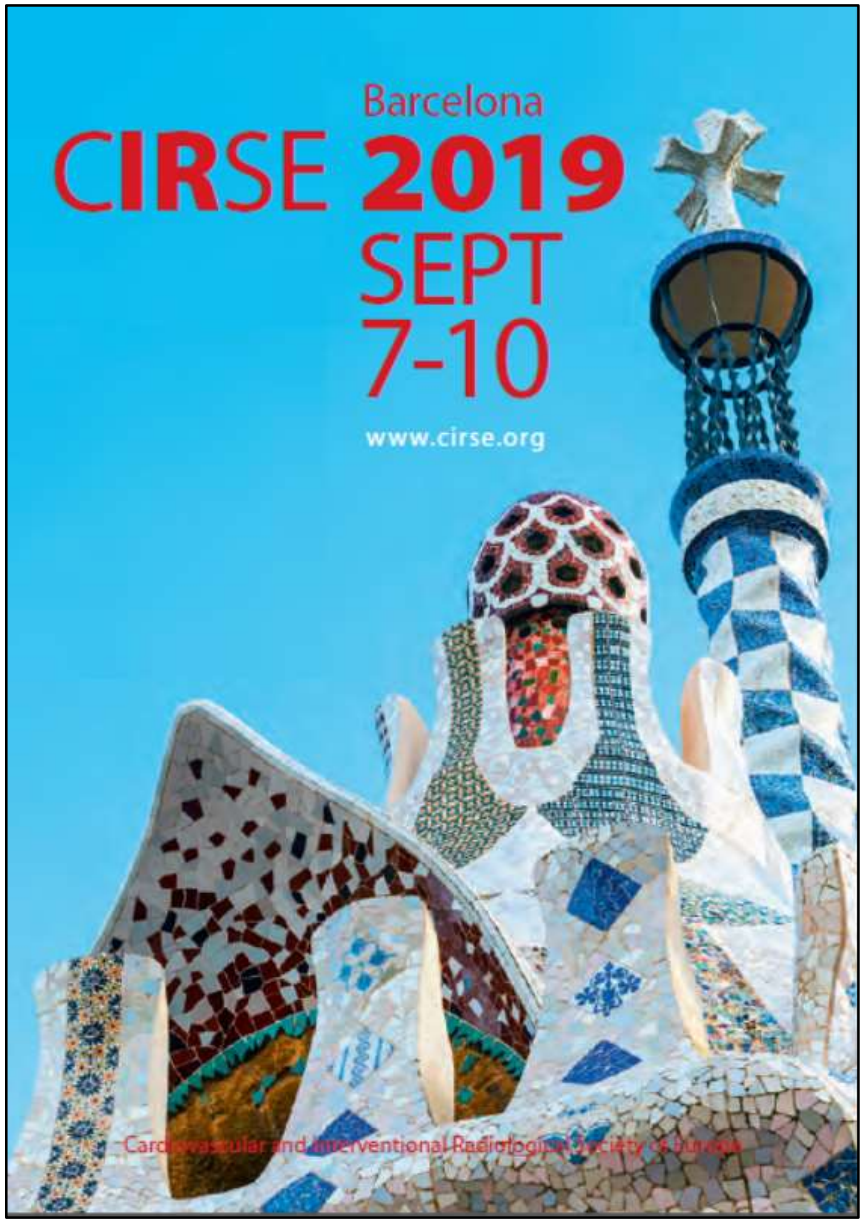
- Compliance was assessed as number of completed visits over number of expected visits through the follow-up periods.
- Follow-up schedule was pre-defined by respective study protocols.

Conclusions

- The IN.PACT Admiral Clinical Program is the largest, independently-adjudicated cohort treated with DCB for femoropopliteal disease, with data through 5 years.

- Results from this independent patient-level meta-analysis demonstrate no correlation between exposure to paclitaxel and mortality through 5 years.
  - No difference in mean paclitaxel dose by survival status
  - No difference in survival between paclitaxel dose levels (lower, mid, or upper)
  - Paclitaxel dose was NOT identified as a predictor of mortality by multivariable cox regression model
  - DCB patients that died were older and had more co-morbidities

- Alternative hypotheses: Preliminary findings suggest follow-up visit compliance (surrogate for repeat touch points with the healthcare system) is associated with lower mortality risk. This needs further evaluation.



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