Why doesn´t existing clinical data initiate a change in the current DVT treatment guidelines?

Dr Michael Lichtenberg, MD, FESC
ARNSBERG VASCULAR CENTER
Disclosure

Speaker name:
Michael Lichtenberg

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
Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Honoraria for lectures:</td>
<td>Inari, Penumbra, Boston Scientific, CR Bard, Veniti, AB Medica, Volcano,</td>
</tr>
<tr>
<td></td>
<td>Optimed GmbH, Straub Medical, Terumo, Biotronik, Veryan</td>
</tr>
<tr>
<td>2. Honoraria for advisory board</td>
<td>Inari, Straub Medical, Biotronik, Veryan, Boston Scientific, Medtronic,</td>
</tr>
<tr>
<td>activities:</td>
<td>Vesper, Vetex, BD Bard</td>
</tr>
<tr>
<td>3. Participation in clinical trials:</td>
<td>Inari, Biotronik, CR Bard, Veryan, Straub Medical, Veniti, TVA Medical,</td>
</tr>
<tr>
<td></td>
<td>Boston Scientific, LimFlow, Terumo</td>
</tr>
<tr>
<td>4. Research funding:</td>
<td>Inari, Biotronik, Boston Scientific, Veryan, Veniti, AB Medica</td>
</tr>
</tbody>
</table>
Venous Thrombus Treatment Options: Traditional Therapy

- Anticoagulation & Compression Stockings only
- Catheter Directed Thrombolysis (CDT)
  - Enhanced CDT (eg, ultrasound)
- Pharmaco-Mechanical Thrombectomy
- Mechanical Thrombectomy
<table>
<thead>
<tr>
<th>Society</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Institute of Healthcare Excellence, 2020 (110)</td>
<td>Consider catheter-directed thrombolytic therapy for people with symptomatic iliofemoral DVT who present with the following: symptoms lasting &lt; 14 d; good functional status; a life expectancy of ≥ 1 y; and a low risk of bleeding</td>
</tr>
<tr>
<td>National Institute of Healthcare Excellence, 2019 (111)</td>
<td>Current evidence on the safety of percutaneous mechanical thrombectomy for acute DVT of the leg shows that there are well-recognized but infrequent complications. For acute iliofemoral DVT, the evidence on efficacy is limited in quality and quantity; therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. For distal DVT that does not extend into the common femoral vein, the evidence on efficacy is inconclusive; therefore, this procedure should only be used in the context of research</td>
</tr>
<tr>
<td>American Society of Hematology, 2020 (66)</td>
<td>In most patients with proximal DVT, the American Society of Hematology guideline panel suggests anticoagulation therapy alone over thrombolytic therapy in addition to anticoagulation (conditional recommendation based on low certainty in the evidence of effects). Remarks: Thrombolysis is reasonable to consider for patients with limb-threatening DVT (phlegmasia cerulea dolens) and for selected younger patients at low risk of bleeding with symptomatic DVT involving the iliac and common femoral veins (higher risk of more severe PTS). Patients in these categories, who value rapid resolution of symptoms, are averse to the possibility of PTS and accept that the added risk of major bleeding may prefer thrombolysis. The use of thrombolysis should be rare for patients with DVT limited to veins below the common femoral vein. For patients with extensive DVT in whom thrombolysis is considered appropriate, the American Society of Hematology guideline panel suggests using catheter-directed thrombolysis over systemic thrombolysis (conditional recommendation based on very low certainty in the evidence of effects)</td>
</tr>
<tr>
<td>European Society of Vascular Surgery, 2021 (112)</td>
<td>In selected patients with symptomatic iliofemoral DVT, early thrombus removal strategies should be considered (Class IIa, Level A). For patients with DVT limited to femoral, popliteal, or calf veins, early thrombus removal is not recommended (Class III, Level B). For patients with DVT treated by early thrombus removal, with or without stent placement, it is recommended that the duration of anticoagulation should be at least as long as if the patients were treated by anticoagulation alone and at the discretion of the treating physician (Class I, Level C).</td>
</tr>
<tr>
<td>American College of Chest Physicians, 2021 (69)</td>
<td>In patients with acute DVT of the leg, anticoagulant therapy alone is suggested over interventional (thrombolytic, mechanical, or pharmacomechanical) therapy (weak recommendation, moderate certainty evidence). Comments: In patients with very severe, limb-threatening DVT (such as those with phlegmasia or threatened venous gangrene), the benefits of more rapid thrombus resolution may outweigh the risk of harm</td>
</tr>
</tbody>
</table>
Ila recommendation!

