OPEN CHALLENGES IN POST-THROMBOTIC PATIENT MANAGEMENT

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Post-thrombotic syndrome

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

Severe PTS 6 – 11%
Ulceration 1 – 6%

Time of symptoms occurrence: 1-10 yrs. /mostly 1-2 yrs. after DVT/


- 1 year - 17.3% (severe PTS - 3%)
- 2 years - 23%
- 5 years - 28% (severe PTS - 9%)

PTS – do we really know the definition?
Post-Thrombotic Syndrome (PTS)

„....chronic venous symptoms and/or signs secondary to deep vein thrombosis.....”

PTS severity assessment (Villalta scale)

**Symptoms**
- Pain
- Cramps
- Heaviness
- Pruritus
- Paresthesia

/patient self reported/

**Signs**
- Oedema
- Skin induration
- Hyperpigmentation
- Venous ectasia
- Redness
- Pain during calf compression

/clinician assessment/

0 - 4: no PTS
5 – 14: mild (5-9) /moderate (10-14) PTS
15 or more, or presence of ulcer: severe PTS

VILLALTA SCORE

Prandoni 1996
Van Dongen 2005
Tick 2008
Kahn 2005
Roumen – Klappe 2009
Kahn 2002
Kahn 2011
Prandoni 1997
Kahn 2008
Kahn 2011
Kahn 2014
O’Donnell 2008
Prandoni 2005
Rodger 2008
Kolbach 2005
Kahn 2006

PTS Diagnosis
PTS Diagnosis
PTS Diagnosis
PTS Diagnosis
PTS Diagnosis
PTS Diagnosis
PTS Severity assessment
PTS Severity assessment
Long term follow up
Long term follow up
Treatment evaluation
Treatment evaluation
Treatment evaluation
Treatment evaluation
Interobserver reliability
Association with pathophysiology
Association with paholophysiology
PTS definition (present/absent):

- PTS is present if the Villalta score is \( \geq 5 \), or a venous ulcer
- is present, in a leg with previous DVT.

Is the Villalta scale a real „gold standard” in PTS assessment?
• Validated clinical and pathophysiological PTS criteria ?

• Objective PTS definition ?

• Validated PTS markers ?
AN IDEAL SCORING SYSTEM FOR PTS EVALUATION

- Easy to use
- Be acceptable to the patients and medical staff
- Have a good inter-observer reliability *

- Specific
- Validated
- Have a clear association with the pathophysiology
- Be able to categorize the disease according to disease severity and identify improvement or deterioration in the condition

Is Villalta scale specific for PTS?
CVD patients or PTS Patients?
Post-thrombotic syndrome (PTS)
PTS - reflux vs. obturation

US Doppler - 6 months after DVT
/180 pts. with PTS/

24% - no abnormalities in US
48% - „residual thrombosis”
37,5% - reflux
54% - reflux + „residual thrombosis”

PTS predictive factors?
### Risk factors related to PTS occurrence?

**Factors related to the patient initial status:**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Risk Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trombophilia</td>
<td>-</td>
</tr>
<tr>
<td>Sex</td>
<td>+/-</td>
</tr>
<tr>
<td>Age*</td>
<td>++</td>
</tr>
<tr>
<td>Obesity**</td>
<td>++</td>
</tr>
<tr>
<td>Preexisting varicose veins</td>
<td>++</td>
</tr>
</tbody>
</table>


*Older age: ↑ PTS risk from 30% to 3 fold
** BMI>30: More than 2-fold ↑ PTS risk
Risk factors related to PTS occurrence?

Factors related to the patient initial status:

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</table>

Preexisting primary CVD – up to 2-fold ↑ risk of PTS

Pre-existing primary venous insufficiency increases the risk of PTS !!!

376 DVT patients after single lower leg DVT episode

Villalta score

Post DVT leg mean: 3.7 ± 3.4 SD

Contralateral leg (no DVT in the past) mean: 1.9 ± 2.5 SD [P < 0.0001]

Up to 40% of all diagnosed PTS might reflect, at least in part, pre-existing symptomatic chronic venous disease !!!

