Drug-Eluting Stents For SFA Interventions

Ehrin J. Armstrong, MD MSc
Director, Interventional Cardiology
Director, Vascular Laboratory
VA Eastern Colorado Healthcare System
Associate Professor of Medicine
University of Colorado School of Medicine

Disclosures

• Consultant and advisory board member to Abbott Vascular, Boston Scientific, Cardiovascular Systems, Medtronic, Spectranetics

Outline

• Rationale for Drug Eluting Stents

• Zilver PTx Drug Eluting Stent
  • Randomized data
  • Real world studies

• Emerging/Investigational Drug Eluting Stents
  • Eluvia DES
  • ESPRIT Biodegradable Scaffold
Drug Eluting Stents

- Traditional nitinol stents have significant limitations
  - Stent fracture
  - Neointimal hyperplasia

- Some scaffold is often required
  - Recoil
  - Significant dissection
  - Calcification?

- DES provide scaffold while limiting neointimal hyperplasia

Restenosis Cascade

- Immediate: Balloon inflation or stent deployment in atherosclerotic vessel
  - Crush plaque
  - Stretch artery
  - Disruption of endothelialization

- Days: Platelets and fibrin deposited at injured site
  - Signaling cascades
  - Inflammatory response

- Weeks: Neointimal Proliferation
  - Smooth muscle cell (SMC) migration
  - Cellular division

- Months: Restenosis
  - Extracellular matrix production
  - Re-endothelialization

Antiproliferative Agents
- Reduce inflammation
- Arrest mitosis
- Inhibit SMC migration

Restenosis in the SFA
**Inhibition of Neointimal Hyperplasia**

<table>
<thead>
<tr>
<th>Device</th>
<th>30 Day</th>
<th>90 Day</th>
<th>180 Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>FP-PES</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
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<td>BMS</td>
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<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
</tr>
</tbody>
</table>

**Zilver PTX Drug Eluting Stent**

- Zilver stent scaffold
- Polymer-free paclitaxel coating at 3 ug/mm²
- Available in lengths up to 120 mm

*Dake et al, Circ Cardiovasc Interv 2011;4:495-504*

**Zilver PTX Study**

- Randomized study of primary DES implantation vs. balloon angioplasty.
- Secondary randomization to DES or BMS after failure of balloon angioplasty.
- Mean lesion length 64 mm.

*Dake et al, Circ Cardiovasc Interv 2011;4:495-504*
Zilver PTX Post-Market Surveillance Study of Paclitaxel-Eluting Stents for Treating Femoropopliteal Artery Disease in Japan

12-Month Results

- 907 patients at 95 institutions in Japan.
- No exclusion criteria.
  - 44% CKD, 22% CLI
- Mean lesion length 147 mm
  - 42% CTOs
  - 19% ISR

Yokoi et al, J Am Coll Cardiol Intv 2016;9:271-277

Freedom From TLR

Yokoi et al, J Am Coll Cardiol Intv 2016;9:271-277

Zilver PTX ZEPHYR Registry

- Real-world multicenter study of 831 FP lesions treated with Zilver PTX.
  - 32% of patients with CLI
- Mean lesion length 170 mm.
- 45% CTOs, 65% with significant calcification.

Iida et al, J Am Coll Cardiol Intv 2015;8:1105-1112
ZEPHYR Registry Outcomes

- Stent thrombosis rate of 2%
- Predictors of restenosis included length > 160 mm, IVUS characteristics.

Iida et al, J Am Coll Cardiol Intv 2015;8:1105-1112

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ZEPHYR Registry

Iida et al, J Am Coll Cardiol Intv 2015;8:1105-1112

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Restenosis Patterns After DES

Iida et al, J Am Coll Cardiol Intv 2015;9:828-834
Eluvia DES

- Inova stent platform
  - Low fracture rates
- Biostable PROMUS polymer matrix
  - Longer elution time
- Paclitaxel
  - $0.167 \mu g \text{ PTx/mm}^2$

MAJESTIC Study

- Prospective, multicenter, single arm study
- 57 patients with femoropoliteal disease
- Mean length 71 mm
  - 46% CTOs
  - 65% severe calcification

![MAJESTIC 24-Month Freedom from TLR](chart)

Primary patency 96% at 12 months 78% at 24 months
Ongoing Studies of Eluvia DES

- **IMPERIAL**
  - RCT of Eluvia vs. Zilver PTx (2:1)
  - 485 patients, enrollment completed

- **EMINENT**
  - RCT of Eluvia vs. BMS (2:1)
  - 750 patients, enrolling

- **REGAL**
  - Open label registry
  - 500 patients

ESPRIT Bioresorbable Scaffold

- Poly L-lactide Scaffold
- Poly D, L-lactide polymer coating
- Everolimus elution
- Balloon expandable

ESPRIT I Study

- Mean lesion length 36 mm
- Binary restenosis 12.1% at one year, 16.1% at two years.
- TLR 8.8% at one year, 11.8% at two years.

