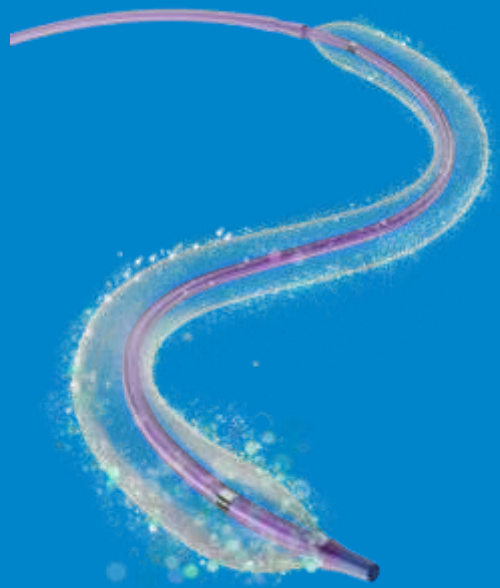
IN.PACT DCB

Science Behind the Outcomes



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UNC-REX Hospital
University of North Carolina
Raleigh, NC

Medtronic
Further, Together

DC00062713

SFA Treatment

- SFA disease remains a challenge to manage with no uniformly accepted evidence-based standard
- PTA is associated with high incidence of restenosis when used for anything but focal, noncomplex lesions
- Reported long-term patency rates with stents range from 60-75%,[1,2] but concerns persist about in-stent restenosis and stent fractures
- While drug-coated balloons (DCBs) have demonstrated promising results at 1- and 2-years in randomized trials,[3-5] long-term data for commercially available DCBs are limited.

1. Dake MD, et al. J Am Coll Cardiol 2013;61:2417-27.
2. Rocha-Singh KJ, et al. Catheter Cardiovasc Interv 2015;86: 164-70.
3. Presented by Laurich C, SVS Chicago, USA 2015.
4. Laird J, et al., J Am Coll Cardiol 2015;66:2329-38.
5. Presented by Brodmann M, VIVA Las Vegas, USA 2017.

IN.PACT DCB SFA Clinical Program

Robust Adjudicated Series of 1837 Subjects

IN.PACT DCB Clinical Program

RCTs + Pivotal Registration Studies

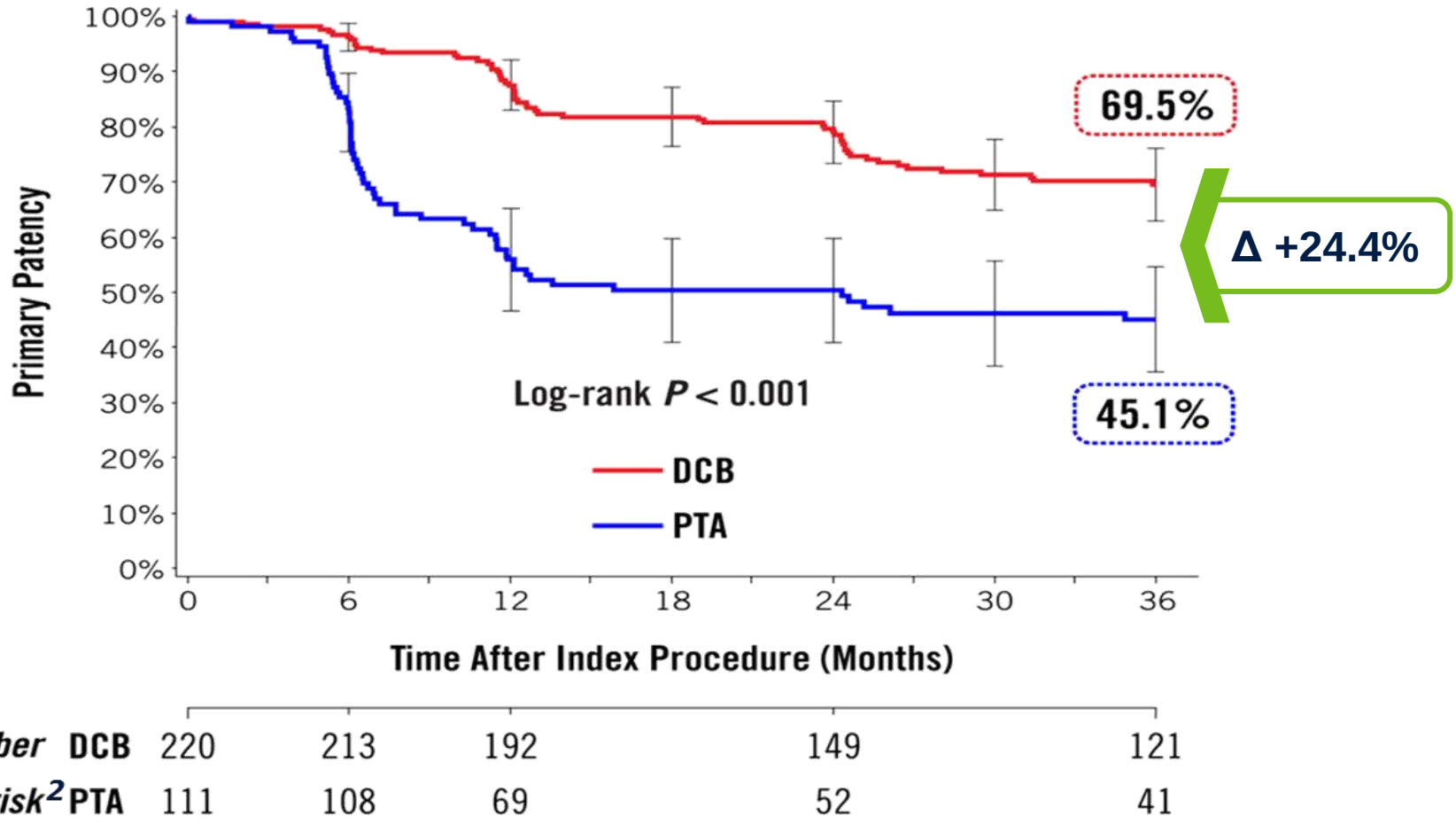
- IN.PACT SFA (EU+US) RCT[1]
  - Gender Subset
  - Diabetic Subset
- IN.PACT JAPAN RCT[1]
- IN.PACT China[1]

Real-World Study

- IN.PACT Global Study[2]
  - Pre-specified Imaging Cohorts
    - Long Lesion[1]
    - ISR[1]
    - CTO[1]
  - Regional Subset
    - Belgian
    - ASEAN

