Sulodexide for signs, symptoms and beyond

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Disclosure

- Educative lectures supported by Alfasigma
CHRONIC VENOUS DISEASE TREATMENT

- Pharmacological treatment
- Invasive treatment
- Compression

+ Risk factor elimination
Do we have the real disease oriented treatment?
The care of patients with varicose veins and associated chronic venous diseases: Clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum

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The Society for Vascular Surgery (SVS) and the American Venous Forum (AVF) have developed clinical practice guidelines for the care of patients with advanced chronic venous disease. The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system was used to rate the quality of evidence and to assign grades of recommendations. The evidence is presented for treatment of venous disease and for treatment of chronic venous disease in patients with chronic venous disease in the lower extremities. The evidence is based on systematic reviews of randomized controlled trials, meta-analyses, and other types of evidence. The guidelines are intended for use by healthcare professionals who are involved in the care of patients with chronic venous disease. The guidelines are not intended to be used as the sole source of information for the treatment of patients with chronic venous disease.

Guideline 8. Medical treatment

<table>
<thead>
<tr>
<th>Guideline No.</th>
<th>8. Medical treatment</th>
<th>GRADE of recommendation</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.1</td>
<td>We suggest venoactive drugs (diosmin, hesperidin, rutosides, sulodexide, micronized purified flavonoid fraction, or horse chesnut seed extract [aescin]) for patients with chronic venous disease, in countries where these drugs are available.</td>
<td>2</td>
<td>B</td>
</tr>
</tbody>
</table>

Guideline 8.1 We suggest venoactive drugs (diosmin, hesperidin, rutosides, sulodexide, micronized purified flavonoid fraction or horse chesnut seed extract for patients with pain and swelling due to chronic venous disease, in countries where these drugs are available [2B]
Recommendation 34

Venotonic drugs should be considered as a treatment option for swelling and pain caused by chronic venous disease [2A]
Normal saphenous vein

Incompetent saphenous vein
Vein wall changes in CVD patients

- Vasa vasorum compression
- Hypoxia
- Fibroblasts
- TGF beta 1
- Mast cells
- MMPs/TIMP
- VEGF
- Oxydative stress
- Extracellular matrix changes

- Flow disturbance
- ICAM expression
- Hypertension
- Hypertension and venostasis related ischemia
- Endothelial cell activation
- Leukocyte adhesion, activation and migration

Nicolaides AN.: From Symptoms to leg edema. Angiology 2003
Multi-target activity of sulodexide

- Antithrombotic and profibrinolytic activity
- Protects endothelial cells
- Oxidative stress suppression
- Inflammatory reaction suppression
- Metalloproteinase expression decrease
- Growth factor expression modulation
- Capillary permeability control
NEWS

Sulodexide effects

Venotonic activity

/venous contraction increase/

**Sulodexide Promotes Venous Contraction in Rat Inferior Vena Cava**

Joseph D. Raffetto, MD, Fiorella Calanni, Paolo Mattana, Reouf Khalil.

**Objective:** Sulodexide (SDX) is a highly purified glycosaminoglycan composed of fast-moving heparin (80%) and dermatan sulfate (20%). SDX has both antithrombotic and profibrinolytic properties with reported benefits in chronic venous disease and other thrombotic and atherosclerotic vascular disorders. However, the effects of SDX on the vein wall structure and function are unclear. We have previously shown that matrix metalloproteinases 2 and 9 cause venous relaxation, and other studies have suggested that SDX may inhibit matrix metalloproteinase 9. The purpose of this study was to test whether SDX affects venous function and whether its venous effects are different from those in the arteries.

**Methods:** Male rat inferior vena cava (IVC), abdominal aorta, and mesenteric artery were harvested and 3-mm circular segments were equilibrated under 0.5g, 2g, and 1g basal tension, respectively, in a tissue bath containing Krebs solution bubbled with 95% O₂ 5% CO₂ at 37°C, and the changes in isometric contraction were recorded. Vessel segments were precontracted with the α-adrenergic receptor agonist phenylephrine (PHE, 3 × 10⁻⁷ M), and the changes in the vessel response to SDX (0.001-1 mg/mL) were measured. The % venous/arterial contraction or relaxation was calculated, and the data were presented as means ±

In phenyleprine precontracted inferior vena cava, SDX caused concentration - dependent increases in contraction

Conclusions: SDX potentiates contraction in veins while causing relaxation in arteries. The mechanisms may involve differential effects of SDX on different matrix metalloproteinase subtypes, protease-activated receptors, and integrins in the veins vs arteries and need to be further examined. The results may have clinical implications as SDX may be helpful as a venotonic agent for chronic venous disease while promoting arterial dilation and decreasing arterial pressure.
Chronic venous disease

