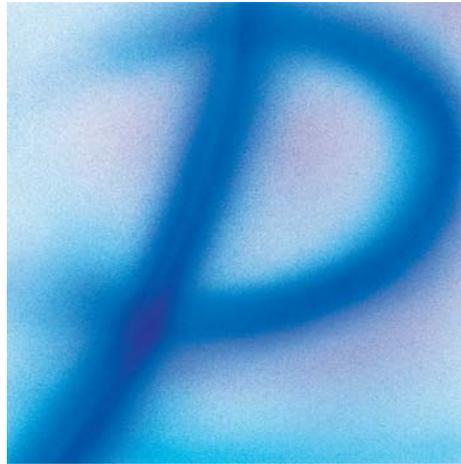


# PHLEBOLOGY

ISSN 1286-0107



Vol 20 • No.2 • 2013 • P85-124

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# LYMPHOLOGY

## AIMS AND SCOPE

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

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

*Phlebology* is scientifically supported by a prestigious editorial board.

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

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

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Indexed in EMBASE,  
Index Copernicus, and Scopus.

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ISSN 1286-0107

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**CONGRESS**

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**Marc Vuylsteke**  
Tielt, Belgium

**D**ear Readers,

*This issue contains some very good review articles about venous anatomy, the thrombotic risks of patients undergoing varicose vein surgery, conservative treatment of chronic venous disease, and the value of venous endoscopy.*

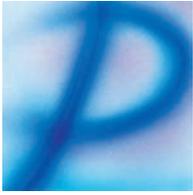
*The first article, written by Dr **Alberto Caggiati** from Rome, gives a very interesting description of the distribution of the valves in the deep, superficial, and perforating veins of the lower limb. This review article explains the embryology of venous valve development as well as the age-related changes in valves which can explain why aging is an important risk factor for vein thrombosis. These data also afford some insights into varicose disease development. There is a relationship between the mean number of valves and the risk of developing varicose disease. There is support for the hypothesis that, for skin changes to occur, valve incompetence in both the larger vessel network and the microvenous network is necessary.*

*Dr **Andreas Oesch** from Bern has written an excellent survey of thrombosis and pulmonary embolism risk in patients undergoing varicose vein surgery. Thromboembolism cases seem to be underreported for several reasons. The incidence can reach 5.3% after stripping of the great saphenous vein. Most thromboses are localized in the calf, are very often asymptomatic, and the potential damage is limited. Pulmonary embolism is exceptional. Therefore, the use of antithrombotic prophylaxis could be restricted to high-risk patients. A postoperative thrombotic event can occur up to 2 months after the procedure. Ten days of prophylaxis had no advantage over the use of an oral nonsteroidal anti-inflammatory agent. Therefore, if the prophylaxis is started, it should be continued for longer. Patients should also be motivated to undergo early and extensive mobilization post-treatment.*

*The third article, by Dr **Giovanni Agus** from Milan, emphasizes the importance of the conservative treatment option for chronic venous disease. The prevalence of chronic venous disease seems to be higher than expected and reaches 64% of the population when considering patients classified between the C1 class and the C6 class. The aim of treating patients is to relieve symptoms and to prevent or treat complications. The troublesome problem of varicose vein recurrence after surgery and the increasing costs of this treatment reopen the discussion about the indications for surgery. Conservative therapy includes three tenets: lifestyle changes, pharmacological treatment, and compression therapy. Venoactive drugs can be administered at all stages of chronic venous disease to decrease symptoms, to reduce edema, and to promote ulcer healing. Compression therapy is a basic treatment for chronic venous disease of the lower limbs for its effects on venous hemodynamics, hydrostatic pressure, and edema reduction.*

*Finally, Dr **Firmilian Calota** from Craiova explains the benefits of using venous endoscopy. It allows the visualization of normal and pathological structures. A classification of normal venous valves and valvular lesions is presented. Phleboendoscopic observations have revealed that the deep venous system is more valvular than the superficial venous system and has a higher number of tributaries. The use of venous endoscopy can have some unexpected therapeutic potential. Adapted instruments inserted through a working channel can be used for endoscopic valvuloplasty, embolectomy, stent placement, etc, thereby promoting better and faster recovery for patients with chronic venous disease. In the future, early treatment of deep venous thrombosis will benefit from this new option.*

*Have an enjoyable read!*



# The venous valves of the lower limbs

Alberto CAGGIATI

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## ABSTRACT

Venous valves appear after the heart begins to beat and the primordial muscles begin to move the limb buds. The pressure gradient due to heart beats and muscle movements triggers the process of venous valve development. Prenatal, postnatal, and senile morphological and numerical rearrangements have been described. However, the signaling pathways related to venous valve morphogenesis have yet to be clearly demonstrated.

