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AIMS AND SCOPE

Phlebolymphology is an international scientific journal entirely devoted to venous and lymphatic diseases.

The aim of *Phlebolymphology* is to provide doctors with updated information on phlebology and lymphology written by well-known international specialists.

Phlebolymphology is scientifically supported by a prestigious editorial board.

Phlebolymphology has been published four times per year since 1994, and, thanks to its high scientific level, was included in several databases.

Phlebolymphology comprises an editorial, articles on phlebology and lymphology, reviews, news, and a congress calendar.

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Phlebolymphology

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PHLEBOLYMPHOLOGY

Hugo Partsch
Editor in Chief

Dear Readers,

Many roads lead to Rome and many routes may be chosen to treat varicose veins...

*In this issue of Phlebolymphology, guidelines on the treatment of varicose veins elaborated by a group of prominent American vascular surgeons are reported and commented on by prominent European vascular surgeons (**Marzia Lugli** and **Oscar Maleti** from Modena, and **Michel Perrin** from Lyon). Those who are looking for clear recommendations on which method is the most successful to treat varicose veins in a specific clinical setting will be disappointed. However, the comments of our European colleagues on the American suggestions are quite stimulating. It is interesting to note that the American surgeons have also included statements regarding the role of drug treatment and have recommended the use of micronized purified flavonoid fraction in both symptomatic venous patients and venous ulcer patients to accelerate healing. Together with the recently published reviews of randomized controlled trials in the treatment of varicose veins written by Michel Perrin and Bo Eklöf (Phlebolymphology. 2011,18:(4)196-207 [Part I] and Phlebolymphology. 2012,13:(2)91-99 [Part II]), the reader now has a substantial amount of information that critically reviews the current concepts in the treatment of varicose veins.*

*The prevalence of chronic cerebrospinal venous insufficiency (CCSVI) and the relationship between CCSVI and multiple sclerosis (MS) remain controversial topics. **Marian Simka**, Katowice, Poland, gives a well-balanced overview of the present knowledge, elegantly putting the diagnostic weight on phlebography rather than ultrasound, and clearly stating that only a few small open-label studies investigating the clinical efficacy of endovascular treatment for CCSVI in MS patients have been published. He estimates that so far, about 12 000 MS patients have had endovascular therapy worldwide.*

The present issue of Phlebolymphology *also contains interesting results from an interim report on some outcomes of the large international VEIN CONSULT program, a joint initiative between the International Union of Phlebology and Servier. This is the first survey to make the distinction between C0a (healthy people) and C0s participants (patients complaining of symptoms in the absence of chronic venous disease signs). To ascertain whether C0s patients, who do not present with a detectable venous pathophysiology (Pn) have a venous disorder, medical questioning should delve deeper into the symptoms since we know that many subjective leg symptoms (eg, night cramps) can have other causes as well.*

***Amanda D. Shepherd, Tristan R. Lane** and **Alun H. Davies,** from London, have written an excellent review documenting the natural history of venous disorders. The authors have not only provided a comprehensive overview of the longitudinal studies dealing with clinical disease progression and the effects of intervention on disease progression, but also included longitudinal studies evaluating the venous hemodynamics and risk factors for the development of venous ulceration. A real gem, this article summarizes all the data published to date in this field of high socioeconomic importance.*

This issue of Phlebolymphology *concludes with a basic-science article from **Geert W. Schmid-Schönbein**, University of San Diego, USA, demonstrating the complex relationships between metabolic syndrome, insulin resistance, hypertension, chronic inflammation in chronic venous disease, and the multifaceted cell dysfunctions described in the genetic model of the spontaneously hypertensive rat. Pharmacological approaches against some of these complex mechanisms need to be carefully selected since some players (eg, certain metalloproteinases) are an integral part of tissue repair in the inflammatory process.*

Happy reading!

Review and Comment of the 2011 Clinical Practice Guidelines of the Society for Vascular Surgery and the American Venous Forum

Gloviczki P, Comerota AJ, Dalsing MC, et al. The care of patients with varicose veins and associated chronic venous diseases: Clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. *J Vasc Surg*. 2011;53:2S-48S.

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ABSTRACT

The Clinical Practice Guidelines of The Society for Vascular Surgery and The American Venous Forum, published in the 2011 *Journal of Vascular Surgery* supplement, is the most complete document on the management of varicose veins ever published in English. It is the work of leading members of the American Venous Forum, who are major contributors to advances in this field. However, most of them are vascular surgeons and this may have influenced their recommendations.

A total of 14 guidelines are recommended or suggested using the recommendation grading system of Guyatt et al. The present article will specifically review these recommendations, bearing in mind that as Europeans we may have some divergence of opinion with our American colleagues.

Abbreviations used

VVs, varicose veins; PREVAIT: PREsence of Varices (residual or recurrent) After InTervention; REVAS: REcurrence of Varices After Surgery; RCT, randomized clinical trial

Keywords:
chemical ablation; endovenous laser ablation; endovenous radiofrequency ablation; sclerotherapy; varices; varicose vein surgery

INTRODUCTION

The Clinical Practice Guidelines of The Society for Vascular Surgery and The American Venous Forum, published in the 2011 *Journal of Vascular Surgery* supplement, is the most complete document on the management of varicose veins (VVs) ever published in English. It is the work of leading members of the American Venous Forum, whose knowledge in this field is undisputed. However, most of them are vascular surgeons and this may have influenced their recommendations.

Phlebolymphology. 2012;19(3):107-120.

The article is 47 pages long and includes:

- 2 figures depicting the superficial, deep, and perforator veins of the lower limbs.

- 8 tables, including:

The different levels of evidence-based recommendations as described by Guyatt et al[1] *(Table I)*.

- The CEAP classification[2] *(Table II)*.
- The venous anatomic segment classification[2] *(Table III)*.
- The Revised Venous Clinical Severity Score[3] *(Table IV)*.
- A definition of the major and minor complications of endovenous ablation[4] *(Table V)*.
- The main manufacturers of endovenous ablation devices and the laser wavelengths of these devices.
- A comparison of sclerosing agents.
- The indications for sclerosing agents and the concentrations used.

No fewer than 376 references are quoted, a veritable gold mine for readers and fellow writers, especially considering that very few major articles are missing.

In total, 14 guidelines are recommended or suggested using the recommendation grading system mentioned above.[1]

In this review, we will focus on these guidelines, bearing in mind that our European practice may account for some divergence of opinion with our American colleagues.

Grade of Recommendation/Description	Benefit vs Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
1A/strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/strong recommendation, low-quality or very low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
2A/weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B/weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendation; other alternatives may be equally reasonable

Table I. *Grading Recommendations According to Evidence (Chest. 2006;129:174-181)*

CEAP classification and description
1. Clinical classification
C_0: No visible or palpable signs of venous disease
C_1: Telangiectases or reticular veins
C_2: Varicose veins
C_3: Edema
C_{4a}: Pigmentation and/or eczema
C_{4b}: Lipodermatosclerosis and/or atrophy
C_5: Healed venous ulcer
C_6: Active venous ulcer
C_S: Symptoms, including ache, pain, tightness, skin irritation, heaviness, muscle cramps, as well as other complaints attributable to venous dysfunction
C_A: Asymptomatic
2. Etiologic classification
E_c: Congenital
E_p: Primary
E_s: Secondary (postthrombotic)
E_n: No venous etiology identified
3. Anatomic classification
A_s: Superficial veins
A_p: Perforator veins
A_d: Deep veins
A_n: No venous location identified
4. Pathophysiologic classification
P_r: Reflux
P_o: Obstruction
$P_{r,o}$: Reflux and obstruction
P_n: No venous pathophysiology identifiable

Table II. *The CEAP classification*[2]

Anatomic classification and venous segment description
Superficial veins
1. Telangiectases/reticular veins
2. GSV above knee
3. GSV below knee
4. Short saphenous vein
5. Nonsaphenous veins
Deep veins
6. Inferior vena cava
7. Common iliac vein
8. Internal iliac vein
9. External iliac vein
10. Pelvic: gonadal, broad ligament veins, other
11. Common femoral vein
12. Deep femoral vein
13. Femoral vein
14. Popliteal vein
15. Crural veins: anterior tibial, posterior tibial, peroneal veins (all paired)
16. Muscular veins: gastrocnemius, soleal, other
Perforating veins
17. Thigh perforator veins
18. Calf perforator veins

Table III. *Venous anatomic segment classification*

Pain	None: 0	Mild: 1	Moderate: 2	Severe: 3
or other discomfort (ie, aching, heaviness, fatigue, soreness, burning) Presumes venous origin		Occasional pain or other discomfort (ie, not restricting regular daily activity)	Daily pain or other discomfort (ie, interfering with but not preventing, regular daily activities)	Daily pain or discomfort (ie, limits most regular daily activities)

Varicose Veins	None: 0	Mild: 1	Moderate: 2	Severe: 3
"Varicose" veins must be ≥3 mm in diameter to qualify		Few: scattered (ie, isolated branch varicosities or clusters) Also includes corona phlebectatica (ankle flare)	Confined to calf or thigh	Involves calf and thigh

Venous Edema	None: 0	Mild: 1	Moderate: 2	Severe: 3
Presumes venous origin		Limited to foot and ankle area	Extends above ankle but below knee	Extends to knee and above

Skin Pigmentation	None: 0	Mild: 1	Moderate: 2	Severe: 3
Presumes venous origin Does not include focal pigmentation over varicose veins or pigmentation due to other chronic diseases (ie, vasculitis purpura)	None or focal	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf

Inflammation	None: 0	Mild: 1	Moderate: 2	Severe: 3
More than just recent pigmentation (ie, erythema, cellulitis, venous eczema, dermatitis)		Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf

Induration	None: 0	Mild: 1	Moderate: 2	Severe: 3
Presumes venous origin of secondary skin and subcutaneous changes (ie, chronic edema with fibrosis, hypodermitis) Includes white atrophy and lipodermatosclerosis		Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf

Active Ulcer Number	0	1	2	≥3
Active Ulcer Duration (longest active)	N/A	<3 mo	>3 mo but <1 y	Not healed for >1 y
Active Ulcer Size (largest active)	N/A	Diameter <2 cm	Diameter 2-6 cm	Diameter >6 cm
Use of Compression Therapy	0 Not used	1 Intermittent use of stockings	2 Wears stockings most days	3 Full compliance: stockings

Adapted from Vasquez et al.[3] Used with permission.

Table IV. *Revised Venous Clinical Severity Score.[3]*

Minor complications
No therapy, no consequence
Nominal therapy, no consequence; includes overnight admission for observation only
Major complications
Requires therapy, minor hospitalization (<48 h)
Requires major therapy, unplanned increase in level of care, prolonged hospitalization (>48 h)
Permanent adverse sequelae
Death

Adapted from Kundu et al.[4] Used with permission.

Table V. *Definition of complications.[4]*

RECOMMENDATIONS REVIEW AND COMMENTS

Guideline 1

Title and guideline number	Recommendation formulation	Grade of recommendation	Level of evidence
Clinical examination 1.1	For clinical examination of the lower limbs for chronic venous disease, we recommend inspection (telangiectasia, varicosity, edema, skin discoloration, corona phlebectatica, lipodermatosclerosis, ulcer), palpation (cord, varicosity, tenderness, induration, reflux, pulses, thrill, groin or abdominal masses) auscultation (bruit), and examination of ankle mobility. Patients should be asked for symptoms of chronic venous disease, which may include tingling, aching, burning, pain, muscle cramps, swelling, sensations of throbbing or heaviness, itching skin, restless legs, leg tiredness, and fatigue.	1. Strong 2. Weak **1**	A. High quality B. Moderate quality C. Low or very low quality **A**

Comments

Full agreement with the **grade 1A recommendation.**

Guideline 2

Title and guideline number	Recommendation formulation	Grade of recommendation	Level of evidence
Duplex scanning 2.1	We recommend that in patients with chronic venous disease, a complete history and detailed physical examination are complemented by duplex scanning of the deep and superficial veins. The test is safe, noninvasive, cost-effective, and reliable.	1. Strong 2. Weak **1**	A. High quality B. Moderate quality C. Low or very low quality **A**
2.2	We recommend that the four components of a complete duplex scanning examination for chronic venous disease should be visualization, compressibility, venous flow, including measurement of duration of reflux, and augmentation.	**1**	**A**
2.3	We recommend that reflux to confirm valvular incompetence in the upright position of the patients be elicited in one of two ways: either with increased intra-abdominal pressure using a Valsalva maneuver to assess the common femoral vein and the saphenofemoral junction, or for the more distal veins, use of manual or cuff compression and release of the limb distal to the point of examination.	**1**	**A**
2.4	We recommend a cutoff value of 1 second for abnormally reversed flow (reflux) in the femoral and popliteal veins and of 500 ms for the great saphenous vein, the small saphenous vein, the tibial, deep femoral, and perforating veins.	**1**	**B**
2.5	We recommend that in patients with chronic venous insufficiency, duplex scanning of the perforating veins is performed selectively. We recommend that the definition of "pathologic" perforating veins includes those with an outward flow of duration of ≥500 ms, with a diameter of ≥3.5 mm and a location beneath healed or open venous ulcers (CEAP class C_5-C_6).	**1**	**B**

Comments

Guidelines 2-1 to 2-4: Full agreement with **the quoted recommendations.**

Guideline 2-5: **grade 1B recommendation.** One wonders why the term "pathologic" is restricted to the perforator in the presence of healed or open venous ulcer (VU). Does this mean that in the absence of VU, outward flow is not pathologic? (*Figure 1*)

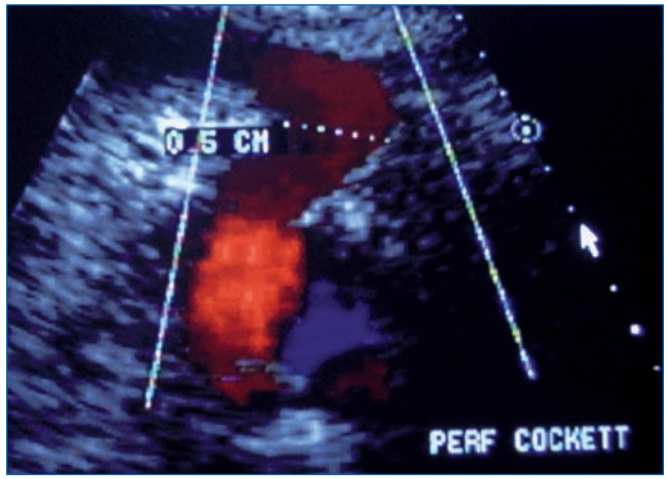

Figure 1. *Duplex ultrasound of a large incompetent medial leg perforator in a patient presenting lipodermatosclerosis (C4b). Why is this perforator not classified as pathologic?*

Guideline 3

Title and guideline number	Recommendation formulation	Grade of recommendation	Level of evidence
Plethysmography 3.1	We suggest that venous plethysmography be used selectively for the noninvasive evaluation of the venous system in patients with simple varicose veins (CEAP class C_2).	1. Strong 2. Weak **2**	A. High quality B. Moderate quality C. Low or very low quality **C**
3.2	We recommend that venous plethysmography be used for the noninvasive evaluation of the venous system in patients with advanced chronic venous disease if duplex scanning does not provide definitive information on pathophysiology (CEAP class C_3-C_6).	**1**	**B**

Comments

Full agreement with:
Guideline 3.1: **grade 2C recommendation** in C2 (uncomplicated VVs).
Guideline 3.2: **grade 1B recommendation** in C3-6 (complicated VVs).

Guideline 4

Title and guideline number	Recommendation formulation	Grade of recommendation	Level of evidence
Imaging studies 4.1	We recommend that in patients with varicose veins and more advanced chronic venous disease, computed tomography venography, magnetic resonance venography, ascending and descending contrast venography, and intravascular ultrasonography are used selectively, including but not limited to postthrombotic syndrome, thrombotic or nonthrombotic iliac vein obstruction (May-Thurner syndrome), pelvic congestion syndrome, nutcracker syndrome, vascular malformations, venous trauma, tumors, and planned open or endovascular venous interventions.	1. Strong 2. Weak **1**	A. High quality B. Moderate quality C. Low or very low quality **B**

Comments

Guideline 4.1: Full agreement with **the grade 1B recommendation.**

Guideline 5

Title and guideline number	Recommendation formulation	Grade of recommendation	Level of evidence
Laboratory evaluation 5.1	We recommend that in patients with varicose veins, evaluation for thrombophilia is needed selectively for those with recurrent deep venous thrombosis, thrombosis at a young age, or thrombosis in an unusual site. Laboratory examinations are needed in patients with long-standing venous stasis ulcers and in selected patients who undergo general anesthesia for the treatment of chronic venous disease.	1. Strong 2. Weak **1**	A. High quality B. Moderate quality C. Low or very low quality **B**

Comments

Guideline 5.1: Agreement with the **grade 1B recommendation** although some clinical situations are not sufficiently detailed.