Primary

Secondary

Both of them can be symptomatic
Bonn Vein Study /Germany/

CVD Symptomatic patients /including leg pain and heaviness sensation/

M – 49%  F – 62%

Sulodexide in CVD symptoms treatment

450 patients with CVD treated 3 months with sulodexide (2x250 LSU)

Evaluation of subjective/heaviness, pain, cramps, paresthesia/ and objective/erythema, skin temperature, induration/ CVD symptoms

/severity score (mean):
0 = abstent; 3 very severe/

Sulodexide
QoL of life improvement after 3 months therapy

450 patients with CVD treated 3 months with sulodexide

Conclusion: Oral sulodexide significantly improves both objective and subjective symptoms, as well as functional and psychological aspects of QoL in patients with CVD.

Sulodexide therapy presents significant improvement in CVD symptoms relief /including pain, heaviness, paresthesias, edema and cramps/.

476 pts. with primary (50%) and secondary (50%) CVD
/Sulodexide in doses: 250, 500LSU 2x daily & 1000LSU 1x daily /60 days/

Symptoms and signs evaluated: limb heaviness, paresthesias, nocturnal cramps, orthostatic and clinostatic pain, pain in effort, oedema of the foot, of the leg and general, skin pigmentation, desquamation, eczema, alteration of skin annexes, hypodermitis, stasis ulcer lymphangitis, cyanosis and venous ectasia/

Sulodexide in CVD symptom and sign treatment

Sulodexide in doses: 250, 500 LSU 2x daily & 1000 LSU 1x daily /60 days/

**Efficacy of SDX therapy is dose dependent.**

- The high dose 1000 LSU daily provided significantly greater relief than the dose 500LSU.
Sulodexide in CVD symptom and sign treatment

434 CVD patients (C0- C6) followed for 4 months in 30 d. intervals
/sulodexide treatment/

Signs and symptoms rated at each examination:
/SCORE 0 (none) – 5 (very intense)/

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean score</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st visit</td>
<td>4th visit</td>
<td></td>
</tr>
<tr>
<td>Leg heaviness</td>
<td>413</td>
<td>3.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Itching</td>
<td>400</td>
<td>3.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Pain burning sensation</td>
<td>414</td>
<td>3.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Cramps</td>
<td>370</td>
<td>2.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Edema</td>
<td>337</td>
<td>3.1</td>
<td>0.7</td>
</tr>
</tbody>
</table>
6 months sulodexide treatment (500 LSU/day) in varicose vein patients after endovascular or hemodynamic venous treatment

Clinical assessment /patient questionnaire/

... results show that Sulodexide *improves signs and symptoms of legs by reducing heaviness, swelling and inflammation, both after 30 days and 6 months after venous treatment, with a better QOL compared with patients who were treated with only the hemodynamic pattern.*

P. Casoni, F. Villa, P Corona /Italy/
Post-thrombotic syndrome (PTS)
PTS predictive factors?
Potential risk factors related to PTS occurrence?

Factors related to the patient initial status:

- Trombophilia
- Sex
- Age
- Obesity
- Preexisting varicose veins

Potential 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/ *
### Potential risk factors related to PTS occurrence

#### Factors related to the treatment phase

<table>
<thead>
<tr>
<th>Factor</th>
<th>Impact</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>&quot;Residual thrombosis&quot; /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>Poor INR control in the treatment phase /especially within first 3 months/</td>
<td>++</td>
</tr>
<tr>
<td>LMWH vs VKA /in favor of LMWH/</td>
<td>+</td>
</tr>
</tbody>
</table>

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Major known risk factor !!!

DVT recurrence (ipsilateral)

Post – thrombotic syndrome risk 3-6x↑
VTE recurrence

- Postthrombotic syndrome occurrence risk ^^
- DVT symptom aggraviation
- PE risk
VTE recurrence prevention

• Full anticoagulation
  VKA, DOACS /high efficacy, continuous risk of bleeding/
VTE recurrence prevention

• Full anticoagulation
  VKA, DOACS /high efficacy, continuous risk of bleeding/

• Reduced doses of anticoagulants
  VKA INR 1.5-2.0,
  Rivaroxaban 10 mg /EINSTEIN CHOICE/
  Apixaban 2x 2.5 mg /AMPLIFY EXTENSION/
VTE recurrence prevention

