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## PACLITAXEL - COATED
## PTA BALLOON CATHETER

INVAMED | RD GLOBAL Research & Development

# Revolutions in Interventional Stenosis Treatments

**1977**

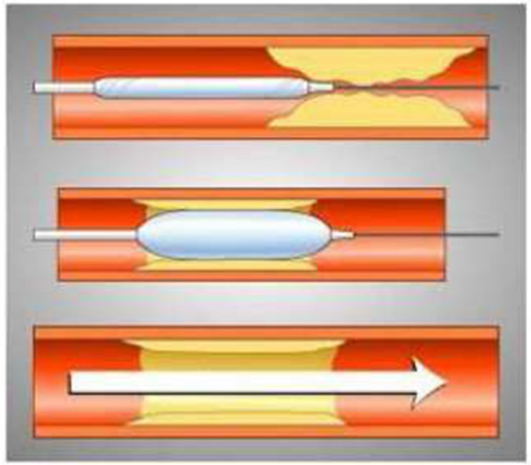
**1. Balloon (PTCA):**
Andreas Gruntzig performs the first PTCA in Zurich, Switzerland

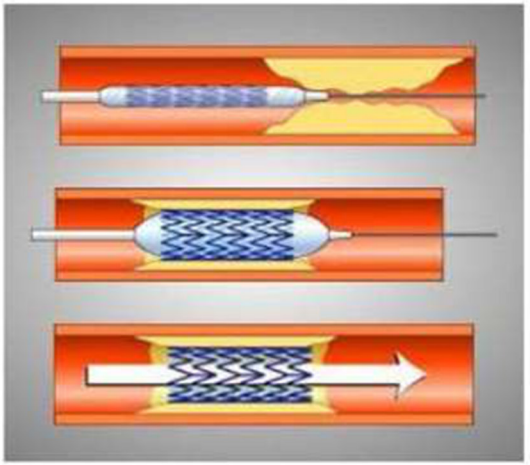
**1988**

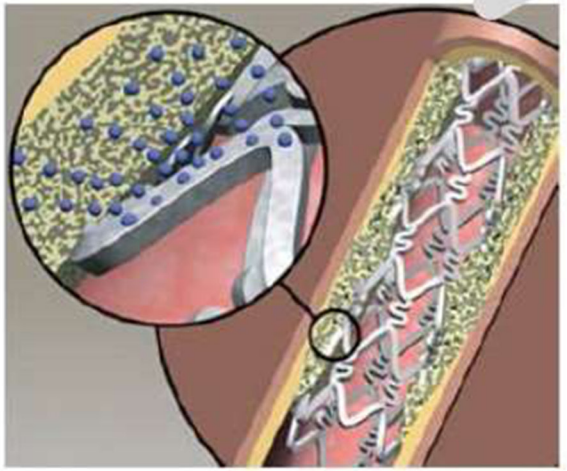
**2. Bare Metal Stent (BMS):**
Julio Palmaz and Richard Schatz develop a stainless steel stent for coronary applications

