Drug Coated Balloons: Technology, Clinical Outcomes and Future Promise

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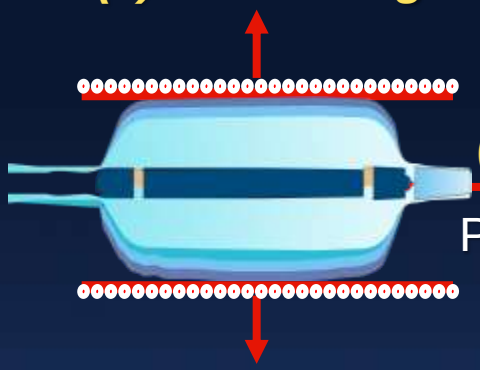
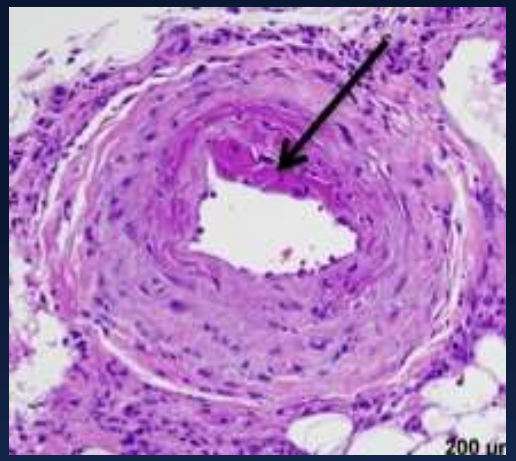
Technical Features of Current DCB Technologies

Mechanism of Action of DCB
Technical Drivers for Clinical Success





(1) Acute Drug Transfer

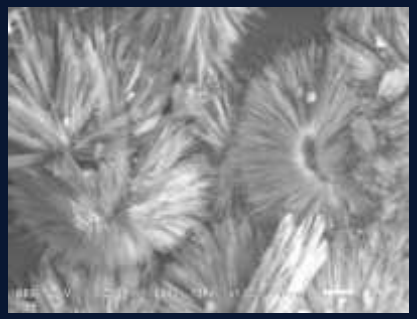
Tissue Transfer* ~1 to 10%	Distal Circulation* ~60 to 70%

(3) Biological Effect
Paclitaxel Tissue Residency

PCB Coating Loss (Insertion-Transit-Inflation)

- Distal Tissue Effect (Acute Occlusion)
  - Acute Micro-vascular Occlusions
  - Chronic Muscle Toxicity
- Systemic Tissue Effects
  - End Organ Toxicity

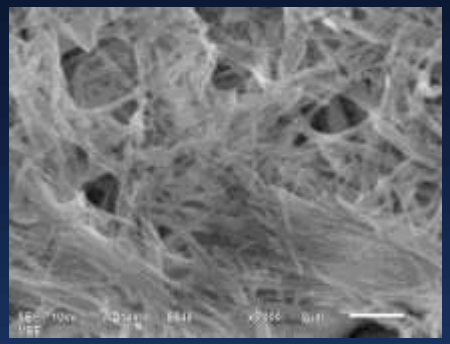
Paclitaxel Coated Balloon Evolution



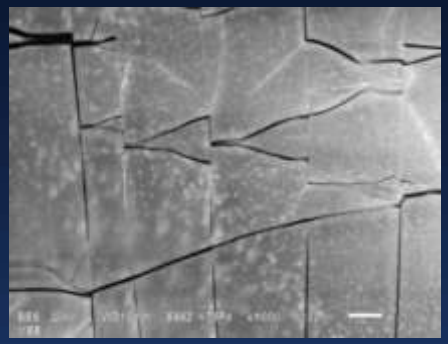
Crystalline Coating

1ST GENERATION PCB COATINGS

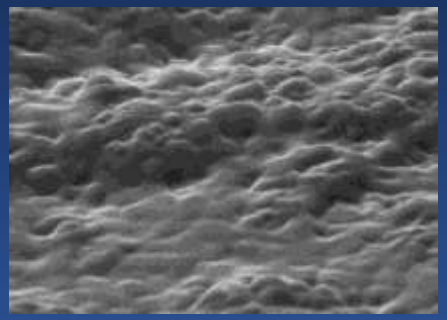
- Drug Processing
- Solvent Characterization
- Surface Deposition Methods
- Drying Process



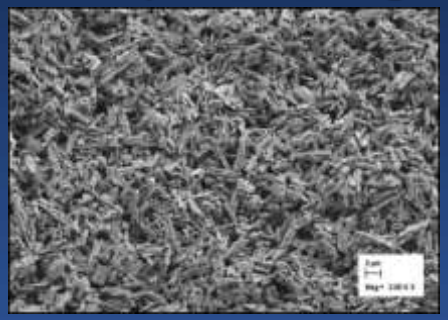
Hybrid Coating



Amorphous Coating



Nano-Spheres Coating



Micro-Crystals Coating

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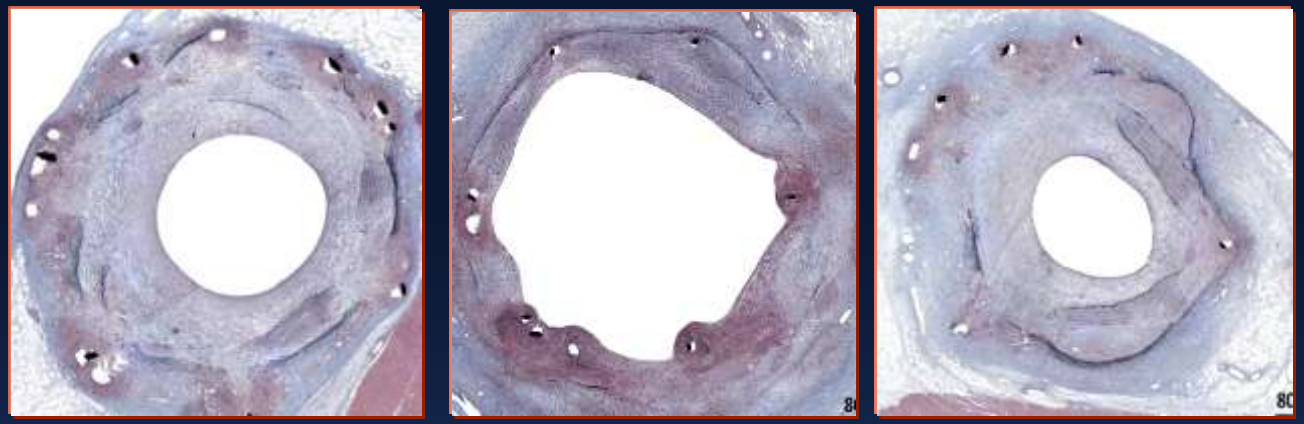
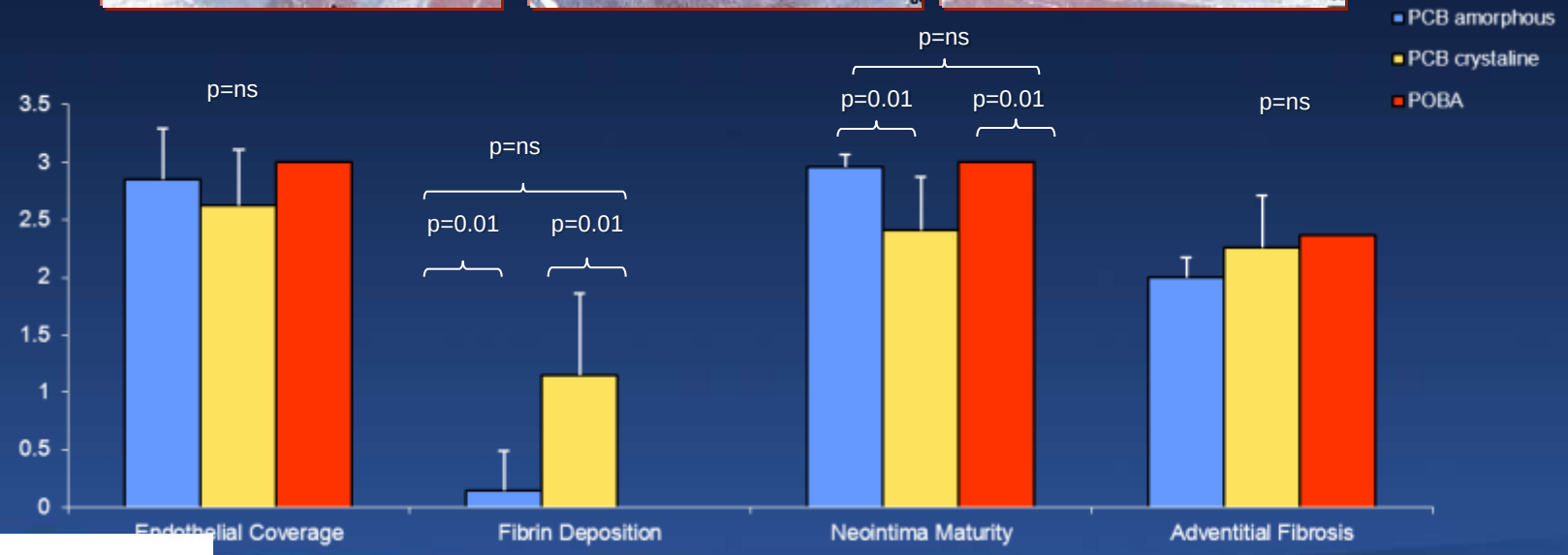
Coating Type Influences Neointimal Growth Inhibition and Healing