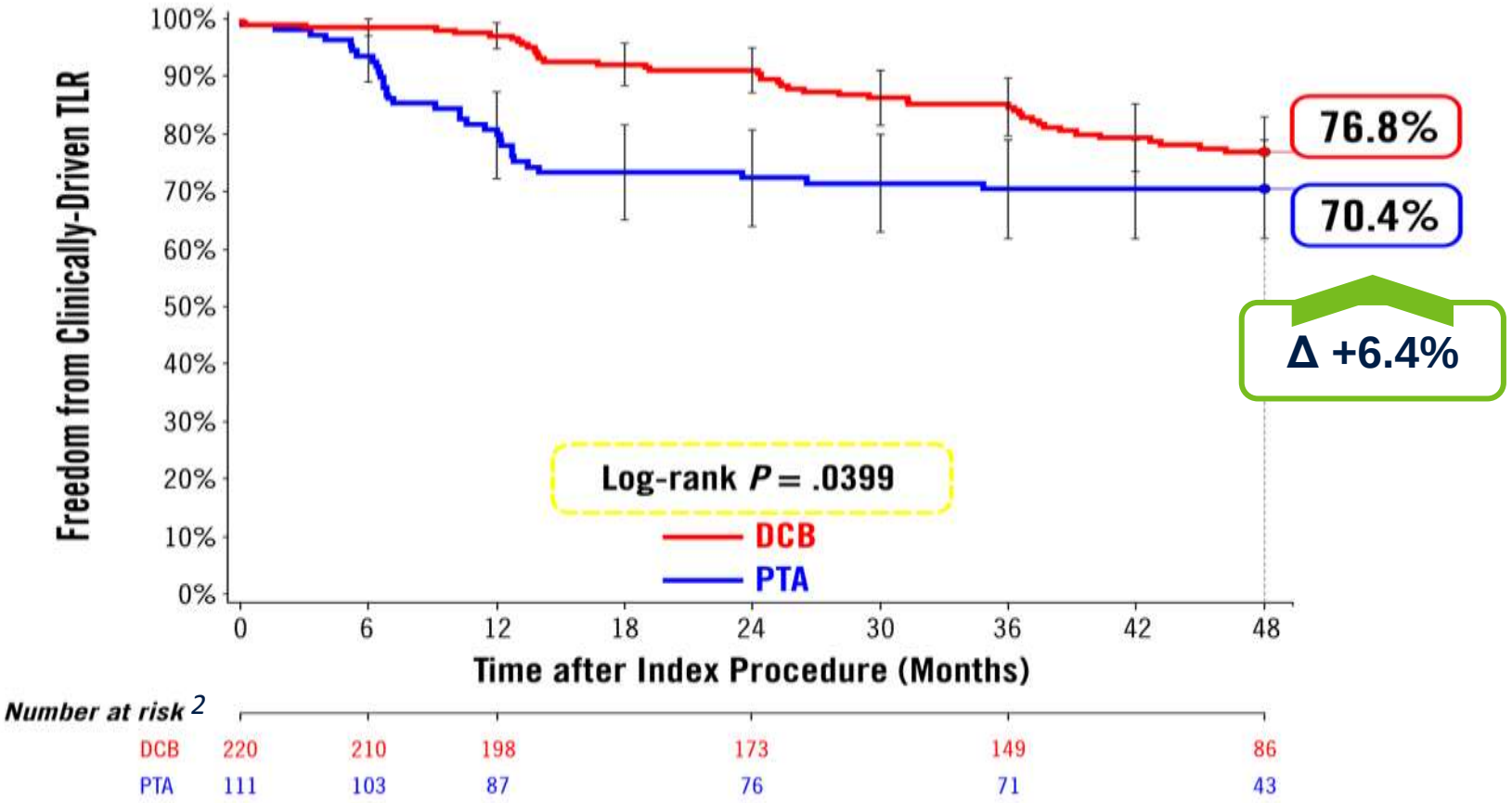
1. Core lab-adjudicated with clinical events committee oversight (IN.PACT Admiral DCB)
2. Clinical events committee oversight (IN.PACT Admiral DCB)

IN.PACT SFA Trial:
Primary Patency[1] through 3 Years



1. Freedom from core laboratory-assessed restenosis (duplex ultrasound PSVR ≤2.4) or clinically-driven target lesion revascularization through 36 months (adjudicated by a Clinical Events Committee blinded to the assigned treatment).
2. Number at risk represents the number of evaluable subjects at the beginning of each 30-day window.

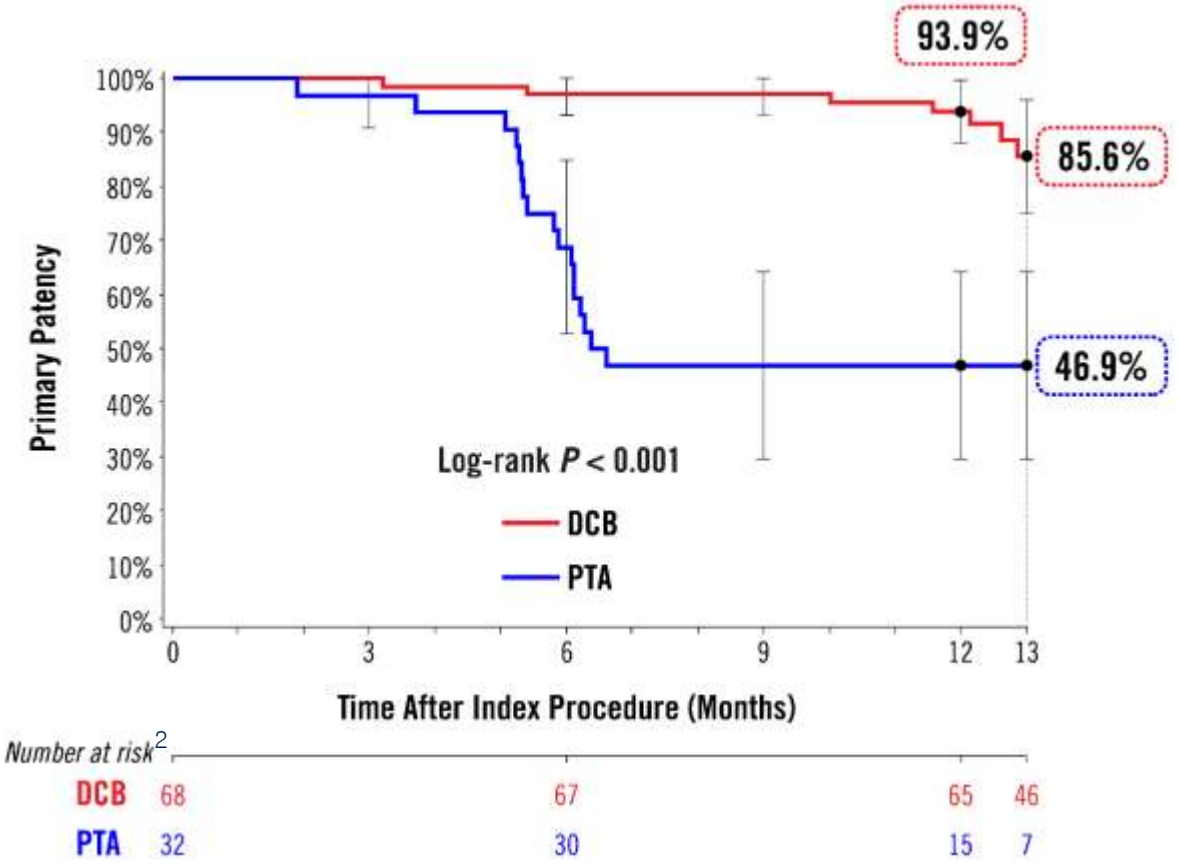
IN.PACT SFA Trial:
Freedom from CD-TLR[1] through 4 Years



1. Clinically-driven TLR adjudicated by an independent Clinical Events Committee, 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.
2. Number at risk represents the number of evaluable subjects at the beginning of each 30-day window.

