Leg pain: taking center stage in chronic venous disorders

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According to the VEIN-TERM consensus document, venous symptoms are complaints related to venous disease, which may include tingling, aching, burning, pain, muscle cramps, swelling, sensations of throbbing or heaviness, itching skin, restless legs, and leg tiredness and/or fatigue. Although not pathognomonic, these symptoms may be suggestive of chronic venous disorders, particularly if they are exacerbated by heat or dependency, worsened with the course of the day, and relieved with leg rest and/or elevation. In several epidemiologic surveys, up to 75% of adults complain of venous symptoms, and in the worldwide Vein Consult Program comprising almost 100,000 individuals, venous symptoms were perceived similarly in all regions surveyed, with pain reported in 60% to 77%. There is a significant correlation between venous pain/symptoms and worsening of chronic venous disorder signs, with a significant influence on quality of life (QoL). A particular group of patients complain of symptoms, but have no clinical signs or venous reflux (C0s according to the class, clinical, etiological, anatomical, physiological [CEAP] classification). These patients were found to represent about 15% of all patients in several surveys. The commonest complaint in chronic venous disorders is leg pain, which may be difficult to understand because its intensity is not correlated with the severity of venous disease, and patients sometimes complain of symptoms without signs. A mistaken conception of venous pain is widespread in the medical world and frequently causes misunderstanding in physician-patient relations.

Focus on leg pain
In this issue of Medicographia, the editor focuses on “Leg pain: taking center stage in chronic venous disorders,” inviting European experts (including Nicos Labropoulos, who originates from Greece) to share their experiences. In 2013, Servier published a book entitled From Venous Pain to Surgery, where the French neurologist Nicolas Danzinger from La Pitié-Salpêtrière, Paris, wrote an excellent chapter on “How to describe venous pain.” In the general mechanisms of venous pain he describes the anatomy, venous innervation, and physiological properties of venous and perivenous nociceptors, and the role of neuromediators involved in their activation. To understand the pathophysiology of venous pain, we need to take into account the properties of the nociceptors, as well as the inflammatory mechanisms that characterize venous disease from its early stages. The likely trigger for these mechanisms is local hypoxia caused by venous hypertension. This hypoxia activates endothelial cells, which results in the synthesis and local release of mediators that modulate pain through activation of proinflammatory nociceptors. Evidence of such an inflammatory reaction in the varicose veins of patients has accumulated in recent years.
years, and the biochemical changes identified suggest that endothelial cells and neutrophils are the source of inflammation. Danzinger questions why pain is not correlated with clinical severity and refers to Bradbury’s findings in the Edinburgh Vein Study, showing a poor correlation between symptoms and the presence or absence of varicose veins. He offers an explanation that this lack of correlation suggests that venous nociceptors may not be activated in the large veins, but rather in the microcirculation. Venous hypertension is transmitted to the microcirculation, which prompts leukocyte adhesion to the capillary endothelium. This initiates an inflammatory reaction that increases capillary permeability, leading to interstitial edema. This theory is supported by van RiJ’s work on failure of microvalvular valves in small superficial veins as a key to skin changes in venous insufficiency, which may also explain pain in C0s patients.

Characterizing venous symptoms

This is difficult and frequently leads to misunderstanding. It is often difficult for patients to find the right words for their complaints; in addition to heaviness and swelling, other descriptions (such as sensations of tension, aching, congestive pain, and tired legs) are also encountered. Physicians often underestimate the degree of pain that patients suffer and its impact on their lives. This is especially true if the pain is chronic and poorly defined, and when no signs of venous insufficiency and reflex are obvious. Physicians lack tools to measure the degree and impact on patient’s daily activities. The CEAP classification should aid the physician in diagnosing the severity of chronic venous disorders, where clinical class C0 has no visible or palpable signs of venous disease, up to C4 with an active venous ulcer. Each clinical class is characterized by “S” for symptomatic or “A” for asymptomatic. The severity of symptoms is not assessed and this needs to be addressed at the next revision of CEAP. In the Venous Clinical Severity Score (VCSS), with which you can follow the effect of treatment, pain correlation to proven effectiveness. At the present time there is no effective, but must also take into consideration the cost in relation to proven effectiveness. At the present time there is no way to effectively prevent the onset of varicose veins. Much

Neglén et al have reported substantial improvement of pain after stenting of iliofemoral obstruction using the VAS, confirmed by several studies using VCSS. Delis reported elimination of venous claudication, evaluated by treadmill in 55 patients with previous iliofemoral deep vein thrombosis (DVT), after stenting. There is no relationship between clinical severity and magnitude of venous pain, and a poor correlation between pain and the presence of deep or superficial reflex. However, QoL questionnaires correlate well with generic and clinical outcomes.

Socioeconomic impact

In the guidelines according to scientific evidence on management of chronic venous disorders of the lower limbs, it is stated that the considerable socioeconomic impact of chronic venous disorders is due to the large numbers concerned, cost of investigations and management, morbidity, and suffering. This in turn is reflected in a deterioration in QoL and loss of working days. The problem is compounded by the fact that chronic venous disorders are progressive and has a propensity to recur. Measures to reduce the magnitude of the problem include increasing the awareness of the problem, early diagnosis and care, careful consideration of the necessity and choice of investigations, discipline in the choice of management based on clinical effectiveness, and cost. These requirements imply specific training in all aspects of this condition. Direct costs are associated with medical, nursing, and ancillary manpower together with costs for investigation and treatment, whether in hospital or as an outpatient. Indirect costs relate to loss of working days. The cost in human terms must also be considered, and this can be quantified by assessment of QoL. Estimation of the overall annual costs of chronic venous disorders vary from 600-900 million euros in Western European countries, representing 1% to 2% of the total health budget. Indirect costs of venous disease in terms of working days lost is quoted as “the most important cost factor,” amounting to 270 million euros in Germany (1990).

A study from France, 2005, found that about 7% of the working population is off work because of venous disease. These costs are higher than the amount spent for arterial disease. The need to contain the increasing costs of chronic venous disorders is evident. The methods used, whether aimed at prevention or treatment, must essentially be shown to be effective, but must also take into consideration the cost in relation to proven effectiveness. At the present time there is no way to effectively prevent the onset of varicose veins. Much
work has been done to prevent chronic venous disorders developing in patients with early varicose veins or following DVT, and all measures that contribute to preventing a venous ulcer will have a strong impact on the human and socioeconomic costs.

**Further research needed**

Despite the increased interest in the pathophysiological mechanisms for chronic venous disorders, our knowledge remains limited according to the above mentioned guidelines. The genetic and molecular determinants for the development of chronic venous disorders are still largely undetermined. The relationship between the macrohemodynamics and endothelial function/ dysfunction in the vein wall, and the actual impact of flow dynamics on capillary, valve, and vein wall remodeling, white-cell activation, smooth muscle cell proliferation and migration, as well as extracellular matrix alteration, require further investigation.

Evidence for the role of senescence and apoptosis in the development of chronic venous disorders-related cellular and molecular alterations in the presence of venous hypertension remain poorly understood. The variable manifestations of signs and symptoms in chronic venous disorders among individuals with similar reflux sites, extent of disease and global hemodynamic impairment have not been explained. In addition, the pathophysiological and molecular bases for lipodermatosclerosis and ulceration are only partially understood, and the pathophysiology behind venous pain in patients without signs of venous disease or reflux/obstruction also needs further study. The significance of corona phlebectatica in relation to progression of chronic venous disorders remains undetermined.

It is critically important that recommendations for change in the CEAP classification are supported by research, enabling progress on the level of evidence rather than the level of investigation. There is a need to include a severity grading of venous disease or reflux/obstruction also needs further study. The comparison between symptom severity in chronic venous disorders, our knowledge remains limited and further research is needed. I encourage you to read the following eight themes written by excellent experts in chronic venous disorders.

**Conclusion**

Several epidemiological studies have shown that up to 75% of adults complain of venous symptoms. There is a significant correlation between venous symptoms and worsening of the clinical ("C") class of CEAP or QoL. However, 15% of these individuals complain of symptoms without signs of chronic venous disorders. The commonest symptom in chronic venous disorders is pain that is not correlated to the severity of chronic venous disorders. The likely trigger is venous, and probably capillary, hypertension causing an interaction between leukocytes and the venous endothelium, which results in the synthesis and release of mediators that modulate pain through activation of proinflammatory nociceptors. Despite the increased interest in the pathophysiological mechanisms for chronic venous disorders, our knowledge remains limited and further research is needed. I encourage you to read the following eight themes written by excellent experts in chronic venous disorders.

**References**


**Keywords:** CEAP classification; chronic venous disorder; Venous Clinical Severity Score; venous pain; venous symptom
Selon le document de consensus VEIN-TERM, les symptômes veineux sont des plaintes liées à l’insuffisance veineuse, qui peuvent inclure des fourmillements, un endolorissement, des brûlures, des douleurs, des crampes musculaires, un œdème, des sensations de pulsation ou de lourdeur, un prurit, un syndrome des jambes sans repos et une fatigue au niveau des jambes\(^1\). Bien qu’ils ne soient pas pathognomoniques, ces symptômes peuvent suggérer un trouble veineux chronique (TVC), en particulier s’ils sont exacerbés par la chaleur ou la déclivité, s’ils s’aggravent au cours de la journée, et s’ils sont soulagés par le repos et/ou l élévation des jambes. Dans plusieurs enquêtes épidémiologiques, jusqu’à 75 % des adultes se plaignent de symptômes veineux, et dans le programme Vein Consult, qui a porté sur près de 100 000 personnes dans le monde, les symptômes veineux ont été perçus de manière similaire dans toutes les régions ayant répondu à l’enquête, la douleur étant mentionnée dans 60 à 77 % des cas\(^2\). Il a été observé une corrélation significative entre la douleur et les symptômes veineux d’une part et l’aggravation des signes de TVC d’autre part, avec une influence significative sur la qualité de vie (QdV). Toutefois, un groupe particulier de patients se plaint de symptômes, mais ne présente ni signes cliniques ni reflux veineux (C\(_0\) selon la classification CEAP [clinique, étiologique, anatomique, physiopathologique]). Il a été constaté que ces personnes représentaient environ 15 % de l’ensemble des patients dans plusieurs enquêtes\(^3\). Le symptôme le plus fréquent de TVC est la douleur des jambes, qui peut être difficile à comprendre, parce que d’une part son intensité ne montre pas de corrélation avec la sévérité de la maladie veineuse, et que d’autre part les patients se plaignent parfois de symptômes sans montrer de signes. Une conception erronée de la douleur veineuse est largement répandue dans le monde médical et provoque fréquemment des malentendus dans la relation médecin-patient.

Analyse de la douleur des jambes
Dans ce numéro de Medicographia, consacré au thème « Insuffisance veineuse : les douleurs de jambe au devant de la scène », plusieurs experts européens (notamment Nicos Labropoulos, Grèce) partagent leur expérience. En 2013, Servier a publié un ouvrage intitulé De la douleur veineuse à la chirurgie, dans lequel le neurologue français Nicolas Danzinger, de La Pitié-Salpêtrière à Paris, a écrit un excellent chapitre sur le sujet suivant : « Comment décrire la douleur veineuse ». Dans la partie consacrée aux mécanismes généraux de la douleur veineuse, il décrit l’anatomie, l’innervation veineuse, les propriétés physiologiques des nocicepteurs veineux et périveineux et le rôle des neuromédiateurs participant à leur activation\(^4\). Comprendre la physiopathologie de la douleur veineuse nécessite que nous prenions en compte les propriétés des nocicepteurs, ainsi que les mécanismes inflammatoires...
qui caractérisent l’insuffisance veineuse dès ses stades précoces. Le déclencheur de ces mécanismes est vraisemblablement l’hypoxie locale provoquée par l’hypertension veineuse. Cette hypoxie active les cellules endothéliales, ce qui entraîne la synthèse et la libération locale de médiateurs qui modulent la douleur par l’activation des nocicepteurs pro-inflammatoires. Des indices d’une telle réaction inflammatoire dans les varices de patients se sont accumulés au cours des dernières années, et les changements biochimiques identifiés suggèrent que les cellules endothéliales et les neutrophiles sont à la source de l’inflammation. Le docteur Danzinger s’intéresse à la raison pour laquelle la douleur ne montre pas de corrélation avec la sévérité clinique, et se réfère aux travaux de Bradbury dans l’Étude Veineuse d’Édimbourg (Edinburgh Vein Study), qui mettaient en évidence une faible corrélation entre les symptômes et la présence ou l’absence de varices. Il suggère que ce manque de corrélation pourrait s’expliquer par le fait que les nocicepteurs veineux ne seraient pas actifs dans les veines de gros calibre, mais plutôt dans la microcirculation. L’hypertension veineuse est transmise à la microcirculation, ce qui déclenche l’adhésion des leucocytes à l’endothélium capillaire. Ce phénomène déclenche une réaction inflammatoire qui augmente la perméabilité capillaire, entraînant un œdème interstitiel. Cette théorie est confirmée par les travaux de van Rij sur l’insuffisance des valves microveineuses dans les petites veines superficielles, qui constitue un élément essentiel des changements cutanés dans l’insuffisance veineuse, ce qui pourrait aussi expliquer la douleur chez les patients de classe clinique C0.

**Caractérisation des symptômes veineux**

Elle s’avère difficile et conduit fréquemment à des malentendus. Il est souvent difficile pour les patients de trouver les mots exacts pour décrire leurs symptômes ; outre la lourdeur et l’œdème, d’autres descriptions (notamment des sensations de tension, de douleur sourde, de douleur congestive et de repos, ou bien à une hypertension veineuse provoquant une douleur inflammatoire. Chez les patients présentant une douleur invalidante, le débit pelvien doit être exploré, en particulier chez les patients atteints d’une maladie post-thrombotique sans aucun changement cutané, se plaignant d’une douleur horizontale. Le débit pelvien doit être exploré, en particulier chez les patients atteints d’une maladie post-thrombotique sans aucun changement cutané, se plaignant d’une douleur horizontale.

Les patients présentant uniquement des symptômes veineux (C0), mais chez lesquels aucun dysfonctionnement veineux ne peut être mis en évidence, sont classés C0EAPn. Une échelle visuelle analogique (EVA) est un outil utile pour la douleur. Lorsque la douleur est sévère et non proportionnée aux résultats cliniques et à l’écho-Doppler, nous devons envisager une obstruction du débit veineux. Cela peut conduire à une claudication veineuse réelle avec des élancements douloureux lors de la marche, et un temps de résolution prolongé au repos, ou bien à une hypertension veineuse provoquant une douleur inflammatoire. Chez les patients présentant une douleur invalidante, le débit pelvien doit être exploré, en particulier chez les patients atteints d’une maladie post-thrombotique sans aucun changement cutané, se plaignant d’une douleur horizontale.

Néglen et al. ont observé une amélioration substantielle de la douleur en utilisant une EVA, après avoir mis en place une endoprothèse sur une obstruction iliofémorale, ces résultats étant confirmés par plusieurs études utilisant le VCSS. Delis a rapporté la suppression d’une claudication veineuse, évaluée par tapis roulant chez 55 patients présentant des antécédents de thrombose veineuse profonde (TVP) iliofémorale, après la mise en place d’une endoprothèse. Il n’existe aucune relation entre la sévérité clinique et l’amplitude de la douleur veineuse, et seule une faible corrélation est constatée entre la douleur et la présence d’un reflux profond ou superficiel. Cependant, les questionnaires de QoV montrent une bonne corrélation avec les résultats généraux et cliniques.

**Impact socio-économique**


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**Abréviations et acronymies principaux**

- CEAP : clinical, etiological, anatomical, pathophysiological [clinique, étiologique, anatomique, physiopathologique]
- TVC : trouble veineux chronique
- EVA : échelle visuelle analogique
- VCSS : Venous Clinical Severity Score [Score de Sévérité Clinique Veineux]
neuse Chronique des Membres Inférieurs : Directives Basées sur les Données Scientifiques], il est indiqué que l’impact socio-économique considérable du TVC est dû au grand nombre de patients concernés, au coût des investigations et de la prise en charge, à la morbidité et à la souffrance1. Ces éléments se reflètent dans la détérioration de la QdV et la perte de jours de travail. Le fait que le TVC soit progressif et présente une propension à récidiver rend le problème compliqué. Les mesures destinées à réduire l’amplitude du problème comprennent une meilleure prise de conscience, un diagnostic et des soins précoce, l’examen minutieux de la nécessité et du choix des investigations, la discipline pour le choix de la prise en charge basé sur l’efficacité clinique et les coûts. Ces exigences impliquent une formation spécifique dans tous les aspects de cette maladie. Les coûts directs sont associés au personnel médical, infirmier et auxiliaire ainsi qu’aux coûts des investigations et des traitements, qu’ils soient délivrés au cours d’une hospitalisation ou en consultation externe. Les coûts indirects sont liés à la perte des jours de travail. Le coût en termes humains doit également être pris en compte, et celui-ci peut être quantifié par l’évaluation de la QdV. L’estimation des coûts annuels globaux du TVC varie de 600 à 900 millions d’euros dans les pays d’Europe de l’Ouest, qui représente 1 à 2 % du budget total de la santé. Les coûts indirects de la maladie veineuse en ce qui concerne la perte des jours de travail sont qualifiés de « plus important facteur de coût », atteignant 270 millions d’euros en Allemagne (1990). Une étude française de 2005 a observé qu’environ 7 % de la population active ne travaillait pas à cause de la maladie veineuse.

Ces coûts sont supérieurs à la somme dépensée pour les maladies artérielles. La nécessité de limiter l’augmentation des coûts du TVC apparaît évidente. Les méthodes utilisées, qu’elles soient destinées à la prévention ou au traitement, doivent se caractériser essentiellement par une efficacité démontrée, mais elles doivent également prendre en considération le coût par rapport à celle-ci. À l’heure actuelle, il n’existe aucun moyen de prévenir efficacement la survenue de varices. Beaucoup d’efforts ont été consacrés pour la prévention du développement du TVC chez des patients présentant des varices précoces ou des antécédents de TVP et toutes les mesures qui contribueraient à la prévention d’un ulcère veineux exerceront un impact important sur les coûts humains et socio-économiques.

Nécessité de recherches complémentaires
Malgré l’intérêt croissant que suscitent les mécanismes physiopathologiques du TVC, notre connaissance reste limitée selon les directives mentionnées ci-dessus. Les déterminants génétiques et moléculaires du développement du TVC sont encore largement méconnus. La relation entre les paramètres macrohémodynamiques et le fonctionnement ou le dysfonctionnement endothélial dans la paroi veineuse, nécessite des investigations complémentaires tout comme l’impact réel de la dynamique des flux sur le remodelage capillaire, valvulaire et de la paroi veineuse, l’activation des globules blancs, la prolifération et la migration des cellules musculaires lisses, et l’altération de la matrice extracellulaire.

Les preuves du rôle de la sénescence et de l’apoptose dans le développement des altérations cellulaires et moléculaires liées au TVC en présence d’une hypertension veineuse restent mal comprises. Les manifestations variables des signes et des symptômes dans le TVC chez les personnes présentant des sites de reflux similaires, une améliorabilité comparable de la maladie et une altération hémodynamique globale équivalente n’ont pas été expliquées. En outre, les bases physiopathologiques et moléculaires de la lipodermatosclérose et de l’ulcération ne sont que partiellement explicitées, et la physiopathologie sous-jacente de la douleur veineuse chez les patients ne présentant aucun signe de maladie veineuse ou de reflux/obstruction doit également faire l’objet d’études supplémentaires. La signification de la corona phlebectatica en relation avec la progression du TVC reste mal déterminée.

Il est essentiel que les recommandations relatives au changement de la classification CEAP soient soutenues par des recherches, afin de permettre des progrès concernant le niveau de preuve plutôt que le niveau d’investigation. Il est nécessaire d’inclure une cotation de la sévérité des symptômes, comme dans le VCSS par exemple. La comparabilité descriptive permise par la stratification CEAP doit être utilisée en association avec les scores VCSS et de QdV, lesquels sont des instruments pour des recherches longitudinales offrant une évaluation objective des résultats. La relation entre la sévérité des symptômes dans le TVC et les paramètres hémodynamiques veineux globaux dans tout le spectre de la classification CEAP nécessite d’être étudiée plus avant. Les méthodes permettant de mesurer le degré d’une obstruction veineuse significative sur le plan hémodynamique restent à déterminer. L’introduction d’un test non invasif fiable permettant de détecter une altération cliniquement significative du flux constitue un besoin important.


Conclusion
Plusieurs études épidémiologiques ont montré que jusqu’à 75 % des adultes présentent des symptômes veineux. Il existe une corrélation significative entre les symptômes veineux et l’aggravation de la classe clinique (« C ») de la classification.
CEAP ou de la QdV. Cependant, 15 % des personnes se plaignant de symptômes ne présentent aucun signe de TVC. Le symptôme le plus fréquent du TVC est la douleur, et elle ne présente pas de corrélation avec la sévérité du TVC. Son déclencheur probable est une hypertension veineuse et probablement capillaire, provoquant une interaction entre les leucocytes et l’endothélium veineux, qui entraîne la synthèse et la libération de médiateurs modulant la douleur par l’activation de nocicepteurs pro-inflammatoires. Malgré l’intérêt croissant porté aux mécanismes physiopathologiques du TVC, notre connaissance reste limitée et des recherches complémentaires sont nécessaires. Je vous encourage à vous plonger dans ce numéro de Medicographia rédigé par d’excellents experts du TVC.

Mots clés : classification CEAP ; trouble veineux chronique ; Score de Sévérité Clinique Veineux ; douleur veineuse ; symptôme veineux
The precise description of venous disorders is lacking in most books or treatises devoted to venous disorders, and confusingly, there are times when both signs and symptoms are included within the same heading of “symptoms.” The absence of an accurate description may be related to the fact that most venous symptoms are nonspecific, and more or less identical to symptoms arising from nonvenous causes. Symptoms listed in various venous classifications are often not the same, and the different terms are sometimes difficult to describe accurately. Some frequently noted symptoms may also be difficult to differentiate, as they are very similar to each other, for example, pain and aching. This review aims to, firstly, describe symptoms as precisely as possible and, secondly, define the circumstances favoring their occurrence. The relationship between symptoms and signs, reflux, quality of life, venous clinical score, and inflammatory markers is reviewed. Some attempts to better ascribe leg symptoms to venous etiology are analyzed, and their value is questioned. In conclusion, an international consensus concerning the definition of venous symptoms and causes is recommended, with the knowledge that this should, in turn, improve the management of patients.

Confusingly in English literature, signs and symptoms sometimes appear under the same heading of “symptoms.” In this article, the term “symptom” only incorporates unpleasant phenomenon felt by the patient that arise from and accompany a particular disease or disorder. Consequently, the presence and severity of symptoms is subjective.

Venous symptoms remain a challenge to deal with for multiple reasons. Firstly, very few books or treatises dedicated to chronic venous disorders give a precise description and definition of so-called “venous symptoms.” This may be due to difficulty in defining these symptoms, as they are not pathognomonic. This point increases the difficulty of attributing a venous etiology or cause to these symptoms, knowing that all classes of venous disorders can be associated with venous symptoms.
List of venous symptoms

- **CEAP classification**
  The CEAP classification includes aching, pain, tightness, skin irritation, heaviness, muscle cramps, and other complaints attributable to venous dysfunction in its list of venous symptoms. 1

- **VCSS classification**
  The Venous Clinical Severity Score (VCSS) reports pain or other discomfort (ie, aching, heaviness, fatigue, soreness, and burning) presumed of venous origin. 2 Interestingly, the symptom list is not limited as it is in the CEAP classification, as venous dysfunction may be identified (which is not always possible in daily practice). In the VCSS, the symptoms described are reported as possibly venous, which is not discriminative as it depends how venous function is investigated.

- **Bonn Vein Study**
  The Bonn Vein Study (BVS) recognizes symptoms such as swelling; feeling of swelling, tightness, and heaviness; pain during prolonged walking, sitting, or standing; cramps; itching; and restless legs. 3,4

- **VEINES-QoL/Sym questionnaire**
  The subscale of the VEnous Insufficiency Epidemiological and economic Study (VEINES) called VEINES-Quality of life/Symptoms (VEINES-QoL/Sym) listed nine venous symptoms: heavy legs, aching legs, swelling, night cramps, heat or burning sensation, restless legs, throbbing, itching, and tingling sensation. Although built to evaluate the quality of life in primary chronic venous disorders, 5 the tool has been mainly used to assess the quality of life of patients with postthrombotic syndrome. 6 From this bibliographic research, it appears that the term "venous symptoms" needs to be better determined and clarified.

Description of venous symptoms

As previously mentioned venous symptoms are nonspecific, but there are some features that may help to attribute them to a venous origin.

- **Pain or aching**
  Venous pain may take on the following patterns:
  - Pain along the varicose vein course (phlebalgia) and, more frequently, diffuse pain in the lower leg, mainly in the calves.
  - Venous claudication due to an obstructive lesion of the deep vein usually located in the iliofemoral axis. 7 Intermittent claudication is defined as the outcome of a painful or bursting sensation that occurs only when the patient is walking or running and is located either in the lower limb or in the buttock. This pain disappears progressively when the patient stops, or by leg elevation that allows differentiating from arterial claudication and nonvenous neurologic compression. According to Blättler and Blättler, pure venous claudication related to axial vein obstruction can be distinguished from venous neurogenic claudication caused by dilated veins in the spinal canal that arise from the collateral circulation, by magnetic resonance imaging or contrast enhanced computed tomography. Both are cured by venous stenting. 8
  - Presence of painful lipodermatosclerosis or an open ulcer.

- **Throbbing**
  This infrequent symptom is depicted by patients as a pulsing pain along the pathway of varices, mainly the incompetent saphenous trunks or their major tributaries.

- **Tightness**
  Tightness is a term rarely used by patients, but may correspond to the feeling that their leg is caught in a stranglehold.

- **Heaviness**
  This symptom is described as heavy legs occurring in a long-term standing or seated position.

- **Fatigue**
  This symptom is a little bit different from heaviness and is described by patients as a feeling of tiredness, occurring after any kind of activity using the lower limb, but also after prolonged motionless standing.

- **Impression of swelling**
  This symptom is different from the sign edema, which can be measured. Some patients describe the impression of swelling with no evident edema on clinical examination.

- **Cramps**
  Cramp is an involuntary, painful, contraction of muscles. Venous cramps are usually located in the calf (gastrocnemius and soleus muscles) and occur at night.

- **Itching**
  Itching may be present in a number of different circumstances, such as in association with: (i) dermatitis (including stasis dermatitis and contact eczema); and (ii) noncomplicated varices. Duque et al showed that in the latter group, 97% complained of itching in the evening and night, 50% had some difficulty falling asleep almost every night, and 40% were awakened by itching. Itching is a frequent and intense symptom. 9

- **Restless legs**
  This symptom, usually quoted as restless legs syndrome, is described by patients as a disagreeable and indefinable feeling,
frequently reported as “having the fidgets” in the lower limb, and accompanied by an irresistible need to move the legs.

◆ Tingling
This symptom is described as a sensation of prickling or stinging in the leg.

Methods allowing identification of venous etiology
In some cases, symptoms or physical signs are highly suspect for venous etiology, but most often, circumstance of apparition and instrumental investigations are crucial for attributing a venous cause to symptoms.

◆ Clinical circumstances of appearance
There is a consensus for agreeing that venous symptoms:
- Are influenced by the standing position, which is often considered as a trigger, or immobility in orthostatic position.
- Worsen progressively during the course of the day and are worst in the evening.
- Are exacerbated by warmth or when the ambient temperature and atmospheric humidity are high (eg, during the summer season, hot baths, floor-based heating systems, or hot waxing to remove body hair), but less intense in winter and/or with cold temperatures.
- Are exacerbated during the luteal phase of the menstrual cycle, in other words, more intense during the period immediately prior to menstruation, and may decrease once menstruation begins.
- May occur with hormonal therapy (eg, oral contraceptive, or hormone replacement therapy), but disappear with discontinuation of such treatment.10-12

Consequently, when symptoms occur or are enhanced by the circumstances described above, a venous origin is highly probable. Nevertheless, instrumental investigations are undertaken to identify venous pathophysiological anomalies, in order to objectively diagnose venous etiology.

◆ Instrumental investigations
Instrumental investigations are often carried out in all patients presenting with any kind of venous disorder from C0s to C6.

◆ Duplex scanning
Duplex scanning (DS) is the first-line investigation for suspected venous disorders. This noninvasive investigation explores saphenous trunks and their first order tributaries, lower-limb deep axial veins, as well as deep femoral, gastrocnemius veins, and lower-limb perforators. Conversely, tributaries beyond the first-generation tributaries and the iliac vein in obese patients are either impossible or difficult to investigate in routine DS examination.

◆ Venography
Venography includes ascending or descending phlebography, with or without lower-limb tourniquet use. This investigation explores the same veins, but less precisely in terms of pathophysiological disorders such as reflux.

◆ Computed tomography and magnetic resonance imaging
These two investigations are rarely used in primary chronic venous disorders, except in pelvic congestion syndrome combined with varices or when non-postthrombotic suprainguinal vein obstruction is suspected.

◆ Iliac vein intravascular ultrasound examination
This investigation is only undertaken in primary venous disorders, in patients presenting with severe symptomatology without severe varices and in the absence of postthrombotic syndrome.13

◆ Microcirculation investigations
Microcirculation is not investigated routinely in the presence of primary venous disease, except in the few cases of severe chronic venous insufficiency.

◆ Conclusion
Venous investigations, particularly DS, are very useful in patients for attributing symptoms to venous etiology in the CEAP C2 class, although there is a weak correlation between varices and symptom severity. Conversely in C0s patients, who represent 19.6% of the Vein Consult Program,12 venous valve competence of the second to the sixth generation are not investigated. We know that microscopic venous valves in the small superficial venous veins of human lower limbs can be incompetent, independent of reflux into the great saphenous vein and major tributaries (Figure 1).14,15 A plausible hypothesis is that symptoms present in C0s patient might be caused by reflux in the second to sixth generation of microvalves. Such “microrefluxes” are not currently assessable by physical examination or by DS investigation.

Relationship between symptoms and/or signs, and other markers

◆ Venous symptoms and reflux
Pain is particularly poorly associated with the presence or absence of trunk varices and reflux, according to the Edinburgh Vein cross-sectional survey. Firstly, in men, only itching was significantly related to the presence and severity of trunk varices. In women, the correlation between symptoms and trunk varices is better: heaviness or tension (P<0.001), aching (P<0.001), and itching (P<0.005).16 Of note, this correlation was established only for saphenous varices, P=0.02 according to the CEAP classification.17 The highest prevalence of symptoms was found when varices and telangiectasias were both present.17 Secondly, reflux in the saphenous trunks was not correlated with venous symptoms in men. In women, only heaviness (P<0.025) and itching (P=0.002; left leg) are correlated with saphenous reflux.18

Chiesa et al showed that approximately 80% of subjects with no visible signs of venous disease, including absence of varices, complain of symptoms. In contrast to the Edinburgh Vein cross-sectional survey, reflux related to valve incompetence correlated positively with worsening symptoms.19
- **Venous symptoms and venous disease severity**
  There is a significant correlation between venous symptoms, particularly pain and worsening of clinical chronic venous disorder signs (CEAP classes), in many articles.\(^{20-23}\) Conversely, Howlader and Smith found no correlation between symptoms and clinical classes (CEAP classification C\(_2\) to C\(_5\)).\(^{24}\)

- **Venous symptoms and health-related quality of life**
  Impact of venous symptoms on health-related quality of life has been clearly established in noncomplicated varices (CEAP classification C\(_0\)). To assess quality of life, Duque et al curiously used a specific dermatologic questionnaire (Skindex-16),\(^9\) while Darvall et al used the generic Short Form 12 (SF-12).\(^{25}\)

- **Venous symptoms and inflammation**
  According to Howlader and Smith, there is no correlation between levels of inflammatory mediators and venous symptoms.\(^{24}\) However, Danziger, in his article on venous pain physiology, underlines that capillary and venule stasis activates endothelial cells, resulting in the synthesis and local release of inflammatory mediators such as bradykinin, platelet-activating factor, prostaglandins, and leukotriene B\(_4\), etc. In turn, these inflammatory mediators activate C nociceptors in the capillary and vein walls, resulting in diffuse pain often described as discomfort, tightness, or heaviness.\(^{26,27}\)

**Attempts to better ascribe leg symptoms to venous etiology**

As venous symptoms are often nonpathognomonic and non-specific, the task of attributing these symptoms to venous etiology is not easy. Carpentier et al suggested the creation of a diagnostic score in order to facilitate this process, by classifying the patients in two groups.\(^{28}\) The first group includes patients presenting with leg symptoms and no clinical evidence of arterial, rheumatic, or neurological disorders, but with venous dysfunction documented both clinically and by DS examination. This group was named CVD\(^+\). The second group included patients with leg symptoms and documented arterial, rheumatic, or neurological disorders, but no signs of clinical disorders or venous reflux at DS examination. This group was identified as CVD\(^-\).

In a validation series of 92 patients (67 CVD\(^+\) and 25 CVD\(^-\)), Carpentier et al found that the combination of four symptoms, worsened by circumstances of apparition, was reliable in terms of high specificity (0.95) and fair sensitivity (0.75) for identifying chronic venous disorders. Unfortunately, no other paper using this score has been reported and consequently the score proposed by Carpentier and al has not yet been validated. In theory, the Carpentier's evaluation has two biases: firstly C\(_0\) patients are difficult to classify, as they have no venous dysfunction identifiable by clinical examination or routine DS. Secondly, the same difficulty exist in patients with non-thrombotic iliac vein obstructive lesions, which are not identified by DS examination according to Neglen.\(^{29}\)

Another approach to identifying venous responsibility has recently been used. In 2013, the BVS was reanalyzed to try to distinguish between a psychic component and somatic component by using a short questionnaire; the psychic vs somatic venous disease questionnaire (PsySoVDQ).\(^{30}\) The conclusion of this study is that the PsySoVDQ identified somatic and psychic components of the widespread and frequently reported leg symptoms in the general population. Nevertheless, in the majority of subjects, symptoms remained unexplained. The authors suggest a neuropsychological and neurobiological hypothesis.

**Conclusion**

Precise definition and description of venous symptoms are suggested in this review, in order to identify a venous origin of the so-called venous symptoms. This is crucial in providing better care for symptomatic patients. However, there are several issues that still need to be clarified.
Firstly, it is still unclear whether venous symptoms are caused by a primary etiology in alterations of the major veins—related to reflux in superficial or/deep veins or compression above the inguinal ligament axial veins—or in anomalies within the veinules or capillaries. Secondly, it is still unclear whether the presence or severity of symptoms independently of signs allows us to forecast worsening venous disease. If we rely on VCSS, the maximum score attributed to symptoms is only 3/30; in other words venous symptoms count for very little in venous disorder scoring.2 Venous symptoms in epidemiological studies are very common: in the BVS more than half of the 1800 participants reported such symptoms.3,4 We know that operative treatment, particularly in noncomplicated, but symptomatic, varices does not relieve venous symptomatology in many cases. It would be a step forward to identify the patients that could potentially experience improved symptoms following operative treatment. Patients that are unlikely to improve should be recommended an alternative treatment.

References

Keywords: CEAP classification; chronic venous disease; chronic venous disorder; varices; Venous Clinical Severity Score; venous symptom
La plupart des ouvrages consacrés aux troubles veineux ne les décrivent pas précisément et parfois, les signes et les symptômes sont regroupés de façon confuse sous la même rubrique « symptômes ». Cette absence de description précise peut être liée à la non-spécificité de la majorité des symptômes veineux et à leur relative similitude avec des symptômes qui sont dus à des causes non veineuses. Les symptômes énumérés dans les classifications veineuses multiples sont souvent différents et les termes utilisés pour décrire les symptômes dans les différentes classifications des affections veineuses chroniques ne sont pas toujours les mêmes. Certains symptômes fréquemment rapportés peuvent être difficiles à différencier car très similaires comme, par exemple, la douleur et l’endolorissement. Cet article décrit tout d’abord les symptômes aussi précisément que possible, pour ensuite définir leurs circonstances de survenue. Les relations entre les symptômes et les signes, le reflux, la qualité de vie, le score veineux clinique et les marqueurs inflammatoires sont étudiées. Les tentatives d’une meilleure attribution d’un symptôme du membre inférieur à une étiologie veineuse sont analysées et leur valeur est discutée. Pour conclure, nous recommandons un consensus international sur la définition des causes et des symptômes veineux dont la connaissance pourra, en retour, améliorer la prise en charge des patients.
The prevalence of lower-limb venous symptoms in recent epidemiological surveys

by E. Rabe, Germany

Introduction

Chronic venous disorders of the lower limbs are amongst the most common diseases all over the world. In contrast to older studies, recent epidemiological studies have used the clinical, etiological, anatomical, pathophysiological (CEAP) classification to make results more comparable.

