Can we prevent the progression of chronic venous disease?

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Chronic venous disease: a disease whose severity is underestimated

by R. K. Pinjala, India

Introduction

Chronic venous disease (CVD) is an umbrella term that comprises wide varieties of clinical manifestations such as varicose veins, venous ulcers, edema, venous eczema, telangiectasia, hyperpigmentation of the skin, atrophie blanche, and lipodermatosclerosis.1,2 It is mostly individuals involved in occupations requiring long periods of standing that are affected with CVD.3 In order to eliminate the ambiguity in the diagnosis of CVD and to establish a valid and reliable methodology for such diagnosis across the world, the CEAP (clinical-etiology-anatomy-physiology) classification system was developed and subsequently revised by the American Venous Forum.4 According to this classification, CVD is identified on the basis of various features, including clinical symptoms (C, graded as C0–C6, see Figure 1), etiologic factors (E), anatomical features (A), and pathophysiological events (P). The CVD stages C3 and above are considered to be chronic venous insufficiency (CVI).

Prevalence of CVD

Incidence of CVD has been comprehensively determined by the Vein Consult Program through a meticulously designed approach using the CEAP classification system and involving 6232 general practitioners from 20 countries across five geographical regions of the world.5 Of the 91545 subjects analyzed in the study, prevalence of CVD (clinical symptoms C1–C6) was determined to be 63.9%. Figure 2 depicts prevalence rates by class, as observed in that study.5 However, studies evaluating the incidence of CVD in India are limited. An epidemiological survey carried out way back in 1972 on Indian railroad workers determined the prevalence of varicose veins to be 25% in South India and 6.8% in North India.6

Quality of life and CVD

An individual’s quality of life (QOL) is largely influenced by CVD. Several independent studies from different countries on diverse subjects have unequivocally established that CVD drastically reduces the QOL of an individual.7-10 In a prospective observation study on Indian patients, QOL was approximately 50% at baseline and improved significantly (P<0.001) after treatment with micromized purified flavonoid fraction.11 Furthermore, data suggests that the higher the degree of CVD the lower the QOL.

Morbidities associated with CVD

Associations between CVD and various other morbidities have been shown in different studies. A significantly elevated prevalence of CVD was observed with various cardiovascular risk factors, as well as diabetic neuropathic foot.12-15 Furthermore, em-
Physema/chronic obstructive pulmonary disease and skeletal/joint diseases were also frequently found with venous disorders. Rarely, chronic venous ulcers could develop into potentially life threatening Marjolin's ulcer. Apart from this, venous endothelial cells isolated from CVD patients strongly express various proinflammatory markers, which might contribute to systemic inflammation in CVD patients. Psychosocial disorders such as anxiety and depression are frequently observed in CVD patients. Economic burden due to CVD
High prevalence, cost of investigation and treatment, and loss of working days due to CVD have a significant socioeconomic impact, and the problem is compounded because CVI is progressive and has a propensity to recur. The economic burden of CVD treatment is attributed to direct costs, such as medical and nursing costs and costs of investigation and treatment, and indirect costs, such as those related to loss of working days. Several studies carried out in different countries have shown that CVD incurs a significant economic burden.

Conclusion
CVD is one of the most common vascular disorders observed across the world and can severely impact QOL, reduce patients’ working hours, and impose a socioeconomic burden. Moreover, the Bonn Vein study reveals that the progression rates of CVD from lower to higher grades increases with time (in a span of 6.6 years, the prevalence for varicose veins rose from 22.7% to 25.1%, and CVD increased from 14.5% to 16%). Despite the increased disease burden with prolonged duration, a high level of acceptance prevails among patients suffering with venous disorders, and both patients and physicians often trivialize the presence and severity of CVD. Nonetheless, despite the capability of CVD to cause grave consequences, it remains one of the prominently underestimated and neglected diseases. Knowing CVD’s potent disruptive nature, it is paramount to give it serious consideration and to define proper measures to prevent and/or manage it.
Keywords: chronic venous disease; chronic venous insufficiency; quality of life; varicose vein; venous ulcer; socioeconomic burden; underestimation
Many authors believe that valvular insufficiency is the principal cause for the development of varicosities... In fact, we now know that veins are exposed to various biomechanical forces other than the traditional intraluminal pressure. Extraluminal pressure, flowing blood, and longitudinal tensile load originating from the presence of different blood volumes in different valve-separated vein segments also influence the biomechanical properties of veins.”

Chronic venous disease (CVD) comprises a set of conditions that cause long-term suffering in the population, with known negative effects on mood and well-being documented in multiple quality of life assessment studies. Given its high prevalence, the management of this pathology is also very expensive, particularly when venous ulceration is present, making proper identification of at-risk patients an increasing necessity. Several risk factors, such as older age, female sex, family history, long periods in the upright position, and obesity, have been positively linked with higher disease prevalence, although data regarding disease progression is still sparse. Recent long-term longitudinal studies such as the Bonn Vein Study and the Edinburgh Vein Study have provided some insight into this matter, with documented yearly progression rates as high as 4.3%. Also, risk factors identified in the Edinburgh Vein Study – family history, previous deep venous thrombosis, and presence of venous reflux – were associated with higher progression rates. Nevertheless, prediction of which patients will develop aggravated disease based on baseline risk factors remains impossible; consequently, the benefit of early intervention is unknown. Considering the current demographic characteristics of the Western world, an increase in CVD prevalence in the near future can be expected; therefore, data on CVD progression is now more important than ever. Further studies are required.

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Introduction

Chronic venous disease (CVD) comprises a set of conditions that cause long-term suffering in the population. The majority of these conditions impair quality of life but do not cause a threat to life. This somewhat influences public opinion in that the problem is frequently considered more of a cosmetic embarrassment than a burdening disease. This belief is reflected in the policies of public health systems, ultimately leading to less attention and funding directed to this disease.

Nonetheless, CVD is one of the most commonly reported chronic medical conditions and represents a substantial source of morbidity in the Western world, consuming up to 1% to 2% of the health care budgets of European countries. Little epidemiological data regarding the progression of this pathology in the general population is known, partially due to the lack of uniformity in venous terminology, which
makes it difficult to compare and analyze data in different epidemiological studies. This lack of knowledge about the natural history and prognostic factors has meant that few advances have been made in identifying patients who might benefit from early intervention, as well as in evaluating preventive measures. Fortunately, introduction of a consensus on venous terminology and recent longitudinal studies have improved the understanding of this pathology’s natural history. Here, we review the current data on the progression of venous pathology.

**Primary venous insufficiency: current epidemiological data on patterns and progression**

For many years, the management of CVD was mainly empirical, given that its pathophysiology, distribution, and natural history were not fully understood. More recently, with the advent of Doppler ultrasound (DUS), the study of venous insufficiency, as well as its progression, has been possible, and the historical perceptions of the venous disease patterns have been challenged.

In fact, according to the traditional “retrograde theory,” it was believed that primary venous insufficiency starts in the saphenofemoral junction, with distal retrograde sequential progression due to an increase in the hydrostatic pressure in the upright position. This common notion was challenged by Labropoulos et al, who, in 1997, studied 125 limbs by DUS in order to assess patterns of insufficiency. His group demonstrated that although reflux could be found in all segments of the saphenous veins and their tributaries, the below-knee segment of the greater saphenous vein was the most common site for reflux (68%), with saphenofemoral junction insufficiency present in only 32% of the cases. Later, Engelhorn et al, in a larger cohort of patients with CVD (472 limbs with reflux), confirmed Labropoulos’ study findings, reporting single or multiple great saphenous vein segmental reflux without saphenofemoral junction involvement in 53% of the patients. These findings changed current lines of thought and influenced several studies that were later undertaken. From here, two theories on venous insufficiency progression have emerged, with some authors defending a segmental to multisegmental progression, whereas others believe in an ascending disease progression. Evidence supporting both theories is available.

In 2012, Engelhorn et al repeated duplex investigations in 92 women (184 limbs) with previous known C1 or C2 disease (according to the CEAP classification system stratifying patients according to severity of presentation; C, clinical; E, etiologic; A, anatomic; P, pathophysiologic), after a mean follow-up period of 33 months. Segmental reflux, which was present in 41% of the patients in the first examination, decreased to 28% at follow-up DUS. On the other hand, a significant increase in multisegmental reflux on control DUS was noted (26% in the first DUS; 40% at follow-up), suggesting that CVD progresses with a pattern of progression from segmental to multisegmental. In this study, the progression was slow: in approximately 3 years of follow-up, there was no significant progression of reflux in about two-thirds of the great saphenous veins. On the other hand, and supporting the ascending theory, Bernardini et al studied 99 patients (104 limbs) with varicose veins for a mean follow-up period of 4 years. During this period, 94% of the patients had evidence of progression of reflux, and all the progressions, when present, extended to reach one or more venous segments at an upper level uninvolved before.

Although CVD progression was confirmed in several other studies, there has been conflicting evidence regarding the rate of progression of the disease, as well as the risk factors influencing it. This is partly a consequence of the lack of uniform venous terminology, which is essential for epidemiological studies, as it serves as a framework for consistency and standardization. The unstandardized use of the term chronic venous insufficiency (CVI), for example, often leads to confusion in epidemiological studies. This clinical venous term was defined in the terminology consensus document as “advanced chronic venous disorder, which is applied to functional abnormalities of the venous system, producing moderate or severe edema, skin changes, or venous ulcers.” Therefore, patients with CEAP C1 to C2 varicose veins do not fit this definition. The indiscriminate use of this term in certain publications regardless of clinical severity, as well as unrepresentative study populations and variable follow-up periods, leads to misinterpretation of epidemiological data. Nevertheless, some population-based studies performed during this period provided more solid information on CVD prevalence and progression.

In the Basel study, 1441 workers in the chemical industry in the 1970s were observed for a period of 11 years. In this study, one-third of the patients with “mild” varicose veins (trunk, reticular, or hyphen web) progressed to more severe varicosities or CVI at a rate of 2.9% annually. On the other hand, the rate of progression in patients with “pronounced” varicose veins was higher, with 50% progressing to CVI at a rate of 4.7% annually. Although this study provided some insight on CVD progression, no uniform venous terminology was available at the time, and the investigated population was...
not based on a random sample of the general population, which of course deeply limits this study's epidemiological value, as previously stated.

More recently, another population-based study was performed, the Bonn Vein Study.\(^1\) In Bonn Vein Study I, conducted in the year 2000, 3072 participants (1350 men, 1722 women) of the general population of the city of Bonn and two rural townships (Germany), aged 18 to 79 years, took part. Participants were selected by simple random sampling from the registries of residents. In Bonn Vein Study II, the same population was investigated again 6.6 years later in order to determine the incidence of newly developed CVD, as well as the progression of the preexisting one. It was observed that, for the considered follow-up period, the prevalence of varicose veins rose from 22.7% to 25.1% and the prevalence of CVI from 14.5% to 16%.\(^2\) This resulted in an incidence of varicose veins and CVI of about 2% per year and suggested that, if left untreated, a significant proportion of patients will move along the spectrum of venous disease from varicose veins to edema, progressing to skin changes and, ultimately, ulceration.\(^2\)

In 2015, the Edinburgh Vein Study accurately reported the progression of CVD during a 13-year follow-up period, granting new insights on disease progression in a larger cohort of patients.\(^3\) This was a population-based cohort study, in which an age- and sex-stratified random sample of adults aged from 18 to 64 years old were first examined at baseline from 1994 to 1996, and later underwent a follow-up examination from 2007 to 2009. The response rate was 52.8%, with 1566 subjects taking part in the study. Participants had a social class distribution similar to that of residents in Edinburgh but were slightly older, from more affluent areas, and more likely to be female than were nonresponders. From the 1566 subjects that were initially assessed, 880 underwent follow-up examination, of whom 334 had trunk varicose veins or CVI at baseline; these made up the study sample. Progression was found in 57.8% of the patients, with an annual progression rate of 4.3%, similar to previous studies. It was noted that progression happened regardless of the baseline CEAP C classification, with 31.9% of the patients with baseline varicose veins (CEAP C1-C2) developing CVI (2.4% annually), and 98% of the subjects with previous varicose veins and concomitant CVI experiencing clinical deterioration.\(^3\) These findings were broadly similar to the Bonn Vein Study and indicated that in around one-third to one-half of the patients with CVD, disease progresses during a 10-year period.\(^3\)

**Risk factors for CVD progression**

Throughout the years, several risk factors have been related to the development of CVD.