MDT-2113 SFA Japan Trial

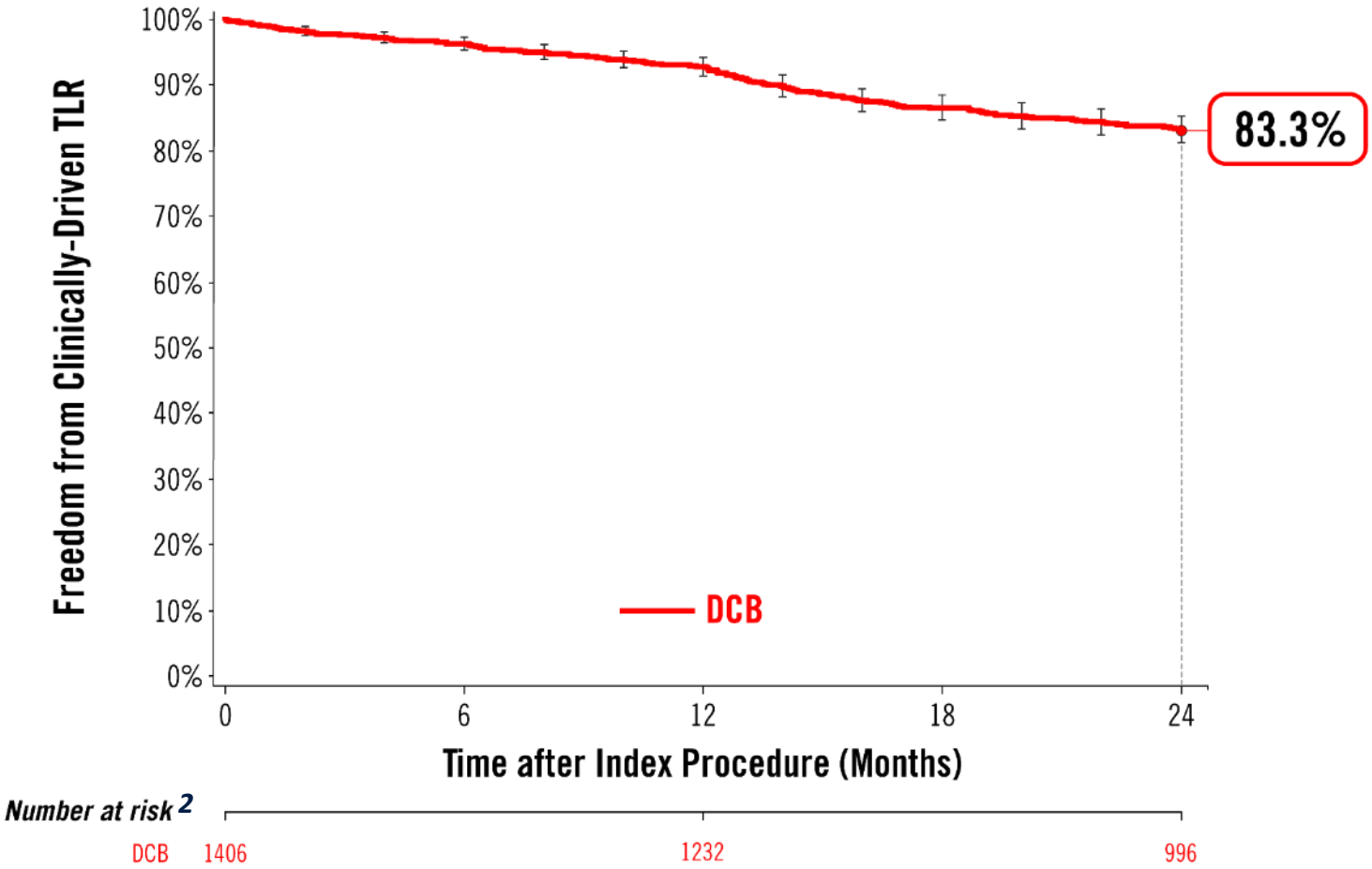
Primary Patency[1] at 12 Months



1. Freedom from core laboratory-assessed restenosis (duplex ultrasound PSVR ≤2.4) and clinically-driven target lesion revascularization through 12 months (adjudicated by a Clinical Events Committee blinded to the assigned treatment)
2. Number at risk represents the number of evaluable subjects at the beginning of the 30-day window prior to each follow-up interval

Medtronic

IN.PACT Global Study:
24-month Freedom from CD-TLR[1]



1. Clinically-driven TLR adjudicated by an independent Clinical Event Committee, 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.
2. Number at risk represents the number of evaluable subjects at the beginning of each 60-day window.

12-month Results across IN.PACT Admiral DCB Clinical Studies

	RCTs		Pivotal Registration Study	GLOBAL					
				Pre-Specified Imaging Cohorts				Regional Subset	
	IN.PACT SFA[1]	**IN.PACT Japan[2]**	IN.PACT China[3]	IN.PACT Global[4]	IN.PACT Global Long Lesion Imaging Cohort[5]	IN.PACT Global ISR Imaging Cohort[6]	IN.PACT Global CTO Imaging Cohort[7]	IN.PACT Global Belgium Subset[8]	IN.PACT Global ASEAN Subset[9]
N	220	68	143	1406	157	131	126	305	114
Lesion Length (Mean ± SD, cm)	8.9 ±4.5	9.2 ± 5.9	10.4 ± 6.5	12.1 ± 9.5	26.4 ± 8.6	17.2 ± 10.5	22.8 ± 9.8	9.5 ± 7.9	17.4 ± 12.3
Primary Patency (KM @ 360 days)	**87.5%**	**93.9%**	**90.9%**	NA	**91.1%**	**88.7%**	**85.3%**	NA	NA
Primary Safety Endpoint	95.7%	95.6%	99.3%*	92.1%	94.0%	91.1%	87.7%	90.6%	96.2%
CD-TLR	**2.4%**	**2.9%**	**2.9%**	**7.5%**	**6.0%**	**7.3%**	**11.3%**	**7.6%**	**2.9%**
Major Target Limb Amputation	0.0%	0.0%	0.0%	0.2%	0.0%	0.0%	0.0%	0.7%	0.0%
Thrombosis	1.4%	0.0%	2.2%	2.9%	3.7%	0.8%	4.3%	3.8%	0.9%

1. Tepe et al., Circulation 2015; Medtronic Data on File
2. Iida et al., JEVT 2018
3. Chen, Z, VEITH 2017
4. Jaff, M. VIVA 2016
5. Scheinert, D. EuroPCR 2015.
6. Brodmann, M. VIVA 2015
7. Tepe, G. Charing Cross 2016
8. DeLoose, K LINC 2017
9. Choi, D. LINC 2017.

*30-day Safety composite

DCB Pivotal Trial Comparisons:
Primary Patency of FDA-Approved DCBs[1]

IN.PACT SFA

LEVANT II

ILLUMENATE Pivotal RCT

1. Primary patency and target lesion revascularization (TLR) rates may be calculated differently, and therefore may not be directly comparable; chart is for illustration only.
2. IN.PACT SFA Trial values represent IN.PACT™ Admiral™ DCB arm as evaluated by 36-mo Kaplan-Meier, patency defined as PSVR ≤ 2.4 and freedom from TLR defined here as clinically-driven TLR; IN.PACT Admiral Instructions for Use M052624T001 Rev 1F.
3. LEVANT II values represent Lutonix 035 arm as evaluated by 730-day Kaplan-Meier, patency defined as PSVR ≤ 2.5 and freedom from TLR defined here as all TLR; Lutonix 035 Instructions for Use BAW1387400r3..
4. ILLUMENATE RCT Pivotal values represent Stellarex as evaluated by 410-day Kaplan-Meier, patency defined as PSVR ≤ 2.5 and freedom from clinically-driven TLR; Stellarex Instructions for Use No. P011966-C Rev 07/2017.

Drug-Coated Balloons

Seeing the Differences through the Mechanisms of Action

Medtronic
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Drug-Coated Balloon (DCB) System

IN.PACT™ Admiral™ DCB

Platform	**Admiral™ PTA balloon** 4-7 mm diameters 40, 60, 80, 120, 150 mm lengths[1]
Drug	**Paclitaxel** Proven anti-proliferative drug 3.5 µg/mm^2
Excipient	**Urea** Facilitates drug transfer Naturally occurring, non-toxic
Process	**Medtronic** Reliable, scalable, uniform drug coating process

1. The IN.PACT™ Admiral™ 120 and 150 mm long balloons have 4,5 & 6 mm diameters only.

Key Elements of IN.PACT™ Admiral™ Design

Providing over 180 days of Therapeutic Drug Levels[1]

Balloon

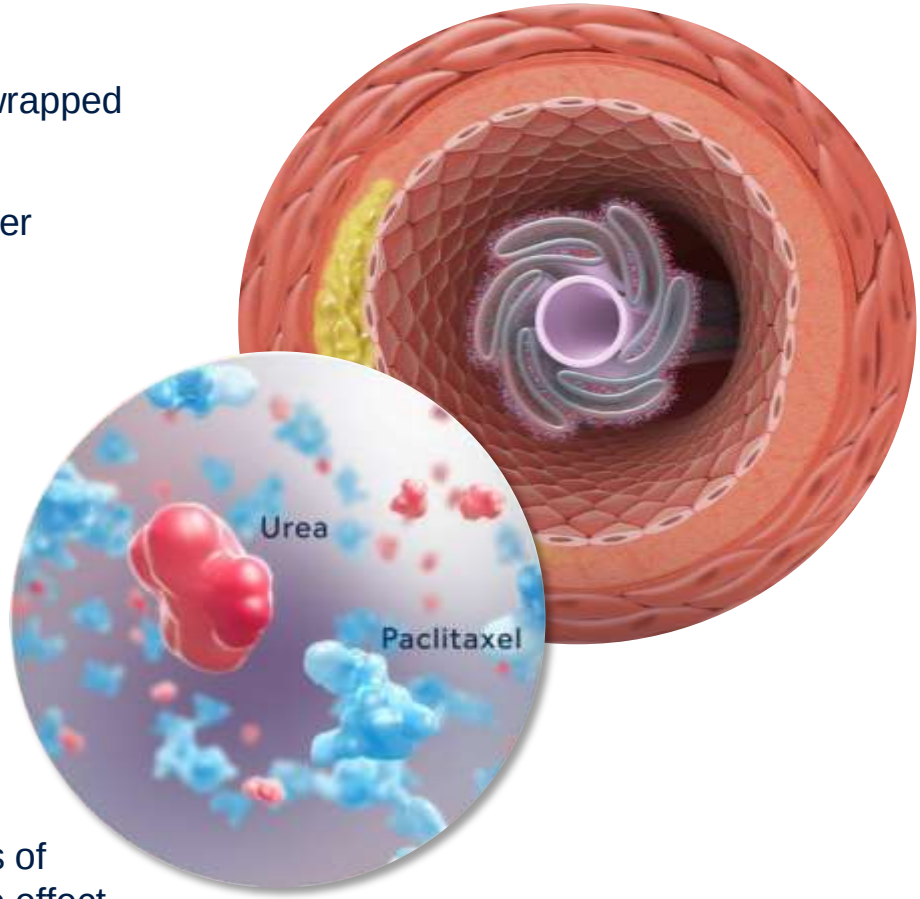
- Coated with matrix in semi-inflated state, then wrapped
- Protects majority of matrix within folds
- Moderates urea dispersion and paclitaxel transfer