**Table 2. Classes of recommendations**

<table>
<thead>
<tr>
<th>Class of recommendation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective</td>
</tr>
<tr>
<td>Class II</td>
<td>Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure</td>
</tr>
<tr>
<td>Class IIa</td>
<td>Weight of evidence/opinion in favour of usefulness/efficacy</td>
</tr>
<tr>
<td>Class IIb</td>
<td>Usefulness/efficacy is less well established by evidence/opinion</td>
</tr>
<tr>
<td>Class III</td>
<td>Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful</td>
</tr>
</tbody>
</table>
Conclusions

SIR considers endovascular thrombus removal to be an acceptable treatment option in selected patients with acute iliofemoral DVT. Careful individualized risk assessment, high-quality general DVT care, and close monitoring during and after procedures should be provided.
Endovascular mechanical thrombectomy versus thrombolysis in patients with iliofemoral deep vein thrombosis – a systematic review and meta-analysis

Michael K. W. Lichtenberg¹, Stefan Stahlhoff¹, Katarzyna Młyńczak²,³, Dominik Golicki²,³, Paul Gagne⁴, Mahmood K. Razavi⁵, Rick de Graaf⁶, Raghu Kolluri⁷, and Katarzyna Kolasa⁸

¹ Angiology Clinic, Venous Center Klinikum Arnsberg, Arnsberg, Germany
² Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, Warsaw, Poland
³ HealthQuest, Warsaw, Poland
⁴ The Vascular Experts, Danlen, CT, USA
⁵ Heart and Vascular Center, St Joseph Hospital, Orange, CA, USA
⁶ Clinic for Diagnostic and Interventional Radiology/Nuclear Medicine, Clinical Center of Friedrichshafen, Friedrichshafen, Germany
⁷ Ohio Health Heart and Vascular, Columbus, Ohio, USA
⁸ Health Economics and Healthcare Management Division, Kozminski University, Warsaw, Poland
Included Literature for Metaanalysis

77 records identified by database search

2 potentially eligible studies identified through other sources

79 identified for title and abstract screening

43 excluded
- literature review, commentary, meta-analysis, or protocol

36 full-text articles reviewed

16 excluded
- inadequate intervention (6)
- inadequate thrombus localization (6)
- no results of the intervention (2)
- inadequate study type (2)

20 articles and 19 studies included
- randomized, controlled (7)
- observational (12)
Lysis grade II/III

Meta analysis (random effect models)

Lysis grade II/III

CDT

PMT

n.s.
Recurrent DVT

**Meta analysis** (random effect models)

- **Recurrent DVT**
  - Song 2014 (CDT, 24 mo.)
  - Lee 2018 (CDT, 5 mo.)
  - Zhang 2014 (CDT + heparin, 24 mo.)

**Meta-analysis for thrombolysis** (random effects)

- (I² = 0%)
  - Song 2014 (angiojet, max 7 mo.)
  - Song 2014 (angiojet in cancer, max 8 mo.)
  - Liu 2018 (angiojet + direct stent, 12 mo.)
  - Liu 2018 (angiojet + CDT + staged stent, 12 mo.)
  - Camm 2018 (PCIT, 24 mo.)

**Proportion (95% confidence interval)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Proportion</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang 2014 (CDT, 24 mo.)</td>
<td>0.0158</td>
<td>(0.0035, 0.0454)</td>
</tr>
<tr>
<td>Lee 2018 (CDT, 8 mo.)</td>
<td>0.0385</td>
<td>(0.0010, 0.1964)</td>
</tr>
<tr>
<td>Zhang 2014 (CDT + heparin, 24 mo.)</td>
<td>0.0215</td>
<td>(0.0055, 0.0541)</td>
</tr>
<tr>
<td>Yoon 2018 (angiojet, max 7 mo.)</td>
<td>0.0000</td>
<td>(0.0000, 0.0180)</td>
</tr>
<tr>
<td>Yoon 2018 (angiojet in cancer, max 8 mo.)</td>
<td>0.0000</td>
<td>(0.0000, 0.0090)</td>
</tr>
<tr>
<td>Liu 2018 (angiojet + direct stent, 12 mo.)</td>
<td>0.0435</td>
<td>(0.0053, 0.1434)</td>
</tr>
<tr>
<td>Liu 2018 (angiojet + CDT + staged stent, 12 mo.)</td>
<td>0.0000</td>
<td>(0.0000, 0.0787)</td>
</tr>
<tr>
<td>Camm 2018 (PCIT, 24 mo.)</td>
<td>0.1327</td>
<td>(0.0685, 0.1962)</td>
</tr>
</tbody>
</table>

