Ultrasound-assisted catheter-directed thrombolysis: Does it really work?
The BERNUTIFUL trial

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Disclosure

Speaker name: Rolf P. ENGELBERGER.

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

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2. Indications for early thrombus removal
   2.1. We suggest a strategy of early thrombus removal in selected patients meeting the following criteria: (a) a first episode of acute iliofemoral deep venous thrombosis, (b) symptoms <14 days in duration, (c) a low risk of bleeding, and (d) ambulatory with good functional capacity and an acceptable life expectancy.
   2.2. We recommend early thrombus removal strategies as the treatment of choice in patients with limb-threatening venous ischemia due to iliofemoral deep venous thrombosis with or without associated femoropopliteal venous thrombosis (phlegmasia cerulea dolens).
   2.3. We recommend that patients with isolated femoropopliteal deep venous thrombosis be managed with conventional anticoagulation therapy because there is currently insufficient evidence to support early thrombus removal strategies in this patient population.
3. Techniques for early thrombus removal
   3.1. We suggest percutaneous catheter-based techniques (pharmacologic or
        pharmacomechanical) as first-line therapy for early thrombus removal in
        patients meeting the criteria in 1.1.
   3.2. We suggest a strategy of pharmacomechanical thrombolysis be considered over
        catheter-directed pharmacologic thrombolysis alone if expertise and resources
        are available.
   3.3. We suggest open surgical venous thrombectomy in selected patients who are
        candidates for anticoagulation but in whom thrombolytic therapy is
        contraindicated.
Pharmacomechanical thrombolysis

**PMT**

**AngioJet**  Power Pulse thrombolysis
+ thrombectomy (Venturi effect)

**Trellis**  Fragmentation + local thrombolysis
+ aspiration with embolic protection

**EKOS**  Ultrasound-assisted thrombolysis
Ultrasound-assisted thrombolysis

**Mechanism of Action**

**Ultrasound pulses**
- High frequency (2.2 MHz)
- Low power (0.5 W per element)
- Pulses of varying waveforms

**Fibrin separation**
- Fibrin without Ultrasound
- Fibrin With Ultrasound

**Active drug delivery by acoustic streaming**

Ultrasound-assisted thrombolysis

- EkoSonic MACH4 Endovascular System catheters (EKOS Corporation)
Figure 1  Tip of the ultrasound-assisted thrombolysis catheter, EkoSonic® Endovascular System (EKOS Corporation; Bothell, WA, USA). The catheter is composed of a 5.2-Fr multi-sidehole drug infusion catheter (treatment zone marker delineated with an arrow head) and a microsonic core wire containing the ultrasound elements (marked with small arrows). During ultrasound-assisted thrombolysis, the multi-element ultrasound core wire is placed inside the infusion catheter.
BERNUTIFUL

the BERN Ultrasound-assisted Thrombolysis for Ilio-Femoral deep vein thrombosis versus standard catheter directed thrombolysis trial

• Aim: to investigate if the addition of intravascular high-frequency, low-power ultrasound energy facilitates the resolution of thrombosis during catheter-directed thrombolysis (CDT)

Engelberger, Kucher et al. Circulation Cardiovasc Interv, in press
supported by the Swiss National Science Foundation: 32003B_140804
BERNUTIFUL Methods

• Single center randomized controlled trial

• **Inclusion criteria:**
  – symptomatic proximal DVT involving the iliac and/or common femoral veins with symptom duration of <2 weeks

• **Exclusion criteria:**
  – age <18 y or >75 y; established PTS or previous symptomatic DVT <2 years in the index leg; limb-threatening circulatory compromise; massive PE; active bleeding or increased bleeding risk, intolerance/allergy to study drugs/contrast medium, eGFR <30 mL/min; pregnancy, lactation, or parturition within the previous 30 days; life expectancy <24 months or chronic nonambulatory status
Primary endpoint

Percentage of thrombus load reduction from baseline to 15 hours of CDT according to the length-adjusted thrombus (LAT) score

\[
\text{Thrombolysis in } \% = \left( \frac{\text{total score } \textit{before} \text{ treatment}}{\text{total score } \textit{before} \text{ treatment}} \right) - \left( \frac{\text{total score } \textit{after} \text{ treatment}}{\text{total score } \textit{before} \text{ treatment}} \right) \times 100 \%
\]

Engelberger, Kucher et al. Circulation Cardiovasc Interv, in press
Lengths-adjusted thrombus (LAT) score