Urea

- Naturally occurring molecule
- Hydrates during contact with blood
- Facilitates drug transfer

Paclitaxel

- Proven anti-proliferative drug
- 3.5 μg/mm^2
- Embedded solid phase drug provides reservoirs of soluble phase drug which exert anti-proliferative effect



1. Data on file at Medtronic (GLP Study FS208; GLP Study PS516).

Design Summary of the FDA-Approved DCBs

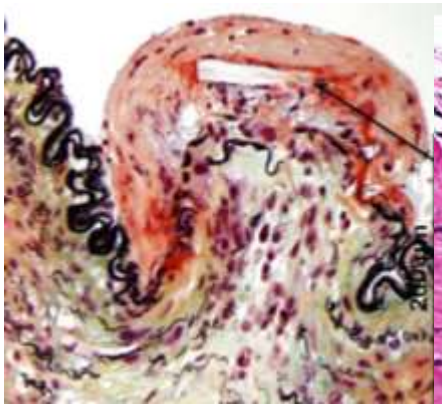
Excipient is critical in delivering and sustaining paclitaxel in the tissue.

- All three devices use paclitaxel dosing significantly lower than other medical applications[1]
- Excipient is unique to each DCB

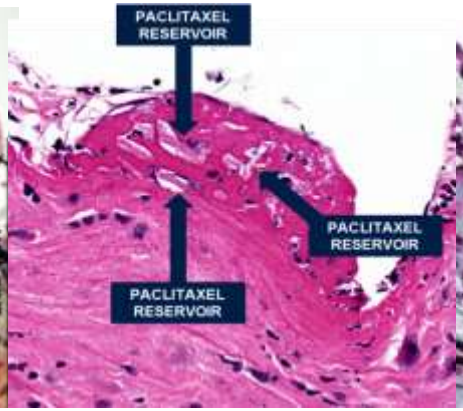
	Drug (Dose)	Excipient
IN.PACT™ Admiral™ DCB	Paclitaxel (3.5µg/mm^2)	Urea
Lutonix™* 035 DCB	Paclitaxel (2.0µg/mm^2)	Polysorbate-Sorbitol
Stellarex™* DCB	Paclitaxel (2.0µg/mm^2)	Polyethylene Glycol

1. Ng, Vivian. Eur J Clinical Investigation 2015;45(3):333-345

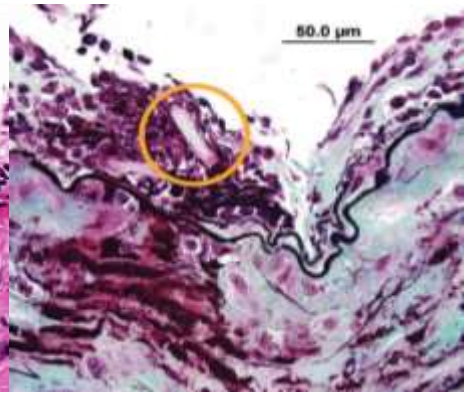
Proposed Mechanism of Action



PACCOCATH (2009)
Granada JF. Open Heart. 2014



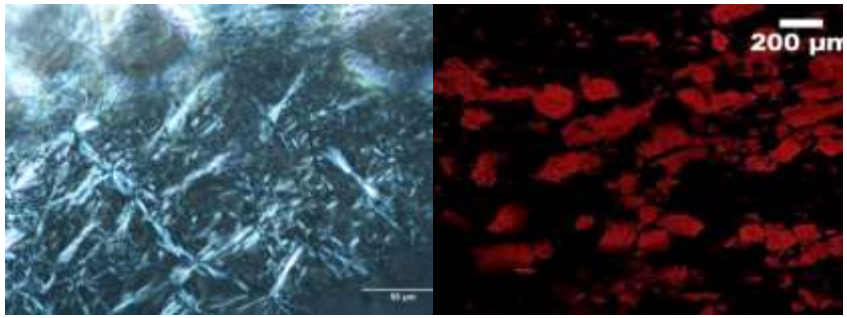
IN.PACT



STELLAREX

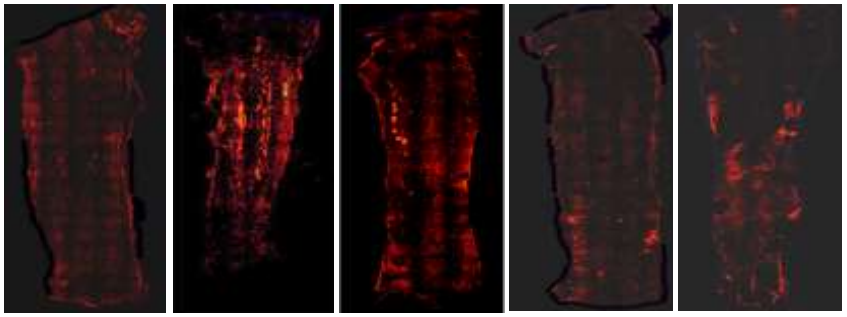
Particle Type, Adhesion and Solubility Determines Tissue Pharmacokinetics

STELLAREX (SPECTRANETICS)



Cheng Y. Expert Opin Drug Deliv 2016; 13:859-72

RANGER (BOSTON SCIENTIFIC)

