Decision making of treatment strategy in patients with CLI
- Learn from Priority and SPINACH study -

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Disclosure

Speaker name: Osamu Iida

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)

☒ I do not have any potential conflict of interest
Two major topics in **PAD** era

**SFA** intervention

**CLI** treatment by endovascular therapy
What is the goal in CLI treatment by endovascular therapy for well-being?

Final goal for CLI patient is to improve Pt’s mortality.
We should establish evidence of CLI treatment in latest endovascular era.
Subjects: CLI due to **isolated BTK lesions**

(884 patients with 1067 Rutherford 4-6)
Efficacy Endpoint: **Amputation-free survival**

**Baseline characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>71 ± 10</td>
</tr>
<tr>
<td>Nonambulatory</td>
<td>38%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>71%</td>
</tr>
<tr>
<td>ESRD</td>
<td>64%</td>
</tr>
<tr>
<td>EF, %</td>
<td>59 ± 14</td>
</tr>
<tr>
<td>Rutherford 5, 6</td>
<td>74%</td>
</tr>
</tbody>
</table>

1-year data: 71%=71% efficacy OPG

![Graph showing amputation-free survival over follow-up period](chart.png)
Five-year AFS stratified by number of risk factors

General factors
1. Impaired ADL
2. BMI < 18.5 kg/m²
3. Albumin < 3 g/dl
4. Creatinine ≥ 2 mg/dl
5. EF < 50%

Lower limb factors
6. Rutherford class 6
7. CRP ≥ 3 mg/dl

Anatomical factors
8. Diseased BA arteries

Table Vb. Summary of efficacy outcomes (one year) for overall CLI cohort and suggested OPG for each endpoint

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Point (95% CI)</th>
<th>Efficacy OPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFS</td>
<td>76.5% (73.7-79.5)</td>
<td>71%</td>
</tr>
</tbody>
</table>
What we learn from \textit{j beat} II registry?

- General and wound conditions were more important than intervention quality
Learn from registry

Endovascular Treatment for Infrainguinal Vessels in Patients With Critical Limb Ischemia
OLIVE Registry, a Prospective, Multicenter Study in Japan With 12-Month Follow-up

3-Year Outcomes of the OLIVE Registry, a Prospective Multicenter Study of Patients with Critical Limb Ischemia
A Prospective, Multi-Center, Three-Year Follow-Up Study on Endovascular Treatment for Infra-Inguinal Vessel in Patients With Critical Limb Ischemia
• **Procedural success:** 93%
  
  * Definition: one straight flow to foot

• **Perioperative complication:** 4% (12)
  
  – Perforation: 5, hematoma: 4, vascular rapture: 2 and dissection: 1

• **Hemodynamic success:** 74%
  
  – Both dorsal and plantar ≥40 mmHg: 48%
  – Either dorsal or plantar: 26%, neither dorsal nor plantar: 26%

Secondary Endpoint:
Time to wound healing

Median time requiring complete wound healing was 97±10 days. The proportion of not-healed patients was 54±3%, 29±3%, 18±3%, and 14±3% at 3, 6, 9, and 12 months, respectively.

Factors predicting failure to achieve healing after 97 days

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &lt;18.5</td>
<td>0.54(0.31-0.96)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>0.79(0.58-1.09)</td>
<td>0.15</td>
</tr>
<tr>
<td>Wound infection</td>
<td>0.60(0.36-0.98)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Secondary Endpoint:
Wound recurrence and its predictors

<table>
<thead>
<tr>
<th>Stepwise analysis for recurrence of wound</th>
<th>OR</th>
<th>95%CI</th>
<th>Wald p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>ALL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male Gender</td>
<td>1.61</td>
<td>0.74</td>
<td>3.52</td>
</tr>
<tr>
<td>Serum albumin&lt;3.0g.dL</td>
<td>2.72</td>
<td>0.42</td>
<td>17.61</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.75</td>
<td>0.76</td>
<td>4.01</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>1.52</td>
<td>0.74</td>
<td>3.14</td>
</tr>
<tr>
<td><strong>Isolated below-the knee lesions</strong></td>
<td>4.54</td>
<td>2.20</td>
<td>9.37</td>
</tr>
</tbody>
</table>

