Prevention and treatment of venous ulcers in primary chronic venous insufficiency

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Primary chronic venous disease (PCVD) is a progressive degenerative condition that usually results in vein wall weakness, producing valvular incompetence. The disease most frequently occurs in the superficial veins and presents as asymptomatic cosmetic varicose veins. PCVD may also advance to symptomatic stages with pain, edema, skin changes, or venous ulcerations.

Primary venous reflux can also develop in the deep and perforating veins. PCVD may also include a symptomatic obstructive element when a nonthrombotic iliac vein lesion (NIVL) is present. PCVD is defined by the basic CEAP classification as: $C_{2\text{-}6}$ E_p $A_{s,d,p}$ $P_{o,r}$.[1] The letter p (primary) refers to nonthrombotic, noncongenital etiology. The pathology is mainly related to deep and/or superficial valve incompetence creating an axial reflux projecting into the ulcer area.[2] Symptomatic NIVL has previously been described as May-Thurner syndrome, Cockett's, or "iliac vein compression" syndrome.[3,4] The existence of marked iliac vein compressions (more than 50% obstruction) with or without intraluminal lesions has been shown to be more pathogenic than previously thought. In the past, these lesions have been considered a common finding of little clinical importance.[5] Primary venous insufficiency should be differentiated from secondary postthrombotic venous insufficiency because the two conditions differ in pathophysiology, management, and prognosis. "Hydrostatic" leg ulcers without venous reflux and/or obstruction (eg, in morbidly obese patients [$C_{5\text{-}6}$ E_s A_n P_n]) are excluded in this discussion.[6]

As early as 1948, the Swedish surgeon Gunnar Bauer found a group of patients with venous leg ulceration who had no history of previous deep venous thrombosis (DVT) but a family history of varicose veins. Descending transfemoral venography showed a patent, uniformly wide, deep vein with plentiful valve stations identified, which allowed the contrast to descend into the calf veins.[7] No postthrombotic changes, such as irregular lumen, collaterals, or poorly identified valve stations, were noted. Bauer's interpretation was that there was a loss of elasticity in the vein wall leading to dilatation and subsequent incompetence of the valve. He termed this condition idiopathic deep vein incompetence; this condition today is defined as primary valvular incompetence. Hach et al have later suggested an additional hypothesis (ie, the deep veins will dilate secondary to massive superficial reflux because of "overloading").[8] Treatment of the superficial reflux in these patients may correct the deep venous reflux. This normalization of venous flow is frequently seen with segmental primary deep incompetence, but rarely with axial deep reflux.[9-12] Mapping of reflux by duplex ultrasound scanning in limbs with primary or secondary reflux and leg ulceration has shown that superficial reflux is present in approximately 80% of limbs, and in half of these limbs it is combined with deep venous reflux.[13-15] The prevalence of significant NIVL in these patients is not known.

Current evidence suggests that multiple factors may lead to intrinsic structural and biochemical abnormalities of the vein wall in PCVD resulting in remodeling of the venous wall and valvular incompetence in PCVD (see Critical Issue 2). This process appears to be multicentric; thus, primary valve incompetence develops simultaneously in discontinuous vein segments. Valves may not fail in a progressive descending or ascending uninterrupted order as previously thought.[16]

PCVD is widespread in the population and is far more prevalent than secondary (postthrombotic) disease. It is responsible for the development of chronic venous insufficiency (C3-C6) in 20% of the older population. A meta-analysis comprising 390 ulcer patients with PCVD having duplex ultrasound scanning revealed superficial incompetence alone and combination of deep and superficial reflux in 44% and 43% of ulcerated limbs, respectively.[17,18] The clinical expression of PCVD is indistinguishable from that of postthrombotic disease in its late stages, but the medical and surgical treatment considerations are distinctly different.

We have identified four critical issues concerning primary chronic venous disease, which are central in the endeavor to decrease the prevalence of venous leg ulcers by 50% at 10 years.