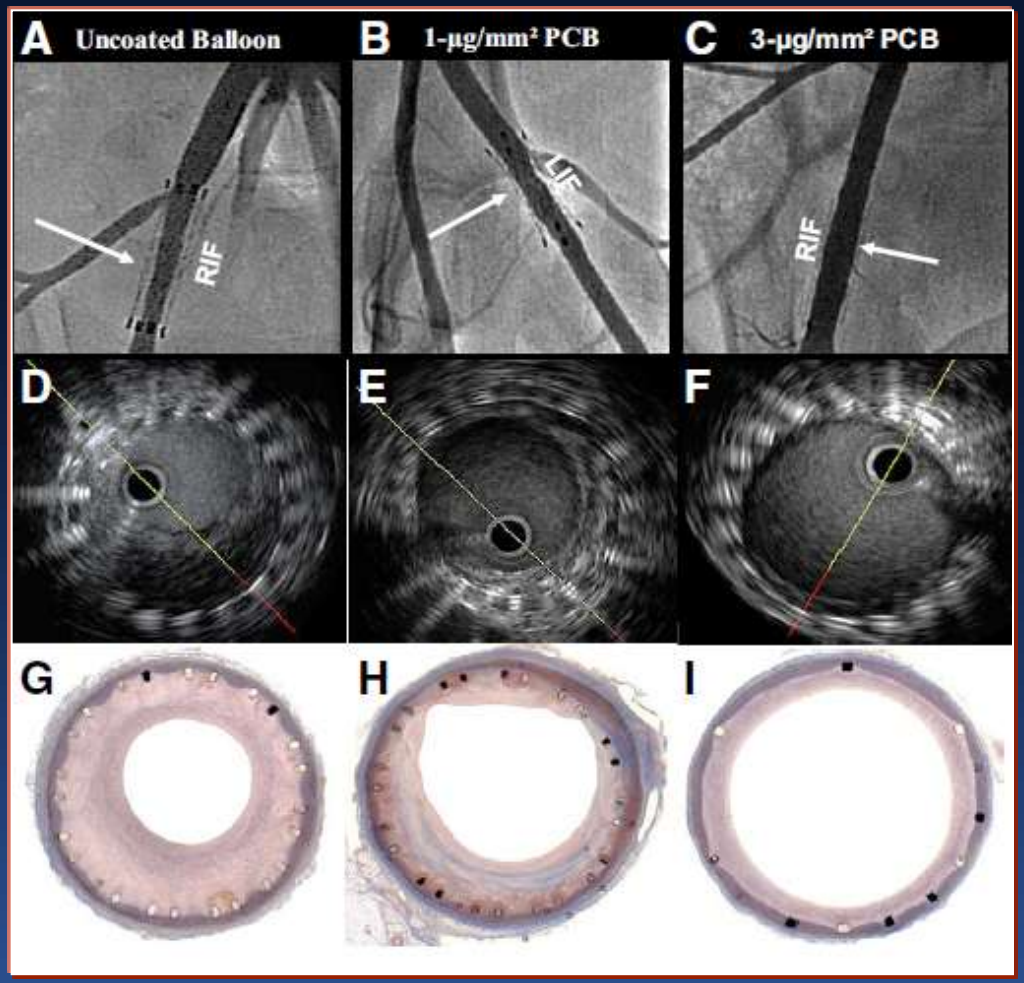
Amorphous Coating | Crystalline Coating | POBA Control





Granada JF, Open Heart. 2014 Aug 6;1(1)

Effect of Paclitaxel Dose on Neointimal Inhibition



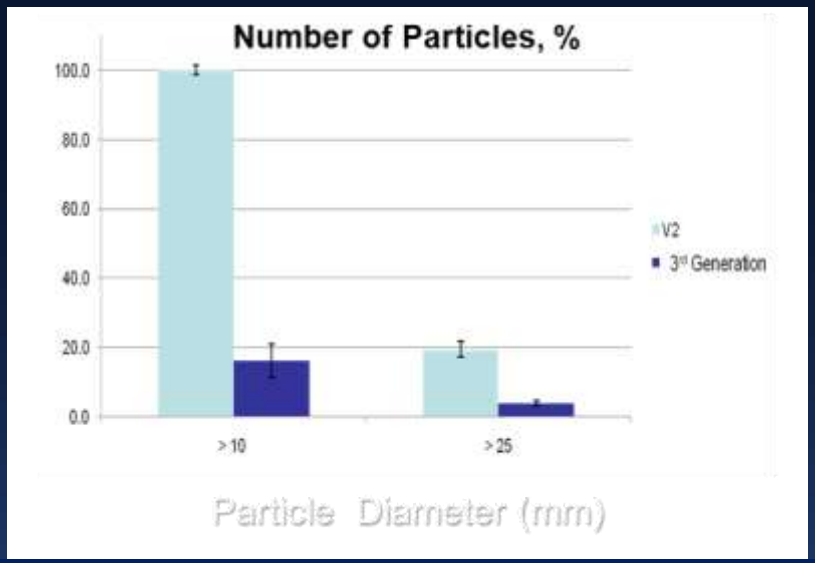
Reduction in %AS
(50% ↓ in Efficacy)

- SFA, ISR-Model
- High-cholesterol swine
- 1-µg/mm^2: 13.2% (p=0.5)
- 3-µg/mm^2: 26% (p<0.04)
- Compared to PTA uncoated controls

Granada JF. JACC Cardiovasc Interv, Oct 2012

Paclitaxel Coating Type and Particulate Formation (Safety)

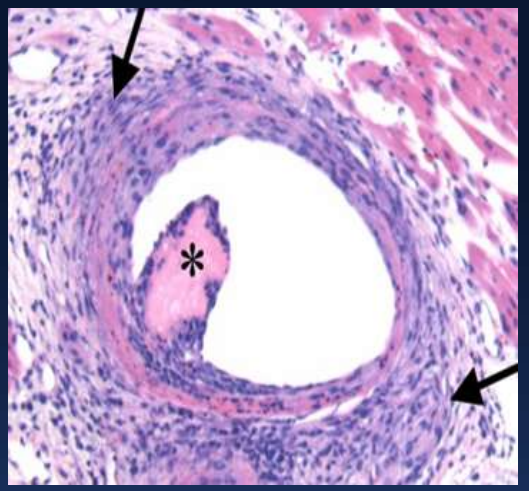
Coating Embolization Following PCB Inflation Is a Real Phenomenon



PCB Coating Loss (Insertion-Transit-Inflation)

- Distal tissue effect (acute occlusion)
  - Acute microvascular occlusions
  - Chronic muscle toxicity
- Systemic tissue effects
  - End organ toxicity