**2002 - 2003**

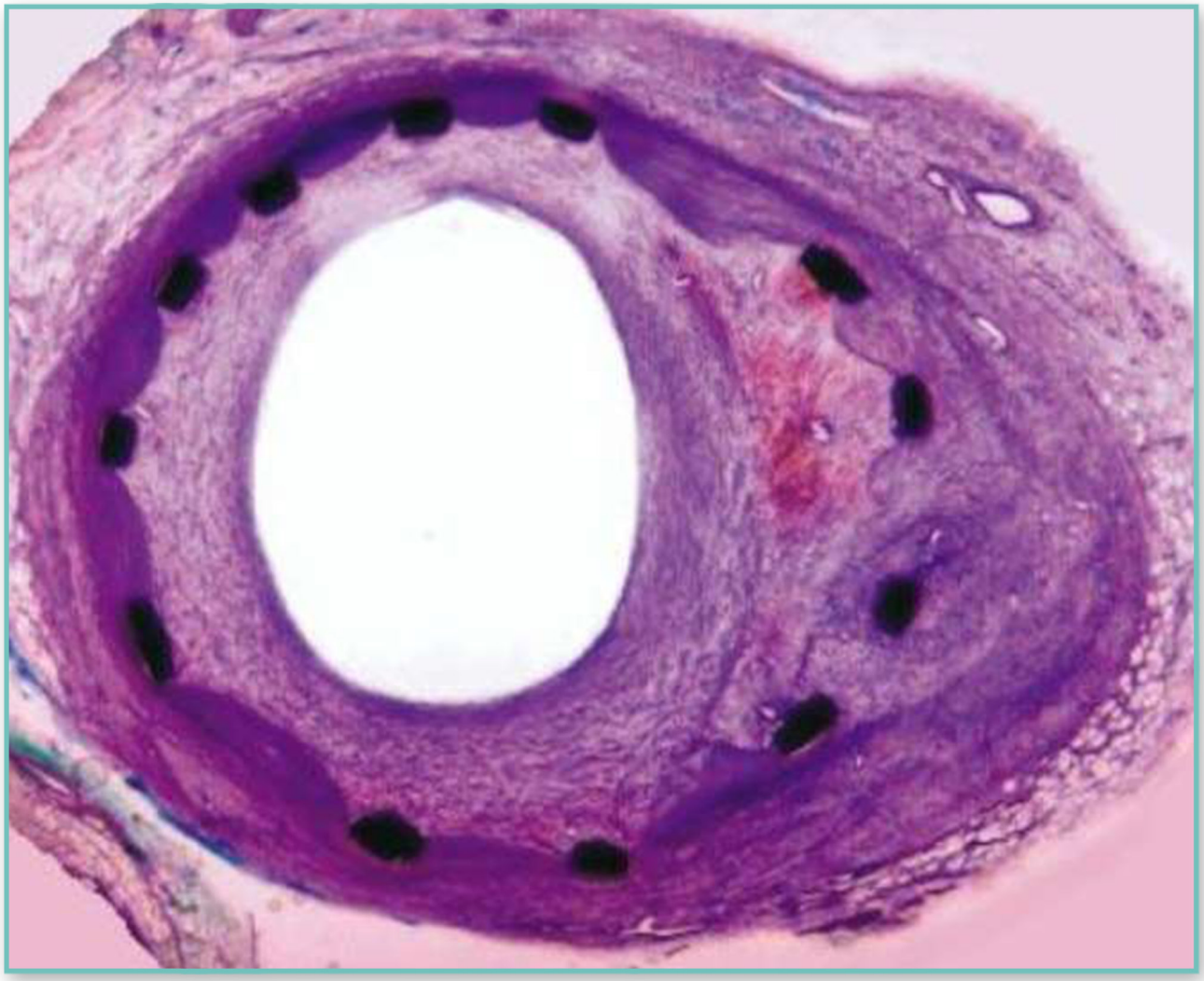
**3. Drug-eluting stents (DES):**
introduced to the European and U.S. markets







# Restenosis After BMS



# Effect of DES

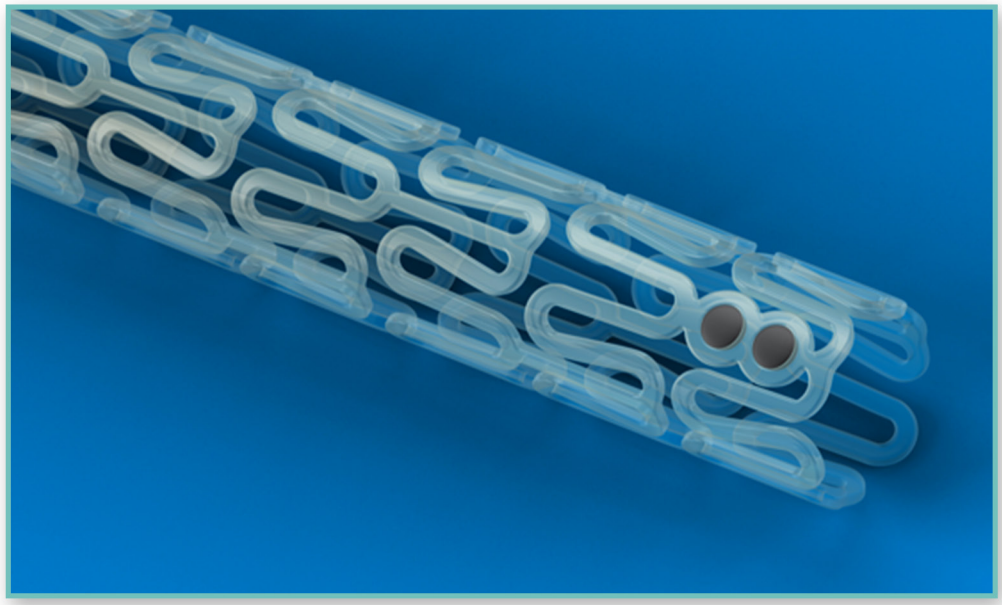
Without Drug Coating

With Drug Coating

# Revolutions in Interventional Stenosis Treatments

- 4th Generation: Leave Nothing Behind!

