Beyond Drug Eluting Stents: New Technology of Local Drug Delivery

An Overview of Drug Eluting Balloon Technologies

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New Drug Carrier Systems
A Simplified Classification Roadmap

Common Features of New Drug Carrier Systems

- Minimal polymeric load.
- Biodegradable matrixes.
- Natural carriers (i.e., collagen).
- Non-polymeric based surfaces or carriers.
- Direct deposition on the device surface.
- Direct "burst" delivery into the vessel wall.

High loading doses, shorter vessel retention, more "erratic" and uncontrollable tissue levels.

Classification Roadmap
Delivery Method (Technology)

Stent Based

Coating Based Technologies
- Bioabsorbable Polymers
  - Uniform (Biosensors)
  - Abluminal (LabCoat)
- Biological Coatings (MIV)

Direct Surface Deposition
- Physical Deposition
  - Carrier Based (Atrium)
  - Surf. Modification (Biosensors)
- Ligand-Based Deposition (PC)

Non-Stent Based

Direct Drug Deposition
- Sequent Please™ (B. Braun)
- Paccocath™ (Medrad)

Stopped-Flow Delivery Catheters
- Genie™ (Acrostak)

Pressure-Enhanced Delivery
- Remedy™ (BSCI)
- Clearway™ (Atrium Medical)

Micro-Infusion to the Adventitia
- Cricket™ and Bullfrog™ (Mercator)

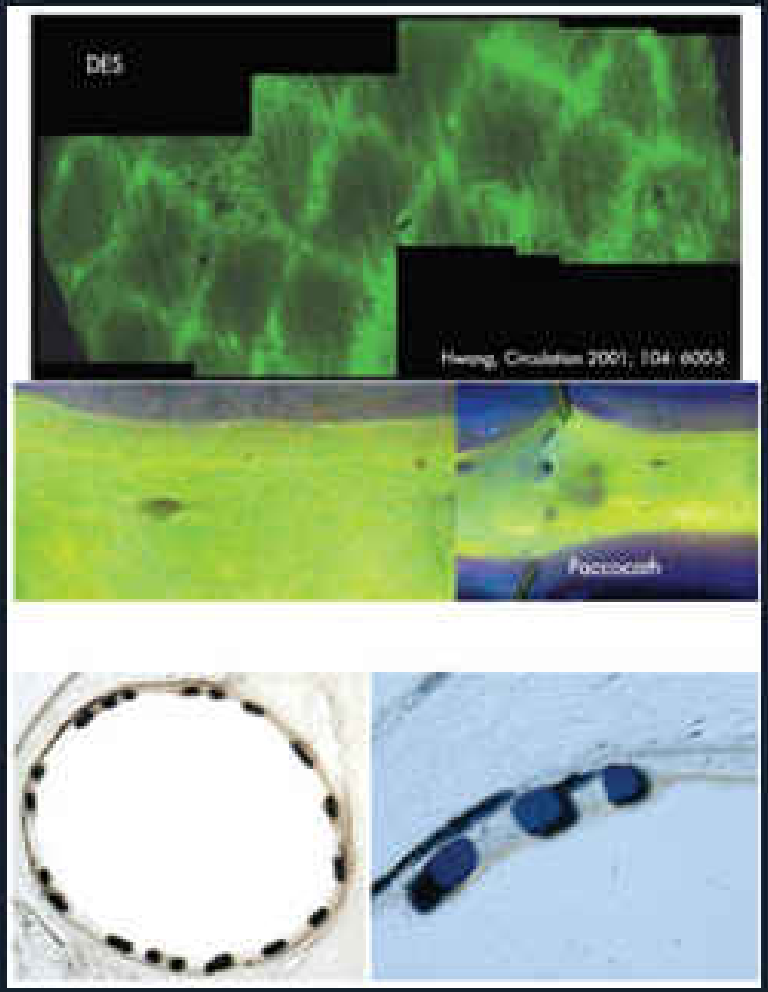
Technological Assumptions

Emerging Drug Carrier Systems

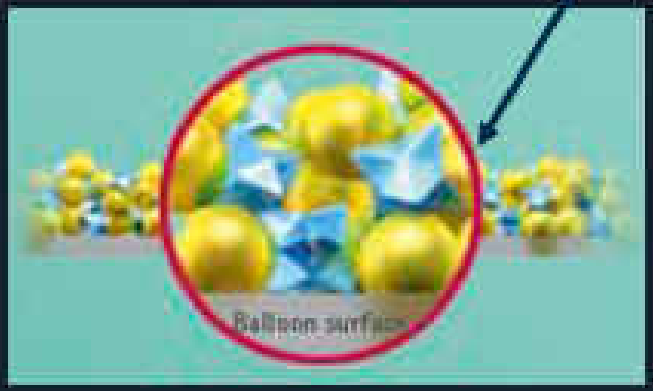
- **In general…a permanent drug carrier is just not completely needed.**
- **Total vessel delivery is a function of the effective *contact* surface area (delivery device-vessel target area).**
- **A single initial burst dose may be sufficient.**
- ***Shorter tissue retention may do the "trick".***
- **Cumulative lower effective doses (compared to DES) may be effective.**
- ***Early modification of the repair mechanisms may lead to less restenosis.***

PACCOCATH Technology

Matrix Coating Description



Paclitaxel + Hydrophilic Spacer (Iopromide)



The hydrophilic spacer leads to:

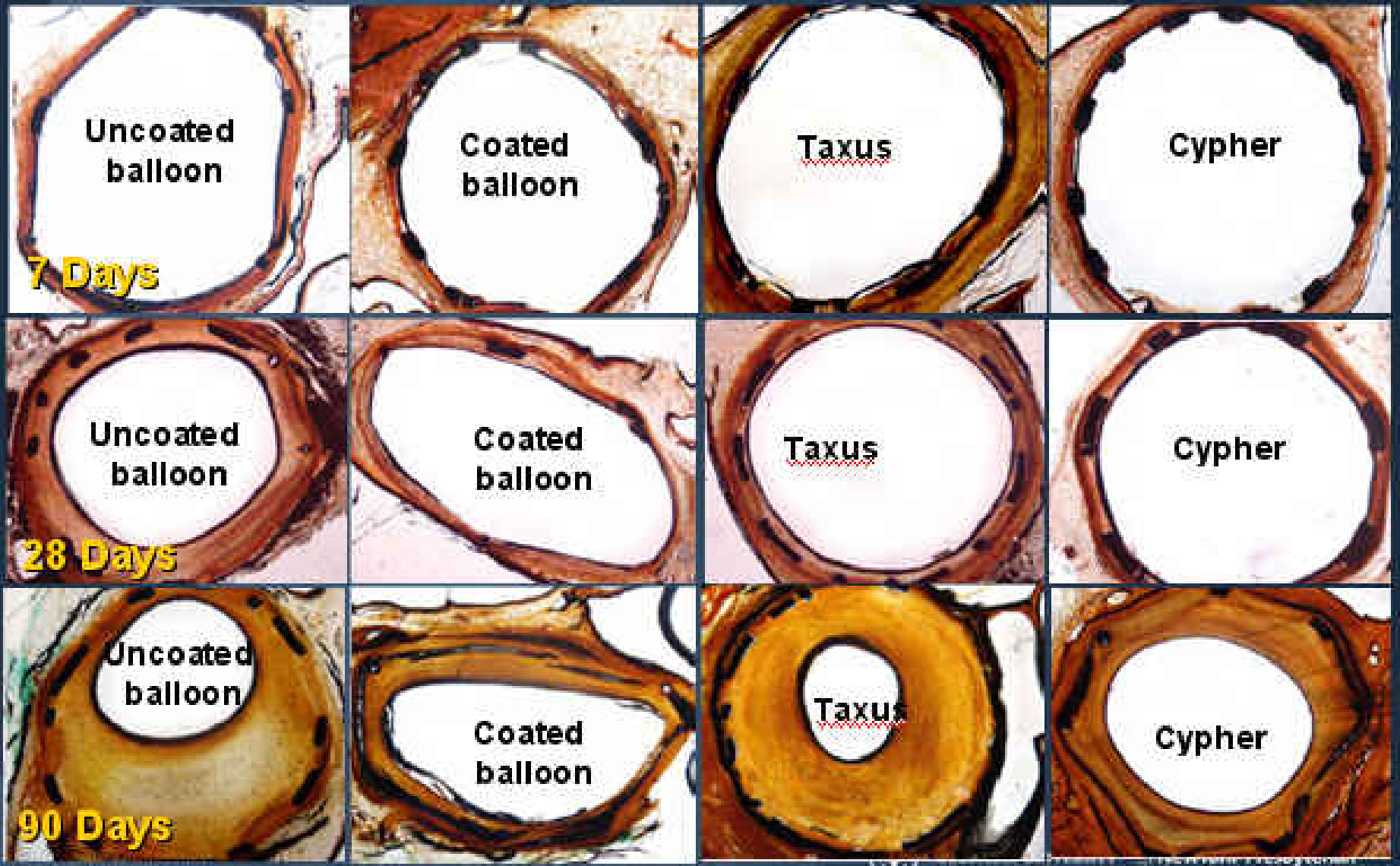
- Porous coating with a ***high contact surface*** between the lipophilic drug molecules and the vessel wall.
- Drug release through vessel contact following balloon expansion.
- High bioavailability of Paclitaxel on the target side for rapid drug absorption by the vessel wall

