Long-term Safety of Drug-Coated Devices for Peripheral Artery Revascularization: Insights from VOYAGER-PAD


TCT Connect 2020
Late-Breaking Clinical Trials and Science
18 October 2020
## Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant/Research Support to CPC Clinical Research</td>
<td>Bayer, Janssen, Amgen, Merck</td>
</tr>
<tr>
<td>Grant/Research Support to CPC Clinical Research</td>
<td>Pan-Industry Consortium (Medtronic, Boston Scientific, Cook, Philips, Bard, Surmodics, TriReme) to support statistical analyses at CPC</td>
</tr>
</tbody>
</table>

Faculty disclosure information can be found on the app.
Background

• Endovascular revascularization is indicated for improvement of symptoms and limb salvage in symptomatic peripheral artery disease (PAD)

• Success of endovascular revascularization is limited by restenosis

• Paclitaxel drug-coated devices (DCD) were designed to attenuate restenosis and improve patency
Long-term Mortality Associated with DCD Use

<table>
<thead>
<tr>
<th></th>
<th>PTX</th>
<th>Control</th>
<th>1 Year</th>
<th>2 Years</th>
<th>4-5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed effect model</td>
<td>2506</td>
<td>1926</td>
<td>1.06 [0.73; 1.55] 100.0%</td>
<td>1.08 [0.72; 1.61] 100.0%</td>
<td>1.93 [1.27; 2.93] 100.0%</td>
</tr>
<tr>
<td>Random effects model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 0%$, $\tau^2 = 0$, $p = 0.98$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths:</td>
<td>58</td>
<td>35</td>
<td>45</td>
<td>101</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>10</td>
<td>100</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Pivotal trials with ~14-38% missing data at 5 years

Katsanos K, et al. JAHA 2018
Long-term Mortality Associated with DCD Use

Pivotal trials with ~14-38% missing data at 5 years

Katsanos K, et al. JAHA 2018
Additional studies have provided mixed results

Increased mortality

Others...

Dake MD et al. Cardiovasc Intervent Radiol 2019
Gray WA et al. Circulation 2019
Freisinger E et al. Eur Heart J 2019
Ouriel K et al. JACC Cardiovasc Interv 2019
Secemsky EA et al. J Am Coll Cardiol 2019
Secemsky EA et al. JAMA Cardiol 2019
Schneider PA et al. J Am Coll Cardiol 2019
Schneider PA et al. Catheter Cardiovasc Interv 2020
Others...

No increased mortality

Limitations

RCTs
Limited sample size
Variable follow up
Variable outcome ascertainment
No standardized adjudication of death

Meta-analyses
Mostly study-level
Heterogeneity of population/design
Variable follow up
Variable outcome ascertainment
No standardized adjudication of death

Observational analyses
Non-randomized
Limited baseline characterization
Heterogenous population
Variable follow-up
Outcomes not adjudicated
VOYAGER PAD

Trial Design

6,564 Patients with Symptomatic Lower Extremity PAD* Undergoing Peripheral Revascularization

ASA 100 daily for all Patients
Clopidogrel at Investigator’s Discretion

Randomized 1:1 Double Blind

Stratified by Revascularization Approach (Surgical or Endovascular) and Use of Clopidogrel

Follow up Q6 Months, Event Driven, Median f/u 28 Months

Primary Efficacy Endpoint: Acute limb ischemia, major amputation of vascular etiology, myocardial infarction, ischemic stroke or cardiovascular death

Principal Safety Endpoint: TIMI Major Bleeding

Primary Endpoint

Acute limb ischemia, major amputation for vascular cause, myocardial infarction, ischemic stroke, CV death

Cumulative Incidence (%)

Placebo
Rivaroxaban

6 Months
3.6%
2.0%
1.5%
NNT 65

1 Year
ARR 2.0%
NNT 50

3 Year
ARR 2.6%
NNT 39

HR 0.85
95% CI 0.76 – 0.96
P=0.0085

ARR – absolute risk reduction, NNT number needed to treat

Bonaca MP, et al. NEJM 2020
VOYAGER PAD - Disposition

6,772 Patients Enrolled
Not Randomized = 208
Inclusion/Exclusion 167
Subject decision 29
Adverse event 2
Physician decision 1
Other 9

6,564 Patients Randomized

Rivaroxaban
N=3286

Premature Drug Discontinuation = 1080 (33.2%)
14.2% Annualized
Withdrawal of Consent = 32 (0.97%)
0.42% Annualized
Vital status unknown = 8 (0.24%)
Lost to Follow up = 3 (0.09%)
Vital Status Known = 3275 (99.7%)
Analyzed
ITT = 3286 (100%)
Safety = 3256 (99.1%)

