

# Classification of CVD: CEAP Class 0-6

CEAP Class	0	1	2	3	4	5	6
Description	No visual or palpable signs of CVD	Telangiectasia or reticular veins	Varicose Veins	Edema	Pigmentation: Skin changes assigned to venous disease	Skin changes with healed ulceration	Skin changes with active ulceration
Visual							

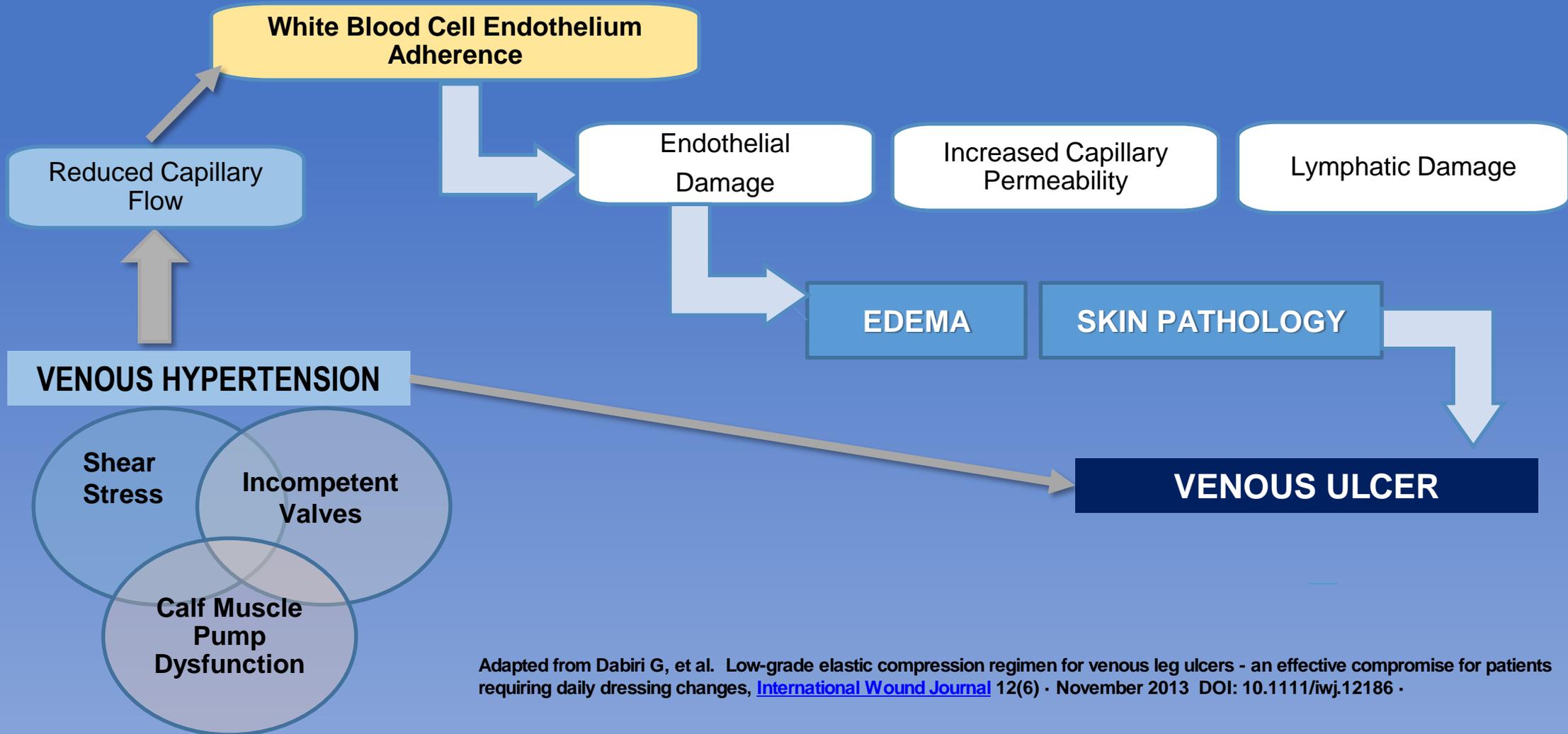
# Risk factors for CVD

## Predisposition to CVD based on environmental or genetic factors

Female gender	Long periods of standing or sitting
Obesity	Constipation
Older age	History of DVT or previous leg injury
Pregnancy	Family history