Paclitaxel Delivery Directly into the Vessel Wall Using a DEB: PACCOCATH

DEB followed by BMS, 22 pigs, 28 days observation

Minimal lumen diameter (mm)			
1.43 ± 0.79	1.98 ± 0.70	2.48 ± 0.89	2.81 ± 0.78
Late lumen loss (mm)			
2.02 ± 0.77	1.84 ± 1.06	0.87 ± 0.92	0.49 ± 0.83
Luminal area (mm^2)			
2.85 ± 0.82	2.72 ± 1.11	3.96 ± 0.93	5.62 ± 1.02
Neointimal area (mm^2)			
4.05 ± 1.07	4.40 ± 1.32	2.35 ± 0.87	1.49 ± 0.41

Paclitaxel Delivery Directly into the Vessel Wall Using a DEB: PACCOCATH



PACCOCATH ISR I/II: 2 Years Follow Up

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Treatment of Coronary In-Stent Restenosis with a Paclitaxel-Coated Balloon Catheter

Bruno Scheller, M.D., Christoph Hehrlein, M.D., Wolfgang Bocksch, M.D., Wolfgang Rutsch, M.D., Dariush Haghi, M.D., Ulrich Dietz, M.D., Michael Böhm, M.D., and Ulrich Speck, Ph.D.

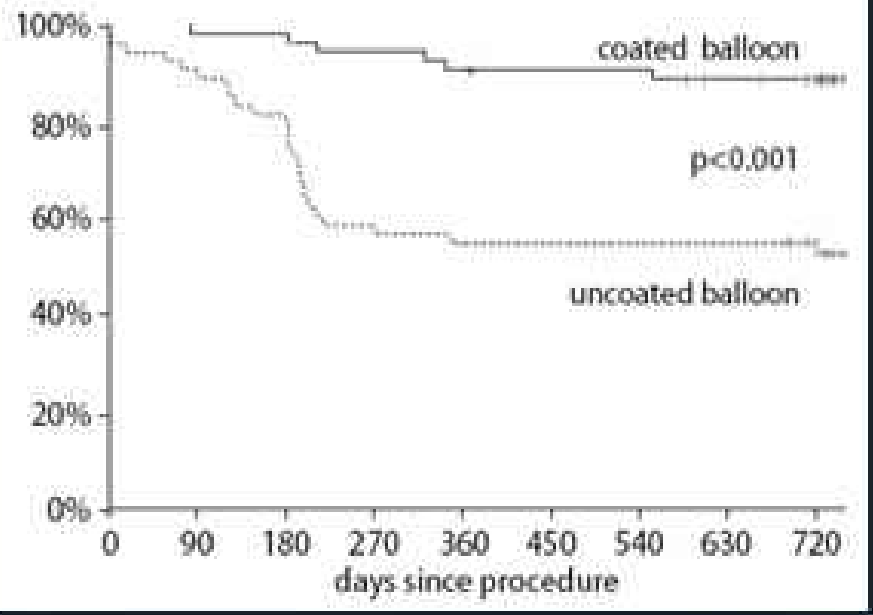
ORIGINAL PAPER

Two year follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter

Primary Endpoint (Late Lumen Loss In-Segment)

Uncoated balloon	PACCOCATH
0.74 ± 0.86 mm	0.03 ± 0.48 mm

New Engl J Med 2006, 355: 2113-24
Clin Res Cardiol 2008; 97: 779-81



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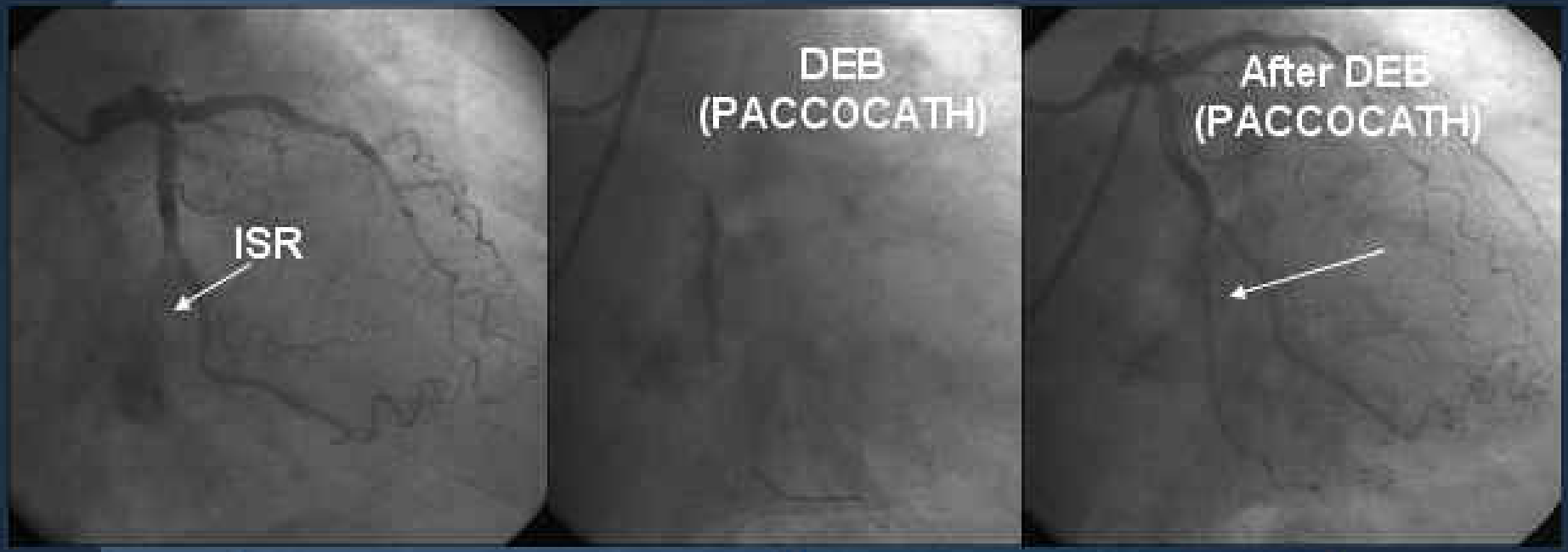
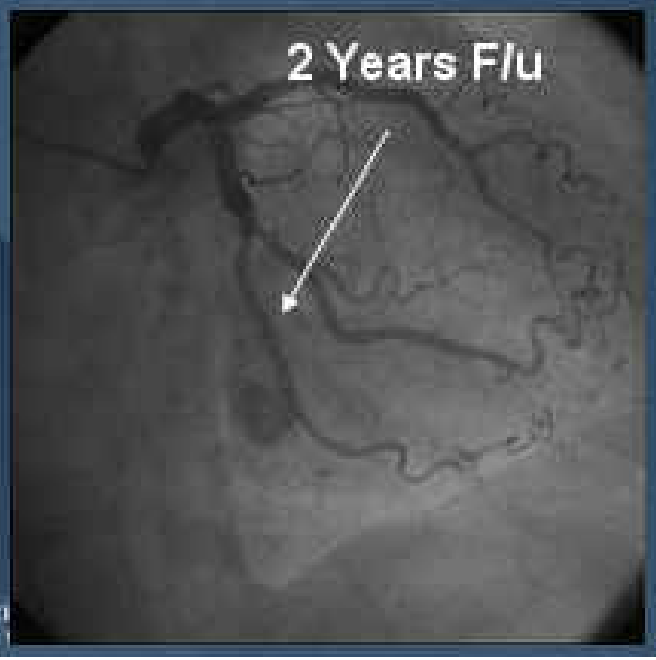
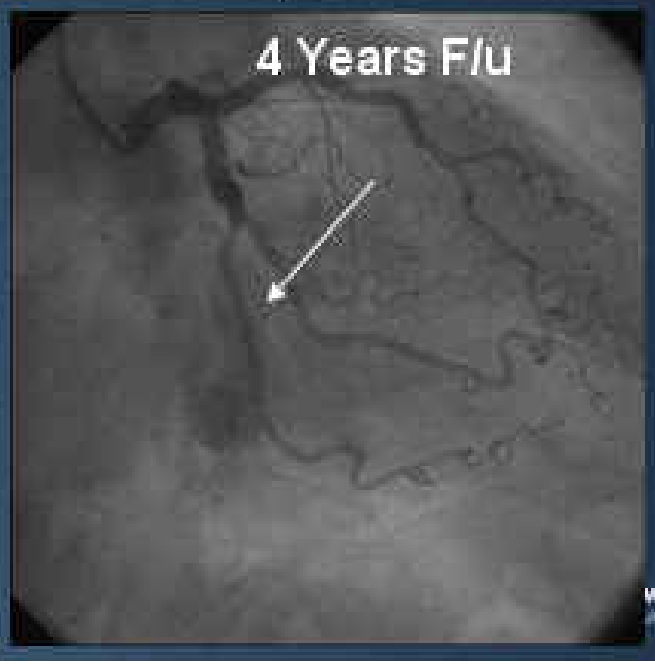
PACCOCATH ISR I & II – Follow-up 4 Years