In 2007, the San Diego Population Study revealed that age, sex, and ethnicity were important risk factors for venous disease,\(^4\) confirming previous findings by Adhikari et al\(^4\) and Criqui et al.\(^2\) Several other studies also revealed that female sex,\(^5,6\) family history,\(^5,7\) standing occupation,\(^7\) obesity,\(^7\) and multiparity\(^7\) were also associated with the development of this condition. Even smoking was found to be a risk factor for varicose veins, first described exclusively in men in the Framingham study,\(^8\) and later confirmed in both sexes by Gourgou et al,\(^9\) particularly in patients from the CEAP C4-C6 category.\(^10\)

Although various risk factors for CVD have been identified, most of the available information came from cross-sectional studies with target populations, therefore deeply limiting conclusions regarding the impact of these risk factors in disease progression. Also, improper control of potential predisposing factors represents a major methodological issue in some of these studies.\(^11\) Fortunately, more solid data from recent longitudinal studies regarding this subject is also available, although sparse and often conflicting.

In 2010, Kostas et al\(^11\) evaluated the long-term characteristics of CVD progression and its correlation with the modification of specific risk factors. In his work, the contralateral limbs of 73 patients undergoing unilateral varicose vein surgery were prospectively evaluated during a 5-year follow-up period, by use of physical as well as color duplex examination. In about 50% of the patients, CVD developed in the contralateral limb during the considered period. Obesity, orthostatism, and nonadherence to treatment with compression elastic stockings were found to be independent risk factors for disease progression, as previously stated in cross-sectional studies, but multiparity was not.\(^12\) Although a longitudinal study, the sample was not population-based, and therefore generalization of the findings of this study to all patients with CVD was not possible.

The Edinburgh Vein Study later overcame these limitations.\(^13\) In this study, as in previous ones, family history of varicose veins was found to be strongly and independently related to worse prognosis, as well as with the development of CVI in subjects with varicose veins, reinforcing the possibility of a strong genetic predisposition to progression (although family environmental factors could also be involved). History of deep venous thrombosis (DVT) was also found to be independently related to CVD progression, as previously stated by Labropoulos et al,\(^12\) who concluded that progression of CVD was more rapid in postthrombotic limbs than in those with primary CVD, due to the probable combination of reflux and obstruction, as well as multisegmental venous involvement. More importantly, the Edinburgh Vein Study demonstrated that several other factors that were considered to be related to CVD development were not significantly related to CVD progression. In this study, obesity was not related to progression of CVD, although it is considered a risk factor for CVI. The same was found for multiparity, as in this study, there was no relation to progression. Cigarette smoking, bowel habits, and mobility at work were also not related to progression, in accor-
dance with the lack of well-established evidence for their roles in CVD development. Finally, this same study also demonstrated that in patients with varicose veins, the presence of superficial venous reflux was more than twice as likely to induce progression than in patients with varicose veins and no reflux. The risk of progression was related to the number of venous segments affected, with reflux in small saphenous veins being particularly important, as progression was found in 85.7% of the cases. Similar evidence had been identified in a previous study by Labropoulos et al., although in a smaller sample with shorter follow-up. These findings strongly suggest that duplex scanning could be a useful prognostic tool in selected patients.

**Risk factors in predicting benefit of early intervention**

CVD is an expensive and burdensome pathology, with high economic costs and a great impact on general quality of life. Evidence demonstrates that this pathology progresses in more than 50% of the patients, and several clinical risk factors for progression have been identified. Some of these risk factors are immutable, such as family history or female sex, but others are modifiable, eventually changing the disease’s natural history. Also, hemodynamic risk factors such as superficial venous reflux were found to be associated with higher disease progression, although with a variable risk, depending on the number of insufficient venous segments present.

Knowing that CVD progresses in certain subgroups of patients when left untreated has important implications in terms of health care planning and raises the obvious question of potential for benefit of early intervention. Nonetheless, it is still difficult to predict which patients will develop aggravated disease and, more importantly, how fast it will occur. In 2012, Engelhorn et al. reported that a subset of patients with segmental saphenous reflux (CEAP C1-C2) did not need treatment for an average of at least 3 years, but more solid evidence regarding this matter is still lacking.

Maybe one day we will be able to accurately predict which patients with CVD are at higher risk of progression and would benefit from an early intervention, but for now, more longitudinal long-term follow-up studies are required to better understand this subject.

**Etiology of venous insufficiency and varicose veins—ongoing debate and future perspectives**

The pathogenesis of primary venous reflux and the etiologic mechanism of morphologic changes in the vein wall still haven’t been totally explained.

Evidence states that venous pathology develops when venous pressure is increased and return of blood is impaired. These phenomena can be a consequence of valvular insufficiency, venous obstruction, or a combination of both and when present, determine global or regional venous hypertension that when left untreated can ultimately lead to the diverse clinical manifestations traditionally associated with CVD.

Many authors believe that valvular insufficiency is the principal cause for the development of varicosities, in line with what Moore et al. had previously stated in 1951. Nonetheless, conflicting evidence exists and has led to frequent debate regarding the scientific value of this theory. In fact, we now know that veins are exposed to various biomechanical forces other than the traditional intraluminal pressure. Extraluminal pressure, flowing blood, and longitudinal tensile load originating from the presence of different blood volumes in different valve-separat ed vein segments also influence the biomechanical properties of veins. Depending on their magnitude, these physical determinants may either stabilize the architecture of the vessel wall or stimulate maladaptive remodeling processes. In the latter case, a chronic rise in biomechanical load may induce pathophysiological responses of the venous wall, promoting its weakening and eventually leading to the development of venous insufficiency and/or varicose veins, which, as we know, predominantly occurs in the lower extremities.

Taking into account these observations, one must consider that although the development of venous insufficiency may be associated with varicose veins, these venous diseases may simply be coincidental and not necessarily causally related. In fact, there is an ongoing discussion as to whether valve dysfunction initiates these venous diseases or is a secondary event to venous remodeling, since, for example, the weakening of the structural integrity of the venous wall may simultaneously be a consequence of and the cause for dysfunction of the venous valves. The mechanisms that induce these maladaptive responses are also now coming to light, with particular importance being placed on inflammatory markers. In fact, there is increasing evidence to support the notion that among several possible trigger mechanisms, CVI is to a considerable degree a blood-pressure-driven inflammatory disease. Elevated venous pressure and a shift in fluid shear stress generate an abnormal biomechanical environment in venules, in their walls and in valves. This may induce the activation of lytic enzyme activity, with the production of matrix metalloproteinases, as well as set in motion a chronic inflammatory cascade that ultimately leads to the degenerative process involved with venous insufficiency. Certain genetic polymorphisms can also be involved in this process, increasing the susceptibility to these biomechanical changes in affected individuals and therefore serving as risk factors for CVD.

Despite detailed knowledge regarding CVD clinical presentation and treatment options, still not much is known about the underlying cellular mechanisms that ultimately trigger its onset. Better understanding of these phenomena is therefore essential, as targeted pharmacologic anti-inflammatory treat-
ments might one day allow for the blockage of the inflammatory cascades involved in these processes, therefore stopping the chronic progression of this debilitating disease.

Conclusion

CVD is a common, progressive, and burdening disease, often overlooked by health care providers because of an under-appreciation of the magnitude and impact of the problem, as well as incomplete recognition of their various presenting manifestations. Several risk factors, such as older age, female sex, family history, long periods in the upright position, and obesity, have been positively linked with higher disease prevalence, although data regarding risk factors for disease progression are still sparse. Recent long-term longitudinal follow-up studies gave some insight on this matter, by demonstrating that family history, previous DVT, and presence of venous reflux were associated with higher disease progression rates, although it is still difficult to determine which patients will develop aggravated disease and how fast it will happen. Nonetheless, taking into account the current demographic characteristics of the Western world, with an aging population and an ongoing obesity epidemic, it is predictable that the prevalence of CVD will rise, and therefore, better awareness for this condition is necessary in order to prevent patient morbidity and excessive economic costs. More long-term longitudinal studies are needed in order to assess the benefit of early intervention in CVD patients, as well as to assess the risk of deterioration from varicose veins to more advanced stages of venous disease, such as leg ulcers. Better understanding of the etiologic mechanisms causing morphologic vein wall changes is also necessary, as targeted pharmacological treatments could one day be used in at-risk patients in order to block inflammatory cascades that ultimately cause CVD.

References


Keywords: chronic venous disease; epidemiologic data; progression; venous insufficiency
In order to discuss which symptoms may best predict progression of chronic venous disease (CVD) to advanced stages we must first consider the complexity of the disease and the diversity of symptoms, and the terms used to describe these symptoms should be clarified. It is also necessary that leg symptoms can be correctly attributed to venous disorders, as the association of leg symptoms with CVD is known to be difficult. The SYM Vein Group has tackled this challenge, making easier the identification of patients at risk of developing ulcers. Nevertheless, so far there is only preliminary data, which seem to suggest that some venous symptoms can increase the risk of developing chronic venous insufficiency; however, findings are influenced by the methodology used for assessment of venous symptoms in those studies, which were carried out before publication of the SYM Vein consensus statement. Here, we highlight the need for new assessment and new surveys that take each symptom and its severity into account individually.

Introduction

Chronic venous disease (CVD) is a common problem affecting a large number of individuals in Western societies, and over at least half a century, heredity, occupation, and pregnancy have been implicated as risk factors. Irrespective of its clinical presentation—ie, in asymptomatic patients (though the disease very often still causes cosmetic concerns); in patients with symptoms or signs related to CVD; in patients that have developed specific complications, such as superficial vein thrombosis or external bleeding—both the physician and patients are usually aware of the progressive nature of CVD. This fact in turn aggravates the potential distress associated with CVD because it is seen as a precursor of deterioration in cosmetic appearance, quality of life, and health status in general. It is well-known that progression of CVD occurs rapidly during pregnancy due to hemodynamic and hormonal reasons and that there is potential for regression after delivery.

Description of symptoms attributed to CVD

Before making any association between an individual symptom and disease progression in patients with CVD, it is imperative to briefly discuss the symptoms, as described in the 2016 SYM Vein consensus statement developed under the auspices of the European Venous Forum. SYM Vein provided the first detailed description and definition of venous symptoms. Venous symptoms have been underestimated for decades, although clearly described in the literature for a long time. This was...
probably because priority had been given to prevention of leg ulceration, which occurs more frequently in CEAP class C3 and C4 patients (class based on presentation severity in the following areas: C, clinical; E, etiology; A, anatomy; P, pathophysiology) and is not related to the presence of CVD symptoms that are improved with elastic stockings or venoactive drugs.\textsuperscript{2,3} It is also possible that because of the subjective nature of CVD symptoms, often exaggerated by patients seeking treatment, these symptoms were not taken seriously. Nevertheless, the wide use of minimally invasive methods, such as endovenous methods and foam sclerotherapy, grew to include treatment of patient groups previously turned down for saphenectomy. In the SYM Vein consensus statement, the process of attributing leg symptoms to venous disorders was described, and the pathophysiology of individual venous symptoms was extensively reviewed. Individual symptoms described in SYM Vein were pain or aching, throbbing, tightness, heaviness, fatigue, feeling of swelling, cramps, itching, restless legs, tingling sensation, and heat or burning sensation. Equally important are the secondary symptoms (eg, feelings of disquiet, malaise, insomnia, ill-being, etc) and the specific complaint of venous claudication. In a large study on 6009 patients, the most common symptoms were leg heaviness (70.4%), pain (64.0%), and sensation of swelling (52.7%).\textsuperscript{5}

Major issues in the assessment of venous symptoms include the difficulty at times in distinguishing them from symptoms related to other diseases.\textsuperscript{7} Furthermore, human factors may influence how both patients and practitioners describe, interpret, express, and use these symptoms, and are clearly discussed in the SYM Vein consensus statement.\textsuperscript{2} These factors include the following:

- Language and culture.
- Levels of tolerance to unpleasant experiences. This determines whether or not a symptom and its level of effect are reported.
- Previous experience—duration and intensity. This influences the choice of words.
- Psychosocial gains. This may influence the choice of symptoms reported, in order to obtain empathy and support.
- Economic gains. This also affects how symptoms are described.
- A patient’s or practitioner’s belief regarding the relationship of symptoms to a CVD. This influences the symptom described and its severity.
- The perceived importance of venous disorders.
- Psychological dysfunction. This may at times contribute to misperceptions of symptom cause and severity.
- Influence of fear due to family history, for example, a fear of future risk of developing ulceration.

