Effect of venoactive compounds in post-thrombotic syndrome

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VEITH SYMPOSIUM
Connecting The Vascular Community

Disclosure

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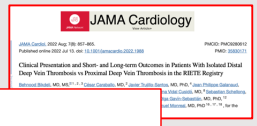
Post-thrombotic syndrome (PTS)

Predictors of Post-Thrombotic Ulcer after Acute DVT: The RIETE Registry



JAMA Cardiology

Clinical Presentation and Short- and Long-term Outcomes in Patients With Isolated Distal Deep Vein Thrombosis vs Proximal Deep Vein Thrombosis in the RIETE Registry

RIETE registry

- 33,897 patients with acute DVTs
- 3 years follow-up
- PTS prevalence:
  - 48% after infrapopliteal DVT
  - 60% after iliofemoral or popliteal DVT
- Venous ulcers: 2.7% at 1 year, 7.1% at 3 years

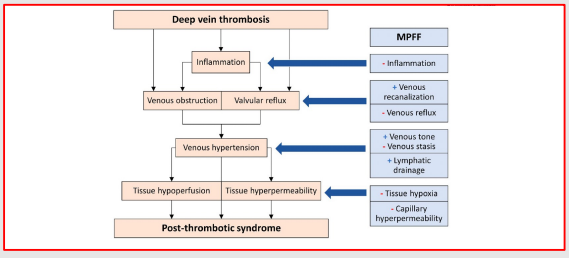
Post-thrombotic syndrome (PTS)

Risk of developing post thrombotic syndrome after deep vein thrombosis with different anticoagulant regimens: A systematic review and pooled analysis

- 21 articles/4342 patients
- Incidence of PTS:
  - 15.1% with VKA
  - 18.2% with DOACs
  - 24.6% with LMWH
- PTS may be lower among patients receiving a DOAC

Treatment of Post-Thrombotic Syndrome

- Venous interventions for superficial veins incompetence and deep veins occlusion
- Compression therapy
- Venoactive compounds (VAC)



Li KX et al. Res Pract Thromb Haemost 2021;5:e12527

BMJ Open. 2021 Sep 13;11(9):e049557. doi: 10.1136/bmjopen-2021-049557.

MUFFIN-PTS trial, Micronized Purified Flavonoid Fraction for the Treatment of Post-Thrombotic Syndrome: protocol of a randomised controlled trial

Jean Philippe Galanaud [1], Jameel Abdulrehman [2], A Lazo-Langner [3], Grégoire Le Gal [4], Sudeep Shivakumar [5], Sam Schulman [6], Susan Kahn [7]

Affiliations + expand

PMID: 34518263 PMCID: PMC8438950 DOI: 10.1136/bmjopen-2021-049557

Abstract

Introduction: After deep vein thrombosis, up to 50% of patients develop post-thrombotic syndrome (PTS). PTS is a chronic condition that reduces quality of life (QOL). Cornerstones of PTS treatment include the use of elastic compression stockings but this treatment is usually incompletely effective and is burdensome. Venoactive drugs have been reported to be effective to treat chronic venous insufficiency (CVI). However, the level of evidence supporting their use in CVI in general and in PTS in particular is low.

Methods and analysis: The MUFFIN-PTS trial is an academic, publically funded, multicentre randomised placebo-controlled trial assessing the efficacy of micronised purified flavonoid fraction (MPFF, Venilexa), a venoactive drug, to treat PTS. Eighty-six patients with PTS (Villalta score (VS) ≥5) and experiencing at least two of the following PTS manifestations among daily leg heaviness, cramps, pain or oedema will be randomised to receive 1000 mg of oral MPFF or a similar appearing placebo for 6 months, in addition to their usual PTS treatment. Total study follow-up will be 9 months, with visits at inclusion/baseline, 3, 6 and 9 months. Primary outcome is the proportion of patients with improvement in VS in each group, where improvement is defined as a decrease of at least 30% in VS or a VS <5 in the PTS-affected leg. Main secondary outcomes include QOL and patient satisfaction.

