Emerging Technologies for SFA Disease: How Do You Incorporate it in Your Practice and With Cost Constraints?

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DISCLOSURE

John Laird, MD

• **Consulting Fee:** Bard/Becton Dickinson, Abbott, Boston Scientific, Medtronic and Philips
• **Research Grants:** Reflow Medical
• **Stocks:** Syntervention, Shockwave Medical, Eximo Medical, Reflow Medical, PQ Bypass
The Challenge of Intrainguinal PAD

• Diffuse disease
• Long occlusions
• Heavy calcification
• Poor run off
• Thrombus containing lesions
• Aneurysms
The Challenge of Infrainguinal PAD

• Numerous approaches are necessary to treat complex disease
  - Better stents and stent grafts
  - Specialty balloons
  - CTO devices
  - Thrombus removal devices
  - Debulking/plaque modification devices
  - Anti-restenosis therapies
How Do We Incorporate New Therapies into Practice?

• New devices address unmet needs: dissections, restenosis, thrombus, calcium

• Reality is that multiple devices are needed to treat real-world lesions.

• Variable reimbursement for new devices.

• The speed of device development is outpacing research: need for data on combination therapy, comparative effectiveness
Reimbursement for New Technologies

Additional Reimbursement
• Stents, covered stents, drug eluting stents
• Atherectomy devices
• Thrombectomy devices

No Additional Reimbursement
• Specialty balloons (cutting, scoring, lithoplasty)
• Drug coated balloons
• CTO devices
• Embolic protection devices
New Devices as Part of Program Development

- Being a “new adopter” in your community
- Optimizing procedural success rates in complex lesions
- Taking on the toughest cases
- Marketing/growing the program (“Limb Salvage Program”)

What New SFA Therapies are Available?

• Tack-Assisted Angioplasty

• Intravascular Lithotripsy

• Adventitial Drug Delivery
Dissections Are the Mechanism of Angioplasty

Balloon angioplasty uses multi-axis stress to increase arterial lumen, causing intimal rupture and variable deeper injury.
Dissections Are Frequent and Severe

Post-PTA Dissection

- D: 24%
- A: 19%
- B: 23%
- C: 5%
- E: 9%
- F: 4%
- None: 16%

Up to 84% of PTA results in a visible dissection¹,²
Up to 42% of PTA results in Grade C or higher¹,²

Regardless of severity, all dissections affect clinical outcome

¹Fujihara, J Endovasc Ther 2017
²Kobayashi, Circ Cardiovasc Interv 2016
Dissections Impact Clinical Outcome

- Hazard ratio for restenosis

**Dissection Severity (NHLBI)**

<table>
<thead>
<tr>
<th>None</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>[95% CI]</td>
<td>(p value)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.58</td>
<td>[0.79, 3.16]</td>
<td>(p = 0.193)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>1.00 (Ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>1.81</td>
<td>[0.88, 3.73]</td>
<td>(p = 0.108)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>4.45</td>
<td>[1.22, 16.2]</td>
<td>(p = 0.024)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>6.37</td>
<td>[2.99, 13.6]</td>
<td>(p &lt; 0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>22.9</td>
<td>[7.33, 71.6]</td>
<td>(p &lt; 0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>297</td>
<td>[34.9, 2527]</td>
<td>(p &lt; 0.001)</td>
<td></td>
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</tr>
</tbody>
</table>

1Fujihara, J Endovasc Ther 2017
2Manual of Operations NHLBI PTCA Registry 1985
Tack Endovascular System®

Tack® Implant
- Adaptive Sizing™ fits vessel diameters 2.5 – 6.0mm
- Nitinol with gold RO markers for visibility
- Unique anchoring system prevents migration
- 6mm deployed length

Delivery System
- 6F/0.035”
- 6 implants pre-loaded on a single catheter
- Designed for highly accurate (≤1mm) deployment
## The Tack Implant is Unique

<table>
<thead>
<tr>
<th></th>
<th>Tack Implant</th>
<th>Stent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radial force</strong></td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td>Minimal</td>
<td>Chronic hyperplastic changes</td>
</tr>
<tr>
<td><strong>Pre-clinical study</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>histology images</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Proximal Tissue" /></td>
<td><img src="image" alt="Proximal Tissue" /></td>
</tr>
<tr>
<td><strong>Sizing</strong></td>
<td>Adaptive Sizing allows a single Tack implant to fit a range of vessel diameters</td>
<td>Force increases with vessel diameter; requires precise sizing</td>
</tr>
<tr>
<td><strong>Metal burden</strong></td>
<td>Focal, biologically “silent” dissection repair therapy</td>
<td>&gt;70% more metal to treat the same dissection(^1)</td>
</tr>
</tbody>
</table>

