Medtronic Presentation
IN.PACT™ Admiral™ Drug-Coated Balloon

Circulatory System Devices Panel Meeting
June 19-20, 2019

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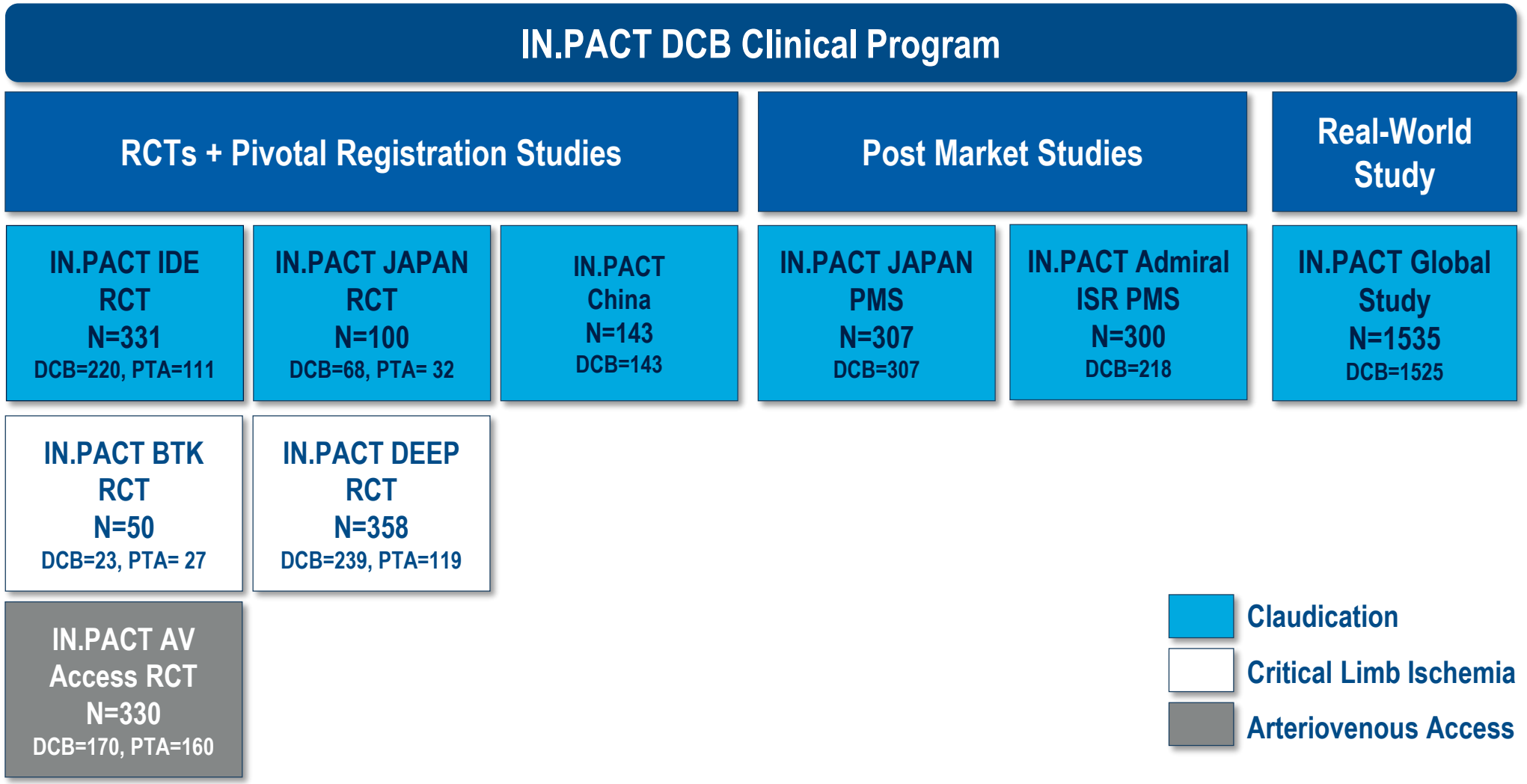
Introduction

Simona Zannetti, MD
Vice President Clinical Research, Medical Affairs, and Medical Education
Aortic, Peripheral, and Venous
Medtronic

IN.PACT CLINICAL PROGRAM: ~ 3000 PATIENTS TREATED WITH IN.PACT DCB ACROSS 9 TRIALS



All studies incorporated independent core laboratory and clinical events committee (CEC) adjudication

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MEDTRONIC COMMITMENT TO DCB SAFETY

- Medtronic previously published on differences in mortality in IN.PACT IDE trial at 2 and 3 years of follow-up in favor of PTA vs DCB[1]
- Medtronic recent steps
  - Independent patient-level meta-analysis to examine correlation of paclitaxel dose and mortality (N=1980)[2]
  - New adjudication of death and relatedness to paclitaxel by independent committee with paclitaxel toxicity expertise
  - 97% vital status data collected across IN.PACT IDE and IN.PACT Japan trials

1. IN.PACT IDE 2 Year: Laird, et al, JACC 2015; IN.PACT IDE 3 Year: Schneider, et al, Circ CI 2017
2. Schneider, et al, JACC 2019

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MULTIPLE STUDIES AND ANALYSES SUPPORT SAFETY AND EFFECTIVENESS OF IN.PACT ADMIRAL DCB

- No significant difference in mortality between IN.PACT DCB and PTA through 5 years
- No correlation between paclitaxel dose and mortality
- No paclitaxel-driven mortality signal
- Superior, consistent, and durable effectiveness across multiple randomized trials and in real-world use
- Study design and conduct might explain observed transient mortality signal

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AGENDA

IN.PACT DCB Effectiveness Analysis	**Peter A. Schneider, MD** Professor of Surgery Division of Vascular & Endovascular Surgery UCSF
IN.PACT DCB Safety Analysis	**Laura Mauri, MD, MSc** Vice President Global Clinical Research & Analytics Medtronic

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IN.PACT DCB Effectiveness Analysis

Peter A. Schneider, MD
Professor of Surgery
Division of Vascular & Endovascular Surgery
UCSF

