Overcoming the Meta-Analysis: Moving forward

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For the 12 months preceding this presentation, I disclose the following types of financial relationships:

- **Honoraria received from:** Abbott Vascular, Veryan, Biotronik, Boston Scientific Corp., Cook Medical, Gore & Associates, Medtronic, Philips-Spectranetics, TriReme, Veryan, Shockwave, Biotronik, B. Braun

- **Consulted for:** Boston Scientific Corp., Cook Medical, Gore & Associates, Medtronic, Spectranetics, Veryan, Intact Vascular, Veryan

- **Common stock:** QT Medical
Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Konstantinos Katsanos, MD, PhD, MSc, EBIR; Stavros Spiliopoulos, MD, PhD; Panagiotis Kitrou, MD, PhD; Miltiadis Krokidis, MD, PhD; Dimitrios Kamabatidis, MD, PhD

Background—Several randomized controlled trials (RCTs) have already shown that paclitaxel-coated balloons and stents significantly reduce the rates of vessel restenosis and target lesion revascularization after lower extremity interventions.

Methods and Results—A systematic review and meta-analysis of RCTs investigating paclitaxel-coated devices in the femoral and/or popliteal arteries was performed. The primary safety measure was all-cause patient death. Risk ratios and risk differences were pooled with a random effects model. In all, 28 RCTs with 4663 patients (89% intermittent claudication) were analyzed. All-cause patient death at 1 year (28 RCTs with 4432 cases) was similar between paclitaxel-coated devices and control arms (2.3% versus 2.3% crude risk of death; risk ratio, 1.08; 95% CI, 0.72–1.61). All-cause death at 2 years (12 RCTs with 2316 cases) was significantly increased in the case of paclitaxel versus control (7.2% versus 3.8% crude risk of death; risk ratio, 1.68; 95% CI, 1.15–2.47; number-needed-to-harm, 29 patients [95% CI, 19–59]). All-cause death up to 5 years (3 RCTs with 863 cases) increased further in the case of paclitaxel (14.7% versus 8.1% crude risk of death; risk ratio, 1.93; 95% CI, 1.27–2.93; number-needed-to-harm, 14 patients [95% CI, 9–32]). Meta-regression showed a significant relationship between exposure to paclitaxel (dose-time product) and absolute risk of death (0.4±0.1% excess risk of death per paclitaxel mg-year; P<0.001). Trial sequential analysis excluded false-positive findings with 99% certainty (2-sided α, 1.0%).

Conclusions—There is increased risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the lower limbs. Further investigations are urgently warranted.

Clinical Trial Registration—URL: www.crd.york.ac.uk/PROSPERO. Unique identifier: CRD42018099447. (J Am Heart Assoc. 2018;7:e011245. DOI: 10.1161/JAHA.118.011245.)
Presentation Overview

• What is a high risk patient with PAD, what is the definition?
• How do you analyse the risk/benefit for paclitaxel?
• Is CLI high risk?
• Why has my treatment algorithm not changed?
• Sufficient follow up to meet the current expectations from regulators
• Current Analysis of Real World Data
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Third FDA Announcement Following the Meta-Analysis
August 7th, 2019

August 7th FDA letter provided the following recommendations:

- Discuss the risks and benefits of all available PAD treatment options with your patients. For many patients, alternative treatment options to paclitaxel-coated balloons and paclitaxel-eluting stents provide a more favorable benefit-risk profile based on currently available information.

- For individual patients judged to be at particularly high risk for restenosis and repeat femoropopliteal interventions, clinicians may determine that the benefits of using a paclitaxel-coated device outweigh the risk of late mortality.
High Risk Patient / Lesion Definition
Based on the FDA Recommendation

• Femoro-popliteal lesions at high risk for restenosis
  – Long lesions
  – Restenotic lesions
  – ISR
  – CTOs

• Lesions at low risk should be treated with standard treatment tools such as POBA, atherectomy or BMS

• However, the strongest evidence for efficacy of paclitaxel coated devices exists for TASC II A & B lesions
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How do you analyse the risk/benefit for paclitaxel?

