2018 MID-ATLANTIC
CONFERENCE

8th ANNUAL CURRENT CONCEPTS IN
VASCULAR THERAPIES

Medical Management of Venous Ulcers

When a Vascular Consult Isn't Enough

Michael F. Amendola MD FACS
Hunter Holmes McGuire VA Medical Center
Virginia Commonwealth University Health System

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"Non-Surgical" Management of Venous Ulcers

When a Vascular Consult Isn't Enough

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Disclaimer

- Although the information contained in this session is focused on a disease state with details as it pertains to practice in the Department of Veterans Affairs, it is not intended to provide interpretation of VA policy nor specific details about how individual VA Medical Centers operate services within their jurisdiction.

- The contents do not represent the views of the United States Department of Veterans Affairs nor the United States Government.

Outline

- General Philosophy
- Common Ground
- Components of Non-Operative Management
- Food for Thought
- Conclusions

https://vignette.wikia.nocookie.net/community-sitcom/images/f/f2/Ghostbusters.jpg/revision/latest?cb=20121024074008&format=original

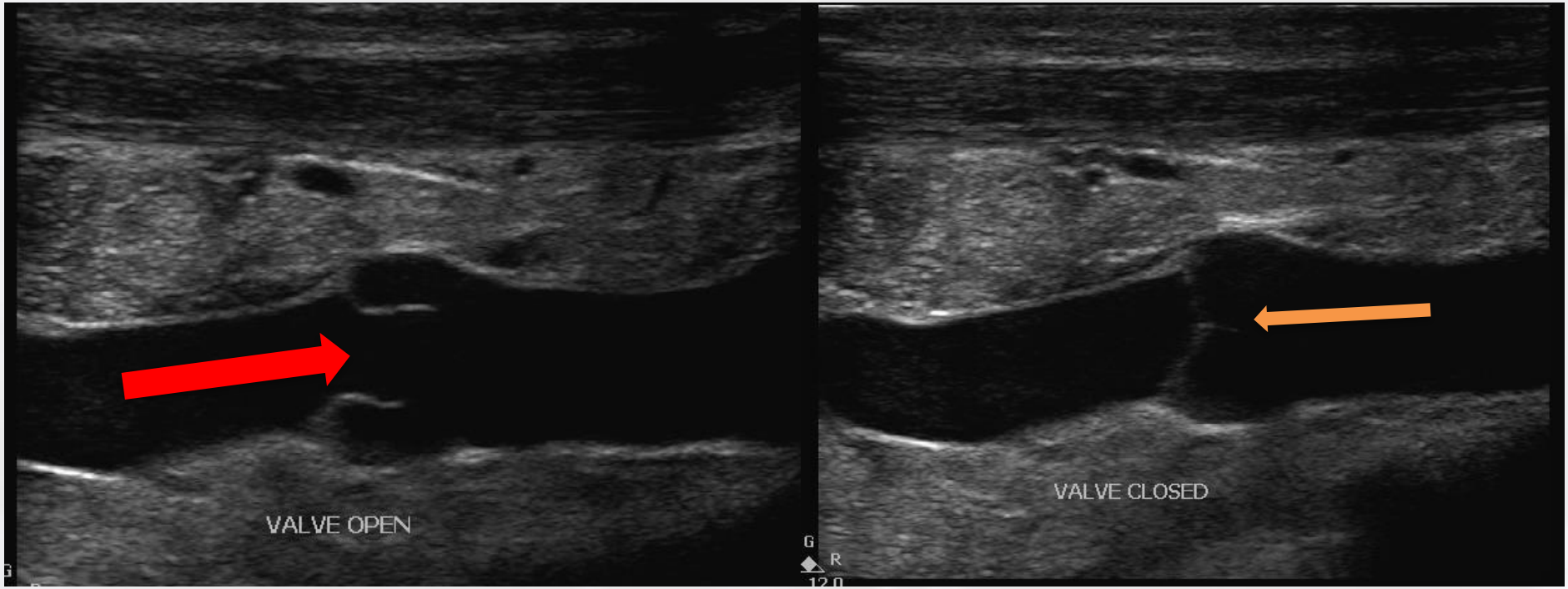
COMMON GROUND

Hydrostatic

Weight of the column of blood from the right atrium to the foot

Hydrodynamic

Related to the pressures generated by contractions of the skeletal muscles of the leg in the capillary network



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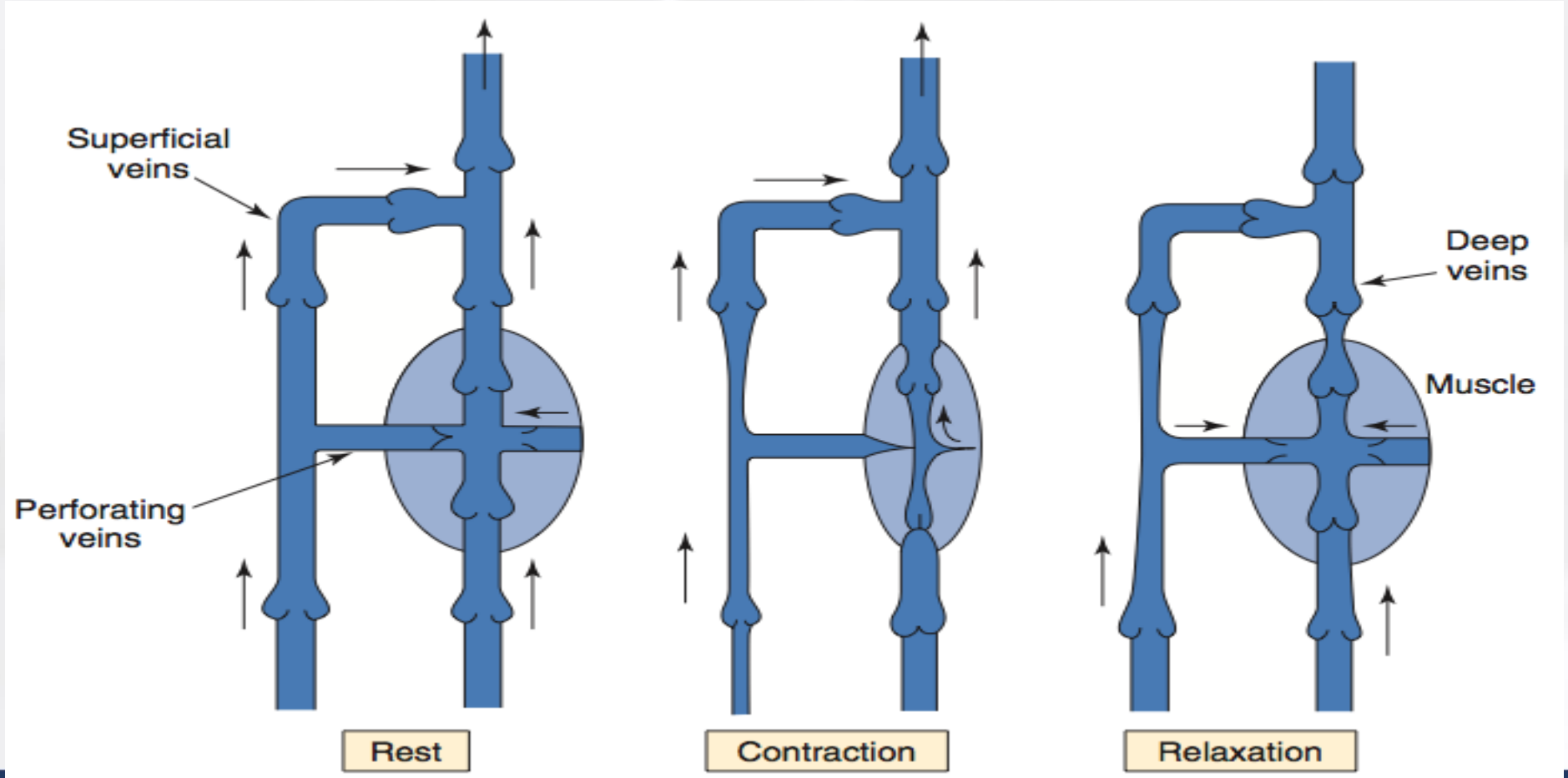
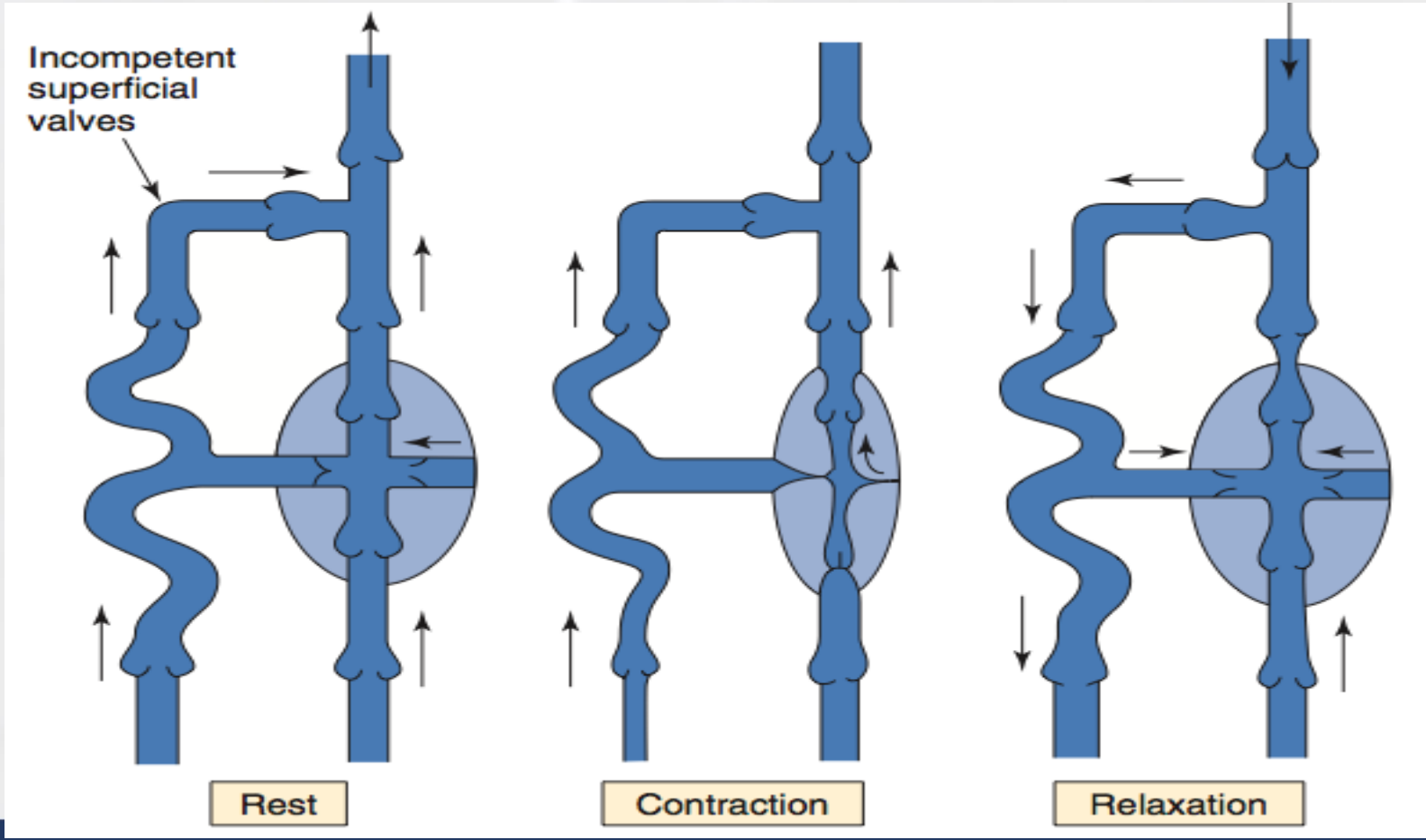


Rutherford's Vascular Surgery, 7th ed, p 156.