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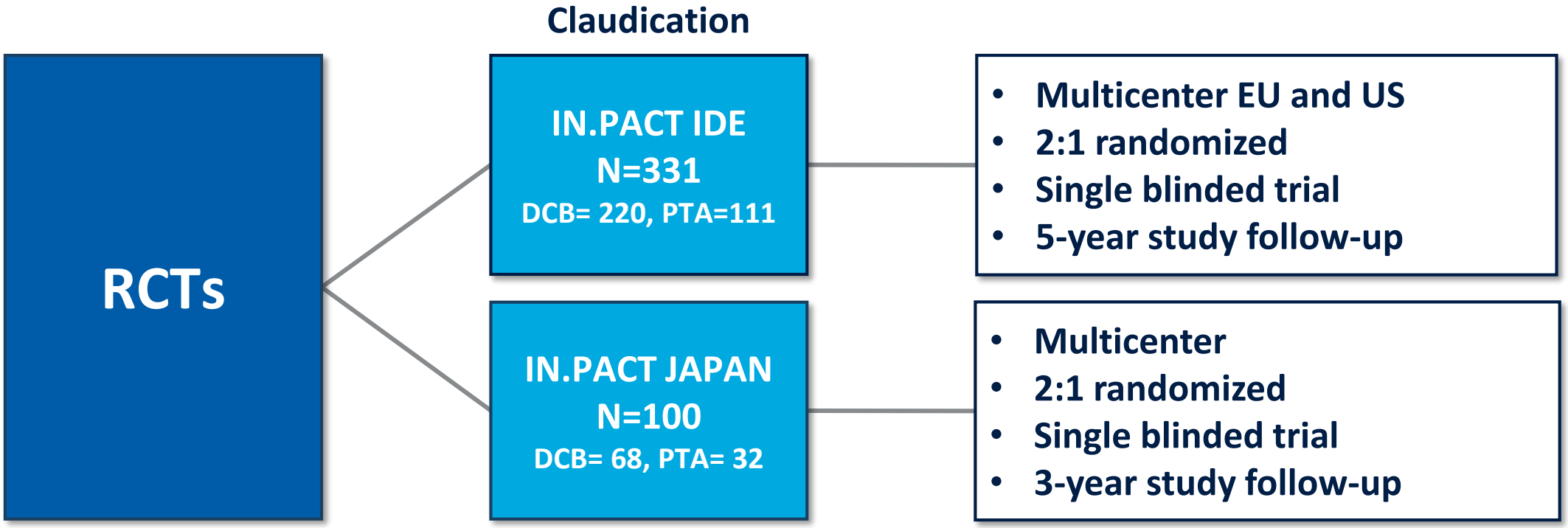
IN.PACT DCB RANDOMIZED CONTROL TRIALS



- Same inclusion criteria (with exception of maximum lesion length which was 2 cm longer for IN.PACT Japan) and same endpoints
- Same core labs, CEC, and DSMB

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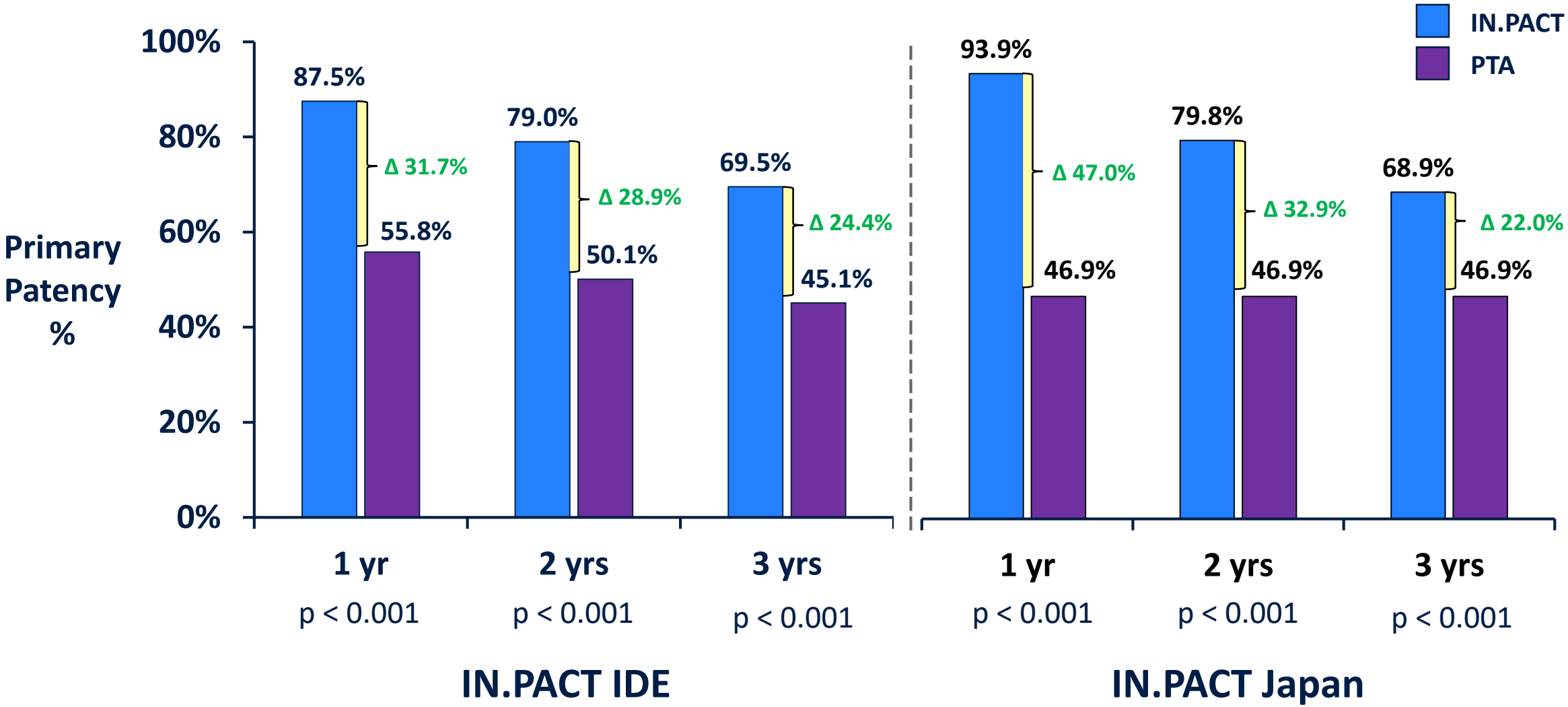
IN.PACT IDE AND JAPAN: CHARACTERISTICS OF PATIENTS ENROLLED

IN.PACT IDE and Japan	Pooled IN.PACT IDE and Japan 431 patients 434 lesions	IN.PACT IDE 331 patients 334 lesions	IN.PACT Japan 100 patients 100 lesions
Age (mean)*	69.0	67.6	73.6
Male	68.2%	65.9%	76.0%
Obesity (BMI ≥ 30 kg/m^2)*	21.3%	26.9%	3.0%
Hyperlipidemia*	81.2%	83.7%	73.0%
Diabetes*	46.6%	43.2%	58.0%
Insulin dependent diabetes mellitus	17.2%	17.5%	16.0%
Coronary heart disease	54.8%	56.3%	50.0%
Carotid artery disease*	30.0%	33.9%	17.7%
Current smoker	35.5%	37.8%	28.0%
Renal insufficiency†	8.2%	7.7%	10.0%
Lesion length (cm)	8.92	8.88	9.07
Total occlusion	21.9%	23.7%	16.0%
Severe calcification	7.6%	7.5%	8.0%

* p-value statistically significant between IN.PACT IDE and IN.PACT Japan

† Baseline serum creatinine ≥ 1.5 ng/dL

IN.PACT IDE AND JAPAN: PRIMARY PATENCY* THROUGH 3 YEARS



*Primary patency defined as freedom from CD-TLR and freedom from restenosis as determined by duplex ultrasound (DUS) Peak Systolic Velocity Ratio (PSVR) ≤ 2.4