Drug Eluting Balloon (DEB)

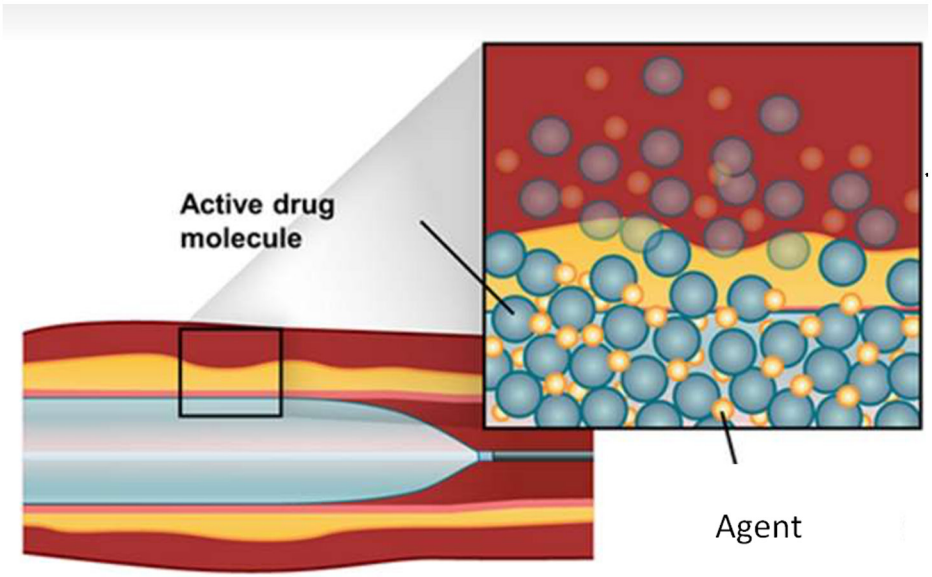


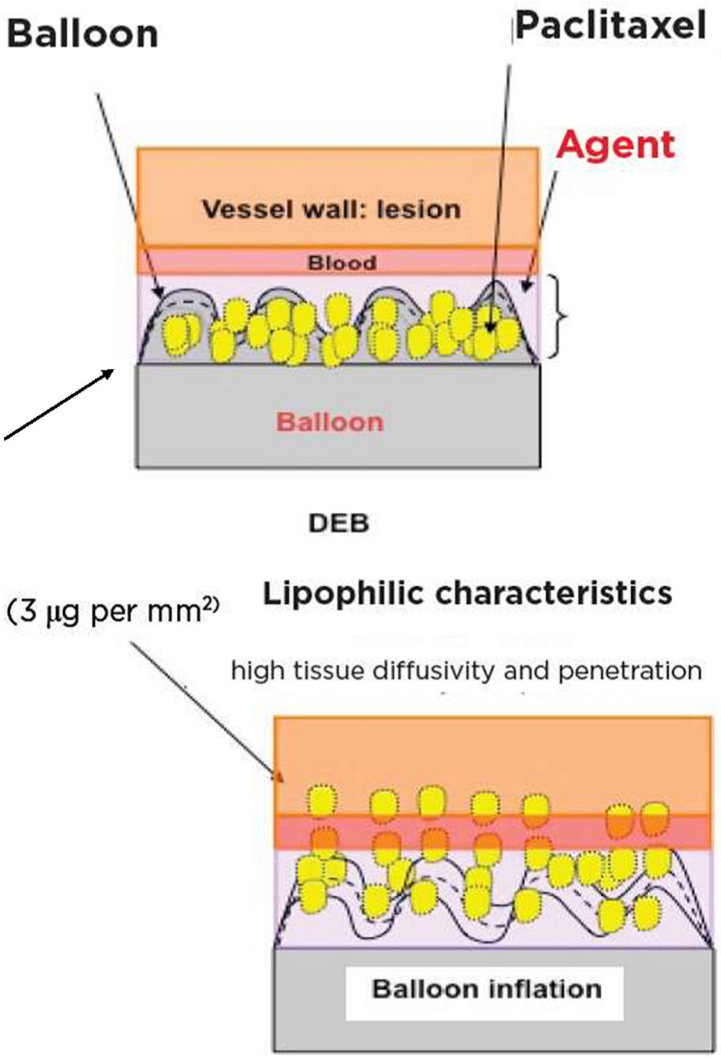
Biodegradable Stent

# Drug Eluting Ballon (DEB)

- Conventional semi-compliant angioplasty balloons
- Covered with an anti-proliferative drug which is released into the vessel wall during inflation of the balloon
- Inflation usually at nominal pressures with a specific minimal inflation time
- Active substance on the DEB is lipophilic with high absorption rate through vessel wall (to compensate for the short period of contact between the inflated balloon and the vessel wall)

# Components of DEB



# DEB

## 1st Generation DEBs

- Paclitaxel (3 ug/mm$^2$)
- Drug Carrier Buffer: Iopromide, an iodinated hydrophilic contrast
- IOPROMIDE - increases drug solubility and speeds uptake

