Atherectomy and Anti-restenotic Therapy

Evidence and Future

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Value of Atherectomy + Anti restenotic Therapy

- Mechanical
  - Lumen gain without overstretch
  - Less dissection/implant
  - Less recoil/implant
- Improved drug intake
  - Homogenous
  - Retention
Pre-clinical Cadaveric Study - OAS + DCB

$^{14}$C-labeled or fluorescent-labeled Paclitaxel

For Fem-Pop:
- 26% **Deeper** Paclitaxel Penetration and
- 70% **Larger** effective Diffusion Coefficient

Rationale of Directional atherectomy + DCB (DAART) may overcome main limitations of stand-alone SFA therapies

<table>
<thead>
<tr>
<th>Unmet Need</th>
<th>PTA</th>
<th>BMS</th>
<th>DES</th>
<th>DCB</th>
<th>DA</th>
<th>DA+DCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address recoil, dissections and Ca^{++}</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Prevent Neointimal Proliferation/Restenosis</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Minimize permanent implants + preserve future options</td>
<td>✔</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

- DA mechanically re-canalize vessel without overstretch
- DA remove calcium barrier for better drug uptake
- DA reduce likelihood of bailout stenting & preserve native vessel
# Atherectomy + DCB Data

few reports - 2 single-center studies – 1 randomized feasibility study

<table>
<thead>
<tr>
<th>Study (* Core Lab)</th>
<th>Type</th>
<th>Patients</th>
<th>Lesions</th>
<th>Dissection(^6)</th>
<th>BO Stent</th>
<th>30-day MAE</th>
<th>Patency 1-year</th>
<th>&gt;1-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>*DEFINITIVE AR(^1)</td>
<td>DCB(^1), DAART(^1), DAART-Ca</td>
<td>54</td>
<td>54</td>
<td>19% (10/54)</td>
<td>3.7% (2/54)</td>
<td>NR</td>
<td>89.6%</td>
<td>93.4%</td>
</tr>
<tr>
<td>Cioppa(^2)</td>
<td>DAART</td>
<td>30</td>
<td>30</td>
<td>6.7% (2/30)</td>
<td>6.7% (2/30)</td>
<td>13% (4/30) (1-year)</td>
<td>90%</td>
<td>?</td>
</tr>
<tr>
<td>Stavrouakis(^3) (Popliteal)</td>
<td>DAART</td>
<td>21</td>
<td>26</td>
<td>NR</td>
<td>NR</td>
<td>14% (3/21)</td>
<td>95%</td>
<td>90% (18-mo)</td>
</tr>
<tr>
<td>Foley(^4)</td>
<td>DCB OA+DCB</td>
<td>61</td>
<td>99</td>
<td>14% (14/99)</td>
<td>39% (39/99)</td>
<td>NR</td>
<td>81%</td>
<td>77%</td>
</tr>
<tr>
<td>Stavrouakis(^5) (CFA)</td>
<td>DCB DAART</td>
<td>26</td>
<td>26</td>
<td>31% (8/26)</td>
<td>4% (1/26)</td>
<td>NR</td>
<td>68%</td>
<td>88%</td>
</tr>
</tbody>
</table>

1. T. Zeller – VIVA 2014
4. TR. Foley – Cath Cardiovasc Interv 2017
5. K. Stavrouakis – J Endovasc Ther 2017

Courtesy Zeller
DEFINITIVE AR\textsuperscript{1}

Prospective, multicenter, randomized (DAART v DCB); plus non-randomized DAART arm for severely calcified lesions

- 121 subjects (10 sites)
- RCC 2-4; lesion lengths 7-15cm [excluding ISR, aneurysmal target sites and multi-lesion limbs]
- Independent CEC, angiographic & DUS core labs
- Pilot study designed to assess effect of DAART v DCB

DEFINITIVE AR

Significantly higher technical success rate
Significantly lower dissection rate
Trend towards improved patency for DAART in long or calcified lesions but not statistically significant

Lower residual stenosis trended toward higher patency rates
DEFINITIVE AR: 2-year Extension