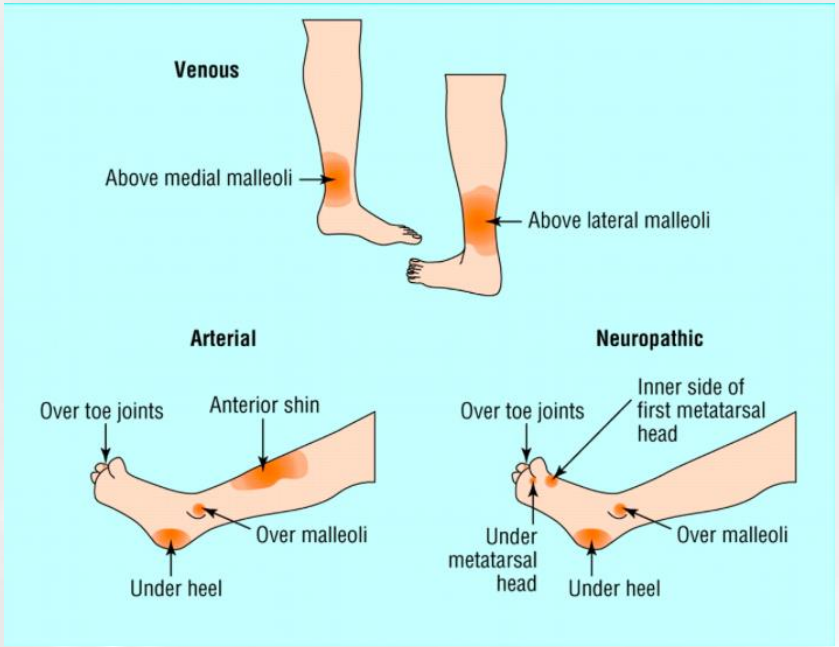

Venous
Insufficiency

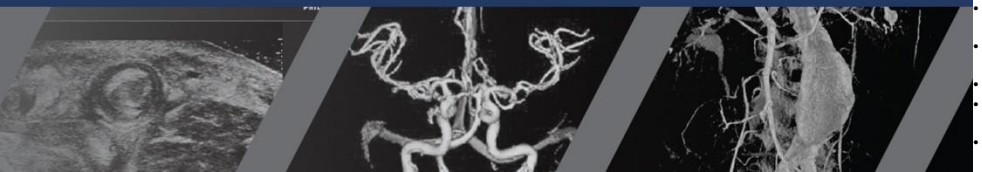


Rutherford's Vascular Surgery, 7th ed, p 156.

Pathogenesis

- Disrupting of microcirculation
- Increasing permeability
- Leakage of plasma and erythrocytes into the surrounding tissue
- Increased levels of leukocytes in the dependent limbs of patients with chronic venous insufficiency





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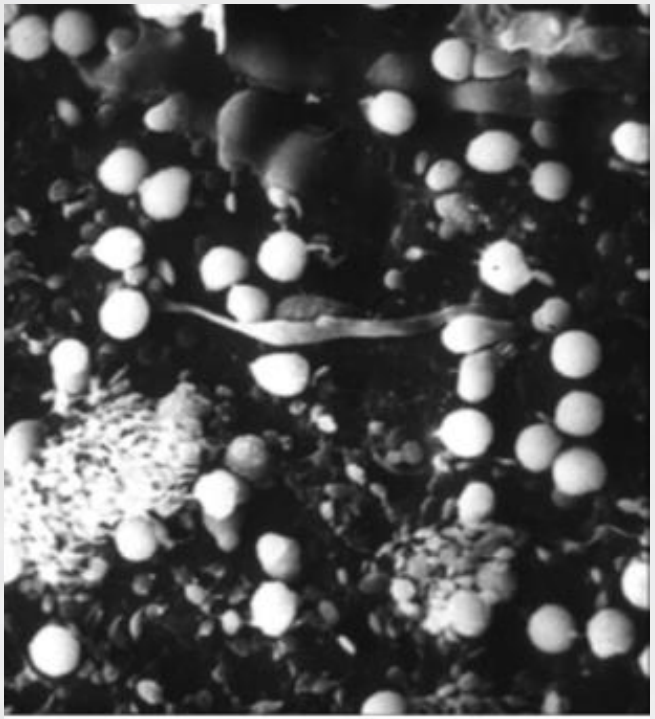
- Thomas PR, Nash GB, Dormandy JA. White cell accumulation in dependent legs of patients with venous hypertension: a possible mechanism for trophic changes in the skin. BMJ 1988;296:1693– 1695

White Cell Trapping

- Localized hypertension ➞ leukocyte trapping/activation
- Releasing free radicals and promotes cell death/tissue damage
- Capillary bed hypertension macromolecules leaking in dermis
- Traps growth factors and cytokines necessary for tissue repair



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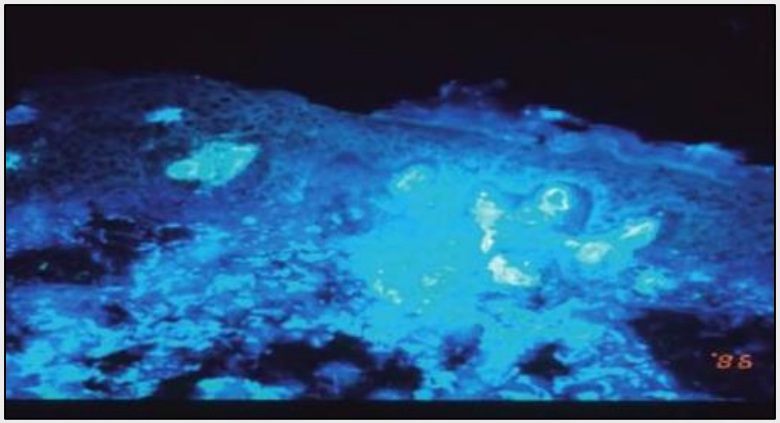
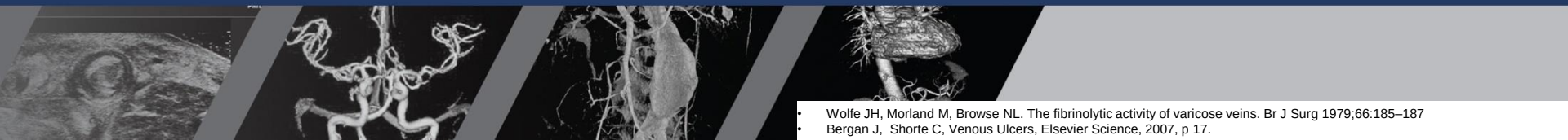
- Bergan J, Shorte C, Venous Ulcers, Elsevier Science, 2007, p 15.
- Comerota A, Lurie F, Pathogenesis of venous ulcer, Seminars in Vascular Surgery. 28(1) 2015, p 6-14.

Fibrin Cuff Theory



- Pericapillary fibrin cuffs that result from venous hypertension
- Extravasation of fibrinogen
- Barriers to the diffusion
- Leading to tissue hypoxia, cell death and ulceration
- However ☞discontinuous, and ulcers can heal



- Wolfe JH, Morland M, Browse NL. The fibrinolytic activity of varicose veins. Br J Surg 1979;66:185–187
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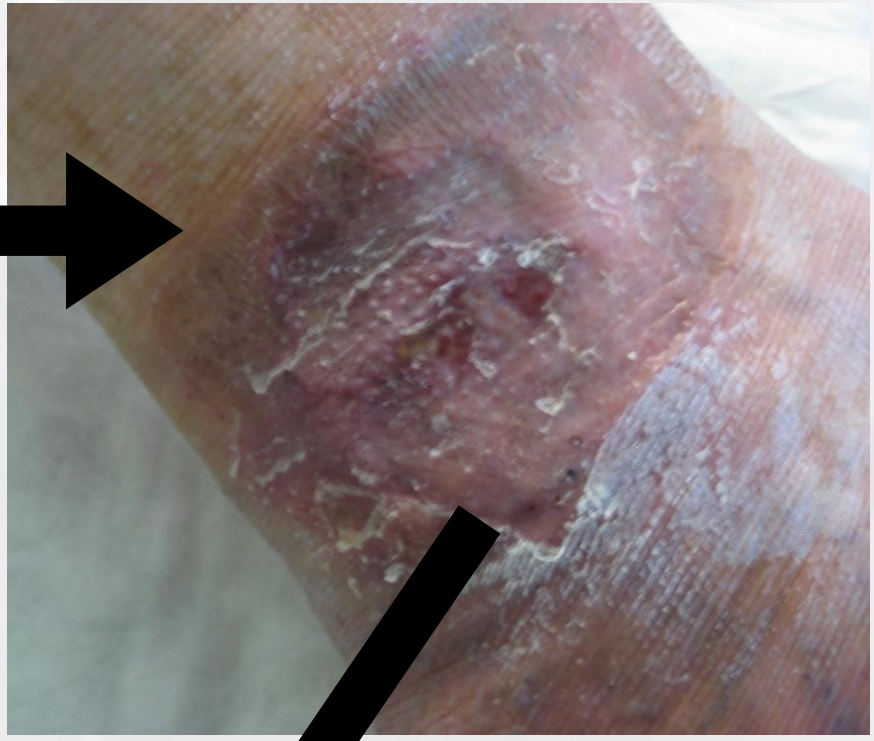
Clinical Classification

C0	No visible sign of venous disease
C1	Telangiectases and/or reticular veins
C2	Varicose veins
C3	Edema
C4‡	Changes in skin and subcutaneous tissue
A	Pigmentation or eczema
B	Lipodermatosclerosis or atrophie blanche
C5	Healed ulcer
C6	Active ulcer

Rutherford's Vascular Surgery, 7th ed, p 156.


