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Legflow DCB Safety / outcomes from the clinical trial program

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Diclosure

Speaker's name: Peter Goverde

- **I have the following** potential conflicts of interest to report:
  - **Consulting**:

Abbott Vascular; Angioslide; Bentley; Bard Peripheral Vascular; Cardionovum; Cordis Cardinal Health; IMDS; Ivascular; Maquet Getinge group; Stille; Veyran; Ziehm Imaging

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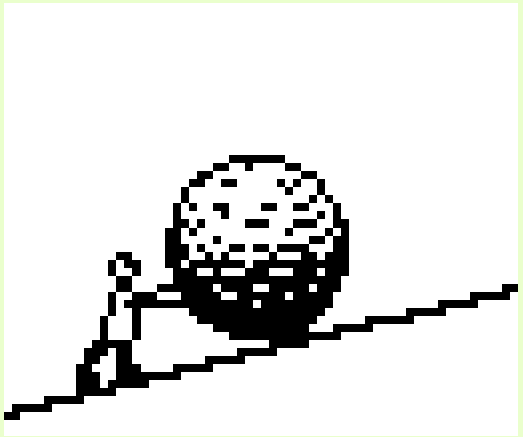
The fight against restenosis….

- PTA /PTCA
- Artherectomy
- Cutting Balloon
- Scoring Balloon
- Laser
- Nitinol Stent
- Drug Eluting Stent
- Covered Stent
- Drug Coated Balloon



….a fight for Sisyphos?

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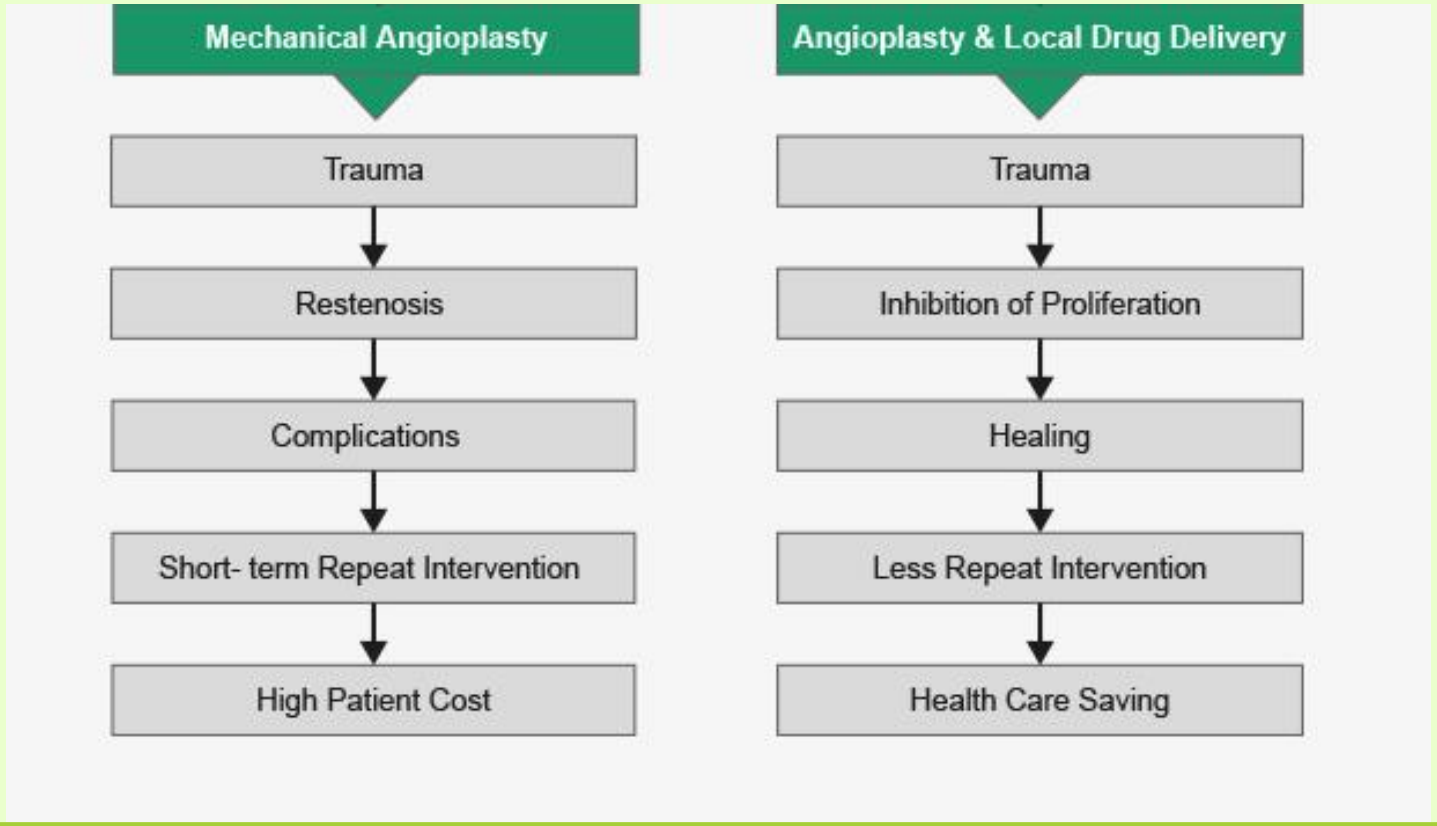
The New Dimension of Drug Releasing Angioplasty



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DCB Design Goals

DES-like Efficacy + BMS-like Safety + Balloon-like Deliverability + Nothing Left Behind

- ⇓ LLL /neointima mm²
- ⇓ Duration of DAPT
- ⇑ Technical Success rate
- ⇓ % Stenting rate

Potential benefits of DCB well-suited to lower extremity challenges

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DCB: Components and Function

Components	Function
PLATFORM	PTA Dilatation, Drug Carriers
DRUG	Restenosis prevention
EXCIPIENT	Drug retention and release control
COATING TECHNOLOGY	Drug layer uniformity, + process reproducibility

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Why is the balloon of importance?