DEFINITIVE AR was extended beyond its originally-designed 1-year follow-up to 2 years

Extended endpoints included:
- Major Adverse Event Rate at 2 Years
  Defined as major unplanned amputation of the treated limb, all-cause mortality or clinically-driven target lesion revascularization.
- Change in WIQ/EQ-5D Score at 2 Years
- Target Lesion Revascularization (TLR) at 2 Years

121 Patients
1 year

53 Patients
2 years

DEFINITIVE AR: 2-year Extension

2. MAE (Major Adverse Event) defined as major unplanned amputation of the treated limb, all-cause mortality or clinically-driven target lesion revascularization.
3. Clinically-driven TLR (target lesion revascularization) defined as any reintervention or artery bypass graft surgery involving the target lesion in which the subject has a ≥ 70% diameter stenosis (Peak Systolic Velocity Ratio (PSVR) > 3.5 may substitute if a pre-intervention angiogram is not available) and at least two of the following: worsening RCC, worsening WIQ score, or an ABI drop > 0.15 from baseline.
DEFINITIVE AR: 2-year Extension

Trend towards lower TLR with ≤30% residual stenosis after DA\(^1\)

Meta analysis of DAART

5 studies
189 patients
53% severe calcification
98% distal protection

Pooled Results:
Technical Success = 90.4%
Bailout stent = 4.8%
Primary Patency (12m) = 85.3%
TLR (12m) = 5.5%
Perforation = 2.6%

Technical success = < 30% residual stenosis without stent
Primary patency = DUS PSVR < 2.5

Table 1. Characteristics of Studies Included in Meta-Analysis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Quality</th>
<th>N</th>
<th>PCB</th>
<th>DA Device</th>
<th>Distal Protection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cioppa et al, 2012 (22)</td>
<td>PC</td>
<td>Moderate</td>
<td>30</td>
<td>IN.PACT Admiral</td>
<td>TurboHawk</td>
<td>100</td>
</tr>
<tr>
<td>Cioppa et al, 2017 (23)</td>
<td>PC</td>
<td>Moderate</td>
<td>30</td>
<td>IN.PACT Admiral</td>
<td>TurboHawk</td>
<td>100</td>
</tr>
<tr>
<td>Zeller et al, 2017 (26)</td>
<td>RCT</td>
<td>High</td>
<td>121</td>
<td>Cotaveance</td>
<td>TurboHawk</td>
<td>95</td>
</tr>
<tr>
<td>Stavroulakis et al, 2017 (25)</td>
<td>RC</td>
<td>Moderate</td>
<td>72</td>
<td>IN.PACT Admiral, Pacific FREEWAY LUTONIX Passeo Lux</td>
<td>TurboHawk</td>
<td>100</td>
</tr>
<tr>
<td>Stavroulakis et al, 2018 (24)</td>
<td>RC</td>
<td>Moderate</td>
<td>47</td>
<td>IN.PACT Admiral, Passeo Lux</td>
<td>TurboHawk</td>
<td>100</td>
</tr>
</tbody>
</table>

Note: IN.PACT Admiral (Medtronic); Cotaveance (Bayer AG, Berlin, Germany); IN.PACT Pacific (Medtronic); FREEWAY (Eurocor Tech GmbH, Bonn, Germany); LUTONIX balloon (Bard Peripheral Vascular, Inc, Tempe, Arizona); Passeo Lux (Biotronik AG, Bülach, Switzerland); TurboHawk (Medtronic); SilverHawk (Medtronic); Pantheris (AviServe Inc); HawkOne (Medtronic).
DA = directional atherectomy; PC = prospective cohort; PCB = paclitaxel-coated balloon; RC = retrospective cohort; RCT = randomized controlled trial.
Meta analysis of DAART

3 studies compared DAART vs DCB

1 RCT, 2 Retro cohort

DAART vs DCB had **trend towards**:
- lower bailout stent placement rate
- higher primary patency
- decreased TLR at 12 months

