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SPECIAL ARTICLE

# Venous symptoms: the SYM Vein Consensus statement developed under the auspices of the European Venous Forum

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## TERMINOLOGY

Chronic venous disease (CVD): Any morphological and functional abnormalities of the venous system of long duration manifested either by symptoms and/or signs indicating the need for investigation and/or care.

Chronic venous disorders (CVDs): This term includes the full spectrum of morphological and functional abnormalities of the venous system.

Chronic venous insufficiency (CVI): A term reserved for advanced CVD, which is applied to functional abnormalities of the venous system producing edema, skin changes, or venous ulcers. ($C_3$-$C_6$ in CEAP classification).

The above three terms are used in this consensus document according to the definitions provided by the VEIN-TERM Transatlantic Interdisciplinary Consensus document. Because they are different, they are not interchangeable and are listed here as a reminder to the reader.

For reference see: Eklöf B, Perrin M, Delis KT, Rutherford RB, Gloviczki P. Updated terminology of chronic venous disorders: the VEIN-TERM Transatlantic Interdisciplinary Consensus document. J Vasc Surg 2009;49:498-501.

## PREFACE

Descriptions of venous symptoms of the legs and their relationship to chronic venous disorders (CVDs) are a controversial issue. All classes of CVDs ($C_{0s}$-$C_6$) can be associated with venous symptoms. Several

TABLE I.—*The consensus group and assignment of topics.*

| Topic | Coordinator | Writer | Members |
|---|---|---|---|
| Preface | | B. Eklöf | |
| PART I. Description and definition of venous symptoms | B. Eklöf | M. Perrin | D. Bouhassira, W. Blättler, R. Launois |
| PART II. Attributing leg symptoms to venous disorders | A. van Rij | P. Carpentier | E. Rabe, A. Mansilha, W. Blättler, K. Darvall, M. Flour |
| PART III. Pathophysiology of venous symptoms | N. Labropoulos | S. Kakkos | M. de Maeseneer, E. Bouskela, D. Bouhassira |
| PART IV. Scoring of venous symptoms | M. Vasquez | M. Vasquez | J.J. Guex, P. Neglen, R. Launois, E. Rabe |
| PART V. Clinical examination and investigations | A. Nicolaides | A. Nicolaides | O. Maleti, M. Lugli, E. Bouskela, C. Hamel, E. Shaidakov |
| PART VI. Conclusion | | M. Perrin | |

studies have found a significant correlation between venous symptoms and worsening of CVD signs with a strong influence on health-related quality of life (HRQoL). On the other hand, the Edinburgh Vein Study did not demonstrate an association between "venous" leg symptoms and varicose veins (VV) and concluded that most of these symptoms probably had a non-venous cause. In addition, there seems to be a poor correlation between symptoms and signs and the results of routine investigations. These controversies prompted this consensus statement on venous symptoms — SYM Vein.

At the annual meeting of the European Venous Forum (EVF) in Paris in June 2014 a consensus group was formed, with members representing Europe, North and South America, and New Zealand (Table I), with the aim of producing a document on symptoms in CVDs of the legs based on available scientific evidence. The members were assigned the following topics:

— description and definition of venous symptoms since these are scarcely described in books and articles;

— attributing leg symptoms to venous disorders as they are not pathognomonic, given the poor correlation between the presence of venous symptoms and visible signs or results of investigations;

— pathophysiology of venous symptoms which is mainly due to venous hypertension, but additional pathophysiological mechanisms can result in poor correlation between degree of symptoms and magnitude of venous hypertension;

— scoring of venous symptoms where a valuable assessment tool should be able to measure and stratify venous symptoms and evaluate the results of therapy;

— investigations in patients with symptoms presumed to be from venous disorders are requested to supplement the history and clinical examination in order to confirm the presence or absence of a venous abnormality, and to determine the anatomic extent and severity.

At the EVF annual meeting in Saint Petersburg in July 2015 the majority of the members spent two days deliberating the development of a consensus statement for the above five topics. Intense work has since continued, on a correspondence basis, with a plan for publication in International Angiology at the end of 2016 after more than two years of work.

## PART I
## Description and definition of venous symptoms

### 1. Introduction

In the medical literature the terms "signs" and "symptoms" often appear under the same heading of "symptoms", which is very confusing. Symptoms, and their intensity, are described by the patient, while signs are elicited by the physician who can in many cases use a validated tool to quantify their severity.

In this chapter, the term "symptom" will be assigned to an unpleasant sensation felt by the patient. Consequently, the presence and severity of symptoms are subjective.

Venous symptoms remain a challenge to deal with for multiple reasons. Firstly, few books or articles in the literature dedicated to CVDs give a precise description and definition of the so-called "venous symptoms". The reason may be the difficulty in doing it, as these symptoms are not pathognomonic. This increases the difficulty in attributing symptoms to a venous etiology as all clinical classes from $C_{0s}$ to $C_6$ [1] can be associated with the same venous symptoms. Secondly, there is poor correlation between the presence of venous symptoms and signs, and between symptoms and routine investigations, particularly duplex scanning.

## 2. List and description of venous symptoms

### *2.1 List of venous symptoms*

#### 2.1.1 Common symptoms described in the literature

The commonest leg symptoms in CVDs are ache, pain, heaviness and discomfort. The intensity of pain/ache does not correlate with the clinical severity and the pain/ache is often dull, diffuse and difficult to describe or localize with precision. Patients often experience difficulty in defining the quality of the pain and frequently use vague terms that are not usually used to describe pain. Further symptoms are throbbing, tightness, fatigue, impression of swelling, cramps, itching, restless legs and tingling sensation. A confused concept of symptoms and inappropriate use of terms is widespread in the medical world and frequently causes misunderstanding in physician-patient relationship.

#### 2.1.2 Venous symptoms according to the CEAP classification

The CEAP classification includes "aching, pain, tightness, skin irritation, heaviness, muscle cramps, and other complaints attributable to venous dysfunction".[1] Because identification of venous dysfunction may not always be possible in daily practice, the CEAP classification remains open to a limitless list of symptoms.

#### 2.1.3 Venous symptoms according to the Venous Clinical Severity Score (VCSS)

Pain or other discomfort (*i.e.* aching, heaviness, fatigue, soreness, and burning) of presumed venous origin are assessable variables of the VCSS.[2] Contrary to the CEAP classification, which allows an unlimited list of symptoms, symptoms in the VCSS, although well-defined, are limited to pain or other discomforts, knowing that the latter are not listed.

#### 2.1.4 Symptoms recognized in the Bonn Vein Study

The Bonn Vein Study listed the following symptoms: feeling of swelling, tightness, heaviness, pain during prolonged walking, sitting, or standing, cramps, itching, and restless legs.[3, 4]

#### 2.1.5 Symptoms listed in the VEINES-Sym, part of the VEINES-QOL

Nine venous symptoms are listed in the VEINES-SYM questionnaire: heavy legs, aching legs, swelling, night cramps, heat or burning sensation, restless legs, throbbing, itching, and tingling sensation. Although this questionnaire was designed for the evaluation of the HRQoL in primary CVDs, it can also be used in patients with deep vein thrombosis (DVT).[5, 6]

Obviously, the term "venous symptoms" needs clarification.

### *2.2 Description of venous symptoms*

The symptoms previously mentioned are not specific to CVDs, but some features may help to attribute them to a venous origin.

#### 2.2.1 Pain or aching

Venous pain may be located along the course of a VV (phlebalgia), but it is usually diffuse in the lower limb, mainly at calf level. However, pain may be related to other causes, such as presence of painful lipodermatosclerosis, open ulcer or venous claudication.

Venous claudication is defined as the development of pain or a bursting sensation that occurs when the patient is walking or running. The pain is localized in the leg, thigh or buttock, and disappears slowly when the patient stops, facilitated by leg elevation, a finding that allows differentiation from arterial or neurogenic claudication. Venous claudication is mainly seen in patients with iliocaval obstruction, but it can also occur in patients with venous neurogenic claudication caused by dilated veins in the spinal canal that arise from collaterals secondary to iliocaval obstruction. It can be differentiated by MRI or CT.[9] A rare form of venous claudication of the calf is due to popliteal vein entrapment.

#### 2.2.2 Throbbing

Throbbing is an infrequent symptom, which is depicted by patients as a pulsating pain along the lower limb.

#### 2.2.3 Tightness

According to a patient's description, tightness is as if they had their legs caught in a stranglehold.

#### 2.2.4 Heaviness

Patients describe this symptom as heavy legs occurring after a prolonged time in the standing or seated position, or when changing from lying to standing.

#### 2.2.5 Fatigue

Fatigue is slightly different from heaviness and is described by patients as a feeling of tiredness occurring after any kind of physical activity. It may also occur after standing still for a long time.