Lammer et al, J Am Coll Cardiol Intv 2016;9:1178-1187
Conclusions

• DES provide superior outcomes to balloon angioplasty or standard nitinol stents in the SFA.

• Real world studies demonstrate some limitations of current DES technology.

• Emerging DES may provide improved scaffold stability and inhibition of neointimal proliferation.

• Potential role for bioresorbable drug eluting scaffolds.

Thank You

Ehrin J. Armstrong, MD MSc
Director, Interventional Cardiology
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VA Eastern Colorado Healthcare System
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Atherectomy for Superficial Femoral Artery Disease

PRAKASH KRISHNAN, MD

INDICATIONS FOR INFRAINGUINAL REVASCULARIZATION

- Claudication
  - Lifestyle limiting
  - Failed medical therapy and exercise regimen
- Critical limb ischemia
- Preservation of bypass graft or stent graft patency in an asymptomatic patient

REVASCULARIZATION OPTIONS

- PTA
- Atherectomy
  - Directional Atherectomy (Silver Hawk)
  - Orbital Atherectomy (CSI)
  - Jetstream/Pathway Rotational Atherectomy
  - Laser Atherectomy (TurboElite)
- Nitinol Stents
- Drug Eluting Stents
- Drug Coated Balloons
Endovascular Treatment of SFA
Nitinol-Stenting

Schillinger et al. NEJM 2006

Theoretical Background of Atherectomy

To avoid the induction of a potentially restenosis promoting barotrauma

Atherectomy removes the plaque without overstretch of the vessel wall

Available Devices

- Directional Atherectomy
  - Hawk portfolio, Silverhawk, Turbolink, & HawkOne
  - Medtronic
  - Pantheris (Abbott)
- Orbital Atherectomy
  - Diamondback (Cook)
- Rotational Atherectomy
  - Jetstream (Boston Scientific)
  - Phoenix (Volcano)
  - Rotablator (BSC)
- Photoblation Atherectomy
  - Turbo Elite & Turbo Tandem (Spectranetics)
MEDTRONIC TURBOHAWK

DEFINITIVE LE CLINICAL TRIAL SUMMARY

1. Trial Design
   - Global, prospective, non-randomized, multi-center study (n = 113 subjects)
   - PI: Dr. James McGovern, Dr. Lawrence Garcia, Prof. Thomas Zeller
   - Patency was evaluated using PIVR
   - Secondary endpoint: angiography and duplex ultrasound
   - Rabbit-ear stents (made for pig patients (N=12))
   - Nearest medicated was excluded

2. Trial Results
   - Primary Patency for SFA of 73% at 12 months (K-M, PIVR 2.5)
   - No re-intervention rate (PIVR) rate was published
   - SFA Primary Patency for lesion length (n=134)
   - Short ≤ 3.5 cm: 79% at 12 months (K-M, PIVR 2.5)
   - Medium 3.6 cm: 87% at 12 months (K-M, PIVR 2.5)
   - Long 4.5 cm: 87% at 12 months (K-M, PIVR 2.5)
   - Overall: 74%

3. Complication Rate
   - Distal embolization: 2.8%
   - Dissection: 2.9%
   - Perforation: 0.4%
   - Overall: 7.9%

12-month Primary Patency

<table>
<thead>
<tr>
<th>SFA 2.5 cm (K-M)</th>
<th>SFA 6.5 cm (K-M)</th>
<th>SFA 8.5 cm (K-M)</th>
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<tr>
<td>78%</td>
<td>83%</td>
<td>85%</td>
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Patient Baseline

<table>
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<tr>
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<tbody>
<tr>
<td>Avg. Lesion Length (cm)</td>
<td>5.2</td>
<td>6.3</td>
<td>6.6</td>
</tr>
<tr>
<td>Occlusion (%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Secular Clot (%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Restenosis (%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>PVK</td>
<td>0.4</td>
<td>0.4</td>
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</table>
### DEFINITIVE AR

#### Inclusion Criteria
- HC C 2.4
- 370% stenosis of SFA and/or popliteal artery
- Lesion Length 7-15 cm
- Reference Vessel 4-6 mm and ≤ 7 mm

#### Exclusion Criteria
- In-ident: restenosis
- Anatomical target vessel
- Multiple lesions in target limb that require treatment

#### General and Angiographic Criteria Assessment
- Lesion severely calcified
  - YES
  - NO
- Randomization
  - DAART
  - DCB
  - DAARt