Guideline 6

Title and guideline number	Recommendation formulation	Grade of recommendation	Level of evidence
Classification 6.1	We recommend that the CEAP classification be used for patients with chronic venous disease. The basic CEAP classification is used for clinical practice, and the full CEAP classification system is used for clinical research.	1. Strong 2. Weak **1**	A. High quality B. Moderate quality C. Low or very low quality **A**
6.2	We recommend that primary venous disorders, including simple varicose veins, be differentiated from secondary venous insufficiency and from congenital venous disorders because the three conditions differ in pathophysiology and management.	**1**	**B**

Comments

Guideline 6.1: Use of the basic and advanced CEAP classifications according to clinical practice and clinical research.[2]

We agree with the use of C for clinical class **(grade 1A recommendation),** but it should be underlined that C_2 does not describe in detail the extension and importance of VVs.

Guideline 6.2: We agree with the **grade 1B recommendation** for the classification of VV etiology as primary, secondary, and congenital, knowing that this classification is not fully satisfying in some other types of chronic venous disease. It seems advisable to rename "secondary" as "postthrombotic."

Guideline 7

Title and guideline number	Recommendation formulation	Grade of recommendation	Level of evidence
Outcome assessment 7.1	We recommend that the revised Venous Clinical Severity Score is used for assessment of clinical outcome after therapy for varicose veins and more advanced chronic venous disease.	1. Strong 2. Weak **1**	A. High quality B. Moderate quality C. Low or very low quality **B**
7.2	We recommend that a quality-of-life assessment is performed with a disease-specific instrument to evaluate patient-reported outcome and the severity of chronic venous disease.	**1**	**B**
7.3	We recommend duplex scanning for the follow-up of patients after venous procedures who have symptoms or recurrence of varicose veins	**1**	**B**
7.4	We recommend reporting procedure-related minor and major complications after therapy.	**1**	**B**

Comments

Four recommendations are listed in this section

Guideline 7.1: As previously stated in various articles—including one published in *VEINews* on March 22nd, 2011—the revised venous clinical severity score is an excellent tool in chronic venous insufficiency patients, but its effectiveness in C_2 patients including those who are symptomatic does not deserve a **grade 1B recommendation.**

Guidelines 7.2-7.4: Full agreement with the **grade 1B recommendation**.

Guideline 8

Title and guideline number	Recommendation formulation	Grade of recommendation	Level of evidence
Medical treatment 8.1	We suggest venoactive drugs (diosmin, hesperidin, rutosides, sulodexide, micronized purified flavonoid fraction, or horse chestnut seed extract [aescin]) for patients with pain and swelling due to chronic venous disease, in countries where these drugs are available.	1. Strong 2. Weak **2**	A. High quality B. Moderate quality C. Low or very low quality **B**
8.2	We suggest using pentoxifylline or micronized purified flavonoid fraction, if available, in combination with compression, to accelerate healing of venous ulcers.	**2**	**B**

Comments

Guidelines 8.1 and 8.2: Full agreement with the **grade 2B recommendation**

Guideline 9

Title and guideline number	Recommendation formulation	Grade of recommendation	Level of evidence
Compression treatment 9.1	We suggest compression therapy using moderate pressure (20 to 30 mm Hg) for patients with symptomatic varicose veins.	1. Strong 2. Weak **2**	A. High quality B. Moderate quality C. Low or very low quality **C**
9.2	We recommend against compression therapy as the primary treatment of symptomatic varicose veins in patients who are candidates for saphenous vein ablation.	**1**	**B**
9.3	We recommend compression as the primary therapeutic modality for healing venous ulcers.	**1**	**B**
9.4	We recommend compression as an adjuvant treatment to superficial vein ablation for the prevention of ulcer recurrence.	**1**	**A**

Comments

Guideline 9.1: **grade 2 C recommendation**. Full agreement with this very weak recommendation, as other treatments should be considered.

Guideline 9.2 and 9.3: **grade 1B recommendation.** Full agreement.

Guideline 9.4. To prevent ulcer recurrence in C_5 patients, the **grade 1A recommendation** is unsatisfactory. In our opinion, if after superficial ablation no superficial/perforator/deep anomaly is present, and in the absence of edema, lipodermatosclerosis compression is not beneficial.

Guideline 10

Title and guideline number	Recommendation formulation	Grade of recommendation	Level of evidence
Open venous surgery 10.1	For treatment of the incompetent great saphenous vein, we suggest high ligation and inversion stripping of the saphenous vein to the level of the knee.	1. Strong 2. Weak **2**	A. High quality B. Moderate quality C. Low or very low quality **B**
10.2	To reduce hematoma formation, pain, and swelling, we recommend postoperative compression. The recommended period of compression in C_2 patients is 1 week.	**1**	**B**
10.3	For treatment of small saphenous vein incompetence, we recommend high ligation of the vein at the knee crease, about 3 to 5 cm distal to the saphenopopliteal junction, with selective invagination stripping of the incompetent portion of the vein.	**1**	**B**
10.4	To decrease recurrence of venous ulcers, we recommend ablation of the incompetent superficial veins in addition to compression therapy.	**1**	**A**
10.5	We suggest preservation of the saphenous vein using the ambulatory conservative hemodynamic treatment of varicose veins (CHIVA) technique only selectively in patients with varicose veins, when performed by trained venous interventionists.	**2**	**B**
10.6	We suggest preservation of the saphenous vein using the ambulatory selective varicose vein ablation under local anesthesia (ASVAL) procedure only selectively in patients with varicose veins.	**2**	**C**

10.7	We recommend ambulatory phlebectomy for treatment of varicose veins, performed with saphenous vein ablation, either during the same procedure or at a later stage. If general anesthesia is required for phlebectomy, we suggest concomitant saphenous ablation.	**1**	**B**
10.8	We suggest transilluminated powered phlebectomy using lower oscillation speeds and extended tumescence as an alternative to traditional phlebectomy for extensive varicose veins.	**2**	**C**
10.9	For treatment of recurrent varicose veins, we suggest ligation of the saphenous stump, ambulatory phlebectomy, sclerotherapy, or endovenous thermal ablation, depending on the etiology, source, location, and extent of varicosity.	**2**	**C**

Comments

Guideline 10.1: The **grade 2B recommendation** seems harsh for classic GSV surgery for two reasons; firstly, because long-term RCTs comparing open surgery with thermal ablation are not available, and secondly, because open surgery performed under local tumescent anesthesia and using atraumatic techniques is less invasive than traditional procedures.

Guideline 10.2: **grade 1B recommendation**. Full agreement.

Guideline 10.3: **grade 1B recommendation**. What is the rationale for recommending nonflush ligation of the saphenopopliteal junction? As far as we know, there is no RCT comparing flush and nonflush ligation.

Guideline 10.4: **grade 1A recommendation**. See the comment on classic surgery in guideline 10.1.

Guideline 10.5 to 10-8: Full agreement.

Guideline 10.9 deals with VV recurrence after open surgery termed REVAS,[5] but not PREVAIT, as defined in the VEIN-TERM consensus article.[6] We agree with the **grade 1C recommendation** as there are very few RCTs comparing the various operative treatments in this situation. Nevertheless, in practice, ultrasound-guided foam sclerotherapy is the first-line treatment used, except perhaps in the presence of a large refluxing saphenous stump (*figures 2a, 2b*).

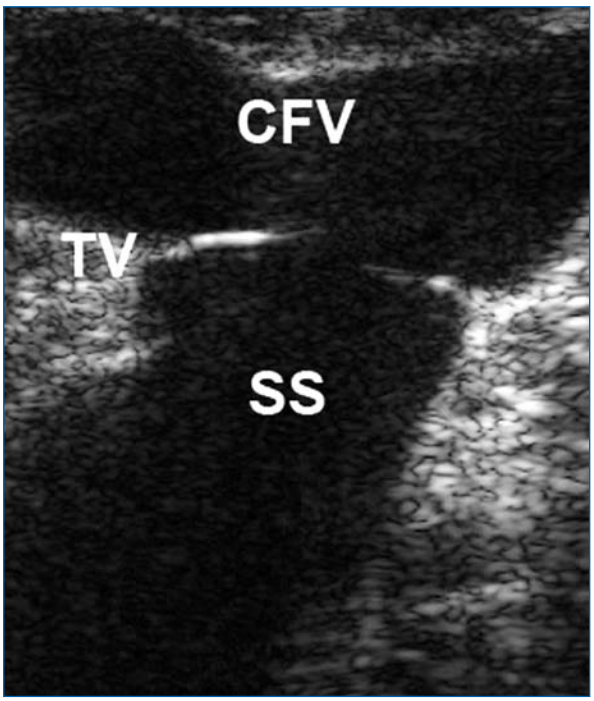

Figure 2a.
B mode. The terminal valve is identified at the saphenofemoral junction.
CFV: common femoral vein;
SS: saphenous stump; TV: terminal valve.

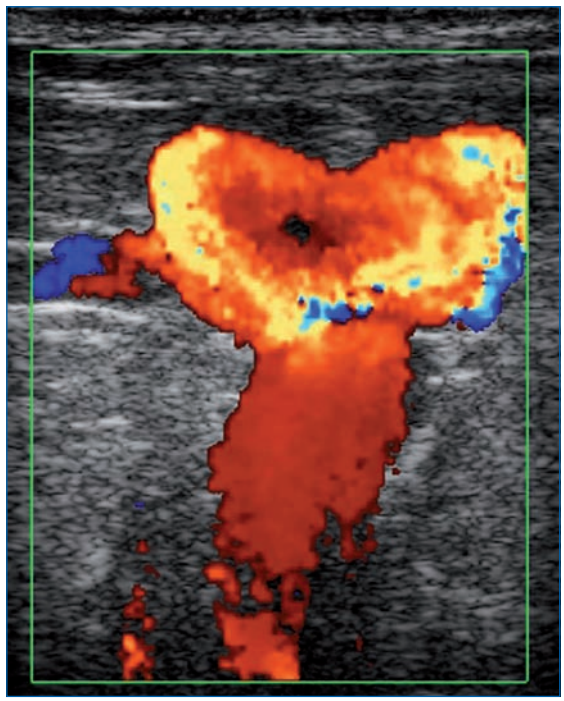

Figure 2b. *Color duplex ultrasound. Massive reflux induced by a Valsalva maneuver.*

Guideline 11

Title and guideline number	Recommendation formulation	Grade of recommendation	Level of evidence
Endovenous thermal ablation 11.1	Endovenous thermal ablations (laser and radiofrequency ablations) are safe and effective, and we recommend them for treatment of saphenous incompetence.	1. Strong 2. Weak **1**	A. High quality B. Moderate quality C. Low or very low quality **B**
11.2	Because of reduced convalescence and less pain and morbidity, we recommend endovenous thermal ablation of the incompetent saphenous vein over open surgery	**1**	**B**

Comments

Guideline 11.1: **grade 1B recommendation**. Full agreement. It is worth noting that, for the authors, endothermal ablation has now become the gold standard for treating saphenous incompetence operatively, instead of HL+ stripping.
Guideline 11.2. See the comment on classic surgery in guideline 10.1

Guideline 12

Title and guideline number	Recommendation formulation	Grade of recommendation	Level of evidence
Sclerotherapy of varicose veins 12.1	We recommend liquid or foam sclerotherapy for telangiectasia, reticular veins, and varicose veins.	1. Strong 2. Weak **1**	A. High quality B. Moderate quality C. Low or very low quality **B**
12.2	For treatment of the incompetent saphenous vein, we recommend endovenous thermal ablation over chemical ablation with foam.	**1**	**B**

Comments

Guideline 12.1: **grade 1B recommendation.** Agreement for telangectasias and reticular veins, but not VVs. According to many articles, foam has given better results than liquid.
Guideline 12.2: **grade 2B recommendation**. Agreement with this weak recommendation, as there is no RCT comparing the long-term outcome after chemical ablation and thermal ablation.

Guideline 13

Title and guideline number	Recommendation formulation	Grade of recommendation	Level of evidence
Treatment of perforating veins 13.1	We recommend against selective treatment of incompetent perforating veins in patients with simple varicose veins (CEAP class C_2).	1. Strong 2. Weak **1**	A. High quality B. Moderate quality C. Low or very low quality **B**

13.2	We suggest treatment of "pathologic" perforating veins that includes those with an outward flow duration of ≥500 ms, with a diameter of ≥3.5 mm, located beneath a healed or open venous ulcer (CEAP class C_5-C_6).	**2**	**B**
13.3	For treatment of "pathologic" perforating veins, we suggest subfascial endoscopic perforating vein surgery, ultrasonographically guided sclerotherapy, or thermal ablations.	**2**	**C**

Comments

Guideline 13.1: **grade 1B recommendation.** Agreement
Guideline 13.2: **grade 2B recommendation.** Agreement
Guideline 13.3: **grade 2C recommendation.** Agreement
There is no RCT comparing the outcome after the different procedures.

Guideline 14

Title and guideline number	Recommendation formulation	Grade of recommendation	Level of evidence
Treatment of pelvic varicose veins 14.1		1. Strong 2. Weak	A. High quality B. Moderate quality C. Low or very low quality
	We recommend noninvasive imaging with transabdominal and/or transvaginal ultrasonography, computed tomography, or magnetic resonance venography in selected patients with symptoms of pelvic congestion syndrome or symptomatic varices in the distribution of the pubis, labia, perineum, or buttocks.	**1**	**C**
14.2	We recommend retrograde ovarian and internal iliac venography in patients with pelvic venous disease, confirmed or suspected by noninvasive imaging studies, in whom an intervention is planned.	**1**	**C**
14.3	We suggest treatment of pelvic congestion syndrome and pelvic varices with coil embolization, plugs, or transcatheter sclerotherapy, used alone or together.	**2**	**B**
14.4	If less invasive treatment is not available or has failed, we suggest surgical ligation and excision of ovarian veins to treat reflux.	**2**	**B**

Comments

Guideline 14.1: **grade 1C recommendation**. Full agreement.
Guideline 14.2: **grade 1C recommendation.** We suggest **1B.**
Guideline 14.3: **grade 2B recommendation**. We suggest **1C.**
Guideline 14.4: **grade 2B recommendation.** Agreement.

CONCLUSION

The Clinical Practice Guidelines of The Society for Vascular Surgery and The American Venous Forum, published in the 2011 *Journal of Vascular Surgery* supplement, gathers information that had never been analyzed in depth before, and the authors deserve to be congratulated for their outstanding work.

The recommendations stated in this document should be commented by members of the international phlebology community according to their specialization, ie, angiology, surgery, dermatology, internal medicine, and phlebology, as well as in light of the health regulations in their respective countries.

Nevertheless, knowing how fast interventional procedures evolve with the development of new techniques or devices, one can bet that some of these recommendations will quickly become outdated.

The main problem with varicose veins can be summarized as follows: on the one hand, chronic venous disease—including varicose veins—evolves slowly and long-term follow-up is required to assess its outcome and management, and on the other hand, investigation and operative procedures change very fast. In other words, by the time RCT results become available, the procedures they compare have become obsolete.

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Chronic cerebrospinal venous insufficiency: state of the art and research challenges

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ABSTRACT

This review discusses a potential vascular basis for multiple sclerosis (MS). The idea that MS could be related to vascular disease is not new, with the first reports describing connections between veins and MS plaques dating from the 19th century. The venous abnormalities found in MS patients, the so-called chronic cerebrospinal venous insufficiency, are currently interpreted as congenital venous malformations. Catheter venography is regarded as the gold standard to assess these lesions, while other tests, such as Doppler sonography and magnetic resonance venography, are much less accurate. Importantly, a relationship between venous pathologies and MS has not yet been proven, especially regarding the causative role of compromised venous outflow in the pathogenesis of MS. Although the results of small open-label studies are promising and treatments have been found to be safe, well-designed clinical trials will be needed to validate the efficacy of endovascular procedures of malformed veins for the treatment of MS.