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Technological Assumptions
Emerging Drug Carrier Systems

- In general…a drug carrier is just not completely needed.
- Total vessel delivery is a function of the effective *contact* surface area (delivery device-vessel target area).
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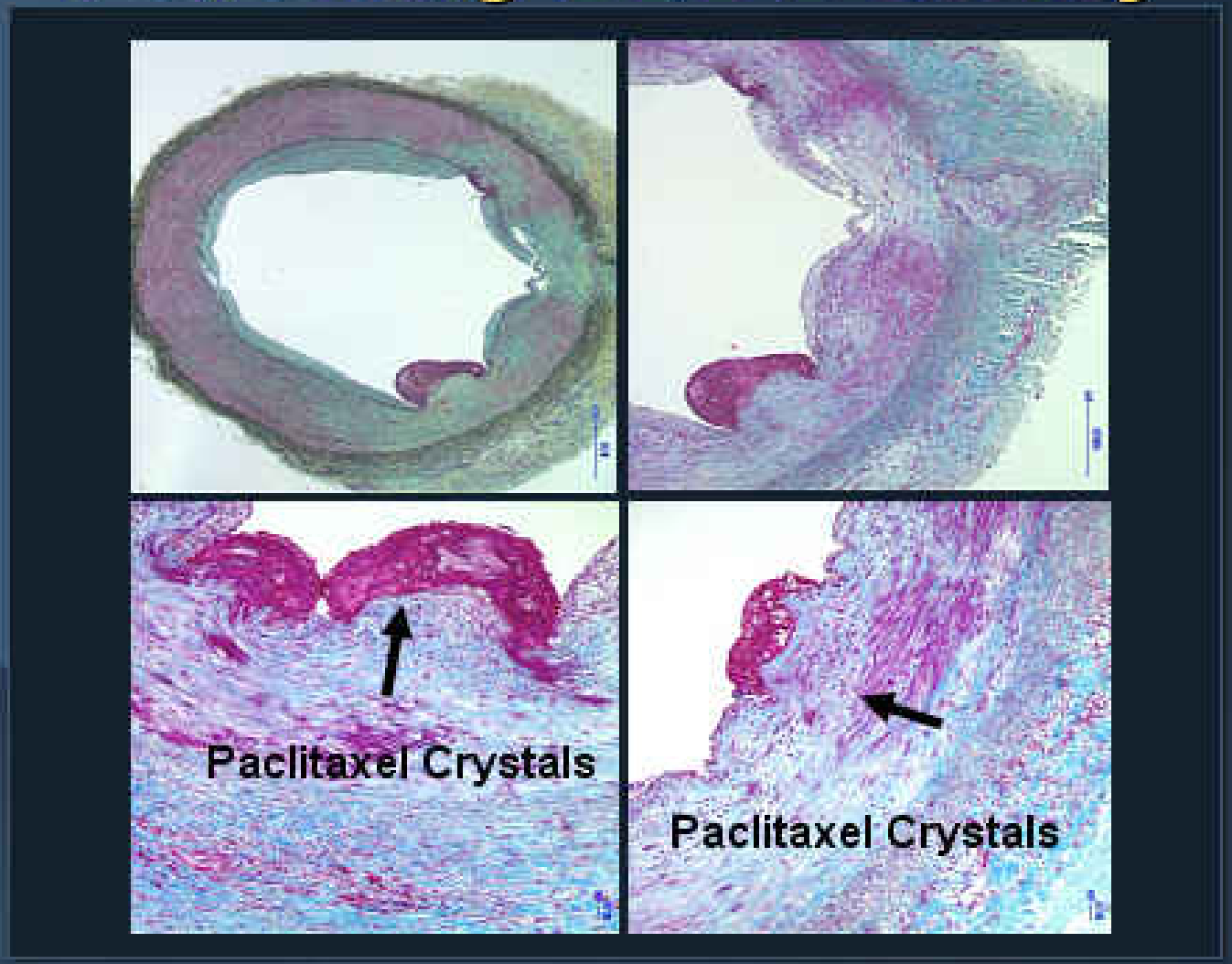
- *Early modification of the repair mechanisms may lead to less restenosis.*

What Do Most of Emergent Stent Carriers Still Have in Common?

Asymmetric Deposition of Paclitaxel Following DEB Delivery



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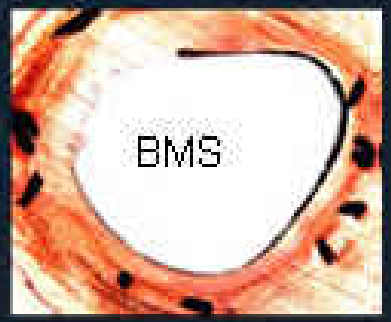
Comparison of Several Non-Polymeric Drug Delivery Stent Based Technologies

	Compatibility with Drugs	*Low-Residue Process*	*Surface Feature*	*Same Material as Stent*	*In vivo Drug Release Kinetics/ Residual tissue [drug]*	*Comments*
Setagon	High	Yes	Smooth	Yes	Days/Wks	Nanoporous metal
Translumina	High	Yes	Rough	Yes	Days/Wks	Roughened surface, surface drug application
Blue Membranes	High	Yes	Rough	No	Days/Wks	Micro- to macro-porous carbon/carbon composite
MIV Therapeutics	High	Yes	Rough	No	Days/Wks	Thin hydroxy-apatite coating
Electroformed Stents Inc.	High	No	Rough	No	Days/Wks	Electroplated coating
Medtronics/NTI	Low	No	Rough	No	Days/Wks	Electrolysis co-deposition
Atrium	High	Yes	Smooth	No	Days/Wks	OFA surface deposition