**PMT**: 0.0448 (0.0045, 0.1233)

**CDT**: n.s.
Overall PTS rate

A Post-thrombotic syndrome

Bias assessment plot

Egger bias = -1.16. 95% CI: -1.66 to -6.5, p < 0.001

PTS

Enden 2012 [CDT] 0.300 (0.208, 0.406)
Engelberger 2017 [CDT] 0.045 (0.001, 0.228)
Haig 2013 [CDT] 0.391 (0.291, 0.499)
Lee 2013 [CDT] 0.192 (0.066, 0.394)
Tichelaar 2016 [CDT] 0.553 (0.401, 0.698)
Engelberger 2017 (USG CDT) 0.174 (0.050, 0.388)
Gombert 2018 (USG CDT) 0.300 (0.147, 0.494)
Tichelaar 2016 (USG CDT) 0.524 (0.298, 0.743)

Metaanalysis for thrombolysis (random effects) 0.311 (0.210, 0.422)
Yoon 2018 [Angiojet] 0.000 (0.000, 0.218)
Yoon 2018 [Angiojet in cancer] 0.000 (0.000, 0.410)
Camrota 2018 [PCDT] 0.490 (0.418, 0.562)
Dopheide 2018 [Angiojet] (modified) 0.091 (0.002, 0.413)
Dopheide 2018 [Ball out Angiojet] (modified) 0.000 (0.000, 0.247)
Dopheide 2018 [Angiojet stent] (modified) 0.500 (0.247, 0.753)

Metaanalysis for PMT (random effects) 0.157 (0.014, 0.412)

CDT

PMT
Moderate/Severe PTS

Meta analysis (random effect models)

PTS moderate/severe

<table>
<thead>
<tr>
<th>Study</th>
<th>Proportion (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engelberger 2017</td>
<td>0.000 (0.000, 0.154)</td>
</tr>
<tr>
<td>Nickel 2016</td>
<td>0.294 (0.128, 0.380)</td>
</tr>
<tr>
<td>Engelbrecht 2017</td>
<td>0.043 (0.001, 0.219)</td>
</tr>
<tr>
<td>Bunkers 2018</td>
<td>0.139 (0.047, 0.275)</td>
</tr>
<tr>
<td>Nickel 2015</td>
<td>0.258 (0.082, 0.472)</td>
</tr>
<tr>
<td>Bunkers 2018 [RCT]</td>
<td>0.127 (0.045, 0.241)</td>
</tr>
<tr>
<td>Bunkers 2018 [PCOR]</td>
<td>0.194 (0.132, 0.245)</td>
</tr>
</tbody>
</table>

$n.s.$

Egger: bias = 1.45 (95% CI: -4.81 to 7.71), p = 0.58
Pulmonary embolism

Meta analysis (fixed effect models)

Pulmonary emboli

Proportion (95% confidence interval)

- Haig 2013 [CDT]
  - 0.0217 (0.0026, 0.0763)

- Lee 2013 [CDT]
  - 0.0000 (0.0000, 0.1323)

- AbuRahma 2001 [CDT]
  - 0.0000 (0.0000, 0.1853)

- Elshefawy 2002 [CDT]
  - 0.0000 (0.0000, 0.1853)

Metsanalysis for thrombolysis (fixed effects)

- (P = 0.0%)
  - 0.0197 (0.0039, 0.0471)

- Liu 2018 [AngioJet + direct stent]
  - 0.0000 (0.0000, 0.0771)

- Liu 2018 [AngioJet + CDT + staged stent]
  - 0.0000 (0.0000, 0.0787)

Metsanalysis for PMT (fixed effects)

- (P = 0.9939)
  - 0.0054 (0.0008, 0.0304)

