What are the right clinical trial endpoints for CLTI?

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COI Disclosure

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I have the following potential conflicts of interest to report:

- Consulting; BD, Boston Scientific, COOK, Medtronic, Century Medical Inc., Cordis, NIPRO, OrbusNeich
- Employment in industry
- Stockholder of a healthcare company
- Owner of a healthcare company
- Other(s): Honorarium: Abbot Vascular, Asahi Intecc., Boston Scientific, BD, COOK, Cordis, KANEKA, NIPRO, Medtronic, OrbusNeichi, Terumo
What are the right endpoints of CLTI patients
In the clinical settings, “endpoint” = purpose of treatment

- ✓ Limb salvage
- ✓ Free from pain
- ✓ Wound healing
- ✓ Survival
In the nationwide CLTI registry in the world

<table>
<thead>
<tr>
<th>Study name</th>
<th>OLIVE</th>
<th>SPINACH</th>
<th>RENDEZVOU</th>
<th>J-BEAT</th>
<th>PRVENT III</th>
<th>CIRCULASE</th>
<th>BASIL</th>
<th>CRITISH</th>
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</thead>
<tbody>
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<td>EVT</td>
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<td>BSX+Drug</td>
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<td>BSX</td>
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</tbody>
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| Age>80 yrs     | 26%   | 18%     | 18%       | 18%    | 18%        | 26%       | 63%   | 68%     |
| Male           | 65%   | 66%     | 72%       | 68%    | 69%        | 65%       | 66%   | 63%     |
| DM             | 71%   | 74%     | 73%       | 73%    | 71%        | 62%       | 39%   | 48%     |
| Hemodialysis   | 52%   | 51%     | 51%       | 62%    | 64%        | 10%       | 10%   | 5%      |
| Tissue loss    | 88%   | 88%     | 85%       | 100%   | 74%        | 74%       | 75%   | 78%     |
| Isolated BTK lesions | 42% | 77%     | 75%       | 53%    | 100%       |           |       |         |
| 1-year AFS     | 74%   | 52%@3-year | 74%  | 71%    | 74.0% - 79.9% | 75%         | 72%   |         |

*Courtesy from Dr. Iida O. And make small modify*
CLTI is the end-stage of atherosclerotic disease
High aged, frail, with severe comorbidities
Dedicated purpose of treatment should be defined for each CLTI patients in daily clinical practice.
In the scientific field (for clinical trial): dedicated endpoint setting should be needed
The RENDEZVOUS registry proved the implication of Inframalleolar intervention.

Our hypothesis is “IM angioplasty may improve the wound healing rate.”
Wrong endpoint setting sometimes make strange result
Hot topics of the CLTI revascularization
BASIL-2 trial

A vein bypass first versus a best endovascular treatment first revascularisation strategy for patients with chronic limb threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal revascularisation procedure to restore limb perfusion (BASIL-2): an open-label, randomised, multicentre, phase 3 trial


BEST CLI trial

Surgery or Endovascular Therapy for Chronic Limb-Threatening Ischemia


Randomized control trial

Surgical bypass vs. endovascular therapy


Surgery or Endovascular Therapy for Chronic Limb-Threatening Ischemia

Best CLI trial: Surgical bypass is superior to endovascular therapy.

Basil-2 trial: Endovascular therapy is superior to surgical bypass.

Two large-scale randomized trials showed different results.


A vein bypass first versus a best endovascular treatment first revascularisation strategy for patients with chronic limb threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal revascularisation procedure to restore limb perfusion (Basil-2 trial) - a randomised, multicentre, phase 3 trial.
**BEST CLI trial**

Surgery of Endovascular Therapy for Chronic Limb-Threatening Ischemia


**Primary endpoint**

**MALE free survival**
Defined as composite of

✓ major amputation
✓ re-intervention


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**BASIL-2 trial**

Primary endpoint

Amputation free survival
Defined as composite of

✓ major amputation
✓ any cause of death


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A vein bypass first versus a best endovascular treatment first randomized trial in patients with chronic limb threatening ischemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal revascularization procedure to restore limb perfusion (BASIL-2): an open-label, randomised, multicentre, phase 3 trial

A vein bypass first versus a best endovascular treatment first review: a randomised controlled trial of 893 patients with chronic limb threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infrainguinal revascularisation procedure to restore limb perfusion (BASIL-2): an open-label, randomised, multicentre, phase 3 trial


Primary endpoint
MALE-free survival
Defined as composite of
✓ major amputation
✓ re-intervention

Amputation-free survival
Defined as composite of
✓ major amputation
✓ any cause of death
Impact of each endpoint is completely different!!!
Blood supply difference between bypass and EVT

Blood supply to wounds

- **Onset of CLTI**
- **Bypass**
- **EVT**
- **Time**

- **Peak after the bypass**
  - Stronger point of the bypass is higher volume of blood supply and longer durability than EVT.

- **Peak after the EVT**
  - Blood supply after EVT is poor, durability is insufficient. However, stronger point of EVT is low-invasiveness and repeatability.
Repeat EVT is not clinical failure!

✓ In daily clinical settings, clinical success cases (Achievement of Limb salvage, amputation free survival and complete wound healing) after repeat EVT is frequently observed!!

✓ Re-intervention is **NOT a clinical failure** of CLTI management!!

✓ Therefore, **free from re-intervention** should **NOT** be defined as a **MAIN CLINICAL ENDPOINT** of CLTI study, especially in comparison to bypass
What are the right clinical trial endpoints for CLTI

**Amputation free survival**

survival and free-from amputation is main hope for most CLTI patient
Thank you for your kind attention
What are the right clinical trial endpoints for CLTI?

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