Placebo
N=3278

Premature Drug Discontinuation = 1011 (31.1%)
13.2% Annualized
Withdrawal of Consent = 37 (1.13%)
0.48% Annualized
Vital status unknown = 12 (0.37%)
Lost to Follow up = 3 (0.09%)
Vital Status Known = 3263 (99.5%)
Analyzed
ITT = 3278 (100%)
Safety = 3248 (99.1%)

Median Follow-up 28 Months

Bonaca MP, et al. NEJM 2020
Objectives

In VOYAGER PAD patients undergoing endovascular lower extremity revascularization for symptomatic PAD:

- To assess whether use of paclitaxel drug-coated devices versus non drug-coated devices is associated with all-cause mortality

- To evaluate whether the effect of rivaroxaban 2.5 mg twice daily plus low dose aspirin versus low dose aspirin alone on the primary efficacy endpoint is consistent with versus without DCD use
Methods

Outcomes

- Prospectively ascertained and independently adjudicated
- All-cause mortality for DCD vs. no DCD
- VOYAGER PAD primary endpoint (acute limb ischemia, major amputation of vascular etiology, myocardial infarction, ischemic stroke, or cardiovascular death) for Rivaroxaban vs. Placebo

Statistical Analysis

- Prespecified analysis of VOYAGER PAD
- Inverse Probability Treatment Weighting (IPTW)
- Two independent statistical teams
- Sensitivity analysis using stabilized weights
- Cox proportional hazards to assess for consistency of efficacy of rivaroxaban in those with and without DCD
Results

Median follow-up 31 months (IQR 25 – 37)

Complete ascertainment of vital status in 99.6% of patients

An affiliate of:
# Baseline Characteristics

## Propensity Model Comparisons

<table>
<thead>
<tr>
<th>Characteristics at Randomization</th>
<th>Unweighted Model*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drug-coated</td>
</tr>
<tr>
<td></td>
<td>N=1342*</td>
</tr>
<tr>
<td></td>
<td>%</td>
</tr>
<tr>
<td>Age, Yrs Mean</td>
<td>67</td>
</tr>
<tr>
<td>Female</td>
<td>28</td>
</tr>
<tr>
<td>Caucasian</td>
<td>84</td>
</tr>
<tr>
<td>Geographic Region</td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>19</td>
</tr>
<tr>
<td>Western Europe</td>
<td>41</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>24</td>
</tr>
<tr>
<td>Asia Pacific</td>
<td>11</td>
</tr>
<tr>
<td>South America</td>
<td>5</td>
</tr>
<tr>
<td>Current/Former Smoking</td>
<td>80</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>46</td>
</tr>
<tr>
<td>COPD</td>
<td>12</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>27</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>35</td>
</tr>
<tr>
<td>Carotid Artery Disease</td>
<td>11</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>67</td>
</tr>
<tr>
<td>DAPT</td>
<td>62</td>
</tr>
<tr>
<td>Statin</td>
<td>86</td>
</tr>
<tr>
<td>Rivaroxaban 2.5mg BID + Aspirin</td>
<td>49</td>
</tr>
</tbody>
</table>

*4,379 patients underwent endovascular revascularization; 63 patients excluded for missing baseline data (16 DCD, 47 non DCD)

** ≥0.10 considered meaningful imbalance
### PAD & Procedural Characteristics

#### Propensity Model Comparisons

<table>
<thead>
<tr>
<th>Characteristics at Randomization</th>
<th>Drug-coated N=1342</th>
<th>Not Drug-coated N=2974</th>
<th>Standardized Difference**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PAD History</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior Endovascular Revascularization</td>
<td>43</td>
<td>32</td>
<td>0.22</td>
</tr>
<tr>
<td>Prior Surgical Revascularization</td>
<td>6</td>
<td>7</td>
<td>0.03</td>
</tr>
<tr>
<td>Prior Amputation</td>
<td>4</td>
<td>7</td>
<td>0.10</td>
</tr>
<tr>
<td>Ankle Brachial Index, Mean (SD)</td>
<td>0.64 (0.22)</td>
<td>0.62 (0.23)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Indication for Revascularization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Critical limb ischemia</td>
<td>15</td>
<td>22</td>
<td>0.18</td>
</tr>
<tr>
<td>Claudication</td>
<td>85</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td><strong>Endovascular Revascularization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atherectomy</td>
<td>11</td>
<td>6</td>
<td>0.20</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>1</td>
<td>1</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Target Lesion Length</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short (&lt;5cm)</td>
<td>21</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Intermediate (5cm to &lt;15cm)</td>
<td>44</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Long (≥15cm)</td>
<td>33</td>
<td>28</td>
<td></td>
</tr>
</tbody>
</table>