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### DEFINITIVE AR

**Baseline Patient / Clinical Characteristics**

<table>
<thead>
<tr>
<th>SilverHawk and TurboHawk Directional Atherectomy (Medtronic) plus PercuSurge DCB ( Bayer)</th>
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<tbody>
<tr>
<td>Patient #</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>BMI</td>
</tr>
<tr>
<td>Angina</td>
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<tr>
<td>DHI</td>
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<tr>
<td>Hypertension</td>
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<tr>
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<td>RCC</td>
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### DEFINITIVE AR

**Baseline Lesion Characteristics**

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<tbody>
<tr>
<td>Lesion #</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Length (mm)</td>
</tr>
<tr>
<td>Diameter Stenosis (%)</td>
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<tr>
<td>Sizing (mm)</td>
</tr>
<tr>
<td>Calcification</td>
</tr>
<tr>
<td>Severe calcification</td>
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**DEFINITIVE AR Conclusions**

DEFINITIVE AR was a pilot study designed to assess the effect of treating lesions with DA followed by DCB (DAART).

- Results suggested trends favoring DAART:
  - Added benefit of DA in lesions ≥10 cm (RCT)
    - DU5: DAART 98.8% DCB 85.9% (p = 0.01)
  - Angiographic patency: DAART 91.0% DCB 68.8% (p = 0.01)
  - Added benefit of DA in severely calcified lesions (All DAART)
    - DAART 76.4% DCB 56.9%
  - Added patency benefit with increased post-procedure MLD

- 24-month follow-up is ongoing to assess long-term effect of DAART. Larger, statistically-powered, randomized studies are needed to further validate the benefits of DAART.

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**Cioppa, et al., DAART Study**

Prospective, single-center study to characterize conjunction of DA + DCB use in severely calcified lesions

**Design and Inclusion**

- Prospective, single-center study
- N = 30 patients (RCC 3.6)
- Enrolled only heavily calcified lesions (≥+++ on both sides of vessel wall > 1 cm in length)

**Specific Technical Details**

- All procedures included distal protection with SpiderFX™ embolic protection device and IVUS-guided atherectomy with TurboJet™ peripheral plaque excision system
- Once ≤ 30% residual stenosis was achieved (via IVUS and Angio) a DCB was used for post-dilatation

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**Cioppa, et al., DAART Study**

Prospective, single-center study to characterize conjunction of DA + DCB use in severely calcified lesions

**Procedural Characteristics (n=30)**

- Mean lesion length: 115 mm
- Total occlusion: 13.3% (4)
- < 30% residual stenosis achieved in all cases
- No procedure-related AEs
- Provisional stenting rate: 6.7% [2 due to flow limiting dissections]

**12-mo Results (n=30)**

- TF patency (PSVR < 2.5): 90% (27)
- TLR: 10.3% (3)
- Limb salvage: 100% (12 CLI Pts)
Silverhawk - Where to use

- Eccentric lesions & bifurcations.
- Vessel diameter ≤ 7mm.
- Diabetic patients?
- Diagnosis of vasculitis.
- Preparation of the artery for endoprosthesis implantation.
- Instent restenoses (cave: acute thrombus containing occlusions).
- Controlled studies warranted.

Silverhawk - Where not to use

- Severely fractured stents.
- Highly calcified lesions without predilatation.
- Bended vessel segments (limited steerability).
- Vessel diameter ≤ 2mm below the knee.

CSI DIAMONDBACK

CSI DIAMONDBACK 360°
COMPLIANCE 360
CLINICAL TRIAL SUMMARY

1 Trial Design
- Prospective, randomized, multicenter study (n = 38 orbital, n = 27 PTCA)
- PFR cutoff of ≥ 2.5 (secondary endpoint) was used to determine restenosis
- 3-year lab was not indicated
- Rutherford classifications were not indicated
- Primary endpoint: freedom from TLR at 6 months

2 Trial Results
- Primary Patency
  - 77.5% at 6 months (K-M, PFR 2.0 ± 22 patients available)
  - 84.6% at 12 months (K-M, PFR 2.5 ± 22 patients available)
High Speed Rotational Atherectomy
Rotablator and Diamondback

Where to use:
- Highly calcified lesions of infra-popliteal arteries

Where not to use:
- Vessel diameters > 3mm because of
  - limited device diameter
  - risk of hemolysis

Atherectomy – When to use

Conclusions
- Different debulking concepts are now available for specific lesion morphologies.
- Debulking reduces the need of stents.
- Diabetics may benefit from debulking.
Pathway Atherectomy - Where to use

- Total subacute occlusions with mixed composition of occlusive material (e.g. thrombus).
- Vessel diameter > 3mm and ≤ 5mm due to device size restrictions.
- Calcified lesions.
- Acute occlusions?
- Diabetic patients?
- Preparation of the artery for endoprosthesis implantation.
- Instent restenosis.
- Controlled comparative studies warranted.
Pathway Atherectomy - Where not to use

- Severely fractured stents.
- Subintimal course of the guide wire (risk of perforation).
- Bended below the knee vessels, especially if vessel diameter ≤ 3mm.

