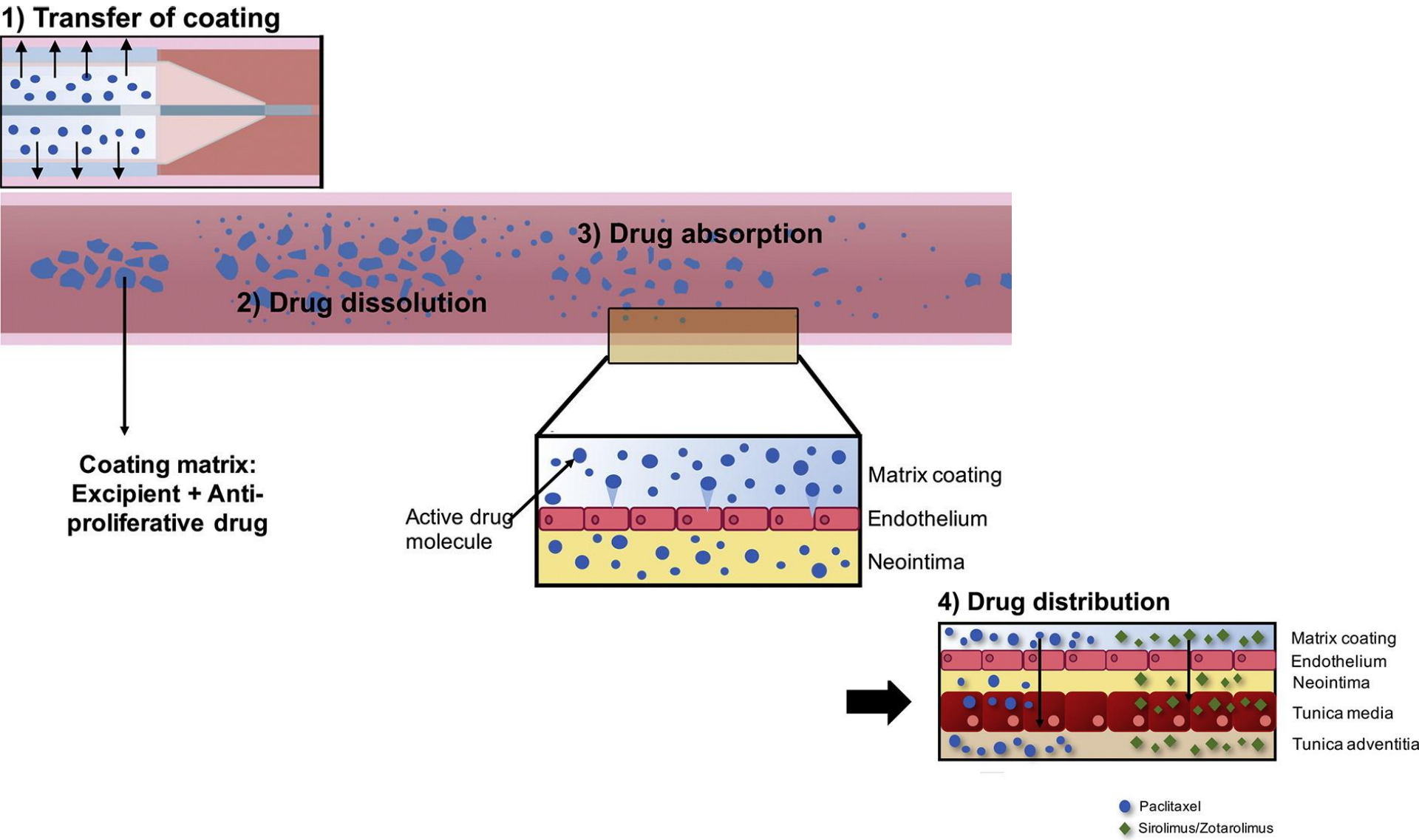
*18th Joint meeting of Coronary Revascularization*

# New drug-coated balloon: new carriers and new drugs

Yun-Kyeong Cho
Keimyung University Dongsan Hospital

# The concept of drug-coated balloon (DCB)



# **Advantage of DCB** (over DES)

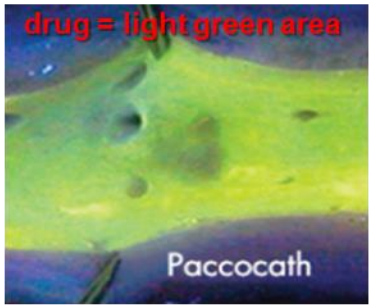
- Absence of an implanted drug delivery system → high initial drug delivery
- Homogeneous drug transfer not limited to areas covered by the balloon

