When the Benefit of Paclitaxel Outweighs the Risk

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Disclosure

Speaker name: Thomas Zeller

I have the following potential conflicts of interest to report:

- Consulting
- Employment in industry
- Stockholder of a healthcare company
- Owner of a healthcare company
- Other(s)
DCB vs DES 5-year Freedom from TLR

IN.PACT SFA Trial: Freedom from CD-TLR through 5 Years

Laird J. VIVA 2018.

Freedom from CD-TLR through 5 years

Kaplan-Meier Freedom From TLR

Rutherford category at 5 year

Scheinert D, LINC NY June 2019
IN.PACT Global Study Full Clinical Cohort
Freedom from CD-TLR Through the Years

1-Year: 92.6%  \( \Delta 9.3\% \)
2-Years: 83.3%  \( \Delta 6.4\% \)
3-Years: 76.9%  \( \Delta 3.5\% \)
4-Years: 73.4%  \( \Delta 4.0\% \)
5-Years: 69.4%

4. Zeller T. IN.PACT Global 4-year Results VIVA 2019
5. Zeller T. IN.PACT Global 5-year Results VIVA 2020
Drug-eluting therapies associated with improved clinical outcomes, at 24-month cost-savings between 10-14% compared to PTA
Drug-Coated Balloons & Stents

Long-term Safety
Insight from AcoArt I-5 Year Follow Up

Dierk Scheinert, MD on behalf of
Guo Wei, MD

Department of Vascular and Endovascular Surgery,
Chinese PLA General Hospital, Beijing, China
On behalf of AcoArt I Trial investigators
Kaplan-Meier Freedom from All-Cause Death by Paclitaxel Dose in All DCB Patients

Peter A. Schneider, MD; John R. Laird, MD; Gheorghe Doros, PhD; Qi Gao, MS; Gary Ansel, MD; Marianne Brodmann, MD; Antonio Micari, MD, PhD; Mehdi H. Shishehbor, DO, MPH, PhD; Gunnar Tepe, MD; Thomas Zeller, MD. Mortality not correlated with paclitaxel exposure: an independent patient-level meta-analysis of IN.PACT Admiral drug-coated balloon. JACC 2019
Mortality after use of paclitaxel-based devices in peripheral arteries: a real-world safety analysis

Eva Freisinger 1, Jeanette Koepp 2, Joachim Gers 1, Dennis Goerlich 1, Nasser M. Malyar 1, Ursula Marschall 1, Andreas Faldum 2, and Holger Reinecke 1

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Methods and results

In 92 million insureds of the German BARMER Health Insurance, data on the application of paclitaxel-based drug-eluting stents (DES) and drug-coated balloons (DCB) were retrieved from their introduction on the market in 2007 until present. All patients with first EVR between 2007 and 2015 were indexed and followed until 31 December 2017. Each subsequently applied DES, DCB, bare-metal stent, and uncoated balloon was included in further analyses. Multivariable Cox regression analysis considered potential non-linear time-dependent hazard ratios (HRs) of DES and DCB over 11 years. We identified 64,771 patients who underwent 107,112 EVR procedures using 23,137 DED. Multivariable Cox regression analysis showed paclitaxel-based DES not to be associated with increased long-term mortality for over 11 years past application (all P > 0.057). DCB was associated with decreased long-term mortality for the first year past application (HR 0.92; P < 0.001), and indifferent correlation in the years thereafter (all P > 0.202).
Long Term Survival after Femoropopliteal Artery Revascularisation with Paclitaxel Coated Devices: A Propensity Score Matched Cohort Analysis

Christian-Alexander Behrendt a, *, Art Sedrakyan b, Frederik Peters a, Thea Kreutzburg a, Marc Schermerhorn c, Daniel J. Bertges f, Axel Larena-Avellaned a, Helmut L’Hoest a, Tilo Kölbl a, Eiko Sebastian Debus d

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bHealthcare Policy and Research, Weill Cornell Medical College, New York, NY, USA
cDepartment of Vascular and Endovascular Surgery, Beth Israel Deaconess Medical Centre, Boston, MA, USA
dDivision of Vascular Surgery, University of Vermont Medical Centre, Burlington, VT, USA
eBARMER, Wuppertal, Germany

WHAT THIS PAPER ADDS
In this retrospective cohort study of 37,914 patients and 21,546 propensity score matched patients, revascularisation between 1 January 2010 and 31 December 2018, rapid adoption of paclitaxel and higher long term survival at five years was observed after their use for the treatment of peripheral arterial occlusive disease. Among BARMER patients, no sign of increased all cause mortality use of paclitaxel coated devices was found, emphasising differences between population based randomised trials.