LASER ATERECTOMY

Spectranetics CVX-300® Excimer Laser

CEGLO
CLINICAL TRIAL SUMMARY

1. Trial Design
   - U.S. multicenter, single-arm, prospective registry (n = 63 subjects)
   - Classification study in de-novo lesions
   - Core lab was used to verify duplex ultrasound and angiograms
   - DUS was used to approximate 50% stenosis
   - All patients were Rutherford classification 1-3
   - SFA lesions represented 96% of vessels treated
   - Popliteal lesions represented 8% of vessels treated

2. Trial Results
   - Primary Patency (non-restenosis rate)
     - 54.3% at 12 months

Primary Patency (K-M)

<table>
<thead>
<tr>
<th>12 Months</th>
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<tbody>
<tr>
<td>54.3%</td>
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<table>
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<th>Test Type</th>
<th>Value</th>
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<tbody>
<tr>
<td>Patient Baseline</td>
<td>65</td>
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<tr>
<td>Avg. Lesion Length (cm)</td>
<td>5.6</td>
</tr>
<tr>
<td>Occlusions (%)</td>
<td>28</td>
</tr>
<tr>
<td>Moderate- to-severe Calcium (%)</td>
<td>65</td>
</tr>
<tr>
<td>Rutherford 3-5 (%)</td>
<td>93</td>
</tr>
<tr>
<td>PSVR</td>
<td>3.8</td>
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</tbody>
</table>
Excimer Laser - Where to use

- Excimer laser might be useful in small vessels such as BTK arteries (LACI trial).
- In larger vessels only in conjunction with the Turbo Booster catheter.
- Special indication instent restenosis?
- Preparation of the artery for endoprosthesis implantation.
- Controlled studies warranted.

Excimer Laser - Where not to use

- Severely fractured stents.
- Highly calcified lesions.
- Acute occlusions? – better: mechanical thrombectomy or PVS.
- Long lesions (time restrictions).

[Image of Lithoplasty®]
Case Study

Clinical Program Overview

Objective: To study the safety and effectiveness of the Shockwave Medical Lithoplasty system in the treatment of calcified, stenotic infragenital peripheral arteries.
- 2 phase, prospective, non-randomized, multicenter study
- Monitoring with 100% source document verification
- Independent angioographic and duplex ultrasound core labs
- Independent clinical events committee

DISRUPT PAD Study Design

Key Eligibility Criteria
- Intermittent claudication: Rutherford Classification 2–4
- Ankle-brachial index ≥0.9
- SFA/Popliteal lesions ≥70% stenosis
- RVD 3.5–7.0 mm, ≤150 mm length
- Moderate and severe calcification by angiography

Study Device
- Shockwave Medical Peripheral Lithoplasty Catheter
- Diameters: 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0 mm
- Length: 60 mm
**DISRUPT PAD Study Endpoints**

Procedural
- Procedural success: <50% residual stenosis
- Exploratory endpoint: ≤30% residual stenosis

Follow Up: 30 days, 6 mo, & 12 mo
- Major adverse events
- Target lesion patency by DUS (stenosis <50%)
- Target lesion revascularization (TLR)
- Functional outcomes

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**DISRUPT PAD Effectiveness**

By angiographic and DUS core labs

- % Stenosis
- Acute Gain

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**DISRUPT PAD: Procedural Characteristics**

| Adjunctive Therapy N| Adjunctive Therapy N%
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Pre-dilatation</td>
<td>11.6% (11)</td>
</tr>
<tr>
<td>Post-dilatation</td>
<td>7.4% (7)</td>
</tr>
<tr>
<td>Provisional stenting</td>
<td>1.1% (1)</td>
</tr>
</tbody>
</table>
Conclusions

- The DISRUPT PAD Program has successfully treated a calcified PAD population with limited adjunctive balloon and implants required.
- Compelling safety in a difficult-to-treat population.
- Effectiveness results show consistent procedural success, high acute gain, and minimal acute injury.
- Sustained patency and TLR results through 6 months.
- Sustained functional improvement through 6 months.
- Consistent effectiveness across all subgroups.