#### 2.2.6 Feeling of swelling

The feeling of swelling is different from the sign of edema that can be measured. Despite the fact that patients feel that their legs are swollen, edema is not always present at clinical examination.

#### 2.2.7 Cramps

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

#### 2.2.8 Itching

Itching can be present in association with dermatitis, including stasis dermatitis or contact eczema, and in association with non-complicated varices. It has been reported that among patients complaining of leg itching, 97% felt the symptom in the evening and at night to such a degree that half of them had sleep difficulties with 40% waking up because of itching. Itching is considered a frequent and intense symptom.[10]

#### 2.2.9 Restless legs

This symptom, often called restless legs syndrome is described by patients as a disagreeable and indefinable feeling, frequently reported as "having the fidgets" in the lower limb and accompanied by an irresistible need to move the legs.

#### 2.2.10 Tingling

Tingling is the sensation of prickling or "pins and needles" in the legs.

#### 2.2.11 Heat or burning sensation

A burning sensation is usually described as diffuse heat in the legs, but sometimes as a burning comparable to the feeling perceived when in contact with a hot object.

#### 2.2.12 Secondary symptoms

Rarely mentioned, secondary symptoms are the subjective feelings of disquiet, malaise, insomnia, ill-being, etc. that can be induced by CVDs whatever the clinical class and the etiology. Both physical and mental HRQoL) may be negatively affected. Data is available for complicated and non-complicated VV,[11] and for post thrombotic syndrome.[12]

## 3. Definition of venous symptoms

By definition, venous symptoms are related to venous etiology, but as venous symptoms are rarely specific, this makes their definition difficult.

In order to solve this challenge, we need to clarify some points and answer the following questions:

1) are venous symptoms of primary etiology caused by alteration of the major veins or by venule and capillary anomalies? Would major vein alterations be related to reflux in superficial and/or deep veins or to compression of proximal veins? Could small venules or capillaries be involved in $C_{0S}$ patients, knowing that both anomalies (major veins and venules) may be combined in $C_6$ patients?[13]

2) Should the absence of clinical venous signs and the absence of reflux on duplex scanning or air plethysmography (APG) systematically rule out a venous etiology?

3) Is the presence or the intensity of symptoms, independently of the presence of signs, predictive of CVDs progression? If we refer to VCSS, the maximum score attributed to symptoms is only 3/30; in other words, venous symptoms count for very little in CVDs scoring systems.[2] In the Bonn Vein Study II, "sensation of swelling" significantly increased the risk for the development of chronic venous insufficiency (CVI).[15]

These questions will be addressed in Parts II to V of the present document.

## 4. Conclusion

Precise description and definition of venous symptoms are provided above in an attempt to specify venous origin. This point is crucial for the provision of better care to symptomatic patients.

In epidemiological studies venous symptoms are very common. In the Bonn Vein Study more than half of the 1800 participants reported such symptoms.[3, 4, 14] In the worldwide Vein Consult Program, more than 80% of screened subjects presented with symptomatic CVDs, of which 20% were in $C_{0s}$.[15]

Operative treatment, particularly in patients with non-complicated symptomatic varices, is reported as not relieving venous symptomatology in many cases. Identifying which symptoms can be relieved by operative treatments would be a great step forward. In patients with other symptoms, an alternative treatment could then be recommended.

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# PART II
# Attributing leg symptoms to venous disorders

## 1. Introduction

As indicated in Part I, leg symptoms are common and therefore to relate them to a specific CVDs may be difficult. The magnitude of this challenge is amplified by the complexity of CVDs and the diversity of symptoms and terms used to describe these symptoms.[1-3] In this chapter, the different factors influencing how symptoms are perceived by patients and how well they are associated with CVDs will help determine their value in attributing the symptom to a specific venous cause.

There are two important caveats to consider: 1) leg symptoms are of themselves not diagnostic of a venous disease, and 2) leg symptoms deserve to be assessed and treated appropriately.

## 2. Understanding symptoms

Patients may complain about many different kinds of leg symptoms. They are unique, personally-felt experiences. These feelings are variously expressed and with differing intensity, and they may mean many different things to different patients. It is important firstly to have a general understanding of how symptoms may be expressed and interpreted as well as how they might or might not be related to venous disease.

### *2.1 Human factors*

There are many factors which influence how both patients and practitioners describe, interpret, express and use these symptoms. These include the following:

1) language and culture. The words used to describe symptoms are influenced by cultural and linguistic experience both of doctors and their patients so that often they do not have exactly the same meaning.

2) Levels of tolerance to unpleasant experiences determine whether a symptom and its level of effect is reported or not.

3) Prior experience, duration and intensity influence the choice of words as well as the way such words are used to describe symptoms.

4) Psychosocial gains may influence the choice of symptoms to obtain empathy and support.

5) Economic gains will also affect how symptoms are described. What is "heaviness" for one patient may be "discomfort" for another and "pain" for yet another for whom this will be associated with easier access to treatment or reimbursement for its cost. Most patients consulting for VV also put forward the discomfort linked to these symptoms as the reason why they want their VV to be treated operatively.

6) The belief regarding the relationship of symptoms to a CVDs by the patient or practitioner will influence the symptom described and its severity. This is irrespective of whether the patient understands the disease or not.

7) The perceived importance of the venous disorders. In most cases, patients with venous symptoms such as heavy/swollen legs acknowledge a mild to moderate intensity (Visual Analogue Scale, VAS of 2 to 6 out of 10). They can be even milder and, for example, many people only experience a sensation of heavy/swollen legs in exceptional circumstances such as long-haul flights or even only realize they had such symptoms when they experience their relief through wearing compression stockings.[4] By contrast, people who have cosmetic concerns about VV, reticular veins or telangiectasiae pay more attention to any leg symptom, which may explain the high prevalence of venous symptoms reported in these populations.[5]

8) Psychological dysfunction may at times contribute to misperceptions of symptom cause and severity. However, in those with anxiety or with depression who may have a lower pain threshold, a statistically greater association of their symptoms with CVDs does not mean that they have symptoms of a purely psychogenic origin.[6]

9) Influence of fear due to family history, for example, for future risk of developing ulceration.

### *2.2 The story and clinical context of symptoms*

— Symptoms are generally not just feelings but they occur in a clinical context and they have a story. This may include how they started and progressed as well as their timing, duration, frequency, precipitating and relieving situations and anatomical location. Consequently, careful clinical interrogation to establish the story clarifies the meaning of the symptom and its significance relative to venous disease. Furthermore, a symptom may not occur alone but along with other relevant symptoms and together they may clearly establish an association with CVDs.

### *2.3. The specificity of symptoms: leg symptoms are not unique to CVDs*

In one of the most informative papers about venous symptoms reporting the results of a cross-sectional population study, there was a weak or an unclear relationship between most symptoms and VV.[7] The authors extrapolated their results to the provocative conclusion that "most lower limb symptoms probably have a non-venous cause". This is consistent with the substantial relative risk (OR=3.04) of so called venous symptoms in subjects from the general population who have sedentary work even after adjustment in a multivariate analysis.[8]

When considering the leg symptoms associated with CVDs, it should be kept into consideration that:

— Many of these symptoms are very common in the general population where VV are also highly prevalent, especially in the elderly. Therefore, the specificity of these symptoms for CVDs is low.[9, 10] Similarly these leg symptoms may be observed in numerous other disorders with a similar lack of specificity.

— These leg symptoms may also be the symptoms of other conditions not directly related to any venous dysfunction. There are many instances of this especially in the elderly. Some examples include heaviness in cardiovascular and renal disease because of edema, restless legs in multiple sclerosis, itching as

with adverse reactions to medications, limb swelling with drug therapy such as calcium channel blockers and pain in a large number of other conditions including those seen in orthopedic and podiatry practice.[11-13]

— Symptoms of CVDs may be confounded by coexisting conditions which have a direct effect on the manifestation of CVDs and associated symptoms. The coexistence of venous and arterial diseases has been well documented in the studies exploring the etiologies and outcomes of leg ulcers. There is also a strong association of VV and other kinds of CVD with musculoskeletal (locomotor) disorders such as osteoarthritis of the knee and ankle as well as foot arch problems. These conditions may directly affect venous function. They can alter the efficacy of the calf muscle venous pump function as well as that of the accessory venous pumps. This makes the association of venous symptoms and locomotor disorders quite plausible.[11]

### *2.4. Determining the strength of the association of symptoms to CVDs*

There is a wide variability in the specificity of leg symptoms to CVDs. Consequently, they generally cannot be considered as specifically diagnostic of CVDs but may direct the further clinical assessment to a venous diagnosis. The strengths of association are established from published observational and epidemiological studies.[7, 8, 14]

It is useful to consider three situations.