**DCB**

- Immediate release
  : drug release < 1 min
- 300~600ug dose
- No polymer

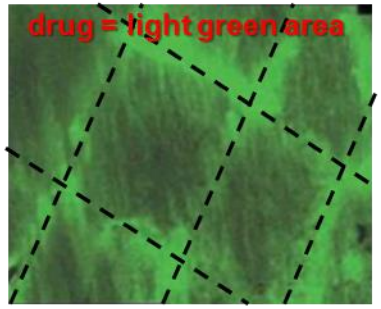
**DES**

- Slow release
  : initial drug release up to 30 days
- 100~200ug dose
- Medium or longterm polymer

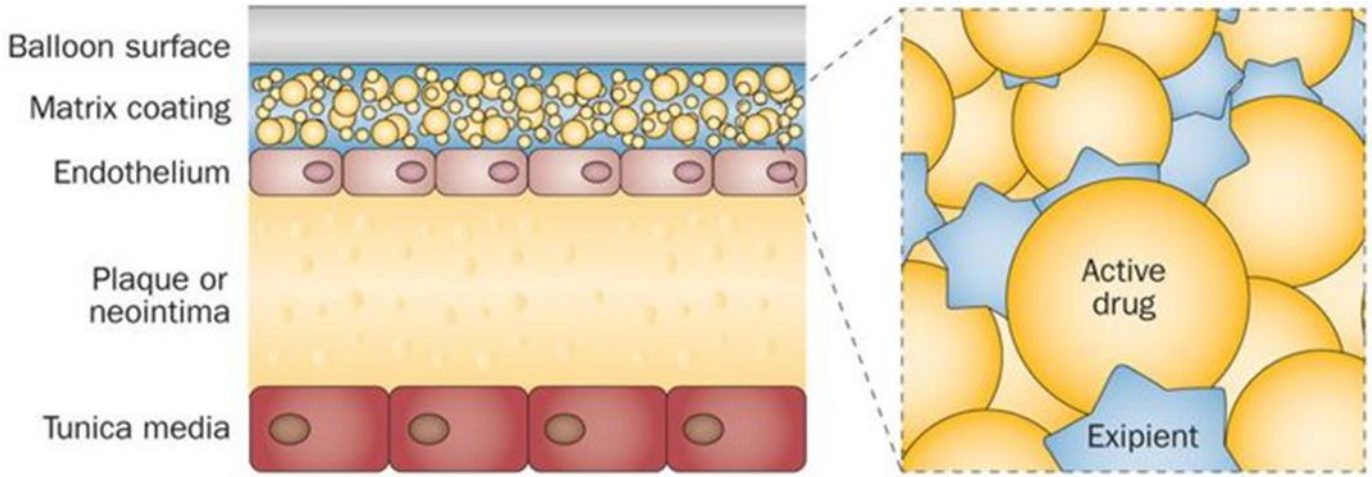



**Drug dispersion pattern**

⇦ artery interior surface ⇨



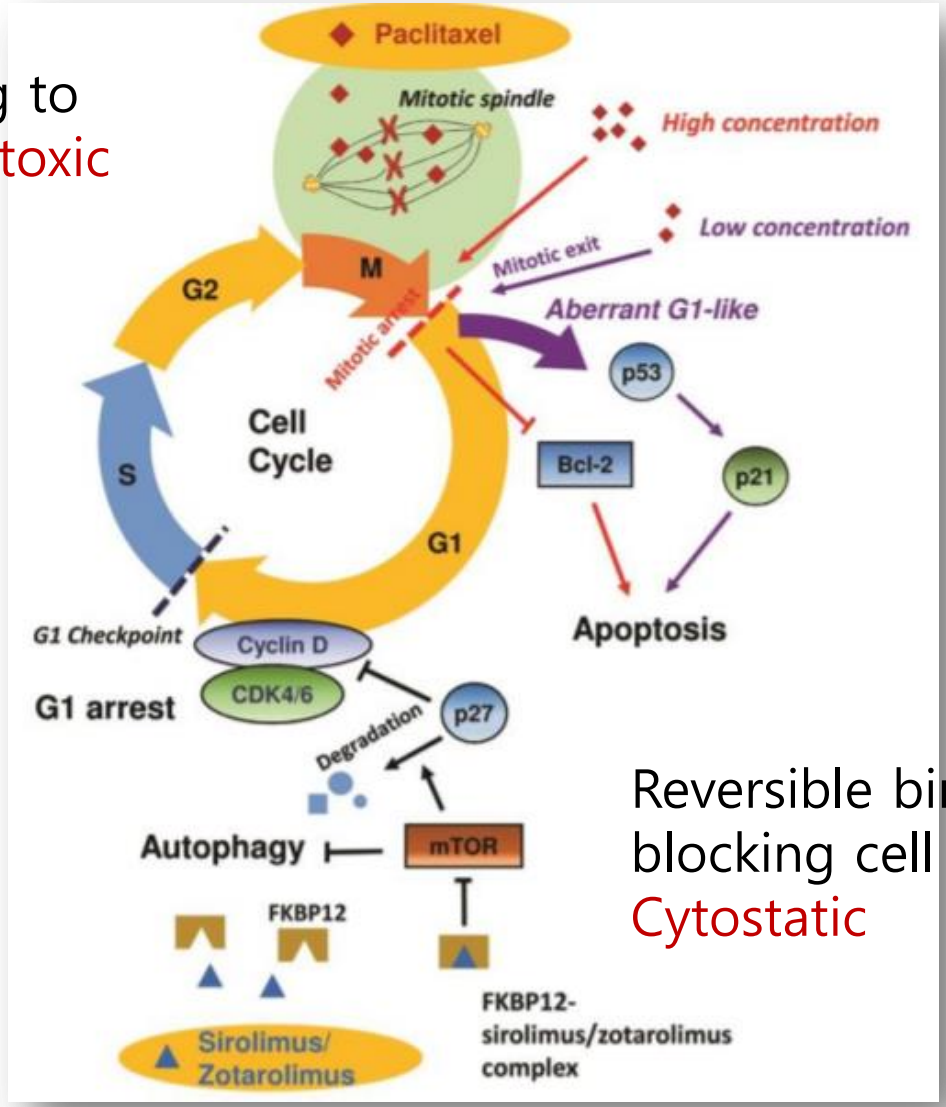
# Component of DCB




- **Active drug**: anti-proliferative drug
- **Excipient** (부형제): substance formulated alongside the active ingredient for the purpose of long-term stabilization, bulking up solid formulations or to confer a therapeutic enhancement on the active ingredient