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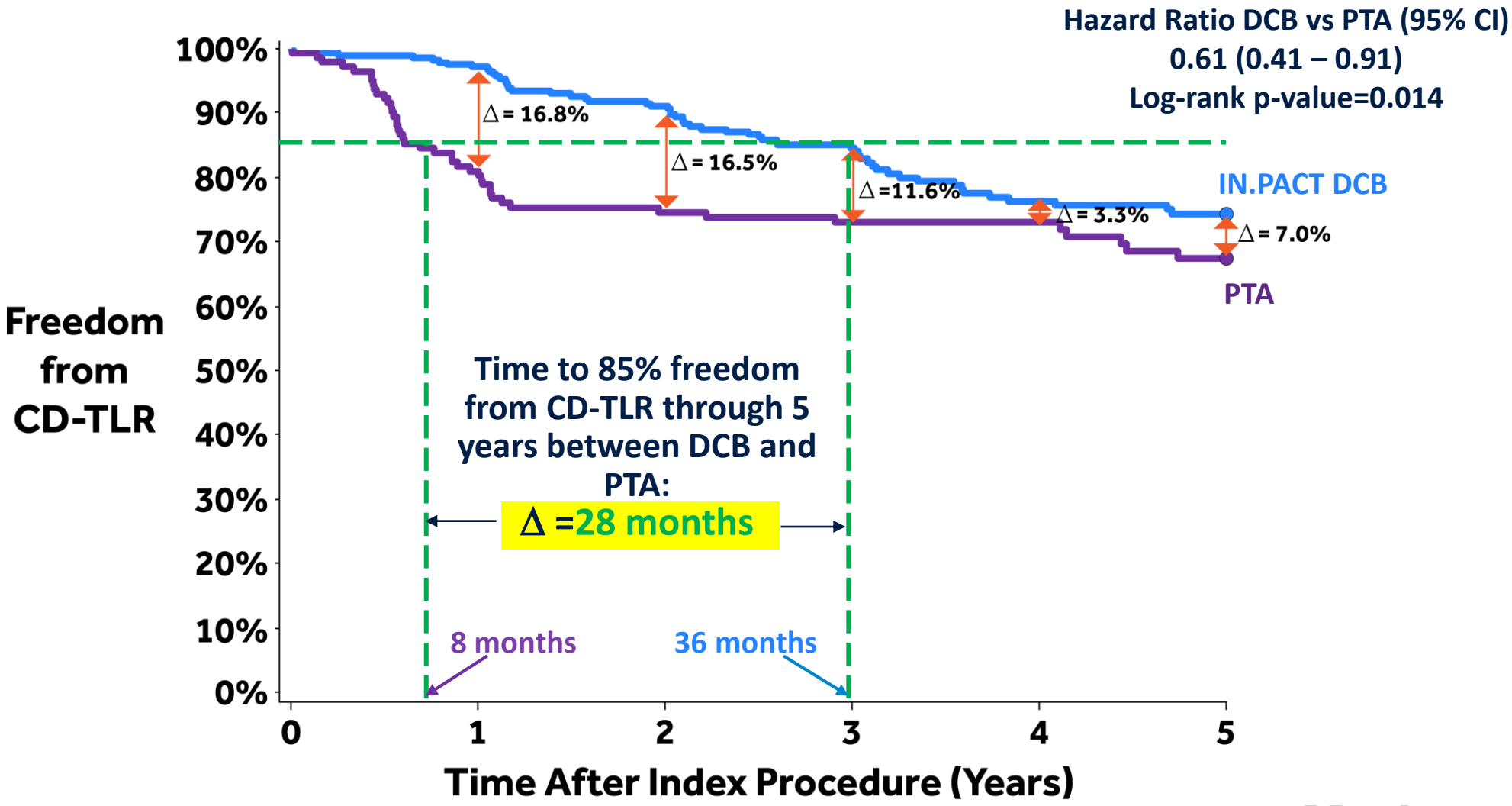
POOLED IN.PACT IDE AND JAPAN: TIME TO REINTERVENTION SUBSTANTIALLY LONGER WITH DCB vs PTA



Clinically-driven TLR adjudicated by an independent CEC, blinded to the assigned treatment based on any re-intervention at the target lesion due to symptoms or drop of ABI of ≥20% or >0.15 when compared to post-procedure baseline ABI

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EVIDENCE SUPPORTS BENEFITS WITH IN.PACT DCB

- DCBs are vast improvement over PTA
  - Integrated into standard of care
- IN.PACT DCB provides durable treatment benefit over PTA
  - 3 of 4 patients treated remain reintervention-free through 5 years
- Major step backwards will lead to more re-interventions
  - Thousands of patients likely to receive less efficacious treatments that would result in repeat interventions