The CEAP classification of chronic venous disorders, in its updated version from 2004, gives clear definitions of venous findings and specifies venous symptoms. All clinical classes can be asymptomatic (A) or symptomatic (S). Symptoms include aching, pain, tightness, skin irritation, heaviness, muscle cramps, and other complaints attributable to venous dysfunction. The subjective symptomatic course can point to a venous etiology, particularly if the abovementioned symptoms are exacerbated, eg, by heat and/or the course of the day, or relieved with leg rest and/or elevation. Lower-limb symptoms may be associated with venous pathology, but may not be specific for venous disease. Van der Velden recently found that other leg diseases like arterial occlusive disease, knee or hip arthrosis, or spinal disc herniation may be associated with identical symptoms as venous disease. In the Edinburgh Vein Study, Bradbury found that the correlation of trunk varices with venous symptoms is weak and that venous symptoms do not correlate well with venous reflux. How-
ever, Darvell showed a worsening of health-related quality of life with the number of reported venous symptoms.\textsuperscript{15} The aim of the paper is to review venous symptom findings in recent epidemiologic studies that used the CEAP classification.

### The Bonn Vein Study
The Bonn Vein Study investigated 3072 participants aged between 18 and 79 years, selected by a simple random sample from population registers of the city of Bonn and two rural townships.\textsuperscript{4} The overall prevalence of varicose veins was 23.2% (19.8% in men, 25.8% in women), and of chronic venous insufficiency (C\textsubscript{3} to C\textsubscript{6}) 17% (15.4% in men, 18.3% in women). A total of 56.4% of the participants claimed leg symptoms assignable to chronic venous disorders in the prior 4 weeks (Table I).\textsuperscript{4} Venous symptoms were more frequent in the female population (62.1%) compared with the male population. Except for restless legs, all symptoms increased with the severity of the disease. The prevalence of all symptoms, except of restless legs, was significantly higher in participants with trophic venous changes.

### The San Diego Population Study
The San Diego Population Study investigated 2408 men and women, aged between 29 to 91 years, who were employees, retirees, or spouses of a large state university. This population was randomly selected within strata by age, sex, and ethnicity.\textsuperscript{5} In the whole population, 23.3% had varicose veins (15% in men, 27.7% in women).\textsuperscript{5} Trophic changes were present in 6.2% of the population (7.8% in men, 5.3% in women). As a part of the standard interview, participants were asked if they had any kind of venous symptoms in the past or present. The most frequent symptom was aching (17.7%), followed by cramping (14.3%), tired legs (12.8%), and feeling of swelling (12.2%) (Table II).\textsuperscript{6}

Symptoms were more common in the female population compared with the male population. Except for restless legs, all symptoms increased with the severity of the disease. The prevalence of all symptoms, except of restless legs, was significantly higher in participants with trophic venous changes.

### The Italian Study
In Italy, Chiesa and coworkers published the 24-cities cohort study on venous diseases, including 4457 women and 730 men aged 18 to 90 years.\textsuperscript{7} The participants were selected during spring and summer 2003 by advertising on television, in newspapers, and by leaflets in 24 Italian cities. Only 22.7% had no clinical signs of chronic venous disease (CVD). A total of 64.8% had telangiectasias or reticular veins, 29.4% had varicosities other than saphenous veins, and 13.6% saphenous varicose veins. In the C\textsubscript{0} class, 13.6% had edema, 13.4% venous eczema, and 8.6% preulcer skin changes like white atrophy and dermatoliposclerosis, or healed or active venous ulcers. Venous symptoms were reported in 96.3% of the women and 90.1% of the men. The authors suspected that this high prevalence might be partly due to the method of recruitment for the study.\textsuperscript{7} There were no differences in prevalence by age or by region of living for most of the symptoms. The most frequent complaints were tired legs (77.5%) and heavy legs (75.5%). Except for tingling sensation, women reported symptoms significantly more often than men (Table III, page 18).\textsuperscript{7}

### The Polish Study
In this multicenter cross-sectional study, 803 participating primary care physicians in Poland screened 40 095 consecutive patients using a standardized interview and assigned them to

### Table I. Leg symptoms in the Bonn Vein Study I.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>All (%)</th>
<th>Men (%)</th>
<th>Women (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heaviness</td>
<td>18.2</td>
<td>11.1</td>
<td>23.8</td>
</tr>
<tr>
<td>Tension</td>
<td>12.6</td>
<td>9.1</td>
<td>15.3</td>
</tr>
<tr>
<td>Swelling</td>
<td>11.4</td>
<td>5.7</td>
<td>15.8</td>
</tr>
<tr>
<td>Aching on standing</td>
<td>19.9</td>
<td>14.4</td>
<td>24.2</td>
</tr>
<tr>
<td>Aching on walking</td>
<td>11.6</td>
<td>11.3</td>
<td>11.8</td>
</tr>
<tr>
<td>Itching</td>
<td>9.5</td>
<td>10.3</td>
<td>8.9</td>
</tr>
<tr>
<td>Cramps</td>
<td>25.5</td>
<td>21.9</td>
<td>28.2</td>
</tr>
<tr>
<td>Restless legs</td>
<td>9.6</td>
<td>6.4</td>
<td>12.1</td>
</tr>
</tbody>
</table>

### Table II. Percentage of participants with leg symptoms in the San Diego Population Study by visible disease.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>All (%)</th>
<th>No CVD (%)</th>
<th>C\textsubscript{1} (%)</th>
<th>VV (%)</th>
<th>TC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heaviness</td>
<td>7.5</td>
<td>4.4</td>
<td>6.7</td>
<td>11.8</td>
<td>16.0</td>
</tr>
<tr>
<td>Swelling</td>
<td>12.2</td>
<td>7.2</td>
<td>10.1</td>
<td>19.1</td>
<td>35.7</td>
</tr>
<tr>
<td>Tired legs</td>
<td>12.8</td>
<td>10.6</td>
<td>11.1</td>
<td>18.3</td>
<td>21.1</td>
</tr>
<tr>
<td>Aching</td>
<td>17.7</td>
<td>14.2</td>
<td>15.7</td>
<td>25.5</td>
<td>29.1</td>
</tr>
<tr>
<td>Itching</td>
<td>5.4</td>
<td>4.0</td>
<td>4.3</td>
<td>8.7</td>
<td>13.1</td>
</tr>
<tr>
<td>Cramps</td>
<td>14.3</td>
<td>12.9</td>
<td>13.2</td>
<td>17.7</td>
<td>19.7</td>
</tr>
<tr>
<td>Restless legs</td>
<td>7.4</td>
<td>5.8</td>
<td>7.5</td>
<td>9.0</td>
<td>8.0</td>
</tr>
</tbody>
</table>

### Table III. Leg symptoms in the Polish Study.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telangiectasias or reticular veins</td>
<td>29.4%</td>
</tr>
<tr>
<td>Varicosities other than saphenous veins</td>
<td>13.6%</td>
</tr>
<tr>
<td>Saphenous varicose veins</td>
<td>13.6%</td>
</tr>
<tr>
<td>Edema</td>
<td>13.6%</td>
</tr>
<tr>
<td>Venous eczema</td>
<td>8.6%</td>
</tr>
<tr>
<td>Preulcer skin changes</td>
<td>8.6%</td>
</tr>
</tbody>
</table>

### Selected Abbreviations and Acronyms

- **CEAP**: clinical, etiological, anatomical, pathophysiological
- **CVD**: chronic venous disease

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The prevalence of lower-limb venous symptoms in recent epidemiological surveys – Rabe
a clinical class, “C”, according to the CEAP classification. Of the participants, 16% were men and 84% were female. The age ranged from 16 to 97 years with a mean of 44.8 years. A total of 51.1% were assigned to C0, 16.5% to C1, 21.8% to C2, 4.5% to C3, 4.6% to C4, 1% to C5, and 0.5% to C6.

In patients assigned to the clinical levels C1 to C6, symptoms like heaviness, cramps, and aching were very frequent compared with those assigned to C0 (heaviness 73.7% vs 23.3%, cramps 57.5% vs 20.0%, aching 75.7% vs 27.5%, respectively). In the chronic venous disorder group (CEAP C1 to C6), in most cases the symptoms intensified at the end of the day (73.4%), during standing position (67.4%), and during summer time (66.1%), compared with the C0 patients, where this dynamic could only be observed in the minority of participants (24.6%, 20.0%, 19.5%, respectively). In the chronic venous disorder population, the symptoms were chronic in 23.8%, whereas this was only the case in 4.4% of the C0 group.

The Brazilian Study
From March 1998 to December 2000, in the cities of Sorocaba and Campinas, 2104 consecutive patients from general ambulatory departments in the University Hospital and from the Public Health Centers were screened for venous disease and assigned to the “C” class of CEAP. They were asked about the presence of subjective symptoms such as feelings of heaviness in the legs, edema, tired legs, burning feet, and paresthesia. In the female age group of 14 to 22 years, 12.29% were classified as symptomatic. In the male population, only 6.0% were classified as symptomatic. In the male population, only 13.97% were classified as symptomatic.

The Vein Consult Program
The most recent data derive from the Vein Consult Program (VCP). The VGP is a large international observational prospective survey that has been carried out on the initiative of the Union Internationale de Phlébologie (International Union of Phlebology) to raise awareness of CVD, thanks to an unrestricted grant from Servier, France. A total of 6232 general practitioners in Western, Central, and Eastern Europe, Latin America, and the Middle East screened 91 545 consecutive patients for the presence of chronic venous disorders. The mean age was 50.6 years, with 16.4% of all participants in an asymptomatic C0 class and 19.7% with venous symptoms, but no clinical signs of chronic venous disorders (C0s). A total of 21.7% had reticular veins or telangiectasias, 17.9% were in class C2, 14.7% in C3, 7.5% in C4, 1.4% in C5, and 0.7% in C6. The majority of the population screened had venous symptoms, the most prevalent being heavy legs (72.4%) and pain (67.7%) (Table IV).

In the majority, symptoms increased at the end of the day. Venous symptoms were more prevalent in the female population and the prevalence increased with higher “C” classification.

Discussion
Recent epidemiologic studies show that venous symptoms defined in the updated CEAP classification are very common in the general population. These symptoms, eg, feeling heaviness, swelling, and pain in the legs, are more prevalent in the female population compared with the male population. They increase with age and are more frequent in higher clinical stages of chronic venous disorders, except for restless legs and similar complaints. These symptoms increase during the course of the day and with warm temperatures in the chronic venous disorder population.

These symptoms are not limited to venous disease alone. As Van der Velden showed, similar symptoms may also be present in other pathologies, such as orthopedic back and knee diseases, and arterial occlusive disease. However, in these cases the typical dynamics with increased intensity during the course of the day and during warm periods may not be present.

Even in the C0 patients without any clinical signs of CVD so-called venous symptoms may be present. It is possible in these cases that the symptoms are definitely not of venous origin and therefore may have an alternative cause. However,
the clinical level C0 does not mean that no venous pathology exists. One such example is of postthrombotic patients with obstruction or valve incompetence in the deep venous system, but without varicose veins, edema, or skin changes. In these patients, the symptoms are even part of the Villalta system, but without varicose veins, edema, or skin changes. With obstruction or valve incompetence in the deep venous system, swelling, or pain, like venous claudication, may also be symptoms of primary or secondary iliac vein obstruction without visible signs of chronic venous disorders. In obese patients may develop a functional venous disease without reflux, but with nonpermanent iliac vein obstruction during sitting periods. They may also develop venous symptoms without clinical signs of chronic venous disorders. We have to consider that there may also be a psychogenic component of leg symptoms, as reported by Ami r et al. in 7.3% of the Bonn Vein Study symptomatic participants. 19

References
15. Darvall KA, Bate GR, Adam DJ, Bradford AW. Generic health-related quality of life is significantly worse in varicose vein patients with lower limb symptoms independent of CEAP clinical grade. Eur J Vasc Endovasc Surg. 2012;44(3):341-344.

Keywords: CEAP classification; chronic venous disease; chronic venous disorder; venous symptom

La prévalence des symptômes des membres inférieurs dans les études épidémiologiques récentes

La classe clinique « C » de la classification CEAP (clinique, étiologique, anatomique, physiopathologique) divise les cas en symptômes et asymptomatiques, les symptômes comprenant douleur, raideur, irritation de la peau, lourdeur et crampes musculaires, en particulier s’ils sont exacerbés par exemple par la chaleur ou au cours de la journée, ou soulagés par l’élévation ou le repos des jambes. Dans des études épidémiologiques récentes, ces symptômes sont très fréquents dans la population générale et ne sont pas spécifiques de la maladie veineuse. Leur prévalence augmente avec l’âge et elle est plus élevée chez les femmes. Ces symptômes sont cependant significativement associés à une pathologie veineuse et leur fréquence augmente aussi avec les stades « C » plus élevés. Les symptômes veineux chez ceux qui n’ont pas de signes cliniques de maladie veineuse chronique (MVC) peuvent évoquer une pathologie veineuse structurelle ou fonctionnelle cachée, comme des modifications post-thrombotiques ou une obstruction veineuse induite par l’obésité. Il ne faut cependant pas négliger les autres raisons des symptômes de jambes, comme les maladies orthopédiques ou l’influence psychique.
Association of so-called venous symptoms (aching, itching, tingling, burning sensation, swelling, easily fatigued legs, leg heaviness, and leg restlessness) with chronic venous disease (CVD) still remains a controversial issue. Although these symptoms and decreased quality of life are common in patients with venous incompetence, and are even more frequent in those with a history of venous thrombosis or recurrent and bilateral varicose veins, research has actually revealed that these complaints are poorly correlated with objective signs of venous insufficiency. A venous source for these complaints is quite obvious in patients with advanced CVD, but a substantial part of venous symptoms, especially in patients with telangiectasias and uncomplicated varicose veins, is actually not of venous origin. In addition, such symptoms can be reported by many patients presenting with nonvenous diseases, while uncomplicated varicose veins can cause few symptoms or be asymptomatic. In many venous patients these symptoms are not permanent, but can only be seen at the end of the day. Therefore, it is important to consider and investigate an alternative cause of such “venous” complaints, especially because other pathologies can accompany CVD and produce similar symptoms. The most common pathologies that may be responsible and should be taken into account include: spinal disc herniation, hip and knee arthrosis, peripheral arterial disease, joint and ligament overload due to obesity, peripheral neuropathy, and adverse drug reactions.

Medicographia. 2015;37:20-25 (see French abstract on page 25)

There is a great deal of controversy surrounding association of so-called venous symptoms with chronic venous disease (CVD). An uncertain association of the presence of uncomplicated varicosities with these symptoms has even lead some health care providers to restrict access to treatment for asymptomatic varicose vein patients or those experiencing few symptoms. Clinical symptoms that are thought to be caused by chronic venous insufficiency include: aching leg pain, itching, tingling, burning sensation, swelling, easily fatigued legs, leg heaviness, and restlessness. All of these symptoms typically worsen as the day progresses. The presence of such complaints usually correlates with a decreased quality of life (QoL). An association of these symptoms with CVD is not as obvious as is usually believed. While some researchers found significant correlations between venous symptoms and the signs of CVD (venous reflux revealed by means of Doppler sonography, visible varicose veins, or skin changes typical for venous incompetence [hyperpigmentation, lipodermatosclerosis, and ulcers]), others argued that these symp-
Symptoms and signs of chronic venous disorders – Simka

Correlating symptoms and signs

The majority of patients with severe forms of CVD—those with leg edema (C3 according to the clinical, etiological, anatomical, pathophysiological [CEAP] classification), skin changes (C4), and venous ulcers (C5 and C6)—present with some of the above symptoms. The proportion of patients with venous symptoms significantly increases with the “C” class of the CEAP classification. Usually, in patients with advanced CVD an association of these symptoms with venous incompetence is not questioned, even if other pathologies can accompany chronic venous insufficiency and may produce similar symptoms. Also, it has been demonstrated that these patients present with decreased QoL, with progressive impairment of QoL from C3 to C6/C7.

Less severe chronic venous disease

Venous background of clinical symptoms in patients with less severe forms of CVD, C1, and C2, remains controversial. Many of these patients are asymptomatic despite the presence of an obvious venous pathology. In many C1/C2 patients these complaints may actually be rooted in another coexisting pathology, such as osteoarticular, neurologic, or arterial pathology. For example, in the VEnous Insufficiency Epidemiologic and economic Study (VEINES; 1531 patients with CVD and 1313 controls assessed) the authors did not find significant differences in terms of venous symptoms between the controls and patients with varicose veins (C2). Thus, the authors speculated that clinical symptoms in varicose vein patients probably resulted from concomitant aspects of CVD and not from varicosities, per se.

Poor correlation between symptoms and signs

In the Edinburgh Vein Study (a cross-sectional population study, 1566 individuals assessed) the authors did not demonstrate an association between lower-limb symptoms (leg heaviness, aching, and itching) and the presence of visible varicose veins. Nor did they reveal a significant correlation between venous reflux and lower-limb symptoms. Consequently they concluded that most of these symptoms probably had a non-venous cause. A similar conclusion came from another study, where itching and burning sensations in the legs were not correlated with the severity of venous insufficiency. Also, an observational study by Howlager et al, looking at patients attending a vascular clinic (132 individuals assessed), did not reveal an association between severity of the symptoms and anatomic distribution of venous reflux.

Potential correlation between symptoms and signs

On the contrary, in the San Diego population study (a cross-sectional study on 2209 individuals) the researchers revealed an association between clinical symptoms and the presence of venous disease. Leg edema was the most specific symptom related to venous incompetence. Other symptoms, comprising leg heaviness, aching, and itching, although more common in the patients with venous disease, were also found quite often (5% to 15%) in individuals without CVD.

Similar results were demonstrated by a recent Dutch study. The authors revealed small and—except for swelling of the leg and itching—nonsignificant differences in prevalence of venous symptoms between the patients with CVD and those suffering from other pathologies (arthritis, peripheral arterial disease, or spinal disc herniation). However, the patients with

Selected abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CEAP</td>
<td>clinical, etiological, anatomical, pathophysiological</td>
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<tr>
<td>CVD</td>
<td>chronic venous disease</td>
</tr>
<tr>
<td>QoL</td>
<td>quality of life</td>
</tr>
<tr>
<td>VEINES</td>
<td>VEnous Insufficiency Epidemiologic and economic Study</td>
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</table>
Venous incompetence were more likely to experience symptoms at the end of the day, which was atypical in patients with other pathologies. In another study, the researchers found more frequent venous symptoms among patients with telangiectasias, and even more such symptoms in patients with varicose veins. However, a substantial proportion of the individuals without venous disease also reported “venous” complaints (heaviness, swelling, aching, restless legs, cramps, itching, and tingling) and differences between the subjects with no visible venous pathology and those with either telangiectasias or varicose veins were modest.

Much the same conclusions came from another survey. The authors of this cross-sectional study revealed venous symptoms in 60% of patients with varicose veins and demonstrated that this association was statistically significant. However, 33% of subjects without varicose veins also suffered from venous symptoms. Risk factors that were significantly associated with these symptoms included prolonged sitting or standing, and history of thromboembolism. These symptoms were more common in older women and in tall (height >175 cm) and overweight (body mass index [BMI] >25 kg/m²) men. Consequently, the authors concluded that varicose veins were not the only cause of venous symptoms. Other factors, primarily prolonged sitting and standing, could be a source of such symptoms, and improper clothes and shoes may also play a role. Of note, the researchers did not demonstrate a statistically significant correlation between these symptoms and a history of osteoarthritis. Still, venous symptoms were more common in such patients (20% vs 15% in patients with a negative history of osteoarthritis). Notably, in this study the patients were not clinically examined to reveal an osteoarticular pathology.

In another cross-sectional study on clinical features of CVD in Italian patients (16 251 individuals assessed) the researchers found a statistically significant positive correlation between the symptoms (such as tired and heavy legs, leg pain, or leg edema) and severity of venous disease (defined by the “C” grade of CEAP). These venous symptoms were more prevalent in women and in patients with an increased BMI. However, almost all participants of this survey reported some complaints and only about 10% of the individuals surveyed were free of venous symptoms. An actual venous background of these complaints in the population studied remains questionable. Moreover, it was likely that relevant selection bias occurred in this study, since the individuals attending this survey were attracted by means of advertising in mass media. Therefore, the population was probably skewed towards people with some—not necessarily vascular—leg complaints.

To add to the confusion, in one study patients with benign venous disease (C2/C3) reported more symptoms than those with complicated varicose veins (C4/C5). Venous background of leg symptoms in patients with telangiectasias and small epifascial veins (C, in the CEAP classification) is even less certain. In a cross-sectional study aimed at the evaluation of the clinical impact of small cutaneous veins, researchers found that venous symptoms, comprising leg edema, muscle cramps, and restless legs, were more common in patients with small varicosities in comparison with healthy controls (C3), except for itching, which was less prevalent in the individuals with dilated veins. However, when adjusted for age and sex, these differences—except for leg swelling—were no longer statistically significant. Thus, the authors concluded that although venous symptoms were quite common, also in the C class patients, patients’ age (older subjects) and sex (women) seemed to be a better explanation for these complaints than the presence of small cutaneous varicosities. Leg swelling can be related to such dilated veins, yet their clinical relevance in the development of this symptom seemed to be low (odds ratio, 1.3).

Chronic venous disease and quality of life

Clinical stage

There are also conflicting results for studies on QoL in early stages of CVD. In the San Diego population study the presence of venous disease, even of uncomplicated varicose veins, was associated with significant limitations of all functional scales (physical functioning, role functioning, pain, and general health perception) of the Short Form 36 (SF-36) QoL questionnaire. In another study, female sex was associated with a worse QoL in the patients referred to the varicose vein clinic, but this effect was no longer seen when only C2 patients were analyzed.

Similarly, the VEINES study did not reveal significant differences in QoL between C2 patients and controls, and there was no association between the “C” class and QoL impairment in a study assessing the patients qualified for surgical treatment of varicose veins. Also, an observational study on patients assessed in vascular laboratories did not demonstrate a decreased QoL in the individuals with C1 and C2 classes. Some QoL scores were even higher in varicose vein patients than in healthy people. Likewise, in a study evaluating patients qualified for invasive varicose vein treatment, the authors found an impaired QoL that was independent of the clinical stage of venous disease. However, a similar cross-sectional study (570 venous patients from Serbia) revealed a progressive worsening of QoL from C1 to C6 class. Even those patients presenting with C1 and C2 classes reported an impairment of QoL and did not consider their venous incompetence as a benign cosmetic problem, but rather as a real disease.

Worsening of QoL in C3 to C6 patients compared with the C1/C2 classes was also found in another study.

Venous reflux and inflammatory markers

Similarly, a correlation between the degree of venous reflux with QoL reduction is uncertain. Although one would expect profound venous reflux or an increased diameter of incompe-
tent saphenous trunk to be associated with more severe clinical symptoms and decreased QoL, research does not always confirm such a relationship. In one study, incompetence of the great or small saphenous veins had a greater impact on QoL than nonsaphenous varicosities. Another study revealed either a weak or no correlation between the diameter of incompetent great saphenous vein and impaired QoL in patients with varicose veins. Similarly, there was no association between venous symptoms and systemic inflammatory markers, such as von Willebrand factor, intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion protein 1 (VCAM-1), E-selectin, P-selectin, L-selectin, vascular endothelial growth factor (VEGF), interleukin 1α (IL-1α), IL-1β, IL-6, and tumour necrosis factor α (TNF-α).

**Interventions**

Some studies examined the impact of interventions aimed at the reduction of venous incompetence (compression therapy or ablation of varicose veins) on venous symptoms and QoL. It might be assumed that if the symptoms were indeed produced by venous disease, then such treatments should result in fewer complaints and a better QoL. However, only some of the patients studied were free of symptoms after otherwise successful treatment of varicose veins. On the other hand, a recurrence of venous incompetence was not always accompanied by a return of the symptoms.

**Compression stockings and radiofrequency ablation**

As expected, wearing compression stockings resulted in improved QoL, not only in advanced (C_3 to C_6) venous patients, but also in those with early (C_2) disease. A similar improvement of QoL was demonstrated by another study in patients with incompetent great saphenous veins (clinically C_2 to C_3). The authors of this study revealed that improvement of QoL was mainly due to the relief of venous symptoms. In this study, an invasive treatment (radiofrequency ablation of the great saphenous vein together with phlebectomies of superficial varicosities) resulted in an even greater improvement of QoL. An important finding of this study was that relief of symptoms by compression therapy was a good predictor of successful surgical treatment. Patients who improved their symptoms with compression therapy were more likely to experience further clinical improvement after ablation of varicose veins. However, a substantial proportion of patients who did not improve their QoL after compression therapy benefited from surgical treatment of varicose veins. Thus, not all clinical symptoms of CVD could be relieved by compression alone.

**Surgical excision**

In another interventional study, QoL significantly improved (71% of the patients got better) after surgical excision of varicose veins. Patients with uncomplicated (C_2 to C_3) and complicated (C_4 to C_6) venous disease experienced a similar improvement in their QoL. In this study the patients with a poorer QoL before surgery were more likely to benefit from the treatment. Similarly, in an observational study on patients receiving ultrasound-guided foam sclerotherapy of symptomatic incompetent great or small saphenous veins (patients with asymptomatic varicosities were not included) there was a significant improvement of QoL after the treatment. This improvement was seen in both C_2 to C_3 and C_4 to C_6 patients. Improvement of QoL was similar in patients with great and small saphenous vein varicosities. Also, considering mental domains of the QoL questionnaire, there was no difference in terms of QoL according to whether uncomplicated (C_2 to C_3) or complicated (C_4 to C_6) varicose veins were treated. On the contrary, physical aspects of QoL were significantly worse in patients with C_2 to C_3 venous disease. Interestingly, regarding physical domains of QoL, the patients with uncomplicated varicosities benefited more from the treatment in comparison with those with complicated varicose veins.

**Other influencing factors**

It seems that CVD is not a uniform clinical entity in terms of clinical symptoms and impaired QoL. Thrombotic events, bilateral varicosities, and the recurrence of varicose veins significantly affect natural history of the disease. In the VEINES study, a multivariable regression analysis revealed that previous venous thromboembolism was a predictor of poorer QoL, independent of variables such as age, sex, country of residence, education, BMI, duration of CVD, and the presence of comorbidities. In this study, an analysis adjusted for the CEAP clinical class confirmed a previous thromboembolism as an independent predictor of decreased QoL. Bilateral varicose veins were demonstrated to be associated with worse QoL than unilateral venous incompetence, while some studies demonstrated that QoL was significantly reduced in patients with recurrent varicosities in comparison with those with primary varicose veins. In one study, QoL impairment was no worse in recurrent varicosities than primary varicosities.

**Conclusion**

A reasonable explanation of the enigma of venous symptoms—considering inconsistent results of the above-presented studies—is not easy. Certainly, in many of these studies a selection bias took place, either skewing the cohorts studied towards the patients presenting with real symptomatic CVD (clinical symptoms indeed caused by venous disease), or towards the patients suffering from alternative sources of complaints, primarily osteoarticular pathologies. The first scenario was more likely if the patients qualifying for surgical treatment of varicose veins were evaluated, since they were initially screened by an experienced clinician and those with nonvenous complaints were not very likely to enter such a study. A second scenario could take place in the surveys that used advertising in mass media to select participants, thus mostly attracting people with pain or other leg symptoms primarily associated with neurological and orthopedic problems, and not with venous incompetence. Some researchers speculated that differences between the studies in terms of association of venous symp-
toms with CVD could result from different expressions of such complaints in particular languages, making a comparison of the studies conducted in different countries difficult. 8

Nonetheless, venous symptoms seem to be nonspecific for CVD and can also be reported by patients presenting with other diseases. Many uncomplicated varicose veins can indeed be asymptomatic or cause very few symptoms. 11,12 In some varicose vein patients, the symptoms and impaired QoL may result from concomitant components of venous disease, such as inflammatory skin changes, and are not directly caused by dilated veins. In many of these patients, clinical symptoms are not permanent, but can be seen at the end of the day (when clinical trials are not routinely performed) or only during hot periods of the year (again, not a typical season to perform studies). Moreover, the research is telling us that a large proportion of venous symptoms have their sources in coexisting nonvenous pathologies. 2,11,15 This is of particular importance in patients in classes C 1 and C 2 , since those with more severe forms of venous incompetence usually experience symptoms caused by venous disease. The majority of symptoms in the patients with telangectasias and uncomplicated varicose veins do not seem to be of venous origin. Rather, especially if such symptoms are severe, an alternative cause should be considered.

Unfortunately, available QoL questionnaires do not include questions that facilitate recognition of the real cause of symptoms. Also, a thorough medical history and clinical examination, together with vascular sonographic assessment, were not used by most of the studies that evaluated an association of venous symptoms with the presence of venous disease. Instead, rather nonspecific QoL questionnaires and simple clinical tests were utilized.

Better constructed studies (such as a recent Dutch study) 2 may put an end to the controversy over this problem. For the time being, from a practical point of view, it is important to distinguish patients with actual symptomatic varicosities from those patients with other sources of pain and other “venous” complaints. If such patients are initially not properly diagnosed, it is inevitable that some of them will be dissatisfied by the treatment for varicose veins, since the real cause of their complaints (eg, hip arthrosis) will not be addressed by a vascular procedure. At the moment, we lack solid information on prevalences of pathologies being the cause of such “venous” symptoms in the population of patients with CVD. Still, the most common pathologies that may be responsible and should be considered in clinical practice comprise spinal disc herniation, hip and knee arthrosis, peripheral arterial disease, joint and ligament overload due to obesity, and peripheral neuropathy.

There are also many patients who suffer from leg pain and edema after the use of different medications, especially calcium channel blockers. 21 In the case of such a drug-related adverse event occurring in varicose vein patients, an invasive or pharmacological treatment for venous incompetence will not relieve symptoms. Instead, the medication should be discontinued. Similarly, in patients complaining of symptoms caused by osteoarticular, neurological, or arterial pathology, the disease that is a source of the complaints should primarily be addressed.

References

20. Darvall KA, Bate GR, Adam DJ, Bradford AW. Generic health-related quality of life in...
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**Signes et symptômes de la maladie veineuse chronique : peut-on mettre fin à la controverse ?**

L’association de la maladie veineuse chronique (MVC) à ce que l’on appelle les symptômes veineux (douleur, démangeaison, picotement, sensation de brûlure, gonflement, fatigue et lourdeur des jambes et syndrome des jambes sans repos) est toujours un problème controversé. Ces symptômes et la diminution de la qualité de vie sont courants chez les patients ayant une atteinte veineuse, et sont même plus fréquents chez ceux ayant des antécédents de thrombose veineuse ou de varices bilatérales ou récidivantes, mais d’après la recherche, ces plaintes sont très peu liées à des signes objectifs d’insuffisance veineuse. Pour les patients ayant une MVC avancée, une cause veineuse à ces plaintes est presque évidente, mais une partie importante des symptômes veineux, en particulier chez les patients ayant des télangiectasies et des varices non compliquées, n’est en fait pas d’origine veineuse. De plus, de nombreux patients ayant des maladies non veineuses peuvent avoir de tels symptômes, tandis que des varices non compliquées peuvent n’entrainer que de légers symptômes ou être asymptomatiques. Chez de nombreux patients ayant des symptômes veineux, ceux-ci ne sont pas permanents, mais peuvent n’être vus qu’à la fin de la journée. Il est donc important d’envisager et de rechercher une cause alternative à de telles plaintes, en particulier parce que d’autres pathologies peuvent accompagner la MVC et provoquer des symptômes similaires. Les pathologies les plus courantes pouvant être responsables et qui devraient être prises en compte sont : hernie discale, arthrose de la hanche et du genou, maladie articulaire périphérique, surcharge aux niveaux articulaire et ligamentaire due à l’obésité, neuropathie périphérique et événements indésirables dus aux médicaments.
The authors’ studies on an eventual psychic cause of venous-type leg symptoms are reviewed. Construction of the nine-item psychic vs somatic venous disease questionnaire (PsySoVDQ) is described. The instrument has been applied to participants of the population-based Bonn Vein Study (BVS) II and found able to group 77.3% of the 962 subjects with symptoms according to the presence of a psychic cause or a somatic cause of the symptoms. The groups showed different demographic and disease-related characteristics. Elevated scores in the psychic component (PC) were correlated with the absence of true venous disease. Elevated scores in the somatic component (SC) showed high sensitivity and specificity for true venous disease. The PsySoVDQ clearly recognizes the particularities of subjects with a somatic and a psychic condition behind their symptoms. However, it has a limited discriminatory power. This is due to the fact that subjects with an emotional or psychic problem use the same expressions for their feelings as those with clear organic venous disease. This is an inalterable phenomenon implying that questionnaires may not be appropriate tools to assess feelings.

Data of studies on symptoms of leg swelling, heaviness, tension, and pain

The hallmark of venous-type leg symptoms are feelings of swelling and heaviness, and poorly located pain that is difficult to explain. In addition, a wide spectrum of individual complaints are brought up by afflicted persons. The various symptoms show a high inter-item consistency and a strong correlation of each with the core symptoms. The symptoms are poorly associated with venous disease severity and clearly have a good prognosis. This is discordant with the impaired quality of life readily observed in individual patients and documented in many observational studies.

We studied the many aspects of the disorder in four cohorts: (i) patients who consulted because of symptoms, with no objective signs and laboratory findings of venous or any other disease; (ii) healthy persons at a presumed elevated risk of becoming symptomatic.
because of their occupation; (iii) healthy subjects who served as controls in a study on normal anatomy of veins; and (iv) subjects from the general population.

**Symptoms only**

In-depth psychiatric work-up of patients showed a high incidence of feelings of heaviness of legs, tiredness, and sleeplessness (73%, 88%, and 65%, respectively) and no other somatic symptoms of above-normal prevalence or intensity. The “psychic syndrome” featured hypochondria, anxiety, disturbance of vital feelings (85%, 77%, and 73%, respectively) and depression (84% overall, 42% severe depression). Psychiatric analysis revealed a low self-esteem, high dependence on the opinion of others, a wish to run away, and the inability to attribute to the legs their libidinous role, among others.6-9

We conclude that leg symptoms can be associated with characteristic and comprehensible psychiatric symptoms and frank depression.

**At-risk population**

The most interesting finding gathered from persons at risk of developing venous leg symptoms was the response to wearing light compression stockings for three weeks in a randomized crossover trial. We also found that both the psychic and somatic end points were improved at the end of the period during which the persons were not wearing compression stockings, but were looking forward to using them. The phenomenon was understood as a Hawthorne effect. The term labels the pervasive phenomenon that any promise of change for the better results in feelings of hope and faith, and thereby leads to an improvement in the symptoms.

We conclude that leg symptoms are related to leg volume and can be prevented with light leg compression. The expectation of such treatment already exerts a positive effect on both somatic and psychic phenomena.

**Healthy controls**

The examination of healthy volunteers participating in a population-based cross-sectional study on normal vein anatomy revealed that leg symptoms were equally prevalent in subjects with fears of one day developing varicose veins, in subjects with a refluxing great saphenous vein that was only uncovered during the study, and in patients who consulted a vein clinic for overt venous disease (Figure 2).10

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**Figure 1.** Medical compression stockings and lower limb symptoms.
(A) Pain and feeling of leg swelling and (B) change of lower leg volume during the period of awaiting the designated use of low-strength medical compression stockings (in dotted lines) and during the period of wearing them (in plain lines). Data of a crossover trial in hairdressers.


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**Figure 2.** Correlating symptoms and disease.
Feelings of leg swelling and heaviness in healthy volunteers with a fear of developing varicose veins (bar 3); with reflux in the great saphenous vein (GSV) unknown at the time of the study (bar 2); with both features (bar 4); with neither feature (bar 1); and in patients with GSV varicose disease (bar 5).

Abbreviation: SD, standard deviation.


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We conclude that leg symptoms of similar intensity can be caused by specific fears, the presence of a previously unknown and clinically undetectable varicose great saphenous vein, and a varicose disorder for which treatment is deemed necessary.

**General population**

*The psychic vs somatic venous disease questionnaire (PsySoVDQ)*

Based on both our psychometric and psychoanalytical data and in due consideration of the literature, we worked out a comprehensive questionnaire (62 items) and used it in a previous study. A version shortened to 12 items was applied to participants in the Bonn Vein Study (BVS) II, the follow up of the BVS I. Finally, a nine-item questionnaire was constructed with the data gathered in this large population-based study. The statistical methods applied were a factor analysis of principal components with varimax rotation and Cronbach’s α calculation to assess inter-item consistency. This version was labeled the PsySoVDQ and used to distinguish between a psychic and a somatic cause of the symptoms on the basis of symptoms alone (Table I). The BVS symptom score, used for comparison, took the presence of signs into account.

