Chronic venous disease guidelines and daily clinical practice

EDITORIAL

231 Guidelines in chronic venous disease: providing clinicians with better decision-making tools. Directives sur l’insuffisance veineuse chronique : fournir aux cliniciens de meilleurs outils de décision
A. J. Comerota, USA

THEMED ARTICLES

238 Updating guidelines in chronic venous disease: what is needed?
C. Allegra, Italy

245 Chronic venous disease guidelines and terminology: sharing a common language
M. R. Perrin, France, and B. Eklöf, Sweden

253 Prevalence and socioeconomic data in chronic venous disease: how useful are they in planning appropriate management?
D. J. Milic, Serbia

259 Treatment of chronic venous disease: pathophysiological underpinnings
R. D. Malgor, N. Labropoulos, USA

268 Classifications, severity scorings, and chronic venous disease guidelines
M. Kurtoğlu, M. Aksoy, Turkey

274 Current status of patient-reported outcomes and chronic venous disease guidelines
A. Mansilha, Portugal

280 Rating the quality of evidence and the strength of recommendations: the new GRADE system in venous disease
G. Le Gal, Z. Alavi, France

285 European and American guidelines on primary chronic venous disease: what’s new?
J.-L. Gillet, France

Contents continued on next page
CONTROVERSIAL QUESTION
293  Are chronic venous disease guidelines adapted to daily practice?
K. A. Aal, Egypt - H. S. Caldevilla, Argentina - R. Costa-Val, Brazil -
H. S. Yuwono, Indonesia - H. N. T. H. Le, Vietnam - S. M. Kulišić,
Croatia - A. Puskás, Romania - K. Roztočil, Czech Republic -
M. Salah, Saudi Arabia - I. S. Escotto, Mexico - J.-F. Uhl, France -
I. A. Zolotukhin, Russia

DAFLO N 500 MG
306  The place of Daflon 500 mg in recent guidelines on the management of
chronic venous disease
F. Pitsch, France

INTERVIEW
315  Are we any better at identifying the risk factors for chronic venous
disease progression?
M. Flour, Belgium

FOCUS
320  Identifying and accessing patients with chronic venous disease:
the large-scale VCP International Study
E. Rabe, Germany

UPDATE
325  Pain in chronic venous disease: perspectives for research
N. Danziger, France

A TOUCH OF FRANCE
334  Theory and practice: European Renaissance medicine
S. Daynes-Diallo, France

344  Écouen: from château to museum, or Beauty is in the detail
S. Deprouw, France
Chronic venous disease (CVD) is the most prevalent vascular disorder in developed countries and it may be the single most common chronic disease overall. Therefore, standard descriptors of the disease—its location, presentation, etiology, pathophysiology, impact on patients, response to therapy, and cost—are crucial, if not mandatory. Reporting standards and guidelines for the above measures organize patient evaluation and treatment, standardize nomenclature, and offer tools to evaluate the severity, natural history, and response to treatment of the disease. Unfortunately, the reporting of outcomes of therapy for venous disease has lagged behind other disease categories. During the past several years, there has been growing interest in the development of guidelines for venous anatomy (nomenclature), the description of patient presentation, the severity of venous disease, and the outcome measures following therapy.

Use of guidelines for disease description and measurement of treatment outcomes is the first step in the process of implementing evidence-based care. Evidence-based medicine has been defined as “the conscientious, explicit, and judicious use of the current best evidence in making decisions about the care of individual patients.”

This article highlights areas of standardized nomenclature, patient presentation, severity of venous disease, and standardized and validated outcome measures following therapy. It is hoped that all physicians will incorporate these guidelines into their clinical care of patients with CVD.

Need for standard definitions
For many years, the description of patients with venous disease and measurement of outcomes were subjective and arbitrary. Ambiguity in clinical descriptors led to confusion and misunderstanding. Standardized nomenclature is the first step to developing clear, objective documentation and communication regarding patients, disease status, and outcome measures.

◆ Anatomic nomenclature
Guidelines for venous disease must begin with a standard nomenclature regarding the anatomy of the venous system. Until 2002, the veins of the lower extremity were often incorrectly characterized, and physicians used numerous eponyms to refer to specific veins. Caggiati et al made an important contribution to the field when they proposed a standard international nomenclature for the veins of the lower extremity.
er extremity. Examples of their contribution include precise definitions of perforating veins, which penetrate the muscular fascia to connect superficial veins to deep veins, and communicating veins, which connect veins within the same compartment.

A major misnomer that existed for decades was the term “superficial femoral vein,” referring to the major deep vein of the thigh that connects the popliteal vein to the common femoral vein. That vein is now appropriately termed the femoral vein. Noninvasive imaging has led to our increased understanding of the saphenous subcompartment and saphenous fascia. Standardization of the terms “great saphenous vein” and “small saphenous vein” has added greater clarity to the superficial venous nomenclature.

The saphenofemoral junction, previously a major point of contention, is now called the confluence of the superficial inguinal veins, which refers to that segment of the great saphenous vein extending from the inferior epigastric vein to its junction with the common femoral vein.

International nomenclature has discarded eponyms and renamed veins appropriately, according to proper anatomic terms, eg, by replacing the name “vein of Giacomini” with “intersaphenous vein.”

This international nomenclature consensus statement is an important reference that allows us to ensure that a standardized nomenclature is incorporated into all our communication regarding patient care, clinical studies, and reports of patient outcomes.

Standardizing investigations
Tools are necessary to build strong and enduring structures. With few exceptions, the better the tools available, the more rapidly the job is done and the more enduring the product. Investigative tools have been developed to describe, characterize, and monitor the outcome of venous disease. Perhaps the most important metric is patients’ view of how the disease has affected their life. Just as no single tool can build a large and durable building, no single tool fully meets the investigative needs in CVD.

It is appropriate to identify what is needed and then to choose the appropriate instrument. Instruments can be broadly categorized into discriminative and evaluative instruments. A discriminative instrument is one that clearly describes the patient (current status of venous disease) and is capable of identifying differences between patients, whereas evaluative instruments are designed to detect changes over time, either deterioration due to disease or improvement with treatment.

Perhaps the best discriminative instrument available is the CEAP (Clinical-Etiological-Anatomical-Pathophysiological) classification. The CEAP classification describes the clinical severity of a patient’s venous disease, its etiology, its anatomical location, and the patient’s underlying pathophysiology. Patients presenting with venous disease should be classified according to the CEAP classification.

One potential weakness of current discriminative instruments is our inability to identify and quantify venous obstruction. Since noninvasive evaluation of venous disease is now standard for most patients, we know that imaging methods underestimate the magnitude of venous luminal obstruction (short of showing venous occlusion), with the possible exception of intravascular ultrasound. Noninvasive physiological testing using maximal venous outflow techniques are notoriously insensitive at detecting venous obstruction; much more work is required to identify a noninvasive method to more clearly delineate this element of venous pathophysiology.

Other deficiencies include our inadequate understanding of the effects of venous disease on the microcirculation and why microcirculatory dysfunction occurs in some patients and not in others. This likely explains why there are different clinical venous categories of CVD in patients with similar venous hemodynamics. It becomes evident that until we develop diagnostic techniques to assess these important end points, classification systems that include pathophysiology as part of their description will remain potentially inaccurate if not misleading.

A number of good evaluative instruments exist that can monitor changes in patients’ status over time and are responsive to disease progression or therapeutic intervention. Each instrument should be carefully studied to ensure that it is valid (capable of quantifying what it is intended to measure), reliable (produces consistent results when used repeatedly on stable subjects), and responsive (capable of detecting clinically important changes). Two of the better evaluative instruments are the Venous Clinical Severity Score (VCSS) and the Villalta scale. Other evaluative instruments focus on patients’ quality of life, arguably the most important outcome of

**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CEAP</td>
<td>Clinical-Etiological-Anatomical-Pathophysiological</td>
</tr>
<tr>
<td>CIVIQ-20</td>
<td>Chronic Venous disease quality of life Questionnaire [20]</td>
</tr>
<tr>
<td>CVD</td>
<td>chronic venous disease</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short Form 36 [health survey]</td>
</tr>
<tr>
<td>VCSS</td>
<td>Venous Clinical Severity Score</td>
</tr>
<tr>
<td>VDS</td>
<td>Venous Disability Score</td>
</tr>
<tr>
<td>VEINES-QOL</td>
<td>Venous Insufficiency Epidemiological and economic Study–Quality Of Life</td>
</tr>
<tr>
<td>VSDS</td>
<td>Venous Segmental Disease Score</td>
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all. Examples include the SF-36 (Short Form 36 [health survey]),17,18 VEINES-QOL (Venous Insufficiency Epidemiological and economic Study–Quality Of Life),11 CIVIQ-20 (Chronic Venous disease quality of life Questionnaire [20]),19 and Aberdeen questionnaires.20

Adjuncts to the VCSS are the Venous Segmental Disease Score (VSDS) and the Venous Disability Score (VDS).21 The VSDS is designed to anatomically localize venous disease and describe whether the identified segment has reflux or is obstructed. Points have been arbitrarily assigned for each segment. The VSDS has not yet been validated, and it is likely that further modification will be required after appropriate prospective clinical studies are performed.

The VDS is a 4-point scale (4 categories) of disability ranging from 0 (asymptomatic) to 3 (unable to carry out usual activities, even with compression and/or limb elevation). Like the VSDS, the VDS requires validation. However, in light of its broad categories and their limited number, the VDS is likely to be insensitive as an evaluative instrument and more appropriately used as a descriptive measure.

Guidelines and the treatment of CVD

Objective outcome measures and guidelines for the management of patients with venous disease are more important now than ever and will assume even greater importance in the future. Management of patients with CVD is rapidly evolving from open surgical procedures to endovascular techniques. In patients with the most complex forms of CVD, hybrid procedures that include both open and endovascular components are being performed.22 To assess whether a particular treatment is appropriate, reliable, standardized, and objective, evaluation instruments are required. These should be prospectively applied to all patients; that is, prior to treatment, patients should be objectively classified according to the CEAP classification and a validated quality-of-life instrument and a good evaluative instrument should be used. Following treatment at appropriate time intervals, evaluative and quality-of-life measures should be repeated. These objective measures can then be assessed and integrated into a cost analysis to determine the true value of a treatment for specific patient groups.

Handbook of Venous Disorders: Guidelines of the American Venous Forum

An excellent source of guidelines for the clinician to follow is the 3rd edition of the Handbook of Venous Disorders: Guidelines of the American Venous Forum, edited by Peter Giovi-
czki, MD.23 This is perhaps the best single volume of guidelines for the management of venous disease available today. The handbook, comprised of 65 chapters divided into seven sections, contains the latest information on epidemiology, basic science, and investigation of venous and lymphatic diseases, as well as modern venous imaging techniques. Both acute and chronic venous diseases are covered, and the increasing enthusiasm for minimally invasive and endovenous technology is appropriately addressed.

Perhaps the most important and enduring aspect of this volume is the addition to each chapter of evidence-based clinical guidelines regarding the evaluation and management of venous disease. Evidence scores are given to assist the reader in assessing the strength of the evidence and the grade of recommendation. In the final chapter, the volume culminates with a list of all the evidence-based guidelines of the American Venous Forum.

Summary

The important topics in Medicographia No.108 are addressed in a timely manner by an international collection of experts focusing on areas of venous disease in which they have a special interest and have made major contributions. The specific topics are important for all of us to recognize, as they will have practical implications for the care of patients with CVD as we move forward. I recommend this issue of Medicographia to each of you and I am sure you will find it as valuable as I have.

References


Keywords: guidelines; chronic venous disease; decision-making
Directives sur l’insuffisance veineuse chronique : fournir aux cliniciens de meilleurs outils de décision

par A. J. Comerota, États-Unis

L’insuffisance veineuse chronique (IVC) est l’affection vasculaire la plus fréquente dans les pays développés1,2, et pourrait constituer la pathologie chronique individuelle la plus fréquemment rencontrée. Par conséquent, les descriptions standard de la maladie, qui comprennent la localisation, le tableau clinique, l’étiologie, la physiopathologie, l’impact sur les patients, la réponse au traitement et les coûts, sont essentielles, si ce n’est obligatoire. Les normes et les directives de notification des paramètres précédents organisent l’évaluation et le traitement des patients, standardisent la nomenclature et offrent des outils d’évaluation de la sévérité et de l’histoire naturelle de la maladie, ainsi que de la réponse au traitement. Malheureusement, l’expression des résultats thérapeutiques dans l’insuffisance veineuse est restée en retrait par rapport aux autres domaines pathologiques3. Au cours de ces dernières années, un intérêt croissant est né pour le développement de directives sur l’anatomie veineuse (nomenclature)4, la description du tableau clinique5, la sévérité de l’insuffisance veineuse6-8, et la mesure des résultats thérapeutiques9,10.

L’utilisation de directives pour la description de la maladie et la mesure des résultats thérapeutiques est le premier pas dans le processus de mise en œuvre des soins factuels. La médecine factuelle est définie comme « l’utilisation consciencieuse, explicite et judicieuse des meilleures preuves actuelles dans la prise de décision pour les soins prodigués aux patients11. » Cet article présente certains aspects d’une nomenclature standardisée, du tableau clinique, de la sévérité de l’insuffisance veineuse et des mesures standardisées et validées des résultats thérapeutiques. Il faut espérer que tous les médecins tiendront compte de ces directives dans les soins qu’ils prodigueront à leurs patients atteints d’IVC.

Nécessité de définitions standard

Depuis de nombreuses années, la description des symptômes de l’insuffisance veineuse et la mesure des résultats thérapeutiques étaient subjectives et arbitraires. L’ambiguïté des descriptions cliniques a conduit à la confusion et à l’incompréhension. Une nomenclature standardisée constitue la première étape pour développer une documentation et une communication claires et objectives sur les patients, le stade de la maladie et les critères d’évaluation.

N° Nomenclature anatomique

Les directives sur l’insuffisance veineuse doivent débuter par une nomenclature standard concernant l’anatomie du système veineux. Jusqu’en 2002, les veines des membres inférieurs ont été souvent caractérisées de manière incorrecte, et les mé-
Les outils d’investigation ont été développés pour décrire, caractériser et contrôler l’évolution de l’insuffisance veineuse. L’une des mesures peut-être la plus importante est l’opinion des patients concernant la manière dont leur maladie a affecté leur vie. Exactement de la même manière qu’un seul outil ne permet pas de construire un édifice important et durable, de même aucun outil isolé ne pourra répondre aux besoins d’investigation dans l’IVC.

Il convient d’identifier ce qui est nécessaire, puis de choisir l’instrument approprié. Les instruments peuvent être classés globalement en instruments de distinction et d’évaluation. Un instrument de distinction permettra de décrire clairement le patient (stade actuel de l’insuffisance veineuse) et d’identifier les différences entre les patients, tandis qu’un instrument d’évaluation sera conçu pour détecter des changements au cours du temps, ou une détérioration due à la maladie ou une amélioration apportée par le traitement.

La classification CEAP (clinique – étiologique – anatomique – physiopathologique) peut être considérée comme le meilleur instrument de discrimination disponible. La classification CEAP décrit la sévérité clinique de l’insuffisance veineuse, son étiologie, sa localisation anatomique et les processus physiopathologiques sous-jacents chez le patient. Tous les patients présentant une insuffisance veineuse devraient être classés avec la classification CEAP.

L’une des faiblesses potentielles des instruments actuels de distinction est notre incapacité à identifier et quantifier l’obstruction veineuse. Dans la mesure où l’évaluation non invasive de l’insuffisance veineuse est désormais la norme pour la plupart des patients, nous savons que les méthodes d’imagerie minimisent l’ampleur de l’obstruction luminaire veineuse (réduction de l’importance de l’occlusion veineuse), à l’exception éventuelle de l’échographie intravasculaire. Il est également établi que les épreuves physiologiques invasives utilisant les techniques de débit veineux maximal ne sont pas sensibles à la détection de l’obstruction veineuse; beaucoup d’efforts doivent encore être accomplis pour identifier une méthode non invasive permettant de définir clairement cet élément de la physiopathologie veineuse.

La clarté de la nomenclature des veines superficielles a apporté une plus grande clarté à la nomenclature des veines superficielles. La jonction saphéno-fémorale, un point litigieux important au-delà de la veine fémorale superficielle, qui fai- sait référence à la principale veine profonde de la cuisse qui connecte la veine poplitée à la veine fémorale commune. Cette veine porte désormais l’appellation appropriée de veine fé- morale. L’imagerie non invasive a permis d’améliorer notre connaissance du sous-compartment saphène et de l’aponé- vrose saphène. La standardisation des termes « veine grande saphène » et « veine petite saphène » a apporté une plus grande clarté à la nomenclature des veines superficielles.

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La nomenclature internationale a éliminé les éponymes et a renommé les veines de façon appropriée, en leur donnant des termes anatomiques propres, par exemple en remplaçant le nom de « veine de Giacomini » par « veine intersaphène ».

Cette déclaration de consensus concernant une nomenclature internationale est une référence importante qui nous permet d’assurer qu’une nomenclature standardisée sera utilisée dans toutes nos communications concernant les soins aux patients, les études cliniques et les notifications de résultats.

**Standardiser les investigations**

Des outils sont nécessaires pour élaborer des structures fortes et durables. À quelques exceptions près, plus les outils sont efficaces, plus le travail est fait rapidement et plus le produit est durable.

Des outils d’investigation ont été développés pour décrire, caractériser et contrôler l’évolution de l’insuffisance veineuse. L’une des mesures peut-être la plus importante est l’opinion des patients concernant la manière dont leur maladie a affecté leur vie. Exactement de la même manière qu’un seul outil ne permet pas de construire un édifice important et durable, de même aucun outil isolé ne pourra répondre aux besoins d’investigation dans l’IVC.

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Les autres inconvénients comprennent notre mauvaise compréhension des effets de l’insuffisance veineuse sur la microcirculation, et les raisons de la survenue d’un dysfonctionnement microcirculatoire chez certains patients et non chez d’autres. Cela explique vraisemblablement pourquoi il existe différentes catégories cliniques d’IVC chez des patients présentant des caractéristiques hémodynamiques veineuses similaires. Il est certain que, jusqu’à ce que nous développons des techniques diagnostiques permettant d’évaluer ces critères importants, les systèmes de classification incluant la physiopathologie dans leur description resteront potentiellement inexacts, si ce n’est tropmeurs.

Un certain nombre d’instruments d’évaluation satisfaisants permettent actuellement de surveiller l’évolution de l’état des patients avec le temps, et sont sensibles à une progression de la maladie ou à une intervention thérapeutique. Chaque instrument doit être étudié avec attention pour s’assurer de sa validité (capacité de quantifier ce qu’il est supposé mesurer), fiable (produisant des résultats constants lorsqu’il est utilisé de façon répétée chez des sujets stables) et sensible...
(en mesure de détecter des changements cliniquement importants)\textsuperscript{12}. Deux des meilleurs instruments d’évaluation sont le score de sévérité clinique de l’insuffisance veineuse (Venous Clinical Severity Score, VCSS)\textsuperscript{6,15} et l’échelle de Villalta\textsuperscript{7,16}.

D’autres instruments d’évaluation portent sur la qualité de vie du patient, qui peut être considérée comme le paramètre le plus important, par exemple : le questionnaire de santé SF-36 (Short Form 36)\textsuperscript{17,18}, le questionnaire de l’étude épidémiologique et économique sur l’insuffisance veineuse – qualité de vie (Venous Insufficiency Epidemiological and Economic Study–Quality Of Life, VEINES-QOL)\textsuperscript{19}, le questionnaire de qualité de vie dans l’insuffisance veineuse chronique (Chronic Venous disease quality of life Questionnaire, CI/VQ-20)\textsuperscript{20}, et le questionnaire d’Aberdeen\textsuperscript{21}.

Deux outils supplémentaires complètent le VCSS, le score segmentaire de l’insuffisance veineuse (Venous Segmental Disease Score, VSDS) et le score d’incapacité veineuse (Venous Disability Score, VDS)\textsuperscript{21}. Le VSDS est conçu pour localiser anatomiquement l’insuffisance veineuse et décrire si le segment identifié présente un reflux ou une obstruction. Des points ont été arbitrairement assignés à chaque segment. Le VSDS n’a pas encore été validé, et il est probable que certaines modifications seront nécessaires après la réalisation des études cliniques prospectives appropriées.

Le VDS est une échelle en 4 points (4 catégories) pour l’évaluation de l’incapacité, comprise entre 0 (asymptomatique) et 3 (incapable d’effectuer les activités usuelles, même avec une compression et/ou une élévation des membres). Comme le VSDS, le VDS nécessite une validation. Cependant, compte tenu de ses larges catégories et de leur nombre limité, le VDS ne sera probablement pas assez sensible comme instrument d’évaluation, et sera utilisé de façon plus appropriée comme mesure descriptive.

**Directives et traitement de l’IVC**

Des mesures objectives des résultats thérapeutiques et des directives pour la prise en charge des patients atteints d’insuffisance veineuse sont aujourd’hui plus importantes que jamais, et le seront encore davantage à l’avenir. La prise en charge des patients atteints d’IVC évolue rapidement des procédures chirurgicales ouvertes vers les techniques endovasculaires. Chez les patients souffrant de formes plus complexes d’IVC, des procédures hybrides comprenant des composantes ouvertes et endovasculaires sont actuellement réalisées\textsuperscript{22}. Afin d’évaluer si un traitement particulier est approprié, fiable, standardisé et objectif, des instruments d’évaluation sont nécessaires. Ils devront être appliqués de façon prospective à tous les patients ; cela signifie qu’avant le traitement les patients devront être classés de manière objective selon la classification CEAP, et qu’un instrument de qualité de vie validé et un instrument d’évaluation satisfaisant devront être utilisés. Après le traitement, à intervalles déterminés, les mesures d’évaluation et de qualité de vie devront être répétées. Ces mesures objectives pourront ensuite être évaluées et intégrées dans une analyse coût-efficacité afin de déterminer la valeur réelle d’un traitement dans des groupes de patients spécifiques.

**Manuel des troubles veineux : directives du forum américain sur l’insuffisance veineuse**


L’aspect le plus important et pérenne de ce manuel pourrait être l’ajout à chaque chapitre des directives cliniques factuelles concernant l’évaluation et la prise en charge de l’insuffisance veineuse. Les scores de preuves sont fournis pour aider le lecteur à évaluer le niveau de la preuve et la classe de recommandation. Dans son dernier chapitre, le livre présente une liste de l’ensemble des directives factuelles de l’American Venous Forum.

**Résumé**

Les sujets importants abordés dans le nº 108 de Medicographia sont traités à point nommé par un groupe international d’experts spécialisés dans le domaine de l’insuffisance veineuse, et auquel ils ont apporté des contributions majeures. Les sujets spécifiques sont particulièrement importants, car ils nous font comprendre qu’ils auront des applications pratiques dans les soins des patients atteints d’IVC à l’avenir. Je recommande fortement à chacun d’entre vous la lecture de ce numéro de Medicographia, et je suis persuadé qu’il suscitera pour vous autant d’intérêt qu’il en a fait naitre chez moi.
The setting up of the CEAP classification and its adjuncts was a great leap forward in the management of CVD. The CEAP classification can be used by physicians to keep records of diagnostic information, while the adjuncts to CEAP (VCSS, VSDS, and VDS) are scoring schemes that are quantifiable and include elements that change in response to treatment. These instruments may be used to evaluate any stage of CVD in patients, although they are imperfect in the early stages.”

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Because the venous system is in many respects more complex than the arterial system, chronic venous disease (CVD) is common in Western populations. Both specialists and general practitioners have to deal with this disease, and there is a need for practical support regarding CVD management in daily practice. The most recent guidelines have considered the many possible treatments of CVD, including vasoactive drugs such as Daflon 500 mg. First, it must be stressed that no consensus on guidelines is possible without the sharing of a common international scientific language for the investigation and management of CVD.

What is also important for building guidelines is to have reliable prevalence data that can serve as a valuable basis for the planning of appropriate actions to deal with problems, and by repeating an epidemiological survey within a defined geographical area to allow the assessment of the effect of treatment changes. Better knowl-
edge of the underlying mechanisms of CVD will create the basis for correctly targeted treatment and, in a certain way, will improve the recommendations in guidelines. In addition, validated assessment tools to measure changes to treatment and their proper use would improve the management of CVD. A rigorous system for rating the quality of evidence and grading the strength of a recommendation has to be used in order to offer proper recommendations to the clinical community that are easy to understand, transparent, and pragmatic. This is challenging.

All the above aspects are of the utmost importance for guidelines to be adopted and will be reviewed in the present article.

**Terminology, classifications, and severity scoring of CVD**

A great leap forward, a consensus on the use of common venous anatomical terminology1-3 for a standardized classification system—CEAP (Clinical-Etiological-Anatomical-Pathophysiological)—and on the use of duplex ultrasound investigation to assess the anatomy of superficial and perforating veins by ultrasound imaging4 and its derivatives has now been universally adopted, which has facilitated and improved communication on and served as a foundation for the accurate reporting of the severity of CVD.4,5,6

Because the CEAP classification is descriptive, with static components that do not change in response to treatment, it cannot be used for venous severity scoring. As a result, a Venous Severity Scoring System (VSSS) has been proposed by the American Venous Forum (AVF) Ad Hoc Committee on Venous Segmental Disease Score (VSDS), which assesses the ability to work with or without a “support device.”7

VCSS, one of the components of the VSSS, has been studied and shown to be valid, in that its score increases in a linear fashion with CEAP clinical class, and VCSS is reliable, as demonstrated in tests of intraobserver variability.8 A change in the score of this instrument could therefore be used as an outcome measure to assess treatment. Unfortunately, the responsiveness of VCSS has not been adequately evaluated; therefore, it cannot as yet be used to calculate sample sizes for clinical trials.

Updated definitions of terms related to CVD by the Vein-Term Transatlantic Interdisciplinary Consensus Group of international experts have decreased problems of interpretation and improved communication and reporting in the investigation and management of CVD.9 The consensus document includes 33 broadly used venous terms relating to the management of CVD of the lower extremities, which were agreed to have variable applicability and interpretation in reports in venous literature. The terms selected for inclusion in the VEIN-Term consensus document are stratified into three different groups: clinical, physiological, and descriptive. It is worth noting that 13 terms had not to our knowledge been previously defined in venous literature. They are: the acronym PREVAIT (PREsence of Varices (residual or recurrent) After InTervention), axial reflux, venous occlusion, venous obstruction, venous compression, recanalization, iliac vein obstruction syndrome, venous ablation, perforating vein interruption, perforating vein ligation, perforating vein ablation, miniphihlebectomy, and sclerotherapy.

**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ACCP</td>
<td>American College of Chest Physicians</td>
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<tr>
<td>AVF</td>
<td>American Venous Forum</td>
</tr>
<tr>
<td>AVVQ</td>
<td>Aberdeen Varicose Veins Questionnaire</td>
</tr>
<tr>
<td>CEAP</td>
<td>Clinical-Etiological-Anatomical-Pathophysiological</td>
</tr>
<tr>
<td>CIVIQ</td>
<td>Chronic Venous disease quality of life Questionnaire</td>
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<tr>
<td>CVD</td>
<td>chronic venous disease</td>
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<tr>
<td>GRADE</td>
<td>Grading of Recommendations Assessment, Development and Evaluation</td>
</tr>
<tr>
<td>MOS SF-36</td>
<td>Medical Outcome Study health survey Short Form 36</td>
</tr>
<tr>
<td>PREVAIT</td>
<td>PREsence of Varices (residual or recurrent) After InTervention</td>
</tr>
<tr>
<td>QOL</td>
<td>quality of life</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>VCSS</td>
<td>Venous Clinical Severity Score</td>
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<tr>
<td>VDS</td>
<td>Venous Disability Score</td>
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<tr>
<td>VEINES</td>
<td>VEnous INsufficiency Epidemiological and economic Study</td>
</tr>
<tr>
<td>VSDS</td>
<td>Venous Segmental Disease Score</td>
</tr>
<tr>
<td>VSSS</td>
<td>Venous Severity Scoring System</td>
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ed by heat or worsen during the course of the day, and are relieved by leg rest and/or elevation.” The VEIN-Term consensus document is intended to clarify venous terminology. It is to be hoped that it will result in a more precise use of venous terms in English-language articles and guidelines on CVD in the future. Nevertheless, one challenge still remains, and that is to translate the English definitions as accurately as possible into other languages for national documents. This is not easy, although it has already been done for CEAP classification and anatomic nomenclature. Lastly, VEIN-Term has not covered all the imprecise terms in phlebology, and further refinements are needed to complete this work.

Prevalence data
CVD is a common condition with a major socioeconomic impact due to its high prevalence. The cost of CVD includes its pact due to its high prevalence. The cost of CVD includes its impact on the patient, the health-care system, and the family. Chronic venous leg ulcers that can introduce a risk of misinterpretation of the true prevalence. For prevalence data to be reliable, the study has to be large enough. By calculating the 95% confidence interval, certainty is possible when examining a smaller population. Validation of all or a randomly selected sample of the reported patients is mandatory to determine the number of false positives and to establish the diagnosis, which is usually done nowadays by performing a duplex scan investigation in combination with a clinical examination. Without objective validation, there is a high risk of overestimating the prevalence of CVD.

The use of only the “C” of CEAP, as is usually done in prevalence studies, presents weaknesses because of the difficulty in distinguishing between C1 and C2 patients, as shown by the wide variation in disease prevalence in epidemiological studies from one paper to another; it is not clearly stated in the CEAP classification whether the edema of C3 patients is a permanent edema (ie, a preliminary stage leading to skin changes and CVD complications) or if it is a reversible edema that occurs at the end of the day and disappears after rest. Despite corona phlebectatica (corona) being a clinical sign associated with CVD, it is not yet included in the CEAP classification. Corona is defined by fan-shaped intradermal telangiectasias in the medial and sometimes lateral portions of the ankle and foot. It has been shown that corona strongly correlates with the clinical severity and hemodynamic disturbances of the disease. The inclusion of corona in the C3 class would probably improve the reliability of the clinical classes of CEAP.

Pathophysiology of CVD
Understanding the pathophysiology of a disease state is basic to effective treatment. Results from studies that demonstrate treatment efficacy lead to guideline recommendations. CVD is defined as: “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.” It is caused by venous valvular incompetence with or without associated venous outflow obstruction, which may affect the superficial venous system, the deep venous system, or both. Venous dysfunction may result from either a congenital or an acquired disorder. CVD is the consequence of venous hypertension.

Chronic venous hypertension leads to disturbances of the microcirculation, which is responsible for exchange with interstitial tissues. This results in a local inflammatory reaction, which is associated with an increase in capillary permeability.
and fragility. The lymphatic system can compensate for the increase in fluid outflow into the surrounding tissues in the early stages of the disease.\textsuperscript{24,26} However, if CVD persists or worsens, edema develops because the lymphatic system becomes overloaded and can no longer handle the drainage of excess fluid. Studies of the mechanism of tissue injury at the different stages of CVD show how changes in venous pressure and hemodynamic forces (particularly fluid shear stress, the force exerted on venous walls that is predominantly linked to blood speed) lead to cellular and biochemical disorders.

Leukocytes, due to their ability to respond to physical stimulation, are now known to play a key role in the resultant tissue injury that leads to the development of CVD symptoms, varicose veins, edema, and ulcers.\textsuperscript{26} Recent data suggest that valve damage may be acquired rather than congenital and may be caused by inflammatory factors, notably leukocyte activation triggered by venous hypertension. Immunohistochemical studies using monoclonal antibodies have demonstrated monocyte/macrophage infiltration into the valve leaflets and venous walls of patients with varicose veins, and leukocyte infiltration was found to be greater on proximal surfaces of venous valves. A key event in CVD is valve failure, which leads to increased venous hypertension, maintains a vicious circle of inflammatory events, and causes eventual venous complications.\textsuperscript{27}

**Assessment tools in CVD**

Both general practitioners and specialist doctors have to deal with CVD. The treatments of this pathology are usually evaluated on the basis of clinical outcomes, but such evaluation does not take into account patients’ perception of the disease and the impact of treatment on their QOL, which is significantly altered by the disease. Specific tools capable of assessing the full spectrum of CVD, its signs and symptoms, impact on QOL, and treatment effects are key to the efficient management of the disease.

Assessment tools in CVD can be categorized into two classes (those for symptoms and those for CVD-related signs) and are summarized below.\textsuperscript{20}

- **Regarding symptom assessment**
  
  The first step should be to ascribe symptoms to CVD, since they are not pathognomonic. The scoring system by P. Carpenter is a patient-administered diagnostic tool combining 4 criteria worth 1 mark each, which allows leg symptoms to be ascribed to CVD if the threshold level is equal to or greater than 3. The VEINES-Sym (VEnous INSufficiency Epidemiological and Economic Study), developed by D. L. Lamping, is a 10-item self-administered questionnaire that includes questions on the frequency of 9 symptoms encountered in CVD, while the 11-item Phleboscore\textsuperscript{20} of P. Blanchemainson, which includes questions about the frequency of symptoms, helps predict the risk of developing CVD.

Of the various instruments that are available to physicians to measure symptoms such as pain, the most widely validated is the 10-cm visual analogue scale. This type of scale provides patients with an easy and rapid means to express the intensity of their pain and has numerous applications, including in CVD. Other types of scale, such as numerical rating scales, are usually graded from 0 to 4, 0 to 5, or 0 to 10. These scales allow the measurement of pain both during the medical visit and retrospectively, and are also used in the evaluation of treatment in CVD.

Besides physician-guided tools, there is an increasing need for patients’ impressions of treatment outcomes and consequently a need for patient-reported outcome tools. The tools used to assess patient-reported outcomes consist mainly of QOL scales that may be either generic or disease-specific. Of the specific QOL scales, the following are noteworthy: the 13-item Aberdeen Varicose Veins Questionnaire (AVVQ), the Charing Cross Venous Ulceration Questionnaire, the VEINES questionnaire, and the 20-item Chronic Venous disease quality of life Questionnaire (CIVIQ-20) and its recently shortened version, CIVIQ-14. CIVIQ has been used extensively, as reported in numerous studies some of which included large samples of patients.\textsuperscript{28}

All four specific questionnaires above were used in conjunction with the 36-item Medical Outcome Study health survey Short Form (MOS SF-36), a generic health-related QOL instrument whose validity, reproducibility, and responsiveness to changes over time have been well demonstrated.

- **Regarding assessment of signs**
  
  As mentioned in the section, “Terminology, classifications and severity scoring of CVD,” above, the setting up of the CEAP classification and its adjuncts was a great leap forward in the management of CVD. The CEAP classification can be used by physicians to keep records of diagnostic information, while the adjuncts to CEAP (VCSS, VSDS, and VDS) are scoring schemes that are quantifiable and include elements that change in response to treatment. These instruments may be used to evaluate any stage of CVD in patients, although they are imperfect in the early stages.\textsuperscript{29} Besides these “global” assessment tools, signs such as varicose veins, edema, and venous ulcers can be specifically assessed. Vein diameter can be measured on duplex scan investigation. Leg edema can be assessed by measuring either leg circumference (tape, Leg-o-Meter\textsuperscript{29}) or volume (water displacement volumetry, optoelectronic methods, computed tomography [CT] scanning, magnetic resonance imaging [MRI], or dual x-ray absorptiometry).\textsuperscript{20}

Numerous techniques are available for the assessment of venous ulcers, ranging from the simple use of tracings to more sophisticated methods requiring the use of cameras, videos, and computers.\textsuperscript{20} The parameters most frequently
used to measure a wound are the length of the principal axes (length and width of the wound), the projected surface area, and the perimeter.  

**Invasive therapy**

New minimally invasive techniques for the treatment of primary and secondary varicose veins, such as radio frequency ablation and Endolaser, have existed for some years. Both these techniques are designed to eliminate the larger and/or lesser saphenous veins, collateral vances, or recurrent varicosity. With either treatment of the greater saphenous vein, the tributary veins at the femoral saphenous junction are spared, leaving a long saphenous stump. Currently, two of the most frequently cited causes of restripping are inadequate sectioning of saphenous vein tributaries at the saphenous junction and leaving too long a saphenous stump. Despite this, it would seem that the 5-year results using these techniques are at least similar to and in fact often better than those of traditional stripping.  

Another great addition to these techniques is foam sclerotherapy, which gives the same excellent results at remarkably low cost. A comparative consensus conference is needed to clarify the specific indications and the long-term effectiveness and complications of each of these different methods, so that we are able to better inform patients and help them choose the most appropriate treatment for them.

**Methods of determining the strength and quality of the recommendations**

Guideline developers have used a bewildering variety of systems to rate the quality of the evidence underlying their recommendations. Some are facile, some confused, and others sophisticated but complex. The recent documents that reported recommendations in CVD used several systems.

The one used by Cochrane’s group consists of applying a random effects statistical model as used in meta-analyses to a selection of randomized controlled trials (RCTs). Selection of RCTs is done by classifying trials as level A (low risk of bias), level B (moderate risk of bias), or level C (high risk of bias). A total of 10 Cochrane reviews have been published in CVD since 2000.

In European guidelines on CVD management, studies were classified as: grade A (at least two RCTs with large sample sizes, meta-analyses combining homogeneous results), grade B (RCTs with small sample sizes, single RCT), or grade C (other controlled trials, nonrandomized controlled trials). This was the case in an important document on the “Management of Chronic Venous Disorders of the Lower Limbs: Guidelines According to Scientific Evidence,” prepared by an international consensus group under the auspices of the leading societies for venous disease. Another recent document, “Antithrombotic Therapy for Venous Thromboembolic Disease,” from the American College of Chest Physicians (ACCP) 8th consensus conference, has recently been published to help physicians care for patients with venous disease.

These recent ACCP guidelines have made specific changes with recommendations and suggestions linked to objective grades. The so-called “Grading of Recommendations Assessment, Development and Evaluation” (GRADE) method of determining the strength and quality of the recommendations deserves mention. The strength of the recommendation (1: “We recommend,” or 2: “We suggest”) is no longer based, as was the case only a few years ago, solely on the type and quality of available studies. It is a true judgement of the overall value of the balance between the benefits and risks incurred by following this recommendation, a judgement based

- Developed by a widely representative group of international guideline developers
- Clear separation between quality of evidence and strength of recommendations
- Explicit evaluation of the importance of outcomes of alternative management strategies
- Explicit, comprehensive criteria for downgrading and upgrading quality of evidence ratings
- Transparent process of moving from evidence to recommendations
- Explicit acknowledgment of values and preferences
- Clear, pragmatic interpretation of strong versus weak recommendations for clinicians, patients, and policy makers
- Useful for systematic reviews and health technology assessments, as well as guidelines

**Table I. Advantages of GRADE over other systems.**

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<tr>
<th>Advantage</th>
<th>GRADE (Grading of Recommendations Assessment, Development and Evaluation)</th>
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<tr>
<td>Clear, pragmatic interpretation of strong versus weak recommendations for clinicians, patients, and policy makers.</td>
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<tr>
<td>Useful for systematic reviews and health technology assessments, as well as guidelines.</td>
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not only on the expected health benefits, treatment-related risks, and patients’ values and preferences, but also on economic considerations and the allocation of resources. In the later document, recommendations are accompanied by a number which refers to the strength of the recommendation (1: for a strong and 2: for a weak recommendation), and a letter, which refers to the quality of evidence supporting the recommendation (A for “high quality,” which is consistent evidence from randomized trials; B for “moderate quality,” which is evidence from nonrandomized trials or inconsistent evidence from randomized trials; and C for “low quality,” which is suggestive evidence from nonrandomized trials, observational reports, or expert opinion).

The advantages of GRADE over other systems are summarized by the developers themselves in Table I. This new approach provides a system for rating the quality of evidence and the strength of recommendations that is explicit, com-
prehensive, transparent, and pragmatic. That is why it is wide-
ly used in North America: 25 organizations have already
adopted it, and it is increasingly being adopted by other or-
ganizations worldwide.