Experimental Evidence of Downstream Myocardial Embolization



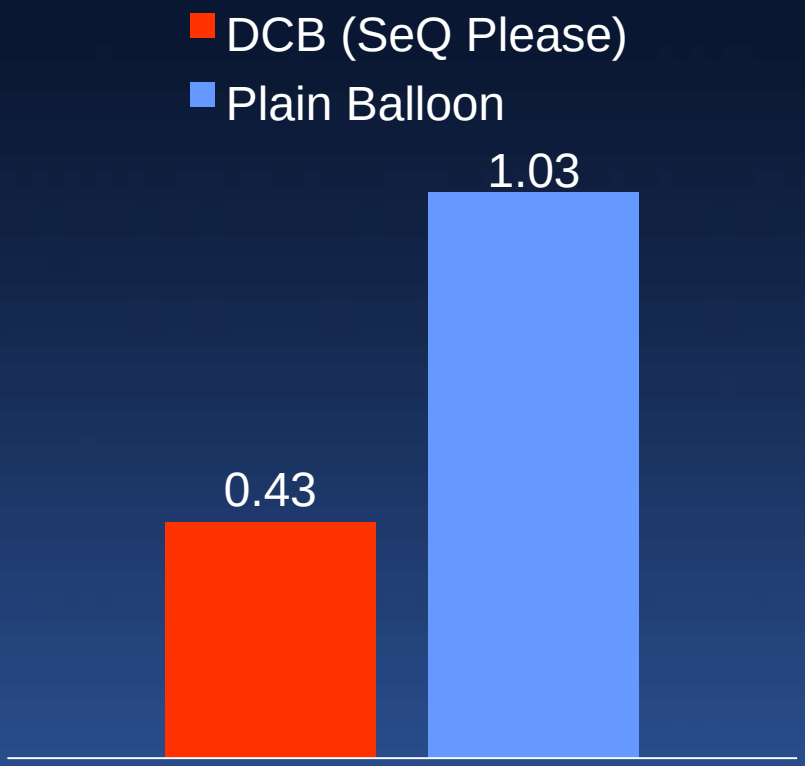
Clinical Implications of Particulate Distal Embolization Appear to be Minimal in the SFA Territory

Efficacy in Coronary Drug Eluting In-Stent Restenosis

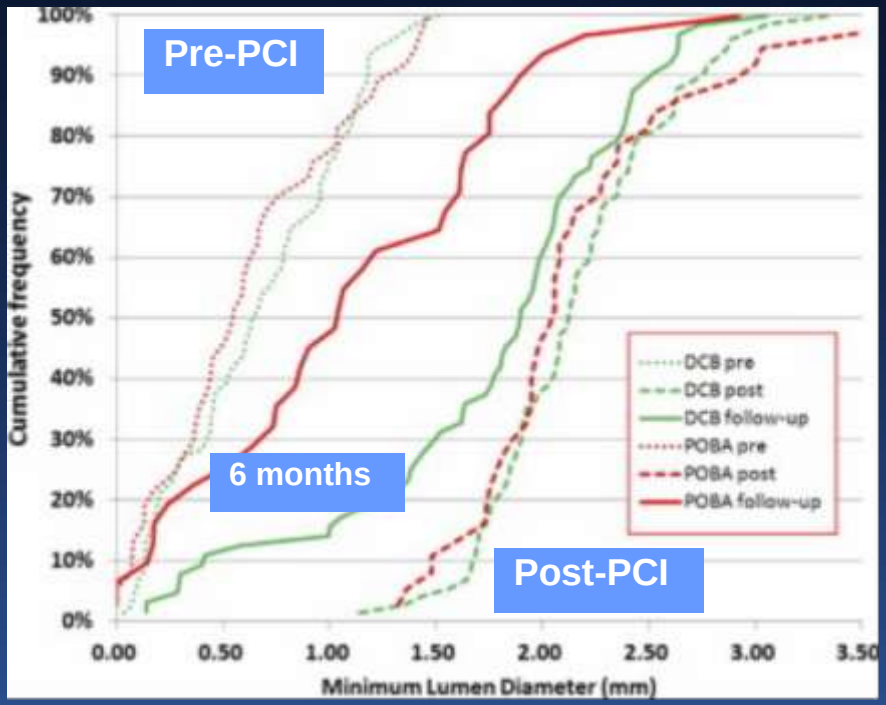
DCB versus POBA
PEPCAD-DES: Primary Results

95/110 patients with angiographic follow-up

Late Loss (mm)



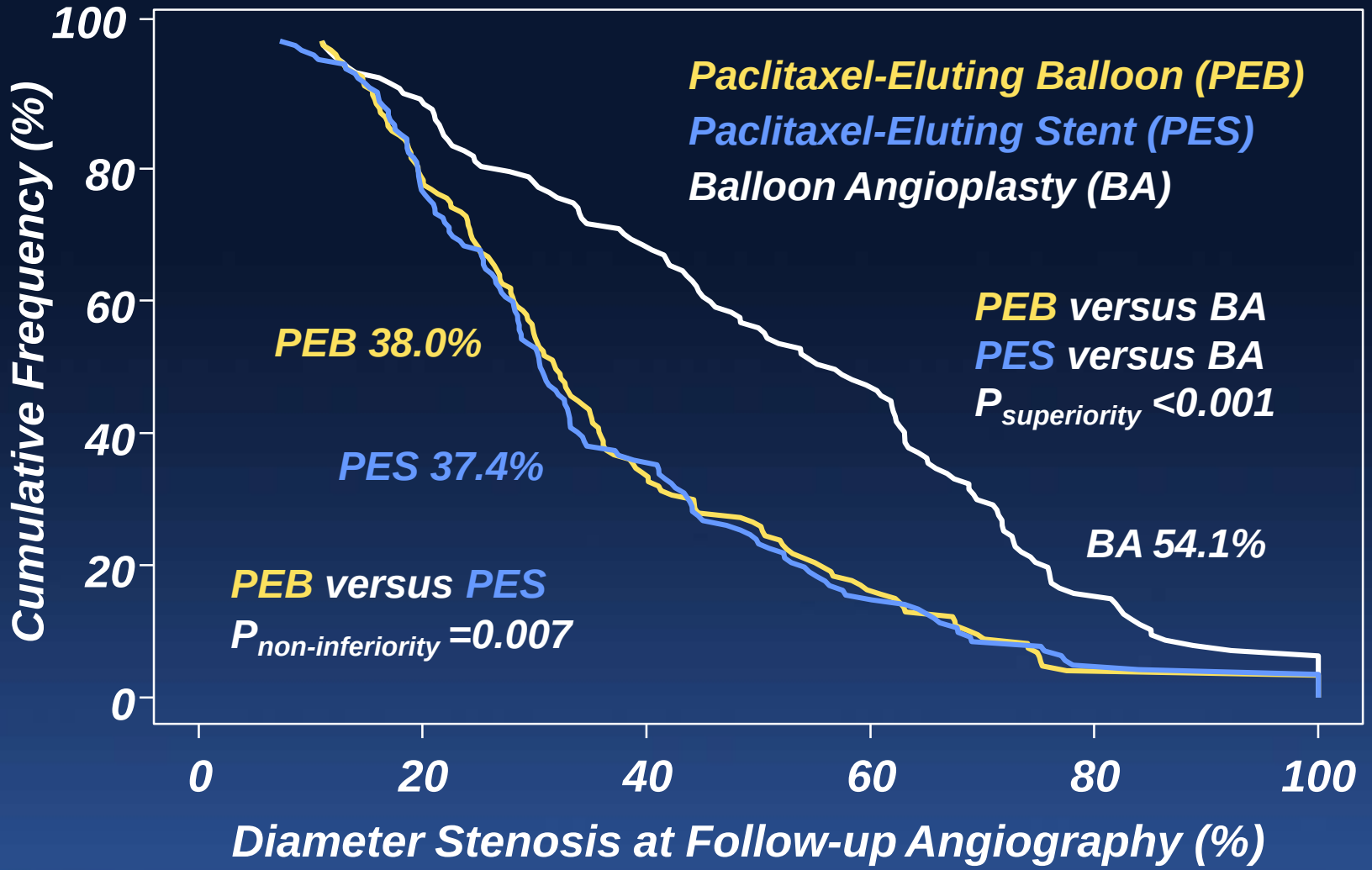
Min. Lumen Diameter (mm)