The PsySoVDQ was administered to 1,800 subjects of which 962 (53.4%) had an elevated BVS symptom score and 1,111 (61.7%) had an elevated PsySoVDQ score. The psychic component (PC) score alone was elevated in 437 subjects (24.3%) and not correlated with an elevated BVS symptom score. Subjects with CEAP (clinical, etiological, anatomical, pathophysiological) class C2 or C3 showed higher PC scores than those with C0 or C1; indeed, an elevated PC score showed a negative predictive value for the presence of C2 or C3 disease (P<0.001). The somatic component (SC) score alone was elevated in 395 subjects (21.9%). It showed the same predictive value for the presence of C2 or C3 as the BVS symptom score (receiver operating characteristic [ROC] analysis, area under the curve 0.604 and 0.627 respectively, both P<0.001). Elevation of the SC score did not depend on the presence of varices, but on the presence of edema (P<0.001).

The use of the questionnaire as an algorithm to identify the cause of the symptoms was reasonably limited in subjects who experienced symptoms in the recent past (Figure 3). Of the 607 subjects with an elevated SC score, 59% had a normal PC score, while 41% had an elevated PC score at the same time. The concomitant increase of the PC score reduced the likelihood of a somatic origin (C2/C3) of the symptoms from 58% to 45%. Of the 355 subjects with a normal SC score, 39% had an elevated PC score. Thus, 58% had a psychic origin of their symptoms, while 42% had a somatic origin. In the subjects with normal SC and PC scores, the origin of the symptoms remained unexplained in 61% and were attributed to a somatic condition in 39%.

The personal and disease-specific data of subjects scoring high on either component of the PsySoVDQ differed significantly from the data obtained from asymptomatic study participants and formed two distinct groups (Table II). The typical interviewees with an elevated PC score were younger, slim women, with a higher education and social status, who felt that their general health was jeopardized and that their psychiatric quality of life reduced. The symptoms were of the same type as those reported by the subjects scoring high in the SC, but were much less intense.

We conclude that the PC of the PsySoVDQ identified subjects with the psychiatric syndrome, as described in the previous studies. Thus, this particular dysfunction is present subconsciously in some healthy subjects with venous-type leg symptoms. The SC identified the subjects with C2/C3 disease as

<table>
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<tr>
<th>Factors</th>
<th>Factor loadings</th>
<th>Internal consistency</th>
<th>Descriptive statistics</th>
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<tr>
<td></td>
<td>Factor 1 (PC)</td>
<td>Factor 2 (SC)</td>
<td>Cronbach α</td>
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<tr>
<td>Psychic component (PC)</td>
<td>0.73</td>
<td>0.76</td>
<td>0.54</td>
</tr>
<tr>
<td>1. Melancholic person</td>
<td>0.79</td>
<td>0.03</td>
<td></td>
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<tr>
<td>2. Anxious person</td>
<td>0.74</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>3. Feels like running away</td>
<td>0.65</td>
<td>0.08</td>
<td></td>
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<tr>
<td>4. Stressed because of unresolved issues</td>
<td>0.62</td>
<td>0.03</td>
<td></td>
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<tr>
<td>5. Interested what other people think of me</td>
<td>0.53</td>
<td>-0.10</td>
<td></td>
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<tr>
<td>Somatic component (SC)</td>
<td>0.67</td>
<td>0.40</td>
<td>0.62</td>
</tr>
<tr>
<td>6. Feelings of leg heaviness</td>
<td>-0.01</td>
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<td></td>
</tr>
<tr>
<td>7. Feelings of leg swelling</td>
<td>-0.02</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>8. Leg pain at various sites</td>
<td>0.03</td>
<td>0.62</td>
<td></td>
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<tr>
<td>9. Leg pain at one site</td>
<td>0.16</td>
<td>0.57</td>
<td></td>
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Possible answers: Questions 1-7: 0=never, 1=rarely, 2=often, 3=very often; Questions 8-9: 0=never, 1=monthly, 2=weekly, 3=daily

Elevated scores defined as PC ≥1 and SC >0
Leg pain: somatic or psychogenic? – Blättler and Amser

Figure 3. Use of the PsySoVDQ as an algorithm to explain the cause of symptoms in participants of the Bonn Vein Study (BVS) II.

Use: Symptomatic subjects, consider somatic component (SC) first and consider psychic component (PC) second. Interpretation: SC+/PC+, no separation of the two components possible (the SC is less strong); SC+/PC-, elevation of the SC score with no elevation of the PC score speaks for the presence of an organic venous condition; SC-/PC+, elevation of the PC score with no elevation of the SC score speaks for the presence of a psychic condition; SC-/PC-, normal values of both components mean that the PsySoVDQ cannot identify the cause of the symptoms in these subjects. Some subjects have asymptomatic C2/C3 disease. Abbreviation: PsySoVDQ, psychic vs somatic venous disease questionnaire.


Table II. Univariate correlations of the psychic component (PC) and somatic component (SC) with personal and disease-related findings (n=1800). *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001.

<table>
<thead>
<tr>
<th>Item</th>
<th>PC Pearson’s r</th>
<th>SC Pearson’s r</th>
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<tbody>
<tr>
<td>Personal data</td>
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<tr>
<td>Women</td>
<td>+0.18****</td>
<td>+0.17****</td>
</tr>
<tr>
<td>Age</td>
<td>-0.19****</td>
<td>+0.10****</td>
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<td>Job exhausting</td>
<td>-0.07*</td>
<td>+0.10**</td>
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<tr>
<td>Fears losing job</td>
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<td>Reduced</td>
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<td>+0.24****</td>
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<td>Getting worse</td>
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<td>+0.09****</td>
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<tr>
<td>Any symptoms</td>
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<tr>
<td>BVS symptom score</td>
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<td>+0.67****</td>
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<td>Restlessness of legs</td>
<td>+0.05*</td>
<td>+0.35****</td>
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<td>Feelings of swelling</td>
<td>+0.05*</td>
<td>+0.51****</td>
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<tr>
<td>Feelings of heaviness</td>
<td>+0.09****</td>
<td>+0.58****</td>
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<td>Feelings of tension</td>
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<td>CEAP classification</td>
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<td>C2/C3</td>
<td>-0.07**</td>
<td>+0.24****</td>
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<td>Pain</td>
<td>ns</td>
<td>+0.36****</td>
</tr>
<tr>
<td>Varices</td>
<td>-0.06**</td>
<td>+0.12****</td>
</tr>
<tr>
<td>Edema</td>
<td>-0.05*</td>
<td>+0.30****</td>
</tr>
<tr>
<td>Compression therapy</td>
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<tr>
<td>CIVIQ Quality of Life</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>+0.05*</td>
<td>+0.45****</td>
</tr>
<tr>
<td>Somatic</td>
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<tr>
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<td>ns</td>
<td>+0.32****</td>
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<tr>
<td>Psychic</td>
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<td>+0.36****</td>
</tr>
<tr>
<td>CIVIQ total</td>
<td>+0.15****</td>
<td>+0.44****</td>
</tr>
</tbody>
</table>

The PsySoVDQ was administered to the whole BVS cohort, and not only to the symptomatic participants. Under this condition, its potential to diagnose a venous disorder with a psychic or somatic origin was found to be very low. We conclude that the PsySoVDQ is of no use to assess a cohort that includes asymptomatic patients.

A hypothesis on the origins of symptoms of leg swelling and heaviness

Venous leg symptoms investigated in multiple studies worldwide and in all imaginable situations turned out to be the same everywhere, and merit the label of a somatoform or functional disorder as they are capable of affecting the subjects’ self. Often dismissed as “just feelings,” the symptoms mimic true venous disease, but remain medically unexplained in many cases as well as the comprehensive BVS questionnaire administered separately and serving for comparison. However, the discriminatory power of the two components is low, as many subjects had both an elevated PC and SC (858 of 962; 89%). As will be discussed below, many subjects take certain notice of phenomena going on in their peripheral veins. The intensity of the bodily signal depends on the shape of the venous system and its environment, while the intensity of the mental reaction depends on momentary emotions and the individual’s psychic condition. The PsySoVDQ covers the two extremes of this continuum. Other questionnaires will undoubtedly encounter the same facts.

The PsySoVDQ was administered to the whole BVS cohort, and not only to the symptomatic participants. Under this condition, its potential to diagnose a venous disorder with a psychic or somatic origin was found to be very low. We conclude that the PsySoVDQ is of no use to assess a cohort that includes asymptomatic patients.
Leg pain: somatic or psychogenic? – Blättler and Amsler

Feelings are the highest manifestation of the homeostatic control, clearly a mental endeavor providing awareness of something potentially noxious threatening the body from inside or out. A hypothesis shall be set forth on how venous function is connected with the emergence of feelings. Involved in the process are the venous circulation, where the bodily signal is produced, the peripheral nervous system, which carries the message, and the central nervous system, which modifies the information on its way to the insular cortex, from where the feelings are expressed.

In a resting person, venous return stagnates because of inactivity of the muscle pump. Although arterial inflow is reduced simultaneously because of low demand, increase of blood volume in the legs inevitably occurs. Standing immobile after rising from the supine or sitting position leads to an increase of leg volume by an average of 30 mL within a few seconds and by about 150 mL, or 2.5%, within 9 minutes (Figure 3). The rapid and readily reversible volume load is attributed to dilatation of veins rather than to fluid extravasation. Vein distension or wall stretch can activate vegetative sensory nerves (unmyelinated C fibers, sympathetic nerve fibers) whose endings are located within the vein wall. Prolonged venous stasis can activate leukocytes, which release noxious substances. Chronic venous hypertension will occur when the venous capacity reaches its limits regularly or permanently. These phenomena are associated with feelings of discomfort illustrating the fact that the information is transported to the central nervous system. On their way to the brain, bodily signals are subject to continuous modification by interperception, until they ultimately arrive at the specific somatosensory areas of the brain cortex that are mainly located in the insula. The primarily unconscious process is subject to much interference from other sources as well (exteroperception) and to comparisons with the body image created by somatoperception. Interference can bring about defensive reactions, from repetitive leg movements to polite excuses like “I have to move my legs for a moment.” Reasons for (mis)perceptions contributing to negative feelings can be either amplified bodily signals (as in physical deconditioning) or decreased filter activity (as in anxiety and depressive moods). Feelings conveyed with words like heaviness and tension, rightly put emphasis on the somatic origin of the problem, and not on their aggravating modification by emotions and psychic conditions. In some cases, however, patients may well use expressions that allow one to elucidate the autobiographic context of their complaints (such as the feeling to have to run away). The hypothetical concept of venoneuronal coupling is depicted in Figure 4.

Recognition of the venoneuronal coupling has therapeutic implications

Feelings of venous origin are empathized if they are reported in association with a visible venous pathology. If no somatic problem can be identified, the model of venoneuronal coupling can offer an explanation that even low-strength signals from the peripheral venous system can be perceived as noxious and described with appropriate terms. Using a colloquial expression, one could say that these persons “hear the grass grow.” Successful therapeutic intervention with this oversensitivity requires an in-depth diagnosis, which includes both a venous workup and the search for the presence of a psychic problem. Treatment with light compression stockings allevi-
mates the symptoms reliably by reducing the venous distension and/or by direct action on the afferent nerves that control the input from the venous milieu. Empathy of the consulted person toward the symptomatic subject plays an important role. The fact that anticipation of a benefit can give relief already originating in the body are meaningful, and should help to ward off misunderstandings of the cause of the symptoms and over-estimations of the efficacy of interventions on veins.

References

Keywords: chronic venous disease; chronic venous disorder; PsySoVDQ; venoneuronal coupling; venous symptom


DOULEURS DE JAMBE S : SOMATIQUES OU PSYCHOGÈNES ?

Nous analysons les études d’auteurs sur une éventuelle cause psychique des symptômes de jambes de type vei- neux. Nous décrivons la mise en place du questionnaire psychique vs somatique à 9 items sur la maladie veineuse (PsySoVDQ). Cet outil a été appliqué aux participants de l’étude BVS II (Bonn Vein Study) basée sur la population et capable de grouper 77,3 % des 962 personnes ayant des symptômes selon la présence d’une cause psychique ou somatique des symptômes. Les groupes ont montré différentes caractéristiques démographiques et liées à la maladie. Des scores élevés de la composante psychique (CP) sont corrélés à l’absence de véritable maladie veineuse. Des scores élevés de la composante somatique (CS) montrent une sensibilité et une spécificité élevées pour une vé- ritable maladie veineuse. Le questionnaire PsySoVDQ reconnaît clairement les particularités des personnes ayant une pathologie somatique ou psychique derrière leurs symptômes. Il a cependant une puissance discriminatoire liée à la personne ayant un problème émotionnel ou psychique utilisant les mêmes expressions pour leurs sensa- tions que ceux ayant une maladie veineuse organique évidente. Ce phénomène non modifiable montre que les questionnaires ne sont pas des outils appropriés pour évaluer les sensations.
Patients with chronic venous disease (CVD) present with a variety of signs and symptoms. Pain, and similar symptoms such as the feeling of bursting, tiredness, and a burning sensation, is very common in these patients. Many epidemiological and clinical studies have demonstrated that there is a high prevalence of such symptoms and that these symptoms are found in all clinical stages of CVD. The feeling of the symptoms is evident in multiple studies showing that different types of treatment such as medications, compression, and surgical procedures can improve or alleviate pain. The range of pain sensation varies from mild to severe and can be present at rest or during physical activity. The association of pain intensity with the clinical severity of CVD may be weak, as many factors determine the development of pain sensation. The mechanisms of venous pain are not well understood. However, inflammatory mediators seem to have an important role in the activation of the nerve endings. Many inflammatory cells and molecules have been found in the venous wall and perivenous space, both in experimental animal studies and in humans. As inflammation is found in early stages of venous disease this could explain why patients in classes C₀ and C₁ (clinical, etiological, anatomical, pathophysiological [CEAP] classification) report pain. The diffuse character of venous pain makes it difficult for the patient to define and, therefore, to describe. This is a significant challenge for the practitioners who deal with venous disease. More studies are needed in order to elucidate the strength of the association of pain in CVD and unravel its pathways.
the venous symptoms in patients with clinical, etiological, anatomical, pathophysiological (CEAP) classification C 0 and C 1 disease do not correlate well with the level of pain.

In a recent consensus document from the significant level of pain in patients with venous claudication. 10-12

In early life. "13 The sensation of pain appears early in life in aching usually found in patients with early stages of CVD, to a significant level of pain in patients with venous claudication. This paper focuses on the pathophysiological underpinnings of pain of venous origin in order to elucidate what is known and define the questions that we still need to answer.

**Definition of pain and its relation to chronic venous disease**

Pain has been defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” They also wrote that “Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life.”13 The sensation of pain appears early in life in order to serve as a signaling system for tissue damage.15 In patients with CVD, pain is a very common symptom with different degrees of intensity. As the perception of pain is subjective and the thresholds vary significantly among individuals, the clinical presentation and extent of underlying venous disease do not correlate well with the level of pain.

In a recent consensus document from the Union Internationale de Phlébologie (UIP; International Union of Phlebology) the venous symptoms in patients with clinical, etiological, anatomical, pathophysiological (CEAP) classification C 0 and C 1 disease were discussed.11 The data presented in the consensus were on the following: heaviness, tightness, feeling of swelling, pain after standing, pain during walking, cramps, itching, and restless legs. The prevalence of the symptoms (each examined alone) ranged from 9.5% to 25%, with women being affected more often. Risk factors for developing these symptoms were female sex, higher age, obesity, and a sitting or standing profession. It was stated that symptoms of patients with CVD are not very specific and thus it is essential to differentiate them from other causes. The association of symptoms in the early stages of CVD has been a controversial topic. In our clinics, we have evidence from many patients that pain is present in a good number of patients at the early stages of CVD, after having excluded other causes for pain. However, the degree of this association is not known, since we did not study it in an objective manner. Multiple studies, both epidemiologic and clinical, have indicated that such an association exists and therefore cannot be ignored.14-17

In patients in CEAP class C 2, pain is reported more often. Typically, such pain is located along the varicose veins and is more often perceived below the knee. In patients who have pelvic congestion syndrome and present with C 2 disease, the pain may sometimes be localized only to the area of varicosities in the groin and perineum. Pain in the pelvis alone may also be found in patients with pelvic congestion syndrome that is associated with the reflux in varicosities after all other causes have been excluded.15,16 Multiple studies have reported relief of pain after treatment with medication, elastic compression stockings, or invasive procedures. The greatest relief has been achieved with the latter, which also has the support of many prospective randomized trials.20-23

In patients with C 3 to C 6 disease, pain is often seen and can be independent of the presence of varicose veins, as deep vein obstruction and postthrombotic luminal damage are more common in these patients.24,25 Obviously, many of these patients have varicose veins as well and the pain is most likely a result of both pathologies. When both reflux and obstruction are present, the chance of developing signs and symptoms of CVD is higher.24,26 Pain intensity is usually higher in this group of patients. In fact, venous claudication is exclusively seen in patients with proximal venous obstruction, particularly when the iliofemoral veins are involved.12,27,28 Also, the distribution of pain is more extensive and can be found in both the calf and the thigh.

Representative images of patients with CVD and pain, with the location and daily presentation, are seen in the examples of Figure 2 (page 34). It needs to be emphasized that although the majority of CVD patients present with symptoms, a large
number of them are asymptomatic. This is also true for patients who present with ulcers. The reasons for which patients develop symptoms, and more importantly pain, are largely unknown. It is interesting to see that two different patients with a similar history, duration, and extent of CVD, and the same age and sex, can present very differently. One could have itching along the varicose veins and the other, leg heaviness and pain. This is a frequent scenario that leads us to question why this occurs and what triggers symptoms to be present. Precise history and clinical examination are important before assigning certain signs and symptoms to patients with CVD. It is not uncommon to see patients presenting with joint or sciatic pain that is unrelated to CVD.

Clinical relevance of pain in patients with chronic venous disease

One of the most common complaints of patients with CVD is pain. Patients describe different types of pain and in different locations, with variable extent and intensity in the lower extremities. The importance of pain in patients with CVD, despite the lack of understanding of its origin, is well perceived, as all instruments of evaluation such as scales, clinical severity scores, and quality of life questionnaires have included pain assessment. In most published reports, pain has been the most significant factor affecting the health-related instruments mentioned above. Studies in multiple countries have demonstrated that CVD has a major socioeconomic impact, affecting millions of patients worldwide. One of the most frequent symptoms involved in these studies is pain. Despite the subjectivity in reporting and describing pain, it is still the dominant symptom that affects most patients’ quality of life. This is clearly evident from all the clinical trials where treatment has reduced or abolished pain and has significantly improved most measurements, as recorded by the different instruments of pre- and posttreatment assessment. 20-23,29,30

Pain and inflammation

Venous pain is closely linked to inflammation. Multiple studies have shown that CVD is an inflammatory disease. The inflammation is evident in the vein wall and the perivenous space. 31,32 Infiltration of monocytes/macrophages in the proximal vein wall, wall base of valve leaflet, and in the valve sinus has been demonstrated, while macrophage-monocytes and mast cells were found widely distributed throughout the vein wall. 33,34 Endothelial cell activation, with expression of several molecules and inflammatory infiltrates, has been found in several papers. 35-37 These inflammatory changes are more pronounced in patients with skin damage, ie, CEAP classes C4 to C6. It has been shown that inflammation parallels the severity of CVD. 38 Significant changes are observed in small venous networks and capillaries, which are more apparent in patients with skin damage. 39 The venous flow in areas of inflammation becomes more pulsatile.

When inflammation is more intense, the cutaneous and perforating arteries have a high flow with increased diastolic velocity and loss of the reverse flow component. 7 There are also more lymph nodes, which are enlarged, seen in the groin. 7 The skin blood flux is increased and the ability to increase the local flow to thermal stimuli is reduced. 38 A schematic diagram of the role of inflammation on the development of CVD is shown in Figure 3. 31

Venous pain is linked to the activation of nerve endings that are found on the venous wall and are called nociceptors. 40 Perivascular nerves terminating on the adventitia layer of the veins in animal preparations have been mapped. Although, nerve fibers have been illustrated in a few papers in the lower extremity of patients with CVD, the nerve pathways, precise architecture, and function have not been reported. Therefore, the description and associations for venous pain are based on hypothesis and indirect relations. The current hypothesis on the mechanisms of venous pain emphasizes an inflammatory reaction and an interaction on venous nociceptors. 40 The association of pain with other unpleasant sensations that are related to nociception such as tightness, feeling of swelling, heaviness, and cramps is very common in patients with CVD, regardless of the clinical class. This may explain why it is difficult to assess how symptoms are related to CVD. Currently, the hypothesis on the mechanism of development of pain

![Figure 2. Examples of patients with chronic venous disease and different types of symptoms. (A) Male patient with varicose veins in the medial and posterior calf. He had itching only, at the mid-calf at the area of the bulging varicocities. (B) Female patient who presented with varicose veins in the anterior and medial thigh. She had mild pain along the lower part of the varicocities of the leg, with an itching and burning sensation. (C) Male patient with extensive skin damage. He had previous thrombosis with partial recanalization in the deep veins. Axial reflux was found in the deep superficial veins and two pathological perforator veins were found in the calf.](image-url)
and unpleasant perception of the other symptoms discussed may be described as follows. Venous stasis, genetic predisposition, and environmental factors lead to altered shear stress and wall behavior, which results in the activation of endothelial cells and leucocytes. This in turn promotes secretion of algogenic and proinflammatory mediators that induce local inflammation, which stimulates the nerve endings and leads to a pain sensation.

The degree of stimulation may depend on the status of the nerve endings (healthy, damaged, nonfunctional) and on transient stimuli, for example, at the end of the day, menstrual cycle, prolonged standing or sitting. The condition of the nerve patient may not correlate with CVD severity, as many factors present, nerve endings may become less functional and therefore the pain intensity could be less comparable to those with earlier stages of CVD. In contrast, some patients with advanced CVD have more pain than usual and can be sensitive to touch, without having an infection. This could be explained by partial nerve damage that may lead to a reduction of the threshold of pain.

Pathophysiologic underpinnings of lower-limb pain of venous origin – Labropoulos

Clinical implications

Venous pain may resemble visceral pain. When compared with pain in the cutaneous space, the nociceptive messages that are developed at a visceral level are less localized, may have the same pain intensity, can be perceived as more unpleasant, and may have a more significant emotional impact. The diffuse character of venous pain, with the feeling of aching, tiredness, tightness, discomfort, bursting, heaviness, and burning sensation, which is difficult for the patient to define and thus challenging for the physician to deal with, has a significant impact on patients’ quality of life. There is a need to enhance our knowledge of these associations, and better define venous pain and related symptoms. We need to improve the instruments of evaluation, and further understand the ultrastructural and functional changes observed at the microcirculation. Moreover, a more detailed workup is needed to define the nerve pathways and their function in the lower-limb veins.

Conclusion

It is evident from many epidemiological and clinical studies that venous pain is found in all stages of CVD. The intensity of pain may not correlate with CVD severity, as many factors play a role in the development and sensation of pain. The underlying mechanisms of pain are not well understood. However, inflammatory mediators seem to have an important role. As inflammation starts early in venous disease, this could explain why patients in CEAP classes C0 and C1 may have pain. Experimental studies, together with functional and clinical studies, are needed to further elucidate pain development and its association with CVD. This will help us to better manage patients with CVD and improve their quality of life.

References

aux stades précoces de la maladie veineuse. Le patient définit et donc décrit difficilement la douleur veineuse à cause de son caractère diffus. Traiter la maladie veineuse est un enjeu significatif pour les médecins. Il faut d'autres études nombreuses études dans lesquelles les symptômes sont ressentis. La gamme des sensations de douleur varie de anatomique, physiopathologique) rapportent des douleurs, qui peuvent s'expliquer par une inflammation retrouvée chez les patients. De nombreuses études épidémiologiques et cliniques ont montré la haute prévalence de ces symptômes et leur présence à tous les stades cliniques de la maladie. Différents types de traitement comme les médicaments, symptômes similaires, comme la sensation de brûlure, de fatigue et l'impression de chaleur sont très courants chez ces patients. Le développement et la sensation de douleur, l'association de l'intensité de la douleur à la sévérité clinique de la MVC peut être faible. Les mécanismes de la douleur veineuse ne sont pas bien compris. Les médiateurs inflammatoires semblent cependant avoir un rôle important dans l'activation des terminaisons nerveuses. Chez les humains comme dans les études expérimentales animales, la paroi veineuse et l'espace périveineux contiennent de nombreuses cellules et molécules inflammatoires. Les patients des classes C7 et C8 de la CEAP (classification clinique, étiologique, anatomique, physiopathologique) rapportent des douleurs, qui peuvent s'expliquer par une inflammation retrouvée aux stades précoces de la maladie veineuse. Le patient définit et donc décrit difficilement la douleur veineuse à cause de son caractère diffus. Traiter la maladie veineuse est un enjeu significatif pour les médecins. Il faut d'autres études pour éclairer l'association de la douleur dans la MVC et éclaircir son parcours.
Lower-limb venous symptoms and assessment of quality of life: existing tools

by F. Mariani, Italy

Chronic venous disease (CVD) may affect several aspects of quality of life (QoL). These functional effects are usually operationalized as (limitations in) physical, psychological, and social functioning. CVD can negatively affect patients’ QoL, as it is a painful and disabling disease that can restrict physical functioning and mobility, and that is associated with depression and social isolation. Instruments used to measure QoL can be classified into generic instruments and disease-specific instruments. A number of good evaluative instruments exist that can monitor changes in patients’ status over time and are responsive to disease progression or therapeutic intervention. Each instrument should be carefully studied to ensure that it is valid (capable of quantifying what it is intended to measure), reliable (produces consistent results when used repeatedly on stable subjects), and responsive (capable of detecting clinically important changes). Objective outcome measures and guidelines for the management of patients with venous disease are more important now than ever and will assume even greater importance in the future. Management of patients with CVD is rapidly evolving, and to assess whether a particular treatment is appropriate, reliable, standardized, and objective, evaluation instruments are required. It would be helpful to promote and validate new specific assessment tools about the medical procedures and QoL in venous leg ulcers, in postthrombotic syndrome and in CVD. Specific tools capable of assessing the full spectrum of CVD, its signs and symptoms, impact on QoL, and treatment effects are key to the efficient management of the disease. Secondly, there should be a focus on longitudinal research about the long-term effect of CVD on QoL and on the effect of CVD on the well-being of the partners of the affected individual. In future, it will be necessary to promote an international consensus to approve the same instruments for all clinical studies on CVD/QoL.

Medicographia. 2015;37:37-44 (see French abstract on page 44)

Q uality of life (QoL) can be defined as “the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient.” Chronic venous disease (CVD) may affect several aspects of QoL.

These functional effects are usually operationalized as (limitations in) physical, psychological, and social functioning. CVD can negatively affect patients’ QoL, as it is a painful and disabling disease that can restrict physical functioning and mobility, and that is associated with depression and social isolation.
In consequence, CVD can result in limitation to daily activities, decreased productivity at work, and patients needing to take sick leave, as well as having a negative effect on their self-esteem. The higher the clinical, etiological, anatomical, pathophysiological (CEAP) clinical class, the poorer the disease-specific QoL, as demonstrated by low scores for physical and social functioning in QoL questionnaires. QoL is increasingly seen as an important outcome measure because of the publication of several clinical trials showing that it is responsive to important clinical changes. In addition to relieving clinical symptoms and prolonging survival, the primary objective of any health care intervention should be the enhancement of the QoL of the patient. Instruments used to measure QoL can be classified into generic instruments and disease-specific instruments. Generic instruments allow comparison across populations of patients with different diseases, whereas disease-specific instruments are sensitive to key dimensions of QoL that are impaired by specific diseases. A number of good evaluative instruments exist that can monitor changes in patients' status over time and are responsive to disease progression or therapeutic intervention. Each instrument should be carefully studied to ensure that it is valid (capable of quantifying what it is intended to measure), reliable (produces consistent results when used repeatedly on stable subjects), and responsive (capable of detecting clinically important changes).

Objective outcome measures and guidelines for the management of patients with venous disease are more important now than ever and will assume even greater importance in the future. Management of patients with CVD is rapidly evolving and to assess whether a particular treatment is appropriate, reliable, standardized, and objective, evaluation instruments are required. Patients should be objectively classified according to the CEAP classification and a validated QoL instrument combining generic and disease-specific instruments. Following treatment at appropriate time intervals, evaluative and QoL measures should be repeated.

### Review of available instruments

An instrument is reliable when it consistently produces the same results when applied to the same subjects with no evidence of change (Table I). One way to assess reliability is to determine the internal consistency reliability coefficient, which reflects the degree of relatedness between the individual items that make up a scale. The items should all measure the same concept, and therefore be correlated with each other. A measure of overall internal consistency reliability is the Cronbach α coefficient; in general, for comparing groups a reliability coefficient higher than 0.70 is acceptable. Validity of a QoL measure is usually determined by examining correlations between conceptually-related measures and by studying associations between the measure and various clinical characteristics. The tools can be summarized as:

- clinical, CVD-related signs—assessed by the physicians (CEAP and VSS [Venous Severity Scoring]);
- functional (measuring QoL) or CVD-related symptoms—the symptoms are self-assessed, using patient-related outcome or patient-reported outcome tools.

The VEIN-TERM consensus document has clarified venous terminology; venous symptoms may include tingling, aching, burning, pain, muscle cramps, swelling, sensations of throbbing or heaviness, itching skin, restless legs, and leg tiredness, and/or fatigue. Although not pathognomonic, these may be suggestive of CVD, particularly if they are exacerbated by heat or worsen during the course of the day, and are relieved by leg rest and/or elevation.

### Table I. Main features of an assessment tool instrument.

<table>
<thead>
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<th>Appropriateness</th>
<th>The content of the instrument corresponds to the intended purpose of their specific trial</th>
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<tbody>
<tr>
<td>Acceptability</td>
<td>This instrument is acceptable to patients</td>
</tr>
<tr>
<td>Feasibility</td>
<td>The impact of different measures upon staff and researchers in collecting and processing information</td>
</tr>
<tr>
<td>Interpretability</td>
<td>The meaning of the instrument’s score</td>
</tr>
<tr>
<td>Precision</td>
<td>The capacity of the instrument to make numerous distinctions</td>
</tr>
<tr>
<td>Reliability</td>
<td>The reproducibility and internal consistency of the instrument, it assesses the extent to which the instrument is free from random error</td>
</tr>
<tr>
<td>Responsiveness</td>
<td>The ability of the instrument to detect important clinical changes</td>
</tr>
<tr>
<td>Validity</td>
<td>The assessment of the extent to which the instrument measures what it is supposed to measure</td>
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Clinical investigations
There are three main clinical investigation methods: CEAP, VSS, and Villalta Scale, specific for postthrombotic syndrome (PTS). The CEAP classification was first developed in 1995. The original classification was modified in 2004, since at the time it was not adequately dynamic nor did it adequately correlate with symptoms. The modified version continued to be physician-centered and hence did not always correlate with patient symptoms. Furthermore, the symptoms related to lymphatic failure in CVD are not considered in the classification. This is a pitfall in all the cases in which the patients have edema of the lower limb. The CEAP classification is descriptive, but many of its components are static and do not change in response to treatment. A disease severity scoring scheme needs to be quantifiable, with gradable elements that can change in response to treatment. The American Venous Forum developed the VSS, which was designed to supplement CEAP scoring and to provide a method for serial assessment. VSS is mainly used for longitudinal follow-up of a patient's condition during and following treatment, it has recently undergone a revision to increase its sensitivity and value.

The VSS scoring system has three components:
- Venous Disability Score (VDS)—this component evaluates the level of work-based disability, disability is scored from 0 to 3;
- Venous Segmental Disease Score (VSDS)—this is based on anatomical and pathophysiological components of CEAP, obstruction, and reflux;
- Venous Clinical Severity Score (VCSS)—this is a dynamic form of CEAP evaluation that has been designed to include the most severe complications of CVD, each hallmark is scored on a severity scale ranging from 0 to 3; VCSS is an easy-to-apply, stand-alone scoring system.

A number of clinical tools or scales have been used in clinical investigations to measure the PTS. The International Society on Thrombosis and Haemostasis recommended that the Villalta Scale be adopted in clinical studies to diagnose and grade the severity of PTS. The Villalta Scale is a reliable and valid clinical scoring system that is based on severity ratings of PTS symptoms and signs.

Functional investigation
These are generic and disease-specific assessments of QoL. The generic assessments are Short Form 36 (SF-36; 36-item health survey), SF-12 (12-item health survey), and EuroQol 5 Dimension (EQ-5D; mobility, self-care, usual activities, pain/discomfort, anxiety/depression health survey). The disease-specific assessments include the Aberdeen Varicose Vein Questionnaire (AVVQ), Specific Quality of life and Outcomes Response-Venous (SOQR-V), Chronic Venous Insufficiency quality of life Questionnaire (CIVIQ), and VEnous Insufficiency Epidemiological and economic Study (VEINES). Since the latter ones are more specific in their scope, they have become more popular in evaluating CVD management.

Generic instruments
- SF-36
  The SF-36 is a valid assessment of QoL. The scoring system is based on two types of health aspects: physical health and mental health. The former is assessed via the patient's level of functioning, whilst the latter is assessed via an indicator of well-being. These two types include eight domains: assessment of physical and social functioning, role limitations due to physical and emotional problems, mental health, pain, vitality, and health perception. The survey generates a score ranging from 0 to 100, with higher scores indicating better general health perception. The SF-36 is a good way of assessing changes in QoL in CVD.
- Nottingham Health Profile
  The Nottingham Health Profile (NHP) is intended for primary health care to provide a brief indication of a patient's perceived emotional, social, and physical health problems. It consists of two parts. Part I contains 38 yes/no items in six domains: pain, physical mobility, emotional reaction, energy, social isolation, and sleep. Part II contains seven general yes/no questions concerning problems of daily living.

Disease-specific instruments
- CIVIQ
  The CIVIQ was developed and validated (relevance, acceptability, reliability, construct validity, and sensitivity) by a French group in 1996. The CIVIQ is a 20-item self-reported instrument that includes four categories of questions: physical (4 items), psychological (9 items), social (4 items), and pain (3 items). Its score ranges from 0, the worst score, to 100, the best. There are five possible answers (from 1 to 5) to describe each symptom and the sensation of discomfort.

In a great number of patients the CIVIQ showed good internal consistency, reliability (above 0.80), and discriminating power of items. Factor analysis identified physical, psychological, and pain factors as important, but revealed instability of the social factor. The CIVIQ was highly sensitive to changes in the QoL of patients clinically improved after drug treatment.

The first version of the CIVIQ questionnaire, CIVIQ 1 (where 1 denotes the first draft) included different numbers of questions in each category. The second version, the CIVIQ 2 (where 2 denotes the second draft of the same questionnaire) provides a global score covering all aspects of the questionnaire and weighs the categories equally. Recently, a new short form of the CIVIQ with a stable factorial structure was validated; the CIVIQ-14 (14-item QoL questionnaire). The RELIEF (Reflux assessment and quality of life improvement with micronized flavonoids) study, which was conducted in 23 countries worldwide and included the participation of more than 10,000 patients suffering from CVD, validated the CIVIQ, the first QoL scale specific to CVD, and...
assessed changes in the QoL of patients suffering from CVD, with or without venous reflux, treated with micronized flavonoids (MF).

The DECIDE study\textsuperscript{26} evaluated the predictive value of a symptom checklist for CVD in patients seen by general practitioners. The secondary objectives were to assess the relationship between the checklist data and the patient’s QoL evaluated using the CIVIQ, and to monitor the medium-term evolution of this relationship amongst patients prescribed a venoactive drug. A total of 13 131 patients were included, whose acceptance of the symptom checklist was good, since the completion rate was high. The correlation between a positive diagnosis of CVD and positive answer to the symptom checklist was 98.9% (95% confidence interval [CI], 98.3% to 99.3%), indicating that the symptom checklist is of predictive value for CVD. The CIVIQ-20 was of discriminatory value since there was a 12-point difference between patients with and without CVD (64.4±17.9 vs 76.2±16.4, respectively; \( P<0.001 \)).

Of 9953 patients followed up for an average of 63 days, 88.7% received MF 500 mg, 5.1% received another venoactive drug, and 3.5% were left untreated. After the 63-day follow-up, a significant decrease in CVD symptoms was observed in all patients treated with MF 500 mg. Amongst the 7103 patients to whom the CIVIQ-20 was readministered, a significantly greater improvement in QoL was seen in the group treated with MF compared with the other treatment groups.