n.s.
### Safety: Major bleeding complications

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Proportion (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AbuRahma 2001</td>
<td>THR (CDT)</td>
<td>2</td>
<td>18</td>
<td>4.1%</td>
<td>0.11 (0.01 - 0.35)</td>
</tr>
<tr>
<td>Enden 2009</td>
<td>THR (CDT)</td>
<td>2</td>
<td>50</td>
<td>11.0%</td>
<td>0.04 (0.01 - 0.14)</td>
</tr>
<tr>
<td>Enden 2009</td>
<td>THR (CDT)</td>
<td>3</td>
<td>50</td>
<td>19.7%</td>
<td>0.03 (0.01 - 0.09)</td>
</tr>
<tr>
<td>Tichelaar 2016</td>
<td>THR (CDT)</td>
<td>2</td>
<td>62</td>
<td>13.6%</td>
<td>0.03 (0.00 - 0.11)</td>
</tr>
<tr>
<td>Engelberger 2015</td>
<td>THR (CDT)</td>
<td>0</td>
<td>24</td>
<td>5.4%</td>
<td>0.00 (0.00 - 0.14)</td>
</tr>
<tr>
<td>Haig 2013</td>
<td>THR (CDT)</td>
<td>3</td>
<td>92</td>
<td>20.1%</td>
<td>0.03 (0.01 - 0.09)</td>
</tr>
<tr>
<td>Laiho 2004</td>
<td>THR (CDT)</td>
<td>2</td>
<td>16</td>
<td>3.7%</td>
<td>0.13 (0.02 - 0.38)</td>
</tr>
<tr>
<td>Lee 2013</td>
<td>THR (CDT)</td>
<td>2</td>
<td>26</td>
<td>5.8%</td>
<td>0.08 (0.01 - 0.25)</td>
</tr>
<tr>
<td>Engelberger 2015</td>
<td>THR (UA CDT)</td>
<td>1</td>
<td>24</td>
<td>5.4%</td>
<td>0.04 (0.00 - 0.21)</td>
</tr>
<tr>
<td>Tichelaar 2016</td>
<td>THR (UA CDT)</td>
<td>3</td>
<td>33</td>
<td>7.4%</td>
<td>0.09 (0.02 - 0.24)</td>
</tr>
<tr>
<td>Laiho 2004</td>
<td>THR (systemic)</td>
<td>1</td>
<td>16</td>
<td>3.7%</td>
<td>0.06 (0.00 - 0.30)</td>
</tr>
</tbody>
</table>

**Pooled proportion THR (fixed effects)**

- THR (CDT): 21 events, 451 total, proportion: 0.05 (0.03 - 0.07)
- THR (UA CDT): 1 event, 24 total, proportion: 0.04 (0.00 - 0.21)
- THR (systemic): 1 event, 16 total, proportion: 0.06 (0.00 - 0.30)

Cochran's $Q = 8.3, p = 0.06, I^2 = 0$

---

**Pooled proportion PMT (fixed effects)**

- PMT (AngioJet): 3 events, 379 total, proportion: 0.01 (0.00 - 0.03)

Cochran's $Q = 12.4, p = 0.001, I^2 = 0$
### ClotTriever system outcomes in lower extremity DVT patients

**CLOUT Registry in-hospital and 30-day outcomes (N=500)**

#### Session metrics
- **99.4%**
  - Single-session treatment
  - \(n = 499\)
- **40mL**
  - Median estimated blood loss
  - \(n = 446\)
- **0.4%**
  - Adjunctive thrombolytics used
  - Per limb; \(n = 520\)
- **2.2%**
  - Post-procedure ICU stay
  - \(n = 494\)

#### Safety outcomes
- **0.2%**
  - Device-related SAEs
  - \(n = 499\)
- **0**
  - Vessel damage
  - Valve damage
  - Acute kidney injury (AKI)
  - \(n = 424\)

#### 6-month outcomes on 250 patients

- **90%**
  - Flow via duplex ultrasound
  - \(n = 142\)
- **100%**
  - Median reduction in pain
  - \(n = 150\)
- **91%**
  - Free of moderate or severe PTS symptoms*
  - \(n = 160\)

---

1. In-hospital and 30-day Outcomes from the Fully-enrolled Multicenter Prospective CLOUT Registry presented by Dr. David Dexter at VEINS 2022

---

*24.4% of patients had PTS symptoms at 6 months*
(ClinicalTrials.gov Identifier: NCT05740410)

ClinicalTrials.gov Identifier: NCT05740410

Patency@6 months 92%

<table>
<thead>
<tr>
<th>Symptom Improved</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>25</td>
<td>100.0%</td>
</tr>
<tr>
<td>patients</td>
<td>25</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICU stay (days)</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 days</td>
<td>25</td>
<td>100.0%</td>
</tr>
<tr>
<td>patients</td>
<td>25</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
ClinicalTrials.gov Identifier: NCT05740410

Figure 1 – Villalta score (mean ± Standard Deviation) over the course of time.