Rittger et al. J Am Coll Cardiol 2012

DCB vs. 1st Generation DES; n=402

Diameter Stenosis at Follow-up Angiography



ISAR-DESIRE 3: Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis: 3 Treatment Approaches; Byrne et al. Lancet 2013

DCB vs. 2nd Generation DES: RIBS IV

(January 2010 – August 2013 at 23 centers)

Inclusion Criteria
Informed Consent

309 Pts DES-ISR Randomization

Rx Centralized
Stratification:
ISR Length & Edge

Xience Prime
(Abbott Vascular)

155 Pts **EES**

154 Pts **DEB**

SeQuent Please
(B. Braun)

100% Angiographic Success

4 Died
18 Refused

3 Died
12 Refused

133 Pts Angio FU

139 Pts Angio FU

Mean: 279 days
(Median: 248)

QCA Primary End-point

Mean: 266 days
(Median: 246)

(272 Patients: 90% of Eligible)

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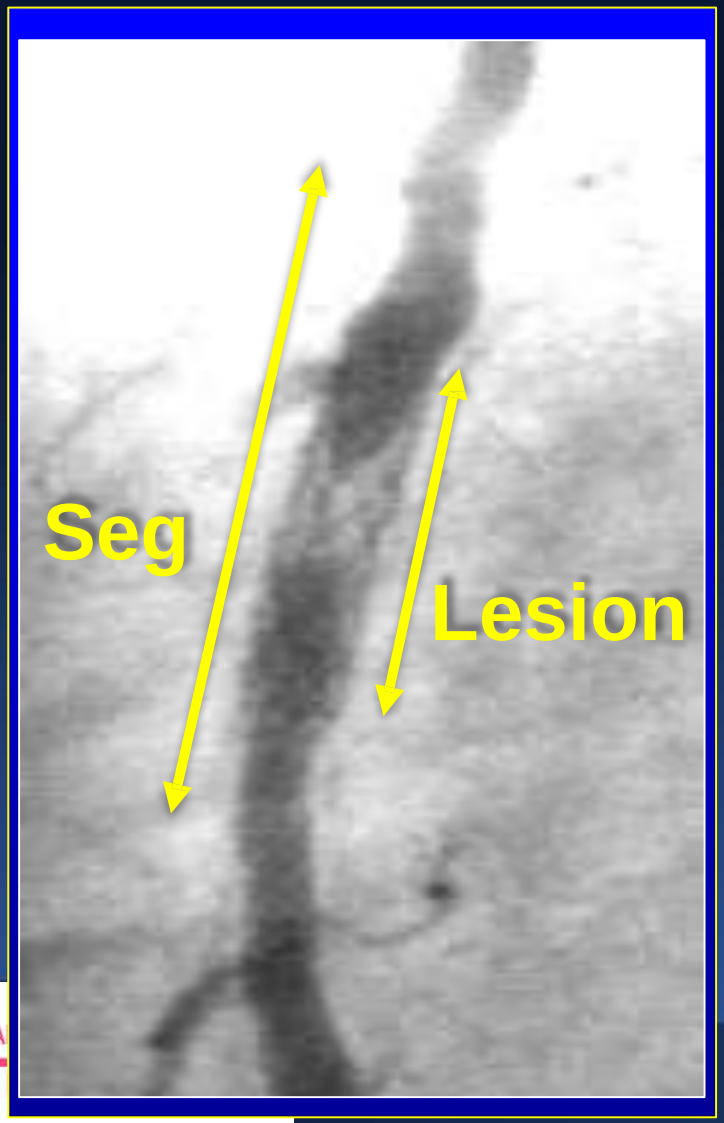
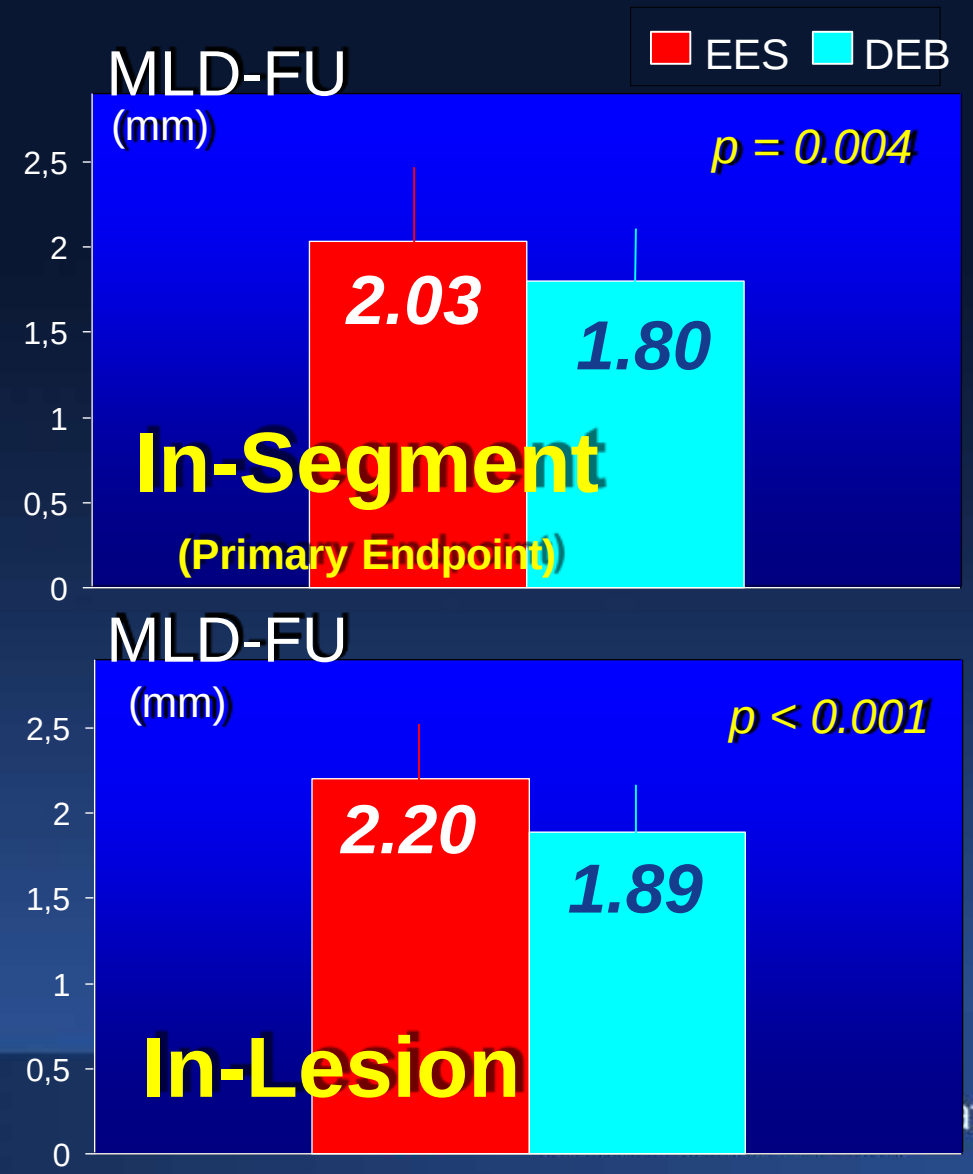
RIBS-IV: DES-ISR: DCB v G2 DES