As a result of the bias introduced, associations between the various venous symptoms and end points of research may not be clearly significant, as a different amount of bias may exist for different symptoms.

**Pathophysiology insights**

Pain or aching, tightness, heaviness, and feeling of swelling are more likely to be the result of venous hypertension, although pain may be the result of coexisting vascular inflammation. On the other hand, cramps, restless legs, tingling sensation, and heat or burning sensation may be related to secondary neuropathy as a result of CVD. Itching and a heat (or burning) sensation are probably related to the local temperature of the skin and might represent localized vascular inflammation aggravated by increased ambient temperature. Leg fatigue is thought to be the end result of the presence of one or more symptoms.\textsuperscript{8}

A key component of vascular inflammation leading to certain symptoms is leukocyte-endothelium interaction, which includes a sequence of events, ie, leukocyte trapping/adhesion, migration, endothelial activation, and release of inflammatory mediators in the microcirculation.\textsuperscript{9} Venous hypertension, venous stasis with hypoxia, and altered shear stress are considered the key reasons responsible for the initiation of the vascular inflammation process described above. Inflammatory mediators such as bradykinin, serotonin, prostaglandin, leukotrienes, platelet-activating factor (PAF), and interleukins secreted by leukocytes have been implicated in the activation of nociceptors, which results in diffuse nonlocalized pain. It is thought that pain is the result of activation of sensory multimodal nociceptors of myelinated A\textsubscript{δ} and unmyelinated C nerve fibers. Vascular inflammation may be responsible not only for patient symptomatology but also for alterations in the macrocirculation with remodeling of the venous wall and valves (elastic fiber fragmentation, smooth muscle differentiation and migration with extracellular matrix alteration and fibrosis), which in turn aggravates venous hypertension, ie, is related to CVD development and progression. More work on the genetics of varicose veins and progression is required.\textsuperscript{10} As a positive family history of CVD is a predictor of progression.\textsuperscript{11}

**Ultrasonographic progression**

In a prospective study of progression of reflux patterns in saphenous veins of 92 women with chronic venous valvular insufficiency, great saphenous vein segmental reflux was most prevalent initially, progressing to great saphenous vein multisegmental reflux.\textsuperscript{12} Unfortunately, the frequency and role of symptoms was not reported. In another study, 73 limbs in patients who had venous surgery in the contralateral leg were followed-up for 5 years, and 48 new sites of reflux (affecting the superficial system in 37 cases) were observed in 38 limbs (52%).\textsuperscript{13} Obesity, prolonged standing, and noncompliance with elastic stockings were independent risk factors for CVD progression. Unfortunately, the correlation between overall venous ultrasound findings (reflux + obstruction) and venous clinical severity score was weak in one study ($r=0.23$, $P<0.0001$),\textsuperscript{14} indicating a poor prognostic role of venous symptoms, a constituent of venous clinical severity. However, another study on the progression of CVD showed that in patients with new
signs or symptoms during reexamination, new ultrasound findings were encountered in 54%, compared with 23% in patients without new symptoms (P=0.04), although a predictive role for any baseline symptom was not reported.15 In the same study, progression affected mostly the saphenous trunks or their tributaries.

Association of symptomatology with CVD clinical class and severity scoring
In everyday clinical practice, phlebologists and other vascular specialists are faced with the multifaceted presentation of venous disease. Extensive varicosities are very often entirely asymptomatic; on the other hand, relatively small varicosities can cause significant symptoms. Although exaggeration of symptoms may hold true for those patients seeking active treatment (systemic bias) and there may be variability in patient perception (random bias), these are valid observations. Additionally, a seeming paradox may exist: symptoms in patients with CVD occur more frequently in those with advanced stages of CVD,14,15 but these tend to be less severe in advanced CEP clinical classes.16 This apparent paradox is thought to be a result of an altered perception of pain during the course of the disease or to an increased threshold as a result of neuropathy. Furthermore, venous symptoms are not specific and are sometimes difficult to distinguish from symptoms caused by other diseases. It is obvious that all of the above associations, observations, and facts should be viewed as confounders in the quest for candidate symptoms associated with CVD progression. In general, it has been reported that CVD symptoms did not change in a large series of patients awaiting surgery with a high frequency of progression to skin changes and ulceration.17 However, the association of a specific symptom with progression was not reported.

Frequency of progression
In a study involving 304 patients with varicose veins, 4% of them developed venous ulceration and 22%, skin changes while on the waiting list for a median of 4 years.17 In a cross-sectional study in 114 patients with venous ulcers and a control group of 352 patients with varicose veins and without leg ulceration, venous ulceration developed mainly due to primary varicose veins, and its risk increased with age.18 In the Edinburgh vein study in 334 subjects with varicose veins followed-up for 13 years, progression was observed in 58% (4.3% per year).19 Assuming that the last study included mostly asymptomatic individuals with a CVD, the lower rate of progression than that observed in the previously mentioned study on symptomatic patients (6.5%)17 indicates that progression of varicose veins occurs irrespectively of the presence or absence of symptoms, albeit at a higher rate in the former group, acknowledging the fact that these two studies are not directly comparable. As a result, the asymptomatic individuals may still be offered regular follow-up appointments or at least warned to come back if they experience deterioration of their clinical status, including development of symptoms. This otherwise simplistic observation requires confirmation before formal advice is given to stakeholders and interested individuals.

Bonn Vein Study I, conducted in the year 2000, included 3072 participants—aged 18 to 79 years—of the general population of the city of Bonn and two rural townships. Participants were selected by simple random sampling from the registries of residents. In this follow-up study, 6.6 years later, the same population was investigated again to identify the incidence of newly developed CVD and of progression of preexisting CVD. Between May 2007 and September 2008, all Bonn Vein Study I participants were invited for a reinvestigation. The response at follow-up after 6.6 years was 84.6%, and 1978 participants were reinvestigated. The incidence for new varicose veins was 13.7% per 6.6 years, and for new chronic vein insufficiency (CVI), it was 13% per 6.6 years.20 The authors concluded that there was a high incidence of about 2% per year for varicose veins and for CVI.

Factors associated with progression of CVD
It is very important to clearly define the baseline CVD stage of patients who progress, and it is equally essential to report the CVD stage these patients progress to, as previously reported by others.10,13 Therefore, C0s and C1s patients may progress to C2s disease. Similarly, C2s patients may progress directly to C3, C4, or C6 disease; C3s patients may progress to C4 or C6 disease, and C4s patients may progress to C6 disease. Obviously, in very few patients, symptoms may fade away after evolution, which explains the absence of a designation for symptoms after progression in these examples.

Although not explicitly stated in studies on CVD progression, the presence of edema, which is the hallmark of C3 disease, is usually accompanied by patient complaints, including sensation of leg edema and heaviness. C3 patients, including those with sensation of leg edema and heaviness, are prone to develop progression to a venous ulcer. A well-known source of information on progression of varicose veins is the waiting list for surgery11; however, this is biased because of the selected population. Having said that, these lists mostly contain symptomatic patients, and it is a pity that specific information in the form of stratification by type of symptoms was not provided.21

In a case-control study involving 120 patients with an active or healed venous leg ulcer and 120 controls with varicose veins and no history of venous ulceration, skin changes including lipodermatosclerosis, corona phlebectatica, and eczema; higher body mass index (BMI); and popliteal vein reflux remained independently associated with increased risk of ulceration.22 On the other hand, good dorsiflexion of the ankle and an effective calf muscle pump remained protective factors. Obviously, these predictors should be verified in a longitudinal study, which should additionally evaluate the predictive role of venous symptoms.
In a prospective 5-year study of 96 limbs, the progression of CVD was reported to be more rapid in postthrombotic limbs than in those with primary CVD. Prognostic factors for progression to advanced CVD were the combination of reflux and obstruction, ipsilateral recurrent deep venous thrombosis (DVT), and multisegmental involvement.23

In the large Edinburgh Vein study in 334 subjects with varicose veins followed-up for 13 years, family history was the only independent risk factor for progression in patients with varicose veins at baseline.22 The presence of reflux in the superficial system increased the possibility of progression, particularly when it was combined with deep reflux and affected the small saphenous vein.23 Again, baseline symptoms were not reported.

Additional information may be taken from studies on the general risk factors for development or recurrence of varicose veins. In a study on risk factors, female sex, increasing age, a reported positive family history for varicose veins, increasing number of births, standing posture at work, and increased weight and height were associated with varicose veins.21 In the Edinburgh Vein Study, the incidence of CVI increased consistently with age and obesity, and participants with a family history of venous disease were more likely to develop C2 varicose veins.20 Residual, uncorrected venous hypertension—in the form of a failed open surgery or endovascular ablation of the superficial venous system, intentionally untreated saphenous stems,27,28 or deep vein incompetence or obstruction—is strongly correlated with recurrent CVD. These observations strongly support the notion that underlying major hemodynamic mechanisms are related to postintervention recurrent CVD. Similarly, the severity of underlying hemodynamic pathology may be well associated with CVD progression. Having said that, the fast progression of CVD observed in pregnant women is attributed to hemodynamic (and hormonal) reasons, which supports the above statement.

A reanalysis of the Basel study (1441 participants with follow-up in 1982, i.e., 11 years after recruitment in 1971) was presented several years ago at the 21st Annual Meeting of the American Venous Forum in Phoenix, Arizona, in the United States and was published in the abstract book of the meeting.24 This study reported that on multivariate logistic regression analysis, venous symptoms predicted the development of venous edema (odds ratio 4.08) but not that of varicose veins in patients we nowadays would call C0s or C1s. Unfortunately, no information was given on the predictive role of specific venous symptoms. Nevertheless, the results are in agreement with the clinical experience of C3 patients without visible or palpable varicose veins; this is probably a result of variation in CVD distribution affecting mainly the large veins. Corona phlebectatica, on the other hand, predicted the development of skin changes. A preliminary analysis of the Bonn Vein study published in an abstract form reported that age, obesity, and hypertension were the only predictors of progression, but it was not specified whether venous symptoms were taken into account.

Micronized purified flavonoid fraction (MPFF), consisting of diosmin plus hesperidin, is an effective medication to improve not only patients’ symptoms but also quality of life.29,30 Incompetent valves in small veins and venules may be the target of MPFF and other venaocclusive medications in order to reduce vascular inflammation related to symptomatology and potentially to CVD progression.25,31 Also, transient venous reflux (i.e., reflux observed only in the evening after prolonged periods of standing), which occurs in about 50% of C0s and C1s patients, can be eliminated with MPFF in 93% of all patients, leading to symptomatic improvement in 89%.32 Potentially, progression of venous disease may be halted with MPFF, but obviously, this hypothesis needs formal testing by a double-blind placebo-controlled trial. Similarly, MPFF may be used after ASVAL treatment (ambulatory selective ablation of varicosities under local anesthesia), known to improve venous function,29 or knee-length stripping of the great saphenous vein, known to be associated with residual reflux below the knee and symptoms,33 in an effort to reduce disease progression, pending proper testing of these hypotheses.

**Interpretation of the available evidence**

Symptoms of CVD have been known for decades if not centuries. However, it is only recently that a systematic description of them was published in the form of a consensus statement.2 Very often, one or more coexisting symptoms are intense enough to affect quality of life, calling for medical, surgical, or endovascular intervention. Since CVD is a progressive disease, patients frequently ask about this risk and if it is associated with existing symptoms in the hope of receiving treatment that eliminates these two issues. So far, there is no direct evidence that the presence of symptoms or the type of symptom is related to progression rates. Patients on a waiting list for saphenectomy probably have a higher progression rate than patients who entered the study through screening of the general population,19 indicative of a more aggressive form of disease. C3 patients, with edema, often complain of the sensation of leg edema and heaviness. Such patients seem prone to progression to a venous ulcer, but this common observation requires formal testing. Also, symptomatic C0s and C1s patients have a risk of developing venous edema that is fourfold that observed in C0a and C1a (a, asymptomatic) patients, but no details on specific symptoms were presented. The results of the Bonn Vein study, which will investigate the possible predictive role of venous symptoms on progression of venous disease,41 are eagerly awaited.