- I don’t do it because I am confident that the meta-analysis outcome is an artefact resulting from inappropriate statistical methods and patient selection bias.
Zilver PTX RCT – **Intent to Treat**
5-year Mortality Analysis

- **PTA***
  - n = 237
  - Died = 24
  - KM = 15.3%

- **Zilver PTX**
  - n = 242
  - Died = 41
  - KM = 22.1%

- \( p = 0.04 \)

*40% of PTA group = Zilver PTX

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Zilver PTX RCT – **As-Treated**
Final 5-year Mortality

- **PTA/BMS**
  - n = 143
  - Died = 23
  - KM = 17.1%
  - p = 0.60

- **Zilver PTX**
  - n = 336
  - Died = 61
  - KM = 19.1%
Covariate analysis for treatment in the Zilver PTX RCT

- Tissue Loss: Hazard Ratio = 2.257 (1.121, 4.543), P Value = 0.023
- Congestive Heart Failure: Hazard Ratio = 1.995 (1.108, 3.592), P Value = 0.021
- Still Smokes vs Never Smoked: Hazard Ratio = 1.776 (0.770, 4.096), P Value = 0.402
- Renal Disease: Hazard Ratio = 1.735 (0.959, 3.141), P Value = 0.069
- Arrhythmia: Hazard Ratio = 1.666 (0.908, 3.057), P Value = 0.099
- Pulmonary Disease: Hazard Ratio = 1.499 (0.884, 2.543), P Value = 0.133
- Carotid Disease: Hazard Ratio = 1.491 (0.892, 2.494), P Value = 0.128
- Diabetes Mellitus: Hazard Ratio = 1.455 (0.908, 2.330), P Value = 0.119
- Quit Smoking vs Never Smoked: Hazard Ratio = 1.445 (0.690, 3.029), P Value = 0.402
- CLI vs Claudicant: Hazard Ratio = 1.423 (0.685, 2.957), P Value = 0.344
- US vs Japan: Hazard Ratio = 1.411 (0.583, 3.419), P Value = 0.690
- US vs Germany: Hazard Ratio = 1.334 (0.446, 3.992), P Value = 0.690
- Hypercholesterolemia: Hazard Ratio = 1.259 (0.706, 2.246), P Value = 0.436
- Zilver PTX: Hazard Ratio = 1.214 (0.729, 2.021), P Value = 0.457
- Male vs Female: Hazard Ratio = 1.144 (0.694, 1.887), P Value = 0.599
- Hypertension: Hazard Ratio = 1.071 (0.519, 2.209), P Value = 0.854
- Age (yr): Hazard Ratio = 1.060 (1.029, 1.092), P Value < .001
- Total Lesion Length (cm): Hazard Ratio = 1.066 (0.958, 1.078), P Value = 0.810
- Body Mass Index: Hazard Ratio = 0.952 (0.905, 1.002), P Value = 0.060
- Previous Myocardial Infarction: Hazard Ratio = 0.898 (0.505, 1.596), P Value = 0.714
• 5-year Follow-up: Significant Loss for Follow-up
  – POBA: \[13 + 12 = 25 \text{ (46\%)}\] vs. DCB: \[7 + 4 = 11 \text{ (23\%)}\]

• Patient Population at Baseline:
  – POBA: 54 vs. DCB: 48

• 5-year Number of Reported Deaths:
  – POBA: 8 vs. DCB: 12

• Katsanos et al. Mortality Rate and Risk Ratio:
  – POBA 14.8\% (8/54) vs. DCB: 25\% (12/48) RR 1.69

• Correct Correlation of Events to the Numbers at Risk:
  – POBA: 27.6\% (8/29) vs. DCB: 32.4\% (12/37) RR 1.17
Kaplan-Meier Freedom from All-Cause Death by Paclitaxel Dose in All DCB Patients

Adjusted p-value* = 0.731

* p-value was from log rank test with study on random effect and PPM adjusted

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
Dose Exposure Analysis – RCT

<table>
<thead>
<tr>
<th>Dose Group</th>
<th>5-year Mortality Rate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11.5%</td>
<td>~0.3 mg</td>
</tr>
<tr>
<td>2</td>
<td>13.6%</td>
<td>~3 mg</td>
</tr>
<tr>
<td>3</td>
<td>13.4%</td>
<td>~30 mm</td>
</tr>
<tr>
<td>4</td>
<td>20.0%</td>
<td>Increasing Total Paclitaxel Dose</td>
</tr>
<tr>
<td>5</td>
<td>13.2%</td>
<td>~300 mm</td>
</tr>
</tbody>
</table>

No impact of Zilver PTX paclitaxel dose on mortality rate
• Why is the dose argument so critical?
• It is because in pharmacology, dose escalation studies have clearly shown a relationship between dose and the magnitude of therapeutic and adverse effects.
• If there is no dose effect, there is no causation argument and the relationship must be an association.
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CLI Mortality in Context