\(^1\)Schneider, *JACC: Cardiovasc Interv* 2015
Tack Device for Post-Angioplasty Dissection

Tack Device for Post-Angioplasty Dissection

## Robust Clinical Trial Program

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Design</th>
<th>Sites</th>
<th>Key Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATK</strong></td>
<td></td>
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</table>
| **First in Human** (N=11) | ATK and BTK Safety, Feasibility | Prospective, single arm | 2 Paraguay sites | JACC: Cardiovascular Interventions\(^1\) Safety, feasibility demonstrated SFA to Tibial  
- 83.3% 12-month patency |
| **TOBA** (N=138) | Prospective, single arm | 13 European sites |       | Journal of Vascular Surgery\(^2\)  
- 89.5% K-M freedom from CD-TLR  
- 76.4% K-M patency rate  
- 98.5% technical success rate |
| **TOBA II** (N=213) | Prospective, single arm | 33 US/European sites |       | 12-month pivotal trial data late 2018  
POBA or Lutonix® DCB |
| **TOBA III** (N=201) | Prospective, single arm | 15 European sites | Long lesion subset (>150–250mm) | Enrollment Complete  
IN.PACT™ Admiral™ DCB |
| **TOBA BTK** (N=35) | Prospective, single arm | 6 Europe/New Zealand sites |       | Catheterization and Cardiovascular Intervention\(^3\)  
- 93.5% K-M freedom from CD-TLR  
- 84.5% Amputation-free survival  
- 78.4% K-M patency rate |
| **TOBA II BTK** (N=232) | Prospective, single arm | 60 US and international sites |       | Rapidly enrolling in US, Europe and New Zealand |

Over 2500 Tacks implanted in over 750 subjects
**TOBA II Study Design**

**Tack Optimized Balloon Angioplasty Study for Post-Dissection Repair of the Superficial Femoral and Proximal Popliteal Arteries (TOBA II)**

**Prospective, multi-center, single-arm, non-blinded study in US, Europe**

**213 subjects, all with post-PTA dissection** following POBA (n=90) or Lutonix® angioplasty (n=123)

<table>
<thead>
<tr>
<th>Primary Safety Endpoint:</th>
<th>Freedom from the occurrence of any new-onset MAE(s) at 30 days:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Index limb amputation (above the ankle)</td>
</tr>
<tr>
<td></td>
<td>• CEC adjudicated CD-TLR</td>
</tr>
<tr>
<td></td>
<td>• All-cause death at 30 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Efficacy Endpoint:</th>
<th>Primary patency at 12 months:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Freedom from CEC adjudicated CD-TLR and</td>
</tr>
<tr>
<td></td>
<td>• Freedom from core lab adjudicated DUS-derived binary restenosis (PSVR ≥ 2.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Key Observational Endpoints:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Freedom from CEC adjudicated CD-TLR</td>
</tr>
<tr>
<td></td>
<td>• Tack Performance: Dissection Resolution, Migration and Fracture</td>
</tr>
<tr>
<td></td>
<td>• Changes in Rutherford, ABI and Quality of Life measures</td>
</tr>
</tbody>
</table>

Angiographic Core Laboratory/Clinical Events Committee: Yale Cardiovascular Research Group (New Haven, CT)
Vascular Ultrasound Core Laboratory: VasCore (Boston, MA)
12 Month Kaplan-Meier Estimates
(Core lab adjudicated)

Primary Patency 79.3%

Freedom from CD-TLR 86.5%

100% Dissected Vessel Population
60% Moderate/Severe Calcium

Dissections are site-reported (visual estimate during index procedure); 99.5% core-lab adjudicated dissection rate
The Bullfrog Micro-Infusion Device

"Painting" the vessel with 0.5 mL per cm of lesion:
Current Clinical Trials of Adventitial-Perivascular Therapy with Bullfrog Delivery

- Trauma
- Recoil
- Signaling
- Recruitment
- Proliferation
- Migration
- Obstruction

**Vonapanitase**
- PRT201-115
  - 40 subjects
  - Dose-escalation RCT
  - Enrolling

**Dexamethasone**
- DANCE
  - 283 limbs
  - Open-label
  - COMPLETED

**Temsroliimus**
- TANGO
  - 60 total subjects
  - Dose-escalation RCT
  - Enrolling

**LIMBO**
- LIMBO-ATX
  - 120 total subjects
  - 1:1 RCT
  - Enrolling

- LIMBO-PTA
  - 120 total subjects
  - 1:1 RCT
  - Enrolling
The DANCE Trial
Dexamethasone to the Adventitia to eNhance Clinical Efficacy in fem/pop disease