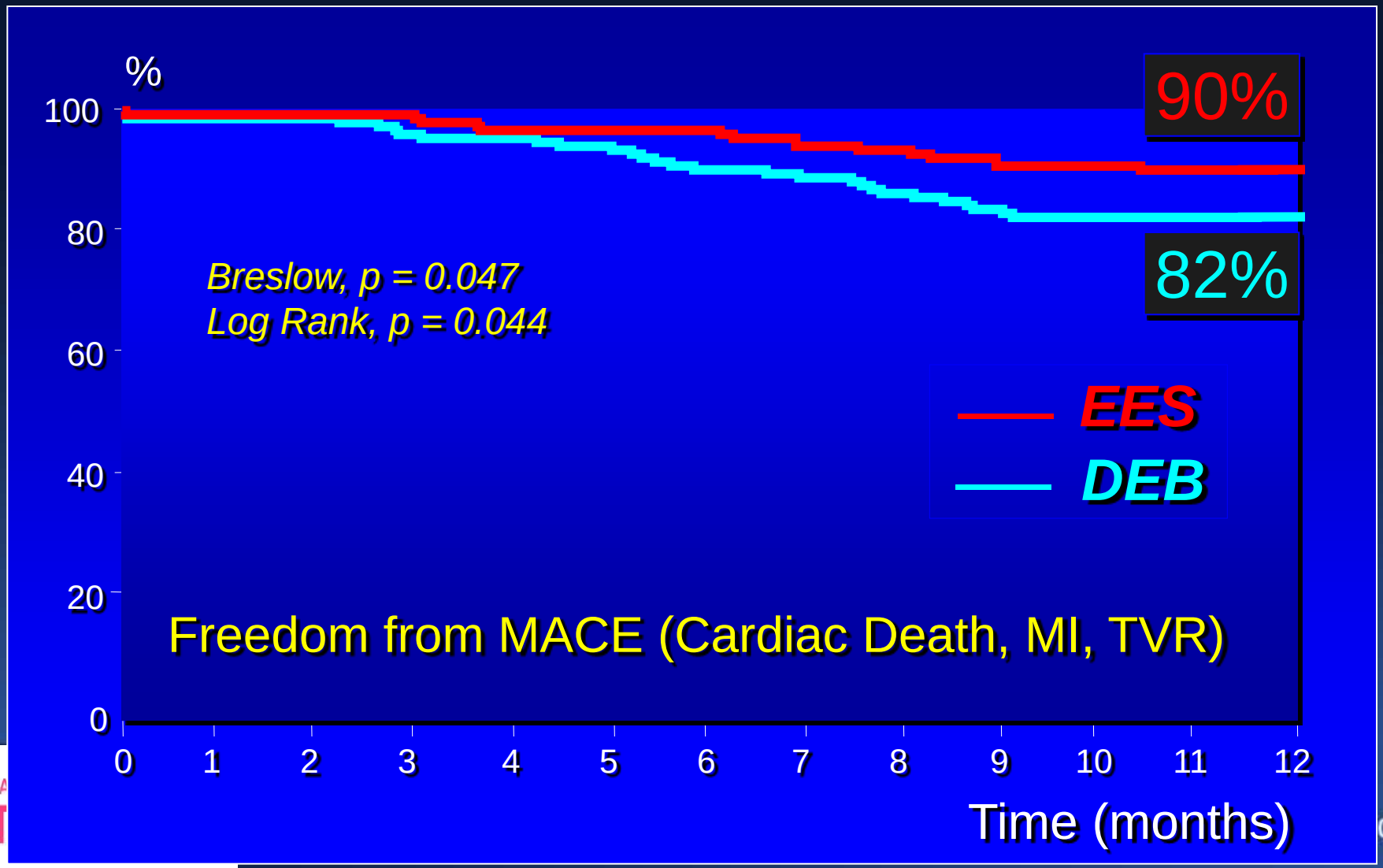
QCA: MLD at FU





Clinical Follow-up:

