How Paclitaxel is perceived in Japan

Osamu Iida, MD, FACC
Amagasaki, Hyogo, Japan
Kansai Rosai Hospital, Cardiovascular Center
COI Disclosure

Speaker name: Osamu Iida, MD

I have the following potential conflicts of interest to report:

- Consulting: NIPRO, Canon
- Employment in industry
- Stockholder of a healthcare company
- Owner of a healthcare company
- Other(s) Honoraria: Medtronic, Boston Scientific, Gore, NIPRO, Canon, Kaneka, Cook
- I do not have any potential conflict of interest
Approved products for femoropopliteal Tx in Japan

**Leave nothing behind strategy (DCB-based treatment)**
- Lutonix 35DCB (BARD)
- IN.PACT 35DCB (Medtronic)
- Ranger 18DCB (Boston Scientific)
- Standard PTA

**Leave scaffold behind strategy (Stent-based treatment)**
- ZilverPTX (COOK)
- VIABAHN (GORE)
- Eluvia (Boston Scientific)
- SUPERA (Abbott)

Although FDA had specific statement for appropriate use of paclitaxel-based devices, in Japan, PMDA (Pharmaceuticals and Medical Devices Agency) doesn't have a specific announcement for reducing the use of Paclitaxel-based devices.
On going clinical trial for approval in Japan

**Femoropopliteal disease**

- **Kanshas DCB (Terumo)**
  - Single arm study,
  - total number 120 cases

- **SeQuet Please DCB (B. Braun)**
  - Single arm study,
  - total number 207 cases

**Infrapopliteal disease**

- **SAVAL BTK-DES (Boston Scientific)**
  - RCT study, total number: 201 cases

Recruitment in these clinical trials (DCB for SFA and DES for BTK) don’t pause after JAHA paper.
PTX issue in Japan

• No-mortality signal was found in
  • IN.PACT Japan 3-year data
  • CARROT 5-year registry

• No-amputation signal was found in
  • Real-world case
  • RADISH registry
The 3-Year primary patency was significantly different between the two groups in favor of DCB with a rate of 68.9% compared to 46.9% in PTA. The 3-year cumulative incidence of all-cause death was not statistically different between two groups.
Follow-up compliance is higher in OUS than US. Crude mortality rates in PTA group in IN. PACT SFA study was numerically lower compared to other studies.
Study Design: A multicenter, Retrospective Clinical Study

Inclusion Criteria:
✓ Age >20 years old
✓ Rutherford category 2-4
✓ de novo lesions
✓ Successfully EVT for SFA lesions

Exclusion Criteria:
✓ CFA lesions
✓ In stent restenosis
✓ Rutherford 5-6

Endpoint: The risk of all-caused mortality were compared between patients treated with PTX-coated stent (Zilver PTX, Cook) and those without PTX-coated devices.

Patients: Consecutive 1554 patients (2010-2016)

Centers:
Kokura Memorial HP (700)  Kishiwada Tokushukai HP (383)
Kansai Rosai HP (435)    Morinomiya HP (101)

ZilverPTX (COOK)

CAuses of death after femoro-popliteal intervention

# Mortality vs. PTX dosage

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio (PS-matched model)</th>
<th>Hazard ratio (PS-stratified model)</th>
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<tbody>
<tr>
<td>PTX-coated device use</td>
<td>1.01 [0.72, 1.40] (P=0.98)</td>
<td>0.86 [0.64, 1.17] (P=0.33)</td>
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<tr>
<td>PTX dose (versus no PTX use)</td>
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<tr>
<td>Q1 (&lt;552 μg)</td>
<td>0.40 [0.13, 1.22] (P=0.11)</td>
<td>0.39 [0.14, 1.05] (P=0.062)</td>
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<td>Q2 (552 to 1104 μg)</td>
<td>1.49 [0.85, 2.63] (P=0.16)</td>
<td>1.08 [0.70, 1.67] (P=0.73)</td>
</tr>
<tr>
<td>Q3 (1104 to 2589 μg)</td>
<td>0.81 [0.42, 1.57] (P=0.53)</td>
<td>0.91 [0.53, 1.57] (P=0.73)</td>
</tr>
<tr>
<td>Q4 (≥2589 μg)</td>
<td>1.11 [0.62, 2.00] (P=0.73)</td>
<td>0.82 [0.48, 1.39] (P=0.46)</td>
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</table>
PTX vs. BNS

PTX vs. PTA

PTX issue in Japan

No-mortality signal was found in
- IN.PACT Japan 3-year data
- CARROT 5-year registry

No-amputation signal was found in
- Real-world case
- RADISH registry
Clinical question (CQ) in DCB era
-Does DCB use adversely impact on limb prognosis?- 

Fiction or fact of DCB use in CLI practice

**Best scenario**
- Accelerated wound healing
- Limb salvage

**Worst scenario**
- Delayed wound healing
- Major amputation

DCB use → Downstream
Clinical question (CQ) in DCB era

-Does DCB use adversely impact on limb prognosis?- 

Fiction or fact of DCB use in CLI practice

DCB use 

Downstream 

Best scenario 

Accelerated wound healing 

Limb salvage

Worst scenario 

Delayed wound healing 

Major amputation
Clinical scenario: Just after procedure, color of plantar surface was unexpectedly worsened due to downstream effect. However, color was immediately recovered to baseline status.