The Vein Consult Program,\textsuperscript{27} which started in 2009, is an international observational, multicenter, descriptive survey of CVD. In step two of the program, the patients were asked to complete the CIVIQ-14. A total of 69 866 subjects were screened for the first 13 countries participating in the program. It is demonstrated that there is good correlation between two vein-specific QoL tools (AVVQ and CIVIQ-14) across the whole spectrum of disease severity.\textsuperscript{28}

The CIVIQ and CIVIQ-14 have been used extensively as reported in numerous studies, some of which included large samples of patients, and have been validated in seventeen linguistic versions.\textsuperscript{29}

\textbf{VEINES-QoL/Sym}

The VEINES,\textsuperscript{30} an international prospective cohort study conducted in Belgium, France, Italy, and Canada, has developed the VEINES-QoL/Sym to evaluate QoL and symptoms across the range of conditions (eg, telangiectasias, varicose veins, edema, skin changes, leg ulcers) in CVD. It consists of 35 items distributed in two categories to generate two summary scores: the questionnaire comprises 25 items that estimate the effect of disease on QoL, and 10 items that measure symptoms. The focus of this instrument is on physical discomfort as opposed to psychological and social aspects. This measure of QoL and symptoms is available in four languages (English, French, Italian, and Canadian French). Compared with the CIVIQ, this method focuses more on symptoms than the psychological and social aspects of the disease; furthermore, it was validated for DVT symptoms.\textsuperscript{30}

\textbf{Phleboscore®}

The Phleboscore\textsuperscript{28} is an 11-item self-administered questionnaire that helps predict the risk of developing CVD.\textsuperscript{27} It includes questions about risk factors as well as questions about the frequency of symptoms and the circumstances in which symptoms worsen (heat, contraceptive pill, long-distance travel). The scores range from 0 to 31. A score >12 identifies patients at risk of CVD, while a score >23 pinpoints a need for venous investigation.

\textbf{AVVQ}

The AVVQ\textsuperscript{18} addresses multiple aspects of varicose disease, including physical symptoms, social issues, and the cosmetic manifestations of treatment outcomes. The overall evaluation consists of a score with a range of 0 to 100. The AVVQ is a 13-question survey addressing multiple elements of varicose vein disease. Physical symptoms and social issues, including pain, ankle edema, ulcers, compression therapy use, and limitations on daily activities are examined, as well as the cosmetic effect of varicose veins. The questionnaire is scored from 0 (no effect) to 100 (severe effect). A high correlation was found between the AVVQ and the SF-36 for CVD patients, with health perception lower in patients with varicose vein disease. Physical symptoms and social issues, including pain, ankle edema, ulcers, compression therapy use, and limitations on daily activities are examined, as well as the cosmetic effect of varicose veins. The questionnaire is scored from 0 (no effect) to 100 (severe effect). A high correlation was found between the AVVQ and the SF-36 for CVD patients, with health perception lower in patients with varicose veins than in the general population. Two recent studies\textsuperscript{22,23} show that the AVVQ may be the preferred method of rationalizing patients for varicose vein surgery. It could be used to help inform a patient pathway for referral and treatment of varicose veins.

\textbf{Charing Cross Venous Ulcer Questionnaire (CXXUQ)}

The CXXUQ was developed to provide a valid QoL measurement of venous ulcers. This method may be combined with the SF-36 to generate valuable information on the progression of ulcers and their treatment. This questionnaire has been mainly designed for patients with venous ulcers.\textsuperscript{34} Although it can be intuitively assessed that venous stasis ulcers negatively affect patient QoL, there was no reliable instrument to evaluate the effects of venous ulcer therapies.

\textbf{Venkatraman Ulcer-specific QoL Questionnaire (VUQ)}

In 2005, a cross-sectional survey\textsuperscript{25} conducted on a representative sample of patients suffering from venous leg ulcers was published. A self-administered six-page questionnaire, Freiburger Lebensqualitats Fragebogen Assessment (FLQA), was used to collect data. The pilot survey showed the reliability and the reproducibility of the questionnaire and indicated that the VUQ is suitable and has the potential to reflect the perspective on compression therapy and overall QoL of patients suffering from venous leg ulcers. The VUQ was tested in some randomized studies to evaluate compression therapy for venous ulcers or venous surgery, and QoL.\textsuperscript{36,37}
Discussion

A number of findings stand out when reviewing the topic of QoL in patients with CVD:

- patients with varicose veins report a real impairment of QoL;
- patients with venous leg ulceration report impairment of their physical functioning and mobility similar to patients suffering from congestive heart failure, and suffer from negative emotions and social isolation;
- patients with venous thrombosis and PTS report pain and impairment of their physical functioning, they also report low health perceptions and high health distress;
- improvement of QoL in CVD after treatment with MF is well demonstrated.

The majority of studies about PTS applied generic QoL measures, in particular the SF-36, which provide the possibility to characterize patients with deep venous thrombosis (DVT) in comparison with other clinical samples and the healthy population. However, the SF-36 could not detect any differences between patients with and without PTS, whereas the VEINES-QoL/Sym did detect some differences. The generic measure, SF-36, is also not sensitive to any specific effects of compression therapies. Some studies about the effects of compression and QoL used disease-specific measures, but only a few have been adequately validated in large groups of patients. In most of these instruments, the social dimension has been neglected or only partially captured. Because we feel that this is an important issue, we recommend the use of an instrument that also assesses this domain and that is well validated, such as the CIVIQ, VEINES-QoL/Sym, and VUQ, in association with CEAP classification and the VSS system. There are recognized limitations in questionnaire studies including patients with low literacy skills or poor eyesight who might not be able to complete them, and that long and demanding questionnaires might reduce compliance. In addition, the responses on questionnaires that were administered retrospectively could suffer from a response bias, and most of the used questionnaires have not been formally evaluated for reliability.

The following questions are concerned with your views on compression therapy (bandages or elastic stockings). Please put a cross in the box provided to indicate your feelings (*scores).

<table>
<thead>
<tr>
<th></th>
<th>Not at all (1)*</th>
<th>Sometimes (2)*</th>
<th>Occasionally (3)*</th>
<th>Always (4)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Do you experience pain when compression is applied?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Do you experience pain when compression is removed?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Do you experience pain when wearing shoes with compression?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Do you experience pain when walking wearing compression?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Do you have painful constrictions after wearing compression?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Does wearing compression prevent you from normal activities?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Does wearing compression prevent you from visiting friends and families?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Do you feel any discomfort while wearing compression during the day?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Do you wear compression when you are asleep?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Do you feel any discomfort while wearing compression when you are asleep?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>How many times do you wear compression?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Does your compression device slip?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Do you have dryness of the skin?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Do you feel itching?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Do you wear compression at all times or when the nurse or families help you?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What is your opinion about the compression therapy?

<table>
<thead>
<tr>
<th></th>
<th>It helps to improve my symptoms (1)*</th>
<th>It does not improve my symptoms (4)*</th>
<th>It prevents my symptoms (1)*</th>
<th>It helps to heal my ulcer (1)*</th>
<th>It does not improve my ulcer (4)*</th>
<th>It is comfortable (1)*</th>
</tr>
</thead>
</table>

Table II. A proposal for a modified Venkatraman Ulcer-specific Questionnaire (VUQ) for compression therapy.
and validity. Furthermore, no symptoms seemed to vary according to the severity of varicose veins and the complaints related to CVD. They can be very complex to detect at the first stages of the CEAP classification and they can have many pathological causes (eg, edema or pain). Early stages of CVD are difficult to assess objectively, particularly in C0s to C1 patients, as symptoms are by definition subjective.

The QoL of CVD patients is greatly affected by pain, the complaint that most often leads to the diagnosis of venous disease. The intensity of pain can also fluctuate, from patient to patient or in the same patient with progression of the disease over a period of time. A causal relationship between CVD and pain of venous origin remains difficult to clarify. In the Edinburgh Vein Study, 40 the correlation observed between pathologic superficial venous reflux and sensation of swelling, heaviness, or tension was low. In addition, this correlation was limited either solely to men (sensation of swelling) or solely to women (sensation of heaviness or tension). No significant correlation was observed between superficial or deep venous reflux and venous symptoms or pain. Furthermore, no statistical relation is found between the pain score or heaviness score of a patient, evaluated on a 10-point visual analogue scale (VAS), and the clinical severity of venous disease. 41,42 There are multiple measures available to assess pain in adult populations. 43 Each measure has its own strengths and weaknesses. The VAS and the Numeric Rating Scale for Pain (NRS) are unidimensional single-item scales that provide an estimate of patients’ pain intensity. The VAS is usually a horizontal or vertical line, 10 cm in length, anchored by word descriptors at each end. On this line, the patient marks the point that they feel represents their perception of their current state. To evaluate the multiple dimensions of acute and chronic pain, a number of fore most suitable for use in making comparisons across populations and between subgroups within populations. The VAS and SF-36 BPS are the preferred generic assessment instruments for pain. Regarding CVD, since pain is mostly below the half scale, the adequacy of the VAS may be questioned because the amplitude of pain may not be large enough in CVD to assess the therapeutic effects using such means. The CIVIQ questionnaire evaluates pain in CVD with a specific approach, but for everyone involved in CVD, pain is difficult to measure.

Another important question is to distinguish the psychic from somatic components in CVD symptoms. Recently the psychic vs somatic venous disease questionnaire (PsySoVDQ) was applied to 1800 participants of the Bonn Vein Study II. 44 Factor analysis of the PsySoVDQ distinguishes a psychic component separate from a somatic component. The PsySoVDQ identified somatic and psychic components of the widespread and frequently reported leg symptoms in the general population.

**Conclusion**

It would be helpful to promote and validate new specific assessment tools for the medical procedures and QoL in venous leg ulcers, PTS, and CVD. We propose to assess a modified VUQ for compression therapy (Table II, page 41). The section of the questionnaire regarding compression therapy is modified and could be validated for the general assessment of QoL with compression bandages and stockings. This questionnaire could be used in association with the Norton Scale (for mental state and joint mobility; Table III), 45 the CIVIQ (or VEINES) and CEAP/VSS classification to assess, at the same time, CVD and the effects of compression therapy on QoL. Specific tools capable of assessing the full spectrum of CVD, its signs and symptoms, impact on QoL, and treatment effects are key to the efficient management of the disease.

The European Organization for Research and Treatment of Cancer (EORTC) took the initiative to develop a QoL instrument for patients with cancer, the QLQ-C30, which is validated in 81 languages and used in more than 3000 studies worldwide. It would be an idea for the future if a similar instrument was developed for patients with CVD and applied as a standard measurement in all clinical studies. Until that day, a combination of well-validated clinical investigations and disease-specific measures would be the preferred approach. Secondly, there should be a focus on longitudinal research on the long-term effect of CVD on QoL and on the effect of CVD on the well-being of the partners of the affected individual. In future, it will be necessary to promote an international consensus to approve the same instruments for all clinical studies on CVD/QoL.
References


Keywords: CEAP classification; primary venous disorder; varices; Venous Clinical Severity Score; venous symptom
SYMPTÔMES VEINEUX DES MEMBRES INFÉRIEURS ET ÉVALUATION DE LA QUALITÉ DE VIE : LES OUTILS EXISTANTS

La maladie veineuse chronique (MVC) peut influer sur plusieurs aspects de la qualité de vie (QdV), les effets sur le fonctionnement étant habituellement concrétisés comme des limitations physiques, psychologiques et sociales. La MVC, maladie douloureuse et handicapante pouvant restreindre le fonctionnement physique et la mobilité, influe négativement sur la QdV et s’associe à la dépression et à un isolement social. Les instruments de mesure de la QdV peuvent être classés en instruments généraux et instruments spécifiques de la maladie. Certains bons instruments d’évaluation peuvent suivre les changements de l’état des patients dans le temps et réagissent à la progression de la maladie ou au traitement. Chaque instrument devrait faire l’objet d’une étude soigneeuse pour s’assurer de sa validité (capable de quantifier ce qu’il est supposé mesurer), de sa fiabilité (fournit des résultats réguliers lorsqu’il est utilisé de façon répétée chez des sujets stables), de sa réactivité (capable de détecter cliniquement des changements importants). Des mesures objectives des résultats et des recommandations pour la prise en charge des patients atteints de maladie veineuse sont plus importantes maintenant que jamais, et le seront encore plus dans l’avenir. La prise en charge des patients souffrant de MVC évolue rapidement et des instruments d’évaluation fiables, standardisés et objectifs sont nécessaires pour juger de l’efficacité d’un traitement particulier. Promouvoir et valider de nouveaux outils d’évaluation spécifiques sur les procédures médicales et la QdV dans les ulcères veineux de jambe, le syndrome post-thrombotique et la MVC, seraient d’une grande aide. Des outils spécifiques d’évaluation de la gamme complète de la MVC, de ses signes et de ses symptômes, de son impact sur la QdV et des effets des traitements sont des éléments clés de la prise en charge efficace de la maladie. L’effet à long terme de la MVC sur la QdV et sur le bien-être des partenaires des sujets atteints devrait être étudié de façon longitudinale. À l’avenir, un consensus international d’approbation des mêmes instruments pour toutes les études cliniques sur la MVC et la QdV sera nécessaire.
Recent developments in the number and quality of treatment modalities have increased health provider interest in appropriate outcome assessment. Uniform outcome data are also desirable to establish medical necessity for third party payers. A valuable assessment tool will measure and stratify venous symptoms and elucidate the results of therapy. While general categories of physician-assessed or patient-reported instruments form the framework for evaluation, specific tools have emerged as valid, reproducible methods for the continuum of diagnosis, treatment, and follow-up. Physician-generated instruments including the clinical, etiological, anatomical, pathophysiological (CEAP) classification and Venous Clinical Severity Score (VCSS) measure objective data. The revised VCSS is now the most widely used physician-derived assessment tool in chronic venous disease. More subjective patient-reported assessments have also increased in popularity. There are four measurement tools frequently referenced in venous literature and one promising newcomer. The VEnous Insufficiency Epidemiological and economic Study—Quality of Life/Symptoms (VEINES-QoL/Sym), Chronic Venous Insufficiency quality of life Questionnaire (CIVIQ), Aberdeen Varicose Vein Questionnaire (AVVQ), Charing Cross Venous Ulcer Questionnaire (C XVUQ), and some modifications are reviewed. The Varicose Vein Symptom Questionnaire (VVSymQ®) is introduced. The novel idea of combining physician-generated and patient-reported assessment instruments is being explored. The benefit of a combination approach to following outcomes may be a more accurate evaluation of both symptoms and treatment results in the same patient. A model that combines the elements attributed to symptoms, treatment results, and ultrasound findings may lay the framework for medical necessity and reimbursement in the future.

Lower-limb venous symptoms: combining physician and patient reporting tools

by M. A. Vasquez, C. Munschauer, and D. Panza, USA

The number of available outcome assessment tools has increased dramatically in recent years. There is a genuine interest in following the results of the increasing modalities of treatment available. Arising with this are the demands of an increasingly restrictive payer network. The end result is a tangle of similar, yet different, assessment tools that reflect what is meant to be measured. We will attempt to sift through the currently available, validated tools for the assessment of symptoms and manifestations of chronic venous disease (CVD), focusing on instruments that evaluate the results of therapy. Beyond a systematic review of outcome assessment, we will address the predicted future value of these instruments in light of emerging therapies.

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Currently available assessment tools

Things have certainly changed in the 6 years since we were first asked to write a review of outcome assessment methods in venous disease. While the two broadest categories of physician-assessed or patient-reported instruments remain, the tools available have increased and undergone further validation. They have been used in numerous studies and have benefited from increased exposure and discussion. We now have a clearer picture of the specific benefits and drawbacks of many of the instruments. We also have models for combining assessment tools to gather as much relevant information as possible from patient and physician perspectives.

With so many instruments available, one important question is how to best choose the tool to provide the desired information without it becoming cumbersome to complete and onerous to evaluate. With this in mind, many clinicians forego the generic quality of life (QoL) instruments, including the Short Form 36 (SF-36). While this survey has been well validated, it yields mainly population-based data and collective treatment results. With more attention being paid to combining physician-generated tools and patient-reported outcomes (PRO) instruments, the focus seems to have settled on combining instruments that are specific for venous disease symptoms and course of therapy.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Absent (0)</th>
<th>Mild (1)</th>
<th>Moderate (2)</th>
<th>Severe (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain or other discomfort (ie, aching, heaviness, fatigue, soreness, burning), presumed venous origin</td>
<td>None</td>
<td>Occasional pain or other discomfort (ie, not restricting regular daily activity)</td>
<td>Daily pain or other discomfort (ie, interfering with, but not preventing regular daily activities)</td>
<td>Daily pain or discomfort (ie, limits most regular daily activities)</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>None</td>
<td>Few: scattered (ie, isolated branch varicosities or clusters), also includes corona phlebectatica (ankle flare)</td>
<td>Confined to calf or thigh</td>
<td>Involves calf and thigh</td>
</tr>
<tr>
<td>Venous edema</td>
<td>None</td>
<td>Limited to foot and ankle area</td>
<td>Extends above ankle, but below knee</td>
<td>Extends to knee and above</td>
</tr>
<tr>
<td>Skin pigmentation</td>
<td>None or focal</td>
<td>Limited to perimalleolar area</td>
<td>Diffuse over lower third of calf</td>
<td>Wider distribution above lower third of calf</td>
</tr>
<tr>
<td>Inflammation</td>
<td>None</td>
<td>Limited to perimalleolar area</td>
<td>Diffuse over lower third of calf</td>
<td>Wider distribution above lower third of calf</td>
</tr>
<tr>
<td>Induration</td>
<td>None</td>
<td>Limited to perimalleolar area</td>
<td>Diffuse over lower third of calf</td>
<td>Wider distribution above lower third of calf</td>
</tr>
<tr>
<td>Number of active ulcers</td>
<td>None</td>
<td>1</td>
<td>2</td>
<td>≥3</td>
</tr>
<tr>
<td>Duration of active ulcer (longest active)</td>
<td>None</td>
<td>&lt;3 months</td>
<td>&gt;3 months, but &lt;1 year</td>
<td>Not healed for &gt;1 year</td>
</tr>
<tr>
<td>Size of active ulcer (largest active)</td>
<td>None</td>
<td>Diameter &lt;2 cm</td>
<td>Diameter 2-6 cm</td>
<td>Diameter &gt;6 cm</td>
</tr>
<tr>
<td>Use of compression therapy</td>
<td>None</td>
<td>Intermittent use of stockings</td>
<td>Wears stockings most days</td>
<td>Full compliance with stockings</td>
</tr>
</tbody>
</table>

Several physician-generated instruments are ideally suited to provide valid, reliable data on the objective criteria of venous disease. The clinical, etiological, anatomical, pathophysiological (CEAP) classification and Venous Clinical Severity Score (VCSS) both provide measurement of clinical parameters in the progression of venous disease (Table I). CEAP is foremost only a classification tool and a less responsive peri-procedural representation of CVD. The revised VCSS is a more dynamic representation of the course of venous disease through serial reporting. Both of these instruments have gained acceptance due to the common descriptive platforms they provide and their ease of use. Both also have strong recommendations for use in the clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. The CEAP classification is not to be used to assess treatment results as a stand-alone tool. CEAP has limited responsiveness to changes in condition with therapy, especially at the C4 and C5 levels. The original VCSS was criticized early on for the precision of language used and the degree of interobserver variability. The VCSS was revised in 2010, and has been widely regarded as improved in specificity of language, nomenclature, and observer variability, especially with regards to pigmentation change. It is intuitive and is now the most widely used physician-derived venous score to date, and has been incorporated into European and American venous registries. It is made readily available on the American Venous Forum Web site. There remains debate about whether the VCSS should include the largely subjective category of compression therapy use, and this may be addressed in future revisions.

Patient-reported, venous disease–specific outcome-reporting tools have gained popularity recently as a subjective measure of the benefits of therapy. The five assessments that we encounter most often are the VEnous INsufficiency Epidemiological and Economic Study—Quality of Life/Symptoms (VEINES-QoL/Sym), the Chronic Venous Insufficiency quality of life Questionnaire (CIVIQ), the Aberdeen Varicose Vein Questionnaire (AVVQ), the Charing Cross Venous Ulceration Questionnaire (CXVUQ)1 and the VVSymQ® Score (Varicose Vein Symptom Questionnaire). All of these PRO instruments are focused primarily on symptoms as opposed to assessing or comparing therapies. As they measure symptoms at a given point in time, they are effective measures for evaluating the effects of treatment.

CIVIQ has been validated and is used effectively as a global measure of venous disease. Some critics have said that it does not address the specific manifestations of venous disease, but is more valuable in the overall assessment of venous disease. However, CIVIQ has been linguistically validated in 17 versions. There are two versions of CIVIQ: the CIVIQ-14 and the CIVIQ-20. For CIVIQ-20, patient-generated reports of signs and symptoms of venous disease were specifically used to generate the questionnaire. The final 20-item questionnaire shows a comprehensive collection of relevant parameters: pain, physical, psychological, and social (Table II). Patient recall of symptoms was set at 4 weeks.

CIVIQ-20 was felt to be incomplete in assessing social factors in divergent populations, so a new questionnaire, the CIVIQ-14 was developed, which combined social factors with pain to yield three categories: pain, physical, and psychological (Table III, page 48). This questionnaire was validated across international lines.

### Table II. Dimensions and items used in the Chronic Venous Insufficiency quality of life Questionnaire (CIVIQ)-20.

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Pain in the legs, Impairment at work, Sleeping poorly, Standing for long periods of time</td>
</tr>
<tr>
<td>Physical</td>
<td>Climbing several floors, Squatting/kneeling, Walking at a good pace, Doing the housework</td>
</tr>
<tr>
<td>Psychological</td>
<td>Feeling nervous, Having the impression of being a burden, Being embarrassed to show legs, Becoming irritable easily, Having the impression of being disabled, Having no desire to go out, Having to take precautions, Getting tired easily, Difficulty in getting going</td>
</tr>
<tr>
<td>Social</td>
<td>Going to parties, Performing athletic activity, Traveling by car, plane, etc</td>
</tr>
</tbody>
</table>

### Table III. Dimensions and items used in the Chronic Venous Insufficiency Epidemiological and Economic Study—Quality of Life/Symptoms (VEINES-QoL/Sym).

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVVQ</td>
<td>Aberdeen Varicose Vein Questionnaire</td>
</tr>
<tr>
<td>CEAP</td>
<td>clinical, etiological, anatomical, pathophysiological</td>
</tr>
<tr>
<td>CIVIQ</td>
<td>Chronic Venous Insufficiency quality of life Questionnaire</td>
</tr>
<tr>
<td>CVD</td>
<td>chronic venous disease</td>
</tr>
<tr>
<td>CXVUQ</td>
<td>Charing Cross Venous Ulceration Questionnaire</td>
</tr>
<tr>
<td>MPFF</td>
<td>micrized purified flavonoid fraction</td>
</tr>
<tr>
<td>PRO</td>
<td>patient-reported outcomes</td>
</tr>
<tr>
<td>QoL</td>
<td>quality of life</td>
</tr>
<tr>
<td>VCSS</td>
<td>Venous Clinical Severity Score</td>
</tr>
<tr>
<td>VEINES-QoL/Sym</td>
<td>VEnous Insufficiency Epidemiological and Economic Study—Quality of Life/Symptoms</td>
</tr>
<tr>
<td>VVSymQ®</td>
<td>Varicose Vein Symptom Questionnaire</td>
</tr>
</tbody>
</table>
Because of this specificity, in order for CXVUQ to give a complete venous disease assessment in patients with ulcers it probably needs to be combined with a traditional clinical outcome measure or a generic instrument. The new kid on the block is the VVSymQ® Score. It is a symptom-focused PRO instrument that was designed to evaluate the symptom burden of varicose veins before and after treatment of the great saphenous vein in the BTG Varithena® (polidocanol injectable foam) randomized controlled trials. In fact, it is the only PRO instrument that meets the exacting standards set out in the US Food and Drug Administration (FDA) guidance document titled Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. The VVSymQ® score is based on daily patient assessment of the varicose vein symptoms determined through research to be most important to patients: heaviness, achiness, swelling, throbbing, and itching (Table IV).

There is a demonstrated intercorrelation with known instruments such as the VCSS, VEINES-QoL, and CIVIQ-20. In the Varithena® trials, VVSymQ®, VCSS, and VEINES-QoL were highly sensitive to change. The moderate correlation with VCSS seems to indicate that both instruments measure different aspects of the same disease. This falls in line with our understanding of the complementary nature of physician-generated and patient-reported tools.

With regards to vеноactive drug use in a patient with CVD, key assessment tools have been used to assess efficacy. The most commonly used include CIVIQ-14, CIVIQ-20, and the 10-point Visual Analog Scale (VAS) which assesses pain intensity. CEAP has been used to classify patients in these studies. The revised VCSS has not been directly used with venoactive drugs to date. The investigators of the studies found that the use of valid, reliable assessment tools was very useful in determining both the clinical effect of vеноactive drug therapy and to measure the QoL of a venous disease patient using vеноactive drug therapy.

### Table III. Dimensions and items used in the Chronic Venous Insufficiency quality of life Questionnaire (CIVIQ)–14.


<table>
<thead>
<tr>
<th>Dimension</th>
<th>Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Pain in the legs, Impairment at work, Sleeping poorly</td>
</tr>
<tr>
<td>Physical</td>
<td>Climbing several floors, Squatting/kneeling, Going to parties, Performing athletic activities</td>
</tr>
<tr>
<td>Psychological</td>
<td>Feeling nervous, Having the impression of being a burden, Being embarrassed to show legs, Becoming irritable easily, Having the impression of being disabled, Having no desire to go out</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Heaviness, Achiness, Swelling, Throbbing, Itching</th>
</tr>
</thead>
</table>

### Table IV. Dimensions and items used in the Varicose Vein Symptom Questionnaire (VVSymQ®).

*Data from reference 7.*

The issues addressed in the CIVIQ questionnaire assess patients across the spectrum of venous disease, through C6, although CIVIQ-20 targets C0 to C2. Patients with ulcers are excluded, since factors relevant to patients in the earlier stages of chronic vascular disease may not be relevant to patients with ulceration, including questions relating to participation in sports or limitations on social activities. CIVIQ-20 showed a strong ability to track changes following therapy. This has been validated through its use in comparing treatment methods and conservative therapies.

VEINES-QoL/Sym is applicable in a wide range of clinical conditions. It focuses on the underlying condition and changes in associated symptoms, not on the therapy itself. It has proven useful in elucidating symptomatic changes in studies utilizing multiple treatments. However, because it focuses on diagnostic elements, it is difficult to assess change in response to a specific therapy. Also, there is less focus on anatomic and physiologic elements, which also might clarify beneficial treatment options.

AVVQ considers all elements of venous disease, including cosmetic manifestations. Because of this wide-reaching approach, AVVQ is useful in many applications and in consideration of many venous disease findings. However, because of this wide focus, it lacks some sensitivity in elucidating change over time in individual patients, especially those with milder disease.

CXVUQ is an instrument that considers venous stasis ulcers and their course. Because of its specific focus, it is a consistent measure of QoL factors in patients with venous ulcers, regardless of the treatment option selected. However, largely because of this specificity, in order for CXVUQ to give a
One thought-provoking combined study, the DECISION study, evaluated whether the addition of micronized purified flavonoid fraction (MPFF) to patients undergoing endovenous treatment for varicose veins of the lower extremities improves postoperative symptoms and signs of CVD and patient QoL. They found that the “reduction in VCSS score during the first 2 weeks after the endovenous procedure was significantly greater in the MPFF group compared with the control group.” The reason for this is not entirely clear and elicits further questions. What changes would be seen if MPFF were used along with medical compression? A valid alternative may be offered for those patients with symptomatic deep reflux or postthrombotic syndrome.

Conclusion
There are a range of valid, reliable assessment instruments to measure CVD symptoms and results of treatment. New modalities of treatment are ever present. Comparison of ablation outcomes is best performed when the same outcome measures are used no matter what the mode of treatment. Physician assessment and patient self-assessment serve complementary functions and should be combined to provide a more accurate clinical scenario. We will even go so far as to profess that a combined scoring system, inclusive of duplex findings, would be a preferred manner to establish medical necessity for those considering treatment and insurance reimbursement.

References

Keywords: CEAP; chronic venous disease; CIVIQ; C XVU Q; lower limb; VCSS; venous symptom
Venous hypertension eventually leads to extravasation of macromolecules into dermal interstitium and to chronic inflammation. Initially, vein walls become distended and valve leaflets deform, resulting in valve failure. Valve failure leads to turbulent flow, blood stasis, or reflux, which can provoke local inflammatory and thrombotic responses. These responses include the production of prothrombotic agents (monocyte chemoattractant protein 1 and vascular cell adhesion molecule 1) and growth-promoting agents (angiotensin II, endothelin 1, and platelet-derived growth factor), leukocyte and neutrophil migration, and promotion of apoptosis.

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Chronic reflux, along with venous hypertension, raises blood pressure in capillaries of the microcirculation. Capillary hyperton tension leads to a vicious circle of leakage, edema, and inflammation, which ultimately result in pathological skin changes and venous ulceration. Chronic reflux, which is evident before large veins become visible, is a preclinical sign of CVD in at-risk individuals. As CVD progresses, common symptoms that manifest include aching legs, heaviness, tension, cramp, swelling, itching, and restless legs. The clinical, etiological, anatomical, pathophysiological (CEAP) classification is today used worldwide to classify CVD.

### Development of current chronic venous disease guidelines

As CVD symptoms can appear in the absence of clinical signs of venous disease and at every clinical stage of CVD, symptom control in CVD is critical. Venoactive drugs (VADs), of which there are different types with different effects (Table I), are one of the pillars of the symptomatic management of CVD in the latest guidelines. The way in which evidence quality and recommendations for VADs are determined has evolved greatly over the last decade.

In 2005, a Cochrane review of 59 randomized controlled trials showed that treatment with VADs reduced most symptomatic CVD outcomes without increasing the incidence of adverse events vs placebo. In the same year, a panel of CVD experts set out to determine the efficacy of VADs by assessing 83 randomized controlled trials and meta-analyses in the literature. Evidence quality was graded A (randomized clinical trials with large sample sizes, meta-analyses combining homogeneous results), B (randomized clinical trials with small sample sizes, single randomized trial only), or C (other controlled trials, nonrandomized controlled trials).

On this basis, micronized purified flavonoid fraction (MPFF), calcium dobesilate, and hydroxyethylrutosides were classified grade A, horse chestnut seed extract and Ruscus extract grade B, and other VADs grade C. These experts also concluded that VADs should be indicated to relieve symptoms in all clinical classifications of CVD, from class C0s to C6s. Guidelines in 2008 amalgamated the grade recommendations of the 2005 International Consensus Statement with the drug indications of the 2005 Cochrane review. The 2008 guidelines also provided more information on the use of VADs in C6 patients and safety of VADs. Importantly, they proposed that VADs could be used as a first-line treatment for symptoms and edema in CVD. In 2011, a new set of recommendations for the use of VADs, based on the Grading of Rec-

### Table I. Evidence-based modes of action of the main venoactive drugs.

<table>
<thead>
<tr>
<th>Venoactive drug</th>
<th>Category</th>
<th>Venous tone</th>
<th>Venous wall/valve leakage</th>
<th>Capillary leakage</th>
<th>Lymphatic drainage</th>
<th>Hemorrhological disorders</th>
<th>Free radical scavengers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micronized purified flavonoid fraction</td>
<td>Flavonoid (γ-benzopyrone)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nonmicronized or synthetic diosmins*</td>
<td>Flavonoid (γ-benzopyrone)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Rutin and rutosides O-β-hydroxyethyl-rutosides (roxerutin, HR)</td>
<td>Flavonoid (γ-benzopyrone)</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Anthocynans (Vitis vinifera)</td>
<td>Flavonoid (γ-benzopyrone)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Proanthocyanidins (Vitis vinifera)</td>
<td>Flavonoid (γ-benzopyrone)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Coumarin</td>
<td>α-benzopyrone</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Horse chestnut seed extract; escin</td>
<td>Saponin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ruscus extract</td>
<td>Saponin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Gingko extracts*</td>
<td>Other plant extract</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Calcium dobesilate</td>
<td>Synthetic product</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Benzaroni*</td>
<td>Synthetic product</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nattazone*</td>
<td>Synthetic product</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>


### Selected abbreviations and acronyms

- **CEAP**: clinical, etiological, anatomical, pathophysiological
- **CVD**: chronic venous disease
- **GRADE**: Grading of Recommendations Assessment, Development, and Evaluation
- **MPFF**: micronized purified flavonoid fraction
- **VAD**: venoactive drug
Table II. Summary of the present guideline recommendations for the use of venoactive drugs for symptom relief, according to the GRADE system.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Venoactive drug</th>
<th>Recommendation</th>
<th>Evidence quality</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relief of symptoms associated with CVD in patients in CEAP classes C0 to C6s and in those with CVD-related edema (CEAP class C0)</td>
<td>Micronized purified flavonoid fraction</td>
<td>Strong</td>
<td>Moderate</td>
<td>1B</td>
</tr>
<tr>
<td></td>
<td>Nonmicronized diosmins or synthetic diosmins</td>
<td>Weak</td>
<td>Poor</td>
<td>2C</td>
</tr>
<tr>
<td></td>
<td>Rutosides (O-β-hydroxyethyl)</td>
<td>Weak</td>
<td>Moderate</td>
<td>2B</td>
</tr>
<tr>
<td></td>
<td>Red vine leaf extracts (Vitis vinifera)</td>
<td>Weak</td>
<td>Moderate</td>
<td>2B</td>
</tr>
<tr>
<td></td>
<td>Calcium dobesilate</td>
<td>Weak</td>
<td>Moderate</td>
<td>2B</td>
</tr>
<tr>
<td></td>
<td>Horse chestnut seed extract</td>
<td>Weak</td>
<td>Moderate</td>
<td>2B</td>
</tr>
<tr>
<td></td>
<td>Ruscus extracts</td>
<td>Weak</td>
<td>Moderate</td>
<td>2B</td>
</tr>
<tr>
<td></td>
<td>Gingko biloba</td>
<td>Weak</td>
<td>Poor</td>
<td>2C</td>
</tr>
<tr>
<td></td>
<td>Other VADs</td>
<td>Weak</td>
<td>Poor</td>
<td>2C</td>
</tr>
</tbody>
</table>

The 2014 guidelines contain a comprehensive section on the role of venoactive drugs (VADs) in the management of chronic venous disorders (CVD). The guidelines address various aspects of venous disease, including edema, pain, and cramps. The table above summarizes the recommendations for the use of specific venoactive drugs for symptom relief, based on the GRADE system. The table lists the indication, the specific venoactive drug, the recommendation strength, the quality of evidence, and the GRADE code.

The 2014 guidelines, like their predecessors, emphasize the importance of addressing the underlying causes of CVD and recommend a multidisciplinary approach to treatment. Key points from the guidelines include:

- **The C0s patient**
  - The revised 2004 CEAP classification drew attention to the existence of C0s patients, or more specifically C0sEnAnPn patients, with no detectable reflux or visible signs. These patients are often overlooked but can still benefit from targeted treatments.

- **Management of lower-limb venous symptoms**
  - The overall prevalence of CVD symptoms in C0s patients was less common: 58.5% vs 80.0% for pain in the legs; 52.4% vs 73.9% for sensation of swelling; and 29.1% vs 62.7% for night cramps (all P<0.0001). C0s patients also present with fewer symptoms (2.1±1.1 vs 3.1±1.0; P<0.0001).

- **Pain**
  - Pain, which is induced by inflammation and/or vein wall distension, is one of the most oppressive symptoms in C0s patients. Numerous different factors can provoke venous inflammation: oxidative stress, shear stress, toxicity, bacterial infection, venous hypertension, hypoxia, and mechanical injury, among others. These factors are often silent and difficult to detect. Excessive distension of veins can be due to prolonged standing, pregnancy, heavy labor, or hereditary deficiency of elastic and/or muscular vein wall components. Distension and inflammation lead to the activation of nociceptors.
(sympathetic C fibers) found in venous intima and media. Management of pain and other CVD symptoms in C_{ve} patients includes oral VADs, compression hosiery, and patient reassurance and lifestyle modification.