The task of building international guidelines is challenging,
particularly in the venous field. This is because of the large
spectrum of disease manifestations and either the lack of
validated methods or the weak consensus for methods that
have been adopted for assessing symptoms, signs, and QOL,
not to mention the resource constraints that vary consider-
ably from region to region. Even if much still remains to be
done to get the high-quality scientific studies needed to sup-
port the development of guidelines, we are at a point where
a lot of progress in standardization, classification, fundamen-
tal research, and assessment methods has been made in a
short time. Let us hope that we can continue to advance in the
same way. ■

References
1. Caggiati A, Bergan JJ, Gloviczki P, et al. Nomenclature of the veins of the low-
2002;36:436-442.
2. Caggiati A, Bergan JJ, Gloviczki P, et al. Nomenclature of the veins of the low-
41:719-724.
and refinements: an International Union of Phlebology conference of experts.
the veins in chronic venous disease of the lower limbs–UIP Consensus Docu-
5. Porter JM, Moneta GL, International Consensus Committee on Chronic Venous
21:635-645.
1252.
8. Comerota AJ. Treatment of chronic venous disease of the lower extremities: 
ders: the Vein Term Transatlantic Interdisciplinary Consensus Document. J Vasc
demiology, outcomes, diagnosis and management. Summary of an evidence-
based report of the VIENES task force. Venous Insufficiency Epidemiologic and
11. Evans CJ, Foxwes FG, Ruckley CV, Lee AJ. Prevalence of varicose veins and
chronic venous insufficiency in men and women in the general population: Ed-
12. Alguire PC, Mathes BM. Chronic venous insufficiency and venous ulceration.
13. International Task Force. The management of chronic venous disorders of the
leg: an evidence-based report of an international task force. Epidemiology.
insufficiency. An Italian pilot study of the Triveneto Region. Int Angiol. 2005;24:
272-277.
18. Forsgren A, Fransson I, Neblén O. Leg ulcer point prevalence can be decreased by
broad-scale intervention: a follow-up cross-sectional study of a defined ge-
19. Neblén O. Prevalence of venous leg ulcer: the importance of the data collection
20. Jawien A. Unmet needs in the assessment of symptoms and signs related to
chronic venous disease. Application to Dalfon 500 mg. Phlebology. 2009;
16:331-339.
22. Allegra C. Patients with chronic venous disease–related symptoms without signs:
23. Uri JF, Comu-Thénard A, Carpenter PH, et al. Clinical and hematologic sig-
2006;42:1163-1168.
24. Allegra C, Bartolo M J, Cariot B, Cassiani D. 6th World Congress for Microcir-
500 mg on microlymphatics in chronic veins insufficiency. Int J Micro-
laries pressure in human skin with patients with chronic venous insufficiency.
of its use in chronic venous insufficiency, venous ulcers and haemorrhoids.
Drugs. 2003;63:71-100.
27. Bergan JJ, Schmid-Schönbein G, Coleridge-Smith P, Nicolaides A, Boisseau M,
28. Lurato R, Marsillia A, Jantet G. International psychometric validation of the
Chronic Venous Disease Quality of life Questionnaire (CVIQ-D). Eur J Vasc
29. Perrin M, Diedeau F, Jessert V, Blanc MP. Evaluation of the new severity scoring
system in chronic venous disease of the lower limbs: an observational study
2004;47:312-319.
randomized controlled trial of VNUS closure versus surgery for the treatment of
32. Perrin M. Lower limb varicose veins endothermal treatment by endovenous laser
and radiofrequency. A literature analysis at March 1st 2004 [in French]. Phle-
33. Nicolini P. Closure Group. Treatment of primary varicose veins by endovenous
obliteration with the VNUS Closure system: results of a prospective multicenter
34. Hinchiffe RJ, Ulthi J, Beech A, Ellison J, Braithwaite BD. A prospective ran-
domized controlled trial of VNUS closure versus surgery for the treatment of re-
current long saphenous varicose veins. Eur J Vasc Endovasc Surg. 2006;31:
212-218.
35. Merchant RF, DePalma RG, Kabnick LS. Endovenous obliteration of saphe-
19:4-6.
37. Brue FX, Suggenbichler S. European Consensus Meeting on Foam Sclero-
therapy, April, 4-6, 2003, Tegernsee, Germany.
38. Nicolini P. Venoactive medications and the place of Dalfon 500 mg in re-
cent guidelines on the management of chronic venous disease. Phlebolymphol-
ders of the lower limbs. Guidelines according to scientific evidence. Int An-
40. Keanor C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ; Amer-
ican College of Chest Physicians. Antithrombotic therapy for venous thrombo-
embolic disease: American College of Chest Physicians Evidence-Based Clin-
41. Guyatt GH, Oxman AD, Kunz R, et al. GRADE: an emerging consensus on
developing quality of evidence and strength of recommendations. BMJ. 2008;336:
923-926.
MISE À JOUR DES RECOMMANDATIONS DANS
LA MALADIE VEINEUSE CHRONIQUE : DE QUOI AVONS-NOUS BESOIN ?

La maladie veineuse chronique (MVC) est un trouble très fréquent dans la population occidentale, que doivent traiter à la fois les généralistes et les spécialistes. Un manque de précision dans la description de la MVC (qui entraîne douleur, gêne et altérations significatives de la qualité de vie des patients), et dans les résultats des études, a conduit à des conclusions contradictoires et à compréhension limitée de la prise en charge de la pathologie veineuse. Dans le but de rectifier ces manques, la communauté médicale s’efforce actuellement de mieux définir le domaine de la MVC, de clarifier la terminologie et la nomenclature anatomique et clinique, de standardiser les examens et d’introduire de nouvelles approches thérapeutiques, qui seront présentées dans cet article. En plus, à ces prérequis importants pour l’élaboration de recommandations sur la maladie veineuse, s’ajoute la nécessité de données de prévalence adéquates pour mieux appréhender l’amplitude du problème, tout en reconnaissant les mécanismes sous-tendant les manifestations de la maladie veineuse afin de développer des traitements appropriés. Afin d’établir des recommandations, il faut obligatoirement un accord général sur des outils d’évaluation pouvant mesurer les changements induits par le traitement en utilisant soit des outils de médecin soit des questionnaires de patients, encore à valider. Enfin et surtout, le principal outil nécessaire est un système optimal de cotation facilement compréhensible par tous les cliniciens afin que la communauté médicale accepte toutes les recommandations proposées.
One of the important lessons from the biblical story of the Tower of Babel is that a common language allows men to achieve extraordinary things. For all those involved in the management of chronic venous disease (CVD), the American Venous Forum (AVF) has created a “common language” in the classification of CVD, the CEAP (Clinical-Etiological-Anatomical-Pathophysiological) classification. The need for an accurate classification system is fundamental to understanding the clinical disease processes and to interinstitutional communication about the disease. The CEAP classification system was established in 1994 and was followed by REVAS (Recurrent after Varicose vein Surgery), created in Paris in 1998, and the Venous Clinical Severity Score (VCSS), in 2000. Several consensus documents from the Union Internationale de Phlébologie (UIP) led to the revision of the CEAP classification system in 2004. The latest update of terminology for CVD was the VEIN-TERM consensus document published in the Journal of Vascular Surgery in 2009. All these efforts have led to the creation of a common language in CVD, which is essential for the establishment of clinical practice guidelines.

Hidden within the main story of the Tower of Babel (Figure 1, page 246) from the Bible lies an interesting and valuable lesson: that with a common language, men can achieve extraordinary things. Without a common language, not only would this project have been impossible (as it later transpires), but it also would have been unimaginable. In creating the CEAP (Clinical-Etiological-Anatomical-Pathophysiological) classification as a “common language” for chronic venous disorders, the American Venous Forum (AVF) has laid the foundations for future progress in chronic venous disease (CVD).

The need for an accurate classification system in venous disease is fundamental to the understanding of the clinical disease processes and to interinstitutional communication about the separate entities. The imprecise diagnoses that were the norm in venous disease in the past have been replaced by accurate imaging studies, since the introduction of noninvasive ultrasound scans in the 1980s.

Once presented with the ability to make accurate diagnoses of the causes and mechanisms of chronic disease in individual segments of the lower extremity veins, it became necessary to devise a classification system capable of organizing the data in a meaningful way.
In 1994, the AVF convened a subcommittee of world experts in CVD to address this challenge. Recognizing that a modern classification of CVD must now embrace more than just the clinical state of the patient, this committee created the CEAP classification, which provides a system whereby the multiple variations of CVD can be communicated in a clinically and scientifically meaningful manner, allowing analysis and comparison of treatment modalities for like conditions.1

Because identical clinical presentations of CVD spring from different etiologies, and the distribution of specific pathological processes have different implications for treatment and long-term prognosis, the CEAP classification organizes these elements into the methodology. In the CEAP system, the "C"-clinical state is complemented by the "E"-etiological basis for the disease in each case, and this is described in terms of the "A"-anatomical distribution of the "P"-pathophysiological process throughout the axial venous drainage system, from the calf to the diaphragm. This organization of information has been successfully promulgated around the world by the international body that devised it. Its widespread acceptance has become fundamental to interinstitutional communication and to describing chronic venous disorders.

**Development of the CEAP classification**

The CEAP classification provides a framework around which the clinical manifestations found in CVD are paired with key pathological elements of causation and physiological mechanisms in specific anatomical locations of the lower extremity. Specifically, for each clinical condition it distinguishes:

- Reflux from obstructive pathophysiology;
- And identifies the precise anatomical segments affected by reflux or obstruction using 18 named segments of the lower extremity venous tree.

In this way, clinical manifestations can be coupled with the precise pathological entity. Using this, the natural history of the pathological processes and the effects of management alternatives for like clinical states can be identified and studied. The classification describes the status of the disease process at a point in time; these details can change over time with the introduction of interval treatments and with the natural history of the disease process. By CEAP examination at regular intervals, the longitudinal changes that occur over time or after interventions can be documented.

This classification addressed the considerations imposed by modern diagnostic and treatment capabilities. It was incorporated into the updated Reporting Standards for Venous Disease in 1995 and became known as the CEAP classification. Its acceptance was engendered around the world by venous authorities in America, Asia, Australia, and Europe, and the classification has now been published in at least 11 languages (Chinese, English, French, German, Greek, Italian, Japanese, Polish, Portuguese, Spanish, and Swedish). The worldwide dissemination addresses the need for a universal classification that enables accurate communication between institutions and countries about the details of CVD and the results of different forms of treatment. The CEAP classification was originally intended as a preliminary document; it was meant to be amended in light of future experience with usage. Since this time, several evaluations of the clinical categories and of the appended scoring systems based upon CEAP have been published, which have both validated and appraised their content.

In 1998, at an international consensus meeting in Paris, Perrin et al established a classification for recurrent varicose veins (REcurrent Varices After Surgery [REVAS]).2 Two years later in

**Selected abbreviations and acronyms**

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<th>Definition</th>
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<td>AVF</td>
<td>American Venous Forum</td>
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<tr>
<td>CEAP</td>
<td>Clinical-Etiological-Anatomical-Pathophysiological</td>
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<td>CVD</td>
<td>chronic venous disease</td>
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<tr>
<td>LDS</td>
<td>lipodermatosclerosis</td>
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<tr>
<td>REVAS</td>
<td>REcurrent Varices After Surgery</td>
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<tr>
<td>UIP</td>
<td>Union Internationale de Phlébologie [International Union of Phlebology]</td>
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2000, Rutherford et al and the Ad Hoc Outcomes Committee of the AVF published an upgraded version of the original venous severity scoring system. Uhl et al established a European Venous Registry based on CEAP and reported studies on intraobserver and interobserver variability that showed significant discrepancies in the clinical classification of CEAP, which prompted the improvement of definitions of clinical classes C0 to C6. Further changes regarding definitions and refinements of the clinical classification, the “C” in CEAP, were suggested soon after at the Union Internationale de Phlébologie [International Union of Phlebology] (UIP) international consensus meeting in Rome in 2001, which not only contributed to CEAP, but ultimately formed the basis for its modification. At the same meeting, Caggiati et al published a consensus document on nomenclature of the veins of the lower limbs, which was updated a couple of years later.

After a decade (in 2004), a new international subcommittee of the American Venous Forum decided to review the validity and usefulness of CEAP and to make revisions if needed. This new version affirmed and retained the fundamental structure of the CEAP categories, but included additions to classification, such as specific definitions of terms, clarification of details within the “C” class, and improvements in the method of recording of findings to render classification more complete in its long form, and more user-friendly in its short form.

**Terminology and new definitions**

The CEAP classification deals with all forms of CVD. The term “chronic venous disorder” includes the full spectrum of morphologic and functional abnormalities of the venous system, from telangiectasias to venous ulcers. Some of these, such as telangiectasias, are highly prevalent in the healthy adult population, and in many cases use of the term “disease” is not appropriate. The term “chronic venous insufficiency” implies a functional abnormality of the venous system, and is usually reserved for more advanced disease, including edema (C3), skin changes (C4), and venous ulcers (C5-C6).

It was agreed to maintain the present overall structure of the CEAP classification, but to add more precise definitions. The following recommended definitions apply to the clinical (“C”) class of CEAP:

- **Atrophie blanche (white atrophy)** Localized, often circular whitish and atrophic skin areas surrounded by dilated capillaries and sometimes hyperpigmentation. Sign of severe CVD, and not to be confused with healed ulcer scars. Scars of healed ulceration may also exhibit atrophic skin with pigmentary changes, but are distinguishable by history of ulceration and appearance from atrophie blanche, and are excluded from this definition (Figure 2).

- **Corona phlebectatica** Fan-shaped pattern of numerous small intradermal veins on medial or lateral aspects of ankle and foot. Commonly thought to be an early sign of advanced venous disease. Synonyms include malleolar flare and ankle flare (Figure 3).

- **Eczema** An erythematous dermatitis that may progress to blistering, weeping, or scaling eruption of skin of the leg. Most often located near varicose veins, but may be located anywhere on the leg. Usually seen in uncontrolled CVD, but may reflect sensitization to local therapy.

- **Edema** Perceptible increase in volume of fluid in skin and subcutaneous tissue, which is characteristically indented with pressure. Venous edema usually occurs in the ankle region, but may extend to the leg and foot (Figure 4, page 248).

- **Lipodermatosclerosis** Lipodermatosclerosis (LDS) is a localized chronic inflammation and fibrosis of the skin and subcutaneous tissues of the lower leg, sometimes associated with scarring or contracture of the Achilles tendon. LDS is sometimes preceded by diffuse inflammatory edema of the skin, which may be painful and which often is referred to as hypodermitis. Lymphangitis, erysipelas, or cellulitis must be differentiated from LDS by their characteristically different local signs and systemic features. LDS is a sign of severe CVD (Figure 5, page 248).
**Pigmentation**
Brownish darkening of skin, resulting from extravasated blood. Usually occurs in the ankle region, but may extend to the leg and foot (Figure 6).

**Reticular vein**
Dilated bluish subdermal vein, usually 1 mm to less than 3 mm in diameter. Usually tortuous. Excludes normal visible veins in persons with thin, transparent skin. Synonyms include blue veins, subdermal varices, and venulectasias.

**Telangiectasia**
Confluence of dilated intradermal venules less than 1 mm in caliber. Synonyms include spider veins, hyphen webs, and thread veins (Figure 7).

**Varicose vein**
Subcutaneous dilated vein 3 mm in diameter or larger, measured in upright position, may involve saphenous veins, saphenous tributaries, or nonsaphenous superficial leg veins.

Varicose veins are usually tortuous, but tubular saphenous veins with demonstrated reflux may be classified as varicose veins. Synonyms include varix, varices, and varicosities (Figure 8).

**Venous ulcer**
Full-thickness defect of skin, most frequently in the ankle region, that fails to heal spontaneously and is sustained by CVD (Figure 9).
### Table I. VEIN-TERM definitions/Clinical venous terms.2,3,5,8-13

<table>
<thead>
<tr>
<th>Previous definitions</th>
<th>VEIN-TERM update9</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic venous disorders:</strong> include all clinical abnormalities (symptoms or signs) resulting from disease of the lower limb veins and progressing chronically.8</td>
<td><strong>Chronic venous disorders:</strong> this term includes the full spectrum of morphological and functional abnormalities of the venous system.</td>
</tr>
<tr>
<td><strong>Chronic venous disease:</strong> is defined as an abnormally functioning venous system caused by venous valvular incompetence with or without associated venous outflow obstruction, which may affect the superficial venous system, the deep venous system, or both.10</td>
<td><strong>Chronic venous disease:</strong> 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.</td>
</tr>
<tr>
<td><strong>Chronic venous insufficiency:</strong> implies a functional abnormality of the venous system, and is usually reserved for more advanced disease, including edema (C3), skin changes (C4), or venous ulcers (C5-C6).8</td>
<td><em><em>Chronic venous insufficiency (C3</em>-C6):</em>* a term reserved for advanced chronic venous disorders, which is applied to functional abnormalities of the venous system producing edema,* skin changes, or venous ulcers, [C3*: moderate or severe edema, as stratified by Rutherford et al9]</td>
</tr>
<tr>
<td><strong>Venous symptoms:</strong> may be associated with telangiectasic, reticular, or varicose veins and include lower extremity aching, pain, and skin irritation.10</td>
<td><strong>Venous symptoms:</strong> complaints related to venous disease, which may include tingling, aching, burning, pain, muscle cramps, swelling, sensations of throbbing or heaviness, itching skin, restless legs, and leg tiredness and/or fatigue. Although not pathognomonic, these may be suggestive of chronic venous disease, particularly if they are exacerbated by heat or dependency in the day’s course, and relieved with leg rest and/or elevation.</td>
</tr>
<tr>
<td><strong>Venous signs:</strong> described in the “C” of the CEAP classification.5,10</td>
<td><strong>Venous signs:</strong> visible manifestations of venous disorders, which include dilated veins (telangiectasiae, reticular veins, varicose veins), leg edema, skin changes, and ulcers, as included in the CEAP classification.8</td>
</tr>
<tr>
<td><strong>Recurrent varices:</strong> the presence of varicose veins in a lower limb previously operated on for varices (with or without adjuvant therapies).2</td>
<td><strong>Recurrent varices:</strong> reappearance of varicose veins in an area previously treated successfully.</td>
</tr>
<tr>
<td><strong>Persisting or residual varices:</strong> original varicosities that may persist so that the failure of treatment is apparent from an early stage after surgery.11</td>
<td><strong>Residual varices:</strong> varicose veins remaining after treatment.</td>
</tr>
<tr>
<td><strong>No previous definition</strong></td>
<td><strong>New acronym PREVAIT:</strong> this acronym stands for: PREsence of Varices (residual or recurrent) After operative Treatment</td>
</tr>
<tr>
<td><strong>Postthrombotic syndrome:</strong> the term may be used if the patient has experienced an objectively documented prior episode of deep vein thrombosis.10</td>
<td><strong>Postthrombotic syndrome:</strong> chronic venous symptoms and/or signs secondary to deep vein thrombosis.</td>
</tr>
<tr>
<td><strong>Pelvic congestion syndrome:</strong> characterized by chronic pelvic pain in the setting of pelvic venous varicosities. The syndrome has been shown to be the result of engorgement of the pelvis due to gross dilatation and incompetence of one or both the ovarian veins.12</td>
<td><strong>Pelvic congestion syndrome:</strong> chronic symptoms, which may include pelvic pain, perineal heaviness, urgency of micturition, and postcoital pain, caused by ovarian and/or pelvic vein reflux and/or obstruction, and which may be associated with vulvar, perineal, and/or lower extremity varices.</td>
</tr>
<tr>
<td><strong>No venous literature definition</strong></td>
<td><strong>Varicocele:</strong> presence of scrotal varicose veins.</td>
</tr>
<tr>
<td><strong>Venous aneurysm:</strong> the diameter above which a vein is considered to be aneurysmal is debated: it is generally accepted that its diameter must be twice that of the normal vein. Aneurysms are classified into saccular and fusiform.13</td>
<td><strong>Venous aneurysm:</strong> localized saccular or fusiform dilatation of a venous segment with a caliber at least 50% greater than the normal trunk.</td>
</tr>
</tbody>
</table>

*In the original article, the definition is followed by the sentence: “Existing venous signs and/or (noninvasive) laboratory evidence are crucial in associating these symptoms with chronic venous disorder,” which conflicts with the acknowledged existence of the clinical CEAP category C0s En An Pn, corresponding to patients complaining of leg symptoms, but presenting with no visible signs and without detectable pathophysiological abnormalities identifiable by routine investigations. This is why we removed this paragraph from the present brochure.
### Table II. VEIN-TERM definitions/Physiological venous terms 9,13-20

<table>
<thead>
<tr>
<th>Previous Definitions</th>
<th>VEIN-TERM Update 13</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Venous valvular incompetence:</strong> abnormal functioning of the veins of the lower extremities is recognized clinically as venous dysfunction.14</td>
<td><strong>Venous valvular incompetence:</strong> venous valve dysfunction resulting in retrograde venous flow of abnormal duration.</td>
</tr>
<tr>
<td><strong>Venous reflux:</strong> reversal of flow in a segment of vein following its dilatation and/or anatomical or functional incompetence of its valves.15</td>
<td><strong>Venous reflux:</strong> retrograde venous flow of abnormal duration in any venous segment.</td>
</tr>
<tr>
<td>Primary valve dysfunction: absence of complete closure of the valves.15</td>
<td>Primary: caused by idiopathic venous valve dysfunction.</td>
</tr>
<tr>
<td>Secondary valve dysfunction: valves irreversibly damaged by the thrombotic process.15</td>
<td>Secondary: caused by thrombosis, trauma, or mechanical, thermal, or chemical etiologies.</td>
</tr>
<tr>
<td>Congenital valve dysfunction: atrophy or absence of valve.15</td>
<td>Congenital: caused by the absence or abnormal development of venous valves.</td>
</tr>
<tr>
<td><strong>Axial reflux:</strong> uninterrupted retrograde venous flow from the groin to the calf.</td>
<td><strong>Axial reflux:</strong> uninterrupted retrograde venous flow from the groin to the calf.</td>
</tr>
<tr>
<td><strong>Superficial:</strong> confined to the superficial venous system.</td>
<td><strong>Superficial:</strong> confined to the superficial venous system.</td>
</tr>
<tr>
<td><strong>Deep:</strong> confined to the deep venous system.</td>
<td><strong>Deep:</strong> confined to the deep venous system.</td>
</tr>
<tr>
<td><strong>Combined:</strong> involving any combination of the three venous systems (superficial, deep, perforating)</td>
<td><strong>Combined:</strong> involving any combination of the three venous systems (superficial, deep, perforating)</td>
</tr>
<tr>
<td><strong>Perforator incompetence:</strong> retrograde (outward) outflow flow lasting greater than 0.3 s or longer than antegrade flow during the relaxation phase after release of manual compression.18</td>
<td><strong>Perforator incompetence:</strong> perforating veins with outward flow of abnormal duration.</td>
</tr>
<tr>
<td><strong>Neovascularization:</strong> recurrence of varices after vein transection restored by growth of new vessels in the surrounding tissue and vein wall.19</td>
<td><strong>Neovascularization:</strong> presence of multiple new, small tortuous veins in anatomic proximity to a previous venous intervention.</td>
</tr>
<tr>
<td><strong>Venous occlusion:</strong> total obliteration of the venous lumen.</td>
<td><strong>Venous occlusion:</strong> total obliteration of the venous lumen.</td>
</tr>
<tr>
<td><strong>Venous obstruction:</strong> partial or total blockage of venous flow.</td>
<td><strong>Venous obstruction:</strong> partial or total blockage of venous flow.</td>
</tr>
<tr>
<td><strong>Venous compression:</strong> compression by external structures.20</td>
<td><strong>Venous compression:</strong> narrowing or occlusion of the venous lumen as a result of extraluminal pressure.</td>
</tr>
<tr>
<td><strong>Recanalization:</strong> development of a new lumen in a previously obstructed vein.</td>
<td><strong>Recanalization:</strong> development of a new lumen in a previously obstructed vein.</td>
</tr>
<tr>
<td><strong>Iliac vein obstruction syndrome:</strong> venous symptoms and signs caused by narrowing or occlusion of the common or external iliac vein</td>
<td><strong>Iliac vein obstruction syndrome:</strong> venous symptoms and signs caused by obstruction of the left common iliac vein due to external compression at its crossing posterior to the right common iliac artery.</td>
</tr>
</tbody>
</table>

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**May-Thurner syndrome:** Compression of the left common iliac vein by vascular bone entrapment. The anterior surface entrapment is the common iliac artery, the posterior is formed by vertebral column.13
Need for updated CVD terminology

Despite the revision of the CEAP classification and the updated nomenclature of the venous anatomy of the leg, many terms need a better definition to create a common scientific language for the investigation and management of CVD. In October 2007 onboard M/S Trollfjord, we organized the Arctic Fjords Conference and workshops on CVD. During this voyage, an interdisciplinary faculty of experts under the auspices of the European Venous Forum, the AVF, the UIP, the International Union of Angiology, the American College of Phlebology, and the Society for Vascular Surgery met in order to provide recommendations for fundamental venous terminology. The group met again in February 2008 at the of AVF meeting in Charleston, South Carolina, to finalize the document that was endorsed by the organizations and published in the Journal of Vascular Surgery as the VEIN-TERM consensus document.

The venous terms defined in this document are presented under three headings: clinical, physiological, and descriptive, alongside the previous literature definitions when available. Some may not have been used in any previous publication. Most of the terms previously defined in CEAP documents and prior venous nomenclature refinements were excluded.9

The aim of Table I (page 249),2,3,5,8-13 Table II,9,13-20 and Table III9,21-23 is to summarize the venous terms relating to the management of chronic venous disorders of the lower extremities that are widely used and recognized to vary in applicability and interpretation in reports in the venous literature. The venous terms newly defined in the VEIN-TERM consensus document are compared with those in previous literature definitions. The definitions presented in VEIN-TERM testify to a continued effort to create a common language upon which we can build clinical practice guidelines (presented by Peter Gloviczki in his editorial).9

Table III. VEIN-TERM definitions/Descriptive venous terms.9,21-23

Abbreviation: GSV, great saphenous vein.

<table>
<thead>
<tr>
<th>PREVIOUS DEFINITIONS</th>
<th>VEIN-TERM UPDATE9</th>
</tr>
</thead>
<tbody>
<tr>
<td>High ligation and division: ligation and division of the long saphenous vein and its tributaries at the saphenofemoral junction.21</td>
<td>High ligation and division: ligation and division of the great saphenous vein (GSV) at its confluence with the common femoral vein, including interruption of all upper GSV tributaries.</td>
</tr>
<tr>
<td>Stripping: removal of the saphenous vein.22</td>
<td>Stripping: removal of a long vein segment, usually most of the GSV or the small saphenous vein by means of a device.</td>
</tr>
<tr>
<td>No precise previous definition</td>
<td>Venous ablation: removal or destruction of a vein by mechanical, thermal, or chemical means.</td>
</tr>
<tr>
<td>No precise previous definition</td>
<td>Perforating vein interruption: disconnection of a perforating vein by mechanical, chemical, or thermal means.</td>
</tr>
<tr>
<td>No precise previous definition</td>
<td>Perforating vein ligation: interruption of a perforating vein by mechanical means.</td>
</tr>
<tr>
<td>No precise previous definition</td>
<td>Perforating vein ablation: disconnection or destruction of a perforating vein by mechanical, chemical, or thermal means.</td>
</tr>
<tr>
<td>No precise previous definition</td>
<td>Miniphlebectomy: removal of a vein segment through a small skin incision.</td>
</tr>
<tr>
<td>No precise previous definition</td>
<td>Sclerotherapy: obliteration of a vein by introduction of a chemical (liquid or foam).</td>
</tr>
<tr>
<td>Endophlebectomy: surgical disobliteration of chronically obstructed venous segment.23</td>
<td>Endophlebectomy: removal of postthrombotic residue from the venous lumen.</td>
</tr>
</tbody>
</table>

References


Keywords: chronic venous disease; definition; terminology

**Terminologie et recommandations dans la maladie veineuse chronique : partager un langage commun**

The exact prevalence of chronic venous disease (CVD) remains difficult to determine because of variations in study population, selection criteria, and disease definition between different studies. The prevalence of CVD, as reported in studies, ranges from 2%-56% in men and from 1%-60% in women. Despite the fact that it has a huge impact on health-care budgets and patients’ quality of life, it is still an underestimated condition. CVD is more common with increasing age, and in recently published studies there were no significant sex differences. Family history, obesity, prolonged standing, and diet have been proposed as risk factors, but further studies are needed to clarify the influence of potential risk factors on the development of CVD. The financial burden on the health-care system is enormous, with recent estimates placing the cost of CVD treatment at $3 billion per year in the United States, or up to 2% of the total health-care budget of all Western countries. Existing evidence highlights the need for good quality longitudinal and cross-sectional studies measuring the incidence and prevalence of CVD. These studies may help to reduce the magnitude of the problem of CVD by raising awareness among public and health-care authorities, and health-care professionals. Furthermore, prevalence and socioeconomic data may serve as a valuable basis for the planning of appropriate steps to deal with CVD and for the education and hire of skilled personnel.

Medicographia. 2011;33:253-258 (see French abstract on page 258)
Published studies
Data from available epidemiological literature published during the last 30 years are very difficult to compare due to the fact that different evaluation criteria of CVD were used. Lawrence1 confirms that the prevalence of varicose veins depends on the definition of this disease because dilated veins ranging from telangiectasias to massive varicosities come under the general category of varicose veins. In order to standardize the evaluation of severity of venous disease in 1994, a new classification system was suggested by the American Venous Forum. The CEAP (Clinical-Etiological-Anatomical-Pathophysiological) classification system includes not only the clinical symptoms of CVD, but also considers the etiology, anatomical distribution, and the pathogenic mechanisms and produces a score based on the severity of the disease.2 The clinical signs in the affected leg are categorized into seven classes designated C0 to C6. CVD encompasses the full spectrum of signs and symptoms associated with classes C0 to C6, whereas the term “chronic venous insufficiency” is generally restricted to disease of greater severity, such as edema, trophic skin changes (such as pigmentation and lipodermatosclerosis), and ulceration.3

CVD is extremely common, although the prevalence estimates in the literature vary because of differences in the methods of evaluation, criteria for definition, and the geographic regions analyzed.4 In order to establish the magnitude of the problem, epidemiological studies are used to assess the prevalence of diseases or disorders within a population. Cross-sectional studies have usually been used to assess the number of patients with a certain disease within a health-care system. Large random samples have been used to assess populations and have the advantage of including people who self-treat, whereas the term “chronic venous insufficiency” is generally restricted to disease of greater severity, such as edema, trophic skin changes (such as pigmentation and lipodermatosclerosis), and ulceration.3

Prevalence data from such studies are a valuable basis for the planning of appropriate actions to deal with the problem. By repeating a prevalence study within a defined geographical area, we have an opportunity to assess the effect of treatment changes, which is important.5 Unfortunately, published epidemiological studies often misuse prevalence data by mixing overall prevalence figures with point prevalence data, giving an inaccurately wide range that leads to incorrect interpretations of prevalence data between countries and studies. Therefore, in order to provide the most reliable data and to generate accurate comparisons, it is essential to analyze the methods used in various epidemiological studies. However, we still have many pitfalls that can lead to inaccurate conclusions and interpretations6 (Table I).

Prevalence data are often harvested from cross-sectional studies or large population samples. The former investigate a defined cohort, generally all patients receiving treatment from health-care professionals within a relatively short time frame, usually one to three months. The latter usually consist of randomly selected people in a certain age range who have not necessarily been in previous contact with the health-care system. The benefit of population samples is that people who self-treat are included, unlike cross-sectional studies.6 The drawback of a population sample is that usually not all age groups are represented.5

To facilitate recruitment, it is important to avoid approaching carers and patients with lengthy questionnaires. Such forms take time to fill in and introduce a risk of dropout because of lack of time of the carer, patient, or both. A cross-sectional study involves selection bias since only patients treated within the health-care system will be included. Such a study will give an indication of the workload for health-care professionals, but there are, in addition, people who treat the disease on their own. A population sample overcomes this by including all people within the selected sample. The biggest problem of population sample studies is that they need to be fairly large (more than 10 000 people) in order to detect enough

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**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>CEAP</td>
<td>Clinical-Etiological-Anatomical-Pathophysiological</td>
</tr>
<tr>
<td>CIVIQ</td>
<td>Chronic Venous disease Questionnaire</td>
</tr>
<tr>
<td>CVD</td>
<td>chronic venous disease</td>
</tr>
<tr>
<td>CVI</td>
<td>chronic venous insufficiency</td>
</tr>
<tr>
<td>DALY</td>
<td>disability-adjusted life year</td>
</tr>
<tr>
<td>GIS</td>
<td>global index score</td>
</tr>
<tr>
<td>QALY</td>
<td>quality-adjusted life year</td>
</tr>
<tr>
<td>QOL</td>
<td>quality of life</td>
</tr>
<tr>
<td>RELIEF</td>
<td>Reflex assEssment and quaLitY of life improvEment with micronized Flavonoids [study]</td>
</tr>
<tr>
<td>YLD</td>
<td>years lived with disability</td>
</tr>
<tr>
<td>YLL</td>
<td>years of life lost</td>
</tr>
</tbody>
</table>

**Table I. Pitfalls in performing prevalence studies and their effects on the results.**

<table>
<thead>
<tr>
<th>Pitfall</th>
<th>Effect on results of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population sample</td>
<td>Not all age groups are represented</td>
</tr>
<tr>
<td>Cross-sectional studies</td>
<td>Patients who self-treat are not included</td>
</tr>
<tr>
<td>Follow-up studies</td>
<td>May affect patient recruitment negatively</td>
</tr>
<tr>
<td>Different evaluation criteria of CVD</td>
<td>Possible high drop-out rate</td>
</tr>
<tr>
<td>Too small a sample</td>
<td>Uncertain prevalence estimate</td>
</tr>
<tr>
<td>Selection bias</td>
<td>Prevalence not representative for the general population</td>
</tr>
<tr>
<td>Low response rate</td>
<td>Risk of underestimation of prevalence</td>
</tr>
<tr>
<td>Extensive primary questionnaire</td>
<td>Noncomparable results</td>
</tr>
</tbody>
</table>

Abbreviation: CVD, chronic venous disease.
patients with the disease so that a reliable prevalence estimate can be made. These studies are expensive, time consuming, and difficult to perform.6

Prevalence of chronic venous insufficiency

The prevalence of varicose veins reported in studies ranges from 2%-56% in men and from 1%-60% in women7 (Table II). Seven general population surveys have been conducted to date,7-13 and only a few studies have measured the incidence of varicose veins. The Framingham Study was a longitudinal study that followed up men and women living in Framingham, USA, over a 16-year period from 1966.14 Every second year over this period, subjects were examined for varicose veins, defined as “the presence of distended and tortuous veins, clearly visible on the lower limbs with the subject standing.” Over the 16-year period, 396 out of the 1720 men and 629 out of the 1202 women who were free from venous disease in 1966 developed varicose veins. On average, the two-year incidence rate of varicose veins was 39.4 per 1000 for men and 51.9 per 1000 for women. However, further studies are required to determine the incidence and progression of venous disease in the general population. One such study is the Edinburgh Vein Follow-Up Study. Subjects examined at baseline in 1994-1996 are currently undergoing a follow-up examination to determine the incidence and natural history of CVD as well as to establish the risk factors relating to progression.

A cross-sectional study of a random sample of 1566 subjects 18 to 64 years of age from the general population in Edinburgh, Scotland,12 found that telangiectasias and reticular veins were each present in approximately 80% of men and 85% of women. Varicose veins were present in 40% of men and 16% of women, whereas ankle edema was present in 7% of men and 16% of women.12 In this study, duplex ultrasound found reflux in 9.4% of men and 6.6% of women and after age adjustment, reflux rose significantly with age (21.2% in men >50 years old, and 12.0% in women >50 years old).15 Interestingly, it appears that certain treatments can reduce venous reflux. Jantet16 in the RELIEF (Reflux assessment and quality of life improvement with micronized flavonoids) study found that venous reflux was absent in 57% of patients diagnosed as suffering from CVI belonging to CEAP classes C0 to C4. Moreover, during treatment with micronized purified flavonoid fraction, all symptoms showed a decrease in both groups of patients (with and without venous reflux).16

The balance of evidence supports the finding that the prevalence of venous disease increases with increasing age.7,9,11,13,17-20 The magnitude of risk appears to differ depending on the classification criteria, and estimates vary in published studies. The prevalence of varicose veins in men aged 30 to 40 years old is about 3%, while in the age group over 70 years old, it increases up to about 40%.11,13 Similar results were also found in women: a prevalence of 20% at the age of 30 to 40 years old increases gradually with age and by 70 years of age, it exceeds 50%.12 The prevalence of trunk varices rose from 11.5% in persons aged 18 to 24 years old to 55.7% in the population between 55 to 64 years of age.12 The occurrence of skin changes in CVI depends on the patient’s age as well. In the Tecumseh Health Study,7 the prevalence of skin changes in women aged 30 to 39 years old was 1.8%, whereas in patients aged over 70 years old a prevalence of 20.7% was reported.

The San Valentino Vascular Screening Project found a prevalence of 7% for varicose veins and 0.86% for “symptomatic” CVI among the 30 000 subjects evaluated by clinical assessment and duplex ultrasound.21 As in previous studies, CVI was more common with increasing age, but there was no significant sex difference.

Active or healed venous leg ulcers occur in approximately 1% of the general population.12,22 Although not restricted to the elderly, the prevalence of CVD, especially leg ulcers, increases with age.22,23 It has been estimated that 2.5 million people have CVI in the United States, and of those, 20% develop venous ulcers.24 The overall prognosis of venous ulcers is poor with delayed healing and recurrent ulceration.25 More than 50% of venous ulcers require prolonged therapy lasting more than 1 year.26

Most studies have shown that CVI is more prevalent among women, although in a recent study, the difference between sexes was small.4 Selection bias may be a problem in some of these studies, as more women than men may be aware of their varicose veins or consider them to be a problem and, thus, may be more likely to participate in such studies. Moreover, many of the results from these studies have not been adjusted for age, a factor that may contribute to the observed gender differences.3 In the Framingham Study,14 the annual

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Country</th>
<th>Study sample size</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mekky</td>
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<td>Egypt</td>
<td>467</td>
<td>–</td>
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<tr>
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<td>6399</td>
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<td>Abramson</td>
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<td>Israel</td>
<td>4802</td>
<td>10.4</td>
<td>29.5</td>
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<td>1986</td>
<td>Brazil</td>
<td>1755</td>
<td>37.9</td>
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<td>1992</td>
<td>England</td>
<td>1338</td>
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<tr>
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<td>Turkey</td>
<td>850</td>
<td>34.5</td>
<td>38.3</td>
</tr>
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<td>Sisto</td>
<td>1995</td>
<td>Finland</td>
<td>8000</td>
<td>6.8</td>
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The high prevalence of CVI, cost of investigation and treatment, and loss of working days mean that CVI has a considerable socioeconomic impact. The problem is compounded by the fact that CVI is progressive and has a propensity to recur. In France, 2.24 billion Euros are spent for the treatment of CVI, of which 41% was for drugs, 34% for hospital care, and 13% for medical fees. In France in 1991, there were 200,000 hospitalizations for CVI (50% were for varicose veins), which was the eighth most common cause of hospitalization. The cost of treatment represented 2.6% of the total healthcare budget for that year. In Germany, in-patient direct costs were 250 million Euros, out-patient costs were 234 million Euros, and drug costs were 207 million Euros.

In Sweden, the average weekly cost of treating venous leg ulcers in 2002 was 101 Euros, with an estimated annual cost of 73 million Euros. Indirect costs of venous disease in terms of working days lost were the most important cost factor in 1990 in Germany, amounting to 270 million Euros. In the USA, venous ulcers cause the loss of 2 million workdays per year, while in France 6.4 million workdays were lost in 1991 due to venous disease. The socioeconomic impact of venous ulceration is dramatic, resulting in an impaired ability to engage in social and occupational activities, a reduction in patients’ QOL, and the imposition of financial constraints. In a population study in the United Kingdom, the median duration of ulceration was nine months, but 20% of ulcers had episodes of ulceration lasting longer than five years. Published data show that venous ulcers may cause the early retirement of a substantial portion, up to 12.5%, of workers with this condition.

A useful tool to determine the burden of CVI in population is to calculate health expectancies, which are population indicators that estimate the average time (in years) that a person could expect to live in a defined state of health. Health gaps measure the difference between actual population health and some specified norm or goal. The principle characteristic defining a health gap measure is the population norm (age) chosen to define the period before which death or disability is considered premature. Methods for defining health states and for eliciting health state valuations, as well as incorporation of other social values also affect the calculation and interpretation of health gaps, as for health expectancies. The best known of the health gap measures is the disability-adjusted life year (DALY), developed for use in burden of disease studies by Murray and Lopez. The DALY combines a measurement of premature mortality and disability and expresses years of life lost to premature death together with years lived with disability of specified severity and duration. One DALY is thus one lost year of healthy life. This indicator is the aggregate of years of life lost (YLL) and years lived with disability (YLD) at a population level, and reflects the burden of disease in a population: 

$$\text{DALY} = \text{YLL} + \text{YLD}.$$ 

An even more useful tool for assessing the importance of CVI is the quality-adjusted life year (QALY), a measure of disease burden that includes both the quality and the quantity of life lived. It can be used to assess the value for money of a medical intervention. Unfortunately, to date, there are no studies that have assessed DALYs and QALYs in patients with CVI.