- When an individual receives a first diagnosis of CLI, the mortality risk is 24% of 1 year and 60% over 5 years.¹

- Among 22 different types of malignancy, only six have a 5-year mortality rate higher than that of CLI.²

- Thus, a “mortality signal” following paclitaxel exposure – if it exists - does not play a relevant role in such a high mortality risk population

¹ Mustapha JA et al JACC CI 2018
² American Cancer Society Cancer Statistics Center 2018
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DCB vs DES 5-year Freedom from TLR

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

Log-rank $p = 0.0196$

Number at risk

<table>
<thead>
<tr>
<th>Time After Index Procedure (Months)</th>
<th>IN.PACT DCB</th>
<th>Standard PTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>220</td>
<td>111</td>
</tr>
<tr>
<td>12</td>
<td>198</td>
<td>88</td>
</tr>
<tr>
<td>24</td>
<td>173</td>
<td>77</td>
</tr>
<tr>
<td>36</td>
<td>149</td>
<td>72</td>
</tr>
<tr>
<td>48</td>
<td>121</td>
<td>67</td>
</tr>
<tr>
<td>60</td>
<td>58</td>
<td>22</td>
</tr>
</tbody>
</table>

Laird J. VIVA 2018.

5-year Freedom from TLR
Zilver® PTX® vs Standard Care

Log-rank $p < 0.01$

83.1%

67.6%

Freedom from CD-TLR through 5 years

Kaplan-Meier Freedom From TLR

Rutherford category at 5 year

P-value of Log-rank (Mantel-Cox) < 0.001
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

Freedom from All-cause Death through 5 years

No significant statistical difference on mortality between DCB and PTA over 5-years follow up, even more patients died in PTA group Vs. DCB group (24 vs. 17)

Kaplan-Meier Curves of Freedom From All-cause Death Between the DCB Group and PTA Group
Illuminate RCTs 3-Year Mortality

Figure 1. Hazard rates for mortality for drug-coated balloon arms of the 2 randomized, controlled trials (RCTs). The Pivotal study and EU RCT had nearly identical hazard rates with an overall $I^2$ of 0.0%, indicative of homogeneity. EU RCT indicates CVI Drug-coated Balloon European Randomized Clinical Trial; and PIVOTAL, Pivotal Trial of a Novel Paclitaxel-coated Percutaneous Angioplasty Balloon.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Hazard Rate (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIVOTAL RCT</td>
<td>3.81 (2.57, 5.63)</td>
<td>44.64</td>
<td></td>
</tr>
<tr>
<td>EU RCT RCT</td>
<td>3.95 (2.78, 5.62)</td>
<td>55.36</td>
<td></td>
</tr>
<tr>
<td>Overall ($I^2$ = 0.0%, $p = 0.887)</td>
<td>3.89 (2.99, 5.05)</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effect analysis

Figure 3. Survival in the pooled randomized, controlled trials (RCTs). The pooled RCTs show no significant differences in the survival rates in the 2 groups through 3-year (1080-day) follow-up. For further information about pooling, refer to the combining data sets section of the article. The $P$ value tests the null hypothesis that restricted mean survival time (RMST) for the 2 curves are equal vs the alternative that they are not equal. DCB indicates drug-coated balloon; and PTA, uncoated percutaneous transluminal angioplasty.
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POBA vs. DCB Use Femoropopliteal Lesions
Bad Krozingen 2011 - 2016

01/2011 - 06/2016

POBA  
n = 2860

DCB  
n = 4497

POBA vs. DCB Use Femoropopliteal Lesions
Bad Krozingen 2011 - 2016

01/2011 - 06/2016

POBA  
n = 2860

DCB  
n = 4497
**POBA vs. DCB Mortality Bad Krozingen**

**DCB**
- 01/2013 - 03/2016
- n = 1178
- FU < 36 months
  - n = 111 (9.4%)
  - ↓
- n = 1067

**POBA**
- 01/2011 - 06/2016
- n = 580
- FU < 36 months
  - n = 65 (11.2%)
  - ↓
- n = 515
<table>
<thead>
<tr>
<th></th>
<th>DCB</th>
<th>POBA</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>184</td>
<td>176</td>
</tr>
<tr>
<td>Mortality</td>
<td>17.2%</td>
<td>34.2%</td>
</tr>
<tr>
<td>360 patients</td>
<td>22.8%</td>
<td></td>
</tr>
<tr>
<td>died</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Mortality after use of paclitaxel-based devices in peripheral arteries: a real-world safety analysis

