Update on Balloon Technologies

John R. Laird
Professor of Medicine
Medical Director of the Vascular Center
UC Davis Medical Center
Charles Dotter, MD
50th Anniversary of Angioplasty

August 1964
MEDICINE

With a lack of competing options, Dr. Davis forces his own “snake”—a specially designed catheter—through the artery supplying the main artery in a patient's leg. The patient was given a sedative and local anesthetics before treatment, which lasted half an hour.

Plumbing-style ‘snake’ restores blocked circulation

CLEARING AN ARTERY

Dr. Charles Potter, of the University of Oregon Medical School, had every reason to be elated. By applying a bit of knowledge straight out of the practices’ manual, he had just saved his patient’s life by restoring a leg.

The man on the treatment table, George Gerhardt, 75, was suffering from acute abdominal pain, which had completely blocked a main artery of his left leg with fatty deposits. Gerhardt had told his wife, and unless the vessel could be opened immediately, the man’s life was in danger. Fortunately for Gerhardt, Dr. Potter had developed—a tool specifically designed for a new technique employing a miniature device similar to the “snake” with which he had restored a leg.

In an attempt to free the arteries in the man’s left leg artery, the doctor inserted a catheter on the affected vessel and inserted a new channel for the blood. He hopes that eventually his technique can be used in arteries supplying the brain and heart to prevent strokes and heart attacks.

AN X-RAY WATCH ON THE PROGRESS

As he converses with his leading physician, Dr. Potter explains the advantages of using a new X-ray equipment, which allows him to monitor the progress of other medical procedures. He emphasizes the importance of using the latest technology in medical practice.

Continued...
The First Angioplasty

82 year old female with toe gangrene who refused amputation
The Father of Balloon Angioplasty
Andreas Gruentzig, MD
Gruentzig Balloon
The Co-Axial (over the wire) Angioplasty Balloon

John Simpson, MD
The Rapid Exchange Balloon

Paul Yock, MD
The RX “Monorail” Balloon
Iterative Improvements

- Lower and lower profile
- More flexible and easy to deliver
- Compliant vs. non-compliant
- Longer balloons
- High pressure balloons for post stent dilation
The Hits and Misses of Balloon Angioplasty

- PLOSA – Physiologic Low Stress Angioplasty
- Laser (Spears) Balloon
- Perfusion (Stack) Balloon
- Cutting (Barath) Balloon
- Scoring Balloon
- Cold Balloon (Cryoplasty)
- Embolic Capture Angioplasty
Role for Cutting/Scoring Balloons

- Focal, calcified lesions
  - Diabetes
  - ESRD
- Ostial stenoses
- Bypass graft stenoses
- Instent restenosis
- Lesion preparation prior to stenting
AngioSculpt®

- 2 component system
- OTW or rapid exchange balloon
- Nitinol spiral cage
Cutting Balloon
Embolic Capture Angioplasty

Angioplasty

A. Guide Wire Insertion

B. Balloon Inflation

Embolic Capture

C. Folding Inward

D. Negative Pressure

E. Debris Capture

F. Debris Removal
Multicenter Trial Highlights

Particles Removed in Every Procedure
- Total of 45,665 particles were counted
- Individual specimen (devices): 47 - 3849 particles
- Average of 319 particles per device
- Particle counts per subject: 63 - 4361

Clinically Relevant Particles in 25% of Procedures
- 25% of patients had a particle > 2 mm
- 11% of patients had a particle > 4 mm
- 7% of patients had a particle > 5 mm
- 6% of patients had a particle > 6 mm

1 year clinical follow-up demonstrated lower revascularization rate in comparison to historical controls
SFA Instent Restenosis
Atherectomy and ECA
STAY CALM! WINE IS HERE!