- **Not only the technical features such as deliverability and pressures are of importance!**
- ***Balloon material can react with matrix and drug***
- ***Balloon material can cause inflammatory reactions (In.Pact Deep – Phtalat reaction)***
- ***Balloon material dependent whether***
  - *coating is possible at all and*
  - *how effective the drug release will be*
- ***Balloon material influences treatment algorithm of physician***

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Unique PTA /PTCA balloonTechnology

- High class OEM PTA / PTCA technology
  - Standard polymeric material without more smootheners than needed
  - High pushability and kink stability due to “phased out” hypotube
  - Low guide wire friction due to special extrusion of GW lumen
  - Atraumatic tip
  - High pressure balloon for APERTO

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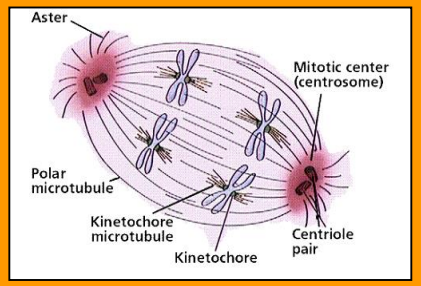
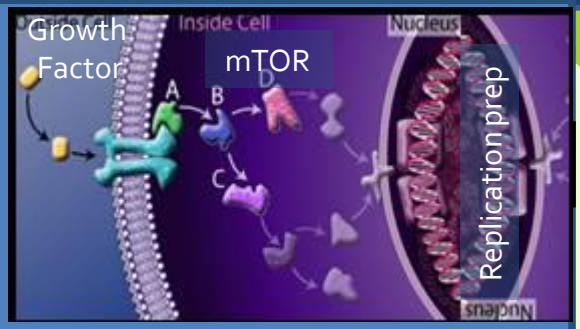
Why Paclitaxel for DCB?

Paclitaxel

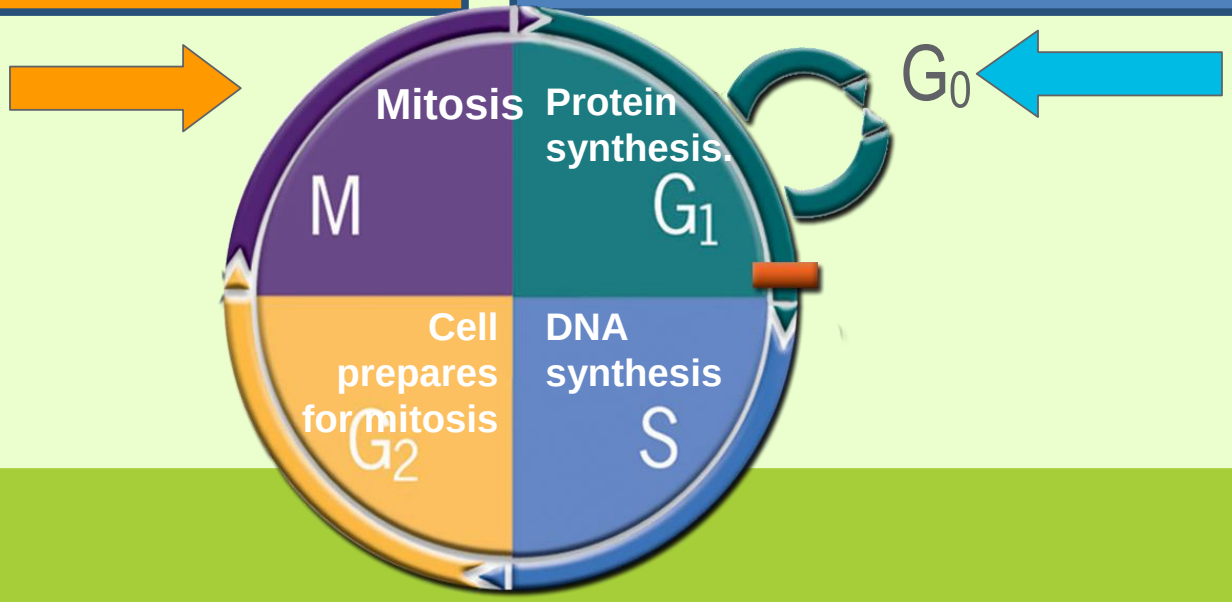


Interferes with cell division at the M phase, after DNA synthesis has occurred. Cells are in an abnormal state with twice the normal DNA content, which leads to cell death by apoptosis

ABT-578 Rapamycin Everolimus



Interfere with cell growth at the G1/S transition, before DNA synthesis has occurred.
Cells return to the resting phase (Go) without dying and can reenter the cell cycle later again



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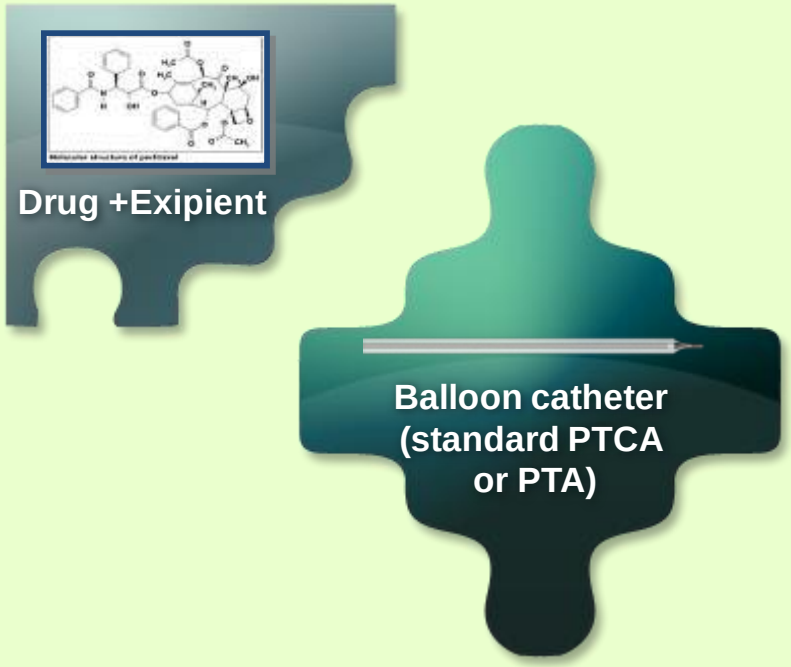
DCB Components: Drug