### Quality of life in patients with chronic venous insufficiency

CVI has a huge impact on patients’ QOL. Clinical assessment of CVI severity may be carried out using different reported outcome tools: physician reported outcomes (VDS [Venous Disability Score], VCSS [Venous Clinical Severity Score]) and patient reported outcomes, such as QOL scales (generic: SF-12 and SF-36 [Short Form 12 and 36]; or specific: VEINES [Venous Insufficiency Epidemiological and Economic Study], AVVQ [Aberdeen Varicose Veins Questionnaire], CIVIQ [Chronic Venous disease Questionnaire], SQOR-V [Specific Quality Of life Response–Venous]). In the study published by Jantet, patients with venous reflux had lower CIVIQ scores than patients without reflux, reflecting a poorer QOL (62.2 versus 66.7; \(P=0.0001\)). This was observed not only for the global index scores (GIS), but for all aspects of the CIVIQ (psychological, pain, physical, and social). The subgroup with both short and long saphenous vein involvement had significantly lower QOL scores, and hence poorer QOLs, than the subgroups of patients with isolated reflux of the short saphenous vein or of the long saphenous vein only (GIS = 59.3 versus 64.1 and 64.7, respectively; \(P=0.0001\)). It is also interesting to observe from this study that only 21.8% of all patients with CVI were treated for this condition.

The CIVIQ questionnaire is a specific instrument for assessing the impact of venous disease on patients’ QOL. This scale consists of 20 items that assess physical limitation (4 items),
physical pain (4 items), social relationships (3 items), and psychological limitations (9 items). The CIVIQ questionnaire uses a Likert response scale, in which each item is scored from 0 to 10. A score per item (a value of 1-5) or a global score (a value of 0-100) can then be calculated. These questionnaires have been successfully used in previous studies.38,40

Conclusion
The exact prevalence of CVD remains difficult to determine because of variations in study population, selection criteria, and disease definition between different studies. The prevalence of varicose veins, as reported in studies, ranges from 2%-56% in men and from 1%-60% in women. Evidence suggests that the prevalence of venous disease increases with age. Varicose veins appear to be more prevalent in women, but pregnancy and the fact that women report the presence of varicose veins more often than men may play a role in this variation. Family history, obesity, prolonged standing, and diet have been proposed as risk factors, but further studies are needed to clarify the influence of potential risk factors on the development of CVI. Existing evidence highlights the need for good quality longitudinal studies measuring the incidence and prevalence of CVD. Varicose veins and CVI are often ignored as a serious public health issue even though evidence from research indicates that venous disease affects a significant proportion of the population, causes considerable morbidity, and adversely impacts the QoL of those affected. All of these factors have an influence on health-care budgets and public spending.

Future prevalence and socioeconomic studies may help to reduce the magnitude of the problem of CVI. This type of CVI assessment could raise awareness among the public, health-care authorities, and health-care professionals. In turn, this could mean that patients in the early stages of CVI receive adequate treatment preventing the development of more severe stages of CVI. Furthermore, prevalence and socioeconomic data may serve as a valuable basis for the planning of appropriate actions to deal with CVD and for the education and hire of skilled personnel. By repeating an epidemiological survey within a defined geographical area, these studies make it possible to assess the effects of treatment protocols.

References

Prevalence and socioeconomic data in chronic venous disease – Millic

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257


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**PRÉVALENCE ET DONNÉES SOCIO-ÉCONOMIQUES DANS LA MALADIE VEINEUSE CHRONIQUE : QUELLE EST LEUR UTILITÉ POUR UNE PRISE EN CHARGE APPROPRIÉE ?**

La prévalence exacte de la maladie veineuse chronique (MVC) reste difficile à déterminer à cause de la variation des populations des études, des critères de sélection et de la définition de la maladie entre les différentes études. La prévalence de la MVC, rapportée dans les études, varie de 2 % à 56 % chez les hommes et de 1 % à 60 % chez les femmes. Cette pathologie reste encore sous-estimée malgré son impact énorme sur les dépenses de santé et sur la qualité de vie des patients. La MVC augmente avec l’âge et d’après des études récemment publiées, il n’y avait aucune différence significative entre les sexes. Les antécédents familiaux, l’obésité, la station debout prolongée et le régime alimentaire sont des facteurs de risque, mais d’autres études sont nécessaires pour évaluer l’influence des facteurs de risque potentiels sur le développement de la MVC. Le poids financier sur le système de santé est énorme, de récentes estimations plaçant le coût du traitement de la MVC à 3 milliards de $ par an aux États-Unis, ou à plus de 2 % du budget total de la santé dans tous les pays occidentaux. L’état actuel des connaissances souligne le besoin d’études croisées et longitudinales de bonne qualité permettant de mesurer l’incidence et la prévalence de la MVC. Ces études pourraient permettre de réduire l’ampleur du problème de la MVC en éveillant la conscience du public, des autorités et des professionnels de santé. De plus, la prévalence et les données socio-économiques pourraient servir de base précieuse à la mise en œuvre d’étapes appropriées pour la prise en charge de la MVC et pour éduquer et recruter du personnel qualifié.
Treatment of chronic venous disease: pathophysiological underpinnings

by R. D. Malgor and N. Labropoulos, USA

Chronic venous disease (CVD) causes a significant negative socioeconomic impact in society. Its indolent course confers a high tolerance until treatment is pursued. The initial phase of the disease is often neglected by most patients and many seek treatment when the disease is advanced. The most common pathology is reflux in the superficial veins, while isolated deep vein reflux is uncommon. Obstruction alone is rare, but is frequently found in combination with reflux, a scenario that has the worst prognosis. Several modalities of treatment are available, from medication using venoactive drugs through to open and endovenous interventions. A comprehensive understanding of the causative mechanisms involved in the development of CVD is mandatory for choosing the most appropriate and tailored treatment for each patient. This review focuses on the pathophysiological underpinnings involved in the treatment of CVD.

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Primary and secondary venous disease

Chronic venous disease (CVD) is a worldwide affliction affecting a great portion of the world’s population. Despite its widespread prevalence, there are several reasons why CVD treatment is delayed and why it attracts little attention for major research funding: it has an indolent course; clinical presentation is late, with skin changes; and there is no risk of loss of limbs or mortality. There are several factors involved in the pathophysiology of CVD. In recent years, the inflammatory pathway in CVD, on which certain medications act, has become better known. Inflammatory processes, such as leukocyte migration, plasma-granulocyte activation, and increased metalloproteinase activity, all cause degradation of the valve leaflets. Another factor involved in the pathophysiology of the CVD is calf pump function. The calf pump increases blood flow velocity and maintains fluid balance. Patients with dysfunctional calf pumps are more prone to develop skin changes and more severe venous ulcer disease.

CVD is classified into two types: primary and secondary. Essentially, primary venous disease is caused by venous reflux and affects two-third of limbs with CVD. Initially, increased venous pressure causes smooth muscle relaxation, endothelial damage, and extracellular matrix degradation. Subsequently, the vein wall becomes weak and eventually dilated. Superficial vein reflux, in the great saphenous vein (GSV) and small saphenous vein (SSV), is the most common type of reflux, occurring in 80% of cases, followed by reflux in perforator veins (PVs) and deep veins. Isolated
involvement of deep veins is rare. Likely deep vein reflux is noted when longstanding superficial vein reflux affects the venous junctions (Figure 1) and the PVs in turn render the deep veins incompetent. Often, isolated primary deep vein reflux is found in the common femoral vein, followed by the femoral and popliteal vein. Deep vein reflux can be found in association with superficial vein reflux in up to 40% of cases. PV reflux is another component of CVD commonly related to superficial vein reflux. Two mechanisms have been proposed to explain how PV valves become incompetent. The first mechanism is an ascending extension of superficial vein reflux causing progressive vein dilation and reflux that propagates proximally rendering the perforator vein dilated and incompetent. The second mechanism is a descending propagation where re-entry PVs drain reflux blood into the deep veins. Over a long period of time, the high flow volume in the PVs causes dilatation and reflux in these veins. PV reflux most often originates in the GSV system and may render the deep veins incompetent. In cases of deep vein reflux secondary to PV reflux, frequently only a short segment is affected.

Secondary venous disease is less common than primary CVD and is caused by either a thrombotic event or arteriovenous fistula (AVF). Trauma has been mentioned as a cause of secondary CVD, but this occurs through deep venous thrombosis (DVT) of an AVF that can occur after trauma. Increasing venous pressure secondary to AVF formation creates local venous hypertension causing endothelium damage, vein wall weakening, and dilation faster but similar to that observed in primary CVD.

DVT is the most common cause of secondary CVD. Many risk factors are involved in the development of DVTs, such as pregnancy, operations, immobilization, malignancy, trauma, and obesity. In addition, patients who have a hypercoagulation disorder (ie, mutation of coagulation factors, active protein C resistance, protein S and antithrombin III deficiency) are likely to develop DVT. Reflux, obstruction, and a combination of reflux and obstruction are the three possible patterns present in secondary CVD. The worst prognosis is when reflux and
obstruction are present in the same limb, rendering the limb prone to skin changes, such as discoloration, and to venous ulcers. Ipsilateral recurrent DVT, iliofemoral thrombosis, and persistent intensity of signs and symptoms in the first month after the episode of DVT are important predictors for developing postthrombotic syndrome (PTS).15-17

Partial recanalization (Figure 2) is seen more frequently than total recanalization or complete occlusion of veins after an episode of thrombosis.18 The location of reflux and obstruction also plays a role in the development of PTS, which is defined as a group of signs and symptoms comprising heaviness, edema, itching, and eventually skin damage including venous ulcers.18 Lastly, in a minority of cases, congenital venous malformations are to blame for CVD. Agenesis, hypoplasia, and the absence of valves in a short or long segment of superficial or deep veins are the most common findings.19

Although the clinical course of CVD is indolent, over time it causes a negative impact on health and quality of life. In order to create a standardized method to describe patients with CVD, a classification based on clinical ("C"—telangiectasias to skin damage), etiological ("E"—primary, secondary, or congenital), anatomical ("A"—superficial, deep, or perforators), and pathophysiological ("P"—reflux, obstruction, or both) findings has been created, which is known by the acronym CEAP: Clinical-Etiological-Anatomical-Pathophysiological. The majority of patients are at an initial stage of the disease (C1-C2) and have telangiectasias and varicose veins. Chronic venous insufficiency (CVI) occurs when patients present with edema or skin damage (discoloration or venous ulcers).

**Treatment**

Treatment modalities for CVD, for which there are many, should be tailored to the specifics of each patient based on pathophysiological findings. Patients should then be stratified according to disease severity, and nonoperative and invasive treatments used alone or in combination. All patients with CVD should be referred to specialists for general and focused history taking and physical examination. Many options for venous disease workup are available, including direct and indirect noninvasive methods and other imaging studies, such as computed tomography (CT)/CT venograms, magnetic resonance (MR) imaging/MR venograms, and contrast venography (ascending and descending).

The identification and location of reflux can be accurately assessed with duplex ultrasound, so the vascular laboratory should be the first stop for a workup to obtain a noninvasive, comprehensive, and dynamic assessment of the superficial, perforator, and deep veins. It is recommended that not only patients with CVI, but those with telangiectasias and varicose veins undergo duplex ultrasound examination of the superficial, deep, and (selectively) perforator veins to evaluate valvular incompetence prior to initial treatment of CVD. Laboratory workup for screening of patients with positive familial histories of hypercoagulation states or venous ulcers should be individually tailored.

Recently, the role of CT venograms and MR venograms for the identification of iliofemoral and caval obstructions in patients with skin damage has been investigated. A positive result showing significant stenosis or obstruction can change
the treatment approach and therapy and potentially reduce the recurrence of the venous disease. However, the routine indication of noninvasive and invasive treatments with intravascular ultrasound assessment of iliofemoral and caval obstructive disease is not yet recommended for routine use.

◆ Medication (venoactive drugs)
Many different categories of medication have been used for the treatment of CVD: alpha-benzopyrones (coumarin), gamma-benzopyrones (ie, purified flavonoids), saponins (escin and ruscus extract), plant extracts (ie, ginkgo biloba), and synthetic products (ie, benzaron).20 The use of medication for varicose veins is based on the targeting of inflammatory pathways involved in the development of CVD. The best results of all the medication regimens are achieved in early cases of CVD where no significant structural changes of the vein wall and valves have occurred. However, certain venoactive drugs have been used successfully in patients with more advanced disease (with edema and venous ulcers). A meta-analysis of 5 prospective, randomized trials in 723 patients demonstrated encouraging results with the adjuvant use of Daflon 500 mg, reporting a 32% improvement in venous ulcer healing rates.21

In an experimental study in rats, purified flavonoid (Daflon 500 mg) was found to decrease the levels of granulocyte and macrophage infiltration in the valves preventing valve damage and delaying the development of reflux.22 Another class of flavonoids, the oxerutins, are also utilized for their anti-inflammatory properties. Low cost, widespread availability, and rare side effects are advantages of treating CVD with medication. The only contraindication to the use of venoactive drugs is allergy to one of the components of the formula, but this is rare.

◆ Compression therapy, structured exercise, and wound care
Compression therapy has long been considered the first-line treatment for all symptomatic patients with CVD (C1-C6) where venoactive drugs are unavailable (USA, for example). The rationale for using compression hosiery is to increase venous blood flow velocity, thus improving venous reflux, and also to assist the calf muscle pump, therefore reducing leg edema.23,24 The local inflammatory response also decreases with a reduction in cytokine production and the shift of local cutaneous fluid from the interstitial space to the lymphatic system.25,26 There are several advantages of compression therapy. First, all patients are eligible for use except for those with severe peripheral arterial insufficiency (ankle-brachial index [ABI] <0.5). Second, patients with CVI (C3-C6), especially those with venous stasis ulcers, benefit significantly from therapy with good levels of ulcer healing and they remain ulcer-free for a reasonable length of time. In a prospective, multicenter randomized study that examined 200 limbs with venous ulcers that were randomized for compression or surgical treatment, the ulcer healing rate was similar in both groups (53%).27 A larger prospective, randomized trial of 500 patients, the ESCHAR (Effect of Surgery and Compression on Healing And Recurrence) trial, demonstrated that compression therapy is as effective as surgery plus compression therapy for ulcer healing, but recurrence rates were higher when compression was used alone.28 A document detailing multiple modalities of compression therapy (ie, simple component, two- or four-component, elastic, nonelastic) was produced by the Cochrane Collaborative Group. The results of the Cochrane systematic review show that elastic multicomponent systems, ie, containing an elastic bandage, appear more effective than those that have inelastic components.29 Regardless of the high efficacy of the different compression garments and techniques in ulcer healing and preventing ulcer recurrence, the most challenging aspect of treatment remains the lack of compliance: four in five patients are noncompliant.30

Exercises to strengthen the calf muscle pump and intermittent pneumatic devices have proven beneficial as an adjuvant therapy in patients with CVD. Calf muscle pump conditioning can lead to a subsequent improvement in venous blood return.31 A randomized controlled trial in 31 patients with skin damage or ulcers who were divided into two groups (a structured exercise group [n=18] and controls [n=13]) showed that the calf pump function did improve venous blood return, but the quality of life and severity scores of the groups were similar.32 However, this study only provides short-term results with a 6-month follow-up. Large trials with mid- and long-term follow-ups are warranted to gauge the actual impact of calf pump function on quality of life, venous ulcer healing, and ulcer recurrence. Compression therapy should not be viewed as a definitive therapy, but rather as a valuable adjuvant tool that can be utilized in all asymptomatic patients with CVD to hinder the progress and prevent the recurrence of venous ulcers.

Venous ulcers are responsible for lost work productivity and high health-care costs.33,34 Patients with skin damage who develop ulcers must be evaluated and treated in specialized wound care centers by a multidisciplinary team.35 The initial treatment of venous ulcers targets the underlying cause of CVD (venous obstruction, reflux, or a combination of obstruction and reflux).36 In addition, infected areas require treatment with appropriate antibiotic regimens (guided by culture biopsies) and debridement, which is performed in operating rooms.37 There has been progress in the field of ulcer debridement recently. A new technique for the debridement of venous ulcers, low-frequency ultrasound, has been developed, but for the moment limited experience and low-quality evidence mean the routine use of this technique is not recommended.38

◆ Sclerotherapy
Venous injection of sclerosing agents has gained popularity due to the minimal material, low cost, and short learning curve required. Currently, two types of sclerotherapy are available:
liquid and foam (Figure 3). Whatever formulation is utilized for the ablation of the GSV or SSV, ultrasound guidance is mandatory in order to gauge the amount of foam necessary to obliterate the segment of interest and, more importantly, to control the extent of sclerotherapy.

The advantages of foam over liquid are better control during injection, less volume required to fill the target vessel, greater circumferential contact area between the treatment and endothelial cells, and a longer sclerosing time due to a slower absorption compared to the liquid preparation. A multicenter randomized controlled trial of 95 patients showed that a polidocanol foam preparation was twice as effective at achieving and maintaining venous occlusion over a 2-year follow-up as the liquid version.38 Furthermore, other studies have demonstrated that more dilute solutions, such as 1% polidocanol, are as effective as stronger solutions of 3% in obliterating GSV <8 mm.39

The drawback of the technique is the possible inadvertent passage of sclerosing agent into the deep veins, which is not completely prevented either with ligation or compression of the saphenofemoral junction (SFJ) with the ultrasound probe during the intervention.40 Fortunately, complications of sclerotherapy are rare because they can be serious41: lung and brain emboli have been reported.41,42 Long-term results from large multicenter, randomized controlled trials are still warranted to assess the durability of treatment and to define potential predictive factors to prevent adverse outcomes.

Stripping, stab phlebectomy, and ablation procedures

The treatment of superficial venous reflux has evolved greatly over the past three decades. The old standard of care, ligation of the SFJ or saphenopopliteal junction (SPJ) with or without stripping of the GSV or SSV, has been replaced by radiofrequency ablation (RFA) or endovenous laser therapy (EVLT). The stripping of the GSV consisted of dissection and isolation of the SFJ and the distal segment of the GSV or SSV at the end point of reflux with insertion of a metallic or plastic wire through the isolated segment with subsequent stripping of the vein. The disadvantages of the technique included the risk of wound infection, postoperative pain, longer recovery time, and a significant inflammatory response in the SFJ or SPJ leading to neovascularization and the recurrence of the varicose veins.43 Modifications to the traditional stripping with invagination technique and the use of tumescence have reduced complications of this technique and have made it an outpatient procedure.44 EVLT and RFA are ultrasound-guided, catheter-based techniques that obliterate the lumen of the GSV and SSV and occasionally perforator veins via a totally endovascular approach. First, diluted local anesthetic in saline solution is injected abundantly prior to the venous ablation in the subcutaneous tissue around the GSV, SSV, or accessory veins to create a fluid barrier between the vein and the skin and to reduce the size of the vein lumen. The purpose of the tumescent local anesthesia is to prevent skin damage (such as thermal injury or discoloration), to increase the effectiveness of the procedure (via vein wall compression), and to provide intra- and postoperative analgesia.

The RFA or EVLT catheter is then inserted into the vein and positioned up to 2 cm away from the SFJ or SPJ in order to avoid thermal injury or extension of the thrombus into the common femoral or popliteal vein. Different wavelengths of laser (ie, 810-1470 nm) and two different types of energy transmission (ie, pulsed or continuous) are commercially available in the USA.

Endovenous interventions have some advantages over vein stripping as an ambulatory-based intervention with same-day discharge. These include the feasibility of performing the intervention under local anesthesia with light sedation and a faster return to work. Modified stripping techniques with ultrasound guidance and local perivenous anesthesia without ligation of the junction and its tributaries may have similar results.44–46 Several trials have reported similar efficacies with GSV and SSV ablation and the resolution of symptoms using either EVLT or RFA.48–50 Complications of endovenous ablation include skin burns and the propagation of the thrombus into the deep veins causing DVT and pulmonary embolism. Venous thromboembolic events have also been reported with ligation and stripping.51 Recent studies have demonstrated that thermal ablation procedures and surgical techniques have similar outcomes in abolishing reflux and improving quality of life.52

Figure 3. Nonsaphenous vein reflux.

(A) Prolonged reflux in the left ovarian vein in a patient who presented with pelvic congestion syndrome and varicose veins in the groin medial to the saphenofemoral junction extending down to posteromedial thigh. The patient was treated with selective catheterization of the left ovarian vein. Foam sclerotherapy was used for the distal tributaries in the pelvis and the ovarian vein was coiled with long coils. The varicocities in the thigh were removed with phlebectomy and those in the inner groin with foam sclerotherapy. (B) Prolonged reflux in the vein of the popliteal fossa in a patient who presented with varicocities in the posterior and later calf. The small saphenous vein was intact. Phlebectomies were performed with adjunct foam sclerotherapy.
Two other innovative alternatives to vein ablation are the Clari-Vein™ (Vascular Insights, Madison, Connecticut) and the Steam Vein Sclerosis (SVS) system™ (Guttman Medical Services GmbH, Geretsried, Germany). The former consists of a percutaneous 0.035” infusion catheter that contains a rotating wire operated and activated from a DC battery-powered handheld device. The pharmacomechanical effects cause endothelial damage, intense vasospasm, and eventually thrombosis of the lumen. The SVS™ system delivers water vapor through a heating catheter that does not require a wire inside the vein causing thermoablation comparable to that of RFA or EVLT. Like EVLT or RFA, ultrasound guidance is needed for both ClariVein™ and SVS™, but tumescent local anesthesia is only required for the SVS™ system. The initial results of Clarivein™53 and SVS™ 54 for venous ablation are promising, but further research is still needed.

In light of the fact that the varicosities of tributaries and accessory veins are far more prevalent than those of saphenous trunks, these veins can be treated alone or in combination with the saphenous veins.55 Treatment of varicose veins may also be treated with stab phlebectomies alone.44,56 In a study of 303 limbs, the incompetent GSV was not removed, but only the varicose veins linked to the zones of reflux. In this series, 78% of the patients reported an improvement in symptoms or no symptoms at 4-year follow-up.57

The role of PV treatment has been controversial. Although the number and size of incompetent PVs increases with CVD severity, evidence for treating most of these veins is lacking with the exception of a few cases.13,28,58,59 The role of superficial venous reflux on the development of deep venous incompetence has been investigated. Since isolated deep venous reflux is rare, the concept of volume overload in the superficial venous system causing valve dysfunction in the perforator and deep veins has been reported.11 Treatment of superficial vein reflux has been shown to correct valve function in deep veins.9,10 Patients with skin damage or secondary CVD have worse results because of chronic inflammatory changes, severe valve dysfunction, and vein wall dilation.

**Open and endovascular venous reconstruction**

Venous reconstructions are frequently indicated in symptomatic patients with secondary CVD who have significant venous stenosis, obstruction, or a residual thrombus (Figure 5). Before the endovenous era all patients with ilio-femoral and caval obstruction were treated with open procedures including bypass graft, spiral vein interposition graft, and veinoplasty. Initially, an arteriovenous fistula (AVF) is frequently associated with venous bypass construction aimed at reducing venous stasis and therefore increasing the patency of the repair. The
shortcoming of AVFs is that the venous hypertension generated causes vein wall dilation, valve destruction, and venous reflux if the AVF is not monitored and ligated in a timely fashion. A series of 44 patients with nonmalignant venous obstruction who underwent different types of reconstructions (ie, spiral vein, bypass, venoplasty, Palma procedure) reported an overall primary and secondary patency at 3-years of 54% and 62%, respectively. Lower primary and secondary patency rates were found for iliofemoral and iliocaval bypasses when analyzed separately, only 38% and 54% at 2-year follow-up, respectively, likely because the majority of repairs were done using extended polytetrafluoroethylene (PTFE) grafts.

Endovenous treatment of common femoral and ilio caval obstruction comprise angioplasty and stenting. The big advantage of percutaneous treatment compared with transperitoneal or retroperitoneal approaches under general anesthesia is the lower morbidity and mortality. In a series of 982 chronic nonmalignant obstructive lesions of the common femoral and ilio caval veins that were stented, complete relief of pain and swelling occurred in 62% and 32% of cases, respectively, and ulcer healing in 58% of the patients at 5-year follow-up.

Several open surgical valve reconstruction techniques have been proposed to correct venous reflux and obstruction. The main procedures described are internal and external (transcommissural) valvuloplasty, axillary vein transfer, vein transplantation, and valve transplant. Surgical expertise, postprocedural care, and referral to a high-volume specialized center for these specific procedures are essential.

Briefly, with an internal valvuloplasty, the incompetent valve is exposed and the leaflets are approximated suturing the intercommissural space with subsequent closure of the venotomy. The external (transcommissural) valvuloplasty is performed without doing a venotomy with interrupted sutures placed externally transfixing the venous wall to approximate the intercommissural space. The advantage of the transcommissural repair is the possibility of treating long segments in a shorter operating time. Valve transfer is often carried out while dissecting, dividing, and resecting a segment of vein that serves as a graft (ie, axillary vein) for replacement of a diseased venous segment in a lower extremity. Neovalve creation is now feasible with a technique developed by Maletti and colleagues. In this technique, an endophlebectomy of the venous segment is performed with dissection of the intima layer creating a flap that is positioned as a mono- or bicuspid valve with subsequent venorrhaphy in a transverse fashion.

The use of an external sleeve of Dacron or PTFE wrapped around the incompetent valve has been advocated by some authors in order to narrow and approximate the valve leaflets or as an adjunct after a vein transfer to prevent future vein obstruction.
wall dilation. Satisfactory results have been reported using all techniques, although limited experiences in a few specialized centers are available for comparison in the US and Europe.

Conclusion CVD is a multifaceted entity responsible for significant negative socioeconomic impact. Treatment of the CVD requires a complete understanding of the pathophysiological underpinnings of the disease in order to offer the most appropriate treatment tailored to the disease specific of each patient. Combinations of different types of treatment may be necessary in the majority of the patients. Given that over 25% of patients with CVD have skin damage, treatment at earlier stages may be important to slow down the progression and to reduce the prevalence of skin damage from CVD.

References
Keywords: chronic venous disease; treatment; pathophysiology

TRAITEMENT DE LA MALADIE VEINUSE CHRONIQUE : BASES PHYSIOPATHOLOGIQUES

L’impact socio-économique de la maladie veineuse chronique (MVC) est significativement négatif dans la société. Peu douloureuse, elle est bien tolérée jusqu’à la mise en route du traitement. La plupart des patients négligent souvent la phase initiale de la maladie et sont demandeurs d’un traitement lorsque la maladie est évoluée. Le reflux veineux superficiel est la pathologie la plus courante, contrairement au reflux veineux profond isolé. L’obstruction isolée est rare mais fréquemment retrouvée en association avec un reflux, scénario au plus mauvais pronostic. Il existe plusieurs modalités de traitement, des phlébotomies aux interventions endoveinées ou à ciel ouvert. Il faut une compréhension complète des mécanismes impliqués dans le développement de la MVC pour choisir le traitement le plus approprié et personnalisé pour chaque patient. Cet article traite des bases physiopathologiques impliquées dans le traitement de la MVC.
chronic venous disease (CVD) continues to impose a significant burden on both patients and physicians since the way to manage it most effectively still remains elusive. A great deal of research has revealed that the long-term outcomes of highly distinct treatment methods, including invasive and completely noninvasive techniques, yield comparable results overall. The rationales behind these techniques are very different from each other, which raises a concern about the validity of the methods that are used to calculate the severity of CVD before and after treatment. One of the major obstacles to collecting consistent CVD management data is that CVD severity can be evaluated in many different ways. While a patient’s quality of life is perhaps the most important measurement, physician-centered parameters exist and they are primarily based on the pathophysiology of the disease. Furthermore, the variability in the perception of the disease among different groups of patients presents another challenge in drawing conclusions from various studies. These scoring systems need to be dynamic, since CVD management comprises the treatment of clinical issues that evolve over a long period of time. Realization of these pitfalls has resulted in a number of modifications to previously established scoring systems. However, even today, the modified versions individually fail to indicate the overall severity of the disease. Thus, there is still the need to generate a universally acceptable scoring system in CVD that combines the most significant parameters of the current investigation methods.

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Recently, management of chronic venous disease (CVD) has embraced new methods of treatment. In the 20th century, the only treatment for CVD was various methods of surgery with some forms of conservative therapy, ie, stockings. Although all of these methods were claimed to be effective, the long-term outcomes as well as the efficacy of these treatments have never been compared to each other. Until recently, it was assumed that surgery was more efficacious than conservative approaches, and therefore the latter form of treatment was saved for patients who were not eligible for surgery.

The move towards surgical management of CVD has generated newer forms of methods, such as ASVAL (incompetent sAphenouS Vein preservAtion with phLebectomy [Ablation Sélective des Varices sous Anesthésie Locale]) and CHIVA (Conservative ambulatory Hemodynamic management of Varicose veins [Cure conser-
Clasifications, severity scorings, and chronic venous disease guidelines – Kurtoglu and Aksoy

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VENOUS DISEASE GUIDELINES AND DAILY CLINICAL PRACTICE

venous insufficiency, involvement. However, postoperative analysis of these methods by Doppler ultrasonography has revealed that all of the surgical approaches were comparable. This finding is interesting since the methodologies of these surgical approaches were distinct from each other; CHIVA is based on correcting descending venous reflux, while ASVAL is based on the ascending negative pressure steal phenomenon. Despite these differences, the early anatomical, clinical, and hemodynamic results of these methods were surprisingly similar. In addition to surgical methods, newer approaches using radiofrequency, lasers, and sclerotherapy to ablate veins have further expanded the range of methods to manage CVD. These newer approaches are reported to be at least as effective as conventional surgical methods. It appears that methods that are grossly different from each other claim to have similar outcomes. The question then becomes: “How should we define the effectiveness or success of CVD management?” From the patient’s point of view, success and satisfaction is usually based on improving quality of life, while physicians would also focus on resolving the anatomical and hemodynamical pathologies of CVD. Another measure of effectiveness comes from an economic standpoint: cost-effectiveness of management. Lastly, it should not be forgotten that the severity of recurrence has its own role in defining the efficacy and success of a treatment method.

What current instruments can assess the efficacy of CVD treatment?

Since all methods of CVD management claim to be efficacious, we need to elaborate on what kind of assessment tools can be used to evaluate the efficacy of CVD management. The following section will focus on defining these tools as well as their validity in assessing the efficacy of CVD management.

In contrast, anatomical assessment is an outstanding way of evaluating the disease. Anatomical assessment of CVD is mainly based on color duplex imaging of veins. This instrument-based approach generates both morphological and functional results to evaluate CVD management. There is a widely accepted terminology used in this method, which is based on the obstruction and reflux of superficial, perforating, and deep veins. Therefore, color duplex imaging allows both quantitative and qualitative assessment of the severity of pathology in these veins. The diameter of the incompetent vein can be measured by duplex imaging. However, diameter alone is not a valid method of assessment. This measurement may be of value in cases where an increase is detected during follow-up because it may be indicative of a recently developed connection between the greater saphenous vein and pelvic sources of reflux. Measurement of diameter is recommended at the junction and along the great saphenous vein if there is reflux. Although a definitive cutoff for all vein segments has not been agreed, venous reflux is considered to be retrograde flow in the reverse direction to physiological flow if it lasts for more than 0.5 s. Finally, diameter is not a marker for indication, but may help in deciding the type of intervention required, such as sclerotherapy, laser, or radiofrequency ablation.

Clinical investigation

Clinical investigations are based on the assessment of visible pathologies that result from CVD, such as edema, varicose veins, and ulcers. The clinical evaluation of these pathologies is further supplemented by color duplex imaging of veins. In the course of CVD management, these visible pathologies can be partially or completely resolved, and clinical investigations score the level of this improvement. However, it is important to note that these investigations are not sufficiently dynamic to assess the durability of wellness.

SELECTED ABBREVIATIONS AND ACRONYMS

- ASVAL: incompetent sAphenous Vein preservAtion with phLebectomy [Ablation Sélèctive des Varices sous Anesthésie Locale]
- AVVQ: Aberdeen Varicose Veins Questionnaire
- CEAP: Clinical-Etiological-Anatomical-Pathophysiological
- CHIVA: Conservative ambulatory Hemodynamic management of VRicose veins [Cure conservatrice et Hémodynamique de l’Insuffisance Veineuse en Ambulatoire]
- CIVIQ: Chronic Venous disease Questionnaire
- CVD: chronic venous disease
- CVI: chronic venous insufficiency
- CXVUQ: Charing X [cross] Venous Ulceration Questionnaire
- EQ-5D: EuroQol 5 Dimension [mobility, self-care, usual activities, pain/discomfort, anxiety/depression health survey]
- NHP: Nottingham Health Profile
- RELIEF: Reflex assEssment and quaLity of life improvEment with micronized Flavonoids
- SF-12: Short Form 12 [-item health survey]
- SF-36: Short Form 36 [-item health survey]
- SOOR-V: Specific Quality Of life Response–Venous
- VCSS: Venous Clinical Severity Score
- VDS: Venous Disability Score
- VEINES: VEncous INSufficiency Epidemiological and economic Study
- VSDS: Venous Segmental Disease Score
- VSS: Venous Severity Score
There are two main clinical investigation methods: CEAP and VSS. The CEAP classification was first developed in the 1990s. The original classification was modified in 2004, since at the time it was not adequately dynamic nor did it adequately correlate with symptoms. This modification allowed better communication between physicians, which led to improved assessment of CVD management efficacy. However, even the modified version continued to be physician-centered and hence did not always correlate with patient symptoms. These investigations are not necessarily responsive to improvements following treatment.

Upon realization of the pitfalls of CEAP, the American Venous Forum developed the VSS, which was designed to supplement CEAP scoring and to provide a method for serial assessment. VSS is mainly used for longitudinal follow-up of a patient’s condition during and following treatment. The scoring system has three components:

- Venous Disability Score (VDS)
  This method is an extension of CEAP that evaluates the level of work-based disability. Based on the ability to work with or without support, disability is scored from 0 to 3. The total result will show the disability associated with venous disease.

- Venous Segmental Disease Score (VSDS)
  This score is based on anatomical and pathophysiological components of CEAP obstruction and reflux. This part requires assessment with Doppler ultrasonography or phlebography.

- Venous Clinical Severity Score (VCSS)
  This is a dynamic form of CEAP evaluation that has been designed to include 9 hallmarks of the most severe complications of CVD. These include skin changes, inflammation, induration, and ulcers. Each hallmark is scored on a severity scale ranging from 0 to 3. VCSS is an easy-to-apply, stand-alone scoring system. This part of the VSS has been studied expansively and is frequently used for longitudinal surveillance of venous disease.

**Physiological investigation**
These are hemodynamic investigations that are usually performed for academic purposes. This method uses plethysmography, which monitors the change in ambulatory venous pressures following treatment of CVD. The patterns of venous flow in different vein segments are also evaluated by either duplex scan or phlebography.

**Functional investigation**
These are generic and disease-specific assessments of quality of life. The generic assessments are SF-36 (Short Form 36 [10-item health survey]), SF-12 (Short Form 12 [12-item health survey]), EQ-5D (EuroQol 5 Dimension [mobility, self-care, usual activities, pain/discomfort, anxiety/depression health survey]), while the disease specific ones are AVVQ (Aberdeen Varicose Veins Questionnaire), SQOR-V (Specific Quality Of Life Response–Venous), CIVIQ-2 (Chronic Venous disease Questionnaire 2), and VEINES (Venous Insufficiency Epidemiological and Economic Study). Generic methods are geared toward evaluating the subjective assessment of quality of life, while the disease-related surveys examine specific elements associated with a particular disease process. Since the latter ones are more specific in their scope, they have become more popular in evaluating CVD management.

- **Generic instruments**
  - SF-36
    The SF-36 is a valid assessment of quality of life. The scoring system is based on two types of health aspect: physical health and mental health. The former is assessed via the patient’s level of functioning, whilst the latter is assessed via an indicator of well-being. These two types include eight domains: assessment of physical and social functioning, role limitations due to physical and emotional problems, mental health, pain, vitality, and health perception. The SF-36 is a good way of assessing changes in quality of life in CVD. It has been widely used in studies concerning patients affected with venous disorders.
  - Nottingham Health Profile
    The Nottingham Health Profile (NHP) is intended for primary health care to provide a brief indication of a patient’s perceived emotional, social, and physical health problems. It consists of two parts. Part I contains 38 yes/no items in 6 domains: pain, physical mobility, emotional reaction, energy, social isolation, and sleep. Part II contains 7 general yes/no questions concerning daily-living problems. It can be applicable to other diseases as well as to CVD.

- **Disease-specific instruments**
  - CIVIQ
    This method contains questions to assess the psychological, social, and pain aspects of CVD. The first version of this questionnaire included different numbers of questions in each category. The second version, CIVIQ 2, provides a global score covering all aspects of the questionnaire and weighs the categories equally. Both versions of the questionnaire are reported to be valid quality-of-life measurements. The RELIEF (Reflux assessmnt and quaLity of lIfe improvEment with micronized Flavonoids) study, which was conducted in 23 countries worldwide and included the participation of more than 10,000 patients suffering from chronic venous insufficiency (CVI), validated CIVIQ, the first quality-of-life scale specific to chronic venous insufficiency, and assessed changes in the quality of life of patients suffering from CVI, with or without venous reflux, treated with micronized purified flavonoid fraction.

- **VEINES**
  Compared with CIVIQ, this method focuses more on symptoms than the psychological and social aspects of the dis-
ease. The VEINES questionnaire consists of 25 items that estimate the effect of disease on quality of life, and the VEINES symptom questionnaire consists of 10 items that measure symptoms.14

- **Aberdeen Varicose Vein Questionnaire**
  AVVQ addresses multiple aspects of varicose disease, including physical symptoms, social issues, as well as the cosmetic manifestations of treatment outcome. The overall evaluation consists of a score with a range of 0 to 100.15

- **Charing Cross Venous Ulceration Questionnaire**
  The CXVUQ was developed to provide a valid quality-of-life measurement of venous ulcers. This method may be combined with the SF-36 to generate valuable information on the progression of ulcers and their treatment. This questionnaire has been mainly designed for patients with venous ulcers.16

- **Cost-effectiveness investigation**
  This type of investigation is independent of patient- or physician-centered assessments and plays an important role in selecting effective treatment, although it is currently underutilized. As the use of new technologies in CVD management becomes more widespread, their current high costs are expected to decrease, which may affect physicians’ decision on what appropriate treatment of CVD they choose. It is important to include early economic impact measures in this investigation, such as time away from work following treatment as well as possible costs due to recurrences. These economic aspects of CVD are currently underemphasized and require more attention.

**Discussion**

The main dilemma in evaluating these investigative methods is whether patient- or physician-centered evaluation methods are superior. In other words, should we rely on indicators from the perspective of the physician or the patient? Perhaps more importantly, can we develop methods to satisfy both?

It is important to note that venous diseases are individual-based pathologies, such that patient satisfaction becomes a hallmark of effective treatment. However, evaluation of patient satisfaction can contain obvious subjective measures, which generate an obstacle to standardizing the method of reporting CVD management outcomes.17

It is evident that combining methods geared toward patients and physicians would generate more satisfactory results.12 However, combining methods would likely compromise effective communication of results, since the methodologies would be cumbersome and somewhat complicated. However, it is our opinion that the combination of CEAP and VCSS yields the most complete evaluation of CVD treatment methods without compromising effective communication between various centers.

The prevalence of venous disease is approaching 30%, as reported in various studies worldwide.10 However, the effectiveness of the treatment of CVD is still unsatisfactory, despite the recent development of various techniques to provide alternatives to conventional surgery. As a matter of fact, these new techniques have raised further questions, since early, short-period, ie, 3 weeks, posttreatment follow-up has demonstrated no differences in patient satisfaction compared with either surgery or with other new techniques.20,21 Thus with this equivalence, cost-effectiveness becomes an important factor, since these new technologies cost more than surgical methods. Balancing this, we cannot exclude the fact that these newer technologies provide better comfort in the early posttreatment period and shorter delays in returning to work.22 As a result, patients and therefore physicians continue to want to utilize these techniques, which may reduce their cost in the near future. These arguments provide a basis for why more dynamic treatment evaluation methods are needed since in addition to early outcomes in CVD management, long-term effects and recurrences need to be factored in to draw better balanced conclusions from studies.

Different surgical approaches as well as new technology-based techniques are designed to ablate superficial venous system and to resolve obstructions in the deep venous system. However, a fundamental difference between surgical and newer approaches is that the former focuses on preventing saphenofemoral junction reflux with high ligation, while the latter minimally invasive techniques ablate the vein at least 2.5 cm below the junction in order to prevent potential complications of the common femoral vein, including deep vein thrombosis. Interestingly, as mentioned above, these therapeutic methods are reported to result in similar outcomes,20,21 which raises the question of whether reflux of the saphenofemoral junction plays a significant role in progression of venous disease.

Anatomical investigations, ie, Doppler ultrasound, indicate the severity of venous disease based on the investigation of the pathway of the saphenous trunk and saphenofemoral junction reflux. If reversing the reflux appears to play no role in the outcome of CVD management, are anatomical investigation methods biased? On the other hand, in the deep venous system, resolving postthrombotic obstructions improves patient symptoms, since recanalization via stents without prevent-
ing reflux has been shown to resolve symptoms of CVD. Yet again, there is another perspective: CVD primarily due to reflux is treated by obliterating this pathology via reconstruction of the valves. These contradictions in the use of CVD management techniques and their results reveal the lack of understanding of how venous disease progresses and show that evaluation techniques that mainly rely on anatomical investigations, such as CEAP, may give biased results.