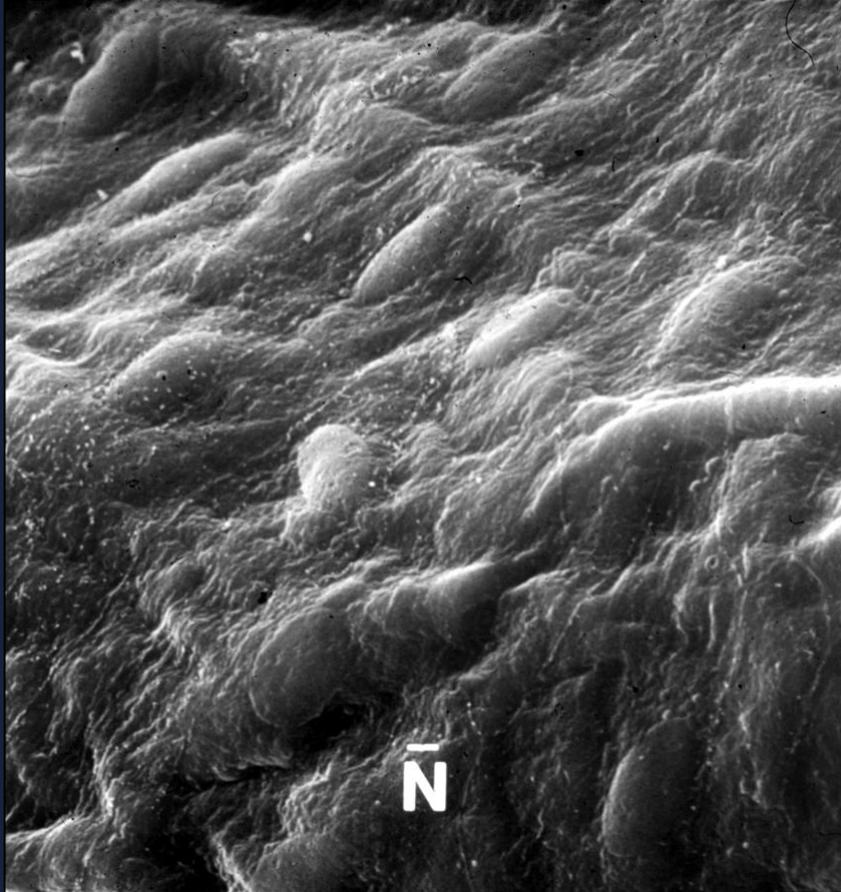
1. Coleridge Smith P. The causes of skin damage and leg ulceration in chronic venous disease. *Lower Extrem Wounds* 2006; 5(3): 160–168. 2. Jawien A. Influence of environmental factors in chronic venous insufficiency. *Angiology* 2003; 54(Suppl. 1): S19–S31. 3. Jawien A, Grzela T and Ochwat A. Prevalence of chronic insufficiency in men and women in Poland: Multicenter cross-sectional study in 40,095 patients. *Phlebology* 2003;18: 110–121. 4. Evans CJ, Fowkes FGR, Ruckley CV, et al. Prevalence of varicose veins and chronic venous insufficiency in men and women in the general population: Edinburgh Vein Study. *J Epidemiol Community Health* 1999; 53: 149–153. 5. Criqui MH, Jamoskos M, Fronek A, et al. Chronic venous disease in an ethnically diverse population: The San Diego Population Study. *Am J Epidemiol* 2003; 158:448–456. 6. Maurins U, Hoffmann BH, Lössch C, et al. Distribution and prevalence of reflux in the superficial and deep venous system in the general population – Results from the Bonn Vein Study, Germany. *J Vasc Surg* 2008; 48(3):680–687. 7. Carpentier PH, Maricq HR, Biro C, et al. Prevalence, risk factors, and clinical patterns of chronic venous disorders of lower limbs: A population-based study in France. *J Vasc Surg* 2004; 40: 650–659.