Drug Matrix On Balloon

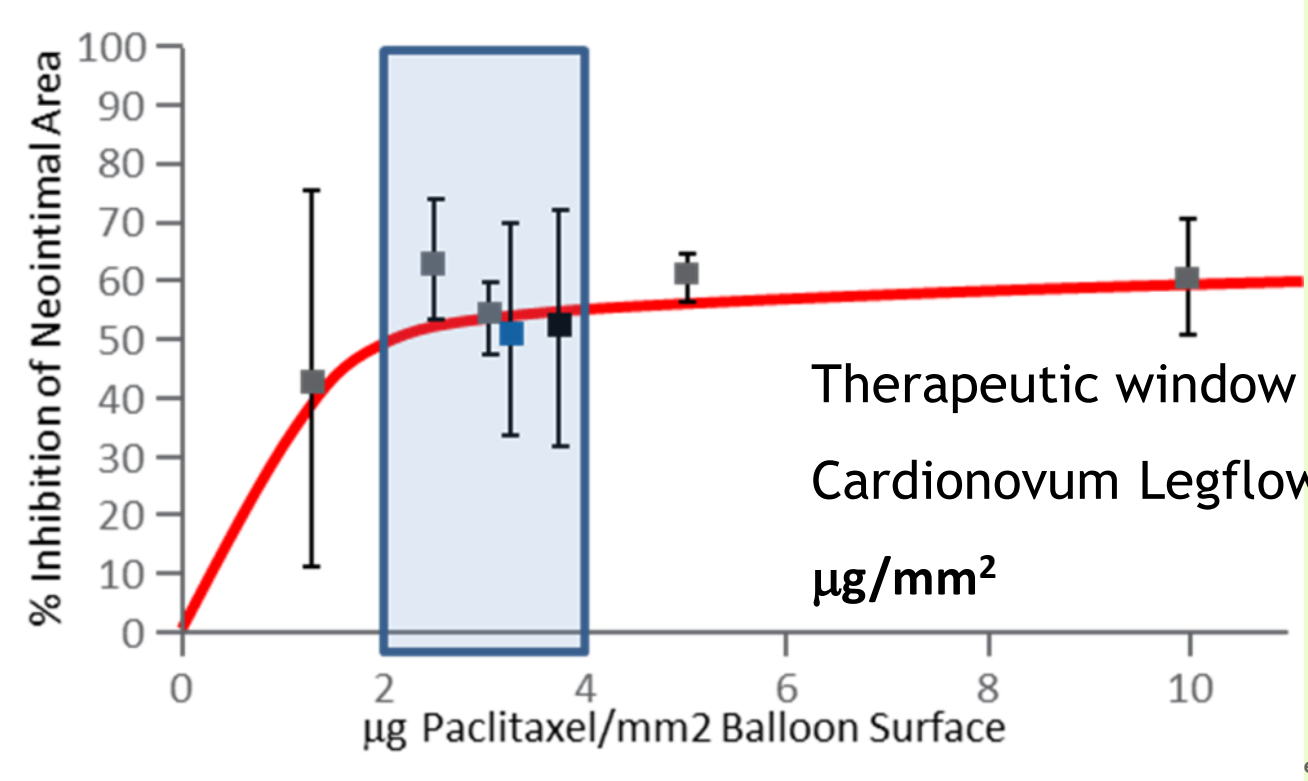
THERAPY



Paclitaxel:

- Provides appropriate antirestenotic drug therapy for an *acute* delivery system such as a DCB
- Facilitates *acute* delivery with *chronic* results due to its hydrophobicity and lipophilicy and tight binding to the microtubule subunit
- Allows for increased potency for *single-shot* therapy
- Limits drug toxicity with DCB delivery

Dose Selection



Therapeutic window 2-4 µg/mm²

Cardionovum Legflow DCB: **3 µg/mm²**

1. Sch emers B, et al.*Clin Res Cardiol*. 2009;98:325-330.

4. Cremers B, et al *Thromb Haemost*. 2009; 101: 201-206. 5. Rowinsky EK, Donehower RC. *N Engl J Med*. 1995;332:1004-1014. 6. Margolis J, McDonald J, Heuser R, et al. *Clin Cardiol*. 2007;30:165-170

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60-70 % of dose protected within balloon folds

DCB drug excipients

- Substances which are used as a carrier / matrix for PXL
- ideal & effective excipient act as safe binding of the PXL in the excipient until drug release in the vessel
- necessary to achieve therapeutic PXL levels
  - PTX without excipient = no bio-availability of PXL
    (Scheller 2004 Circ 110:810-814, Fig.1)
- Excipient can be:
  - mixed with Drug Excipient = Dispersion *(actual DCBs)*
  - embedded under the Matrix Surface = Encapsulation *(earlier generations)*

Ideal DCB drug excipients

- **Hydrophobic** = controls and minimizes drug loss during transit
- **Lipophilic** = accelerates drug release, facilitates tissue uptake (i.e. drug transfer into vessel wall)
- **Elastic** = stability, controls & maintains & provides coating integrity
- **Low Viscosity**