## 2nd Generation DEBs

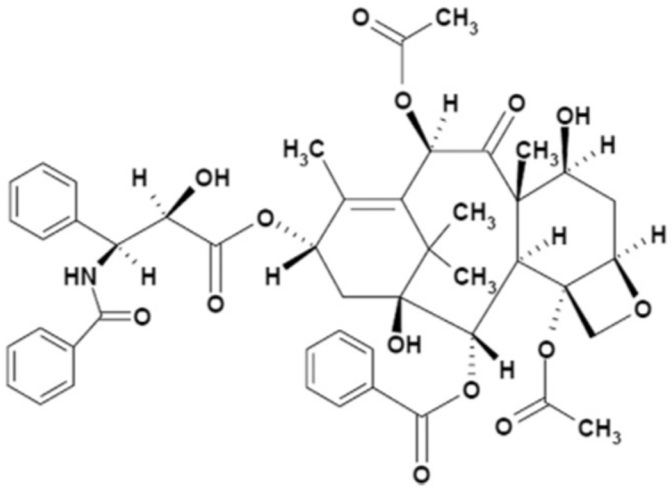
- Paclitaxel or Sirolimus
- New Drug Carrier Buffers
  - Urea
  - Shellac
  - BTHC (Butyry Trihexyl Citrate)

## 3rd Generation DEBs

- No drug carrier buffers
  - Paclitaxel (2 ug/mm$^2$) and hydrogel coat
  - Very tight bound paclitaxel in between balloon folds

# Why Paclitaxel?

- Highly lipophilic – Rapid intracellular uptake and retention in vessel wall for nearly a week
- Acts by irreversible binding to microtubules, inhibiting cell division and migration - structural intracellular changes cause long-lasting effects
- Short incubation time (3 minutes) with paclitaxel almost completely inhibits vascular smooth muscle cell proliferation for up to 12-14 days



Vaquerizo B etal. Update on drug-eluting balloons for percutaneous coronary interventions. EMJ Int Cardiol. 2013;1:80-90

# Why this concentration?

- Concentration of paclitaxel on DEB – 3 μg/mm2 – 3x higher compared with paclitaxel- eluting stents (PES)
- This specific dose is the same for all DEB - based on in vitro studies
  - 10% of the dose lost while catheter is advanced through haemostatic valve and guiding catheter
  - 70-80% dose released at the target site is washed away in the blood stream during inflation
  - Only 10 to 20% of the paclitaxel transferred from balloon surface to the vessel wall
- Thus, PCB delivers a dose to target in a very short time that is higher than total dose released by DES over many weeks
- With this immediate drug release - no need for a polymer for drug administration - thus avoiding chronic inflammation and late thrombosis

Vaquerizo B etal. Update on drug-eluting balloons for percutaneous coronary interventions. EMJ Int Cardiol. 2013;1:80-90

# Available Elution Characteristics

| Name of PEB | Type of Coating | Formulation | Realease from balloon surface 30/60(s) | Vessel wall paclitaxel concentration & time of inflation | Company | Procedure |
|---|---|---|---|---|---|---|
| Paccocath™ | Iopromide | 3 µg paclitaxel/mm² balloon surface, admixed iopromide (Ultravist 370™) | | | Bavaria Medizin Technology | - BMS-ISR (RCT): PEB vs POBA (11) |
| SeQuent™ Please | Iopromide | 3 µg paclitaxel/mm² balloon surface, modified Paccocath™ | NA/93% | 45-95 µg- 60 s | B. Braun, Melsungen, Germany | - BMS-ISR (RCT): PEB vs PES (14)<br>- DES-ISR (RCT): PEB vs POBA (12, 13). PEB vs PES vs POBA(16)<br>- *De novo* lesions (r) (16, 17) |
| Cotavance™ | Iopromide | 3 µg paclitaxel/ mm² balloon surface, modified Paccocath™ | NA | NA | MEDRAD Inc, Warrendale, PA | NA |
| DIOR I | No carrier | Paclitaxel micro-crystals coated onto a 3-fold-microporous balloon surface structure | 20/25% | 1.5-6 µg – 60 s | Eurocor, GmbH, Ger-many | BMS/DES-ISR (r) (20)<br>*De novo* lesions (RCT) (30) |
| DIOR II | Shellac | 3 µg paclitaxel/mm² balloon surface, 1:1 mixture of paclitaxel and shellac | 75/85% | 167 µg – 30 s | Eurocor, GmbH, Germany | BMS/DES-ISR (r) (20, 21)<br>*De novo* lesions |