**Conclusions**

There is evidence to suggest that venous symptoms in general in patients with CVD are predictors of progression in C0s or C1s patients, but there is no information with regard to a
particular type of venous symptom. Sensation of swelling in the subset of C3 patients with venous edema per definition may be viewed as a risk for future ulceration, although this hypothesis should be confirmed by a controlled study. Un-
til a definite study becomes available, the pathophysiology of CVD symptoms and progression should be viewed as distinct steps of the complex process responsible for the development of varicose veins.

References
Risk factors and possible therapeutic options to delay the progression of chronic venous disease

by M. Vuylsteke, Belgium

Chronic venous disease (CVD) is a very common and progressive disease. This means that untreated patients will develop more signs and symptoms of CVD, and this will have an impact on their health-related quality of life (HRQOL). The underlying mechanism of this progression is persistent venous hypertension and local inflammation of the vessel wall. Epidemiological data show the important influence of risk factors on the progression of CVD. Some risk factors, which are mostly lifestyle related, can be influenced. Unfortunately, however, the most important risk factors—such as having a positive family history, age, and sex—are not modifiable. Treating patients with compression and medication does have a positive influence on the symptomatology of CVD and on ulcer healing. Interventional treatment, either surgical or endovenous, does have an important impact on the venous disease. Signs and symptoms will diminish and the patients’ HRQOL will improve significantly. Unfortunately, this will be temporary, as recurrence can be expected. One of the major causes of recurrence is progression of the disease. There is no evidence at present that early intervention has an impact on the underlying progression of CVD.

Introduction

Chronic venous disease (CVD) is a very common disorder in Western societies1-4 and even worldwide.5 Estimates of its prevalence vary depending on the population, selection criteria, disease definition, and imaging techniques used. Its severity changes dynamically within the adult population. The age-stratified prevalence of truncal varicose veins measured in the Edinburgh Vein study was 11.5% in the 18-to-24–year age group, increasing to 55.7% in the 55-to-64–year age group.2,4,5

In order to report more precisely on the extent of venous disease, the CEAP classification was introduced in 19947 and updated in 2004.8 This classification is based on clinical manifestations (C), etiological factors (E), anatomic distribution of disease (A), and underlying pathophysiologic findings (P).

According to the results of the Vein Consult Program, the prevalence of CVD (C1-C6) and chronic venous insufficiency (CVI, C3-C6) are respectively 63.7% and 25.9% worldwide.5 Increasing age results in a higher C-classification, with more symptoms and a lower disease-related quality of life (QOL).9 Venous disease is a progressive...
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Clinical progression of CVD is accompanied by progression of reflux in the superficial veins, and both clinical progression and progression of superficial venous reflux are significantly correlated with age. The underlying pathophysiology is persistent venous hypertension and a local inflammatory process. These are significantly influenced by other risk factors, such as obesity, orthostatism, lack of regular exercise, pregnancy, smoking, having a positive family history (genetics?), and female sex. So, what can we do to delay this progression?

Risk factor assessment

The most important risk factors include having a positive family history for venous disease, obesity, age, and sex, and these do have an important influence on the predicted probability of having CVD (all P < 0.001).

Having a positive family history of CVD is the most common risk factor. The expected risk of developing venous disease is about 90% if both parents are affected. If only one parent is affected, the risk drops to 25% in males and to 62% in females. The heritability of CVD is high, which suggests a notable genetic component in the etiology of the disease. To date, no specific gene loci associated with the development of varicose veins have been identified, although mutations in the FOXC2 gene (encoding forkhead box protein C2) are strongly associated with primary valve failure in lower limb veins. In any case, there is no way of altering this risk factor. But family history may remain important even if genetic variants are elucidated, because it also reflects interactions between genetic and environmental risk factors.

Family members may have common habits and may be exposed to similar environmental risks.

The estimated probabilities for having CVD and CVI for each sex increase with age. Older age means an increased number of insufficient venous segments and increased risk of clinical progression of CVD from varicose veins to CVI. The pathogenesis of CVD and the influence of age are still debated. Although most experts agree that valve reflux is the principal determinant of varicose veins and CVD, there is no consensus as to whether primary valve incompetence is the initiating event in the pathogenesis of venous disease or whether the incompetence is secondary to vein wall dilatation. Some evidence indicates that reflux likely occurs due to weakening of vein walls and subsequent venous dilatation, resulting in incompetence of the valve. In varicose veins, the vein wall is highly heterogeneous and can be separated into hypertrophic and atrophic areas. The hypertrophic areas, containing de-differentiated smooth muscle cells and increased extracellular matrix content, are the result of a "wound-healing" response. The atrophic segments may represent a final stage in the evolution of hypertrophic segments in which the smooth muscle cells have degenerated and disappeared.

One histological study showed that total collagen content and, particularly, intimal collagen decrease with advancing age. Furthermore, the collagen fiber types demonstrated a statistically significant alteration with age. The compliance of the venous vessel wall decreases, and it becomes incapable of elastic expansion to cope with changes in blood volume and flow. The age-associated decrease in both collagen and elastin may ultimately contribute to an age-associated decrease in venous compliance, leading to an increased risk of venous diseases such as CVD and varicose veins.

Degeneration of the vein wall is associated with a local inflammatory reaction. Vein wall degeneration results in modification of local shear stress. Local venous hypertension also causes some hypoxia of the vein wall. This triggers the local inflammatory reaction resulting in leukocyte activation and local release of inflammatory regulators. Endothelial destruction results from leukocyte attachment. This increases capillary permeability, again leading to release of free radicals and matrix metalloproteases (MMPs). Further degradation of extracellular matrix and destruction of valve leaflets and vein wall structure again leads to increased venous hypertension. This is a continuous self-exacerbating and ongoing process affecting the vein wall, which is altered with age.

Age-related degeneration is of course not modifiable, but some medication can decrease the local inflammatory reaction, resulting in improved venous tone. This is associated with a decrease in symptomatology and edema among the patients with CVD. However, the question of whether these vasoactive drugs really have a significant influence on the progression of the venous disease remains unresolved.

Female sex is, in most epidemiological studies, also associated with an increased prevalence of CVD. Although evidence is not consistent, pregnancy is presumed to be a major contributory factor in the increased incidence of varicose veins.

Selected abbreviations and acronyms

- CEAP: classification system to stratify patients according to severity of presentation; C, clinical; E, etiologic; A, anatomic; P, pathophysiologic
- CVD: chronic venous disease
- CVI: chronic venous insufficiency
- HRQOL: health-related quality of life

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Pregnancy is associated with a number of physiological changes that contribute to the development of venous distention and thus, potentially, to varicose veins. There is a significant increase in blood volume, caused primarily by plasma volume expansion. In addition, fetal growth and weight gain increase intra-abdominal pressure and impair venous return. Hormonal changes, such as increases in relaxin and progesterone levels, will also weaken the blood vessel wall and have a vasodilator effect. This increases the pressure on the venous valves in the lower limbs.

Interestingly, one study found a significant difference when comparing male patients with female patients who had never become pregnant. Those female patients had a significantly larger number of symptoms (all female patients) and a higher C-classification (in age groups <50 years) than male patients. This means that pregnancies are not the only reason why female patients have a higher CVD severity on average. Genetic factors and hormone state probably play an important part as well.

Obesity has been associated with a more advanced clinical stage of venous disease than observed in nonobese people. This can be explained by increased intra-abdominal pressure, which creates a relative obstruction to centripetal venous flow. This leads to venous hypertension and increased risk of CVD progression.

Many obese patients also have right cardiac failure, which impairs venous return. However, in severely obese patients, approximately two-thirds of limbs have no anatomic evidence of venous disease. The association of increasing limb symptoms with increasing obesity suggests that the obesity itself contributes to the morbidity.

On average, obese patients also take less regular exercise and sit down for longer periods, which contributes to venous hypertension. Interestingly, edema and skin changes decrease after bariatric surgery. This suggests that correcting obesity can have an influence on the progression of venous disease. Cross-sectional epidemiological studies show that risk factors such as prolonged orthostatism and lack of regular exercise are correlated with a higher C-classification. This can be explained by a decreased calf pump function, which increases venous pressure and thus impairs venous flow. Smoking, particularly in males, may also be associated with a higher risk of developing CVD. These behavioral factors can be modified and could have a positive effect on the progression of the venous disease. However, more longitudinal studies are necessary to prove that effect.

**Compression**

Compression is widely used in the treatment of venous disease. It improves venous pump function and enhances venous flow velocities. At various stages, compression significantly reduces symptoms and has a positive effect on patients' health-related QOL. Unfortunately, there is insufficient information from randomized trials on the prevention of CVD progression by compression. However, in one study by Kostas et al., it was shown that patients adherent to compression therapy experienced slower progression of their CVD than those who did not adhere to such therapy. More studies including large cohorts of patients and long follow-up periods are necessary to make any final conclusions on the effect of compression on the progression of CVD.

**Medical therapy**

Persistent venous hypertension is widely accepted to be the predominant cause of the progression of CVD. This is accompanied by a local inflammatory reaction in the vein wall and valve leaflets. This is a self-sustaining reaction leading to progressive leaflet destruction and scarring of the vein wall. It has been shown that medical therapy using micronized purified flavonoid fractions (MPFF), reduces this inflammation. These venotonics reduce expression of adhesion molecules, reduce adhesion of leukocytes to the endothelium, and decrease capillary permeability.

One study in which patients were treated at an early stage of venous disease (C0s) showed that MPFF is able to reverse transient segmental reflex in the GSV. This resulted in a reduction in symptoms in the affected patients. However, more double-blind, randomized controlled clinical trials with long follow-up are necessary before any final conclusions can be reached on the effect of medical therapy on the progression of venous disease. Meanwhile, venotonic drugs should only be considered as a treatment option for swelling and pain caused by CVD.

**Interventional therapy**

Varicose vein surgery is among the most commonly performed medical interventions and accounts for 1.5% to 2% of total health care expenditure. A large proportion of patients looking for interventional treatment are C2 patients, with signs and symptoms of venous disease but without edema or skin changes. Patients with mainly cosmetic problems also receive treatment. However, a certain number of patients with early stage venous disease (C2) will progress to a higher clinical stage (see introduction). Untreated patients will develop more signs and symptoms, which has an impact on patients' HRQOL. Unfortunately, it is difficult to predict which patients will progress to the higher clinical stages. HRQOL studies show that venous disease does have a significant influence on patients' QOL, independent of the CEAP clinical classification. Results from a randomized trial have also shown that surgery for uncomplicated varicose veins gives a signifi-
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Can we prevent the progression of chronic venous disease in terms of HRQOL, health status, and patient satisfaction at a relatively small cost? Therefore, patients with varicose veins with CVI (C3-C6), as well as those C2 patients with severe clinical symptoms and impaired QOL due to CVD, should be treated with ablation of the varicose veins in a refunded care system.10

Varicose vein surgery does have a positive influence on the signs and symptoms, decreases the clinical C-classification, and improves HRQOL. However, can varicose vein surgery prevent extension of venous incompetence over time?

The reduction in venous hypertension by surgery or endovenous techniques is considered the mainstay of therapy for the treatment of CVD and for avoiding recurrences. Experience has taught us that patients treated at an advanced stage, with huge amounts of tributaries, do have more postoperative pain and complaints than those treated in an early stage. They have more postoperative hematomas, induration, pain, and hyperpigmentation.