MULTIPLE SCLEROSIS – A PARADIGM SHIFT?

This review discusses a potential vascular basis for multiple sclerosis (MS), an idea that has been hotly debated by both neurologists and vascular specialists.[1-7] MS is a chronic neurological disease characterized by multifocal areas of inflammation, demyelination, and neurodegeneration within the central nervous system. The current ruling paradigm is that MS is an autoimmune disease, which means that it is caused by an autoimmune attack against nervous tissue, primarily against myelin antigens, a process carried out by reactive T cells. Therapeutic strategies predominantly target—unfortunately, not very effectively[8-11]—the inflammatory cascade or modify the immune response. However, a mechanism triggering this hypothetical autoimmune reaction remains elusive. For the time being, concepts regarding the pathophysiology of MS and mechanisms responsible for its initiation and progression, as well as the philosophy of its treatment, are all based on an animal model of the disease: experimental autoimmune encephalomyelitis

Keywords:
doppler ultrasonography; jugular veins; multiple sclerosis; phlebography; ultrasound applications; vascular malformations.

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(EAE). Yet, there are substantial differences in the size, timing, localization, and composition of the cellular infiltrate between MS and EAE. Although the EAE model has been widely accepted by neurologists, it actually poorly mirrors MS in humans. EAE, unlike MS, is an acute monophasic illness, and even the chronic subtypes of EAE contrast with human disease.[12] The autoimmune origin of MS is undermined by the fact that no autoantigen responsible for MS immunity has been identified and by the lack of clonally expanded T cells.[13-17] Moreover, although most of the current research on MS is focused on its autoimmune aspects, it should be stressed that during the last century, researchers had considered the roles of other potential factors (infectious, environmental, genetic and— importantly—vascular).

Italian vascular surgeon Paolo Zamboni has recently stridden into this murky milieu with his chronic cerebrospinal venous insufficiency (CCSVI) theory,[18] which has managed to stoke the ongoing debate in the scientific community. The CCSVI paradigm claims that venous blockages have a primary role in initiating the immune reactions of MS. In addition, this hypothesis suggests that venous insufficiency may also contribute to MS pathology by causing chronic ischemia of the brain or iron toxicity.[19,20]

Zamboni insists that his CCSVI theory offers important insight into the pathophysiology of MS, a contention supported by some studies,[21-25] while others vigorously challenge it.[1,26,27] However, an hypothetical role for venous blockages in the pathogenesis of MS is not necessarily contrary to the currently accepted paradigm. It is possible that both vascular and immune mechanisms may play synergistic roles in pathology—similarly to chronic venous insufficiency of the lower extremities, where pathological venous flow is primarily responsible, but for which immune reactions seem to be an auxiliary mechanism leading to cellular infiltrates in the skin and, finally, to the development of venous ulcers.[28,29]

VASCULAR ETIOLOGY OF MS – HISTORICAL BACKGROUND

The idea that MS could be related to vascular disease is not new. The first observations relating the presence of pathological blood vessels, or a connection between cerebral veins and the location of MS plaques were made in the 19th century. Plaques—the foci of pathological nervous tissue, a hallmark of MS—preferentially localize around small cerebral veins or extend along the axis of these vessels. This venocentric characteristic of MS plaques has been known since the first histopathological descriptions of MS. The vascular paradigm of MS has been extensively studied during the first part of the 20th century, when Dawson described periventricular MS plaques extending along the cerebral veins. Another neurologist, Putnam, tried to validate the idea of a venous etiology of MS. To prove this hypothesis, he carried out an experimental animal study in which he obstructed the intracranial veins of 14 dogs. On autopsy the majority of these animals exhibited demyelinated cerebral lesions that were very similar to those seen in MS.[30] Unfortunately, Putnam's research was not continued and has since largely been forgotten. With autoimmunity becoming a leading topic in MS research, and due to the difficulty in demonstrating occlusions in the intracranial veins, this first attempt to investigate a relationship between the venous system and MS was abandoned.

The next studies on this topic were not carried out until the 1970s. Schelling observed a widening of the main venous passages through the skull and hypothesized that these dilated veins could be a consequence of venous hypertension, with the cause of this venous pathology situated outside the cranium.[31] Ogleznev et al described stenoses and occlusions in the internal jugular and brachiocephalic veins in patients with myelopathies of unknown origin (perhaps these patients actually presented with MS, since a definite diagnosis for MS was not made in this Russian study).[32,33] Similar observations were also published by French authors.[34] There were also some reports by neuroradiologists, who had measured abnormal cerebral flow with MR techniques.[35-41] These flow disturbances could not be explained within the autoimmune paradigm of MS and their characteristics suggested a venous origin.

RESEARCH BY ZAMBONI'S GROUP

Much controversy has emerged since the first article published by Zamboni. In 2006, he published a review paper in which he hypothesized that there may be some common features between MS and venous leg ulcers.[20] The following year, his team detected flow abnormalities in the intracranial veins of a group of MS patients. This type of pathological venous flow is not frequently seen

in healthy subjects.[42] Two years later, the same group published a study that demonstrated the presence of significant stenoses and occlusions in the main veins draining the central nervous system: the internal jugular veins (IJVs) and the azygous vein.[18] Importantly, these blockages were situated outside the skull and spinal canal, while the abnormal intracerebral flow seemed to be a secondary effect resulting from these extracranial blockages. In another important study, Zamboni et al proposed the following set of sonographic criteria:

- *Reflux.* Constant reflux (>0.8 s) in a single IJV or the vertebral veins, in the sitting or supine position.
- *Reflux in intracranial veins.* Reflux >0.5 s in the deep cerebral veins in the sitting and supine position.
- *Stenosis.* A reduction of the cross-sectional area (CSA) of the IJV of less than 0.3 cm^2 in both body positions, or the presence of intraluminal defects (such as webs, septa, or malformed valves).
- *No flow.* Absence of Doppler signal in the IJV or vertebral veins in both the supine and upright body positions.
- *Negative ΔCSA.* A cross-sectional area of the IJV that is greater in the sitting position than in the lying position, or that appears unchanged despite a change in posture.[43-45]

They found at least two positive criteria in all the MS patients they examined and found none in the healthy controls. Moreover, they described four distinct patterns of abnormal outflow: type A – obstruction of the proximal azygous vein accompanied by a stenosis of one of the IJVs; type B – obstruction of the proximal azygous vein together with bilateral stenoses of the IJVs; type C – stenoses of both IJVs; type D – numerous stenoses or occlusions in the azygous vein system. Interestingly, distinct flow patterns were seen in different clinical types of MS patients: types A, B, and C were seen primarily in patients with relapsing-remitting MS and secondary progressive MS, while type D was seen in patients with primary progressive MS.[18,46] The following year, a study reporting the results of endovascular treatment of these venous blockages was published. The results of this small open-label trial were promising, especially in patients with relapsing-remitting MS. In addition, another study from this team showed a reduced number of new plaques and a trend toward a decreased number of new relapses.[47,48]

NATURE OF VASCULAR LESIONS IN CCSVI

Although long-term and pediatric observations are currently missing, it is suspected that CCSVI patients present with congenital venous malformations of the veins draining the brain or spinal cord.[49,50] Taking into account the embryologic development of the IJVs and brachiocephalic veins, one should expect a higher prevalence of these pathologies on the left side. IJVs develop from the precardinal veins, which must join the common cardinal veins during embryological development. In some cases this process may go awry, especially on the left side, where part of the left common cardinal vein involutes. In addition, in some patients, the development of the jugular valves may not be perfect, resulting in structural abnormalities and stenoses. Indeed, some researchers have found a higher prevalence of CCSVI lesions in the left IJV.[51-53] Similarly, most of the abnormalities in the azygous vein are found slightly distally from the arch, in the area where, during embryological development, the proximal part of the left postcardinal vein joins the left supracardinal vein. In some cases this fusion of the fetal veins may be imperfect, resulting in twisting or focal hypoplasia of the vein. For the time being, it remains controversial whether impaired outflow from other veins could influence the functioning of the central nervous system. Theoretically, in case of significant occlusion of the left iliac vein or the left renal vein, the azygous system could be overloaded by collateral flow coming from the lower part of the body. Yet, MS patients rarely present with plaques in the thoracic and lumbar segments of the spinal cord, which are drained by the azygous vein, thus making this potential iliac or renal source of neurological pathology unlikely.

CURRENT DIAGNOSTICS FOR CCSVI

CCSVI patients present with obstructive venous lesions, a unique vascular pathology (*Figure 1*). The most frequently found abnormalities are stenotic "overcompetent" jugular valves. Other vascular lesions—for example stenoses not related to the valves—are rarely encountered. Since this type of vascular pathology is not often seen in other vascular territories, a

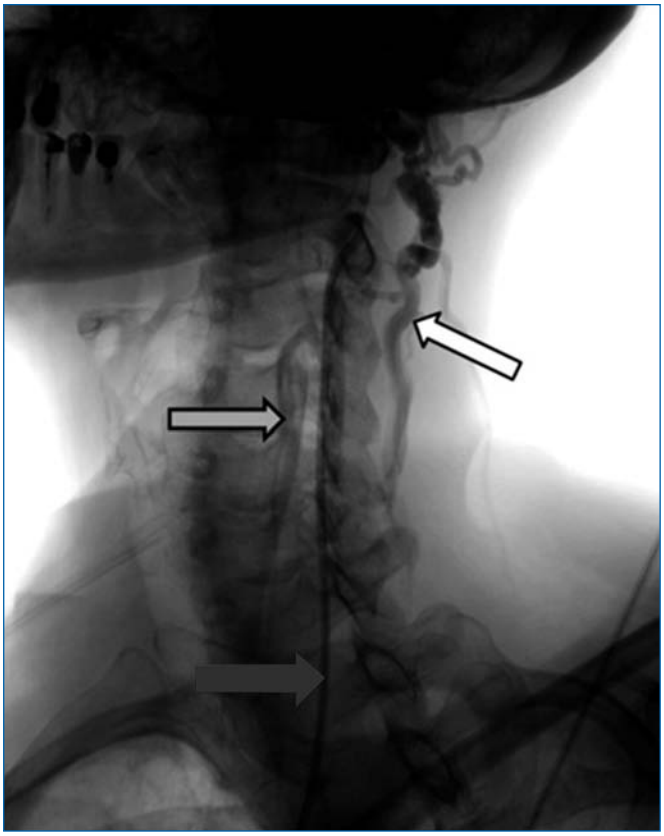

Figure 1. *Severe stenosis of the left internal jugular vein. A catheter has been placed in this vein (black arrow), but contrast is flowing out through the vertebral vein (white arrow) and deep cervical veins (grey arrow).*

noninvasive method for their assessment has not been established yet. For the time being, only Zamboni's CCSVI criteria have been validated. Still, the inconsistent results obtained in the studies that have used these criteria indicate that they are probably far from perfect and may need revising. Contrary to Zamboni, who found a 100% prevalence of CCSVI in MS patients,[45] Zivadinov[54] and Centonze,[26] who used the same sonographic criteria, demonstrated a 50-60% prevalence of CCSVI. In addition, these authors found sonographic features of CCSVI in many healthy controls. Recently, revised sonographic criteria have been proposed,[55] but their diagnostic accuracy was not found to be much better than that of the previous ones.[56] Obviously, more research is needed to understand flow disturbances in this unique venous territory and, consequently, the sonographic features of such a disturbed flow. Until a reliable set of criteria is developed, the results of screening using Doppler sonography should be interpreted with caution. The localization of the azygous vein makes its assessment using traditional sonography virtually impossible. Some authors nevertheless believe that lesions in the azygous vein can be diagnosed indirectly by evaluating the flow in the vertebral veins.[43] Yet, according to the anatomy of the venous system, it would be rather unlikely to detect a change in the flow pattern of the vertebral veins resulting from compromised azygous flow. The other diagnostic option is to evaluate the azygous vein using a transesophageal approach, since such an examination is currently performed in patients with portal hypertension. But, as yet, no published reports exist on transesophageal assessment of this vein in CCSVI patients.

Magnetic resonance venography (MRV) is another noninvasive diagnostic method (*Figure 2*), which seems to be less operator-dependent than Doppler sonography. It also enables the assessment of the intracranial veins, as well as the azygous vein. However, the currently available MR protocols are the source of significant imaging artifacts. Consequently, the diagnostic accuracy of MRV is even lower than that of Doppler sonography.[7,54,57,58]

Catheter venography (CV) is currently regarded as the gold standard reference test for the assessment of CCSVI. Using CV, at least 90% of MS patients were found to

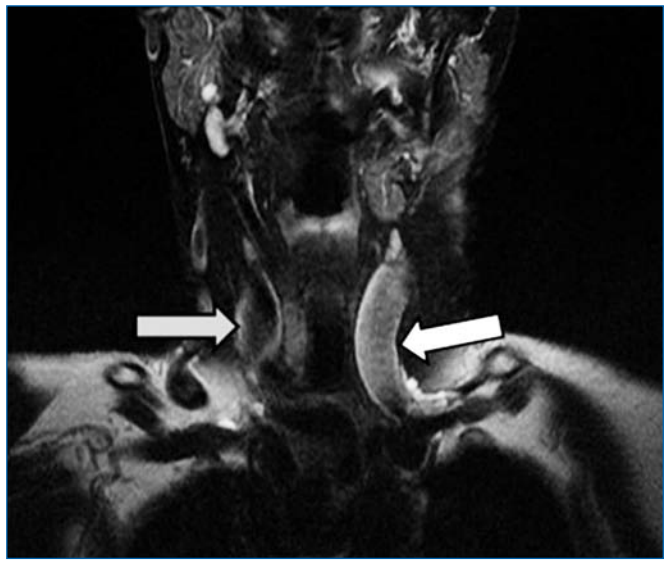

Figure 2. *The flow in the left internal jugular vein (white arrow) is slowed down, as demonstrated by fast-spin-echo-T2-weighted sequences with fat-saturation MR imaging. With this imaging modality, blood vessels with slow flow appear whitish, while those with normal flow are black, as shown in the right internal jugular vein (grey arrow). Please note that the left internal jugular vein is of normal size, and therefore may appear unchanged on conventional MR venography.*

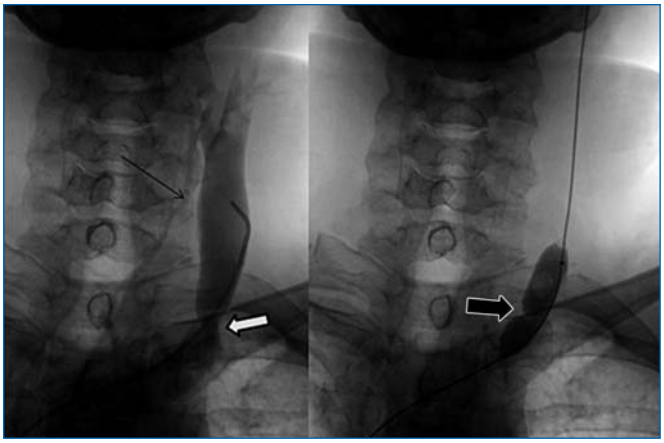

Figure 3. *Stenotic valve of the left internal jugular vein. Contrast is flowing out through the deep cervical veins (thin arrow); although the valve (white arrow) does not seem too significantly stenosed on venography, there is actually a tight stenosis, as indicated by an indentation in the angioplastic balloon (black arrow).*

have venous occlusive abnormalities.[18,27,51-53] The main problem related to the use of CV is the technique used and the interpretation of venographic images (*Figure 3*). Since CCSVI is primarily a functional pathology, venographic tests should mirror blood flow in the examined veins. Thus, contrast should be injected under low pressure (as in the case of venous blood flow) and the injection of large volumes of contrast should be avoided (in order not to overload the vein and not to induce artifactual collateral outflow). Therefore, contrast should be injected by hand and not with an automatic syringe. Similarly to the generally accepted venographic signs of impaired venous outflow in other venous obstructive pathologies, when assessing the IJVs or the azygous vein, the following venographic patterns should be regarded as abnormal:

- slowed down venous outflow (retention of injected contrast in the examined vein);
- reversed flow direction;
- outflow through collaterals;
- complete occlusion or agenesia of the vein.