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CRITICAL ISSUE 1

Standardization of diagnostic testing (especially ultrasound scanning) for chronic venous disease and criteria for interpretation of the results

Background. Studies on how to identify patients with PCVD that will progress to ulceration do not exist. It has been shown to be important to correct the underlying pathology in patients with established venous ulcer disease to prevent recurrence.[19] However, there is no standard for evaluation of reflux/obstruction and changes of the microcirculation in CVD by Intersocietal Commission for Accreditation of Vascular Laboratories (ICAVL) in the United States. Standardization is vital to move forward because of its importance to direct treatment in clinical practice as well as to perform research. There is also a lack of basic information on ambulatory venous pressure and hemodynamic changes in the microcirculation.[20]

Evidence. Many laboratories have developed protocols for evaluating reflux and obstruction in the lower limbs, but there is no standardization of method and interpretation.

Discussion highlights. Duplex ultrasound scanning (DUS) is the most common and available test, and, therefore, central in evaluation of CVD, regardless of etiology, in clinical practice. Standardizing the method of scanning and the interpretation of the results would quickly have a major impact on CVD treatment. Primary care physicians would learn when to consult a vascular specialist for assessment and possible intervention. Since DUS of the ilio-caval vein segment is frequently difficult to perform, additional imaging studies may be needed to detect iliofemoral venous outflow obstruction as per institutional preference (eg, transfemoral contrast venography, magnetic resonance venography, computed tomography venography, or intravascular ultrasonography [IVUS]). There are no standard methods of quantification of hemodynamically significant venous outflow obstruction.[21] Methods of measuring outflow resistance also need to be developed.

There are no known hemodynamic methods to identify which patient with PCVD and limbs with C-class 2 to 4 will progress to develop leg ulcers. To achieve this goal, other hemodynamic tests in addition to ultrasound scanning should be utilized. Duplex ultrasound scanning parameters of interest would be the anatomic extent and distribution of reflux and obstruction (such as the system proposed by Hach),[22] and quantification of reflux by peak volume reflux, peak reflux, etc.[23] Hemodynamic tests, such as plethysmography (air plethysmography, foot volumetry, or strain-gauge)[24] and laser Doppler measurements, such as veno-arterial response (VAR) and vasomotor activity (VA),[25,26] need further evaluation. When these hemodynamic tests are used, the patients need to be followed with clinical severity scores (venous clinical severity, segmental disease, and disability scores or others), which are more sensitive than C-classification to detect symptomatic progression.

Conclusion. It is necessary to develop first a protocol for CVD investigation for clinical practice, and then introduce a more sophisticated protocol for longitudinal research of CVD.

Recommendations. Standardize venous duplex studies for clinical practice and reimbursement in the U.S. by:

1. Establishing a protocol for DUS to detect venous reflux and obstruction in CVD, regardless of etiology. The scanning should include the inferior vena cava and iliac veins as able.
2. Achieving ICAVL approval: For research purposes, it is important to develop ultrasound measurements, which identify not only presence but also provide quantification of reflux and obstruction. The ultimate goal will be to assess the contribution of reflux/obstruction in each system (superficial/deep/perforator) and at various levels (axial/segmental; ilio-femoral/femoro-popliteal) to the global hemodynamics of the lower limb. This would enable directed treatment. Additional methods of studying venous hemodynamics and the microcirculation should also be used in longitudinal studies. With regards to PCVD, it is essential to identify measurements that would predict progression of limbs of C-class 2-4 to active leg ulcers.

Action. The American Venous Forum (AVF) is well positioned to take the lead and to coordinate with other societies the development of a clinical protocol for ultrasound scanning. Members can be identified with contacts in ICAVL, and societies of interest could shoulder this responsibility. This goal should be possible to achieve in a relatively short time frame (1 year) and reached with ICAVL approval. This would impact on the overall goal to achieve reduction of leg ulcer prevalence by 50% in 10 years.

Protocols for research will be performed by individual institutions or cooperation between interested institutions. Central to this would be cooperation between members of AVF and other societies with special interest in evaluation of the hemodynamics of CVD and vascular laboratories in general. This task is more challenging. First, the hemodynamic parameters have to be identified and then applied in longitudinal studies. The time span is at least 5 years. It is doubtful that, by this stage, this will have an impact on the overall goal of the present endeavor.

CRITICAL ISSUE 2

Identification of factors (other than hemodynamic) that identify patients with PCVD and C-class 2, 3, and 4 limbs, who are at risk for progression to C-class 6

Background. There is a lack of information on the natural history of PCVD. If factors for disease progression in patients with primary chronic venous disease could be identified, a modification of these factors, if feasible, may prevent development of venous ulcer.