**Paclitaxel + Iopromid**
**90% Drug Release**

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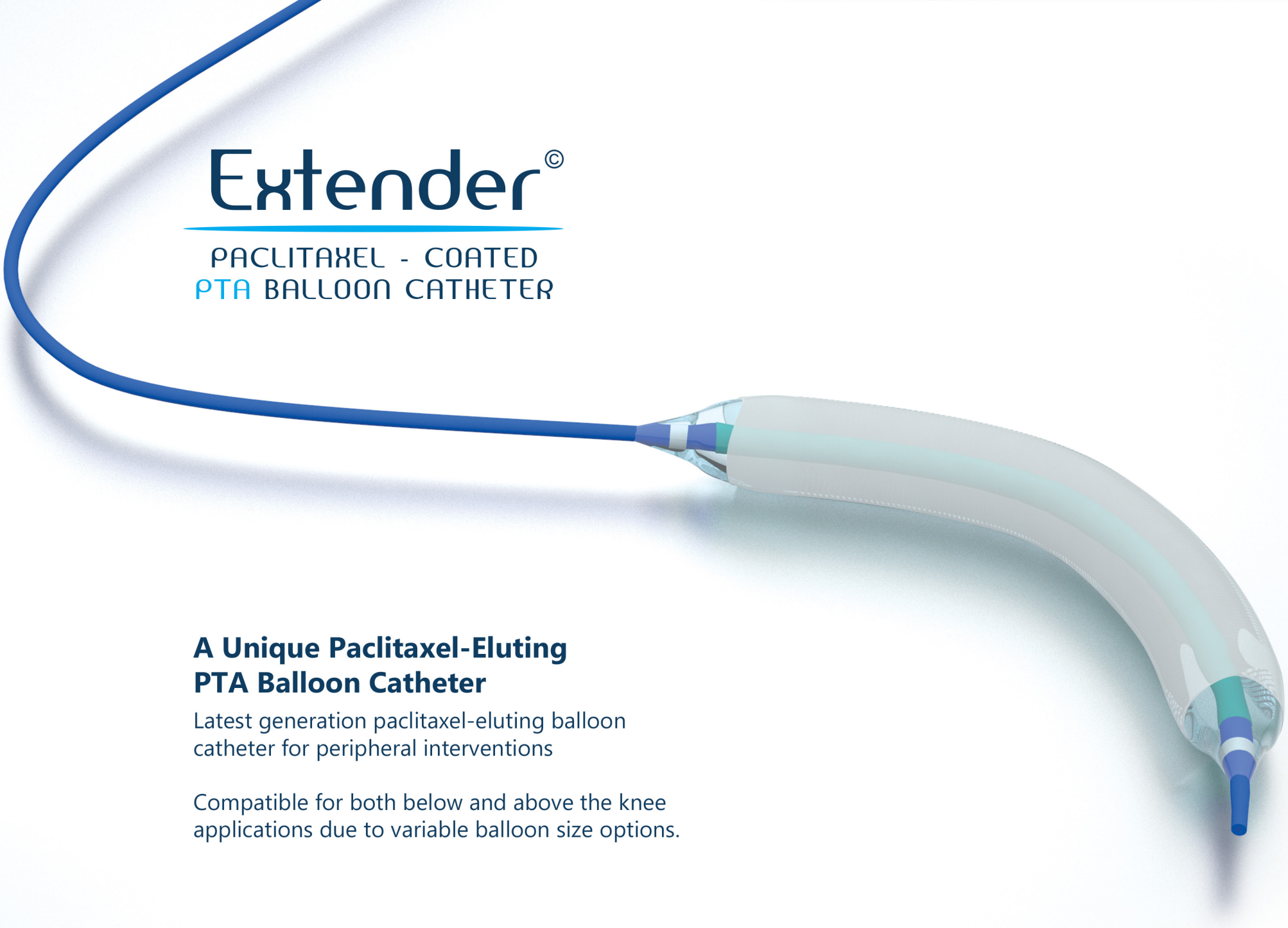
PACLITAXEL - COATED
PTA BALLOON CATHETER



## A Unique Paclitaxel-Eluting PTA Balloon Catheter

Latest generation paclitaxel-eluting balloon catheter for peripheral interventions

Compatible for both below and above the knee applications due to variable balloon size options.

# Extender

- 3 ug/mm2 Paclitaxel + Iopromid
- <2 um particle size
- Minimal drug loss during advancing into the lession (< %5)
- Over %90 drug transfer to the target lession
- Both over and below the knee balloon sizes (2-10 mm)
- Over 16 atn high pressure (Burst pressure 27 atm)

# Practical points before DEB use

- Proper vessel preparation with predilation balloon 0.5-1.0 mm smaller than intended DEB
- Ensure adequate 1:1 sizing between vessel and DEB
- Shorten transfer time from access sheath to DEB inflation
- Single prolonged inflation for complete drug release till manufacturer's recommended time (60 or 30 sec) – if not tolerated, fractional release in quick intermittent inflations till recommended time is complete

# DEB in Peripheral Arterial Diseases (PAD)

# PAD Current Treatment Options

- Surgical by-pass
- PTA Balloon
- Bare Metal Stent
- Endovascular Stent-Greft
- Drug Eluting Stent
- Drug Eluting Balloon
- Atherectomy

