Long term durability of DCB treatment in the SFA: 4-year results of the IN.PACT SFA study

John Laird, MD
Adventist Heart & Vascular Institute
St. Helena, California, USA
Disclosure

Speaker name: John R. Laird

I have the following potential conflicts of interest to report:

- Consulting: Abbott Vascular, Bard Peripheral Vascular, Boston Scientific, Cordis, Medtronic
- Employment in industry
- Stockholder of a healthcare company: Syntervention, Shockwave, Eximo, Reflow, PQ Bypass
- Owner of a healthcare company
- Other(s)
Background

- DCBs have significantly changed the treatment landscape for SFA disease, showing improved outcomes over PTA in randomized trials $^{1,2,3}$
- IN.PACT™ Admiral™ DCB has demonstrated best in class safety and efficacy results at 1, 2 and 3 years $^{1,4,5}$
- Long term randomized data for commercially available DCBs are limited

1. Tepe G et al 12-Month Result of IN.PACT SFA. Circulation 2014
3. Schroeder H et al. 1-Year Result of the ILLUMENATE EU RCT. Circulation 2017
5. IN.PACT SFA 3-Year Results. Krishnan VIVA 2016
Drug-Coated Balloon Versus Standard Percutaneous Transluminal Angioplasty for the Treatment of Superficial Femoral and Popliteal Peripheral Artery Disease

12-Month Results From the IN.PACT SFA Randomized Trial

Gunnar Tepe, MD; John Laird, MD; Peter Schneider, MD; Marianne Brodmann, MD; Prakash Krishnan, MD; Antonio Micari, MD; Christopher Metzger, MD; Dierk Scheinert, MD; Thomas Zeller, MD; David J. Cohen, MD, MSc; David B. Snead, PhD; Beaux Alexander, MBA; Mario Landini, MS; Michael R. Jaff, DO; for the IN.PACT SFA Trial Investigators*

Background—Drug-coated balloons (DCBs) have shown promise in improving the outcomes for patients with peripheral artery disease. We compared a paclitaxel-coated balloon with percutaneous transluminal angioplasty (PTA) for the treatment of symptomatic superficial femoral and popliteal artery disease.

Methods and Results—The IN.PACT SFA Trial is a prospective, multicenter, single-blinded, randomized trial in which 331 patients with intermittent claudication or ischemic rest pain attributable to superficial femoral and popliteal peripheral artery disease were randomly assigned in a 2:1 ratio to treatment with DCB or PTA. The primary efficacy end point was primary patency, defined as freedom from restenosis or clinically driven target lesion revascularization at 12 months. Baseline characteristics were similar between the 2 groups. Mean lesion length and the percentage of total occlusions for the DCB and PTA arms were 8.94±4.89 and 8.81±5.12 cm (P=0.82) and 25.8% and 19.5% (P=0.22), respectively. DCB resulted in higher primary patency versus PTA (82.2% versus 52.4%; P<0.001). The rate of clinically driven target lesion revascularization was 2.4% in the DCB arm in comparison with 20.6% in the PTA arm (P<0.001). There was a low rate of vessel thrombosis in both arms (1.4% after DCB and 3.7% after PTA [P=0.10]). There were no device- or procedure-related deaths and no major amputations.

Conclusions—In this prospective, multicenter, randomized trial, DCB was superior to PTA and had a favorable safety profile for the treatment of patients with symptomatic femoropopliteal peripheral artery disease.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique Identifiers: NCT01175850 and NCT01566461. (Circulation. 2015;131:495-502. DOI: 10.1161/CIRCULATIONAHA.114.011004.)

Key Words: drug-eluting balloons • peripheral arterial disease • peripheral vascular diseases
Sustained Durability of Treatment Effect Using a Drug-Coated Balloon for Femoropopliteal Lesions
24-Month Results of IN.PACT SFA

John R. Laird, MD,* Peter A. Schneider, MD,† Gunnar Tepe, MD,‡ Marianne Brodmann, MD,§ Thomas Zeller, MD,∥
Christopher Metzger, MD,¶ Prakash Krishnan, MD,‖ Dirk Scheinert, MD,¶* Antonio Micari, MD, PhD,‖†
David J. Cohen, MD, MSC,‖ Hong Wang, MD, MPH,‖‖ Melissa S. Hasenbank, PhD,‖‖ Michael R. Jaff, DO,‖‖‖ for the IN.PACT SFA Trial Investigators

ABSTRACT

BACKGROUND Evidence from large, randomized, controlled peripheral artery disease trials reporting long-term outcomes using drug-coated balloons (DCBs) is limited. Previously, the DCB showed favorable 1-year outcomes compared with conventional percutaneous transluminal angioplasty (PTA), yet durability of the treatment effect with DCBs remains unknown.