IN.PACT DCB Safety Analysis

Laura Mauri, MD, MSc
Vice President, Global Clinical Research & Analytics
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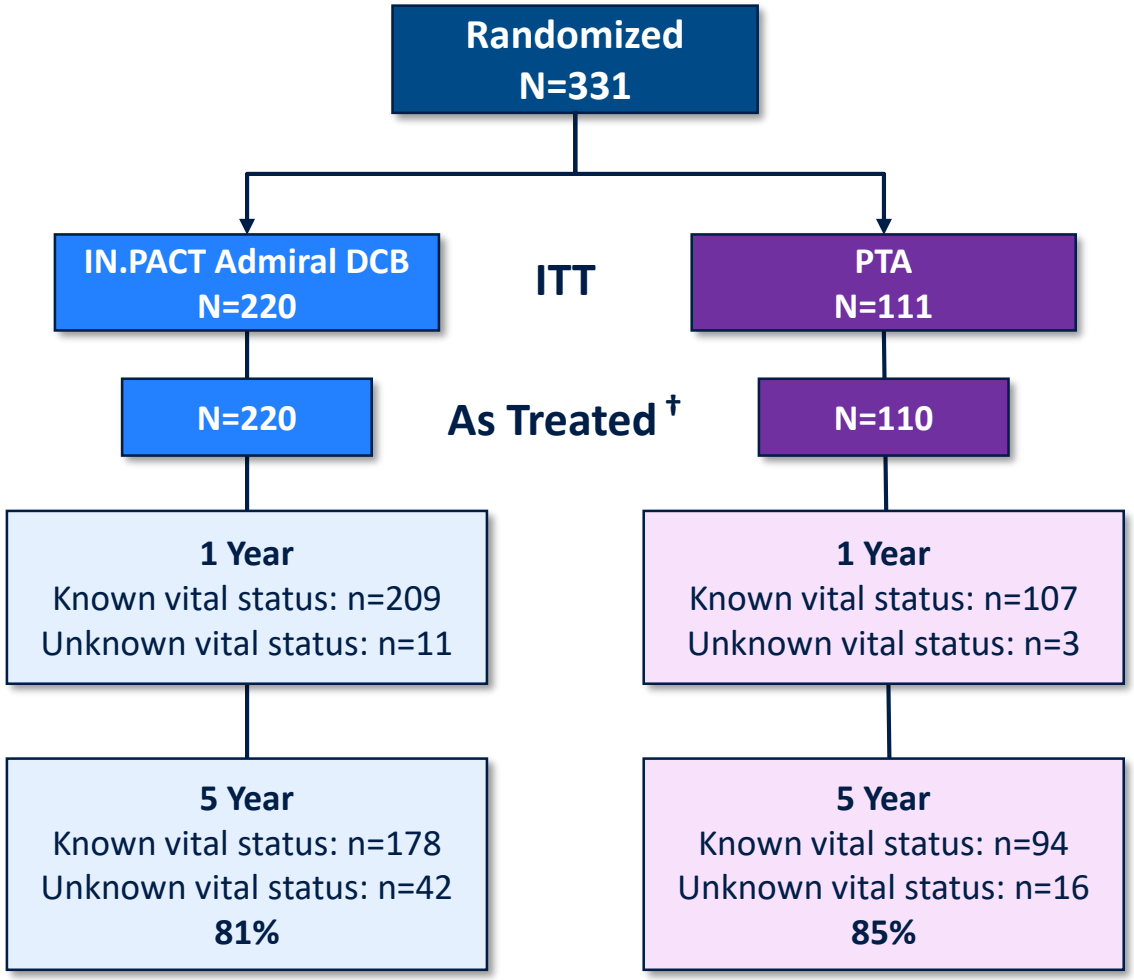
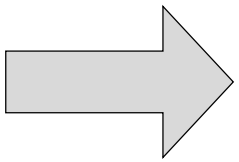
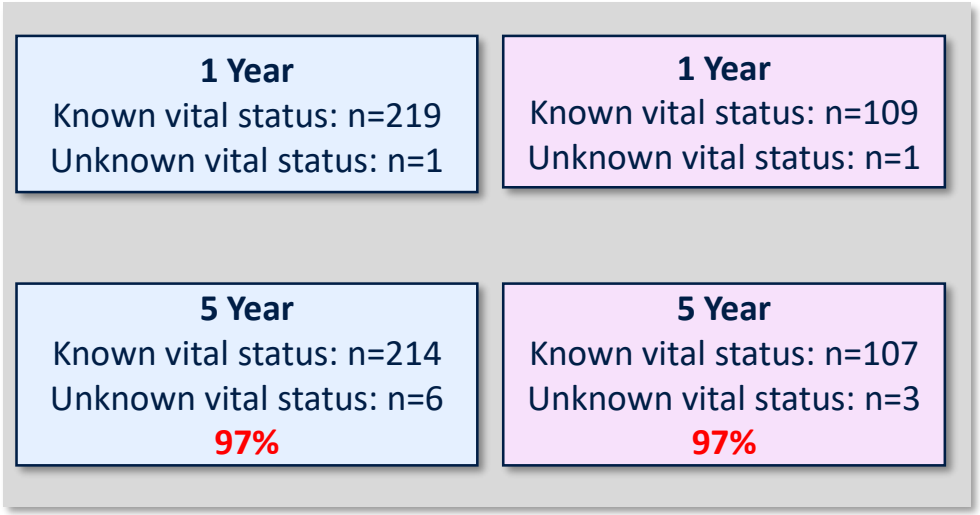
IN.PACT IDE TRIAL: UPDATED PATIENT ACCOUNTABILITY



After Vital Status Ascertainment*





†1 patient randomized to the DCB arm received PTA treatment. 1 patient randomized to the PTA arm received DCB treatment. 1 PTA patient did not receive randomized treatment.

* As of 24 April 2019

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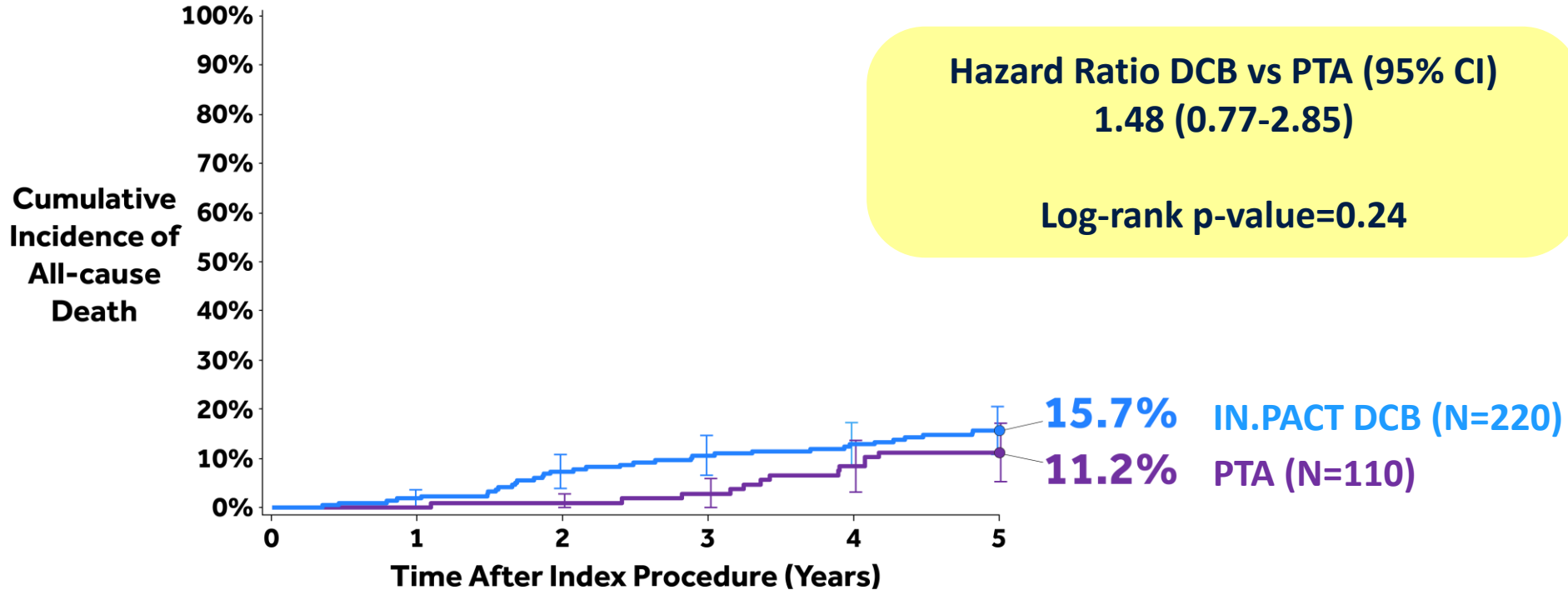
IN.PACT IDE: 5-YEAR CUMULATIVE INCIDENCE OF MORTALITY DCB vs PTA (AS TREATED)