Impact of Exposure Time on Paclitaxel Drug Delivery

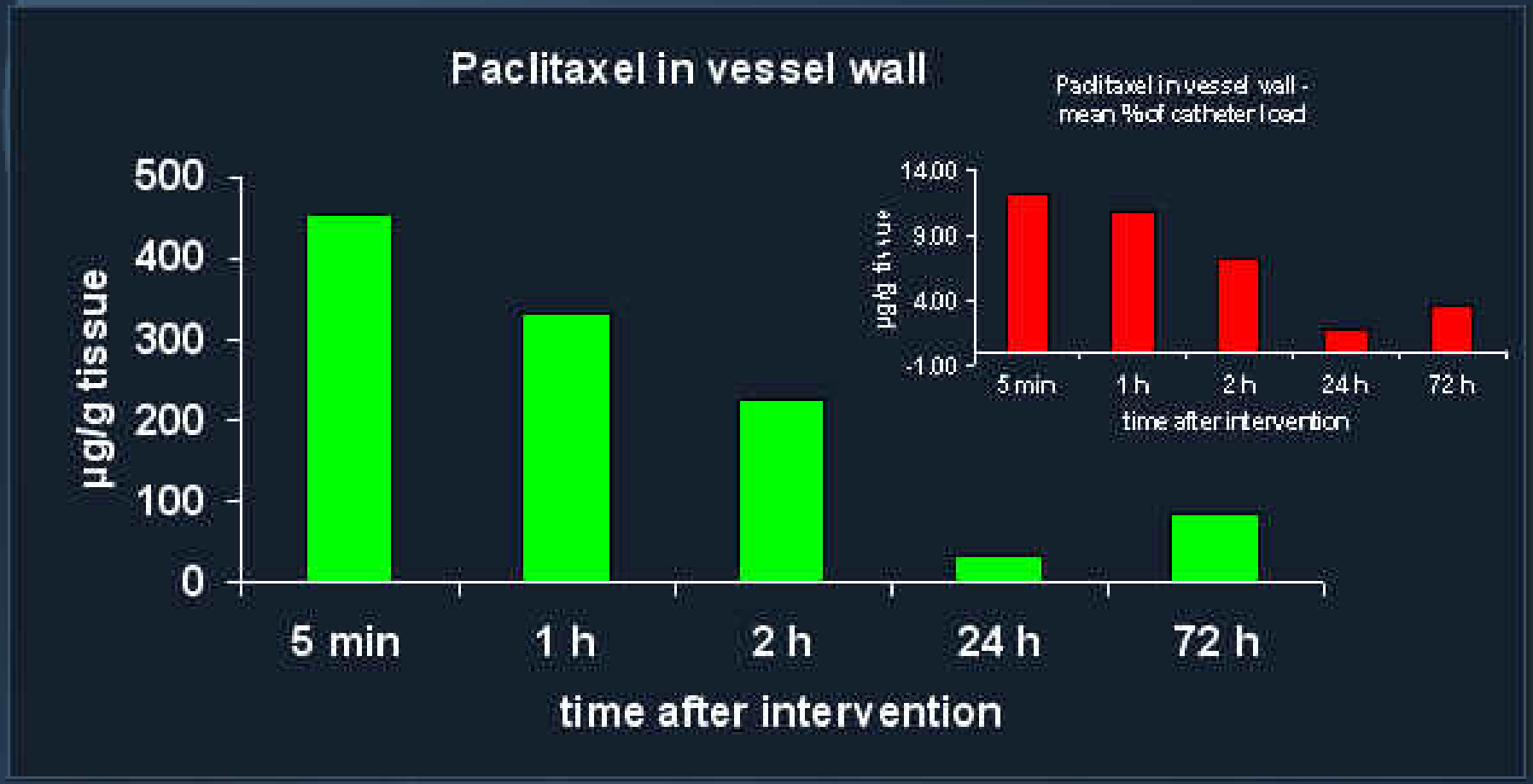
- *33 Pigs*
- *28 Days*
- *5 mcg/mm²*



	BMS	DES	DEB 10s
Luminal Area (mm²)	3.14 ± 0.93	3.70 ± 0.96	5.66 ± 0.89
Neointimal Area (mm²)	4.26 ± 1.18	3.31 ± 1.04	1.83 ± 0.40

	2 x DEB 60s	DEB 2 x 60s	2 x DEB 60s
Luminal Area (mm²)	5.97 ± 0.97	5.95 ± 1.31	6.26 ± 0.90
Neointimal Area (mm²)	1.68 ± 0.23	1.86 ± 0.33	1.67 ± 0.46

Paclitaxel Delivery Directly into the Vessel Wall Using a DEB: PACCOCATH



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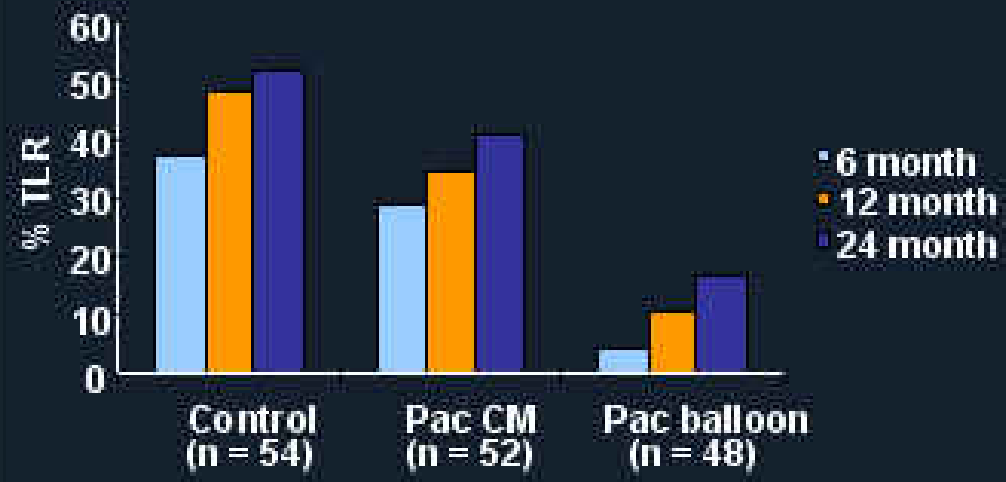
PEPCAD II ISR
Angiographic Follow-Up

	SeQuent Please	Taxus	p
n	66	65	
Angiographic Follow-up	57 (86.4%)	59 (90.8%)	0.43
Late Lumen Loss			
In-Stent	0.19 ± 0.39 mm	0.45 ± 0.68 mm	0.01
In-Segment	0.17 ± 0.42 mm	0.38 ± 0.61 mm	0.03
Late LL Index			
In-Stent	0.12 ± 0.26 mm	0.28 ± 0.48 mm	0.03
In-Segment	0.11 ± 0.29 mm	0.30 ± 0.53 mm	0.02
Binary Restenosis			
In-Stent	4 (7%)	10 (16.9%)	0.10
In-Segment	4 (7%)	12 (20.3%)	0.04

Thunder Trial: Re-Intervention Rate by Target Lesion Revascularization

	PTX Balloon (n = 48)		PTX i.c (n = 52)		Control (n = 54)	
	N*	%	N*	%	N*	%
6-Month Follow-up	2	4.2	15	28.8	20	37
12-Month Follow-up	5	10.4	18	34.6	26	48.1
24-Month Follow-up	8+	16.7	21	40.4	28	51.9



* N = cumulative number of patients during the 24-month follow-up period

+ In the publication of the results in the N Engl J Med (2008) there are only 7 patients with TLR because at the timepoint of publication the database was not yet closed and the data correction phase was not yet finished.