C5

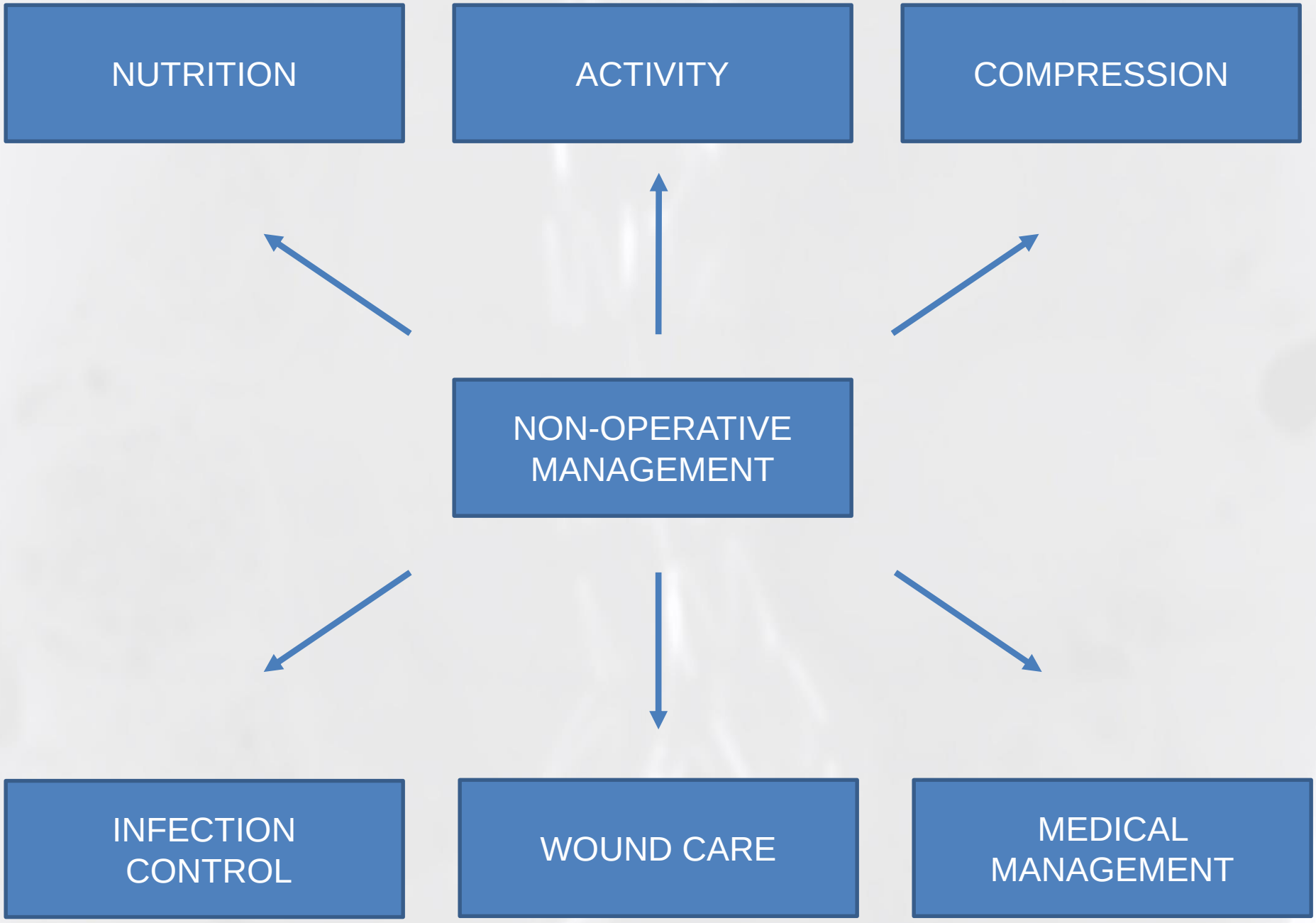


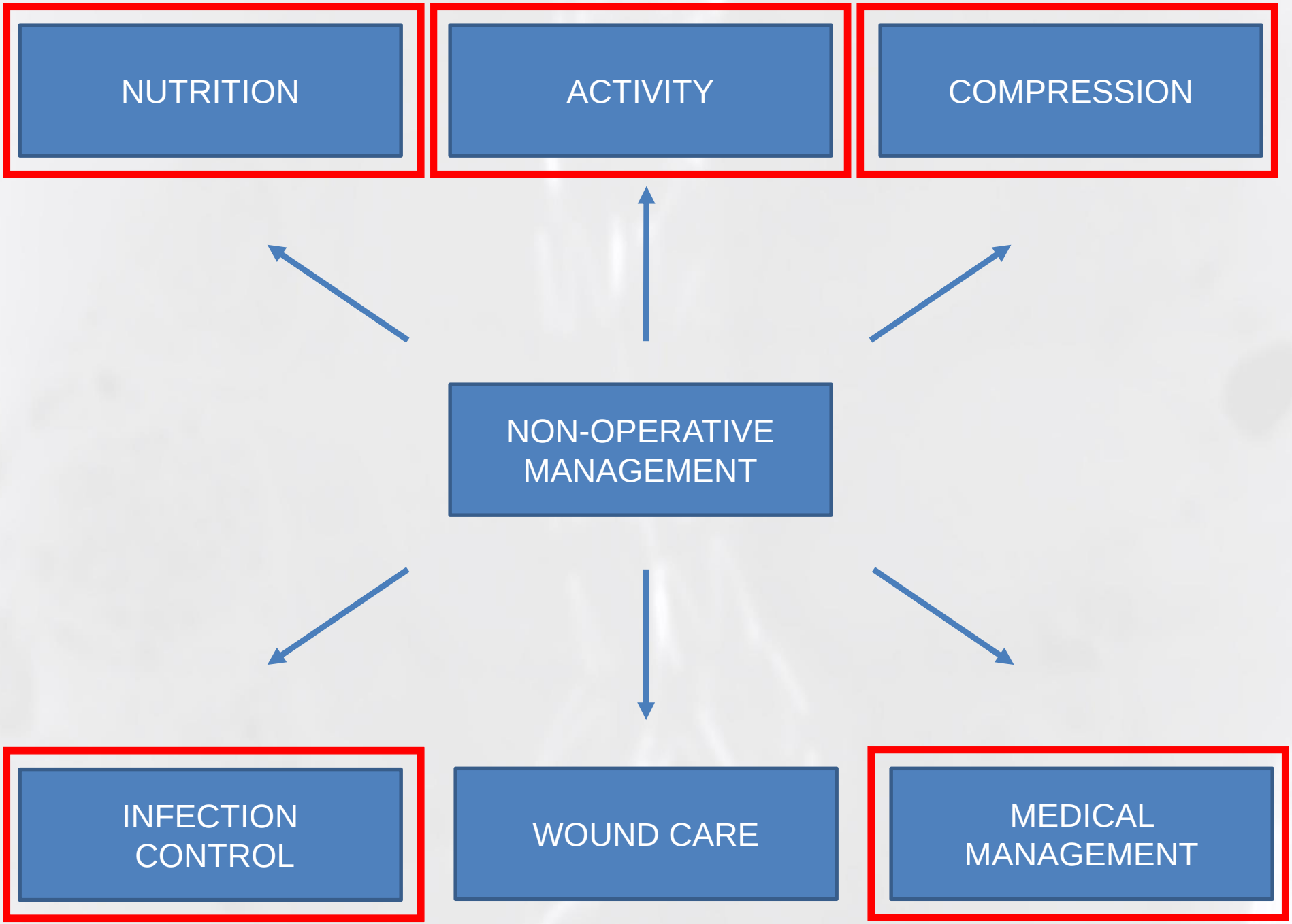

C6


C5


C6

NON-OPERATIVE MANAGEMENT

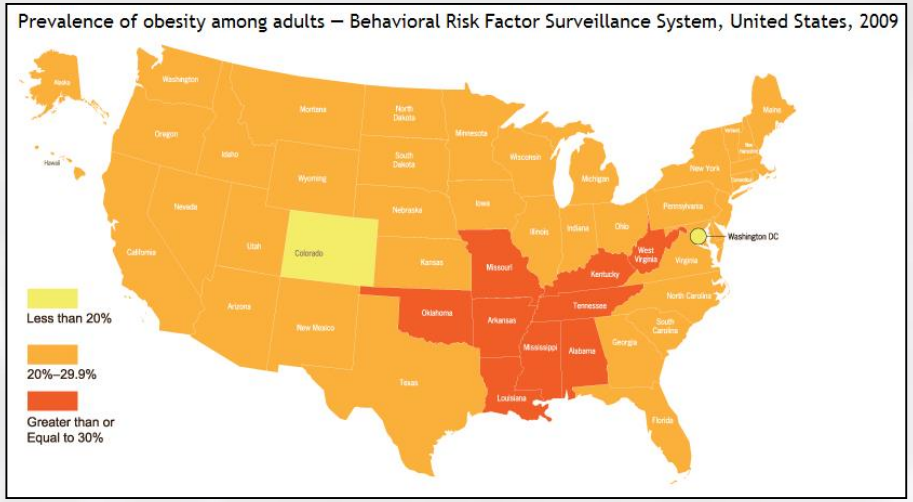

NUTRITION
ACTIVITY
COMPRESSION
NON-OPERATIVE MANAGEMENT
INFECTION CONTROL
WOUND CARE
MEDICAL MANAGEMENT

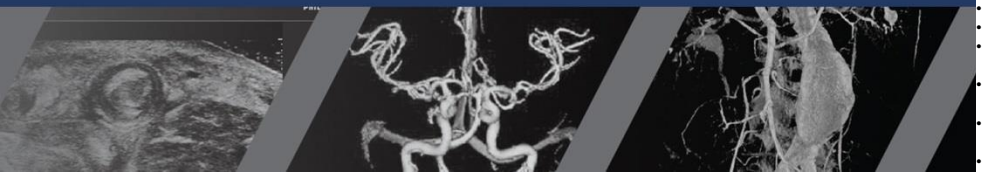

NUTRITION
ACTIVITY
COMPRESSION
NON-OPERATIVE MANAGEMENT
INFECTION CONTROL
WOUND CARE
MEDICAL MANAGEMENT

NUTRITIONAL

The Effect of Weight

- Obese increases the risk of chronic venous disease and varicose veins
- ⇩ reduces pressure on leg veins
- ⇩micro-circulation
- ⇩ energy
- ⇩ mobility





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- Scherger J. First Consult. Varicose Veins. www.clinicalkey.com. Last updated 6/18/2012.

Diet

- Low fiber diet ~ bowel movement strain
- Straining
  - ☝ abdominal pressure
  - ☝ venous pressure
  - ☟ venous wall strength
  - ☝ varicose veins

- MacKay D. Hemorrhoids and varicose veins: a review of treatment options. Alternative medicine review : a journal of clinical therapeutic. Apr 2001;6(2):126-140.
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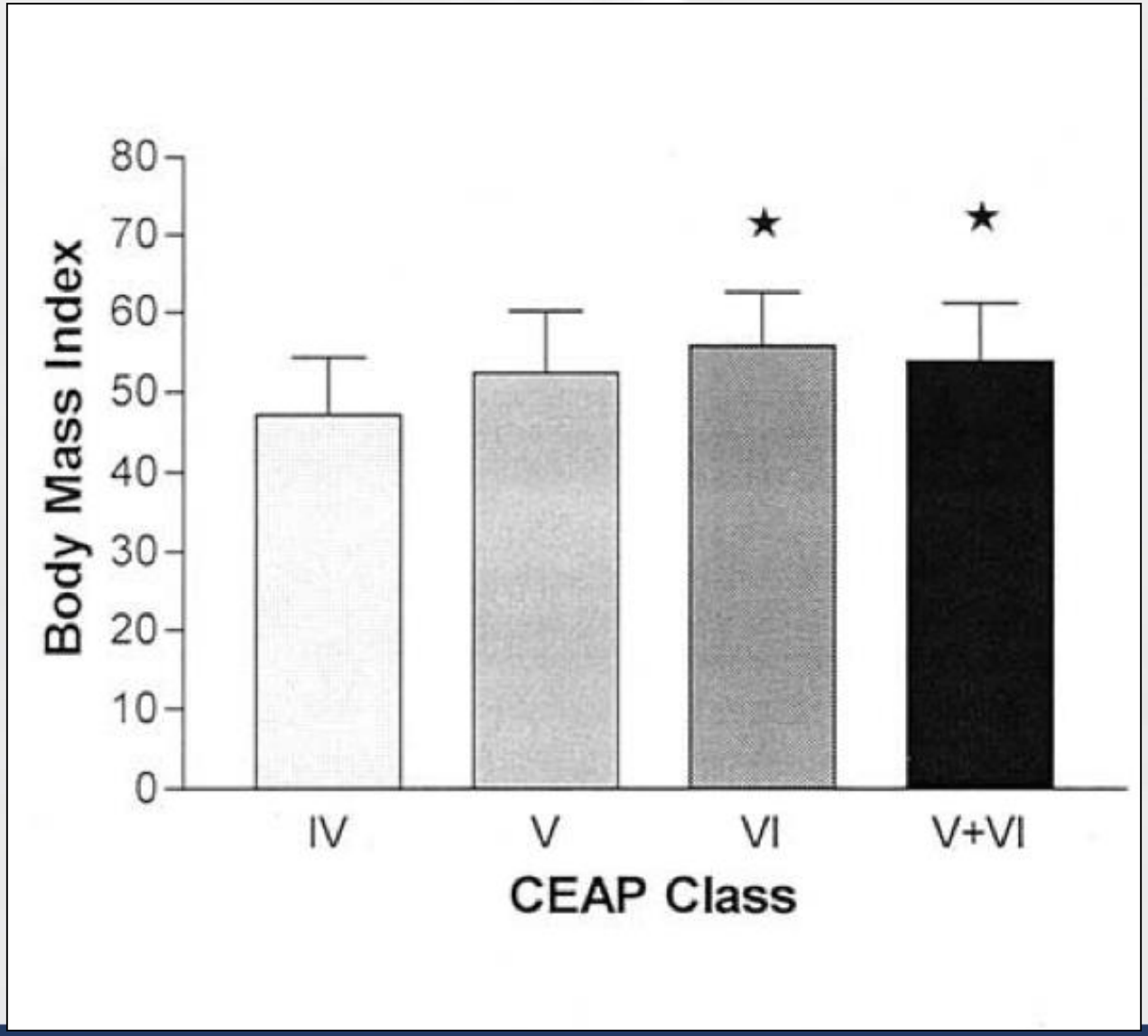