OBJECTIVES This study sought to investigate the longer-term outcomes of a paclitaxel-eluting DCB compared to PTA for femoropopliteal lesions.

METHODS We enrolled 331 patients with symptomatic (Rutherford 2 to 4) femoropopliteal lesions up to 18 cm in length. Patients were randomly assigned in a 2:1 ratio to treatment with DCB or PTA. The 24-month assessments included primary patency, freedom from clinically driven target lesion revascularization (CD-TLR), major adverse events, and quality of life and functional outcomes as assessed by the EuroQoL-5D quality-of-life questionnaire, walking impairment questionnaire, and 6-min walk test.

RESULTS At 24 months, patients treated with DCB showed significantly higher primary patency when compared with PTA (78.9% vs. 50.1%; p < 0.001). The rates of CD-TLR were 9.1% and 28.3% (p < 0.001) for the DCB and PTA groups, respectively. The overall mortality rate in the DCB group was 8.1% versus 0.9% in the PTA group (p = 0.008). There were no device- or procedure-related deaths and no major amputations in either group through 24-month follow-up. The rate of vessel thrombosis was low (1.5% DCB vs. 3.8% PTA; p = 0.243), with no new events reported between 1 and 2 years. Both groups showed similar functional improvement at 2 years, although DCB patients achieved this level of function with 58% fewer reinterventions.

CONCLUSIONS The 24-month outcomes from the trial demonstrate a durable and superior treatment effect of DCB versus PTA with significantly higher primary patency, lower CD-TLR, and similar functional status improvement with fewer repeat interventions. (Randomized Trial of IN.PACT Admiral Drug Eluting Balloon vs Standard PTA for the Treatment of SFA and Proximal Popliteal Arterial Disease [IN.PACT SFA I]; NCT01758850; and IN.PACT Admiral Drug-Coated Balloon vs. Standard Balloon Angioplasty for the Treatment of Superficial Femoral Artery [SFA] and Proximal Popliteal Artery [PPA] [IN.PACT SFA II]; NCT01566461) (J Am Coll Cardiol 2015;11:13-22) © 2015 by the American College of Cardiology Foundation.
Peripheral Vascular Disease

Treatment Effect of Drug-Coated Balloons Is Durable to 3 Years in the Femoropopliteal Arteries
Long-Term Results of the IN.PACT SFA Randomized Trial

Peter A. Schneider, MD; John R. Laird, MD; Gunnar Tepe, MD; Marianne Brodmann, MD; Thomas Zeller, MD; Dierk Scheinert, MD; Christopher Metzger, MD; Antonio Micari, MD; Ravish Sachar, MD; Michael R. Jaff, DO; Hong Wang, MD, MH; Melissa S. Hasenbank, PhD; Prakash Krishnan, MD; for the IN.PACT SFA Trial Investigators

Background—Randomized controlled trials have reported favorable 1-year outcomes with drug-coated balloons (DCBs) for the treatment of symptomatic peripheral arterial disease when compared with standard percutaneous transluminal angioplasty (PTA). Evidence remains limited on the durability of the treatment effect with DCBs in the longer term.

Methods and Results—IN.PACT SFA is a single-blind, randomized trial (Randomized Trial of IN.PACT Admiral Paclitaxel-Coated Percutaneous Transluminal Angioplasty [PTA] Balloon Catheter vs Standard PTA for the Treatment of Atherosclerotic Lesions in the Superficial Femoral Artery [SFA] and/or Proximal Popliteal Artery [PPA]) that enrolled 331 patients with symptomatic (Rutherford 2-4) femoropopliteal lesions up to 18 cm in length. Patients were randomized 2:1 to receive treatment with DCB or PTA. The 36-month assessments included primary patency, freedom from clinically driven target lesion revascularization, major adverse events, and functional outcomes. At 36 months, primary patency remained significantly higher among patients treated with DCB compared with PTA (69.5% versus 45.1%; log rank $P<0.001$). The rates of clinically driven target lesion revascularization were 15.2% and 31.1% ($P=0.002$) for the DCB and PTA groups, respectively. Functional outcomes were similarly improved between treatment groups even though subjects in the DCB group required significantly fewer reinterventions versus those in the PTA group ($P<0.001$ for target lesion revascularization, $P=0.001$ for target vessel revascularization). There were no device- or procedure-related deaths as adjudicated by an independent Clinical Events Committee.

Conclusions—Three-year results demonstrate a durable and superior treatment effect among patients treated with DCB versus standard PTA, with significantly higher primary patency and lower clinically driven target lesion revascularization, resulting in similar functional improvements with reduced need for repeat interventions.


Key Words: angioplasty ■ peripheral arterial disease ■ target lesion revascularization
Objective: Assess the safety and efficacy of IN.PACT Admiral DCB vs. standard PTA for the treatment of superficial femoral and proximal popliteal artery disease due to claudication and rest pain.