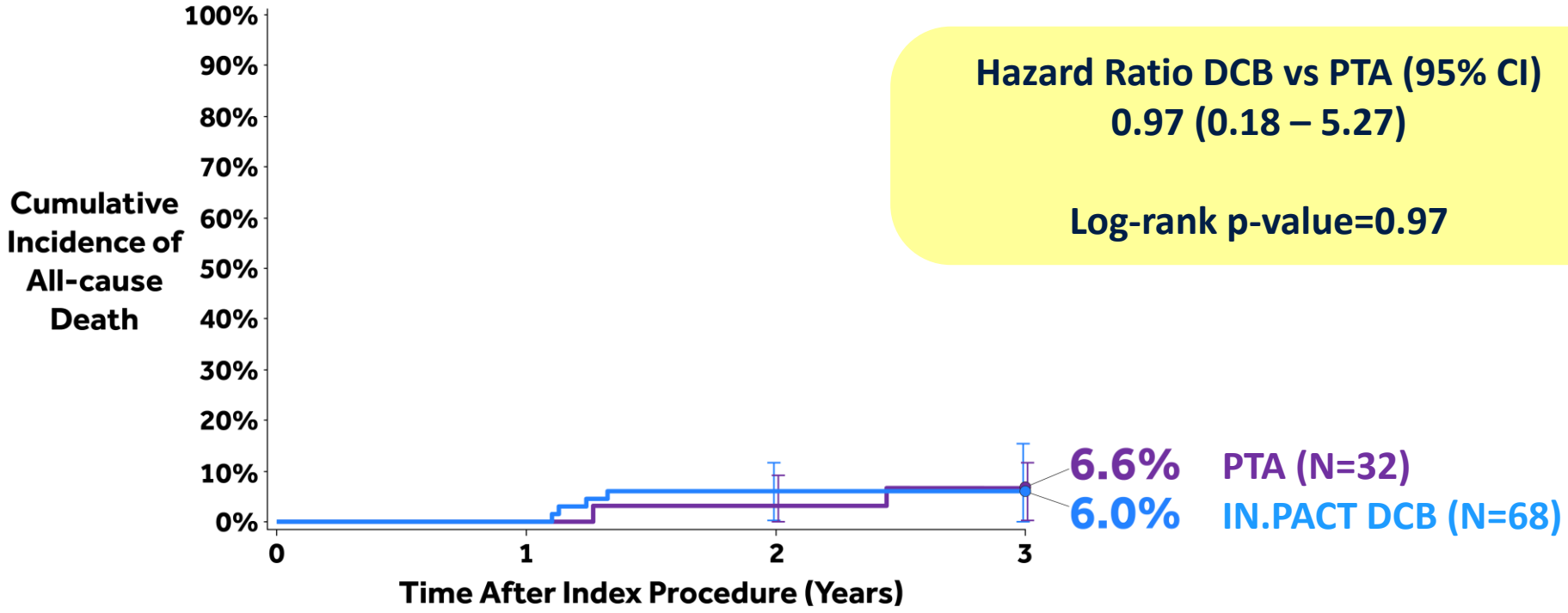
Hazard Ratio DCB vs PTA (95% CI)
1.48 (0.77-2.85)

Log-rank p-value=0.24

N at Risk						
IN.PACT DCB	220	215	203	194	186	72
PTA	110	109	107	105	98	29
Cumulative Incidence (Cumulative Deaths)						
IN.PACT DCB	0.0% (0)	1.8% (4)	7.3% (16)	10.5% (23)	12.8% (28)	15.7% (34)
PTA	0.0% (0)	0.0% (0)	0.9% (1)	2.8% (3)	8.4% (9)	11.2% (12)

- 5-year mortality cut off was 1825 days. Error bars represent 95% confidence intervals
- 7 deaths (5 DCB and 2 PTA) were reported beyond 5-year cut-off. 5 DCB deaths occurred on day 1894,1946, 2003, 2045, 2185. 2 PTA deaths occurred on day 1962, 2938

IN.PACT JAPAN: 3-YEAR CUMULATIVE INCIDENCE OF MORTALITY DCB vs PTA (AS TREATED)



Hazard Ratio DCB vs PTA (95% CI)
0.97 (0.18 – 5.27)

Log-rank p-value=0.97

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)

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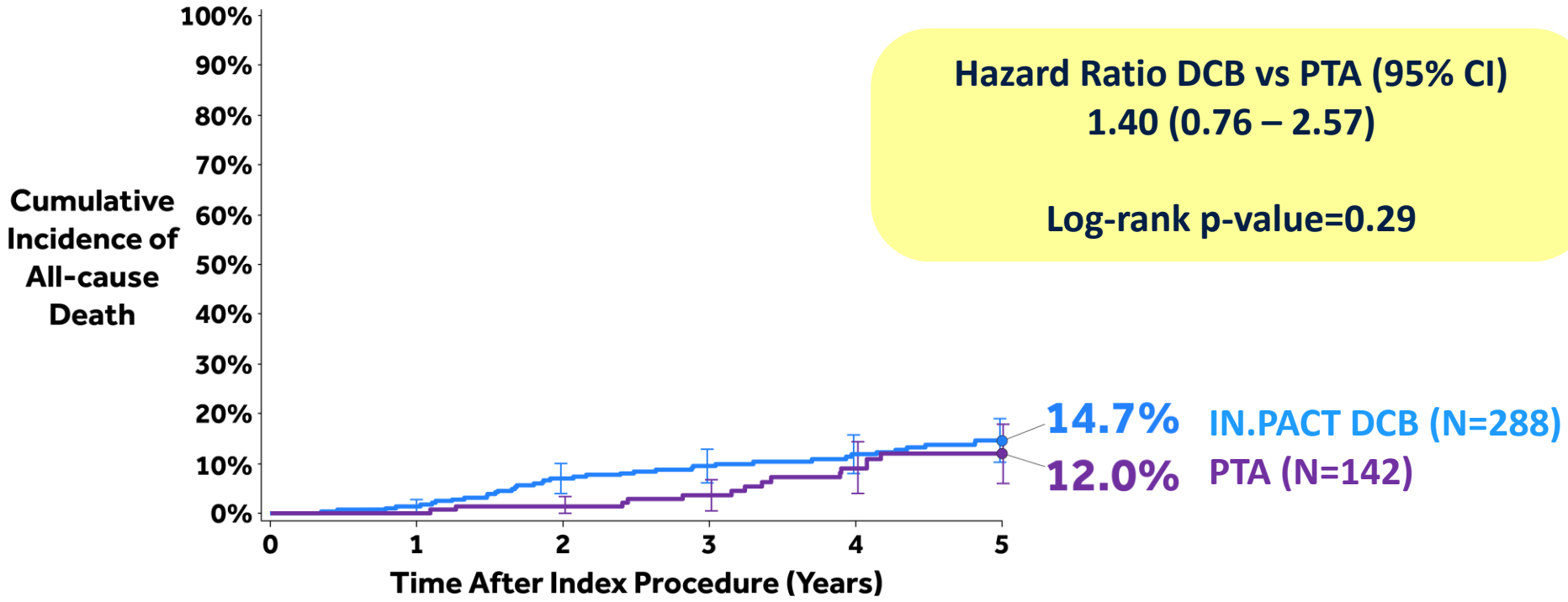
- 3-year mortality cut off was 1095 days. Error bars represent 95% confidence intervals