**Oral venoactive drugs**

VADs have been shown to be an effective way of alleviating pain in CVD and of treating nearly all CVD symptoms. Most VADs have been shown to reduce capillary leakage and improve venous tone (Table I). Agents that improve venous tone act by modulating noradrenergic signaling, either by reducing noradrenaline metabolism (MPFF and hydroxyethylrutosides) or by stimulating venous α_{1}-adrenergic receptors (Ruscus extracts). Horse chestnut seed extract has a different mechanism of action for improving venous tone, inducing calcium-dependent contractions in vena cava in a rat model. Most VADs also have free-radical scavenging properties and have now been demonstrated to have anti-inflammatory effects in CVD; several acting at more than one step of inflammatory pathways. VADs can also reduce capillary permeability, prevent skin degeneration related to abnormal capillaries, improve lymphatic drainage, and reduce blood viscosity and/or erythrocyte aggregation. Fewer VADs (flavonoids, α-benzopyrones, and calcium dobesilate) have been shown to have an effect on lymphatic drainage or hemorheological disorders (Table I). Only while MPFF has been shown to prevent the degradation of venous wall and venous valves. VADs also have a role in chronic venous insufficiency (CEAP C_{ve} to C_{ve}). MPFF used alongside compression and local wound care has been shown to increase the rate of healing of larger ulcers (5 cm to 10 cm) and established ulcers (6 months to 12 months) vs standard wound treatment alone.

There are five main categories of VAD: flavonoids (γ-benzopyrones), α-benzopyrones, saponins, other plant extracts, and synthetic products (Table I). The largest of these categories is the flavonoids (hesperidin, diosmin, oxerutins, β-hydroxyethylrutosides, quercetin, kaempferol, and proanthocyanidins), which are known to have potent antioxidant properties. Flavonoids prevent the production of oxidizing agents, scavenge free radicals (thus avoiding cellular damage), block the propagation of oxidative reactions, and strengthen inherent cellular antioxidant capacity. All flavonoids reduce leg edema and many also improve symptoms (Table III). The flavonoids in red vine leaf extract have been shown to improve venous blood flow, while those in MPFF improve quality of life, ulcer healing, and clinical severity of CVD (reduction in CEAP class).

VAD mixtures are common; examples include MPFF, Gingko extracts, and Ruscus extracts. MPFF is made of a 90%/10% micronized mixture of the flavonoid diosmin and other flavonoids (hesperidin, diosmetin, linarin, andisorhoifolin). Gingko extracts contain Gingko biloba, heptaminol, and troxerutin; and Ruscus extracts contain Ruscus aculeatus, hesperidin, methyl chalcone, and ascorbic acid.

<table>
<thead>
<tr>
<th>Product</th>
<th>Origin</th>
<th>Active ingredient</th>
<th>Clinical benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micronized purified flavonoid fraction</td>
<td>Rutacea aurantiae</td>
<td>Hesperedin, Diosmin</td>
<td>↓ leg edema, ↓ quality of life, ↑ ulcer healing</td>
</tr>
<tr>
<td>Oexertin</td>
<td>Sophera japonica, Eucaliptus spp, Fagopyrum esculentum, Moench</td>
<td>Oexertin</td>
<td>↓ symptoms, ↓ leg edema</td>
</tr>
<tr>
<td>β-hydroxyethylrutosides</td>
<td>Sophera japonica, Eucaliptus spp, Fagopyrum esculentum, Moench</td>
<td>β-hydroxyethylrutosides</td>
<td>↓ symptoms, ↓ leg edema</td>
</tr>
<tr>
<td>Read vine leaf extract</td>
<td>Vitis vinifera</td>
<td>Quercetin glucoside, Quercetin glucuronides, Kaempferol glucoside</td>
<td>↓ symptoms, ↓ leg edema, ↑ blood flow</td>
</tr>
<tr>
<td>Pycnogenol</td>
<td>Maritime pine</td>
<td>Proanthocyanidins</td>
<td>↓ leg edema</td>
</tr>
</tbody>
</table>

Table III. Flavonoid products prescribed for the treatment of chronic venous disorders and chronic venous insufficiency and their origins, active ingredients, and clinical benefits.

**Abbreviations:** CEAP: clinical, etiological, anatomical, pathophysiological.

**Modified from reference 1:** Int Angiol. 2014;33:87-208. © 2014, Edizioni Minerva Medica.
Compression therapy
Medical compression therapy is also considered an option in C0s patients,12 and the rationale for its use is explained in the 2014 guidelines.1 However, a recent review of the literature highlighted the lack of good quality evidence for determining the effectiveness of compression stockings or for making comparisons between the different types available.26 Furthermore, more data are needed to show that the real-life efficacy of compression therapy is comparable with that observed in trials, as treatment compliance may be an issue.27,28

Topical treatment and lifestyle
The cooling sensation of topical preparations containing VADs or heparinoids can sometimes provide relief for symptoms of heaviness or swelling.1 Although there is no evidence to substantiate the benefit of modifying lifestyle, the everyday experience of phlebologists indicates that many simple measures could reduce symptoms in C0s patients. Measures such as weight loss, raising the legs at night or during breaks, swimming, substituting walking for driving, and calf exercises could all play a valuable role.

Conclusion
Over the last decade, a constant message has emerged in chronic venous disorder guidelines, reviews, and consensus statements: VADs are effective for controlling symptoms at all stages in CVD. This includes the earliest stage of chronic venous disorders, where patients show no visible or palpable signs of disease (C0). The major symptom in C0 patients, pain, can be alleviated by VADs. The role of VADs in the management of CVD in the 2014 guidelines is described as "central and unique." These guidelines also advocate lifestyle modification in C0 patients, but call for further assessment of compression therapy. Treatment regimens in CVD should be based on VADs, like MPFF, with higher levels of guideline recommendation.

References

Keywords: chronic venous disease; chronic venous disorder; compression therapy; guideline; venoactive drug; venous symptom
PRISE EN CHARGE DES SYMPTÔMES VEINEUX DES MEMBRES INFÉRIEURS : 
QUE NOUS DISENT LES RECOMMANDATIONS ?

Les phlébotropes (ou veinotoniques) font partie intégrante du traitement de la maladie veineuse chronique symptomatique (MVC), surtout aux stades précoces. Ces 10 dernières années, les recommandations sur l’utilisation des phlébotropes pour le traitement symptomatique de la MVC ont considérablement évolué. Les événements marquants du développement des recommandations actuelles sont les suivants : la revue Cochrane 2005, la déclaration de consensus international 2005, les recommandations 2008 pour la prise en charge des troubles veineux chroniques des membres inférieurs, la revue Perrin et Ramelet 2011 et plus récemment, les recommandations actuelles 2014. À chaque étape, de nouvelles données ont été ajoutées et le statu quo réévalué. La plupart des phlébotropes améliorent le tonus veineux, piègent les radicaux libres et réduisent la fuite capillaire, tandis que très peu d’entre eux diminuent la perméabilité capillaire, empêchent la dégénérescence cutanée, améliorent le drainage lymphatique et diminuent la viscosité sanguine et/ou l’agrégation érythrocytaire. Les phlébotropes diminuent aussi la douleur dans la MVC. La douleur, induite par l’inflammation et/ou la distension de la paroi veineuse, est un symptôme majeur des patients C₀s, patients symptomatiques sans signe visible ou palpable de maladie veineuse. Un cinquième des patients MVC pourrait appartenir au stade C₀s de la CEAP (Clinical, Étiological, Anatomical, Physiopathological). Le réconfort et les modifications du style de vie peuvent aussi être utiles à ces patients, mais l’argumentaire du traitement par compression se fonde sur de faibles données. Les recommandations de 2014 soulignent le « rôle central et unique » des phlébotropes, en particulier dans la MVC précoce. Il faut utiliser de préférence les phlébotropes de haut niveau de recommandation.
THE QUESTION

Lower-limb pain of venous origin and clinical/investigation findings have often been shown to be incongruous, yet it is acknowledged that this symptom greatly worsens patients’ quality of life. The question is, is there appropriate emphasis placed on the reduction of lower-limb pain symptoms in the treatment of chronic venous disorders and is this ultimately a meaningful treatment outcome?

Is lower-limb pain reduction a meaningful treatment outcome?

1. S. Agarwal, India
2. Y. Akcali, Turkey
3. M. Bokuchava, Georgia
4. D. Branisteanu, Romania
5. E. Ferreira, Portugal
6. F. F. Haddad, Lebanon
7. D. T. T. Huong, Vietnam
8. D. Karetová, Czech Republic
9. G. Lessiani, Italy
10. H. Lotfy, Egypt
11. C. Ruangsetakit, Thailand
12. C. E. Virgini-Magalhães, Brazil
13. I. A. Zolotukhin, Russia
The syndrome of chronic venous disease (CVD) is common. In India, about 15% of the population has varicose veins, and 2.5% venous leg ulcers. However, among outpatients in the general practice setting, the frequency is much higher. Leg pain is a major symptom of CVD. In a cross-sectional survey of 300 patients with CVD, clinical, etiological, anatomical, pathophysiological (CEAP) classification C0 to C4, 97% complained of lower-limb pain, and their quality of life (QoL) assessed by a visual analogue scale was reduced by one-fourth. The most severe pain and loss of QoL is in patients with leg ulcers (CEAP C5 and C6).

The origin of lower-limb pain in CVD is microvascular inflammation. This pathogenic process is initiated by an idiopathic loss of venous tone or thrombophlebitis involving the veins of the lower limb. The resulting valvular incompetence and venous reflux leads to venous hypertension and venous stasis in the lower limb. Venous stasis acts as a signal for the marginalization of white cells and their adhesion to the vein wall. This triggers white-cell activation and release of inflammatory mediators such as free radicals, thromboxane, and prostaglandins. A sterile inflammation develops in the wall of capillaries making them more permeable and friable. This micro-circulatory inflammation gives rise to pain and the other cardinal symptoms of CVD, such as heaviness, cramps, and sensation of swelling in the leg.

The leg pain of CVD is responsive to specific treatment. Measures to improve venous tone, reduce venous hypertension, suppress microvascular inflammation, and increase lymphatic drainage are effective. In experimental studies, micronized purified flavonoid fraction (MPFF) has been shown to significantly increase venous tone, augment lymphatic drainage, suppress inflammatory mediators (free radicals, thromboxane B2, and prostaglandins E2 and F2α), and reduce capillary hyperpermeability. When patients with CVD were randomly treated with MPFF 1000 mg or placebo for 3 months, there was a significant improvement in lower-limb pain together with plathesmographic increase in venous tone with MPFF 1000 mg treatment compared with placebo. This has since been demonstrated in several studies. In India, QoL was first assessed in a 6-month study on patients with CVD (CEAP C0 to C4) in 1998. Treatment with MPFF 1000 mg together with leg elevation reduced pain by 76%, and improved QoL by 65%.

Against this background of high prevalence, and availability of effective treatment, it is worthwhile to treat leg pain due to CVD.

Reference
Venous disorders in the legs, which may be considered a nearly normal part of the aging process, are perhaps the most common afflictions of the bipedal human. Venous leg pain is the most important differentiation between “venous disorder” and “venous disease.” Therefore, it should be systematically asked whether a patient is suffering from venous leg pain. In the event of a painful leg, other vascular, neurogenic, orthopedic, or rheumatologic disorders should be considered as differential diagnoses.

Leg pain related to chronic venous disease (CVD) can be exacerbated by a standing position in the course of the day, immobility (for example, in a prolonged sitting position), warmth, and menstrual cycle, and can be relieved with resting, leg elevation, and cold exposure. However, patients complaining of severe venous pain should be investigated for venous intermittent claudication (IC) and coexisting peripheral arterial disease (PAD). Venous IC is a rare consequence following hemodynamically significant obstruction of the deep venous system, especially after iliofemoral deep venous thrombosis (DVT) without adequate collateralization. Patients often experience severe thigh “bursting” pain or cramps and the sensation of tightness with walking or exercise, sometimes mimicking claudication secondary to PAD. However, in contrast to arterial claudication, 15 to 20 minutes of rest combined with leg elevation often relieve the pain.

Venous pain, which is the main symptom that guides the diagnosis of CVD, has a substantial impact on patients’ quality of life. Therefore, the absence of venous pain is considered to be the most important outcome after venous treatment.

Pain is a symptom of chronic venous “disease,” but not of chronic venous “disorder.” Most patients who have visible signs in the leg(s) do not need referral to the hospital. Furthermore, visible signs, pain, or reflux in the affected vein may interact in the pathophysiological process, and consequently, is as important as the appearance of visible signs on the legs and reflux in the affected vein. Hence, in my clinical practice I do not perform surgical or endovenous saphenous ablation unless all of the following indications are present: (i) clinical indication: CVD-related symptoms, mainly pain; (ii) anatomic indication: dilated, tortuous and/or elongated superficial veins ≥6 mm; and (iii) pathophysiologic indication: reflux in the affected vein >0.5 seconds. So I consider that pain relief, disappearance of visible signs on the legs, and the absence of reflux in the diseased veins after the treatment of CVD are the most important therapeutic outcomes.

If a patient who has been treated for their diseased veins or skin (clinical, etiological, anatomical, pathophysiological [CEAP] class C4 to C6) with satisfactory clinical and duplex ultrasound outcomes continues to complain of leg pain, they should be re-evaluated meticulously for other vascular or nonvascular diseases (obesity, calf muscle venous pump dysfunction, etc). After the diagnosis of coexisting PAD, which increases with advanced age just as in CVD, have been excluded, the deep venous system is reinvestigated for thrombotic or nonthrombotic insufficiency. Sometimes a saphenous vein can function as a collateral pathway in a patient who has deep vein aplasia or hypoplasia with Klippel-Trenaunay syndrome. Then, if saphenous ablation is performed without an adequate clinical and radiological evaluation, venous leg pain can continue and even augment postoperatively. A similar clinical picture is discussed for postthrombotic syndrome, which is primarily diagnosed on clinical grounds.

References
Leg pain is the complaint that occurs in 80% of patients with chronic venous disease (CVD)\textsuperscript{1-3} and has a significant impact on patient’s quality of life (QoL). This pain is mostly associated with a feeling of heaviness or tiredness in the legs, numbness, burning, or a sensation of swelling.\textsuperscript{4,5}

In my clinical practice, the first thing to do is to gain the anamnesis of a venous patient and to find out whether there is a family history of varicose disease, thromboembolism, or thrombophilia. I systematically ask patients about leg pain and its origin—symptoms, when and under what circumstances the pain appears, and its correlation with patient’s daily activities. In women, it is important to have information about the number of pregnancies, and the use of contraceptives and hormonal therapy.

Venous pain is usually diffuse, with no clear location. Also, it is known that the intensity of pain is not correlated with the severity of venous disease—many patients suffering from venous pain have no objective clinical or paraclinical abnormalities.\textsuperscript{4,6} The pain must be differentiated from other lower-limb pain of different etiologies: mechanical factors usually related to activities and movements such as walking up the stairs and lifting, “intermittent claudication” (in patients with chronic ischemic peripheral arterial disease), or by the pain associated with joint disease. A complaint of severe venous pain requires further investigation. For me as a specialist, the most important thing is to adapt the treatment to the patient. For this purpose we must start with an analysis of the patient’s clinical status, taking into account his expectations, and of course to have a good knowledge of the indications and outcomes of various treatment options. So, the most important outcome after CVD treatment is not only the disappearance of one clinical sign or symptom, but a disappearance of all—visible signs, pain, reflux in the affected vein, and severity of heavy or tired legs.

In the case of continuous leg pain despite venous pathology having been successfully treated (including ulcer healing), with good clinical and duplex ultrasound results, I suggest further investigations with other specialists, eg, neurology or orthopedics/traumatology, in order to exclude other pathology.

The treatment strategy used for the management of chronic venous pathology is complex, including medical treatment (such as venoactive drugs to prevent the progression of the disease and to avoid complications), elastic compression therapy, and surgery.

To conclude, leg pain affects 80% of patients with CVD, so it is important to consider this kind of venous pain as a therapeutic target to improve the QoL of these patients.\textsuperscript{2,4}

References
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Venous pain was and still is an issue of intense debate among phlebologists because of its clinical and pathophysiological particularities. There were, and probably still are, doctors who believe that leg pain is difficult to attribute to venous disease. On the other hand, venous pain is difficult to describe by patients, the sensation of pain being associated with other multiple symptoms of chronic venous disease (CVD): cramps, pruritus, sensation of swelling, feelings of heaviness, tension in the legs, etc.

Recent studies provide information on the physiological mechanism underlying venous pain and elucidate some cellular and biochemical processes. Still, incomplete and even erroneous concepts of the importance of venous pain persist in the medical community. More precisely, patients find it difficult to describe and even to realize that leg pain is related to venous disease. A detailed, targeted history may lead to the active detection of this complex symptom of venous disease.

However, the insidious onset and chronicity of venous pain means that the importance of venous pain in the diagnosis, course, and effectiveness of therapy for venous disease is often underestimated by both patient and doctor.

Venous pain is poorly quantified in the clinical, etiological, anatomical, pathophysiological (CEAP) classification; there is no concrete scientific assessment of venous pain intensity, only the differentiation between the presence or absence of venous pain. The Venous Clinical Severity Score (VCSS) also doesn’t consider venous pain as a criterion for assessing the severity of venous disease, although the fact that venous pain leads to a change in the quality of life of patients with venous disease is recognized.

Practical clinical experience suggests a great diversity of venous pain expression in patients with venous disease. Thus, some patients with advanced CVD (CEAP class C4 or C5) presenting with significant and diverse trophic skin changes and severe duplex ultrasound findings do not have significant venous pain. On the other hand, there are patients who complain of significant leg pain in the absence of consistent clinical or ultrasound changes. These clinical findings suggest that there is no correlation between the presence and intensity of venous pain, and between pain and the severity of pathophysiological, clinical, and ultrasound changes, thus further complicating the correct diagnosis, and short- and long-term management of CVD.

In daily practice, active detection of leg pain is very important in all patients with venous disease. This way, the doctor-patient relationship related to leg pain as a symptom of venous disease can be improved. Assessment of leg pain as “severe” on the Visual Analogue Scale should prompt the physician to refer the patient to more complex ultrasound examinations for an accurate diagnosis.

The most important outcome after venous treatment is halting the progression of CVD to advanced stages, and even regression in less severe stages of disease. Given this goal, reducing venous hypertension in leg circulation and the disappearance of reflux in the affected vein are essential. Depending on the CVD stage, it is desirable that visible signs on the leg disappear or diminish. From a patient’s point of view, I believe that the most important outcome after venous treatment is the disappearance, or at least the relief, of CVD symptoms, especially leg pain, followed by healing of clinical signs visible on the legs.

If leg pain persists despite correct and complex treatment for CVD, controlled clinical signs, and satisfactory duplex ultrasound results, I think it is appropriate to investigate for other etiology (e.g., arterial, neurological, articular, muscular, infectious, etc.). Large epidemiological studies are needed to determine the true incidence and intensity of venous pain in CVD, such as detecting the factors that cause variations in pain intensity from one patient to another.
C hronic venous disease (CVD) is the most prevalent vascular disorder in developed countries and is associated with significant costs (2% to 3% of the health budget of Western countries). According to the clinical, etiological, anatomical, pathophysiological (CEAP) classification, all classes of CVD can be associated with symptoms, and there is no direct relationship between symptoms and stage of disease.

One of the symptoms of CVD is leg pain. Quality of life (QoL) has been reported to be negatively affected by leg pain among patients with CVD. The prevalence of leg pain in CVD is often underestimated by physicians, since it is difficult to evaluate and could suggest different diagnoses (rheumatic, orthopedic, neuropathic, etc). However, we can describe some features that may suggest CVD:

◆ Symptoms worsen towards the end of the day.
◆ Symptoms are more intense during the hot season.
◆ Symptoms show an activity-related variation throughout the day-night cycle; usually unresponsive to analgesics or non-steroidal anti-inflammatory drugs.
◆ Venous obstruction or reflux removal, as well as the use of compression stockings and venoactive drugs, leads to improvement.

Until recently, treatment effectiveness did not take into account patient-centered outcomes such as QoL. Currently, modern medicine has greatly shifted its focus to the patient’s perspective of the disease and it has become indispensable when treatment outcomes are assessed. So, on the first contact with the patient, it is essential to clarify the reason for consultation including cosmetic complaints, symptoms (pain, edema, restless legs, pruritus), impact on QoL, fear of disease progression, and patient expectations (this is our most important outcome measure).

A complete clinical history, physical examination, and a continuous wave Doppler evaluation, are then performed. According to the findings, we can have a diagnosis, classify the severity of CVD, and propose a treatment regimen. Duplex ultrasound is generally reserved for patients with C3 or more advanced stages of the CEAP classification. Patient education on healthy lifestyle is fundamental. The following instructions must be convincing and regularly repeated to the patient: (i) walk daily, as often as possible; (ii) elevate legs by 30° during rest periods throughout the day; (iii) elevate the foot of the bed, 10 cm to 15 cm during the night; (iv) take cold showers; (v) regular participation in sports—walking, cycling, swimming, running, etc; and (vi) regular use of compression stockings.

If leg pain is the main complaint, and if its severity has an impact on patient lifestyle, venoactive drugs should also be prescribed.

At this time, according to the CVD classification, sclerotherapy or classic vs endovenous surgery will be discussed. If a patient that has been satisfactorily treated (according to clinical and ultrasound results) continues to complain of leg pain, the physician should investigate further.

Therefore, it is mandatory to confirm if the etiology of the pain is just a symptom of venous disease or whether there are other objective causes for these symptoms. If all other causes, including psychological, have been excluded, venoactive drugs are prescribed. The most important outcome after venous treatment is measured by the satisfaction of the patient.

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since before ancient times, mankind described, suffered from, and treated varicose veins; clearly not all for cosmetic reasons. The San Diego Population Study reported data on symptoms of venous disease: aching was the most commonly reported venous symptoms with a prevalence of 17.7% (though swelling was slightly more specific). Symptons increased in severity with the increase in functional and visible disease.

It is established that symptoms in varicose veins play a key role in overall assessment, as stressed by class C0 in the clinical, etiological, anatomical, pathophysiological (CEAP) classification; however, pain does not stand out specifically in this grading. The symptom of pain, despite the mixed reporting in relation to the physical signs and severity of disease, does carry serious medical implications. Indeed, recent onset pain, warmth, and erythema in the distal leg can be signs of early lipodermatosclerosis at the level of the perforators and a prelude for future ulceration. Not surprisingly, in the most recent NICE guidance, patients are to be referred for vascular specialist care if varicose veins are associated with any “troubleshooting symptoms” such as “pain.” In addition, the fact that venous pain may not be correlated with incompetent valves or absence of reflux (CEAP class C0) supports the findings of microvalvular incompetence at very distal tributaries. Failure of microvenous valves in small superficial veins is a key to the skin changes of venous insufficiency. The ultimate assessment of disease impact and treatment outcomes is quality of life (QoL); looking at the recently revised Chronic Venous Insufficiency quality of life Questionnaire (CIVIQ)–14 score, one of the three dimensions of this tool is “pain.” Currently, this is one of the most reliable and validated QoL scores in chronic venous disease.

Importantly, varicose veins are one of the rare etiologies of pain in the legs that are actually visualized by the patient. Hence, any complaint in the presence of varicocities is automatically related to the latter. Having pain assessment and reassessment, initially and at follow-up, is an important outcome tool. If this is unchanged after treatment, it is likely that further investigation is warranted to explore possible etiologies. Regardless, as with any other pathology, outcome assessment should cover the original complaint that brought the patient for consult. This issue was addressed partly with the revised Venous Clinical Severity Score, which is also endorsed by the Society for Vascular Surgery and the American Venous Forum recommendation. This does not, unfortunately, include staging of the disease, and CEAP classification would still be in order. Ideally, a single venous assessment and outcome tool should be available that looks at the patient stage, well-being, and QoL, with a fair representation of the pain scale in its component.

References
As a cardiovascular doctor, I have to examine patients who have heart and vascular diseases. While examining these patients, I tend to investigate potential risk factors for these diseases. Clinical practice has shown that many patients suffering unpleasant sensations in their legs (including heaviness, cramps, and tension) at the end of the day show absence of reflux in the superficial or deep veins on duplex ultrasound.

In contrast, patients with varicose veins often do not complain about leg pain. It is clear that there is no correlation between the clinical state and the presence of reflux, or between the intensity of the pain and the severity of venous disease.

In practice, while examining patients, I often concentrate on asking them to describe and rate the intensity and the property of pain, and clarify whether their pain is stimulated by physical activities or not. These questions help to differentiate leg pain due to venous disease from leg pain caused by other stimuli, such as arthropathy, nervous pain, etc.

Careful investigation is essential in examining venous disease. Many patients are still diagnosed as having chronic venous disease by general practitioners, even though they do not have chronic varicose veins, and vice versa. For all patients who complain about leg pain, to orientate medical treatment, intervention, or surgical treatment, I always ensure a duplex ultrasound scan is carried out by vascular ultrasound specialists. I believe the quality of evaluation of treatment results depends on numerous criteria:

◆ For young women with high esthetic requirements, it is important to provide a treatment that improves the esthetics of the legs.
◆ For the vast majority of patients, the absence of leg pain, which thus enables them to enjoy daily life without the feeling of heaviness or cramps at the end of the day, is the best treatment outcome.
◆ For patients with varicose veins treated with radiofrequency or laser, the good treatment outcome is no reperfusion or reflux in the treated veins.

However, in clinical practice there are many patients who, after being treated by a cardiovascular intervention or surgery, still complain of leg pain, despite the absence of clinical signs or duplex ultrasound results of varicose. These patients still need to continue using venotonic drugs, because the mechanism of venous pain is complex. Studies on the mechanism of skin pain have clearly shown that inflammatory mediators may activate nociceptors in the skin. Among the peripheral mediators involved, protons, bradykinin, serotonin, prostaglandins, and leukotrienes appear to be the most potent activators of cutaneous nociceptors. Other substances, such as platelet-activating factor, histamine (pruriginous at low concentration, painful at high concentration), certain interleukins, and neuromediators also play a major role in the activation of cutaneous nociceptors. These data on cutaneous nociceptors have led to several studies of the neuromediators involved in the activation of venous and perivenous nociceptors in human subjects. Study of the painful feeling induced by bradykinin’s intravenous or perivenous application unambiguously shows that bradykinin is involved in the generation of venous pain. In view of this response to chemical stimulation, venous nociceptors can be considered to be chemoreceptors.
Chronic venous disease (CVD) is often accompanied by "venous pain," which is a consequence of the over-pressure in microcirculation. Current hypotheses on pain mechanisms in venous disease are focused on a local inflammatory origin related to venous stasis, and on a local activation of nociceptors in the microcirculation, where contact between nerve endings and the capillary is probably much closer than on the macrovascular level. The diminution of pain in the advanced stages of venous disease may be related to peripheral sensory neuropathy induced by venous microangiopathy.

The chief complaint of pain has a significant impact on patients' quality of life. However, pain is difficult to assess, both because of its multifaceted nature and because of the lack of a precise correlation between pain as a symptom and severity of venous disease. There are at least three other reasons.

First, pain of venous origin is frequently associated with other unpleasant sensations such as heaviness, cramps, tension in the legs, or pruritus. It is also often difficult to describe. Second, the intensity of pain can fluctuate substantially, both from patient to patient or in the same patient with progression of the disease over a period of time. Lastly, although the neurophysiological mechanisms of pain of venous origin are better understood, and some biochemical and cellular processes involved in varicose vein remodeling have been explained by recent studies, the causal relationship between CVD and pain of venous origin remains difficult to understand.

Many scoring systems for evaluation of the severity of CVD have been developed. Although these systems are used especially in clinical studies (eg, Chronic Venous Insufficiency quality of life Questionnaire [CIVIQ]), they are too complicated for everyday practice. Instead of these complicated sets of questionnaires, a much more helpful tool is a set of simple questions allowing physicians to conclude whether the patient really suffers from venous hypertension.

Examples of these questions are as follows: Is it more comfortable to have your legs up or down? Do you have more pain in your legs early in the morning or later in the afternoon? Do you have problems while walking?

The evaluation of these answers is much more important for the decision of whether to treat CVD than the extent of the disease determined by physical or ultrasound examination. Once physicians come to the conclusion that the problem could be venous hypertension, then therapeutic testing with a potent venoactive drug, such as micronized purified flavonoid fraction can be done. The relief of pain is the best proof of hitting the target.

In conclusion, there is a huge discrepancy between the severity of pain in venous disease based on clinical findings and the degree of pain reported by patients. This discrepancy complicates the objective evaluation of the result of therapies in venous disease. The evaluation of leg pain requires a proper history and physical examination, as well as neurologic evaluation in some cases. Vascular evaluation should include general screening with noninvasive vascular studies. The localized release of proinflammatory mediators seems to play a decisive role in the activation of venous and perivenous nociceptors and may account for the occurrence of pain at early stages of venous disease.
Chronic venous disease (CVD) is one of the most widespread conditions afflicting a great part of the world’s population. The exact prevalence of CVD is difficult to determine because there is a wide variation in study population, selection criteria, and disease definition between different studies. Generally, symptoms ascribed to CVD are: heaviness, cramps, aching, itching, feeling of swelling, tinging, etc.

Pain is the most frequent reason for medical evaluation by patients with CVD, and generally is the complaint that leads to the diagnosis of venous disease. Quality of life (QoL) of patients with CVD is greatly affected, especially by pain. However, pain in CVD is very difficult to understand. Indeed, epidemiological studies have established that the presence and intensity of leg symptoms related to CVD, are not correlated with the clinical assessment of severity disease. Bradbury et al showed in the Edinburgh Vein Study that about 40% of asymptomatic patients had varicose veins on clinical examination and 45% of the patients complaining of leg pain compatible with CVD had no varicose veins on examination. Moreover, no correlation was observed between the presence of pain and the observation by Doppler ultrasound of superficial or deep venous reflux. Also, many patients complain of pain at an early stage of venous disease, when they also have a normal clinical and Doppler examination. Howlader and Smith reported no statistical relation between the pain score or heaviness score of a patient, evaluated with a 10-point visual analogue scale, and the clinical severity of venous disease.

Pain of venous origin is often associated with other disagreeable sensations that are very difficult to describe (tension in the leg, pruritus, feeling of heaviness). Pain in venous disease may vary over time in intensity, within the same patients. Generally in clinical practice, physicians tend to underestimate the intensity of pain in venous disease, especially when it is chronic, poorly defined, poorly located, and when underlying mechanisms are not clearly identified. Moreover, clinical, etiological, anatomical, pathophysiological (CEAP) classification and the Venous Clinical Severity Score (VCSS) underestimate pain. The CEAP classification only differentiates between symptomatic or asymptomatic patients, and VCSS defines venous pain in a generic way. For these reasons, there is a growing interest in patient-reported outcomes (PROs), which are considered to be key outcomes that cover several aspects: preference of care received, outcome of care (health-related QoL, patient satisfaction, subjective symptoms), and allows monitoring of pain and the progression of the disease. The use of QoL questionnaires in patients suffering from CVD can provide relevant and more complete information, also in relation to psychology, social aspects, and pain.

Interesting neurophysiological mechanisms of pain in CVD, and some biochemical and cellular process involved in pain and vein remodeling have been explained. The strong trigger for these mechanisms is local hypoxia caused by venous stasis. The hypoxia activates endothelial cells resulting in the synthesis and local release of mediators that modulate pain (activation of venous and perivenous nociceptors) and are pro-inflammatory. Over time, this process also leads to venous remodeling characterized by cellular and matrix alterations resulting in loss of structural integrity of the vein wall and its elastic properties. Activation of venous and perivenous nociceptors plays a relevant role in determining pain, even in the early stage of disease.

In clinical practice, we consider it very important to focus on venous pain during evaluation of the patient, at initial evaluation and on follow-up. For this reason, we systematically perform a QoL questionnaire and visual analogue scale for pain. With a complaint of severe venous pain, we perform a thorough clinical and haemodynamic evaluation, and try to exclude other causes. After venous treatment, we consider relevant outcomes, correction of haemodynamic alterations, and absence of pain, rather than disappearance of visible signs. If the patient continues to complain of leg pain despite satisfactory treatment (clinical and ultrasound results), we re-evaluate for other possible causes, and review pharmacological therapy, taking into account drugs with proven efficacy against venous pain.

References
Is low er-lim b pain reduction a m eaningful treatm ent outcome?

Pain!! Is it some sort of punishm ent from G od, is it an evil spirit intruding the body, is it a gift from The Lord to be able to recognize that there is something going wrong, or is it due to chemical mediators and noxious stimuli either from within or from outside the body? All these questions have mystified scientists and philosophers over the ages; each tries to explain pain according to his own point of view.

So, what is pain? Pain—as we all know—is that unpleasant sensory and/or emotional feeling caused by an underlying pathology. Pain can be acute or chronic according to the duration of suffering. It varies in severity from mild discomfort that may affect the patient’s quality of life, to severe pain that significantly affects normal daily activity and disturbs sleep. The lower limb is the most common site to experience tiredness and pain. It is the price paid for the upright position of mankind. Venous pathology, as a cause for pain, is considered the most common factor resulting in muscle fatigue and venous congestion after standing idle for a long time.

It is not surprising that pain is the most common complaint of patients and the most common reason to seek medical advice. Pain is ranked first in vascular complaints. It may precede cosmetic concern. In my opinion, vascular surgeons must focus on the analysis of pain to probe the real cause of pain and to exclude other causes that mimic venous pain.

It is strange to find that different sophisticated scoring systems for venous disease, such as the clinical, etiological, anatomical, pathophysiological (CEAP) classification and the Venous Clinical Severity Score (VCSS), do not address pain as a main component. They just consider whether pain or discomfort is present, regardless of its severity.

It is not uncommon to find patients with remarkable venous problems free from pain or discomfort, meanwhile patients with mild pathology may have pain out of proportion to their problem. It is essential to investigate the depth of the condition to find out the actual cause of pain. The most important issue is to handle the patient’s complaints in view of the presented pathology, considering that the most important outcome is to alleviate pain. It is not worth removing dilated veins or alleviating venous reflux while the patient is still suffering. Answering a patient’s question of “How can I reduce my leg pain?” by an answer such as “You have had your veins ablated and are free from varicosities, so there is nothing else that can be done—you have to live with it,” is very frustrating and disappointing. The patient will certainly wonder why he has had all these tedious and expensive investigations and procedures.

A large number of patients go to work in spite of the presence of pain. This may be attributed to the difference between populations with regards to pain threshold. The financial aspect also plays an important role as many individuals are breadwinners for their families.

In conclusion, pain relief must be considered as a human right for every patient to end his suffering and improve quality of life. Physicians and medical personnel must consider pain alleviation as the main target that must be achieved while simultaneously treating the causative factor.
The incidence and prevalence of chronic venous disease (CVD) varies widely depending on the definition of disease and studied geographic area. In Thailand, the incidence and prevalence have not yet been established. CVD is a common problem in our vascular clinic, at Siriraj Hospital, Mahidol University, and the patients who visit our clinic have varied clinical manifestations. Common clinical manifestations are limb swelling, pain, varicose veins, dermatitis, and venous ulcers. Leg pain in venous patients can be due to venous or other causes. Other causes may coexist, such as arthritis, neuropathy, claudication, and spinal stenosis. In these patients, it is important to determine the likelihood that leg pain is related to venous insufficiency, to enable appropriate venous management.

For venous patients suffering from leg pain, a physician needs to study the details of their history and physical examination to identify the cause. Onset, duration, characteristic of pain, aggravating and releasing factors, and associated symptoms—all these details of leg pain usually point to the etiology. In the case of patients where the etiology is not evident from history and examination, investigations need to be done, especially in patients with severe venous pain.

Venous physiological tests are very useful for chronic venous insufficiency. Photoplethysmography can demonstrate the presence or absence of venous insufficiency. Air plethysmography can not only identify venous insufficiency, but also demonstrates severity of venous insufficiency and the outcome of venous treatment. Duplex ultrasonography is necessary to identify the cause of venous insufficiency such as deep vein thrombosis (DVT), the site of reflux, evaluate the deep and perforator systems, and guide intervention. It is necessary to promptly identify the cause of severe venous pain, as it may be due to deep vein occlusion or a complication of primary CVD and can disturb daily activities.

When patients with CVD are diagnosed, they can undergo treatment. At present, venous treatment can be categorized into conventional and endovenous treatment for superficial and deep venous systems. The outcomes after venous treatment depend on the patient’s symptoms and concerns. These include leg swelling, leg pain, visible varicose vein, hyperpigmentation, dermatitis, and leg ulcers. The disappearance or improvement of visible signs on the leg and of leg pain are satisfactory outcomes for the patients. Even though the improvement of the patient’s symptoms and concerns can be demonstrated, some patients still have reflux in the affected vein. Conversely, some patients show absent reflux in the affected vein, but still have the symptoms.