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ACTIVITY

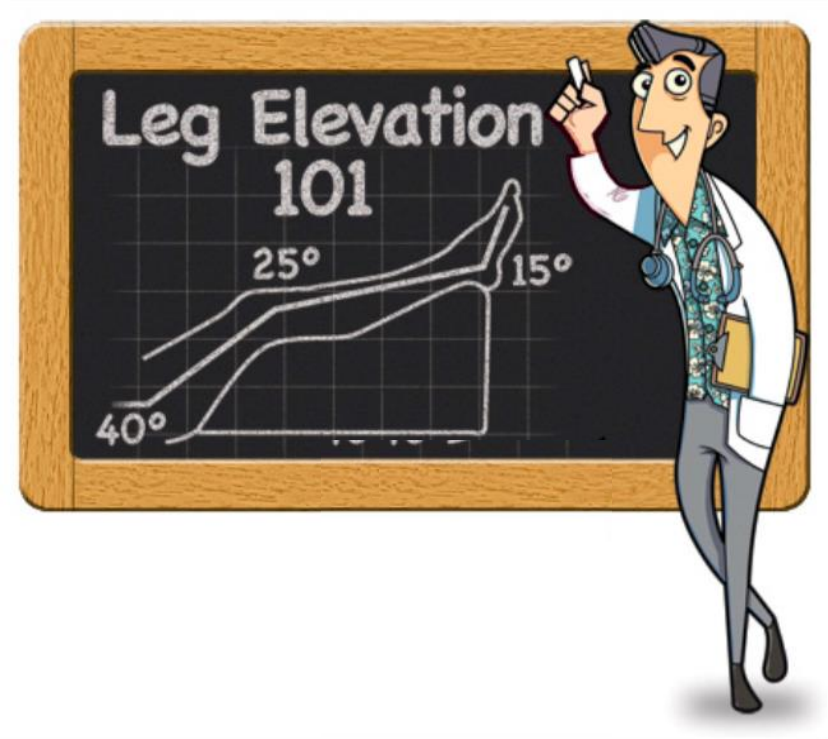
How Active is Active?

- Advanced chronic venous disease is associated with overall poor mobility status
- Increased mobility promotes ulcer healing and to be an adjunct to compression therapy
- Aged matched controls (> 60 years) to those with VU
  - walking speed, endurance, and self- perceived exertion were severely impaired
  - ankle plantar flexion and dorsiflexion were significantly reduced if active ulcers were present ☞ pain

- Brown A. Life-style advice and self-care strategies for venous leg ulcer patients: what is the evidence? J Wound Care 2012;21:342–4, 346, 348–50.

Leg Elevation

- Venous drainage
- Blood return to the heart
- Ankle edema
- Cutaneous microcirculation
- C5 recurrence with
  - compression
  - leg elevation times of 33 minutes per day



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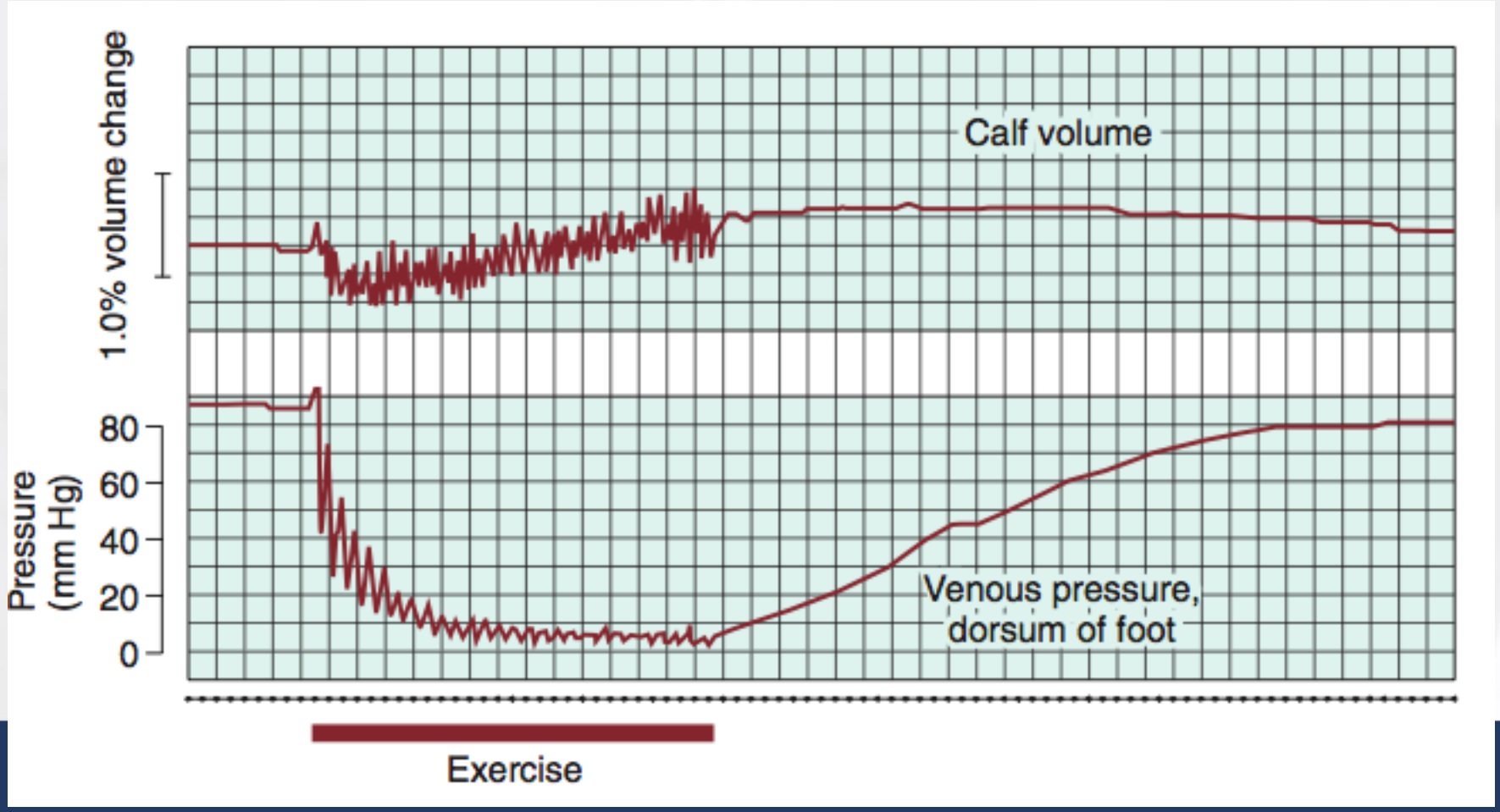
- https://www.loungedoctor.com/classroom.html

Ambulatory Venous Pressure



Rutherford's Vascular Surgery, 7th ed, p 157.

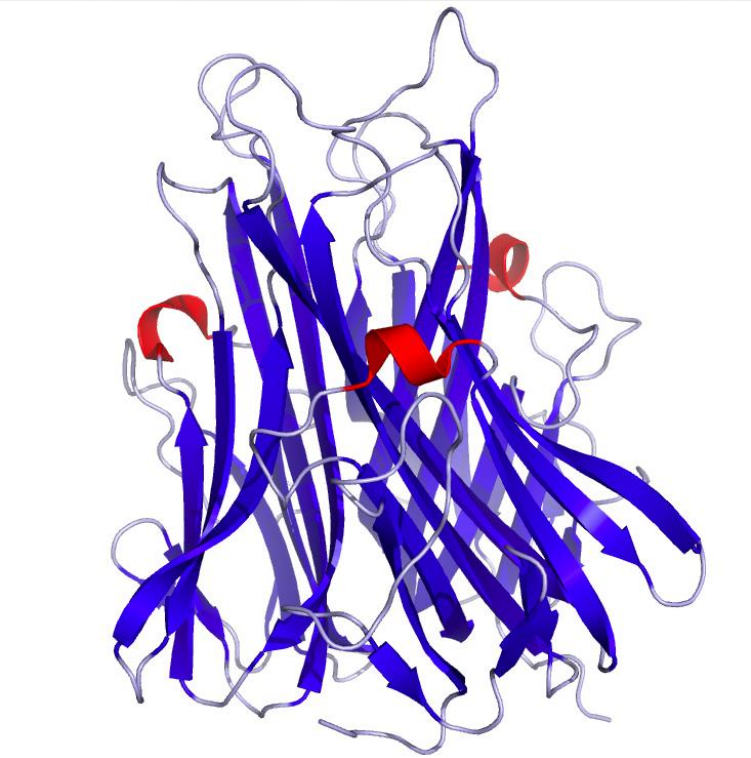
COMPRESSION

Rationale

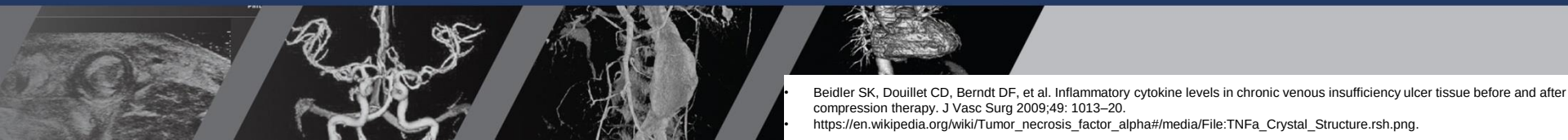
- Foundation of the treatment
- Attenuate reflux-induced venous hypertension.
- Normal standing resting venous pressure ~ 60 to 80 mmHg
- Compression between 35 - 40 mmHg
- Safe limit ~ 60 mm Hg has been shown to the safe upper limit (ABI > 0.5)

- Partsch B, Partsch H. Calf compression pressure required to achieve venous closure from supine to standing positions. J Vasc Surg 2005;42:734–8.
- http://actionmedical.ca/aids-daily-living/dressing-aids/compression-stocking-aid.

Biochemical Effects



- ↓ Capillary density
- ↓ Transcutaneous oxygen
- ↑ Inflammatory cytokines
- ↑ Tumor necrosis factor α
- ↑ Endothelial growth factor
- ↑ Interleukin 1β

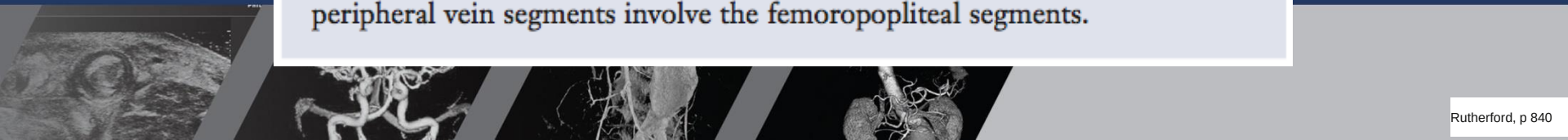


- Beidler SK, Douillet CD, Berndt DF, et al. Inflammatory cytokine levels in chronic venous insufficiency ulcer tissue before and after compression therapy. J Vasc Surg 2009;49: 1013–20.
- https://en.wikipedia.org/wiki/Tumor_necrosis_factor_alpha#/media/File:TNFa_Crystal_Structure.rsh.png.