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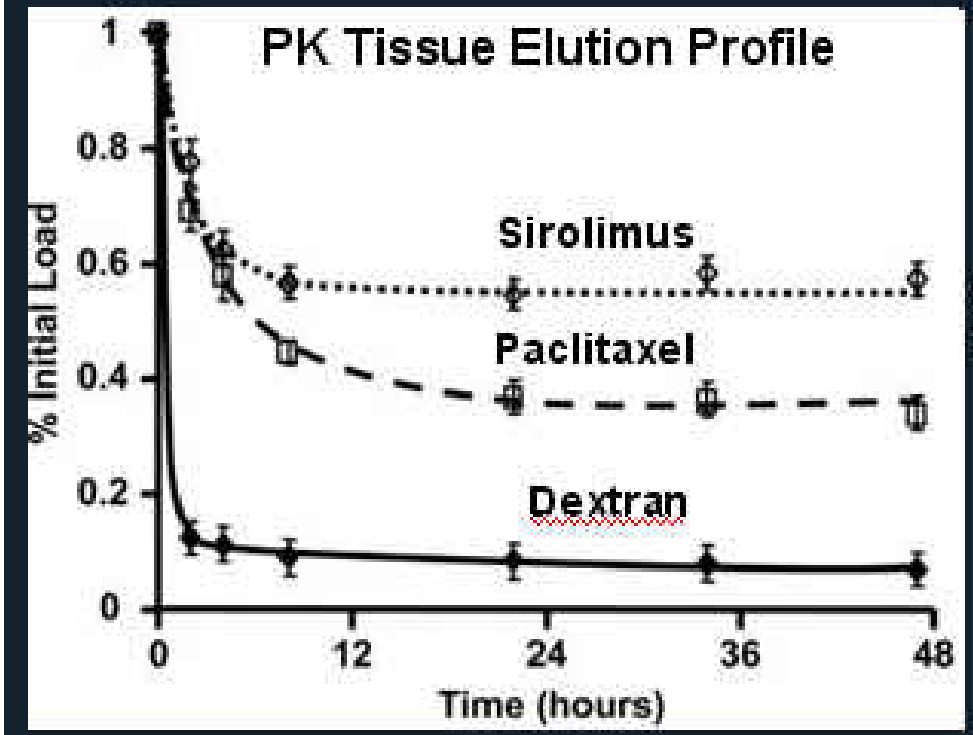
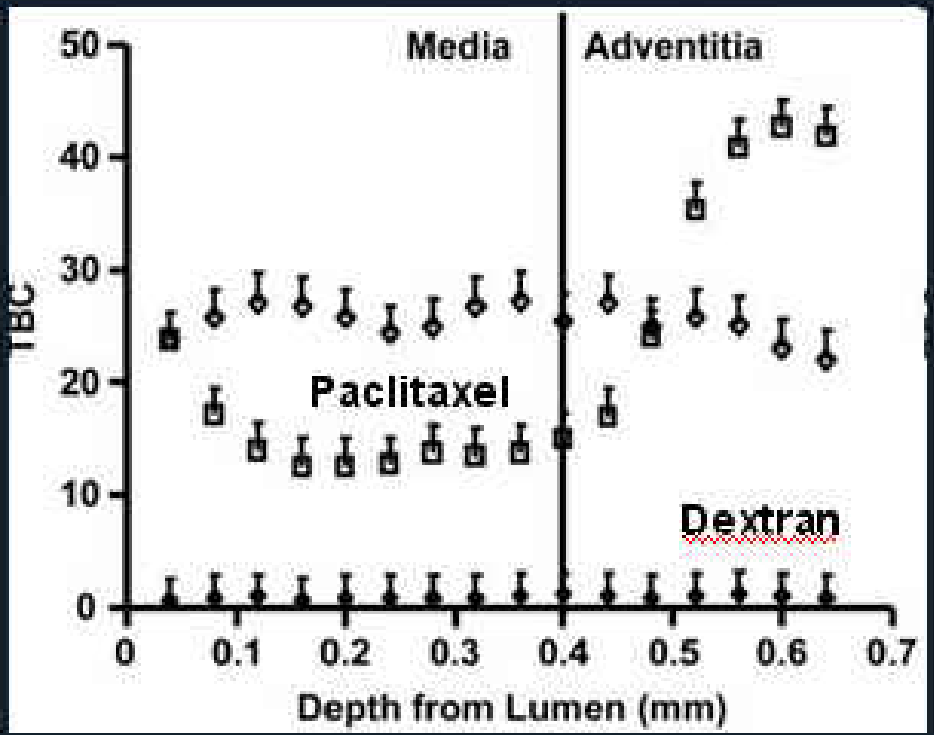
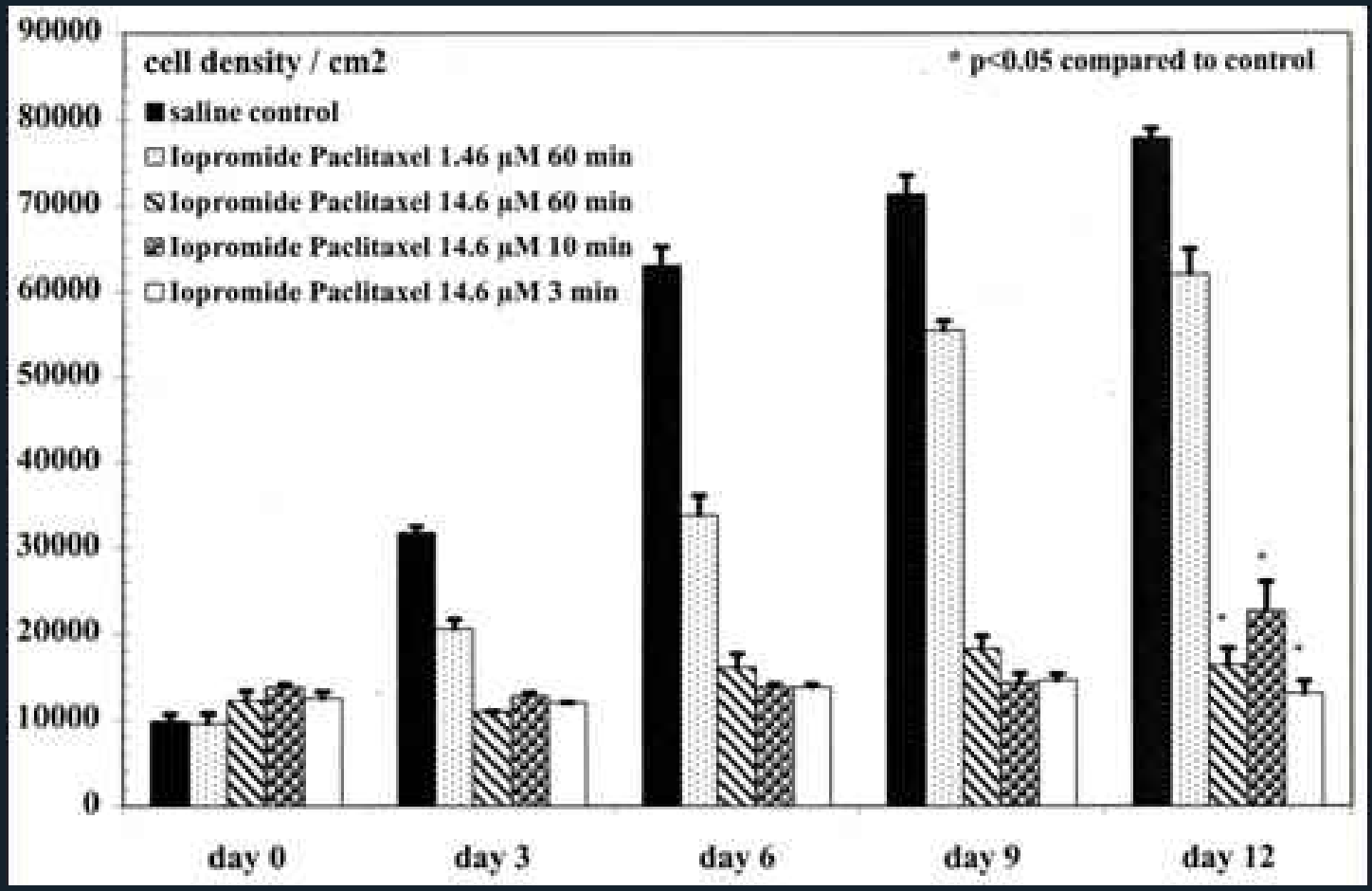
Specific Binding to Intracellular Proteins Determines Arterial Transport for Rapamycin & Paclitaxel





