Overview of CLI treatment
Evidence vs. Experience

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Disclosure

Speaker name: Osamu Iida, MD

I have the following potential conflicts of interest to report:

- [ ] Consulting
- [ ] Employment in industry
- [ ] Stockholder of a healthcare company
- [ ] Owner of a healthcare company
- [X] I do not have any potential conflict of interest
Three clinical questions in CLI era

- Revascularization vs. medication
- Angiosome Concept Yes or No?
- Endovascular Tx vs. Surgical Tx
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

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One-year survival rate in both groups

- Revascularization: $P = 0.007$
- Non-revascularization: $P = 0.120$
Impact of revascularization on mortality in subgroups

Advantage of revascularization is found in subgroup with below variables.

1. Non-older age
2. Non-HF
3. Rutherford 5 or 6

In other words, poor-risk CLI patients with

1. Old age (M>85, F>90)
2. HF
3. rest pain

should be carefully considered for revascularization
What we learn from Priority registry?

Advantage of revascularization would attenuate in poor-risk CLI patients with 1) older age, 2) heart failure, and 3) rest pain.
Angiosomes of the lower extremity

Angiosome is an anatomical concept, defined as the blood supply from a main, secondary or distributing artery to a specific tissue area.

### Quality of intervention would impact wound healing

<table>
<thead>
<tr>
<th>Angiosome</th>
<th>Pedal Arch Angioplasty</th>
<th>Wound brush</th>
<th>Indigo carmine angiography</th>
<th>Vascular Flow Reserve (VFR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iida O.</td>
<td>Kawarada O.</td>
<td>Nakama T.</td>
<td>Utsunomiya M.</td>
<td>Higashimori A.</td>
</tr>
</tbody>
</table>

**Direct flow by revascularization to angiosome-related artery is important.**

**Indirect flow by revascularization is good enough.**

**Adjunctive pedal arch angioplasty improved the 1-year rate of wound healing.**

**Wound blush is the most important endpoint to predict ulcer healing.**

**Indigo carmine angiography can be considered an important predictor for wound healing by EVT in patients with CLI.**

**VFR is useful in clinical risk stratification for patients with CLI after EVT.**

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Although there are several concepts and endpoints assessed its impact on limb-related outcomes in BTK revascularization, these still have insufficient power for definitive recommendations.
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
The number of patients enrolled

- BSX
- EVT

- Oct 2017
- Nov 2017
- Dec 2017
- Jan 2018
- Feb 2018
- Mar 2018
- Apr 2018
- May 2018
- Jun 2018
- Jul 2018
- Aug 2018
- Sep 2018
- Oct 2018
- Nov 2018
- Dec 2018

- 40
- 169
- 209
Surgical reconstruction versus Peripheral Intervention in pAtients with Critical limb ischHemia - prospective multicenter registry in Japan:

The SPINACH registry

Osamu Iida, MD¹, Mitsuyoshi Takahara, MD, PhD², Yoshimitsu Soga, MD, PhD³, Akio Kodama MD, PhD⁴, Hiroto Terashi, MD, PhD⁵, Nobuyoshi Azuma, MD, PhD⁶, 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

Primary endpoint: Amputation-free survival at 36 months
EVT or BSX? (Risk stratification)

**Factors less favorable for surgical reconstruction** (-1 point for each):
- Non-adherence to CV risk management
- Hemoglobin < 10 g/dL
- Diabetes mellitus
- Renal failure (including Dialysis)
- Contralateral major amputation

**Factors more favorable for surgical reconstruction** (+1 for each):
- WIfI Classification W-3
- WIfI Classification fI2/3
- History of minor amputation
- Prior revascularization after CLI onset
- Bilateral CLI

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Case 55 yrs, Male, W3fI2I2

History
- ESRD on hemodialysis, Hypertension,
- AP (undergo bypass surgery), AF,
- Nondrinking, Nonsmoking,
- ADL: ambulatory

Medication
- Aspirin 100mg, Clopidogrel 75mg, Warfarin 2mg,
- Rabeprazole 10mg, Bisoprolol fumarate 3mg,
- Cinacalcet hydrochloride 25mg, Telmisartan 20mg
Choice of revascularization

Factors **less favorable** for surgical reconstruction (-1 point for each)

- Non-adherence to CV risk management
- Hemoglobin < 10 g/dL
- Diabetes mellitus
- Renal failure (including Dialysis)
- Contralateral major amputation

Factors **more favorable** for surgical reconstruction (+1 for each)

- WIfI Classification W-3
- WIfI Classification fI2/3
- History of minor amputation
- Prior revascularization after CLI onset
- Bilateral CLI

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Because of extremely poor BTA run-off, surgical approach is considered as first line therapy for this type of patient in the view of durability and sustained sufficient blood flow.
Time course of ischemic wound after bypass surgery

Judging from this time course of wound healing, treatment with both durable and sufficient blood supplying to the ischemic and infective wound is clinically mandatory for accomplishing wound healing.
What we learn from **SPINACH** registry?