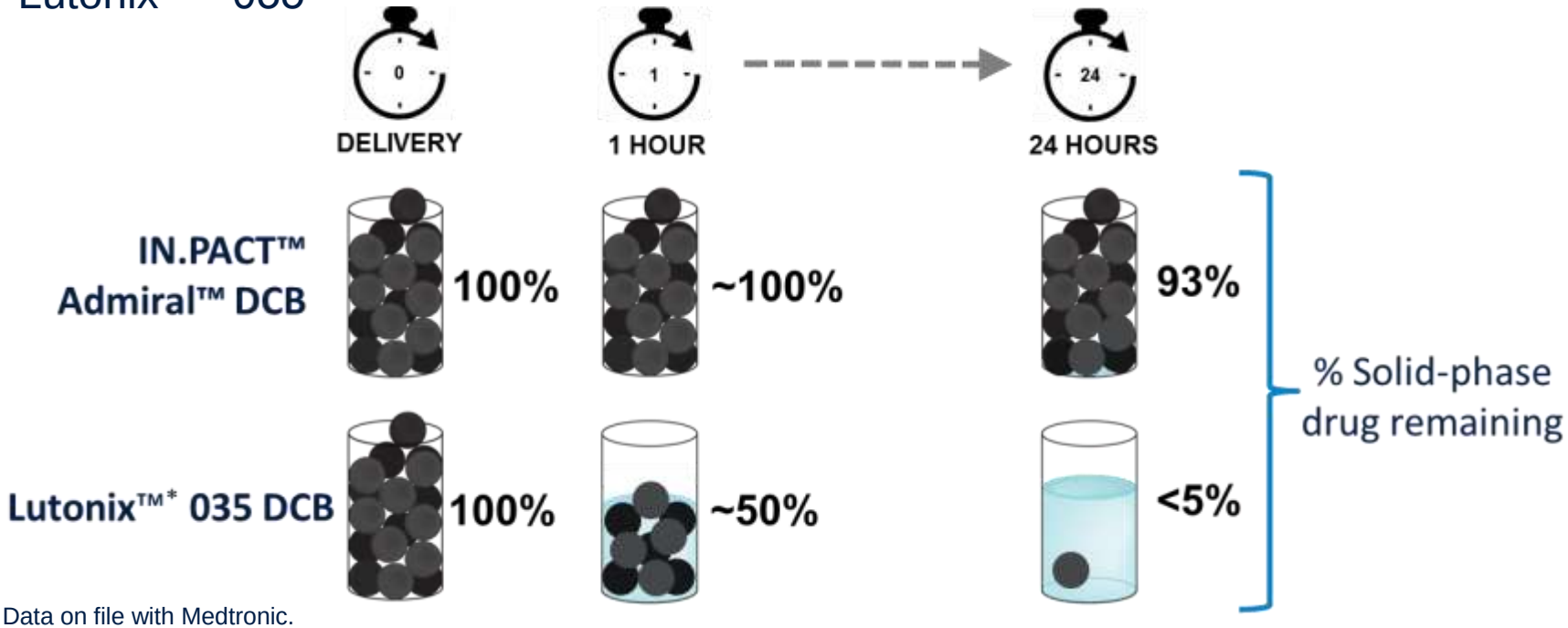


15 Min | 1 Day | 3 Days | 7 Days | 14 Days

Solid-Phase Drug Transition

Transition from solid- to soluble-phase is different through 24 hours.[1-2]

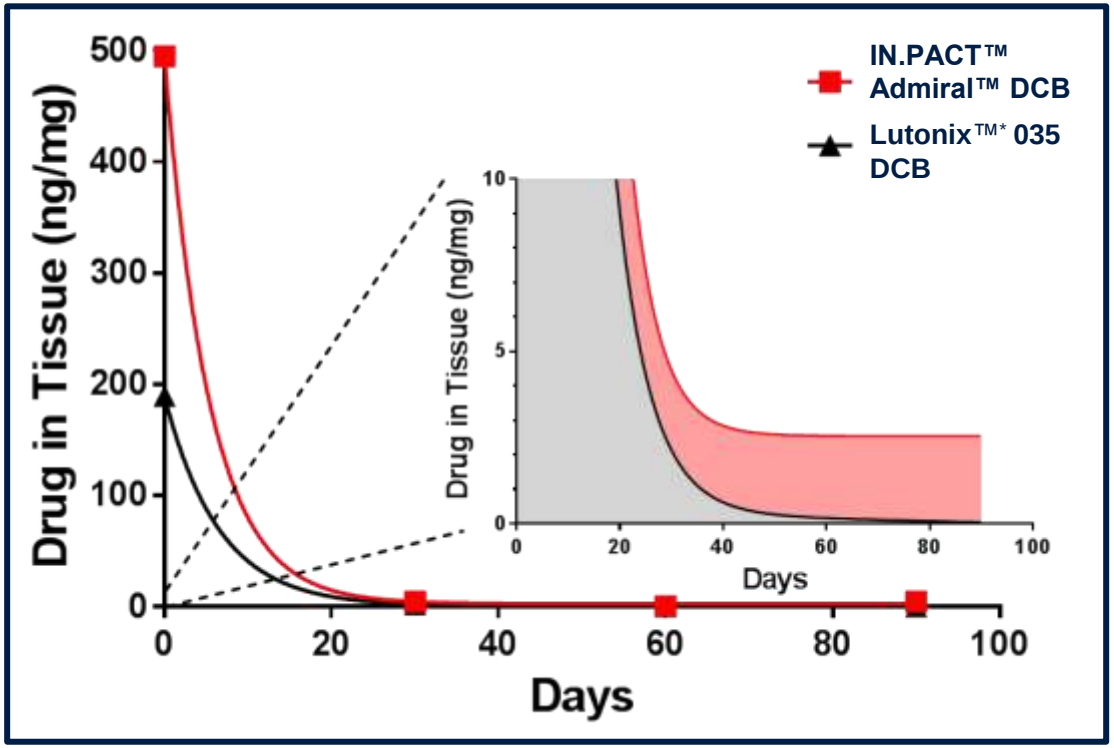
- Bench-top porcine plasma model reveals that both devices transfer solid-phase paclitaxel from the DCB
- Subsequent transition from solid-phase to soluble-phase occurs at different rates
- At 24 hours, IN.PACT™ Admiral™ DCB retains more drug in solid-phase than Lutonix™* 035



1. Data on file with Medtronic.
2. Virmani R, "Arterial wall response to drug-coated balloon use" presented at Charing Cross, London 2016.

Sustained Drug Availability

Higher percentage of solid-phase drug is associated with higher drug tissue concentration through 90 days.[1-2]



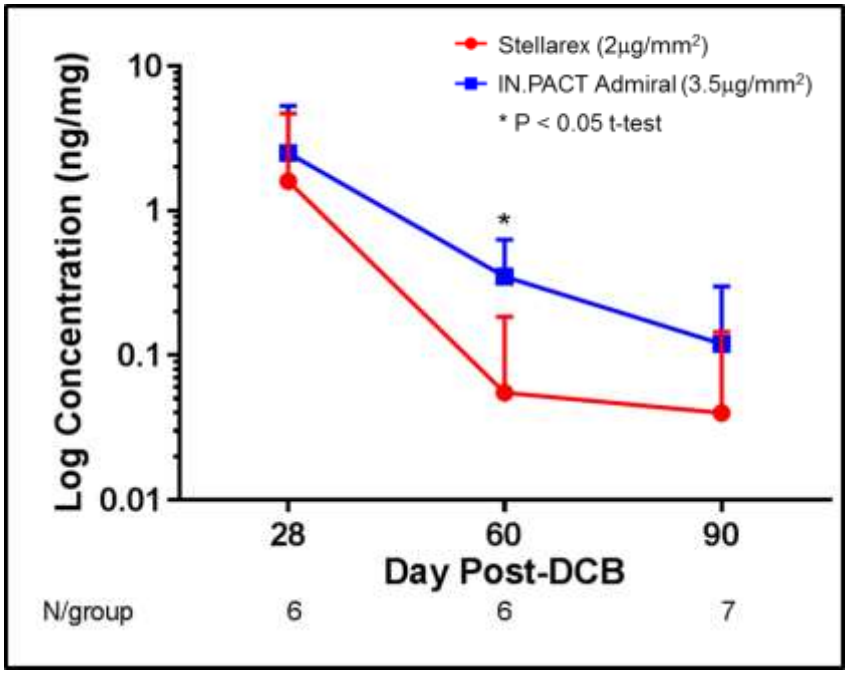
In vivo porcine model used to quantify sustained drug residence in tissue

1. Data on file with Medtronic; Study PS747.
2. Virmani R, "Arterial wall response to drug-coated balloon use" presented at Charing Cross, London 2016.