# Molecular mechanisms of active drug (anti-proliferative drug)

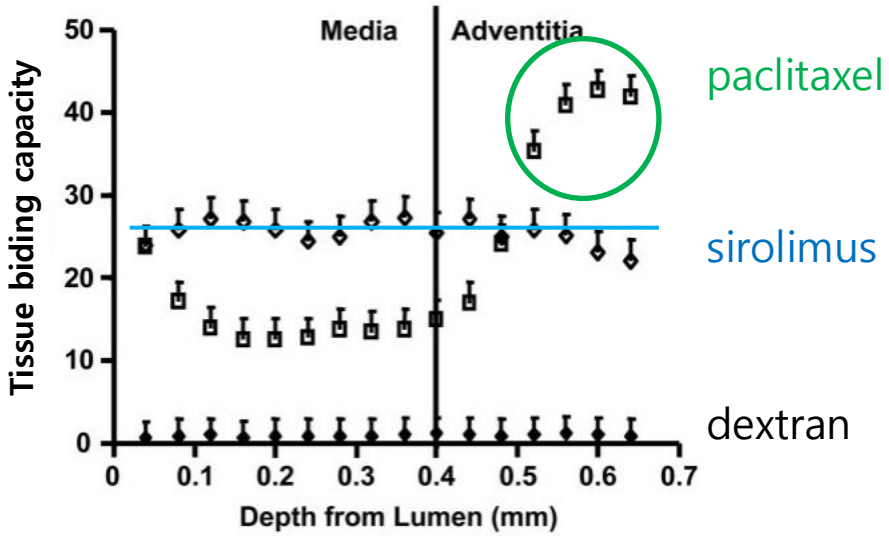
Irreversible binding to microtubules: Cytotoxic




Reversible binding to FKBP12, blocking cell cycle progression: Cytostatic

# Transmural equilibrium distribution in bovine internal carotid tissue segments

- The modes of tissue binding by limus and taxane compounds result in different transmural drug distribution.

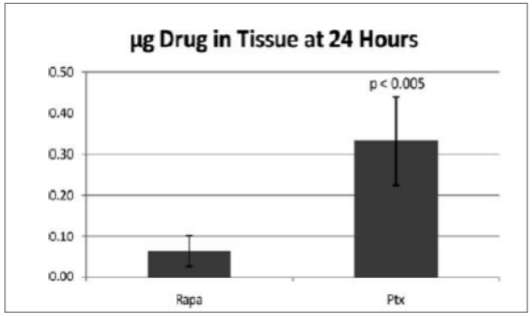


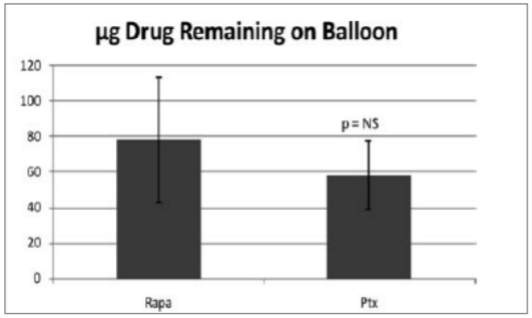

- Lipophilic drugs are able to cross the inner hydrophobic core of cell plasma membranes in the endothelium.
- The retention of paclitaxel in the deep arterial tissues helps to prolong therapeutic drug levels in the tissue.