- Known distance between 2 radio-opaque ultrasound elements (= 1 ultrasound-segment)
- Scoring for each ultrasound-element
  - 0 point if (near) completely free of filling defects
  - 1 point if partially thrombosed
  - 2 points if (near) completely thrombosed

- Total LAT score = sum of ultrasound-element scores * ultrasound-element lengths in cm
Patients with objectively confirmed **symptomatic acute ilio-femoral DVT** (n=92)

Patients excluded:
- DVT symptom duration >14 days: 20
- Age <18 (2) or >75 years (5)
- Significant bleeding risk, or known coagulation disorder: 3
- Established PTS or previous symptomatic DVT within the last 2 years in the index leg: 3
- Limb-threatening circulatory compromise: 2
- History intracranial bleed: 2
- Pregnancy: 2
- Life expectancy < 24 months or chronic non-ambulatory status: 2
- Inability to tolerate catheter procedure due to severe dyspnea or acute systemic illness: 2
- Major surgery <10 days: 1

**Patients included and Randomized** (N=48, mean age 50±20y, 52% women)

**USAT (n = 24):** 20 mg r-tPA in 15 hours

**CDT (n = 24):** 20 mg r-tPA in 15 hours

**Primary endpoint (assessed by blinded core laboratory):**
Percentage of thrombus load reduction from baseline to 15 hours of catheter thrombolysis

**2nd endpoints (non-blinded):** Adjunctive thrombus removal, stenting rate, bleedings (n=48)

**Follow-up at 3, 6, 12 m (non-blinded):** Duplex for patency, Villalta score for PTS severity, CEAP
BERNUTIFUL Results
Primary Endpoint: Percentage of Thrombus Load Reduction

- **USAT**
  - N=24
  - 55±27%

- **CDT**
  - N=24
  - 54±27%

$p=0.91$
### BERNUTIFUL Results

**Secondary outcomes: Adjunctive therapy**

<table>
<thead>
<tr>
<th>Secondary Outcome</th>
<th>USAT N = 24</th>
<th>CDT N = 24</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjunctive catheter thrombus removal therapy</td>
<td>7 (29%)</td>
<td>11 (46%)</td>
<td>0.37</td>
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<tr>
<td>Adjunctive stenting</td>
<td>19 (80%)</td>
<td>20 (83%)</td>
<td>0.99</td>
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<tr>
<td>Number of implanted stents</td>
<td>1.3±1.0</td>
<td>1.4±1.1</td>
<td>0.67</td>
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BERNUTIFUL Results

Safety outcomes

<table>
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<tr>
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<th>USAT N = 24</th>
<th>CDT N = 24</th>
<th>p</th>
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<tbody>
<tr>
<td>Major bleeding</td>
<td>1 (4.2%)</td>
<td>0</td>
<td>0.99</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>1 (4.2%)</td>
<td>2 (8.3%)</td>
<td>0.99</td>
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BERNUTIFUL Results
Secondary outcomes at 3 months

<table>
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<tr>
<th></th>
<th>USAT N = 24</th>
<th>CDT N = 24</th>
<th>p</th>
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<tbody>
<tr>
<td>Primary patency 3 months</td>
<td>100%</td>
<td>96%</td>
<td>0.33</td>
</tr>
<tr>
<td>Secondary patency 3 months</td>
<td>100%</td>
<td>100%</td>
<td>1.00</td>
</tr>
<tr>
<td>Mean Villalta score 3 months</td>
<td>3.0±3.9 [range 0-15]</td>
<td>1.9±1.9 [range 0-7]</td>
<td>0.21</td>
</tr>
</tbody>
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Conclusions

• A standardized thrombolysis regimen with 20 mg r-tPA over 15 hours for the treatment of patients with acute ilio-femoral DVT is safe and associated with a high degree of thrombus load reduction.

• The addition of high-frequency (2.2 MHz), low-power (0.5 W) intravascular ultrasound did not facilitate thrombus resolution.
Ultrasound-assisted catheter-directed thrombolysis: Does it really work?

• BERNUTIFUL Trial with negative results for patients with acute ilio-femoral DVT
• Potential advantage in non-acute DVT?
• Better results with increased ultrasound energy?
• Better in other vascular beds?
  • RCT in patients with thrombosed infrainguinal native arteries or bypass grafts (ISRCTN72676102) ongoing
  • ULTIMA trial in pulmonary embolism

Thank you for your attention