POOLED IN.PACT IDE AND JAPAN: 5-YEAR CUMULATIVE INCIDENCE OF MORTALITY DCB vs PTA (AS TREATED)



Hazard Ratio DCB vs PTA (95% CI)
1.40 (0.76 – 2.57)

Log-rank p-value=0.29

N at Risk						
IN.PACT DCB	288	282	265	225	186	72
PTA	142	141	135	117	98	29
Cumulative Incidence (Cumulative Deaths)						
IN.PACT DCB	0.0% (0)	1.4% (4)	7.0% (20)	9.5% (27)	11.8%(32)	14.7% (38)
PTA	0.0% (0)	0.0% (0)	1.4% (2)	3.6% (5)	9.2% (11)	12.0% (14)

- 5-year mortality cut off for IN.PACT IDE was 1825 days and for IN.PACT Japan was 1095 days. Error bars represent 95% confidence intervals
- 7 deaths (5 DCB and 2 PTA) were reported beyond the 5-year cut-off. 5 DCB deaths occurred on day 1894, 1946, 2003, 2045, 2185. 2 PTA deaths occurred on day 1962, 2938

POOLED IN.PACT IDE AND JAPAN: PACLITAXEL RELATED ADVERSE EVENTS [1] (AS TREATED)

Adverse Event[2]	1 Year		3 Years		5 Years[5]	
	DCB	PTA	DCB	PTA	DCB	PTA
Bradycardia	**0.7%** (2)	**0.7%** (1)	**1.1%** (3)	**1.5%** (2)	**2.4%** (5)	**1.5%** (2)
Neurotoxicity[3] (peripheral neuropathy)	**0.0%** (0)	**2.8%** (4)	**0.0%** (0)	**2.8%** (4)	**0.0%** (0)	**2.8%** (4)
Hematologic	**3.5%** (10)	**3.6%** (5)	**7.1%** (19)	**4.3%** (6)	**9.5%** (23)	**5.5%** (7)
Anemia	**3.5%** (10)	**2.1%** (3)	**7.1%** (19)	**2.9%** (4)	**9.5%** (23)	**4.0%** (5)
Leukopenia	**0.0%** (0)	**0.0%** (0)	**0.0%** (0)	**0.0%** (0)	**0.0%** (0)	**0.0%** (0)
Neutropenia[4]	**0.0%** (0)	**1.4%** (2)	**0.0%** (0)	**1.4%** (2)	**0.0%** (0)	**1.4%** (2)
Thrombocytopenia	**0.4%** (1)	**0.0%** (0)	**0.4%** (1)	**0.0%** (0)	**0.4%** (1)	**0.0%** (0)
Myalgia	**0.3%** (1)	**0.0%** (0)	**0.3%** (1)	**0.0%** (0)	**0.3%** (1)	**0.0%** (0)

1. Mekhail TM, Markman M. Paclitaxel in cancer therapy. Expert Opin Pharmacother 2002;3:755-66

2. Numbers are Kaplan-Meier estimate (number of patients with event)
3. Peripheral Neuropathy log-rank p-value=0.004 at 1 yr, 3 yrs and 5yrs
4. Neutropenia log-rank p-value=0.045 at 1 yr, 3 yrs, and 5 yrs. All other subgroups of Hematologic events were not significant
5. IN.PACT IDE follow-up through 5 years and IN.PACT Japan follow-up through 3 years

Note: DCB vs PTA patients were randomized in a 2:1 fashion (288 DCB vs 142 PTA)

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POOLED IN.PACT IDE AND JAPAN: CAUSE OF DEATH (AS TREATED)

Cause of Death[1]	IN.PACT DCB (N= 34)	PTA (N= 11)
Cardiovascular deaths	**4.0%** (10)	**3.2%** (3)
Acute myocardial infarction	**0.4%** (1)	**0.0%** (0)
Sudden cardiac death	**1.1%** (3)	**1.0%** (1)
Heart failure	**1.2%** (3)	**0.0%** (0)
Stroke	**0.8%** (2)	**0.0%** (0)
CV hemorrhage	**0.0%** (0)	**1.1%** (1)
Other CV cause	**0.6%** (1)	**1.1%** (1)

Cause of Death[1]	IN.PACT DCB (N= 34)	PTA (N= 11)
Non-cardiovascular deaths	**8.9%** (20)	**4.7%** (5)
Pulmonary	**0.4%** (1)	**0.0%** (0)
Renal	**0.6%** (1)	**0.0%** (0)
Gastrointestinal	**0.4%** (1)	**0.0%** (0)
Infection/sepsis (inc'l inflammatory)	**2.0%** (5)	**1.8%** (2)
Suicide	**0.7%** (1)	**0.0%** (0)
Neurological (non-CV)	**1.0%** (2)	**0.0%** (0)
Malignancy	**4.3%** (9)	**2.9%** (3)
Undetermined cause	**1.8%** (4)	**2.7%** (3)

No treatment comparisons were significant

Note: 7 additional deaths found through vital status data collection were not adjudicated as source documentation limited
Note: Numbers are Kaplan-Meier estimate (number of patients with event)

1.Hicks, et al. JACC 2018
Note: DCB vs PTA patients were randomized in 2:1 fashion (288 DCB vs 142 PTA)