High probability of a symptom being attributed to CVDs. In this situation the relationship appears straight forward. This may be due to a clear temporal and/or spatial association. Unfortunately, few symptoms fall easily into this group. Examples are:

— venous claudication, a clear indication of venous obstruction resulting from a venous proximal obstruction or thrombosis;

— the phlebalgia of superficial thrombophlebitis;

— the throbbing pain associated with chronic venous ulceration.

Low probability of a symptom being attributed to CVDs. This is more common particularly as a result of more recent careful studies. In this instance, apart from a sound clinical evaluation, extensive investigations for CVDs and invasive treatments based on these symptoms alone are not warranted. Examples are:

— "impatient legs", mimicking a minor form of restless legs syndrome restricted to the first part of the night and eliciting the subject to move his legs, but with no uncontrolled movements;[11, 13]

— sensation of warm feet mainly in the first ten minutes after going to bed, much milder than true erythromelalgia.[14]

Moderate probability of a symptom being attributed to CVDs. This is the most common situation and leads to confusion and frequent dilemmas in decision making. It is helpful here to be reminded that these symptoms are not diagnostic for CVDs but point to the need for further venous assessment. Treatment based on these symptoms alone as if they were due to CVDs is not appropriate. The implication is that these symptoms may equally be attributable to other causes which also need to be excluded. An example of this is the sensation of heavy/swollen legs, one of the most widespread symptoms in CVDs patients.[9] It is described by the patient as a diffuse and often bilateral sensation of heaviness in the calf and lower leg or a feeling of swollen legs of mild to moderate intensity, worsened by a warm environment and by inactivity, and increasing through the day. It may also be reported as fatigue in the legs by some patients. Unfortunately, these symptoms are not unique to CVDs or the presence of VV, but also occur in $C_{0s}$ patients in whom there is no demonstrable venous dysfunction by routine investigations. (Pn patients). They also occur in the "otherwise well" population, and also as a feature in those with other clinical conditions such as knee osteoarthritis or plantar static disturbances.[12] What is clear is that patients with these symptoms, with a moderate probability of CVDs, deserve careful venous evaluation.

## 3. Controversies

There remain some controversial areas in the relationship of CVDs and symptoms which require comment as they cause considerable misunderstanding.

### *3.1 The absence of symptoms does not exclude CVD*

Epidemiological studies have shown that venous dysfunction, such as venous reflux, can be found in

subjects from the general population without symptoms or clinical consequences.[15, 16] More generally speaking even the physical signs of CVD may remain undetected or truly absent so it is not surprising that patients may not experience any corresponding symptoms. Changes seen with capillaroscopy with CVI precede clinical signs of skin changes and associated symptoms.[17]

Similarly, the lack of sensitivity in clinical detection of edema suggests that the significance of the symptom of "swollen" legs in this setting would be difficult to correlate. In contrast there is a relationship of heavy/swollen leg symptoms to the presence of overt edema.[18] However, as described in the Bonn Vein Study, those initially with heavy legs without CVDs ($C_{0s}$) were the most likely to go on to develop overt edema when seen 11 years later and not those with other symptoms.[7]

Other symptoms may also be absent despite extensive venous abnormalities depending on high patient threshold to experiencing the symptom. This may also be true where hemodynamic adaptation to the venous disease has occurred.

When there is absence of symptoms and absence of clinical signs of $C_3$ to $C_6$ or evidence of significant advancing venous disease then conservative management, and in particular avoidance of invasive treatment, is a reasonable course of action.

### *3.2 Leg symptoms that might have a high probability of being venous, but venous dysfunction is not demonstrable*

Despite the increased sophistication in venous diagnostic tests, in particular the high sensitivity of duplex scanning there are still circumstances when the demonstration of venous dysfunction remains elusive. This is well illustrated by the recent recognition of the importance of the question of venous obstruction. Similarly, the limitations of assessment of calf venous pump function, the interpretation of perforator disease or implications of microvenous pathology create significant gaps in which to fit symptoms.

In the absence of acceptable evidence, invasive treatment for such an implied venous disorder is not recommended outside of an ethically approved research investigation.

### *3.3 Leg symptoms that are not associated with demonstrable venous dysfunction which may respond to noninvasive treatment methods commonly used in CVDs*

These symptoms occur in a significant proportion of patients attending for assessment of CVDs and may be relieved by noninvasive therapies.

## 4. Ascribing a venous origin of leg symptoms in a given patient

With such complexity in understanding how symptoms may or may not relate to CVDs some guiding principles to help both patient and clinician are needed to progress sound clinical decision making. These can be considered in three components.

### *4.1 Clinical evaluation looking for association of symptoms to a venous etiology (see Part V)*

#### 4.1.1 Patient interrogation and interpretation of symptoms — the symptom story

Establish temporal relationship, identify accentuating and relieving circumstances, determine influence of temperature and other environmental factors, evaluate lifestyle, occupational factors, postural change, circadian variations and identify associated co-morbidities with similar symptoms and those which affect CVDs.

The use of structured definitions, scoring systems and guidelines may be helpful.[4, 8]

#### 4.1.2 Examination which relates symptoms to a physical venous problem in the same territory

#### 4.1.3 Imaging and functional testing to confirm whether CVDs exists and can be related to the symptoms

### *4.2 Knowing the evidence*

This requires a knowledge of the published literature regarding the evidence relating symptoms to CVDs. It includes: 1) the clinical evidence base which is largely derived from observational studies, 2) the basic physical science and psychology of symptoms, 3) the scientific basis of pathophysiology of CVDs and how they may relate to each other (see Part III).

### *4.3 Making the decision*

This should take into account: 1) probability and strengths of the clinical association of symptoms to identified CVDs in the face of alternative explanations; 2) probability of the association from published evidence; and 3) accounting for patient and practitioner bias for diagnostic, treatment choice and reimbursement opportunity.

### *4.4 An example*

A patient complaining of a chronic sensation of heavy/swollen legs (data from Carpentier *et al*.[8]):

— a venous origin is the most probable explanation (basal specificity = 0.55);

— a temporal association with any factor influencing edema formation should be taken into account; the association with an influence of both a warm environment and physical inactivity has a specificity of 0.95;

— the association of a venous dysfunction with a topography consistent with the symptoms is an additional argument, but its absence does not have any significant negative predictive value;

— the association with VV should be analyzed cautiously, as they can be influenced by the patients representations and wishes;

— the association of a locomotor disturbance (osteoarthritis in the lower limbs, foot arch problems etc.) should be carefully analyzed in the light of a possible interaction with the venous function, and cannot systematically be considered as a negative argument for a venous cause;

— the positive influence of rehabilitation, compression stockings or venoactive drugs is of practical importance for the well-being of the patient, but should not be considered as an effective "therapeutic test" for the venous origin of symptoms.

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# PART III
# Pathophysiology of venous symptoms

## 1. Introduction

Regardless of the cause of CVD, venous symptoms are frequently absent despite the presence of large VV or advanced CVD such as lipodermatosclerosis or atrophie blanche (CEAP $C_{4b}$). On the other hand, symptomatic CVD in patients with recurrent or small caliber VV can have normal hemodynamic on air plethysmog-

raphy.[1] The above observations indicate that venous symptoms do not necessarily correlate with the presence or magnitude of venous hypertension (venous pressure during exercise) and that although the latter is their main causative factor, some additional pathophysiological mechanisms are present. The ultimate effect of venous symptoms is deterioration of quality of life with impaired physical and mental generic HRQoL being reported.[2]

## 2. Primary symptoms

### *2.1 Pain or aching*

A differential diagnosis and exclusion of other non-venous conditions causing leg pain are essential,[3] bearing in mind that CVD complications such as pain due to ulceration, superficial vein thrombosis with or without deep vein thrombosis and venous neuropathy can all cause considerable symptoms, affecting quality of life. It should be also kept in mind that frequently-reported leg symptoms in the general population, including those found with CVDs, often have somatic and psychological components,[4] and that pain perception can be different among individual patients. Nevertheless, VV operative treatment including thermal or chemical ablation and stripping largely improve patient pain and symptoms in general,[5, 6] including heaviness, fatigue, itching, tingling and burning.[5]

It is thought that pain is the result of pressure increase that is also transmitted to the microcirculation and activation of sensory multimodal nociceptors of myelinated Aδ and unmyelinated C nerve fibres.[7, 8] Different stimuli activate these venous nociceptors, but in CVDs the main mechanism is local inflammation related to venous capillary stasis resulting in hypoxia and release of proinflammatory and, subsequently, inflammatory mediators.[8] 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 non-localized pain.[9]

Pain sensation can be local over the area of VV but often is diffuse and poorly localized,[10] probably due to increased diameter of the dermal papillae, which occurs in the entire leg.