Evidence. Evidence is lacking as most studies on risk factors look at risk of ulceration regardless of etiology and not the risk of progression between C-classes in limbs with PCVD. No validation of risk factors in class progression exists. However, risk factors for ulcer recurrence (other than presence of postthrombotic disease) have been identified and some may be helpful (eg, residual iliofemoral vein obstruction; residual deep incompetence, particularly axial deep reflux; residual or recurrent superficial reflux; and persistent venous hypertension).[27-30]

Discussion highlights. There are many proposed clinical risk factors, which need clarification of their role in progression of the disease.[31] Some of these are age, obesity, smoking, pregnancy, gender, hypertension, use of hormones, "feeling of swelling," and occupation. In addition, clinical signs (eg, corona phlebectatica and other skin changes) may warrant early intervention to prevent later ulcer formation. In the Bonn Vein Study I, conducted in 2000, 3072 participants of the general population of the city of Bonn and two rural townships, aged 18 to 79 years took part (1350 men, 1722 women).[32] Participants were selected via simple random sampling from the registries of residents. In a follow-up study (Bonn Vein Study II) 6.6 years later, the same population was investigated again. The incidence of progress to chronic venous insufficiency (C3-C6) was approximately 2.0% per year. In a multivariate analysis, the main risk factors for developing severe stages (C4-C6) were age, arterial hypertension, and obesity. Further, does development of symptoms in limbs with C2 to C4 signal a risk of progression to ulcer formation? Databases with some of this information are available, but as yet not published (www.heonline.nhs.uk).[24] In the Bonn Vein Study II, the "feeling of swelling" increased the risk for the development of CVI significantly (unpublished data).

There are studies showing that mechanical dysfunction of the calf muscle pump may enhance the development of leg ulceration.[33] It will be important to investigate ankle range of motion,[34] calf muscle pump function, and patient activity in relation to progression of disease. The data that are presently available need to be correlated to progression of the disease.

Genetic factors may also play a role in progression to advanced chronic venous disease. A relationship between the C282Y polymorphism in hemochromatosis (HFE gene) and venous ulceration has been described.[35] Gene polymorphisms and biomarkers that may identify high-risk patients for progression to ulceration should be investigated (some studies are in progress). Bio-banks for subsequent analysis in longitudinal studies need to be established. Patients with ulcers have a 2- to 30-times higher prevalence rate of thrombophilia than the general population, despite no previous DVT. Presence of certain thrombophilias, such as antithrombin deficiency, may be a risk factor for ulcer development.[36]

It would be of value to identify biomarkers signaling an increased risk of ulcer formation. Most agree that universal markers such as IL-6 are elevated, but it is uncertain whether or not they may indicate progression of the disease.[37,38]

Most would agree that wall dilation and valve incompetence in PCVD is related to venous endothelial dysfunction. Endothelial cellular injury and activation increase the expression of inflammatory markers and leukocyte recruitment in varicosities, and venous wall changes are thought to contribute to the weakening, dilatation, and valve reflux. Varicose vein patients demonstrate imbalances in the humoral mediators of vasoconstriction and venous dilatation. Plasma levels of endothelin-1 are increased in those with varicose veins and rise disproportionately in the response to venous stasis. Plasma levels of nitric oxide, a potent mediator of vascular relaxation, may also be modulated. Matrix metalloproteinase (MMP) 2 may also lead to alterations in the extracellular matrix as well as venous relaxation. Most of the studies are observational.[16,39] The understanding of the natural history and progression of PCVD remains incomplete. Current evidence suggests the multifactorial origin of PCVD, leading to tissue remodeling of the venous wall with changes in the microcirculation and dermis. More studies to identify markers of endothelial dysfunction of prognostic value are necessary.

Are there differences in skin type/metabolism/race that may place patients at an increased risk of ulceration? Some studies indicate this.[24,40-42]

Do quality of life (QoL) measurements correlate with disease severity (overall, yes),[43,44] and in turn correlate with those patients that are at increased risk for disease progression (presently no evidence)? Can QoL assessment be used as a surrogate marker for patients at risk for disease progression? Currently there is no evidence that QoL can be used to identify who will progress since QoL is not directly related to venous incompetence.

Conclusions. There is a need for additional studies on the natural history of PCVD and factors responsible for disease progression to ulcer formation, such as clinical, mechanical, humoral, genetic, and endothelial risk factors.