I consider that symptoms, concerns, and venous hemodynamics make patients visit the clinic. In my opinion, the patients’ symptoms and concerns are more important than the absence of reflux in the affected vein. In patients whose clinical and duplex ultrasound results are satisfactory, but who still continue to complain about leg pain, I explain and discuss the possible causes of leg pain, and give recommendations about avoiding or reducing activity that increases venous stasis and pressure. I also advise regular calf muscle exercises. Occasionally, these patients need muscle relaxants, painkillers, and venoactive drugs. In my practice, leg pain may improve or disappear in patients who receive treatment. Lower-limb pain in venous patients can limit their activity and work. Identifying the cause of pain and managing appropriately could bring about good outcomes. However, pathogenesis of pain in venous disease is still not clearly understood.
Despite recent advances in pathophysiology and mechanisms involved in the clinical expression of chronic venous disorders, scientific understanding is still disappointing. Such deficiency becomes even more expressive in daily practice, where we are currently challenged with diverse clinical presentations. Many patients present with a typical history and symptoms, but without any objective signs of chronic venous disorders. On the other hand, some present with varicose veins and venous hypertension stigma without any clinical complaints.

Leg pain is probably the earliest symptom of chronic venous disorders. Although many patients with venous disease do not complain of leg pain, several epidemiological studies indicate that it is a very common symptom, even in the early stages of the clinical, etiological, anatomical, pathophysiological (CEAP) classification. It seems intuitive to associate the degree of the inflammatory process associated to chronic venous disorders to the intensity of pain in these patients, since pain is a common symptom associated with inflammation in other medical conditions. However, recent studies failed to show a clear correlation between pain intensity and venous disease severity.

The concept of pain relates to an unpleasant sensory and emotional experience associated with actual or potential damage. Several aspects are involved in the expression and modulation of pain, which attributes great subjectivity and individuality to this sensation. However, this symptom has a direct impact on perceived quality of life among these patients, and this is an important issue that should be considered. Lack of specificity means that venous pain is underestimated by many physicians, and the eventual absence of a clear anatomical substrate leads to the neglect of diagnostic investigations or even disregard of the possibility of treating these individuals. Certainly, chronic venous disorders have multifactorial caus-
es that vary from one individual to another, but a significant group of patients slowly evolve a vicious cycle fueled by the inflammatory cascade that gradually promotes remodeling of macro- and microcirculation, worsening the consequences of stasis and venous hypertension.

We believe that venous pain is the first clinical evidence of this inflammatory process. Therefore, the most effective way to approach chronic venous disorders seems to be the early identification and management of this inflammatory cascade. Any patient with typical venous disease complaints associated with a prolonged orthostatic position such as itching, burning or swelling should be investigated for chronic venous disorders. Patients with typical venous pain should have a duplex scan study searching for venous truncal reflux, insufficient tributaries, and perforating veins in the lower limbs.

In addition, leg pain should be considered a therapeutic target for chronic venous disorder treatment and we believe that the disappearance of pain should be a good and interesting parameter to evaluate therapeutic success, as we recurrently see, for example, patients presenting with painful venous ulcers that improve after a session of foam sclerotherapy or saphenous thermal ablation procedure.

It is possible that in a few years we will understand more about the natural history and evolution of chronic venous disorder patients. Meanwhile, it seems reasonable to use clinical parameters such as pain as a therapeutic premise and as a clinical reference of an ongoing inflammatory process that may extend over a long period of time, if not treated.

References
This topic has been of interest to me for many years and it is a great idea to raise it in discussion among specialists in venous diseases. In thinking about what is a meaningful outcome in chronic venous disease (CVD), I prefer not to refer to reflux at all, as reflux is not a disease, but only a hemodynamic phenomenon that is quite often not correlated with the presence and severity of symptoms and signs.

So, the dynamic of symptoms and signs is my choice in estimating treatment efficacy. In my point of view, venous pain is absolutely a meaningful outcome. It should be taken into account in any case of CVD, regardless of whether or not the patient has it at the time of consultation, because lack of pain today does not mean lack of pain tomorrow. Wide acceptance of this symptom as a useful tool in clinical practice or even in clinical trials faces many challenges.

The most important is the precise definition and description of venous pain. Every patient with CVD that I see in clinic is asked about symptoms; nearly four out of five are symptomatic. Most patients with venous symptoms say that they have leg pain.

However, when asked in detail, they frequently say that this symptom is not exactly pain. They describe it as a complex sensation consisting of a mix of symptoms such as discomfort, heaviness, tiredness, etc. This is not only my observation, but that of my colleagues too. Maybe the problem is discrepancy in interpretation of the pain in different languages. If it is, the commonly accepted definition of venous pain may need validation in different countries, as by the example of quality of life (QoL) questionnaires.

The next problem is the choice of patients for whom pain would be a valuable outcome. Some, especially young patients with both venous pain and cosmetic complaints, look above all for the disappearance of visible signs. For senior patients, cosmetic results are usually less meaningful and we have to concentrate upon eliminating symptoms rather than signs. Therefore, using the same main clinical outcome in different groups of patients seems to be really controversial.

Rarely, venous pain can be severe. On the one hand, this helps in differential diagnostics—if a patient has severe lower-limb pain we should suspect an alternative origin rather than venous. As a result, we have to make further diagnostic steps to exclude other pathology. On the other hand, if the pain is really venous, it barely exceeds 4 cm to 5 cm on a visual analog scale (VAS) and the next question arises—how can we estimate a positive impact of our treatment with such a tool? Of course, if pain completely disappears after treatment, the result is undeniably positive. But if we only see the regression of pain, what should be considered as a success? Is 2 cm of pain significantly better than 3 cm on the VAS? Other aspects that are not usually taken into account are the frequency of pain and its duration. One patient may have 4 cm of pain on a VAS, but it appears once or twice a week, while another patient may have 2 cm of pain daily. In some patients, 4 cm of pain starts after several hours of orthostasis, while others experience such a pain only at the end of the day. Of course, there are QoL instruments we now use, but they are not venous pain specific.

It seems that the development of a complex tool for the measurement and estimation of venous pain would be of great value for both investigators and practitioners.
Use of international guidelines for disease description and measurement of treatment outcomes is the first step in the process of implementing evidence-based care. The aim of this review article is to address some of the new guidelines that include drug management of chronic venous disorders. A review of the accepted definitions in the disease field, standardized nomenclature, patient presentation, severity of venous disease, and validated outcome measures following therapy are presented. Also, the prevalence, burden, and pathophysiological underpinnings of chronic venous disorders, and the classification of the most prescribed venoactive drugs are broached in the present article. It appears that venous hypertension underlies all clinical manifestations of the disease. Inflammation is key in wall remodeling, valve failure, and subsequent venous hypertension, which is transmitted to the microcirculation. This results in capillary alteration leading to edema, skin changes, and eventually venous ulceration. Venous symptoms may be the result of interplays between proinflammatory mediators and nerve fibers located in the periphery of capillaries. Therefore, venous inflammation constitutes a therapeutic target for pharmacological intervention, more particularly for venoactive drugs. A discussion of recent guidelines that have evaluated the benefits of venoactive drugs (reviews, book chapters, and international guidelines on the management of chronic venous disorders) follows. Based on recent studies, reviews, and meta-analyses, a strong recommendation was given to micronized purified flavonoid fraction (Daflon 500 mg). The conclusion looks at what remains to be done in order to update guidelines on the management of chronic venous disorders with venoactive drugs, with particular emphasis on the need for larger and more definitive clinical trials to improve the existing recommendations.

Medicographia. 2015;37:71-79 (see French abstract on page 79)

**Introduction**

This article addresses some of the newer guidelines on venoactive drugs (VADs) in general, and Daflon 500 mg in particular, in the management of chronic venous disorders, to help clinicians better manage patients with venous disorders of the lower extremity.

Intentionally, only the primary disease will be tackled in this review, putting post-thrombotic venous disease aside.
A common language is needed before building guidelines in chronic venous disorders

It should first be stressed that no consensus on guidelines is possible without the use of a common language. A leap forward was recently made thanks to: (i) a common terminology on venous anatomy,1 the clinical, etiological, anatomical, pathophysiological (CEAP) classification proposed by the ad hoc committee of the American Venous Forum in 1994 and revised in 2004,2 which was subsequently adopted worldwide as a basis for improved patient description; and (ii) a consensus on terminology related to chronic venous disorders to avoid misunderstanding and lack of precision in publications. The last consensus document (VEIN Term) provides the definition of 33 widely used clinical venous terms and was published in The Journal of Vascular Surgery, 2009, under the aegis of the main American and European scientific societies (American Venous Forum, American College of Phlebology, European Venous Forum, Union Internationale de Phlébologie [UIP; International Union of Phlebology], International Union of Angiology, and Society for Vascular Surgery).³

The CEAP classification includes a clinical assessment (C), an etiological assessment of the patient’s disease (E), an anatomical assessment of location of the pathology (A), and the pathophysiological basis for the underlying disease (P). It provides a broad-based, objective, anatomic, and physiologic basis for classification of venous disease. This is why CEAP has improved standardization, communication, decision making, and reporting of venous disease.

What does the term “chronic venous disorders” cover?

The term “chronic venous disorders” covers a full spectrum of venous conditions ranging from patients with symptoms only (C₀) of the CEAP classification) and telangiectasias to the ultimate complications, venous ulcers. Symptoms are commonly associated with signs of chronic venous disorders. Venous symptoms are defined as tingling, aching, burning, pain, muscle cramps, swelling, sensations of throbbing or heaviness, itching skin, restless legs, leg tiredness and/or fatigue, all of which may be exacerbated during the course of the day or by heat, but relieved with leg rest, elevation, or both.² Venous signs are visible manifestations of chronic venous disorders, which include dilated veins (telangiectasias, reticular veins, varicose veins), leg edema, skin changes, and ulcers, as described in the CEAP classification.²

Chronic venous disorders include those patients with symptoms only, but presenting no signs at clinical examination or ultrasound investigation (the so-called C₀ patients), and those with venous signs as described in the CEAP classification. The latter may be either symptomatic or asymptomatic.

The burden of chronic venous disorders

Chronic venous disorders are common conditions in Western countries that have a significant impact on affected individuals and the health care system. In the French survey by Carpenter et al.,⁴ the percentage of symptomatic patients with chronic venous disease (CVD) varied between 25% and 84%, depending on the severity of the disease (the magnitude of symptoms increased with severity). According to population-based epidemiological studies in various countries, telangiectasias and reticular veins are present in approximately 80% of men and 85% of women, and varicose veins in 25% to 32% of women and 7% to 40% of men. The prevalence of open plus healed venous ulceration is estimated at approximately 1% of the population.⁵

In the recent Vein Consult Program initiated with the UIP, which surveyed 91 545 subjects of 20 countries worldwide, the prevalence of chronic venous disorders was 83.6%: 63.9% of the subjects ranging from C₁ to C₃, and 19.7% being C₀ subjects. C₀ patients were more frequent men, whatever the age or geographical zone. C₁ to C₃ appeared to be more frequent among women, whatever the country, but the rate of severe stages (C₄ to C₆) did not differ between men and women.⁶

The high prevalence of varicose veins and the chronicity of leg ulcers mean that CVD has a considerable impact on health care resources. It has been estimated that venous ulcers cause the loss of approximately 2 million working days and incur treatment costs of approximately $3 billion per year in the United States. In European countries, medical care costs associated with the disease have been estimated to account for 1% to 3% of total annual health care budgets.⁷

CVD is associated with a reduced quality of life, particularly in relation to pain, physical function, and mobility. It is also associated with depression and social isolation. The impairment associated with venous leg ulcers, the most severe manifestation of CVD, has been likened to the impairment associated with stage II to III of heart failure.⁸

The main categories of vеноactive drugs

VADs, also known as phlebotonic agents, are often used to treat chronic venous disorders. Main classes of VADs include coumarin, flavonoids, saponins, and synthetic products (calcium dobesilate, benzaron, and naftazon). On the basis of randomized controlled trials (RCTs) and meta-analyses, previous guidelines concluded that VADs should be used as an adjunct treatment for symptomatic C₀ to C₆ chronic venous

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**Selected Abbreviations and Acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEAP</td>
<td>clinical, etiological, anatomical, pathophysiological</td>
</tr>
<tr>
<td>CVD</td>
<td>chronic venous disease</td>
</tr>
<tr>
<td>UIP</td>
<td>Union Internationale de Phlébologie (International Union of Phlebology)</td>
</tr>
<tr>
<td>VAD</td>
<td>vеноactive drug</td>
</tr>
</tbody>
</table>
disorders except in specific situations, such as hot climates, where they may be used in place of compression. Flavonoids are VADs of particular interest in the treatment of chronic venous disorders. Flavonoids were initially described as "vitamin P" (for permeability) because their deficiency causes capillary fragility and increases vessel wall permeability. Flavonoids are naturally occurring polyphenolic compounds widely found in nature, especially as plant pigments. Main classes include flavones, flavonols, flavanes, flavanones, anthocyanadins, isoflavonoids, and neo flavonoids. Flavonoid products used for the treatment of chronic venous disorders include micronized purified flavonoid fraction (MPFF), oxerutin, and O-(β-hydroxyethyl) rutosides (Table I).

MPFF contains purified flavonoids, mostly hesperidin and diosmin, from Rutaceae aurantiae (orange) micronized into 2 mm particles to help improve intestinal absorption. Oxerutin and O-(β-hydroxyethyl) rutosides are derived by hydroxyethylation of rutin, a naturally occurring glycoside of quercetin and the disaccharide rutinose. Red vine leaf extract is a preparation made from the leaves of wine grape (Vitis vinifera) containing the flavonols quercetin glucoside, quercetin glucuronides, and kaempferol glucoside. Pycnogenol is an extract of maritime pine bark containing proanthocyanidins, which are polymers of flavonoids.

Pathophysiological mechanisms and pharmacological treatment of chronic venous disorders

◆ Valve and vein wall changes

Results from studies that demonstrate treatment efficacy lead to guideline recommendations. Ambulatory venous hypertension is the hemodynamic disease that is related to all symptoms and signs of chronic venous disorders, the underlying components of venous hypertension mainly being failure of the calf muscle pump, venous valvular incompetence, and luminal obstruction. Venous hypertension is the underlying cause of chronic venous disorders and lies in the complex cellular and molecular processes set in motion by abnormal venous hemodynamics. When venous pressures in the leg reach higher-than-normal levels and remain elevated for prolonged periods, a progressive increase in skin damage occurs. Nicolaides reported that nearly all patients with exercising venous pressures of >90 mm Hg experienced venous ulceration. Primary chronic venous disorders are the result of increased and unabated venous hypertension caused mostly by reflux through incompetent valves. To be efficient, any treatment should prevent or decrease superficial valve incompetency in order to counteract venous hypertension. It is only recently that research interest has focused on the action of VADs on chronic inflammatory processes that can affect large and small venous vessels and valves of the superficial venous system.

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug</th>
<th>Venous tone</th>
<th>Venous wall and valve</th>
<th>Capillary leakage</th>
<th>Lymphatic drainage</th>
<th>Hemorheological disorders</th>
<th>Free radical scavengers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flavonoids (flavons, flavonols, flavanons)</td>
<td>Micronised purified flavonoid fraction</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Nonmicronised or synthetic diosmins*</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rutin and rutosides, O-(β-hydroxyethyl) rutosides (troxerutin)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>Anthocyanins</td>
<td>Vitis vinifera extracts*</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Proanthocyanidins</td>
<td>Vitis vinifera extracts, grape seed extracts</td>
<td>+</td>
<td></td>
<td></td>
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<td>+</td>
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<tr>
<td>Coumarin</td>
<td>Melilotus officinalis</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
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<tr>
<td>Saponins</td>
<td>Horse chestnut seed extract, escin</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
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<tr>
<td></td>
<td>Ruscus extract</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Other plant extracts</td>
<td>Gingko extracts*</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic products</td>
<td>Calcium dobesilate</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Benzarone*</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Naftazon*</td>
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Table I. Evidence-based modes of action of the main venoactive drugs.*No data available. Data from references 5 and 10.
Evidence has accumulated over the past years showing that inflammation could be key in wall remodeling, valve failure, and subsequent venous hypertension. Various types of inflammatory mediators and growth factors are released (Figure 1), including vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), transforming growth factor β1 (TGF-β1), fibroblast growth factor β1 (FGF-β1), and vascular endothelial growth factor (VEGF). The inflammatory cascades in the vein wall and venous valves can cause progressive valvular incompetence and eventual valvular destruction. Once initiated, venous valve damage will be self-reinforcing, exacerbating venous hypertension and disturbance of venous flow, and causing further inflammation. As a result, reflux appears and may occur in the superficial or deep venous system or in both.

Flavonoids are known to have potent antioxidant properties that have been investigated in several therapeutic areas other than CVD, including cancer, arthritis, and cardiovascular disease. More specifically, the VADs MPFF and rutosides have shown powerful free-radical scavenging properties in various assay systems, and VADs from other groups have also shown similar properties, including escins, proanthocyanidines from grape seeds and French maritime pine bark, and calcium dobesilate.

In addition to actions that reduce oxidative stress, several VADs also act at various points in inflammatory cascades. As examples, grape seed proanthocyanidin reduced expression of cell adhesion molecules by activated cultured vein endothelial cells, and MPFF decreased expression of adhesion molecules by neutrophils and monocytes in patients with chronic venous disorders.

**Capillary alteration**

Venous hypertension increases hydrostatic pressure in capillaries resulting in transcapsillary filtration that exceeds lymphatic flow. This contributes to the formation of interstitial edema. Venous hypertension alters blood flow in capillaries, prompting leukocyte adhesion to capillary endothelium and initiating an inflammatory reaction. The capillary gaps would become very large, greatly raising capillary permeability to fluid, macromolecules, and extravasated red blood cells, resulting in their flow into the interstitial space and in edema formation (Figure 2).

Fragmentation and destruction of lymphatic vessels may further impair drainage from the extremity, whereas dysfunction of local nerve fibers may alter regulatory mechanisms. Given their antioxidant and anti-inflammatory effects, it is not surprising that many of the major VADs have been shown to reduce capillary hyperpermeability, including MPFF, rutosides, escin, *Ruscus* extract, grape seed extract, and calcium dobesilate.

**Skin changes and venous ulceration**

Several mechanisms for the development of venous ulceration have been postulated, of which the theory of "leucocyte trapping" is the most likely, although challenged today. It is hypothesised that the primary injury to the skin (which is the final target of chronic venous hypertension) is extravasation of macromolecules, such as fibrinogen and α-macroglobulin.
and red blood cells into the dermal interstitium. Red blood cell degradation products and extravasated interstitial protein are potent chemoattractants and presumably generate the initial inflammatory signal, which results in leukocyte recruitment and migration into the dermis. Pathologic events occur during leucocyte migration into the dermis and the end product of these is dermal fibrosis. A cascade of inflammatory events results in cutaneous changes, which include skin hyperpigmentation caused by hemosiderin deposition and eczematous dermatitis. Fibrosis may develop in the dermis and subcutaneous tissue (lipodermatosclerosis).

Interest in the mechanisms underlying skin changes has received new impetus with the increasing recognition of the importance of venous valves in small veins and venules. It is now appreciated that small superficial veins of the human lower limb contain abundant, typical bicuspid venous valves, with the majority occurring in vessels less than 100 μm in diameter and present in vessels as small as 18 μm. A recent study has shown that incompetence can occur in human small superficial venous valves independently of reflux within the great saphenous vein and major tributaries. Importantly, degenerative changes and incompetence in these microvenous valves...

<table>
<thead>
<tr>
<th>Pharmacodynamic effects</th>
<th>Clinical consequences</th>
</tr>
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</table>
| **MPFF preserves valves structure** | • Reduces the number of activated leukocytes in venous valves in an animal model of arteriovenous fistula (AVF).  
• Maintains the valve diameter in an AVF model.  
• Reduces reflux rate in an AVF model.  
• Prolongs the vasoconstrictor effect of noradrenaline (norepinephrine) on the vessel wall, reduces gap between valve leaflets, and reduces blood venous stasis in vitro.  
• Increases mechanical tension on bovine metacarpal vein rings in vitro. |
| **MPFF protects microcirculation** | • Struggles against superficial venous hypertension and might hamper disease progression.  
• Compared with control, improves postoperative pain and quality of life of C2 patients having undergone stripping surgery. |
| **MPFF increases lymphatic drainage** | • As adjunctive treatment to compression therapy, accelerates ulcer healing by 32% and shortens time to healing by 5 weeks in C6 patients.  
• Shows at least a 25% better decrease of ankle edema compared with Ruscus extract, hydroxyethylrutoside, or diosmin in C6 patients.  
• Reduces edema by half a liter by lower limb in C2 patients.  
• Reduces hematomas by 30% compared with controls in C2 patients after stripping surgery. |
| **MPFF has potent venous anti-inflammatory effects** | • Significantly ameliorates skin hardness and heaviness of upper limbs at 6 months of treatment in patients with lymphedema.  
• Significantly decreases upper-limb circumference at 6 months of treatment in patients with lymphedema.  
• Improves symptoms in patients with filariasis. |

Table II. Overview of the pharmacodynamics and clinical properties of micronized purified flavonoid fraction (MPFF).

Data from references 12, 15, 17, and 20.
can allow reflux into the microvenous networks in the skin, which may be critical in the development of severe skin changes in chronic venous disorders.\textsuperscript{18}

The ability of VADs to reduce inflammation and oxidative stress could protect small venous valves and prevent reflux, and also act at the level of preventing the adverse remodeling of skin tissue that ultimately may lead to the development of active ulcers in chronic venous disorders.

\textbf{Symptoms and the role of C nociceptors}

Typical leg symptoms of chronic venous disorders are common in those with even the least severe forms (CEAP C\textsubscript{0k} and C\textsubscript{1}). In a recent report from the Vein Consult Program, a large cohort of over 90,000 consecutive outpatients from 20 countries, who were consulting their general practitioner for any reason, were screened for chronic venous disorders. Of these, 19.7\% had typical chronic venous disorder leg symptoms without signs and were assigned to CEAP class C\textsubscript{0k}, and a further 21.7\% were assigned to class C\textsubscript{1}.\textsuperscript{6} The exact mechanisms by which chronic venous disorders, particularly the earliest stages, give rise to pain and other typical venous symptoms are not yet understood, but recent studies suggest inflammation plays a key role.\textsuperscript{19,20} Sympathetic C fibers are found in the venous intima and media, and wrapped around cutaneous venules, and act as nociceptors that can respond to inflammatory mediators.

Inflammatory processes seem to be involved in all stages and severities of chronic venous disorders, even before obvious tissue damage has occurred, and could be responsible for many of the symptoms experienced. Thus, the anti-inflammatory properties of VADs have the potential to improve symptoms in patients at all stages of the disease, including those in CEAP class C\textsubscript{0k}.

\textbf{Lymphatic drainage}

Lymphatic function is known to be compromised in patients with especially the more advanced stages of chronic venous disorders, and has been shown to improve in patients with varicose veins after reduction of venous reflux by saphenous vein ablation.\textsuperscript{21} Several VADs, including alpha-benzopyrones (coumarin) either alone or combined with rutin,\textsuperscript{22,23} MPFF,\textsuperscript{24} and calcium dobesilate\textsuperscript{25} have all been shown to improve lymphatic drainage in animal models.

\textbf{Hemorheological disorders}

Hemorheological changes, including increased blood viscosity and erythrocyte aggregation, are common in chronic venous disorders. Several VADs have been shown to reduce blood viscosity and/or erythrocyte aggregation, including MPFF,\textsuperscript{26} troxerutin\textsuperscript{27} and calcium dobesilate.\textsuperscript{28} The pharmacological effects of VADs are summarized in Table I.\textsuperscript{5,10} The mode of action more specifically related to MPFF is described in Table II (page 75).\textsuperscript{12,13,17,20}

| Table III. GRADE: a new system to rate the strength of recommendation. |
|-----------------------------|-----------------------------|-----------------------------|
| Grade of recommendation     | 1 = strong                  | Based on the author’s opinion depending on the balance between desirable/undesirable effects, cost of treatment, and patients’ preferences |
| Quality of evidence         | A = high                    | Depending on the methodological quality of supporting evidence |
|                             | B = medium                  | |
|                             | C = low                     | |

A new grading system for recommendations in guidelines

The method of determining the strength and quality of the recommendations in American guidelines deserves mention. Recommendations are generally accompanied by a number, which refers to the strength of the recommendation, and a letter, which refers to the quality of the evidence supporting the recommendation. Recent guidelines for venous disease have used two levels for the strength of their recommendations depending mainly on the benefit/risk ratio: grade 1 for strong and grade 2 for weak. They further indicate that statements accompanied by a grade 1 level are “recommendations” and statements accompanied by a grade 2 level are “suggestions” (Table III).\textsuperscript{23}

The quality of evidence upon which the strength of the recommendation is based ranges from “A” for high quality, which is consistent evidence from randomized trials, to “B” for moderate quality, which is evidence from nonrandomized trials or inconsistent evidence from randomized trials. Level “C” is low quality, which is suggestive evidence from randomized trials, observational reports, or expert opinion. Writing committees are increasingly aware of the cost of care and patient values and preferences, as are physicians. These are also considered in the strength of recommendation.

The recent guidelines on the management of chronic venous disorders

Recent reviews and guidelines on chronic venous disorders have used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (Figure 3):

\begin{itemize}
  \item The article by Perrin et al published in The European Journal of Vascular and Endovascular Surgery, 2011, which reviews the evidence for pharmacological therapies of primary chronic venous disorders together with the rationale for such treatment and the questions that remain unanswered.\textsuperscript{12}
  \item The latest (second) edition of The Vein Book edited by Bergan and Bunke, which covers the entire spectrum of venous conditions from clarification of the pathophysiology of chronic venous disorders, molecular mechanisms in the cause of
\end{itemize}
varicose veins, new treatment options for varicose veins and spider veins, starting new treatment for venous thromboembolic disease, and effective treatment for leg ulcers. 30
◆ The updated recommendations on the management of chronic venous disorders, results of a consensus conference initiated by the European Venous Forum (EVF) and held in 2012 in Cyprus with renown experts. The consensus document was published under the auspices of the EVF; the International Union of Angiology (IUA), the Union Internationale de Phlébologie (UIP; International Union of Phlebology), and the Cardiovascular Disease Educational and Research Trust (CDIRT). 10

In summary and based on the quality of evidence, the authors found it possible to propose a strong recommendation, based on evidence of moderate quality (1B), for the use of MPFF in symptoms and edema. Rutosides, horse chestnut seed extract, and Ruscus extracts have also proven effective against CVD-related symptoms and lower limb edema, although the volume and quality of evidence is less than for the previous drug.

Calcium dobesilate has been associated with a potential safety concern relating to rare cases of agranulocytosis. Authors of guidelines have considered that it is only possible to give a weak recommendation for its use, given the uncertainty over the balance between benefits and harms (2B). There is evidence from a meta-analysis of RCTs that MPFF is effective in the healing of venous ulcers. In the absence of important safety concerns, its use in this indication can be given a strong recommendation for its use in combination with compression in long-standing or large venous ulcers of primary etiology (1B; Table IV, page 78). 10

**Figure 3.** Reviews and guidelines on the management of primary chronic venous disorders that have used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.

Data from references 10, 12, and 30.

**Updating guidelines on chronic venous disorders**

An update of the Guidelines for Testing Drugs for Chronic Venous Insufficiency is needed to allow the pharmaceutical industry investing the necessary resources to perform large and definitive clinical trials that could improve the recommendations, which are useful for clinicians and organizations involved in decision making in this important field of chronic venous disorders. Such guidelines could:

◆ Reiterate the basic principles that should prevail when reporting from (and setting up) any RCT, using the Consolidated Standards of Reporting Trials (CONSORT) statement, as for meta-analyses with the QUORUM checklist.

◆ Comprehensively describe patients at selection in a study,
using the advanced CEAP classification,2 which implies that all classes of the CEAP must be completed, and that duplex scan investigation, with or without plethysmography (level 2 investigation) is mandatory.

◆ Include larger sample sizes (>200 patients in each group), having in mind the high incidence of the placebo effect.12 For instance, the most recent studies on VADs included only between 30 and 125 patients in each group.9

◆ Promote the use of validated tools to assess symptoms, edema, and venous leg ulcers, and have a consensus on end points.33

◆ Encourage the adoption of a simple and universally understood system of grading.39

◆ Perform long-term studies in order to examine the prevention of chronic venous disorder progression and assess the cost-effectiveness of VADs.39

### Table IV. Summary of the updated recommendations for the use of venoactive drugs, according to the GRADE system.

<table>
<thead>
<tr>
<th>Indication</th>
<th>VAD</th>
<th>Recommendation for use</th>
<th>Quality of evidence</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relief of symptoms associated with chronic venous disorders in patients in CEAP classes C0 to C6, and those with CVD-related edema (CEAP class C6).</td>
<td>Micronized purified flavonoid fraction</td>
<td>Strong</td>
<td>Moderate</td>
<td>1B</td>
</tr>
<tr>
<td></td>
<td>Nonmicronized diosmins or synthetic diosmins</td>
<td>Weak</td>
<td>Poor</td>
<td>2C</td>
</tr>
<tr>
<td></td>
<td>O-[(β-hydroxyethyl)] rutosides</td>
<td>Weak</td>
<td>Moderate</td>
<td>2B</td>
</tr>
<tr>
<td></td>
<td>Red vine leaf extracts (Vitis vinifera)</td>
<td>Weak</td>
<td>Moderate</td>
<td>2B</td>
</tr>
<tr>
<td></td>
<td>Calcium docusate</td>
<td>Weak</td>
<td>Moderate</td>
<td>2B</td>
</tr>
<tr>
<td></td>
<td>Horse chestnut seed extract</td>
<td>Weak</td>
<td>Moderate</td>
<td>2B</td>
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<td></td>
<td><em>Ruscus</em> extracts</td>
<td>Weak</td>
<td>Moderate</td>
<td>2B</td>
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<tr>
<td></td>
<td>Gingko biloba</td>
<td>Weak</td>
<td>Poor</td>
<td>2C</td>
</tr>
<tr>
<td></td>
<td>Other venoactive drugs</td>
<td>Weak</td>
<td>Poor</td>
<td>2C</td>
</tr>
<tr>
<td>Healing of primary venous ulcer (CEAP class C6), as an adjunct to compressive and local therapy.</td>
<td>Micronized purified flavonoid fraction</td>
<td>Strong</td>
<td>Moderate</td>
<td>1B</td>
</tr>
</tbody>
</table>

**References**


Keywords: chronic venous disease; chronic venous disorder; edema; guideline; management; micronized purified flavonoid fraction; recommendation; symptom; venoactive drug

PLACE DE DAFLON 500 MG DANS LES RECOMMANDATIONS INTERNATIONALES RÉCENTES POUR LA PRISE EN CHARGE DE LA MALADIE VEINEUSE CHRONIQUE SYMPTOMATIQUE

La première étape dans la mise en œuvre de la médecine basée sur les preuves passe par l’utilisation des recommandations internationales dont le but est d’évaluer les résultats des différentes options thérapeutiques. Le présent article traite des dernières recommandations relatives du traitement de la maladie veineuse chronique. Nous présentons ici les définitions acceptées dans le domaine de la maladie, la nomenclature standardisée, le tableau clinique du patient, la sévérité de la maladie veineuse et les mesures validées de résultats après traitement. L’article aborde aussi la prévalence et le coût de la maladie veineuse chronique, ses fondements physiopathologiques et la classification des phlébotropes les plus prescrits. L’hypertension veineuse apparaît être la base de toutes les manifestations cliniques de la maladie. L’inflammation joue un rôle clé dans le remodelage pariétal, l’insuffisance valvulaire et l’hypertension veineuse qui en résulte et qui est transmise à la microcirculation. Les modifications capillaires qui s’en suivent entraînent un œdème, des modifications cutanées et enfin l’apparition d’ulcères veineux. Les interactions entre médiateurs pro-inflammatoires et fibres nerveuses de la périphérie des capillaires pourraient être à l’origine des symptômes veineux. L’inflammation veineuse est donc une cible thérapeutique, tout particulièrement en ce qui concerne les phlébotropes. Les recommandations récentes ayant évalué le bénéfice des phlébotropes (mises au point, chapitres de livre et recommandations internationales sur la prise en charge des troubles veineux chroniques) sont analysées. Il ressort des études récentes, des mises au point et des métaanalyses que le médicament constitué de la fraction flavonoïque purifiée micronisée (Daflon 500 mg) est celui qui a obtenu la plus forte recommandation. L’article conclut sur ce qu’il reste à faire afin d’actualiser les recommandations sur la prise en charge des troubles veineux chroniques par les phlébotropes, en insistant sur la nécessité d’études cliniques plus importantes et précises pour améliorer les recommandations existantes.
Advances in research have drawn attention to the role of chronic inflammatory processes affecting the valves and walls of veins of all sizes and also in the skin, leading to the development of varicose veins and chronic venous insufficiency. The role of inflammation in the occurrence of venous pain has also been highlighted in recent research and the presence of nociceptors stimulated by inflammatory mediators completes the picture. Investigations into the pathophysiology of chronic venous disease have only focused on the competence of macroscopic valves present in large veins. However, some researchers have recently demonstrated that incompetence of the smaller valves located in the third to sixth generation of tributaries can be involved in the occurrence of chronic venous disease. Small vein incompetence is not necessarily associated with valve incompetence in the main venous trunk, thus justifying the possible occurrence of venous symptoms in patients not affected by varicose veins or axial reflux. Moreover, it is well known that venous symptoms and leg pain are only loosely correlated with alterations in the main venous trunks. Therefore, it can be hypothesized that these symptoms actually stem from incompetence in smaller veins and capillaries.

Why has venous pain been so poorly studied in the literature?

Venous pain is a very common complaint in chronic venous disorders and its chronic nature greatly worsens the quality of life of affected people. Although frequently encountered in daily practice, venous pain is hard to understand. The wording used by patients to describe leg pain is vague and is associated with other unpleasant sensations, such as feelings of swelling, tension, burning, heaviness, and tingling, etc. Venous pain is diffuse, not localized, and more similar to visceral pain. Frequently, the relatively low intensity of venous pain seems to not justify its impact on quality of life, leading to suggestions that venous pain may be more psychogenic than biological in origin. Consequently, venous pain is difficult to define, identify, locate, and quantify. Moreover, the intensity of venous pain is not related to chronic venous disorder severity, so that suffering patients often present with no clinical or pathophysiological anomalies.

When pain occurs in the context of venous disease, such as postthrombotic syndrome or varicose veins, the pain is usually attributed to the disease itself. This is a common attitude, despite the fact that several well conducted epidemiological stud-
ies have shown that the presence and the intensity of pain likely to be related to chronic venous insufficiency are not correlated with the clinical assessment of disease severity. The Edinburgh Vein Study has shown that approximately 40% of asymptomatic patients presented with varicose veins, whereas 45% of patients complaining of pain compatible with chronic venous insufficiency did not present with varicose veins. Moreover, no significant correlation was proven between the presence of pain and the presence of superficial and/or deep reflux detected at Doppler ultrasound examination.

What do we know about the mechanisms at work in venous pain occurrence?

Leg pain is associated with all stages of chronic venous disorders, and has the tendency to increase with severity of disease. However, correlation between pain intensity and severity of venous signs is weak, as is correlation between pain and the presence of inflammatory markers. It is fully accepted that primary chronic venous disorders are caused by the occurrence of venous hypertension determined by reflux through incompetent valves (mostly in superficial veins) and sometimes by primary non-postthrombotic obstruction and reflux in the deep system. Venous hypertension is a key point to help understand alterations in superficial veins, deep veins, capillaries, and eventually skin. There is now a body of evidence showing that all stages of primary chronic venous disorders are linked to inflammatory processes that can affect large and small venous vessels and their valves. In patients affected by varicose veins, superficial valves are incompetent and present a highly remodeled wall. Several studies have found that valve flaps are often infiltrated with inflammatory cells, mainly granulocytes and neutrophils. The trigger event for venous inflammation and the cascade of events that leads to valve degradation and disease progression is not clear. It can be hypothesized that the postural pressure changes that are frequent in daily life might lead to vein distension and valve distortion. This could be the starting mechanism of endothelial and leukocyte activation, and consequently of inflammation. Lifelong repeated inflammatory stresses might lead to valve and wall injuries, thus determining reflux and consequently venous hypertension.

Changes in the hemodynamics of large veins and venous hypertension are transmitted into the microcirculatory level, increasing permeability and leading to the accumulation of fluid, macromolecules, and extravasated red blood cells into the interstitial space. This pathological process results in the production of the interstitial edema. Eventually, the many changes result in the development of venous microangiopathy, which could be due to white blood cell trapping. The last stage in disease progression is venous ulceration.