Not statistically significant
Previous DCB ➔ occluded in 6 months
Bullfrog with Dex ➔ Occluded in 12 months

Vessel Preparation with DAART InPact DCB
B Laser + POBA vs DCB

- AngioDynamics/Eximo Medical B-Laser /AURYON
- a 355 nm laser with a very short pulse width to selectively ablate mixed-morphology plaque including calcification
- CE mark and US IDE patients compared
- B-Laser + either POBA (n = 46) or DCB (n = 51)
- Core lab–adjudicated duplex patency at six months
- POBA arm more popliteal and tibial lesions treated (77.8 and 84.2% vs. 11.1 and 15.8% in the DCB group), but other lesion characteristics were similar

John Runback VIVA 2019 Late Breaker
Results

• no major procedural complications, including no embolization and no grade C–E dissections
• Core lab–adjudicated duplex patency at six months was 89.5% in the POBA group and 85.2% in the DCB group
• One-year clinical improvement (ankle-brachial index, Rutherford score) identical
• no differences in measurable short-term outcomes following B-Laser atherectomy regardless of subsequent mode of angioplasty
Atherectomy combined with DCB

**OPTIMISE BTK (RCT)**  
OAS ± LUTONIX

**ADCAT (RCT)**  
TURBOHAWK ± LUTONIX

**PRESTIGE**  
PHOENIX + STELLAREX

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**OPTIMIZE Primary Outcome Measures**

- LLL of the target lesion by QVA at 6 months post-procedure or at the time of TLR
- Patency of the target lesion by DUS at 6 mo and 12 mo post-procedure
- Freedom from Major Adverse Events at 30 days, 3, 6, 12, and 24 months post-procedure
  - MACEs include: clinically-driven TLR; unplanned, unavoidable major amputation of the index limb; and death within 30 days of the index procedure
- Freedom from clinically driven TLR at follow up (core lab adjudicated)
- Freedom from unplanned, unavoidable major amputation of the index limb follow up

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**Atherectomy and Drug-Coated Balloon Angioplasty in Treatment of Long Infrapopliteal Lesions (ADCAT-Study)**

Atherectomy (Turbohawk, Medtronic) and paclitaxel-coated balloon angioplasty (Lutonix 6, Bard) for treatment of long atherosclerotic BTK lesions

- Prospective, randomized, multicentric study

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**PRESTIGE**

- Prospective, single-arm, multi-center
- N=75
- Objective: assess safety and efficacy of an IVUS-guided lesion preparation strategy with Phoenix atherectomy before DCB in CLI patients with T2K disease and moderate/severe calcium
- Primary Endpoints:
  - Efficacy: Patency at 6 months (freedom from TLR and TL occlusion by DUS)
  - Safety: freedom from MALE and/or 30-day perioperative death
  - Angio, IVUS, DUS Core-lab adjudication

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**PRESTIGE 42**

- Clinical eligibility criteria met and signed
- Angiographic eligibility criteria met (incl. moderate/severe calcification)

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**Outcomes**

- **Baseline**
- **Post-procedure**
- **FU 30-day**
- **FU 6-months**
- **FU 12-months**
- **FU 24-months**

- **Angio, IVUS, DUS Core-lab adjudication**

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**Results**

- **RCA 4-5**
  - Clinical eligibility criteria met and signed
  - Angiographic eligibility criteria met (incl. moderate/severe calcification)

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- **FU 30-day**
- **FU 6-months**
- **FU 12-months**
- **FU 24-months**

- **Clincal / IVUS**
Primary Effectiveness Endpoint:
Primary patency (PSVR < 2.4) and freedom from CDTLR at one-year in subjects with long, moderate and severely calcified symptomatic femoropopliteal lesions and/or occlusions after treatment with DA + DCB

Primary Safety Endpoint:
Freedom from (MAEs) defined as freedom from flow-limiting dissections (D-F), vessel perforations requiring stenting or stent-grafts, unplanned amputation, intra-procedure distal atheroembolization and clinically-driven TVR in subjects with long, moderate and severely calcified FP lesions and/or occlusions through 30-day follow-up visit.