Table 53-5 Treatment of Venous Disorders Based on Pathophysiology

Venous Pathophysiology	Primary Treatment	Secondary Treatment*
Reflux		
Superficial	Compression	Ablation, HLS, sclerotherapy, foam, phlebectomy, pharmacologic
Deep	Compression	Valve reconstruction
Perforator	Compression	Ablation, foam, ligation, SEPS
Obstruction (nonacute)		
Central	Compression, venous stenting	Venous stenting
Peripheral	Compression	Valve reconstruction
Muscle pump dysfunction	Compression	Structured exercise

*Ablation indicates endovenous radiofrequency and laser ablation. HLS indicates high ligation and stripping. Pharmacologic includes the micronized purified flavonoid fraction (Daflon), horse chestnut seed extract. SEPS indicates subfascial endoscopic perforator surgery. Central obstruction indicates vein segments involving the femoroiliocaval segments, and peripheral vein segments involve the femoropopliteal segments.



Rutherford, p 840

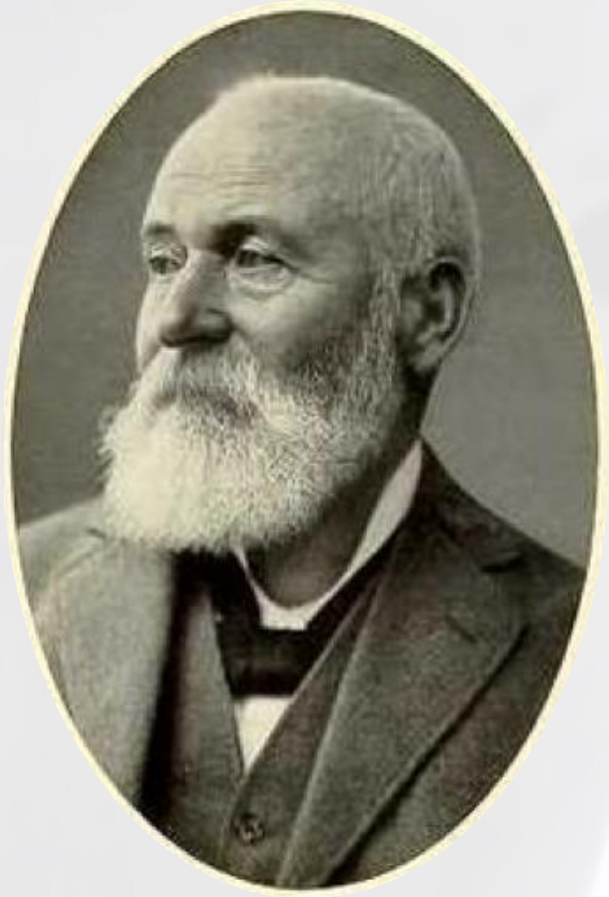
Lets Get Real

- Thrombo-Embolic Deterrent Hose (TED)
- Gradient compression stockings
- Anti-embolism compression stockings
- Knee-high
- Thigh-high length
- 10 to 15 mmHg

https://hillcrestsouth.com/news/when-should-you-wear-ted-hose-or-compression-socks

Paul Gerson Unna

- 1850 to 1929
- Private Dermatology practice
- Strong interest in venous disease
- “Unna Boot”



What is Unna's Boot?

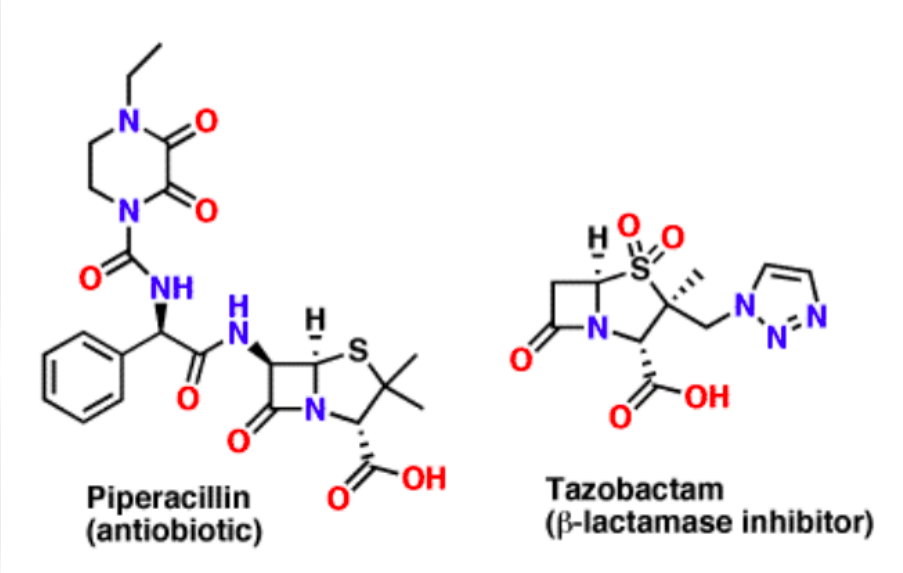
- 4 inches wide
- 10 yards long
- Thick creamy mixture
  - zinc oxide
  - calamine
  - acacia
  - glycerin
  - castor oil and white petrolatum

- www.en.wikipedia.org
- www.amazon.com/Covidien-8034-Curity-Unna-Bandage/dp/B00PTZOKZW/ref=sr_1_9_s_it?s=hpc&ie=UTF8&qid=1523015867&sr=1-9&keywords=unna+boot

INFECTION CONTROL

To Treat or Not To Treat

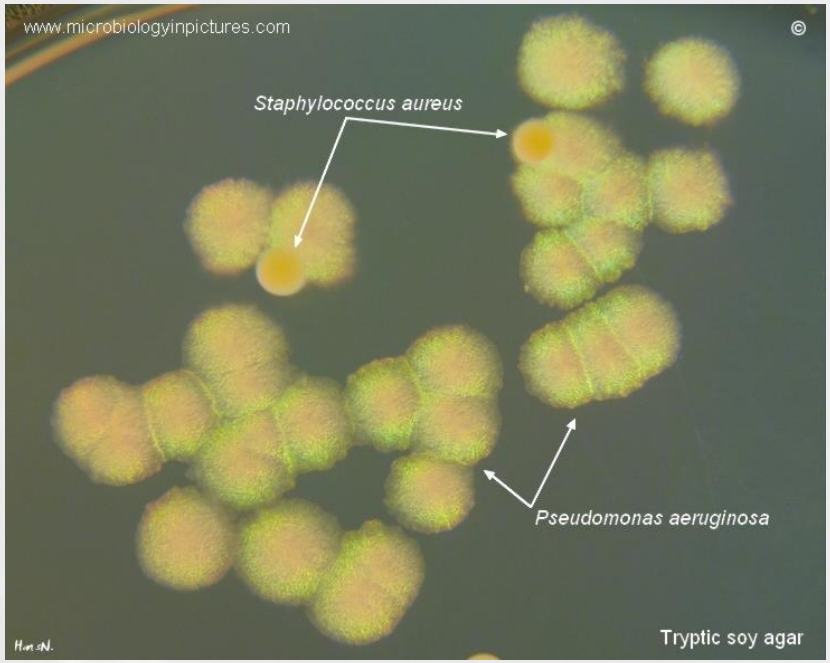
- Complex
- Bacterial colonization
- Superimposed bacterial infections
- Cochrane review of 22 RCTs
  - Systemic antibiotics?
  - Topical antibiotics?
  - Antiseptics?
  - No evidence that routine use of oral antibiotics improves healing



https://www.masterorganicchemistry.com/2015/01/06/my-recent-absence-explained-with-9-molecules/

Bugs Bugs Bugs

- Staphylococcus aureus
- Pseudomonas aeruginosa
- Beta-haemolytic streptococci
- Broad spectrum penicillin
- Macrolide
- Quinolone
- Two-week course



- Grey J, Enoch S, Harding K. ABC of wound healing Venous and arterial leg ulcers. BMJ. 2006 Feb 11; 332(7537): 364.
- www.microbiologyinpictures.com/bacteria-photos/pseudomonas-aeruginosa-photos/pseudomonas-green-colonies.html

Antibiotics

- Topical antiseptic agent cadexomer iodine - increased healing rate at four to six weeks compared with placebo.
- Oral antibiotics are recommended to treat venous ulcers only in cases of suspected cellulitis.
- Consider IV antibiotics for failed outpatient management

- Grey J, Enoch S, Harding K. ABC of wound healing Venous and arterial leg ulcers. BMJ. 2006 Feb 11; 332(7537): 364.
- http://thesportenergy.me/augmentin-profile/

MEDICAL MANAGEMENT

Pentoxifylline

- Competitive nonselective inhibitor of the enzyme adenylate cyclase
  - ↓ intracellular cyclic adenosine monophosphate
  - ↓ protein kinase A
  - ↓inhibition of tumor necrosis factor
  - ↓ leukotriene synthesis

https://granulomaannulare.wordpress.com/2016/03/29/pentoxifylline/

Pentoxifylline

A factorial, randomized trial of pentoxifylline or placebo, four-layer or single-layer compression, and knitted viscose or hydrocolloid dressings for venous ulcers

E. Andrea Nelson, PhD, RN,[a,b] Robin J. Prescott, PhD, BSc,[b,c] Douglas R. Harper, MD, BSc, FRCSEd, FRCSGlas,[b] Barbara Gibson, RN,[b] Dorothy Brown, RN,[b] and C. Vaughan Ruckley, MB, ChM, FRCPE, FRCSE[b,d] *Leeds and Edinburgh, United Kingdom*

Objective: We evaluated the effectiveness of pentoxifylline, knitted viscose or hydrocolloid dressings, and single-layer or four-layer bandaging for venous ulceration.

Method: A factorial randomized controlled trial with 24-week follow-up was conducted in legular clinics in Scotland with blinded allocation to pentoxifylline (1200 mg) or placebo, knitted viscose or hydrocolloid dressings, and single-layer or four-layer bandages. The study enrolled 245 adults with venous ulcers. The main outcome measure was time to complete healing. Secondary outcomes included proportion healed, withdrawals, and adverse events. Analysis was by intention to treat.

Results: There was no evidence of interaction between the drug, bandages, and dressings. Pentoxifylline was associated with nonsignificant increased ulcer healing (62% vs 53%; *P* = .21). Four-layer bandages were associated with significantly higher healing rates (67% vs 49%; *P* = .009). There was no difference in healing between knitted viscose and hydrocolloid dressings (58% and 57%; *P* = .88). Cox regression models increased the significance of the pentoxifylline effect (relative risk of healing, 1.4; 95% confidence interval, 1.0 to 2.0).

Conclusions: Pentoxifylline increased the proportion healing compared with placebo to the same extent as shown in recent systematic reviews, although this finding was only statistically significant when a secondary adjusted analysis was conducted. Four-layer bandaging produced higher healing rates than single-layer bandaging. There was no difference in time to healing between knitted viscose and hydrocolloid dressings. (J Vasc Surg 2007;45:134-41.)

Leg ulceration is a chronic, recurring condition affecting about 1% of the adult population in industrialized countries.[1,2] Most ulcers are secondary to venous insufficiency, others are due to arterial insufficiency, diabetes mellitus, rheumatoid arthritis, and connective tissue disorders. The primary functional abnormality in venous ulceration is ambulatory venous hypertension caused by venous reflux or obstruction that gives rise to changes at the tissue level, including white cell trapping, capillary fuffing, and pericapillary fibrin cuffs.[3] Externally applied compression, such as bandages, stockings, or pneumatic boots, reduces venous hypertension and promotes healing.[4]

A systematic review has found that compression heals more ulcers than dressings alone.[5] It has not been possible, however, to determine the dose-response relationship between compression levels and healing rates, and whether, for example, multiple layers of bandage are necessary.[4] Four-layer bandaging is widely used but it can be bulky, and we sought to compare it with a single layered bandage that can supply and sustain high levels of pressure.[6]

Ulcer management includes wound dressings to prevent bandages from adhering to the wound and to provide a moist environment for wound healing.[7] Modern dressings such as hydrocolloids promote moist wound healing by restricting moisture loss from the wound. The role of such semi-occlusive dressings in venous ulcers is unclear; however, because bandages also restrict moisture loss,[7] and a moist wound environment can thus be achieved with a dry dressing. Hydrocolloids cost more and have higher rates of contact sensitivity than simple dressings[8]; therefore, we set out to compare the relative effectiveness of knitted viscose and hydrocolloid dressings.