1 Year FU 309 P (100%); FU Time 360±35 days

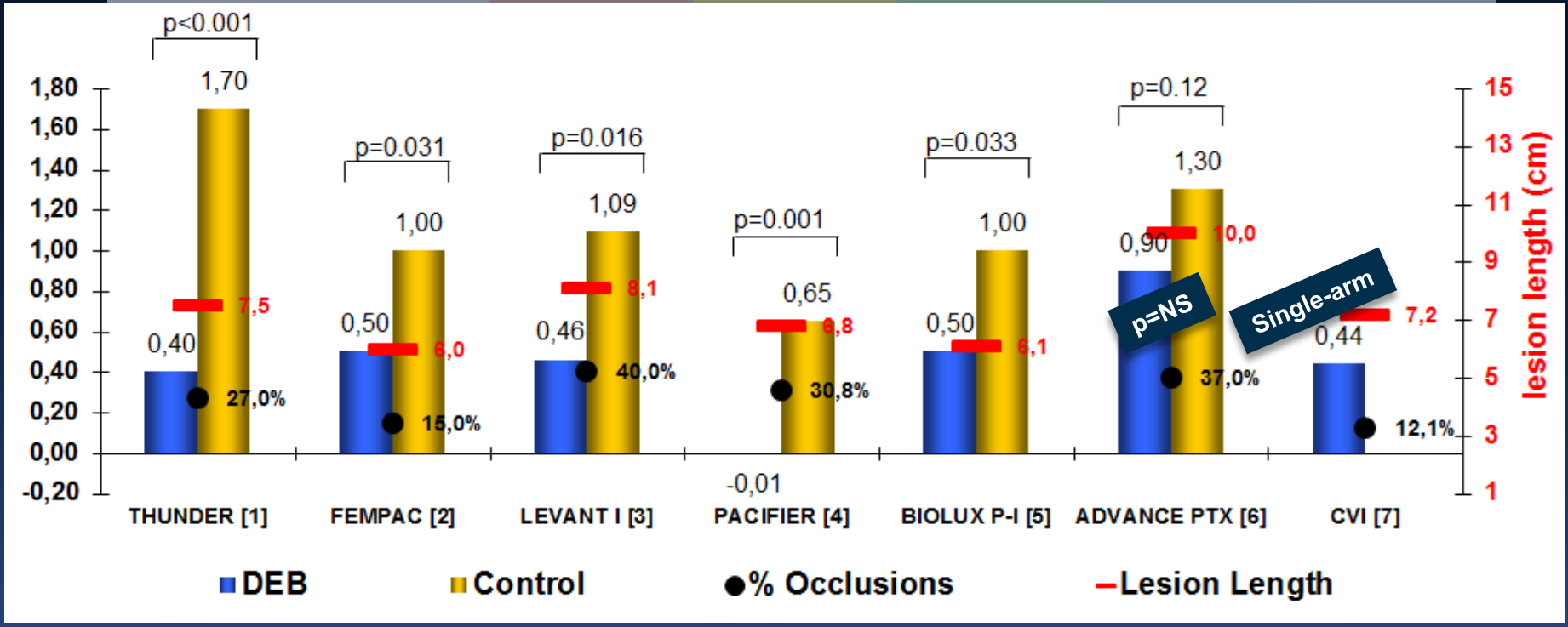


Efficacy in Femoro-Popliteal Arterial Vascular Disease

DEB in SFA Evidence: FIH Trials

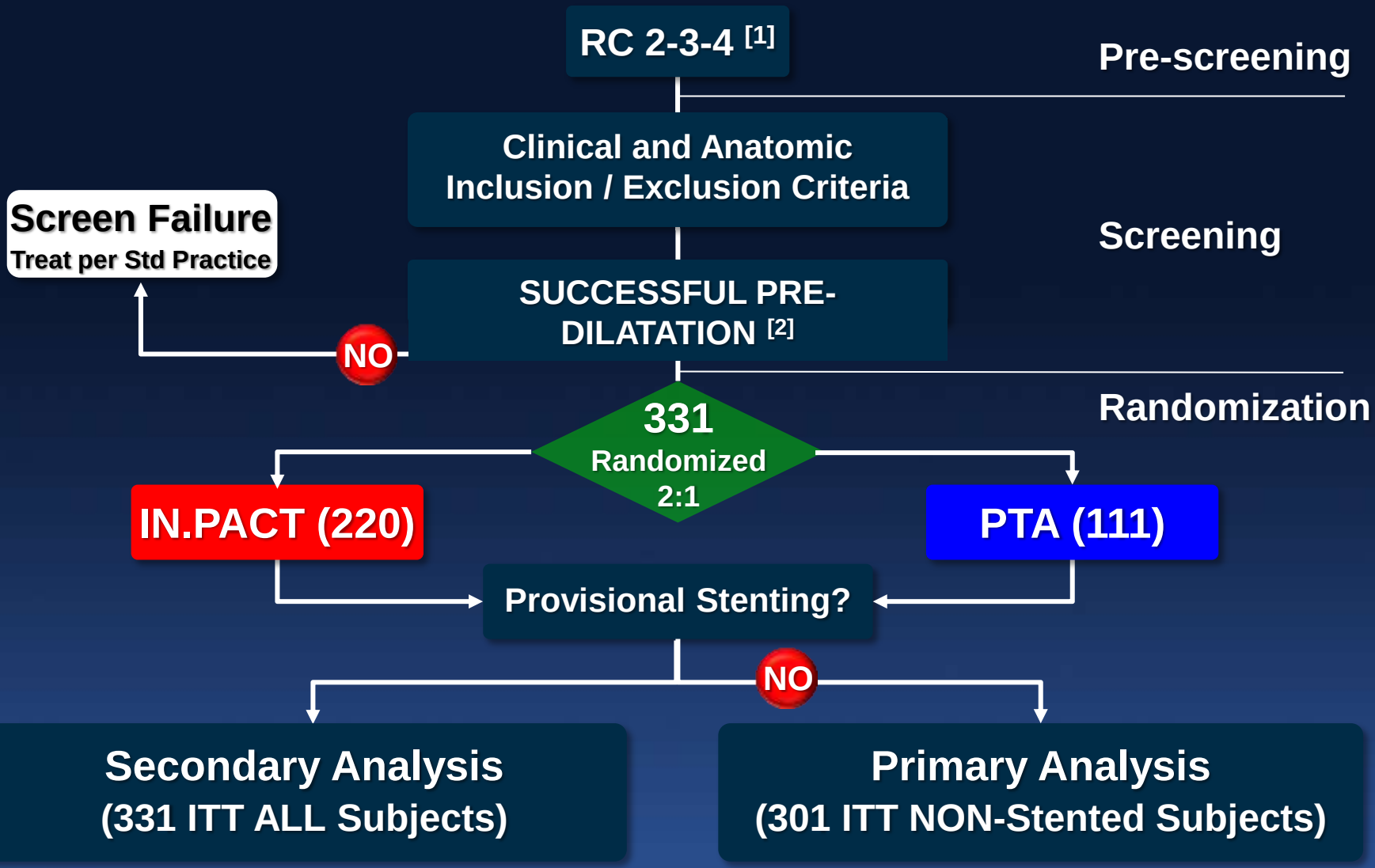
7 Trials / 6 DEB Technologies; 6-month LLL (Primary Endpoint)

PACCOCATH	LUTONIX	INVATEC-MDE	PASSEO 18 LUX	ADVANCE PTX	STELLAREX
PTX 3µgr/mm² + Ultravist	PTX 2µgr/mm² + Sorbitol	PTX 3µgr/mm² + Urea	PTX 3µgr/mm² + BTHC	PTX 3µgr/mm² NO Excipient	PTX 2µgr/mm² Polymer-Based



[1] G.Tepe et al. - NEJM 2008; [2] M.Werk et al. - Circulation 2008; [3] D.Scheinert - TCT 2012 oral presentation; [4] M.Werk et al. - Circulation CI 2012; [5] D.Scheinert – EuroPCR 2012 oral presentation; [6] D.Scheinert – LINC 2013 oral presentation; [7] S.Duda – EuroPCR 2013 oral presentation

IN.PACT SFA: Trial Design



1. With symptoms of claudication and/or rest pain and angiographic evidence of SFA/PPA stenosis
2. Pre-dilatation mandatory for all subjects in IN.PACT SFA II phase only

Per Protocol-12-Month Outcomes

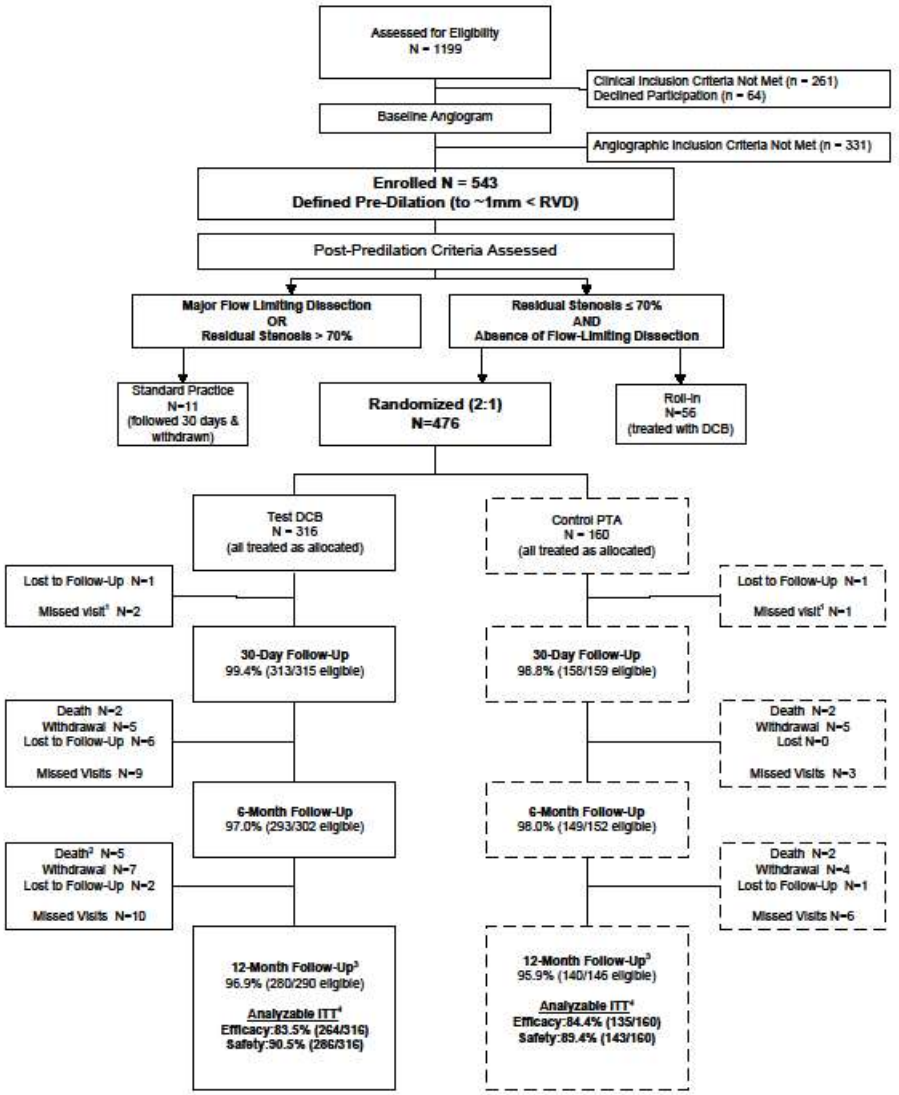
Primary Efficacy Primary Patency [1]	IN.PACT	PTA	Difference [95% CI] [2]	*p* [2]
Non-Stented ITT	82.9%	52.2%	29.0% [16.2%, 41.8%]	*<0.001*
All ITT	82.2%	52.4%	26.2% [15.1%, 37.3%]	*<0.001*

Primary Safety Composite[3]	IN.PACT	PTA	Difference [97.5% CI] [4]	*p*
Non-Stented ITT	95.8%	77.7%	12.2% [1.2%, ∞] [4, 5]	*NA*
			18.2% [9.3%, 27.0%]	*<0.001* [6]
All ITT	95.7%	76.6%	19.0% [11.5%, ∞] [4]	*NA*
			19.0% [10.5%, 27.5%]	*<0.001* [6]

1. Primary patency is defined as freedom from clinically-driven TLR and freedom from restenosis as determined by duplex ultrasound (DUS) Peak Systolic Velocity Ratio (PSVR) ≤ 2.4
2. Primary patency comparative statistics imputed missing data and non-stented ITT were adjusted for Propensity Score
3. Primary safety composite is defined as freedom from device and procedure-related 30-day death and freedom from target limb major amputation and clinically-driven TVR through 12 months
4. Non-inferiority margin −10%
5. Non-stented ITT cohort difference adjusted for Propensity Score
6. p-value associated with sequential superiority test