It remains a matter of debate if findings such as:

- intraluminal structures (webs, septa, membranes);
- hypoplasia or narrowing of the vein;
- prestenotic dilation of the vein

should always be regarded as abnormal, or should be interpreted as a pathology only when associated with other signs of compromised outflow. Perhaps in most cases, CV should be accompanied by intravascular ultrasonography (IVUS) to resolve these uncertainties.

Since patients present with different degrees of venous pathology, a four-grade venographic classification of CCSVI has been proposed:

- Grade 1: slowed down venous outflow, no reflux detected;
- Grade 2: slowed down venous outflow, mild reflux and/or pre-stenotic dilation of the vein;
- Grade 3: slowed down venous outflow, with reversed flow direction and outflow through collaterals;
- Grade 4: no outflow through the vein, huge outflow through collaterals.[51]

Taking into account the low accuracy of a single test, many doctors opt for multimodal diagnostics, including: Doppler sonography, MR venography, catheter venography, and IVUS.

CCSVI: DOES THE SYNDROME ACTUALLY EXIST?

The CCSVI theory attracted vigorous criticism from neurologists.[3] Some researchers tried to replicate Zamboni's findings, using a modified sonographic protocol. While some of them demonstrated results similar to Zamboni's,[21-25] others were unable to demonstrate venous lesions.[59-62] Other researchers looked for potential MRI markers of CCSVI and did not find any signs of pathology.[63,64] Consequently, they claimed that CCSVI does not exist, and that the results of Zamboni are mere artifacts.

However, these "negative" studies were carried out either on a small group of MS patients—thus, with a high probability that non-CCSVI patients were assessed

just by chance—or using improper diagnostic tools. Nevertheless, only a minority of researchers now question the existence of venous abnormalities in MS patients (irrespective of the clinical meaning of the findings) and research performed with the use of reliable diagnostic tools (eg, catheter venography) has demonstrated the presence of lesions in about 90% of patients.[27,51-53]

However, it is important to emphasize that the actual prevalence of venous abnormalities in the IJVs and the azygous vein in a healthy population is not known. Reliable data should be obtained using CV, which—due to the invasive nature of this test—will not be an easy task. However, some already published data indicate that such flow disturbances could be found in as many as 30% of healthy people.[26,54] Thus, the total number of the so-called "CCSVI" patients in the general population may be much higher than the number of MS patients. Consequently, these vascular abnormalities should probably not be regarded as the pathology *per se*, but rather as a permissive lesion. This would mean that MS may be more likely to evolve from its preclinical form into clinically overt disease in the presence of venous abnormalities, while the triggering factor (eg, genetic predisposition or viral infection) may not be related to the vascular system.[65]

The CCSVI hypothesis is a perfect example of the haphazard nature of science, which often produces progress ahead of our understanding. Our knowledge of the anatomy and physiology of the veins draining the central nervous system is rather scarce. Most previous research has focused on the arterial side of the cerebral and spinal circulation, and also on the competence of the jugular valves.[66-70] Nevertheless, we have some data regarding the localization and diameter of the IJVs. For example, Troianos et al measured the diameter of IJVs in a group of 1136 non-MS patients. He did not observe occluded or severely narrowed veins.[71] Similarly, Denys et al found patent and normal-sized right IJVs in 96.4% of 928 critically ill patients. In the remaining 3% of patients, the vein was occluded by iatrogenic thrombi resulting from many previous cannulations.[72] Likewise, Lin et al found a 1.0% prevalence of occluded IJVs in a group of 104 uremic patients.[73] In contrast, except for a few case reports, we have no information on malformed azygous veins.[74] What is more, we do not know how often vascular malformations occur in "healthy" individuals nor what the clinical meaning of finding a "lesion" is.

The main problem related to the CCSVI concept is the difficulty in defining this clinical entity. According to Zamboni, CCSVI is a syndrome characterized by stenoses of the IJVs and/or the azygous vein, with opening of the collaterals and insufficient venous drainage, demonstrated by reduced cerebral blood flow and pathologic perfusion MR parameters (eg, prolonged cerebral mean transit time).[44,75,76] Currently, CCSVI is primarily defined in terms of pathologic Doppler sonography parameters. But should CCSVI be exclusively seen as a state of impaired venous outflow? An alternative view is that, in order to diagnose the pathology, venous outflow impairment should be accompanied by abnormalities of the central nervous system. It would appear to be more than a mere semantic problem. If this dilemma were solved, it would help decide which anatomical or structural lesions should be managed, and which ones should be considered only as anatomic variants with no potential clinical impact.

IMPLICATIONS OF THE CCSVI HYPOTHESIS

According to the Consensus Document of the International Union of Phlebology on the diagnosis and treatment of venous malformations, CCSVI is interpreted as a truncular venous malformation.[50] These lesions obstruct the main outflow routes from the central nervous system: the brain and spinal cord. Yet, it remains elusive whether these vascular abnormalities actually contribute to neurological pathology. Irrespective of these controversies, since CCSVI compromises the blood outflow from a vital organ, for many doctors it seems reasonable to unblock these obstructions. Others, however, argue that such interventions should only be accepted as a valid treatment option for MS on condition that:

- the impact of venous insufficiency on MS is demonstrated;
- procedures to alleviate these vascular pathologies have been proven to be technically feasible and safe;
- treatments have been shown to result in clinical benefit.

CAUSATIVE RELATIONSHIPS BETWEEN MS AND CCSVI

So far, an unquestionable relationship between CCSVI and MS has not been proven yet, especially regarding a causative role of venous abnormalities. Some data even support the idea of a secondary nature of CCSVI, ie, that these lesions develop due to the action of proinflammatory agents released by the diseased brain, or that they result from brain atrophy.[27,60] However, taking into account the morphological characteristics of CCSVI lesions (primarily: malformed valves) and that these malformations are seen more frequently on the left side,[51-53] it is very difficult to suggest a reasonable mechanism by which these vascular abnormalities could develop secondarily. It seems far more likely that the CCSVI lesions are of a congenital nature. Indeed, a recent study showed no correlation between the duration of MS and the severity of venous pathology, backing the idea of the primary nature of these vascular lesions.[65]

There are several theoretical mechanisms by which CCSVI could trigger or exacerbate MS-associated inflammation and neurodegeneration. In addition to a potential role for iron[19,77,78] —although it is possible that an increased concentration of iron within the cerebral parenchyma is only an epiphenomenon and the sign of a weakened blood-brain barrier—it has been hypothesized that CCSVI augments neurological disability through chronic brain hypoxia resulting from the blockage of venous outflow.[39] Current research favors this idea. Measurements of pO_2 and pCO_2 in blood samples obtained from the IJVs before and after angioplasty of the stenotic jugular valve have demonstrated dramatic improvements of these blood gas parameters, indicating a better oxygenation of the brain after the procedure.[79]

It is also possible that venous reflux in the cerebral circulation elicits disintegration of the blood-brain barrier, which in turn initiates an autoimmune attack against nervous tissue.[80-82] Moreover, in the setting of chronic ischemia and a leaky blood-brain barrier, the axons could be injured via glutamate-mediated excitotoxicity. A potentially deleterious role of glutamate has long been suspected to be important in the pathogenesis of MS-related neurodegeneration, but it was difficult to find a factor that may be responsible for the increased susceptibility of axons to this amino acid.[83-87] Perhaps CCSVI is the missing piece of the puzzle.

THERAPEUTIC OPTIONS FOR CCSVI AND THEIR SAFETY

Currently, balloon angioplasty remains the first-line option for the treatment of malformations of the veins draining the central nervous system (*Figure 4*). This procedure has been demonstrated to be safe.[48,51,52,88] Only a few major complications have been observed. However, balloon angioplasties of IJVs are associated with a high rate of restenosis. Stenting of a stenotic vein was found more effective in the short term but—unfortunately—also associated with a higher risk of complications, which may even be life-threatening. Moreover, problems with maintaining long-term patency of the stents, which can be occluded by thrombi or intimal hyperplasia, have been reported (*Figure 5*).[89] Therefore, stents should not be regarded as the preferred

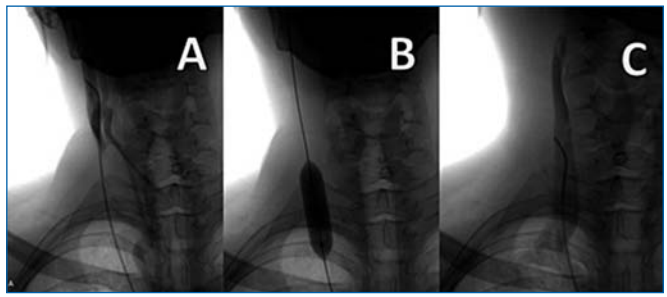

Figure 4. *Severely narrowed right internal jugular vein. Injected contrast flows out from this vein only through the collateral network (A); balloon angioplasty of the malformed jugular valve (B) resulting in physiologic outflow after the procedure (C).*

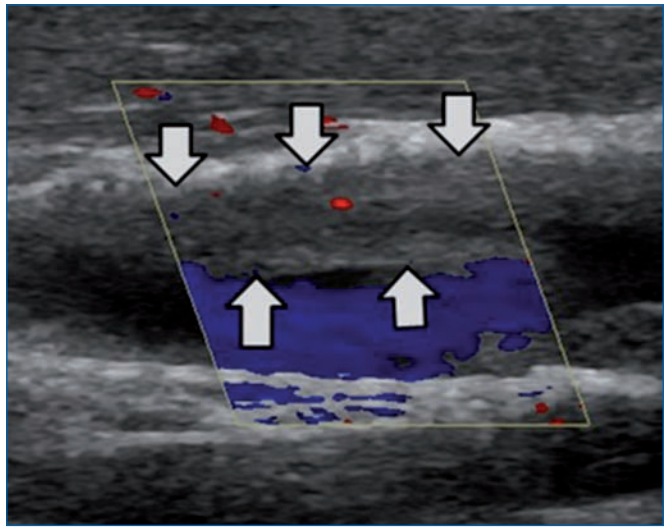

Figure 5. *Intimal hyperplasia (arrows) inside the stent implanted into the internal jugular vein. There is sufficient flow through the free part of the stent, but sometimes the stent can be completely blocked by ingrown tissue.*

treatment option. Perhaps, the use of cutting balloons (angioplastic balloons with small blades that cut the restricting annulus)—instead of stents—will be a better solution,[90] but as yet no reports on the efficacy of this method have been published. Other endovascular techniques, such as drug-coated balloons, drug-eluting stents, or dissolvable stents, may become useful in the future, but they have not yet been tested in this new indication.

The other unsolved problem related to endovascular treatment for CCSVI is the choice of optimal postprocedural medication. All reported fatal complications following the treatment of CCSVI were not directly related to the procedure, but were associated with the use of antithrombotic drugs. On the other hand, insufficient antithrombotic or antiplatelet medication can potentially result in thrombotic occlusion of the treated vein.[91,92] Thus, an optimal (ie, safe and effective) posttreatment medication scheme should be established. Taking this into account and until an optimal protocol is established, endovascular techniques that require more aggressive anticoagulation (primarily the use of stents) should be avoided whenever possible, since MS patients seem to be at higher risk of serious bleeding complications.

CLINICAL EFFICACY OF ENDOVASCULAR TREATMENTS

For the time being, only a few small open-label studies investigating the clinical efficacy of endovascular treatment for CCSVI in MS patients have been published. The results of these open-label studies were promising, especially in patients with relapsing-remitting clinical MS.[47,48,93-96] It has also been found that only some MS-related symptoms (eg, chronic fatigue, bladder control, impaired balance) may improve after the treatment, while others, especially walking ability, are not very likely to get better. Therefore, in patients with Extended Disability Severity Scores above 5 points, one should not expect an improvement in this scale. Unfortunately, high rates of restenoses of the treated veins have been observed, which may explain the fact that some authors observed only temporary benefits following angioplasty.[90,96] Still, only prospective randomized sham-surgery-arm or crossover trials, assessing objective and widely accepted neurological parameters (eg, the number of new plaques, number of relapses, or EDSS scores) would unequivocally prove or disprove the clinical efficacy of endovascular procedures for CCSVI.

ONGOING RESEARCH AND FUTURE PERSPECTIVES

The association of MS with impaired venous outflow from the central nervous system has shed new light on the cause and potential treatment options for this incurable neurological disease. There has been a shift away from viewing MS solely as an autoimmune disease, with no other potential treatment options. It is estimated that about 12 000 MS patients have already received endovascular treatment worldwide,[97] with only a few serious complications reported. Even if only a subgroup of MS patients actually benefited from vascular treatment, these procedures could potentially be a breakthrough in the management of MS.

In addition, perhaps some "vascular" drugs may improve venous insufficiency and—in turn—modify the clinical course of MS. Therefore, these pharmaceutical agents should be tested for potential anti-MS effects. Moreover, the discovery of CCSVI has shown another possible research avenue. It is known that only a minority of MS patients improve after administration of immunomodulating drugs. It cannot be ruled out that these "responders" actually represent a unique subset of CCSVI. If it were the case, these drugs should be given only to this group of MS patients. This hypothesis may also be validated by ongoing research.

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VEIN CONSULT Program: interim results from the first 70 000 screened patients in 13 countries

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ABSTRACT

The VEIN CONSULT Program, a joint initiative between the *Union Internationale de Phlébologie* and Servier, is the largest global effort to raise awareness of chronic venous disease (CVD) among patients, health care professionals, and health authorities. The aim is to update information on the prevalence of primary CVD in different geographic areas, to compare the management of the disease between countries, and to improve our understanding of the relationship between general practitioners and venous specialists, in order to propose a straightforward approach to earlier diagnosis. The survey was conducted in primary care centers as face-to-face interviews. Questionnaires were completed by practitioners and established the subjects' characteristics and risk factors for venous disease. Complaints likely to be of venous origin and when they were most likely to occur were reported together with the presence of visible signs on the legs. All data were pooled according to geographic area. Thirteen countries have already completed the survey, in Eastern Europe, Western Europe, South and Latin America (Brazil, Mexico), and the Middle and Far East, totaling almost 70 000 patients.

Primary care patients were mostly women (>66%) except in Pakistan (48%) and were older in Europe (mean age >52 years) than in the other geographic areas (≤45 years). A majority (>60%) said they had a maternal history of primary CVD and around 10% had a personal history of venous thrombosis. Reported symptoms in order of importance were heaviness, pain, sensation of swelling, and night cramps, and were found to intensify mainly at the end of the day or after prolonged standing. Symptoms significantly increased with age and with severity of disease.

Most screened subjects (>52%) believed they had leg problems at the time of consultation, while 19% to 26% presented spontaneously for venous care. After examination of the legs by physicians, it appeared that more than 61% of subjects had visible signs on at least one leg. Around 17% of them

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CEAP, chronic venous disease, CIVIQ, epidemiology, prevalence, symptoms

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complained of venous symptoms only. Patients consulting specially for venous problems had more severe signs compared with the whole sample.

Regarding costs, it appeared that CVD is responsible for large productivity losses, as well as the physical and psychological suffering of patients, which is reflected in worsened quality of life.

THE NEED FOR THE VEIN CONSULT PROGRAM

CVD is a common condition that has a significant impact on both the individuals affected and the health care system. It is estimated that 30%-35% of the general population are categorized as C_0 and C_1 of the CEAP classification system. This includes people with venous symptoms but no visible or palpable signs of venous disease (C_{0S}) and those with telangiectasias or reticular veins.[1,2] One epidemiological study in Germany found that only 10% of the population was free of some form of CVD.[3] According to epidemiological studies over 10 years, varicose veins affect 30% of adult women and 15% of men.[4] In Europe, venous disorders may affect 25% to 50% of people, for all types and degrees of varicose veins, 10% to 15% for marked varicose veins, and 5% to 15% for more severe stages of the disease.[5] In countries with developed health care systems, CVD has been estimated to account for 1 to 3% of the total health care budgets,[6] and the annual direct plus indirect costs of CVD in Germany, France, and the UK are approximately 800 million euros in each country.[7] CVD is no longer considered a disorder related to age as the first symptoms can develop between the ages of 15 and 25 years. CVD is associated with a reduced quality of life.[8] Despite being such an expensive disease with high levels of morbidity, few people recognize that early diagnosis, patient monitoring, and treatment of CVD can prevent disease-related complications.