There are, unfortunately, no data available showing any difference in recurrence rates between patients treated in an early stage compared with those treated in an advanced stage of venous disease. Independent of the clinical severity of the patient treated, recurrence can be expected in 40% to 50% at 5 years and 70% at 10 years.49,50 These recurrences are multifactorial, but progression of the disease should account for 20% to 50% of all recurrences. This may be due to anatomical extension of previous incompetent truncal segments, reflux in new segments, or a combination of both. Varicose vein reflux can develop in any vein, with or without an apparent feeding source.51,52

Neovascularization is also a major cause of the recurrence of reflux. At 5 years, it is found in 32% and 50% of cases at the saphenofemoral and saphenopopliteal junctions, respectively.49,53 Many theories exist explaining the underlying cause of neovascularization as a cause of recurrence. One interesting theory is the hemodynamic paradox proposed by C Recek. After elimination of the incompetent truncal vein and the tributaries, some small communicating channels might persist. Due to a pressure difference between the femoral vein and the remaining veins in the saphenous system in the thigh during calf pump activity, these minor channels may grow and develop into tortuous diluted veins. The pressure difference increases flow and enhances fluid shear stress on the endothelium in preexisting minor communicating channels between the femoral vein and the saphenous system in the thigh, which triggers release of the biochemical agents nitric oxide and vascular endothelial growth factor; the consequence is enlargement (vascular remodeling) of the communicating channels and, ultimately, reflux recurrence. Hence, the abolition of saphenous reflux creates the conditions for the recurrence of the previous pathological situation.54

In a study on the efficacy of surgery of the superficial venous system and compression at early stages of CVD for the prevention of chronic venous ulceration, no difference in terms of avoiding recurrences of ulcerations could be found between patients who were adherent to treatment and those who were not.55 It appears that interventions have no effect on the natural progression toward higher C-classifications.

Conclusions

CVD is a progressive disease. Its progression is influenced by risk factors. Some risk factors, especially lifestyle-correlated ones such as obesity, smoking, orthostatism, and lack of regular exercise can be influenced, whereas others cannot. Early interventions will have a positive influence on patients’ signs and symptoms of CVD and their HRQOL. This positive effect will be temporary. In the meantime, patients will feel better until recurrence occurs. Unfortunately, there is no evidence that intervention can delay the underlying progression of CVD.

References


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**Keywords:** chronic venous disease; compression; health-related quality of life; inflammation; purified flavonoid fraction; risk factor; surgery

Options to delay chronic venous disease progression – Uppståke

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The last fellowship was awarded at the:
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In your clinical practice, what makes you initiate the management of chronic venous disease: signs or symptoms?

1. L. M. Chernukha, *Ukraine*
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4. E. Kolossváry, *Hungary*
5. D. Pratama, *Indonesia*
6. S. Tzaneva, *Austria*
7. I. A. Zolotukhin, *Russian Federation*
8. M. Zummo, *Canada*
Whether it’s the signs or symptoms of chronic venous disease (CVD) that lead me to initiate treatment can be considered from a philosophical viewpoint. Development of CVD in lower limbs (LL) is a consequence of pathological venous hypertension. Macrohemodynamic changes associated with valvular failure in the superficial (deep) veins initiate a cascade of inflammatory reactions. The inflammation, initiated by venous hypertension, is a key moment in the prolongation of the development of pathological processes; clinically, it is manifested by CVD symptoms and signs.1

Patients with initial symptoms, indicating the development of a disease, do not always consult a doctor; very often, patients ignore this “symptomatic” stage. In most cases, the patients that consult doctors have already developed external disease signs, the progression of which may overshadow the symptoms or make them seem less obvious.

If we look past the general “philosophy” and consider a specific clinical condition that is pathognomonic for CVD (especially the most common nosology—varicose vein deformation of primary etiology), we must first focus on the definition of “symptoms and signs.” A misunderstanding of this terminology is the basis for the subsequent misunderstanding not only between the patient and the doctor, but also between doctors themselves.2 Second, we need to assess the patient’s clinical status and complaints, knowing it is often difficult for patients to find the right words for their interpretation.3

The fact is despite the high prevalence and frequency of occurrence, more than 75% of adults present characteristic venous symptoms2 that are not always caused by CVDs of the LL (monopathognomonic), but can be “mixed,” and can be initiated by concomitant diseases (comorbidities such as musculoskeletal diseases). Doctors often see patients who have typical CVD signs but do not have symptoms or simply do not recognize them. It can be assumed that the stage of expressed symptoms was missed (eg, with the development of varicose veins, at the stage of venous wall stretching, the “activity” of nociceptors—which react intensively to the venous wall stretching at the initial stages of disease—is lost).4

In turn, studies show that 19% of patients (every fifth patient!) at the C0s stage have a severe pain syndrome with no clinical signs. Again, it’s important that the link between symptoms and their onset together with CVD of the LL is made at the early stages of disease development. At that point, there are no CVD signs, and the symptoms can be more pronounced than with “severe” CVD of the LL.

Ideally, we should not wait for signs of CVD of the LL to manifest before treatment is begun; treatment should begin as soon as symptoms appear. However, patients do not always come for treatment at the preclinical stage, without signs of disease. Sometimes, it is the doctors that do not pay proper attention to patients without signs of disease, thinking “nothing to operate on; therefore, nothing to treat.”

Discussion with the patient, consideration of clinical and instrumental examination findings, and, necessarily, active medical thinking are key to achieving a correct diagnosis and determining correct treatment approaches; at the appearance of initial symptoms, pathogenetically based treatment can slow down or prevent the development of the disease, even more so its severe forms.

Treatment regimens in CVD should be based on venoactive drugs, such as micronized purified flavonoid fraction, with higher levels of guideline recommendation.5 This includes the earliest stage of CVD, where there are no visible or palpable signs (C0s). Treatment to inhibit inflammation and improve venous hypertension may offer the greatest opportunity to prevent CVD progression and related complications.

The key importance of symptoms is undeniable—one should not wait for signs to appear. It is necessary to prescribe pathogenetic treatment!6

References
Chronic venous disease (CVD) is the most common vascular pathology seen during the daily practice of vascular surgeons. It encompasses a wide spectrum of manifestations, including symptoms that can sometimes be incapacitating, usually resulting from dysfunctional drainage of blood from the lower limbs. Left untreated, it can be a progressive disease, which can also become complicated (bleeding, thrombosis, or ulceration), affecting the patient’s quality of life. So every vascular surgeon nowadays is aware that CVD is much more than just a cosmetic concern.

A variety of treatment options are currently available, including noninterventional treatment in the form of compression stockings and vasoactive drugs; interventional procedures in the form of sclerotherapy for spider or reticular veins; reflux ablation by laser, radiofrequency, or glue; and deep venous reconstructions by endovenous stenting, surgical endophlebectomy, or bypass. Choosing the proper modality for treatment in modern practice should be tailored following careful analysis of each patient’s history, clinical presentation, and after investigating the underlying pathophysiologic cause(s).

The question remains, however, whether we should base our decision to treat patients solely on the presence of signs, ie, “what we see,” or according to a patient’s symptoms, ie, “how the patient feels.” The fact that some patients with early varicose veins remain asymptomatic should not withhold us from investigating patients for any underlying pathophysiologic abnormality. There is no evidence that asymptomatic CVD cannot become complicated. Besides, CVD has been shown to develop and progress in about half of unilateral-treated CVD patients in their contralateral previously asymptomatic limbs in 5 years. Although the natural history of CVD progression has not yet been clearly established, it is estimated to be somewhere between 3.5% and 7% per annum. Furthermore, symptoms related to venous insufficiency can be present in nearly a fifth of the screened population in epidemiological studies denoted as COs, even in the absence of any signs of CVD. This subgroup of patients can benefit from vasoactive drugs, eg, flavonoids, which can be quite effective in improving symptoms of uncomplicated CVD and improve the quality of life of treated patients. Although their role in preventing complications or progression of disease remains to be explored, flavonoids have also been shown to promote venous leg ulcer healing.

In conclusion, CVD is a disease with variable patterns of presentation, can progress, and can become complicated. The decision to initiate management should be taken once CVD is diagnosed, regardless of whether patients have signs, symptoms, or both. Treatment should be tailored according to each patient’s presentation and should not be delayed in asymptomatic patients until signs develop or vice versa.

References
Chronic venous disease (CVD) leads to substantial socioeconomic costs, accounting for more than 2% of the healthcare budgets in Western countries. Its prevalence increases linearly with age.

CVD should be managed from the very first functional signs and symptoms: heavy legs, pain, swelling, tingling in the feet and ankles, restless legs, etc. These signs and symptoms are not trivial, as complications may arise and become aggravated with time. They have a strong negative impact on patients’ quality of life, are a source of discomfort, and impair daily activities. CVD can rapidly become a true handicap, limiting or even obliging to discontinue certain activities. Trophic disorders, such as cutaneous pigmentation, eczema, and even ulcerations, appear later in the course of its evolution.

CVD treatment should not be limited to the surgical stripping or the endovenous obliteration of a varicose vein. It should take into account all patients’ complaints and is not limited to a medical prescription. A healthy lifestyle is of the utmost importance: it’s effective and inexpensive, it aims to encourage movement: walking, exercises to prevent venostasis, deep breathing, etc.

Treatment aims to relieve patients’ symptoms, prevent CVD complications, and limit the progression of the disease.

In the initial stage of the disease, the evidence provided by physical examination is scanty. Thus, there is a risk that the physician might consider the condition trivial. Functional signs reported by the patient are at the forefront; they are a consequence of tissue damage due to venous stasis in the capillaries with hemorheological disturbance, an increase in capillary leakage, and inflammation within the interstitial fluid, clinically resulting in evening ankle edema, which disappears during the night in the lying position.

The initial stage of the disease represents the best moment for the prescription of venoactive medicines. Indeed, no other treatment can be proposed at this stage. sclerotherapy is not useful in the absence of significant hemodynamic involvement, and venous contention measures are often poorly accepted at the initial stage, particularly by young women in countries with a warm climate.

Venoactive medicines will act, according to their mode of action, on the different components responsible for the functional signs of venous disease. Varicose disease will unfortunately continue its evolution; however, thanks to these medicines, this will be delayed and controlled.

Treatment should last a sufficient time and, most importantly, should be continued throughout the warm season, from April or May until the end of September. During the winter, treatment every other month will be useful in order to ensure effective tissue drainage, in combination with appropriate venous contention.

Venous disease should therefore be managed from the very first stages of its evolution. Treatment should ideally be initiated when patients are not too advanced in age and before the development of complications that characterize neglected CVD.

CVD should therefore be regarded as a whole. A rigorous approach to its diagnosis and treatment can only be beneficial to the patient and, as a consequence, also allow healthcare savings.

References
In medical and even in colloquial communication, the terms of symptoms and signs are widely used. According to the common definitions in the medical dictionaries, the distinction between symptoms and signs is basically related to the individual who notices something abnormal in relation to a medical condition. According to this concept, whereas symptoms are detected by the patient, signs are discovered by the physician by any means of examination.1

However, numerous examples may be given showing that this distinction is not accurate and that the exact nature of contrast is not clear. We may reject the view of distinguishing signs from symptoms based on patient-subjective versus clinician-objective attitude or that signs are visible externally and symptoms are internal feelings. The essential feature of a sign, according to Lester S. King, is that there is both a sign (or “signifier”) and a “thing signified.” So “the essence of a sign is to convey information”; it can only be a sign, properly speaking, if it has a meaning.2

Besides the ontological problem of lacking an exact definition of symptoms and signs, the challenge in using these terms is more pronounced in asymptomatic cases when only signs can be detected. There are also conditions with symptoms and no objectively detectable signs.

In reference to chronic venous disease (CVD), orientation by focusing on the pattern of symptoms and signs is rather challenging, as the provocative title indicates.

This problem is especially characteristic in the case of functional disease. Functional CVD (FCVD) corresponds to the first C class (C0, no visible or palpable signs) in the CEAP classification (C, clinical; E, etiologic; A, anatomic; P, pathophysiological).3 The prevalence of FCVD was close to 20% in the Vein Consult Program.4 Andreozzi et al recommended a typology of FCVD, with four groups showing patency and no reflux by ultrasound examination and different duration of symptoms. The prevalence of symptoms in these cases were mainly heavy legs (74.39%), followed by night (resting) cramps and restless leg syndrome (29.26%).5

In these cases, the dilemma is even more complex in contrast to examples where we may base our clinical decisions on existing symptoms and signs with a different pattern.