CALL: 01249 602 727
The New Era of Drug Eluting Balloons

Paclitaxel Balloon Coating, a Novel Method for Prevention and Therapy of Restenosis

Bruno Scheller, MD; Ulrich Speck, PhD; Claudia Abramjuk, DVM; Ulrich Bernhardt, PhD; Michael Böhm, MD; Georg Nickenig MD

Background—Drug-eluting stents have shown promising antirestenotic effects in clinical trials. Non-stent-based local delivery of antiproliferative drugs may offer additional flexibility and also reach vessel areas beyond the immediate stent coverage. The aim of the present study was to evaluate a novel method of local drug delivery based on angioplasty balloons.

Methods and Results—Stainless steel stents (n=40; diameter, 3.0 to 3.5 mm; length, 18 mm) were implanted in the left anterior descending and circumflex coronary arteries of domestic pigs. Both conventional uncoated and 3 different types of paclitaxel-coated, percutaneous transluminal coronary angioplasty balloons (contact with vessel wall for 1 minute) were used. No difference in short-term tolerance between coated and uncoated balloons and no signs of thrombotic events were observed. Quantitative angiography and histomorphometry of the stented arteries asserted the statistical equality of the baseline parameters between the control and the 3 treatment groups. Paclitaxel balloon coating led to a marked, dose-dependent reduction of parameters characterizing in-stent restenosis (reduction of neointimal area up to 63%). Despite the marked reduction in neointimal proliferation, endothelialization of stent struts was present in all samples. There was no evidence of a significant inflammatory response in the neighborhood of the stent struts.

Conclusions—Paclitaxel balloon coating is safe, and it effectively inhibits restenosis after coronary angioplasty with stent implantation in the porcine model. The degree of reduction in neointimal formation was comparable to that achieved with drug-eluting stents. (Circulation. 2004;110:810-814.)

Key Words: restenosis ■ angioplasty ■ paclitaxel
Thunder Trial
Study Design

Fem-pop Disease
N = 154

Uncoated Balloon
N = 54

Iopromid + Paclitaxel I.A.
N = 52

Paclitaxel Balloon*
N = 48

*3 micrograms/mm2 Paclitaxel

Six Month Angiographic Follow-up

12 and 24 Month Duplex Follow-up
Thunder Trial

Binary Restenosis Rate

- Uncoated balloon
- Uncoated balloon/Paclitaxel i.a.
- Paccocath

Comparing results at 6 months and 12 months.
Thunder Trial
Case Study
## DCB with PTX- Early Results

<table>
<thead>
<tr>
<th>Trial</th>
<th>Comparator</th>
<th>Vessel</th>
<th>1° Endpoint</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEMPAC</td>
<td>PACCOCATH™ vs. PTA</td>
<td>SFA de-novo</td>
<td>6M LLL</td>
<td>Werk et al, Circulation 2008;118:1356-1365</td>
</tr>
<tr>
<td>LEVANT I</td>
<td>MOXY™ vs. PTA</td>
<td>SFA de-novo</td>
<td>6M LLL</td>
<td>D. Scheinert, TCT 2010</td>
</tr>
</tbody>
</table>
### Durable TLR benefit at 2 and 5 years

<table>
<thead>
<tr>
<th></th>
<th>DEB</th>
<th>PTA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEMPAC 2Y</td>
<td>6/45 (13%)</td>
<td>21/42 (50%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**THUNDER 5Y**

G. Tepe ISET 2012

Freedom from TLR: Kaplan-Meier

[Logrank p=0.0003]