Leukocyte-endothelium interaction (trapping/adhesion, migration, endothelial activation, release of inflammatory mediators) in the microcirculation is not only responsible 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. Increasing hypertension aggravates the microcirculation even further. However, a better understanding of the molecular mechanisms responsible for the development of symptoms is necessary.

Oral micronized flavonoid therapy improves pain without changes in venous filling index (VFI), ejection fraction (EF), and residual volume fraction (RVF); observations that imply that macrocirculation is only partially responsible for the development of this symptom.[11] Hydroxyethylrutosides have been shown to have a beneficial effect on decreasing capillary macromolecular permeability in abnormal blood flow with a significant increase in oxygen levels, an observation that is associated with an improvement in leg symptoms attributable to CVDs (throbbing, aching, tingling, cramps, itch associated with eczema, heaviness, burning, and in some instances pain).[12]

Venous hypertension responsible for capillary stasis, which is itself the result of obstruction, reflux or a combination of both, produces symptoms in the majority of patients. Venous hypertension is transmitted to the microcirculation producing an increase in capillary diameter and permeability and change in morphology as well as endothelial activation with white cell trapping, and increased leakage of plasma and red cells.[13]

As expected, symptoms occur during standing due to the increased blood pooling and trans-wall pressure increase. Additionally, symptoms (aching but also swelling, throbbing, etc.) are reported to be more intense at the end of the day,[3] likely to be at least partially the result of great saphenous vein (GSV) enlargement associated with standing for a prolonged time.[14] Another well-known provoking factor is a hot environment (with improvement in a cold environment), presumably due to venodilatation,[10] although the exact mechanism has not been elucidated.

Conflicting evidence exists for the pre-menstrual period in women.[10, 15] As a result of the hemodynamic causes of ache and pain, these symptoms are improved with leg elevation, walking (due to leg muscle pump

activation),[15] and the use of elastic compression.[16]

Leg symptoms, including pain and aching, occur more frequently in patients with advanced stages of CVD,[17, 18] in the elderly,[19] and in the presence of extensive axial reflux of the GSV.[20] Patients with VV due to pelvic congestion syndrome complain for leg pain more often than patients with VV without pelvic congestion syndrome, possibly because of the presence of worse venous hypertension in the former group associated with a larger column of blood.[21] A linear trend towards more severe skin damage in patients with CVI and increasing ambulatory venous pressure (AVP) has been reported,[22] however such a link between symptoms and AVP has not been studied.

Although symptoms occur more often in patients with advanced CVD, it seems that these tend to be less severe in patients with advanced CEAP clinical class.[23] This apparent paradox might be the result of an altered perception of pain during the course of the disease or to an increased threshold as a result of neuropathy.[9]

### *2.2 Throbbing*

This otherwise typical symptom of CVDs has not been the subject of a thorough investigation. Throbbing occurs more often in patients with VV compared to $C_1$ patients, indicative of a hemodynamic mechanism.[24]

### *2.3 Tightness*

The exact nature of this particular symptom is unknown, but it is likely to be related to the presence of fluid inside the anatomical compartments.[25] It is a common symptom in patients with iliocaval obstruction and venous claudication.

### *2.4 Heaviness*

The nature of this symptom is closely related to the feeling of swelling,[10] and swelling itself. Heaviness has been reported to occur more often in patients with CVI and higher BMI.[18, 26] However, venous macro-hemodynamics are not the sole determinant of this symptom since, as mentioned above, oral micronized flavonoid therapy improves heaviness and swelling without changes in VFI, EF, and RVF, implying that the microcirculation is mainly responsible for the development of these symptoms.[11] Data obtained from experimental animals and *in-vivo* observation of the microcirculation have shown that oral treatment with micronized purified flavonoid fraction (MPFF), as well as with the extract of *Ruscus aculeatus*, decreases macromolecular permeability induced by histamine, bradykinin, $LTB_4$ and ischemia/reperfusion as well as leukocyte-endothelium interactions evaluated by the number of rolling and sticking leukocytes in control as well as streptozotocin-induced diabetic hamsters.[27-38]

### *2.5 Fatigue*

Fatigue may be the result of leg pain, ache, throbbing, tightness and heaviness.[15] Further work is needed.

### *2.6 Feeling of swelling*

This symptom is usually related to edema formation and is worse in warm weather. A complex process takes place and involves not only the obvious effects of transmission of venous hypertension and consequent increase in microvascular permeability mediated through leucocytes in experimental studies,[39] and reduced veno-arteriolar reflex.[40] Microcirculatory dysfunction caused by chronic venous hypertension is usually not taken into account in CVDs, probably due to the difficulty in observing it. Virgini-Magalhães *et al.* have examined 44 patients and thirteen healthy subjects, 48±8 years, using orthogonal polarization spectral (OPS) imaging and evaluated the following microcirculatory parameters at the internal perimalleolar region: functional capillary density (number of capillaries with flowing red blood cells/mm$^2$), capillary morphology (percentage of abnormal capillaries), diameter (μm) of dermal papilla to quantify edema, diameter of capillary bulk (μm) to assess the degree of change, and diameter of capillary limb to detect enlargement. These microcirculatory parameters were significantly different from control values: capillary diameter and capillary morphology from $C_2$ to $C_5$; diameter of dermal papilla and diameter of capillary bulk from $C_3$ to $C_5$ and functional capillary density only from $C_4$ to $C_5$. In a separate investigation, also using OPS imaging, Porto and co-workers have demonstrated that 4 weeks oral treatment with the extract of *Ruscus aculeatus* was able to decrease capillary

diameter of women with $C_{2s}$ or $C_{2,3s}$ CVD. It is important to note that alterations in microcirculatory parameters could be considered the earliest damage occurring in CVDs patients.[41, 42]

Some patients complain of local swelling that corresponds to the area of VV; this is different from the ankle swelling mentioned above, although the feeling of local edema might be aggravated by local venous hypertension and edema. Venous edema has a characteristic appearance on magnetic resonance imaging, involving not only the subcutaneous tissue but also the muscles,[25] perhaps increasing the pressure inside the leg compartments.

Changing position from lying or sitting to standing leads to a rapid and significant increase in the volume of the leg. The volume increase follows a bi-exponential function fitting to a fast filling compartment (venous pooling) and a slow filling compartment reflecting extravasation.[43] During the course of the day additional tissue fluid may accumulate in the subcutaneous tissue but also inside the leg compartments.[25] The feeling of swelling occurs more often in patients with CVD, recurrent VV affecting the main trunk and also higher BMI.[18, 26, 44] The exact nature of the latter association is not known, however obesity has been shown to be associated with CVI involving a mechanism separate from local effects on venous reflux.[45] In CVI, secondary lymphedema may coexist aggravating patient symptoms.

Improvement of the feeling of swelling by elastic compression suggests that this symptom is the result of hemodynamic causes or microedema.[16]

### *2.7 Cramps*

In the Edinburgh Vein Study, combined superficial and deep reflux was related to leg cramps (P=0.026, left leg) in women.[46] Alternatively, neuropathy (see below) might also be responsible. In the Bonn Vein Study, leg cramps were not associated with CVDs.[47]

### *2.8 Itching*

Itching occurs in association with eczema, but often it is an isolated symptom. Inflammation, cytokine and matrix metalloproteinase activation, and altered cellular function have all been implicated in the pathophysiology of dermal pathology in patients with lipodermatosclerosis or leg ulceration,[48] but for patients with venous eczema the available information is limited. It is thought that a systemic factor or susceptibility apart from venous hypertension is required, while in patients with eczema, allergy is often a common cofactor because of use of topical antibiotics, lanolin in emollients and rubber in elastic bandages.[49]

Itching has been reported to occur more often in patients with CVD,[18, 44] women with isolated superficial reflux (P=0.002, left leg) and men with combined superficial and deep reflux (P=0.0043, left leg),[46] and in patients with recurrent VV.[44] In another study itching was closely associated with localized pain over VV,[10] indicative of the presence of a focal process, while others have demonstrated an association between itching and pain intensity in a study where slightly less than half of all patients with itching also had pain and/or a burning sensation over the itchy area.[50]

### *2.9 Restless legs*

It is thought that afferent nerve fibers triggered by the dilatation of VV are responsible for these involuntary leg movements that are not specific for CVDs and a characteristic of neurological disorders. Sclerotherapy of VV has good short-term results,[51] which indicates that CVD could be one of the causes of restless legs. However, no association between restless legs and the presence of CVD,[47] or CVD severity has been shown.[18]

### *2.10 Tingling*

Tingling sensation may well be a result of peripheral neuropathy due to venous hypertension as previously described.[52-55] In CVI skin biopsy demonstrates marked perineural degeneration, edema, and collagen replacement.[52] In one study, patients with $C_5$ and $C_6$ CVI had a higher Neuropathy Symptom Score and also a higher Neuropathy Disability Score compared with $C_1$ and $C_2$ patients, indicating the presence of peripheral sensory neuropathy. This is probably due to venous microangiopathy, as is also suggested by the presence of reduced vibration sense as well as perception of warmth and cold.[54, 56] Others have demonstrated the presence of a

polyneuropathy in patients with CVI.[53] More specifically, nerve conduction studies showed statistically significant prolongation of distal motor latency in patients with CVI as compared with the controls (median, 5.4 *versus* 4.5 ms; P=0.001). On vibration testing, vibration thresholds were significantly reduced in patients with CVI as compared with the controls (median vibration threshold, 2.9 *versus* 1.1; P<0.0005), indicating dysfunction of A-beta fibers. On thermal sensory testing, warm perception was significantly reduced in patients with CVI (median, 9.6 *versus* 5.2; P=0.001), showing dysfunction of peripheral thermoafferent-C fibers, while cold perception was also affected, indicating a disturbance of A-delta fibers (median, 3.5 *versus* 1.6; P=0.001).