# Pathway from Venous Hypertension to Ulcer



Adapted from Dabiri G, et al. Low-grade elastic compression regimen for venous leg ulcers - an effective compromise for patients requiring daily dressing changes, [International Wound Journal](https://doi.org/10.1111/iwj.12186) 12(6) - November 2013 DOI: 10.1111/iwj.12186 -

## Normal Venous Pressure



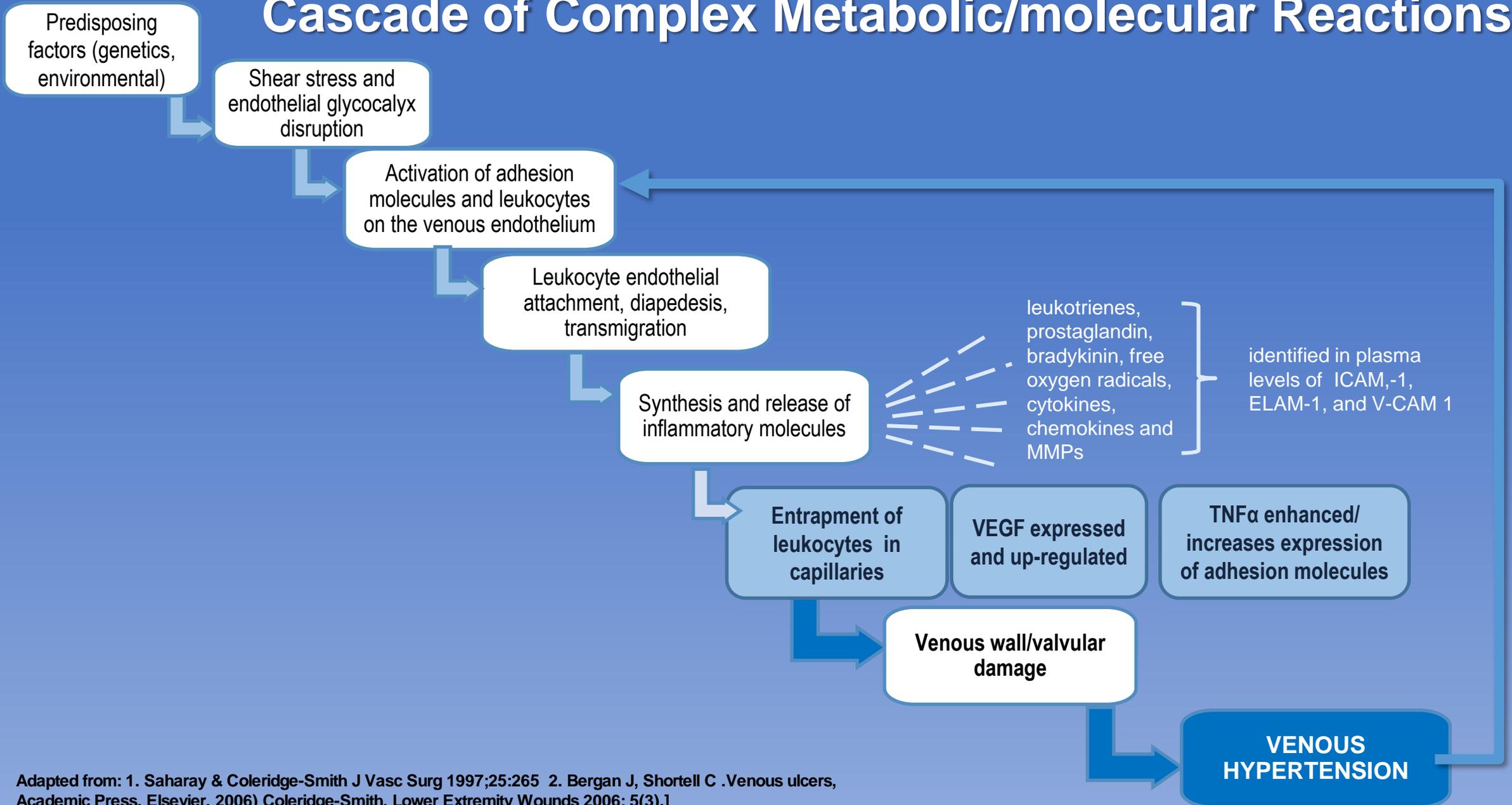