AIMS OF THE VEIN CONSULT PROGRAM

The VEIN CONSULT Program is the greatest global effort to raise awareness about CVD among patients, health care professionals, and health authorities. It aims to assess the prevalence of CVD and to provide a picture of the typical adult patient and the management of their disease, in varying geographical areas. This will help to evaluate how general practitioners (GPs) and venous specialists manage patients with CVD and to understand better at which stage of the disease specialists take over from GPs in the management process.

The program is designed to detect CVD early, with the goal of improving the management process of this chronic disease, and to assess the impact of CVD on the quality of life of patients, health care resources, and the economy (eg, number of work days lost).

VEIN CONSULT PROGRAM METHODOLOGY

In Step 1 of the program, GPs screen patients consulting them for any medical reason (except an emergency). The GPs must assess whether the patients are suitable for involvement in the program using set criteria: men or women over 18 years old, informed of their involvement in a screening program and who agree to take part; informed that they have the right to refuse to participate fully or partly; not consulting for an emergency or for an acute episode of an ongoing event. The patients need to be enrolled consecutively within a short period of time.

If the patient meets these criteria, each participating GP then completes a case report form assessing the patient's history, listing any CVD risk factors, screening for CVD symptoms, and performing a routine leg examination. If the patient shows symptoms or signs of CVD and the GP considers him or her to be eligible to participate in Step 2 of the program, the patient is asked to complete a short, self-administered quality-of-life questionnaire—the **C**hron**I**c **V**enous **I**nsufficiency **Q**uestionnaire-14 (CIVIQ-14), a 14-item questionnaire. The GP then recommends a follow-up consultation with a venous specialist.

Step 2 is the follow-up consultation with a venous specialist. The specialist completes a 21-item questionnaire to establish the patient's history of CVD and risk factors, carries out a lower leg examination, and assesses whether treatment is required.

FIRST RESULTS FROM THE VEIN CONSULT PROGRAM

Results for the first 13 countries participating in the VEIN CONSULT Program were pooled (out of the 20

participating in total) by geographical region, as patient profiles varied from one region to another. These were Western Europe (France, Spain), Eastern Europe (Georgia, Hungary, Romania, Russia, Serbia, Slovakia), Latin and Central America (Brazil, Mexico), and the Middle and Far East (Emirates, Pakistan, Singapore). Sample size varied from one region to another. Western Europe totaled 36 004 subjects, Eastern Europe had 23 412 subjects, while there were 6385 and 4065 subjects, respectively, in Latin and Central America and the Middle and Far East. A total of 69 866 subjects were screened between October 2009 and March 2011.

The mean age of patients consulting for CVD was 51.6 years. Mean age decreased across regions as follows: Eastern Europe, 53.4 years > Western Europe, 52.5 years > Central and Latin America, 46.2 years > Middle and Far East, 39.4 years. On the latter continent, Pakistan influenced the results with a higher proportion of young men.

On average, the percentage of women consulting was 67.8%, the number of women being 2.5- to 3-fold higher than the number of men, with the exception of the Middle and Far East where there were 52.8% women.

Almost 42% of subjects remembered a family problem of reticular veins, varicose veins, swollen legs, or venous ulcer. Whatever the continent, participants were more likely to remember leg problems, if they were present, in the mother (64.8%) than the father (13.9%). This was a little less likely in the Middle and Far East, but in this region men were proportionally more numerous. Personal history of venous thrombosis concerned 8.3% of participants. Subjects were spending a mean of 6.6+3.1 hours a day in a standing position, and 67.8% did not exercise regularly.

CEAP classification

The distribution of the study population as a function of CEAP class is shown in *Figure 1*. Nearly 58% of subjects were between C0s and C2, stages of CVD that can be considered as early, while nearly 24% were at the stage of chronic venous insufficiency (C3-C6). The prevalence of ulcers, healed and active (2.1%), is in agreement with published data. A total of 61.2% of subjects were at stages C1-C6.

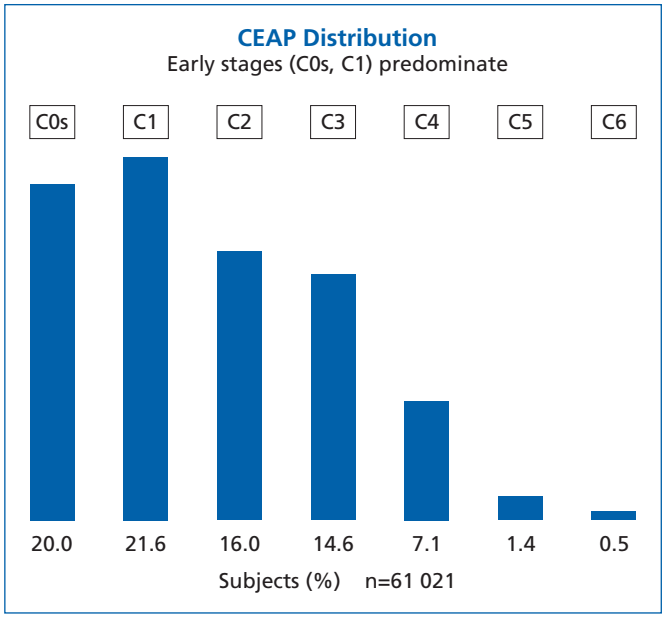

Figure 1. *CEAP distribution in the subjects screened in the VEIN CONSULT Program*

Symptoms encountered

A high proportion of subjects complained of leg heaviness (75.4%) and pain (67.3%); a sensation of swelling (54.8%) and night cramp (42.6%) were also common. The rank order of these symptoms varied from one country to another.

To be ascribed to CVD, symptoms had to vary with the time of day, temperature, and position. *Figure 2* shows that CVD symptoms were usually most intense at the end of the day (58.3%) and after prolonged standing (44.2%), and less intense during the night (36.8%). Summer is associated with the appearance of symptoms in countries where the seasons are well defined (34.2%), namely in Europe.

In the Middle and Far East, summer had less climatic variation and this question remained largely unanswered (5.4%). In addition, in this region, symptoms were more likely to be felt with greater intensity during the night (52.5%) than at the end of the day (36.6%).

The proportion of patients complaining of symptoms increased with disease severity in accordance with the CEAP classification. Similarly, the mean number of symptoms per patient also increased with disease severity (*Table I*). This tendency was observed in all countries.

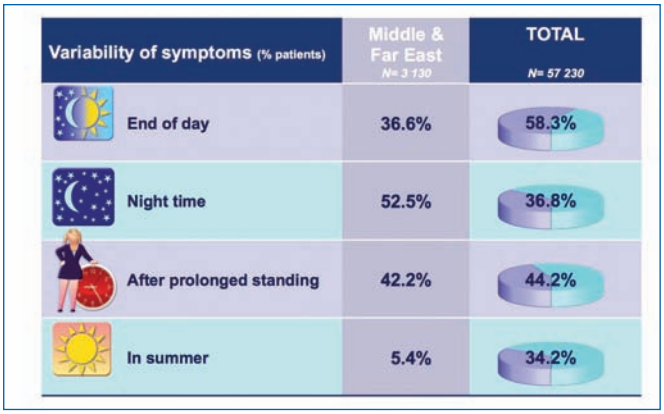

Figure 2. Variability of symptoms according to time, temperature, and position.

% heaviness in:	Global participants	Mean number of symptoms of which subjects were complaining
C0S	67,00%	2.3
C1	76,80%	3.0
C2	83,00%	3.6
C3	88,00%	3.8
C4	90,00%	4.4
C5	93,00%	4.9
C6	93,80%	5.0

Table I. Percentage of participants with heaviness, and mean number of symptoms reported according to CEAP classification.

Consideration of chronic venous disease by patients and practitioners

A total of 25.9% of participants consulted a practitioner spontaneously because of leg problems, of which 2% were at stage C0s. If we consider that 61% were assigned stages C1-C6, this means that nearly 40% of C1-C6 patients would not have been detected without VEIN CONSULT Program. As shown in *Figure 3*, the more advanced the severity of CVD, the more likely patients were to consult spontaneously. It is when the disease worsens (especially from stage C5) that the majority of patients decide to consult a general practitioner (GP).

On the other hand, GPs do not consider patients as having CVD before they present with a sign. Underestimation of CVD by GPs is especially clear at the C0S stage (27% of C0s patients were considered to have CVD), and to a lesser extent at C1 (82%), but is

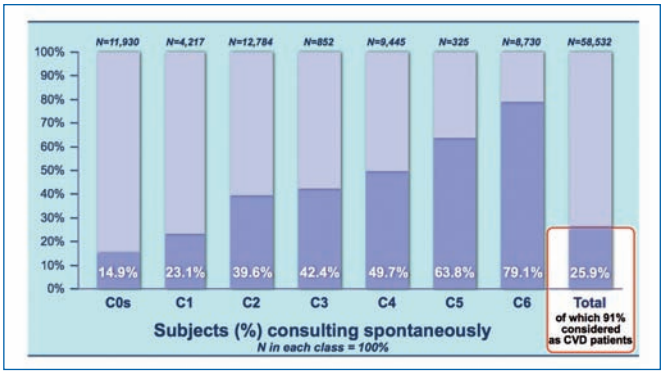

Figure 3. Percentage of subjects consulting spontaneously because of leg problems according to the CEAP classification.

recognized more from stage C2 (92% to 100% of patients considered to have CVD). C0s patients are generally not included in the CVD category (except in France where 1 in 3 patients in this category are considered to have CVD).

When asked "Do you presently have spider veins, varicose veins, ankle swelling, or ankle ulcer," 52.8% of patients answered that they had one or several of these signs, but when examined by GPs, 61.2% presented with such signs. CVD seems to be underestimated by patients themselves.

Impact of chronic venous disease on costs and quality of life

Only patients considered by GPs as having CVD completed the questionnaire about costs and impact on the quality of life. CIVIQ-14 was used to assess the quality of life of patients using the Global Index Score (GIS). A GIS=100 means a very good quality of life and GIS=0 a very bad quality of life.

Among the 25 436 patients who replied to the questionnaire, more than 12%, that is to say more than 3000 patients, had already undergone surgical treatment or sclerotherapy. Nearly 6% of patients had been hospitalized and 3.7% had changed their professional activities because of venous leg problems. Loss of work days was reported in 15% of CVD patients. Number of lost work days did not exceed 1 week for most (45.2%), while 30% of them lost more (18%>1 week and 12%>1 month). Quality-of-life scores decreased with higher frequency of lost work days (from 68.40±19.50 for 1 time to 43.04±22.32 for >3 times) and with duration of the absence from work (from 77.25±18.84 for <1 week to 56.97±22.19 for >1 month).

As CVD increases in severity, GIS scores range from 80.71±16.15 in patients with telangiectasias to 44.17±23.51 in those with an ulcer (*Table II*), and with the presence of a symptom (84.77±15.96 in patients without pain versus 66.86±19.80 in those with pain).

CEAP clinical class	C0s	C1	C2	C3	C4	C5-6
Global Index Score (GIS) with CIVIQ-14	83.2	80.7	72.6	67.5	60.0	47.5

Table II. *Assessment of Global Index Score with CIVIQ-14 according to CEAP classes*

Whatever the symptom concerned, the quality of life score was significantly better in the absence of symptoms. The more symptoms a patient had, the more quality of life deteriorated (*Table III*).

Number of reported symptoms	0	1	2	3	>3
Global Index Score (GIS) with CIVIQ-14	92.5	87.0	88.8	75.1	62.7

Table III. *Assessment of Global Index Score with CIVIQ-14 according to the number of reported symptoms.*

Discussion

This international epidemiological survey provides a snapshot of CVD in adults consulting primary care physicians. This is the first survey that has used the same questionnaire and the same CEAP classification whatever the country involved. Patients consulting spontaneously for leg problems (>25% of the study population) seem to be numerous. It appears they sought medical advice from stage C2 (varicose veins), but not much before. With 61.2% of participants at stages C1-C6, the prevalence of CVD in the study population was very high. VEIN CONSULT Program data are in line with previous surveys.[3,9-15] Prevalence varied with area, age, and sex. It should be emphasized that CVD was present worldwide and not only in the western world. Subjects complaining of symptoms were numerous. The questionnaire focused on symptoms first before examination of legs, which might have introduced a bias. The VEIN CONSULT Program is the first survey that has distinguished between C0a (healthy people) and C0s (complaining of symptoms without CVD signs) participants. Of particular interest is the high prevalence of the C0s population (20%) particularly in the Middle East where participants were younger than in the whole sample. Considering the high prevalence of the C0s population (20%) particularly in Middle East, more than 50 % complaining about symptoms during night time, it is debatable, if these complaints are really caused by venous problems, justifying the description C0 or to other, non-specific ailments. (The CEAP classification is by definition a classification of chronic venous disorders which should exclude non- venous pathologies. To ascertain whether C0s patients, who do not present with a detectable venous pathophysiology (Pn) have a venous disorder, medical questioning should delve deeper into the symptoms since we know that many subjective leg symptoms (eg, night cramps) can have other causes as well. Complaints for leg problems may occur whatever the country and culture, even if symptoms increase with the severity of CVD. The VEIN CONSULT Program confirms that CVD is a costly disease that may cause considerable suffering to patients.

Despite these facts, CVD remains underdiagnosed, as confirmed in the VEIN CONSULT Program, which detected nearly 40% of C1-C6 patients. The reasons for this are multiple[16] and include inadequate graduate and postgraduate training, diffuse nature of the disease presentation, intervention of numerous specialities, lack of understanding of preventability and treatment, lack of focused interest by many practitioners. The role of GPs in the diagnosis of CVD is critical as early intervention may prevent progression of this chronic disease, and treatment of early skin changes increases the chances of preserving the tissues of the lower leg, and referral of patients to a specialist is crucial in obtaining venous testing, particularly at advanced disease stages.

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The natural progression of chronic venous disorders: An overview of available information from longitudinal studies

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ABSTRACT

Chronic venous disorders remain a common problem worldwide; however, despite increasing research into novel endovenous therapies for the treatment of superficial venous disease, the natural history of primary venous disorders remains poorly understood. The following article provides a review of the longitudinal studies evaluating the progression of chronic venous disorders in the published literature. This includes a summary of the rate of development of venous disease in asymptomatic limbs and the rate of progression of venous disease in terms of hemodynamic, anatomical, and clinical progression including the development of skin changes and venous ulceration.

Venous disorders, including varicose veins and superficial venous insufficiency, are a common pathology, thought to affect between 15% and 40% of the adult population.[1-2] They have plagued mankind for thousands of years and there is documentation of their existence from as early as 3500 BC.[3] In the last decade, the development of endovenous techniques has led to a rapid increase in the popularity of many novel therapies including thermal and chemical ablation techniques.[4-7] Yet, despite the large number of research studies supporting the use of new devices, the etiology and natural history of the progression of venous disease remains poorly understood. Evidence from clinical ultrasonographic and histological studies supports a multicentric theory for the development of venous disorders due to abnormalities in the composition of the vein wall leading to functional changes.[8-9] However, the investigation of the progression of venous disease is complex and can be measured in a number of different ways. In recent years, there has been a move away from the use of surrogate end points to grade disease severity, such as the presence or absence of reflux, or the use of hemodynamic parameters such as venous refill times. A greater emphasis is now placed on the clinical assessment of disease severity and its functional impact on the individual patient. The association between the presence of superficial reflux and venous hemodynamic measurements with clinical and functional outcomes has been shown to be weak,[2,10,11] and the relationship between these parameters remains poorly understood.

Keywords:
CEAP classification; natural history; varicose veins

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To date, there have been few studies that have investigated the natural history of the progression of primary venous disease. Much of the current information is based on patients self-reporting their symptoms, many of whom subsequently undergo treatment, and the natural history of the condition is infrequently documented. In the current financial climate, the natural history of patients presenting with mild or moderate venous disease becomes increasingly important in order to justify the allocation of scarce resources. The overall societal burden of venous disease is unknown; however, chronic venous ulceration is debilitating for patients and costly for society and therefore preventative treatments are likely to be cost effective.[12,13] This article includes a review of the available information from longitudinal studies to date.