In summary, it is clear that one investigational method does not suffice to evaluate the management of CVD. Both physician- and patient-centered methods need to be utilized to generate satisfactory conclusions. However, using all these methods together produces complex results that are cumbersome to interpret and communicate. Thus, we need to revisit our understanding of the etiopathogenesis of CVD to guide us in designing evaluation methods that focus on pathologic factors that play a significant role in the progression of venous disease. All reports indicate that current treatment of pathologies that are thought to underlie CVD does not prevent recurrence of the disease. Furthermore, every recurrence appears to demonstrate distinct clinical and anatomical features in each patient: generalization of CVD treatment outcome may be challenging in an individual-based disease. Moreover, since CVD is a life-long progressive disease, all investigation methods should be adequately dynamic to work in parallel with the progression of management.

**Conclusion**

Currently, there are several investigational methods available that provide somewhat limited, but nevertheless adequate, information regarding the management outcomes of CVD. We believe that the reason for developing significantly distinct investigation methods is the diversity of ways in which CVD manifests in each individual and therefore methods like CEAP and VCSS, which are dynamic and patient- and physician-centered, appear to provide sufficient data to evaluate the efficacy of CVD management. A better understanding of the etiopathogenesis of CVD will facilitate further modification of investigational methods.

**Keywords:** chronic venous disease; guidelines; scoring systems; classifications

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**References**

La maladie veineuse chronique (MVC) représente toujours une charge significative pour les patients et les médecins puisque la façon la plus efficace de la prendre en charge reste difficile à déterminer. De nombreuses recherches ont montré que les résultats à long terme de méthodes de traitement très différentes, y compris des techniques invasives ou non invasives, étaient globalement identiques. Les argumentaires de ces techniques sont très différents les uns des autres, ce qui pose la question de la validité des méthodes utilisées pour calculer la sévérité de la MVC avant et après traitement. Le fait que cette sévérité puisse être évaluée de différentes façons est un des principaux obstacles au recueil de données pertinentes sur la prise en charge de la MVC. La qualité de vie du patient est probablement le critère le plus important mais il existe des paramètres centrés sur le médecin et basés principalement sur la physiopathologie de la maladie. De plus, la variabilité de la perception de la maladie dans les différents groupes de patients est une autre difficulté pour tirer des conclusions des diverses études. Ces systèmes de cotation doivent être dynamiques puisque la prise en charge de la MVC prend en compte le traitement des problèmes cliniques qui apparaissent sur une longue période. La compréhension de ces obstacles a entraîné de nombreuses modifications des systèmes de cotation précédents. Cependant, même aujourd’hui, les versions modifiées prises séparément ne parviennent pas à indiquer la sévérité de la maladie dans sa totalité. Il faut donc créer un système de cotation universel dans la MVC qui réunirait les critères les plus importants de toutes les méthodes d’investigation actuelles.
Chronic venous disease (CVD) is highly prevalent in the Western world and is associated with significant costs. Outcome studies promote understanding of the disease and the results of treatment. The use of patient-reported outcomes (PROs) by patients suffering from CVD is thought to be an important step forward in the assessment of patients’ perspective of the disease, quality-of-life (QOL) questionnaires being the best adapted instruments. Despite some limitations in the evidence available, there are eight criteria that provide an explicit framework for selecting PROs. Eight simple questions can help choose PROs, each question being linked to a specific criterion: appropriateness, reliability, validity, responsiveness, precision, interpretability, acceptability, and feasibility. Concerning the evaluation of patients’ QOL, two types of questionnaires can be used: generic and disease-specific. Generic instruments are designed to be applicable across a wide range of populations and treatments and are able to capture information on a broad range of aspects of health status and disease consequences. On the other hand, specific QOL instruments have been developed to provide patients’ perception of a specific disease, health problem, or intervention. In the latest guidelines published in the area of venous disease, it is clear that PRO assessment is already a priority, CIVIQ (Chronic Venous Disease Questionnaire) being the most recent and validated specific questionnaire with psychometric criteria.

It is widely recognized that traditional outcomes (clinical and laboratory measures) need to be complemented by measures that focus on patients’ concerns in order to evaluate interventions and identify more appropriate forms of health care. In this regard, patient-reported outcomes are unique and complementary indicators of traditional outcomes, providing additional information about disease and treatment efficacy.
regard, PROs are unique and complementary indicators of traditional outcomes, providing additional information about disease and treatment efficacy.4

Types and application of PROs
An enormous range of instruments in the form of questionnaires, interviews, and rating and assessment forms were created with the objective of evaluating states of health and illness from a patient’s perspective.7 Maybe because no exclusive and rigid classification exists, several authors have proposed dividing these instruments into seven major types (Table I).7

With regard to their application, PROs can be applied in different fields, particularly generic and disease-specific QOL questionnaires. However, the majority have been developed for clinical trials and economic evaluation to assess the healthcare needs of populations and to assist health-care professionals in the treatment of individual patients.

Clinical trials and cost-utility studies
The number of trials and cost-utility studies that include PRO measures is progressively increasing. Nowadays, the majority of studies include determinations of health status or QOL, unless these outcomes are not relevant to the study.7 PRO measures have been used as primary outcomes (eg, in the evaluation of a drug’s treatment effect on QOL) in randomized controlled trials or in nonrandomized research designs, despite their more complex interpretation.7

In a different way, when investigators need to obtain an overall evidence value for a health-care intervention that allows comparisons with other interventions, in the same treatment area or across areas, outcomes in the form of utilities are required. The most widely known form of a summary value for the purpose of comparing treatments is the quality-adjusted life year (QALY).7

Assessing health-care needs of populations
Apart from conventional data such as mortality and morbidity rates, there are other measures that may also indicate health-care needs. Among them, PRO measures provide a feasible and valid measure of health status, particularly if such assessments are based on questionnaires with proven acceptability. There is growing evidence reinforcing the idea that poor scores on health-status measures may be associated with elevated rates of subsequent health service use and mortality.7

Health authorities and those responsible for purchasing or providing health care are increasingly expected to base their decisions about health-care resource allocation on evidence, and PRO measures add invaluable material to existing sources of health status information, helping these decision-makers.7

Even though the value of patients’ input is acknowledged, there is some resistance to including PROs as one of the key sources of information among health-care decision-makers owing to issues related to the measurement and interpretation of patients’ perspective.8

Individual patient care
PROs offer an important aid to physicians in patient care. Self-completed questionnaires, with proven reliability and validity, offer quick and consistent evidence of a patient’s view about his health that complements the clinical data of physicians.7 Using PROs, health-care professionals can screen health problems that would otherwise not be apparent and can monitor the progression of disease as perceived by the patient and the outcomes of any treatment.7 Nevertheless, it is necessary to consider that in the context of clinical care, an individual score is less precise than the one obtained for a group of patients.7 As a consequence, the applicability of PROs in individual patient care is more difficult.7

<table>
<thead>
<tr>
<th>Type of PRO</th>
<th>Examples of this type of PRO</th>
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<tbody>
<tr>
<td>Generic</td>
<td>Medical Outcomes Study 36-Item Short Form health survey, Functional Limitations Profile</td>
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<tr>
<td>Disease-specific</td>
<td>Asthma Quality of Life Questionnaire, Arthritis Impact Measurement Scales</td>
</tr>
<tr>
<td>Population-, site-, or region-specific</td>
<td>Child Health and Illness Profile-Child Edition, Oxford Hip Score, Shoulder Disability Questionnaire</td>
</tr>
<tr>
<td>Dimension-specific</td>
<td>Beck Depression Inventory, McGill Pain Questionnaire</td>
</tr>
<tr>
<td>Summary items</td>
<td>Question about limiting, long-standing illness in the General Household Survey</td>
</tr>
<tr>
<td>Individualized</td>
<td>McMaster Toronto Arthritis Patient Preference Disability Questionnaire, Schedule for the Evaluation of Individual Quality of Life</td>
</tr>
<tr>
<td>Utility measures</td>
<td>EuroQol 5D, Health Utility Index</td>
</tr>
</tbody>
</table>

Table I. The seven major types of PROs and examples of each type.

Abbreviations: PRO, patient-reported outcome.
Choosing a PRO
Despite clear limitations in the evidence available, there are eight criteria that provide an explicit framework for selecting PROs. Eight simple questions can be formulated in order to help choose PROs, each question being linked to a specific criterion (Table II).7,9

Chronic venous disease
In Western countries, chronic venous disease (CVD) has a high prevalence and morbidity. Recent data indicate that the prevalence of varicose veins is estimated to be 25% to 33% in women and 10% to 20% in men.10 The prevalence of more severe stages of CVD, such as edema and skin changes (hyperpigmentation and eczema), varies from 3% to 11% of the population,10 and it is estimated that the assessment and treatment of patients with varicose veins and leg ulcers consume 2% to 3% of the health budget of Western countries.11 For instance, the costs of dressing a leg ulcer in the UK National Health Service reaches £6000 to £20 000 per year.12

As a result of the complexity and chronicity of venous disease, the application of PROs to patients suffering from CVD is thought to be an important step forward in the assessment of patients’ perspective of disease, QOL questionnaires being the most adapted instruments.1 The use of QOL questionnaires in patients suffering from CVD can provide important information regarding disease burden in patients that would otherwise be unobtainable.1,13

Quality of life
QOL is a broad ranging concept that has been changing over the years and, depending on the perspective, different definitions of QOL are acceptable. In 1947, the World Health Organization (WHO) defined QOL as a “state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity,” while, in 1984, Calman wrote: “Quality of life measures the difference, or the gap, at a particular period of time, between the hopes and expectations of the individual and that individual’s experiences.” Although no single definition or theory can be considered more correct than another, it is clear that the WHO provides the most coherent and comprehensive definition. In 1998, the WHO updated its definition of QOL to: “Individuals’ perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person’s physical health, psychological state, level of independence, social relationships, person-

<table>
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<tr>
<th>PRO selection criterion</th>
<th>Comment on criterion</th>
<th>Question to ask when choosing a PRO</th>
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<tbody>
<tr>
<td>Appropriateness</td>
<td>This criterion requires that investigators consider as directly as possible how well the content of an instrument corresponds to the intended purpose of their specific trial.7</td>
<td>Is the content of the instrument appropriate to the questions which the clinical trial is intended to address?</td>
</tr>
<tr>
<td>Reliability</td>
<td>Reliability is related to the reproducibility and internal consistency of an instrument. It assesses the extent to which the instrument is free from random error and can be considered as the amount of a score that is signal rather than noise.</td>
<td>Does the instrument produce results that are reproducible and internally consistent?</td>
</tr>
<tr>
<td>Validity</td>
<td>The validity of a measure is an assessment of the extent to which it measures what it purports to measure.7</td>
<td>Does the instrument measure what it claims to measure?</td>
</tr>
<tr>
<td>Responsiveness</td>
<td>It is essential for a health status questionnaire to detect important changes over time within individuals, which might reflect therapeutic effects. Responsiveness could be defined as the ability of an instrument to detect important clinical changes.</td>
<td>Does the instrument detect changes over time that matter to patients?</td>
</tr>
<tr>
<td>Precision</td>
<td>Precision refers to the number of distinctions that an instrument makes. It is related to the capacity to make numerous distinctions.</td>
<td>How precise are the scores of the instrument?</td>
</tr>
<tr>
<td>Interpretability</td>
<td>Interpretability is concerned with how meaningful the scores of an instrument are.</td>
<td>How interpretable are the scores of an instrument?</td>
</tr>
<tr>
<td>Acceptability</td>
<td>This criterion requires that an instrument is acceptable to patients.</td>
<td>Is the instrument acceptable to patients?</td>
</tr>
<tr>
<td>Feasibility</td>
<td>Feasibility is related to the impact of different PRO measures upon staff and researchers in collecting and processing information. The time and resources required to collect, process, and analyze a PRO measure.</td>
<td>Is the instrument easy to administer and process?</td>
</tr>
</tbody>
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Table II. PRO selection criteria and questions to ask when choosing a PRO. Based on reference 7.
Abbreviations: PRO, patient-reported outcome.
al beliefs and their relationship to salient features of their environment. This definition is the one most commonly used. Regarding clinical trials and health-care interventions, QOL is considered an important outcome that provides an overall assessment of the effect of both the disease and treatment on the patient. More simply, QOL has been defined as: “the extent to which our hopes and ambitions are matched by experience,” while improving patients’ QOL through medical care has been defined as: “narrow[ing] the gap between a patient’s hopes and expectations and what actually happens.” Concerning the evaluation of patients’ QOL, two types of questionnaires can be used: generic and disease-specific QOL questionnaires.

Generic quality-of-life questionnaires

Generic instruments are designed to be applicable across a broad range of populations and treatments and to be able to capture information on a wide range of aspects of health status and disease consequences. Due to their broad range of content and more general applicability, these instruments have been used more frequently than disease-specific instruments to assess health status of nonhospital samples in the general population.

Regarding generic QOL questionnaires, those most used and mentioned in international literature are: the Medical Outcomes Study Short Form 36-item (SF-36) health survey, Nottingham Health Profile (NHP), Functional Limitations Profile (FLP), Sickness Impact Profile (SIP), and EuroQol Instrument (EQ-5D). For example, SF-36 was designed to be used in clinical practice and research, health policy evaluations, and general population surveys. This questionnaire has 36 items that measure health status in eight categories. Another example is FLP, which is the English version of SIP, which was developed in the United States. It consists of 136 items grouped into 12 categories.

Advantages

Regarding the advantages and drawbacks of the different types of questionnaires, what will be mentioned are suppositions rather than firm statements, and the generalizations are difficult to substantiate because there is little evidence available, particularly from direct comparisons of their use. The main advantage of generic instruments is that they can be used for a broad range of health problems, allowing comparisons between different treatments and their respective effectiveness. With a generic QOL questionnaire, it is possible to calculate “normative values,” which give scores for patients with distinct health problems and allow comparisons to be made. Another advantage of the generic QOL questionnaire is its broad scope, so they may be of value in detecting the unexpected positive or negative effects of an intervention. Finally, even though they cover a wide range of different categories, they are relatively economic and reduce patients’ burden.

Drawbacks

By including items that cover a broad range of aspects about health status, generic instruments lose some level of detail in terms of a particular disease’s relevance.

Disease-specific quality-of-life questionnaires

Specific QOL instruments have been developed to provide patients’ perception of a specific disease, health problem, or intervention. An example is the Asthma Quality of Life Questionnaire that contains 32 questions in four different categories or the Arthritis Impact Measurement Scale, a self-administered questionnaire for use in rheumatic diseases, which covers 45 items in nine categories. Both instruments clearly have a specific range of applications in each disease, respectively. In relation to CVD, some specific instruments exist: the Chronic Venous disease Questionnaire (CIVIQ), the Venous Insufficiency Epidemiological and economic Study (VEINES), the Aberdeen Varicose Vein Questionnaire (AVVQ), and the Charing Cross Venous Ulceration Questionnaire (CXVUQ).

Advantages

The content of specific QOL questionnaires is relevant for a particular disease, as all items of the instrument were developed specifically to assess a specific health problem. These instruments are more likely to detect important changes that occur over time in a particular disease. Another important advantage is that with specific QOL questionnaires, acceptability and conclusion rates are usually higher compared with generic instruments. This occurs because specific instruments are clearly relevant to a patient’s problem.

Drawbacks

Generally, it is not possible to use a disease-specific instrument in samples of patients that do not have a specific condition or disease because logically it is not possible to ask a person about a problem or condition that he/she does not have. In the same way, disease-specific instruments do not allow easy comparison between outcomes of different treatments for patients with different health problems. This situation is a problem when certain data from a general sample of healthy individuals must be compared with the health status scores of a study or when comparative judgments on the relative effectiveness of different treatments in different diseases are required in order to propose resource allocation.

Another problem of disease-specific instruments is that they may not capture certain data associated with a disease or a treatment when these have not been anticipated. An instrument with a broader scope may be more effective in detecting unexpected effects.

CIVIQ

In CVD, there are several reasons, mostly linked to disease characteristics, which justify the creation and development of a specific questionnaire to assess patients’ QOL. Among
them, we could highlight that CVD has a high and growing prevalence, as one in two adults complains about symptoms and/or signs of the disease. CVD has a considerable socioeconomic impact representing around 1% to 3% of the total health-care budget of countries with developed health-care systems, and CVD’s negative impact on patients’ daily life is usually underestimated by physicians due to its indolent clinical course and the absence of a relation between symptoms and signs. Taking into account these previously mentioned reasons and knowing that disease-specific instruments are usually more sensitive in key categories of QOL than generic scales, it was crucial to develop a specific QOL questionnaire for widespread use in CVD.

The CIVIQ questionnaire was developed and validated (relevance, acceptability, reliability, construct validity, and sensitivity) by a French group in 1996. Later in 2000, it was translated, adapted to the cultural habits of 18 countries, and then revalidated in different languages to give high significant validity and reproducibility (P<0.0001). The CIVIQ questionnaire is a 20-item self-reported instrument that includes four categories of questions: physical (4 items), psychological (9 items), social (3 items), and pain (4 items). Its score ranges from 0, the worst score, to 100, the best.

As the number of publications including the CIVIQ questionnaire has increased, it has become possible to confirm that it is extremely reliable, easy to use, and shows an excellent ability to detect changes of state among CVD patients. For all these reasons, the CIVIQ questionnaire represents a step forward in the assessment of patients’ QOL in CVD.

**PROs and current guidelines in venous disease**

In the latest guidelines published in venous disease, it is evident that PRO assessment is already a priority and that several instruments are mentioned. In the third edition of the *Handbook of Venous Disorders: Guidelines of the American Venous Forum*, there are 2 chapters dedicated to PROs in which the CIVIQ questionnaire is mentioned (chapter 62, “Outcome assessment in acute venous disease,” and chapter 63, “Outcome assessment in chronic venous disease.”). Chapter 61 details how the CIVIQ questionnaire has been successfully validated in several groups of patients, including those with severe postthrombotic syndrome. In chapter 62, the CIVIQ questionnaire is referred to as one of the four venous disease–specific instruments developed for evaluating CVD and one with excellent internal consistency and stability.

The latest guidelines of European Venous Forum, *Management of Chronic Venous Disorders of the Lower Limbs: Guidelines according to Scientific Evidence*, also highlight PROs. In the part on the assessment of efficacy of therapies, it states that QOL has been assessed by generic and disease-specific measures in CVD patients. However, considering the fact that specific complaints of patients with CVD have not been identified by currently used generic QOL questionnaires, specific questionnaires have been developed to assess the functional and psychological effects of venous disease. The unique specific QOL instrument mentioned is the CIVIQ questionnaire, which is referred to as the most recent, validated questionnaire with psychometric criteria, including reliability, content, construct validity, and responsiveness.

**Conclusion**

In the last few years, the rapid expansion in the assessment of outcomes from the patients’ perspective has resulted in hundreds of instruments. In this time, PROs have undergone an incredible evolution from being nearly “irrelevant” to being a “priority” in population health assessment and are now being applied in various contexts, particularly generic and disease-specific QOL questionnaires. This marked improvement in the importance of PROs is related to their potential for monitoring disease progression and response to treatment, assessing quality of care provided, and providing important information that is not properly expressed by the statistical values of morbidity and mortality that physicians traditionally use. Furthermore, these data are assessed directly from the patients’ perspective and are invaluable outcomes that complement more conventional data, such as clinical and laboratory measures.

In CVD, the use of QOL instruments has already proven to be reliable and much appreciated by practitioners, especially the CIVIQ questionnaire, which is a disease-specific instrument that has been validated in different languages with high significant validity and reproducibility. Furthermore, this questionnaire has been used successfully in different situations: in the RELIEF (Reflux assEssment and quaLity of lIfe improvEment with micronized Flavonoids) study, a worldwide study performed in CVD; the Vein Consult Program, an international educational survey carried out under the auspices of the International Union of Phlebology (UIP [Union Internationale de Phlébologie]); and the study, “What do you know about your veins?”, the first Portuguese study to evaluate the impact of CVD on the QOL of the Portuguese population.

All the cumulative experience with the CIVIQ questionnaire, in addition to the knowledge that QOL is likely to be responsive to clinical changes, leads us to conclude that PROs, especially CIVIQ, could be widely used by the medical community to improve patient health care by eliciting earlier diagnosis and treatment, particularly in CVD.
La maladie veineuse chronique (MVC) est hautement prévalente dans les pays occidentaux et est associée à des coûts significatifs. Les études d’impact insistent sur la compréhension de la maladie et les résultats du traitement. L’utilisation des résultats rapportés par les patients (RRP) permet de faire un important pas en avant dans l’évaluation de la perspective de sa maladie par le patient, les questionnaires de qualité de vie (QDV) étant les instruments les mieux adaptés. Malgré des limites concernant les preuves disponibles, huit critères fournissent un cadre explicite pour sélectionner les RRP. Huit questions simples peuvent aider à choisir les RRP, chaque question étant reliée à un critère spécifique : opportunité, fiabilité, validité, réactivité, précision, capacité d’interprétation, acceptabilité et faisabilité. En ce qui concerne l’évaluation de la QDV des patients, deux types de questionnaires peuvent être utilisés : les questionnaires génériques et ceux spécifiques à la maladie. Les instruments génériques sont conçus pour être utilisés pour toutes sortes de population et de traitements et peuvent collecter de l’information sur l’état de santé et les conséquences de la maladie. Par ailleurs, des instruments spécifiques de la QDV ont été développés pour donner aux patients la mesure d’une maladie spécifique, d’un problème de santé ou d’un traitement. Dans les dernières recommandations publiées sur la maladie veineuse, il est clair que l’évaluation des RRP est déjà une priorité, le questionnaire CIVIQ (Chronic Venous disease Questionnaire) étant le questionnaire spécifique le plus récent doté de critères psychométriques.
The Grades of Recommendation Assessment, Development and Evaluation (GRADE) system was developed in 2004 as an attempt to provide systematic and explicit methods of building guidelines for clinicians. The system was adopted by the American College of Chest Physicians (ACCP) in the latest edition of the ACCP Evidence-Based Clinical Practice Guidelines on Antithrombotic and Thrombolytic Therapy. The ACCP grades its recommendations both in terms of the strength of recommendation (1 = strong; 2 = weak) and of the quality of evidence (A = high; B = intermediate; and C = low). Although the numbers and letters used in the grading system remain unchanged compared with previous editions, there have been significant changes in the underlying definitions and criteria leading to these grading recommendations over the latest few editions of these guidelines. In particular, the methodological quality of available studies is no longer the only determinant of the quality of evidence, while the strength of a recommendation is no longer only based on the quality of evidence, but also on the balance between benefit and harm, on values and preferences, and on cost. Guideline users need to be aware of the way grades of recommendations are obtained in order to fully understand and take advantage of guidelines for their patients’ care.

Many guidelines are published by medical societies, public health agencies, or journals around the world. Unfortunately, they often use different ways of rating the quality of evidence and of grading the strength of recommendations. As a result, clinicians, patients, managers of health-care systems, and policy makers face challenges in understanding the messages that grading systems are trying to convey when they need to compare alternative strategies and diagnostic tests and weigh up their benefits and downsides. A lot of effort has been spent coming up with the much anticipated criteria and approaches for an optimal worldwide grading system, reflecting greater awareness of the variability in patients’ values and preferences. In addition to minimizing bias and aiding interpretation, following a systematic approach to grad-

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www.medicographia.com
ing the strength of recommendations enhances the usefulness of clinical guidelines. The Grades of Recommendation Assessment, Development and Evaluation (GRADE) system was developed in 2004 as an attempt to provide systematic and explicit methods of making judgements.1

The American College of Chest Physicians (ACCP) Evidence-Based Practice Guidelines on Antithrombotic and Thrombolytic Therapy is “bedtime reading work” for physicians involved in the management of patients with venous disease. In its latest edition released in 2008, the ACCP committee of methodologists and guideline developers adopted a grading system based on the GRADE approach. The criteria, displayed in Table I, have been placed in an order that approximates their relative significance.2 The ACCP team in charge of the task agreed on these criteria for defining a grading system that would be consistent with the latest developments in the field.

In this paper, we will focus on the GRADE approach to recommendations and on how the GRADE system categorizes the quality of evidence and strength of recommendations, and explore the implications of these grading categories for patients, clinicians, and policy makers.

What makes a good grading system?
For an optimal grading system, decisions regarding quality of evidence should be separate from those regarding strength of recommendations. Not all grading systems succeed in doing this. For instance, early systems of grading methodological quality relied primarily on the basic study design (ie, randomized control trials [RCTs] or observational studies). Study design was used by these early grading systems as an essential component for determining our level of confidence in estimates of beneficial and adverse treatment effects.

Over the past few years, there has been increased awareness of a number of other factors that require consideration in order for us to be confident in the estimation of benefits, risks, burden, and costs.

What differentiates GRADE from previous grading systems?
Compared with previous/other grading systems, the GRADE working group wanted a system that used explicit definitions of strength of recommendation and of quality of evidence. Their system takes into account various factors that can affect the quality of evidence, not only the study design and quality, but also study limitations, imprecision, and possible confounding. It assesses the relative importance of outcomes, clarifies the judgement on benefit and harm by providing an explicit definition for trade-offs between benefit and harm, and includes judgement on whether the incremental health benefits are worth the costs. Finally, it provides a clear interpretation of the recommendation.

Table I. Criteria for an optimal grading system, according to the ACCP Task Force.
Abbreviations: ACCP, American College of Chest Physicians.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Separation of grades of recommendations from quality of evidence</td>
</tr>
<tr>
<td>2</td>
<td>Simplicity and transparency for clinician consumer</td>
</tr>
<tr>
<td>3</td>
<td>Sufficient (but not too many) categories</td>
</tr>
<tr>
<td>4</td>
<td>Explicitness of methodology for guideline developers</td>
</tr>
<tr>
<td>5</td>
<td>Simplicity for guideline developers</td>
</tr>
<tr>
<td>6</td>
<td>Consistent with general trends in grading systems</td>
</tr>
<tr>
<td>7</td>
<td>Explicit approach to different levels of evidence for different outcomes</td>
</tr>
</tbody>
</table>

Quality of evidence in the GRADE system
“Quality of evidence” reflects the extent to which the confidence in an estimate of an effect is adequate in supporting a recommendation. To achieve transparency and simplicity, the GRADE system classifies the quality of evidence at one of four levels: high, moderate, low, and very low.

As with early systems for grading the quality of evidence, GRADE initially focuses on study design. In this way, RCTs without limitations constitute high-quality evidence, observational studies without special strengths or with important limitations constitute low-quality evidence, while any other study (case series) constitutes very low-quality evidence.

Negative factors affecting quality of evidence
There are, however, negative factors that affect the quality of evidence that can downgrade the quality of observational studies as well as RCTs:

a) Study limitations
If studies have major limitations that may bias their estimates of the treatment effect, confidence in the evidence decreases. Such limitations include a lack of allocation concealment, a lack of blinding, a significant number of patients lost to follow-up, failure in the intention-to-treat analysis, failure to report outcomes, and early ending of a study due to benefit.

Selected abbreviations and acronyms
ACCP American College of Chest Physicians
GRADE Grades of Recommendation Assessment, Development and Evaluation
RCT randomized controlled trial
VTE venous thromboembolism
b) Inconsistency of results
Heterogeneity or variability in results across studies suggests true differences in underlying treatment effect. This variability may come from differences in populations, interventions (larger effects with higher drug doses), or outcomes (decreasing treatment effect with time). The quality of evidence diminishes when there is heterogeneity of results, but investigators fail to identify a credible explanation.

c) Indirectness of evidence
Two types of indirectness of evidence addressed by the guideline developers are:
- When considering the use of one of two active drugs. In the absence of a randomized comparison of the drugs, randomized trials may compare one drug with placebo and the other with placebo. This leads to a comparison of the magnitude of effect of both drugs, therefore, the evidence is of a lower quality than it would have been had there been a direct head-to-head comparison of the drugs.
- When there are discrepancies between the population, intervention, intervention comparator, or outcome of interest and those included in the applicable studies.

d) Imprecision
The quality of evidence is reduced in cases where studies use relatively few patients or have few events, leading to wide confidence intervals.

e) Publication bias
Not reporting studies, especially those that show no effect, downgrades the quality of evidence. A prototypical situation would be when published evidence is limited to a small number of trials, all of which are financed by industry.

Positive factors affecting quality of evidence
Conversely, there are also some factors that might increase quality of evidence.

a) Even though observational studies usually result in a low quality of evidence, strong observational studies can methodologically provide large or very large and consistent estimates of the magnitude of a treatment effect. This gives good confidence in the results, in particular when there is no major plausible confounder. The larger the magnitude of effect, the stronger the evidence becomes.

b) If all the plausible confounders tend to reduce the estimation of the effect, the confidence in the evidence increases.

c) Finally, the existence of a dose-response gradient also increases confidence in the authenticity of the effect.

The GRADE system has four levels of quality of evidence: A = high; B = moderate; C = low; and D = very low. A “high quality of evidence” means that further research is unlikely to change our confidence in the estimate of effect. A “moderate quality of evidence” means that further higher-quality research may have an impact on our confidence in the estimate of effect or to change this estimate. A “low quality of evidence” is used when further higher-quality research is likely to have an important impact on our confidence in the estimate of effect, or to change the estimate. Finally, the evidence is graded “very low” when any estimate of effect is highly uncertain.

Strength of a recommendation in the GRADE system
The “strength of recommendation” reflects the extent to which we can be confident that the desirable effects of adhering to an intervention outweigh its undesirable effects. There are two grades of recommendations: strong (1) and weak (2). A strong recommendation means that benefits clearly outweigh risks, while a weak recommendation means that one can’t be sure that benefits outweigh risks.

The strength of a recommendation is no longer exclusively based on the quality of evidence. It is also determined by:

a) The balance between desirable and undesirable effects
This takes into account the incidence rate of the target event, the importance of the event that treatment prevents, the magnitude of treatment effect, the precision of estimates of treatment effect, and the risks associated with therapy.

b) Burdens of therapy

c) Costs
A judgement may be made on whether the net benefits are worth the incremental cost.

d) Patients’ varying values and preferences
Strong and weak recommendations may be interpreted as follows. If the recommendation is strong, benefits clearly outweigh risks, or vice versa, and apply to most patients in most circumstances. The use of a decision aid tool is not needed, and the patient only needs to be informed. In the case of a weak recommendation, the best action may differ and other alternatives may be equally reasonable. In this case, decision aid tools may be useful, and the physician needs to make sure that the choice is in accordance with the patient’s values. While almost all patients would make the same choice for strong recommendations, the choice may significantly vary for a weak recommendation.

Rating evidence and recommendations in venous disease
The GRADE system has been implemented in the 8th edition of the ACCP Evidence-Based Clinical Practice Guidelines on Antithrombotic and Thrombolytic Therapy. There are two levels of strength of recommendation (1 = strong, “We recommend”; and 2 = weak, “We suggest”), and three levels of quality of evidence (A = high; B = moderate; and C = low).
In 2001, for first time,6 the primacy of the judgement on the efficacy of an intervention was replaced by the importance of the methodological quality of available studies. Back in 1989,7 panelists would first rate the level of evidence from “large trials with clear-cut results and low risk of error” to “case series only,” and the grade of recommendation depended on the level of evidence, with no other parameter taken into account. Interestingly, until the 6th edition in 2001, the quality of evidence rating preceded the strength of recommendation rating in the grading system (from A1 to C2), and the assessment of quality of evidence was mainly based on study design, the highest level being limited to RCTs and meta-analyses of RCTs.

Therefore, six different grades may be used to grade a recommendation (Table II).7 The reader needs to understand the importance changes made in the way the final recommendations are obtained. The most dramatic change is that the strength of recommendation is no longer based, as was the case only a few years ago, solely on the type and quality of available studies. Back in 1989,7 panelists would first rate the level of evidence from “large trials with clear-cut results and low risk of error” to “case series only,” and the grade of recommendation depended on the level of evidence, with no other parameter taken into account. Interestingly, until the 6th edition in 2001, the quality of evidence rating preceded the strength of recommendation rating in the grading system (from A1 to C2), and the assessment of quality of evidence was mainly based on study design, the highest level being limited to RCTs and meta-analyses of RCTs.

### Table II. ACCP grades for recommendations.

**Abbreviations:** ACCP, American College of Chest Physicians; RCT, randomized controlled trial.


<table>
<thead>
<tr>
<th>Grade</th>
<th>Benefit vs risk</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Benefits clearly outweigh risks, or vice versa; recommendation can apply to most patients in most circumstances.</td>
<td>RCTs with no important limitations, or exceptionally strong evidence from observational studies. Further research is unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>1B</td>
<td>Benefits balanced with risks; best action may differ depending on circumstances or patient/society values.</td>
<td>RCTs with no important limitations, or exceptionally strong evidence from observational studies. Further research is unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>1C</td>
<td>At least one critical outcome from RCTs with serious flaws, observational studies, case series, or indirect evidence. Further higher-quality research may have an important impact.</td>
<td>At least one critical outcome from RCTs with serious flaws, observational studies, case series, or indirect evidence. Further higher-quality research may have an important impact.</td>
</tr>
<tr>
<td>2A</td>
<td>Benefits balanced with risks; other alternatives may be equally reasonable.</td>
<td>RCTs with no important limitations, or exceptionally strong evidence from observational studies. Further research is unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>2B</td>
<td>At least one critical outcome from RCTs with serious flaws, observational studies, case series, or indirect evidence. Further higher-quality research may have an important impact.</td>
<td>RCTs with no important limitations, or exceptionally strong evidence from observational studies. Further research is unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>2C</td>
<td>Benefits balanced with risks; other alternatives may be equally reasonable.</td>
<td>At least one critical outcome from RCTs with serious flaws, observational studies, case series, or indirect evidence. Further higher-quality research may have an important impact.</td>
</tr>
</tbody>
</table>

The GRADE system certainly represents a major improvement in clinical guideline methodology. It provides the clinician with recommendations based not only on the methodological quality of available studies, but also on other important criteria (see above). However, one could consider that recommendations based on the GRADE system are more demanding for the reader. In fact, it is crucial for guideline users to carefully read and understand the way recommendations are made. Above all, to fully appraise a recommendation, they need to read not only the final summary sentence, but the whole text giving the explicit criteria leading to the recommendation.

### Limitations and misunderstandings

The GRADE system certainly represents a major improvement in clinical guideline methodology. It provides the clinician with recommendations based not only on the methodological quality of available studies, but also on other important criteria (see above). However, one could consider that recommendations based on the GRADE system are more demanding for the reader. In fact, it is crucial for guideline users to carefully read and understand the way recommendations are made. Above all, to fully appraise a recommendation, they need to read not only the final summary sentence, but the whole text giving the explicit criteria leading to the recommendation.

For example, the latest edition of the ACCP guidelines is often quoted as strongly recommending long-term treatment in patients who experience a first unprovoked deep vein throm-
basis or pulmonary embolism. However, the exact recommendation reads: “For patients with a first unprovoked VTE [venous thromboembolism], and in whom risk factors for bleeding are absent and for whom good anticoagulant monitoring is achievable, we recommend long-term treatment (Grade 1A).” In terms of values and preferences, this recommendation attaches a relatively high value to the prevention of recurrent VTE and a lower value to the burden of long-term anticoagulant therapy. This is obviously very different to the quick summary and reveals the thinking behind how decisions are made.\

Moreover, GRADE authors insist that recommendations apply to specific settings, groups of patients, and economic contexts. There may be significant variations across countries or hospitals that may influence the decision of whether to adhere to a recommendation. Costs, for example, as well as the way costs influence clinical decisions, differ widely between countries. Most of all, no recommendation can take into account all individual clinical circumstances. The ACCP guideline authors warn that any grade other than a grade 1A recommendation indicates that the authors acknowledge that other interpretations of evidence and other clinical policies may be appropriate. Furthermore, they suggest that even grade 1A recommendations may not apply to all patients and circumstances, either because of resource constraints or because of patients’ atypical values and preferences. Finally, physicians must use their judgement and consider local and individual circumstances along with their patients’ values and preferences to achieve the best-tailored decisions.

**Conclusion**
Clinical decision-making is not simple. Guidelines help clinicians and patients facing complex choices to choose informed options, to improve quality of care, and to make the best use of limited resources. The GRADE system provides a standardized and explicit way of compiling recommendations, of which physicians must be aware in order to fully make the most of guidelines in the care of their patients.

**Acknowledgements:** the author would like to thank Mrs Alavi for her useful assistance.

**References**

**Keywords:** evidence-based medicine; review; recommendations
SERVIER / UIP RESEARCH FELLOWSHIP

Objectives of the UIP/Servier Fellowship
The objectives come within the scope of the UIP goals and are threefold
▶ to encourage innovation and research in the field,
▶ to create vocations among young researchers,
▶ to advocate venous and lymphatic diseases as disabling diseases, reducing quality of life and expensive to treat.

Description of the UIP/Servier Fellowship
Every other year, the Prize is granted to a young candidate by a selection committee of reknown specialists for a research project in the field of venous or lymphatic diseases. The project can be fundamental or clinical. The amount of the research grant is 25 000 Euros

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2001: Tomasz URBANEK (Poland)

2003: Gemma Maria PASCUAL GONZALEZ (Spain)

2005: Gregory Thomas JONES (New Zealand)

2007: Caterina ROSI (Italy)

2009: Anwar AHMAD (UK)
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**How to apply:** Instructions available on the IOF Web site: [www.iофbonehealth.org](http://www.iофbonehealth.org) and [www.servier.com](http://www.servier.com).

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**Aim and grant:** This prize was set up to promote research in the field of metabolism and awards one gold medal (€20 000) and two silver medals, each worth €8000.

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**How to apply:** Instructions available from Prof Gaetano Crepaldi, The G.B. Morgagni Prizes Committee, Centro Studi per l’Invecchiamento, Ospedale Giustiniano, Via Giustiniani 2, 35128 Padova (Italy). E-mail: crepaldi.metabolism@unipd.it and [www.servier.com](http://www.servier.com).

**American Venous Forum**

**Aim and grant:** This grant for €20 000 was set up to promote the know-how of French experts in the fields of phlebology and vascular surgery and to encourage exchanges between Europe and the USA.

**Who may apply:** Young Fellows, under 45 years.

**How to apply:** Instructions available on the AVF Web site: [www.venous-info.com](http://www.venous-info.com) and on [www.servier.com](http://www.servier.com).

**Jean Delay Prize awarded by the World Psychiatric Association**

**Aim and grant:** This prize of €40 000 is intended as a reward for contributions fostering links between the clinical, biological, and social aspects of psychiatry, or between psychotherapy and pharmacotherapy.

**Who may apply:** Any individual who has made a major contribution in these fields or has built bridges between these domains is eligible to apply.

**How to apply:** Instructions available at [www.wpanet.org](http://www.wpanet.org) and [www.servier.com](http://www.servier.com).

For further information and deadline applications, please visit our Web site: [www.servier.com](http://www.servier.com).
Primary chronic venous disease (CVD) is defined as morphological and functional abnormalities of the venous system of long duration, manifested by symptoms, signs, or both. CVD is extremely common in most countries and has a considerable socioeconomic impact in Western countries. Venoactive drugs (VADs) are a heterogenic group of drugs of vegetal or synthetic origin. The objective of this article is to highlight the role and impact of VADs in the management of primary CVD according to recent European and American guidelines. Following analysis of the recent guidelines on primary CVD and their recommendations regarding the place of VADs in the management of primary CVD, three VADs were given the highest level of recommendation. Calcium dobesilate, micronized purified flavonoid fraction (MPFF), and hydroxyethylrutoside (ie, oxerutins) were assigned a Grade A recommendation, the highest level of recommendation by the International Consensus Statement (Siena, 2005) and the Consensus Statement led by Nicolaides in 2008, with regard to CVD-related symptoms. The guidelines detailed evidence of the efficacy of several VADs in CVD-related edema, and the efficacy of MPFF as an adjunct to standard treatment in the healing of venous ulcers. The use of MPFF and pentoxifylline in combination with compression in long-standing or large venous ulcers was recommended and assigned Grade 1B in the latest edition of the Handbook of Venous Disorders (2009). Suggestions regarding expected improvements in future guideline documents are also presented.
toms (A, asymptomatic). All classes of CVD can be associated with symptoms. Epidemiological studies have shown that CVD is extremely common in most countries and has a considerable socioeconomic impact in Western countries. In some studies, the majority of the adult population showed some degree of CVD. In the Edinburgh Vein Study, more than 80% of people aged 8 to 64 years had mild hyphen-web or reticular varices, while a study carried out in 24 Italian cities showed that only 3% of subjects examined were free of visible signs of CVD. In the San Diego Population Study, featuring 2211 people, visible disease was present in 84% of women and 57% of men.

Reported prevalences of the clinical manifestations of CVD vary widely. The prevalence of edema and skin changes, such as hyperpigmentation and eczema, due to CVD varies from 3% to 11% of the population. In Western countries, it is estimated that 1% of the population will develop one or more episode(s) of leg ulcer.