** ≥0.10 considered meaningful imbalance
Inverse Probability Treatment Weighting
Standardized Differences

Unweighted
- Baseline DAPT
- Baseline ACEI/ARB
- Baseline Statin
- Smoking
- Baseline ABI
- Diastolic BP
- Systolic BP
- BMI
- Ethnicity
- Race
- Sex
- Age
- Logit Propensity Score
- Randomized Treatment
- Carotid Artery Disease
- Diabetes
- Chronic Kidney Disease
- COPD
- Prior Endovascular Revasc
- Baseline critical limb ischemia
- Hyperlipidemia
- Hypertension
- Heart Failure
- Coronary Artery Disease
- Prior Peripheral Surgical Bypass
- Prior Amputation
- Thrombolysis
- Atherectomy

Weighted

Difference (Treated-Control)
All-cause Mortality

Unweighted

N=4,379
401 deaths

Cumulative Incidence (%)

Not drug-coated
Drug-coated

Months from Randomization

# at risk DCD 1358 1347 1344 1336 1325 1313 1301 1290 1127 923 728 536 373 243 104
# at risk no DCD 3021 2992 2970 2938 2911 2891 2864 2829 2491 2023 1639 1253 882 544 220

13.5%
10.2%
All-cause Mortality

Weighted

N=4,316
394 deaths

Not drug-coated
Drug-coated

Cumulative Incidence (%)

Months from Randomization

HR 0.95
95% CI 0.83 – 1.09
P=0.49

Stabilized weights
HR 0.95
95% CI 0.77 – 1.18
P=0.66
Causes of Mortality

Cardiovascular
Non-cardiovascular

No DCD
185 (62%)
114 (38%)

DCD
55 (54%)
47 (46%)
# Mortality and DCD Use by Device Type

*Weighted Hazard*

<table>
<thead>
<tr>
<th>Device Type</th>
<th><strong>DCD</strong> n/N (%)</th>
<th><strong>No DCD</strong> n/N (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>102/1342 (7.6)</td>
<td>292/2974 (9.8)</td>
<td>0.95 (0.83, 1.09)</td>
</tr>
<tr>
<td><strong>DCB vs. PTA</strong></td>
<td>61/820 (7.4)</td>
<td>144/1479 (9.7)</td>
<td>0.99 (0.82, 1.20)</td>
</tr>
<tr>
<td><strong>DES vs. BMS</strong></td>
<td>19/231 (8.2)</td>
<td>148/1495 (9.9)</td>
<td>1.04 (0.84, 1.28)</td>
</tr>
</tbody>
</table>

Favors DCD

Favors no DCD

DCB = drug-coated balloon  
PTA = percutaneous transluminal angioplasty  
DES = drug-eluting stent  
BMS = bare metal stent
Effect of Rivaroxaban According to DCD Use

Acute limb ischemia, major amputation of vascular etiology, myocardial infarction, ischemic stroke, or cardiovascular death

Overall HR 0.85 for Rivaroxaban vs. Placebo (95% CI 0.76 – 0.96), p=0.0085

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rivaroxaban n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>Absolute Difference (%)</th>
<th>HR (95% CI)</th>
<th>P-interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>No DCD use</td>
<td>221/1536 (14.4)</td>
<td>238/1485 (16.0)</td>
<td>1.6</td>
<td>0.89 (0.74, 1.07)</td>
<td>0.88</td>
</tr>
<tr>
<td>DCD use</td>
<td>88/666 (13.2)</td>
<td>104/692 (15.0)</td>
<td>1.8</td>
<td>0.87 (0.65, 1.15)</td>
<td></td>
</tr>
</tbody>
</table>
Summary

• Among >4300 VOYAGER PAD patients undergoing endovascular revascularization with 99.6% ascertainment of mortality

• IPTW successfully adjusted for known confounders and showed no mortality risk or benefit associated with DCD, including in subgroups by device type

• The benefit of rivaroxaban 2.5 mg twice daily with aspirin versus aspirin alone on reducing ischemic limb and cardiovascular outcomes after revascularization for symptomatic PAD is consistent regardless of DCD use
Conclusions

- Large sample size
- Well characterized cohort
- 99.6% ascertainment of vital status with ~400 deaths in this sub-analysis
- Long-term follow-up
- Adjudicated outcomes

No association of mortality with paclitaxel DCD
Thank You