In my view, two points may be raised that can potentially contribute to a reinterpretation of the seemingly contradictory approach that is hidden in the conflict of symptom or sign conception.

Firstly, aching, night cramping, and restless legs are not visible indeed. However, the pattern of these findings, especially after excluding other conditions not related to CVD, in fact, conveys information for venous specialists. In this sense, the exact distinction between symptoms and signs just fades out.

Secondly, the exclusion of functional alteration in the venous system as essential criteria for FCVD, represents a probably more complex challenge than outlined in the work of Tsukanov et al.6 In their study, in almost half of C0 patients, transitory reflux was detected by duplex ultrasound examination in the evening only and not in the morning, with an association of larger great saphenous vein (GSV) diameter in the evenings. After micronized purified flavonoid fraction (MPFF) treatment for 2 months, the signs of transitory reflux and GSV diameter difference disappeared in parallel with diminishing symptoms. This analysis draws attention to the importance of functional investigations and the difficulties of detection of early signs of CVD.

In conclusion, answering the question about symptoms or signs as a priority in the management of CVD, I recommend pondering over the deeper meaning of this distinction and closely following the new results of research on functional alteration in CVD. I would not argue for preference for either of these two terms.

References
In Indonesia, the incidence of chronic venous disease (CVD) increases every year. Although there currently is not sufficient data available from national-scale studies from the Indonesian Ministry of Health, the prevalence of CVD is assumed to be as high as that in developed countries, considering the similar risk factors in society such as lifestyle, less exercise, smoking, high pregnancy rate, and use of hormonal contraceptive. Due to the worsening progression of the disease, the economical effect arising from it, and the significant decrease in quality of life, management of CVD is of immediate concern.

The prognosis of CVD will worsen drastically if it reaches the late stage: chronic venous insufficiency (CVI) or postthrombotic syndrome (PTS). With a limited number of experts—especially vascular surgeons—and limitations in physicians' knowledge, early care of the disease can be suboptimal, influencing disease progression significantly. In my experience, the patients who come to the vascular surgery clinic are usually in stage C3 (having edema) based on the CEAP classification (stratifying patients according to severity of presentation; C, clinical; E, etiologic; A, anatomic; P, pathophysiologic). Most of them have had complications such as dermatitis, hyperpigmentation, lipodermatosclerosis, thrombophlebitis, leg ulcer, and deep vein thrombosis. The patients in such condition could not be treated by conventional or minimal invasive surgery alone. Some come in with even worse conditions that can only be managed conservatively by compression stockings and a micronized purified flavonoid fraction (MPFF) drug, such as diosmin plus hesperidin. The prognosis for CVD patients with complications is not satisfying.

Unfortunately, Indonesian national health insurance cannot cover both conservative therapies. Compression stockings are not covered because they are considered cosmetic therapy, and MPFF is categorized as traditional medicine. As the symptoms' recurrence is frequent and the treatment duration is for a lifetime, CVD therapy is a financial burden. From the macroeconomic point of view, the treatment of CVD would be costly and could account for 1% of the national health expenditure. The loss of work hours is estimated to be more than 2 million hours annually, either due to morbidities or to clinic visiting schedules. Furthermore, if the psychological impact on influencing productivity is taken into consideration, CVD would cause significant losses for the economy in a developing nation.

It should be kept in mind that the most important thing in managing chronic diseases, including CVD, is the quality of life. The losses described above supposedly trigger us to manage the patients' condition comprehensively by considering physical, economical, and psychological aspects. We believe that it is urgent to treat CVD before the disease progresses and incurs further complications.

So, when should we initiate therapy? Is it when the patient feels the symptoms or when the signs appear on physical examination? On the basis of the reasons above and also to emphasize the importance of quality of life, we believe that CVD management should begin with the presence of symptoms.

The earliest classification stage of CVD is C0, either with or without symptoms (C0s or C0a, respectively). Generally, patients start to seek medical help at the C0s stage. Diagnostic procedures must be used to determine the causes of symptoms, even in the absence of signs. Next, therapy in accordance with the pathophysiology and complaints must be started immediately to get rid of the symptoms, to prevent further progression of CVD, and to enhance the overall quality of life. If we refer to the 2015 European Society for Vascular Surgery guidelines for CVD management, the earliest management is recommended to start when symptoms are present, even if no signs are found, as this prevents progression of the disease. We can at least educate patients about preventive efforts, such as physical exercise and the control of patient risk factors.

We believe that the patients' quality of life is still the first priority in the management of CVD.

Dedy PRATAMA, MD
President of Indonesian Society for Vascular and Endovascular Surgery (ISVS)
Division of Vascular and Endovascular Surgery
Dr. Cipto Mangunkusumo Hospital / Faculty of Medicine, University of Indonesia
INDONESIA
(email: dedypratama@yahoo.com)
There is still some controversy and discussion in the phlebological community regarding the optimal time for treatment of a patient with chronic venous disease (CVD). In this short article, I will share my thoughts and the procedure that I follow when I have diagnosed CVD in a patient.

In general, signs are defined as the physical manifestation of a medical condition and can be objectively observed, whereas symptoms can only be felt and described by the patient. Thus, signs are visible externally and symptoms are internal feelings.

Nevertheless, medical signs aren’t always diagnosed by seeing, but also by touching, listening, or smelling. Some of the most common signs I assess in my medical field are the skin signs: color, temperature, structure, surface, and moisture. For example, increased local temperature could be a sign of erysipelas; hardening and immobility of the skin, a sign of lipodermatosclerosis; and foul-smelling odor of a leg ulcer, a sign of wound infection. Another aspect is that signs do not always correlate with the symptoms. In my clinical practice, there are patients with CVD who report considerable complaints but have few objective signs. On the other hand, some patients with evident clinical signs do not describe any subjective complaints.

The decision whether to treat a patient with CVD is pretty complex. In my opinion, important decision criteria are whether the superficial, the deep venous system, or both are affected, taking the signs into account. Furthermore, it is crucial if the patient has a venous reflux disease, an obstructive venous disease, or the combination of both. In case of a refluxive superficial disease, the distribution plays a key role, depending on whether trunk veins, side branches, or both are affected.

In my view, it is important to weigh the benefits and risks in the specific patient’s situation besides considering the signs and symptoms. For example, the threshold for recommending noninvasive treatments is much lower because the benefit-to-risk ratio is high. This applies especially to compression treatment and therapy with venoactive drugs. If invasive procedures are necessary, it is even more important to consider not only signs and symptoms, but also individual wishes of the patient, life and work situations, compliance, and education of the patient.

Sometimes the symptoms reported by the patient have nothing to do with the current venous disease. In these cases, it is important to objectively assess the signs of the venous problem and to make the decision for treatment. However, if the symptoms indicated by the patient are clearly related to the venous disease, I tend to recommend treatment.

If the patient does not report any symptoms, but tissue damage from stage C4a with skin changes is visible, I strongly recommend treatment. If a large caliber trunk vein insufficiency with significant reflux is present, I recommend treatment, but I do not recommend treatment in patients with isolated side branch varicose disease. If the deep venous system is affected, I strongly recommend treatment in order to prevent further progression of CVD.

In summary, both signs and symptoms are incorporated in my decision to treat or not to treat a patient with CVD, but these are not the only important arguments. Finally, the decision is made individually, depending not only on signs and symptoms, but also on many surrounding factors and information regarding a patient’s life situation and benefit-to-risk analysis.
To be brief, I suggest treatment of chronic venous disease (CVD) if either signs or symptoms are present. For example, for a patient with varicose veins but no symptoms, I suggest treatment; and for a patient with venous symptoms but no signs, I also suggest treatment.

Why is that? For starters, this is a linguistic issue. In the Russian language, the words “symptom” and “sign” have the same meaning; we do not distinguish between them the way a native English speaker would. Furthermore, regardless of whether the patient has symptoms vs signs (or both), having either means there is a disease that has to be managed. This is what all medical doctors in Russia have been taught as students and postgraduates.

On the basis of my understanding of CVD and on my personal experience, treatment should be initiated as soon as symptoms or signs are noted. For example, let’s say I see a patient with primary varicose veins and no complaints. My understanding of the disease tells me that vein-specific inflammation is behind it. The pathological process would have already started, with leukocytes being recruited from the blood flow by endothelial cells, migration of leukocytes into the venous wall, and remodeling of the venous wall underway. What I know of vein-specific inflammation is that it never stops on its own. Leukocytes move to interstitial tissues, causing damage that leads to symptoms, edema, and trophic disorders. Patients left untreated because they are asymptomatic will experience symptoms sooner or later. From my personal experience, this happens in many, if not all, patients. The literature supports this. The greater the age of the patient, the longer the disease duration; thus, we often observe more advanced stages of CVD. I see no reason to wait to initiate treatment if the patient presents with varicose veins only and complains of nothing. It is only a matter of time before symptoms develop.

The choice of treatment for primary varicose veins is rather clear to me. If there are no contraindications, I suggest endovenous ablation or surgery, depending on the situation with compression before and after the procedure and medical treatment with micronized purified flavonoid fraction (MPFF) overlapping the date of procedure. If there are venous symptoms, I prescribe MPFF. I prefer this agent because of my understanding of the disease, which tells me that vein-specific inflammation is the target of treatment. MPFF is known as an agent that has an effect on it, improving venous symptoms and edema. This is corroborated by published data, along with my personal experience.

In some patients with neither signs nor symptoms, I may also suggest treatment. For example, after deep vein thrombosis (DVT), some patients are sign- and symptom-free. I believe that doesn’t mean they are disease-free, especially if DVT was proximal. They have deep venous reflux, which alters shear stress. Uncorrected, this triggers vein-specific inflammation.

There is no way to fully correct such reflux. So, I believe we need to treat postthrombotic patients by compression in order to reduce reflux and by medical treatment with MPFF in order to control venous inflammation so that patients are kept asymptomatic to the greatest extent possible.

In conclusion, regardless of whether the patient has signs vs symptoms, I consider CVD to be a chronic condition with slow but inevitable progression that needs to be managed after it is confirmed.

Igor A. Zolotukhin, MD, PhD
117897, 36-1-381, Novatorov str., Moscow
RUSSIAN FEDERATION
(email: zoloto70@bk.ru)
The decision of whether or not to treat chronic venous disease (CVD) is based on the patient’s quality of life (QOL), which can be impaired either by a change in the cosmetic aspect of his or her legs, especially in classes C1 (having telangiectasias or reticular veins) and C2 (having varicose veins), or by improving the symptoms associated with CVD in all clinical stages. By experience, in the earlier clinical stages of CVD, it is not rare for patients not to realize that they have symptoms related to their venous disease until they’ve undergone treatment.

Since the signs do not always correlate with the symptoms, treatment can be initiated for both types of presentation. A patient with a CEAP class (stratifying patients according to severity of presentation: C, clinical; E, etiologic; A, anatomic; P, pathophysiologic) of C0 (no visible or palpable signs of CVD), C1, or even C2, disease can be quite symptomatic. On the other hand, and not infrequently, we will encounter patients with a more advanced problem (larger varicose veins, dermatitis, atrophie blanche) with or without a minimum of symptoms. The explanation could be that the group C nerve fibers, responsible for the perception of pain, become depleted of their neurotransmitters as the disease progresses, and the involved veins become larger in diameter.

The general perception of the population in regard to varicose vein disease has also changed over time. Thirty years or so ago, varicose veins and CVD were thought to be a medical and/or cosmetic problem affecting primarily, if not exclusively, women. Of course, the prevalence of CVD being estrogen related, it is much more common in women earlier in life, ie, in their reproductive years. Even so, in recent years, the perception that CVD solely affects women has changed, and we see more men in consultation for CVD. They are also consulting at earlier CEAP stages. They also tend to be as preoccupied by the symptoms as by the signs of CVD.