Figure 1. Flow chart of this propensity score matched retrospective analysis of health insurance claims. PAOD = peripheral arterial occlusive disease; PBA = plain balloon angioplasty; RMS = bare metal stent; DCB = drug coated balloon; DES = drug eluting stent.
Kaplan-Meier Estimates of 5-Year Survival Including 95% CI

A: Chronic Limb Threatening Ischemia

B: Intermittent Claudication
Analysis #3

- **152,473 Medicare beneficiaries** who underwent femoropopliteal artery revascularization from **01/1/2015** to **12/31/2017** at 3,042 U.S. institutions
  - Both inpatient and outpatient procedures

- **Drug-coated devices** (DES/DCB) compared with **non-drug-coated devices** (BMS/PTA)

- All-cause mortality was analyzed through **04/30/2019**
  - Median follow-up 799 days, longest 1,573 days
**Device Type: Weighted Results**

**DCB vs PTA**
- Log-rank $P<0.001$
- Adjusted HR 0.93; 95% CI 0.91, 0.95

**DES vs BMS**
- Log-rank $P=0.03$
- Adjusted HR 0.97; 95% CI 0.94, 1.00
Survival of the entire cohort for POBA (n=514) and DCB-group (n=1065)

Survival of matched patients for POBA and DCB-group

Kaplan-Meier analysis with the use of the Mantel-cox log-rank test.

Böhme T et al. JACC CI 2020 epub
IN.PACT Global Study
Long-term All-Cause Mortality in Context

Real-World Study

<table>
<thead>
<tr>
<th>Condition</th>
<th>All-Cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC+CLI</td>
<td>19.5% *</td>
</tr>
<tr>
<td>IN.PACT Global</td>
<td></td>
</tr>
</tbody>
</table>

PAD Epidemiological Studies

<table>
<thead>
<tr>
<th>Country</th>
<th>Condition</th>
<th>All-Cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>N-DM</td>
<td>38.0%</td>
</tr>
<tr>
<td></td>
<td>DM</td>
<td>52.0%</td>
</tr>
<tr>
<td></td>
<td>IC</td>
<td>39.8%</td>
</tr>
<tr>
<td></td>
<td>CLI</td>
<td>29.0%</td>
</tr>
<tr>
<td>UK</td>
<td>N-DM</td>
<td>58.0%</td>
</tr>
<tr>
<td></td>
<td>DM</td>
<td>63.0%</td>
</tr>
<tr>
<td></td>
<td>IC</td>
<td>75.0%</td>
</tr>
<tr>
<td>Sweden</td>
<td>N-DM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CLI</td>
<td></td>
</tr>
</tbody>
</table>

*cumulative incidence K-M estimate
IC = Intermittent Claudication
CLI = Critical Limb Ischemia
N-DM = Non-Diabetes Mellitus
DM = Diabetes Mellitus

2. Heikkila, K et al BJS 2018; 105: 1145–1154
Drug-Coated Balloons

Below-the-Knee
## AcoArt BTK Italy – DCB vs. POBA
### 1-Year Outcomes

### Clinical Outcome at 12-months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LITOS</th>
<th>POBA</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>4(7.7%)</td>
<td>7(13.2%)</td>
<td>0.2</td>
</tr>
<tr>
<td>TLR</td>
<td>6/62(10)</td>
<td>27/66(41)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Major Amputation</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Complete Healing at 12 months</td>
<td>42/47(89.4)</td>
<td>35/47(74.5)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Graph:**
- Sign. Log Rank (Mantel-Cox) p < .001

Liistro F LINC 2020, Leipzig
AcoArt II Study – DCB vs. POBA
1-Year Results

6-month results - Primary Endpoint

<table>
<thead>
<tr>
<th>Primary Patency</th>
<th>DCB (N=48)</th>
<th>PTA (N=46)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>77.1% (37/48)</td>
<td>28.3% (13/46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Occlusion</td>
<td>8 (16.7%)</td>
<td>27 (58.7%)</td>
<td></td>
</tr>
<tr>
<td>TLR</td>
<td>3 (6.3%)</td>
<td>12 (26.1%)</td>
<td></td>
</tr>
<tr>
<td>Amputation</td>
<td>1 (2.1%)</td>
<td>1 (2.2%)</td>
<td></td>
</tr>
</tbody>
</table>

* Primary patency was defined as Freedom from occlusion and CD-TLR and major amputation above ankle.