A. Levin et al., Proc Natl Acad Sci USA, 2004, 101, 9463-9467.

Persistence of Cellular Inhibitory Effect of Paclitaxel After 3 Minutes Exposure



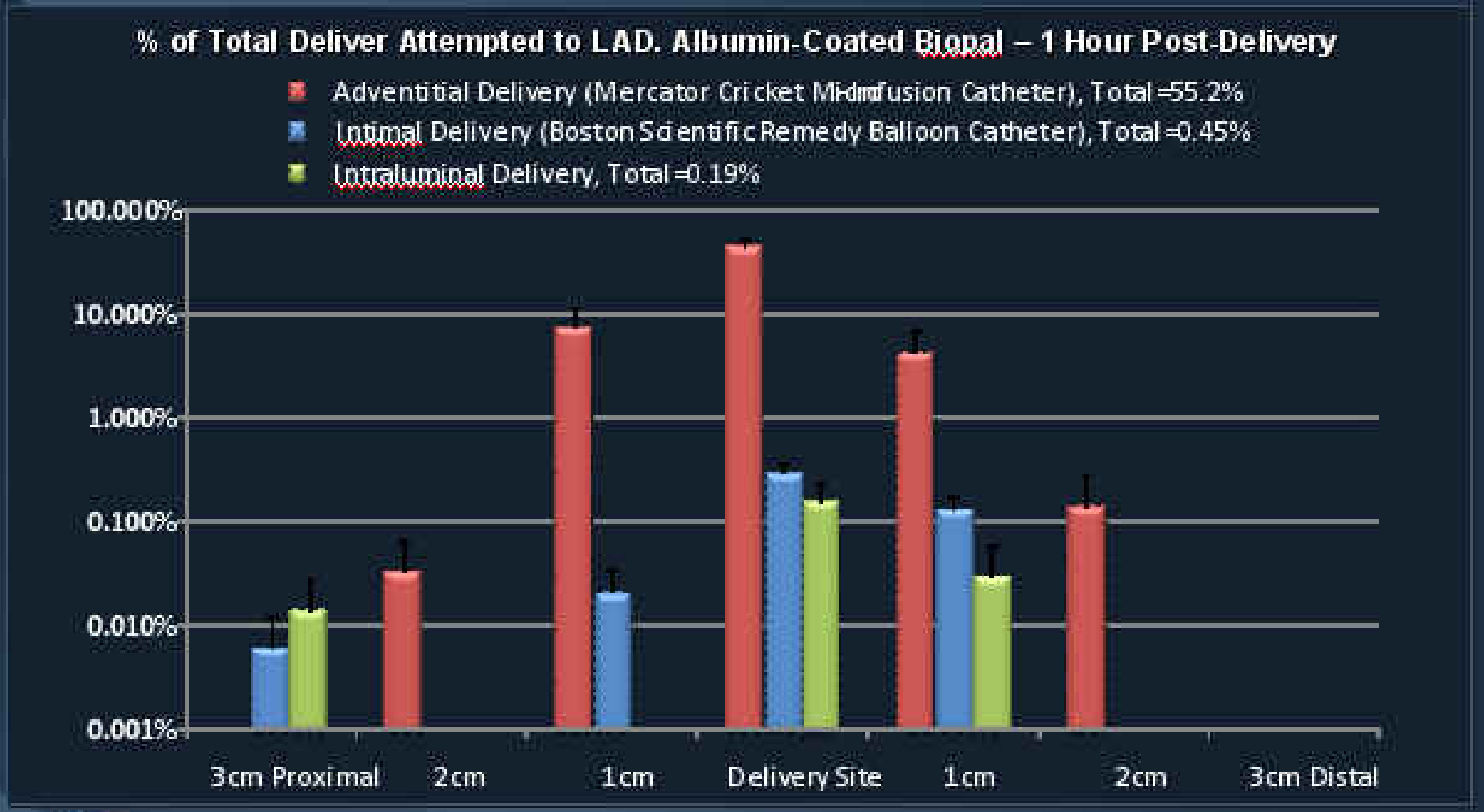
Scheller B. J Am Coll Cardiol, 2003; 42:1415-1420

Impact of the Biological Activity of the Drug in Emergent Drug Delivery Devices

- It is wrong to assume that all drugs will display a biological behavior similar to the Paclitaxel-Iopromide combination.
- The potential of achieving a sustained tissue retention is important.
- However, as the general concept is to "hit and run" the individual biological behavior of the drug may be more critical than the carrier per se.
- In general, the ideal drug profile must include:
- Lipophilic better than hydrophilic.
- Lower molecular weight (more drug per mm^2).
- Very high and rapid intra-cellular uptake.
- Irreversible and durable cellular effect.

What About the Delivery Site?

Drug Delivery Efficiency (Delivery Site)



JW Karanjan, LDDR 2007

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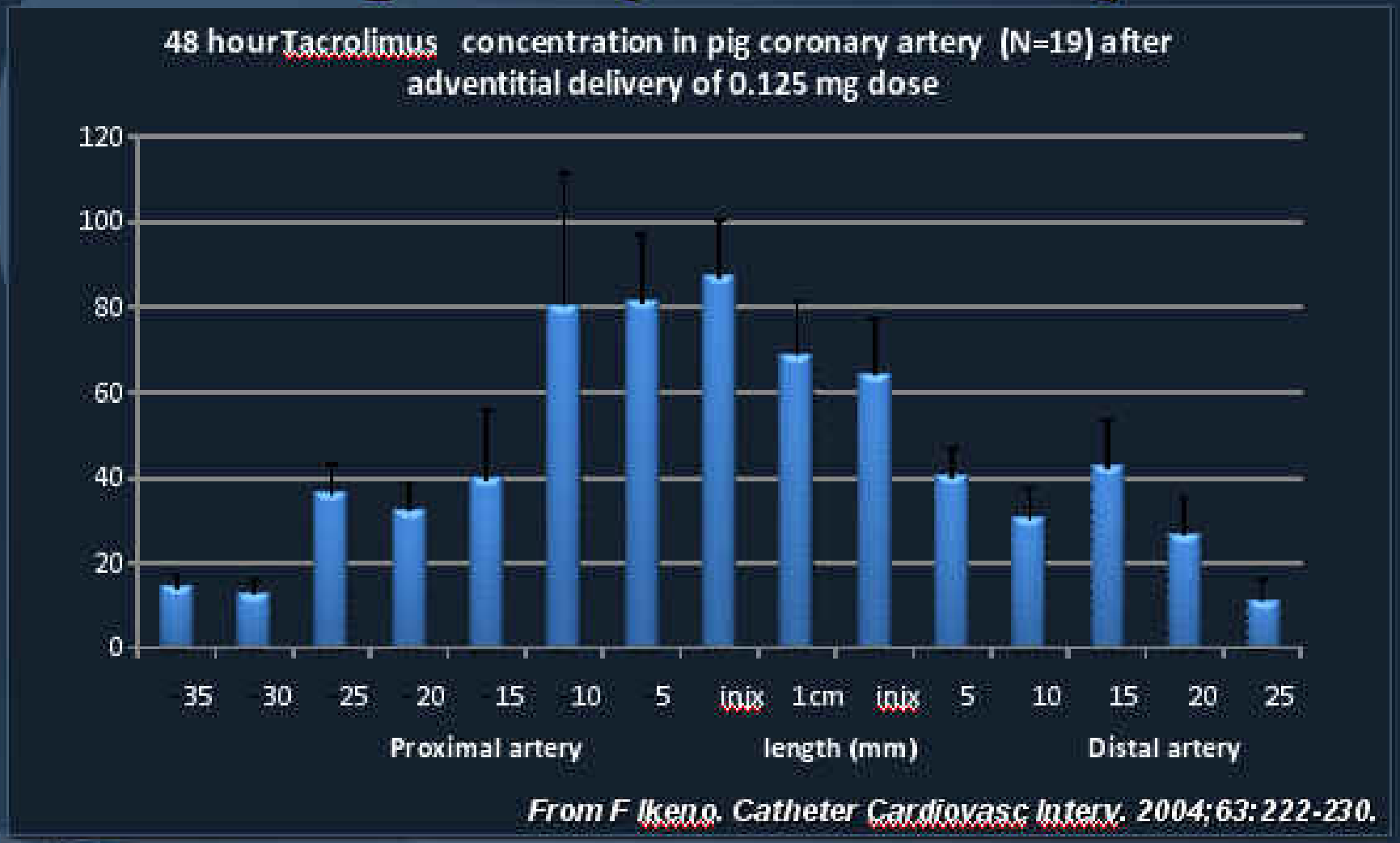
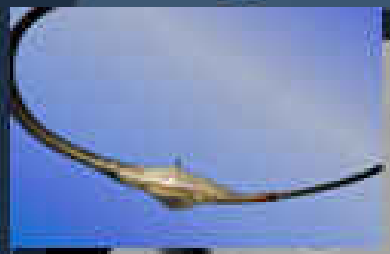
Adventitial Retention of Lipophilic Agents (Tacrolimus)