No WBCs

## Venous Hypertension



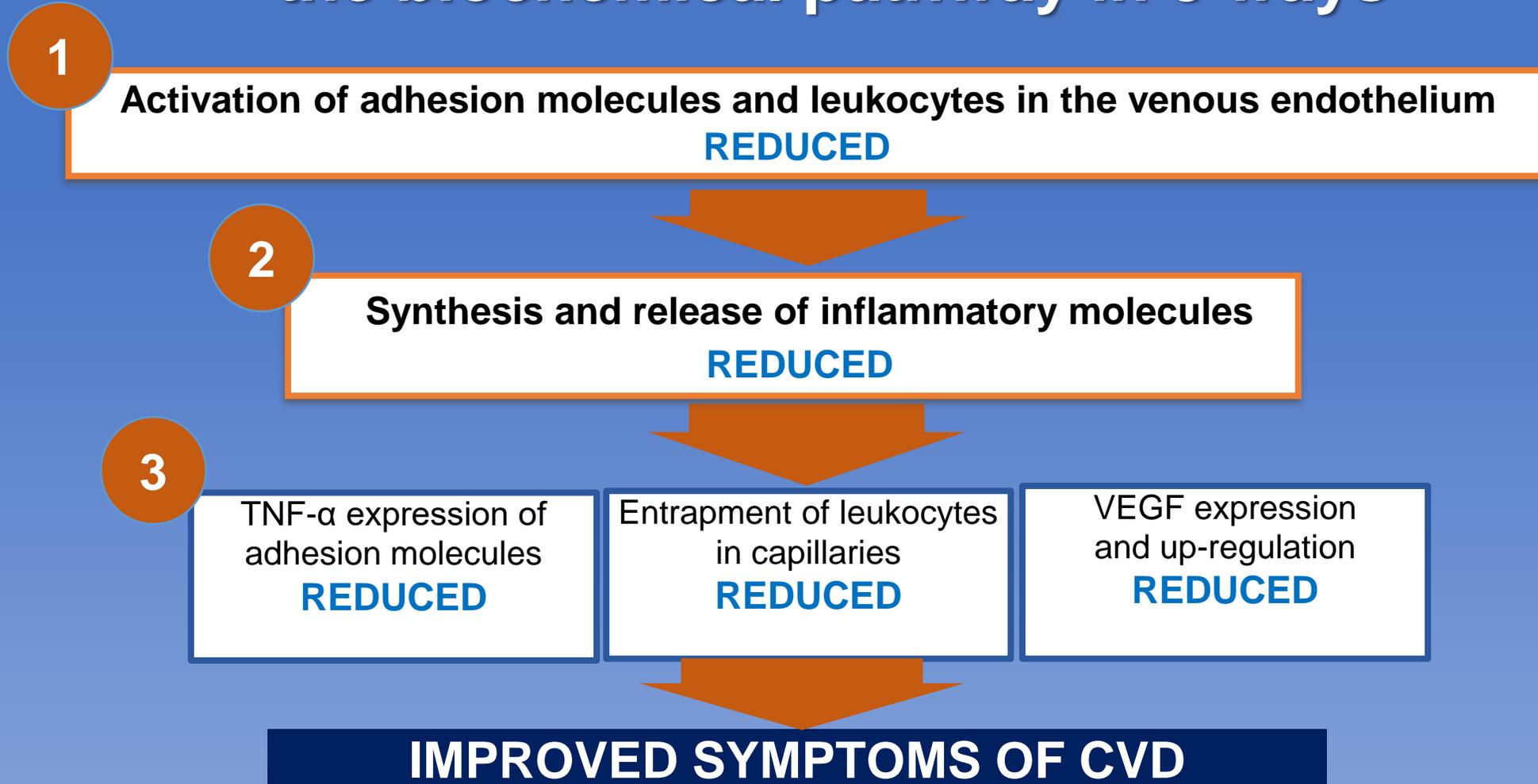
WBC Activation and Adhesion

# Cascade of Complex Metabolic/molecular Reactions



Adapted from: 1. Saharay & Coleridge-Smith J Vasc Surg 1997;25:265 2. Bergan J, Shortell C .Venous ulcers, Academic Press, Elsevier, 2006) Coleridge-Smith, Lower Extremity Wounds 2006; 5(3).]