Recommendations. To perform longitudinal studies evaluating factors responsible for disease progression. In addition, identify genetic and humoral mediators of endothelial dysfunction, which are present in limbs with PCVD and disease progression.

Actions. Studies on clinical risk factors and clinical signs associated with progress of the disease are already in place, and analysis needs to be finalized (see above Bonn Vein Study II). It is possible to reach this goal within 1 year. Further studies regarding other factors have to be initiated. It will probably be difficult to perform longitudinal studies on the influence of these factors on disease progression. An alternative way is to find unique features in limbs with already established ulcers (C6) as compared with limbs with lower severity venous disease, C2 to C4. Modification of some of these risk factors may, however, not be possible. It may not have an impact on ulcer prevalence in 10 years. There is a need to obtain more information on the impact of progression on quality of life by following patients in longitudinal studies.

CRITICAL ISSUE 3

Identification of treatments, which may prevent progression in patients with C2, C3, or C4 limbs to formation of leg ulcers (C6)

Background. By intervening at early stages of PCVD, and so preventing progression of the disease, would lower the prevalence of ulcers within 10 years.

Evidence. No study exists on the efficacy of compression therapy, pharmacotherapy, or endovenous/open interventions on prevention of progression of PCVD.

Discussion highlights. There are older studies giving the prevalence of venous ulceration, although most reports have deficiencies, and regional numbers are difficult to apply to the general population.[45,46] There is a need to establish new point prevalence rates of limbs with venous ulceration, since currently patients with venous disease have generally better care reducing the rate of ulcer incidence. It is possible that even if we add nothing to current practice, the ulcer prevalence will be reduced by 50% in 10 years. It may be of value to compare snapshots of venous ulcer prevalence today with 5 years ago as a baseline.

External compression. External support will result in clinical improvement and help control swelling. There is evidence that stockings help alleviate symptoms of C2 disease in pregnant women.[47] A systematic review of 39 randomized trials concluded that ulcer healing rates are increased when compression therapy is used compared with no compression therapy.[48] There is, however, no report evaluating their effect on progression of PCVD. The main problem when studying efficacy of compression devices, including compression stockings, is how to ensure and track patient compliance of usage. In addition, it is not known whether or not all patients with C2 to C4 limbs should use compression therapy. If only symptomatic patients are to use compression, the assumption is made that only patients with symptomatic disease are at risk for progression to leg ulcer. That may not necessarily be true. The types of stocking or other devices and the adequate pressure gradient have also to be assessed to optimize compression therapy in PCVD. Compression therapy following acute DVT has been shown to reduce the incidence of subsequent postthrombotic syndrome and progression to ulcer formation.[49] The results are not transferable to PCVD, but show that prospective comparative studies with and without compression therapy should be feasible in patients with marked C2 disease.

Drug therapy. There are studies that show pentoxifylline to have a beneficial effect on ulcer healing with or without adjunctive compression therapy.[50,51] Although there is a theoretic possibility that pentoxyfylline or venoactive drugs and statins may prevent progression, no supporting studies exist.

Endovenous procedures including foam sclerotherapy or open surgery. It is important to decide in what sequence to treat primary vein obstruction and reflux and which vein segments to treat. Most agree to control superficial vein reflux first, even in the presence of deep vein reflux. Significant outflow obstruction by NIVL should probably be treated early. There are no data to support that treating perforators in limbs with C2 or C3 disease will have an effect on progression. It would be important to assess whether or not treatment of perforators, deep valve insufficiency, or venous outflow obstruction may prevent progression in limbs with C4 disease to C6.

Conclusions. Substantial need for more information if early intervention with compression therapy, drug therapy, or surgery will prevent progression to ulcer formation.

Recommendations. Studies have to be performed. There may be substantial difficulty to perform this adequately, since it will be difficult not to intervene in symptomatic patients with clinical severity classes below C6.

Actions. With regard to current point prevalence, it may be of value to study Medicare data today and compare with data obtained from 2000 or 2005, to reveal important trends. Data from the Olmsted County epidemiology study showed that the overall incidence of venous ulcers in patients older than 45 years of age are estimated at 3.5 per thousand per year, and the incidence of venous ulcers remains unchanged over 20 years, between 1970 and 1990.[52] This epidemiologic study continues and may soon give us an answer on current trends. Adequate longitudinal studies on impact of intervention may not be possible.