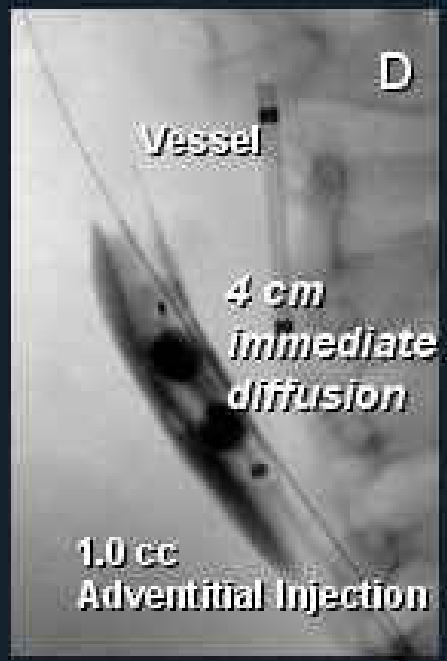


From F Ikeno. Catheter Cardiovasc Interv. 2004;63:222-230.

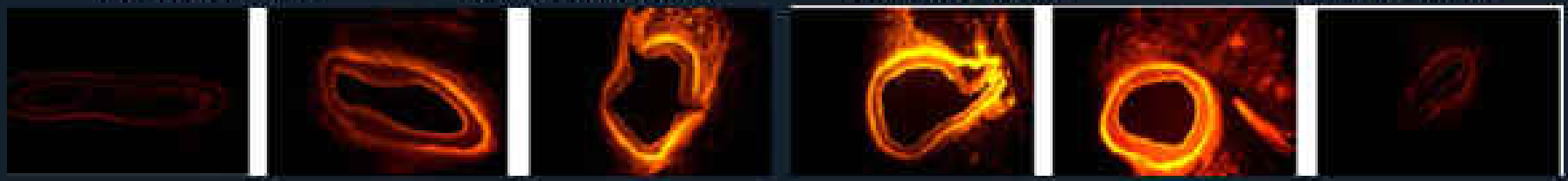
Emerging Drug Carrier Systems

Drug Delivery Efficiency (Delivery Site)





Pre-Treatment | BalloonInflation | Start Injection | 1 cc Injection



1-cm serial sections, 1 hr after adventitial delivery of 0.5 ml rhodamine in a porcine coronary artery

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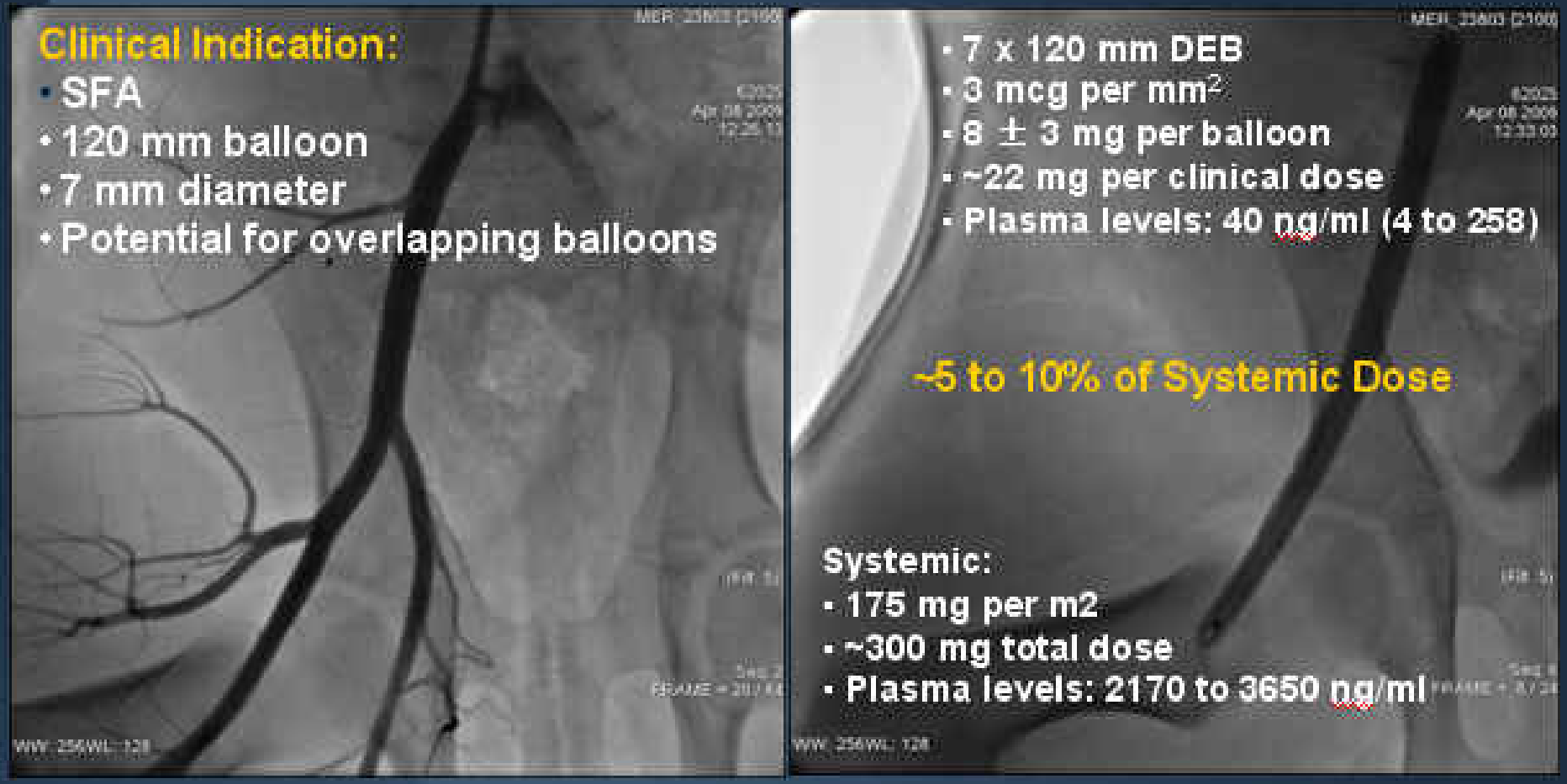
Drug Eluting Balloons and Potential for Systemic Toxicity…