When and how does pain occur during this timeline? It is well known that the walls of veins contain unmyelinated C fibers that may play a key role in the onset of pain. Experimentally, C fibers are activated by different types of stimuli (mechanical, thermal, or chemical), thus they are polymodal nociceptors. Venous dilatation, even when severe, is not by itself a significant source of pain in normal subjects. This statement is confirmed by the evidence of absence of pain of arteriovenous fistulae created for hemodialysis. A balloon dilatation is felt as being painful when the diameter of veins reaches a value that is three times that of normal. Such a situation is not likely to occur in chronic venous disorders, because vein dilatation is not of this amplitude, even if vein dilatation is real and can be assessed. Painful sensations related to temperature variations have been studied in human hands before and after blockade of venous afferents. Intravenous cooling or warming of a cutaneous vein segment of the hand was able to evoke pain after numbing the skin, thus confirming that the sensory elements of veins are polymodal nociceptors.

In chronic venous disorders, the sensation of heat is one of the many complaints expressed by symptomatic patients. Such a sensation is not related to any nociceptive stimuli. Current hypotheses on pain mechanisms in chronic venous disorders are focused on a local inflammatory origin, related to venous stasis. At the end of the full process, inflammatory mediators released by activated leukocytes are strong stimulators of C nociceptors and partly explain why chronic venous disorders can be painful at all disease stages. Interestingly, the same processes assumed to generate pain in venous disease seem to be involved in the long-term period of varicose vein remodeling, defined as the whole qualitative and quantitative alterations in the cellular and matrix components of the venous wall. The starting point for these mechanisms is probably the local hypoxia associated with capillary stasis. A significant fall in the partial pressure of oxygen after 30 minutes in the standing position has been demonstrated in lower-limb veins in venous disease, and several studies have demonstrated that hypoxia induced by capillary stasis has the effect of activating endothelial cells.

The evidence for an inflammatory reaction playing such a main role in patients with varicose veins has increased dramatically over recent years, and the biochemical changes identified suggest that endothelial cells and neutrophils are the source of this local inflammation. The presence of neutrophils, monocytes, and activated T lymphocytes, the accumulation of macrophages and mast cells, the expression of adhesion molecules on the surface of leukocytes and endothelial cells (lymphocyte function–associated antigen 1 [LFA-1], very late

Selected abbreviations and acronyms

CEAP clinical, etiological, anatomical, pathophysiological
GSV great saphenous vein
MVV microscopic venous valve
antigen 4 [VLA-4], endothelial leukocyte adhesion molecule 1 [ELAM-1], intercellular adhesion molecule 1 [ICAM-1], vascular cell adhesion protein 1 [VCAM-1]), and the synthesis of cytokines (interleukin 1β [IL-1β], IL-6, tumor necrosis factor α [TNFα]) and prothrombotic factors (von Willebrand factor) are all indicators of inflammation in venous disease.

What is the rationale that led to the suggestion that microcirculatory reflux is involved in the occurrence of symptoms?

The fact that venous pain is not closely correlated with the presence of varicose veins or axial reflux/obstruction suggests that the primary activation site of venous and/or perivenous nociceptors may not be in the large venous vessels. In this regard, the hypothesis of local activation of nociceptors in the microcirculation, where contact between nerve endings, the arterioles, the vein, and the capillaries is probably much closer than at the macrovascular level, seems entirely plausible. Moreover, edema stems from capillary leakages and is painful due to the pressure it exerts on nerve endings.

Interest in the mechanisms underlying symptoms and signs of chronic venous disorders has received new impetus with the increasing recognition of the role of venous valves in small veins and venules. It is known that small superficial veins of the human lower limb contain abundant, typical bicuspid venous valves, with the majority occurring in vessels less than 100 µm in diameter and present in vessels as small as 18 µm. Such microscopic valves have also been described in human skin. Their role was believed to resist and prevent blood reflux in small-sized veins, from postcapillary venules to the capillary bed.

A recent study by Vincent et al has confirmed the existence of these microscopic venous valves (MVVs) in the small superficial venous veins of human lower limbs, and has shown that incompetence can occur in the MVVs independent of reflux within the great saphenous vein (GSV) and major tributaries. Reflux in MVVs was associated with tortuosity and distension of varicosities in the skin with a normally functioning GSV.

Using light microscopy in retrograde corrosion casts of legs with venous ulcers, MVVs were found from the GSV through to the sixth-generation tributaries. Indeed, to show reflux from the GSV to the small-vessel networks, the resin has to pass a minimum of three generations of incompetent valves. The last valve generation before resin refluxed into the skin capillary bed was designated as the “boundary valve.” Most of these “boundary valves,” assumed to prevent reflux in the small venous network in the skin, were located in the third generation of tributaries. The authors speculated that skin degenerative changes are worse when refluxes in MVVs from the third generation and in GSV occur together, and this would explain why some patients with longstanding varicose veins develop venous ulcers.

At the other extremity of the clinical, etiological, anatomical, and pathophysiological (CEAP) classification, individuals with lower-limb symptoms without signs, assigned to CEAP class C0s, are frequently encountered in clinical practice. In the population of the Vein Consult Program, 19.7% of screened individuals had typical chronic venous disorder leg symptoms without signs. C0s subjects constitute an excellent population to investigate, since they are purely venous symptomatic.

We hypothesize that incompetence in the MVVs from the third to the sixth generation of tributaries may be responsible for the occurrence of venous symptoms, particularly the early symptoms in the C0s subjects.

What are the current methods used to investigate the microcirculation and what do they assess?

Instrumental investigation of any early chronic venous disorder patients, including C0s subjects, usually performed by duplex ultrasound, often proves negative. In the larger number of cases reflux is not detected, neither in the saphenous veins nor its tributaries. In fact, investigations of pathophysiology of primary chronic venous disorders evaluate only the competence of the macroscopic valves present in large veins, usually the GSV and to a lesser extent, short saphenous vein. Duplex ultrasound investigation is not sensitive enough to detect reflux down to more than one level of tributary generations. It is therefore not known whether C0s subjects present with reflux in the MVVs of the GSV and its subsequent tributaries.

Currently, various methods can be used to explore the microcirculation and its alterations over the course of progression of chronic venous disorders. In my knowledge, none of the current assessment tools have been used with the purpose of finding relationships between the presence of venous symptoms and alterations in the microcirculation.

Regarding the assessment of the microcirculation, the following investigations may be applied:

- Videocapillaroscopy: to visualize capillaries in different cutaneous areas of the lateral and medial aspects of the lower leg and in the foot. Some parameters can be measured, such as the capillary density (number of vessels per mm²) and the capillary loop diameter (µ).
- Laser Doppler: to quantify skin perfusion after standardized maneuvers such as the venoarteriolar reflex.
- Light reflection rheography (LRR) plethysmography (static or dynamic): the probe applied in the same cutaneous areas as those mentioned above evaluates the lower-limb venous function by measuring the refilling time.

INTERVIEW
The assessment of reflux in large veins and first generation of tributaries, usually performed by duplex ultrasound examination, can be integrated by adjunctive ultrasound investigations:

- **B-flow ultrasound**: the evaluation of tributaries until the limit of detection of a superficial probe (7.5 to 10 MHz). Exploration can be performed on the whole lower extremity,

- **Continuous-wave Doppler**: with a flat probe applied on visible tributaries to identify flow direction. Continuous-wave Doppler is able to detect small sites of reflux often missed by duplex ultrasound.

What would be an ideal investigation procedure to assess leg pain in symptomatic patients?

Current methods to assess the microcirculation are not sensitive enough to detect symptomatic subjects such as those in class C0s, since these people probably have subliminal perturbations of the capillary bed.

The orthogonal polarization spectral imaging technique used in the CytoScan® has raised hope to better study patients suffering from chronic venous disorders. The CytoScan® has a small handheld probe which can be noninvasively applied to all body surfaces. Chronic venous disorders were previously studied using the orthogonal polarization spectral technique. Five microcirculatory parameters were correlated with CEAP classification (C0 to C5). Moderate microangiopathy was found among all CEAP classes, and microcirculatory alterations were not assessable before CEAP class C2. No microangiopathy could be found in C0.9

References


Keywords: chronic venous disorder; leg pain; microvalve; reflux; vein incompetence; venous disease; venous valve
Les avancées de la recherche ont attiré l’attention sur le rôle des processus chroniques inflammatoires affectant les valvules et les parois des veines de toute taille et aussi de la peau, entraînant le développement de varices et d’une insuffisance veineuse chronique. La recherche récente a souligné également le rôle de l’inflammation dans la survenue de la douleur veineuse, la présence de nocicepteurs stimulés par des médiateurs inflammatoires complétant le tableau. Les études sur la physiopathologie de la maladie veineuse chronique ne se sont intéressées qu’à la continence des valvules macroscopiques des grosses veines. Des chercheurs ont néanmoins montré récemment que l’incontinence des valvules plus petites, situées au niveau des collatérales de 3e à 6e génération, serait impliquée dans la survenue de la maladie veineuse chronique. L’incontinence des petites veines n’est pas nécessairement associée à une incontinence valvulaire des troncs veineux principaux, ce qui explique l’apparition possible de symptômes veineux chez des patients non variqueux ou sans reflux axial. De plus, il est bien connu que symptômes veineux et douleur de jambes sont plus ou moins corréles aux modifications des principaux troncs veineux. On peut donc supposer que ces symptômes proviennent en fait de l’incontinence des veines plus petites et des capillaires.
Venous symptoms are very frequently mentioned during general practitioner or vascular surgeon consultations. Even so, the amount of research conducted on venous sensations is inversely proportional to the frequency of reported symptoms. Today, there is a lack of epidemiological studies concerning this issue. The Vein Consult Program (VCP) was started with a clear mission, with the aim to raise awareness and to deal with a chronic disease that has reached almost pandemic proportion—chronic venous disease (CVD). The most worrying finding of the VCP is that the majority of subjects with or without any clinical signs of CVD have symptoms that significantly affect their daily activities and deteriorate quality of life. Several factors have been proposed as risk factors for the development of symptomatic CVD: age, body mass index, sex, family history of CVD, history of previous venous thromboembolism, hours spent standing, smoking, and lack of daily exercise. Also, aside from traditional risk factors, several comorbidities such as high blood pressure, diabetes mellitus, heart failure, and chronic obstructive pulmonary disease could have an influence on the development and progression of the symptoms in patients with CVD. Most of these risk factors cannot be changed, but a significant number of them could easily be modified. In this article, we present the latest facts related to venous-related symptoms and risk factors for the development of such symptoms, based on the results of the VCP.

Medicographia. 2015;35:85-91 (see French abstract on page 91)
In this article, we present the latest facts related to venous-related symptoms and risk factors for the development of such symptoms, based on the results of the VCP.

**The prevalence of CVD and lower-limb symptoms before the VCP**

As there is not yet an established relationship between symptoms and signs of CVD, opinions diverge, with some believing that symptoms such as venous pain, cramps, etc., simply do not exist, while others believe that all these symptoms should be treated.

The first step in determining the prevalence of lower-limb symptoms related to CVD should be to exclude all patients with symptoms of nonvenous origin. This approach is more complex, especially in the group of patients without clear signs of CVD, or in patients with early stages of visible disease.

Before the first results of the VCP, the prevalence rate of CVD and venous-related leg symptoms was based mainly on cross-sectional epidemiological studies, which were limited to one region or a single country. Most of the studies have inhomogeneous prevalence rates, due to the different classification systems used. Today, epidemiological surveys have adopted the universal clinical, etiological, anatomical, pathophysiological (CEAP) classification, whose purpose is to achieve a better definition of each disease stage. In addition, by using this classification system it is much easier to assess the respective frequency of each disease stage. The international character of the CEAP classification allows precise comparisons between countries and between continents.

However, through our daily practice we observed a large number of limiting factors in the current classification systems. The CEAP classification does not include any assessment of the level of the pain, with the classes only categorized as “symptomatic” or “asymptomatic.” Due to that, symptoms and their levels are often underestimated by physicians. These limitations require additional questionnaires to incorporate levels of symptoms and their change during the time period. In addition, very few epidemiological studies have actually taken venous symptoms into account.

Both the Italian 24-cities cohort study and the Bonn Vein Study found that patients very frequently reported some venous symptoms (approximately 56% of subjects). However, both studies marked one very worrying finding: the vast majority of subjects with leg symptoms could not be given a medical explanation for their condition (up to 80% in the 24-cities cohort study population). Together, these and results of other studies emphasized a very complex issue of the origin of venous-type leg symptoms, especially in patients without any other clinical signs of CVD (C0) or venous reflux/obstruction.

The VCP was organized within the framework of ordinary consultations, with GPs properly trained in the use of the CEAP classification. First results show that CVD affects a significant part of the population worldwide, highlighting the importance of adequate screening for CVD, and training of both GPs and specialist physicians. The VCP revealed some key facts, as presented in the following text.

**Better identification of subjects who are more likely to present with one or several venous leg symptoms**

CVD could be associated with a wide range of symptoms such as pain, heaviness, restless legs, tingling, aching, burning, night muscle cramps, swelling, sensations of throbbing or itching skin, leg tiredness, and/or fatigue. In addition, these symptoms could be a part of other nonvenous chronic and acute conditions, such as obesity, neurological disease, a standing or sitting profession, or arterial occlusive disease.

Results of the VCP show that venous pain could be found in approximately 70% of adults, where heaviness and pain were the most frequent symptoms, mostly affecting women. Once there are visible signs of CVD (C1 class or higher), associated symptoms can be more easily assigned to a venous cause. The risk of developing symptoms increased significantly with disease severity. Individuals with chronic venous insufficiency, C3 to C6, were 16-fold more likely to be symptomatic than individuals in class C0.

It is rational to believe that symptoms of CVD will correlate with Doppler ultrasound findings. However, Chiesa et al. reported that the occurrence of venous symptoms is independent of venous reflux, but also that symptoms correlated positively in both sexes with the CEAP grade, with the exception of pain (no significant correlation was observed in men). Still, a Serbian group of authors found a significant presence of both reflux and obstruction in VCP patients in classes C0 to C1. These findings could justify recommendations for color duplex ultrasound in all patients with symptoms of CVD, regardless of clinical signs.

Patients with no visible sign of disease, but who are reporting venous-like symptoms, represent a real “nightmare” for both GPs and vascular surgeons. Identification of C0 patients could be crucial from a diagnostic and therapeutic point of view and deserves special attention. Revision of the CEAP

**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEAP</td>
<td>clinical, etiological, anatomical, pathophysiological</td>
</tr>
<tr>
<td>CVD</td>
<td>chronic venous disease</td>
</tr>
<tr>
<td>QoL</td>
<td>quality of life</td>
</tr>
<tr>
<td>VCP</td>
<td>Vein Consult Program</td>
</tr>
</tbody>
</table>
classification brought to the public a new profile of patients; those in the C0s class. For the first time, the results of the VCP\textsuperscript{13} show a global prevalence of C0s patients. Approximately 20\% of patients with CVD are in the C0s class. Also, within the new results from the VCP we expect a detailed clinical profile of patients in the C0s class, including information on the quality of life (QoL) of C0s patients, risk factors, etc.

The question still remains: if there is no clinical evidence and functional sign of CVD, do the subjective symptoms have an objective origin, and if so, are we able to find and treat this origin? Several hypotheses have been proposed. Vincent at al\textsuperscript{18} analyzed valvular competence in amputated legs with functional sign of CVD, do the subjective symptoms have an objective origin, and if so, are we able to find and treat this origin? Several hypotheses have been proposed. Vincent at al\textsuperscript{18} analyzed valvular competence in amputated legs without signs of CVD, or evidence of reflux in the deep and superficial venous system (within the great saphenous vein [GSV]). The authors showed that microvalvular incompetence could exist in the small superficial veins of the leg, independent of incompetence in the GSV or its accessories. These findings raise some additional arguments for ascending incompetence, rather than the traditional descending theory and reflux in the saphenofemoral junction.\textsuperscript{18} Incompetence in the microcirculation along with activation of the inflammatory response and nociceptors could be the very first manifestation of CVD. Identification of these patients seems to be crucial, because not only could we identify patients in the early stage of disease, but we could also start with some of the treatment options.

Van der Velden et al\textsuperscript{19} tried to distinguish which symptoms are specific for CVD. However, their results did not have statistical power due to the low number of patients investigated, and the approach and design of the study. This supports the need for future large multicenter studies.

### Table I. Distribution of the prevalence of chronic venous disease (CVD) symptoms according to clinical, etiological, anatomical, pathophysiological (CEAP) class.

<table>
<thead>
<tr>
<th>CEAP class</th>
<th>Total n=77505</th>
<th>C0s n=15290</th>
<th>C1 to C3 n=41838</th>
<th>C4 to C6 n=7421</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of symptoms</td>
<td>2.3±1.5</td>
<td>3.4±1.7</td>
<td>4.7±1.8</td>
<td></td>
</tr>
<tr>
<td>% Symptomatic patients</td>
<td>80.4</td>
<td>100</td>
<td>94.7</td>
<td>96.8</td>
</tr>
<tr>
<td>Heavy legs</td>
<td>72.4</td>
<td>58.1</td>
<td>75.0</td>
<td>81.1</td>
</tr>
<tr>
<td>Pain in the legs</td>
<td>67.7</td>
<td>52.8</td>
<td>68.3</td>
<td>81.1</td>
</tr>
<tr>
<td>Sensation of swelling</td>
<td>52.7</td>
<td>29.3</td>
<td>56.9</td>
<td>75.3</td>
</tr>
<tr>
<td>Night cramps</td>
<td>44.3</td>
<td>32.6</td>
<td>43.4</td>
<td>59.6</td>
</tr>
<tr>
<td>Sensation of &quot;pins and needles&quot; in legs</td>
<td>37.0</td>
<td>27.4</td>
<td>36.6</td>
<td>50.3</td>
</tr>
<tr>
<td>Sensation of burning</td>
<td>29.0</td>
<td>15.8</td>
<td>29.6</td>
<td>52.3</td>
</tr>
<tr>
<td>Itching</td>
<td>23.6</td>
<td>15.3</td>
<td>22.3</td>
<td>42.5</td>
</tr>
</tbody>
</table>

### Identification of risk factors that influence the appearance of symptoms

Risk factors connected to symptomatic CVD are important, from a therapeutic and prognostic point of view. Some risk factors can easily be modified in order to slow the development and progression of CVD.

The VCP is the first international program that has involved a large and varied range of countries and geographical zones. In total, 91 545 subjects were involved; 36 004 from Western Europe; 32 225 from Central and Eastern Europe; 12 686 from Latin America; 3518 from the Middle East; and 7112 from the Far East (Table II).\textsuperscript{13}

The results of the VCP show that CVD is a global phenomenon not solely limited to Western countries, as is often believed.\textsuperscript{20,21} The prevalence of symptoms in the VCP is high in all geographical areas studied. Moreover, the distribution of symptom prevalence (by decreasing frequency: heavy legs, pain, sensation of swelling, night cramps, etc) was similar, whatever the area considered. Heaviness and leg pain were found in up to 72\% and 68\% of VCP participants, respectively. Symptoms, such as the “sensation of swelling,” show the greatest increase between C0s and C4 to C6, and this suggests that the perception of pain is similar in all studied countries and is likely to be disconnected from any cultural phenomenon.\textsuperscript{13} Furthermore, the VCP shows that the classification system of CVD is applicable worldwide and this classification allows the generation and design of a whole battery of new questionnaires, for better identification of patients and for symptom measurement.

### Table II. Vein Consult Program (VCP) study zones with number of subjects.

<table>
<thead>
<tr>
<th>Western Europe</th>
<th>Central and Eastern Europe</th>
<th>Latin America</th>
<th>Middle East</th>
<th>Far East</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=36004</td>
<td>n=32225</td>
<td>n=12686</td>
<td>n=3518</td>
<td>n=7112</td>
</tr>
<tr>
<td>France</td>
<td>Spain</td>
<td>Germany</td>
<td>Brazil</td>
<td>Pakistan</td>
</tr>
<tr>
<td>Spain</td>
<td>Hungary</td>
<td>Romania</td>
<td>Mexico</td>
<td>United Arab Emirates</td>
</tr>
<tr>
<td>Spain</td>
<td>Hungary</td>
<td>Russia</td>
<td>Venezuela</td>
<td>Singapore</td>
</tr>
<tr>
<td>Greece</td>
<td>Hungary</td>
<td>Serbia</td>
<td>Venezuela</td>
<td>Thailand</td>
</tr>
<tr>
<td>Italy</td>
<td>Hungary</td>
<td>Slovak republic</td>
<td>Venezuela</td>
<td>Vietnam</td>
</tr>
<tr>
<td>Ukraine</td>
<td></td>
<td>Slovenia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In the VCP population, 56% of patients in the C_0_ class had leg pain, while almost 90% of patients in C_0_ to C_2_ had significant leg pain. Still, it is quite interesting that even though there is a significant increase of symptom prevalence with CEAP class, some patients with severe forms of CVD (C_6_ and C_7_) do not report any symptoms (Table I).^{14}

Results of the VCP show that risk factors connected to symptomatic CVD are: age, body mass index (BMI), sex, family history of CVD, and the patient’s history of previous venothromboembolism (Table III).^{14} In addition, patient habits play a significant role in the development of venous symptoms, such as hours spent in an upright position, smoking, and lack of daily exercise (Table IV).^{14} Together, all of these facts are traditionally recognized as risk factors for the development of CVD in numerous earlier published studies.^{2,20,22-26} The results of the VCP, for the first time, show the distribution of risk factors on a global level, and in populations with different social habits and economical standards, sometimes living in diametrically different time and weather zones. As we can see from Table III, the sex and age of subjects are two very important factors for symptomatic CVD. In the VCP, screened subjects were divided into four age groups: ≤34 years, 35 to 50 years, 51 to 64 years, and ≥65 years. When the CEAP profile was analyzed according to the age and sex, the authors observed that whatever the age group, there was a significant difference between men and women in the classes C_0_ to C_2_. With the exception of the C_0_ class, which was more frequent in men than in women after the age of 35, other categories were more prevalent among women. Next, the prevalence of severe CVD (C_2_ to C_6_) was found to be similar, whatever the sex and age, and to drastically increase with age in both sexes. C_2_ and C_3_ increased with age in both sexes, but stabilized after the age of 64 years.^{13,14}

A number of studies reported an association between obesity and CVD.^{15,14,22} In the VCP population, mean BMI is significantly higher in men compared with women (P<0.0001). Higher values of BMI are reported in Eastern and Central Europe (27.34±5.64) whereas smaller figures appear among patients in the Far East (22.89±3.59; P<0.0001). In a part of the VCP population, Vlajinac et al^{26} showed that the CEAP “C” categories of CVD were significantly related to being overweight or obese, and this association was independent of age, sex, and some other postulated risk factors in this study. Several other habits were confirmed as very strong CVD risk factors, such as smoking and physical inactivity. The last three mentioned factors (obesity, smoking, and physical inactivity) deserve special attention, since these factors can be easily modified. Standing time increases the risk of symptomatic CVD, especially if that period is more than 10 hours. On the other hand, it seems that sitting time is not a risk factor for symptomatic CVD. Lack of regular exercise has been observed in 67.4% of subjects. Up to 42% of subjects were smokers. The appearance of symptoms was strongly connected to the period of day (end of day) and seasons (summer). Even some regions (Middle and Far East) showed a higher presence of symptoms during the night (52.5% of subjects) and a significantly lower presence of venous symptoms during the summer (only 5.4% of subjects).^{14}

Up to 65% of participants with CVD in the VCP had a positive maternal history of CVD. Also, the role of hormonal factors in the development of CVD has been suggested by several investigations. Under the VCP, a Serbian group of authors^{26} showed that the average number of births was significantly higher in women in classes C_0_ to C_2_ and C_2_ to C_6_ in comparison with those without the disease. The higher number of births was a risk factor for CVD, independent of other observed factors, including age. Menopause was also independently related to all clinical classes, especially C_4_ to C_6_. The same study showed no existing relationship between CVD and either oral contraceptive use or hormonal replace-

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Adjusted odds ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex; female vs male</td>
<td>2.3</td>
<td>2.2-2.4</td>
</tr>
<tr>
<td>Age (years) 35-50 vs ≤34</td>
<td>1.7</td>
<td>1.6-1.8</td>
</tr>
<tr>
<td>Age (years) 51-64 vs ≤34</td>
<td>2.3</td>
<td>2.2-2.5</td>
</tr>
<tr>
<td>Age (years) &gt;65 vs ≤34</td>
<td>2.8</td>
<td>2.6-3.0</td>
</tr>
<tr>
<td>BMI (kg/m^2) 25-30 vs ≤24</td>
<td>1.3</td>
<td>1.2-1.4</td>
</tr>
<tr>
<td>BMI (kg/m^2) ≥30 vs ≤24</td>
<td>1.6</td>
<td>1.5-1.7</td>
</tr>
<tr>
<td>Family history of CVD vs no family history</td>
<td>2.0</td>
<td>1.9-2.1</td>
</tr>
<tr>
<td>Personal history of VT vs no personal history</td>
<td>2.5</td>
<td>2.1-2.8</td>
</tr>
</tbody>
</table>

Table III. Occurrence of venous symptoms and risk factors in the Vein Consult Program (VCP) population (P<0.05).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Adjusted odds ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hours spent standing 5-10 vs &lt;5</td>
<td>1.3</td>
<td>1.2-1.4</td>
</tr>
<tr>
<td>Hours spent standing &gt;10 vs &lt;5</td>
<td>1.4</td>
<td>1.2-1.5</td>
</tr>
<tr>
<td>Hours spent sitting 5-10 or &gt;10 vs &lt;5</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>Smoker vs nonsmoker</td>
<td>1.3</td>
<td>1.2-1.4</td>
</tr>
<tr>
<td>Lack of regular exercise vs regular exercise (≥22 times per week)</td>
<td>1.3</td>
<td>1.2-1.4</td>
</tr>
</tbody>
</table>

Table IV. Occurrence of venous symptoms and risk factors in the Vein Consult Program (VCP) population (P<0.05).

Abbreviations: CVD, chronic venous disease; VT, venothromboembolism.

ment therapy. On a global level, use of birth control pills is significantly more frequent in Western Europe (45.8%, vs 31.1% for the total population of survey), while that of hormone replacement therapy is significantly higher in Latin America (23.2%, vs 8.2% for the total population; P<0.0001); in the Far East, HRT use is significantly less frequent than in the other participating countries (2.3%, vs 8.2% for the overall population of the survey; P=0.0008).

The presence of symptoms increased significantly with disease severity. When considering individual symptoms according to CEAP clinical class, “heaviness” and “sensation of swelling” appeared more related to the C3 class (edema), while itching was related to skin changes.

**Comorbidities as risk factors for symptomatic CVD**

There is a lack of evidence on how comorbidities affect the development and progression of CVD and venous symptoms. CVD is still often associated with chronic conditions such as diabetes mellitus, high blood pressure, heart failure, chronic obstructive pulmonary disease, renal insufficiency, peripheral arterial disease, and many others.

Our preliminary results of the VCP show that other chronic diseases are found in a large number of patients with CVD, primarily in elderly patients. For example, arterial hypertension can be found in up to 70% of patients aged above 65 years in CEAP classes C2 to C6. Presence of arterial hypertension, simultaneously with congestive heart failure, contributes to edema development and the decrease in local defense capabilities of already damaged skin and subcutaneous tissue in patients with severe CVD.

The presence of comorbidities could potentially be a very important risk factor for symptom development in patients with CVD, not only in severe cases, but also in the early stages (C0 to C2). These factors could mislead GPs and vascular surgeons, especially in subjects without visible signs of CVD (C0).

Thus, early recognition and quick treatment of comorbidities is essential, and could dramatically reduce symptoms and slow progression of CVD.

**The attitude of patients and GPs who manage venous symptoms**

The results of the VCP gave us a clearer picture of how GPs deal with patients who have CVD, through every stage of the disease. Two facts have left the strongest impression. Firstly, subjects with symptoms only are not considered by their GPs to have CVD. Globally, 63% of screened subjects in the VCP were considered to have CVD by their GPs. Subjects with symptoms only (C0) were less likely to be considered as having CVD and to be liable for treatment than those with signs. The presence of a symptom was not the trigger for starting CVD treatment. Secondly, while 63% of screened subjects were considered to have CVD by GPs, only 22% (one-third) were referred to venous specialists. Despite this, it appears that a systematic search for venous symptoms, as was performed in the VCP, could help detect CVD in 6 out of 10 subjects (it is of note that 50% of these were C0 or C1).

Even when venous symptoms are recognized by GPs, the question still remains: should all symptomatic patients be treated? The decision is particularly difficult in patients without visible signs of disease. Yet, it is acknowledged that venous pain greatly worsens patients’ QoL. Several questionnaires have been created to compare the effects of different types of CVD therapy, as well as for discriminative purpose, and show very promising results.

In the VCP, subjects diagnosed with CVD after a GP examination, were requested to complete a self-administered questionnaire reporting features about their professional activities and QoL (using the Chronic Venous Insufficiency quality of life Questionnaire [CIVIQ]; 0=poor QoL, 100=very good QoL). A total of 35 495 questionnaires from 17 countries were analyzed. A total of 7% of patients were hospitalized and 4% changed their professional activities as a result of CVD. Loss of work days was reported in 15% of patients.

Besides the traditional venous leg symptoms, some authors have identified depression, anxiety, and hypochondria among patients with CVD.

The authors concluded that a specially designed questionnaire, applied to individuals with venous-type leg symptoms, allows the subjects or patients who have a distinct psychiatric condition to be distinguished from those with a true venous disorder. The rate of patient referrals to specialists increases with disease severity: 4.1% at C0 stage vs 60.2% at C6. In Central and Eastern Europe as well as in Latin America and the Middle East, patients are referred more frequently, starting at the C2 stage, than in the Far East, where even C0 patients are rarely referred.

**Conclusion**

In conclusion, CVD is a global phenomenon that reaches almost pandemic proportions. To deal with this problem, the VCP was established. The most worrying finding of the VCP is that the majority of subjects with or without clinical signs of CVD have symptoms that significantly affect their daily activities and deteriorate QoL. However, several factors and comorbidities have been identified as risk factors for the development of venous symptoms, and some of these can be easily modified, such as BMI, hours spent in an upright position, smoking, and lack of daily exercise. Results of the VCP also show the importance of the role of GPs in early recognition and management of CVD. Venous symptoms may be encountered in numerous fields and calls for a multidisciplinary approach (scientific, eg, neurology, molecular biology, psychometrics, etc; clinical, eg, surgery, dermatology, phlebology, etc) and raised awareness amongst patients and the community as a whole.
References


Keywords: chronic venous disease; chronic venous disorder; comorbidity; prevalence; symptom; risk factor
Les symptômes veineux sont très fréquemment évoqués au cours des consultations de médecine générale ou de chirurgie vasculaire. Pourtant, le nombre de recherches menées sur les sensations veineuses est inversement proportionnel à la fréquence des symptômes rapportés. Nous manquons aujourd’hui d’études épidémiologiques sur cette question. La mission du programme Vein Consult (VCP) était claire : augmenter la vigilance et se consacrer à une maladie chronique ayant presque atteint une dimension pandémique, la maladie veineuse chronique (MVC).

Le résultat le plus préoccupant du VCP est la présence de symptômes affectant significativement les activités quotidiennes et détériorant la qualité de vie d’une majorité de sujets avec ou sans signes cliniques de MVC. Dans les facteurs de risque de développement d’une MVC symptomatique, on retrouve : l’âge, l’indice de masse corporelle, le sexe, les antécédents familiaux de MVC, les antécédents de thromboembolie veineuse, le nombre d’heures en position debout, le tabagisme et le manque d’exercice quotidien. Outre les facteurs de risque traditionnels, il existe aussi des comorbidités tels une pression artérielle élevée, un diabète, une insuffisance cardiaque et une maladie pulmonaire obstructive chronique qui peuvent influer sur le développement et la progression des symptômes chez les patients souffrant de MVC. Si la plupart de ces facteurs de risque ne peuvent être modifiés, un nombre significatif d’entre eux peut aisément être changé. Nous présentons dans cet article, d’après les résultats du VCP, les derniers événements liés aux symptômes veineux et les facteurs de risque de leur développement.
A TOUCH OF FRANCE

Consumption (as tuberculosis was then called) was the scourge of rapidly industrializing overcrowded cities in 19th-century Europe. Among its victims, the disease claimed the lives of many artists, while also inspiring their works (see story by Isabelle Percebois). Tuberculosis triggered research on an unprecedented scale. Robert Koch discovered the culprit, *Mycobacterium tuberculosis*, in 1882. In 1921, Albert Calmette and Camille Guérin developed the vaccine that was to save untold lives (see story by Annick Perrot), and the first effective treatment, streptomycin, was used in 1946. Tuberculosis is making a comeback in Europe due to increased migratory flows and the emergence of treatment-resistant bacteria.

“The Savior of Children”: Albert Calmette and the BCG vaccine
A. Perrot, France
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Blighted destinies: arts, artists, and the Romantic Disease in 19th-century France
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Scanning electron micrograph of *Mycobacterium tuberculosis*.
© 2011, Institut Pasteur/Guadagnini (Ultrastructural Microscopy Platform; Marie Jackson (Mycobacterial Genetics Unit); Jean-Marc Panaud (colorization).
Antituberculosis stamp created in 1934, extolling the BCG vaccination and Calmette, “The Savior of Children.” The first antituberculosis stamp was issued in Denmark in 1904. France followed suit in 1927. In France, these stamps played a special educational role, and booklets of stamps were handed out by schoolteachers to schoolchildren who sold them to the public. The proceeds went towards the fight against tuberculosis. Themes and slogans changed until 1967, the last year such stamps were produced.

© Comité National contre les Maladies Respiratoires.
Growing up in Nice, in southern France, Albert Calmette (1863-1933) gazed across the bay and dreamt of voyages to faraway lands, of sailing o’er the bounding main. Dreams he realized on joining the French navy, not as a mariner, as in his boyhood musings, but a ship’s surgeon. He sailed the China Seas, traveled on assignment to Gabon, and voyaged to Saint Pierre and Miquelon in the Atlantic Ocean near Canada, where, self-taught, he began his microbiological research. On his return to France, in 1890, Calmette took classes at the Pasteur Institute given by Émile Roux, with whom over the years he forged a lasting friendship. On the recommendation of Louis Pasteur, Calmette was sent to Saigon (now Ho Chi Minh City) to set up a laboratory for the preparation of vaccines against rabies and smallpox. In one year, half a million people were vaccinated against smallpox. It was in Saigon that Calmette oversaw the building of the first Pasteur Institute outside France; the second one, also in Vietnam, was founded in Nha Trang by Calmette’s colleague and great friend, Alexandre Yersin (today there are 32 Pasteur Institutes throughout the world). He worked on anti–snake venom serum there and later, back in Paris, developed antivenom serotherapy. Confident in Calmette’s organizational skills, Pasteur entrusted him with setting up and directing a Pasteur Institute in Lille. Calmette turned it into a model of its kind that played a major part in the industrial and agricultural development of Northern France and in the improvement of public health and social hygiene, and above all, in the fight against tuberculosis. With Camille Guérin, Calmette studied the tuberculosis bacillus and developed what came to be known as the BCG vaccine, which has prevented hundreds of millions of premature deaths ever since.

**“The Savior of Children”**

**Albert Calmette and the BCG vaccine**

by A. Perrot, *France*

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www.medicographia.com

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Medicographia. 2015;37:94-103 (see French abstract on page 103)
A scourge since antiquity, tuberculosis is blind to merely mortal distinctions of rank, wealth, and kudos. From Egyptian pharaohs to crossing sweepers, from nabobs to panhandlers, over millennia it killed millions. In recent times, tuberculosis was, for more than half a century until the rise of drug-resistant strains in the 1980s, thwarted by the BCG vaccine. B for Bacillus, C for Calmette, G for Guérin. Bacillus—Mycobacterium tuberculosis—the foe, needs no introduction. Guérin (Camille) we will come to shortly. Here, though, our story is that of Albert Calmette.

Albert, his father exulted, was born “to the booming of cannon saluting the seizure of Mexico City” (instigated by Emperor Napoleon III of France). The year was 1863, the place Nice, in southern France. Albert was the third son, and the last, because before he reached two his mother was dead. Albert’s father then embarked with his children on an itinerant life, following the demands of his career as a high-ranking regional civil servant. Albert grew up at a time when France was building its overseas empire, and his curiosity plunged him into adventure novels and explorers’ tales. Exoticism kindled his taste for discovery, and by the age of 13 Albert had made his choice. A life on the high seas.