Ipsilateral PTS (Villalta total score > 4) - 31.6% (n = 116)

39.7% of patients with ipsilateral PTS had a Villalta score > 4 in the contralateral leg

### Other risk factors related to PTS occurrence

Factors related to the initial DVT characteristic:

<table>
<thead>
<tr>
<th>Symptomatic DVT vs Asymptomatic</th>
<th>+/-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provoked DVT vs Unprovoked</td>
<td>-</td>
</tr>
<tr>
<td>DVT location/massive proximal vs. distal/</td>
<td>* ++</td>
</tr>
</tbody>
</table>

*But distal DVT does not exclude PTS occurrence*


<table>
<thead>
<tr>
<th>Study</th>
<th>Procedure</th>
<th>Time (years)</th>
<th>Compression stocking</th>
<th>PTS</th>
<th>Severe PTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mudge 1988</td>
<td>Abdominal surgery</td>
<td>10</td>
<td>Not reported</td>
<td>8%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Francis 1988</td>
<td>THA/TKA</td>
<td>4</td>
<td>Not reported</td>
<td>58%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Andersen, Wille – Jorgensen 1991</td>
<td>Surgery</td>
<td>5</td>
<td>Not reported</td>
<td>19-50%</td>
<td>Not reported</td>
</tr>
<tr>
<td>McNally 1994</td>
<td>THR</td>
<td>5</td>
<td>100%</td>
<td>88%</td>
<td>25%</td>
</tr>
<tr>
<td>Warwick 1996</td>
<td>THR</td>
<td>16</td>
<td>Not reported</td>
<td>47%</td>
<td>3%</td>
</tr>
<tr>
<td>Siragusa 1997</td>
<td>THR/TKR</td>
<td>3</td>
<td>Not reported</td>
<td>24%</td>
<td>2%</td>
</tr>
<tr>
<td>Ginsberg 2000</td>
<td>THR/TKR</td>
<td>5</td>
<td>Not reported</td>
<td>5%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Ginsberg 2001</td>
<td>O</td>
<td>1</td>
<td>Not reported</td>
<td>4%</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
Other risk factors related to PTS occurrence?

Factors related to the initial DVT characteristic:

- Symptomatic DVT vs Asymptomatic: +/-
- Provoked DVT vs Unprovoked: -
- DVT location /massive proximal vs. distal/: * ++
  
  * 2-3 fold ↑ risk after proximal DVT
  /especially iliac or common femoral vein than distal (calf) DVT/

Post-thrombotic Syndrome
Proximal vs Distal DVT

Higher risk in proximal DVT

No differences (proximal vs distal DVT)
Other risk factors related to PTS occurrence?

Factors related to the treatment phase

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of anticoagulation</td>
<td>-</td>
</tr>
<tr>
<td>Intensity of VKA anticoagulation</td>
<td>-</td>
</tr>
<tr>
<td>Poor INR control in the treatment phase</td>
<td>++</td>
</tr>
<tr>
<td>/especially within first 3 months/</td>
<td></td>
</tr>
<tr>
<td>„Residual thrombosis“ /non complete recanalisation and thrombus resolution/</td>
<td>+</td>
</tr>
<tr>
<td>Incomplete resolution of the symptoms within 1st month of the treatment</td>
<td>+</td>
</tr>
<tr>
<td>LMWH vs VKA /in favor of LMWH/</td>
<td>+</td>
</tr>
</tbody>
</table>

Other risk factors related to PTS occurrence?

Factors related to the treatment phase

- Duration of anticoagulation
- Intensity of VKA anticoagulation

++ Poor INR control in the treatment phase
/especially within first 3 months/

++/- Type of anticoagulation LMWH vs VKA
/in favor of LMWH/

+ „Residual thrombosis” /non complete recanalisation and thrombus resolution/

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


Other risk factors related to PTS occurrence?

Factors related to the treatment phase

Duration of anticoagulation -

Intensity of VKA anticoagulation -

Poor INR control in the treatment phase ++
  /especially within first 3 months/

Type of anticoagulation LMWH vs VKA /in favor of LMWH/ ++/−

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

„Residual thrombosis“ /non complete recanalisation and thrombus resolution/ +

Residual DVT symptoms presence 1 month after the diagnosis of DVT – higher risk of PTS occurrence


Villalta score category at 1 month after DVT and PTS occurrence @ 24 months

- score 5-9: HR 2.74 [95% CI 1.62, 4.64]
- score 10-14: HR 5.81 [95% CI 2.99, 11.29]
- score >14: HR 7.59 [95% CI 3.31, 17.44]

SOX trial secondary analysis


Marker of persistent inflammation or venous outflow obstruction?
Other risk factors related to PTS occurrence?