No association between tingling and CVDs severity has been shown.[18] It has been suggested that dysfunction of local nerve fibers may alter regulatory mechanisms,[57] with further aggravation of venous hypertension, but further work on this topic is required.

### *2.11 Burning sensation*

A burning sensation typically occurs during the warm months of the year and is alleviated by seeking a cool place or by lowering the leg temperature by means of a cold shower or use of local gels or creams with a cooling effect. An increased local skin temperature over VV can be clinically observed in some patients; a finding that has been confirmed and quantified a long time ago.[58-61] It is possible that this raised temperature over VV worsens in hot environments leading to a burning sensation, while an early form of neuropathy might be responsible for the burning sensation in some cases.

### *2.12 Venous claudication*

Venous claudication, an uncommon symptom of CVD that is under-recognized and under-treated, is seen almost exclusively in patients with severe iliofemoral or iliocaval obstruction.[62-65] In such cases the venous obstruction is so severe that during walking the arterial inflow is increased beyond the ability of the venous drainage leading to swelling and pain.[62, 66] Muscular pressures at rest and during exercise in the calf are much higher compared with the contralateral unobstructed limb.[66] Unlike arterial claudication the recovery time to baseline is much longer, taking at least 15 minutes.[62] Femoral vein pressures, venous outflow resistance and arm-foot pressure differential are higher compared with those having obstruction below the common femoral vein.[63, 66-68] These patients are also more likely to have edema and skin damage.[64, 65] It should however be kept in mind that in patients with iliofemoral obstruction, neurogenic claudication (caused by dilated veins in the spinal canal that arise from the collateral circulation) instead of pure venous claudication symptoms can occur in 50%, either as an isolated symptom or usually in combination with venous claudication.[69]

## 3. Secondary symptoms

Depression symptoms have been reported to occur in patients with CVDs.[70] Circulating vascular endothelial growth factor (VEGF) has been associated with primary CVI and also with major depression,[71, 72] the implication being the need for further work to firmly establish a direct link between VEGF and depression in CVDs patients. In an observational study on 100 patients with VV, 29% of them had high depression scores suggestive of depression.[70] Depression scores were not influenced by age or gender and there was no correlation between depression scores and VCSS or between venous disability score.[70] However, weak correlations between depression scores and Aberdeen Varicose Vein Questionnaire (AVVQ, P=0.0009, $r^2$=0.12), EuroQol-5D questionnaire (EQ-5D, P<0.0001, $r^2$=0.32) and EuroQol-Visual Analogue Score (EQ-VAS, P<0.0001, $r^2$=0.25) were observed.[70] The presence of depression has been also reported to occur in patients with venous ulcers.[73] Some 68% of patients reported that venous ulceration had a negative emotional impact on their lives, including feelings of fear, social isolation, anger, depression, and negative self-image.[73] In another study, pain and malodor were associated with anxiety and depression.[74] In a third study including 60 patients with venous ulcers depressive symptoms, including sadness, distorted body image, self-depreciation, decreased libido and social withdrawal, have been reported to occur in 92%.[75] It therefore seems that depression in patients with venous ulcers is multifactorial in origin, with depression associated with pain, sleep disturbance, and fatigue (but not swelling and inflammation) on cluster analysis.[76] More studies are required to elucidate the

pathophysiology of depression in patients with CVDs. Nevertheless, in a randomized crossover trial on the use of elastic stockings (15-20 mmHg) in a cohort of hairdressers (not screened for leg symptoms, varicose veins or evening edema prior to study entry), sleep disturbance (insomnia) and symptoms of depression were improved by wearing elastic stockings, indicating that venous hemodynamics may play some role.[16]

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## PART IV
## Scoring of venous symptoms

### 1. Introduction

CVDs have different types of consequences for the patient including symptoms, signs, complications, impairment of activities, and psychological distress. The global result is known as HRQoL. Symptoms can be evaluated alone, or taken into account in a more global scoring system, whether by the physician or by the patient. The weight of symptoms in each assessment tool is variable.

Recent developments in the number and quality of treatment modalities have increased health provider interest in appropriate outcome assessment. Uniform outcome data is also desirable for establishment of medical necessity for third party payers. A valuable assessment

tool should measure and stratify venous symptoms and assess the results of therapy. While general categories of physician-assessed or patient-reported instruments form the framework for evaluation, specific tools have emerged as valid, reproducible methods for the continuum of diagnosis, treatment and follow up. Physician-generated instruments including CEAP and VCSS measure objective data. Revised CEAP classification is now the most widely-used physician-derived classification tool for CVDs. More subjective patient-reported assessments have also increased in popularity. The novel idea of combining physician-generated and patient-reported assessment instruments is being explored. The benefit of a combination approach to measuring outcomes may be a more accurate evaluation of both symptoms and results of treatment in the same patient. A model that combines the elements attributed to symptoms, treatment results and ultrasound findings may lay the framework for medical necessity and reimbursement in the future.

In this section we present the currently available, validated tools for the assessment of symptoms and manifestations of CVDs, focusing on instruments that evaluate the results of therapy. Beyond a systematic review of outcome assessment, we will address the predicted future value of these instruments in the light of emerging therapies.

## 2. Currently available assessment tools and their relationship to symptoms

While the two broadest categories of physician-assessed or patient-reported instruments remain, the tools available have increased and undergone further validation. They have been used in numerous studies and have benefitted from increased exposure and discussion. We now have a clearer picture of the specific benefits and drawbacks of many of the instruments. We also have models for combining assessment tools to gather as much relevant information as possible from patient and physician perspectives.

With so many instruments available, two questions arise:

1) how to choose the best tool to provide the desired information without becoming cumbersome to complete and onerous to evaluate?

2) How much information about symptoms do these tools provide?

Many clinicians forego the generic HRQoL instruments in favor of using disease-specific physician-reported tools, and VAS.

### *2.1 Physician-generated tools*

Several physician-generated instruments are ideally suited to provide valid, reliable data on the objective criteria of CVDs that rely mainly on signs. CEAP and VCSS both provide information on clinical parameters in the progression of CVD, but not on the symptom severity and type.

CEAP is only a *classification* tool and a less responsive periprocedural representation of CVD. CEAP is not to be used to assess treatment results as a stand-alone tool. CEAP has limited responsiveness to change in condition with therapy, especially at the $C_4$ and $C_5$ levels.

The VCSS and the Revised VCSS (rVCSS) provide a more dynamic representation of the course of CVD through serial reporting.[1, 2] Both CEAP and rVCSS have gained acceptance due to the common descriptive platforms they provide and their ease of use. Both also have strong recommendations for use in the Clinical Practice Guidelines of the Society for Vascular Surgery and the American Venous Forum [3] and the European Society for Vascular Surgery (ESVS) Guidelines [4] on the management of chronic venous disease.

CEAP takes into account "presence of symptoms" simply by addition of a subscript "s" without any information given about severity and type of symptoms.

Only one symptom, pain, is used in the rVCSS, and graded 0-3. Thus, neither CEAP nor rVCSS provide any information on symptoms that can be used to study progression or regression of symptoms especially in relation to therapy.

### *2.2 Patient-reported outcomes*

#### 2.2.1 Generic HRQoL scale

The EQ5D-5L™ questionnaire (www.euroquol.org) is a standardized instrument for use as a generic measure of health outcome. This HRQoL questionnaire uses a 5-level (only 3-level in the initial version EQ5D-3L) assessment of pain/discomfort (none, slight, moderate, severe, extreme) and other dimensions, and a VAS for self-perceived HRQoL (vertical, 20 cm). Each health state measured with EQ5D derives into a valuation fac-

tor which can be used for direct calculation of Quality Adjusted Life Years (QALYs) by the formula: QALY = life expectancy × QoL evaluation. Less sensitive to interventions at $C_1$ and $C_2$ levels than disease-specific HRQoL, it can be used in severe health conditions where it allows a valuable approach to cost-effectiveness analysis.