- Multicenter, open-label trial
- SFA and Popliteal
- Primary atherectomy (ATX) or primary angioplasty (PTA) based on investigator decision
- Adventitial drug delivery of dexamethasone (ADD-DEX) in all subjects
- Primary Endpoints:
  - Safety: A composite of major adverse limb events (MALE) and post operative death (POD) within 30 days from the procedure
  - Efficacy: Primary patency at 12 months
    - Freedom from binary restenosis by duplex ultrasound (PSVR ≤ 2.4) or angiography and
    - Freedom from clinically-driven target lesion revascularization (CD-TLR)

Baseline angiogram and biomarker blood draw

157 ATX
124 PTA

ADD-DEX Treatment

Blood draws for change in biomarkers (~1/3 of patients) at 24 hours and 4 weeks

Clinical, hemodynamic and duplex US follow-up at 6, 12, 18, 24 months
DANCE Atherectomy Group 2-Year Patency and CD-TLR

DANCE-ATX Preliminary 2-Year **Primary Patency** Kaplan-Meier Estimates (per protocol)

DANCE-ATX Preliminary 2-Year **Freedom from CD-TLR** Kaplan-Meier Estimates (per protocol)
Intravascular Lithotripsy (IVL): Localized Lithotripsy to Treat Cardiovascular Calcium

**Lithotripsy**

- 30 years of safety data in kidney stone treatment
- Sonic Pressure Waves preferentially impact hard tissue, disrupt calcium, leave soft tissue undisturbed

**Cardiovascular Lithotripsy**

- Miniaturized and arrayed Lithotripsy Emitters for localized lithotripsy at the site of the vascular calcium
- Optimized for the treatment of cardiovascular calcium

Peripheral IVL Catheters
The Shockwave IVL System consists of an IV pole-mountable generator, a connector cable, and a catheter that houses an array of lithotripsy emitters enclosed in an integrated balloon.
Intravascular Lithotripsy
DISRUPT PAD Study for Femoropopliteal Disease

Objective: To study the safety and effectiveness of the Shockwave Medical Lithoplasty® System in the treatment of calcified, stenotic infrainguinal peripheral arteries.

- Two-phase, prospective, non-randomized, multi-center study
- Monitoring with 100% source document verification
- Independent angiographic and duplex ultrasound core labs
- Independent clinical events committee

DISRUPT PAD I
35 subjects, 3 sites
Jan 2014 – Sep 2014

DISRUPT PAD II
60 subjects, 8 sites
Jun 2015 – Dec 2015
## DISRUPT PAD Safety and Effectiveness

### Safety

All events adjudicated by independent clinical events committee

<table>
<thead>
<tr>
<th>Major adverse events</th>
<th>30 days N=94</th>
<th>6 mo N=93</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target limb emergency surgical revascularization</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Target limb major amputation</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Thrombus or distal emboli with treatment</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Perforations and dissections (≥D) with treatment</td>
<td>1.1% (1)</td>
<td>1.1% (1)</td>
</tr>
</tbody>
</table>

### Dissections (n=95)

| None                                      | 86.3% (82) |
| A                                        | 0.0%       |
| B                                        | 7.4% (7)   |
| C                                        | 6.3% (6)   |
| D                                        | 1.1%*      |

### Freedom From TLR

76.7%

### Patency

100%
10 cm Severely Calcified SFA Stenosis

**Diagnostic Angiogram**
- Total Occlusion 10.2 cm lesion
- Severe Calcium

**Fluoroscopic Image**
- Calcium

**Procedural Angiogram – Lithoplasty in Action**
- Pre-Lithoplasty (6 x 60 mm) Inflation to 4 atm
- Active Lithoplasty (6 x 60 mm) @ 4 atm

Case courtesy of: Prof Marianne Brodmann
Severely Calcified SFA Stenosis

Diagnostic Angiogram

Severe Calcium

Total Occlusion
10.2 cm lesion

Fluoroscopic Image

Procedural Angiogram

6.0 mm Lithoplasty Balloon
Dilatation Catheter @ RVD

Final Angiogram

27% Residual
4.6 mm Acute Gain

Case courtesy of: Prof Marianne Brodmann
Disrupt PAD III Study Design

Study Design: Randomized study of the Shockwave Medical Peripheral Intravascular Lithotripsy (IVL) System with DCB versus standard balloon angioplasty with DCB to treat moderate and severely calcified femoropopliteal arteries (Disrupt PAD III).

Objective: The objective is to assess the optimal therapy to dilate heavily calcified lesions with IVL versus traditional angioplasty, in achieving less than 30% stenosis without the need for a stent. In addition, all patients who do not receive a stent will be treated with a drug-coated balloon.
Conclusions

• The complex nature of infrainguinal PAD mandates new and better solutions to optimize outcomes for our patients

• The speed of development of these new devices often outpaces comparative research and governmental reimbursement strategies

• Incorporating emerging technologies as part of “program development” in your clinical practice will set you apart in your community
Thank You!