Tepe G et al. Circulation 2014, in revision

LEVANT II



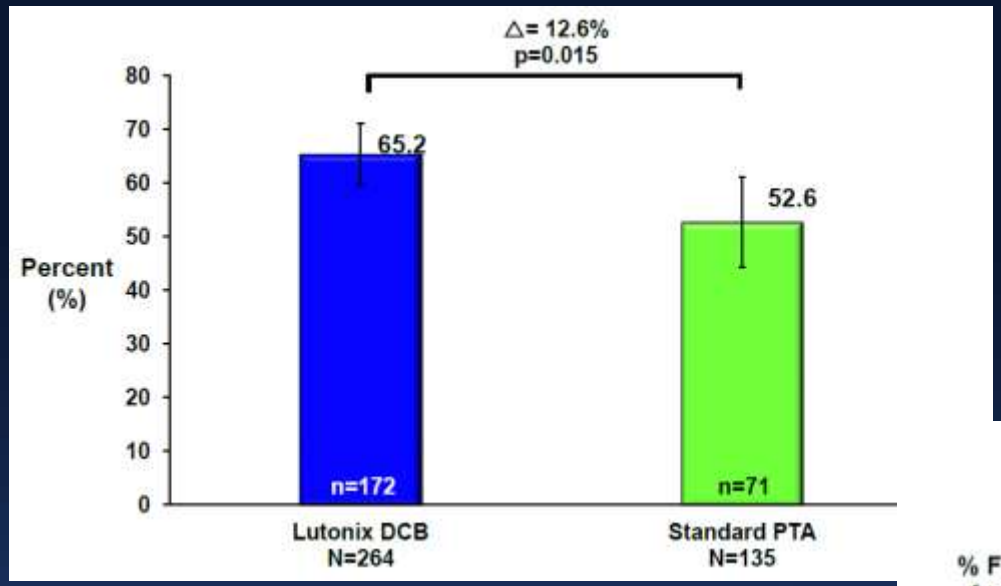
[1] Telephone follow-up allowed at 30 days per protocol 50.3% test vs. 49.7% control patients had in-person clinical visits.
[2] One DCB patient died within the 12-month window after completing a 12-month visit
[3] At 12 months, clinical information was obtained by telephone for n =11 vs 5 patients, and 269 (93.7%) test vs 135 (93.1%) control patients had in-person clinical visits.
[4] All endpoint failures occurring prior to study discontinuation are included as Analyzable ITT. Analysis for Primary Safety requires evaluable clinical follow-up only; Primary Efficacy requires both evaluable Doppler and evaluable clinical follow-up.

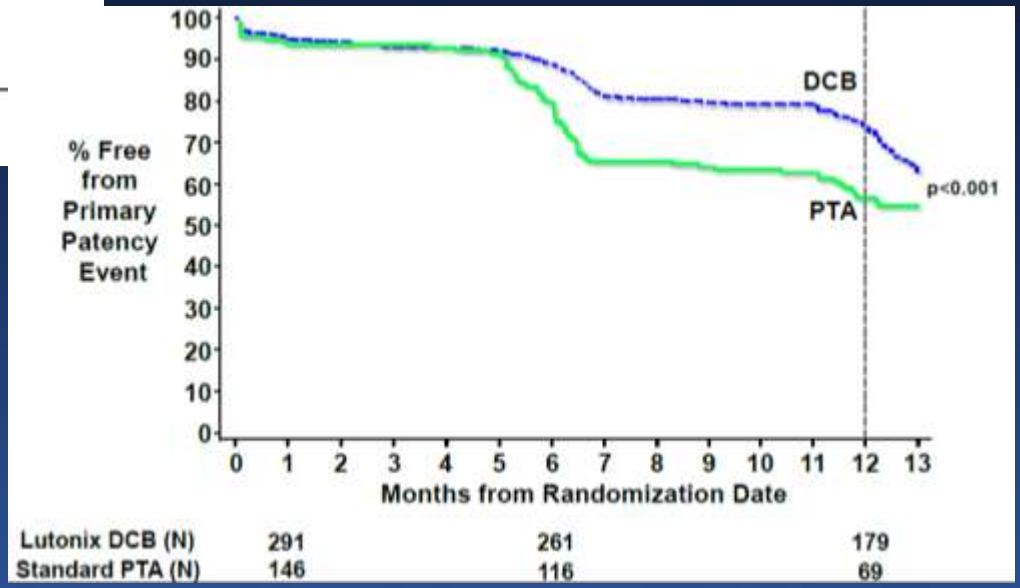
Lesion Characteristics (PCB vs. PTA)

- Number of Lesions Treated, % (no.)
  - One Lesion 98.1(310) vs. 96.9 (155)
  - Two Lesions 1.9 (6) vs. 3.1 (5)
- Total Lesion Length (mm), $\bar{x}\pm SD$
  - 62.7 ± 41.4 vs. 63.2 ± 40.4
- Treated Length (mm), $\bar{x}\pm SD$
  - 107.9 ± 47.0 vs. 107.9 ± 49.4
- Percent Stenosis (%DS), $\bar{x}\pm SD$
  - 80.5 ± 14.8 vs. 80.9 ± 14.9
- TASC II Classification, % (no.)
  - TASC A 76.3 (241) vs. 75.6 (121)
  - TASC B 21.5 (68) vs. 23.8 (38)
  - TASC C 2.2 (7) vs. 0.6 (1)
- Calcification, % (no.)
  - 59.2 (187) vs. 58.1 (93)
- Severe Calcium 10.4 (33) vs. 8.1 (13)
- Total Occlusion, % (no.)
  - 20.6 (65) vs. 21.9 (35)

LEVANT II

1-Year Primary Patency





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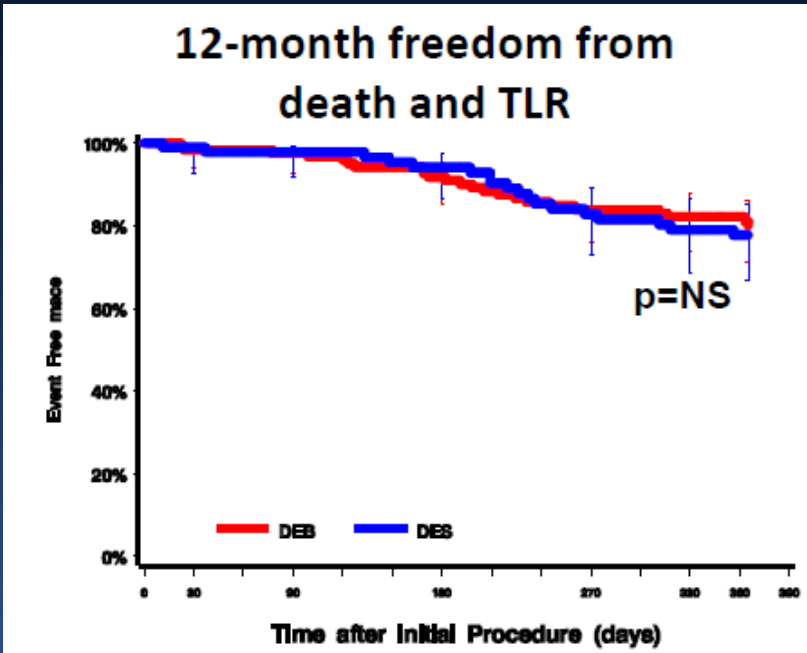
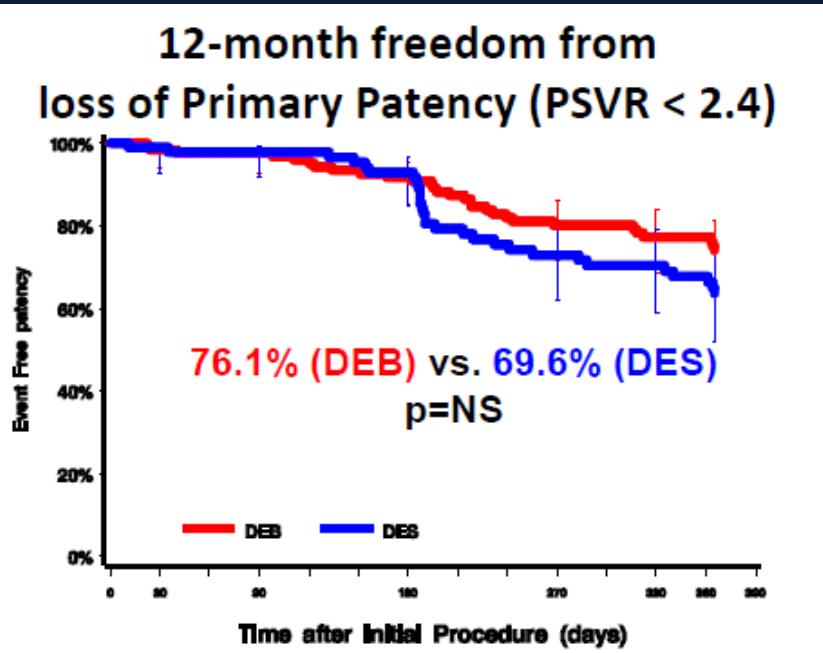
IN.PACT vs. DES in Long SFA Lesions