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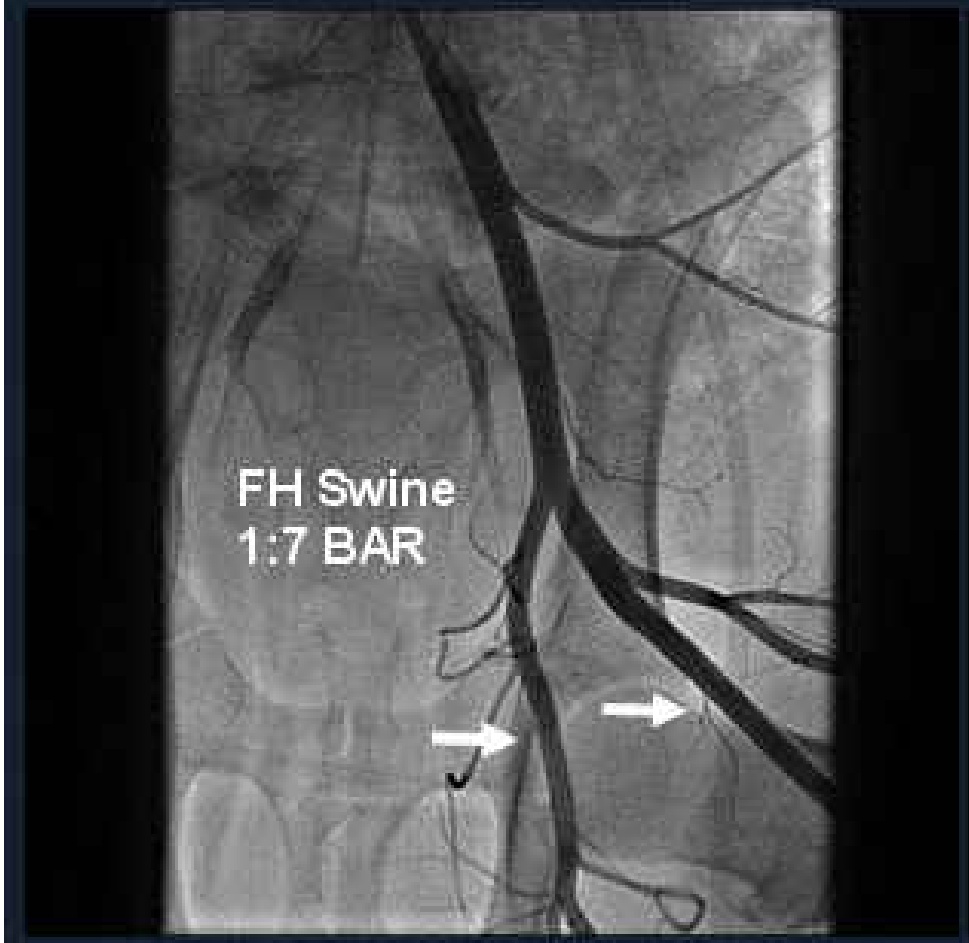
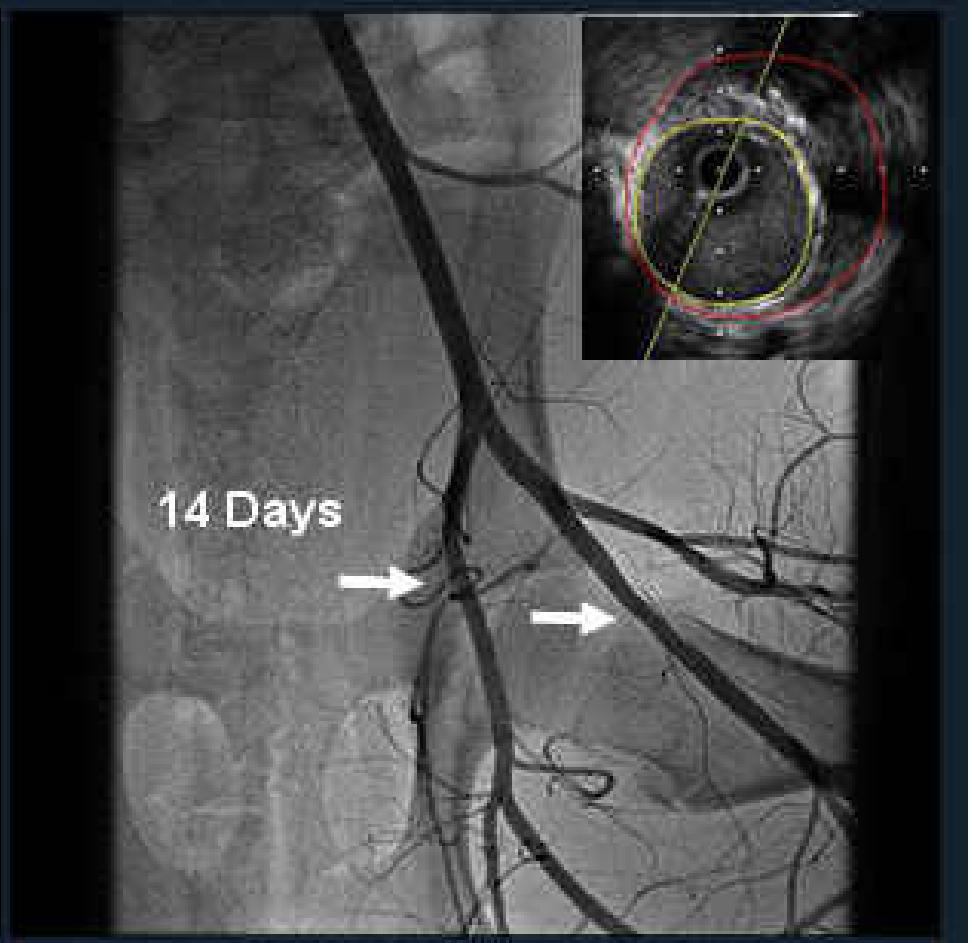
Diseased Animal Models
Familial Hypercholesterolemic Swine





Paclitaxel Coated Balloon

Overview of Clinical Programs

Trial	Countries	PI	Devices used	Lesions	patients	Trial status
PACCOCATH ISR I	Germany	B. Scheller	PACCOCATH vs. uncoated balloon	ISR	52	NEJM 2006 2 years FU completed
PACCOCATH ISR II	Germany	B. Scheller	PACCOCATH vs. uncoated balloon	ISR	56	Clin Res Cardiol 2008 2 years FU completed
PEPCAD I SVD	Germany	M. Unverdorben	SeQuent® Please	De novo, small vessels	120	12 month FU completed
PEPCAD II ISR	Germany	M. Unverdorben	SeQuent® Please vs. Taxus®	ISR	131	12 month FU completed
PEPCAD III	Europe	C. Hamm, B. Scheller	Cocoflex® DEBlue vs. Cypher®	De novo	600	recruitment completed
PEPCAD IV DM	Malaysia, Thailand	MA. Bodi	SeQuent® Please + Cocoflex® Blue vs. Taxus®	De novo, diabetics	128	recruiting
PEPCAD V	Germany	D. Mathey F. X. Kleber	SeQuent® Please + Cocoflex®	Bifurcation	25	recruiting
CTO Pilot	Germany	J. Woebbe G. Werner	SeQuent® Please+ Cocoflex® Blue	CTO	48	recruiting
PEPCAD AMI pilot	Germany	B. Scheller G. Maisch	Cocoflex® DEBlue vs. BMS	STEMI	60	planned
INDICOR	India	U. Kaul	SeQuent® Please + Cocoflex® Blue	Real world	100	recruiting
THUNDER	Germany	G. Tepe	PTA vs. PACCOCATH vs. paclitaxel in contrast	SFA	154	NEJM 2008
Femoral Paclitaxel	Germany	J. Ricke	PTA vs. PACCOCATH	SFA	87	Circulation 2008

Emerging Drug Eluting Devices

Conclusions

- Several well developed emerging drug delivery platforms have already moved from the "proof of concept" stage and are undergoing extensive pre-clinical and clinical testing.
- Most of these technologies have already overcome previous technological challenges and have become viable drug delivery platforms.
- In general, release kinetics and tissue absorption seen with these devices are unique and appear to result in a favorable biological result in animal models and small clinical trials.
- Besides drug delivery, these devices could offer alternative strategies to enhance the process of vascular healing and become strong competitors in the DES market.

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