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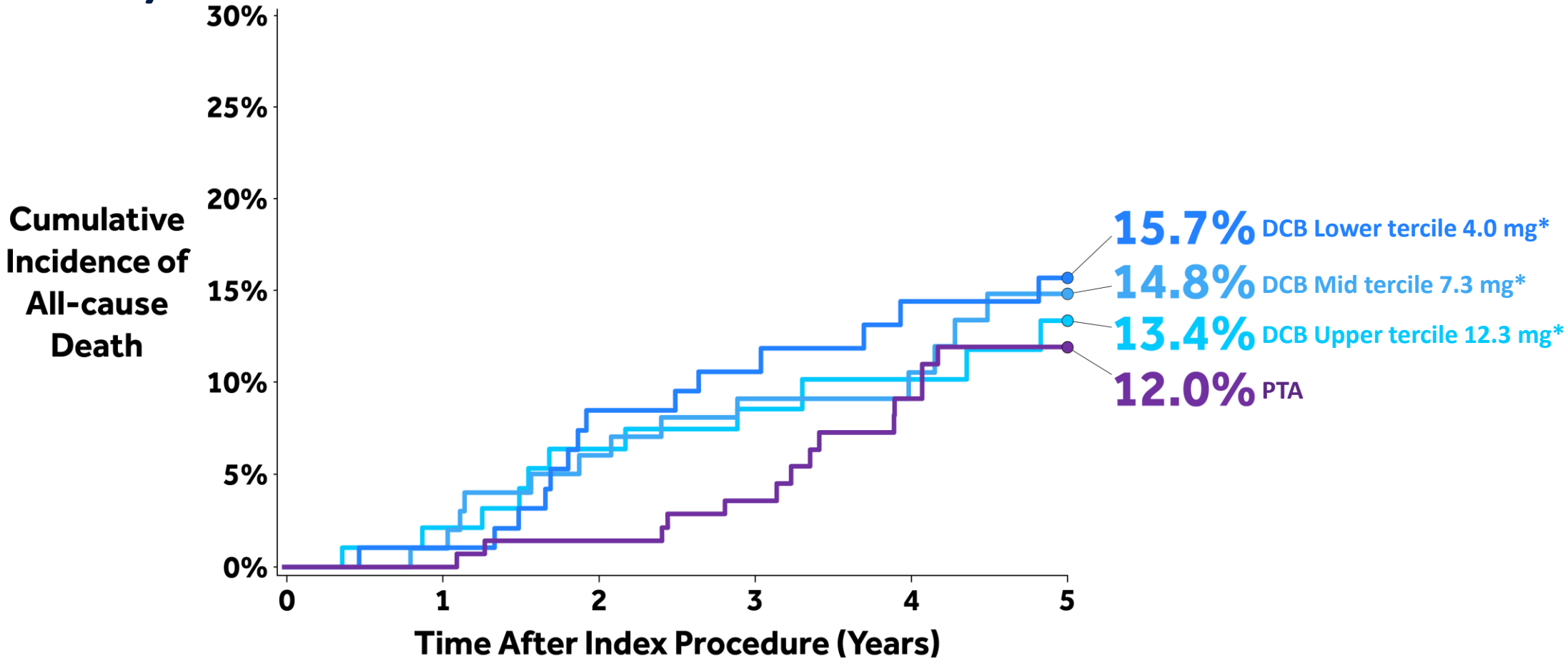
POOLED IN.PACT IDE AND JAPAN: MORTALITY BY DOSE TERCILE (AS TREATED)



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	
DCB Lower Tercile	0.0% (0)	1.1% (1)	8.5% (8)	10.6% (10)	14.4% (13)	15.7% (14)	1.50	p-value 0.73
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	

*Mean doses

POOLED IN.PACT IDE AND JAPAN: MULTIVARIABLE ANALYSIS FOR PREDICTORS OF MORTALITY

Predictors of death through 5 years[1]	Hazard Ratio (95% CI)	p-value[2]
Age (≥ 75 vs <75 yrs)	2.45 [1.37, 4.38]	0.003
Renal insufficiency (baseline serum creatinine ≥ 1.5 ng/dl) (Y vs N)	2.62 [1.28, 5.39]	0.009
Smoking (Current/Previous vs Never)	1.65 [0.86, 3.15]	0.128
Paclitaxel dose tercile in DCB (Lower vs PTA)[3]	1.61 [0.76, 3.38]	0.212
Paclitaxel dose tercile in DCB (Mid vs PTA)[3]	1.44 [0.68, 3.07]	0.344
Paclitaxel dose tercile in DCB (Upper vs PTA)[3]	1.20 [0.54, 2.64]	0.660
Treatment arm (DCB vs PTA)	1.41 [0.76, 2.60]	0.272
Paclitaxel dose (mg)	1.03 [0.97, 1.08]	0.381

1. Analysis includes both the DCB and PTA arm of trials
2. Frailty Cox model with geography (EU, US, Japan) as random effect was conducted to calculate the hazard ratio and p-value
3. The model selection p-value for dose tercile variable set is 0.621

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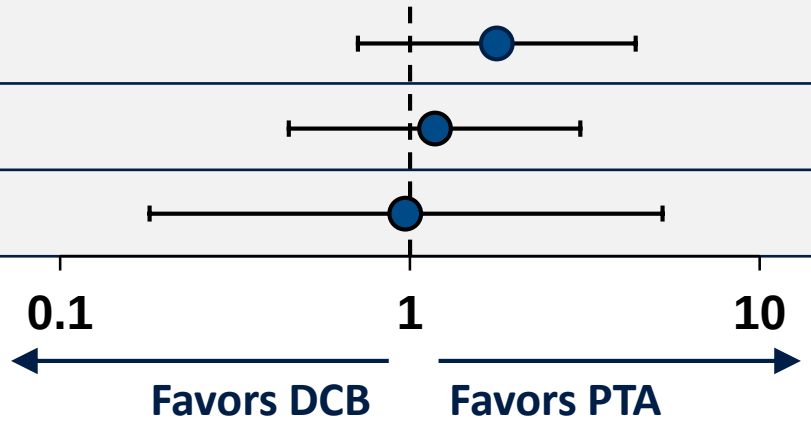
POOLED IN.PACT IDE AND JAPAN: HAZARD RATIO FOR MORTALITY BY REGION DCB vs PTA (AS TREATED)

Subgroup (N_{DCB}/N_{PTA})	IN.PACT DCB (Mortality)	PTA (Mortality)	Hazard Ratio (95% CI)	p-value for interaction*
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)	



*p-value derived from Cox Proportional Hazard model by testing treatment-by-region-interaction term