CRITICAL ISSUE 4

Calculate the number of symptomatic C2, C3, and C4 patients needed to treat to prevent an ulcer

Background. It is necessary to find out how many symptomatic or asymptomatic patients at risk to develop venous ulcer are necessary to treat to avoid one leg ulcer. This is a critical issue since it will be necessary to justify the cost of preventive treatment to payers.

Evidence. Since there is a lack of information to identify the patient at risk, there are also sparse data on prevention. No appropriate data are available since information on early intervention and progression of PCVD largely does not exist. There are some extrapolations made from a Swedish study suggesting that 100 symptomatic patients with varicose veins have to be operated on to prevent one ulcer; however, this number decreases to 10 when limbs with C4 disease are treated.[53]

Discussion highlights. It is important to offer best treatment options for at-risk C2 to C4 patients to optimize prevention of progression. It is likely that a large number of patients may be necessary to treat to prevent one ulcer, which may be relatively costly for society. The most obvious health care saving is made by avoiding a lengthy and costly ulcer treatment owing to decreased incidence of leg ulcer formation. However, it must also be stressed that secondary gains are achieved. The patients receiving preventive treatment are also likely to experience a substantial improvement of quality of life in addition to ulcer prevention.

Conclusion. Any preventive method has to be related to the number of patients treated to prevent one leg ulcer.

The associated cost and possible additional beneficial effects on the patients need to be assessed.

Recommendations. Based on the outcome of Critical Issues 1 to 3, it may be possible to acquire the necessary information to perform cost-benefit analysis.

Actions. This issue is intimately connected with the solution of Critical Issues 1 to 3. Without having the data giving the patients at risk, it is impossible to make a cost-benefit analysis.

CONCLUSION

To summarize, regardless of etiology of venous ulcerations, it is fundamentally necessary to develop first, a protocol for CVD investigation for clinical practice, and second, a more sophisticated protocol for longitudinal research of CVD. The natural history of primary CVD and factors responsible for disease progression to ulcer formation, such as clinical, mechanical, humoral, genetic, and endothelial risk factors must be studied. There is also a lack of information as to whether or not early intervention by compression treatment, drug therapy, or ablative interventions will prevent progression to ulcer formation in primary CVD. Any preventive method has to be related to the number of patients needed to be treated to prevent one venous ulcer, owing to the potential socio-economic impact. The associated costs and additional beneficial effects on the patients' quality of life need to be assessed.