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DCB drug excipients

Excipient	Company	Information
Butyryl-trihexyl citrate (BTHC)	Biotronik	- Plasticizer, used in plastic blood carriers for rendering the plastic smooth, - increases drug uptake in tissue
Sorbitol Sweetner	Bard/ Lutonix	- hydrophilic, non-polymeric carrier (uniform thickness of coating of appx. 7 µm) - Poor PTX drug transfer
Amonium-salt SAFEPAX®	Cardionovum	- Low hydrophilicity – less likely to be washed of - Elastic film - Aids detachment of PTX from balloon & tissue uptake
Citrate ester TRANSPAX®	Boston Scientifix	- Low hydrophilicity – less likely to be whashed off - Elastic - Strong bondage to PTX

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DCB drug excipients

Excipient	Company	Information
Urea FREEPAC®	Medtronic /Invatec	- natural substance; considered as harmless; compound naturally found in the human blood - Highly hydrophilic – high wash off during transit to treatment site / Systemic drug loss - 3.0µm large PTX crystals, risk of micro-embolization
Iopramide	B.Braun Medrad Blue Medical Cook	- Contrast media - hydrophilic - Unpredictable PXL burst release
Shellac	Eurocor	- Low hydrophilicy - Natural resin; FDA approved E904 food additive - Balloon surface hardening, coating brittling - No full PTX release from matrix

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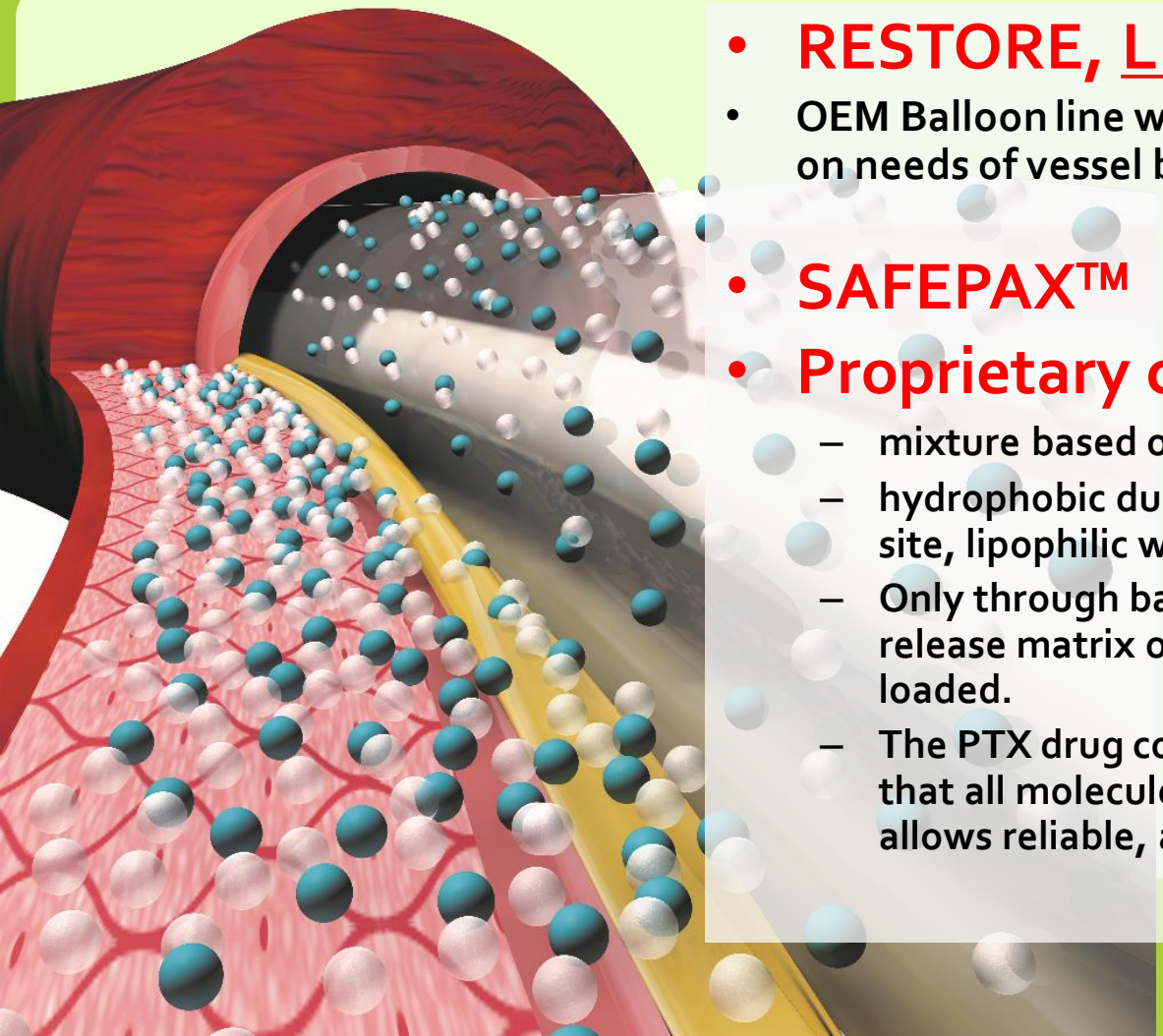
Matrix not equal to Matrix



- **RESTORE, LEGFLOW, APERTO**
- OEM Balloon line with dedicated specifications based on needs of vessel bed

- **SAFEPAX™**
- **Proprietary coating formulation**
  - mixture based on a novel Ammonium Salt compound
  - hydrophobic during catheter tracking to the lesion site, lipophilic when balloon is inflated.
  - Only through balloon inflation the Safepax drug release matrix opens up and releases the Paclitaxel loaded.
  - The PTX drug coating is nano-crystalline. It means that all molecules are in a structured order, which allows reliable, and homogenous drug release.