**STEPWISE**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.05</td>
<td>0.94</td>
<td>4.45</td>
</tr>
<tr>
<td><strong>Isolated below-the knee lesions</strong></td>
<td>4.28</td>
<td>2.15</td>
<td>8.53</td>
</tr>
</tbody>
</table>

Recurrence of wound until 3 years: **43.9 %**

AFS: 55%
- Age: HR 1.43
- BMI < 18.5: HR 2.17
- Hemodialysis: HR 2.91
- Rutherford 6: HR 1.64

Wound healing: 86%
- BMI < 18.5: HR 0.54
- Wound infection: HR 0.60

MALE-free: 84%
- Statin: HR 0.28
- Rutherford 6: HR 2.25
- Heart failure: HR 1.96
- One-straight line: HR 0.27

Wound recurrence: 43%
- Isolated BTK lesions: OR 4.28

3-year clinical results of EVT were reasonable despite high reintervention and moderate ulcer recurrence rate.
What we learn from registry?

• Clinical outcomes after EVT is reasonable. However, if we take a look at wound prognosis, it would be still challenging.
After publication of J-BEAT and OLIVE study, 3 clinical questions are emerged in RW practice.

CQ-1: Revascularization improve the CLI mortality?

CQ-2: EVT is clinically comparable to surgery in CLI Pt?

CQ-3: Angiogenesis yes or no?
Prognostic impact of revascularization in poor-risk patients with critical limb ischemia:

**The PRIORITY registry**

**Poor-Risk patients with and without Revascularization Therapy for critical limb ischemia**

**Osamu Iida**, MD¹, Mitsuyoshi Takahara, MD, PhD², Yoshimitsu Soga, MD³, Nobuyoshi Azuma, MD, PhD⁴, Shinsuke Nanto MD, PhD⁵, Masaaki Uematsu MD, PhD, FACC¹, on behalf of the PRIORITY investigators.

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(2) Department of Diabetes Care Medicine, and Department of Metabolic Medicine, Osaka University Graduate School of Medicine, Suita, Japan
(3) Department of Cardiology, Kokura Memorial Hospital, Kitakyushu, Japan
(4) Department of Vascular Surgery, Asahikawa Medical University, Asahikawa, Japan
(5) Department of Cardiology, Nishinomiya Municipal Central Hospital, Nishinomiya, Japan

Methods

**Objective:** To investigate the prognostic impact of revascularization for poor-risk CLI patients in real-world settings

**Primary endpoint:** One-year survival compared between the revascularization and non-revascularization groups

**Statistical analysis:** The propensity score matching was performed to minimize the intergroup difference in baseline characteristics
Results

• A total of 662 CLI patients were registered. (n = 562 in the revascularization group, and n = 100 in the non-revascularization group)

• 94.4% of patients (625/662) completed the one-year follow-up.

• Death was observed in 33.7% of patients (223/662).
One-year survival rate in both groups

\[ P = 0.007 \]

\[ P = 0.120 \]
Impact of revascularization on mortality in subgroups

Interaction effect

- Non-older age
- Non-HF
- Rutherford 5 or 6

Above variables are in favor for revascularization
What we learn from Priority registry?

Revascularization should be performed with knowledge of those patient’s risk.
Surgical reconstruction versus Peripheral Intervention in patients with Critical limb ischemia - prospective multicenter registry in Japan: The SPINACH registry

Osamu Iida, MD, Mitsuyoshi Takahara, MD, PhD, Yoshimitsu Soga, MD, PhD, Akio Kodama MD, PhD, Hiroto Terashi, MD, PhD, Nobuyoshi Azuma, MD, PhD, on behalf of the SPINACH investigators.

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5) Kobe University Graduate school of Medicine, Department of Plastic Surgery, Kobe, Japan
6) Department of Vascular Surgery, Asahikawa Medical University, Asahikawa, Japan

Methods

**Objective**: To investigate 3-year outcome compared between EVT and BSX for patients with critical limb ischemia in real-world settings

**Primary endpoint**: Amputation-free survival at 3 years compared between EVT and BSX groups

**Statistical analysis**: The propensity score matching was performed to minimize the intergroup difference in baseline characteristics
Results

- A total of **548** CLI patients were followed. (n = **351** in the EVT group, and n = **191** in the BSX group)
- **80%** of patients (n = 437) completed the three-year follow-up.
- Major amputation and death were observed in **47** and **237** patients, respectively.
Primary endpoint: **Amputation-free survival**

