Post – thrombotic Syndrome: 
do We Know the Predictive Factors ?

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Disclosures

□ X - No

Post-thrombotic syndrome (PTS)

Valve damage

Vein obstruction

PTS

Even if we know the pathology ...

......still some doubts how to define and describe PTS ?

/PTS criteria ?/

Post-thrombotic syndrome

10 – 70% of patients after DVT (depends on the way of assessment)

Severe PTS 8 – 14 %

Ulceration 1 – 6 %

Time 3-10 yrs. (mostly 1-2 yrs. after DVT)

PTS severity assessment (Villalta scale)

Symptoms

Pain

Cramps

Heaviness

Pruritus

Paresthesia

Signs

Oedema

Skin induration

Hyperpigmentation

Vein eczema

Redness

Pain during calf compression

0 - absent, 1 – mild, 2 - moderate, 3 - severe

0 – 4: no PTS

5 – 14: mild/moderate PTS

15 or more, or presence of ulcer: severe PTS

PTS assessment

Villalta scale
Villalta /+ visually assisted form/

Ginsberg criteria
- Pain and swelling of limb of ≥ 1 mo. duration, typical character (worse end of day or after prolonged sitting/standing, better after night's rest and leg elevation) that occurs ≥ 6 months after acute DVT
- Objective evidence of valvular incompetence (diagnosed via plethysmography or venous Doppler)

Brandjes score
- 8 subjective criteria – symptoms, 7 objective criteria – signs; score results over two consecutive visits, 3 months apart

PTS non-specific: VCSS, Widmer, CEAP

PTS predictive factors?

SOX trial (class II vs placebo stocking after DVT episode)

PTS in placebo arm:
- Ginsberg criteria (used for primary endpoint assessment): 12.7%
- Villalta scale (secondary endpoint assessment): 52.3%

Use of anticoagulant therapy?

- Probably does not actively dissolve the clot
- 10-30% of patients with proximal clot propagation
- Probably does not prevent valve damage
- Probably does not prevent directly post-thrombotic syndrome
- But decrease the risk of recurrence!

DVT recurrence (ipsilateral)
Post-thrombotic syndrome risk 3-6x

Other risk factors related to PTS occurrence?

Factors related to the patient initial status:
- Trombophilia -
- Sex +/-
- Age ++
- Obesity ++
- Pre-existing varicose veins ++

Factors related to the initial DVT characteristics:
- Symptomatic DVT vs Asymptomatic +/-
- Provoked DVT vs Unprovoked -
- DVT location /massive proximal vs. distal/ * ++

*But distal DVT does not exclude PTS occurrence

Kahn SR. Lancet 2014; 8: 383: 880-8

Other risk factors related to PTS occurrence?

Factors related to the treatment phase

- Duration of anticoagulation
- Intensity of VKA anticoagulation

"Residual thrombosis" (non complete recanalization and thrombus resolution) +

Incomplete resolution of the symptoms within 1st month of the treatment +

Poor INR control in the treatment phase ++

LMWH vs VKA (in favor of LMWH) +

Can we avoid it?

"Open vein" concept?

- Surgical thrombectomy
- Local thrombolysis

Venous thrombectomy (+/- costs)

<table>
<thead>
<tr>
<th>No</th>
<th>follow up (months)</th>
<th>iliac vein patency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plate (1984)</td>
<td>31</td>
<td>6</td>
</tr>
<tr>
<td>Piquet (1984)</td>
<td>57</td>
<td>19</td>
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<tr>
<td>Einarsson (1986)</td>
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<td>10</td>
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<tr>
<td>Vollmar (1988)</td>
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<td>53</td>
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<tr>
<td>Jhun (1990)</td>
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<td>102</td>
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<td>Roessmann (1990)</td>
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<td>20</td>
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<tr>
<td>Eloit/Kornier (1996)</td>
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<td>48</td>
</tr>
<tr>
<td>Neglen (2005)</td>
<td>34</td>
<td>24</td>
</tr>
<tr>
<td>Meissner (1996)</td>
<td>27</td>
<td>12</td>
</tr>
</tbody>
</table>

Insufficient data about subsequent valve injury

Invasiveness of the procedure

Limited access to the experience centres

Local thrombolysis

- Minimal invasive (+/-)
- Relief of DVT related symptoms (+)
- Vein patency restoration (+)

Valve function preservation (?)
Post-thrombotic syndrome avoidance (?)
RCTs: loco-regional thrombolytic treatment (CDT)

PTS in CDT group ↓ - 14.4%

<table>
<thead>
<tr>
<th>CDT (%; 95% CI)</th>
<th>Standard treatment (%; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTS @ 24 months</td>
<td>41.1% (31.5 - 51.4) 55.6% (45.7 - 65.0) p=0.047</td>
</tr>
<tr>
<td>Iliofemoral patency at 6 months</td>
<td>65.9% (55 - 75) 47.4% (37.6-57.3) p=0.012</td>
</tr>
</tbody>
</table>

Ilio-femoral DVT: 209 pts.