We are still unable to predict how the disease is going to evolve in time. Occasionally, we see patients with a dermatitis and even atrophie blanche (CEAP = to C4) without any apparent varicose veins or deep venous insufficiency. We also see patients with large refluxing greater saphenous or short saphenous veins without symptoms or any sign other than apparent varicose veins. So, whether I treat signs or symptoms depends a lot on the patient’s desire for improvement in QOL. However, as a general rule, the decision to initiate treatment is motivated predominantly by the signs of CVD, ie, edema and cutaneous changes, especially in later clinical stages (C3 and over).
Therapeutic options to delay the progress of chronic venous disease: the example of micronized purified flavonoid fraction

by H. P. Yaltirik, France

Chronic venous disease is a global phenomenon that can affect both developed and developing countries, with high prevalence and risk of progression. Recent studies highlight the importance of the early detection of chronic venous disease by proper use of the clinical, etiological, anatomical, and pathophysiological (CEAP) classification system and the necessity for the earlier management of the disease. The causal and temporal sequences of events that occur during the development and progression of chronic venous disease have not been ascertained. Currently available drugs directed toward preventing or limiting the inflammatory response at all stages of the condition may play a significant role in preventing or slowing the development and recurrence of troublesome outward manifestations. More studies are needed to further elucidate the pathophysiology at the early stages of chronic venous disease, investigating the presence of evening reflux in the distal venules due to damage to microvalves, and to determine the role of venoactive drugs in the prevention of the progression of chronic venous disorders: eg, are all vеноactive drugs able to prevent future morbidity? The aim of this article is to provide an overview about the pathophysiology and the possible hypothesis in the progression of chronic venous disease and to illustrate the potential benefits of early management of chronic venous disease in delaying the progression of the disease with micronized purified flavonoid fraction (MPFF).

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Chronic venous disorders have a high prevalence,1–5 which increases further with aging of the population.6 Some population-based surveys from the United States, Brazil, and Northern and Western Europe, based on clinical, etiological, anatomical, and pathophysiological (CEAP) classification, report prevalence rates ranging from 49% to 90%.7–12

The CEAP classification published in 199613 and updated in 200414 describes chronic venous disorder presentations in all its aspects. The classification is based on clinical, etiological, anatomical, and pathophysiological criteria, including the presence or absence of symptoms. Chronic venous disease so defined ranges from disease with no visible or palpable signs of venous disease symptoms (C0) to leg ulcers (C6). Patients complaining of “venous symptoms” but who do not have any clinical signs, anatomical anomalies, or physiological disorders that can be identified using the current complementary investigations involved in the CEAP clas-
sification are assigned to class C0s, En, An, Pn (Table I). The CEAP classification, now commonly used worldwide, has allowed collection of epidemiological data on a more homogeneous basis.

The Vein Consult Program (VCP)—a large-scale international, observational, prospective survey—collected global epidemiological data on chronic venous disorders on the basis of CEAP classification in 20 countries from different geographical zones worldwide. The results allowed reliable comparisons due to the use of the same single protocol, the same internationally accepted classification system, and the centralized data management and processing.

The VCP is one of the rare studies having quantified the proportion of patients classified as C0s among those consulting for potential chronic venous disorders, and it provided an immediate snapshot of a consultation in general practice in real life. According to the results, overall, the prevalence of chronic venous disorders was 83.6%: with 63.9% of the subjects with disease classification C1 to C6 and 19.7% with disease classification C0s. Furthermore, C0s to C3 stages were predominant regardless of the country (Figure 1). These results are similar to those of some other epidemiological studies revealing that patients classified as having early stages of the disease (C0s, C1, C2) are frequently encountered during consultations in the general population.

Besides its high prevalence, chronic venous disease is a progressive disease. If untreated, the disease will probably become more extensive, resulting in more symptoms and a higher C-classification. Clinical progression of chronic venous disease is accompanied by progression of reflux in the superficial veins, and both clinical progression and progression of superficial venous reflux are significantly correlated with age. Notably, 4% of patients with established chronic venous disease progress to a higher CEAP clinical class each year. Lee et al. published the progression results of the Edinburgh Vein study. After a follow-up period of 13.4 years, chronic venous disease was shown to have progressed in more than 58% of the patients. Additionally, up to 30% of the participants of the Bonn Vein study with varicose veins were shown to have progressed to higher clinical classes during the 6.8-year follow-up. Furthermore, in a study by Kostas et al investigating the contralateral limbs of 73 patients undergoing varicose vein surgery, about half of the patients with unilateral varicosities developed chronic venous disease in the contralateral, initially asymptomatic limb within 5 years.

These studies show that chronic venous disease is a global phenomenon that can affect both developed and developing countries.

**Table I. CEAP classification.**

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No visible or palpable signs of venous disease</td>
</tr>
<tr>
<td>1</td>
<td>Telangiectases or reticular veins</td>
</tr>
<tr>
<td>2</td>
<td>Varicose veins</td>
</tr>
<tr>
<td>3</td>
<td>Edema</td>
</tr>
<tr>
<td>4</td>
<td>Skin changes</td>
</tr>
<tr>
<td>4a</td>
<td>Pigmentation and/or eczema</td>
</tr>
<tr>
<td>4b</td>
<td>Lipodermatosclerosis and/or atrophie blanche</td>
</tr>
<tr>
<td>5</td>
<td>Healed venous ulcer</td>
</tr>
<tr>
<td>6</td>
<td>Active venous ulcer</td>
</tr>
</tbody>
</table>

**Figure 1.** Distribution of the CEAP clinical classes according to geographical areas in Vein Consult Program.

countries. They also highlight the importance of the early detection of chronic venous disease by proper use of the CEAP classification system and the necessity for the earlier management of chronic venous disease.

This article provides an overview of the pathophysiology and possible hypothesis for the progression of chronic venous disease and illustrates the potential benefits of early management of the disease with micronized purified flavonoid fraction (MPFF; registered under trade names Ardium, Alvenor, Arvenum 500, Capiven, Daflon, Detralex, Elatec, Flebotropin, Variton, and Venitol) to delay disease progression.

**Pathophysiology**

Although the causal and temporal sequences of events that occur during the development and progression of chronic venous disease have not been ascertained, the emerging twin themes of disturbed venous-flow patterns and chronic inflammation may underlie all the clinical manifestations of the disease (Figure 2). 

Evidence has accumulated in the past years that inflammation could be key in wall remodeling, valve failure, and subsequent venous hypertension. Research interest has recently focused on possible chronic inflammatory processes that can affect large and small venous vessels and valves. In such processes, various types of inflammatory mediators and growth factors are released, including vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), transforming growth factor β (TGF-β1), fibroblast growth factor β (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.

Degenerative changes and incompetence in microvenous valves can create reflux into the microvenous networks in the skin, which may be involved in the development of the severe skin changes that are observed with chronic venous disease. It is unknown whether microvalve alterations could also be responsible for symptoms that appear early in the progression of the disease, particularly in the C0s patients. Research is currently ongoing to determine the origin of the symptoms in C0s patients.

Once initiated, venous valve damage will be self-reinforcing, exacerbating venous hypertension and disturbance of venous flow and causing further inflammation. Therefore, early diagnosis and earlier treatment aiming to prevent venous hypertension, reflux, and inflammation can alleviate symptoms of chronic venous disease and reduce the risk of ulcers, both of which reduce the quality of life and are expensive to treat.

**Role of vеноactive drugs**

Pharmacological treatment with vеноactive drugs and compression therapy are currently used to treat C0s patients. Nevertheless, the role of vеноactive drugs in the prevention of the natural history of chronic venous disease remains to be determined: are all vеноactive drugs able to prevent future morbidity? Research advances have led to an appreciation of the importance of chronic inflammatory processes throughout the course of the condition. Such processes in the valves and walls of veins of all sizes and also in the skin lead toward the development of varicose veins and leg ulcers. Currently available drugs directed

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**Figure 2.** Clinical manifestations of chronic venous disease.

toward preventing or limiting the inflammatory response at all stages of the condition may play a significant role in preventing or slowing the development and recurrence of troublesome outward manifestations. These pharmacological agents deserve detailed study.

Chronic-venous-disease-related symptoms constitute the most important indication for vеноactive drugs in patients at any stage of the disease. There are insufficient data to specify those CEAP clinical classes for which the benefits will be greatest, but it is reasonable to assume that patients at all stages of the disease and particularly at the early C0s stage may benefit.

Indeed, as regards vеноactive drugs, the studies demonstrating the efficacy of MPFF in reducing the initial components of the inflammatory cascade, as well as the recent studies conducted in C0s and C1 patients showing that MPFF alleviated the transitory venous reflux and reduced the venous symptoms, suggest the possibility that MPFF could also be of benefit in the early stage of chronic venous disease and might inhibit inflammation-induced damage and disease progression.

**Pharmacological and therapeutic effects of micronized purified flavonoid fraction**

MPFF is a flavonoid-based vеноactive drug composed of 90% micronized diosmin and 10% other active combined flavonoids (expressed as hesperidin, diosmetin, linarin, and isorhamnetin—which all contribute to the pharmacological effect). This unique composition makes MPFF more potent than diosmin alone. In many guidelines, MPFF is indicated as a first-line treatment for chronic-venous-disease-related symptoms and edema in a broad spectrum of patients at all stages, and it is the only vеноactive drug indicated as an adjunct treatment to conventional therapy for the treatment of venous leg ulcers, owing to its wide range of evidence-based pharmacological and therapeutic effects.

**Effects on venous tone**

MPFF acts on venous tone by modulating noradrenergic signaling and reducing norepinephrine metabolism. The effect of MPFF (two 500-mg tablets daily) on venous tone was shown in an open-label study in women with unilateral varicose veins and, in the other leg, an abnormal elasticity modulus value, as measured using air plethysmography, but no visible varicose veins. The elasticity modulus increased significantly in the treated group, confirming that MPFF improves venous tone in patients with a high risk of developing varicose veins. In another trial, treating patients with MPFF (two 500-mg tablets daily) reduced venous distension and venous capacitance and improved venous tone in women with various grades of venous insufficiency, ie, healthy women, women with venous insufficiency related to postthrombotic syndrome, and pregnant women.

**Antioxidant action and effects on inflammatory mediators**

MPFF inhibits oxygenated free radical production in vitro in zymosan-stimulated human neutrophils, rat leukocytes, and mouse macrophages. Additional trials demonstrated that MPFF normalizes the release of prostaglandin E2 (PGE2) and prostaglandin F2α (PGF2α) and synthesis of thromboxane B2 in inflammatory granulomas in rats; reduces the bradykinin- or ischemia-induced microvascular permeability in rat cremaster muscle; reduces the histamine-, bradykinin-, leukotriene-B4–induced ischemia and reperfusion or oxidant challenge in the hamster cheek pouch; and protects the endothelial cells from lipid peroxidation in bovine aortic endothelial cells and human skin fibroblasts.

**Effects on leukocyte activation and adhesion**

Former pharmacological studies in animals have demonstrated that MPFF inhibits venous inflammation by reducing leukocyte rolling, adhesion, and migration; by decreasing the number of parenchymal dead cells after venular mesenteric occlusion; and by reducing leukocyte adhesion and/or migration after ischemia-reperfusion injury. In clinical studies, MPFF reduced the expression of monocyte or neutrophil CD62L and the endothelial activation markers ICAM-1 and VCAM-1 on human leukocytes from patients with venous ulcers.

**Effects on capillary permeability and resistance**

MPFF decreases the volume of induced edema in the rat paw and improves microvascular reactivity and functional capillary density after ischemia and reperfusion in the hamster cheek pouch. In humans, MPFF significantly improved capillary hyperpermeability compared with placebo in patients with idiopathic cyclic edema, decreased the abnormal capillary filtration rate in patients with chronic venous insufficiency as evaluated using strain gauge plethysmography, and significantly improved capillary resistance compared with placebo in patients with abnormal capillary fragility.

**Effects on lymphatics**

MPFF increases lymphatic drainage owing to its noradrenergic action on the lymphatic system. MPFF increases the frequency and strength of contractions of lymphatic vessels, significantly lowers intralymphatic pressure, limits the diameter of lymphatic capillaries, and increases the number of functional lymphatic capillaries, which results in an improvement in lymphatic drainage in patients suffering from skin changes.