The economic cost of CVD is thought to be very high. It has been estimated that the cost of managing CVD represents 1%-3% of the total health-care budget in Western countries, with treatment costs amounting to approximately US $3 billion annually in the USA. In addition, venous leg ulcers cause the loss of some 2 million working days per year in the USA.

Venoactive drugs

Venoactive drugs (VADs) are a heterogenic group of drugs of vegetal or synthetic origin. They can be classified in 4 major categories (Table II): benzopyrones; saponins; other plant extracts; and synthetics drugs.

### Table I. Clinical descriptions of the revised CEAP classification.

Abbreviations: CEAP, Clinical-Etiological-Anatomical-Pathophysiological; CVD, chronic venous disease.

<table>
<thead>
<tr>
<th>CEAP classification</th>
<th>Clinical description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C0</td>
<td>No visible or palpable signs of venous disease</td>
</tr>
<tr>
<td>C1</td>
<td>Telangiectasias or reticular veins</td>
</tr>
<tr>
<td>C2</td>
<td>Varicose veins; distinguished from reticular veins by a diameter of 3 mm or more</td>
</tr>
<tr>
<td>C3</td>
<td>Edema</td>
</tr>
<tr>
<td>C4</td>
<td>Changes in skin and subcutaneous tissue secondary to CVD, divided into 2 sub-classes to better define the differing severity of venous disease: C4a: pigmentation or eczema C4b: lipodermatosclerosis or atrophie blanche</td>
</tr>
<tr>
<td>C5</td>
<td>Healed venous ulcer</td>
</tr>
<tr>
<td>C6</td>
<td>Active venous ulcer</td>
</tr>
</tbody>
</table>

### Main categories of VADs

#### Benzopyrones

There are two classes of VAD in this category: alpha-benzopyrones and gamma-benzopyrones. Coumarin is the most notable alpha-benzopyrone. Gamma-benzopyrones, which are also known as flavonoids, include diosmin, micronized purified flavonoid fraction (MPFF), and rutosides, such as rutin, troxerutin, and hydroxyethylrutosides (HRs).

#### Saponins

This category includes horse chestnut seed extract (HCSE) and Ruscus extracts.

#### Other plant extracts

All these plant extracts, such as extracts of Ginkgo biloba, Centella asiatica, and Hamamelis, contain flavonoids, such as anthocyans and proanthochyanidins, together with other active substances.

#### Synthetic drugs

The principal synthetic drugs are calcium dobesilate, naftazone, and benzaron.

### Mode of action of VADs

VADs have multiple effects on the venous system. The mode of action varies depending on the drug. They attenuate macrocirculatory changes in the venous wall and venous valves that cause hemodynamic disturbances leading to venous hypertension and attenuate microcirculatory effects of venous hypertension that lead to venous microangiopathy. They also have effects, eg, anti-inflammatory, on venous tone, venous wall, venous valves, capillary leakage, the lymphatic network, and hemorrheologic parameters.

Recently, attention has focused on the roles of oxidative stress and inflammation in causing adverse changes in the vein wall and venous valves, which lead to subsequent skin changes. Some VADs have free-radical scavenging actions and can interfere with inflammatory cascades, notably in the case of MPFF by inhibiting leukocyte-endothelial interactions.

### Abbreviations

- **CEAP**: Clinical-Etiological-Anatomical-Pathophysiological
- **CIVIQ**: Chronic Venous Disease Questionnaire
- **CONSORT**: CONSOLidated standards of Reporting Trials
- **CVD**: chronic venous disease
- **GRADE**: Grades of Recommendation Assessment, Development and Evaluation
- **HCSE**: horse chestnut seed extract
- **HR**: hydroxyethylrutoside
- **MPFF**: micronized purified flavonoid fraction
- **QOL**: quality of life
- **RCT**: randomized controlled trial
- **SF-12**: Short Form 12-item [health survey]
- **SF-36**: Short Form 36-item [health survey]
- **VAD**: venoactive drug

### Selected Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEAP</td>
<td>Clinical-Etiological-Anatomical-Pathophysiological</td>
</tr>
<tr>
<td>CIVIQ</td>
<td>Chronic Venous Disease Questionnaire</td>
</tr>
<tr>
<td>CONSORT</td>
<td>CONSOLidated standards of Reporting Trials</td>
</tr>
<tr>
<td>CVD</td>
<td>chronic venous disease</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grades of Recommendation Assessment, Development and Evaluation</td>
</tr>
<tr>
<td>HCSE</td>
<td>horse chestnut seed extract</td>
</tr>
<tr>
<td>HR</td>
<td>hydroxyethylrutoside</td>
</tr>
<tr>
<td>MPFF</td>
<td>micronized purified flavonoid fraction</td>
</tr>
<tr>
<td>QOL</td>
<td>quality of life</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>SF-12</td>
<td>Short Form 12-item [health survey]</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short Form 36-item [health survey]</td>
</tr>
<tr>
<td>VAD</td>
<td>venoactive drug</td>
</tr>
</tbody>
</table>
imal studies suggest that these actions of VADs can protect the vein wall and valves from deleterious changes, with the potential for slowing or preventing the progression of primary CVD.14

Numerous randomized, controlled, double-blind studies have demonstrated the improvement of CVD-related symptoms by VADs, and the antiedema effect of VADs has also been objectively demonstrated in double-blind trials. The main indications for VADs are symptoms related to CVD and edema in patients at any stage of CVD. VADs may also have a role in the treatment of leg ulcers. A meta-analysis of MPFF, from the benzopyrone category of VADs, confirmed its value as an adjunct to standard treatment for healing leg ulcers.15

This article will assess the role and impact of VADs in the management of primary CVD in light of the recent European and American guidelines. Two guidelines have been published recently discussing the therapeutic efficacy of VADs on CVD-related symptoms and venous edema.11,16,17 The latest edition of the Handbook of Venous Disorders: Guidelines of the American Venous Forum18 includes a chapter on drug treatment of varicose veins, venous edema, and ulcers. Elsewhere, Perrin and Ramelet18 have proposed their own recommendations for the use of VADs, based on the principle of the GRADE (Grades of Recommendation Assessment, Development and Evaluation) system.

**Therapeutic efficacy of VADs and impact on guidelines**
A Cochrane review of VADs by Martinez et al (2005) examined the efficacy of such drugs in detail.20 Clinical trials of a range of different VADs were analyzed. Studies of HCSE were excluded because they were covered in a separate Cochrane review (see below).21 The authors identified 110 randomized, placebo-controlled trials, 44 of which were included in the final analysis. Studies were classified level A (low risk of bias), level B (moderate risk of bias), or level C (high risk of bias). A wide range of outcome variables, including objective signs and subjective symptoms, were analyzed using a random effects statistical model. For every outcome variable except venous ulcer, the analyses showed significant treatment benefits for VADs compared with placebo when analyzed as either a dichotomous or a continuous variable, or both in some cases. The analyses showed that VADs had significant treatment benefits compared with placebo with regard to pain, cramps, heaviness, and sensations of swelling and paresthesia, despite a lack of homogeneity between trials.19 The only nonsignificant effects were for venous ulcer, the analyses showed significant treatment benefits for VADs compared with placebo when analyzed as either a dichotomous or a continuous variable, or both in some cases. The analyses showed that VADs had significant treatment benefits compared with placebo with regard to pain, cramps, heaviness, and sensations of swelling and paresthesia, despite a lack of homogeneity between trials. The only nonsignificant effects were for venous ulcer, itching assessed as a continuous variable, and paresthesias assessed as a continuous variable. For edema (relative risk [RR], 0.72; 95% confidence interval [CI], 0.65-0.81), trophic disorders (RR, 0.88; 95% CI, 0.83-0.94), and restless legs (RR, 0.84; 95% CI, 0.74-0.95), the analyses showed a significant benefit with VAD treatment, with no evidence of heterogeneity among the studies. This was in contrast to most of the analyses, which showed evidence of heterogeneity.19

### Table II. Classification of the main venoactive drugs

<table>
<thead>
<tr>
<th>Group</th>
<th>Substance</th>
<th>Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzopyrones</td>
<td>Coumarin</td>
<td>Melilot (Melilotus officinalis)</td>
</tr>
<tr>
<td>Alpha-benzopyrones</td>
<td></td>
<td>Woodruff (Asperula odorata)</td>
</tr>
<tr>
<td>Gamma-benzopyrones (flavonoids)</td>
<td>Diosmin</td>
<td>Ciprus sp (Sophora japonica)</td>
</tr>
<tr>
<td></td>
<td>Micronised purified flavonoid fraction (MPFF)</td>
<td>Rutaceae aurantiae</td>
</tr>
<tr>
<td></td>
<td>Rutin and rutosides</td>
<td>Sophora japonica</td>
</tr>
<tr>
<td></td>
<td>O-(β-hydroxyethyl)-rutosides</td>
<td>Eucalyptus sp</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fagopyrum esculentum</td>
</tr>
<tr>
<td>Saponins</td>
<td>Escin</td>
<td>Horse chestnut (Aesculus hippocastanum)</td>
</tr>
<tr>
<td></td>
<td>Ruscus extract</td>
<td>Butcher’s broom (Ruscus aculeatus)</td>
</tr>
<tr>
<td>Other plant extracts</td>
<td>Anthocyanins</td>
<td>Bilberry (Vaccinium myrtillus)</td>
</tr>
<tr>
<td></td>
<td>Proanthocyanidins (oligomers)</td>
<td>Grape pips (Vitis vinifera)</td>
</tr>
<tr>
<td></td>
<td>Extracts of ginkgo, heptaminol, and troxerutin</td>
<td>Maritime pine (Pinus maritima)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ginkgo biloba</td>
</tr>
<tr>
<td>Synthetic products</td>
<td>Calcium dobesilate</td>
<td>Synthetic</td>
</tr>
<tr>
<td></td>
<td>Benzaron</td>
<td>Synthetic</td>
</tr>
<tr>
<td></td>
<td>Naftazone</td>
<td>Synthetic</td>
</tr>
</tbody>
</table>

**Recent guidelines on VADs**
Numerous randomized, controlled, double-blind studies have demonstrated the improvement of CVD-related symptoms by VADs, and the antiedema effect of VADs has also been objectively demonstrated in double-blind trials. The main indications for VADs are symptoms related to CVD and edema in patients at any stage of CVD. VADs may also have a role in the treatment of leg ulcers. A meta-analysis of MPFF, from the benzopyrone category of VADs, confirmed its value as an adjunct to standard treatment for healing leg ulcers.
The Cochrane review of horse chestnut seed extract. Randomized clinical trials (RCTs) of HCSE, whose main active component is the triterpenic saponin escin, were the subject of a Cochrane review published by Pittler and Ernst in 2006. Twenty-nine studies were identified, 17 of which were included in the review. The authors concluded that HCSE was efficacious compared with placebo and of similar efficacy to compression therapy in the short-term treatment of CVD. Adverse effects were generally mild and infrequent, so the overall risk/benefit ratio for HCSE was favorable. On the basis of the publications, including Cochrane reviews, VADs as a whole have been assigned a weak recommendation (Grade 2B) for improving symptoms and edema associated with CVD in the latest edition of the Handbook of Venous Disorders.

As a result of the analysis, calcium dobesilate, MPFF, and HR were all assigned the highest level (Grade A) recommendation, while HCSE and Ruscus extracts were assigned Grade B (Table III).

Management of CVD of the lower limbs
A consensus statement on the management of chronic venous disorders of the lower limbs was prepared in 2008 under the auspices of several learned societies, including the American Venous Forum, the American College of Phlebology, and the European Venous Forum. A set of guidelines arising from the consensus statement covers most aspects of the management of CVD, including investigations, treatment, and management strategy.

With respect to VADs, the guidelines largely summarized and endorsed the positive findings of the recent Cochrane reviews and the grades of recommendation of the International Consensus Statement of Siena. These guidelines used the same grading system as the Siena Consensus, except for meta-analyses, which were considered to have a grade B level of evidence. Outcomes this time included not only symptoms, but also edema and venous ulcer healing.

Table IV summarizes VAD effects on symptoms, edema, and skin changes by category of drug. Grade A status was assigned to three VADs: calcium dobesilate, MPFF, and HR, but only symptoms were considered. Generally, no reservations were voiced regarding the safety of VADs, except for a couple of specific cases: coumarin-rutin and benzaron (hepatotoxicity) and calcium dobesilate (some cases of transient agranulocytosis were reported from 1992 to 2005).

Guidelines and VADs for venous edema
Although edema is a nonspecific sign, it is one of the most frequent and typical symptoms and signs in CVD. All other causes of edema should be excluded to confirm its venous origin. CVD-related edema is described as sporadic, unilateral or bilateral, and limited to the legs, which may also involve proximal parts of the lower extremities. It is enhanced by prolonged orthostatic posture, and improved by leg elevation.

Several well-conducted controlled trials versus placebo or stockings have shown the efficacy of oral VADs such as MPFF, rutosides, HCSE, calcium dobesilate, proanthocyanidines, and coumarin-rutin. In these trials, the evaluation of antiedematous efficacy was based on objective measures, such as measurement of leg circumference, strain-gauge plethysmography, and water displacement. Results of meta-analyses, including the Cochrane reviews, have confirmed the antiedematous efficacy of VADs.

The guidelines highlighted the evidence of efficacy of several VADs (calcium dobesilate, MPFF, rutosides, HCSE, proanthocyanidines, and coumarin + rutin) in CVD-related edema, and

<table>
<thead>
<tr>
<th>Compound</th>
<th>Recommendation</th>
<th>Number of influential studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium dobesilate</td>
<td>Grade A</td>
<td>3</td>
</tr>
<tr>
<td>MPFF</td>
<td>Grade A</td>
<td>4</td>
</tr>
<tr>
<td>Hydroxyethylrutosides</td>
<td>Grade A</td>
<td>5</td>
</tr>
<tr>
<td>HCSE (escin)</td>
<td>Grade B</td>
<td>1</td>
</tr>
<tr>
<td>Ruscus extracts</td>
<td>Grade B</td>
<td>2</td>
</tr>
<tr>
<td>Diosmin (synthetic)</td>
<td>Grade C</td>
<td>1</td>
</tr>
<tr>
<td>Troxerutin</td>
<td>Grade C</td>
<td>2</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>Grade C</td>
<td>2</td>
</tr>
<tr>
<td>Proanthocyanidines</td>
<td>Grade C</td>
<td>2</td>
</tr>
<tr>
<td>Troxerutin + coumarin</td>
<td>Grade C</td>
<td>1</td>
</tr>
<tr>
<td>Centella asiatica</td>
<td>Grade C</td>
<td>1</td>
</tr>
<tr>
<td>Naftazone</td>
<td>Grade C</td>
<td>1</td>
</tr>
</tbody>
</table>

Table III. Grades of recommendation of the International Consensus Statement. Based on data from reference 11. Abbreviations: HCSE, horse chestnut seed extract; MPFF, micronized purified flavonoid fraction; RCT, randomized clinical trial.
the efficacy of MPFF as an adjunct to standard treatment in the healing of venous ulcers (although only symptoms have been considered in the assignation of a grade of recommendation) (Table IV).

Guidelines and VADs for venous leg ulcers

Acceleration of venous leg ulcer healing (stage C6 of the CEAP classification) has been demonstrated in a double-blind study using MPFF in combination with compression. This result was confirmed in 2005 by a meta-analysis of five trials in which MPFF was used as an adjunct to standard compression treatment in 723 class C6 patients. HCSE and HRs were not superior to compression in advanced chronic venous insufficiency or in the prevention of venous ulcer recurrence.

The latest edition (3rd edition) of the Handbook of Venous Disorders includes a chapter on drug treatment of varicose veins, venous edema, and ulcers. The method of determining the strength and quality of recommendations in this document was based on GRADE. GRADE recommendations consist of a number ("1" for a "strong" or "we recommend" recommendation, and "2" for a "weak" or "we suggest" recommendation) and a letter, which refers to the "quality of evidence" supporting the recommendation. There are three grades: "A" for high-quality evidence; "B" for moderate-quality evidence; and "C" for low-quality evidence. The GRADE system is based on the distinction between the strength of a recommendation and the quality of the evidence on which it is based, although in practice the separation is not absolute and the quality of evidence is an important determinant of the strength of a GRADE recommendation.

The use of MPFF in combination with compression in long-standing or large venous ulcers was recommended and assigned a grade 1B. The evidence for the addition of MPFF is based on the meta-analysis of 5 trials with MPFF as an adjunct to standard compression treatment in 723 patients mentioned above. At 6 months, complete ulcer healing had occurred in 61% of MPFF patients and in 48% of control patients (RR reduction for persistent ulceration, 32%; 95% CI, 3% to 70%; P=0.03). Subgroup analyses suggested that the benefits of MPFF were greatest in ulcers ≥5 cm² and in ulcers of >6 months’ duration.

Pentoxifylline, a drug indicated for the management of peripheral arterial disease, has also been used in the management of venous ulcers. Its use in combination with compression in long-standing or large venous ulcers has a grade 1B recommendation.

Tentative recommendations for VADs

Building on recent reviews and meta-analyses and taking into account additional evidence that was either not available or not included in them, Perrin and Ramelet have proposed tentative recommendations for the use of VADs based on the principles of the GRADE system. They stress that these recommendations reflect their own opinions and judgements, and have not been endorsed by learned societies or other organizations to date.

These recommendations are summarized in Table V (page 290). A grade 1B was assigned to MPFF and rutosides for the relief of symptoms associated with CVD in C0s to C6s pa-
tients with CVD-related edema. A grade 1B recommendation was also given for the use of MPFF as an adjunct to compressive and local therapy for healing large or long-standing venous ulcers. 18

Future challenges17,19

◆ Assessing the efficacy of treatment

An update of the guidelines for testing drugs for CVD27 is needed to enable the pharmaceutical industry to invest the resources required to perform large and definitive clinical trials, with a view to improving the recommendations. Recommendations are useful to clinicians and organizations involved in decision-making in this important field. Such guidelines could:

◆ Reiterate the basic principles that should prevail when reporting (and setting up) a clinical trial, using the CONSORT (CONsolidated standards of Reporting Trials) statement. This statement is designed to help authors and investigators file reports using a published checklist and flow diagram,28 available on the Web site: www.consort-statement.org.
◆ Describe patients comprehensively at study selection using the advanced CEAP classification. This implies that not only the “C” (Clinical) of CEAP should be completed, but also items “E” (Etiological), “A” (Anatomical), and “P” (Pathophysiological), together with mandatory duplex color, with or without plethysmography (a level 2 investigation, according to Eklöf et al)2, and in certain cases, invasive (level 3) investigations; the addition of new descriptors for the “E”, “A”, and “P” items when no venous abnormality is identified may be useful when describing patients with leg complaints, but no visible or detectable signs of CVD.9
◆ Promote the use of validated tools to assess symptoms,20 edema,21 and venous leg ulcer.17
◆ Reach a consensus on the standard use of dressings, compression therapy, and local antiseptics in venous leg ulcer.

In addition, there is a need for consensus on the following end points:

◆ Symptoms: how great does the decrease on the visual analogue scale have to be in order to consider there is clinical improvement?
◆ Edema: how great does the reduction in ankle volume have to be in order to consider it as clinically relevant?
◆ Varicose veins: which criteria should be used to consider whether a drug treatment for varicose veins works?
◆ Venous leg ulceration: when should we consider the ulcer to be healed?

◆ Adapted patient-reported outcome tools

Early stages of CVD are difficult to assess objectively, particularly in CO, patients, as symptoms are by definition subjective. The assessment of patients’ perception of their quality of life (QOL) is desirable in such cases. Both generic and specific QOL scales should be used: the generic SF-12 (Short Form 12-item [health survey]) or SF-36 (Short Form 36-item [health survey]) are validated tools that could be adopted, while if a specific scale is required, the CIVIQ-20 (Chronic Venous disease Questionnaire) QOL is a good choice. It has been extensively validated,22 is the scale most often used in CVD, and has currently been validated in 13 languages.

Conclusion

The role of VADs in the prevention of the natural history of CVD progression remains to be fully determined: are all VADs able to protect CVD patients against the progression of the disease to severe complications? The use of human-sized experimental animals, such as pigs, might allow for better evaluation of the key processes involved.23 Where grading is concerned, consensus adoption of a simple and universally understood system of grading is desirable.24

References


Table V. Summary of tentative recommendations, according to Perrin and Ramalet.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Venoactive drug</th>
<th>Recommendation for use</th>
<th>Quality of evidence</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relief of symptoms associated with CVD in CO, to C6, patients with CVD-related edema</td>
<td>MPFF</td>
<td>Strong</td>
<td>Moderate</td>
<td>1B</td>
</tr>
<tr>
<td>Rutosides</td>
<td>Strong</td>
<td>Moderate</td>
<td>1B</td>
<td></td>
</tr>
<tr>
<td>Calcium dobesilate</td>
<td>Weak</td>
<td>Moderate</td>
<td>2B</td>
<td></td>
</tr>
<tr>
<td>HCSE</td>
<td>Weak</td>
<td>Low</td>
<td>2C</td>
<td></td>
</tr>
<tr>
<td>Ruscus extracts</td>
<td>Weak</td>
<td>Low</td>
<td>2C</td>
<td></td>
</tr>
<tr>
<td>Healing of large or long-standing venous ulcers as an adjunct to compression and local therapy</td>
<td>MPFF</td>
<td>Strong</td>
<td>Moderate</td>
<td>1B</td>
</tr>
</tbody>
</table>

Abbreviations: CVD, chronic venous disease; HCSE, horse chestnut seed extract; MPFF, micronized purified flavonoid fraction.

L’objectif de cet article est de souligner le rôle et l’impact des MVA dans la prise en charge de la maladie veineuse chronique primaire (MVC). Les médicaments veino-actifs (MVA) sont un groupe hétérogène de médicaments d’origine végétale longue durée touchant le système veineux, se manifestant par des symptômes, des signes ou les deux. La MVC est définie par des anomalies morphologiques et fonctionnelles de la circulation veineuse. Les critères d’admissibilité pour les MVA sont le respect de certaines conditions formelles d’étude. Les preuves de l’efficacité de plusieurs MVA dans l’œdème lié à la MVC et l’efficacité de la FFPM comme additif au traitement standard dans la cicatrisation des ulcères veineux. L’utilisation de la FFPM et de la pentoxifylline associées à la compression dans les ulcères importants ou anciens a été recommandée et classée en grade 1B dans la dernière édition du Hanbook de Venous Disorders (2009). Nous présentons également des améliorations possibles qui devraient être apportées aux futures recommandations.

**Keywords:** chronic venous disease; venoactive drug; guidelines; grade of recommendation

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**Recommandations européennes et américaines sur la maladie veineuse chronique primaire : Quoi de neuf ?**

La maladie veineuse chronique primaire (MVC) se définit par des anomalies morphologiques et fonctionnelles de longue durée touchant le système veineux, se manifestant par des symptômes, des signes ou les deux. La MVC est extrêmement courante dans la plupart des pays et son impact socio-économique est considérable dans les pays occidentaux. Les médicaments vaso-actifs (MVA) sont un groupe hétérogène de médicaments d’origine végétale ou synthétique. L’objectif de cet article est de souligner le rôle de l’impact des MVA dans la prise en charge de la MVC primaire selon les recommandations européennes et américaines récentes. En suivant les analyses des recommandations récentes sur la MVC primaire et leurs directives concernant la place des MVA dans la prise en charge de la MVC primaire, trois MVA ont obtenu le plus haut niveau de recommandation. Le dobesilate de calcium, la fraction flavonique purifiée micronisée (FFPM) et l’hydroxyethylrutoside (c’est-à-dire les oxérutines) ont été classés en recommandation de grade A, le plus haut niveau de recommandation du communiqué de Consensus International (International Consensus Statement) (Sienne, 2005) et du Communiqué de Consensus (Consensus Statement) dirigé par Nicolaides en 2008, en ce qui concerne les symptômes liés à la MVC. Les recommandations ont détaillé les preuves de l’efficacité de plusieurs MVA dans l’œdème lié à la MVC et l’efficacité de la FFPM comme additif au traitement standard dans la cicatrisation des ulcères veineux. L’utilisation de la FFPM et de la pentoxifylline associées à la compression dans les ulcères importants ou anciens a été recommandée et classée en grade 1B dans la dernière édition du Hanbook de Venous Disorders (2009). Nous présentons également des améliorations possibles qui devraient être apportées aux futures recommandations.
Are chronic venous disease guidelines adapted to daily practice?

CVD guidelines are based on well-designed studies that use control groups, have multiple planned follow-up visits, and are performed by skilled personnel in dedicated facilities. However, studies are not perfect and limitations exist: exclusion because of old age, inability or unwillingness to comply with monitoring, and contraindications. So, do CVD guidelines reflect what goes on in real life and are they applicable and useful in all cases of CVD patient management? Our experts give their views.

1. K. A. Aal, *Egypt*
2. H. S. Caldevilla, *Argentina*
3. R. Costa-Val, *Brazil*
4. H. S. Yuwono, *Indonesia*
5. H. N. T. H. Le, *Vietnam*
6. S. M. Kulišić, *Croatia*
7. A. Puskás, *Romania*
8. K. Roztočil, *Czech Republic*
10. I. S. Escotto, *Mexico*
11. J.-F. Uhl, *France*
12. I. A. Zolotukhin, *Russia*
Before answering this question we must first identify our needs. These begin with a comprehensive study that would provide a simple classification of all the signs and symptoms of chronic venous insufficiency. Using evidence-based studies, it would identify and standardize the most appropriate investigation(s) and treatment(s) for each disease stage. It would also be readily applicable in daily practice and sufficiently malleable to incorporate the latest data. The recent guidelines largely satisfy this wish list. They represent a huge amount of work by international experts. They incorporate recent medical and surgical treatments, such as radiofrequency ablation, laser ablation, and foam sclerotherapy, and compare their results with conventional techniques.

But supposing we wished to use the recent Clinical-Etiological-Anatomical-Pathophysiological (CEAP) classification to describe a typical case, how would the classification present it? For example, for a patient with painful swelling of the leg, varicose veins, lipodermatosclerosis, and active ulceration, who had a duplex scan on May 17, 2004, showing axial reflux of the great saphenous vein above and below the knee, incompetent calf perforators, and axial reflux in the femoral and popliteal veins, with no signs of postthrombotic obstruction, we would need to write: C6,S, Ep , As,p,d, Pr in basic CEAP code, and C2,3,4b,6,S, Ep , As,p,d, Pr2,3,18,13,14 (2004-05-17, L II) in advanced CEAP code! These formulae are comprehensive in terms of provision of a detailed patient description for research purposes, but too complicated to be applied in routine practice, as shown by the fact that they were used in only 23% of studies in a recent Cochrane review. Some phlebologists also question their relevance to routine practice. The new guidelines have clearly shown that vasoactive drugs and compression are the cornerstones of treatment. Fitting and applying elastic hosiery can be problematic, however, in particular in the elderly, the obese, and those with painful ulcers. Cost and frequent renewal are other drawbacks.

In France, vasoactive drugs are recommended in symptomatic patients for a maximum duration of 3 months, except if symptoms recur on treatment withdrawal. This recommendation is driven by financial considerations in that vasoactive drugs are widely prescribed in France, where they represent a major drain on the health insurance system, double that in Germany, sevenfold that in Spain, and twentyfold that in Belgium. However, many questions remained unanswered, such as the recommended treatment duration and the management of hepatic and gastric side effects. Some manufacturers claim that long-term treatment makes their drugs more effective against hemorrhoids, but do not mention similar effects for chronic venous disease or varicose veins. The same applies to the treatment of lipodermatosclerosis (many patients complain of disfigurement after postthrombotic disease). Other topics on which we need more information are ulcer recurrence rates and evidence-based trials on methods of prevention.

Each new set of guidelines should make a point of recommending what further studies will be required in order to answer outstanding questions. Meanwhile, we recommend implementing the guidelines worldwide by contacting local societies and organizing frequent workshops (if possible, with research committees collecting data), which will allow improved prediction of ulcer healing, decreased health-care costs, and better quality of life.
If guidelines are understood to be the systematic development of recommendations to help doctors and patients take the best possible decisions in specific clinical circumstances, guidelines have a number of potential benefits, but also disadvantages.

**Benefits**
- Improved outcome
- Increased standardization of medical procedures
- Rejection of old, cost-ineffective treatments
- Scientific validation of diagnostic tests, treatments, and results
- Justification for reimbursement
- Protection of health-care professionals from malpractice suits.

**Disadvantages**
- Disincentive to come up with local solutions
- Absence of legal protection for doctors not following the guidelines
- Poor reproducibility of clinical trial settings in daily practice, due to:
  - Multiple comorbidity
  - Advanced age
  - Polypharmacy
  - Lack of social support
  - Incorrect information from patients about their diseases and treatments
  - Patients’ difficulty in perceiving symptoms and recognizing their importance, eg, “Doctor, are you sure I need to have so many tests and complex treatments because of my ulcer and swollen leg?”
  - Frequent history of treatment nonadherence.

Practicing doctors treating chronic venous disease have to contend with the fact that even with the correct diagnosis and most appropriate treatments, the guidelines are insufficient in themselves to guarantee improvement and control of the disease, in particular in the cases of recurrent varicose veins and postthrombotic syndrome. Payment and cost issues are the most frequently cited obstacles to guideline implementation, as much in venous disease as elsewhere. Stenting is impossible if nobody can afford it. If in a local institution there is no provision for the reimbursement of endovascular procedures, for instance, then there is no possibility of appropriate training and guideline implementation.

Venous disease tends to be cared for by a variety of specialists with different skills. Some may not trust their own ability to implement the guideline recommendations. For example, practice is likely to be biased, independently of the guidelines, by those who happen to specialize only in sclerotherapy or in surgery. Some guideline recommendations may be difficult to implement because of the intrinsic nature of the changes in practice required. Some evidence-based strategies may appear unconventional to certain practitioners, requiring the acquisition of new skills or equipment, and possibly system changes that are expensive or difficult to implement.

Many doctors consider that guidelines restrict their autonomy and flexibility, and depersonalize the doctor-patient relationship. Such doctors prefer to think of the individual patient in front of them, who is often very different from the “typical” patient in the clinical trials that generated the guidelines. Drawing on their own accumulated experience, these doctors often see a tenuous resemblance between “their” patients and those featured in the trials. They are therefore unsure that following the guidelines will necessarily improve their results.

Yet despite these impediments to their use, there is no doubt that, as in other areas, guidelines represent the way ahead in venous disease in terms of patient care, clinical efficacy, health-care costs, and quality of life. Indeed, we need more and better trials to increase the proportion of asymptomatic patients (currently <40%), so that doctors and their patients become confident about what to do. The future in chronic venous disease research lies in elucidating the genetics and epigenetics involved in the transmission, onset, and evolution of the disease. In a few years’ time, the guidelines may well be incorporating the benefits of a personalized healthcare approach made possible by “omic” insights (from genomics, epigenomics, proteomics, and the like) that predict the natural history of the disease in individual patients together with their response to specific treatments.

**References**
The latest guidelines published in journals such as International Angiology and Chest, and in the Handbook of Venous Disorders edited by Gloviczki, feature a new approach to the analysis of clinical trial data, classifying them into three levels of evidence (1, 2, and 3) and three grading treatment recommendations (A, B, and C), according to their impact on the prognosis and quality of life of patients with chronic venous disease (CVD).

Compression therapy is evaluated and classified by evidence grades A to C, depending on indication. It emerges as a well-established recommendation to be used at all stages of CVD. However, it is important to point out that it is often best combined with other treatments, in particular venotropic drugs and various surgical and minimally invasive techniques. Venotropics are a recommended treatment, although the indications for specific agents differ between the European and American guidelines.

Certain venotropics, in particular micronized purified flavonoid fraction (diosmin 450 mg plus hesperidin 50 mg [Daflon® 500 mg]), have well-established effects on symptoms such as pain, cramps, itching, leg heaviness, and restless legs. The American Venous Forum, responsible for the American guidelines, gives venotropics a 2A level recommendation in long-term ulcer therapy. The European guidelines, published in International Angiology on behalf of the International Union of Angiology, International Union of Phlebology, and European Venous Forum, recommend various venotropics for the signs and symptoms of CVD, including ulcers, with micronized purified flavonoid fraction being the only drug carrying a grade A recommendation for almost all signs and symptoms, except edema. The Handbook of Venous Disorders also awards micronized purified flavonoid fraction and pentoxifylline grade 2A recommendations for use in venous ulceration.

The discrepancies in venotropic indications are probably driven by the different experience with these drugs, which is considerably more extensive in Europe than in North America. In addition, the huge variety of apparently similar drugs with multiple differences in physicochemical properties represents a considerable obstacle to serious clinical and scientific analysis of their actions.

In Brazil, venotropics are commonly prescribed for almost all stages of CVD, including ulcers. There are evidence-based national guidelines for this purpose, designed to be applied in daily practice, enabling practitioners to offer their patients a better-grounded therapeutic choice. They recommend compression, venotropics, and surgery, often in combination, especially for the more severe stages of the disease. Indeed, much of the scientific activity undertaken by the Brazilian Angiology and Vascular Surgery Society (SBACV) consists of developing such guidelines within an overarching guideline project coordinated by the Brazilian Medical Association, designed to provide a scientific foundation to clinical practice in a range of areas, including CVD. There are already rumors that the Brazilian Health System will be taking the SBACV guidelines into account in its control of therapeutic procedures. In other words, the Society’s recommendations may soon become the foundation for the official regulation of CVD management by the world’s largest public health-care system. There can be no clearer indication of the importance of these scientific and institutional initiatives involving this challenging disease.

References

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Are chronic venous disease guidelines adapted to daily practice?
Phlebology has benefited from the general advance in vascular diagnostics and therapeutics achieved in the second half of the twentieth century. The lessons of multiple multicenter trials have been encapsulated in clinical guidelines that should accelerate the pace of clinical research by raising and standardizing the level of care worldwide, enabling new lessons to be learned more quickly, which can then be ploughed back into the recommendations to produce ever better informed and relevant updates.

Guidelines play a key socioeconomic role by standardizing best practice, ensuring that all patients with similar disease can expect to receive approximately similar treatment, and be reimbursed accordingly. They also encourage communication and cooperation between specialists, not only in the preparatory stages of elaborating the guidelines themselves, but also in encouraging their uptake by others, whether in journal articles, scientific meetings, or simply hospital case conferences and journal clubs. Guidelines provide a common descriptive language and a point of reference that allows specialists to compare like with like, rather than swap anecdotal, unextrapolative experiences, as tended to be the case in the past. In other words, guidelines are essential to scientific progress.

In chronic venous disease, as in any other area, guidelines need to follow a number of obvious quality criteria if they are to be fit for purpose: they must be robust, in other words based on the evidence contained in randomized controlled trials published in quality journals; they must be nonpartisan, representing a consensus view of best practice; and, perhaps most importantly, they should be updated at regular intervals, ideally by a data collection program incorporated within the guidelines themselves. An important word of warning, however, guidelines must always be applicable to routine clinical practice. They cannot be feasible only in an academic or clinical trial setting. If so, they remain sterile and fail as drivers of progress. This, unfortunately, has been the fate of many guidelines. Time management issues, staffing levels, sociocultural setting, economic and organizational environment—all need to be taken into account if guidelines are to fulfill their purpose.

Guidelines that are not informed by such considerations risk accusations of irrelevance, gathering dust on academia’s shelves. Some accusations go further, referring to potential limitations and possible patient harm. Patients on bed rest for more than 3 days at the Hasan Sadikin General Hospital (Bandung, Indonesia) did not benefit from antiplatelet agents: cases of deep vein thrombosis were confined almost entirely to gynecological patients with cancer.

Elastic compression stockings are a mandatory precaution for reducing the risk of postthrombotic syndrome. However, they find less favor among Indonesians than among inhabitants of more temperate climates. The stockings are difficult to wear in hot and sweaty conditions. This is an instance of a northern recommendation falling foul of a southern geographic location.

For more detailed information on this topic, we interviewed nine doctors treating chronic venous disease in four Bandung hospitals. Almost none ever follow the elastic compression stocking guideline. Only two sometimes implemented the guideline. This decision appeared to alienate all the doctors from the other recommendations in the guideline, with the result that they did not understand why they should follow any such guideline or feel obliged to do so. Instead, they manage their patients according to the relevant textbook and maintain that this produces acceptable results. In this instance, it could be concluded that despite all the arguments in favor of guidelines, there is little evidence of management failing without them.

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**References**

2. Prasetyo E. Deep vein thrombosis: Is malignancy the most dominant risk? Bandung, Indonesia: School of Medicine, Pajajaran University; 2007.

Are chronic venous disease guidelines adapted to daily practice?
The most recent guidelines for managing chronic venous disease (CVD), published in 2009 by the International Union of Angiology, represent a dramatic change in understanding and practice for Vietnam. Their major advantage is that they are grounded in robust scientific and clinical evidence that can be readily extrapolated into daily practice.

The most obvious use of the CEAP (Clinical-Etiological-Anatomical-Pathophysiological) classification is in differentiating between different types of patients. Of the many CVD classifications available, the CEAP is the most useful because it is based on the signs and symptoms characteristic of each stage of the disease course, from onset to ulceration. It provides practitioners and patients with a clear vision of the pathology and its natural history. Unsurprisingly, it has been rapidly adopted by Vietnamese specialists, who have incorporated it into most of the recent epidemiological studies conducted in this region.

CVD is caused by primary abnormalities of the vein wall and valves or secondary abnormalities resulting from deep vein thrombosis. These lead to reflux, obstruction, or both. In my many years of clinical practice, I have seen no case of a congenital malformation resulting in CVD.

CVD was once considered a disease with symptoms, but no signs, especially in the early stages, making it especially difficult to evaluate. Duplex ultrasound has since introduced a range of objective parameters and is the investigative technique most favored by Vietnamese specialists.

As well as providing an aid to diagnosis, the guidelines represent the first comprehensive review of CVD management. They provide an evidence-based evaluation of all CVD treatments. In particular, they discuss the mode of action and efficacy of venoactive drugs, concluding that most fail to meet the requisite criteria and that some should even be withdrawn. Only diosmin, for which there is objective evidence of efficacy and a relevant mode of action, is recommended for all stages of CVD, from incipient disease to ulceration. The guidelines thus provide specialists with an excellent diagnostic and therapeutic framework for their clinical practice.

An understanding of its pathology at the microcirculatory level explains why CVD is a progressive condition and hence requires venoactive treatment. Although surgery may be indicated in particular patients, venoactive drug therapy is essential in arresting changes in the venous microcirculation—a point still not fully appreciated by some members of the Vietnamese medical community. At teaching hospital level, however, diosmin + hesperidin is our first-line therapy in daily CVD practice, although we depart somewhat from the guidelines in tailoring the dosage to the patient’s weight. At the same time as raising awareness among our fellow practitioners, we are also attempting to highlight the profile of CVD among the general public, since this is essential if we are to improve understanding, diagnosis, and treatment of the disease.
Chronic venous disease (CVD) guidelines were developed to help physicians cope with a formidable spectrum of signs, symptoms, and therapeutic approaches. Each fresh revision has brought the guidelines that much closer to grassroots practice, to the extent that the current challenge for the phlebological community may no longer be, “How do we improve the guidelines?”, but, “How do we ensure that clinicians implement the guidelines in their daily practice?”.

Practical implementation of the guidelines requires a widely accepted classification system. The consolidation of several former systems into the Clinical-Etiological-Anatomical-Pathophysiological (CEAP) classification of CVD, revised in 2004, has achieved acceptance in all important international guidelines. It was a big step towards greater accuracy and consistency in diagnosis and better management. However, in Croatia, we have so far failed to convince all our colleagues to adopt the CEAP classification as the basis of the guidelines.

Reasons for this failure include:

- a clear lack of trained phlebologists to promote the guidelines;
- the impossibility of implementing all requisite treatment options within a single institution; and
- medical insurance restrictions that exclude CVD as a public health problem, meaning that the patients concerned are not the official responsibility of any institution or group and are therefore not treated according to international CVD guidelines.

In this setting of low CVD awareness and with our appointment as Croatia’s national reference center pending, our department has decided to issue some basic therapy recommendations and supervise their implementation, before producing complete national guidelines based on the CEAP classification.

The following recommendations constitute our first draft:

1. Compression therapy controls most symptoms of acute and chronic venous disease, slows disease progression, and prevents deep vein thrombosis (DVT) in bedridden patients.
2. Sclerotherapy is suitable for the treatment of smaller varicose veins, reticular veins, and telangiectasiae. It should be avoided in large veins, in the vicinity of small and great saphenous veins, and in perforators, owing to the risk of deep vein thrombosis. It is not an etiological treatment for varicose veins and cannot prevent the emergence of new varicose veins.
3. Surgical options include phlebectomy, stripping, perforator ligation (if it enhances function), paratibial fasciotomy, and ulcer grafting.
4. Medication comprises drugs with synthetic or naturally occurring active ingredients that act on capillary permeability and/or venous tone to relieve chronic venous hypertension.
5. Physical therapy consists of various massage and lymphatic drainage techniques that may temporarily relieve symptoms, provided they are always combined with compression.
6. Local dermatitis therapy is based on physiological skin care, antimicrobial and anti-inflammatory ointments, and corticosteroids. Proper wound care includes debridement of necrotic and infected tissue, exudate control, wound protection, and pain relief. The choice of wound dressing depends on the wound itself, surrounding skin characteristics, allergies, and availability.
7. Prevention includes exercise, compression, and micronized purified flavonoid fraction therapy, all of which are significantly cost-effective.