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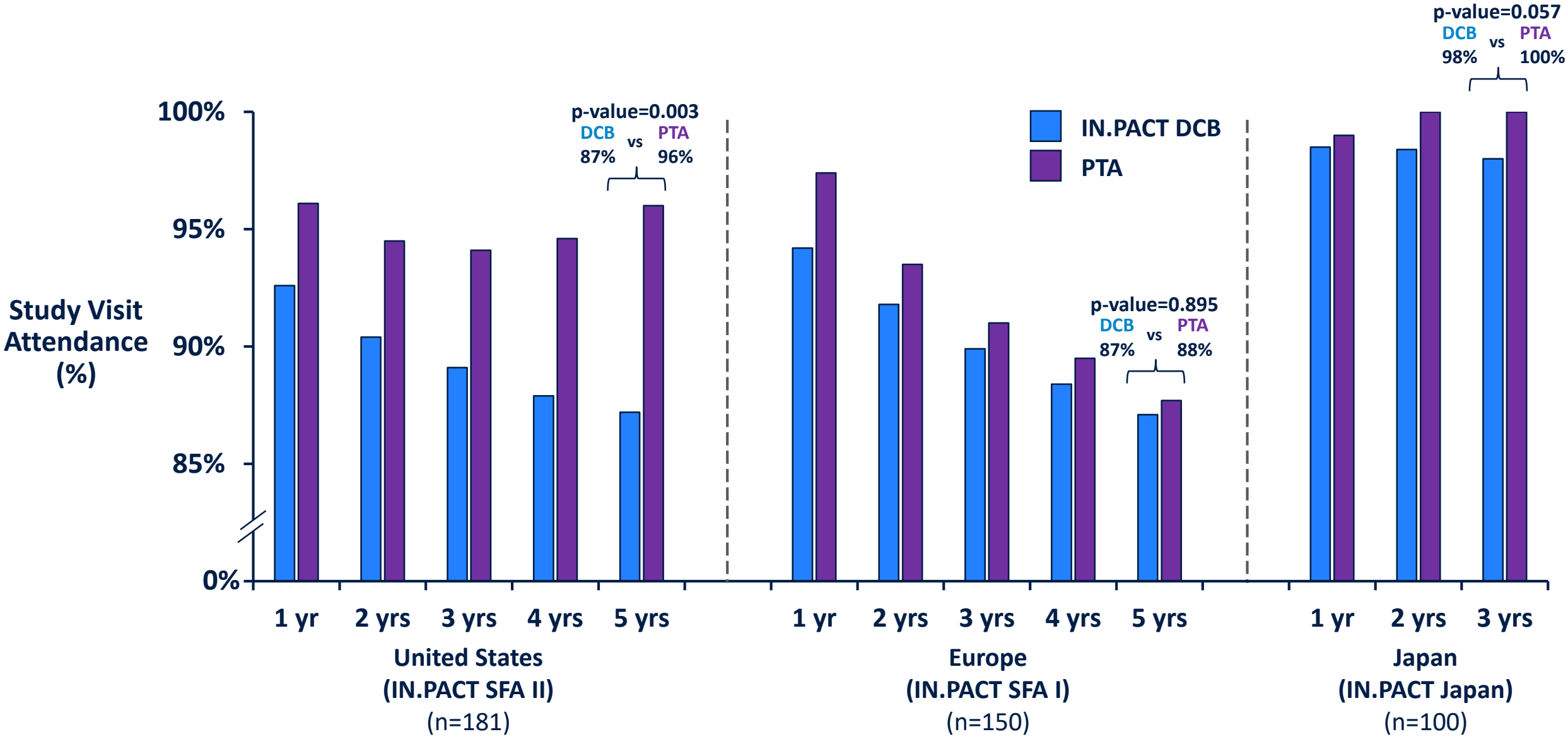
FOLLOW-UP VISIT ATTENDANCE BY REGION



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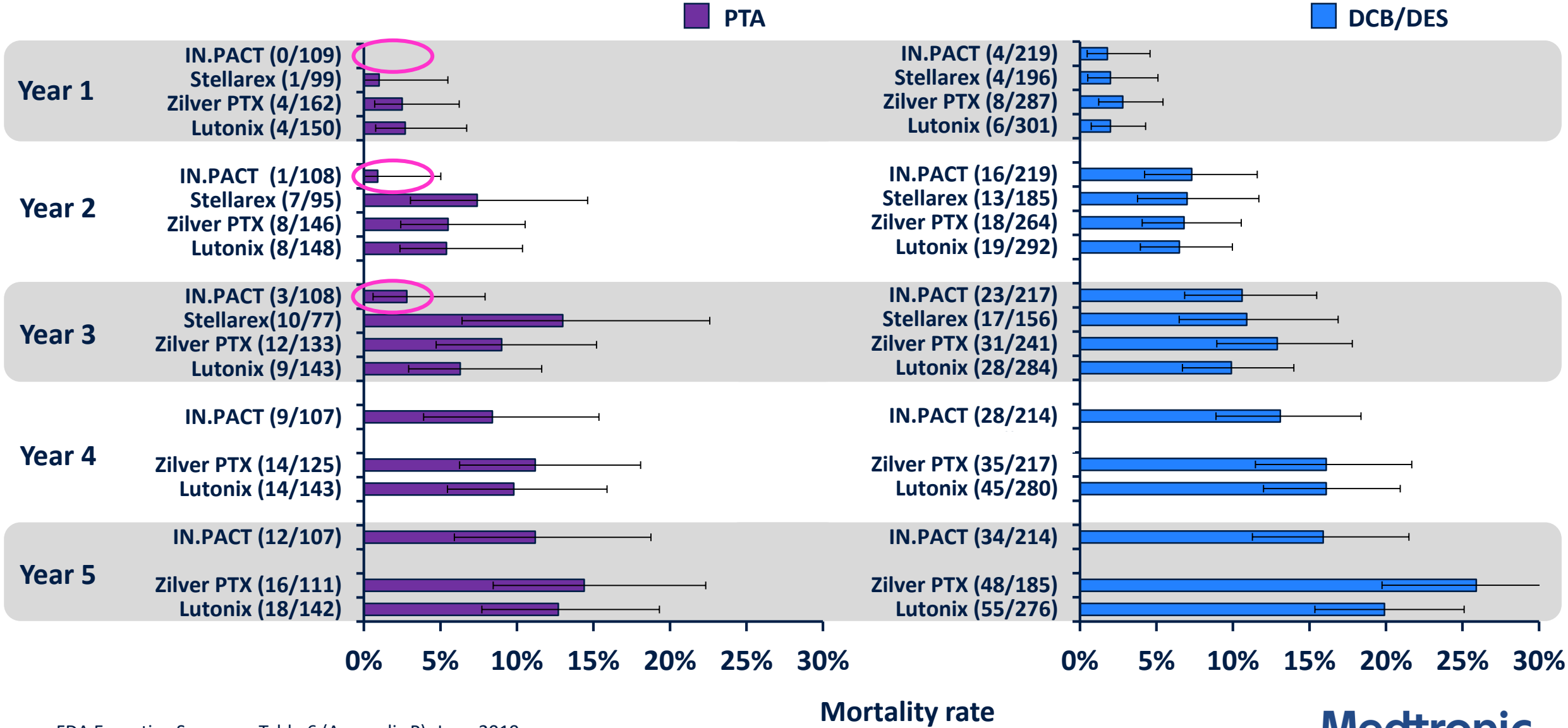
CRUDE MORTALITY RATES FOR PIVOTAL RCTs (AS TREATED)



Source: FDA Executive Summary Table 6 (Appendix P), June 2019
Proportion rate for each study are reported. Error bars are Exact Binomial 95% Confidence Intervals

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IN.PACT DCB – NO RELATIONSHIP BETWEEN PACLITAXEL EXPOSURE AND MORTALITY

- **No drug-related mortality signal**
  - No identifiable pattern of adverse events to suggest a biological mechanism
  - No dose relationship to mortality by multiple methods of investigation
- **Study design and conduct may explain transient mortality signal**
  - Biased follow-up study attendance in US patients
  - Lower than expected early PTA mortality rates because of small sample size
  - Updated vital status reduced differences between two arms at all time points
  - No significant difference in mortality at 5 years
- **Real-world comparative studies followed for sufficient duration may help to better understand long-term safety of paclitaxel products**

IN.PACT DCB IS SAFE AND EFFECTIVE WITH IMPORTANT BENEFITS

- Alleviates pain more effectively for longer duration compared with PTA
- Necessary treatment option for elderly and complex patient population
- Benefit-risk profile supports IN.PACT DCB as first line therapy for treatment of PAD

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