Survival Probability

Time free of TLR (years)
## Peripheral & Coronary DCBs with CE Mark

<table>
<thead>
<tr>
<th>Company</th>
<th>Device Name</th>
<th>Balloon Drug Load</th>
<th>Carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutonix</td>
<td>Moxy DCB</td>
<td>2 µg/mm²</td>
<td>Non-polymeric</td>
</tr>
<tr>
<td>Medrad-Possis</td>
<td>Cotavance</td>
<td>3 µg/mm²</td>
<td>Iopromide</td>
</tr>
<tr>
<td>Medtronic/Invatec</td>
<td>In.Pact</td>
<td>3.5 µg/mm²</td>
<td>Urea</td>
</tr>
<tr>
<td>Biotronik</td>
<td>Pantera Lux, Passeo 18</td>
<td>3 µg/mm²</td>
<td>BTHC</td>
</tr>
<tr>
<td>B. Braun</td>
<td>Sequent Please</td>
<td>3 µg/mm²</td>
<td>Iopromide</td>
</tr>
<tr>
<td>Eurocor</td>
<td>DIOR II, Freeway</td>
<td>3 µg/mm²</td>
<td>Shellac</td>
</tr>
<tr>
<td>Aachen Resonance</td>
<td>Elutax</td>
<td>3 µg/mm²</td>
<td>Unknown</td>
</tr>
<tr>
<td>Blue Medical</td>
<td>Protégé</td>
<td>3 µg/mm²</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
- Low drug-load balloon with 2µg per mm² of paclitaxel
- Hydrophilic, highly transfer-efficient drug carrier
Medtronic DEB Technology

**IN.PACT™**
- Medtronic DEB balloon line

**FREEPAC™**
- proprietary hydrophilic drug coating formulation
  - separates Paclitaxel molecules
  - balances hydrophilic and lipophilic properties
  - facilitates Paclitaxel elution into the vessel wall

**PACLITAXEL (3.5 MCG/MM²)**
The LEVANT I (Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis) Trial for Femoropopliteal Revascularization

First-in-Human Randomized Trial of Low-Dose Drug-Coated Balloon Versus Uncoated Balloon Angioplasty

Objectives This study sought to evaluate the safety and efficacy of the Lutonix drug-coated balloon (DCB) coated with 2 μg/mm² paclitaxel and a polysorbate/sorbitol carrier for treatment of femoropopliteal lesions.

Background Percutaneous treatment of peripheral vascular disease is associated with a high recurrence. Paclitaxel-coated balloons at 3 μg/mm² formulated differently have shown promising results with reduced restenosis.

Methods Subjects at 9 centers with Rutherford class 2 to 5 femoropopliteal lesions were randomized between June 2009 and December 2009 to treatment with Lutonix DCB (n = 49) versus uncoated balloons (control group [n = 52]), stratified by whether balloon-only treatment (n = 75) or stenting (n = 26) was intended. The primary endpoint was angiographic late lumen loss at 6 months. Secondary outcomes included adjudicated major adverse events (death, amputation, target lesion thrombosis, reintervention), functional outcomes, and pharmacokinetics.

Results Demographic, peripheral vascular disease, and lesion characteristics were matched, with mean lesion length of 8.1 ± 3.8 cm and 42% total occlusions. At 6 months, late lumen loss was 58% lower for the Lutonix DCB group (0.46 ± 1.13 mm) than for the control group (1.09 ± 1.07 mm; p = 0.016). Composite 24-month major adverse events were 39% for the DCB group, including 15 target lesion revascularizations, 1 amputation, and 4 deaths versus 46% for uncoated balloon group, with 20 target lesion revascularizations, 1 thrombosis, and 5 deaths. Pharmacokinetics showed biexponential decay with peak concentration (Cmax) of 59 ng/ml and total observed exposure (AUC0-24) of 73 ng h/ml. For successful DCB deployment excluding 8 malfunctions, 6-month late lumen loss was 0.39 mm and the 24-month target lesion revascularization rate was 24%.

Conclusions Treatment of femoropopliteal lesions with the low-dose Lutonix DCB reduced late lumen loss with safety comparable to that of control angioplasty. (LEVANT I, The Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis; NCT00930813) (J Am Coll Cardiol Intv 2014;7:10–9) © 2014 by the American College of Cardiology Foundation
Figure 3. Primary Endpoint