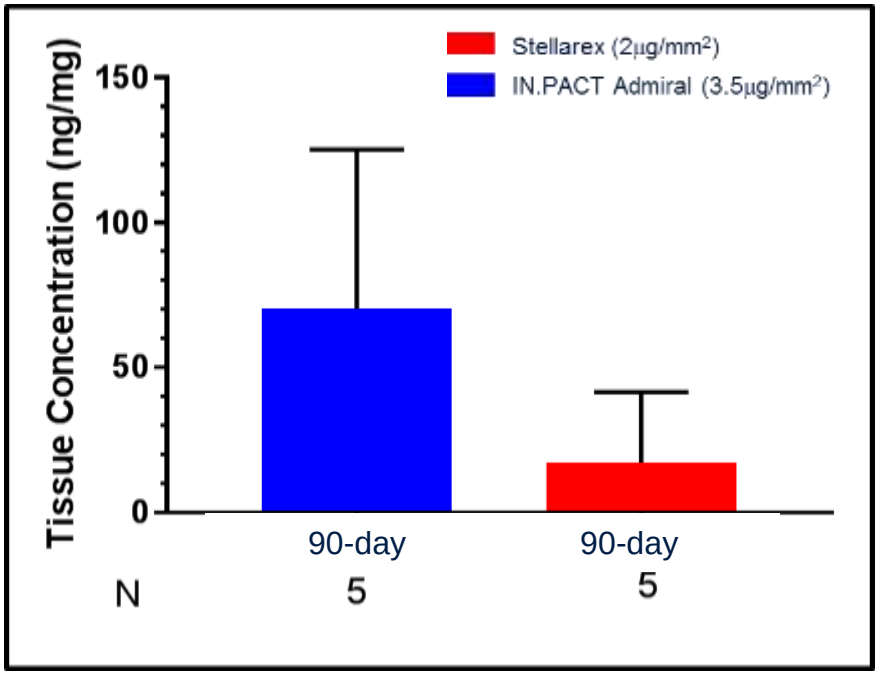
Sustained Drug Availability

Different tissue drug concentrations are also demonstrated in a similar head-to-head experiment as well as porcine arterial neointima model.[1,2]

Healthy Porcine Arterial Model



In-Stent Restenosis Porcine Arterial Model

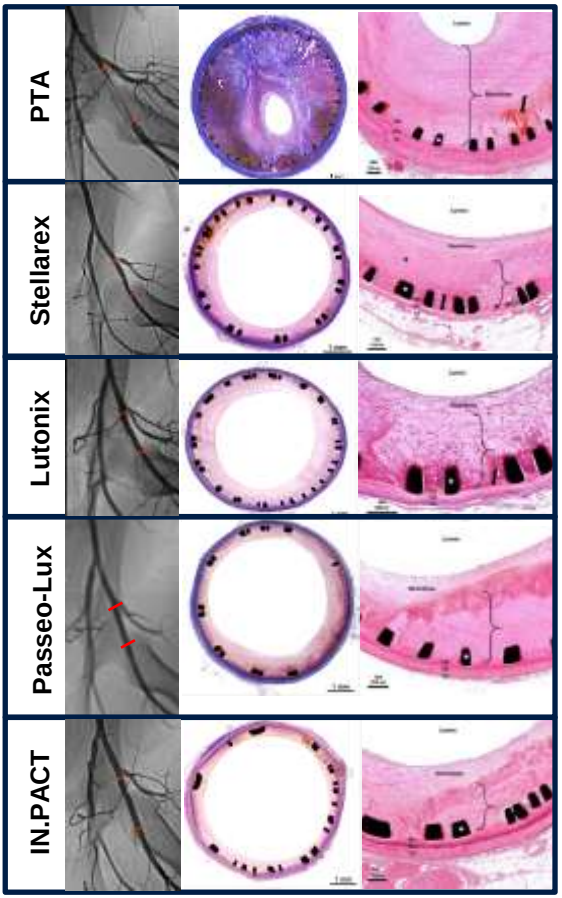


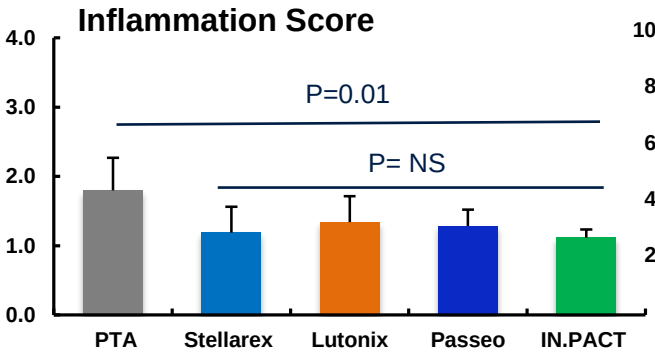
Higher input drug concentration facilitates greater long-term concentrations.

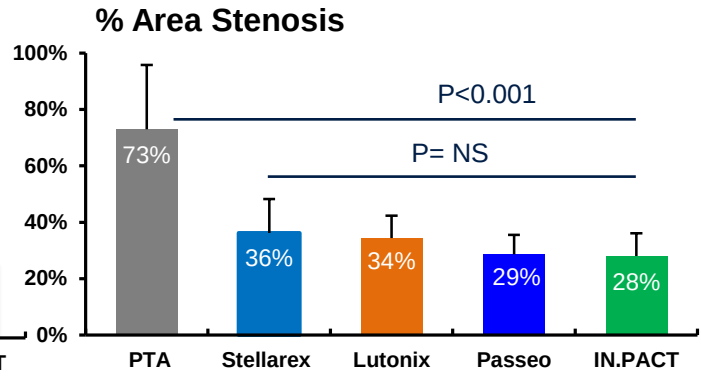
1. Data on file with Medtronic; Study PS767.
2. Data on file with Medtronic; Study PS781.

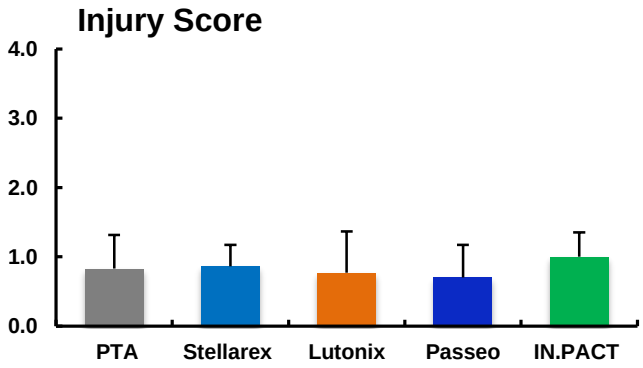
SHORT-TERM Restenosis Prevention Following DCB Treatment in the FHS Model of SFA-ISR