12-month Results

<table>
<thead>
<tr>
<th></th>
<th>DCB</th>
<th>PTA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD-TLR</td>
<td>8.5% (5/59)</td>
<td>23.2% (13/56)</td>
<td>0.030</td>
</tr>
<tr>
<td>Ulcer healing rate</td>
<td>83.9% (26/31)</td>
<td>75.0% (24/32)</td>
<td>0.393</td>
</tr>
<tr>
<td>Major Amputation</td>
<td>1.7% (1/59)</td>
<td>1.8% (1/56)</td>
<td>0.971</td>
</tr>
</tbody>
</table>

Zhidong Ye LINC 2020, Leipzig
IN.PACT DEEP Trial: Safety Outcomes

Kaplan-Meier Freedom from All-Cause Death through 5 Years

No statistically significant difference in mortality at any time point

Zeller T. et al. JACC CI 2020
# IN.PACT DEEP Trial: Multivariable Analysis

## Predictors of All-Cause Death through 5 Years

<table>
<thead>
<tr>
<th>Predictor</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Rutherford Category (&gt;4 vs. &lt;=4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Previous Peripheral Revascularization (Y vs. N)</td>
<td>0.026</td>
</tr>
</tbody>
</table>

After Forcing Dose into the Model: Paclitaxel is Still Not a Predictor

<table>
<thead>
<tr>
<th>PTX Dose (Lower vs. 0)</th>
<th>0.214</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTX Dose (Upper vs. 0)</td>
<td>0.428</td>
</tr>
<tr>
<td>PTX Dose (Mid vs. 0)</td>
<td>0.713</td>
</tr>
</tbody>
</table>
Mortality analysis of patients who underwent endovascular therapy of infrapopliteal lesions (Median follow-up of 46±32 months)

→

Mortality incidence:

Entire cohort
DCB: 46.9%
POBA: 66.9%

Kaplan-Meier survival analysis for different paclitaxel exposure

Initial Paclitaxel Dosage

Total Paclitaxel Dosage

Böhme T et al. In revision
Long Term Outcomes After Revascularisations Below the Knee with Paclitaxel Coated Devices: A Propensity Score Matched Cohort Analysis

WHAT THIS PAPER ADDS
In this retrospective cohort study of 14,738 patients and 6,568 propensity score matched patients with index revascularisation below the knee between 1 January 2010 and 31 December 2018, a reduction was observed in long-term all-cause mortality and the combined endpoints of amputation or death and cardiovascular event or death five years after the use of paclitaxel-coated devices when compared with uncoated devices for the treatment of chronic limb-threatening ischaemia. The study addressed a key question in vascular medicine and using long-term real-world evidence does not confirm the potential harm reported in randomised controlled trials.

Figure 1. Flow chart of this propensity score matched retrospective analysis of health insurance claims to identify the study cohort of patients with peripheral arterial occlusive disease (PAOD) and chronic limb-threatening ischaemia treated endovascularly with plain balloon angioplasty (PBA), bare metal stent (BMS), drug-coated balloon (DCB) or drug-eluting stent (DES) to determine long-term outcomes of below-knee interventions using paclitaxel-coated devices in routine vascular care.
Long Term Outcomes After Revascularisations Below the Knee with Paclitaxel Coated Devices: A Propensity Score Matched Cohort Analysis

Franciska Heidemann 1, Frederik Peters 1, Jenny Kuchenbecker 1, Thea Kreutzburg 1, Art Sedrakyan 1, Ursula Marshall 1, Holmut L’Hoces 2, Elle S. Debis 3, Christian-Alexander Behrendt 4, 5

1 Department of Vascular Medicine, Research Group GermanVasc, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
2 Healthcare Policy and Research, Weill Cornell Medical College, New York, NY, USA
3 BARMER, Wuppertal, Germany

A: All cause mortality

B: Cardiovascular events or death

C: Amputation or death

Figure 2. Forest plots of all cause mortality (A), cardiovascular events or death (B), and amputation or death (C) after five years by treatment approach by drug coated balloon (DCB) or drug eluting stent (DES) in patients with chronic limb threatening ischaemia in the below knee arteries using propensity score matched cohorts with hazards ratios and 95% confidence intervals (balloon vs. stent vs. both approaches merged together).
Paclitaxel – The Benefit Outweighs a Hypothetical Risk

Summary

• The meta-analyses by Katsanos et al. with a suggested excess mortality following paclitaxel coated device treatment for femoro-popliteal artery and BTK disease was a single finding without confirmation in large scale real world studies.

• Paclitaxel coated DCB and DES are to date the most clinically and cost-effective interventional tools for the treatment of even complex femoro-popliteal artery disease.

• Withholding such devices to patients with severe PAOD may even harm them and results in increased global health care costs.

• When will the agencies recall their warning?