Levin AD, et al. Natl Acad Sci U S A. 2004;*101*:9463–9467.

# Active drug of DCB

| Attribute | Limus | Paclitaxel |
|---|---|---|
| Nature of Drug | Less Lipophilic | Highly Lipophilic |
| Tissue Absorption & Elution | More Difficult | Easier |
| Margin of safety | 10,000 fold | 100 fold |
| Level of competition | Low | Very High |




Gray&Granada, Circulation 2010; June 22

- **Limus:** slow drug uptake, hence longer time required at site
- **Paclitaxel:** has been the primary choice of anti-proliferative drug used in DCB

# Commercially available DCB

| Manufacturer | Product Name | Drug, Dose | Excipient |
|---|---|---|---|
| Aachen Resonance GmbH | Elutax | Paclitaxel, 2.2 μg/mm$^2$ | Dextrane |
| B. Braun Interventional Systems, Inc. | SeQuent Please Neo | Paclitaxel, 3 μg/mm$^2$ | Iopromide |
| Biosensors International Group, Ltd. | Biostream | Paclitaxel, 3 μg/mm$^2$ | Shellac |
| Biotronik | Pantera Lux | Paclitaxel, 3 μg/mm$^2$ | Butyryl-tri-hexyl citrate |
| Boston Scientific Corporation | Agent | Paclitaxel, 2 μg/mm$^2$ | Citrate ester |
| Cardionovum GmbH | Restore DEB | Paclitaxel, 3 μg/mm$^2$ | Safepax |
| Eurocor GmbH | Dior | Paclitaxel, 3 μg/mm$^2$ | Shelloic acid |
| iVascular | Essential | Paclitaxel, 3 μg/mm$^2$ | Organic ester |
| Medtronic | In.Pact Falcon | Paclitaxel, 3 μg/mm$^2$ | Urea |


Editorial

Sirolimus is an Usual Drug for Drug-eluting Stents but a New Drug for Drug-eluting Balloons

Rev Bras Cardiol Invasiva. 2012;20(2):123-4

Kaori Nakagawa[1], Fumiaki Ikeno[2]

# Sirolimus DCB

- Limus is **more effective in suppressing reactive hyperplasia**, is associated with less late lumen loss and less restenosis and has a much **wider therapeutic window** as a cytostatic drug.

| Company | Product | Drug | Concentration | Delivery Agent |
|---|---|---|---|---|
| Abbott Vascular | NA | Zotarolimus | 6–7 μg/mm$^2$ | Iopromide matrix |
| Caliber Therapeutics, Inc. | Virtue DCB* | Sirolimus nanoparticles | 3 mg | Porous balloon |
| Concept Medical Inc. | Magic Touch DCB,* Xtreme Touch DCB | Sirolimus nanoparticles | 1.3 μg/mm,$^2$ 3 μg/mm$^2$ | Phospholipid excipient |
| M.A. Med Alliance SA | Selution DCB* | Sirolimus nanoparticles | 1 μg/mm$^2$ | CAT |
| Sahajanand Medical Technologies Pvt. Ltd. | NA | Sirolimus | 0.7 μg/mm$^2$ | PLGA/PVP 50/50 coating |

*The Virtue, Magic Touch, and Selution DCBs are currently in human clinical trials.

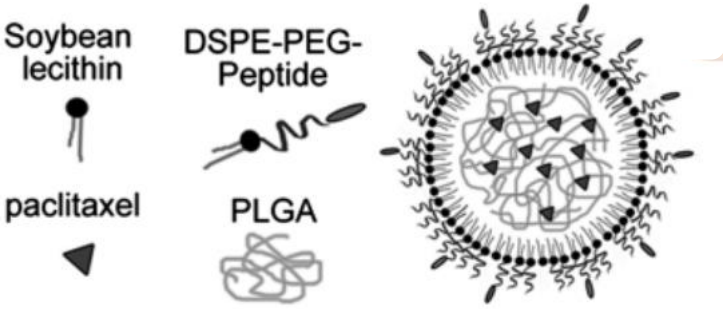
To encapsulate sirolimus in extended-release nanoparticles that facilitate rapid transfer and sustained drug release