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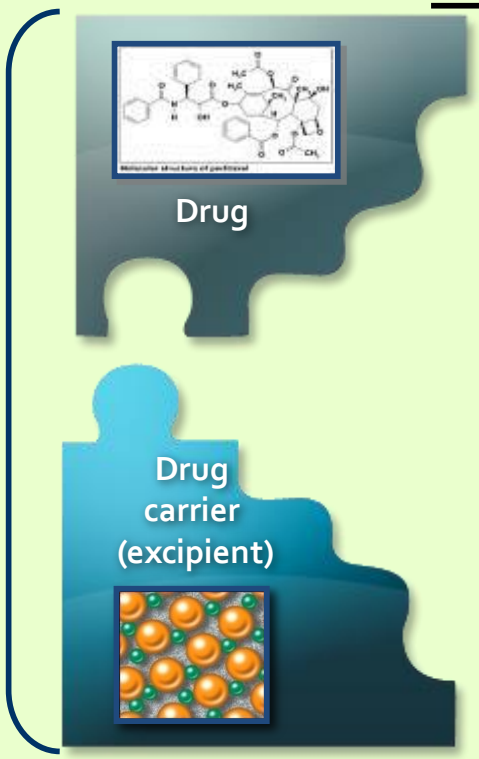
DCB Components: Excipient

Excipient Legflow:



- The balloon surface is homogenously coated (by nano-crystalline structure).
- development of 0.1µm smallest and non visible PTX particles. (contemporary PTX size measures 2.0-3.0µm PTX)
- The smallest PTX particles are easily absorbed intra-murally.
- developed of small PTX particles to avoid any capillary bed blockages

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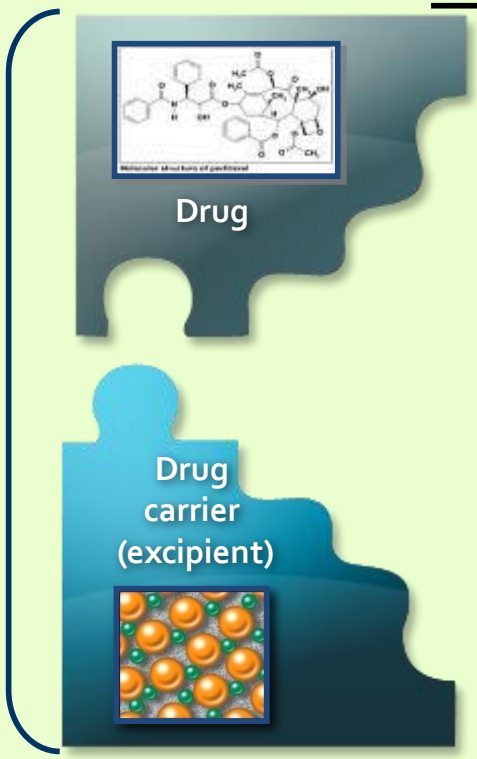
DCB Components: Excipient

Excipient Legflow :



- The SAFEPAX coating avoids the risk potential of micro embolization.
- The minimized risk of micro-embolization allows our DCBs for application in BTK artery lesions.
- The drug release curve (see next slide) proves the reliable drug release, in the animal study model.
- Within 7 days, almost 95% of the absorbed PTX are fully metabolized and gone, while a remaining estimated 5% still provides a sustained in arterial tissue, ant proliferative action up to 28 days Less than 1% , up to 90 days.

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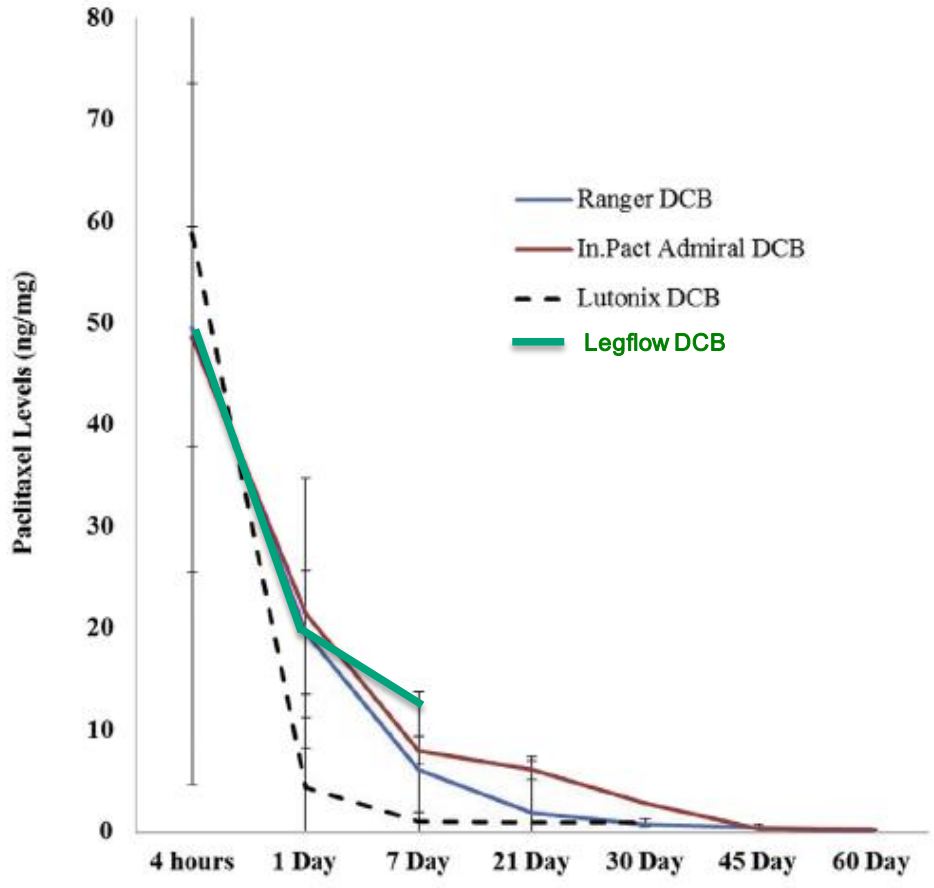
Drug in tissue

WHY IS IT IMPORTANT?