Factors related to the treatment phase

- Duration of anticoagulation
- Intensity of VKA anticoagulation
++ Poor INR control in the treatment phase /especially within first 3 months/
++/-- Type of anticoagulation LMWH vs VKA /in favor of LMWH/
+ Incomplete resolution of the symptoms within 1st month of the treatment

„Residual thrombosis” /non complete recanalisation and thrombus resolution/ +
Post-thrombotic syndrome (PTS)

- Residual thrombosis
  - Vein obstruction
  - Risk of recurrence

Residual thrombosis 1.5 – 2 fold increase of PTS risk
PTS PREVENTION
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 post-thrombotic syndrome
- but decrease the risk of recurrence!

DVT recurrence (ipsilateral)
Post – thrombotic syndrome risk 3-6x↑
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 - Direct Oral Anticoagulants
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).

PTS patients: more frequently recurrent DVT 15% vs 3% (no PTS ); p = 0.03

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* 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?

- Other drugs?

*DOACs - Direct Oral Anticoagulants
SULODEXIDE in Post-thrombotic syndrome prevention

The patients enroled 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 prevention of PTS

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

>40 points = PTS

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

„Open vein” concept?

- surgical thrombectomy

- local thrombolysis
Local thrombolysis

• Minimal invasive (+/-)
• Relief of DVT related symptoms (+)
• Vein patency restoration (+)
• Valve function preservation (?)
• Post-thrombotic syndrome avoidance (?)
Follow-up (median): 5 years (max. up to 14.3 years).

Cumulative rate of patients with deep patent veins without reflux @ 7 years: 79%.

Factors associated with poorer outcome:
- symptom duration >2 weeks (HR 2.78, 95% CI 1.14-6.73)
- chronic post-thrombotic lesions (HR 19.3, 95% CI 7.29-51.2)
CaVenT study
Long term outcome after traditional catheter – directed thrombolysis versus standard treatment for acute ilio-femoral deep vein thrombosis (the CaVenT study): a randomised controlled trial.

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 /
/follow up 189 pts./

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

But no changes in Ilio-femoral patency and QOL scores @ 5 years !!!

<table>
<thead>
<tr>
<th></th>
<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)</td>
<td>55.6% (45.7 - 65.0)</td>
</tr>
<tr>
<td>Iliofemoral patency at 6 months</td>
<td>65.9% (55 - 75)</td>
<td>47.4% (37.6-57.3)</td>
</tr>
</tbody>
</table>

PTS in CDT group ↓ - 14.4%

Enden T et al. Lancet 2012
Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis (ATTRACT)

Primary Outcome Measures:

**Cumulative incidence of Post-Thrombotic Syndrome (Villalta Scale)**
(Time Frame: within 24 months after randomization)

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

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

**CDT associated with a reduced severity of post-thrombotic syndrome - DVT patients who received both blood-thinning drugs and PCDT were 25 % less likely (18 % with CDT vs. 24 % without) to develop moderate-to-severe PTS.**

**Major bleeds** 1.7% vs 0.3% /p=0.049/

**Any bleeding** 4.5% vs. 1.7% /p=0.049/

**Fatal or intracranial bleeds** 0% vs 0%

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* 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
Ilio-femoral DVT results

Moderate and severe PTS /Villalta > 9/
Thrombolysis 18% vs Anticoagulation 28% /p=0.021/

Severe PTS /Villalta >14/
Thrombolysis 8.7% vs Anticoagulation 15% /p=0.048/

Severe PTS by VCSS: 6.6% vs 14 % /p = 0.013/
We will analyse the ATTRACT trial results many times and we will go into study details but ........

„Open vein” concept

is still „open” for the further research in term of PTS prevention.....
Compression use after DVT episode for post-thrombotic syndrome avoidance?

PTS after 49 months (mean): CS - 26% vs Control - 49%  
NNT 5 (3-11)

Proximal DVT
Knee-length elastic CS /30 – 40mmHg/ - 2 yrs.
Follow up - 5 yrs
Class II ECS vs “Placebo stockings”
Post-thrombotic syndrome /Ginsberg Criteria/

Randomization:

ECS - 410 pts vs Placebo ECS

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/ (HR 1.13; 95% CI 0.73-1.76; p=0.58)

Most proximal extent of DVT

<table>
<thead>
<tr>
<th>Location</th>
<th>Active ECS</th>
<th>Placebo ECS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iliac</td>
<td>10.8%</td>
<td>12.4%</td>
</tr>
<tr>
<td>Common femoral</td>
<td>26.7%</td>
<td>27.2%</td>
</tr>
<tr>
<td>Femoral</td>
<td>31.3%</td>
<td>31.2%</td>
</tr>
<tr>
<td>Popliteal</td>
<td>31.3%</td>
<td>29.2%</td>
</tr>
</tbody>
</table>

Active ECS:
Knee – length
30-40 mm Hg compression.