Another goal was to determine whether adjuvant therapy of sustained release pentoxifylline (oxpentifylline) with compression and dressings would increase healing rates, as four previous trials in 247 people receiving compression did not provide conclusive results,[9-12] and one trial found a statistically significant benefit with pentoxifylline.[10]

A factorial trial design allows examination of the interaction between interventions and comparison of a number of independent interventions with no increase in trial size.

From the School of Healthcare, University of Leeds[a]; Lothian and Forth Valley Leg Ulcer Study[b], and the Medical Statistics Unit,[c] and Department of Surgery,[d] University of Edinburgh.

Supported by ConvaTec UK Ltd, Hoechst Roussel Ltd UK, Chief Scientist Office, Scotland.

Competition of interest: The trial was partly funded by the distributors of pentoxifylline (Hoechst), hydrocolloid dressings (ConvaTec), and the single layer bandage (ConvaTec), but the analysis and writing were conducted independently.

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0741-5214/$32.00

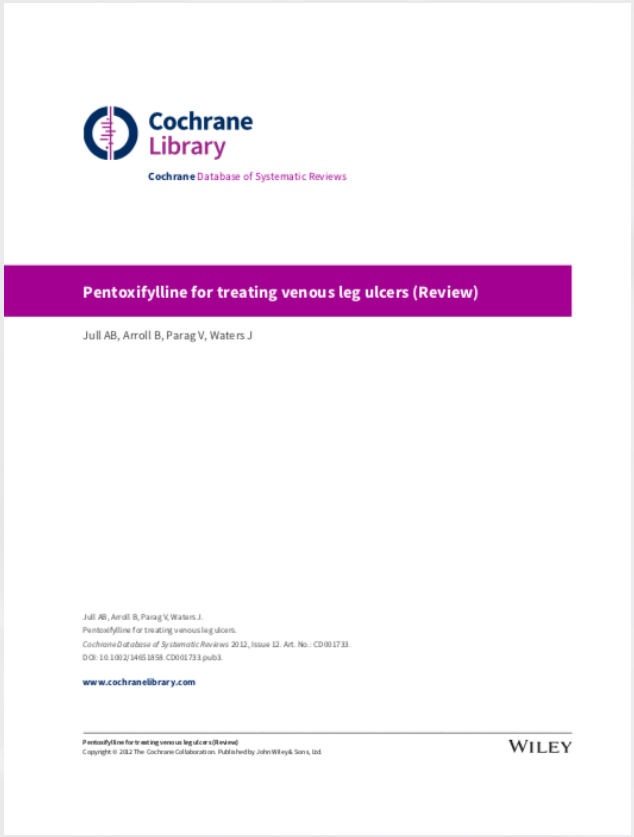
doi:10.1016/j.jvs.2006.09.043

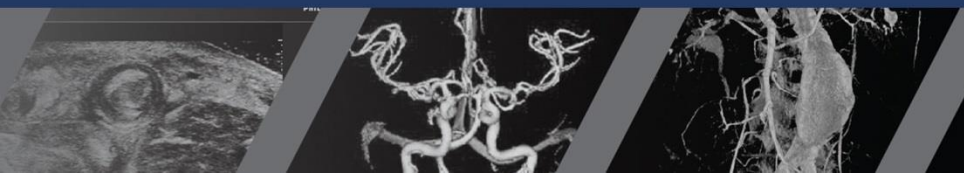
- Prospective randomized trial
  - 245 C_6 patients
  - Pentoxifylline 1200 mg daily
  - Standard dressings
  - Ulcer healing (62% vs 53%; p= NS)
  - Cox regression analysis model resulted in a clinically marginal significant improvement in ulcer healing in the Pentoxifylline group

Nelson EA, Prescott RJ, Harper DR, et al. A factorial, randomized trial of pentoxifylline or placebo, four-layer or single-layer compression, and knitted viscose or hydro- colloid dressings for venous ulcers. J Vasc Surg 2007;45: 134–41.

Pentoxifylline

- Cochrane review
- 12 trials
- 864 patients
- Pentoxifylline plus compression was found to be more effective than compression alone
- Pentoxifylline therapy alone was more effective than placebo or no treatment

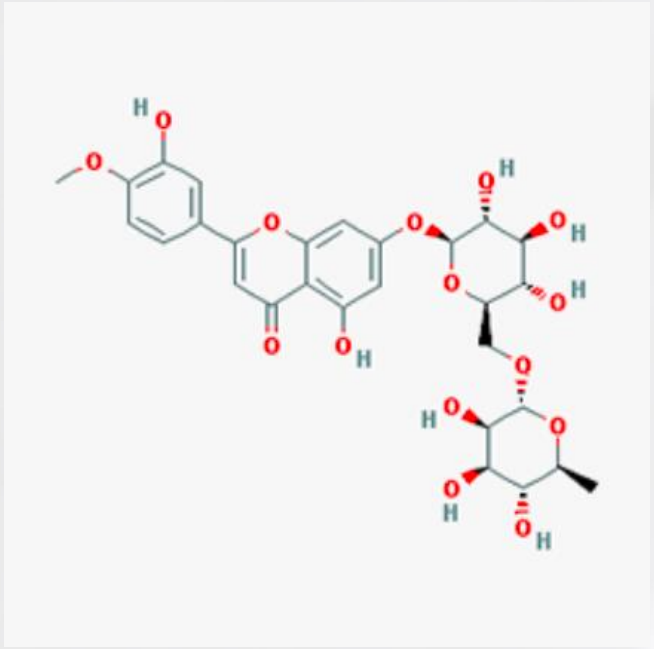




- 1Jull A, Arroll B, Parag V, et al. Pentoxifylline for treating venous leg ulcers. Cochrane Database Syst Rev 2007(3): CD001733.
- https://granulomaannulare.wordpress.com/2016/03/29/pentoxifylline/

Phlebotropic

- Daflon 500
- 90% micronized Diosmin and 10% Flavonoids
- Anti-inflammatory activity with inhibition of granulocytes and macrophage infiltration in the venous parenchyma.
- Animal model
  - leukocyte adhesion/migration into valvular tissue
  - expression of intercellular adhesion molecule-1 and P-selectin
  - apoptosis of endothelial cells
  - venous valve degeneration was attenuated in the treatment group



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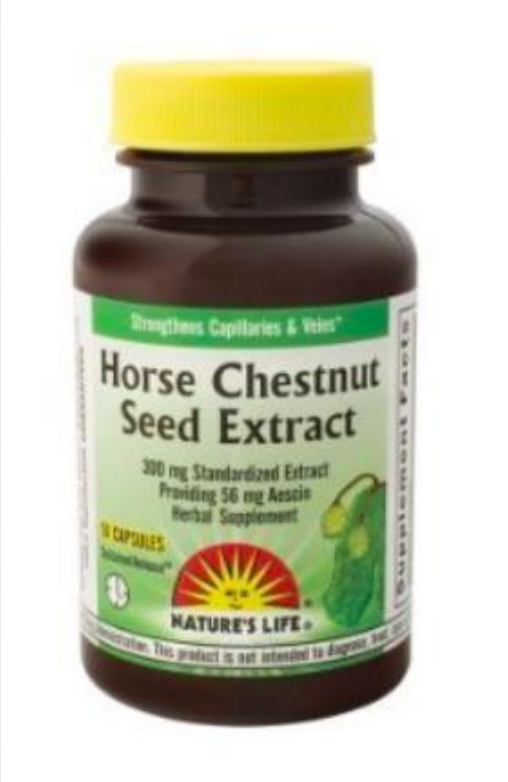
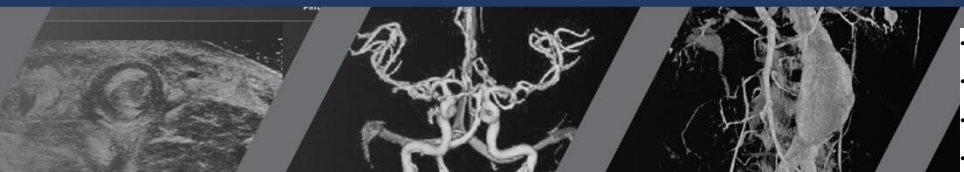
Horse Chestnut Seed Extract



- Aesculus hippocastanum
- Traditional herbal remedy
- Swelling and inflammation
- Used extensively in Europe to treat venous disorders.
- RCT is an effective and safe short-term treatment for chronic venous insufficiency
- Extract contains flavonoids



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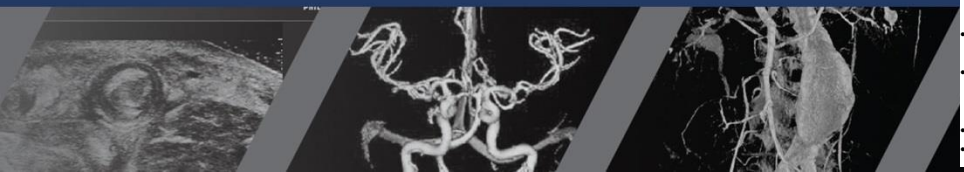
Pycnogenol

- French maritime pine bark.
- Chronic venous insufficiency
- Venous ulcer healing
- Reducing extremity edema
- Anti-inflammatory
- Vasodilating
- Anti-thrombotic properties
- May slow progression to chronic venous insufficiency?



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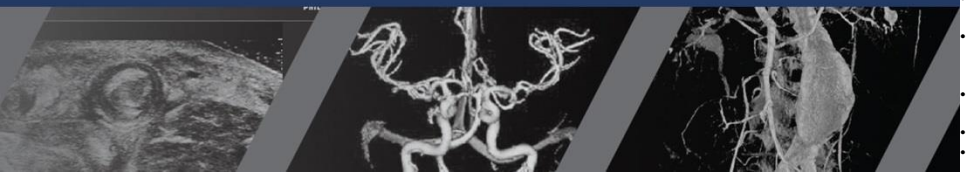
- www.ilactr.com/ilac/daflon.html
- www.pycnogenol.com/about/faq/

Centella Asiatica

- Gotu kola
- Southeast Asia tropical plant
- Carotenoids and Vitamins C and B complex
- RCT
  - likely exerts beneficial effects on the signs and symptoms of chronic venous insufficiency
  - significantly improved edema-related symptoms in patients with venous hypertension
  - ankle edema
  - improved the capacity of veins to stretch or dilate