Comparative tissue levels up to 60 days of a standard dose paclitaxel-coated balloon (PCB) (In.Pact) versus a lower-dose balloon (Ranger) in the superficial femoral artery territory of the swine. **Dashed line** represents the comparative data with the Lutonix PCB (11). DCB = drug-coated balloon.

Drug in tissue can indicate long term results

Drug in tissue describes drug uptake by different Matrix

For good long term results „depots“ are built with PTX – particle size is important for the efficacy of the depots

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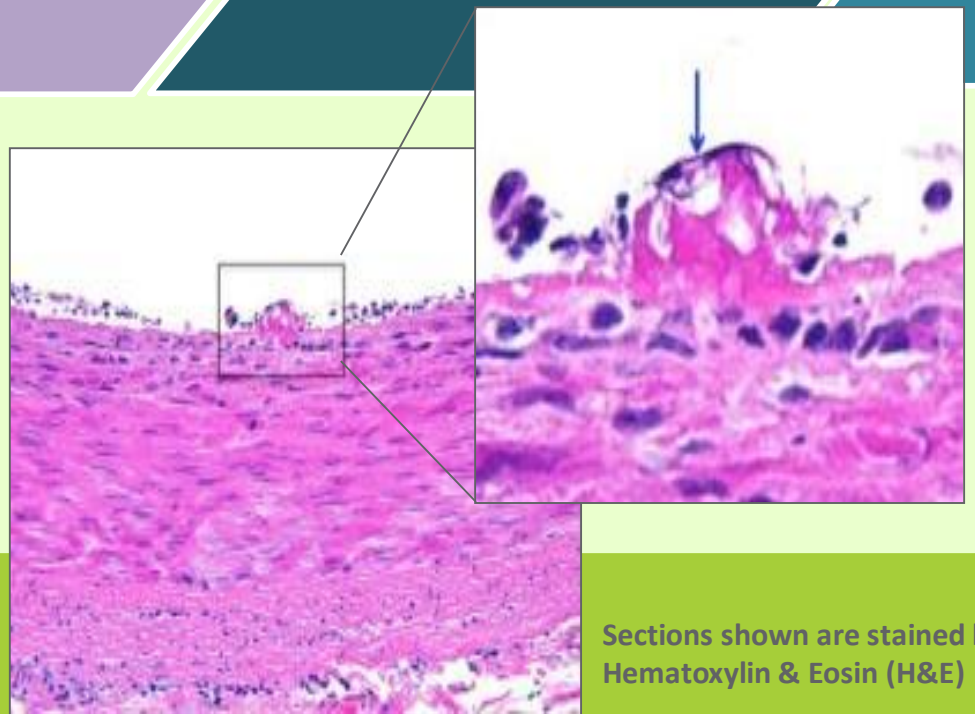
How the matrix builds depots

Paclitaxel is released as matrix hydrates

(importance of natural matrix substance)

Particles are **embedded** into arterial wall and sequestered by tissue

Embedded particles provide **extended drug release** to **surrounding** tissue



Sections shown are stained by Hematoxylin & Eosin (H&E)

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DCB coating pitfalls

- Maintain sufficient drug adherence in dry state
- Drug loss to subsequent folding process
- Uneven Coating of Balloon Surface
- Unpredictable wash off during catheter advancement
- Flaking off of Drug=Risk of PTX contamination !
- Undesired peak in drug uptake, e.g. Iopromide
- Crystallization of Drug to the surface of the matrix
  - Drug outside the Drug Excipient Matrix appears white, is unprotected and might fall off balloon.
  - SMALL Drug Nano-crystals staying embedded in matrix appear clear / transparent like glass

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How to find your way in the DCB „Jungle“

- DCB with NO Matrix do not work!
- All DCB on the market do have a matrix and work, but question is how!
- Matrix decides about the amount of drug released to the vessel wall
  - As more hydrophilic the coating is, as more whash off occurs. The wash off finally decides how much drug will be left on the balloon for delivery to the vessel wall.
- Matrix decides about fast and slow drug uptake
  - our drug release only starts after approx. 30 seconds due to the biochemical bondage of lipophilic PTX to hydrophobic Ammonium Salt where the lipophilic force towards the vessel wall will be stronger when touching the vessel wall with fat cells

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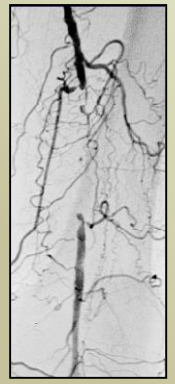
DCB as a choice for Clinical Challenges

- **Clinical Challenges Where DCB is Preferable to POBA or Stenting**

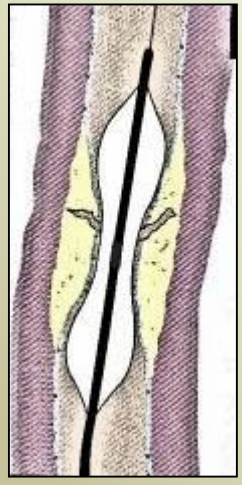
De Novo Lesions

Small Vessels (BtK)
High Movement or Flexion Sites (SFA/Pop)



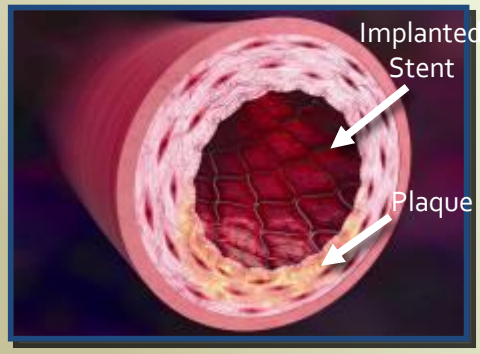
Stent should not be placed or it may not be ideal (e.g., too many stents in SFA)