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REFERENCES

1. Eklöf B, Rutherford RB, Bergan JJ, Carpentier PH, Gloviczki P, Kistner RL, et al; American Venous Forum International Ad Hoc Committee for Revision of the CEAP Classification. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg 2004;40:1248-52.
2. Bergan JJ, Schmid-Schonbein GW, Coleridge-Smith PD, Nicolaides AN, Boisseau MR, Eklof B. Chronic venous disease. N Engl J Med 2006;355:488-98.
3. May R, Thurner J. The cause of the predominantly sinistral occurrence of thrombosis of the pelvic veins. Angiology 1957;8:419-27.
4. Cockett FB. The iliac compression syndrome alias "iliofemoral thrombosis" or "white leg." Proc R Soc Med 1966;59:360-1.
5. Raju S, Neglén P. High prevalence of nonthrombotic iliac vein lesions in chronic venous disease: a permissive role in pathogenicity. J Vasc Surg 2006;44:136-43; discussion 144.
6. Bjellerup M. Determining venous incompetence: a report from a specialised leg ulcer clinic. J Wound Care 2006;15:429-30, 433-6.
7. Bauer G. The etiology of leg ulcers and their treatment by resection of the popliteal vein. J Int Chir 1948;8:937-7.
8. Hach-Wunderle V, Hach W. Invasive therapeutic options in truncal varicosity of the great saphenous vein. Vasa 2006;35:157-66.
9. Adam DJ, Bello M, Hartshorne T, London NJ. Role of superficial venous surgery in patients with combined superficial and segmental deep venous reflux. Eur J Vasc Endovasc Surg 2003;25:469-72.
10. MacKenzie RK, Allan PL, Ruckley CV, Bradbury AW. The effect of long saphenous vein stripping on deep venous reflux. Eur J Vasc Endovasc Surg 2004;28:104-7.
11. Makarova NP, Lurie F, Hmelniker SM. Does surgical correction of the superficial femoral vein valve change the course of varicose disease? J Vasc Surg 2001;33:361-8.
12. Sharp MA, Nawabi DH, Walton J, Hands L. Popliteal venous reflux is not abolished by superficial venous ligation. Phebology 2003;18:143-5.
13. Grabs AJ, Wakely MC, Nyamekye I, Ghauri AS, Poskitt KR. Colour duplex ultrasonography in the rational management of chronic venous leg ulcers. Br J Surg 1996;83:1380-2.
14. Hanrahan LM, Araki CT, Rodriguez AA, Kechejian GJ, LaMorte WW, Menzoian JO. Distribution of valvular incompetence in patients with venous stasis ulceration. J Vasc Surg 1991;13:805-11; discussion 811-2.
15. Labropoulos N, Giannoukas AD, Nicolaides AN, Ramaswami G, Leon M, Burke P. New insights into the pathophysiologic condition of venous ulceration with color-flow duplex imaging: implications for treatment? J Vasc Surg 1995;22:45-50.
16. Lim CS, Davies AH. Pathogenesis of primary varicose veins. Br J Surg 2009;96:1231-42.
17. Perrin M. Rationale for surgery in the treatment of venous ulcer of the leg. Phlebolymphology 2004;45:276-80.
18. Labropoulos N. Hemodynamic changes according to the CEAP classification. Phlebolymphology 2003;40:103-6.
19. Gohel MS, Barwell JR, Taylor M, Chant T, Foy C, Earnshaw JJ, et al. Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomised controlled trial. BMJ 2007;335:83-8.
20. Pascarella L, Schonbein GW, Bergan JJ. Microcirculation and venous ulcers: a review. Ann Vasc Surg 2005;19:921-7.
21. Neglén P, Raju S. Proximal lower extremity chronic venous outflow obstruction: recognition and treatment. Semin Vasc Surg 2002;15:57-64.
22. Hach W. (Diagnosis and surgical methods in primary varicose veins) [in German]. Langenbecks Arch Chir 1988;Suppl 2:145-51.
23. Neglén P, Egger JF 3rd, Olivier J, Raju S. Hemodynamic and clinical impact of ultrasound-derived venous reflux parameters. J Vasc Surg 2004;40:303-10.
24. Nicolaides AN, Allegra C, Bergan J, Bradbury A, Cairols M, Carpentier P, et al. Management of chronic venous disorders of the lower limbs: guidelines according to scientific evidence. Int Angiol 2008;27:1-59.
25. Shami SK, Scurr JH, Smith PD. The veno-arteriolar reflex in chronic venous insufficiency. Vasa 1993;22:227-31.
26. Chittenden SJ, Shami SK, Cheatle TR, Scurr JH, Coleridge Smith PD. Vasomotion in the leg skin of patients with chronic venous insufficiency. Vasa 1992;21:138-42.
27. Magnusson MB, Nelzen O, Volkmann R. Leg ulcer recurrence and its risk factors: a duplex ultrasound study before and after vein surgery. Eur J Vasc Endovasc Surg 2006;32:453-61.
28. Obermayer A, Gostl K, Walli G, Benesch T. Chronic venous leg ulcers benefit from surgery: long-term results from 173 legs. J Vasc Surg 2006;44:572-9.
29. McDaniel HB, Marston WA, Farber MA, Mendes RR, Owens LV, Young ML, et al. Recurrence of chronic venous ulcers on the basis of clinical, etiologic, anatomic, and pathophysiologic criteria and air plethysmography. J Vasc Surg 2002;35:723-8.
30. Tenbrook JA Jr, Iafrati MD, O'Donnell TF Jr, Wolf MP, Hoffman SN, Pauker SG, et al. Systematic review of outcomes after surgical management of venous disease incorporating subfascial endoscopic perforator surgery. J Vasc Surg 2004;39:583-9.
31. Robertson L, Lee AJ, Gallagher K, Carmichael SJ, Evans CJ, McKinstry BH, et al. Risk factors for chronic ulceration in patients with varicose veins: a case control study. J Vasc Surg 2009;49:1490-8.
32. Maurins U, Hoffmann BH, Losch C, Jockel KH, Rabe E, Pannier F. 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;48:680-7.
33. Shiman MI, Pieper B, Templin TN, Birk TJ, Patel AR, Kirsner RS. Venous ulcers: a reappraisal analyzing the effects of neuropathy, muscle