### 2.2.2 Disease-specific HRQoL scales

Patient-reported, venous disease-specific outcome reporting tools (PROs) have gained popularity recently as subjective measures of the benefits of therapy.[2] All of these PROs are focused primarily on symptoms as opposed to signs and therefore more amenable to assessing or comparing therapies. Because they measure symptoms at a given point in time, they are effective measures for evaluating the effects of treatment.

CIVIQ-20 (Table II), which relies predominantly on symptoms, has been validated and is used effectively as a global measure of HRQoL in venous disease. Some critics have said that it does not address the specific manifestations of CVDs, but is more valuable in the overall assessment.[1] However, CIVIQ has been linguistically validated in 17 versions.[7] CIVIQ-20 is among the most comprehensively validated assessment scales in terms of factorial structure, known group validity and responsiveness. This is most important in terms of addressing use in studies in different countries, and in discrimination of severity of patient symptoms as well as response to treatment.[8, 9]

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

The issues addressed in the CIVIQ questionnaires assess patients across the spectrum of CVD, through $C_6$, although CIVIQ-20 targets $C_0$ to $C_4$. Patients with ulcers are excluded, since factors relevant to patients in the earlier stages of CVD may not be relevant to patients with active ulceration, including questions relating to participation in sports or limitations on social activities. CIVIQ-20 showed strong ability to track changes following therapy. This has been validated through its use in comparing treatment methods and conservative therapies.[9]

Table II.—*Dimensions and items used in CIVIQ-20.*

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

Although the CIVIQ questionnaires are extremely useful in assessing HRQoL they do not provide information on different symptoms as listed in Part I.

VEINES-QOL/Sym is applicable in a wide range of clinical conditions. It focuses on the underlying condition and changes in associated symptoms, not on the therapy itself. It has proven useful in elucidating symptomatic changes in studies utilizing multiple treatments. However, because it focuses on diagnostic elements, it is difficult to assess change in response to a specific therapy. Also, there is less focus on anatomic and physiologic elements, which also might clarify beneficial treatment options.[1]

Table III.—*Dimensions and items used in CIVIQ-14.*

| Dimension | Item |
|---|---|
| Pain | Pain in the legs |
| | Impairment at work |
| | Sleeping poorly |
| Physical | Climbing several floors |
| | Squatting/kneeling |
| | Walking at a good pace |
| | Going to parties |
| | Performing athletic activities |
| Psychological | Feeling nervous |
| | Having the impression of being a burden |
| | Being embarrassed to show legs |
| | Becoming irritable easily |
| | Having the impression of being disabled |
| | Having no desire to go out |

AVVQ considers all elements of patients presenting with VV including cosmetic manifestations. Because of this wide reaching approach, AVVQ is useful in such patients. However, because of this wide focus, it lacks some sensitivity in elucidating change over time in individual patients, especially those with milder disease.[1] Also, it is not applicable to patients with deep venous disease.

CXVUQ is an instrument that considers venous ulcers and their course. However, it includes only one symptom: pain in the ulcer. Because of its specific focus, it is a consistent measure of HRQoL factors in patients with venous ulcers, regardless of the treatment option selected. But largely because of this specificity, in order for CXVUQ to give a complete venous disease assessment in patients with ulcers, it probably needs to be combined with a traditional clinical outcome measure or a generic instrument.[1]

The SQOR –V [10-12] is based on a fine clinical appraisal of both symptoms and consequences of CVDs. Symptoms are rated from 2 to 5 and the questionnaire evaluates: global discomfort, pain, heaviness, itching, night cramping, swelling, warm or burning sensations, tingling, stinging or stabbing sensations, restless legs, and worsening by heat. It has been compared to other questionnaires and has allowed observation of the discrepancy between symptoms, signs, and hemodynamic abnormalities.

The newest PRO is the VVSymQ® Score. It is a symptom focused PRO that was designed to evaluate the symptom burden of VV before and after treatment of the GSV in the BTG Varithena® (polidocanol injectable foam) randomized controlled trials (RCTs).[13] In fact it is the first and only symptom PRO that meets the exacting standards for reliability, sensitivity, and content validity as set out in the FDA guidance document titled Patient-reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (US Food and Drug Administration, 2009). The VVSymQ® Score is based on daily patient assessment of the VV symptoms determined through research to be most important to patients: heaviness, achiness, swelling, throbbing, and itching.

## 3. Measuring venous pain

### *3.1 How to measure?*

If looking for a specific evaluation of pain (or any other specific symptom) and not referring to a global assessment of symptoms and their consequences as a whole such as with HRQoL scales, the use of a (self-rated) VAS is the best method.[14] It is specific, sensitive and validated. Pain measurements carried out by the physician underestimate severe pain and overestimate mild pain.[15] Counting painkillers intake is not satisfactory.[16]

Despite some flaws, such as 10-15% of screened patients being unable to use them,[17] VAS have been commonly used in all medical fields including CVDs for a convenient clinical assessment of various types of pain and symptoms.

A VAS usually consists of a 100-mm line, horizontal or vertical, with at one end the indication “No pain” and at the other “Maximal imaginable pain”. The patient is asked to mark the line at the level he thinks describes best the intensity of their pain. Alternate versions and choices do exist such as a choosing a verbal descriptor on a 5- or 7-level scale, or various pain questionnaires. Some may also appear in specific HRQoL scores.

### *3.2 When to measure?*

Like all symptoms, it is important to evaluate pain in similar conditions of time, temperature, activity etc. since venous symptoms vary accordingly.[18] In the SQOR-V questionnaire the timing of symptoms is assessed as follows: day and night, morning, middle of the day, evening, bed-time.

### *3.3 Is it relevant?*

It is relevant and useful but the construction of a RCT should not analyze too many items. An evolution has been observed in recent studies with more importance given to HRQoL scales than to VAS measurement of pain. However, when analyzing specific features of a treatment procedure (pain during procedure, efficacy of local anesthesia, bruising-related pain, etc.) VAS measure of pain is of utmost interest.

## 4. Conclusion

There is a range of valid, reliable assessment instruments to measure CVDs severity using signs and symptoms, but not with the same weight. Physician assessment and patient self-assessment tools deserve

complementary functions and can be combined to provide a more complete clinical picture.

Using the VAS for scoring symptoms, the VCSS for physician evaluation, and HRQoL self-assessment provides information on clinical severity and HRQoL. However, patient satisfaction after treatment remains the ultimate referee and the improvement of venous symptoms should never be missed. Despite this, a validated standard quantitative symptom questionnaire is not yet available.

It follows from the above that quantification of symptoms will be helpful in understanding the natural history of the disease and essential for comparing outcomes and results after different types of therapy. It is obviously better to quantify symptoms using a score instead of using yes or no. In principle, a 10-cm VAS can be used to quantify the severity of a symptom like pain. However, venous symptoms have more dimensions like frequency in which the symptom appears and differences during the day course. A simple score could be used for each symptom with a minimum of 0 and a maximum of 9 points.

We must think about a more precise appraisal of symptoms, and a three-dimensional diagram is suggested:

— frequency: never=0, from time to time=1, several times per week=2, and every day=3;

— daily course: never=0, only in the evening=1, in the afternoon=2, in the morning=3;

— severity: none=0, slightly=1, moderate=2, and severe=3.

This score must be validated before using it in RCTs.

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# PART V
# Clinical examination and investigations

## 1. Introduction

The first question that needs to be posed and answered by a clinician before referring a symptomatic patient presenting with possible CVDs for any investigation should be whether, based on the history and clinical examination, the symptoms are likely to be the result of CVD.

In the presence of CVD and coexisting non-venous disease (elicited from the history and clinical examination), a further question that needs to be answered is which symptoms are attributed to CVD and which to the other coexisting pathology.

The purpose of the initial investigations requested is to provide information that will supplement the history and clinical examination in order to make a diagnosis with adequate understanding of the underlying pathol-

ogy and severity of the problem. Thus, in the case of CVDs the diagnosis includes not only confirmation of presence or absence of a venous abnormality, but also its anatomic extent and severity. In the presence of CVI (CEAP $C_3$-$C_6$), quantification of reflux and obstruction would be a great asset in the development of a rational plan of management.

It should be remembered that every provisional diagnosis (or differential diagnosis) based on the history is a "probability" (or in the case of a differential diagnosis, a list of "probabilities") which can increase or decrease after the clinical examination and may approach a certainty when the results of specific investigations become available. The choice of investigations is determined by the "probabilities" that are formed in the mind of the doctor and suspected pathology based on information from the history and clinical examination.