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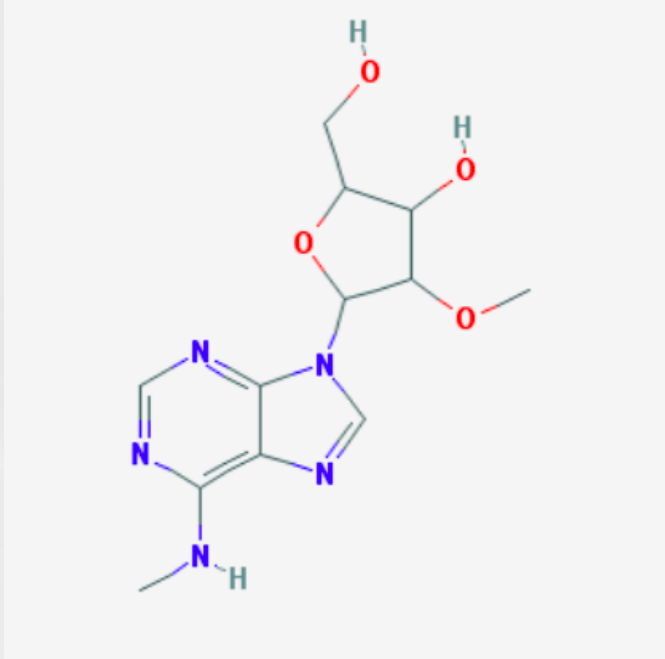
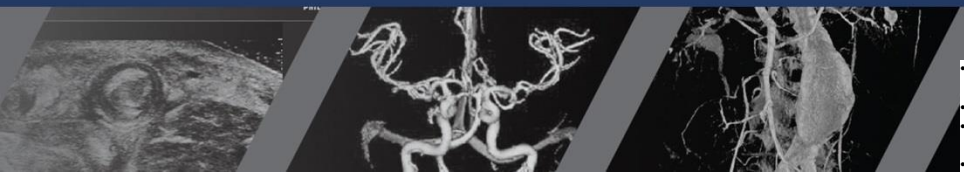
Sulodexide

- Purified complex of glycosaminoglycans
- Naturally occurs in ulcers
- Anticoagulant
- Anti-inflammatory
- Improves healing
- Used in Europe





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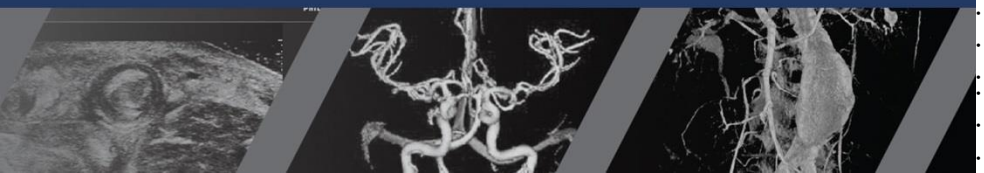
- https://pubchem.ncbi.nlm.nih.gov/compound/14366984.

Oxerutin

- Semisynthetic flavonoids mixture
- Commonly used in Europe
- Clinical trials
  - reduced edema
  - decreased pain
- Reduce excessive venous permeability and improvement in venous micro-circulation



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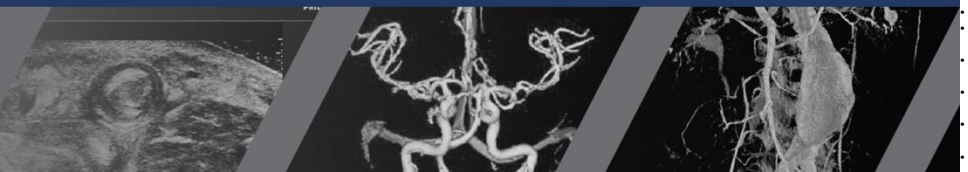
Others

Compound	Comments
Vitamin E	• Fat-soluble vitamin and free radical scavenger/anticoagulant
Grape Seed Extract	• Proanthocyanidins • Inhibit enzymes that degrade collagen and elastin efficacy in enhancing vascular function and circulation.
Vitamin C	• Scavenger of free radicals that also contributes to venous dilation. • Necessary for the synthesis of collagen • important role in wound healing
Butcher's Broom	• Ruscus aculeatus • Inhibit elastase enzymes - reduces vascular permeability • Contributes to edema.
Red Vine Leaf Extract	• Leaves of the wine grape plant (Vitis vinifera) • Powerful flavonoid present in many plants. • Improves pain and sensation of heaviness and swelling



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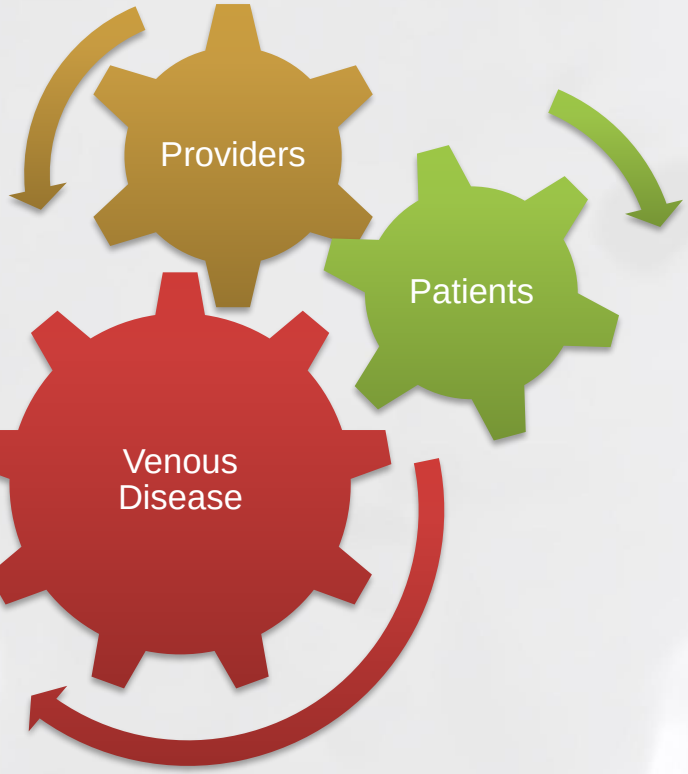
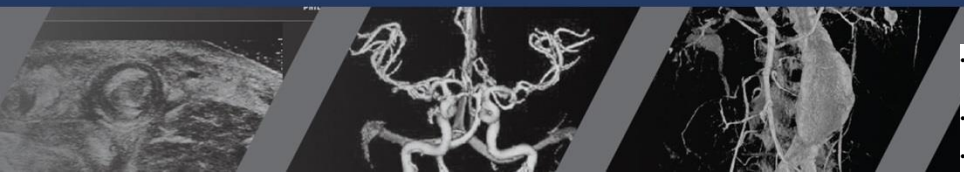
FOOD FOR THOUGHT

Venous Epidemiology

- ~ 1% Western Countries
- ~ 0.3% World Wide
- Active or healed venous ulcer
- Chronic venous disease ☝ prevalence with age - considered a “dose-related risk factor”





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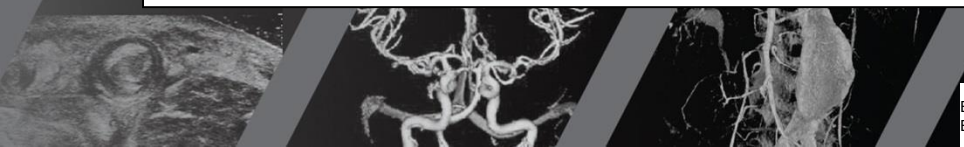
Prevalence

Year of publication	Reference	CVI manifestation	Prevalence (%) Males	Females
1958	Arnoldi (23)	Active or healed ulcer	1.9	5.5
1966	Bobek et al. (99)	Active or healed ulcer	0.9	1.1
1969	Mekky et al. (37)	Hyperpigmentation, ulcer, edema, and eczema		10.0
1973	Coon et al. (54)	Stasis skin change**	3.0	3.7
		Active or healed ulcer	0.1	0.3
1974	DaSilva et al. (56)	Dilated subcutaneous veins	10.0	15.0
		Hyperpigmentation	8.7	9.6
		Active or healed ulcer	1.1	1.4
1978	Widmer (20)	Skin changes*	6.0	5.0
		Active or healed ulcer	1.0	1.0
1986	Maffei et al. (53)	Edema	17.1	20.3
		Hyperpigmentation	7.6	5.2
		Eczema	2.5	1.1
		Fibrosis	1.3	0.5
		Active or healed ulcer	2.5	4.1
1992	Franks et al. (60)	Active or healed ulcer	4.7	4.0
1994	Komsuoglu et al. (42)	Hyperpigmentation	0.3	2.8
		Eczema	0.5	1.8
		Active or healed ulcer	0.6	1.4
1999	Evans et al. (21)	Dilated subcutaneous veins	6.9	5.3
2002	Ruckley et al.† (32)	Hyperpigmentation	1.3	1.1
		Active or healed ulcer	1.0	0.2
2003	Criqui et al. (40)	Trophic changes‡	7.8	5.3
		Edema	7.4	4.9

*Excluding varicose veins.
**Hyperpigmentation, fibrosis, induration, atrophy.
†Edinburgh Vein Study (results published in two manuscripts).
‡Hyperpigmentation, lipodermatosclerosis, ulcer.



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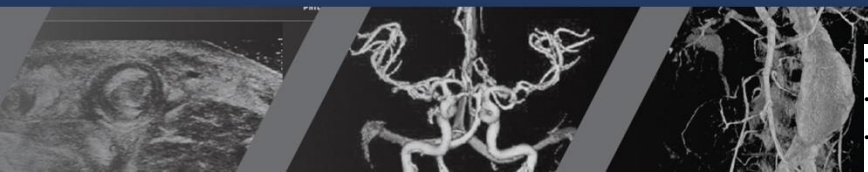
Venous Epidemiology

- Around 400,000 to 600,000 venous ulcers affect the US population
- Rarely fatal and hardly ever progress to amputation ☞ frequent hospitalizations
- 37% to 48% recurrence rate of healed venous stasis wounds at 3 years



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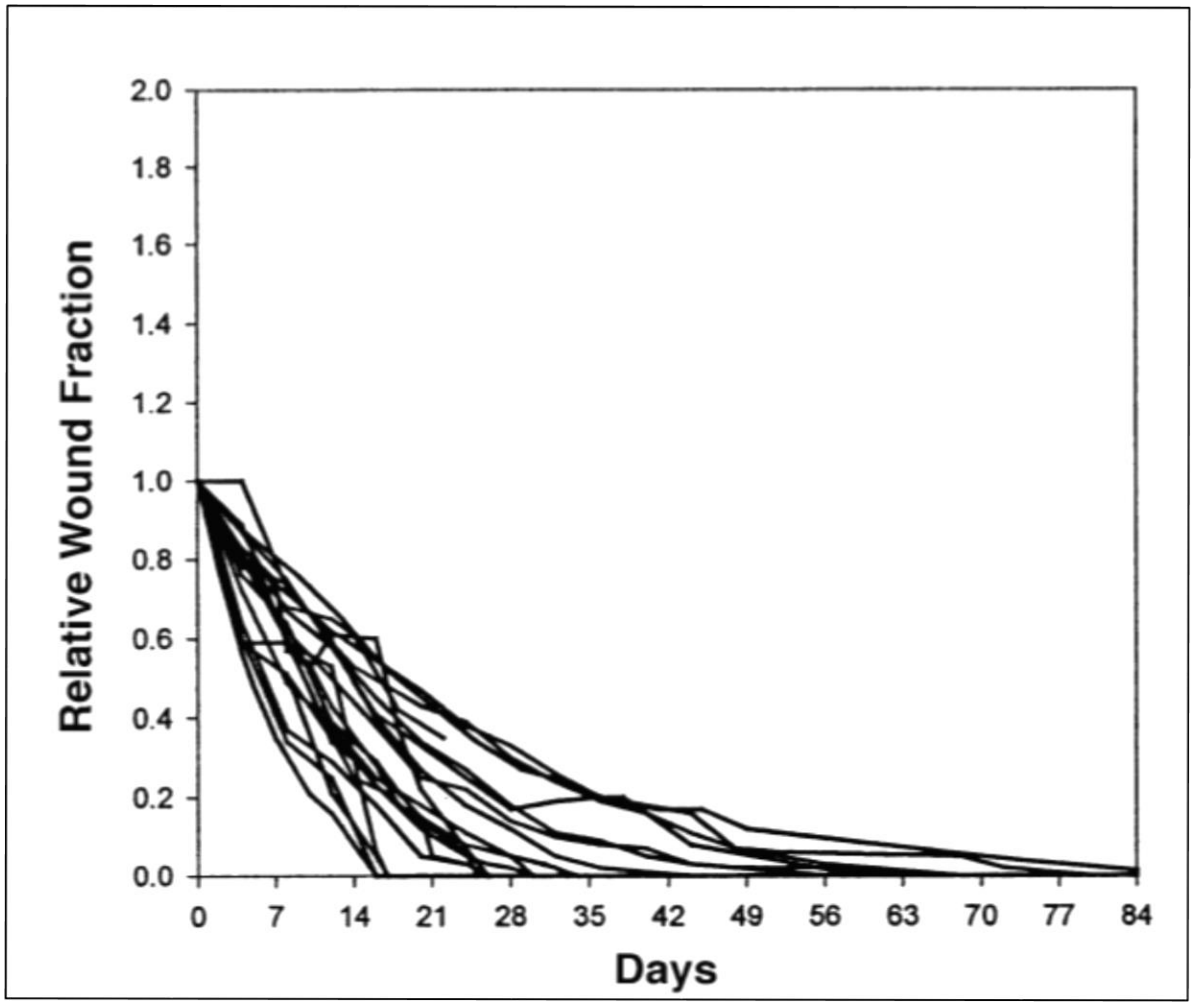