Mean late lumen loss at 6 months is shown for Lutonix drug-coated balloon (DCB) (open bars) versus control uncoated balloon percutaneous balloon angioplasty (solid bars) in the intention-to-treat population (all subjects in pooled strata) and separately for each stratum (intended balloon or stent groups) with p values. Columns are labeled with evaluable sample size (n) at base and mean late lumen loss ± SD (mm) at top.
<table>
<thead>
<tr>
<th><strong>Primary endpoints</strong></th>
<th>Safety and primary patency of target lesion at 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients/sites</strong></td>
<td>476 Randomized (2:1) / 55 global sites</td>
</tr>
</tbody>
</table>
| **Follow-up** | **Clinical:** 6, 12, 24 Months  
**Duplex Ultrasound (DUS):** 0–30 days, 6, 12, 24 months  
**Telephone:** 1, 36, 48, 60 Months |
| **National principal investigators** | **Ken Rosenfield:** Mass General, Boston  
**Dierk Scheinert:** Park Hospital, Leipzig, Germany |
| **Status** | First Patient Enrolled July 2011  
Last Patient Enrolled July 2012  
12 month follow-up visits now complete and monitored |
### 6 MONTH OUTCOMES

<table>
<thead>
<tr>
<th>Measure</th>
<th>DCB % (n/N)</th>
<th>PTA % (n/N)</th>
<th>Difference$^2$</th>
<th>P-value$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Binary Restenosis</strong></td>
<td>17.4% (47/270)</td>
<td>33.8% (47/139)</td>
<td>-16.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Composite Safety Endpoint Failure</strong></td>
<td>8.0% (24/299)</td>
<td>8.6% (13/151)</td>
<td>-0.6%</td>
<td>0.016 (non-inferiority)</td>
</tr>
<tr>
<td>TVR</td>
<td>6.7% (20/298)</td>
<td>7.9% (12/151)</td>
<td>-1.2%</td>
<td>0.633</td>
</tr>
<tr>
<td>Death</td>
<td>0.7% (2/301)</td>
<td>1.3% (2/152)</td>
<td>-0.7%</td>
<td>0.497</td>
</tr>
<tr>
<td>Amputation</td>
<td>0.3% (1/299)</td>
<td>0.0% (0/151)</td>
<td>0.3%</td>
<td>0.366</td>
</tr>
<tr>
<td>Embolization (any during index procedure)</td>
<td>0.6% (2/316)</td>
<td>1.9% (3/160)</td>
<td>-1.2%</td>
<td>0.226</td>
</tr>
<tr>
<td>Re-intervention for Thrombosis or Embolism (target vessel)</td>
<td>0.3% (1/298)</td>
<td>0.7% (1/151)</td>
<td>-0.4%</td>
<td>0.623</td>
</tr>
</tbody>
</table>

$^1$Proportions through close of 6-month follow-up window (212 days)

$^2$Not pre-specified for hypothesis testing and not adjusted for multiplicity
IN.PACT SFA
Randomized Trial of IN.PACT Admiral DCB vs. PTA for the Treatment of Atherosclerotic Lesions in the SFA and/or PPA
1-year Primary Outcomes

Gunnar Tepe - RoMed Klinikum Rosenheim, Rosenheim (Germany)
Peter Schneider - Hawaii Permanente, Honolulu, HI (US)
John Laird - UC Davis Medical Center, Sacramento, CA (US)

on behalf of the IN.PACT SFA Investigators
Trial Design

Pre-screening

Screening

Randomization

Screen Failure
(treat per std practice)

RC 2-3-4 [1]

Clinical and Anatomic
Inclusion / Exclusion Criteria

SUCCESSFUL PRE-DILATATION [2]

331
Randomized
2:1

IN.PACT (220)

PTA (111)

Provisional Stenting?

NO

Secondary Analysis
(331 ITT ALL Subjects)

Primary Analysis
(301 ITT NON-Stented Subjects)