- **Full anticoagulation**
  
  VKA, DOACS /high efficacy, continuous risk of bleeding/

- **Reduced doses of anticoagulants**
  
  VKA INR 1.5-2.0,
  Rivaroxaban 10 mg /EINSTEIN CHOICE/
  Apixaban 2x 2,5 mg /AMPLIFY EXTENSION/

- **Sulodexide**
  
  Sulodexide 2x500 LSU /SURVET/
VTE recurrence prevention

• Full anticoagulation
  
  VKA, DOACS /high efficacy, continuous risk of bleeding/

• Reduced doses of anticoagulants
  
  VKA INR 1.5-2.0,
  
  Rivaroxaban 10 mg /EINSTEIN CHOICE/
  
  Apixaban 2x 2,5 mg /AMPLIFY EXTENSION/

• Sulodexide
  
  Sulodexide 2x500 LSU /SURVET/

• ASA /WARFASA, ASPIRE/
Optimal duration of antithrombotic VTE treatment

Risk of recurrence  Risk of bleeding
SURVET - a multicentre, randomised, double-blind, parallel-group, placebo-controlled trial in adult patients with first-ever unprovoked VTE

Patients aged ≥18 years with first-ever unprovoked VTE who had completed oral anticoagulation therapy

**RANDOMISATION**

- Sulodexide 500 LSU orally twice daily + compression therapy
- Placebo twice daily + compression therapy

Primary efficacy endpoint: Confirmed recurrence of VTE
Primary safety endpoint: Major or clinically relevant non-major bleeding

n=309

Adapted from Andreozzi et al. 2015.

DVT = Deep Vein Thrombosis  LSU = Lipasemic Units  PE = Pulmonary Embolism  VTE = Venous Thromboembolism

* The primary efficacy outcome was symptomatic, objectively confirmed recurrence of VTE, defined as the composite of deep vein thrombosis (DVT) objectively confirmed by compression ultrasonography, or non-fatal or fatal pulmonary embolism (PE) objectively confirmed by computed tomography or lung scanning.

† The principal safety outcome was major or clinically relevant non-major bleeding. An overt bleeding event was defined as major if fatal, or occurred in a critical location, or required a transfusion of ≥2 units of whole blood or red cells. Clinically relevant non-major bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but was associated with the need for medical intervention, contact with a physician, or interruption of the study drug or with discomfort or impairment of activities of daily life.

Statistically significant reduction in risk of recurrent VTE vs placebo

Recurrent VTE occurred in 15 (4.9%) patients treated with sulodexide compared with 30 (9.7%) patients treated with placebo (HR: 0.49; 95% CI: 0.27–0.92; p=0.02)1†

* The analysis adjusted for age, sex, index event, country, duration of exposure to VKA, and delay from end of VKA treatment and randomisation, confirmed that sulodexide treatment reduced the risk of recurrence (adjusted HR: 0.45; 95% CI: 0.24–0.84; p=0.01).1 No association was found between recurrent VTE and length of exposure to VKA (HR: 0.79; 95% CI: 0.41–1.53; p=0.48).1

† Of the 15 episodes of recurrent VTE with sulodexide, 12 (75%) were DVT and 3 (25%) were PE.1 Of the 30 episodes in the placebo group, 24 (80%) were DVT and 6 (20%) were PE.1

Multi-target effects of sulodexide

- Antithrombotic, profibrynolityic
- Endothelial-Protective
- Restoration of endothelial glycocalyx
- Capillary permeability control
- Anti-Inflammatory
- Growth factor release control
- Proteolytic enzyme (MMP) activity control

Potentially valid for PTS prevention and treatment
Post-thrombotic syndrome prevention

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Patients</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>167 pts.</td>
<td>standard management - no coagulation</td>
</tr>
<tr>
<td>Group 2</td>
<td>124 pts.</td>
<td>sulodexide</td>
</tr>
<tr>
<td>Group 3</td>
<td>48 pts.</td>
<td>ASA</td>
</tr>
</tbody>
</table>


Conclusion: Sulodexide administration after DVT appears to be effective in preventing PTS.
Effects of Sulodexide in postthrombotic 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

<table>
<thead>
<tr>
<th>% variation</th>
<th>Pain</th>
<th>Itching</th>
<th>Edema</th>
<th>Skin A.</th>
<th>Paresthesia</th>
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<tbody>
<tr>
<td>20</td>
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<tr>
<td>0</td>
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<td>-20</td>
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<tr>
<td>-100</td>
<td></td>
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</table>

Sulodexide

Placebo

Hemodynamical evaluation: Strain gauge pletysmography + 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)

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

S. Ferrero. NAM. 1990; 6:169-72
VENOUS LEG ULCER TREATMENT
Sulodexide impacts on biomarkers of inflammatory and granulation

=> potential acceleration of ulcer healings.