![Graph showing amputation-free survival over time](image)

- **Follow-up period (months)**: 0, 6, 12, 18, 24, 30, 36
- **Amputation-free survival**
- **Number at risk**:
  - Surg group: 149, 123, 114, 104, 92, 75, 49
  - EVT group: 295, 237, 197, 161, 139, 114, 60
- **P-value**: 0.26

<table>
<thead>
<tr>
<th>Follow-up period (months)</th>
<th>Surg group</th>
<th>EVT group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>6</td>
<td>84%</td>
<td>86%</td>
</tr>
<tr>
<td>12</td>
<td>79%</td>
<td>76%</td>
</tr>
<tr>
<td>18</td>
<td>74%</td>
<td>67%</td>
</tr>
<tr>
<td>24</td>
<td>66%</td>
<td>60%</td>
</tr>
<tr>
<td>30</td>
<td>58%</td>
<td>55%</td>
</tr>
<tr>
<td>36</td>
<td>52%</td>
<td>52%</td>
</tr>
</tbody>
</table>
EVT or BSX? (Risk stratification)

<table>
<thead>
<tr>
<th>Factors less favorable for surgical reconstruction (-1 point for each)</th>
<th>Factors more favorable for surgical reconstruction (+1 for each)</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Non-adherence to CV risk management</td>
<td>✓ WIfI Classification W-3</td>
</tr>
<tr>
<td>✓ Hemoglobin &lt; 10 g/dL</td>
<td>✓ WIfI Classification fI2/3</td>
</tr>
<tr>
<td>✓ Diabetes mellitus</td>
<td>✓ History of minor amputation</td>
</tr>
<tr>
<td>✓ Renal failure (including Dialysis)</td>
<td>✓ Prior revascularization after CLI onset</td>
</tr>
<tr>
<td>✓ Contralateral major amputation</td>
<td>✓ Bilateral CLI</td>
</tr>
</tbody>
</table>

![Graph showing hazard ratio of EVT for primary outcome]
What we learn from SPINACH registry?

Surgical reconstruction should be considered for CLI patients with concomitant of infection and large ulcer.
Angiosome is an anatomical concept, defined as the blood supply from a main, secondary or distributing artery to a specific tissue area.

## 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity PAD: Executive Summary

### Recommendation for Revascularizations for CLI

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-NR</td>
<td>In patients with CLI, revascularization should be performed when possible to minimize tissue loss (260).</td>
</tr>
<tr>
<td>I</td>
<td>C-EO</td>
<td>An evaluation for revascularization options should be performed by an interdisciplinary care team (Table 8) before amputation in the patient with CLI.</td>
</tr>
</tbody>
</table>

### 9.1.1. Endovascular Revascularization for CLI

<table>
<thead>
<tr>
<th>Recommendations for Endovascular Revascularization for CLI</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-R</td>
<td>Endovascular procedures are recommended to establish in-line blood flow to the foot in patients with nonhealing wounds or gangrene (242, 243).</td>
</tr>
<tr>
<td>IIa</td>
<td>C-LD</td>
<td>A staged approach to endovascular procedures is reasonable in patients with ischemic rest pain (261, 262).</td>
</tr>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>Evaluation of lesion characteristics can be useful in selecting the endovascular approach for CLI (263, 264).</td>
</tr>
<tr>
<td>IIb</td>
<td>B-NR</td>
<td>Use of angiosome-directed endovascular therapy may be reasonable for patients with CLI and nonhealing wounds or gangrene (245, 247-249, 251-253, 255-257).</td>
</tr>
</tbody>
</table>
Wound-directed Angiosome Revascularization approach to patients with critical limb ischemia - Prospective multicenter international observational study: The WARRIORS Registry

Principal investigator:
Osamu Iida, MD, and Nobuyoshi Azuma, MD
In order to select appropriate treatment for CLI cases, we needed original research in Japan.

- **CQ-1**: Revascularization would improve CLI mortality?
- **CQ-2**: EVT is clinically comparable to surgery in CLI Pt?
- **CQ-3**: Angiosome yes or no?

**Pros. study** (Cleared)

**Retro. study** (Cleared)
In order to select appropriate treatment for CLI cases, we needed original research in Japan.
Decision making of treatment strategy in patients with CLI
- Learn from Priority and SPINACH study -

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