Restenosis After POBA



Anti-proliferative therapy desired

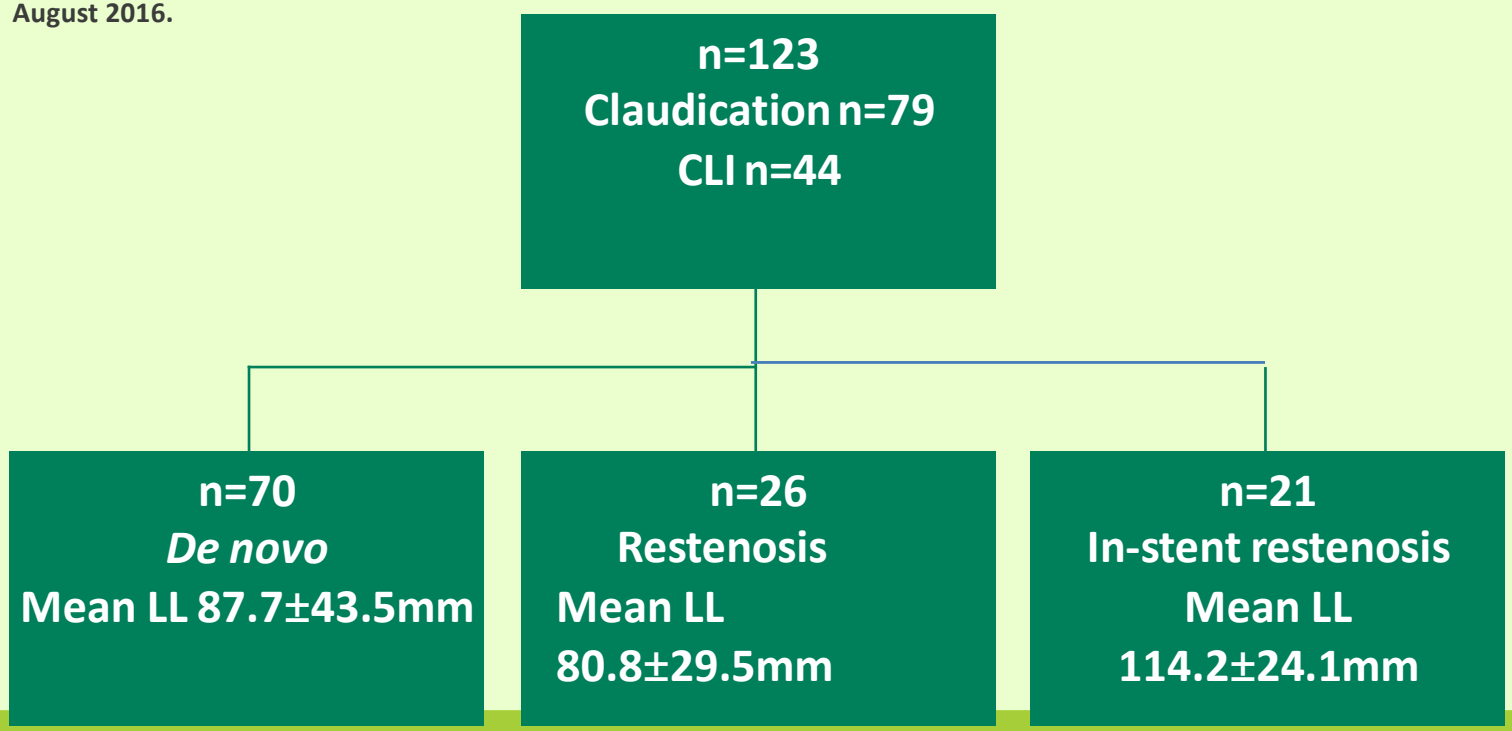
In Stent Restenosis



Stent-in-stent not desired

THE LEG-DEB REGISTRY IN NUMBERS

The LEG-DEB Registry is a prospective, multicentre, single-arm study of the LEGFLOW DCB in femoropopliteal arteries in a real-word population. An interim analysis of the six-month results was published by Stabile *et al* in the *International Journal of Cardiology* in August 2016.



Clinical trials

LEG-DEB six-month freedom from target lesion revascularisation (TLR) and how it compares with other DCB studies

ALL patients	Claudication	CLI	*De novo*	Restenosis	In-stent restenosis
88.6%	93.6%	79.5%	88.1%	80.7%	100%

Superior freedom from TLR

In the LEVANT I study with the Lutonix DCB, freedom from TLR for all patients at six months was 87%, with lesion length 80.8±37mm and most patients having Rutherford class 2–3.

In LEG-DEB the freedom from TLR rate was superior (88.6%) even though the study included restenosis, in-stent restenosis and CLI with lesion length of up to 130mm.

The LEVANT I (Lutonix Paclitaxel- Coated Balloon for the Prevention of Femoropopliteal Restenosis) Trial for Femoropopliteal Revascularization

Scheinert *et al. Jacc Cardiovasc Int* 2014

Claudicants: Similar TLR with lesions 20% longer

In claudicants, LEG-DEB showed a similar rate of freedom from TLR at six months (93.6%) to those from a multicentre Italian registry with the IN.PACT DCB (95.6%) and the ILLUMENATE first-in-human study with the Stellarex DCB (96%).

However, the claudicant group treated with LEG-FLOW had lesions 20% longer (91.3±53.46mm) than those in the Italian registry (76.3±38.3mm) and in ILLUME-NATE (72±47mm).