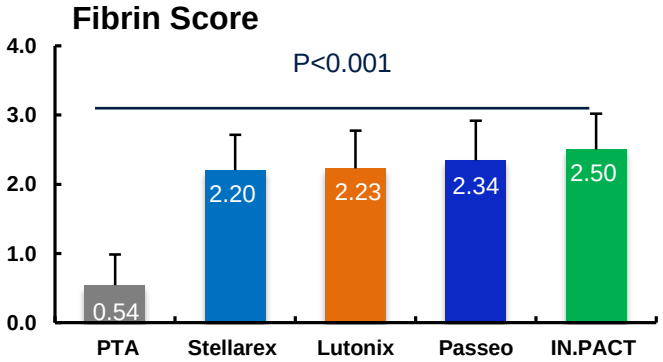
28-Days Following ISR Treatment







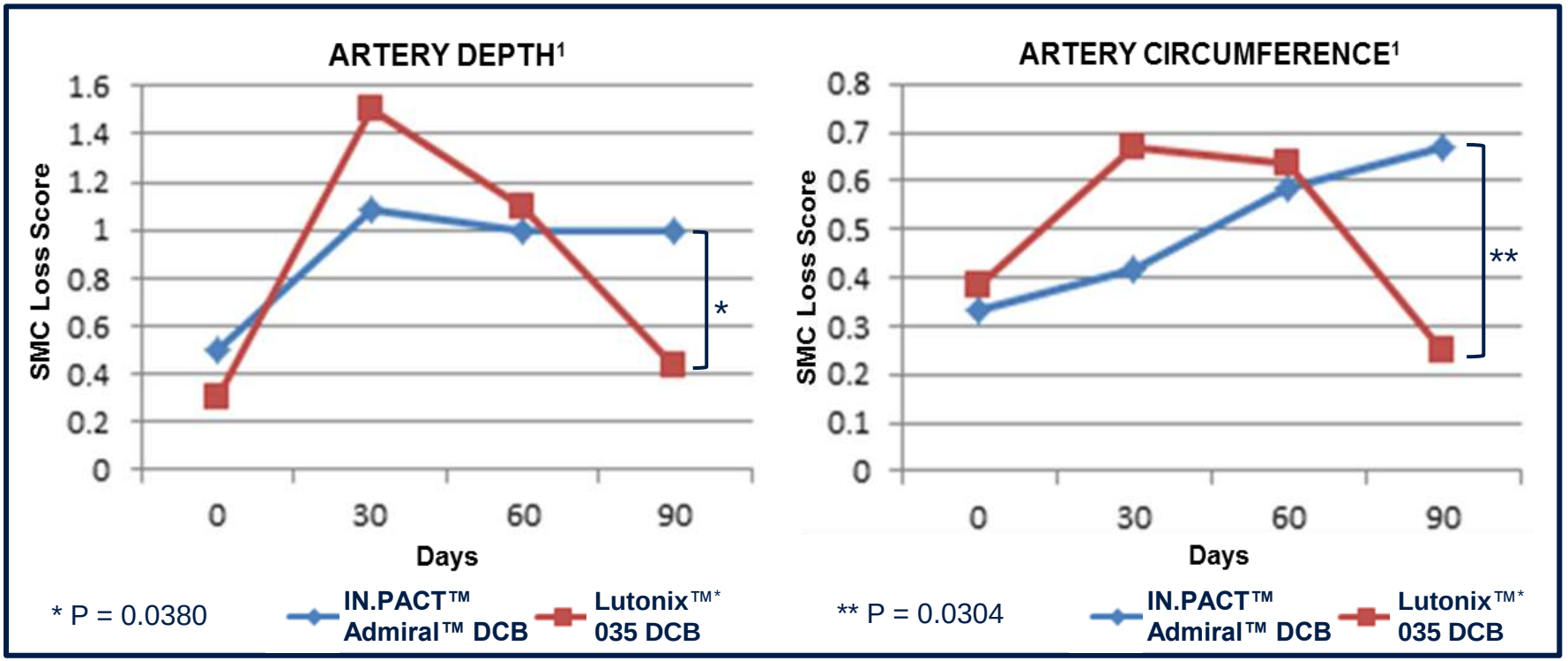




Data Courtesy of Cheng YP. Skirball Center for Innovation 2017

Prolonged Anti-Proliferative Effect

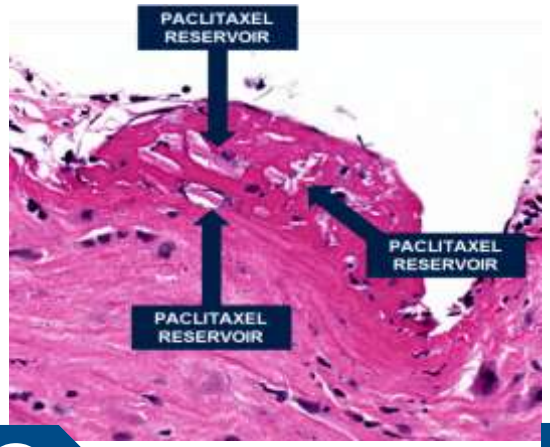
Higher percentage of solid-phase drug is associated with continued trend of smooth muscle cell loss through 90 days.[1-2]



In vivo porcine model used to quantify smooth muscle cell loss through 90 days

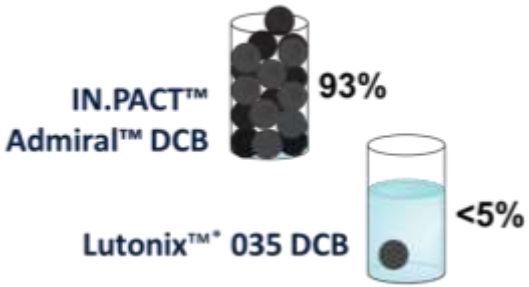
1. Data on file with Medtronic; PS747.
2. Virmani R, "Arterial wall response to drug-coated balloon use" presented at Charing Cross, London 2016.

Keys to Sustained Effect



1

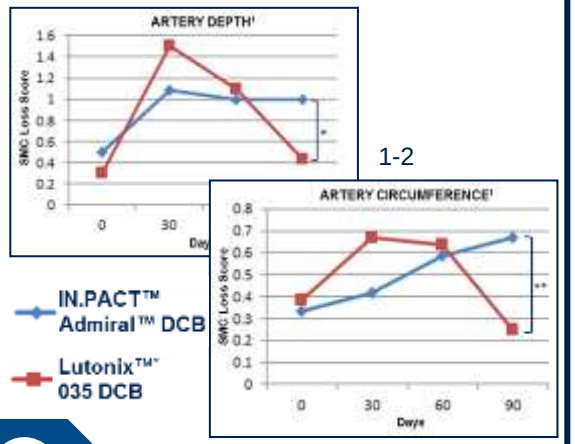
Solid-phase drug delivery



Solid-phase paclitaxel at 24h[1-2]

2

Sustained drug availability



1-2

3

Prolonged anti-proliferative effect

1. Data on file with Medtronic. Ninety-day differences in artery depth delta and artery circumference demonstrate p=0.0380 and p=0.0304, respectively (right panel).
2. Virmani R, "Arterial wall response to drug-coated balloon use" presented at Charing Cross, London 2016.

Key Safety Metrics:
12-Month FDA-Approved DCB Cohorts

	LEVANT II[1]		Global[2]	IN.PACT SFA[3]		Global Clinical Cohort[4]	EU RCT[5]		US Pivotal[6]		Global[7]
	PTA	Lutonix 035		PTA	IN.PACT Admiral		PTA	Stellarex	PTA	Stellarex	Stellarex
Subjects	160	316	691	111	220	1406	72	222	100	200	371
All Thrombosis				3.7% (4/107)	1.4% (3/207)	2.9% (38/1311)			0.0% (0/95)	1.1% (2/189)	
Revasc. due to Thrombosis	0.7% (1/140)	0.4% (1/285)	1.3% (8/634)								
Major Amputation	0.0% (0/140)	0.3% (1/286)	0.5% (3/635)	0.0% (0/107)	0.0% (0/207)	0.2% (3/1311)	0.0% (0/60)	0.0% (0/204)	0.0% (0/95)	0.0% (0/189)	1[7]

Consistently low frequency of thrombosis and major amputation across platforms.

Does distal downstream particle embolization impact wound healing and could affect clinical outcomes?

Paclitaxel Effect on Wound Healing
Experimental Design

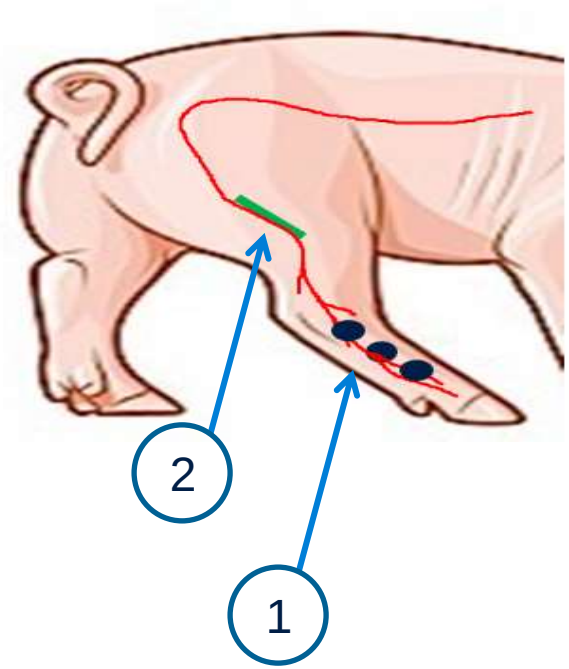
1. Wound creation
2. Bilateral treatment

   PTA or DCB x1 or DCB x3
3. Clinical assessment

   Scoring and wound care (dressing change) three times per week
4. Termination (14 and 28 days)