IN.PACT SFA I
150 subjects enrolled at 13 EU sites
Sep 2010-Apr 2011

IN.PACT SFA II
181 subjects enrolled at 44 US sites
Apr 2012-Jan 2013

Robust Level 1 Evidence
- Prospective, multicenter EU and US, randomized (2:1), single-blinded trial
- 331 patients enrolled: IN.PACT DCB (n = 220) vs. PTA (n = 111)

Rigorous and Unbiased
- Independent and blinded Duplex Ultrasound Core Lab [1], Angiographic Core Lab [2], and Clinical Events Committee [3]
- Independent Safety Monitoring Board
- External monitoring with 100% source data verification

Durability of Outcomes
- Subjects followed up to 5 years

1. VasCore DUS Core Laboratory, Boston, MA, US
2. SynvaCor Angiographic Core Laboratory, Springfield, IL, US
3. Clinical Events Committee and Data Safety Monitoring services provided by HCRI, Boston, MA, US
IN.PACT SFA Trial
Blinded, Independently Assessed Outcomes

- **Primary Efficacy Endpoint**: Primary patency within 12 months, defined as freedom from clinically-driven TLR and DUS-derived restenosis (PSVR ≤ 2.4).

- **Primary Safety Endpoint**: Freedom from device- and procedure-related death through 30 days, and freedom from target limb major amputation and clinically-driven TVR within 12 months.

- MAEs (including all individual components of the primary endpoints and key secondary endpoints) are adjudicated by the blinded CEC through 5 years.

- Restenosis is assessed by the blinded Duplex and Angiographic Core Labs through the 3-year follow-up visits.
IN.PACT SFA Trial
Blinded, Independently Assessed Outcomes

4 Year Follow-up Assessment

- Clinically-driven TLR: CD-TLR was adjudicated by an independent Clinical Event Committee, blinded to the assigned treatment based on any re-intervention at the target lesion due to symptoms or drop of ABI of ≥20% or >0.15 when compared to post-procedure baseline ABI

- Conducted via Telephone Interview

- MAEs (including all individual components of the primary endpoints and key secondary endpoints) are adjudicated by the blinded CEC through 5 years.

- Restenosis is assessed by the blinded Duplex and Angiographic Core Labs through the 3-year follow-up visits.
## IN.PACT SFA Trial
### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>IN.PACT\n(n=220) subjects</th>
<th>PTA\n(n=111) subjects</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Y ± SD</td>
<td>67.5 ± 9.5</td>
<td>68.0 ± 9.2</td>
<td>0.612</td>
</tr>
<tr>
<td>Male, % (n)</td>
<td>65.0% (143/220)</td>
<td>67.6% (75/111)</td>
<td>0.713</td>
</tr>
<tr>
<td>Diabetes, % (n)</td>
<td>40.5% (89/220)</td>
<td>48.6% (54/111)</td>
<td>0.161</td>
</tr>
<tr>
<td>Current smoker, % (n)</td>
<td>38.6% (85/220)</td>
<td>36.0% (40/111)</td>
<td>0.719</td>
</tr>
<tr>
<td>Rutherford class, % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>37.7% (83/220)</td>
<td>37.8% (42/111)</td>
<td>0.898</td>
</tr>
<tr>
<td>3</td>
<td>57.3% (126/220)</td>
<td>55.9% (62/111)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5.0% (11/220)</td>
<td>5.4% (6/111)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.0% (0/220)</td>
<td>0.9% (1/111)</td>
<td></td>
</tr>
<tr>
<td>Lesion length (cm ± SD)</td>
<td>8.94 ± 4.89</td>
<td>8.81 ± 5.12</td>
<td>0.815</td>
</tr>
<tr>
<td>Total occlusions, % (n)</td>
<td>25.8% (57/221)</td>
<td>19.5% (22/113)</td>
<td>0.222</td>
</tr>
<tr>
<td>Calcification, % (n)</td>
<td>59.3% (131/221)</td>
<td>58.4% (66/113)</td>
<td>0.907</td>
</tr>
<tr>
<td>Severe calcification, % (n)</td>
<td>8.1% (18/221)</td>
<td>6.2% (7/113)</td>
<td>0.662</td>
</tr>
<tr>
<td>Provisional stenting, % (n)</td>
<td>7.3% (16/220)</td>
<td>12.6% (14/111)</td>
<td>0.110</td>
</tr>
</tbody>
</table>
IN.PACT SFA Trial
Primary Patency¹ Through 3 Years