Surgical reconstruction should be considered for CLI patients with severe wound status.
Case 68 yrs, Male, W2I3fI2

History

- Hypertension, Diabetes mellitus
- CI (cerebral infarction)
- Complete AV block (post pacemaker)
- ADL: ambulatory

Medication

- Aspirin 100mg, Clopidogrel 75mg,
- Amlodipine 5mg, Lansoprazole 15mg
- Sitagliptin 50mg, Glimepiride 1mg,
## Choice of revascularization

### Factors less favorable for surgical reconstruction (-1 point for each)
- Non-adherence to CV risk management
- Hemoglobin < 10 g/dL
- Diabetes mellitus
- Renal failure (including Dialysis)
- Contralateral major amputation

### Factors more favorable for surgical reconstruction (+1 for each)
- WIfI Classification W-3
- WIfI Classification fI2/3
- History of minor amputation
- Prior revascularization after CLI onset
- Bilateral CLI

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![Graph showing quartiles of favorability score for surgery](image)
Anatomical features (TASC II A) are easily treated by endovascular approach.
What we learn from this case is that endovascular approach is suitable for case with endo-treatable anatomical feature, though it is high risk for major amputation based on our SPINACH stratification score.
Sub analysis from SPINACH study

The association of preoperative characteristics with the **re-intervention risk**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unadjusted hazard ratio (univariate model)</th>
<th>Adjusted hazard ratio (multivariate model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVT (versus surgical reconstruction)</td>
<td>1.52 [1.15-2.01] *</td>
<td>1.51 [1.13-2.01] *</td>
</tr>
<tr>
<td>Hemoglobin (per 1 g/dL)</td>
<td>0.92 [0.85-1.00] *</td>
<td>0.96 [0.88-1.04]</td>
</tr>
<tr>
<td>Renal function (versus eGFR ≥60 mL/min/1.73 m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR &lt;30 mL/min/1.73 m² / On regular dialysis</td>
<td>1.94 [1.35-2.78] *</td>
<td>1.74 [1.20-2.54] *</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.42 [1.04-1.95] *</td>
<td>1.22 [0.88-1.69]</td>
</tr>
<tr>
<td>History of revascularization after CLI onset</td>
<td>1.65 [1.05-2.57] *</td>
<td>1.68 [1.06-2.67] *</td>
</tr>
<tr>
<td>Bilateral CLI</td>
<td>2.01 [1.42-2.85] *</td>
<td>1.83 [1.28-2.61] *</td>
</tr>
<tr>
<td>TASC II aorto-iliac classification</td>
<td>0.95 [0.85-1.07]</td>
<td>N/I</td>
</tr>
<tr>
<td>TASC II femoro-popliteal classification</td>
<td>0.95 [0.87-1.03]</td>
<td>N/I</td>
</tr>
<tr>
<td>TASC infrapopliteal classification</td>
<td>1.01 [0.87-1.18]</td>
<td>N/I</td>
</tr>
</tbody>
</table>

In our SPINACH population, EVT itself was significantly associated with increasing risk of re-intervention. Durable devices especially in below-the-knee and -ankle treatment will be needed.

Iida O, et al. submitted
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.

Case: 60 yrs, male, CLI with recurrent ulcer

Initial angiogram

Lt. SFA

Lt. Pop

Lt. BTK

Recurrent ulcer after EVT and TMA.
DCB treatment for femoropopliteal segment

After pre-dilatation

IN.PACT Admiral 4.0*150 mm
For distal popliteal to proximal SFA
Final angiogram (after DCB angioplasty)

Slow flow phenomenon was found after DCB therapy and ischemic wound was temporarily worsened (day 2).
Follow-up angiogram (day 21)

Lt. SFA

Lt. BTK

Lt. Pop
## Baseline characteristics (DCB Tx vs. conventional Tx)

<table>
<thead>
<tr>
<th></th>
<th>DCB Tx (n=45)</th>
<th>Conventional (n=735)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>119±88</td>
<td>631±572</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>75±10</td>
<td>74±10</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>22.6±4.5</td>
<td>21.4±3.7</td>
</tr>
<tr>
<td>Non-ambulatory status, n (%)</td>
<td>15 (34)</td>
<td>324 (44)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>29 (67)</td>
<td>482 (66)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>14 (33)</td>
<td>130 (18)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>27 (63)</td>
<td>491 (67)</td>
</tr>
<tr>
<td>Hemodialysis, n (%)</td>
<td>23 (51)</td>
<td>398 (54)</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>31 (69)</td>
<td>325 (44)</td>
</tr>
<tr>
<td>Chronic heart failure, n (%)</td>
<td>9 (20)</td>
<td>84 (19)</td>
</tr>
<tr>
<td>Rutherford classification, n (%)</td>
<td>R5</td>
<td>36 (80)</td>
</tr>
<tr>
<td></td>
<td>R6</td>
<td>9 (20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>162 (22)</td>
</tr>
</tbody>
</table>
Wound healing rate (DCB Tx vs. conventional Tx)

Log rank
P=0.14

Follow-up period (month)

Wound healing rate

DCB Tx
Conventional Tx
Conclusions

- The SPINACH study demonstrated that the 3-year AFS were not different between the two treatment strategies in the overall population.

- The subsequent interaction analysis suggested that CLI with severe wound status might be more suited for surgical reconstruction, while those with a poor general condition might benefit more from EVT in terms of AFS.

- What we should do next is to establish anatomical classification (BTK and BTA) in the era of drug-solution.