Co-Principal Investigators
Krishna Rocha-Singh, MD
Chief Scientific Officer
Prairie Heart Institute of Illinois

Brian DeRubertis MD, FACS
Associate Professor of Surgery
UCLA Division of Vascular Surgery

- Consent 250 subjects
- Goal Enrollment 150 subjects
- 10 U.S. Sites
  - Lesion length 8-18cm
  - Occlusion length 6-10cm
- 3 German Sites
  - Lesion length up to 25cm
What we hope to learn from Reality

• Is the directional atherectomy + DCB paradigm safe in long moderate-severely calcified lesions?
• How effective is DA in removing calcified atheroma prior to DCB and what can IVUS teach us regarding optimal technique?
• Does a ≤30% %DS post-DA portend a favorable one year clinical outcome? How is this best assessed?
• What is the appropriate metric to assess ideal vessel prep (residual %DS by angio or luminal gain, residual plaque burden by IVUS)?

Courtesy K Rocha Singh
FUTURE DIRECTIONS
Aneurysms after DAART?

Courtesy Ulrich Beschoner

Follow up
OCT directed Atherectomy + DCB - Pantheris

- 33 patients, 37 lesions
- Claudication 75% de novo 68%, Median LL = 70 mm 35% CTOs
- Technical success 95%
- The mean luminal gain after atherectomy was 52 ± 17% and the median gain after DAART 68% (IQR: 58-91)
- **Primary patency @ 12 month = 93%**
- **Freedom from TLR @ 12 months 100%**
- Complications: perforation 3% (N=1) and 2 embolizations 5% (N=2)
- Bailout stenting 3% (N=1), no flow limiting dissection
- Aneurysmatic change 5% (N=2)

Combining Atherectomy with Novel methods of Drug Delivery

TANGO Trial Design

- TANGO: Temsirolimus adventitial delivery to improve ANGiographic Outcomes below the knee
- Phase II prospective, multi-center, randomized, double-blinded, dose-escalation trial
- FDA IND-regulated
- Dosing concentrations:
  - Low dose: 0.1 mg/mL
  - High dose: 0.4 mg/mL
  - Control: saline
- Dosing volume:
  - Popliteal (P3): 0.5 mL/cm
  - Infrapopliteal: 0.25 mL/cm
  - Injections as needed to provide diffusion coverage
Results from the TANGO Phase 2 Trial

Can the combination of atherectomy and novel drug delivery reduce mechanical failure that confounds effect of anti restenotic therapy??

*Primary Patency is composite freedom from:
• CD-TLR
• Ischemia-driven major amputation
• Occlusion

Notes:
1. Data is pooled for the low-concentration and high-concentration treatment group, since no differences were noted.
2. Data is presented for the Phase 3 eligible population, excluding unstented severe target lesion dissections and inflow occlusions.
SELUTION SLR™ FIRST SIROLIMUS-ELUTING BALOON DESIGNED FOR “SUSTAINED LIMUS RELEASE” DRUG KINETICS

- Use of micro-reservoirs made out of biodegradable polymer intermixed with Sirolimus coated on the balloon:
  - Controlled and sustained drug release mechanism
  - Maintains therapeutic effect in tissue over long period of time

**Can combination atherectomy and prolonged drug elution with a Limus DCB be the answer?**

- Less drug loss during transit to lesion
- Less drug loss during inflation

![Graph showing tissue drug concentration over time](image)

- **Continued ECM formation**

![Bar chart comparing tissue drug concentration](image)

- Therapeutic Effect ≥ 1 µg/g
- **Bard LUTONIX - PAX**
- Medtronic IN.PACT - PAX
Summary

• Combination Atherectomy and anti-restenotic therapy may reduce mechanical failure and allow better drug uptake
• Early data with DAART shows benefit with better lumen gain and less dissections associated with a trend towards better patency and TLR in Fem pop
• We are awaiting data on combination therapy in BTK vessels
• Image guided systems novel drug delivery and Limus DCBs hold promise