LONGITUDINAL STUDIES EVALUATING CLINICAL DISEASE PROGRESSION

The Framingham study (1988)[14]

One of the earliest longitudinal epidemiological studies of varicose veins was the Framingham study, which followed 5209 male and female subjects for 16 years at 2-yearly intervals starting in 1966. Subjects were examined for the presence of varicose veins—defined as dilated tortuous veins on the lower limbs—and potential risk factors were recorded. At the beginning of the study, 1720 men and 2102 women had no clinical evidence of varicose veins. Over the 16-year period, 396 men and 639 women developed varicose veins. The development of varicose veins was significantly greater in obese women. Significant differences were also noted in those with a higher systolic blood pressure, and those who were less physically active. The data suggested an incidence of varicose veins of 39.4 per 1000 men and 51.9 per 1000 women with no significant increase with age; however, there was an increase in prevalence with age due to accumulation. The study provided useful information regarding the incidence and potential risk factors associated with the development of varicose veins; however, it did not provide details of the progression of venous disease.

Brewster et al (1991)[15]

Brewster et al published one of the earliest longitudinal studies documenting the details of venous disease progression in 304 patients on an NHS waiting list for superficial venous surgery. The median waiting time for patients on the waiting list was 4 years (range, 6 months to 13 years) and the median reported length of symptom duration was 28 years (range, 2-47 years). Primary varicose veins were observed in 85.5% of patients while 64% of patients reported that they felt that their venous disease had progressed since their initial presentation, and 5.2% suffered an episode of thrombophlebitis. In the time since their initial presentation, 68 patients (22%) had developed skin changes and 12 patients (3.9%) had developed venous ulceration, although the degree of clinical severity at baseline in those who developed ulceration was not reported.[15] As with previous published studies, the development of further varicosities did not necessarily correlate with worsening of symptoms.

Sarin et al (1993)[16]

In a small study of 56 limbs in 36 patients on an NHS waiting list for treatment of uncomplicated varicose veins (43 primary and 13 recurrent), patients underwent noninvasive imaging and clinical examination at initial presentation and again prior to surgery. Superficial venous surgery was delayed by a median of 20 months (range, 15-27 months). An additional 3 patients had developed varicosities along the distribution of the great saphenous vein (GSV), and 11 had developed new varicosities in the small saphenous vein (SSV) distribution prior to treatment. There were no new cases of venous ulceration; however, 1 patient developed lipodermatosclerosis.[16] Of the 16 previously clinically normal contralateral limbs, 5 (31%) developed varicosities. Duplex ultrasonography demonstrated that an additional 14 patients developed superficial reflux at new sites (27%) and 18% were shown to have progressive reflux compared to initial duplex scans. New reflux developed in 25% of normal contralateral limbs. No significant deterioration in venous refill times was observed.

Labropoulos et al (2005)[17]

Labropoulos et al carried out a longitudinal study comprising 116 limbs from 90 patients presenting with symptomatic chronic venous disease, who—for various reasons—did not undergo immediate treatment for their venous disorder and underwent treatment at a later date.[17] All patients underwent two duplex ultrasound scans prior to intervention and reflux was classified as retrograde flow >0.5 s in truncal veins and >350 ms for perforator veins. All changes were documented and the time in between scans was specified. At the time of the

initial duplex scan, 3.4% of patient had C1 disease, 43.8% had C2 disease, 23.3% had C3 disease, 13.8% had C4 disease, and 6.9% and 4.3% had C5 and C6 disease, respectively.[17] Over a total of 43 months, 27 of 116 limbs (23.3%) had changes on duplex ultrasonography and patients reported worsening symptoms at some point in 13 of 116 limbs (14.4%), although patients underwent scans at different time intervals. In patients who underwent a second duplex between 1 and 3 months, 1 of 15 limbs exhibited noticeable changes on duplex ultrasonography and 5 of 28 limbs showed duplex changes when scanned after 4-6 months, although none of these patients had worsening clinical symptoms. In the patients who underwent their second scan at 7-9 months, 6 of 18 limbs showed duplex changes and worsening symptoms were reported in 1 of 18 limbs. In the patients scanned after 10-12 months, 3 of 15 limbs exhibited duplex changes, and worsening symptoms were reported for 1 of 15 limbs. When scanned after 13-18 months, 3 of 12 limbs showed duplex changes and worsening symptoms were reported for 3 of 12 limbs. At 19-24 months and 25-30 months, scans showed duplex changes in 3 of 10 limbs and 2 of 8 limbs, respectively, while worsening symptoms were reported in 3 of 10 limbs and 2 of 8 limbs, respectively. Between 31 and 36 months, 3 of 7 limbs exhibited duplex changes and worsening symptoms were reported in 2 of 7 limbs, while between 37 and 43 months, 1 of 3 limbs had duplex changes and worsening symptoms were reported in 1 of 3 limbs. New reflux was documented at 14 new sites including the GSV (n=2), SSV (n=1), tributaries (n=4), nonsaphenous vein (n=1), perforator veins (n=4), and deep veins (n=2). Extension of reflux in existing refluxing veins was documented in 17 limbs including at the saphenofemoral junction (SFJ) (n=1), GSV (n=7), SSV (n=4), tributaries (n=7), nonsaphenous veins (n=3), perforator veins (n=6), and deep veins (n=3). Overall when compared separately with other veins, saphenous veins and their tributaries were significantly more likely to have undergone change ($P<0.01$, Fisher exact test). Extension was antegrade in 7 limbs, retrograde in 7 limbs, and in both directions in 3 limbs. Worsening swelling (C2 to C3 change) was reported in 7 cases, worsening skin changes (C3 to C4) in 4 cases, and there were 2 cases of venous ulceration (C4 to C6). Overall 73% of limbs did not undergo any change; in those that did, this was usually after 6 months from the original scan. Approximately half of the patients who had significant changes on duplex ultrasonography reported a change in symptoms that occurred after 1 year. In addition, a number of patients who did not have noticeable changes on duplex ultrasonography were observed to have progressive clinical disease.

The Bonn Vein Study – Rabe et al[18]; Pannier et al[19]

The aim of the Bonn Vein study was to investigate the prevalence of deep and superficial reflux in the general population.[20] The most recent evidence from the Bonn Vein Study—which surveyed over 1978 patients in Germany—showed that over 6.6 years, progression of C2 disease to higher C classes was 31.8% in patients with saphenous reflux and 19.8% in patients with nonsaphenous reflux.[18] The prevalence of varicose veins rose from 22.7% to 25.1%, and the prevalence of CVI increased from 14.6% to 16%. Risk factors for disease progression were identified using a multivariate analysis and included increasing age, obesity, and arterial hypertension.[19]

Kostas et al (2010)[21]

73 patients with primary superficial venous disease who underwent unilateral varicose vein surgery were followed up after 5 years with regard to the contralateral limb, which was either asymptomatic or minimally symptomatic at the time of initial treatment.[21] Patients underwent clinical examination and were graded according to the Clinical-Etiological-Anatomical-Pathophysiological (CEAP) classification. Duplex ultrasonography was performed to establish the presence of retrograde flow >0.5 s in either deep or superficial veins. At initial recruitment, 5 of 73 patients had mild symptoms in the contralateral limb and 56 patients (77%) had no evidence of venous disease, 21% of patients were graded as C1, and 4 patients (5%) were graded as C2. A total of 12 limbs had isolated superficial reflux, and 6 limbs had deep reflux on duplex ultrasonography. At 5 years, 48 new sites of reflux were found in 38 limbs, most frequently in the superficial veins; however, 6 limbs developed deep venous reflux. In the limbs where reflux had propagated, this was antegrade in 10 limbs and retrograde in 8. In the majority of patients, changes in detectable reflux were associated with clinical changes, with 5 limbs progressing from C0 to C1, 5 from C0 to C2, 2 from C0 to C3, and 5 from C0 to C2/3. Progression from C1 to C2 was observed in 6 limbs, while 3 limbs progressed from C1 to C3, and 2 from C2 to C3. There were 2 patients who were initially classified as C2 who developed C4 skin changes. The study found that the progression of CVD

was significantly affected by orthostatism and obesity, and that progression was reduced to some extent with the use of elastic compression stockings. Conversely, parity and estrogen treatments were not associated with progression of CVD. Overall, approximately a third of limbs with mild or asymptomatic reflux developed clinical signs over 5 years. This is similar to the 27% reported by Labropoulos.[17]

Labropoulos et al (2009)[22]

The progressions of primary and secondary venous disorders are noticeably different. A prospective comparison of the rate of progression of primary and secondary venous disease was performed over a 5 year period in 41 patients with a proximal DVT (group A), compared with a cohort of 41 patients with primary venous disease (group B) and followed up at 5 years with duplex ultrasonography. These were also compared with 15 control cases with no evidence of venous disease (group C). At 5 years, CEAP scores for the 3 groups were as follows: group A, C0 n=6, C1 n=0, C2 n=0, C3 n=29, C4 n=8 C5 n=1, C6 n=2; group B, C0/C1 n=0, C2 n=29, C3 n=18, C4 n=3, C5/C6 n=0; group C, C0 n=25, C1 n=3, C2 n=2 C3/C4/C5/C6 n=0. All patients were encouraged to wear compression stockings with 30 to 40mm Hg of graduated compression. Results confirmed that patients with a previous history of DVT developed significantly more skin changes compared with those with primary venous disease (P=0.019), and those with no venous disease (P<0.01) and that the progression was more rapid in patients with a previous history of DVT. Skin changes also occurred significantly more frequently in patients with combined reflux and venous obstruction (P=0.12).[22]

The Edinburgh Vein Study – Robertson et al (2011)[23]

Data from this cohort study included 1566 randomly selected adults between 18 and 64 years of age who were examined at baseline and then at 13 years as part of the Edinburgh Vein Study. Recorded measurements included a questionnaire of lifestyle factors, CEAP grade, and duplex ultrasonography. Of the 1566 patients, 880 were followed up at 13 years. A total of 325 patients had truncal varicosities at baseline, and at 13 years, 154 patients had deterioration in their varicosities (47.4%) while 62 had stayed the same (19.1%). Of the 555 patients with no truncal varices at baseline, 101 developed C2 varices during the 13-year follow-up. The annual incidence of developing trunk varices was 1.35%, the rate of disease progression was 3.54% per annum, and the number of patients with unilateral disease who developed bilateral disease was 25.3%. A total of 109 patients showed improvement (33.5%), of which 16.6% had undergone surgery or sclerotherapy. Patients who had not undergone treatment were all reported to have mild disease and differences in grade may be attributable to interobserver variability.

LONGITUDINAL STUDIES EVALUATING VENOUS HEMODYNAMICS

The Bochum study – Stucker et al (2005)[24]

The Bochum study surveyed 73 pupils over a period of 9 years at the beginning, middle, and end of their schooling. A fourth survey was also performed at 11 years. Pupils underwent clinical examination, duplex ultrasonography, and digital PPG and were classified according to the CEAP classification. Overall venous refill times appeared to lengthen from childhood to adulthood; this was thought to be due to maturation of the venous calf pump during adolescence. Interestingly, no clinical deterioration was observed in this cohort.[24]

LONGITUDINAL STUDIES EVALUATING THE EFFECTS OF INTERVENTION ON DISEASE PROGRESSION

Lurie et al (1998)[25]

This study evaluated 195 limbs in 183 patients with primary chronic venous insufficiency and reflux affecting the femoral vein, the SFJ, and the GSV.[25] Venous ulceration lasting for more than 6 months but less than 3 years was reported in 99 limbs. Patients underwent ascending and descending venograms and duplex scanning, and were randomized to receive one of three treatment options including elastic compression hosiery (n=68), surgical treatment of venous insufficiency/saphenectomy (n=75), or deep vein reconstruction/valvuloplasty with saphenectomy (n=52). Clinical results were recorded based on the clinical severity scoring system recommended by the subcommittee on the reporting standards for venous disease.[26] Over a mean follow-up period of 6.2 years, no significant difference was observed between the results of the three interventions in patients who had a disease duration of less than 5 years. However, in patients with a disease history of greater than 5 years, the results of valvuloplasty were significantly better, and the incidence of recurrent

varicosities was significantly lower after valvuloplasty in comparison with superficial vein repair alone. Recurrent varicosities were observed in 18 patients (14.2%). The authors concluded that valvuloplasty significantly improved the results of superficial venous surgery and that successful treatment was associated with an improvement in valvular function.[25]

LONGITUDINAL STUDIES EVALUATING RISK FACTORS AND THE DEVELOPMENT OF VENOUS ULCERATION

It is known that disease progression is related to the severity of venous reflux and duration of disease.[27] The sensation of leg swelling in otherwise mild disease was found to be an indicator of likely disease progression and poorer prognosis.[28] The number of patients with superficial reflux who are likely to progress to edema, skin changes, lipodermatosclerosis, and venous ulceration is unknown; however, the overall incidence of edema and skin changes in the general UK population is thought to be approximately 1% per year.[27] The incidence of venous ulceration is 1% in the UK and the majority of those presenting with venous ulceration have had venous disease for more than 20 years.[15 29]

Heit et al (2001)[30]

A retrospective population cohort study was conducted in 1131 patients, including 263 patients who had venous ulceration over a 25-year period, to evaluate the incidence of venous stasis syndrome and venous ulceration. The incidence of venous stasis was 76.1 per 100 000 person-years and the incidence of venous ulceration was 18 per 100 000 person-years. Of the 945 patients who had venous reflux alone and no previous history of ulceration, 60 (6.3%) developed venous ulceration and the mean (±SD) time from the diagnosis of venous stasis to the development of a venous ulcer was 5 (±5) years with a range of 14 days to 24 years.[30] Venous ulceration increased with age in linear fashion and was higher in women than men.

A SUMMARY OF THE CLINICAL EVIDENCE ON THE DEVELOPMENT AND PROGRESSION OF VENOUS DISEASE

A number of longitudinal studies have reported the clinical development and progression of venous disease. Regarding the development of venous disease in asymptomatic patients (ie, patients not experiencing any symptomatic discomfort), Kostas et al reported results over a 5-year period where 22% of patients developed new C1 disease, 31% developed new C2 disease, and 27% developed new C3 disease, while Sarin et al reported that 25% of patients on a waiting list developed new varicosities over a median of 20 months and 1 patient (3%) developed lipodermatosclerosis. Regarding the progression of venous disease in patients with early clinical stages, Kostas et al reported that 3% of patients progressed from C2 to C4 disease.[21] In the Bonn Vein Study II, the rate of clinical progression from C2 to higher C stages was 31.8% in patients with saphenous reflux and 19.8% in those with nonsaphenous reflux over an average of 6.6 years.[18] Data from the Edinburgh Vein study suggested that 47.4% of patients with truncal varicosities showed clinical deterioration over a 13-year period and the rate of disease progression was 3.54% per annum.[23] Brewster et al noted that 22% of patients reported skin changes while waiting an average of 4 years for treatment of superficial venous disease. Labropoulos et al reported 7 cases of progression from C2 to C3, 4 cases of progression from C3 to C4, and 2 cases of venous ulceration (C4 to C6) over a period of 43 months.

A SUMMARY OF THE ANATOMICAL AND HEMODYNAMIC EVIDENCE FOR THE PROGRESSION OF VENOUS DISEASE

Although the presence of superficial venous reflux and abnormal venous hemodynamics are associated with symptoms, the degree of symptoms reported and the severity of venous disease frequently correlate poorly with quantitative anatomical or hemodynamic findings. Therefore, it is difficult to interpret the relevance of the observed anatomical progression of venous reflux demonstrated on duplex ultrasonography or the deterioration in hemodynamic function. Nevertheless, the evidence is summarized below.

Sarin et al reported that 27% of patients developed sites of new reflux in limbs where venous reflux previously existed and 25% of normal contralateral limbs had developed new reflux over this time, although no significant deterioration in venous refill times were observed. Labropoulos et al observed that over a total of 43 months, 23.3% of limbs had changes on duplex

ultrasonography and an extension of existing reflux was documented in 14.7% of limbs. Kostas et al reported 48 new sites of reflux in 38 limbs at 5 years (52%) and 6 limbs developed deep venous reflux compared with baseline.