228-Patients *Retrospective, Propensity Score Analysis*

- Lesions ~19 cms in length
- Non significant difference between IN.PACT DCB and Zilver PTX in long SFA lesions
- Provisional stent rate post DCB = 18.3%





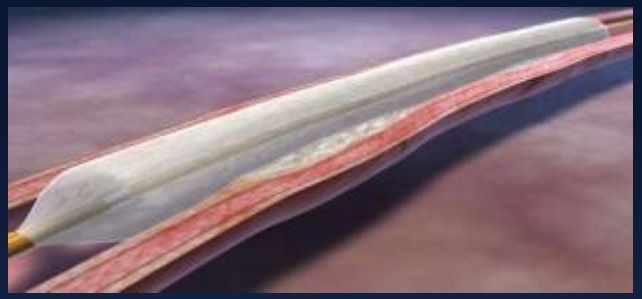
Zeller T, CRT 2015

Zeller T. et al. JEVT 2014

Future Perspectives in Local Drug Delivery

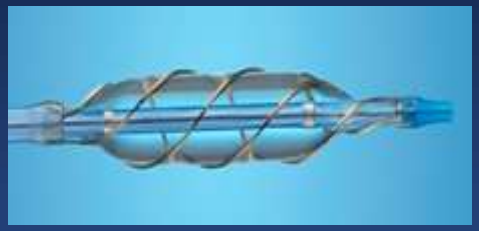
PCB + *Adjunctive* Use with Other Emerging Technologies

Drug Coated Balloons



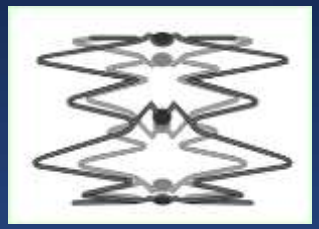
Local Drug Delivery

Scoring Balloons



Plaque Modification

Partial Scaffold



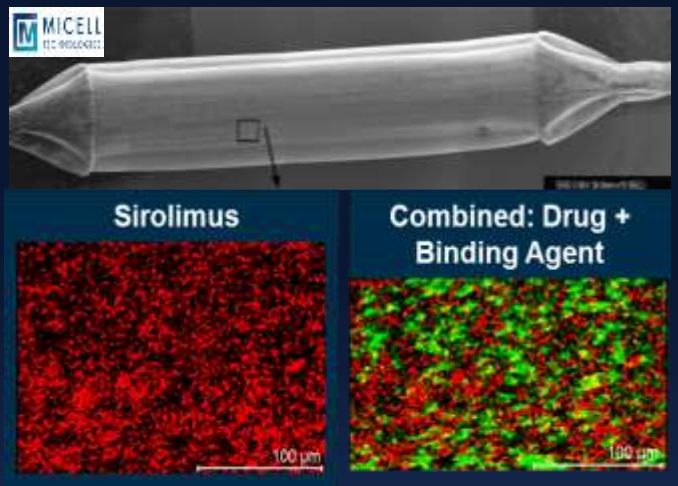
Bioresorbable Scaffolds

- Less Dissections
- No Scaffold Needed?

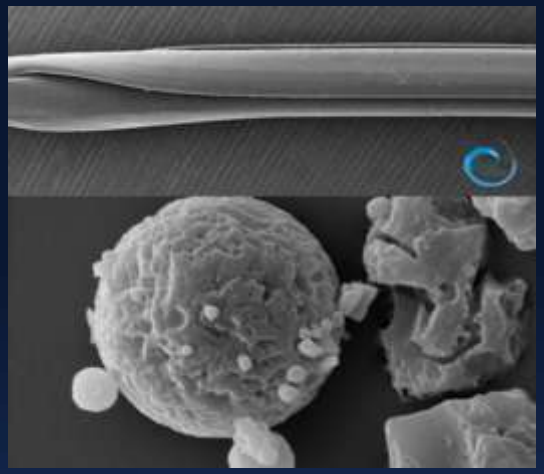
- Minimal vs. Temporal Scaffold
- Bigger Lumen Gains

Sirolimus DCB and DEB Concepts

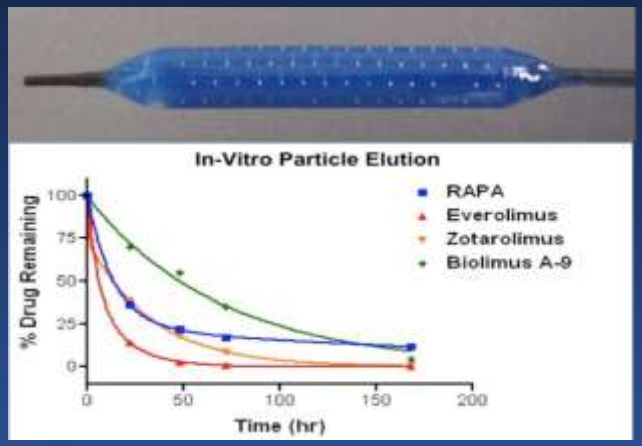
Microcrystalline Coating



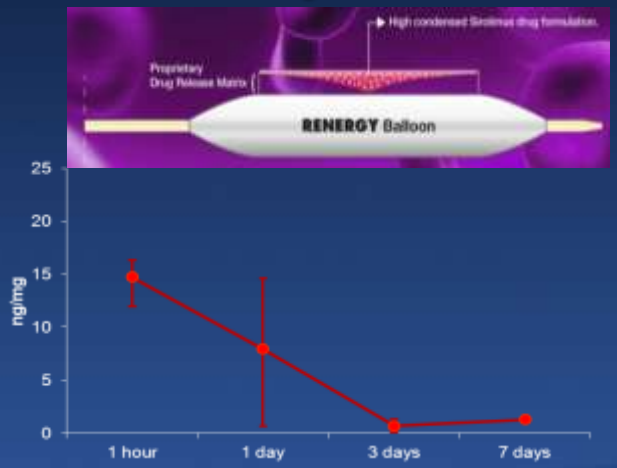
Nano-Carrier Coating



Nano-Encapsulated Delivery



Vitamin-Fatty Acid Coating



Conclusions

- ***DES-ISR*** is the perhaps one of the few ***indications for the use of DCB*** in the coronary territory, consider DCB when:
  - ***Focal ISR***, stent under-expansion is present or high bleeding risk or requiring DAPT interruption
- Level I clinical evidence already exist in regards to the performance ***of DCB in femoro-popliteal lesions*** in ***relatively short lesions (10 cms)***
  - The biological effect on restenosis in longer and complex lesions require further investigation
- DCB coating technologies will continue to evolve focusing on the applications of ***new drugs, carriers and delivery methods*** aiming to achieve:
  - Optimal transfer rates and tissue retention at low doses
  - Lower particulate formation and drug loss in transit