# PTA Balloon & Bare Metal Stent (POBA)

- POBA 1st line treatment for femoro-popliteal disease
- Stenting only for poor outcome – high rate of re-stenosis despite initial technical success rate of 95% even with stenting 1 year restenosis rates have varied between 20-50% depending on an increasing with length of lesion
- Balloon angioplasty for shorter lesions(<4cm)
- Primary stenting in longer lesions

  Secondary stenting if residual stenosis/dissection

# DEB in Femoro-Popliteal Diseases

- Many RCT showing favourable results vs POBA (upto 2 yrs)
- But have short follow up, industry driven
- Secondary stent implantation: 4-21% in DEB; 14-36% in POBA
- Paclitaxel platform demonstrates greater efficacy

Colombo A. Drug eluting balloons for femoro-popliteal artery disease: Emerging research. ESC E journal cardiology practice 2014;13.

# DEB in Femoro-Popliteal Diseases

**Table 4.** Comparison of published freedom from TLR and primary patency following treatment of FP.

| Study/first author | Devices | Follow-up | Lesions (*n*) | Freedom from TLR | Primary patency |
|---|---|---|---|---|---|
| Zilver-PTX[13] | DES | 1 year | 108 | 81% | 79% |
| RELINE study[12] | Viabahn covered stent | 1 year | 39 | 80% | 74% |
| | PTA | 1 year | 44 | 42% | 28% |
| Werner et al.[7] | Brachytherapy | 1 year | 90 | NS | 80% |
| Dick et al.[6] | Cutting balloon | 6 months | 17 | 59% | 35% |
| | PTA | 6 months | 22 | 64% | 27% |
| Shammas et al.[3] | Directional atherectomy | 1 year | 41 | 66% | NS |
| Trentmann et al.[4] | Directional atherectomy | 1 year | 35 | NS | 25% |
| Zeller et al.[5] | Directional atherectomy | 1 year | 43 | 53% | 54% |
| Shammas et al.[8] | Laser atherectomy + PTA | 1 year | 40 | 49% | NS |
| Yeo et al.[9] | Laser atherectomy + PTA | 1 year | 22 | 77% | NS |
| Excite ISR study[11] | Laser atherectomy + PTA | 6 months | 169 | 73.5% | NS |
| | PTA | 6 months | 81 | 51.8% | NS |
| Laird et al.[10] | Laser atherectomy + heparin coated stent | 1 year | 27 | 83% | 48% |
| Van den Berg et al.[26] | Laser atherectomy + DEB | 18 months | 14 | 86% | 86% |
| Stabile et al.[18] | DEB | 1 year | 39 | 100% | 92.1% |
| DEBATE ISR study[17] | DEB | 1 year | 44 | 86.4% | 81.5% |
| DEBATE ISR study[27] | DEB | 3 year | 44 | 60% | NS |
| FAIR study[19] | DEB | 1 year | 62 | 90.8% | 70.5% |
| | PTA | 1 year | 57 | 52.8% | 37.5% |
| PLAISIR study | DEB | 1 year | 55 | 90.2% | 83.7% |

DEB = drug-eluting balloon; DES = drug-eluting stent; FP = femoropopliteal; ISR = in-stent restenosis; PTA = percutaneous transluminal angioplasty.

Bague et Al., Femoropopliteal In-stent Restenosis Repair: Midterm Outcomes After Paclitaxel Eluting Balloon Use (PLAISIR Trial) , Eur J Vasc Endovasc Surg (2017) 53, 106e113