We shall be following up these basic recommendations by:

- formally educating clinicians in the implementation of the CEAP classification for all their CVD patients; and
- providing continuing medical education courses on the pathophysiology of CVD and the advanced treatment options available.

A huge amount of work remains to be done in this field, especially in Croatia. But it is the only solution for improving the management of CVD and patients’ quality of life.
Are chronic venous disease guidelines adapted to daily practice?

Chronic venous disease (CVD) has a high prevalence in the general population and as such represents a major socioeconomic burden. Quality of life in the later stages is distressing: patients with venous ulcers report a quality of life similar to that of patients in heart failure.

CVD is usually caused by primary abnormalities of the vein wall and valves and/or secondary abnormalities resulting from previous deep venous thrombosis (DVT), leading to reflux, obstruction, or both. Congenital malformation is a rare cause.

The good news is that major progress has been made in the last few years in diagnosis, prevention, and treatment. Recommendations are now available for the management and prevention of CVD in recently developed guidelines drawn up in the US and Europe. Physicians caring for patients with venous disease have two important documents at their disposal: “Management of Chronic Venous Disorders of the Lower Limbs: Guidelines According to Scientific Evidence,” published in International Angiology in 2008;1 and “Antithrombotic Therapy for Venous Thromboembolic Disease,” from the American College of Chest Physicians (ACCP) 8th Consensus Conference in 2008.2

So, do these guidelines reflect real life and are they applicable and useful in everyday CVD management?

Answers in the affirmative highlight the systematic approach adopted in the guidelines, with recommendations based on literature evidence and on studies selected for their impeccable design, rigorous criteria, and follow-up visits performed by skilled investigators working in dedicated facilities. Levels of evidence range from 1 to 3, and recommendations are graded A through C. Level 1 and Grade A refer to randomized controlled trials reporting clear-cut results applicable to everyday practice. The guidelines also include meta-analyses, but these need to be used with caution. Some meta-analyses contain studies that have been included without due care, ignore substantive issues and relevant variables, and use heterogeneous findings or interpret results with bias.1

Answers in the negative point to the high proportion of CVD patients excluded from clinical trials because of old age and an inability or unwillingness to comply with regular laboratory monitoring during therapy. Such studies often fail to reflect the reality of a regular outpatient clinic, in rural conditions, or routine general practice. Rarely is there a single test that can provide all the information needed to make a clinical decision and plan a management strategy. A number of patients are likely to require more than one investigation.1 In addition, such investigations may require expertise in ultrasonography/phlebology/vascular medicine that is lacking in many European countries. CVD awareness among general practitioners differs from country to country, and does so even among specialists, to the extent that the general situation is far from ideal. Studies also suggest that patient compliance with compression therapy is also very low in daily practice. In other words, there is a clear discrepancy between guideline recommendations and their application.

Daily phlebological practice remains remote from guideline recommendations in many European countries, making dissemination by field leaders of the essential information contained in these documents all the more crucial if we are to improve the lot of patients with CVD.

References
Clinical guidelines are generally designed with several aims in mind: to educate, to improve management standards, to eliminate inappropriate care, and to reduce costs. Their impact on the ground varies and is rarely satisfactory in all respects. Monitoring adherence to guidelines often reveals surprising gaps between evidence-based recommendations and actual clinical management. Notable examples have included the care of coronary artery disease and the treatment and prophylaxis of venous thromboembolism.1-3

A similar situation exists in the case of chronic venous disease (CVD). Analysis of venoactive drug prescribing by 2092 general practitioners and 432 vascular specialists in the Czech Republic4 showed significant divergence from the conclusions propounded in internationally accepted guidelines.5,6 Over half the drugs prescribed were supported by zero evidence of benefit in randomized controlled clinical trials or by minimal evidence of efficacy from other sources. Drugs with the strongest evidence of efficacy—diosmin-hesperidin (miconized purified flavonoid fraction [MPFF]), calcium dobesilate, hydroxyethylrutoside (oxerutins)—accounted for no more than 10% of overall prescriptions.

There are several reasons for poor guideline adherence. First, practitioner familiarity with the guidelines is low. Publication is insufficient in itself to produce awareness. Second, confidence in the guidelines is low. Adherence is significantly influenced by scientific evidence. Recommendations based on a large number of randomized controlled studies attract greater adherence than those based on expert opinion.7 Other reasons are more subjective, eg, the impression of a nonindividuated approach to the patient or a suspicion that certain recommendations pander to cost-control considerations. There can also be economic reasons for deviating from guidelines. Our own analysis highlighted the important role played in this regard by the reimbursement policy of insurance institutions. Thus, in the case of our study referred to above, prescriptions for cheaper drugs unsupported by evidence from randomized controlled trials were fully or partially reimbursed, in contrast with those for more expensive drugs whose use was backed by scientific evidence. An additional reason for guideline noncompliance, although probably theoretical in the context of CVD, is a fresh discovery—whether a new diagnostic approach or a promising treatment—that has yet to be incorporated in the official text.

Guidelines are most successfully introduced when they are easy to implement, not overly complex, and useful in daily clinical practice. Brief study of the official texts currently available on the treatment of patients with CVD5 confirms their ready applicability to routine clinical practice. All that it is required to circumvent the reasons for noncompliance outlined above is that these guidelines be regularly updated, integrated into continuing medical education programs, and broadcast by field leaders at every opportunity—whether at international meetings or at the grass roots departmental or practice level—with every opportunity for feedback.

**References**

A further consideration is that the studies undertaken in one country, and the guidelines that ensue, may require modification or adaptation before they can be applied in another country. This can be due to differences in patient types, skin types, thresholds of complaint, and many other factors.

Socioeconomic factors are not always helpful when implementing guideline protocols in investigations or treatment. Some practitioners also dislike the more detailed kinds of guidelines that convey, in their view, a cookbook approach to the practice of medicine, which inevitably downgrades the practitioner’s role to that of a technician.

Recommendations that fail to take due account of the evidence can result in suboptimal, ineffective, or harmful practice. Guidelines that are inflexible can have an impact opposite to that intended by leaving insufficient room for clinicians to tailor care to a patient’s personal circumstances and medical history. For these reasons, it is always preferable to promote guidelines as works in progress rather than as definitive statements, as snapshots in a continuously evolving state of the art rather than as pronouncements carved in stone. Guidelines must always be open to ready and rapid amendment in line with advances in basic and clinical research. Many specialists view them less as mandatory or compulsory than as compilations of advice and suggestion, grounded in the best available clinical evidence, to be resorted to in specific sets of circumstances.

In summary, clinical guidelines are excellent compendia of evidence-based medicine and have the potential not only to broaden patient access to optimal strategies, but also, at the socioeconomic level, to improve the cost-effectiveness of CVD management. However, practice guidelines can never substitute for the clinical judgment of a qualified health-care professional. My view, on balance, is one of qualified endorsement: “Yes, the CVD guidelines continue to be applicable to our daily practice in most cases.”

References
Guidelines for chronic venous disease (CVD) need to be considered first in terms of their strengths and then in terms of their weaknesses.

Strengths

The most important CVD guidelines were drawn up by panels of experts. As such, they enshrine an international consensus endorsed by major medical societies and organizations involved in the study and treatment of the disease. They draw upon the most relevant evidence-based studies published in the highest-rated international journals. In addition they grade their recommendations using a system similar to that already used in consecrated guidelines for the major specialties, all of which casts them in a robust scientific structure. As with guidelines in any specialty, the aim is to raise minimum standards among the various categories of healthcare professionals dealing with CVD by reducing subjectivity in diagnosis, treatment, and follow-up. Their main objective is to standardize knowledge and issue best-practice recommendations applicable to routine use.

Most guidelines have adopted well-established clinical classifications, for example the Clinical-Etiological-Anatomical-Pathophysiological (CEAP) system that standardizes disease presentations on the comprehensive basis of the four components indicated in its title. Other systems, such as the Venous Clinical Severity Score (VCSS), have been useful in handling large patient populations in clinical trials and also in evaluating treatment outcomes with greater objectivity.

The guidelines have also helped to elucidate the role and efficacy of specific venoactive drugs in managing the symptoms evaluated in particular studies. In the case of edema, for instance, the venoactive drug most strongly recommended for patients with C0 to C6 disease, including for primary venous ulcer healing, is micronized purified flavonoid fraction (diosmin + hesperidin), which is supported by good-quality evidence compared with other venoactive drugs.

Weaknesses

The range of possible clinical presentations in CVD is very wide. Many patients present with different stages of the disease in one or two lower limbs. Secondary CVD is more frequent in patients with postthrombotic syndrome, which represents a diagnostic and therapeutic challenge. The major guidelines have begun to issue recommendations on the diagnosis of acute deep vein thrombosis, drawing attention to the improved results that can be achieved with more invasive treatment. This can be expected to lower the frequency of this form of secondary CVD.

The guidelines fail to provide a convincing pathophysiological explanation for CVD recurrence in patients who have undergone open surgery or endovascular vein ablation. Nor do they supply clear guidance as to the optimal management of this stage of the disease.

Specialists continue to debate the place of hormone replacement therapy in menopausal patients with CVD. Guideline updates will need to incorporate conclusive recommendations as to patient identification and optimal treatment in this regard, given the rising incidence and prevalence of this combination in numerous populations.

Further study is also required of certain previously established risk factors for CVD, in particular age, being overweight, and female sex, given reports of the increasing prevalence of early CVD in women and the general impact of rising obesity levels in various young populations of both sexes.

Conclusion

CVD guidelines have fulfilled their brief of standardizing the diagnosis and management of most typical presentations of the disease. They simply need tweaking with input from methodologically stronger studies that address less typical disease presentations.

References

Chronic venous disease (CVD) guidelines based on carefully conducted therapeutic trials are very useful in clinical practice. They help us to make the best treatment choices, but there are two main limitations to their application in our daily practice: first, the limitations inherent in the evaluation tools on which they rely (primarily the Clinical-Etiological-Anatomical-Pathophysiological [CEAP] scoring system); and, second, the failure of clinical trials to be universally applicable.

Our main reference points when we use the CVD guidelines are the CEAP parameters: symptoms, clinical class, anatomical venous lesions, and their etiology (reflux or obstruction). Updated venous nomenclature has recently made it easier for CVD specialists to speak a common language.

But from our daily practice we also know that, for any given patient, other parameters are of great importance: way of life and occupation, number of hours during the day spent standing or walking, limitation of ankle movement, static foot disorders, concomitant treatments (hormones, in particular), heredity, and progression of CVD.

Any of these factors can impair venous return and quality of life. They are not usually taken into account in the evaluation tools used either to classify patients or to compare treatments. As a consequence, we don’t find them among the guideline parameters. It is also difficult to standardize venous investigations. The quantification of reflux and reproducibility of “provocative” maneuvers are rarely easy.

As for the second limitation, trials often exclude patients on the grounds of old age, contraindications to therapy, inability or unwillingness to comply with laboratory monitoring during therapy, and other criteria that apply to swathes of the routine population we are called upon to treat.

Our real-life patients do not necessarily fit the ideal clinical trial subject’s profile in other respects. International guidelines are always unlikely to provide an exact match to particular patients rooted in their given sociocultural characteristics, country, occupation, and language. This constitutes a major limitation.

Moreover, new treatments are continually appearing. Rigorous evaluation takes several years, during which time fresh techniques will have appeared, with the result that clinical research is forever playing catch-up. The guidelines therefore require continuous updating, which makes them difficult to apply in everyday clinical practice.

We should keep in mind that CVD is a complex and progressive disease that is both multifactorial and multidimensional, as well as particularly fast-moving. For these reasons CVD guidelines should not be considered as a set of directly applicable rules, but as general guides to good practice providing a conceptual reference frame for the most common cases. It is in the very nature of guidelines that they cannot fully take into account the inevitable specificities of individual patients.
The prevalence of chronic venous disease (CVD) is widespread. Epidemiologic data from industrialized countries, where studies have essentially been centered, indicate that the signs and symptoms of CVD can be found in up to 70%-80% of subjects in some populations, depending on age, gender, ethnicity, etc.

Such a vast pool of potential patients could never be catered for effectively by vascular specialists alone. That is why multidisciplinary competence is required, extending across numerous other specialties, including primary care. This cannot be achieved without the publication and dissemination of contemporary diagnostic and management standards. Hence, the need for guidelines that can be consulted by any healthcare professional called upon to care for a patient with CVD.

The development of the Clinical-Etiological-Anatomical-Pathophysiological (CEAP) classification was the first step in standardizing diagnosis. It proved highly successful and has become accepted worldwide. The next step was the development of guidelines intended to reduce the improper and unnecessary use of various diagnostic and treatment methods and to improve CVD care. We now have a number of comprehensive CVD guidelines available to us, headed by those proposed in 2008 by the expert group of Nicolaides et al., encompassing all aspects of the disease. Three years have passed since the publication of these guidelines, which has given us the time to consider their relevance to our daily practice.

There are two possible views that can be taken. The first is that of the doctors who manage CVD patients on a daily basis (phlebologists, angiologists, etc.). I believe that most of these specialists consider the guidelines as really useful tools for analyzing and systematizing their own approaches and improving their management of CVD. However, the alternative view is that shared by specialists for whom CVD is not central to their practice, even though, epidemiologically, they see and manage (at least in the initial stages) the majority of patients. These specialists are general surgeons, vascular surgeons, and general practitioners. As they are not usually involved in the routine treatment of CVD, they don’t only need a tool for analyzing and systematizing their management, but also clear, strong, and unequivocal recommendations as to how to respond to different clinical situations.

A good example of such a document would be the American College of Chest Physicians’ guidelines. Despite the vagueness and uncertainty of some of the recommendations they contain, most are direct and authoritative, enabling the doctor to make appropriate decisions. CVD guidelines, on the other hand, are less firm and clear-cut. They often fail to provide doctors with ready-made solutions for many clinical situations.

Even in the case of pharmacological therapy, where a high level of evidence exists for the efficacy of venoactive drugs, the current guidelines state that they “may be indicated” or “may be used.” It is probable that such advice, which fails to fully endorse the scientific evidence, will not prevent doctors reaching the right decision, assuming they have expert knowledge in phlebology. But if not, if phlebology is not central to their practice, it may lead them to withhold necessary and useful medication.

Good randomized controlled trials and reliable meta-analyses of the main CVD treatments are few and far between. They are therefore more essential than ever if the current guidelines are to gain in authority, weight, and decisiveness. What doctors need in their daily practice is not discussion, but practice-oriented guidelines as to how to respond to different clinical situations.

References
Chronic venous disease (CVD) is a common condition representing a spectrum of disorders. Much effort has been spent creating a common language, which is essential for the establishment of clinical practice guidelines. In addition to improved methods of defining CVD, there is now also increased understanding of the pathological processes involved in its development. Lack of venous tone, abnormal capillary permeability, and overloaded lymphatic vessels have been put forward as the mechanisms involved in the development of CVD. The leukocyte-endothelium interaction and its association with valvular damage is one of the earliest pathophysiological mechanisms at work in the disease. This has focused attention on Daflon 500 mg, the only available molecule whose activity is known to modify such inflammatory events. Besides its ability to increase venous tone, regulate capillary filtration, and speed up lymphatic drainage, it has been shown to reduce the interaction of leukocytes with the endothelium in acute venous hypertension and inflammation, and it is used clinically to treat CVD. Daflon 500 mg has been intensively investigated in well-designed clinical trials and is well tolerated. Micronization of the particle size of its components to <2 μm improves its oral absorption and bioavailability compared with those of nonmicronized diosmins. These characteristics explain why Daflon 500 mg is listed among the venoactive drugs in recent guidelines on the management of this disease.

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This article addresses some of the newer guidelines on venoactive drugs (VADs) in general, and Daflon 500 mg in particular, in the management of CVD to help clinicians better manage patients with CVD of the lower extremity. Intentionally, only primary CVD will be tackled in this review, putting postthrombotic venous disease aside.
What are the indications of Daflon 500 mg?
Daflon 500 mg, micronized purified flavonoid fraction (MPFF), consists of 90% diosmin and 10% other flavonoids (hesperidin, diosmetin, linarin, and isorhoifolin). Prescribing information may differ between countries, but in general Daflon 500 mg, which is available in more than 100 countries, is indicated as a first-line treatment of symptoms associated with any stage of CVD, and in lower limb edema. In more advanced disease stages, such as venous leg ulcer, Daflon 500 mg may be used in conjunction with sclerotherapy, surgery, and/or compression therapy, or as an alternative treatment when surgery is not indicated or is unfeasible.

Pathophysiology of primary CVD and targets for Daflon 500 mg treatment
Because they provide a rational explanation for the clinical benefits of treatments, it is important to consider the pathophysiological mechanisms underlying any disease in guidelines. Ambulatory venous hypertension is the hemodynamic pathology related to all symptoms and signs of CVD. The underlying components of venous hypertension are failure of the calf muscle pump, venous valvular incompetence, and luminal obstruction.

After prolonged standing, venous pressure in the foot is approximately 90 mm Hg in both a patient with incompetent venous valves and a person with a normal leg. However, ambulatory venous pressures in CVD patients remain high in the lower limbs during walking (more than 40 mm Hg), whereas normally these pressures should fall to a lower level (to 30 mm Hg). Due to valve incompetence, venous refill time on air plethysmography is shorter in CVD patients compared with healthy individuals.

When venous pressures in the leg are at higher-than-normal levels and remain elevated for prolonged periods, a progressive increase in skin damage may occur. Nicolaides reported that nearly all patients with exercising venous pressures of >90 mm Hg experienced venous ulceration. The apparently simple concept of venous hypertension is responsible for CVD lies in the complex cellular and molecular processes set in motion by the abnormal venous hemodynamics it engenders.

What initiates inflammatory events in venous valves and walls has not yet been uncovered. It is likely that venous hypertension and subsequent stasis lead to vein distension, which in turn causes venous flow reversal and areas of low shear stress. Even in the absence of reflux, endothelial cells that are exposed to flow reversal become activated. Leukocytes, on the other hand, are activated by low shear stress.

When leukocytes are activated as a result of venous hypertension, they produce adhesion molecules, which bind to intracellular adhesion molecules (ICAMs) at the endothelial surface. This permits endothelial cell adhesion of leukocytes and initiates their migration through the vessel wall into the extravascular spaces, leading to degranulation and the release of proteolytic enzymes (such as matrix metalloproteinases [MMPs], tissue inhibitors of MMPs [TIMPs], and transforming growth factor β1 [TGFβ1]). This type of leukocyte-endothelial interaction initiates and maintains inflammation.

The consequences of inflammation in primary CVD: the remodeling of vein wall and valves

- **Vein wall and valves**
  Morphologic changes in venous valves occur with prolonged pressure-induced inflammation. Wall and valve remodeling and damage occur as a result of leukocyte infiltration into vein wall and valve leaflets, leading to wall fibrosis together with progressive reflux.

  The production of MMPs and a greater proportion of TIMPs leads to the accumulation of extracellular matrix material. In addition, increased production of TGFβ1 stimulates collagen synthesis and further increases in TIMP production. The cumulative result of these events results in the structural and hypertrophic changes in venous wall that typify patients with varicose veins.

- **Microcirculation**
  An early event that occurs in CVD is elevated endothelial permeability, with the opening of leakage sites between endothelial cells. As a result of this enhanced microvascular permeability, extravasation of water and water-soluble nutrients leads to edema. With further permeability, the extravasation of red blood cells leads to the hyperpigmentation of skin in lipodermatosclerosis.

- **Lymphatic network**
  Fluid transport through the lymphatic vasculature completes the body’s circulatory loop. The lymphatic vessels maintain tissue homeostasis and compensate for capillary leakage by absorbing extravasated interstitial fluid. In the case of intense capillary leakage, the lymphatic drainage capacity be-

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**SELECTED ABBREVIATIONS AND ACRONYMS**

- CEAP: Clinical-Etiological-Anatomical-Pathophysiological
- CVD: chronic venous disease
- ICAM: intracellular adhesion molecule
- MMP: matrix metalloproteinase
- MPFF: micronized purified flavonoid fraction
- RCT: randomized controlled trial
- RELIEF: Reflux assessEment and quaLity of life improvEment with micronized Flavonoids
- TGFβ1: transforming growth factor β1
- TIMP: tissue inhibitor of matrix metalloproteinases
- VAD: venoactive drug
comes insufficient to absorb the excess fluid and macromolecules produced. This leads to venous edema, which spares toes, in contrast to lymphatic edema. The Kaposi-Stemmer test allows us to distinguish between the two types of edema (Figure 1).

**Mechanisms of action of Daflon 500 mg**

Daflon 500 mg belongs to the gamma-benzopyrone class of VADs, which are for the most part of plant origin, but also of synthetic origin, too, as illustrated in Table I. So, what are the mechanisms at work in the treatment of CVD by Daflon 500 mg?

- Daflon 500 mg, like most VADs, increases venous tone, thereby reducing venous distensibility and stasis.
- The beneficial effect of Daflon 500 mg in reducing abnormal capillary permeability has been extensively demonstrated. This effect has also been witnessed in almost all VADs.
- Lymphatic drainage improves with Daflon 500 mg. Only two other VADs have a beneficial effect on lymphatic drainage.

### Table I. Classification of the main venoactive drugs.

<table>
<thead>
<tr>
<th>Group</th>
<th>Substance</th>
<th>Origin</th>
<th>Dosage (mg)</th>
<th>Number of doses/day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzopyrones</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Alpha-benzopyrones</strong></td>
<td>Coumarin</td>
<td>Mellilot (Mellilotus officinalis) Woodruff (Asperula odorata)</td>
<td>90 combined with troxerutin (540)</td>
<td>3</td>
</tr>
<tr>
<td><strong>Gamma-benzopyrones</strong></td>
<td>Diosmin</td>
<td>Citrus sp (Sophora japonica) Rutaceae aurantia</td>
<td>300-600</td>
<td>1 or 2</td>
</tr>
<tr>
<td></td>
<td>Micronized purified flavonoid fraction (MPFF)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rutin and rutosides</td>
<td>Sophora japonica Eucalyptus sp Fagopyrum esculentum</td>
<td>1000</td>
<td>1 or 2</td>
</tr>
<tr>
<td></td>
<td>0-β-Hydroxyethyl-rutosides (troxerutin, HR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Saponins</strong></td>
<td>Escin</td>
<td>Horse chestnut (Aesculus hippocastanum)</td>
<td>Initially 120, then 60</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Ruscus extract</td>
<td>Butcher’s broom (Ruscus aculeatus)</td>
<td>2 to 3 tablets</td>
<td>2 to 3</td>
</tr>
<tr>
<td><strong>Other plant extracts</strong></td>
<td>Anthocyanins</td>
<td>Bilberry (Vaccinium myrtillus)</td>
<td>116</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Proanthocyanidins</td>
<td>Maritime pine (Pinus maritimus) Grape pips (Vitis vinifera)</td>
<td>100 to 300</td>
<td>1 to 3</td>
</tr>
<tr>
<td></td>
<td>Extracts of ginkgo</td>
<td>Ginkgo biloba 2 sachets (extracts of ginkgo, heptaminol, and troxerutin)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Synthetic products</strong></td>
<td>Calcium dobesilate</td>
<td>Synthetic</td>
<td>1000 to 1500</td>
<td>2 to 3</td>
</tr>
<tr>
<td></td>
<td>Benzaronone</td>
<td>Synthetic</td>
<td>400 to 600</td>
<td>2 to 3</td>
</tr>
<tr>
<td></td>
<td>Naftazone</td>
<td>Synthetic</td>
<td>30</td>
<td>1</td>
</tr>
</tbody>
</table>

**Figure 1.** The Kaposi-Stemmer test allows physicians to distinguish between venous and lymphatic edema. Lymphatic edema affects the toes, while venous edema spares them.
Only Daflon 500 mg has documented evidence of the ability to attenuate the effects of various inflammatory cascade mediators, particularly those involved in the leukocyte-endothelial interaction, which are important in the genesis of venous hypertension and its clinical repercussions (Figure 2).14

**Venous tone**

The beneficial effect of Daflon 500 mg on venous tone has been studied in three double-blind, placebo-controlled trials in patient populations with varying degrees of CVD, including women with venous insufficiency related to postthrombotic syndrome,15 with venous insufficiency related to pregnancy,16 and without any venous pathology.17 Daflon 500 mg, at a dose of two tablets per day, had an immediate, positive effect on venous tone, which started to improve 1 hour after administration in all three groups of women. In the trial in women without any venous pathology,17 Daflon 500 mg significantly improved venous distensibility for 4 hours after administration compared with placebo ($P<0.05$). When treatment was continued for 1 week, the significant effect on venous distensibility compared with placebo was maintained for 24 hours ($P<0.05$).

In a study aimed at determining the effect of Daflon 500 mg in 25 female volunteers aged 18-35 years with abnormal venous elasticity but without varicose veins,18 12 women received a single dose of two tablets of Daflon 500 mg for 4 weeks, while 13 women in the control group received no treatment. Venous tone significantly improved in patients receiving Daflon 500 mg ($P<0.02$) compared with baseline. In contrast, venous elasticity did not change significantly versus baseline in patients in the control group.

**Capillary hyperpermeability**

When subjected to prolonged venous hypertension, capillaries become elongated and dilated and develop abnormal permeability. The increased permeability causes interstitial edema. The beneficial effects of Daflon 500 mg on capillary hyperpermeability have been demonstrated in two trials.19,20 In a 6-week, placebo-controlled trial in 30 patients with idiopathic cyclic edema, Daflon 500 mg significantly improved capillary hyperpermeability (as measured by labeled albumin retention) compared with placebo ($P<0.05$).19 This was accompanied by a mean weight loss of at least 1.5 kg and a decreased sensation of swelling, indicating a concomitant decrease in edema. In a 4-week study in patients with venous hypertension, Daflon 500 mg given either two or three times daily significantly decreased the capillary filtration rate versus baseline values in a dose-dependent manner ($P<0.05$).20

**Lymphatic drainage**

In patients with advanced CVD, there is an increase in intralymphatic pressure and diameter, and in permeability of the lymphatic capillaries, leading to the transendothelial diffusion of fluids (Figure 3).21 Daflon 500 mg is thought to improve lymph flow by increasing both the frequency and amplitude of contraction of lymphatic capillaries, as well as by increasing the number of functional capillaries. This reduces edema by facilitating the drainage of interstitial fluid into the lymphatic system. In a 4-week study in 24 patients with severe CVD but no active ulceration, Daflon 500 mg significantly decreased the diameter of lymphatic capillaries and the intralymphatic pressure from baseline ($P<0.001$).22 In addition, the number of functional lymphatic capillaries also significantly increased ($P<0.001$).
The leukocyte-endothelial interaction

The well-established role of leukocytes in the pathophysiology of CVD has focused attention on drugs able to block leukocyte adhesion to the venous valves and wall and thereby stop venous inflammation very early in the disease process.

In this model, venous hypertension caused by a femoral arterial-venous fistula resulted in the development of venous reflux and an inflammatory reaction in venous valves. In animals treated with Daflon 500 mg, there was a significant, dose-dependent reduction in reflux rate. Daflon 500 mg also inhibited the expression of the endothelial cell adhesion molecules P-selectin and ICAM-1, reduced leukocyte infiltration, and decreased the level of apoptosis in valves in a dose-dependent manner. These data suggest that in the rat model of venous hypertension, Daflon 500 mg delays the development of reflux and suppresses damage to valve structures by decreasing the interaction between leukocytes and endothelial cells. The administration of Daflon 500 mg reduced the edema and the fistula blood flow produced by the acute arterial-venous fistula. Daflon 500 mg also reduced granulocyte and macrophage infiltration of valves.

Evidence for the clinical efficacy of Daflon 500 mg

The clinical efficacy of Daflon 500 mg has been evaluated in a number of clinical trials. Many studies with rigorous designs have demonstrated that Daflon 500 mg improves symptoms and signs in patients with CVD.

Improvement of symptoms of CVD

A review of the data show that Daflon 500 mg is effective from the earliest stages of CVD, including in patients with a COG classification, and that symptom relief is achieved rapidly and in a sustained manner. The efficacy of Daflon 500 mg’s relief of clinical symptoms has been evaluated in two placebo-controlled trials in which the following symptoms were considered: functional discomfort, sensation of heaviness, nocturnal cramps, and sensation of swelling. These changes were significant after 4 weeks of treatment. The effects of Daflon 500 mg on the symptoms of CVD have also been compared with nonmicronized diosmin in a study of 88 patients. While statistically significant improvements in all subjective symptoms

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Figure 4A illustrates the rolling and adhesion of leukocytes at the surface of the endothelium before their migration into tissues. Figure 4B shows firm adhesion of leukocytes to and migration into the venous endothelium. This is the starting point of an inflammatory reaction and cascade that causes vein wall and valve remodeling, thereby prolonging venous hypertension and eventually progression to complications. Thanks to its vein-specific anti-inflammatory action, Daflon 500 mg prevents the inflammatory cascade in the venous system.
were noted in both treatment groups at the end of 2 months, Daflon 500 mg was more effective than diosmin for the majority of response measures.

**Reduction of leg edema**

In the three trials assessing the efficacy of Daflon 500 mg for the relief of CVD symptoms, measures of edema were also taken. All three trials demonstrated a significant correlation between the improvements in the symptom score of sensation of swelling and a decrease in ankle circumference.\(^{26-28}\) Three further studies that used different methods to quantify leg edema also demonstrated that Daflon 500 mg has beneficial effects. In two placebo-controlled trials of patients with either symptoms or signs of CVD, the administration of Daflon 500 mg resulted in significant reductions in ankle circumference compared with placebo.\(^{26,28}\)

In a third study, edema was assessed using a volumeter in patients with varicose veins. Administration of Daflon 500 mg was associated with a significant decrease in volume of the more affected lower leg of 263 mL (8%) in all patients and 392 mL (12%) in patients with varicose veins.\(^{29}\) In a Czech study in 213 patients with venous edema receiving two tablets a day of Daflon 500 mg for 6 months, the ankle and calf circumferences were significantly less than those at baseline—24.4 vs 25 cm (P<0.001) for ankle circumference; and 39.9 vs 40.6 cm (P<0.001) for calf circumference.

The reduction in circumferences continued until month 6. Leg volume decreased by an average of 78 cm\(^3\) after 2-months’ treatment with Daflon 500 mg and by 121 cm\(^3\) after 6 months. This was significant both times (P<0.001).\(^{30}\) Finally, edema, as measured by leg circumference, also decreased significantly compared with baseline in the RELIEF (Reflux assessment and quality of life improvement with micronized flavonoids) study.\(^{31}\)

**Leg ulcer healing**

A meta-analysis that pooled 723 patients with venous ulcers treated with Daflon 500 mg confirmed that the rate of venous ulcer healing is accelerated by adding Daflon 500 mg to conventional treatments.\(^{32}\) At 6 months, the chance of healing an ulcer was 32% better in patients treated with adjunctive Daflon 500 mg than in those managed by conventional therapy alone (relative risk reduction, 32%; 95% confidence interval [CI], 3% to 70%; P=0.03). Subgroup analyses suggested that the benefits of Daflon 500 mg were greatest in ulcers >5 cm\(^2\) and >6 months in age.

**Summary of Daflon 500 mg in recent guidelines**

**Cochrane reviews**

In recent Cochrane reviews on VADs, randomized, double-blind, placebo-controlled trials were classified as being level A (low risk of bias), level B (moderate risk of bias), or level C (high risk of bias).\(^{33,34}\) Significant and homogeneous results were found for edema reduction, decrease in restless leg symptoms, and improvement in trophic disorders for most VADs compared with placebo.\(^{13}\) However, for most analyses there was evidence of heterogeneity. No test for heterogeneity was applied in the review of horse chestnut seed extract.\(^{34}\)

In the subgroup analyses of individual VADs, Daflon 500 mg was shown to have significant benefits versus placebo, based on multiple studies, on several dichotomous and continuous outcome variables, such as cramps, heaviness, edema, and skin changes, albeit with evidence of heterogeneity in most cases.\(^{35}\)

**Consensus guidelines**

In most European guidelines, studies are usually classified: grade A (at least two randomized controlled trials [RCTs] with large sample sizes, meta-analyses combining homogeneous results), grade B (RCTs with small sample size, single RCT), or grade C (other controlled trials, nonrandomized controlled trials).\(^{13}\)

Two of these guidelines deal with VADs (Figure 5, page 312). The article of Ramelet et al, published in Clinical Hemorheology and Microcirculation, represents the proceedings of the International Medical Consensus Meeting on Venoactive Drugs in the Management of Symptoms of Chronic Venous Disease, held in Siena.\(^{36}\) Eighty-three publications on the efficacy of VADs on venous symptoms were analyzed. The “Internatioral Guidelines on the Management of Chronic Venous Disease,” published in International Angiology,\(^{13}\) used the same grading system as that of the Siena experts except for meta-analyses, which were graded B. Outcomes included not only symptoms, but also edema and venous ulcer healing. One hundred and twenty-eight publications on VADs were analyzed in this document.

Based on the consistency of the respective evidence from these two recent guidelines on VADs,\(^{13,35}\) a grade A was assigned to two VADs: MPFF (Daflon 500 mg) and hydroxyethylrutosides (ie, oexerutins) for the effects of these VADs on symptoms, edema, and skin changes.

**A new grading system for CVD guidelines**

The method of determining the strength and quality of the recommendations in American guidelines deserves mention. Recommendations are generally accompanied by a number, which refers to the strength of the recommendation, and a letter, which refers to the quality of the evidence supporting the recommendation. Recent guidelines for venous disease have used two levels to specify the strength of their recommendations depending mainly on the benefit/risk ratio: grade 1 for strong and grade 2 for weak. They go on to indicate that statements accompanied by a grade 1 rating are “recommendations,” while statements accompanied by a grade 2 rating are “suggestions.”\(^{36}\)
The quality of evidence upon which the strength of the recommendation is based ranges from “A” for high-quality evidence, which is consistent evidence from randomized trials, to “B” for moderate-quality evidence, which is evidence from nonrandomized trials or inconsistent evidence from randomized trials. Level “C” is low-quality evidence, which is suggestive evidence from nonrandomized trials, observational reports, or expert opinion. Writing committees are increasingly aware of the costs of care and patient values and preferences, as are physicians. These are also considered in the strength of recommendations.

Two guidelines on venous diseases use this system (Figure 5):

- one is a recent educational article on the pharmacological treatment of primary CVD, dealing almost exclusively with VADs and their place in the management of such disease. The educational article proposed a strong recommendation, based on evidence of moderate quality, for the use of Daflon 500 mg to treat CVD symptoms and edema. The recommendations of the article reflect the opinions and judgements of the authors, but have not been endorsed by learned societies or other organizations (Table II).

- the second is the latest edition (3rd edition) of the Handbook of Venous Disorders: Guidelines of the American Venous Forum. The educational article proposed a strong recommendation, based on evidence of moderate quality, for the use of Daflon 500 mg to treat CVD symptoms and edema. The recommendations of the article reflect the opinions and judgements of the authors, but have not been endorsed by learned societies or other organizations (Table II).

There is evidence from a meta-analysis of RCTs that Daflon 500 mg may be effective in healing venous ulcers. In the absence of important safety concerns, its use in this indication was given a strong recommendation in primary ulcers (1B). On the basis of the meta-analysis mentioned above, the au-

<table>
<thead>
<tr>
<th>Indication</th>
<th>Venoactive drug</th>
<th>Recommendation for use</th>
<th>Quality of evidence</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relief of symptoms associated with CVD in patients C0 to C6 and with CVD-related edema</td>
<td>Daflon 500mg (MPFF)</td>
<td>Strong</td>
<td>Moderate</td>
<td>1B</td>
</tr>
<tr>
<td>Rutosides</td>
<td>Strong</td>
<td>Moderate</td>
<td>1B</td>
<td></td>
</tr>
<tr>
<td>Calcium dobesilate</td>
<td>Weak</td>
<td>Moderate</td>
<td>2B</td>
<td></td>
</tr>
<tr>
<td>Horse chestnut extracts</td>
<td>Weak</td>
<td>Low</td>
<td>2C</td>
<td></td>
</tr>
<tr>
<td>Ruscus extracts</td>
<td>Weak</td>
<td>Low</td>
<td>2C</td>
<td></td>
</tr>
</tbody>
</table>

Healing of primary venous ulcer, as an adjunct to compressive and local therapy (Coleridge-Smith, 2009)

Daflon 500mg (MPFF) Strong Moderate 1B

The place of Daflon 500 mg in recent guidelines on the management of CVD – Pitsch
The place of Daflon 500 mg in recent guidelines on the management of CVD – Pitsch

10. in long-standing or large venous ulcers of primary etiology quoted for the pharmacological treatment of venous ulcers. The improvement of symptoms and edema associated with CVD. In the same chapter, only MPFF (Daflon 500 mg) was quoted for the pharmacological treatment of venous ulcers. The use of Daflon 500 mg in combination with compression in long-standing or large venous ulcers of primary etiology was recommended (grade 1B).37

Among the many reasons that make guidelines useful, one is because they provide recommendations that are based on good quality evidence. Another is because they balance the desirable and undesirable effects of a treatment, not to mention the cost-effectiveness of such treatment. A robust strength of recommendation for a treatment indicates that clinicians can offer this treatment to almost all their patients with little or no hesitation. This is the case for Daflon 500 mg, which has received a strong recommendation in national as well as in international guidelines.38

References


Keywords: Daflon 500 mg; guidelines; management; chronic venous disease
La maladie veineuse chronique (MVC) est une pathologie courante constituée d’un ensemble de troubles. De nombreux efforts ont été faits pour créer un langage commun, essentiel pour établir des recommandations pratiques cliniques. En plus de l’amélioration des méthodes pour définir la MVC, la compréhension des processus physiopathologiques impliqués dans son développement a aussi maintenant fait de grands progrès. La perte du tonus veineux, une perméabilité capillaire anormale et des vaisseaux lymphatiques surchargés ont été proposés comme mécanismes impliqués dans le développement de la MVC. L’interaction leucocyte-endothélium et son association aux altérations valvulaires est l’un des mécanismes physiopathologiques les plus précoces impliqué dans la maladie, ce qui a attiré l’attention sur Daflon 500 mg, la seule molécule disponible dont l’activité est connue pour modifier de tels événements inflammatoires. En plus de son aptitude à augmenter le tonus veineux, ajuster la filtration capillaire et accélérer le drainage lymphatique, il réduit l’interaction des leucocytes avec l’endothélium dans l’inflammation et l’hypertension veineuse aiguë. Il est utilisé en pratique clinique pour traiter la MVC. Daflon 500 mg, bien toléré, a été largement étudié dans des études cliniques bien conçues. La micronisation de la taille des particules de ses composés à moins de 2 µm améliore sa biodisponibilité et son absorption orales par rapport à celles des diosmines non micronisées. C’est pourquoi, Daflon 500 mg est répertorié comme traitement veinoactif dans les recommandations récentes sur la prise en charge de cette maladie.
The natural history of chronic venous disease (CVD) is poorly understood. There have been too few longitudinal studies. In Northern and Western Europe the prevalence of varicose veins without skin changes is 20% compared to 3% for advanced CVD. Only 10% of the many individuals with C2 varicose veins progress to ulceration. The risk factors for progression are currently believed to comprise the usual combination of the environmental and the genetic. More specifically, the Bonn Vein Study (2008) identified the main culprits as age, hypertension, and obesity, to which other studies have added previous deep vein thrombosis, absence of etiologic intervention, a positive family history, reduced ankle range of motion, and impaired calf muscle pump function. Both hemochromatosis and thrombophilia predispose to ulceration, while twin studies incriminate the FOXC2 gene on chromosome 16. Female gender barely qualifies. Yet despite an additional plethora of sophisticated studies featuring cytokine arrays and gene polymorphisms, there remains no test, or test battery, that identifies the individual patient with early CVD at risk of ulceration. The evidence suggests that best-practice prophylaxis comprises aggressive intervention early in the course of the disease combined where possible with a structured exercise program to improve ankle range of motion and calf muscle pump function.

Medicographia. 2011;33:315-319 (see French abstract on page 319)
by saphenous reflux. The Bonn Vein Studies I & II, conducted in 3072 women and men, found a 2.0% annual incidence of progression to C3-C6 disease (Table I). Age, hypertension, and obesity were the main risk factors for C4-C6 disease.3

Factors for progression include the combination of reflux and obstruction, ipsilateral recurrent deep venous thrombosis (DVT), multisegmental involvement, and absence of etiologic CVD therapy. Prospective evaluation of the normal contralateral limb in 73 patients undergoing unilateral varicose vein (VV) surgery showed that half experienced clinical deterioration and reflux within 5 years. Independent risk factors were obesity, orthostatism, and noncompliance with the use of elastic stockings.6 However, we have no hemodynamic methods for identifying which patients with primary CVD and C2-C4 disease are likely to develop ulcers, despite the disease progressing to C4-C6 in up to 20% or more of the elderly.