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
## Baseline Angiographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>IN.PACT</th>
<th>PTA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=220 Subjects, N=221 Lesions)</td>
<td>(N=111 Subjects, N=113 Lesions)</td>
<td></td>
</tr>
<tr>
<td><strong>Lesion Type</strong> [1]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De novo</td>
<td>95.0% (209/220)</td>
<td>94.6% (105/111)</td>
<td>0.875</td>
</tr>
<tr>
<td>Restenotic</td>
<td>5.0% (11/220)</td>
<td>5.4% (6/111)</td>
<td></td>
</tr>
<tr>
<td><strong># Patent Runoff Vessels</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3.3% (7/212)</td>
<td>4.5% (5/112)</td>
<td>0.758</td>
</tr>
<tr>
<td>1</td>
<td>13.7% (29/212)</td>
<td>26.8% (30/112)</td>
<td>0.006</td>
</tr>
<tr>
<td>2</td>
<td>41.5% (88/212)</td>
<td>33.0% (37/112)</td>
<td>0.151</td>
</tr>
<tr>
<td>3</td>
<td>41.5% (88/212)</td>
<td>35.7% (40/112)</td>
<td>0.340</td>
</tr>
<tr>
<td><strong>Prox. Popliteal Involvement (%)</strong></td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Lesion Length (cm) II</td>
<td>8.94 ± 4.89</td>
<td>8.81 ± 5.12</td>
<td>0.815</td>
</tr>
<tr>
<td>Total Occlusions (%)</td>
<td>25.8% (57/221)</td>
<td>19.5% (22/113)</td>
<td>0.222</td>
</tr>
<tr>
<td>Severe Calcification (%)</td>
<td>8.1% (18/221)</td>
<td>6.2% (7/113)</td>
<td>0.662</td>
</tr>
<tr>
<td>RVD (mm)</td>
<td>4.647 ± 0.841</td>
<td>4.681 ± 0.828</td>
<td>0.728</td>
</tr>
<tr>
<td>MLD pre (mm)</td>
<td>0.900 ± 0.776</td>
<td>0.933 ± 0.771</td>
<td>0.711</td>
</tr>
<tr>
<td>Diameter Stenosis pre (%)</td>
<td>81.1 ± 15.5</td>
<td>81.3 ± 13.7</td>
<td>0.946</td>
</tr>
</tbody>
</table>

All ITT subjects (stented and non-stented)

1. Site-reported
2. Normal-to-normal by Core Lab QVA evaluation
# Per Protocol, 12-month Outcomes

<table>
<thead>
<tr>
<th>Primary Efficacy, Primary Patency</th>
<th>IN.PACT</th>
<th>PTA</th>
<th>Difference [95% CI]</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-stented ITT</td>
<td>82.9%</td>
<td>52.2%</td>
<td>29.0% [16.2%, 41.8%]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All ITT</td>
<td>82.2%</td>
<td>52.4%</td>
<td>26.2% [15.1%, 37.3%]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Safety Composite</th>
<th>IN.PACT</th>
<th>PTA</th>
<th>Difference [97.5% CI]</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-stented ITT</td>
<td>95.8%</td>
<td>77.7%</td>
<td>12.2% [1.2%, ∞] [4, 5]</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18.2% [9.3%, 27.0%]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All ITT</td>
<td>95.7%</td>
<td>76.6%</td>
<td>19.0% [11.5%, ∞] [4]</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19.0% [10.5%, 27.5%]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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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
ALL ITT, 12-month Primary Patency [1]

(p<0.001 by log-rank test)

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
ALL ITT, 12-month Clinically-driven TLR

<table>
<thead>
<tr>
<th></th>
<th>IN.PACT</th>
<th>PTA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically-driven TLR ([1])</td>
<td>2.4%</td>
<td>20.6%</td>
<td>&lt;0.001 ([2])</td>
</tr>
</tbody>
</table>

![Graph showing cumulative freedom from clinically-driven TLR over days after index procedure.](image)

97.5% 79.3%

(p<0.001 by log-rank test)

1. Clinically-driven TLR defined as any re-intervention due to symptoms or drop of ABI/TBI of >20% or >0.15 compared to post-procedure ABI/TBI
2. Actual event rate by frequency ratio algorithm calculation
Summary

- Significant enhancements in balloon technology since the first coronary balloon angioplasty procedure in 1977
- Specialty angioplasty balloons have important niche applications (calcified, non-dilatable lesions, ostial lesions, vessel prep, etc)
- Drug coated balloons have the potential to be “game changing”