1. Freedom from core laboratory-assessed restenosis (duplex ultrasound PSVR ≤2.4) and clinically-driven target lesion revascularization through 36 months (adjudicated by a Clinical Events Committee blinded to the assigned treatment)
2. Number at risk represents the number of evaluable subjects at the beginning of the each 30-day window
1. Clinically-driven TLR adjudicated by an independent Clinical Events Committee, blinded to the assigned treatment based on any re-intervention at the target lesion due to symptoms or drop of ABI of ≥20% or >0.15 when compared to post-procedure baseline ABI.
2. Number at risk represents the number of evaluable subjects at the beginning of each 30-day window.
IN.PACT SFA Trial
Freedom from CD-TLR through 4 Years

Log-rank $P = .0399$

Number at risk:
- DCB: 220, 210, 198, 173, 149, 86
- PTA: 111, 103, 87, 76, 71, 43

Freedom from Clinically-Driven TLR

Time after Index Procedure (Months)
# IN.PACT SFA Trial
## Effectiveness Outcomes through 4 Years

<table>
<thead>
<tr>
<th></th>
<th>IN.PACT DCB (N=220)</th>
<th>PTA (N=111)</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically-driven TLR [1]</td>
<td>23.4% (43/184)</td>
<td>31.1% (32/103)</td>
<td>0.164</td>
</tr>
<tr>
<td>Any TLR [2]</td>
<td>24.5% (45/184)</td>
<td>34.0% (35/103)</td>
<td>0.100</td>
</tr>
<tr>
<td>Time to First CD-TLR</td>
<td>739.2 ± 384.0</td>
<td>302.9 ± 213.0</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

1. Clinically-driven TLR adjudicated by an independent Clinical Event Committee, blinded to the assigned treatment based on any re-intervention at the target lesion due to symptoms or drop of ABI of ≥20% or >0.15 when compared to post-procedure baseline ABI
2. Any TLR includes clinically-driven and incidental or duplex driven TLR

† Unless otherwise indicated, all tests were for superiority using the Fisher’s exact test for binary variables and t-test for continuous variables.
IN.PACT SFA Trial
Preliminary Time to Event Analysis of DCB and PTA Arms

Hypothesis: Specific baseline subject, lesion, and procedural variables are associated with difference in time to event between treatment groups

Methodology: Perform multivariate and angiographic analyses to identify key variables implicated in time to event rates
• Age, Gender, Co-Morbidities, Lesion characteristics (length, RVD, Ca++)

Conclusions: No apparent factors explaining differences across or within treatment arms
### IN.PACT SFA Trial

**Safety Outcomes through 4 Years**

<table>
<thead>
<tr>
<th></th>
<th>IN.PACT DCB (N=220)</th>
<th>PTA (N=111)</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Safety Composite [1]</td>
<td>73.4% (135/184)</td>
<td>64.1% (66/103)</td>
<td>0.108</td>
</tr>
<tr>
<td>Major Adverse Events [2]</td>
<td>38.0% (70/184)</td>
<td>40.8% (42/103)</td>
<td>0.705</td>
</tr>
<tr>
<td>All-cause Death</td>
<td>13.0% (24/184)</td>
<td>6.8% (7/103)</td>
<td>0.116</td>
</tr>
<tr>
<td>Device- or Procedure-related Death</td>
<td>0.0% (0/219)</td>
<td>0.0% (0/111)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Clinically-driven TVR</td>
<td>26.6% (49/184)</td>
<td>35.9% (37/103)</td>
<td>0.108</td>
</tr>
<tr>
<td>Target Limb Major Amputation</td>
<td>0.0% (0/184)</td>
<td>0.0% (0/103)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>2.2% (4/184)</td>
<td>4.9% (5/103)</td>
<td>0.290</td>
</tr>
</tbody>
</table>

1. Freedom from 30-day device and procedure-related death and target limb major amputation and clinically-driven TVR within 36 months
2. Composite of death, clinically-driven TVR, target limb major amputation, and thrombosis

† P-values are based on Fisher’s exact test for superiority with significance level of 0.05
IN.PACT SFA Trial: Summary

• First independently adjudicated, randomized, blinded pivotal IDE trial to demonstrate superior treatment effect with DCB through four years
  • Favorable freedom from CD-TLR of DCB vs PTA
  • Significantly longer time to first reintervention for DCB, $739.2 \pm 384.0$ vs $302.9 \pm 213.0$ days for PTA group
  • Post hoc analysis of revascularized subjects revealed no obvious factors explaining differences across or within treatment arms at 4 years
• Data continue to demonstrate long-term safety of the IN.PACT™ Admiral™ DCB
• These data stress the importance of follow-up beyond common 1- and 2-year intervals, especially for drug therapies
Long term durability of DCB treatment in the SFA:
4-year results of the IN.PACT SFA study

John Laird, MD
Adventist Heart & Vascular Institute
St. Helena, California, USA