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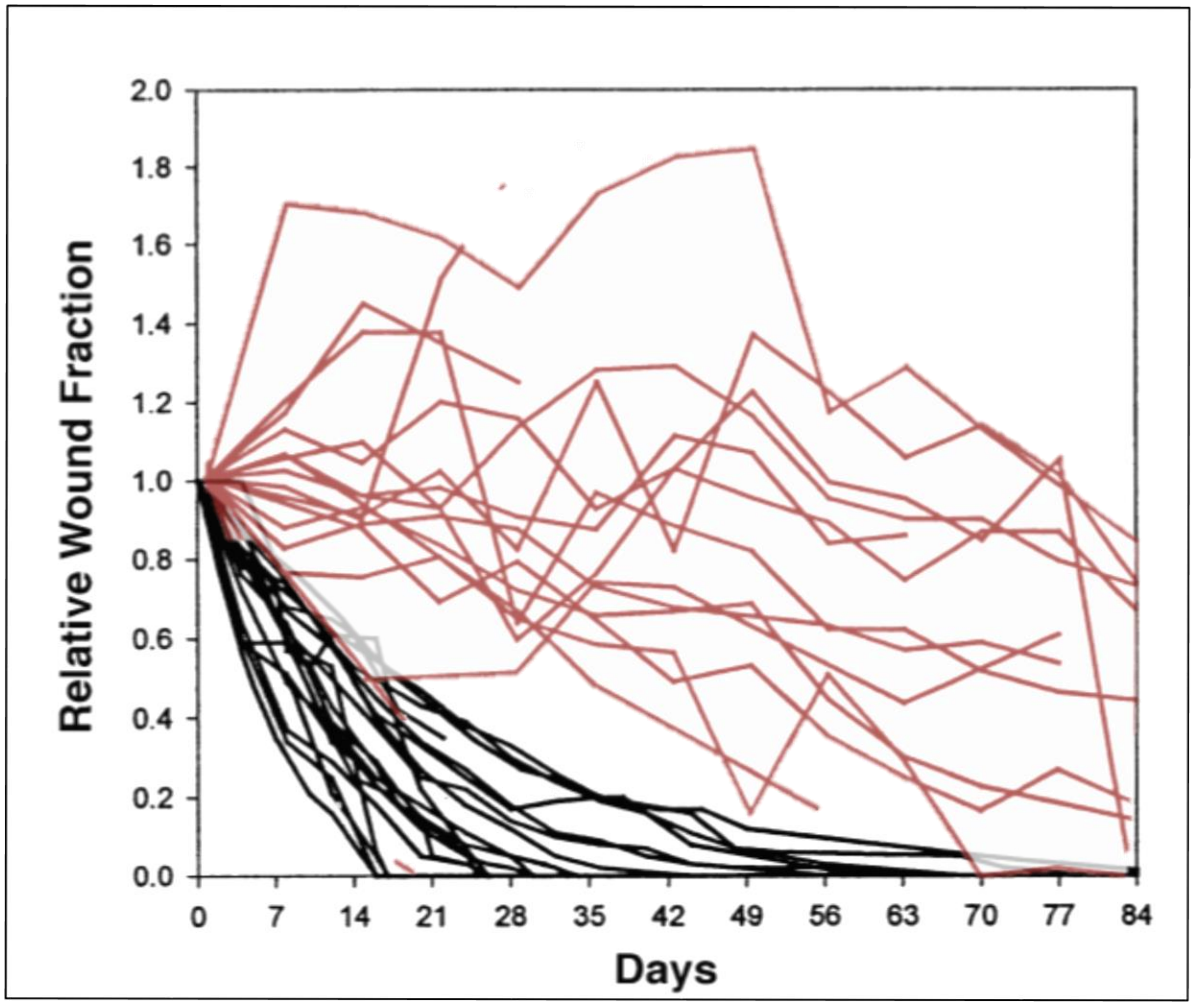
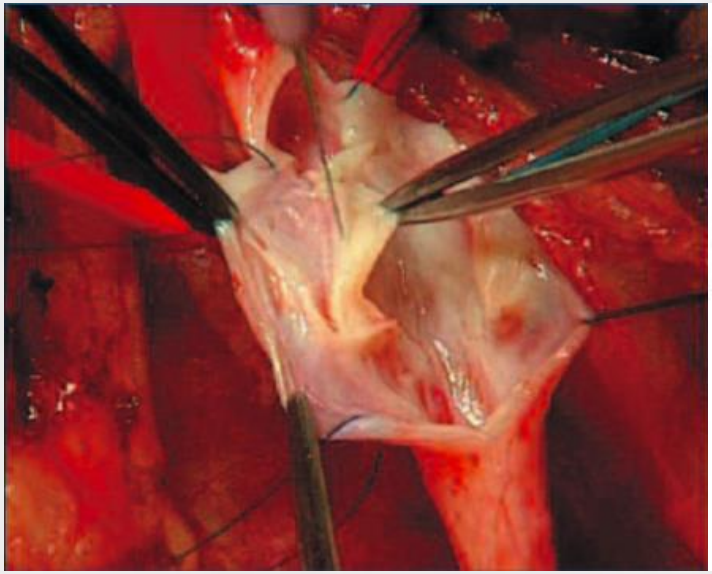
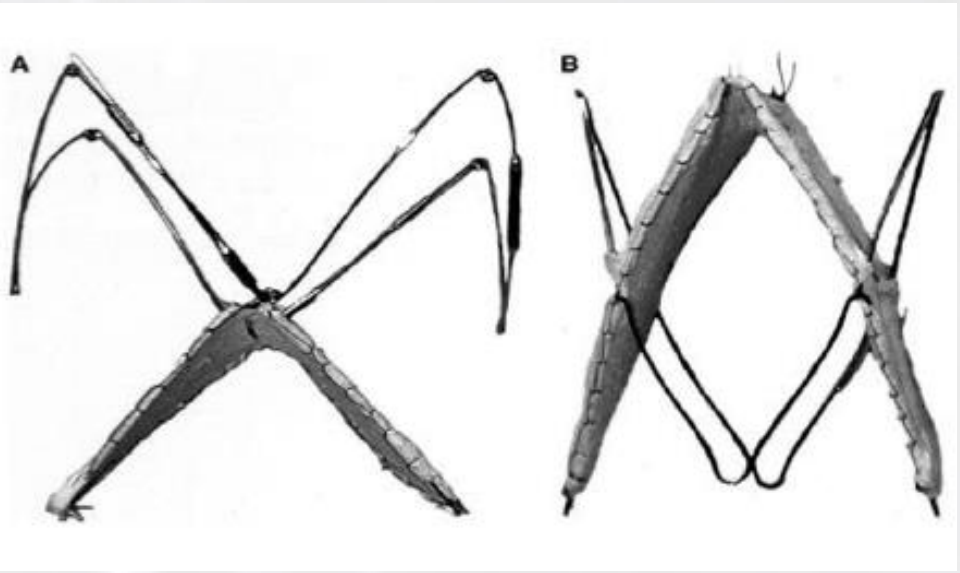


Hill D, Poore S, Wilson J, Robson M, Cherry G, Initial healing rates of venous ulcers: are they useful as predictors of healing? The American Journal of Surgery 2004, 188, 22S–25S.

Percutaneous Valves





Genes

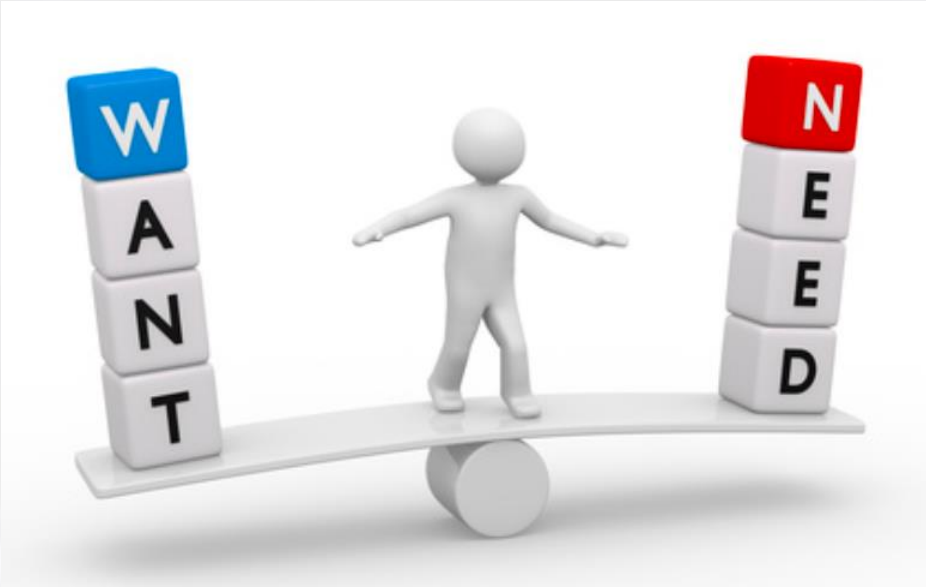
Table 1 – Reports of genetic mutations associated with poor healing and progression of venous leg ulcers.

Study	Type of genetic defect	Phenotypic change	Clinical effect
Toganzzo, 2006 [42]	F13A1 gene	Factor XIII deficiency	Delay in healing of venous ulcers
Zamboni, 2006 [43]	HFE gene	Increased iron deposition	Exacerbation of venous ulcers
Sam, 2003 [44] Sverdlova, 1998 [45]	MTFR gene (SNP C677T)	Reduction in enzyme methylenetetrahydrofolate reductase function	Associated with varicose veins and chronic venous disease (CEAP score 4–6)
Gemmati, 2009 [46]	SLC40A1 (SNP 8CG)	Possible increased iron deposition	Increased the risk of chronic venous disease and primary leg ulcer development
Gemmati, 2009 [46]	MMP-12 (SNP 82AA)	Functional change	Increased risk of ulcer formation
Nagy, 2005 [47]	FGFR-2 (SNP 2451 AG)	Possible messenger RNA instability-reduced mitogenesis	Associated with nonhealing ulcers

Adapted from Anwar et al [10], with permission.
CEAP, clinical, etiology, anatomy, pathophysiology.

Psychological Impact

- 81% patients with venous stasis ulcers experience decreased mobility
- 57% of patients report severely limited mobility
- 68% with fear, anger, depression and social isolation



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CONCLUSIONS

HAMPDEN SYDNEY COLLEGE

Lectures on Surgery

By Aug. L. Warner M.D.

Mr. Aug. Hopkins   Richmond Session   1836-37



to bind up the nation's wounds, to care for him who shall have borne the battle and for his widow, and his orphan, to do all which may achieve and cherish a just and lasting peace among ourselves and with all nations."



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