UTILITY OF VENOACTIVE COMPOUNDS IN POST-THROMBOTIC SYNDROME – A Systematic Review

Monika L. Gloviczki, MD, PhD, DFAVF*, Julianne Stoughton, MD, FACS, DFAVF, ABVLM**, Alessandra Puggioni, MD, DFAVF, RPVI, RPhS***, Joseph D. Raffetto, MD, FACS, DFAVF****

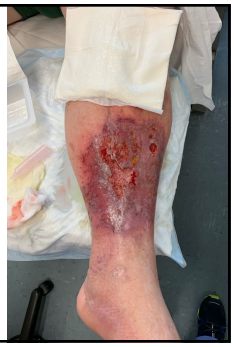
Methods

- A systematic review
- Literature search for VACs, DVT and PTS
- Only 12 RCTs of 94 papers on VACs included

UTILITY OF VENOACTIVE COMPOUNDS IN POST-THROMBOTIC SYNDROME

PTS treatment

- Nine RCTs included 398 (36.5%) PTS patients/1091 patients with chronic venous disease treated with diosmin, hidrosmin/rutosides, MPFF, or sulodexide
- Six of those RCTs included venous ulcers patients



PTS treatment with VACs (diosmin, MPFF, sulodexide)

1st author/ Year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	% of patients with PTS	Total number of patients
Monreal 1994								100%	29
Cospite 1989								23.3%	88
Gilly 1994								15%	160
Glinski 1999								8.6%	140
Guilhou 1997								60%	105
Roztocil 2003								52%	150
Tsouderos 1989								?	?
Cocchieri 2002								?	235
Scondotto 1999								46.8%	94

Low risk of bias | Unclear risk of bias | High risk of bias

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- Nine RCTs (1091 patients, 36.5% with PTS) found that Venoactive Compounds (VACs) significantly improved venous symptoms, edema and venous ulcers healing.
- Most studies on VACs for the treatment of PTS, however, are outdated and lack precision.

CrossMark

From the American Venous Forum

Journal of Vascular Surgery
Venous and Lymphatic Disorders

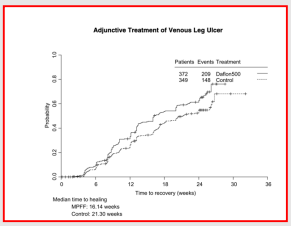
Validity of International Classification of Diseases, Ninth Revision, Clinical Modification codes for estimating the prevalence of venous ulcer

Monika L. Gloviczki, MD, PhD,[a] Henna Kalsi, MD,[a] Peter Gloviczki, MD,[a] Matthew Gibson, MD,[a] Stephen Cha,[b] and John A. Heit, MD,[a,b] *Rochester, Minn*

Post-thrombotic syndrome in 36.6%

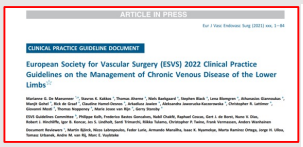
A Meta-analysis of Adjunctive Therapy with Micronized Purified Flavonoid Fraction (MPFF) in Venous Ulcers

- 41% of PTS patients
- Healing rates at 6 months: 61.3% in the MPFF group versus 47.7% in the control group.
- Reduced the median time to healing (16.1 weeks for MPFF vs 21.3 weeks)
- The relative hazard of healing for MPFF group 38% (CI, 11-70) better than control



Coleridge-Smith P et al. Venous leg ulcer: a meta-analysis of adjunctive therapy with micronized purified flavonoid fraction. Eur J Vasc Endovasc Surg 2005;30:198-208

Guidelines in Venous Ulcers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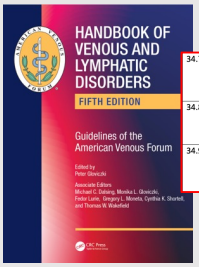
CLINICAL PRACTICE GUIDELINE DOCUMENT

European Society for Vascular Surgery (ESVS) 2022 Clinical Practice Guidelines on the Management of Chronic Venous Disease of the Lower Limbs

6.6. Pharmacotherapy

Recommendation 82			Unchanged
For patients with active venous leg ulceration, micronised purified flavonoid fraction, hydroxyethylrutosides, pentoxifylline, or sulodexide should be considered, as an adjunct to compression and local wound care to improve ulcer healing.			
Class	Level	References	ToE
IIa	A	Coleridge-Smith *et al.* (2005),[463] Jull *et al.* (2012),[464] Scallon *et al.* (2013),[462] Wu *et al.* (2016)[463]	

Venoactive compounds in Venous Ulcers



34.7	We recommend in venous leg ulcers either micronized purified flavonoid fraction, or pentoxifylline, as adjunctive treatment with compression, early intervention and wound local care.	1 (strong)	A (high)
34.8	We recommend sulodexide as adjunctive treatment with compression, early intervention and wound local care.	1 (strong)	B (moderate)
34.9	We suggest in venous leg ulcers hydroxyethylrutosides as adjunctive treatment with compression, early intervention and wound local care.	2 (weak)	C (low to very low)

Gloviczki ML and Raffetto JD. Drug treatment for chronic venous disease. Handbook of Venous and Lymphatic Disorders, 5th Ed.

Conclusions

- Venoactive Compounds (VACs) significantly improved venous symptoms, edema and venous ulcers healing in cohorts of patients including PTS.
- More rigorous and larger RCTs are needed to confirm these effects