Atherectomy – When to use

Conclusions

- Different debulking concepts are now available for specific lesion morphologies.
- Debulking reduces the need of stents.
- Diabetics may benefit from debulking.
DCB for Superficial Femoral Artery Disease

PRAKASH KRISHNAN, MD

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- Claudication
  - Lifestyle limiting
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- PTA
- Atherectomy
  - Directional Atherectomy (Silver Hawk)
  - Orbital Atherectomy (CSI)
  - Jetstream/Pathway Rotational Atherectomy
  - Laser Atherectomy (TurboElite)
- Nitinol Stents
- Drug Eluting Stents
- Drug Coated Balloons
DRUG COATED BALLOONS

Trial of a Paclitaxel-Coated Balloon for Femoropopliteal Artery Disease


ABSTRACT

DESCRIPTION

LEVANT 2 – LUTONIX DCB

LEVANT 2 – LUTONIX DCB
IN.PACT SFA TRIAL - INPACT DCB

IN.PACT SFA TRIAL

ALL ITT, 12-Month Primary Patency [1]
ALL ITT, 12-Month Clinically Driven TLR

1. Clinically driven TLR defined as any re-intervention due to symptoms at days of ABI/TIBA of ≥20% or >10% compared to post procedure ABI/TIBA
2. Acted event rate by binomial distribution calculation

IN.PACT SFA TRIAL
DCB VS PTA 3-YEAR DATA

<table>
<thead>
<tr>
<th>ENDPOINT</th>
<th>12 MONTHS</th>
<th>12 MONTHS</th>
<th>24 MONTHS</th>
<th>24 MONTHS</th>
<th>36 MONTHS</th>
<th>36 MONTHS</th>
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</thead>
<tbody>
<tr>
<td>PRIMARY PATENCY</td>
<td>IN.PACT DCB (%)</td>
<td>PTA (%)</td>
<td>IN.PACT DCB (%)</td>
<td>PTA (%)</td>
<td>IN.PACT DCB (%)</td>
<td>PTA (%)</td>
</tr>
<tr>
<td>PRIMARY PATENCY</td>
<td>82.2</td>
<td>52.4</td>
<td>78.9</td>
<td>69.5</td>
<td>45.1</td>
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<tr>
<td>CD-TLR</td>
<td>2.4</td>
<td>20.6</td>
<td>9.0</td>
<td>27.8</td>
<td>15.5</td>
<td>29.6</td>
</tr>
</tbody>
</table>

3-year IN.PACT SFA data presented at late-breaking trials–TIVA 2016

IN.PACT SFA Trial
Primary Patency Through 3 Years

1. Acted event rate by binomial distribution calculation
ILLUMENATE CLINICAL TRIAL - STELLAREX DCB

ILLUMENATE

Trial design: Patients with superficial femoral artery (SFA) and/or popliteal arterial stenoses were randomized in a 2:1 fashion to either balloon angioplasty with a paclitaxel drug-coated balloon (DCB) or standard balloon. They were followed for 12 months.

Results:
- Primary efficacy outcome: clinically driven target lesion revascularization (DCB vs. standard balloon: 95.4% vs. 87.5%, p = 0.05)
- Primary patency at 12 months: 82.3% vs. 73.9%, p = 0.05

Conclusions:
- Percutaneous transluminal angioplasty (PTA) with a novel low-dose paclitaxel-coated balloon was superior to PTA with standard angioplasty alone in moderately long lesions in the SFA and/or popliteal arteries.
- Data were similar to the LEVANT 2 trial, which used a different balloon but the same drug differences are in balloon design and dose of paclitaxel.

Presented by Dr. Jason Lytle at TCT 2019.

DRUG-COATED BALLOONS SUPERIOR TO PTA IN RANDOMIZED TRIALS
SFA-LONG STUDY
Presenter: Antonio Micari, MD, PhD

- Independent, prospective, multicenter, single-arm study designed to evaluate outcomes with the In.Pact Admiral paclitaxel-coated balloon (Medtronic) in the treatment of long (TASC C and D) femoropopliteal artery disease.

**Key Patient Selection Criteria**

**Inclusions**
- RC 2-3-4
- Reference vessel diameter 4 - 7 mm
- Lesions and occlusions ≥ 15 cm
- ≥ 1 crural vessel run-off either pre-existing or successfully established
- Adequate in-flow

**Exclusions**
- In-stent restenosis
- Aneurysm in the target vessel
- Acute thrombus in the target limb
- Failure to cross the Target Lesion with a guide wire
- Use of alternative therapies (e.g., atherectomy, cutting balloon, laser, radiation therapy, cryoplasty...)

**Endpoints**

**Primary Endpoint:**
The rate of primary patency within 12 months post-index procedure

Primary patency is defined as freedom from the combined endpoints of clinically-driven target lesion revascularization (TLR) and 50% restenosis in the treated lesion.

Clinically-driven TLR is defined as any re-intervention within the target lesion due to symptoms or drop of ABI of ≥20% or <0.5 when compared to post-procedure.