Risk factors for ulcer recurrence include residual iliofemoral vein obstruction, residual deep incompetence (in particular axial deep reflux), residual or recurrent superficial reflux, and persistent venous hypertension. Correction of the underlying pathology reduces the risk of recurrence.

We need large, long-term prospective studies with DU scanning of the anatomic distribution of reflux and obstruction, and serial quantification of reflux. A more sophisticated protocol for longitudinal research is required, using studies of venous hemodynamics and the microcirculation. If we could identify the predictors of progression from C2-C4 to active ulceration, we could plan their modification where feasible.

**What are the clinical risk factors warranting early intervention in stage C2 CVD?**

Risk factor studies have given inconsistent results due to multiple methodological differences. Risk factors are currently thought to combine the environmental with the genetic. Age, a major risk factor, is compounded by a positive family history, although evidence for a mode of inheritance is lacking. Twin studies in Germany point to the FOXC2 gene on chromosome 16.5 Obesity has been incriminated in women, but appears to be aggravating rather than causal. It precipitates severe CVD, perhaps from functional rather than anatomical insufficiency. Female gender is universally cited, but CVD is barely more prevalent in women. Onset is earlier in women, at 30.8 years (36.8 years in men). Pregnancy (multiparity) is a universally recognized risk or aggravating factor, but not oral contraception. Major geographic differences suggest strong environmental influences. Although smoking affects the vascular wall and impairs endothelial function and behavior, its status as a risk factor is inconclusive. In the Framingham Study, women with VVs were more often obese, sedentary, older at menopause, and had higher systolic blood pressure; in men, VVs coexisted with sedentary lifestyle and higher smoking rates, suggesting that increased physical activity and weight control may prevent VVs in high-risk adults.

The Bonn Vein Study II reported the “sensation of swelling” as symptomatic of impending CVD.5 Signs such as corona phlebectatica and other skin changes may warrant early intervention to prevent ulcer formation. Risk relates to the severity of varicosity and increases after DVT. But it may also be increased in smokers, the obese, and those with reduced ankle range of motion (ROM) and calf pump power.

Clinical hardening of the vessel wall is associated with an increase in thick disorganized collagen bundles and elastic fiber fragmentation. Similar changes in the extracellular matrix are found in the vein wall and skin of C2 patients. Follow-up DU after aggressive treatment of superficial CVD supports the case for early recognition and intervention by showing improvement or complete reversal of deep venous insufficiency in most patients. Less aggressive treatment improved reflux valve closure time in only 28%.6

It will be difficult to perform the prospective longitudinal and cross-cultural studies that we need in order to measure the impact of these clinical factors on disease progression. An alternative is to identify features unique to limbs with established ulcers (C6) and compare them to limbs with C2-C4 disease.
Do any gene polymorphisms or biomarkers identify patients at high risk of ulceration?

In Northern and Western Europe the prevalence of WVs without skin changes is 20% compared to 3% for advanced CVD. Only 10% of the many individuals with C2 VVs proceed to ulceration. Genetic factors may play an important causal role in both mild and severe disease, but we need to establish biobanks and bloodbanks for longitudinal analysis.

Gene polymorphism and biomarker data may identify patients at high risk of ulceration:

- Tumor necrosis factor α (TNF-α) gene polymorphism has been associated with increased susceptibility to ulceration. However, others dispute that the A allele of the 308 G/A single nucleotide polymorphism (SNP) located in the promoter region of the TNFA gene is a potential factor for ulcer susceptibility, arguing that this association is secondary and that the primary association is probably with obesity.

- Estrogen receptor-beta polymorphism, associated with impaired healing in the elderly, predisposes to venous ulceration.

- SNPs of the fibroblast growth factor receptor 2 gene are significantly more frequent in CVD patients with chronic nonhealing wounds.

- Hemochromatosis studies suggest a role for iron deposition, iron trafficking genes, transglutaminases, and C282Y polymorphism of the hemochromatosis gene in ulceration. A simple C282Y blood test was highly specific in predicting ulcer development (98%), while ulcer onset was almost 10 years earlier in patients carrying the H63D variant.7

- Thrombophilia: venous ulceration was 2 to 30 times more prevalent in thrombophilia patients, even with no history or DU evidence of DVT, than in the general population.8

- Cytokine gene polymorphisms do not significantly influence venous thrombosis risk, despite the close relationship between venous thrombosis and inflammation.

Ongoing studies, including those using the genome-wide association approach, are looking to identify relevant patterns of SNPs to predict disease states and evaluate gene patterns that relate to multiple phenotypes of complex diseases. Gender, age, ethnicity, and environment appear strong determinants of disease penetration. We need systematic population-based searches for CVD susceptibility genes.

Are there differences in skin type, metabolism, or race that increase the risk of ulceration?

Sociodemographic factors may influence CVD progression. A West London study collected age, sex, and ethnicity data on all leg ulcer patients over one year. Ulceration was more frequent in whites than in South Asians (odds ratio, 4.43; \( P = 0.0004 \)), suggesting either a real difference in prevalence or a South Asian reluctance to seek treatment. The San Diego multiethnic cross-sectional study in 2211 subjects found superficial functional disease to be more common in women, while deep functional disease was more common in men. CVD was more common in non-Hispanic whites than in Hispanics, African Americans, or East Asians.

Humoral or genetic factors responsible for progression to ulcer formation are related to thrombosis and inflammation. Hyperhomocysteinemia, a risk factor for venous thrombosis and CVD development and progression, is present in about 65% of patients with CVD. Mild to moderately elevated plasma homocysteine was closely associated with increasing CVD severity, confirming that various inherited and acquired factors act in concert to raise individuals above the thrombotic threshold. Prevalence of the C677T methylene tetrahydrofolate reductase mutation was higher in complicated C4-C6 disease (20%) than in uncomplicated C2-C3 disease (10%), and more patients overall (15%) were homozygous compared with an estimated 5% of the healthy white population.9

Genetic variations that affect chronic inflammation may differ across ethnic groups. Cytokine SNPs affect cytokine levels and hence the inflammatory response.

Elevation of interleukin 6 is a well-documented inflammatory marker, but does it predict CVD progression?

Most people agree that markers such as interleukin 6 (IL-6) are elevated in CVD. IL-6 is produced and released into the systemic circulation from many different cells. It is the only cytokine to stimulate synthesis of all the acute-phase proteins involved in the inflammatory response. It is a universal marker, hence not specific to nor diagnostic of CVD progression. We need a specific biomarker for increased ulcer risk.

A prospective cohort study of elderly community residents showed an association between sociogeographic segregation and IL-6 levels. Ingredients of social disadvantage (age, African American ethnicity, high prescription drug consumption, body mass index >30, high alcohol consumption, and smoking) were all strong predictors of IL-6 elevation.

Elevated plasma inflammatory mediator levels are also risk factors for venous thrombosis. Several biomarkers reflect functional monocyte-macrophage activation and structural endothelial lesions related to venous stasis and venous hypertension that predispose to CVD. Baseline production of inflammatory markers is only elevated in VV patients, and all cytokine levels sharply increase in response to venous occlusion produced by cuff inflation. However, a systematic review of studies of the association between inflammatory markers and venous thrombosis concluded that plasma C reactive protein levels do not predict venous thrombosis.10
Between August 1995 and June 1997, blood was collected from 66,140 people in the second Norwegian Health (cohort) Study of Nord-Trøndelag (HUNT2); 506 cases were registered with a first venous thrombosis. Levels of IL-1β, IL-6, IL-8, IL-10, IL-12p70, and TNF-α, measured at baseline, showed no relationship between an altered inflammatory profile and venous thrombosis. These results suggest that an altered inflammatory profile is more likely to be a result than a cause of venous thrombosis, although a short-term impact with transient-tory profile is more likely to be a result than a cause of venous thrombosis.

No biomarker that accurately reflects wound healing status in individual patients, singly or in combination, has been identified.

**What information would a test of endothelial dysfunction provide, and what are the prospects of one being developed in the near future?**

Recent studies of CVD etiology have focused on endothelial cell integrity and function. Current evidence favors a multifactorial origin involving vein wall remodeling and changes in the microcirculation and dermis. Venous endothelial dysfunction is almost certainly implicated in the wall dilatation and valve incompetence seen in primary CVD. Markers of endothelial cell dysfunction are predictive of vascular events. They reflect multiple micro- or macrovascular disorders and early vascular changes, precluding clinical pathology by many months or even years. Elevation is associated with aging, endocrinopathy, arterial disease, connective tissue disease, smoking, and exposure to air pollution, in addition to venous disease. Endothelial function testing has great potential in cardiovascular screening, but is not yet feasible in routine assessment: no test is sufficiently sensitive and specific for clinical use. Most studies are observational. We still don’t know how best to investigate the multifaceted aspects of endothelial dysfunction.

Three types of test are available: vascular reactivity, systemic plasma markers, and histological immunostaining.

**Vascular reactivity tests**
Vascular reactivity tests are the most widely used; they are noninvasive, and they evaluate the peripheral macrocirculation (conduit arteries) or microcirculation (resistance arteries and arterioles).

**Systemic plasma markers**
Systemic plasma markers of endothelial damage and repair play a minor role in individual patient assessment:

- Nitric oxide: plasma levels of this potent mediator of vascular relaxation may be modulated in CVD.
- Humoral mediators of vasconstriction and venous dilatation: endothelin 1 levels increase and rise disproportionately in response to venous stasis.
- Pro- and anti-inflammatory cytokines: chronic venous hypertension leading to endothelial cellular injury and activation promotes inflammatory reaction and leukocyte recruitment in venous valves, causing dysfunction, reflux, and upstream venous hypertension.
- Adhesion molecules: despite reflecting early leukocyte-endothelium interaction, intercellular adhesion molecule 1 and E-selectin expression did not differ significantly between VV patients and controls.
- Hypoxia inducible factor 1α: Elevation of this marker of leukocyte-endothelium interaction results from prolonged mechanical stretching and increased vein wall tension, supporting the hypothesis of VV hypoxia.
- Soluble markers are mixtures of truly soluble molecules with membrane-bound forms, eg, endothelial microparticles (EMP). EMP-monocyte conjugates enhance transendothelial leukocyte migration in vitro and reflect several inflammatory diseases. But EMP elevation is not diagnostic for CVD progression or inflammation.
- Enzyme activity (matrix metalloproteinases [MMPs] and their inhibitors) increases in both high and low venous pressure regions. The degree of extracellular matrix remodeling of the venous wall and valve leaflets correlates with macroscopic lesion morphology and changes in the microcirculation and dermis. MMP-2 may induce venous relaxation or inhibit venous contraction.
- Plasma thrombomodulin (TM) is a marker of endothelial injury. Two cohort studies found no difference in the prevalence of the three TM genotypes between thrombosis cases and controls. There was no difference in age-adjusted mean soluble TM values by genotype, nor any association between age-adjusted soluble TM or the TMA455V genotype and overall venous thromboembolism or thrombosis.

**Histological immunostaining**
Immunostaining and real-time polymerase chain reaction (RT-PCR) analysis reveal VV intimal changes, such as focal intimal discontinuity and endothelial denudation. Vein wall changes may precede valvular dysfunction. Total elastin content is lower in WVs than in healthy veins.

We need more longitudinal studies to identify prognostic markers of endothelial dysfunction. We must also identify the genetic and humoral mediators of endothelial dysfunction in limbs with primary CVD and disease progression.

**How reliable are ankle mobility, calf muscle pump function, and patient activity in rating CVD progression?**
Both photoplethysmography and air plethysmography show end-of-day deterioration in calf pump function, suggesting that venous return deteriorates with prolonged standing. Musculoskeletal changes affect calf pump hemodynamics, complicating differentiation between cause and effect.
Goniometry shows significantly reduced ankle ROM across all grades of CVD. ROM decreases with increasing clinical severity, impairing calf pump function, and sustaining ambulatory venous hypertension. Gastrocnemius biopsies reveal morphologic changes suggesting that disuse, denervation, and ischemia lead to muscle dysfunction. The resultant impact on gait and ambulation predisposes to venous ulceration. Over two-thirds of ulcer patients have an impaired calf pump. Use of air plethysmography and color Doppler study to the relationship between degree of venous insufficiency, calf pump dysfunction, and venous ulceration showed significantly poorer pump function in legs with active ulcers than in those with healed ulcers or no history of ulceration. CVD is a necessary but limited cause of ulceration; calf pump dysfunction is a significant contributor to the severity of venous ulceration. 

In addition to known risk factors (longer ulcer duration, large surface area, ankle brachial pressure index <0.85), calf pump dysfunction correlates with delayed ulcer healing even with adequate compression. A study in 189 patients identified that calf/ankle circumference ratio <1.3, a fixed ankle joint, and reduced ankle ROM were the only independent parameters associated with nonhealing. Prospective controlled studies show that supervised exercise programs to improve calf pump function, muscle strength, and endurance improve healing rates and decrease recurrence in C6 disease, with benefit being maintained for at least 3 months.

References

Keywords: risk factors; identification; chronic venous disease

Nous sommes-nous améliorés dans l’identification des facteurs de risque de progression de la maladie veineuse chronique ?

Chronic venous disease (CVD) is defined as morphological and functional abnormalities of the venous system of long duration, manifested either by symptoms and signs indicating the need for investigations and/or care. The impact of CVD in the general population is often underestimated and not well recognized by health systems. In recent studies and according to the CEAP (Clinical-Etiological-Anatomical-Pathophysiological) classification, the C0 and C1 classes together are prevalent in more than 60% of the population. Varicose veins (C2) are prevalent in more than 20%. Skin changes, including venous ulcers, are present in less than 10% of the population. For many countries, no epidemiologic data exist. The worldwide Vein Consult Program aims to assess the prevalence of CVD and provide a picture of the typical adult patient and the management of their disease, in varying geographical areas. This is the largest ever CVD detection program to be undertaken. The Vein Consult Program is being carried out under the auspices of the International Union of Phlebology with the support of an unrestricted grant from Servier. More than 4500 selected general practitioners are participating, and it is estimated that they will screen approximately 95 000 patients. In step 1 of the program, general practitioners screen patients whom they are consulting for any medical reason. Step 2 is a follow-up consultation with a venous specialist. Preliminary results from 69 866 screened patients from 13 countries worldwide are available.

Medicographia. 2011;33:320-324 (see French abstract on page 324)
in turn lead to the appearance of signs of CVD such as varicose veins, skin changes, and leg ulceration.\(^3,4\) CVD is also a risk factor for the development of thromboembolic complications. Disease progress can be prevented by early detection and intervention. The impact of CVD in the general population is often underestimated and not well recognized by health systems. It is also often overlooked in primary care and cardiovascular care because of an underappreciation of its scale and of the impact of the disease.\(^5\)

Prevalence of chronic venous disease

In the last few decades, epidemiological CVD studies have been performed in many countries worldwide, mainly focus-

<table>
<thead>
<tr>
<th>Reference, year</th>
<th>Country</th>
<th>Male/female ratio (%/%)</th>
<th>Age (years)</th>
<th>Sample size</th>
<th>C0 All (%)</th>
<th>M (%)</th>
<th>F (%)</th>
<th>C1 All (%)</th>
<th>M (%)</th>
<th>F (%)</th>
<th>C2 All (%)</th>
<th>M (%)</th>
<th>F (%)</th>
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<tr>
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<td>USA</td>
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<td>40-79</td>
<td>2211</td>
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<td>33.6</td>
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<td>23.3</td>
<td>15.0</td>
<td>27.7</td>
</tr>
<tr>
<td>Jawien,(^*) 2003</td>
<td>Poland</td>
<td>16.0/84.0</td>
<td>16-97</td>
<td>40 095</td>
<td>51.5</td>
<td>16.5</td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Rabe,(^*) 2003</td>
<td>Germany</td>
<td>43.9/56.1</td>
<td>18-79</td>
<td>3072</td>
<td>9.6</td>
<td>13.6</td>
<td>6.4</td>
<td>59.1</td>
<td>58.4</td>
<td>59.5</td>
<td>14.3</td>
<td>12.4</td>
<td>15.8</td>
</tr>
<tr>
<td>Carpentier,(^**) 2004</td>
<td>France</td>
<td>67.7/32.3</td>
<td>&gt;18</td>
<td>409</td>
<td>48.7</td>
<td>(including C0+C1)</td>
<td></td>
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</tr>
<tr>
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<td>Italy</td>
<td>14.1/85.9</td>
<td>18-90</td>
<td>5187</td>
<td>22.7</td>
<td>36.0</td>
<td>20.6</td>
<td>64.8</td>
<td>33.4</td>
<td>69.9</td>
<td>29.4</td>
<td>29.3</td>
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</tbody>
</table>

Table I. CEAP classification: clinical classes and definitions. Abbreviation: CEAP, Clinical-Etiological-Anatomical-Pathophysiological.

Prevalence of CEAP classes C0-C6 in recent studies in Western countries. Based on references 14 to 19. Abbreviation: CEAP, Clinical-Etiological-Anatomical-Pathophysiological.

**Table II (above and left).**

<table>
<thead>
<tr>
<th>Reference, year</th>
<th>Country</th>
<th>Male/female ratio (%/%)</th>
<th>Age (years)</th>
<th>Sample size</th>
<th>C3 All (%)</th>
<th>M (%)</th>
<th>F (%)</th>
<th>C4 All (%)</th>
<th>M (%)</th>
<th>F (%)</th>
<th>C5 All (%)</th>
<th>M (%)</th>
<th>F (%)</th>
<th>C6 All (%)</th>
<th>M (%)</th>
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</thead>
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<td>19.0</td>
<td>4.9****</td>
<td>6.2</td>
<td>7.8</td>
<td>5.3</td>
<td>(including C4-C6)</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Jawien,(^*) 2003</td>
<td>Poland</td>
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<td>4.6</td>
<td></td>
<td>1.0</td>
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<td>0.5</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabe,(^*) 2003</td>
<td>Germany</td>
<td>13.4</td>
<td>14.9</td>
<td></td>
<td>2.9</td>
<td>3.1</td>
<td>2.7</td>
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<td>0.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carpentier,(^**) 2004</td>
<td>France</td>
<td>1.1</td>
<td>2.2</td>
<td></td>
<td>4.0</td>
<td>2.1</td>
<td></td>
<td>1.4</td>
<td>0.7</td>
<td>0.7</td>
<td>0.0</td>
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</tr>
<tr>
<td>Chiesa,(^**) 2005</td>
<td>Italy</td>
<td>13.6</td>
<td>14.1</td>
<td>13.9</td>
<td>3.4</td>
<td>5.2</td>
<td>3.1</td>
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<td>8.1</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* nonsaphenous varicose veins; * saphenous varicose veins; ** highest assigned clinical category; *** all clinical categories listed; **** edema in the whole population.

**Selected Abbreviations and Acronyms**

- **CEAP**: Clinical-Etiological-Anatomical-Pathophysiological
- **CIVIQ**: Chronic Venous Disease Questionnaire
- **CVD**: Chronic venous disease
- **CVI**: Chronic venous insufficiency
- **QOL**: Quality of life
- **UIP**: Union Internationale de Phlébologie (International Union of Phlebology)
are prevalent in more than 20%, with a higher prevalence in women. Skin changes due to venous diseases, including venous ulcers, are present in less than 10% of the population with no significant gender differences. Older age, family history of varicose veins, female gender, and pregnancy are established risk factors for varicose veins; obesity is an important additional risk factor for CVI. Unfortunately, such data is only available for a few countries, and the epidemiologic situation in many regions of the world remains unclear.

Quality of life and burden of chronic venous disease
CVD can negatively affect patients’ quality of life (QOL), as it is a painful and disabling disease that can restrict physical functioning and mobility and that is associated with depression and social isolation. In consequence, CVD can result in limitation to daily activities, decreased productivity at work, and patients needing to take sick leave, as well as having a negative effect on their self-esteem. Disease severity appears to be a good indicator of QOL. The higher the CEAP clinical class, the poorer the disease-specific QOL, as demonstrated by low scores for physical and social functioning in QOL questionnaires.

One such questionnaire, CIVIQ (Chronic Venous disease Questionnaire), is a 20-item questionnaire that provides a global index score and a profile in four different categories: pain, physical, psychological, and social functioning. It is valid across a range of different languages and cultures. A shortened version, CIVIQ-14, has been used in the Vein Consult Program.

CVD represents a significant socioeconomic burden in terms of health-care costs due to its high prevalence, the costs of investigation and treatment of complications, and lost working days. The overall cost of venous disease in Germany was €2.18 billion in 2006. A recent evaluation in Germany revealed the mean total yearly cost of an ulcer patient to be almost €10 000.

International Union of Phlebology
The International Union of Phlebology (Union Internationale de Phlébologie [UIP]), founded in 1959, is an association of national phlebology societies from Europe, North America, Latin America, Asia, Africa, Australia, and New Zealand. The UIP represents 50 phlebology societies in 47 countries. The UIP is governed by its Executive Committee consisting of the president, the president elect/the past president, 5 vice presidents, a general secretary, an assistant general secretary, and a treasurer.

The aims of the UIP are:
- to promote consensus on all aspects of CVD
- to encourage studies and research on disorders of venous origin
- to promote joint meetings or international congresses
- to encourage the creation and activities of national societies or associations and to encourage membership of the UIP.

The UIP’s three main areas of focus are science, education, and communication. The UIP encourages ongoing scientific research in phlebology to help answer some of the many questions that still exist in venous disease. One of the important goals is to gain more information on venous epidemiology and on the burden of disease worldwide. For this reason, the UIP is cooperating with Servier on the Vein Consult Program.

Vein Consult Program
The Vein Consult Program is an international educational effort to raise awareness of CVD amongst physicians, patients, the scientific community, and health authorities. The worldwide screening program aims to assess the prevalence of CVD and provide a picture of the typical adult patient and the management of their disease, in varying geographical areas. This is the largest ever CVD detection program to be undertaken, and it will help to evaluate how general practitioners (GPs) and venous specialists manage patients with CVD and to better understand at which stage of the disease specialists take over from GPs in the management process. The program aims to detect CVD early, with the goal of improving the process of management of this chronic disease. It will also assess the impact of CVD on the QOL of patients, healthcare resources, and the economy.

The Vein Consult Program is being carried out under the auspices of the UIP with the support of an unrestricted grant from Servier. The program will be scientifically validated by the UIP via its operational board members and scientific advisory committee. The research is being coordinated in participating countries by national societies that are affiliated to the UIP. In each country, a local research organization will be responsible for data entry and its validation. An international research organization will then pool all national data and be responsible for statistical analysis of these data, under the supervision of the UIP’s scientific advisory committee.

The Vein Consult Program, which started in 2009, is an international observational, multicenter, descriptive survey of CVD. More than 4500 selected GPs are participating, and it is estimated that they will screen approximately 95 000 patients (Table III). In step 1 of the program, GPs screen patients whom they are consulting for any medical reason (except an emergency) and assess their suitability for inclusion in the program. There are several criteria: the patient (male or female) must be over 18 years old; they must be informed of...
Identifying and accessing patients with CVD: the VCP International Study – Rabe

Table III. Initial procedures in the Vein Consult Program.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Countries</th>
<th>No. of doctors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1 Screening of patients for any medical reason within the framework of general practice</td>
<td>Brazil, Columbia, Brazil, Colombia, France, Georgia, Hungary, Indonesia, Mexico, Pakistan, Romania, Russia, Serbia, Singapore, Slovakia, Slovenia, Spain, Thailand, United Arab Emirates, Ukraine, Venezuela, Vietnam</td>
<td>4500 general practitioners</td>
</tr>
<tr>
<td>Step 2 Diagnosis confirmation by selected specialists</td>
<td>Mexico, Romania, Russia, Spain</td>
<td>500 specialists</td>
</tr>
<tr>
<td>Patient self-questionnaire Examination of quality of life + costs</td>
<td>All</td>
<td></td>
</tr>
</tbody>
</table>

Summary

The Vein Consult Program, a cooperative venture between the International Union of Phlebology and Servier, is the largest ever CVD detection program to be undertaken with 95 000 patients from 20 countries. The program will help us to better understand the prevalence and risk factors of CVD, the impact of CVD on the QOL of patients and health resources, and the burden of the disease on the patient and the economy. The Vein Consult Program will also help to increase the awareness of CVDs among health-care professionals and officials, politicians, and insurance companies. This is vital if we are to prevent an upcoming increase in the prevalence of CVD in the general population caused by demographic changes (eg, an increasing elderly population) and by changes in lifestyle (eg, an increasing prevalence of obesity). The issue of improved awareness needs to be urgently addressed.

References

La maladie veineuse chronique (MVC) se définit par des anomalies morphologiques et fonctionnelles de longue durée touchant le système veineux et se manifestant par des signes et des symptômes nécessitant des examens complémentaires et/ou des soins. L’impact de la MVC dans la population générale est souvent sous-estimé et mal reconnu par les systèmes de santé. Dans les études récentes et selon la classification CEAP (Clinique [sévérité] Étiologie-Anatomie-Physiopathologie), les classes C0 et C1 sont toutes les deux prévalentes dans plus de 60 % de la population. Les varices (C2) sont prévalentes chez plus de 20 % de la population. Les modifications cutanées, y compris les ulcères, se retrouvent dans moins de 10 % de la population. Il n’existe pas de données épidémiologiques pour de nombreux pays. Le Vein Consult Program mondial a pour but d’évaluer la prévalence de la MVC et fournit une image du patient adulte typique et de la prise en charge de sa maladie, dans différentes zones géographiques. C’est le plus vaste programme de détection de la MVC jamais entrepris. Le Vein Consult Program est mis en œuvre sous les auspices de l’Union Internationale de Phlébologie avec le soutien de Servier. Plus de 4500 généralistes sélectionnés y participent, et l’on estime qu’ils dépisteront environ 95 000 patients. À la première étape du programme, les généralistes trient les patients qui consultent pour n’importe quelle raison médicale. La deuxième étape est une consultation de suivi avec un spécialiste veineux. Les premiers résultats du dépistage de 69 866 patients de 13 pays sont disponibles.
Pain in chronic venous disease: perspectives for research

by N. Danziger, France

Pain is the complaint that most often leads to a diagnosis of venous disease, and it has a significant impact on patients’ quality of life. For all those involved with chronic venous disease (CVD), pain is difficult to assess both because of its multidimensional nature and because of the lack of a close relationship between pain as a symptom and severity of venous disease. Current hypotheses on the mechanisms of pain induction in CVD highlight its local inflammatory origin. A variety of inflammatory mediators are released locally in the early stages of CVD, which activate unmyelinated C-fibers in the venous wall, leading to pain. In the last five years, there has been a veritable explosion in the number of indicators suggesting an inflammatory reaction in varicose veins. The precise mechanisms governing the interaction between venous nociceptors and mediators of inflammation, which may account for the variability of pain experienced in venous disease, remain difficult to explain.

The quality of life of chronic venous disease (CVD) patients is greatly affected by pain,1,2 the complaint that most often leads to diagnosis of venous disease.3,4 For everyone involved in CVD, pain is difficult to measure. Often pain of venous origin is found in association with other disagreeable sensations that do not belong in the range of nociceptive symptoms, eg, pruritus or a sensation of cramp, heaviness, or tension in the legs.3 The intensity of pain can also fluctuate substantially, from patient to patient or in the same patient with progression of the disease over a period of time.

A causal relationship between CVD and pain of venous origin remains difficult to clarify, both clinically and experimentally. This difficulty could be attributed to the absence of a close link between pain and the severity of CVD. Nevertheless, the future looks promising as the neurophysiological mechanisms of pain of venous origin are now better understood, and several biochemical and cellular processes involved in varicose vein remodeling have been explained.6-8

Venous innervation and the physiological properties of venous and perivenous nociceptors

Veins are innervated by sensory nerve fibers whose cell body is situated in the dorsal root ganglia of the spinal cord.6 Sensory fibers are located along the venous wall and subdivide into collateral branches. Some cross the tunica adventitia and termi-
nate in the venous wall between endothelial cells and smooth muscle cells of the tunica media. Other collateral branches penetrate the connective tissue of the perivenous space where they branch further into unmyelinated free nerve endings in proximity to the microcirculation. These subendothelial and perivascular nerve endings are nociceptors; their sole purpose is the transmission of nociceptive afferent signals generated both in the venous wall and in the perivenous connective tissue, respectively.

Recently, these types of nerve endings have been shown to be present in the wall of human varicose veins. These nociceptors account for the stimuli that generate pain sensations of venous origin. This type of pain can be induced by a variety of different stimuli. Mechanical stimuli used include traction exerted on a vein, venipuncture, or the presence of a catheter, while nonphysiological chemical stimuli used include the injection of “cold” isotonic saline (<20°C), hyperosmolar saline or a glucose solution, the injection of a strongly acidic (pH <4) or alkaline (pH >11) solution, or the presence of a catheter, venipuncture, or the presence of a catheter, without the participation of cutaneous sensory fibers.

Animal studies have shown that there are two types of afferent fibers that transmit nociceptive signals of venous origin. Electrophysiological tracings of nerve fibers innervating venous wall have shown that there is a type Aδ myelinated afferent nerve fiber and a type C unmyelinated afferent nerve fiber. Aδ fibers, with their higher conduction velocities, are responsible for the acute, sharp sensation of pain that is felt first. They respond to a weaker intensity of stimulus than C-fibers. C-fibers, which are deemed polymodal because they respond to an assortment of stimuli, are responsible for the sensation of longer-lasting, slow, dull pain.

Other sources of acute pain of venous origin include superficial venous inflammation or deep vein thrombosis, both of which are often observed in clinical practice. Traditionally, the properties of venous nociceptors have been elucidated experimentally in humans by mechanically, thermally, or chemically stimulating an isolated venous segment and asking the subject to grade the intensity of the sensation induced (Figure 1). This pain model has shown that a variety of nonphysiological endovenous stimuli, such as the application of cold or heat, balloon dilation of the vein, electrical stimulus, and infusion of hyperosmolar saline, produce a painful sensation that starts at a particular threshold and whose quality is the same whatever the method of stimulation used.

Furthermore, the intensity of the sensation of pain increases exponentially with the intensity of the stimulus and completely disappears after injection of a local anesthetic in the isolated venous segment. Regardless of the source of the pain stimulus, the stimulus-sensation curves (intensity of sensation of pain with increasing intensity of applied stimulus) are all the same. These intriguing results suggest that the different stimuli activate the same venous nociceptors, which means that most nociceptors located in the venous wall are polymodal nociceptors.

These experiments have shown that venous dilation is unlikely to be an important factor in the sensation of venous pain. Mechanical venous balloon dilation has to increase the diameter of a vein by three times its normal value before pain begins to be experienced. If we add to this observation the fact that venous dilation is not normally perceived as painful when induced by pharmacological methods such as the local application of adenosine, it appears that even major venous dilation is not in itself a significant source of venous pain in normal subjects. Moreover, arteriovenous fistulae created for the purpose of hemodialysis are painless, another strand of support for this conclusion.

Pain experienced and clinical severity of venous disease
Numerous epidemiological studies have shown that the existence, intensity, or both of lower limb symptoms associated with CVD do not correlate with the severity of clinically evaluated venous disease. The quantitative evaluation of CVD is normally based on the CEAP (Clinical-Etiological-Anatomical-Pathophysiological) classification, a system for classifying clinical signs in one of seven classes (C0 to C6) (Table I) according to their severity. In a population study of over 1500

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**Selected Abbreviations and Acronyms**

- **CEAP**: Clinical-Etiological-Anatomical-Pathophysiological
- **CVD**: chronic venous disease
- **PAF**: platelet-activating factor
was also the case for deep veins, too. When venous symptoms and pain was not only limited to superficial veins; this addition, this correlation was limited either solely to men (sensation of swelling) or solely to women (sensation of heaviness and sensation of swelling, heaviness, or tension was low. In fact, 45% of patients who complained of lower limb pain compatible with CVD did not have varicose veins, while about 40% of women presenting with varicose veins in the clinical examination were asymptomatic. Moreover, in men, no significant correlation was found between pain and the existence of truncular varices.

### Table I. The CEAP classification.

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
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<tbody>
<tr>
<td>C0</td>
<td>No visible or palpable signs of venous disease</td>
</tr>
<tr>
<td>C1</td>
<td>Telangiectasias or reticular veins</td>
</tr>
<tr>
<td>C2</td>
<td>Varicose veins; distinguished from reticular veins by a diameter of 3 mm or more</td>
</tr>
<tr>
<td>C3</td>
<td>Edema</td>
</tr>
<tr>
<td>C4</td>
<td>Changes in skin and subcutaneous tissue secondary to CVD, divided into 2 subclasses to better define the differing severity of venous disease: C4a: pigmentation or eczema C4b: lipodermatosclerosis or atrophie blanche</td>
</tr>
<tr>
<td>C5</td>
<td>Healed venous ulcer</td>
</tr>
<tr>
<td>C6</td>
<td>Active venous ulcer</td>
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</tbody>
</table>

Regardless of the sex of the patient, no symptoms seemed to vary according to the severity of varicose veins. Several studies of patients with advanced CVD (classes C4 to C6) have shown that there is a relation between the degree of Doppler scanning–identified venous reflux and the severity of venous clinical signs and symptoms. Nonetheless, this does not seem to be the case for early-stage CVD. The search for such a correlation in the Edinburgh Vein Study, which focused primarily on patients presenting with early-stage venous disease, proved disappointing. In the Edinburgh Vein Study, the correlation observed between pathologic superficial venous reflux (duration greater than or equal to 0.5 seconds) and sensation of swelling, heaviness, or tension was low. In addition, this correlation was limited either solely to men (sensation of swelling) or solely to women (sensation of heaviness or tension). Strictly speaking, no significant correlation was observed between superficial venous reflux and pain.

A lack of correlation between the presence of venous symptoms and pain was not only limited to superficial veins; this was also the case for deep veins, too. When venous symptoms were compared with deep venous reflux (popliteal vein), no correlation was found, irrespective of the patient’s sex. Equally, in a study of over 120 patients with mild to moderate CVD, no correlation was seen between pain intensity and clinical severity of venous disease based on the CEAP classification.

Furthermore, Howlader and Smith reported no statistical relation between the pain score or heaviness score of a patient, evaluated on a 10-point visual analogue scale, and the clinical severity of venous disease, in a cohort study of 132 patients. The median pain score was 2.8 in the group of patients with class C2 venous disease, 4.5 in class C3, only 0.5 in class C4 and 0 in patients with class C5 venous disease. No difference was noted in pain scores between patients presenting with superficial venous reflux and those presenting with deep venous reflux. These results fully uphold the findings of a French survey on the frequency of clinical symptoms according to the duration of venous disease.

The French survey illustrated a very significant decrease in the frequency of functional signs of venous disease, in particular pain, over time. So, for example, the frequency of the painful heaviness sensation dropped from 71% in the group with symptoms of less than 5 years’ duration to 50% in the group whose symptoms were of 30 years’ duration or longer. These findings concur with the results of a Swiss epidemiological study that indicate the prevalence of varicose veins increases with age, while pain decreases with age.

### Inflammatory autoamplification and pain mechanisms in venous disease

Present-day hypotheses on how pain mechanisms act in venous disease focus on a local inflammatory origin, related to venous stasis. The processes that generate pain in venous disease in the short term seem to be identical to those involved in the process of varicose vein remodeling, defined as all of the qualitative and quantitative alterations in the cellular and matrix components of the venous wall, in the longer term.

Local hypoxia associated with capillary stasis is probably the origin of these mechanisms. The partial pressure of oxygen has been demonstrated to fall significantly in lower limb veins in venous disease after 30 minutes in a standing position, and many studies have shown that capillary stasis–induced hypoxia activates endothelial cells. This type of activation is signaled by the elevation of calcium concentrations in the cytoplasm of endothelial cells, which upregulate phospholipase A₂ activity.

Activation of phospholipase A₂, in turn, leads to the synthesis and local release of proinflammatory mediators such as platelet-activating factor (PAF), bradykinin, prostaglandins E₂ and D₂, and leukotriene B₄. PAF seems to play a key role: it boosts the local release of histamine and serotonin; it caus-
es abnormal adherence of neutrophils to the venous endothelium, prior to their infiltration through the venous wall itself; and, finally, it stimulates the synthesis of leukotriene B4 by activated neutrophils. In the last few years, the amount of evidence for the existence of this type of inflammatory reaction in patients with varicose veins has snowballed, and the biochemical changes identified point to endothelial cells and neutrophils as the source of this local inflammation.24-29

There are a plethora of indicators of inflammation in venous disease: the presence of neutrophils, monocytes, and activated T lymphocytes; the accumulation of macrophages and mast cells; the expression of adhesion molecules on the surface of leukocytes and endothelial cells (eg, LFA-1, VLA-4, ELAM-1, ICAM-1, VCAM-1); and the synthesis of cytokines (eg, IL-1β, IL-6, TNF-α) and prothrombotic factors (eg, von Willebrand factor) are all indicators of inflammation in venous disease.14,30 Venous nociceptors can be activated by proinflammatory mediators released locally as a result of hypoxia. The intravenous or perivenous application of one such mediator, bradykinin, evoked a sensation of pain in healthy subjects, which unambiguously establishes the role of this neuromediator in venous pain.31

A finding that substantiates this hypothesis comes from a study by Howlader and Smith, which demonstrated that nitric oxide concentrations measured in blood collected in the saphenous vein or in a vein in the dorsal aspect of the foot were significantly higher in patients with the most severe stage of venous disease.35 Likewise, certain studies have reported higher levels of markers of endothelial activation in experimental venous hypertension in the most advanced stages of venous disease.36

Given the importance of these inflammatory processes in pain production as well as in varicose vein remodeling, a correlation between levels of inflammatory markers and the intensity of pain in venous disease might be expected to exist. However, this is not the case, in much the same way that the clinical estimation and evaluation of venous pain by venous Doppler scanning proved negative.17 No significant correlation was found between levels of 12 inflammatory markers (measured in a vein on the dorsal aspect of the foot) and pain intensity score on a visual analogue scale in a population of 132 patients with CVD ranging from class C2 to C5. The relationship between the venous wall inflammatory cascade and pain associated with venous disease seems difficult to demonstrate formally.
Pain and objective markers of venous disease

The intensity of pain of venous origin does not correlate with the extent of truncular varicosities observed in clinical examination, the severity of reflux measured with Doppler scanning, or levels of inflammatory markers measured in a lower limb vein. Could hypoxia offer a possible explanation? It is entirely possible that many painful hypoxia-related conditions may occur transiently in patients, e.g., after standing for a prolonged period, at the end of the day, or during certain periods of the menstrual cycle, if hypoxia is indeed a major factor that triggers pain of venous origin.

If venous and perivenous nociceptor-activating chemical cascades were to occur before significant remodeling of large venous vessels arises, this might explain the frequency of functional signs, such as pain or heaviness in the legs, in patients who do not have varicose veins and the lack of abnormal reflux seen in a Doppler scan, as in the Edinburgh Vein Study. While the same essentially inflammatory biochemical and cellular processes are implicated in pain and varicose vein remodeling, the time frame over which these pathological mechanisms occur is different.

Pain appears to be a short-term consequence of venous hypoxia, while varicose vein remodeling seems to take place at a much later stage of CVD. Because the occurrence of pain does not appear to be closely related to objective parameters of varicose vein remodeling, incompetent venous valves, or inflammation, this suggests the primary site of venous/perivenous nociceptor activation may not be the large venous vessels. In light of this fact, the hypothesis of local activation of nociceptors in the microcirculation, where contact between nerve endings, the arteriole, the vein, and the capillary is probably much closer than at the macrovascular level, seems highly conceivable.

As a result, several studies looked at microcirculatory parameters of venous disease. In addition, several studies using an experimental model of acute venous occlusion in the rat showed that an increase in microvascular pressure triggered an inflammatory reaction characterized by infiltration of neutrophils into the endothelium and adjacent tissues.

Shear stress on the endothelium produced by blood flow is another essential factor that promotes inflammation of the venous wall. Shear stress can influence many intracellular biochemical processes, such as protein G phosphorylation, activation of tyrosine kinases, free radical production, and the synthesis of different nuclear transcription factors, via integrins anchored in the endothelial cell membrane. Physiologically normal shear stress produces a potent, local anti-inflammatory effect, while a reduction or an increase in this force below or above a given physiological threshold can lead to overexpression of proinflammatory genes.

Explaining the disappearance of pain in advanced stages of CVD

Alteration of innervation of the venous wall and the perivenous tissue may explain the significant decrease in the frequency and intensity of pain in the most advanced stages of venous disease. This change in nerve fibers may reflect sensory peripheral neuropathy, perhaps related to ischemia secondary to venous microangiopathy, and an increase in endoneural pressure. The threshold of tactile, vibrational, and thermal sensation in the extremities in patients with CVD is significantly higher than normal, suggesting the loss of sensory axons. This sensory threshold elevation was significantly more distinct in class C5 than in class C2 disease. A reduction in the number of venous and perivenous nociceptors could well account for a lessening of pain in the most advanced stages of venous disease.