Because symptoms associated with CVDs are neither specific nor pathognomonic, the initial "probability" of CVD, if based on the symptoms alone, is by necessity low.[1] However, as indicated above (Parts I to III), a number of characteristics of the symptoms and aggravating or relieving factors can provide clues that increase or decrease the likelihood that these symptoms are produced by CVD.

The prevalence of primary CVDs is high in the population even in the absence of symptoms. In practice, when confronted with a symptomatic patient, there are five possibilities: 1) CVD is present (reflux, obstruction or both); 2) CVD is truly absent and the symptoms are unrelated; 3) both CVD and a different pathology that can produce similar symptoms may coexist; 4) CVD is present but the symptoms are not related, being produced by a different pathology; and 5) CVD is apparently absent because it resides in small caliber distal venules or the microcirculation.

In view of the above, all patients should be investigated at least with duplex scanning to confirm or exclude CVD in the venous macrocirculation. Unfortunately, duplex scanning does not assess 2nd and 3rd order saphenous tributaries. Additional investigation should be considered for patients with clinical CEAP $C_{0s}$, *i.e.* patients with typical venous symptoms and normal duplex examination.

The aims of this chapter are to highlight the relationship between clinical examination, hemodynamic information and symptoms of CVD; and also to recommend investigations according to symptomatic CEAP classes.

## 2. Clues from the history of presenting complaint

Care should be taken to elucidate whether the symptoms described by the patient have the characteristic features associated with CVDs, as described earlier in this document, or are atypical. For example, if pain is the main complaint, it is important to know whether this is vague, involving the whole leg and unpleasant rather than sharp and localized at one point; also, it is important to know whether the pain is "bursting" on walking and associated with a feeling of tension and swelling as found in severe outflow obstruction rather than the typical pain of intermittent claudication in arterial occlusive disease which is not associated with swelling or any feeling of "tension" in the leg (for list of typical characteristics of symptoms, see Parts I and II).

Outflow obstruction is always suspected when a feeling of swelling or tension during walking is the predominant symptom. It may be associated with a past history of DVT and the development of prominent collateral venous channels in the groin, above the pubis or on the anterior abdominal wall. Severe outflow obstruction is particularly suspected in a patient with a post-thrombotic limb and venous claudication.

The probability that the symptoms may be the result of CVDs is increased if other conditions that can produce similar symptoms such as sciatica, osteoarthritis of hip or knee, arterial intermittent claudication, acute superficial thrombosis, acute DVT, allergic dermatitis, ankle edema from cardiac or renal failure, lymphedema or proteinuria, are excluded. This is achieved by a careful clinical examination, not only of the venous system but also of the whole patient and not by any venous investigations at this stage.

Leading questions can be helpful: 1) history of DVT or painful swelling of the leg in the past; 2) history of a leg fracture, an operation with prolonged immobilization or a prolonged immobilization in plaster; and 3) whether there had been any leg problems associated with pregnancies. A positive answer to any of these questions will increase the probability of the post thrombotic syndrome.

A list of previous illnesses, operations and medications will also be helpful. For example, a history of back problems may alert the doctor that the pain on walking may be sciatica. Another example is that calcium channel blockers often produce ankle edema. In the presence of otherwise asymptomatic VV, swelling can be misinterpreted

as being caused by CVD. In such cases, treatment of the VV will not cure the feeling of swelling or the edema, but changing the antihypertensive medication to a different drug may do so.

## 3. Clues provided by the clinical examination

Clinical examination will elicit the presence of signs and determine the clinical CEAP class. If the "clues" from the history indicate pathology other than CVD, then eliciting appropriate signs will confirm or refute such an alternative pathology and investigations or referral to a different specialty will be organized to confirm the presence of this different pathology. For example, pain localized in the region of the knee on walking will prompt the clinician to suspect osteoarthritis of the knee and test for crepitus, presence of patellar tap or painful knee flexion. Pain radiating down the leg will prompt the examiner to perform straight leg raising to test for sciatica. Pain and tenderness localized in an area of VV in the presence of a lump will increase the likelihood of superficial vein thrombosis. The presence of dilated prominent veins in the suprapubic region or lower abdomen will increase the probability of outflow obstruction.

Simple leg elevation with the patient supine can provide an estimate of the resting venous pressure by observing the height (in cm) of the heel from the heart level at which the prominent veins in the foot collapse.

## 4. Investigations according to symptoms present and their severity

There are no investigations specific for different symptoms or their severity. This is because symptoms are subjective and not specific for CVDs. Traditionally, one investigates the suspected underlying disease and the magnitude of its severity as measured by signs rather than symptoms.

### *4.1 Anatomic and functional information that can be obtained from investigations*

#### 4.1.1 Presence of reflux and anatomic extent of reflux

Duplex scanning is the method of choice for assessing venous macrocirculation. However, as indicated above it does not assess secondary tributaries or smaller superficial veins. Descending phlebography will be needed to elucidate the presence of leaky valves and especially if deep venous reconstruction is being considered.

#### 4.1.2 Quantification of reflux

For individual veins, duplex scanning can provide measurements of peak venous velocity and volume flow at peak reflux. Volume flow is obtained from the product of time average velocity and vein diameter.

Global reflux for the whole leg is provided by plethysmography methods. The most popular measurement of reflux in ml/sec is provided by the VFI using air plethysmography.

#### 4.1.3 Tests for presence and anatomic extent of outflow obstruction

Duplex scanning is the first method of choice followed by CT scan, MRI, ascending phlebography or intravascular ultrasound (IVUS) depending on available facilities or expertise.

#### 4.1.4 Quantification of obstruction

IVUS provides the most accurate anatomic information on the extension and severity of the stenosis. Plethysmographic tests using outflow fraction are not able to determine the severity of an iliac stenosis because they measure the combined effect of the stenosis with the collateral circulation. Global measurements of obstruction are provided by the arm-foot pressure differential at rest and with reactive hyperemia, and by measurements of outflow resistance.[2] However, these tests are not currently used in routine clinical practice, based on the dogma that all stenosis associated with symptoms should be considered for stenting.

#### 4.1.5 Test for the presence of an abnormal microcirculation

Laser Doppler provides information on skin blood flow (red cell flux), presence or absence of vasomotor activity (VMA) at rest and venoarteriolar response (VAR) on changing position from horizontal to standing. Absence or reduction of VMA and VAR indicate the presence of an abnormal microcirculation.

#### 4.1.6 Quantification of microcirculation abnormality

The rate of capillary leakage between the 7th and 10th minute after inflating a thigh cuff at 70 mmHg using strain-gauge (mL/100 mL/min) or air plethysmography (mL/min) is used to quantify microcirculatory abnormality.

#### 4.1.7 Quantitative changes in skin capillaries

Quantitative changes in capillaries are strongly related to each CEAP clinical class from $C_1$ to $C_6$ can be provided by orthogonal polarization spectral (OPS) imaging used in the Cytoscan. The Cytoscan has a small handheld probe which can be noninvasively applied to all body surfaces and measure functional capillary density (FCD, capillaries/mm$^2$), diameter of dermal papilla (DDP, μm), edema volume, the largest diameter of the capillary bulk (DCB, μm) (degree of change), capillary limb diameter (CD, μm) and capillary morphology (CM, percentage of abnormal capillaries per field). FCD, DDP, DCB, CD and CM values are progressively altered from $C_1$ to $C_6$ patients and values in CVD patients are significantly different from those of healthy subjects ($P<0.05$).

### *4.2 Applications and usefulness of the above measurements in clinical practice and research*

With the exception of orthogonal polarization spectral (OPS) imaging which became available in the last 10 years, many of the above quantitative plethysmographic measurements were abandoned from routine clinical practice when duplex scanning became available and many others such as arm-foot pressure differential, outflow resistance or laser Doppler have been set aside as research tools. However, with the realization that duplex findings have a poor correlation with severity of CVDs, many investigators have turned their attention to quantitative measurements of reflux, obstruction and skin blood flow. The recent development of quantitative tools for measuring the severity of CVD was very timely and stimulated the planning of many studies correlating function with disease severity. As a result, a large collection of publications has accumulated on the correlation of quantitative measurements from venous investigations and clinical severity based on signs but not with symptoms.

### *4.3 Investigations recommended for different CEAP classes*

#### 4.3.1 Patients within CEAP $C_{0s}$ and CEAP $C_{1s}$ classes (no visible or palpable signs of venous disease; telangiectasiae or reticular veins present)

In the absence of any CVD, or in the presence of telangiectasiae only (absence of signs and a normal duplex examination), the history should be reviewed for clues of any different pathology, with appropriate re-examination and additional investigations. For example, if pain on walking is more typical of intermittent claudication due to arterial disease, then Ankle-Brachial Pressure Index (ABPI) should be measured. If tingling in the feet is the main symptom, enquiry about diabetes, testing the urine for glucose and requesting a blood glucose estimation may reveal the possibility of diabetic peripheral neuritis. If all other possible pathology is excluded the patient is CEAP $C_{0s}$ or $C_{1s}$.