Restenosis = 50% is defined by a peak systolic velocity ratio (PSVR) > 2.4

**SecondaryEndpoints:**
- Composite of all Major Adverse Events (MAE) through 24 months (i.e. first occurrence of any of the following):
  - Death from any cause
  - Major target limb amputation
  - Thrombosis at the target lesion site
  - Non-target lesion target vessel revascularization
  - Incidence of MAE: individual components through 24 months
  - Clinical improvement as assessed by Rutherford Class changes at 6, 12 and 24 months with respect to baseline
Head-to-Head Comparisons of Drug-coated Balloons

Are all DCB created equal?
NO: a lot of differences beyond just the same drug

12+ DCBs available in Europe

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Drug</th>
<th>Dose (μg/mm²)</th>
<th>Excipients</th>
<th>Single Center</th>
<th>TLR Endpoint</th>
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<tr>
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<td>Abbott Vascular</td>
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<td>2.0-3.5</td>
<td>0-5</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sotera</td>
<td>Zynapsis</td>
<td>2.0-3.5</td>
<td>0-5</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

- ≠ Dose (2.0 – 3.5 μg/mm²)
- ≠ Drug Formulation (crystalline vs. amorphous vs. hybrid)
- ≠ Excipients (or no-excipient)
- ≠ Balloon Surface Energies
- ≠ Coating Methods
- ≠ Usage methods per IFU (i.e. with or w/out protective sheath)

12+ DCBs available in Europe

DCB Head-to-Head Trials

- Single center
- Retrospective
- TLR Endpoint

- Two DCBs with proven efficacy in prior RCTs show no significant difference for TLR and sustained clinical improvement in real world data
- Limitations of a non-randomized, monocenter cohort study design
- Head-to-head comparisons preferred but not available
Head-to-Head Trials Watch Outs:

✓ Study hypothesis (superiority vs. non-inferiority)
✓ Statistical power
✓ Appropriate primary endpoint (objective, non-bias, no confounders)
✓ All other classical quality criteria, ie:
  ✓ Multicenter
  ✓ Prospective
  ✓ Independent adjudication
✓ Then watch for:
  ✓ $$$$$$$$
  ✓ Timing

Primary Endpoint Considerations

• Primary Endpoint should be as measurable and objective as possible
• Especially in head-to-head device trials

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Clinical Relevance</th>
<th>Device-specific correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Patency</td>
<td>1:1 correlation to the primary mandate of revascular therapies</td>
<td></td>
</tr>
<tr>
<td>TLR</td>
<td>Highly clinical relevant but subject to bias especially in claudication trials</td>
<td></td>
</tr>
<tr>
<td>QoL / Walk</td>
<td>Most relevant but highly dependent on concomitant, non-lesion related &quot;confounders&quot;</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Evidence Appraisal

Requires Critical Assessments of:
Quality of Evidence & Quality of Outcomes

• In the absence of DCB head-to-head trials a careful cross-trial comparison may only be attempted based on specific requisites:
  • Same PAD profile and vessel district
  • Same endpoint definition
  • Same Rigor, Quality and Clinical Relevance
• And critically assessed based on key differences in baseline characteristics