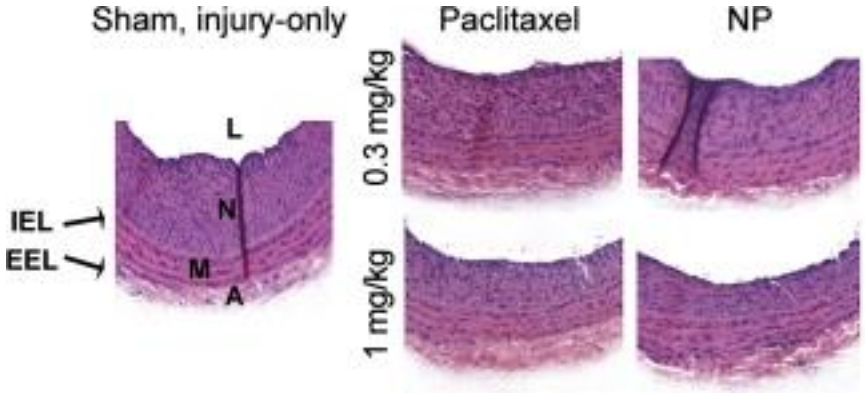
# Novel nanocarriers

- Provision of a “protective shell” to stabilize free drug or to improve its solubility
- Enabling targeted delivery of the drug to tissues
- Improving drug uptake and retention in the arterial wall

# Polymeric nanocarriers

- Entrapment of drugs within biodegradable polymeric matrices
- Migration and distribution: dependent on the size of particle → polystyrene nanoparticles of about 100~200 nm were localized to the inner regions of the arterial wall, 500 nm nanoparticles accumulated primarily at the luminal surface of the aorta



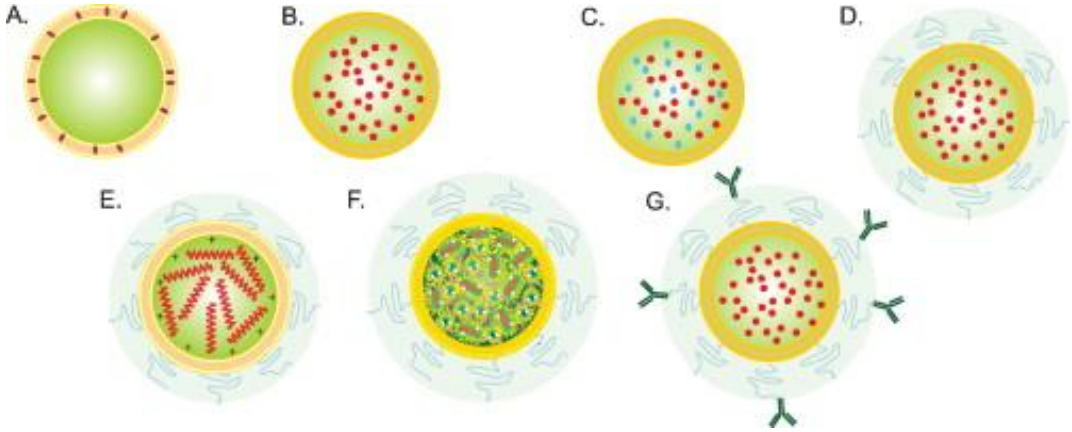




systemically administered, targeted NP system

Proc Natl Acad Sci U S A. 2011;108(48):19347-52

# Nanoliposomes & lipid-based carriers

- Bilayer phospholipid systems
- Similar chemical compositions with cell membrane → excellent biocompatibility and low toxicity
- Liposomal sirolimus?




Adv Drug Deliv Rev. 2013 Jan;65(1):36-48.

# Excipient

- **1st generation DCB**: iodinated hydrophilic contrast (iopromide)
- **2nd generation DCB**: urea, hydrophilic resin "SHELLAC", BTHC (n-Butyryl-tri-n-hexyl citrate), ATBC (Acetyl-tri-n-butyl citrate)……
- **3rd generation DCB**: no carrier

# Iopromide

- Low osmolar, non-ionic contrast agent (Ultravist®)
- Hydrophilic spacer: high contact surface, more uniform & complete release btw the lipophilic drug molecules and vessel wall
- SeQuent™ Please