The presence of "venous-like" symptoms in the absence of signs ($C_{0s}$) are very common. In the Bonn Vein Study 50% of 1800 participants reported such symptoms,[3] and in the worldwide Vein Consult Program 20% of the symptomatic screened subjects presented with $C_{0s}$,[4] In a recent study in Russia of 41 $C_{0s}$ patients with normal duplex in the morning, 26 (63%) had reflux in the evening with an increased GSV diameter.[5] In the Basel longitudinal study, $C_{0s}$ individuals progressed to develop overt edema when seen 11 years later.[4, 6] In such patients duplex scanning is recommended. If venous reflux or obstruction is identified the patient is $C_{0s}$, $E_p$, $A_s$ or $A_p$ or $A_d$, $P_r$ or $P_o$. If these anomalies are isolated and not combined with other non-venous pathology, then conservative treatment should be considered in the first place or more active treatment if symptoms persist. If duplex scan is normal the patient is $C_{0s}$, $E_n$, $A_n$, $P_n$. In these cases, we have little data to guide us whether other examinations for iliac obstruction or reflux in secondary or tertiary tributaries should be pursued. Although valvular incompetence in saphenous tributaries or in the small veins of the skin can exist independently of valvular incompetence in the GSV, and areas of reflux can occur in saphenous tributaries or in the small veins of the skin despite a normally functioning GSV,[7] we do not know how useful high resolution duplex investigations of these veins using high-frequency transducers will be.

The above applies also to patients with venous symp-

toms and telangiectasia or reticular veins ($C_{1s}$). We know very little on the pathophysiology of telangiectasia or reticular veins.

Further studies are needed in patients with $C_{0s}$ and $C_{1s}$ using these methods to elucidate the pathology. In addition, future studies should investigate the presence of reflux in the evening and distal venules due to damage to micro-valves. The more severe the symptoms the greater is the incentive to investigate these patients and the greater is the need to find an underlying cause.

In specialized centers one could test for microangiopathy with laser Doppler (red cell flux and venoarteriolar reflex) or with capillaroscopy using the Cytoscan. If the venoarteriolar reflex is absent or reduced, then elastic compression, intermittent pneumatic compression, electrical calf muscle stimulation, venoactive drugs or a combination of these therapeutic methods should reestablish the venoarteriolar reflex with symptomatic relief. It should be pointed out that these tests are noninvasive and less expensive than duplex. However, in the absence of these facilities treating such patients with venoactive drugs without any investigations apart from duplex is an option with 80% of patients reporting symptomatic relief.

#### 4.3.2 Patients in CEAP $C_{2s}$ class (VV present without any edema or skin changes)

In this group of patients there is a great variability of symptoms and signs. Often, early small VV are associated with severe symptoms and vice versa, patients with large, longstanding VV may present with minimal symptoms. Because of this, the severity of symptoms is not a determinant of type or extent of investigations. Similar to $C_3$-$C_6$ patients, investigations for $C_2$ patients are not performed to confirm venous causes but to plan treatment.

Duplex scanning will determine the presence of reflux, the site or sites of deep to superficial incompetence, the anatomic extent of reflux and re-entry points. It will also assess the state of the deep veins (reflux and/or obstruction). The presence of deep venous obstruction may indicate that the clinically visible VV may be acting as collateral channels.

In the majority of patients with primary VV and normal deep veins, the information provided by the duplex will be enough to plan management. When there is a major discrepancy between venous symptoms and information from investigations, additional investigations should be considered.

The entire superficial and deep venous systems as well as the communicating and perforating veins should be examined. Elements of the examination that are often germane to further management include:

1) Standing position for the femoral and great saphenous veins or sitting position for popliteal and calf veins,
2) Measurement of velocity at peak reflux,
3) Size of perforators,
4) Diameter of saphenous veins,
5) Size and competence of major saphenous tributaries.

#### 4.3.3 Patients in CEAP $C_3$ class (edema with or without varicose veins and without skin changes)

Duplex scanning should be utilized to determine whether or not reflux or obstruction in the deep veins is responsible for the edema. If reflux is present, volume flow in ml/sec at peak reflux should be measured in each axial vein (*e.g.* femoral and GSV) using the automated facility now available on all duplex scanners. An alternative method to measure global reflux is air plethysmography (VFI will provide reflux in ml/sec). Reflux less than 5 mL/s has a good prognosis as it is unlikely to lead to skin changes. Reflux greater than 5 mL/s is likely to lead to skin changes and reflux greater than 10 ml/sec has a poor prognosis because if left untreated is likely to lead to ulceration.

If obstruction is demonstrated or suspected as a result of duplex scanning, then a CT venogram to investigate the deep venous system must be considered.

In the absence of reflux or obstruction on duplex, lymphoscintigraphy may be indicated to confirm the diagnosis of lymphedema in certain patients.

#### 4.3.4 Patients in CEAP $C_4$, $C_5$ or $C_6$ class (skin changes suggestive of venous disease including healed or open ulceration with or without edema and VV)

Duplex scanning should be the initial investigation in all patients. Selected cases, such as those being considered for deep venous intervention, should proceed to further imaging methods (CT scan, ascending and descending phlebography, or IVUS).

If deep venous reconstruction is contemplated, then

quantification of reflux (VFI) and or obstruction (outflow resistance) may help in the development of a rational plan of management.

Duplex scanning alone may be sufficient in some patients with irreversible muscle pump dysfunction due to neurological disease, severe and non-correctable reduction of ankle movement or where there is a contraindication to surgical intervention.

### 5. Management of disease or symptoms?

The paragraphs above indicate how guidelines and current practice are devoted to disease management but not specifically to symptoms. This is because treatment is focused on the underlying pathology and based on the axiom that successful treatment of the underlying cause will relieve symptoms. The major problem is when the underlying suspected pathology is not found. The question, which investigations can help for attributing symptoms to $C_{0s}$ and $C_{1s}$ patients cannot currently be answered fully.

Symptoms disappear in the majority of patients (successful treatment) or improve as shown by the HRQoL scoring systems or VAS used in RCTs. Unfortunately, there are no publications on the use of scoring of symptoms in clinical practice. A clinical scoring system based only on symptoms for use in daily clinical practice is needed. We need to know the amount by which individual symptoms improve after different interventions.

If symptoms do not improve after intervention (treatment failure), the question that needs to be asked is whether the intervention was appropriate but failed due to technical errors or whether it was inappropriate because of diagnosis failure. An example of the first instance is persistent VV after ablation, and in the second persistence of ulceration despite stenting and adequate compression.

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## PART VI
## Conclusion

As stated in the preface, this consensus document on venous symptoms in CVDs is the result of the work of the SYM Vein Group.

The first part on description and definition was not difficult to elaborate, but its translation into different languages may not be easy, as presently some words have no equivalent from one language to the other.

The second part devoted to attribution of "venous symptoms" to a venous cause was the result of a long debate between the participants. The clues for attributing symptoms are multiple and their listing in this document should help physicians in the management of their patients, although medical history, physical examination and instrumental investigations as developed in the last part remain crucial.

With the exception of pain, the pathophysiology of various venous symptoms is poorly documented in the literature. Venous hypertension due to reflux or obstruction leads to capillary stasis and hypoxia but it is not always identified by routine tests. Still the mechanism of increased capillary distension and permeability triggering the inflammatory process appears to be essential for the development of most symptoms. The localized release of proinflammatory mediators seems to play a decisive role in the activation of venous and perivenous nociceptors and may account for the occurrence of pain starting at the early stages of venous disease. The pathophysiology of other symptoms is often the same, but some symptoms such as throbbing, restless legs and cramps are difficult to explain. In contrast, the pathophysiology of venous claudication is clearly identified.

The fourth part analyses in detail the different tools used for scoring chronic venous disorders and indicates which ones are the most useful and precise for scoring venous symptoms.

The last part details how information provided by the patient's history and physical examination is used to as-

cribe symptoms to a venous cause. The role and the value of instrumental investigations to correlate symptoms to various chronic venous disorders and CEAP classification is probably the most original part of this consensus document providing practical advice. In $C_{0s}$ and $C_{1s}$ patients alternative investigations are recommended when routine duplex scan is normal. In $C_{2s}$-$C_{6s}$ patients the main role of instrumental investigations is to plan and implement the most appropriate treatment. However, in terms of symptoms, investigations in these patients are useful when the severity of symptoms does not correlate with anatomical anomalies based on duplex scanning; also when sometimes patients are not improved after treatment although postoperative duplex findings are satisfactory. In these cases, additional investigations need to be considered.

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