# Only VASCULERA addresses the biochemical pathway in 3 ways



# Systematic Review of the Body of Evidence

- Literature review on the use of MPFF for effectiveness and safety
- Databases searched: Medline, Cochrane Database for Systematic Reviews, Google Scholar

Abstracts reviewed	250
Placebo trials	20
Observational studies	9
Comparison studies	16
Meta-analyses	4
Reviews	16
Questionable/Rejected studies	132
Papers Selected for Review	65
Papers included in final Review	10

# Results: Objective and subjective outcomes

## Outcomes of MPFF on CVD can be divided into 2 categories:

- **Objective:** Signs which can be measured objectively, such as: edema, ulceration and trophic changes
- **Subjective:** Symptoms based on patient report, and are subjective such as: pain, sensations of heaviness and swelling, nocturnal cramps, paresthesias, heat or burning and erythema or cyanosis.
- Only randomized, placebo controlled, double-blind studies were considered in evaluating the effect of MPFF on subjective symptoms.

In summary, the general level of evidence supports the recommendation that the use of medical therapy with Micronized Purified Flavanoid Fraction (diosmin) has beneficial outcomes without serious adverse events.

# Study Review: Objective Outcomes

Objective outcomes are assessed through measurable improvements to signs of CVD

Conclusion	Studies
<b>MPFF is of benefit in ulcer healing and reducing ulcer healing time</b> --Greatest benefit seen in ulcers <5cm diameter and <5 years duration <sup>1-3</sup>	4 RCTs; pooled and meta analyses
<b>MPFF showed significant benefit in healing trophic changes<sup>4-6</sup></b> --Pooled analysis showed significant benefit	2/4 RCTs; pooled analysis (Cochrane Review)
<b>MPFF demonstrated a decrease in ankle edema<sup>6-7</sup></b> ---Pooled analysis of statistically significant improvement	4 RCTs; pooled analysis (Cochrane Review)

1. Guilhou JJ, Dereure O, Marzin L et al. Efficacy of Daflon 500 mg in venous leg ulcer healing: a double-blind, randomized, controlled versus placebo trial in 107 patients. *Angiology* 1997;48(1):77-85. 2. Glinski W. The beneficial augmentative effect of micronized purified flavonoid fraction (MPFF) on the healing of leg ulcers: An open, multicenter, controlled, randomized study. *Phlebology* 1999;(4):151-7. 3. Roztocil K, Stvrtinova V, Strejcek J. Efficacy of a 6-month treatment with Daflon 500 mg in patients with venous leg ulcers associated with chronic venous insufficiency. *Int Angiol* 2003;22(1):24-31. 4. Feroso J, Legido AG, Del Pino J, et al. Therapeutic value of hidrosmin in the treatment of venous disorders of the lower limbs. *Curr Ther Res* 1992;52(1):124-34. 5. Gilly R, Pillion G, Frileux C. Evaluation of a New Venoactive Micronized Flavonoid Fraction (S 5682) in Symptomatic Disturbances of the Venolymphatic Circulation of the Lower Limb: A Double-Blind, Placebo-Controlled Study. *Phlebology* 1994; 9(2):67-70. 6. Laurent R, Gilly R, Frileux C. Clinical evaluation of a venotropic drug in man. Example of Daflon 500 mg. *Int Angiol* 1988;7(2S):S1-43. 7. Martinez-Zapata MJ, Vernooij RW, Uriona Tuma SM et al. Phlebotonics for venous insufficiency. *Cochrane Database of Systematic Reviews* 2016;(4).