A SUMMARY OF THE FACTORS AFFECTING THE PROGRESSION OF VENOUS DISEASE

Although the etiology of venous disease is incompletely understood, a number of factors appear to be related to the progression of venous disease. There is good evidence that obesity and arterial hypertension[28] significantly affect disease progression. In addition, there is evidence that prolonged standing increases the rate of disease progression, and that the use of elastic compression hosiery may reduce disease progression.[21] The presence of deep venous reflux, a past history of venous thromboembolism, and the presence of lipodermatosclerosis, corona phlebectatica, or varicose eczema are associated with an increased risk of developing venous ulceration.[31] In patients with secondary venous disease following acute deep venous thrombosis, the natural history of the disease is better understood. Studies suggest that approximately 30% of patients will go on to develop postthrombotic syndrome, with 3% to 6% developing venous ulceration,[32] and that disease progression occurs more rapidly than in those with primary venous disorders.[22]

Improving the diagnosis and treatment of patients with venous ulceration has been shown to significantly improve patient outcomes. Evidence from a Swedish study confirmed that through education and a coordinated multidisciplinary approach—including early diagnosis, thorough investigation, and early use of superficial venous surgery—venous ulceration was reduced by 46% between 2002 and 2005.[33]

PRACTICAL GUIDANCE

Based on the available evidence, the Society of Vascular Surgery and the American Venous Forum have produced practical guidance regarding the management of primary venous disorders.[34] According to this guidance, there is weak evidence for compression hosiery for patients with symptomatic varicose veins and it is not recommended as the primary treatment if a patient is a candidate for saphenous vein ablation. Compression treatment is recommended for patients with primary venous ulceration, with ablation of superficial reflux to reduce the risk of ulcer recurrence. Thermal ablation (radiofrequency or laser) is recommended for the treatment of great saphenous vein reflux in preference to high ligation and stripping, although foam sclerotherapy is also suggested as a treatment option. The treatment of tributaries with phlebectomy or foam sclerotherapy is also recommended. The routine treatment of perforating veins in C2 patients is not supported, although the selective treatment of perforators in patients with ulceration is suggested.

CONCLUSION

Chronic venous insufficiency is a complex disorder with an incompletely understood multifactorial etiology. The majority of patients presenting with venous disorders request treatment, so the natural history of the disorder is difficult to evaluate. At present there is a lack of published evidence from longitudinal studies that have evaluated the natural history of disease progression. Combining data from different studies is difficult due to the heterogeneity of the outcome measures reported in different studies and a lack of understanding of the relationship between them. However, there is promising data from large long-term studies, including the Bonn Vein and Edinburgh Vein studies, which are likely to allow a better understanding of disease progression in the future. Nevertheless, based on the data currently available in the published literature, it could be suggested that in patients with uncomplicated varicose veins, disease progression to higher C stages is likely to be somewhere between 3.5% and 7% per annum[15-17,21,28,35] and is subject to a number of patient and environmental factors. The development of venous ulceration usually occurs in patients who have had venous disease for over 20 years, and skin changes and deep venous incompetence are associated with a significantly higher risk of venous ulceration. The rate of progression from C4 disease in patients with skin changes to venous ulceration is unknown, but based on the available evidence, it is estimated to be in the in the region of 1% to 2% per annum.[15,17,18,25] These figures become highly important when considering the prevalence of venous disease. A recent study evaluating the societal cost of C4-C6 disease in European countries and the USA confirms

First Author	Year of publication	No. of study participants	No. of limbs	Brief study description	Duration of study
Brand[14] (Framingham study)	1988	5209	-	Epidemiological study of the incidence prevalence and risk factors for the development of varicose veins	16 years, patients reviewed at 2-yearly intervals
Brewster[15]	1991	304	-	Patients on an NHS waiting list for varicose vein surgery	Median (range) waiting time of patients was 4 (6-13) years.
Sarin[16]	1993	36	56	Patients on an NHS waiting list for varicose vein surgery	Median (range) waiting time 20 (15-27) months
Labropoulos[17]	2005	90	116	Longitudinal study of patients presenting with venous disease who did not undergo immediate treatment	43 months
Rabe [20,19] (Bonn Vein Study II)	2008-ongoing	1978	-	Longitudinal study of the development and progression of venous disease in the general population	6.6 years
Kostas[21]	2010	73	73	Patients undergoing superficial venous surgery for 5 years were followed with regard to the contralateral limb, which was asymptomatic or minimally symptomatic at the time of surgery	5 years
Labropoulos[22]	2009	97 Group A: Proximal DVT n=41, Group B: primary venous disease n=41, Group C: control group n=15	126	Longitudinal study comparing the progression of primary and secondary venous disease	5 years
Robertson[23] (Edinburgh Vein Study)	2011	880		Longitudinal study of the prevalence of venous disease in the general population	13 years
Stucker[24] (Bochum study)	2005	73		Study of venous refill times and duplex findings in school pupils	9 years
Lurie[25]	1998	183	195	Randomized clinical trial comparing results following treatment with compression hosiery (n=68), valvuloplasty plus saphenectomy (n=52) or saphenectomy (n=75) in patients with reflux of the SFV and superficial reflux.	Mean duration of follow-up 6.2 years
Heit[30]	2001	1131		A retrospective cohort study of patients to estimate the incidence of venous stasis syndrome and venous ulceration.	25 years

Incidence/ Rate of development of venous disease according to CEAP	Rate of progression of C2 disease to higher disease stages	Rate of development of venous ulceration	Duplex findings	Additional outcomes
Incidence of the development of varicose veins-CEAP unspecified 39.4/1000 in males, 51.9/1000 in females	Not specified	Not specified	Not specified	
Not specified	22% developed skin changes/C4 disease from initial presentation	3.9% developed venous ulceration, baseline CEAP unspecified.	Not specified	
25% of contralateral limbs had developed new reflux and 31% developed new varicosities in the contralateral limb	1 patient (2.7%) developed lipodermatosclerosis	No cases of venous ulceration	27% had developed reflux at new sites and 18% of patients had progressive reflux compared to baseline studies	3 patients developed additional varices of the GSV, 11 patients developed new varices of the SSV
A change in either duplex findings or symptoms occurred in 38 limbs at 6 months or later	11.6% progressed from C2 to C3 and 14.8% from C3 to C4	2 patients with C4 disease developed ulceration (12.5%)	31 limbs (26.7) of limbs had progression on venous duplex, of these 29 were symptomatic.	14.4% of patients reported worsening of symptoms
Prevalence of VVS rose from 22.7% to 25.1% over the study duration	31.8% of patients with saphenous reflux and 19.8% of patients with nonsaphenous reflux progressed from C2 disease to higher C stages.	Not specified	Details unpublished	
16 (23.1%) of patients with C0 or C1 disease at baseline developed C2 disease by 5 years.	2 patients with C2 disease developed C3 disease and 2 developed C4 disease	No patients developed C5/C6 disease	48 new sites of reflux were found in 38 limbs, including 6 limbs that showed development of deep reflux.	13 patients with C0 disease at baseline progressed to C3 disease at 5 years.
2 patients in group C developed varicose veins at 5 years (13%)	In group A, the incidence of skin changes at 1 year was 4% (2/46 limbs) and at 5 years was 24%(11/46) In group B, skin changes occurred in 3 patients (6%)	In group A, 9 limbs progressed from C3 to C4 and C6 and 2 limbs from C4 to C5 and C6.		47.4% had deterioration in their varicosities. A change in CEAP clinical class occurred in 14 limbs in group A (30%), of these 11 limbs had progression of reflux or recurrence of DVT.
101/ 555participants with no varices at baseline developed C2 disease. The annual incidence of developing trunk varices was 1.31%	The rate of disease progression was 3.54% per annum	Not specified		25% of those with unilateral disease developed bilateral disease
Not specified	No clinical deterioration was observed.	Not specified	-	Venous refill times lengthened from childhood to adulthood, thought to be due to the maturation of the venous calf pump.
Not specified	Not specified	Not specified	73% of patients had decreased leakage of the femoral vein after valvuloplasty. This did not occur in the saphenectomy or compression hosiery groups.	No significant difference in outcomes was observed between treatment groups in patients with disease duration of greater than 5 years. Results after valvuloplasty were significantly better than saphenectomy or compression. Recurrent varicosis occurred in 7.7% of cases following valvuloplasty compared to 17.3% following saphenectomy alone ($P<0.01$).
Not specified	Not specified	60/945 (6.3%) of subjects with no previous history of ulceration developed venous ulceration over 25 years. The mean (sd) time for the development of ulceration was 5(5) years.	Not specified	The incidence of venous ulceration was 18.0/ 100 000 persons per year. The incidence of venous stasis was 76.1/ 100 000 person-years.

that the costs run to hundreds of millions of euros each year for the treatment of superficial reflux, the treatment of venous ulcers, and the cost of days lost from work due to venous disorders.[36] A better understanding of the rate of progression of venous disease, and the ability to identify patients at risk of venous ulceration will help with the allocation of healthcare resources and ensure the appropriate management of patients with moderate venous disorders, and, therefore, further data from ongoing longitudinal studies is awaited

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Proteolytic degradation and receptor cleavage in the microcirculation

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ABSTRACT

We propose here a previously unrecognized pathogenic mechanism for hypertension and diabetes and the cluster of multifaceted cell dysfunctions characteristic of the metabolic syndrome. The evidence for this new hypothesis is derived from a genetic model with unchecked proteolytic activity, including that of matrix metalloproteinases, which causes cleavage of the extracellular domain of surface receptors and loss of their respective functions. For example, cleavage of the extracellular domain of the β_2-adrenergic receptor promotes arteriolar vasoconstriction and elevates central blood pressure; cleavage of the insulin receptor reduces glucose transport and produces insulin resistance; cleavage of vascular endothelial growth factor receptor 2 induces endothelial apoptosis and loss of microvessels, ie, capillary rarefaction. Similarly, cleavage of leukocyte membrane adhesion molecules (CD18, ICAM-1) and the formyl-peptide receptor attenuates leukocyte-endothelial interactions and promotes immune suppression. Chronic blockade of unchecked proteinase activity attenuates cleavage of each of these receptor types and restores their respective cell functions. The effectiveness of chronic proteinase inhibition for patients with the metabolic syndrome remains to be explored.

INTRODUCTION

A characteristic feature of several vascular diseases is the clustering of multiple cell dysfunctions and organ complications. A classic example is the metabolic syndrome, in which multiple comorbidities are present at the same time.[1] Besides obesity, patients with the metabolic syndrome have leptin resistance, elevated blood pressure, insulin resistance and hyperglycemia, reduced sleep quality and insomnia, dyslipidemia, capillary rarefaction, and immune suppression, to name a few. How is it possible that elevated arterial blood pressure and increased blood glucose levels with signs of insulin resistance[2,3] cluster with microvascular dysfunctions?[4] Furthermore, how can a single intervention against the metabolic syndrome, such as caloric restriction, interfere simultaneously with both hypertension and diabetes?[5]

The mechanism by which each condition arises individually is uncertain and there is as yet no conceptual framework that can explain such a clustering

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inflammation; microcirculation; matrix metalloproteinase; receptor cleavage

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of cell dysfunctions. Consequently, treatments are limited to symptomatic alleviation rather than targeting the underlying fundamental complication. Thus, the development of an overarching concept is potentially of major importance for the effective treatment of patients with multiple symptoms. Different cell dysfunctions may appear in the same individual to varying degrees and involve different receptors and molecular pathways. The condition as a whole predisposes toward enhanced cardiovascular complications, from atherosclerosis to heart and brain infarct, venous disease, and many other ailments.

In this article, we outline a new way of thinking about the multiple complications that may cause cell dysfunction in the metabolic syndrome. Most of the discussion is limited to an animal model, the spontaneously hypertensive rat (SHR). It is the only metabolic syndrome model in which we currently have a body of evidence in favor of this new hypothesis.

A NEW MECHANISM FOR INFLAMMATION: PROTEINASE ACTIVITY AND RECEPTOR CLEAVAGE

The SHR model was originally created as a high blood pressure phenotype.[6] However, besides an elevated blood pressure, this strain exhibits other cell dysfunctions, which include insulin resistance with elevated glucose levels, capillary rarefaction, immune suppression, abnormal red blood cell aggregation, a defective fluid shear stress response, and reduced sleep quality, to name a few.[7] Recent analysis of this model has brought to light a mechanism made possible by two key observations:

(i) a previously unrecognized mechanism for inflammation due to chronically unchecked proteinase activity, and

(ii) a set of new substrate targets for these proteinases.

UNCHECKED PROTEINASE ACTIVITY

In the SHR, in vivo microzymographic measurements and gel zymography—designed to detect proteinase activity in vivo in the microcirculation and in living tissue—reveal the presence of active proteinases, at increased levels compared with the control strains, the Wistar Kyoto rat strain and the Wistar strain. Techniques using a combination of fluorescently quenched proteinase substrates that are specific for individual proteinases, as well as antibody labeling, show enhanced matrix metalloproteinases (MMP) activity in the SHR in vivo. Specific MMPs found in the plasma include gelatinases (MMP-2 and MMP-9) and matrilysin (MMP-7). In addition, MMP-1, MMP-1/-9, MMP-7, and MMP-8 activity can be detected on the endothelium along the mesenteric microvessels whereas less MMP-2 and MMP-3 activity is detected (*Figure 1*).[8] The activity of these proteinases is elevated to a mild but significant degree and is not blocked by tissue inhibitors of metalloproteinases (TIMPs), as in control animals.

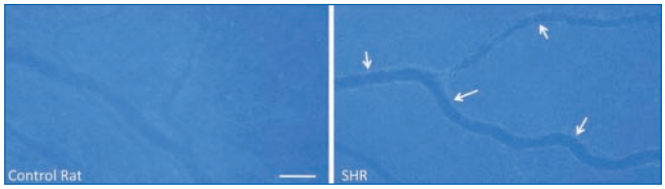

Figure 1. *Proteinase activity in vivo in control and spontaneously hypertensive rat (SHR) mesenteric microvessels. Proteinase activity was detected by fluorescent intensity generated after proteolytic cleavage of a quenched substrate cleaved by both MMP-1 and MMP-9. The proteinase activity is significantly enhanced on the endothelium (arrows). Length bar is 100 µm. Adapted from reference 8.*

What are the mechanisms that can generate such unchecked proteinase activity in the SHR? One clue comes from the observation that the SHR has chronically elevated levels of the nuclear transcription factor NF-κB,[9] one of the transcription factors with multiple binding sites in the promoter region of most members of the MMP family of proteinases.[10] Chronic pharmacological blockade of NF-κB reduces MMP levels in the SHR. The signaling pathway leading to such chronic overexpression of a proinflammatory transcription factor in this genetic form of the metabolic syndrome remains to be clarified.

MMPs are recognized for their ability to restructure the extracellular matrix and any tissue composed of extracellular matrix proteins. In hypertension, arterial hypertrophy and its transition to heart or renal failure, arterial aneurysm, or venous varicosities, are associated with enhanced activity of the members of the MMP family.[11-13] This involvement in diseases has led to a number of clinical trials with new molecules that target

the MMPs with differing levels of specificities. All these clinical trials are faced with the challenge that MMPs are a required component of wound healing. Therefore, chronic and specific inhibition of MMPs interferes with the resolution of inflammation and a more nuanced approach to pharmacological MMP inhibition needs to be developed. There is a need to identify specific MMPs that are associated with tissue damage. Then, ideally, only those particular proteinases should be targeted using graded levels of inhibitors.

RECEPTOR CLEAVAGE

In the SHR, the endothelium and the membranes of the circulating white and red blood cells show multiple signs of receptor cleavage due to unchecked MMP activity. They are diverse and affect a range of cell functions that are often found to be defective in the metabolic syndrome.