**pure paclitaxel**

**high surface adhesion (drug-balloon) and cohesion (drug-drug) → poor bioavailability**


**paclitaxel + hydrophilic spacer**

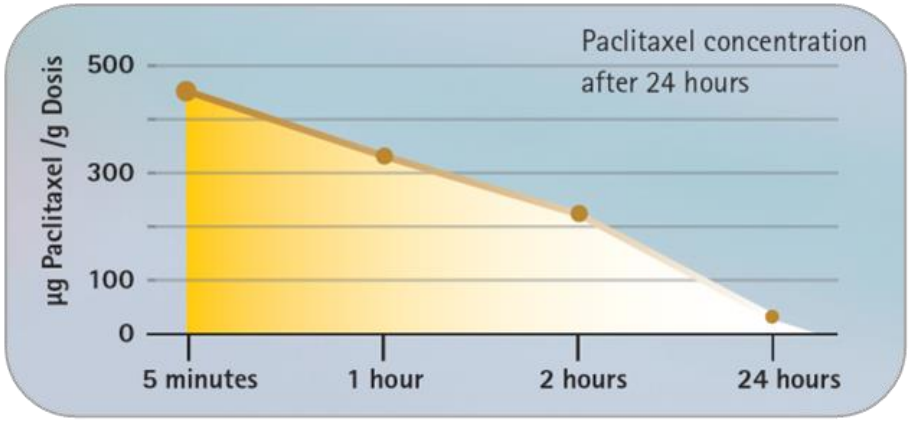
**balanced surface adhesion (drug-balloon) and cohesion (drug-drug) → high bioavailability**

# Iopromide

**Long-term efficacy with short-term release**

Only a “single shot” drug delivery is needed

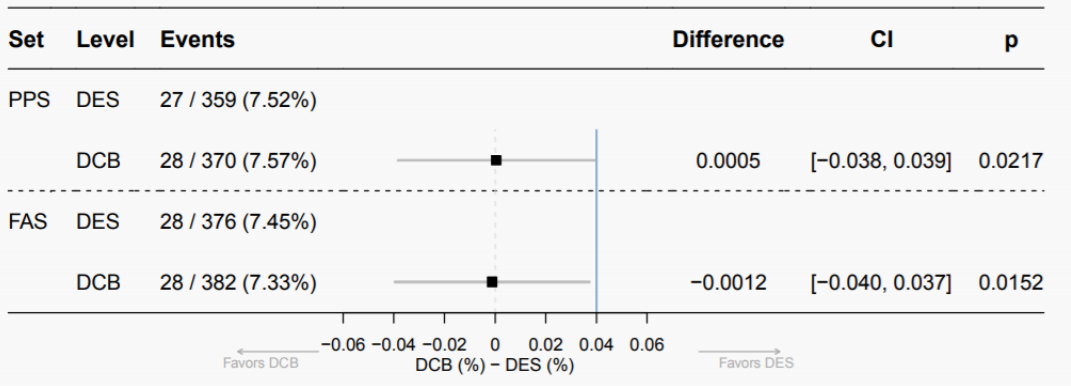
to ensure a sustained antiproliferative effect

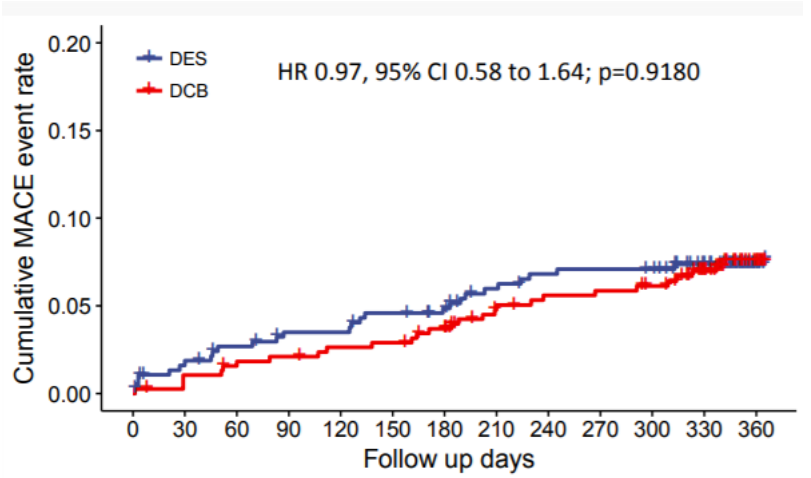


# Iopromide

## Drug-Coated Balloons for Small Coronary Artery Disease: BASKET-SMALL 2

- Multicenter, randomized controlled non-inferiority trial (14 centers in Germany, Switzerland, and Austria)
- Patients undergoing PCI in native coronary arteries <3 mm
- Initial comparison Sequent Please® DCB (B.Braun Melsungen) vs. Taxus Element® DES (Boston Scientific), then changed to Xience® DES (Abbott Vascular) after 25% of patients
- Primary Endpoint: Non-inferiority for major adverse cardiac events (MACE; cardiac death, non-fatal myocardial infarction, and target vessel revascularization) @ 12 months