<table>
<thead>
<tr>
<th>Villalta Score: paired t-test</th>
<th>Baseline</th>
<th>1-month follow-up</th>
<th>6-month follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>7.5 [2.5]</td>
<td>4.4 [2.6]</td>
<td>1.7 [1.4]</td>
</tr>
</tbody>
</table>

Paired t-test:
Baseline vs. 1 month FU: t=4.46, df=16, P<0.001
Baseline vs. 6 month FU: t=10.47, df=24, P<0.001

Wilcoxon test:
Baseline vs. 1 month FU: Z= -3.24, P=0.001
Baseline vs. 6 month FU: Z= -4.33, P<0.001

<table>
<thead>
<tr>
<th>Villalta Score: Wilcoxon test</th>
<th>Baseline</th>
<th>1-month follow-up</th>
<th>6-month follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>8.3 [2.4]</td>
<td>4.4 [2.6]</td>
<td>1.6 [1.3]</td>
</tr>
</tbody>
</table>

No PTS (score < 5)
Baseline 4 (16%) 1-month follow-up 9 (52.9%) 6-month follow-up 24 (96%)
Mld PTS (score 5-9)
Baseline 16 (64%) 1-month follow-up 8 (47.1%) 6-month follow-up 1 (4%)

Significant decrease in patients with PTS symptoms at 30 days

40% ATTRACTION Intervention
27% CLOUT ClotTriever System
Patients with Villalta ≥ 5 P<0.05
ClinicalTrials.gov Identifier: NCT05740410

SAFETY ANALYSIS

<table>
<thead>
<tr>
<th>Adverse Events (AES)</th>
<th>N (%) only patients with AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-stent restenosis target vessel within 30 days</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>Pulmonary embolism (minor symptoms)</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>Post-interventional hematoma</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>Re-thrombosis</td>
<td>1 (6.7%)</td>
</tr>
</tbody>
</table>

No MAEs occurred, and procedural success was attained in 100% of patients. No device-related complications or malfunction occurred during the procedures.
CLOUT Registry in-hospital and 30-day outcomes (N=500)

ClotTriever system outcomes in lower extremity DVT patients

<table>
<thead>
<tr>
<th>Session metrics</th>
<th>Safety outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arnsberg 100%</strong></td>
<td><strong>Arnsberg 0%</strong></td>
</tr>
<tr>
<td><strong>99.4%</strong> Single-session treatment</td>
<td><strong>0.2%</strong> Device-related SAEs</td>
</tr>
<tr>
<td><strong>40mL</strong> Median estimated blood loss</td>
<td><strong>0</strong> Vessel damage, Valve damage, Acute kidney injury (AKI)</td>
</tr>
<tr>
<td><strong>0.4%</strong> Adjuvant thrombolytics used</td>
<td><strong>2.2%</strong> Post-procedure ICU stay</td>
</tr>
<tr>
<td><strong>Arnsberg 0%</strong></td>
<td><strong>Arnsberg 96%</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Significant thrombus removal</th>
<th>Sustained benefits at 30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&gt;90%</strong> Complete or near-complete thrombus removal*</td>
<td><strong>&gt;90%</strong> Freedom from moderate to severe PTS symptoms</td>
</tr>
<tr>
<td><strong>Arnsberg 96%</strong></td>
<td><strong>Arnsberg 96%</strong></td>
</tr>
</tbody>
</table>

6-month outcomes on 250 patients2

- **90%** Flow via duplex ultrasound
- **100%** Median reduction in pain
- **91%** Free of moderate or severe PTS symptoms

*24.4% of patients had PTS symptoms at 6 months

1. In-hospital and 30-day outcomes from the multi-centred prospective CLOUT registry presented by Dr. David Dexter at VHRM 2022
With the safety profile of ClotTriever system, why not consider an intervention-first strategy?

**Traditional Management (AC or Lytics)**

- **No mechanism of action** to address older, chronic clot. And **clot is often older than symptoms suggest.**

- **Up to 50% of patients have RVO**, leading to higher risk of death, recurrent VTE, and PTS

- **Up to 50% of patients develop PTS**

- **Bleeding risk** of lytics

**ClotTriever® System in the ARNSBERG Registry**

- **Effective thrombus removal across all thrombus ages/chronicity**

- **96% freedom from moderate to severe PTS symptoms at 6 months**

- **0 device-related SAEs, 0 valve damage, 0 vessel damage**

---

Conclusions

• Current guidelines are not able to keep with speed of new evidence
  • They may give advise for general treatment
  • Can not include latest technology steps

• Many new PMT devices need prospective data
  • Early stage data are very promising

CDT should be stopped for treatment of iliofemoral DVT