Adrenergic receptor

Using selected antibodies against the extracellular domain of the β_2-adrenergic receptor, and antibodies against its intracellular domain as control, it is possible to show in vivo that, in the SHR, this particular receptor is cleaved at the extracellular domain.[14] (*Figure 2*) The β_2-adrenergic receptor is usually responsible for the vasodilation of the arterioles; thus, proteolytic cleavage of its extracellular domain undermines its ability to dilate the arterioles, a process that makes a major contribution to the elevated arterial blood pressure of the SHR strain. The extracellular domain of the receptor can be cleaved by several MMPs, and plasma of the SHR has even been shown to cleave the extracellular domain of the receptor in naive donor cells. In acute experiments, receptor cleavage can be blocked by several MMP inhibitors. Chronic blockade of the MMPs in the SHR with a mild but broad-acting MMP inhibitor serves to restore the density of the extracellular domain of the receptor, which in turn lowers systemic blood pressure in the SHR.[14]

Insulin receptor

The SHR exhibits characteristic signs of insulin resistance similar to those observed in human hypertensive patients.[15] We found evidence that insulin receptor α is associated with defective glucose transport due to proteolytic cleavage of its extracellular domain

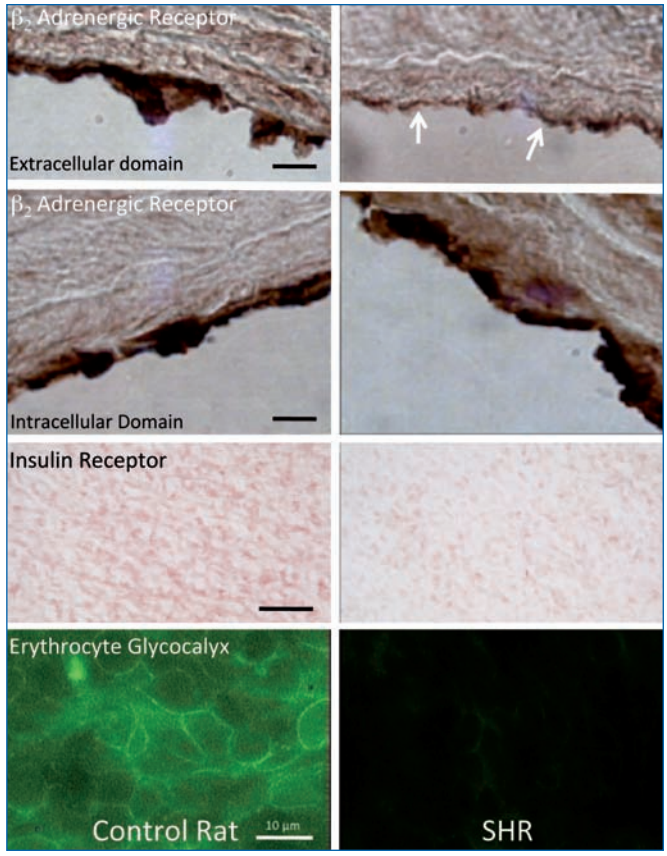

Figure 2. *Micrographs of the β2-adrenergic receptor label density in control and spontaneously hypertensive rat (SHR) aorta. β2-adrenergic receptor label density was detected by antibodies against the extracellular (1st row) and intracellular domains (2nd row) in control and SHR rat aorta. The SHR exhibits a significantly lower expression of extracellular domains of β2-adrenergic receptor (arrows) indicating extracellular receptor cleavage. The extracellular domain label density for the insulin receptor (3rd row) is also reduced in the SHR, and so is the glycocalyx membrane density as detected with a lectin label on fresh tissues (4th row). Length bars are 10 µm, except for the 4th row in which the length bar is 100 µm.*
Adapted from references 14, 16, and 30.

(*Figure 2*).[16] In several cell types of the SHR, the immunolabel density detected on the extracellular domain is lower than in controls. Extracellular domain density is restored by chronic MMP inhibition, a process that normalizes blood glucose values. Proteolytic cleavage of the extracellular domain of the insulin receptor was also observed in other experimental forms of insulin resistance,[17] and was recently documented for the first time in a diabetic patient pilot study.[18] Plasma of the SHR has the ability to cleave insulin receptor α in naive control cells and reduce glucose transport into the cell, a process that can also be blocked by several MMP inhibitors.

Vascular Endothelial Growth Factor Receptor 2 (VEGFR2)

Another major defect in the SHR is extensive endothelial apoptosis associated, in the microcirculation of many organs, with a reduction of arteriolar and venular branching patterns and a loss of capillary networks, ie, capillary rarefaction.[19] The extracellular domain density of VEGFR2, but not its intracellular domain density, is reduced in the SHR.[8] Plasma of the SHR, as well as purified MMP-7 and MMP-9, cleaves the extracellular domain of VEGFR2, which then induces apoptosis. Chronic MMP blockade restores both receptor density and normal growth of the capillary networks.[20]

β_2-Integrin receptor

The SHR exhibits chronically elevated leukocyte counts in the circulation. This is associated with a general "immune suppression" and with reduced numbers of neutrophils and monocytes adhering to the postcapillary venules and migrating into the adjacent tissue.[21] Measurement of the extracellular domain density of the CD18 integrin binding sites of leukocytes shows evidence of reduced density. Again, for this receptor, plasma of the SHR is able to cleave the extracellular integrin binding domain in the leukocyte membrane, a process that can also be inhibited by chronic MMP inhibition.[16] Chronic blockade of the MMP activity in the SHR reduces the circulating leukocyte counts to control values.

ICAM-1

ICAM-1, the counter receptor for CD18 on the endothelium, exhibits a mixed picture of receptor cleavage and overexpression that is organ-dependent.[22] This reflects the fact that receptor density on a cell may be compensated by the overexpression of receptors after cleavage. Extracellular fragments of ICAM-1 accumulate in renal glomeruli, indicating that ultrafiltration in this organ may be associated with the accumulation of cleaved protein fragments, itself a potentially proinflammatory process.

Formyl-peptide receptor (FPR)

The formyl-peptide receptor is involved in the control of pseudopod projection by cytoplasmic actin polymerization as a requirement for the amoeboid migration of leukocytes across the endothelium and into the tissue. The FPR is also required for mechanosensing exposure of leukocytes to fluid shear stress in the circulation.[23,24] The fluid shear stress on the plasma membrane of leukocytes reduces pseudopod formation, a requirement for the normal passage of leukocytes through capillary networks and the stereotypic attachment to the postcapillary endothelium as a part of immune surveillance. While not completely abolished, the ability of SHR neutrophils to retract their pseudopods in response to fluid shear stress is significantly attenuated. This compromised ability to retract pseudopods leads to an increased number of leukocytes with pseudopods in the circulation and, consequently, an increase in capillary hemodynamic resistance.[25] The reduced response of leukocytes to fluid shear stress is accompanied by proteolytic cleavage of the FPR in the plasma membrane, a process that is corrected with chronic blockade of MMPs in the circulation.[26]

Endothelial tight junction proteins

The consequences of unchecked MMP activity in the circulation of the SHR may also include degradation of the tight junctions (occludin and claudin-5) and elevation of microvascular permeability. This was demonstrated in the SHR blood-brain barrier.[27] Elevated permeability is accompanied by the appearance of lower molecular weight fragments of tight junction proteins in the surrounding astrocytes.

Neurotransmitter receptors

Just like many patients with the metabolic syndrome, SHRs have reduced sleep quality with more frequent disruption of their quiet sleep periods.[28] We obtained initial evidence that the antibody label density against the extracellular domain of the 5HT-1A receptor is lower in the hypothalamic region of SHRs compared with the normotensive control rats.[29] Once again, chronic inhibition of MMP activity may serve to reduce cleavage of the receptor and restore normal receptor density in the sleep centers of the brain.

Red blood cell membrane glycoproteins

The proteolytic cleavage of membrane receptors also affects the red blood cells. SHR plasma proteinases cleave the inner core of the red blood cell membrane glycoproteins facilitating dextran- but not fibrinogen-mediated red blood cell aggregation.[30] (*Figure 2*) The cleavage causes swelling of the red blood cells and impaired adhesion to the scavenger receptors of macrophages, and thus may reduce the rate of removal of the old red blood cells in organs like the spleen. In contrast to the cleavage of the fibrinogen binding sites by MMPs, amylases only cleave the carbohydrate portions of the red blood cell glycocalyx, reducing the surface charge on the cell surface and consequently

facilitating fibrinogen-mediated red blood cell aggregation.

In summary, the current evidence in the SHR, a metabolic syndrome experimental model with characteristic hypertension, insulin resistance, etc, is consistent with the hypothesis of uncontrolled proteolytic damage to membrane protein structures and functions (*Figure 3*). Cells respond to the loss of membrane proteins by synthesizing new proteins, which can lead to a notable enhancement of receptor biosynthesis and cell turnover by enhanced mitosis and apoptosis. It is characteristic of the SHR,[31] but at this time largely unexplored in patients.

EVIDENCE FOR MEMBRANE RECEPTOR CLEAVAGE IN HUMANS

Initial evidence that receptor cleavage may also be present in humans has been derived from biomarker studies in diabetes and essential hypertension patients indicating the presence of "soluble receptors." These soluble receptors include the insulin receptor, VEGFR2, the IL-6 receptor, the angiopoietin receptor tie-2, the receptor for advanced glycation end products (RAGE), selectins, and other receptors. In general, soluble receptors are present in low concentrations in the plasma and typically constitute extracellular domain fragments

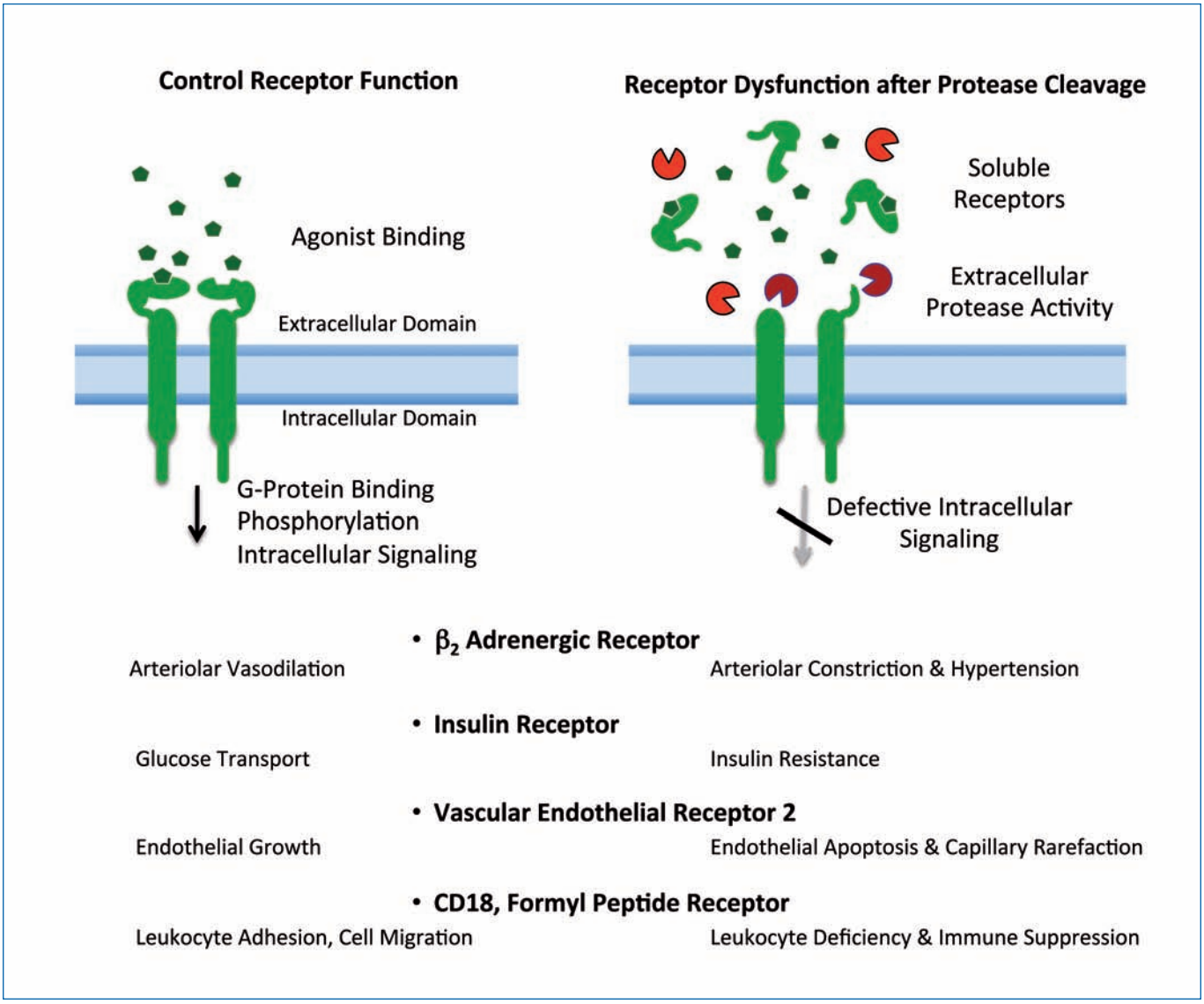

Figure 3. *Schematic diagram for the loss of selected cell functions and generation of soluble receptor fragments by proteolytic cleavage of extracellular receptor domains.*

of intact receptors.[32] Sensitive techniques such as ELISA or mass spectrometry are required for their detection.

As yet, no essential physiological function for normal glucose metabolism or other metabolic needs have been identified for the receptor fragments present in the circulation. Rather, the presence of receptor fragments in plasma may have to be regarded as a consequence of uncontrolled proteolytic receptor cleavage. The fact that the concentration of insulin receptor fragments positively correlates with the glucose levels of diabetic patients[32] supports the receptor cleavage hypothesis, ie, the more cleaved receptors are present in solution, the greater the accumulation of extracellular glucose due to defective insulin receptor function after cleavage.

RECEPTOR CLEAVAGE IN CHRONIC VENOUS DISEASE

Can the concept of proteinase activity and receptor cleavage be applied to chronic venous disease? [33] Already well-established in chronic venous pressure elevation,[34] increased MMP activity (eg, MMP-1, -8, and -9 and tissue inhibitors of metalloproteinases, TIMP-1 and -2) in endothelial cells and in leukocytes adhering to the postcapillary venules is also observed after short-term venous pressure elevations (associated in vivo with a shift in fluid shear stress).[33] This has a direct effect on VEGFR2 expression and may contribute to the loss of endothelial cell response.

Taking all this evidence into account, the question arises of whether receptor cleavage may be one of the early trigger mechanisms for the inflammatory cascade that accompanies chronic venous disease. My hope is that we will be able to clarify this question in the short-term. MMP activation in venules, which may be associated with mechanical distension of veins, may benefit from a combination of approaches: on the one hand by a more effective traditional mechanical counteraction against venous vessel distension and, on the other hand, by a partial blockade of activated MMPs.

In either the metabolic disease or chronic venous disease, a pharmacological approach against MMP activity will require a nuanced approach since MMPs are an integral part of tissue repair in the inflammatory process.

CONFLICT OF INTEREST

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Instructions for authors

AIM AND SCOPE

Phlebolymphology is a quarterly peer-reviewed publication that aims to provide clinicians with updated information on every aspect of the venous and lymphatic disorders: epidemiology, pathophysiology, diagnosis, management, and basic science. Articles are usually in the form of review articles on timely topics with a broad update of recent developments and their clinical applications.

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Articles should discuss a topic of current interest, outline current knowledge of the subject treated, give personal views and also analyze the different opinions regarding the topic discussed, and be up to date on the latest literature data.

The text should be 3000-5000 words, not including references, tables, figures. Illustrations are strongly encouraged. All texts should be submitted in English.

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Examples of style for references

Journal article: Sessa C, Perrin M, Porcu P, et al. Popliteal venous aneurysms. A two-center experience with 21 cases and review of the literature. *Int J Angiol.* 2000;9:164-170.

Article in a supplement: Sansilvestri-Morel P, Rupin A, Badier-Commander C, et al. Chronic venous insufficiency: dysregulation of collagen synthesis. *Angiology.* 2003;(suppl 1):S13-S18.

Chapter in a book: Coleridge Smith PD. The drug treatment of chronic venous insufficiency and venous ulceration. In: Gloviczki P, Yao JST, eds. *Handbook of Venous Disorders: Guidelines of the American Venous Forum.* 2nd ed. London, UK: Arnold; 2001:309-321.

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Presentation at a conference: Jantet G. Epidemiological results of the RELIEF study across different continents. Paper presented at: 15th World Congress of the Union Internationale de Phlébologie; October 2-7, 2005; Rio de Janeiro, Brazil.

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20-23 September 2012	CHINA VASCULAR SURGERY 11th	China	Changsha
27-29 September 2012	VASCULAR SOCIETY OF INDIA	India	Jaipur
26-29 September 2012	20th CONGRESS OF SLOVAK SOCIETY OF ANGIOLOGY WITH INTERNATIONAL PARTICIPATION	Slovak Republic	Tatranská Lomnica
4-6 October 2012	3rd INTERNATIONAL MEETING ON AORTIC DISEASES	Belgium	Liege
4-6 October 2012	16th CONGRESS OF THE ITALIAN COLLEGE OF PHLEBOLOGY - (CIF)	Italy	Naples
Mid-October 2012	XIIIth INTERNATIONAL SYMPOSIUM OF ANGIOLOGY AND VASCULAR SURGERY	Portugal	Oporto

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