3 DCBs with sound, comprehensive Clinical Programs

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>DCB</th>
<th>Drug</th>
<th>Dose (μg/mm²)</th>
<th>Excipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medtronic</td>
<td>IN.PACT</td>
<td>PTX</td>
<td>3.5</td>
<td>Urea</td>
</tr>
<tr>
<td>Spectranetics</td>
<td>LUTONIX</td>
<td>PTX</td>
<td>2.0</td>
<td>Polyethylene Glycol</td>
</tr>
<tr>
<td>Spectranetics</td>
<td>STELLAREX</td>
<td>PTX</td>
<td>2.0</td>
<td>Polysorbate and Sorbitol</td>
</tr>
<tr>
<td>Abbott</td>
<td>ADVANCE LUXE PTX</td>
<td>PTX</td>
<td>1.0</td>
<td>none</td>
</tr>
<tr>
<td>Biosensors</td>
<td>ELUTION PTX</td>
<td>PTX</td>
<td>2.0</td>
<td>2-hydroxypropionic acid</td>
</tr>
<tr>
<td>Biosensors</td>
<td>PROFLO PTX</td>
<td>PTX</td>
<td>1.0</td>
<td>2-hydroxypropionic acid</td>
</tr>
<tr>
<td>Biosensors</td>
<td>CARBODOPIN PTX</td>
<td>PTX</td>
<td>1.0</td>
<td>2-hydroxypropionic acid</td>
</tr>
<tr>
<td>Biosensors</td>
<td>LEGIONAIRE PTX</td>
<td>PTX</td>
<td>1.0</td>
<td>2-hydroxypropionic acid</td>
</tr>
<tr>
<td>Biosensors</td>
<td>LEXICON PTX</td>
<td>PTX</td>
<td>2.0</td>
<td>2-hydroxypropionic acid</td>
</tr>
<tr>
<td>Biosensors</td>
<td>LEXICON PTX</td>
<td>PTX</td>
<td>3.0</td>
<td>Shelloic acid</td>
</tr>
<tr>
<td>Biosensors</td>
<td>LEGEND PTX</td>
<td>PTX</td>
<td>3.0</td>
<td>Shelloic acid</td>
</tr>
<tr>
<td>Biosensors</td>
<td>LEGEND PTX</td>
<td>PTX</td>
<td>3.0</td>
<td>Shelloic acid</td>
</tr>
<tr>
<td>Biosensors</td>
<td>LUMINOR PTX</td>
<td>PTX</td>
<td>3.0</td>
<td>Unknown</td>
</tr>
<tr>
<td>Biosensors</td>
<td>SEQuentia PTX</td>
<td>PTX</td>
<td>3.0</td>
<td>Iopromide</td>
</tr>
<tr>
<td>CoRInnov 1</td>
<td>PASEO 18 LUX</td>
<td>PTX</td>
<td>3.0</td>
<td>Butyryl-trihexyl-Citrate</td>
</tr>
<tr>
<td>CoRInnov 1</td>
<td>ADVANCE 18 LUX</td>
<td>PTX</td>
<td>3.0</td>
<td>none</td>
</tr>
<tr>
<td>CoRInnov 1</td>
<td>ELUTAX PTX</td>
<td>PTX</td>
<td>2.2</td>
<td>Dextrane</td>
</tr>
<tr>
<td>CoRInnov 1</td>
<td>FREEWAY PTX</td>
<td>PTX</td>
<td>3.0</td>
<td>Shellac</td>
</tr>
<tr>
<td>CoRInnov 1</td>
<td>LEGFLOW PTX</td>
<td>PTX</td>
<td>3.0</td>
<td>Shelloic acid</td>
</tr>
<tr>
<td>Biomedtrax</td>
<td>RANGER PTX</td>
<td>PTX</td>
<td>2.0</td>
<td>Citrate ester</td>
</tr>
<tr>
<td>Biomedtrax</td>
<td>LUMINOR PTX</td>
<td>PTX</td>
<td>3.0</td>
<td>Unknown</td>
</tr>
<tr>
<td>Biomedtrax</td>
<td>Biopath PTX</td>
<td>PTX</td>
<td>3.0</td>
<td>Shellac</td>
</tr>
</tbody>
</table>

Level 1 Evidence in Context

In.Pact SFA[1][1], Levant 2[2][2], ILLUMENATE EU RCT[3][3], ILLUMENATE US Pivotal[4][4]: 4 Pivotal DCB vs. PTA randomized trials with highest scientific rigor

- Multicenter, randomized
- Fem-pop / claudication and rest pain
- Independent adjudication of imaging and clinical events by Duplex Core-lab and Clinical Event Committee
- Primary Endpoint: Primary patency @ 1-year
- same Duplex Core laboratory (VasCore, Boston, MA, USA)
- same Primary Patency definition with 2.5 PSVR threshold
- same Kaplan Meier reporting method

Level 1 Evidence in Context

Key Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>40.5%</td>
<td>43.4%</td>
<td>37.4%</td>
<td>48.5%</td>
</tr>
<tr>
<td>Females</td>
<td>35.0%</td>
<td>38.9%</td>
<td>27.9%</td>
<td>44.0%</td>
</tr>
<tr>
<td>Renal Insuff.</td>
<td>8.3%</td>
<td>9.0%</td>
<td>9.0%</td>
<td>18.0%</td>
</tr>
<tr>
<td>RC23</td>
<td>62.3%</td>
<td>70.6%</td>
<td>84.0%</td>
<td>68.5%</td>
</tr>
<tr>
<td>Lesion length</td>
<td>8.9 cm</td>
<td>6.3 cm</td>
<td>7.2 cm</td>
<td>8.0 cm</td>
</tr>
<tr>
<td>Severe Calcium*</td>
<td>25.8%</td>
<td>20.6%</td>
<td>19.2%</td>
<td>19.0%</td>
</tr>
<tr>
<td>CTOs</td>
<td>25.8%</td>
<td>26.0%</td>
<td>19.0%</td>
<td>19.0%</td>
</tr>
</tbody>
</table>