Recommendation 18
Use of medical compression stocking as early as possible after diagnosis of DVT in order to prevent PTS

/1B*/

*downgraded from 1A in the 2008 consensus document*
“...it is still not possible to reliably predict, on an individual basis, who will and who will not develop PTS.”

PTS predictive factors and PTS prevention

Further research is needed, but should probably start with:

• PTS Definition
• validated PTS assessment method
• validated classification of the PTS severity
• PTS prediction models
High risk predictors at baseline:

1 point: iliac vein DVT
2 points: BMI>35
1 point: Vialta score 9-14 at baseline /moderate PTS/
1 point: Villata score >`14 at baseline /severe PTS/

score ≥4 /6 fold ↑ risk of PTS/
[OR 5.9 (95% CI 2.1-16.6)]

SOX – PTS index /range 0-5/

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Risk of post-thrombotic syndrome development

Development and Validation of a Practical Two-Step Prediction Model and Clinical Risk Score for Post-Thrombotic Syndrome
Amin EE, van Kuijk S, Joore M, Prandoni P, Hugo ten Cate H, ten Cate-Hoek AJ

Baseline model:
0–2 points 10%
3–4 points 20%
5 points 40%

Secondary model:
0–2 points 25%
3–4 points 45%
5 points 60%

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline risk assessment</th>
<th>Risk assessment in the sub-acute phasea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 56</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Body mass index &gt; 30</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Smoking</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Residual vein obstruction</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Female sex</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Provoked deep vein thrombosis</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Iliofemoral thrombosis</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>History of deep vein thrombosis</td>
<td>1</td>
<td>–</td>
</tr>
</tbody>
</table>

a) Sub-acute phase – 6 months after diagnosis of deep vein thrombosis
PTS Treatment
Secondary venous disease reflux/obstruction

• Compression
• Risk factors elimination (modification)
• Pharmocological treatment
• Invasive obstruction treatment /PTA, stent placement/
• Local wound treatment /if needed/

/often combined treatment needed/
Consensus Statement for compression stockings in venous & lymphatic disorders

Phlebology 2017

Recommendation 19

Use of medical compression stocking for treatment of symptomatic PTS
Compression in PTS treatment

• How long?

• Which class of compression?

• Does it prevent disease progression?
Guidance Statement

We suggest the following management approach for compression-based therapies:

• Prescribe 20–30 mm Hg ECS to patients with PTS-related leg heaviness or swelling.
• We suggest knee-length ECS, which have similar physiologic effects to thigh-length ECS and are easier to apply, more comfortable and less costly.
• Explain to the patient that these are to be worn daily, from waking to retiring.

• If 20–30 mm Hg ECS do not adequately control PTS symptoms, a stronger pressure stocking (30–40 mm Hg; or 40–50 mm Hg) can be tried.

We suggest that intermittent pneumatic compression sleeve units (e.g. used for 20–30 min sessions, 2–3 times per day) can be used to help severe, intractable PTS symptoms or severe edema, however patients may find these to be cumbersome and the units are expensive.

A Summation Analysis of Compliance and Complications of Compression Hosiery for Patients with Chronic Venous Disease or Post-thrombotic Syndrome

Hadyn K.N. Kankam, Chung S. Lim, Francesca Fiorentino, Alun H. Davies, Manj S. Gohel

Results: From an initial search result of 4303 articles, 58 clinical studies (37 randomised trials and 21 prospective studies) were selected. A total of 10,245 limbs were included, with compression ranging from 15 to 40 mmHg (not stated in 12 studies) and a median follow-up of 12 months (range 1–60 months). In 19 cohorts, compliance was not assessed and in a further nine, compliance was poorly specified. Overall, good compliance with compression was reported for 5371 out of 8104 (66.2%) patients. The mean compliance, weighted by study size, appeared to be greater for compression <25 mmHg (77%) versus > 25 mmHg (65%) and greater in the randomised studies (74%) than in prospective observational studies (64%). Complications of stockings were not mentioned in 43 out of 62 cohorts reviewed. Where complications were considered, skin irritation was a common event.