Mean time of CDT duration - 2,4 days (+/- SD 1,1)

Additional procedures - 39 pts. (23 PTA/15 Stent)

rt-PA 0.01 mg/kg /h max 96 h / ≤ 20 mg /24h /

Primary Outcome Measures:
- Patency after 6 months [Time Frame: 6 months ]
- Post-thrombotic syndrome after 2 years (yrs) [Time Frame: 2 years ]

CaVenT study
Long-term outcome of loco-regional catheter directed thrombolysis versus standard treatment for acute iliofemoral deep venous thrombosis (the CaVenT study): a randomised controlled trial.

Enden T et al. Lancet 2012

Randomization
337 pts. - catheter-directed thrombolysis* vs 355 pts. - anticoagulation alone.

PTS 46.7% vs 48.2% (p=0.56) **

* Catheter-directed rt-PA infusion for up to 24 hours at 0.01 mg/kg/hr (maximum 1.0 mg/hr) via a multisidehole infusion catheter
- Trellis-8 Peripheral Infusion System
- AngioJet Rheolytic Thrombectomy System

What is new in the pharmacotherapy in term of PTS prevention ?

- DOACs* improve the compliance to the effective anticoagulant treatment
  - no need of INR control
  - simplified therapy
  - high clinical efficacy and safety

DOACs and PTS rate decrease ?

DOACs (rivaroxaban) and PTS
Post hoc subgroup analysis of the Einstein DVT trial

Rivaroxaban – 162 pts. (48 %) vs enoxaparin/VKA - 174 pts. (52 %)

PTS cumulative incidence at 60 months follow-up:
29 % /rivaroxaban/ vs 40 % /enoxaparin/VKA group/
adjusted HR 0.76 (95 % CI: 0.51–1.13; p=0.18)*

*Adjusted for covariates: age, gender, body mass index, previous PTS, ipsilateral recurrent DVT, extent of DVT, idiopathic DVT, duration of anticoagulant treatment, compliance to assigned study medication, elastic compression stocking use and active malignancy
DOACs and PTS?

Rivaroxaban (61 pts.) vs Warfarin (39 pts.)
Follow up: 23 months (median) after DVT episode

PTS (Villalta scale): 25% - rivaroxaban vs. 49% - warfarin /p=0.013/
OR 2.9 (1.2-6.8; p=0.014) for PTS development in warfarin group (compared to rivaroxaban)
adjusted OR 3.5 (1.1-11.0; p=0.035).

CONCLUSIONS:
Treatment of DVT with rivaroxaban might be associated with a lower risk for PTS development. A larger randomized trial would be needed for stronger evidence.


What is new in the pharmacotherapy in term of PTS prevention?

• DOACs
• Other drugs?

SULODEXIDE in Post-thrombotic syndrome prevention

The patients enrolled after termination of anticoagulation treatment
5 years follow up

Group 1 167 pts. - standard management - no coagulation
Group 2 124 pts. - sulodexide
Group 3 48 pts. - ASA

Conclusion: Sulodexide administration after DVT appears to be effective in preventing PTS

PTS evaluation based on scoring of:
- swelling
- pain
- heaviness
- itching
- microcirculatory alteration
- permanent skin changes
>10 points = PTS

PTS after 48 months (mean): CS - 28% vs Control - 49%
NNT 5 (3-11)


Compression use after DVT episode for postthrombotic syndrome avoidance?

Class II ECS vs „Placebo stockings”
Post-thrombotic syndrome /Ginsberg Criteria/

Randomization:
ECS - 410 pts vs Placebo ECS
Active ECS: Knee – length
30-40 mmHg compression.

Primary outcome - the cumulative incidence of PTS from 6 to 24 months follow up

Cumulative incidence of PTS
14.2%/active ECS/ vs. 12.7%/placebo ECS/ /p=1.3, HR 0.57 95%CI 0.36-0.92/p=0.03/

In patients with acute DVT of the leg, we suggest not using compression stockings routinely to prevent PTS (Grade 2B).

Comments:
But this does not mean that CS should be not used in symptomatic patients. Further studies needed to emphasize the role of CS in PTS prevention should be designed with proper methodological criteria.
“...it is still not possible to reliably predict, on an individual basis, who will and who will not develop PTS.”


...but further research on PTS required

- Development of PTS risk prediction models
- Evaluation of the role of risk factor modification (e.g., weight reduction)
- The role of CDT and PCDT in PTS prevention
- The role of compression in PTS prevention
- The efficacy of the new anticoagulants in PTS prevention
- Upper extremity PTS prevention
- Pediatric patient PTS prevention