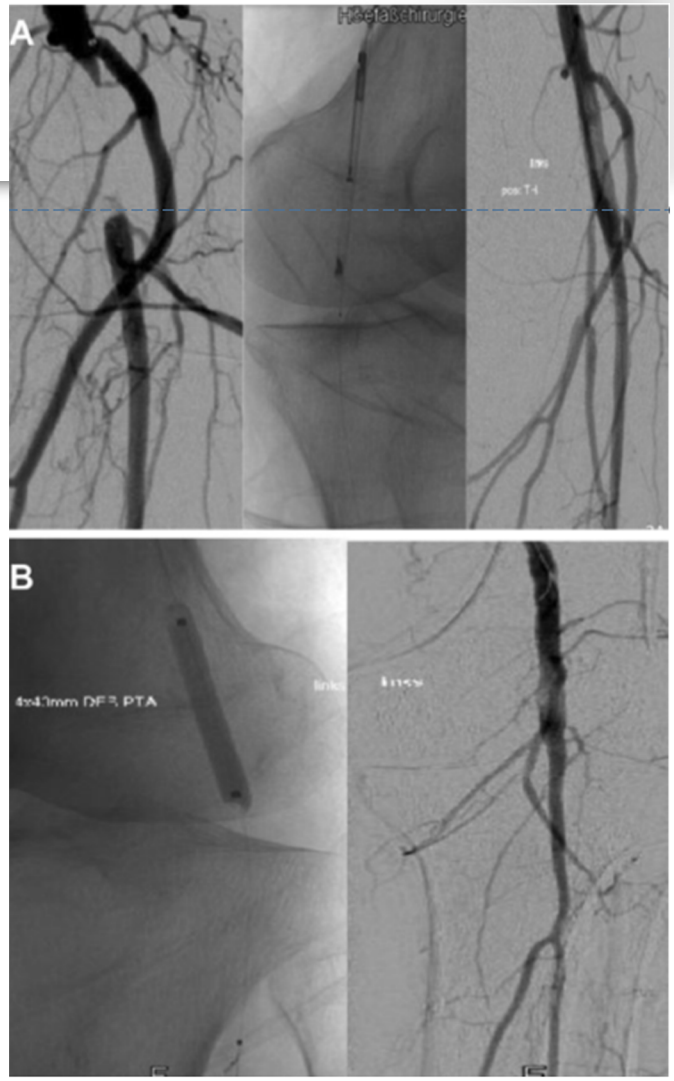
| Study | Year | Study Size | Location | Outcome(s) | Follow-up Time | Results | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Outcome | POBA | DCB | P Value |
| THUNDER | 2008 | 154 | Germany | LLL and TLR | 6 Months | LLL | 1.7mm | 0.4mm | <0.001 |
| | | | | | | TLR | 37% | 4% | <0.001 |
| Werk *et al* | 2008 | 87 | Germany | LLL and TLR | 6 Months | LLL | 0.8mm | 0.3mm | 0.031 |
| | | | | | | TLR | 50% | 13% | 0.001 |
| LEVANT I | 2014 | 101 | Primarily Germany and Belgium | LLL | 6 Months | LLL | 1.09mm | 0.46mm | 0.016 |
| LEVANT II | 2015 | 476 | US and Europe | PP and TLR | 12 Months | PP | 52.6% | 65.2% | 0.02 |
| | | | | | | TLR | 16.8% | 12.3% | 0.21 |
| | | | | | | PP (US) | 56.5% | 69.9% | not given |
| | | | | | | PP (Non-US) | 46% | 69.1% | not given |
| PACIFIER | 2015 | 85 | Germany | LLL and TLR | 12 Months | LLL | 0.65mm | 0.1mm | 0.001 |
| | | | | | | TLR | 27.90% | 7.10% | 0.02 |
| IN.PACT SFA | 2015 | 331 | US and Europe | PP and CD-TLR | 24 Months | PP | 50.10% | 78.9% | <0.001 |
| | | | | | | CD-TLR | 28.30% | 9.10% | <0.001 |

# Atherectomy & DEB

- Rastan et al. Compared the performance of Nitinol stents to isolated balloon angioplasty for isolated popliteal lesions and found a 64% 2-year primer patency in the stent group and 31% ($p < 0.001$) in the angioplasty group.1

- Moreover, application of popliteal lesions (directional atherectomy) in the DEFINITIVE LE study2 provided a 74% primer clearance in mid-length lesions (5.0-9.9 cm) and 74% in longer lesions (≥10 cm). In general, the application of DA alone for Femoropopliteal PAD has failed to demonstrate satisfactory medium-term patency rates in various series.

- Stavroulakis et al. used DA and DEB together in their study3, the mean follow-up period was 18 ± 12 months. The primary clearance remained 95% at 12 months and decreased to 90% due to restenosis at 18 months and occlusion of the treated vessels. The 1-year primary and secondary opening rates (95% and 100%, respectively) were higher than those indicated in the DEFINITIVE LE study, and no amputation was performed.