* Different Ca++ definitions may apply across trials

2. M.Brodmann - ILLUMENATE European Randomized Clinical Trial: 12-month Final Results from the Stellarex DCB – oral presentation, AMP 2016
3. S.Lyden - ILLUMENATE Pivotal Stellarex DCB IDE Study 12-month Results – oral presentation, TCT 2016
Data in Context: DCB RCTs Key Baseline Data
From 4 Core-lab adjudicated randomized DCB trials powered on a Primary Patency primary endpoint

<table>
<thead>
<tr>
<th>DCB</th>
<th>3-month Primary Patency (360-day)</th>
<th>6-month Primary Patency (360-day)</th>
<th>12-month Primary Patency (360-day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stellarex</td>
<td>82.3%</td>
<td>70.9%</td>
<td>55.0%</td>
</tr>
<tr>
<td>P&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In.Pact</td>
<td>86.4%</td>
<td>66.6%</td>
<td>51.0%</td>
</tr>
<tr>
<td>P&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lutonix</td>
<td>75.5%</td>
<td>62.5%</td>
<td>49.3%</td>
</tr>
<tr>
<td>P=0.002</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Core Lab adjudicated (VascCore Laboratories - Boston, MA, USA) Duplex derived Primary Patency based on 2.5 PSVR threshold; † evaluated @ day 360; ‡ evaluated @ day 365

Data in Context: DCB RCTs Cl-driven TLR
12-month clinically-driven TLR* from 4 Core-lab adjudicated DCB randomized trials powered on a Primary Patency primary endpoint

<table>
<thead>
<tr>
<th>DCB</th>
<th>3-month Clinically Driven TLR (360-day)</th>
<th>6-month Clinically Driven TLR (360-day)</th>
<th>12-month Clinically Driven TLR (360-day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stellarex</td>
<td>16.9%</td>
<td>16.1%</td>
<td>16.1%</td>
</tr>
<tr>
<td>P=0.256</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In.Pact</td>
<td>31.3%</td>
<td>31.3%</td>
<td>31.3%</td>
</tr>
<tr>
<td>P=0.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lutonix</td>
<td>15.8%</td>
<td>15.8%</td>
<td>15.8%</td>
</tr>
<tr>
<td>P=0.320</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* CEC adjudicated clinically driven TLR

Conclusions
- DCBs must be appraised on the quality of their own evidence and quality of their own outcomes
- To avoid misleading conclusions RCTs impose highest rigor, what translates in challenges, time and cost
- While there are few head-to-head DCB trials, there are some DCB vs. PTA level 1, with common top rigor, common methodology and similar patient populations that therefore can be placed into context with one another
- Three DCBs have rigorous level 1 evidence, two deserve adoption
Crossing CTOs: Alternative Access or Alternative Devices

Arthur C. Lee, MD
The Cardiac & Vascular Institute
Gainesville, Florida

Disclosures

- Training/speaking/honoraria/advisory board: Cook Medical, CSI, Boston Scientific, Amgen

Strategy

- Clinical Situation
  - Claudication or CLI
- Anatomy
  - Occlusion sites
  - Prox/Distal anatomy
  - Lesion traits, Ca²⁺
- Operator Experience
Chronic Total Occlusions

- CTO common in peripheral intervention
- In order to deliver therapy, CTO has to be crossed
- Antegrade attempts can fail in up to 40% in some reported series\(^1\)
- CTO devices may increase success rate but add additional cost
- Retrograde crossing can increase success rates\(^2\)

---

CTO Crossing Devices

Utilize energy (mechanical, ultrasonic, etc) to advance through CTO and facilitate guidewire placement distal to occlusion

Antegrade Approach to CTO

Proximal Cap

Distal Cap

Re-Entry Devices
Access in 2017

• Antegrade access can mean:
  – Radial/Brachial
  – CFA
  – SFA
  – Tibial
  – and even pedal

Access in 2017

• Retrograde access can mean:
  – CFA
  – SFA
  – Popliteal
  – Tibiopedal
  – Plantar
  – Digital
Reentry Assisted Fenestration

- Accessing an occluded artery using ultrasound
- Can be done in SFA
- Can also be done in tibial and pedal vessels

POP!
- Accessing an occluded artery using ultrasound
- Can be done in SFA
- Can also be done in tibial and DP
Case

71 yo man with previous fem-fem bypass in 2009 with progressive severe claudication and ABI 0.5. Duplex shows flush patent left to right fem-fem bypass and occluded SFA with reconstitution in popliteal artery and occluded PT.

Strategy

- Alternative device or alternative access?
- Antegrade or retrograde?
- Reentry?
• AT access obtained with ultrasound and 2.9F sheath placed

• Support catheter at ostium of SFA is subintimal
  • What now?

• Sheath upsized to 5/6 Slender
  • Outback reentry performed
Wire exteriorized and treatment can be delivered antegrade or retrograde

Zilver PTX placed
A case with alternate access and alternate devices...
Thank you for your attention