Conclusions: In published trials, good compliance with compression is reported in around two thirds of patients, with inferior compliance in those given higher degrees of compression. Further studies are required to identify predictors of non-compliance, to help inform the clinical management of these patients. Complications of compression are not documented in many studies and should be given more consideration in the future.
A trial of ECS may be considered in patients with PTS who have no contraindications (eg, arterial insufficiency) /Class IIb; Level of Evidence C/

For patients with moderate or severe PTS and significant edema, a trial of an intermittent compression device is reasonable /Class IIb; Level of Evidence C/

The Postthrombotic Syndrome: Evidence-Based Prevention, Diagnosis, and Treatment Strategies  
A Scientific Statement From the American Heart Association.
Pharmacotherapy in PTS patients

Venoactive drug RCTs in PTS patients performed with:

• rutosides
• defibrotide
• hidrosmin

Guidance Statement:

• We do not suggest the use of venoactive drugs to treat PTS.
• Also, due to an absence of evidence and potential for harm, we do not suggest the use of diuretics to treat PTS-related edema.

The effectiveness and safety of rutosides, hidrosmin, and defibrotide to treat PTS are uncertain

/Class IIb; Level of Evidence B/
PTS risk factors modification?

- Age
- Obesity reduction?
- Immobilistation?
Excercise training

Guidance Statement:


We suggest that a supervised exercise training program with leg strengthening and aerobic components for 6 or more months be tried in PTS patients who can tolerate it

• calf muscle function improvement

• improvement in term of PTS severity, quality of life, leg strength and leg flexibility

Kahn SR. et al. CMAJ. 2011;183:37–44.
But ........

Current indications for CVD pharmacological treatment

focus on Symptomatic CVD patients
/irrespective if primary or secondary ethiology is recognized/*

SYMPTOMATIC CVD PATIENTS: swelling, pain.....

* No drug which can completly cure the post-thrombotic leg is till now available /complex PTS pathology and irreversible injury of the venous system usually present/, however, the data which suggest the possibilty of the symptoms of the secondary CVD and swelling decrese are available
Effects of Sulodexide in post-thrombotic limbs

30 pts. with postthrombotic limbs: sulodexide 2 x 250 LRU twice daily vs Placebo /3 months/
symptom evaluation: none - 0, severe – 3/

* p < 0.05 vs Placebo and Baseline

- Pain
- Itching
- Edema
- Skin A.
- Paresthesia

Sulodexide
Placebo

Hemodynamical evaluation:
Strain gauge plethysmography + CW Doppler
MVIV - Maximal venous incremental volume
tMVIV - time required to reach a maximal incremental volume
MVO - Maximal venous outflow
dV/dP ratio - venous distensibility
dP/dV ratio - venous tone
CFC - capillary filtration coefficient (index of microcirculatory flow)

Capillary filtration coefficient (CFC) – index of microcirculation

30 pts. with postthrombotic limbs: sulodexide 2 x 250 LRU twice daily vs Placebo /3 months/

47 patients with lower limb thrombophlebitis or thrombosis sequelae:

19 - varicophlebitis
17 - acute superficial thrombophlebitis
12 - post-thrombotic syndrome

Average change in the intensity of the parameters assessed during treatment:

0 = absent
1 = mild
2 = medium
3 = severe

600 LRU i.m./day – 30 days
2 x 250 LRU capsules/day for 60-75 days.

S. Ferrero. NAM. 1990; 6:169-72
Effect of sulodexide on biomarkers in wound healing

Sulodexide impacts on biomarkers of inflammatory and granulation => potential acceleration of ulcer healings.

**Inflammatory Phase**
- IL-1B,
- IL-12,
- IL-8,
- IL-10,
- GM-CSF,
- MMP-9

**Sulodexide**

**Granulation phase**
- IP-10,
- PDGFbb,
- MMP-1,
- MMP-7

**Inhibited biomarkers**

**Stimulated biomarkers**

Adapted from Ligi D et al. 2016
Sulodexide /in addition to standard treatment/ accelerates venous leg ulcer healing process and increases the healing rate

COMPLETE ULCER HEALING IN THE SULODEXIDE GROUP AFTER 3 MONTHS OF THERAPY

- n=235

ACCELERATION OF ULCER HEALING WITH SULODEXIDE

- n=44

Coccheri et al. 2002

Kucharzewski et al., 2003
Placebo (127 pts.) vs Sulodexide (139 pts)
intramuscular injection (60 mg i.m. o.d. for the first 20 days followed by the oral route (100 mg/daily in two 50 mg capsules for 70 days)/previous DVT 25.4% (placebo) vs 38% sulodexide group/

local treatment
/wound care and high compression bandaging: stretch elastic bandages, adhesive bandages, self adherent bandages, zinc oxide bandages, 4-layer bandages/