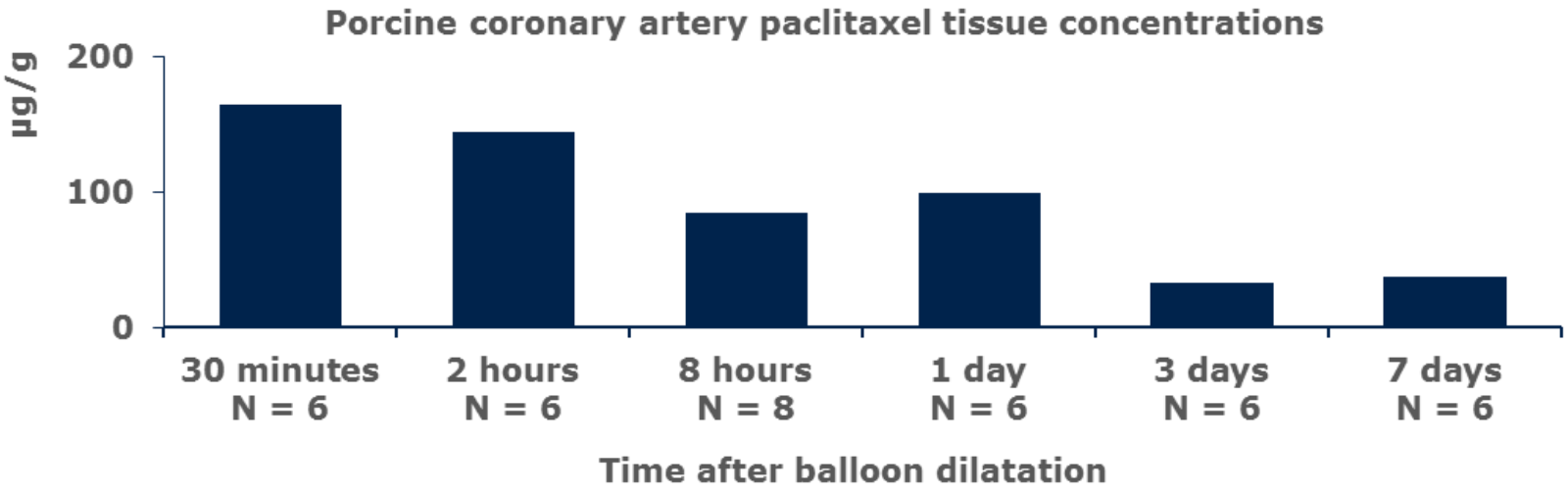



**FAS**, full analysis set;
**PPS**, per-protocol set

# BTHC

- Butyryl-tri-hexyl citrate
- Degrades to citric acid and alcohol
- Biocompatible, approved in blood contacting medical devices such as blood bags
- Hydrophobic nature: less soluble
- Pantera Lux



# BTHC

## Drug REleasing Pantera LUX PTCA Balloon Catheter Registry (DELUX)

Prospective multi-center international registry

1'064 patients enrolled in 62 sites in 12 countries

1'137 lesions treated with the **Pantera Lux**.
Pre-dilation recommended with a uncoated balloon.

Clinical follow-up at 6 months N = 1'033

**Clinical follow-up at 12 months N = 1'008**

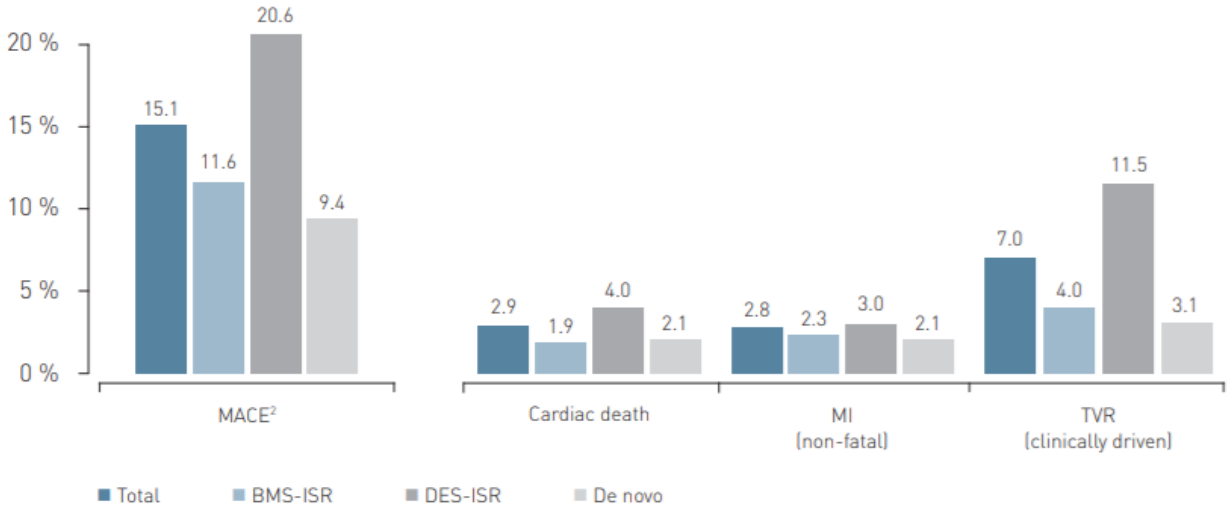
### Major inclusion criteria

- Signed data release form
- Patients with restenotic lesion in a previously stented area of a coronary artery (irrelevant whether BMS or DES related)
- Target reference vessel diameter: 2 - 4.5 mm
- Target lesion length: 8 - 28 mm
- Target lesion stenosis: > 50 % - < 100 %