**Protective effects of MPFF against inflammation-related valve damage in chronic venous disorders**

MPFF blocks the effects of chronic inflammation in the microcirculation and macrocirculation as shown in the pharmacological studies. In a model of venous occlusion and reperfusion, elevation of venous blood pressure increased inflammation and tissue injury. In MPFF-treated animals, markers of inflammation decreased in a dose-dependent manner. MPFF also significantly reduced parenchymal cell death, leukocyte rolling,
adhesion to postcapillary venules, and migration.37 In rats with venous hypertension induced by creating an arteriovenous fistula, Takase et al showed that MPFF treatment resulted in a significant, dose-dependent reduction in the reflux rate in rats with higher than normal venous hypertension, demonstrating the protective effects of MPFF on the macrocirculation.48 These data suggest that by delaying or blocking the inflammatory reaction in venous valves and walls, MPFF may delay the development of venous reflux and suppress damage to valve structures in a rat model of venous hypertension. These outcomes were confirmed in another study using the same animal model. MPFF reduced edema and fistula blood flow produced by an acute arteriovenous fistula and reduced granulocyte and macrophage infiltration into the valves, in line with the previous study.49

In clinical trials, treatment with 1000 mg/day of MPFF for 2 months in patients consulting with complaints related to chronic venous disorders of the lower extremities but without visible signs (therefore, who are categorized as C0s according to the CEAP classification system [Table I]) and who presented with transient evening reflux in the great saphenous vein (GSV) resulted in the elimination of the GSV reflux in most of the treated patients and a decrease in vein diameter; it also had beneficial effects on symptom relief and quality of life (Figure 3).33 In another trial conducted recently with C1s patients presenting with telangiectasia and/or reticular veins and end-of-day leg complaints, a duplex scan examination was performed after a “day orthostatic loading test (DOL-test)” whereby measurements were taken after the patient spent a full day in the standing position. Transient reflux was found in half (55.2%) of the patients. The use of MPFF 1000 mg/day for 3 months significantly decreased the intensity of their chronic-venous-disease–related symptoms and improved their quality of life. In parallel, MPFF eliminated the transient reflux and decreased vein dilation. This provides additional proof of the capacity of MPFF to restore the viscoelastic properties of the venous wall, to protect valve structure at the very early stages of disease, and presumably to protect patients against further complications.32

In addition, a subgroup of patients who were in CEAP class C2 and had GSV reflux even after surgery underwent a 3-month treatment with MPFF 1000 mg/day. After MPFF treatment, the reflux was significantly reduced in 60% of the patients, and the reflux was resolved in 40% of the patients.50

Investigators reported a correlation between the clinical and the ultrasound results of MPFF treatment and stated that of the patients with a situational GSV reflux, patients complained of evening heaviness in their legs (n=77), moderate pain at the end of the day (n=31), and nighttime cramps (n=47). By treatment with MPFF alone for C0s and C1S patients or the combination of MPFF and an elimination of the varicose tributaries and preservation of the GSV for C2 patients, it was possible to recover an impaired GSV function in 78.2% of patients with a situational GSV reflux and to significantly improve the GSV function (ie, reflux extent and duration) in 21.8% of cases. MPFF led to the complete disappearance of leg heaviness in 87.2% of patients, and 12.8% of patients felt a significant decrease in the intensity of the heaviness. Moderate pain at the end of the day and nighttime cramps disappeared in all patients. These clinical changes occurred synchronously with the elimination of GSV reflux (Figure 4).50

Conclusion
Overall, a determined and proactive approach to the treatment of the early stages of chronic venous disease could reduce the number of patients progressing to higher CEAP classes each year. MPFF, owing to its unique composition and features, demonstrates significant anti-inflammatory and venoprotective actions, and it is clearly distinguished from other venoactive drugs in that it provides rapid and substantial relief of chronic-venous-disease–related symptoms at all CEAP stages and also preserves the venous walls and valves both in experimental and clinical studies. Recently, treatment with MPFF has also been shown to reduce the transient orthodependent regional hypervolemia that results from a weakening of the

Figure 3. Symptom intensity on the 10-cm visual analog scale (VAS) before (baseline) and after MPFF treatment (at 2 months).

Abbreviation: MPFF, micronized purified flavonoid fraction.
muscular-tonic function of the venous wall and to eliminate the transient reflux in the GSV in most of the treated patients at the very early stages of chronic venous disease, besides its beneficial effects on symptom relief and quality of life. These data support an approach that aims to prevent chronic venous disease progression from early to severe stages, suggesting MPFF as a basic multipurpose treatment option.

Additional studies with longer follow-up periods are needed in C0s and C1s chronic venous disease patients in order to further elucidate the physiopathology in the early stages of the disease, to investigate the presence of evening reflux in the distal venules due to damage to microvalves, and to determine the role of venoactive drugs in the prevention of the progression of chronic venous disorders.

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Keywords: chronic venous disease; early management; micronized purified flavonoid fraction; prevention; varicose vein; venoactive drug
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Mr. G. SELIUK
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Panorama Business Center
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Alger 16 000
Tel: +213 (0) 21 48 43 05

Argentina
Mr. N. DA CONCEICAO
Servier Argentina S.A.
Av. Libertador 5930, Piso 8
C1429ARP – Buenos Aires
Tel: +54 11 4706 5800

Armenia
Mr. G. VELJANYAN
Les Laboratoires Servier Representative Office
Huyskain Ave. – NORD – Business Centre Building 1, 3rd floor
0301 – Yerevan
Tel: +374 10 505074

Australia
Dr. A. LALLOUETTE
Servier Laboratories Pty Ltd
Servier House, 8 Cato Street
235, boulevard Armand Frappier
Hawthorn – Victoria 3122
Tel: +61 3 8823 7333

Austria
Mr. F. FOUILLOUX
Servier Austria GmbH
Mariahilferstrasse 20/7
1070 Wien
Tel: +43 1 524399900

Belarus
Mr. V. MAXIMENKO
Les Laboratoires Servier 70, Minskova Street
220 030 Minsk
Tel: +375 17 306 54 51

Belgium
Mr. F. BOYER
Servier Benelux SA
Rivendale Business Park
Boulevard International No. 57
1070 Bruxelles
Tel: +32 2 529 43 11

Brazil
Mr. C. SABATHER
Laboratorios Servier do Brasil Ltda, Estrada dos Banderinhas 4211 – Jacarepagua
Rio de Janeiro, RJ
CEP: 22-775-113
Tel: +55 21 3186 1501

Bulgaria
Mr. A. BRETON
Servier Medical EOOD
14 1 tvrd Tor Ceveddelitel
1000 Sofia
Tel: +359 87 11 57 00

Canada
Mr. F. FASANO
Servier Canada Inc.
235, boulevard Armand Frappier
Laval, Québec H7V 4A7
Tel: +1 450 9799 700

China (PRC)
Mr. S. MASCARAU
Servier (Taijin) Pharmaceutical Co., Beijing Office
No. 16 East 3rd Ring, Middle Road
ChaoYang District
Beijing 100020 P.R.C.
Tel: +86 10 5705 0051

Colombia
Dr. F. LEDER
Laboratorios Servier de Colombia SA
Edificio Centro Empresarial 98 x 28, Piso 4°
Transversal 19A – N° 96-28
Bogotá D.C.
Tel: +57 74294341

Croatia
Mr. Z. MITTA
Servier Pharma d.o.o.
Trg banovina 37
10000 Zagreb
Tel: +385 1 3016 222

Czech Republic
Mr. R. AZENCOTH
Servier SPC
Florenciniu
Na Florenci 216/15
310 00 Praha 1
Tel: +420 2 2116 6002

Denmark
Mr. F. TEGER
Servier Danmark A/S
Lyngbyvej 2
2100 Copenhagen
Tel: +45 36 442260

Egypt
Mr. M. TITE
Servier Egypt
Scientific Office
67, El Homya Street, PO Box 123
Heliopolis – Cairo
Tel: +20 2 30 60 77

Estonia
Mr. F. DEBAILLON-VESQUE
Servier Laboratories Ltd, Block 2
West Pier Business Campus Old Dún Laoghaire
Dun Laoghaire, Co. Dublin
Tel: +372 12 2416 2727

Finland
Mr. F. KESSELHUT
Servier Hungaria KFT
Westend Office
B tower, 3rd floor, Váci út 1-3
Budapest 1062
Tel: +36 1 238 7799

France
Mr. F. DRUGUET
Servier Pharma d.o.o.
110 00 Praha 1
Servier SRO
Mr. R. AZENCOTH
Tel: +370 52 638 615

Georgia
Dr. M. KETESURIAN
LLS Representative Office
44 Kote Aptsidze Street
1015 Tbilisi
Tel: +995 32 243 93 90

Germany
Mr. O. KIRST
Servier Deutschland GmbH
Eisenherrenstr. 53
60967 München
Tel: +49 89 5705 0051

Gulf Countries
Mr. P. PEREZ
Les Laboratoires Servier Representative Office
15/F (Level 11), Aramco Tower
Emirates Media City, Sheikh Zayed Road
PO Box 15986 Dubai
United Arab Emirates
Tel: +971 4 332 99 03

Hong Kong
Mr. Y. HARID
Servier Hong Kong Ltd
Room 4201-03, 42/F
249 Queen’s Road East
Wanchai, Hong Kong
Tel: +852 2 5277 1922

Hungary
Mr. F. KESSELHUT
Servier Hungaria KFT
Westend Office
B tower, 3rd floor, Váci út 1-3
Budapest 1062
Tel: +36 1 238 7799

India
Mr. G. JABRE
Serdia Pharmaceuticals
India Pvt Ltd, Servier House
Off Dr. S.S. Rao Road, Parel
Mumbai 400 012
Tel: +91 22 2416 0000

Indonesia
Mr. M. KERTANGLY
Les Laboratoires Servier OÜ
Rotermitte II
Talinn 10111
Tel: +372 640 00 07

Italy
Mr. F. DARCHEZ
Servier Laboratories Ltd, Block 2
West Pier Business Campus Old Dún Laoghaire
Dun Laoghaire, Co. Dublin
Tel: +353 1 663 8110

Japan
Mr. E. DELARGE
Nihon Servier Company Ltd
Hongo MK Building 5F
1-26-34, Hongo, Bunkyo-Ku
113-0033 Tokyo
Tel: +81 3 5921 7111

Kazakhstan
Mr. O. NEGULYAEV
Les Laboratoires Servier Representative Office
310 G DCSTK av, 3rd Floor
050 020 Almaty
Tel: +7 727 386 76 62

Korea
Mr. C. ROUCHES
Servier Korea LTD.
5th Floor, Hong-Ik University Kangnam-Kwan
51-1, Bangpo 4-dong
Seocho-gu – Seoul 137-902
Tel: +82 2 31 85 10

Latvia
Dr. J. LEJA
SIA Servier Latvija
Dundes Namai, Dundes Street 3
LV1013 Riga
Tel: +371 6750 20 39

Lithuania
Mr. P. BOYER
Servier Laboratories OÜ
151 25 Maroussi
7, Fragkoklissias str.
Servier Laboratories OÜ
Mr. F. TEXIER
Tel: +370 52 638 615

Luxembourg
Mr. P. BOYER
Servier Luxembourg SA
178, rue du Chemin de Fer
L-6037 Bertrange
Tel: +352 49 35 35

Mexico
Mr. F. DURGUET
Servier Laboratories S.A. de C.V.
Lomas de Chapultepec
C.P. 11000 – Ciudad de México
Tel: +52 55 52 02 33 59

Morocco
Mr. J. Y. GAL
Les Laboratoires Servier
15/F (Level 115), Arenco Tower
Media City, Sheikh Zayed Road
Representative Office
Tel: +971 4 332 99 03

Netherlands
Mr. J. Y. GAL
Les Laboratoires Servier
15/F (Level 115), Arenco Tower
Media City, Sheikh Zayed Road
Representative Office
Tel: +971 4 332 99 03

Romania
Mr. C. ROUCHÈS
Servier Romania
Mr. O. NEGULYAEV
Les Laboratoires Servier
5967 München
Tel: +49 89 5705 0051

Russia
Mr. F. DARCHEZ
Servier Laboratories Ltd, Block 2
West Pier Business Campus Old Dún Laoghaire
Dun Laoghaire, Co. Dublin
Tel: +353 1 663 8110