A vocation sadly that proved short-lived, curtailed by a severe bout of typhoid fever contracted during his preparatory classes for entry to naval school. By the time his long convalescence was over, the naval school’s doors were closed to him—Albert was already too old. Yet still he dreamed of seeing the world. So instead, he turned to medicine and in October 1881 entered the naval medical school in Brest. Two years later, he was appointed physician assistant in the French navy and enthusiastically wrote to his father: “Now the future is mine.”

His immediate future lay in the China Seas. In November 1883, he boarded the battleship Victorieuse and later the Triomphante in Admiral Courbet’s squadron, which lay at anchor in Halong Bay (meaning, in Vietnamese, “descending dragon bay”), with its myriad islets and grottoes in a karst landscape (now a UNESCO World Heritage Site). The French naval division was on a war footing. Calmette had arrived at a decisive moment of French expansion in the Far East.

China, hostile to the extension to Tonkin of the French protectorate of Annam, was encouraging acts of piracy to which the French responded with an iron fist. Anticipating trouble, the Triomphante cruised along the coast, berthing at various ports, where Calmette had his first glimpse of the vast panorama of Chinese life. Captivated, he observed, studied, and noted. Everything. At Hong Kong, he met the Scottish physician Patrick Manson, who had discovered a developmental phase of filaria in mosquitoes. Under the microscope, Calmette saw the various stages of the life cycle of the nematode worm that was the cause of elephantiasis.

Tensions between France and China continued to mount and the failure of diplomatic negotiations triggered the Sino-French War (August 1884 to April 1885). From his first-aid post, Calmette saw action at the Battles of Fuzhou, on 23 August 1884 (a victory for the French), and Tamsui on 8 October 1884 (a victory for the Chinese), the occupation of Keelung, and the capture of the Pescador Islands. When the signing of a peace protocol ended hostilities, Calmette was recalled to France. Before leaving, he visited Saigon, which he said was “the most agreeable town I’ve seen in the Far East,” adding wistfully “I shall perhaps never return.” Little did he know that Saigon was to play a major part in his career. Back in France, Calmette completed his medical studies, extending Manson’s observations in a doctoral thesis on the “Etiology and pathology of tropical diseases caused by filariae in human blood.”

And then a new departure, this time for Africa, Gabon, where he was to serve aboard the floating hospital the Alceste in Libreville harbor. The year was 1886, and Savorgnan de Brazza, the Italian-born, naturalized French navy officer and explorer, was deploying his legendary energy in preparing an expedition. Calmette’s brother Gaston, the future director of
French (top) and Chinese (bottom) rendering of the naval battle of Fuzhou, on 23 August 1884, during the Sino-French War, eyewitnessed by Albert Calmette. © Musée de l’Image/H. Rouyer – © 华声轮胎/bbs.voc.com.cn. All rights reserved.
Albert, journeys to exotic lands of icy wastes or sweltering heat. Their first port of call was Saint Pierre and Miquelon, in April 1888, an odd destination for the newlyweds, a frozen and deserted archipelago buffeted by violent storms or smothered in fog, where cod fishing was the only resource.

At the Naval Hospital, Calmette had his work cut out. Often unwell (he had caught malaria in Africa), he provided medical care for a local population of 6000, which doubled during the fishing season. He cared for the inhabitants in their homes, the length and breadth of the town, and beyond, delivering babies, medicating, performing surgical interventions—everything from amputations to cataracts. He was unfazed by these numerous initiatives and responsibilities: “It was hard going, but oh so worthwhile in my youthful inexperience!” And on top of all this, he still found the time to fit in two English lessons a week and half an hour of fencing every morning. In the evenings, after a demanding day attending to patients, he studied and marveled at microbiology by reading the Annales de l’Institut Pasteur (created in 1887 by the chemist and microbiologist Émile Duclaux), which he had been receiving since his time in Africa. With an oil immersion objective and an incubator sent from France, he set about his research: “without working, enjoying myself, I gathered together a small collection of preparations of all kinds of microbes.”

To hand there was an intriguing conundrum to be solved: salted cod heaped up in the holds of ships were turning bright red. The contaminated flesh was unfit for sale and so the local economy was ailing. To study this “rouge de la morue” (“cod red”), Calmette isolated the microbe, reproduced the spoilage experimentally, proved that the microbe was in the salt from Atlantic saltworks of Cadiz and Lisbon, and showed that sodium sulfite has a preventive action.

In the meantime Félix Le Dantec, one of Calmette’s colleagues in the navy health corps, preempted him by publishing identical results in 1891, without, however, mentioning transmission by salt. Calmette was only 26 years old and self-taught, yet already he had accomplished laboratory work of great relevance to public health and with an industrial application, as long advocated by Pasteur. Even before he entered the Pasteur Institute, Calmette was well and truly of the same stripe as the great man himself.

The French Colonial Medical Service was created in 1890, and Calmette had no hesitation in joining. His aim was to work on tropical diseases, and in preparation he wished to take a 3-month microbiology course at the Pasteur Institute. Yet word of the course’s repute had spread internationally and no places were left. Calmette, though, came to the attention of Émile Roux, one of Pasteur’s closest disciples, who appreciated his work on “cod red,” his enthusiasm, scientific rigor, and technique, and reserved for him a bench in a small laboratory. Roux’s lab assistant Alexandre Yersin had just left,
having succumbed to the call of distant horizons in the Far
East. And so Calmette joined the course which, he later said,
“opened up attractive vistas towards which I shall strive.”
This was the beginning of a mutual esteem and friendship
between Roux and Calmette that lasted their whole lives.

When the Colonial Medical Service needed someone to set
up a laboratory for the preparation of vaccines against small-
pox and rabies in Indochina, it looked to the Pasteur Institute.
Thus it was that Pasteur summoned Calmette and explained
the mission. “Think it over and let me have an answer soon.”
To Pasteur’s great surprise, the young and eager doctor ac-
cepted forthwith: “There’s nothing to think over. I’ll leave when-
ever you wish.”

In February 1891, Albert and Emilie arrived in Saigon, and Cal-
mette set up his laboratory in two rooms at the military hos-
pital. Great was the contrast after Saint Pierre and Miquelon.
Despite its muggy climate, Saigon appealed to them—the
hospitality of the small French colony, the facilities provided,
their house with the supreme luxury of running water and a
bathroom, plus a garden.

The first problem Calmette faced was storage of his antira-
bies vaccine, which contained attenuated virus taken from
the spinal cord of rabid rabbits. Throughout the long sea voyage,
Calmette had maintained the virus by passing it from rabid
rabbit to healthy rabbit, but now his lagomorph population
was running low. So Calmette implemented one of Roux’s dis-
coveries: storage in glycerol of rabbit spinal cord containing
attenuated virus. Before long, people bitten by “mad dogs”
were sent for treatment to Calmette in Saigon, from all over
Indochina, but also Singapore, Siam, Java, Hong Kong, and
Shanghai.

Calmette also adapted Edward Jenner’s method of vaccina-
tion against smallpox, which was endemic and widespread in
Indochina. Before the French occupation, smallpox was re-
sponsible for 90% of infant deaths, and those that survived
were badly scarred, and many were blind, to the point that
some villages kept a nearby “hamlet of the blind.” Calmette
inoculated the skin of local water buffalos with vaccinia virus
and collected vaccine lymph. This method was quickly adopt-
ed over a large area, including the Indonesian peninsula and
southern China, and 500 000 people were vaccinated against
smallpox in just two years.

Calmette pursued his interest in snakebite envenoming and, in
his first paper on the subject, recounted how a source of ven-
on was found. “A village in the environs of Bac-Lieu (Cochin-
China) was invaded, in October 1891, at the time of the great
rains, by a swarm of venomous snakes belonging to the
species *Naja tripudians* or cobra capel. These animals, driven into the native huts by the flood, bit 40 individuals of whom four, as reported to us, died almost immediately. An Anna-mite was able to capture and enclose in a barrel 19 of these cobras and the administrator of the region, M. Séville, kindly sent them to the laboratory. Fourteen arrived alive. We killed 11 of them immediately to remove their venom glands. Calmette extracted venom from the glands with glycerol and used the solution to prepare anti–snake venom serum.

Calmette also contributed greatly to the local economy, by investigating the so-called “Chinese yeast” used to ferment rice and so produce an alcohol beverage. He doubled the yield of rice alcohol by means of a fungus which he named *Amylomyces rouxii* in honor of his teacher and friend Émile Roux. In this, the heyday of the opium trade, he also showed that another fungus, *Aspergillus niger*, shortened the time needed to ferment opium from one year to 30 days.

And his interests did not stop there. He returned to ideas first formulated in Gabon and began research work on other diseases widespread in Indochina: cholera, dysentery, and filariasis.

Not content with that, Calmette set up the first Pasteur Institute outside France (today, the Pasteur Institute in Ho Chi Minh City). The second, north of Saigon, was the work of Alexandre Yersin, with whom Calmette struck up a real and lasting friendship when they first met in 1891, as Yersin was setting out on an expedition to the Annamite Mountains.

This was the dawn of the Pasteurian epic, which in a few years saw Pasteur’s followers reproduce around the world the model put in place by Calmette, often, like him, in precarious conditions, but always with great adaptability. Researchers, but also hands-on strategists, and military and civilian doctors, all trained in the methods of Pasteur, driven by what amounted almost to fervor. Today, 32 Pasteur Institutes across five continents continue the good work: public health services for local populations, research, and teaching, the only worldwide network of its kind.

After two and a half years in Saigon, Calmette, weakened by dysentery, was recalled to France. At just 30 years old he was appointed a Knight of the Legion of Honor. Keen to continue his research, he wanted to return to the Pasteur Institute where the working atmosphere had so impressed him. Alas, regu-
lations forbade a colonial physician from taking a position outside the colonial office, so instead Calmette accepted a position of secretary to the board of health, where he was given a free hand to conduct his personal research in the morning. For two years he resumed his studies of antivenom serotherapy and worked with Amédée Borrel and Yersin on the preparation of antiplague serum.

Pasteur and Roux then entrusted him with the task of creating a Pasteur Institute in Lille, in the north of France, at the request of the board of health and the city council, which, for this new center of serotherapy, public health, social hygiene, and research, wanted “Mr Roux’s students.” Calmette signed a 10-year contract, but stayed on for a quarter of a century. Inaugurated in 1899, the institute met the needs of physicians and hygienists, but also local industrialists, following Pasteur’s advice that pure science, at its noblest, cannot advance a single step without sooner or later using its precious results for the good of industrial applications.

Calmette turned to problems of public health and hygiene, and started by developing biological treatments to clean up waste water using trickling filters (also known as biofilters). He worked too on hookworm (miner’s anemia), and on his new calling, the study of tuberculosis. Although the disease-causing bacillus (Mycobacterium tuberculosis) had been identified in 1882 by Robert Koch, no treatment had yet been produced to stem the progress of the contagion.

The situation was especially bad in industrial towns, where workers lived in overcrowded, unhealthy conditions. In Lille, for example, a city of 220,000, some 6000 among the poverty-stricken had tuberculosis, which killed 1000 to 1200 of them every year. In affected households, infant mortality was 43%. More generally, in early 20th-century France, “consumption” killed 100,000 to 150,000 people each year, nearly one-quarter of all deaths. Calmette thereafter single-mindedly pursued the scientific and social fight against tuberculosis until the end of his days.

His first priorities in Lille were to focus on the environment and living conditions, to provide the townspeople with safeguards, and to educate them. He set up the first tuberculosis clinic, the Émile Roux Preventorium (for patients infected by a form of tuberculosis not yet active) in 1901, the Ligue du Nord contre la Tuberculose, which raised public awareness and collected funds, a family sanatorium, a school of nursing and hygiene, and an annex for a nonprofit organization that protected children from infected households by sending them to foster homes in the country.

With these treatment and educational networks in place, Calmette focused on the prevention of tuberculosis. The odyssey began in 1900, with at his side Camille Guérin, his research colleague since the early days in Lille. By 1908 they had shown that successive cultures of bovine bacilli (Mycobacterium bovis), on medium containing cooked potato and glycerinated bile, lose their virulence progressively through successive subcultures.

Various types of tuberculosis bacteria cultures: human, bovine, biliary, and aviary tuberculosis on glycerinated potato medium (I to IV); human, bovines and aviary tuberculosis on glycerinated agar-agar (V to VII). Drawing illustrating Calmette’s work, by Demoulin, 1920. © Institut Pasteur – Musée Pasteur.
The Great War and the German occupation of Lille in 1914 interrupted this promising research. During those dark years, Calmette somehow managed to continue making sera for serotherapy and vaccines, in spite of having to cope with the hardships and restrictions imposed by the war and not least the ordeal of having his wife Emilie being taken hostage in 1918 together with a group of twenty-five prominent women from Lille, and deported and interned for seven months in a war prisoner camp in Holzminden, in Lower Saxony.

The war over, Roux called upon Calmette to become an assistant director of the Pasteur Institute in Paris and to run the bacteriology course there, following the death of the previous incumbent Ilya Metchnikov, who had shared the 1908 Nobel Prize in Physiology or Medicine with Paul Ehrlich for his work on immunity. Calmette and Guérin resumed their experiments on tuberculosis and after 13 years of unflagging work, using cultures from 230 passages in the bile/potato medium, they at last had an effective means of vaccination using live attenuated bacillus, thereafter known as Bacillus Calmette-Guérin (BCG). Satisfied that the BCG vaccine was safe, they vaccinated 120 newborn infants of tuberculous mothers with three oral doses of their BCG culture. Thus began the era of vaccination against tuberculosis.

But in 1930, as recognition for his work flowed in from all sides, disaster struck. Terrible news arrived from Lübeck in northern Germany. Seventy-six of 250 children vaccinated with BCG prepared using a strain sent by Calmette in 1929 died of tuberculosis. At the resulting trial, which opened in Octo-
ber 1931, it slowly emerged that the tragedy was not attributable to a recovery of the virulence of BCG, but rather to mistakes perpetrated at the Lübeck laboratory that prepared the vaccine.

Calmette was deeply affected by the Lübeck disaster, which, along with physical exhaustion from years of work and struggle, worsened the heart condition that had afflicted him for some time. Now 70 years old, Calmette was still paying frequent calls on his ailing friend Émile Roux, but declining health forced him to his bed on 24 October 1933, and he died on the morning of 29 October, five days before Roux.

Two years before he died aged 70 in October 1933, Albert Calmette wrote a letter to his children and grandchildren in which he expressed the wish: "I hope that it will be given to me to work until my eyes are closing to the light and that I will fall asleep my soul in peace, conscious of having done that which I have been able." The wish was granted, and since his death Calmette’s main contribution to humanity—the live BCG vaccine—has protected millions of people around the world and, together with antibiotics and improved hygiene, has helped turn the tide against tuberculosis. In its tribute, the Pasteur Institute said of Calmette: “…his death deprives science of one of its most illustrious servants.”

« LE SAUVEUR DES TOUT PETITS » : ALBERT CALMETTE ET LE BCG

Albert Calmette (1863-1933) rêvait, enfant à Nice, d’être marin, il sera médecin de la marine. Il rêvait de contrées lointaines, il naviguera sur la Mer de Chine, dans l’escadre de l’Amiral Courbet, il ira en mission au Gabon, à Saint Pierre et Miquelon où il se distingue par des recherches microbiologiques personnelles. De retour, il suit l’enseignement du Dr Roux à l’Institut Pasteur. Une durable amitié va lier les deux hommes. Il est envoyé à Saigon pour fonder un laboratoire pour la préparation des vaccins contre la rage et la variole. Il pratique en un an 500 000 vaccinations antivarioliques. Il met au point la sérothérapie antivenimeuse. En véritable pionnier, il édifie le premier Institut Pasteur Outre-Mer. Yersin, qu’il a rencontré en Indochine, et à qui l’unira une profonde amitié, crée peu après le deuxième. Il y a aujourd’hui 32 Instituts Pasteur dans le monde. De retour à Paris, confiant dans ses talents d’organisateur, Pasteur lui confie le soin de créer et diriger un Institut Pasteur à Lille. Il en fera un établissement modèle qui participa au développement industriel et agricole et au développement de l’hygiène dans le Nord de la France. Et à la lutte contre la tuberculose, son fer de lance. A Lille, il commence avec Camille Guérin ses recherches sur le bacille de la tuberculose qui aboutira à la vaccination par le BCG. Ce vaccin, qui devait le rendre célèbre dans le monde entier, contribuera à prévenir de la tuberculose des centaines de millions de personnes de par le monde.
In the 19th century, tuberculosis (consumption) struck down countless thousands, acclaimed and nameless alike. Mysterious and incurable, it cut a swathe through the artistic world in France. Prosper Mérimée’s letters bear poignant witness to his fight against the disease; George Sand speaks of Chopin’s decline in her autobiographical writings; in Memoirs from Beyond the Grave, Chateaubriand recounts the consumptive death of his mistress Pauline de Beaumont. Tuberculosis became a major theme in novels of the day. In the works of Eugène Sue, Alexandre Dumas, fils, and Victor Hugo, it assumed a religious character and took the lives of frail heroines seeking to atone for their misdeeds. Realists like the Goncourt brothers and Emile Zola, on the other hand, denied tuberculosis any redeeming value and its depiction served anticlerical ends. Few painters portrayed the disease and it was the Norwegian Edvard Munch, in Paris in 1885, who produced the most explicit and moving representation in The Sick Child. But it was, above all, opera that placed tuberculosis center stage, thereby creating the paradox of the singing consumptive. By adapting the novels of French writers Alexandre Dumas, fils and Henry Murger, the composers Giuseppe Verdi and Giacomo Puccini created La Traviata and La Bohème, two operas whose popularity shows no sign of abating. Thus, it was that tuberculosis came to serve as an artistic trope in 19th-century fiction, painting, and opera, and, latterly, in film adaptations.

Blighted destinies: arts, artists, and the Romantic Disease in 19th-century France

by I. Percebois, France

It plagued 19th-century Europe, sowing death in its wake. Phthisis, the wasting disease, graveyard cough, consumption, call it what you will. Named or nameless it killed all the same. In a world transformed by the industrial revolution, it spread through overcrowded towns, taking the lives of unsung and lauded alike. It was mysterious, hereditary perhaps, incurable. Potions of dog fat and garlic, seaweed placed under the sufferer’s bed, sweltering near a hot stove, fresh air treatment in sanatoria, all proved futile. In France, the world of the arts was not spared and writers, painters, and musicians mythologized the sickness, putting it at the heart of their works, seeing it as a source of febrile creativity, as redemptive, as ennobling.

A case in point is Alexandre Dumas’ 1848 novel La Dame aux Camélias (The Lady of the Camellias), which less than five years later inspired Verdi to compose La Traviata, with Violetta the quintessential victim of the “Romantic Disease.” Not until the end of the 19th century did German microbiologist Robert Koch’s discovery of the tubercle bacillus reveal the true face of the disease, thus sounding the death knell of the consumptive myth and paving the way to a genuine treatment of what came to be known as tuberculosis.

The arts in the time of tuberculosis

Before writers and artists in 19th-century France appropriated it as a fictional device, tuberculosis figured in their correspondence and autobiographical writings in all its blood-spitting wretchedness. Pulmonary tuberculosis, known then as phthisis, forced the dramatist Prosper Mérimée—the author of Carmen, the basis of Bizet’s namesake opera—to divide his twilight years between Paris, where he exercised his office as a senator under the Second Empire, and Cannes, where the mild climate soothed his hacking cough. In his posthumously published Letters to an Unknown Woman, who was in fact Jenny Dacquin, friend and confidante, Mérimée unflinchingly related the progress of his sickness. A letter dated 6 January 1870, less than a year before his death, evoked his repeated fits of breathlessness and nights of pain: “I have tried all remedies, but always find myself back where I started […]. I’m certain a slow and most painful death is approaching.”

Clear-minded, Mérimée dwelled less on the disease, with which he had learned to live, than on the turbulence of history that was dragging France into war with Prussia. In the days following his death, Fanny Lagden, who watched over him till his last breath, wrote that “These horrible political events certainly shortened his life.” Curtailed perhaps, but Mérimée nonetheless died at 69, an age reached by few consumptives.

The composer Frédéric Chopin struggled with consumption for years. His correspondence reveals the daily suffering, but also his humor, as in a letter dated 3 December 1838 to his friend Julian Fontana (also a Polish pianist and composer, and Chopin’s musical executor). Living at the time on the island of Majorca with his lover, the novelist George Sand (pseudonym used by Amandine Aurore Lucile Dupin), Chopin wrote: “Three doctors—the most eminent on the island—examined me. One sniffed my spittle, the other tapped to see where the spit came from, the third palpated me while listening to how I spat. The first said I was going to die, the second that I was dying, the third that I was dead already.”

Cover of journal serializing The Lady of the Camellias, by Alexandre Dumas, fils, showing Marguerite with her bouquet of white camellias. The novel inspired the opera La Traviata, composed by Verdi.

Bibliothèque Nationale de France © Bridgeman Art Library.
that provoked the hostility of the island's inhabitants. Scarcely settled into their lodgings in Palma, the lovers were turfed out by the owner, who demanded from them a large sum of money to disinfect the house soiled by their presence, to whitewash its walls, and to replace its furniture, which was to be burned. Treated as plague victims, they found refuge at the Valldemossa Charterhouse, thanks to help from the French consul. But Chopin's symptoms worsened: "Our stay at the Valldemossa Charterhouse," wrote George Sand, "was a torture for him and a torment for me." The composer seemed already to be dying, but he lived on for another decade, his strength sapped by the disease, which gave birth to works marked by melancholy. In 1849, he died at 39, in his apartment at the Place Vendôme in Paris. His younger sister Emilia too had been carried off by the same disease 22 years before at just 15, and they were reunited in death in her tomb at the Père Lachaise Cemetery in Paris.

The image of the artistic couple as victims of prophylactic measures is redolent of the attitude François-René de Chateaubriand encountered in Rome when looking for a last abode for his consumptive lover Pauline de Beaumont: a dread among those renting accommodation of the contagion of chest diseases. As a young woman, de Beaumont was well known in Parisian salons, but only entered the collective memory after her death in 1803, which Chateaubriand recounted in his Memoirs From Beyond the Grave. Extracts from her own diary testify to deep despair: "Why do I not have the courage to die?" Yet her bravery, heroism even, is celebrated by Chateaubriand when he describes her last moments. While he was in tears, Pauline greeted death with a resolute spirit shaken only by her death throes. Chateaubriand pressed a hand on her thin ribcage and felt her heart flutter: "Oh! Moment of horror and terror, I felt it stop!" Dead at 35, in a foreign land, Pauline de Beaumont, through Memoirs From Beyond the Grave, became a novelistic model for writers like the Goncourt brothers who chose the Eternal City as the setting for their novel Madame Gervaisais.

Pauline de Beaumont's fate foreshadowed that of Marie Bashkirtseff, a Russian painter who died in 1884 aged but 25, in Paris, where she had come to study art at the Académie Julian. Like Pauline de Beaumont, Marie kept a diary, an emotive account of her losing battle against tuberculosis. In it she relates what fiction passes over, to wit medical horrors and treatments that mutilate the female body: "I burnt both sides of my bosom—I was unable to wear a low-cut dress for four months. And these burns have to be repeated from time to time to keep me alive. There's no question of getting better. It seems like I take a dark view of things, but no, it's simply true." Marie's clear-mindedness is striking and a reminder that wisdom is not the prerogative of age. This resignation went hand in hand with unsparing self-criticism because, in her mind, Marie Bashkirtseff despaired of achieving fame and saw tuberculosis as an alternative to mediocrity. In her diary entry for 21 August 1883, she wrote: "I want to live. But I have no genius and it would be better to die." These words fail to do justice to this young polyglot artist and feminist. In a way, Marie's diary summarizes all of 19th-century literature on tuberculosis and through its pages she joins the sisterhood of tragic heroines of this golden age of the novel.

Tuberculosis as a literary device

Strangely, the consumptive young woman became a popular heroine in 19th-century writing, as in Eugène Sue's Les Mystères de Paris (1842-1843), one of the founding texts of the French novel, whose imposing gallery of characters limns the varied faces of the disease. There is Lorraine, the weeping mother who caught the illness while nursing her child. And little Adèle Morel, the daughter of a poor lapidary, who at just four years old appears in the story only long enough to die under the eyes of compassionate readers. Sue does not even spare his heroine, the daughter of the Grand Duke of Gérolstein, who believes her to be dead. Abandoned at six by a moneygrubbing notary public, who passes her off for dead, maltreated by a one-eyed woman nicknamed La Chouette (The Owl), she endures loathsome treatment like a saint under torture. She becomes known as Fleur-de-Marie or Goualeuse (slang for “the Virgin” and “the singer,” respectively) and, inevitably, is stricken by tuberculosis. Far from spoiling her beauty, sickness heightens the delicacy of her face and gives it an
Tomb erected by François René de Chateaubriand, writer, politician, and diplomat, and founder of French Romanticism, for his mistress Pauline de Beaumont, née Montmorin (1768-1803), who died of tuberculosis in Rome. The epitaph reads: “After having seen her entire family, father, mother, two brothers, and sister perish, Pauline de Montmorin, consumed with a languishing disease [consumption] came to die in this foreign land. F. A. Chateaubriand erected this monument in her memory.” © Roger-Violet.
ethereal character: “despite the wasted oval of her face, the expression of her features, her whole bearing, the grace of her attitude were still worthy of the brushes of great painters.” Fleur-de-Marie may be a fallen woman, her body may have been sullied, but her soul is untainted by vice. The more time she spends with her benefactor, the mysterious Rodolphe (who, unbeknown to both, is none other than her natural father, the Grand Duke), the more she becomes aware of her degradation and turns to religion. For Eugène Sue, tuberculosis stems from want, but is also a form of atonement where flesh and spirit merge. Paradoxically, the illness is a deliverance, which, at the very moment when she takes her vows as a nun, enables the heroine’s final apotheosis and frees her from an impure body so she can sit with God.

This conception of tuberculosis had a lasting influence on French writers like Alexandre Dumas, fils, whose The Lady of the Camellias (1848) was a homage to Marie Duplessis, a Parisian courtesan of whom he was enamored and who died of consumption at the age of 23. The novel recounts the tragic passion of the young Armand Duval for the beautiful Marguerite Gautier. The heroine knows only too well, right from the start of the story, that she is doomed, because she says “I am ill, and with one of those diseases that never relent.”

The giddy round of balls, suppers, and lovers was just a diversion, something that serves only to escape boredom, to avoid soul-searching, and above all to forget approaching death. True love alone challenges her licentious behavior, a bewitching interlude with Armand at Bougival, far removed from escapades in Paris. But Marguerite is never more mortal than when she wants to live and regain her health, so as to live fully this passion in which she had lost faith.

Well before death closes its icy fingers on her breast, it is re-nunciation that marks her end. By bending to the will of Armand’s father, by sacrificing her happiness to the honor of her beloved, she commits what is tantamount to suicide. She resumes her life as a courtesan, sells her body to repay debts, and takes refuge in her inner being, her soul, which she knows is pure because of the sacrifice of her love. Her fate is akin to that of Fleur-de-Marie’s, for in sickness both find a form of atonement. Love transforms Marguerite’s heart; tuberculosis enables the elevation of her soul. The priest who hears Marguerite’s deathbed confession is in no doubt: “She lived a sinner, but will die a Christian.”

Marie Duplessis (1824-1847), mistress to Alexandre Dumas, fils, inspired the main character of Marguerite Gautier in La Dame aux Camélias, published in 1848, adapted to the stage in 1852, and set to music by Verdi in 1853 in the opera La Traviata. From the Journal des Romans, 1905, in which the novel, still immensely popular more than 50 years after its first publication, was serialized. © Bibliothèque Nationale de France/Bridgeman Art Library.

As Susan Sontag noted in Illness as Metaphor, “Tuberculosis provided a redemptive death for the fallen, like the young prostitute Fantine in Les Misérables.” Victor Hugo gives us a religious reading of the disease. From the outset, Fantine’s physiognomy seems to predispose her to this malady, for Hugo writes “she is a phantom possessed of the form of a nymph.”

Tuberculosis first becomes manifest in Fantine’s dry cough, which appears while she is breastfeeding her daughter Cosette. No longer able to provide for Cosette, Fantine returns to her birthplace to seek work, confiding her daughter to the loathsome Thénardiers. Fantine works her fingers to the bone striving to meet their insistent demands for money for Cosette’s bed and board. Her symptoms worsen: coughing, cold sweats, and the fever which grips her after a bout of weakness.

The realistic novels of 19th-century France project a contrast- image of illness, which goes hand in hand with anticlericalism and a rejection of the expiatory conception of tuberculosis. Madame Gervaisais, the last novel written jointly by the Goncourt brothers, in 1869, differs in this way from Les Misérables, which preceded it by just 7 years. As in the works...
considered above, the conversion of the heroine is linked to the advance of her illness, but the Goncourts see in this the defeat of the scientific mind, which seeks refuge in religion as death bears down. The mystical fever that grips Madame Gervaisais is also a sickness that gradually isolates her from friends and family. In the last chapters of the book, her life is nothing more than mortification and leads to veritable dehumanization: “the increasing disembodiment of the physical being carried her a little closer to the holy madness and hallucinatory delights of religious love.”10 The spiritual impulse is thus stripped of its aura and constitutes nothing more than one of the symptoms of the illness.

Anticlericalism is apparent also in the last chapter of Émile Zola’s 1878 novel Une Page d’Amour (A Love Episode), an example of French naturalism, when the adulterous passion between Hélène Grandjean, a widow with an 11-year-old daughter, and Dr Deberle is finally consummated. The daughter, Jeanne, jealous of the place Dr Deberle increasingly occupies in her mother’s affections, willfully exposes herself to rain and cold and contracts phthisis (tuberculosis), dying just 3 weeks later. At the end of the novel, the hereditary ill that runs throughout the Rougon-Macquart cycle of 20 novels, of which Une Page d’Amour is one, takes a new form. Symbolically, it is Dr Deberle who pronounces the name of Jeanne’s incurable malady, since in a way he is responsible for it: “It is an acute phthisis, he murmured at last, […] a case he had much studied: the miliary tubercles would multiply fast, the fits of breathlessness would worsen.”11

This medical precision is found in Zola’s description of Jeanne’s death pangs, which are accompanied by violent vomiting, a detail authors often omitted as they deemed it too degrading. Though Jeanne weakens as the days pass, she does not acquire the ethereal character of romantic heroines because her symptoms are rooted in corporeality. Religion is unable to save Jeanne and in Zola’s eyes offers nothing more than the mirage of a first communion, an unattainable dream, the promise of which exacerbates her nervous disorders. Zola’s story describes death, not as an elevation of a soul finally freed of its earthly shell, but as the end of suffering, the final cure.

**Tuberculosis as depicted in the visual arts**

One might expect that this theme of tuberculosis, so vivid in the 19th-century novel, would also flourish in the visual arts. Yet few paintings portray the macabre spectacle of the disease. Marie Bashkirtseff seems to evoke her suffering in the 1883 work *Self-Portrait, a Tear*, where she turns away from the onlooker as if to conceal her pain. Likewise, it would be vain to search for a self-portrait by Eugène Delacroix that reveals his condition. In his canvasses, as in his letters, Delacroix...
was reticent about the disease to which he succumbed in 1863. Perhaps this was why he asked the photographer Gaspard-Félix Tournachon, known as Nadar, not to publish his portrait, taken in 1858, in which Delacroix’s hollow face bears the stigmata of consumption. There is, however, a work by Delacroix that suggests the disease: the portrait of his friend Chopin and George Sand, sketched in 1838, just before the couple left for Majorca. In this unfinished painting, Delacroix sought to show the composer at the piano, while the novel-

ist seems to be lost in thoughts of love. Much later, in 1874, the painting was cut in two, perhaps because the then owner felt that two canvasses would fetch a higher price than one, thus also materializing, as it were, the rupture between the lovers, who had separated in 1845. The portrait of George Sand now hangs in the Ordrupgaard Art Museum in Copenhagen, and the Chopin portrait is in the Louvre in Paris, the shadow of death seemingly fitting over his somber face.

It was a foreign painter staying in Paris who gave us the most doleful image of tuberculosis. In 1885, Edvard Munch won a scholarship to travel from his native Norway to study in Paris. It was there that he developed his ideas for The Sick Child, which was to become a recurrent theme in his painting. While Munch seems to come from the line of Norwegian artists like the naturalist painter Christian Krohg, The Sick Child sets him apart and is above all autobiographical. Tuberculosis killed his mother and then his older sister Sophie, who died in 1877 at only 15: “Disease, madness, and death were the black angels who leaned over the cradle at my birth,”

he declared. Munch alludes to Sophie in The Sick Child, by showing a bedridden girl whose wan face is turned to a distressed mother who hangs her head in distress. Munch painted five other versions of this canvas, ceaselessly reliving his sister’s lingering death while trying to free himself of survivor guilt.

The months that Munch spent in Paris in 1885 were crucial to the gestation of The Sick Child, which the following year shocked at the Autumn Exhibition in Kristiania (the then name of the Norwegian capital), less because of its subject than its execution. Critics just saw “daubings,” blobs of paint, whereas in reality the artist’s brush retranscribed his deep sorrow.
Tuberculosis on the operatic stage

In the 19th century, opera turned tuberculosis into a popular theme, as in La Traviata, the third in Giuseppe Verdi’s trilogy, after Rigoletto and Il Trovatore. Verdi saw a theater production of Alexandre Dumas’ The Lady of the Camellias in 1852 in Paris, where he was staying with his lover, the operatic soprano Giuseppina Strepponi, who became his second wife a few years later. If we are to believe his adoptive daughter, Maria Filomena, as he was leaving the theater Verdi heard in his mind the opening notes of what was to become La Traviata. In the depiction of Violetta “la traviata” (the “woman who strayed” or “the fallen woman”), one sees Giuseppina: she is this woman of easy virtue condemned by the composer’s entourage. Verdi defended Giuseppina in a letter dated 21 January 1852 to his former father-in-law Antonio Barezzi (whose daughter Margherita was Verdi’s first wife, who died suddenly, perhaps of encephalitis, in June 1840 at the age of 26): “I have nothing to hide. In my house there lives a lady, free, independent, like myself a lover of solitude, possessing a fortune that shelters her from all need. Neither I nor she owes...
Stricken Lady With Camellias

The tragic Romantic myth of the young woman falling prey to consumption endures: Venera Gimadieva is Violetta in Verdi’s opera La Traviata, directed by Tom Cairns and conducted by Mark Elder at the Glyndebourne Festival, East Sussex, UK, July-August 2014. The camellia flowers hark back to Alexandre Dumas’ novel La Dame aux Camélias, which inspired the opera. © Robbie Jack/Robbie Jack/Corbis.
to anyone at all an account of our actions." With *La Traviata*, Verdi created a paradox: that of a consumptive woman singing operatic arias, an incongruity that did not escape the audience’s notice. The first performance at La Fenice, in Venice on 6 March 1853, was a sadly foreseeable fiasco, the word Verdi himself used. The composer was obliged to transpose the action to the 17th century to avoid shocking middle-class sensibilities, and had to come to terms with a singer called Fanny Salvini-Donatelli whose stoutness and age (she was 38) were at odds with the portrait of a young woman wasting away from consumption. It was not until Verdi reworked the opera the following year, and then much later when the role of Violetta was sung by sopranos like Maria Callas, that *La Traviata* won acclaim.

Callas also sang the role of the heroine of Puccini’s *La Bohème*, Mimi, who like Verdi’s Violetta died of tuberculosis in her prime. Premiered by Puccini on 1 February 1896, *La Bohème* is an adaptation of *Scènes de la Vie de Bohème* by Henry Murger (1851), which retraces the precarious existence of four young Parisian artists. Unlike his contemporaries, Murger describes a mirthful world of hardship peopled by characters who flit around and fall in love, while living from hand to mouth, trusting in Providence. This unrestrained merriment fades at the death of Mimi, a pretty and flirtatious working-class girl who drudges as a seamstress. Mimi is the fickle lover of the poet Rodolfo, whom she leaves for a viscount, tempted by the hats and dresses he can provide.

Puccini’s opera, which over the years has completely eclipsed Murger’s stories, is rooted in this amorous intrigue and ends with Mimi’s death, unlike the original text. Study of *La Traviata* and *La Bohème* shows them to be sister works and it is little wonder they inspired Baz Luhrmann to direct *Moulin Rouge!* his award-winning 2001 film. As his heroine, Luhrmann chose a courtesan called Satine, who is reminiscent of *The Lady of the Camellias, La Traviata, La Bohème.*
In the 1800s, tuberculosis was seen as the “malady of the century” and as such echoed the melancholy of the Romantics and inspired the Realists. Viewed as the disease of the poor, in reality tuberculosis affected all social classes and ushered many artists, writers, and composers into an early grave, and into legends of blighted destinies. Tragic stories that fire the imagination today, just as they did in the heady days of 19th-century Romanticism.

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