Complete ulcer healing

@ 2 months 35.0% (sulodexide) vs 20.9% (placebo) (p = 0.018) NNT@ 2 months – 7

@ 3 months 52.5% (sulodexide) vs 32.7% (placebo) (p = 0.004) NNT@ 3 months – 5

/The effect of sulodexide at 2 months was especially relevant in ulcers with initial area <10 cm² (p < 0.019) and of more recent (up to 12 months) onset (p = 0.039)/
94 patients with venous leg ulcers secondary to primary CVD or PTS

sulodexide 600 LSU im. od. /30 days/
afterwards 2x 250 LSU orally /30 days/

completely healed ulcers:
sulodexide + local treatment* - 58% vs local treatment* 36%; (p = 0.03)

total healing time
sulodexide + local treatment* - 72 days vs local treatment* 110 days; (p = 0.08)

*Local treatment: wound care + compression

**Key message:**

..... sulodexide might help to improve ulcer healing, as the proportion of ulcers that were completely healed was increased from 29.8% with local treatment to 49.4% when the participants also received sulodexide
Pharmacotherapy in ulcer healing

Recommendation 35

Sulodexide and micronized purified flavonoid fraction should be considered as an adjuvant to compression therapy in patients with venous ulcers

Class IIa, Level A

Management of chronic venous disease
Clinical Practice Guidelines of the European Society for Vascular Surgery
Eur J Vasc Endovasc Surg, 2015; 49: 678-737
Open-label, observational, non-parallel trial

33 patients: multi-layer bandaging + local + DH (diosmin-hesperidin)
37 patients: multi-layer bandaging + local + DH (diosmin-hesperidin) + sulodexide,

/Sulodexide, 60 mg (600 LRU) im. For 10 days, followed by 25 mg (250 LRU) every 12 hours orally until ulcer closure/

GONZÁLEZ OCHOA A. Sulodexide and phlebotonics in the treatment of venous ulcer. Int Angiol 2017; 36: 82-7
Chronic deep vein obstruction

- NIVL /non-thrombotic iliac vein lesion/
- Post-thrombotic /occlusive or non-occlusive/
Post-thrombotic syndrome in patients with venous obstruction

- Asymptomaric course
- Chronic leg heaviness
- Pain
- Venous claudication
- Edema
- Varicose veins
- Trophic skin changes, Ulcer

poor correlation between phlebography results and clinics!
Post-thrombotic syndrome

Interventional treatment of the chronic deep vein obstruction

For the severely symptomatic patient with iliac vein or vena cava occlusion, surgery (eg, femoro-femoral or femoro-caval bypass) (Class IIb; Level of Evidence C) or percutaneous endovenous recanalization (eg, stent, balloon angioplasty) (Class IIb; Level of Evidence B) may be considered.

The Postthrombotic Syndrome: Evidence-Based Prevention, Diagnosis, and Treatment Strategies A Scientific Statement From the American Heart Association.

Difficult aspects of venous obstruction

• Unknown at what degree a obstruction is hemodynamically significant!
  (even with stenosis pressure gradient measurement)

• Morphological stenosis >50% probably significant

• Compression lesions occur in different planes.
Iliac vein compression
The hemodynamical significance of the outflow obstruction

• The degree at which a venous stenosis is critical is not known!
  /Pressure is a function of resistance to flow and quantity of flow/

• No reliable and sensitive non-invasive study is available!
  • A positive result of the test may support further investigations
  • Negative test does not exclude significant stenosis (poor sensitivity)

• Also invasive pressure tests are insensitive
  • hand/foot pressure gradient
  • reactive hyperemia pressure increase
  • femoral vein pressure comparison/gradient/
Arterial stenosis criteria not appropriate directly for venous stenosis

- Lower limb venous flow is complex/collateral circulation, flow and pressure gradient related to the collaterals and pressurized chamber presence/

VENOUS SYSTEM STENOSIS CRITERIA?
Conclusions

• PTS is still very challenging situation

• We have problem to define and to score it properly!

• We have problems to predict its occurrence! (even knowing some of the risk factors)

• Poor clinical correlation of the phlebographic findings and clinical symptoms!

• The further research needed to establish proper prophylaxis and PTS treatment!
CRACOW UIP Chapter Meeting

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