Clinical Evaluation of a Paclitaxel-Eluting Balloon for Treatment of Femoropopliteal Arterial Disease – 12-Month Results From a Multicenter Italian Registry

Micari *et al. Jacc Cardiovasc Int* 2014

Two-Year Results of a Low-Dose Drug- Coated Balloon for Revascularization of the Femoropopliteal Artery: Outcomes From the ILLUMENATE First-In-Human Study

Schroeder *et al. Cath Cardiovasc Int* 2015

In-stent restenosis: No reinterventions at six months

In in-stent restenosis patients, the use of LEGFLOW in the LEG- DEB study showed 100% free- dom from TLR at six months. An earlier experience with the IN.PACT DCB device showed a higher rate of TLR.

Drug-Eluting Balloon for Treatment of Superficial Femoral Artery In-Stent Restenosis

Stabile *et al. J Am Coll Cardiol* 2012

THE RAPID TRIAL IN NUMBERS

RAPID is a randomised controlled trial comparing LEGFLOW DCB vs. plain angioplasty followed by SUPERA stenting in "real-world" long-segment femoropopliteal lesions. The results were presented at LINC 2016.

150/160 patients included (93.8%)

- *De novo* symptomatic lesion in the SFA >5cm. Rutherford class 2–6
- At least one patent below-the-knee artery lesion crossed by guidewire

↓

Randomisation

↙ ↘

LEGFLOW paclitaxel-coated balloon + nitinol stent

Standard PTA balloon + nitinol stent

Follow-up at 1, 6, 12 and 24 months with DUS, ABI, toe pressure, and peripheral arterial questionnaire

Dual antiplatelet regimen for three months

Baseline patient characteristics

	CONTROL	LEGFLOW	p value
Gender (male)	48/74 (64.9%)	45/66 (68.2%)	0.722
Diabetes (yes)	20/70 (28.6%)	18/63 (28.6%)	1.000
Smoking (yes)	35/71 (49.5%)	31/64 (48.4%)	1.000
SVS Risk Score (0–24)			0.923
Rutherford class pre-procedure			
2	33/70 (47.1%)	32/64 (50%)	0.873
3	27/70 (38.6%)	21/64 (32.8%)	
4	4/70 (5.7%)	6/64 (9.4%)	
5	4/70 (5.7%)	4/64 (6.25%)	
6	2/70 (2.8%)	1/64 (1.6%)	
Right leg	38/70 (54.3%)	32/64 (50%)	0.729

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Clinical trials

Baseline lesion characteristics

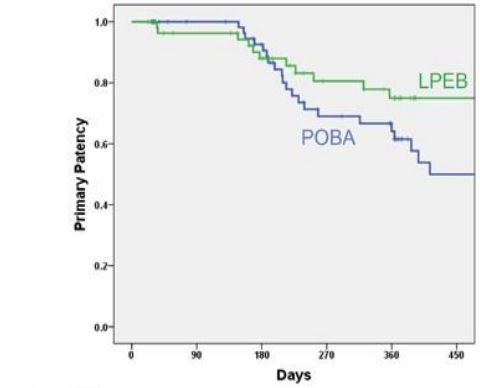
	CONTROL	LPEB	p value
Lesion length on pre-procedural imaging (mm)	116.7±66.7	120.1±69	0.890
Lesion length on angiogram (mm)	155.8±72	157±73.1	0.873
Occlusions	48/69 (69.5%)	43/64 (67.2%)	1.000
Right leg	38/70 (54.3%)	32/64 (50%)	0.729
TASCA	8/69 (11.6%)	7/71 (9.8%)	0.865
TASCB	32/69 (46.4%)	36/71 (50.1%)	
TASCC	29/69 (42.0%)	28/71 (39.4%)	

Lesion length and occlusion rates with other devices were the fol- lowing, respectively: Lutonix 107.9mm and 21%; SUPERA 64.3mm and 24.6%; IN.PACT 89.1mm and 23.7%; Zilver PTX 53.9mm (occlusion N/A)

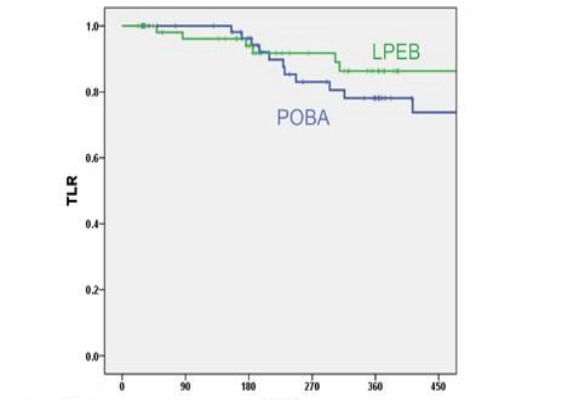
The rate of TASC C lesions with other devices were the following:

Lutonix 1.7%; SUPERA 5.7%; IN.PACT 11.7%; Zilver PTX 36.7%

Primary patency



Freedom from TLR



Clinical trials

THE MAGNIFICENT TRIAL

Magnificent trial is a randomised controlled multicentre trial comparing LEGFLOW DCB vs. plain angioplasty

- multicentre trial being run in Belgium, France and Germany
- including 130 patients
- head-to-head comparison with plain angioplasty for the treatment of *de novo* lesions or restenosis in the superficial femoral artery and in the popliteal artery (P1–P2)
- assessing the binary restenosis rate with duplex ultrasonography at 12 months

Clinical trials

THE MAGNIFICENT TRIAL

Magnificent trial is a randomised controlled multicentre trial comparing LEGFLOW DCB vs. plain angioplasty

- aim to validate the results of our real-life follow-up study
- confirm the excellent data we have seen in several “real-world” registries.
- At the moment > 40 patients enrolled
- Anticipation of enrolment completion by May 2017
- So six-month data by the end of 2017.

Conclusions

- Legflow DCB is from the newest generation of DCB
- Very safe with the SAFEPAX technology
- The early results with Cardionovums Legflow DCB are encouraging for the femoral & popliteal arteries with promising durability biomechanical forces in the different trials

Thank you for your attention