**Inflamatory 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.

Sulodexide + standard treatment vs Placebo + standard treatment

**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. (SUAVIS study) 2002*

*Kucharszewski et al. 2003*
Sulodexide in venous leg ulcer treatment

Oral sulodexide plus compression versus Compression alone

Cocheri /2002/
Scondotto /1999/
Kucharzewski /2003/
Zou /2007/

„...in patients with VLU adequately treated with correct WBP and compression, SDX showed beneficial results by accelerating the rate of wound healing and increasing the proportion of ulcers healed at a predefined time.”

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
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/

Sulodexide group: 100 % of the ulcers healed by week 12
Non-sulodexide group: 100% of the ulcer healed by week 21 /P<0.01/
MIXED ULCER TREATMENT
**Leg ulcers**

**Vascular**

**Chronic venous insufficiency (CVI) - 50%**
- Ulcer location: retromalleolar, mainly medial
- Surroundings: oedema, hypopigmentation, purpura, atrophie blanche. Stasis eczema, allergic contact dermatitis, dermatosclerosis
- History: varicosis, heavy leg, thrombosis, oedema
- Assessment: Doppler sonography/duplex Doppler

**Arterial - 10%**
- Ulcer location: lateral and ventral aspect of leg, dorsum of the foot
- Surrounding skin: atrophic, shiny, hair loss
- History: Cardiovascular risk factors, intermittent claudication
- Assessment: Pulse palpation, ABI, Duplex US, Angiography

**Mixed venous - arterial - 20%**
- Ulcer location: medial and lateral, signs of CVI, ABI <0.8

**Other aetiologies - 20%**

**EWMA clinical practice statements:**
*Statement 5.2.a: All patients presenting with lower leg ulceration must receive a comprehensive assessment.*
Open-label, parallel-groups study

**Standard treatment (compression, local, venous surgery) - Group B vs standard treatment + sulodexide (Group A)**

/600 LRU/day i.m. for 15 days followed by SDX 250 LRU every 12 hours orally for 6 months as adjunctive treatment./

56 pts. with mixed leg ulcers
- presence of venous reflux
- ABPI: >0.5 and <0.8,

MMPs* and NGAL* expression in wound tissue biopsy taken 1 month and 3 months after start of the treatment

*MMP, matrix metalloproteinase; NGAL, neutrophil gelatinase-associated lipocalin;

What else ?
Proportion of patients with ≥ 75% reduction of the lipodermatosclerosis area

<table>
<thead>
<tr>
<th>Duration</th>
<th>Sulodexide + standard treatment</th>
<th>Standard treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks</td>
<td>13.9%</td>
<td>2.6%</td>
</tr>
<tr>
<td>4 weeks</td>
<td>53.4%</td>
<td>19.4%</td>
</tr>
<tr>
<td>6 weeks</td>
<td>79.0%</td>
<td>55.5%</td>
</tr>
<tr>
<td>8 weeks</td>
<td>95.3%</td>
<td>72.6%</td>
</tr>
<tr>
<td>12 weeks</td>
<td>97.6%</td>
<td>83.3%</td>
</tr>
</tbody>
</table>
Sulodexide in post-sclerotherapy hyperpigmentation treatment?

Prospective randomised study
104 C1–C2 sclerotherapy patients treated by aethoxysclerol

Sclerotherapy vs. Sclerotherapy + sulodexide 25mg bid /oral/
/beginning on the day of first evaluation and continue during the three months of follow-up
sclerotherapy treatment begining in less than seven days after first visit/
Photographic computer software based analysis /before the treatment and one month after/

Hyperpigmentation presence at one month:

Control group 22.4% vs. Sulodexide group 13.7% (p=0.001)

[at three months 8.9% vs 3.5% (p=0.04)]

No negative influence of sulodexide on vein clearance

Reducing hyperpigmentation after sclerotherapy using an antithrombotic drug
A Gonzalez Ochoa

CX 2018 book
Sulodexide in Chronic Venous Disease treatment:

- *Primary and secondary CVD symptom decrease*
- *CVD related swelling decrease*
- *Quality of life improvement*
- *Venous and mixed ulcer treatment*
- *Potential new targets for the pharmacological therapy*
9th 2018

HANDS-ON WORKSHOP on VENOUS DISEASE

Grand Resort, Limassol, Cyprus

25-27 Oct, 2018

Register at www.evfvip.com