Interindividual pain variability in venous disease

The range and intricacy of mechanisms involved in the pathogenesis of venous disease pain are a significant source of interindividual variability. Both the reactivity of the cellular components involved (endothelial cells, neutrophils, and venous and perivenous nociceptors) and the ways in which nociceptive stimuli are processed in the brain produce this variability. At a cellular level, for example, experimental studies of human umbilical cord venous endothelial cells have demonstrated that the quantity of different prostaglandins released as a result of hypoxia can differ by a factor of 10 depending on the donor. By the same token, neutrophil reactivity to other inflammatory signals varies with age and previous sensitization (“priming”). What’s more, the density of venous and perivenous innervation as well as the presence of nociceptors in ion channels, which allows the conversion of a chemical message into a nerve impulse relaying nociceptive information, can also vary considerably from one person to another.

Interindividual variability in the way the brain reacts to pain stimuli will also play a part. The intensity of brain modulation of nociceptive signals resulting from the release of endogenous opioids, whose concentrations vary from subject to subject due in part to genetic factors, is also likely to account for some of the pain sensitivity in a given individual with regard to venous nociceptive stimuli. For instance, the genotype of the catechol-O-methyl-transferase enzyme, which determines the quantity of endogenous opioid released during a pain stimulus, significantly affects pain sensitivity.

However, all these variables are just relative obstacles in the elucidation of pain mechanisms in venous disease. In the absence of a correlation between the state of large venous vessels and the degree of pain reported, perhaps we ought to be examining the interaction between the mediators of inflammation and venous nociceptors in more detail, with a mind to developing a method of testing nociceptive function in venous disease microcirculation.
References


Keywords: pain; chronic venous disease; inflammation; nociceptors; C-fibers
La douleur est la plainte qui mène le plus souvent au diagnostic de maladie veineuse et elle influe significativement sur la qualité de vie des patients. Pour tous ceux qui se préoccupent de la MVC, la douleur est difficile à évaluer à la fois à cause de sa nature multidimensionnelle et à cause du manque de relation étroite entre la douleur en tant que symptôme et la sévérité de la maladie veineuse. Des hypothèses actuelles sur le mécanisme d’induction de la douleur dans la MVC soulignent son origine locale inflammatoire. De nombreux médiateurs inflammatoires sont libérés localement aux stades précoces de la MVC, activent des fibres C démyélinisées dans la paroi veineuse, entraînant la douleur. Ces 5 dernières années, on a assisté à une véritable explosion du nombre d’indicateurs suggérant une réaction inflammatoire dans les varices. Il est toujours difficile d’expliquer les mécanismes précis à l’origine de l’interaction entre les nocicepteurs veineux et les médiateurs de l’inflammation, qui pourraient contribuer à la variabilité de la douleur observée dans la maladie veineuse.
Under this heading, each issue of *Medicographia* features two cultural articles. The first one touches on the history of medicine, based around a great figure from French history, while the second one addresses broader aspects of France’s heritage, such as history, art, literature, and the description of museum collections.

Theory and practice: European Renaissance medicine

S. Daynes-Diallo, France


© Archives Charmet/The Bridgeman Art Library.

Écouen: from château to museum, or Beauty is in the detail

S. Deprouw, France

Dish with intertwined flowers (detail).

Iznik, Turkey, circa 1580.

© RMN/René-Gabriel Ojéda.
Although Renaissance medicine has not had the impact of Renaissance art, there were nevertheless major advances in the field of medicine at this time, notably in a Humanist reassessment of the medical legacy from antiquity, a ratification of medical education at medical institutions, and an explosion in the dissemination of medical knowledge. In addition, Renaissance medicine developed the first treatments for firearm wounds and welcomed the arrival in Europe of new remedies from far-flung shores.

Renaissance medicine amalgamated the theory and practice of medical knowledge inherited from Antiquity and the Middle Ages. Although it built on much from the past, it also innovated—Renaissance medicine was determined to shake off its Medieval trappings. In spite of the fact that medicine in the 16th century did not experience a renaissance comparable to that seen in the arts—the medical revolution was still a century away—it could not fail to be caught up in the Humanist wave sweeping through Europe, and it made genuine progress as a result. While the Copernican revolution turned Medieval cosmology on its head, the Reformation undermined Catholic dogma and questioned the relationship between God and Man, and technical advances—spearheaded by printing—led to an unprecedented transformation in knowledge and practice, medicine swung between a form of Humanism that was extremely deferent to the Ancient Greeks and Romans, but which eventually opened the way for textual criticism, and an increasingly empirical form of clinical practice in response to the century’s two main scourges: epidemics and the arquebus—one natural, the other man-made. It was also in the 16th century that medical fraternities organized themselves into institutions and prepared the ground for modern medicine and the completion of the synthesis of theory and practice.
Renaissance medicine amalgamated the theory and practice of medical knowledge inherited from Antiquity and the Middle Ages. In response to the humanism of the age, its attitude constantly oscillated between atavism and innovation, which produced tangible progress and prepared the ground for the blossoming of modern medicine that occurred in the 17th century.

The legacy of the past
The medical world of the Renaissance inevitably bore the stamp of its Medieval counterpart. Medicine in this era was a component of *physica*—the Latin echo of Aristotle’s *τὰ φυσικά*—incorporating the natural sciences, philosophy, and religion. It perceived the world as a macrocosm reflected in the human microcosm, so that the laws governing the one also governed the other. The ambition of Renaissance man was to unveil and understand God’s creation across both spheres. Medical doctrine inherited the synthesis of three great intellectual traditions from the Middle Ages: the Arabic teachings of Antiquity, Christian doctrine, and Middle Eastern culture and science. The corpus of a Renaissance medical library comprised the works of Hippocrates (circa 460 – circa 370 BC), Aulus Cornelius Celsus (circa 25 BC - circa 50 AD), Pseudo-Dioscorides (circa 40-90), and Galen (129-199/217), along with those of Avicenna (circa 980-1037), Averroes (1126-1198), and the teachings of the Salerno School of Medicine from its heyday between the 10th and 13th centuries.

Medical science was based on the doctrine of humors expounded by Hippocrates and his “prophet” Galen. Being a microcosm of the universe, the human body was naturally composed, like the universe itself, of the four “fundamental elements” of earth, water, air, and fire. Each of these elements was in turn characterized by four essential “qualities”: hot, dry, cold, and wet. In addition, the human body was bathed in four “fluids” or “humors,” characterized by two essential “qualities” and one “fundamental element”: blood—hot and wet—was associated with air; phlegm—cold and wet—with water; yellow bile—hot and dry—with fire; and black bile—cold and dry—with earth. In normal circumstances, the humors acted in harmony to produce a healthy, “temperate” individual.

*Decorated initial from the Basel 1555 edition of Andreas Vesalius’s *De Humani Corporis Fabrica* published by Johannes Oporinus. Woodcut. © Wellcome Images.

The Four Humours, from Quinta Essentia by Leonhart Thurneisser zum Thurn (1513-95/6) published in Leipzig, 1574 (engraving) (b/w photo). German School, (16th century)/private collection. © Archives Charmet/Bridge man Giraudon.
Disharmony resulted in illness and disease. Thus an excess of all four humors, especially blood, gave rise to “plethora” (forming the doctrinal basis for bloodletting), while the relative excess of a single humor produced a state of “cacochymy.” The humors were complemented by three spirits animating the body: the “natural” spirit residing in the liver, the “vital” spirit in the heart, and the “animal” spirit in the brain. The aim of Renaissance medicine was to understand more about these humors, recognize their disharmony in patients, and correct them with a set of defined interventions and long-established remedies.

A medley of medical professions and skills
The three guilds of physicians, apothecaries, and surgeons formed the basis of the practice of Renaissance medicine. Over the century, they gradually established themselves into separate institutions, but not without clashes and competition. In addition to these three professions at the top of the medical hierarchy, headed by physicians, 16th century citizens could also access the services of a huge spectrum of artisans prepared, in the absence of the three notables, to undertake medical interventions based essentially on practical experience and folk wisdom. Although Renaissance physicians came from a wide range of social origins, the possession of a university doctorate of medicine conferred a relatively exalted social status on its holder. Attachment to the university was associated with a number of privileges, an oath, and obligations. In provincial cities without a university, organization into corporations or colleges ensured the integrity and protection of the physicians’ guild.

Nevertheless, the gulf in status between the ennobled senior court physician and the provincial physician, or between the private physician of an important figure such as a prince, prelate, or minister and the town-council physician caring for paupers, was huge. In general, however, physicians confined their practice to an urban and well-to-do clientele.

Physicians dressed austerely, in black cassock and cloak, turned down cuffs and collar, and wide-brimmed hat. Above all they were men of letters who taught natural science and literature in universities or at the Collèges de France. They tended to be humanists and poets, and were far more adept in doctoral discourse than in clinical practice or intervention, which they delegated to students, barber surgeons, or even apothecaries.

In France, apothecaries joined with grocers to form the second of the six merchant guilds. Like physicians, they enjoyed important privileges in the Renaissance period, which also came with obligations and an oath very similar to that of the
Folk wisdom based on a combination of magic, religion, and time-honored empiricism enabled everyone either to treat a fellow human being out of charity or neighborliness. But also in towns and villages—a whole range of practitioners served the swathes of population denied access to a physician or surgeon, whether for geographic or financial reasons. Folk remedies, charitable acts by priests or members of religious orders, and recommendations and cure-alls endorsed by ladies in the aristocracy or bourgeoisie were available alongside healers, sorcerers, soothsayers, astrologists, and peddlers of potions. Together they formed a motley army of charlatans purveying an illicit and generally peripatetic medicine that was condemned by the university medical authorities. In addition to this array of dubious practitioners, not forgetting the constant and insistent recourse to faith (ranging from regular devotion to supplications to healer-saints, not to mention a whole gamut of processions, prayers, pilgrimages, and penances), there existed a number of artisans who plied a specialist trade across the class divide: bonesetters, peripatetic barbers, lithotomists (extractors of human kidney, bladder, and gall stones), specialists in hernias and cataracts, toothdrawers, and midwives.

The professional world of surgery during the Renaissance was extremely complex and beset by conflict, the primary although not exclusive source of which lay in the contempt that had been shown for this "manual" discipline by physicians since the Middle Ages: in the 13th century, at a time when medical science was still the privilege of churchmen, Canon 18 of the Fourth Lateran Council forbade the "shedding of blood." This amounted to the de facto exclusion of surgery from both churchmen’s medical practice and the university curriculum. Thus secularized, surgery was left to surgeons, who taught it in schools that varied in the nature of their relationships with the universities.

The second source of conflict in the world of surgery lay in the huge disparities in knowledge and practice within the profession, from the educated master of surgery at the pinnacle of the profession to the barber surgeon, who had learned his craft on the job and who was licensed to practice minor surgery, bloodletting, and the dressing of wounds, at the bottom. In the struggle to obtain recognition for their profession, both groups had to fight off antagonism and encroachment from the university-trained medical profession throughout the 16th century. Below both these groups—mainly in the countryside, but also in towns and villages—a whole range of practitioners served the swaths of population denied access to a physician or surgeon, whether for geographic or financial reasons.

Regulated university medical training

Renaissance universities comprised four faculties. Students had to pass through the first, the faculty of arts—where they studied grammar, the humanities, rhetoric, and philosophy—before they could accede to any of the other three major faculties (theology, medicine, and canon law). From the 13th century onwards, the faculty of medicine was separate from the faculty of arts. Access required the degree of Master of Arts, accompanied by a certificate of baptism in Paris, but granted “regardless of nationality or religion” in Padua. From the second half of the 16th century onwards by the teaching of theory that foreshadowed that dispensing in modern schools of pharmacy. Apothecaries dressed similarly to physicians, whom they served by dispensing their prescriptions.

Studies were conducted in Latin. They consisted essentially of reading and analyzing the texts from Antiquity, mixed in increasing with those of more contemporary authors. In the early 16th century, theoretical teaching was structured around the study of “natural things” (anatomy, physiology, botany), “non-natural things” (hygiene and diet), and “contra-natural
things" (pathology and therapeutics). Theoretical learning was supplemented by practical sessions in botany and anatomy. Paris, Montpellier, Padua, and Bologna were the major 16th century universities and were all originally founded in the Middle Ages. These major centers of learning were not isolated, however. For example, France numbered over twenty faculties of medicine or medical study centers. Students liked to travel from one center to another to study and accumulate qualifications from each.

A number of private medical teaching establishments coexisted with the faculties. In Paris, some colleges that taught medicine gradually merged with the university, such as the Colleges of Tricquet and Cornouailles; similarly, in Montpellier, there was the College of the Twelve Physicians. There were also schools of surgery (colleges of Saint Cosmo), which gradually became incorporated into universities. The Collège de France, set up in 1530 by François I, boasted a chair in medicine from as early as 1542.

Universities were thus not the only institutions that taught medicine. But in addition to teaching and conducting research, they had other prerogatives. For example, they were consulted on issues of general interest to the State, such as public health and hygiene. They also produced the majority of physicians employed by royalty. Universities were also given the duty of overseeing apothecaries, barber surgeons (to a lesser extent), and midwives.

A change of intellectual direction: medical Humanism

Humanism informed the entire Renaissance, most visibly in the arts and sciences. Positioning Man and human values at the center of thought, the new philosophy was characterized by a return to the writings and practices of the Ancient Greeks and Romans, deliberately breaking from the supposed legacy of the Middle Ages. The change of intellectual direction that took place initially in Italy between the late 14th and mid-15th centuries spread rapidly throughout Europe. Humanism took its name from the Latin humanitas, meaning the "humanities" or the study of Latin and Greek in the broadest sense: the idea was to follow the paths laid down by the Ancient Greeks and Romans in knowledge, ethics, philosophy, and politics.

The Humanism of the Renaissance was thus characterized by a desire to return to the writings and practices of the ancients stripped of their Medieval dross: these writings had, after all, been translated, annotated, and added to throughout the Middle Ages. Humanists in all branches of knowledge therefore embarked on the vast undertaking of rereading, reanalyzing, and republishing the texts of Antiquity that had been handed down to them. In medicine, for example, the last quarter of the 15th century saw the republication of De re medica by Aulus Cornelius Celsus, along with central works by Hippocrates and Galen.
Consequently, the entire century witnessed a vast dissemination of Humanist thought, aided and abetted by the development of printing in particular, but also by university teaching and Humanist practice. Magnificent testimony to the movement comes in the form of manuscripts and printed works specifically composed and published for the great Humanist libraries founded by princes and prelates, kings and emperors, and the religious foundations of which the universities were a part. Two compendia of Greek and Roman surgical writings organized by the celebrated Florentine physician Guido Guidi (aka Vidus Vidius [1508-1569]) for the Humanist library of François I and illustrated by the Florentine artist Francesco Salviati (1510-1563) are exemplary in this regard. This sublime work, published in 1544, was a crystallization of the scientific and artistic excellence to which Humanists aspired. Reproduction of its plates throughout the 16th century to adorn multiple works on allied topics, such as those by the French royal surgeon Ambroise Paré (circa 1510-1590), provide a perfect illustration of the dissemination of the Humanist movement.

**Emergence and celebration of anatomy as a discipline**

The Renaissance updated the practice of anatomy to Humanist times. Anatomical dissection, a practice inherited from Antiquity, had been officially conducted in Italy since the 13th century and in France since the 14th century. The papal bull issued by Boniface VIII in the 13th century had secured its approval by the Church for the sole purposes of legal autopsy and university demonstration.

At the start of the 16th century, dissection was only used in university teaching to illustrate the writings of Antiquity. Its role and status grew steadily throughout the century. It began to be performed outside universities, for instance, in independent colleges, at the Collège de France, in schools of surgery, by private individuals (students and barber surgeons), and also by artists. The practice was almost always illegal, but generally tolerated. The details of cadaver provenance remain murky. Andreas Vesalius (1514-1564) is believed to have fetched his supplies from the multistorey gibbet of Montfaucon in what is now the 10th arrondissement of Paris. Other objects of dissection included animals, colleagues, and even friends (who could thus be said to have bequeathed their bodies to science!). An additional source of bodies was pauper cadavers from hospices.

The most remarkable expression of the new anatomy was the masterpiece by Vesalius, *De humani corporis fabrica libri septem*. Published in 1543, the same year as *De revolutionibus orbium coelestium* by Copernicus, it incarnated the urge to question the all-powerful work of Galen and its reverential exponents, which had begun at the turn of the century with the first pre-Vesalian anatomists: members of the Padua School, the English Humanist Thomas Linacre (circa 1460-1524), and the Paris School, one of whose graduates, Charles Estienne (1504-1564), produced (some time before 1539) *De dissectione partium corporis humani*. This work was very similar to *Fabrica*, except that unlike Vesalius, Estienne did not engage a pupil of Titian to take care of the illustrations.

Such fastidiousness was emblematic of the Vesalian revolution: at the same time as Vesalius was insisting on the necessity of the teaching of anatomy and the superiority of hands-on experience over medical scripture and its associated iconography, he was calling on one of the great art workshops of his day for illustrations, regardless of the expense. After all, it was the workshops of Leonardo da Vinci, Verrocchio, Michelangelo, and Dürer that had pioneered the study of anatomy, in terms of representing the human body, in the very early Renaissance. These studies originated mainly from...
Scenes of medical life during the Renaissance.
Frontispiece of Der Gantzen Artzenei, by Johann Eichmann (Dryander) (1500-1560), published by Christian Egenolph, 1542, Frankfurt am Main. Engravings outside frame—upper left: doctor examining a patient’s urine; upper right: bloodletting; main engraving, clockwise from top left: examining a bedridden patient; selection, picking, and preparation of medical herbs; discussion among doctors; apothecary preparing medicines.
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Leonardo’s workshop and were unknown to immediate contemporaries. But their direct influence was displayed for all to see in Fabrica, in an explosion of magnificent yet elegant detail that symbolized the quest for meaning by an entire epoch obsessed with the human body.

Anatomy thus came into its own in the 16th century, as pictorial representation, descriptive treatise, and clinical method. It was to retain its central status for centuries to come. In addition, by encouraging the investigation and elucidation of the human body, the commitment to research and empirical method that drove Vesalius and those who came after him put clinical intervention and hands-on experience back into the heart of medical practice, thereby opening the door to the surgeons.

**Surgical progress: the impact of the arquebus**

Surgery in the 16th century was marked by the beginning of a rise in the social status of surgeons and the normalization of their profession. In addition to celebrated anatomists and surgeon-physicians such as Vesalius, a number of barber surgeons helped their specialty to recover its scientific status. Under the direct challenge of their century’s two main scourges—epidemics and the first firearms—these surgeons led a revolution in surgery that extended way beyond the battlefield and the hospitals where they practiced.

Battlefield surgeons such as Paré, their most celebrated representative, were also responsible for the extensive dissemination of surgical knowledge. In direct contrast to the illiterate caricatures disdained by faculty physicians, they produced surgery and anatomy manuals in vernacular language, which were often richly illustrated and went hand in hand with Humanists’ dissemination of knowledge in similar areas.

It was the battlefield that generated the major surgical advances of the 16th century. Surgeons routinely joined army units, replacing the charlatans that had been used up to that time. Their presence was a necessary response to the increasing violence of battle due to the development of short-range firearms—the arquebus, then the musket—and the novel wounds they produced.

Paré introduced new methods of treating multiple wounds, and a new approach to firearm wounds. Like the personal physician to Henri III, Laurent Joubert (1529-1582), the Swiss surgeon Félix Würtz (dates uncertain), and Hans von Gersdorf (circa 1455-1529) in Strasbourg, he also had an interest in amputations, prostheses, and orthopedic corrective techniques, making some striking contributions in these fields. He published his studies in a large number of works with illustrations combining realism, clarity, sobriety, and a talent for disseminating knowledge. The works are also a treasure trove of the surgical arsenal of the time, only very rare items of which have come down to us. They are particularly valuable for identifying contemporary surgical implements because these can be difficult to tell apart from the tools used by butchers, hunters, and even gardeners.
Ordinary medical practice

On the ground, far from the lofty heights of major surgery and anatomical research, there existed during the Renaissance, as at any other time, ordinary medical practice comprising a set of medical interventions and remedies. Patients were attended in their homes by all levels of practitioner, whether by the prestigious doctors of medicine, who once at the bedside mutated into practicing physicians, or by the humbler physicians themselves, along with their assistants (apothecaries, barbers, and students). The consultation consisted of eliciting and interpreting signs and symptoms, issuing recommendations as to diet or hygiene, performing medical interventions, and writing an extemporaneous prescription for medication.

In addition to the patient interview, the consultation used the following techniques to elicit signs and symptoms: inspection and interpretation of the pulse, urine, and feces, and in some cases blood; and assessment of the patient’s “heat” (temperature), appearance, and complaints. Once interpreted, the condition could be treated with a variety of interventions: bleeding, enema, and cauterization, selected according to the most propitious planetary movement or sign of the zodiac.

The documentary evidence for the ordinary medical practice described above is fairly extensive. In particular, it is backed by an impressive catalogue of iconography. It is also documented in brilliant detail in the remarkable diary of Jean Héroard (1551-1628), physician to Louis XIII, which is held at the Bibliothèque nationale de France.

Apothecaries and their therapeutic arsenal

Designed to restore humoral harmony, the therapeutic arsenal available in the Renaissance was boosted by new ingredients from the Americas (such as tobacco or the hardwood lignum vitae) and by increasing trade relationships with other distant lands. The basis of apothecary practice nevertheless remained the Antidotarium by Nicholas of Salerno (12th century), along with numerous pharmacopoeias, compendia, and recipes.

The remedies made up by apothecaries against physicians’ prescriptions fell into three main classes, termed “alterative,” “evacuative,” and “specific.” Although almost all were of plant or animal origin, some preparations were mineral (e.g., metals such as the antimony prized by Paracelsus [1493-1541], pearls and precious stones, marble, crystal, chalk, and various earths) and a few were of human origin (e.g., milk, blood, bone, urine, excrement, and a mellified human mummy confection known, in a variety of spellings, as *mumie*). Distillation was increasingly used to obtain active ingredients and led to advances in medicinal chemistry. Panaceas were taken as infusions, decoctions, tinctures, syrups, pills, preserves, and confections (the most famous of which was the theriac of Andromachus [1st century] or *theriaca Andromachi*). Alternatively, they were applied top-
ically as ointments, cerates, plasters, poultices, or eye salves; inserted as suppositories or pessaries; or pinned to the clothes or attached to the skin as powder-filled bonnets and sachets.

**Explosion in the dissemination of medical knowledge**

The discovery and rapid development of printing proved extraordinarily effective in disseminating medical science and distributing the texts required for its practice: antidotaria; manuals of surgery, day-to-day medicine, and pharmacy; and almanachs of planetary movements and signs of the zodiac to guide the selection and timing of interventions. As Humanist scholars, physicians saw the dissemination of medical knowledge as an honorable mission. Writing in everyday language also made them accessible to humbler colleagues: French or German editions of works by Paracelsus, Jean-François Fer- nel (1497-1558), or Paré could be read by apothecaries and barber surgeons. Humanist reinterpretations and republications of works by the ancients (to which some physicians, such as Niccolo Leoniceno [1428-1524], devoted themselves almost exclusively) not only transmitted the knowledge inherited from Classical antiquity along with some critical reflection, but were also paralleled by the dissemination of a rich body of contemporary literature that improved rapidly in terms of illustrations and structure as the century unfolded. Thus, 16th century medicine may not have undergone a true Renaissance, but it was nevertheless a true child of its time. Viewing its twin Classical and Medieval inheritance through the prism of Humanism, it inevitably reflected the influence of contemporary religious and philosophical debate. In addition, it managed to bring about a synthesis of the key components in its heritage and, thanks to some remarkable men, to prepare the ground for the blossoming of modern Western medicine the following century.

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**Théorie et pratique : la médecine dans l’Europe de la Renaissance**

*Entre théorie et pratique, la médecine à la Renaissance opère une synthèse du savoir hérité de l’Antiquité et du Moyen Âge. Elle reçoit beaucoup de son passé mais innove également et va, de manière forte, vouloir se défaire de ses limbes médiévales. Si l’on ne peut pas parler de Renaissance médicale au sens où l’on parle de Renaissance des Arts, car la révolution en ce domaine se fera au siècle suivant, la médecine au siècle de la Renaissance n’échappe pas pour autant à la vague humaniste qui anime le siècle, et connaît de réels progrès. Alors que l’ébranlement du cosmos médiéval se produit avec la révolution copernicienne, que la Réforme bouscule le dogme catholique et questionne le rapport entre Dieu et les hommes, que l’on assiste à des progrès techniques qui – imprimerie en tête – permettent une révolution du savoir et des pratiques sans précédent, la médecine oscille entre un humanisme faisant preuve d’une extrême déférence envers les Anciens mais ouvrant enfin la porte à la critique textuelle et une pratique médicale progressivement décomplexée et enhardie par les fléaux du siècle : l’arquebuse et les épidémies. C’est en effet au XVIe siècle que les corps médicaux s’institutionnalisent et construisent le berceau de la médecine moderne, dans laquelle théorie et pratique se seront réconciliées.*
The Château d’Écouen, where the prestigious Renaissance collections from the former Cluny Museum in Paris (today the French National Museum of the Middle Ages) are now held, was converted into a museum at the behest of De Gaulle’s Minister of Culture, André Malraux, and opened to the public in 1977. It is home to a wide range of artwork—tapestries, paintings, ceramics, stained glass, furniture, gold antiques, and silverware—from the Age of Discovery until the early 17th century.
Located 20 km north of Paris, the Château d’Écouen was built in several stages beginning in 1538 for the French soldier, statesman, and diplomat Anne de Montmorency (1493-1567)—Anne being not uncommon at the time as a name for boys—shortly after his childhood friend, King François I, appointed him Constable of France, a post that combined the functions of First Officer of the Crown and Commander-in-Chief of the Army. Montmorency had the existing medieval structure demolished to make way for an unabashedly modern château on top of a hill overlooking the flat region just north of Paris, known as the Plain of France.

A palace to host the Royal Court
A proponent of sustainable development centuries before the concept was coined, Montmorency installed a particularly sophisticated rainwater conveyance and harvesting system, much of it underground, to supply his vaulted bathrooms in the basement of the north wing: this suite dedicated to relaxation—after exertion following hunting or tennis, for example—is one of the last two remaining in France, the other being in the Château de Maulnes in the department of Yonne. It epitomizes the Château d’Écouen’s claim to refinement.

In opting for an architectural style that was both sober and radical—originally a square bounded by projecting rectangular wings—the Château d’Écouen resembles the Château d’Ancy-le-Franc (Yonne) built by Sebastiano Serlio for Antoine de Clermont (1498-1578) during the same period (1542 to around 1550). There is no record of Écouen’s first architect or
project manager. Jean Bullant, who was to become Anne de Montmorency’s favorite architect and who later built the Petit Château for him at Chantilly, appears only to have been involved at Écouen at a later stage (1552), when he redesigned the staircase and north front to accommodate the frequent visits of the King and his Court. The accounts of the château’s construction were unfortunately lost during the French Revolution, but we know that work continued on the château almost until Montmorency’s death in 1567. Although built primarily for gracious living, the château remained defensive in appearance at least, in particular because of its moats, which were dry from the outset. A distinctive feature of the building is the elaborate classical ornamentation of the windows set in the sloping roof. The Constable’s coat of arms (a sword with the motto “APLANOS”—“Unswerving”) is repeated all along the south wing, which housed his apartments and those of his wife, Madeleine de Savoie, on the second floor. Opposite these apartments were the royal apartments, with Catherine de Médicis on the first floor and Henri II on the second floor. Each set of apartments was identified by the occupant’s respective coats of arms, a rainbow and double K for Catherine and an H double D (for “deux,” ie, second) for Henri.
As Constable, Montmorency was the second most important figure in the kingdom, as is borne out by the place of his name next to Henri II’s signature on some royal decrees. It was therefore entirely appropriate for him to have a palace fit to receive a king. Henri was particularly close to Anne de Montmorency, who returned to royal favor after losing the confidence of Henri’s father François I, following his failure to secure the Duchy of Milan, a state in northern Italy from 1395 to 1797, in his negotiations with the Holy Roman Emperor Charles V.

The château’s finest ornamental sculptures were the two slave statues that Michelangelo had designed for the tomb of Pope Julius II, but which he left unfinished. Two members of the Florentine Strozzi family had acquired them from Michelangelo and gifted them to the French king, Henri II, when requesting the protection of their cousin Catherine de Médicis. Gifted in turn to Montmorency by Henri II shortly after he acceded to the throne in 1547, they were set in the recesses of the south wing’s courtyard portico. The originals, now in the Louvre, have been replaced by casts. The columns flanking them, inspired by the Pantheon in Rome, are the first recorded example in France of the colossal order (spanning two floors).

Moving between his home in Paris and his châteaux at Écouen, Chantilly, and Fère-en-Tardenois (Aisne)—the latter a wedding present from François I—Montmorency displayed the same remarkable curiosity in each, along with a deep appreciation of works of art. His collection included paintings by the Florentine master Rosso Fiorentino (1494-1540), sculptures by Jean Goujon (circa 1510 - circa 1572), painted enamels by Léonard Limosin (circa 1505 - circa 1577), illuminated manuscripts and other sumptuously bound books, and items of the rare Saint-Porchaire pottery produced between the 1520s and 1540s, which were too Mannerist, light, and fragile to be of practical use.

Anne de Montmorency was also the first to discover the rustic potter, Bernard Palissy (circa 1510 - circa 1589), who found inspiration in Saint-Porchaire ware. He commissioned Palissy to create a make-believe ceramic grotto, perhaps for the gardens at Écouen, except that it appeared that it was never completed. Partly as a result of his wide breadth of interest in art, Montmorency was one of the principal patrons of the French Renaissance. Not only could he spot young talent, but he seems on occasion to have been instrumental in guiding their choice of subject matter. Although a fervent Catholic, he displayed, like his Protestant rivals, a taste for the rarer Old Testament subjects. He had these painted on the château’s fireplaces by members of the family workshop, founded by Jean Cousin the Elder (born in 1500). One example, the story of Jacob and Esau, relates to his own story as a younger sibling on whom destiny had smiled. Similarly in the chapel he commissioned a relief, Abraham’s Sacrifice, from Goujon, which has since been removed to the Château de Chantilly. The Château of Écouen comprised a gallery connecting the apartments of Madeleine de Savoie to those of the King, running right the way along the west wing. The decoration of this gallery was sumptuously colorful: stained glass windows told the story of Psyche; under foot were ornamental tiled floors from the workshops of Masséot Abaquesne (circa 1500-1564) in Rouen; while the walls would have been hung with tapestries, not to mention the painted ceilings. The stained glass and tiled floors are inscribed with the date “1542”. A contemporary portrait of the château has come down to us in Les Plus Excellents Bastiments de France (1576-1579), a priceless work by the engraver-architect Jacques l'Androuet du Cerceau (circa 1515-1585) that depicts all the most daring architectural innovations of the French Renaissance. His engravings give us an idea of what the east wing must have looked like. It was demolished at the end of the Ancien Régime for esthetic reasons, and also no doubt because it had been heavily damaged. The wing is believed to have contained a gallery with frescos by Nicolo dell’Abbate (died 1571) and a multicolored tiled floor. Through the portico could be glimpsed a life-sized statue of Montmorency on horseback. There was also a tennis court built on sloping ground below the north wing, close to the bathing suite. Further below were the stables, which now house municipal offices.

Écouen: from château to museum, or Beauty is in the detail – Deprouw

Painted fireplace in Anne de Montmorency’s bedroom (oil, mid-16th century, detail). © RMN/Gérard Blot.
The château remained in the family’s hands until the line was cut short in 1632 by the execution for lèse-majesté, treason, of Montmorency’s grandson, Henri. It then passed to the House of Joyeuse, ennobled by Henri III, and was subsequently inherited by the House of Condé. It underwent few modifications apart from the demolition of the east wing. The château escaped the Revolution relatively unscathed, although it was put to various characteristically novel uses, such as a patriots’ club, a prison, and finally a hospital. It embarked on a new chapter, however, when Napoleon, in a decree dated December 15, 1805, turned it into a school for educating the daughters of members of the Legion of Honor. He returned the Château to its original four-square design by building a new, but lower, east wing, which was designed by Antoine-François Peyre (1739-1823).

The building opened for the 1807 academic year. Except for the period between 1814 and 1850, when ownership reverted to the House of Condé and it became increasingly neglected, the château has remained the official property of the Legion of Honor to this day. The marble courtyard, which was no doubt in very poor condition, was repaved with the Legion’s arms at its center. Students were accommodated in new mezzanines and shielded from unhealthy thoughts by

the whitewashing of the painted chimney-pieces and grottesche friezes, thereby mercifully preserving them for posterity, save for some damage to the fireplaces caused by the insertion of stove pipes into the flues. The last students left the château in 1962.

The sharing of the Château’s fate between the Houses of Montmorency and Condé accounts for the presence at the Château de Chantilly of many artifacts and works of art from Écouen. Prince Henri, Duke of Aumale (1822-1897), who inherited the lands and colossal wealth of the House of Condé at the tender age of 8, may have lost possession of the Château d’Écouen, but he was driven by a passionate interest in art and history. He amassed a superb collection in an attempt to retrieve and recreate his ancestors’ heritage. The collection included books bound with the arms of Anne de Montmorency, including Anne’s Book of Hours, but also, more strikingly, the stained glass windows from the Psyche gallery, Goujon’s bas-reliefs, wall tiling by Masséot Abaquesne, and the altar and stained glass windows that had adorned the chapel at Écouen. In fact, the chapel at Chantilly sought to reproduce the dimensions and decorations of its counterpart at Écouen, which has fortunately been preserved and retains its fine ogival vaults, painted with the coats of arms of Anne de Montmorency and his wife. Écouen was inaccessible to researchers during the development of historical studies in French Renaissance architecture. As a result, its virtues were never extolled in a full monograph or promoted as much as it deserved. The first director of the museum, Alain Erlande-Brandenburg, produced a useful introductory work. The current director, Thierry Crépin-Leblond, is working on a weightier presentation that will assemble all the available documentation and give a clearer idea of the château’s interior design, which is still largely unknown.
The Château d'Écouen as a showcase for national collections

The French National Museum of the Renaissance is a young museum, a contemporary of the Pompidou Center—both opened to the public in 1977. The idea of devoting the Château d'Écouen to Renaissance civilization was for André Malraux, De Gaulle's minister for cultural affairs, a solution to two problems.

It found a use for the château, which had stood silent since the academy for young girls closed in 1962, and it was a place to display the Renaissance collections from the Museum of Cluny. The former Paris residence of the abbots of Cluny had, since the 19th century, housed the collection built up by the archeologist Alexandre Du Sommerard (1779-1842), which comprised essentially decorative art works ranging from Greco-Roman antiquity to the end of the Middle Ages. After the Second World War, when all the works put into safekeeping had to be put back on display, it was decided to devote the Hôtel de Cluny exclusively to the Middle Ages. As a result, collections of works from later periods remained in their crates for some 15 further years, while the State looked for a suitable setting in which to display them.

An initial proposal was the Château de Chambord, but Malraux rejected the idea as he wanted to keep the material closer to Paris. Eventually, in 1972, the State agreed to an ultralong lease on Écouen with the Legion of Honor, undertaking to upgrade the building. As a result, the Ministry of Cultural Affairs became its quasi-proprietor. Écouen had the advantage of possessing the Gallery of Psyche, which was ideally suited for displaying a 75-meter masterpiece, the Tapestry of David and Bathsheba (circa 1510-1515). After extensive conversion, a part of the Château opened as a museum in 1977.

Subsequent work resulted in the near-complete opening that we have today, with 36 rooms open to the public.

In addition to the tapestry already mentioned, the collections reflect the variety and complexity of Renaissance art, principally from Europe, but also from further afield. Striking examples include ivory carvings from Portuguese Africa, a feather mosaic triptych created by Aztecs under the Spanish occupation, and, above all, a set of 400 Ottoman ceramic pieces, the most important collection of Iznik ceramics in Europe.

The tastes of the Du Sommerard family were highly eclectic: painting, sculpture, tapestry and other textile work, weapons, precious metalwork, ceramics, glass, enamels, ironwork, furniture, marquetry, manuscripts, and scientific instruments. Only the graphic arts are truly underrepresented in the Museum's collections. Bolstered by the many pieces acquired since 1977, the collections total some 11 000 works, on top of which there are some 14 000 fragments from Bernard Palissy's ceramic workshop in the Tuileries that came to light during the archeological excavations of the Louvre in the 1980s. With no real place for them in the Louvre, they were transferred to the Museum of the Renaissance to be studied and displayed in a new set of rooms.

The Écouen collections range from the rarest of objects to pieces representative of a shared pan-European Renaissance taste. The rare objects are on a par with those in the great museums in Europe (the Victoria and Albert Museum and British Museum in London, the Dresden museums, and the Kunsthistorisches Museum in Vienna) or the United States (the Metropolitan Museum of Art in
Charles V's mechanical galleon. Table ornament constructed by Hans Schlottheim, Augsburg, circa 1580. © RMN/Gérard Blot.
New York, Walters Art Museum in Baltimore, or the Philadelphia Museum of Art). One such object is the famed silver-gilt mechanical galleon made for Holy Roman Emperor Charles V (Nef de Charles Quint), an intricate clock cum automaton built by Hans Schlottheim (1545-1625), a German goldsmith and clockmaker, of which there are only three extant models in the world, the two others being at the British Museum in London and the Kunst-historisches Museum in Vienna. There is of course a clock—though quite small, which a keen eye will discover at the base of the middle mast, with bells ringing the hours in the crow’s nests. But this was a mere excuse for the mechanical marvels displayed by the ship: set on a dinner table, with princely guests agog, it would roll on wheels, playing mechanical music and firing its cannon, amidst flares and smoke, the sailors on board moving and revolving to the beating of a drum and the blowing of trumpets.

The fact that the Écouen collection complements other major French collections so well (those in the Departments of Painting, Sculpture, and Objets d’art in the Louvre, the Château de Fontainebleau Museum, the National Ceramics Museum in Sèvres, the Army Museum, the Arts et Métiers Museum, etc) probably explains Écouen’s inclusion in the network of French national museums.

In recent years, several major acquisitions have added to this core of masterpieces. In particular, two tapestries from the Tapestry of the Story of Diana produced for Diane de Poitiers around 1550, in a remarkable state of preservation that sets off their sharp colors to good effect. The second tapestry in the set represents the birth of Apollo—the nymph Latona gives birth to the god between a palm tree and olive tree with help from his elder twin Diana, a midwife already although just born!

Another notable acquisition was the ornamental flooring from the Château de Polisy in Champagne. This is a skilful combination: a ceiling design published by the Italian Mannerist Sebastiano Serlio (1475- circa 1554) with alternating crosses, octagons, and diamonds, each bordered by different foliage, allegories of virtues engraved by a pupil of Albrecht Dürer, Georg Pencz (circa 1500-1550), and ancient and modern battle trophies, each encircled by strapwork design, broken by an ornamental fleuron at each corner. Designed for one of the bishops of Auxerre, François de Dinteville, brother of the ambassador immortalized by Holbein a few years later (National Gallery, London, 1533), the tiled floor suggests that attaining virtue is a slow process, even a struggle: “VIRTVTI FORTVNA COMES”—“Good fortune attendant on virtue,” runs the motto. This moralistic work was acquired in 2008 as a national treasure, thanks to a contribution from the AXA insurance group.


Pair of spectacles and pear-shaped leather case. France, 17th century. © RMN/Stéphane Maréchal.
We need to don a pair of spectacles if we’re to do justice to the quality of smaller works, such as a superb enameled dish by Léonard Limosin, bearing a discreet signature, “LL”, and the date “1562” on the back; the obverse reproduces Raphael’s Judgment of Paris. Decorated with a female upper body in profile serenaded by trumpeting putti, there is almost as much work on this side as on the other—a frequent characteristic of the Renaissance decorative arts, particularly in France. Smaller still is a sheath that typifies the extreme refinement of Renaissance textile work, often difficult to appreciate today as most such pieces are worn or destroyed.

Far from being anecdotal, the detail inscribed on everyday objects reflects a mentality preoccupied with the grandest of principles. A marriage chest from the 1470s brings together the moral lesson in Plutarch’s tale of Tiberius Gracchus—who sacrificed himself in order to save his much younger wife Cornelia—and the fashionable dress of the contemporary Florentine elite set against the backdrop of Santa Maria Novella just after its completion by Leone Battista Alberti (1404-1472), one of the first theoreticians of perspective.

It was in such decorative detail that Renaissance art so often staged an ongoing dialogue of opposites, between internal and external, sacred and profane, large and small, natural and artificial, typically recounted with wisdom and humor. Similarly, the essence of Écouen invites us to cross the multiple bridges leading to the tastes and skills of an era of cultural upheaval that remains our close and still recognizable forebear.

Further reading