involvement, and range of motion upon gait and calf muscle function. Wound Repair Regen 2009;17:147-52.
34. Davies JA, Bull RH, Farrelly IJ, Wakelin MJ. A home-based exercise programme improves ankle range of motion in long-term venous ulcer patients. Phlebology 2007;22:86-9.
35. Gemmati D, Federici F, Catozzi L, Gianesini S, Tacconi G, Scapoli GL, et al. DNA-array of gene variants in venous leg ulcers: detection of prognostic indicators. J Vasc Surg 2009;50:1444-51.
36. Mackenzie RK, Ludlam CA, Ruckley CV, Allan PL, Burns P, Bradbury AW. The prevalence of thrombophilia in patients with chronic venous leg ulceration. J Vasc Surg 2002;35:718-22.
37. Pappas PJ, Fallek SR, Garcia A, Araki CT, Back TL, Durán WN, et al. Role of leukocyte activation in patients with venous stasis ulcers. J Surg Res 1995;59:553-9.
38. Moore K, Huddleston E, Stacey MC, Harding KG. Venous leg ulcers - the search for a prognostic indicator. Int Wound J 2007;4:163-72.
39. Raffetto JD, Khalil RA. Mechanisms of varicose vein formation: valve dysfunction and wall dilation. Phlebology 2008;23:85-98.
40. Franks PJ, Morton N, Campbell A, Moffatt CJ. Leg ulceration and ethnicity: a study in West London. Public Health 1997;111:327-9.
41. Sam RC, Burns PJ, Hobbs SD, Marshall T, Wilmink AB, Silverman SH, et al. The prevalence of hyperhomocysteinemia, methylene tetrahydrofolate reductase C677T mutation, and vitamin B12 and folate deficiency in patients with chronic venous insufficiency. J Vasc Surg 2003; 38:904-8.
42. Criqui MH, Jamosmos M, Fronek A, Denenberg JO, Langer RD, Bergan J, et al. Chronic venous disease in an ethnically diverse population: the San Diego Population Study. Am J Epidemiol 2003;158:448-56.
43. Vasquez MA, Munschauer CE. Venous Clinical Severity Score and quality-of-life assessment tools: application to vein practice. Phlebology 2008;23:259-75.
44. Kaplan RM, Criqui MH, Denenberg JO, Bergan J, Fronek A. Quality of life in patients with chronic venous disease: San Diego population study. J Vasc Surg 2003;37:1047-53.
45. Nelzen O, Bergqvist D, Lindhagen A. The prevalence of chronic lower-limb ulceration has been underestimated: results of a validated population questionnaire. Br J Surg 1996;83:255-8.
46. Fowkes FG, Evans CJ, Lee AJ. Prevalence and risk factors of chronic venous insufficiency. Angiology 2001;52(Suppl 1):S5-15.
47. Partsch H, Flour M, Smith PC. Indications for compression therapy in venous and lymphatic disease consensus based on experimental data and scientific evidence. Under the auspices of the IUP. Int Angiol 2008;27: 193-219.
48. O'Meara S, Cullum NA, Nelson EA. Compression for venous leg ulcers. Cochrane Database Syst Rev 2009;CD000265.
49. Brandjes DP, Büller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet 1997; 349:759-62.
50. Falanga V, Fujitani RM, Diaz C, Hunter G, Jorizzo J, Lawrence PF, et al. Systemic treatment of venous leg ulcers with high doses of pentoxifylline: efficacy in a randomized, placebo-controlled trial. Wound Repair Regen 1999;7:208-13.
51. Jull A, Arroll B, Parag V, Waters J. Pentoxifylline for treating venous leg ulcers. Cochrane Database Syst Rev 2007;CD001733.
52. Heit JA, Rooke TW, Silverstein MD, Mohr DN, Lohse CM, Petterson TM, et al. Trends in the incidence of venous stasis syndrome and venous ulcer: a 25-year population-based study. J Vasc Surg 2001;33:1022-7.
53. Nelzen, O. Kirurgins gökunge eller kanske snarare dess fula ankunge [in Swedish]. Svensk Kirurgi 2009;32:1-14.

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