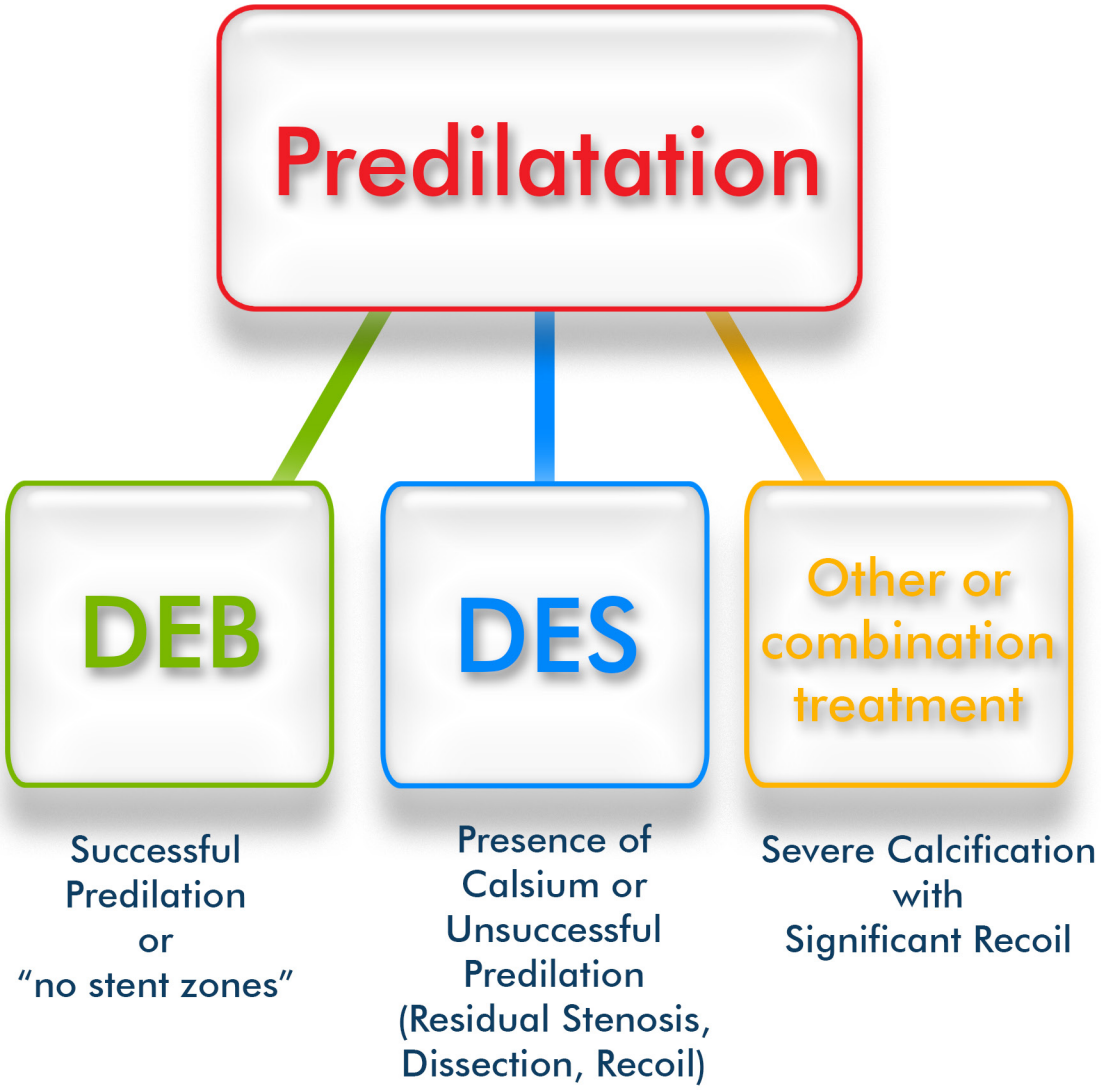

1- Rastan A, Krankenberg H, Baumgartner I, et al. Stent place- ment vs. balloon angioplasty for popliteal artery treatment: two-year results of a prospective, multicenter, randomized trial. J Endovasc Ther. 2015;22:22–27.
2- McKinsey JF, Zeller T, Rocha-Singh KJ, et al. Lower extrem- ity revascularization using directional atherectomy 12-month prospective results of the DEFINITIVE LE study. JACC Cardiovasc Interv. 2014;7:923–933.
3- Stavroulakis et al., Combined Directional Atherectomy and Drug-Eluting Balloon Angioplasty for Isolated Popliteal Artery Lesions in Patients With Peripheral Artery Disease, Journal of Endovascular Therapy, 1–6, 2015

# Atherectomy & DEB

- Theoretically, combined therapy leads to better penetration of the antiproliferative drug into the arterial wall, minimizing the development of drug delivery and excessive neointimal development.
- Administration of DEB after DA can also reduce the local inflammatory response, with subsequent platelet activation, after a more aggressive mechanical plaque excision.
- In this context, Sixt et al.1 Found that the combination of DE with DEB for restenotic femoropoplasic arteries was associated with better patency at 12 months, following DA than balloon angioplasty. In addition, combined therapy provided good results in a small series of femoropopliteal lesions.
- Recently, the results of the DEFINITIVE AR2 trial suggest that combined administration of DEB and femoropopliteal lesions results in a higher rate of patency over 1 year compared to DEB alone.

1- Sixt S, Cancino O, Treszl A, et al. Drug-coated balloon angioplasty after directional atherectomy improves outcome in restenotic femoropopliteal arteries. J Vasc Surg. 2013;58: 682–686.
2- Zeller T. 12 Month DEFINITIVE AR results. Presented at: VIVA 2014: Vascular Interventional Advances; November 4-7, 2014; Las Vegas, NV.

# General Guideline



# Conclusions

- DEB is a promising technology in both coronary and peripheral artery disease
- NOT suitable for all
  - For technical success, requires proper patient selection
  - Clinical and angiographic characteristics, proper preparation of vessel before use

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