### Major exclusion criteria

- Patient with allergy against appropriate anticoagulation/antiplatelet therapy
- Patients with allergy against paclitaxel or BTHC
- Patients with a target lesion that was previously treated by brachytherapy

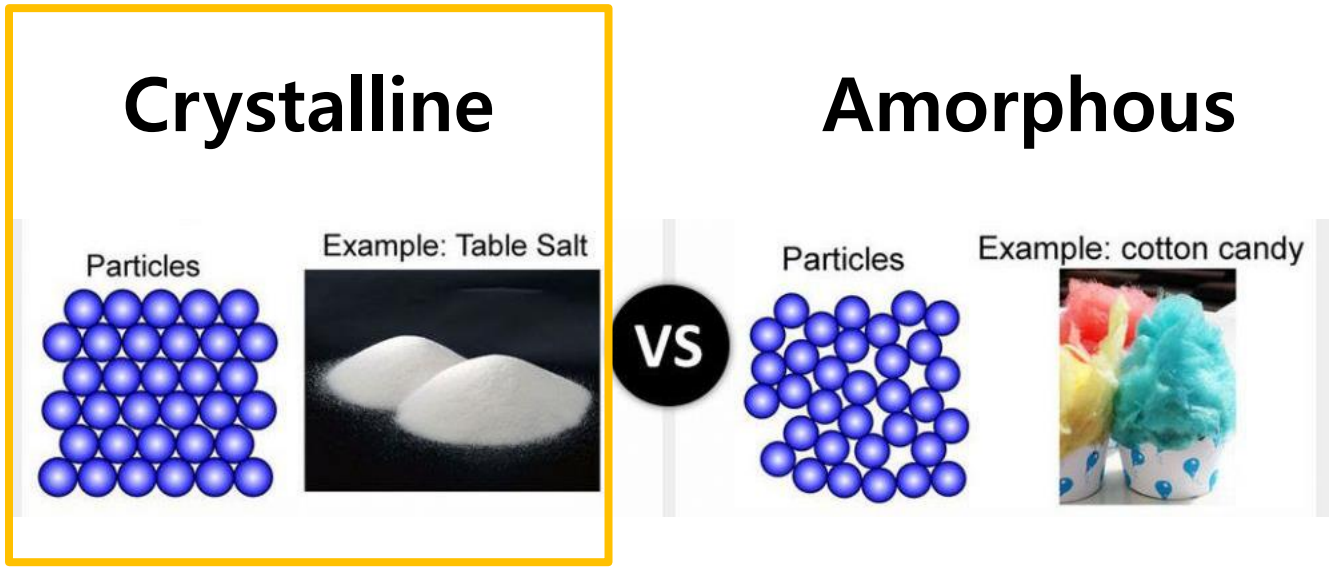
### 12-month results




### Conlusions

- Treatment with the Pantera Lux paclitaxel-coated balloon showed good 12-month outcomes in an international real-world setting in a predominantly difficult ISR population.
- Efficacy and safety are demonstrated by low revascularization, MI and cardiac death rates and confirm previous clinical results of this device using Butyryl tri-hexyl citrate (BTHC) as an inert excipient.
- Results are favorable both in the overall population and in the de novo lesion subgroup.

# Morphology of drug coating




- Slow dissolution
- Sustained drug transfer to the tissues
- Prolonged shelf-life d/t increased stability

# Coating methodology

| Require-ment | Dose control | Reproducibility | Homo-geneity | Effort | Etc. |
|---|---|---|---|---|---|
| Spray coating | Poor | Good | Very good | Mid | SeQuent Please<br>The amount of drug loss during refolding is unclear |
| Dip coating | Very poor | Poor | Poor | Very low | |
| Micro-pipetting | Very good | Very good | good | High | M/C technique<br>Pantera Lux<br>Specific localization of the drug/excipient solution into pockets under folds |

# Summary

- Opportunities for DCB improvement
  1) **New drug**
     * Change in paclitaxel form, size or chemical features
     * Micro encapsulation or advanced drug systems
     * Alternative drugs (limus-based)
  2) **New carrier**
     * Reduce total drug concentration
     * Enhance tissue transfer
     * Increasing tissue drug retention