Learn from case 1: Downstream effect was found, it was not sustained and was subclinical.
Case 2: 60 y/o Tissue loss (Rutherford 5)
- Target lesion: Lt SFA-Pop severe stenosis with ISR (TASC II C)

Recurrence of ulcer after EVT and TMA (day 1)
Case 2: 60 y/o Tissue loss (Rutherford 5)
- Target lesion: Lt SFA-Pop severe stenosis with ISR (TASC II C)

IN.PACT Admiral 4.0*150 mm*3 for distal popliteal to proximal SFA

After successful pre-dilatation

Just after 3 DCBs dilatation (slow-flow phenomenon)
Case 2: 60 y/o Tissue loss (Rutherford 5)
- Target lesion: Lt SFA-Pop severe stenosis with ISR (TASC II C)

Recurrence of ulcer after EVT and TMA (day 1)

Slow-flow phenomenon was found after DCB therapy and ischemic wound (dorsalis surface) was spontaneously worsened (day 3).
Case 2: 60 y/o Tissue loss (Rutherford 5)
-Target lesion: It SFA-Pop severe stenosis with ISR (TASC II C)
Clinical scenario:
Just after procedure, ischemic wound (dorsalis surface) was unexpectedly worsened due to downstream effect. However, wound was going well to complete wound healing as usual time course.

Learn from case 2:
Downstream effect angiographically found, it didn’t affect time course of wound healing.
Case 3: 80 y/o Tissue loss (Rutherford 5)
Target lesion: Lt Pop severe stenosis (TASC II B)

Courtesy of Dr. Inoue
Downstream Findings in Porcine Skeletal Muscle

High (20x and 40x) power images of vascular changes in skeletal muscle at 28 days.

Vascular changes include pyknotic nuclei embedded in homogenous pink material (yellow arrow), representing fibrinoid necrosis (black arrows), with surrounding inflammatory cells (blue arrows).

High (40x) power images of crystalline material (red arrows) at 28d

presented by Finn AV
Two Major Pathological Findings

1: Crystalline material (as similar to Dr. Fin’s report in previous paper)
2: Coil-shaped material (??)
Hydrophilic polymer emboli: an under-recognized iatrogenic cause of ischemia and infarct

Our findings

Hydrophilic polymer emboli: an under-recognized iatrogenic cause of ischemia and infarct

Schematic representation of cross section of bilaminar hydrophilic coating mechanism on a guidewire.

Vascular Response

- **Occlusion with Minimal Inflammation**
- **Mild Macrophagic Reaction**
- **Moderate Macrophagic, Giant Cell and Lymphocytic Reaction**
- **Severe Neutrophilic, Giant cell and Macrophagic Reaction**

Intravascular Fibrous Obliteration with Adjacent Scattered Thrombi (not shown)

Embolic Phenomena

- **1 hour - 3 days**
- **3 days - 2 months**
- **2 months - 9 months and Beyond**

Post Procedure Time

Courtesy of Dr. Inoue
Clinical question (CQ) in DCB era - Does DCB use adversely impact on limb prognosis? -

Fiction or fact of DCB use in CLI practice

DCB use → Downstream

Best scenario:
- Accelerated wound healing
- Limb salvage

Worst scenario:
- Delayed wound healing
- Major amputation
On going project for DCB use in CLI with tissue loss

Roles of Angioplasty with Drug-coated balloon for chronic ISchemia in wound Healing
A multicenter, retrospective clinical investigation

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**Endpoint:** The wound healing rate of CLTI patients undergoing EVT is compared between patients treated with Drug-coated balloon (DCB) and those without DCB.

**Patients:** Consecutive 281 patients (2018.01-2019.03) and historical 725 patients (2014.01-2017.12)

**Center:** MK4

- Morinomiya Hospital
- Kansai Rosai Hospital
- Kokura Memorial Hospital
- Kishiwada Tokushukai Hospital
- Saiseikai NaKatsu Hospital
Interim Analysis of RADISH study

**Wound healing**
- Non-DCB (n=140): 46.6%
- DCB (n=141): 45.6%
- Historical control (n=725): 50.9%

Log rank P=0.71

**Amputation-free survival**
- Non-DCB (n=140): 79.3%
- DCB (n=141): 79.2%
- Historical control (n=725): 80.3%

Log rank P=0.93
Summary

Long-Term Safety And Effectiveness Of Paclitaxel Coated Devices Versus Non-Coated Devices For Fempop Occlusive Lesions from Japanese RCTs And Registries.

1. PMDA (Pharmaceuticals and Medical Devices Agency) doesn't have a specific announcement for reducing the use of Paclitaxel-based devices.
2. Recruitment in clinical trials (DCB for SFA and DES for BTK) don’t pause after JAHA paper.
3. Three-year data of DCB-RCT and large cohort of Zilver PTX vs. PTX-free registry showed no mortality signal in 3-5 years.
4. Downstream phenomenon was found after DCB use in FP lesions but it is subclinical in real-world CLI case.
5. Our retrospective study doesn't show an increased risk of amputation following application of DCB in CLI presenting femoropopliteal disease.
How Paclitaxel is perceived in Japan

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