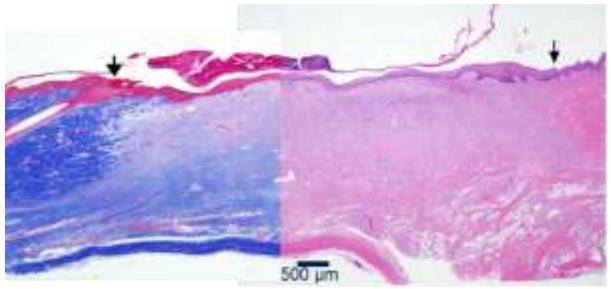
   Histopathological assessment

   Quantification of drug in tissue

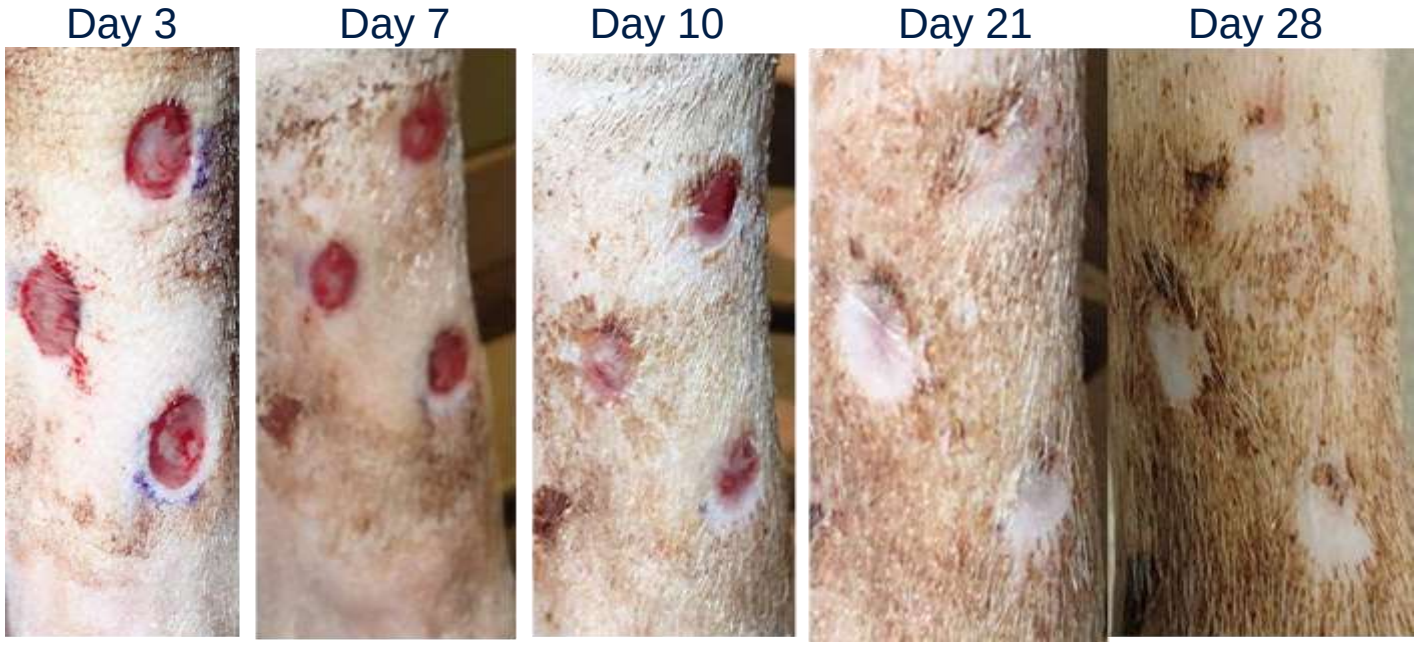


3

4



Wound Healing
Clinical Evaluation



Wound healing (Three times per week)

- Modified Draize wound healing score rank (0-4)
- Modified Hollander Cosmesis score rank (0-4)

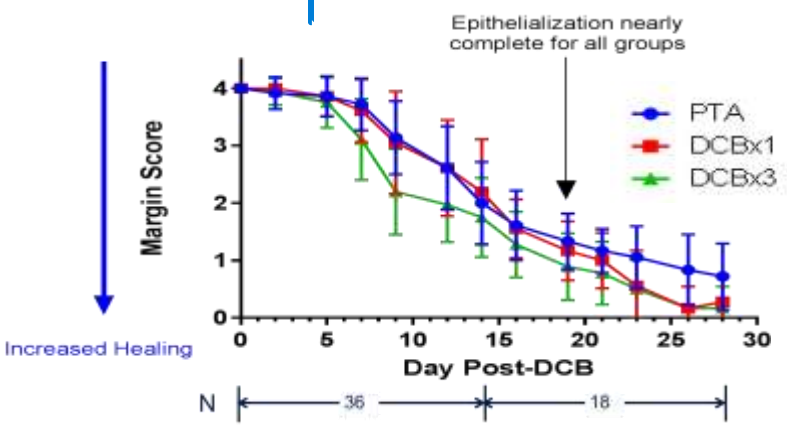
Histopathology (14 & 28 days)

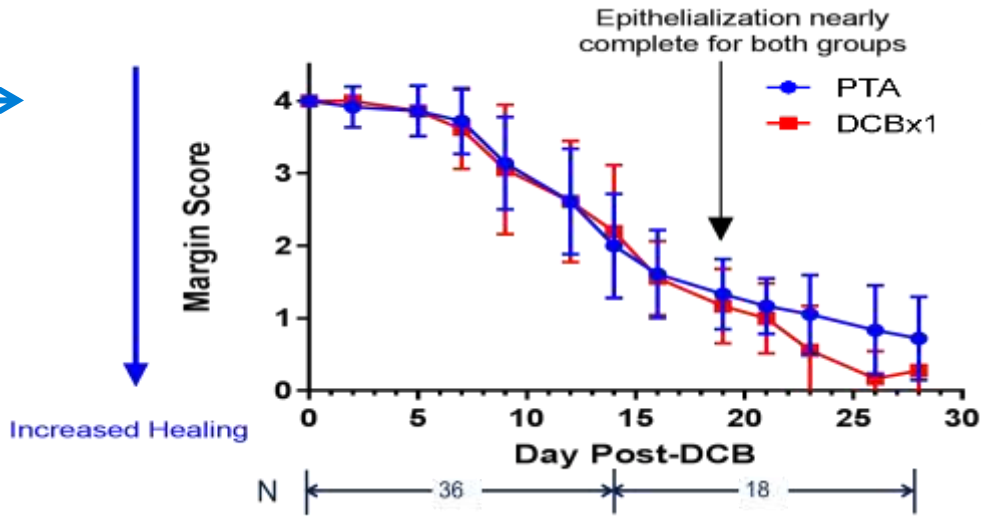
- Re-epithelialization
- Collagen deposition or scar formation
- Neovascularization or granulation
- Wound contraction and/or inflammation

Wound Healing

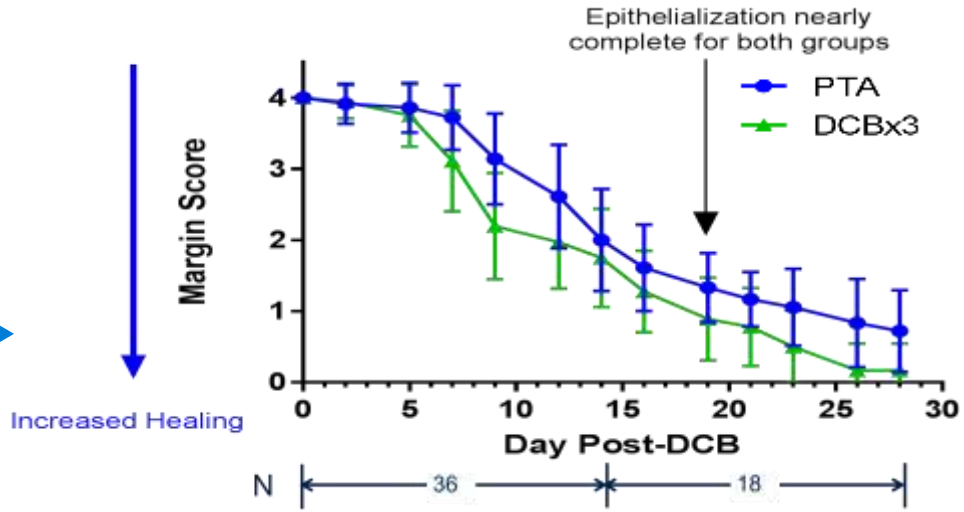
Hollander Score: Direct Indicator of Wound Closure

DCB x1 versus PTA





DCB x3 versus PTA



Conclusions

- There does not appear to be a Class Effect in DCBs
- The In.Pact Admiral is the only DCB to demonstrate a superior treatment effect over PTA through four years
- Continued safety of IN.PACT™ Admiral™ DCB through four years
- The ability to maintain a sustained biological response over time appears to be the main driver of clinical success of DCBs
- Not only paclitaxel dosing but also particle solubility are important technological drivers to achieve long-term suppression of restenosis
- Particulate embolization does not seem to affect wound healing at the experimental level, its effect in humans requires further studies

Thank You!