Eva Freisinger, Jeanette Koepe, Joachim Gerass, Dennis Goerlich, Nasser M. Malyar, Ursula Marschall, Andreas Faldum, and Holger Reinecke

Methods and results

In 9.2 million insurants 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).
Analysis #3

ADVISORY COMMITTEE MEETING

June 19-20, 2019: Circulatory System Devices Panel of the Medical Devices Advisory Committee Meeting Announcement

June 19-20, 2019

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
All Patients, All Devices

Total, Unweighted

HR 0.84; 95% CI 0.82-0.85
Log-rank P<0.001

Total, Weighted

Adjusted HR 0.94; 95% CI 0.93-0.96
Log-rank P<0.001

No difference in survival in subgroups: CLI vs no CLI; Inpatient vs Outpatient

Device Type: Weighted Results

DCB: 23.9% (N=36,410); PTA: 37.2% (N=56,720)

DCB vs PTA

Log-rank P<0.001
Adjusted HR 0.93; 95% CI 0.91, 0.95

DES: 16.5% (N=25,097); BMS: 22.5% (N=34,246)

DES vs BMS

Log-rank P=0.03
Adjusted HR 0.97; 95% CI 0.94, 1.00
Presentation Overview

• Has my treatment algorithm changed?
• What is the criteria of patients that are qualified to receive paclitaxel releasing devices?
• How do you analyse the risk/benefit for paclitaxel?
• How does the risk / benefit look for bare technologies?
• Sufficient follow up to meet the current expectations from regulators
Sufficient follow up to meet the current expectations from regulators

• As a consequence of the FDA request for longer term follow-up study protocols of almost all DES & DCB trials not yet having already finished 5-year follow-up are now amended according to this recommendation

• Even single arm studies
  – What will be the comparator?
  – Wide range of mortality rates in historic studies (0.9 -15% at 2 years)
Mortality Rates From Trials of SFA Therapy
All-Cause Death at 2 Years - Claudicants

<table>
<thead>
<tr>
<th>Trial</th>
<th>Mortality Rate</th>
<th>Study Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEVANT 2</td>
<td>PTA 7.6%</td>
<td>Presented by Lutonix IFU</td>
</tr>
<tr>
<td>ILLUMENATE US</td>
<td>DCB 6.5%</td>
<td>Presented by Mathews S, NCVH 2018, New Orleans, USA</td>
</tr>
<tr>
<td>ILLUMENATE EU</td>
<td>DES 8.3%</td>
<td>Presented by Schroder H, CIRSE 2017, Copenhagen, Denmark</td>
</tr>
<tr>
<td>ACOART-I</td>
<td>BMS 7.6%</td>
<td>Presented by Guo W, LINC 2017, Leipzig, Germany</td>
</tr>
<tr>
<td>CONSEQUENT</td>
<td>PTA 3.5%</td>
<td>Presented by Albrecht T, et al. Cardiovasc Intervent Radiol 2018: 41; 1008-14</td>
</tr>
<tr>
<td>SMART SES and BMS</td>
<td>BMS 7.5%</td>
<td>Presented by Duda et al. J Endovasc Ther 2006: 14; 701-710</td>
</tr>
<tr>
<td>Complete SE SFA</td>
<td>PTA 3.4%</td>
<td>Data on file. Medtronic, Inc.</td>
</tr>
<tr>
<td>RESILIENT BMS</td>
<td>DCB 2.9%</td>
<td>LifeStent IFU. Revised 2/04-16.</td>
</tr>
</tbody>
</table>

ZILVER PTX
Majestic
SMART SES and BMS
Complete SE SFA
Durability II
ETAP BMS
RESILIENT BMS
Dashed Line:
Paclitaxel Devices in Femoro-Popliteal Lesions - Summary

- Paclitaxel may be a locally toxic drug (cell death, aneurysm / pseudoaneurysm formation)
- Systemic toxicity with low dose paclitaxel release via DES seems to be unlikely
- Therefore excess mortality reported in the meta-analysis is most likely an association and no causation
  - Follow-up compliance and inappropriate statistics
- Real world data (e.g. insurance company data, single center data) show a trend to or even a significant higher survival rate for paclitaxel coated devices
- DES (like DCB) seem to overcome historic limitations of femoro-popliteal angioplasty such as long lesions, calcification, and ISR
  - High risk lesions for restenosis
Overcoming the Meta-Analysis: Moving forward

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