The cusps of the venous valves consist of thin collagen half-moon-shaped folds covered by endothelium, which spring from the wall of the vein very close to each other. The vein wall is thicker at the base of the valve cusps, due to an increase in the number of smooth muscle cells in the media. With increasing age, the loose areolar collagen stroma of the cusp is gradually replaced by thick and fibrous tissue.

This article first describes the distribution of the valves in the deep, superficial, and perforating veins of the lower limbs. Finally, the morphology and location of valves in the microveins and their possible role in the pathogenesis of skin changes related to venous insufficiency are described.

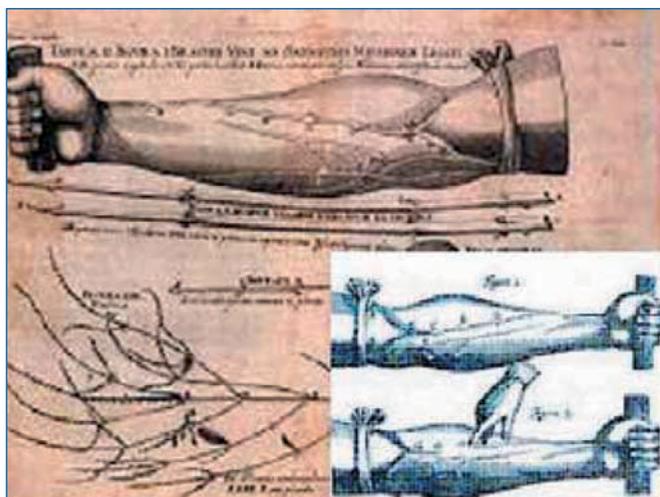
## 1. THE DISCOVERY OF VENOUS VALVES

In his *In Anatomien Corporis Humani Tabulae Quatuor* published in 1544, Ludovicus Vassaeus was the first to mention the existence of valves within the veins.<sup>1</sup> Vesalius did not mention the existence of venous valves (VVs) in the first edition of his *De Humanis Corporis Fabrica*, but included them after Sylvius Ambianus (1478-1555) described the presence of valves in the veins of the lower limbs. The function of the valves was clearly identified in 1559 by Andrea Cesalpino in his *De Re Anatomica*: "certain membranes placed at the openings of the vessels prevent the blood from returning." A few decades later (1585), the German Salomon Alberti published the first drawings of a VV. In 1603, Hyeronimus Fabricius ab Aquapendente (1533-1619) published the first treatise on VVs entitled *De Venarum Ostiolis*, which included the description of the anatomy and topography of VVs in the whole venous system. More importantly, Fabricius described a test to evaluate VV location and competence (*Figure 1*) that led his student William Harvey (*De Motu Cordis*, 1628) to discover the circulation of the blood.<sup>2</sup>

### Keywords:

human venous valve; morphology; aging; microvein; varicose disease

*Phlebology*. 2013;20(2):87-95.

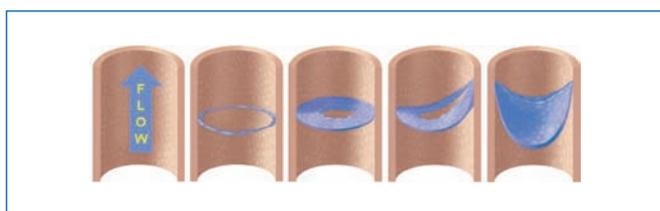


**Figure 1.** Plate 2 of Fabricius’ *De Venarum Ostiolis* was modified by William Harvey (insert) to demonstrate the direction of flow into the veins.

## 2. EMBRYOLOGY AND GENETICS OF VENOUS VALVES

Very few studies have investigated the development of VVs in the human embryo. In 1927, Kampmeier and Birch<sup>3</sup> described the basic morphogenic events involved in VV development as a five-step process: (i) thickening of the endothelium, which forms a pair of ridges placed transverse to the axis of the vessel; (ii) growth of the endothelial ridges due to their invasion by the underlying mesenchyma, which bulges out of the valvular anlage; (iii) the evolving valve directs itself toward the heart; (iv) The valvular cusps widen into a nodular shape, while the valvular sac gains in capacity; and (v) the venous wall thins down considerably in the region of the valvular sinus, mainly due to thickening of the media (*Figure 2*).

This pattern of VV development has been confirmed by a recent investigation performed in mice by Bazigou and colleagues.<sup>4</sup> The same authors also demonstrated a strong similarity in the morphogenesis and signaling pathways involved in the processes of valve formation in



**Figure 2.** The five steps of venous valve development (modified from reference 4, Bazigou et al, 2011).

the veins and lymphatics.<sup>5</sup> In fact, as well as ephrin-B2 (a key marker of arterial identity), VVs express a repertoire of proteins previously characterized as specific and critical regulators of lymphangiogenesis (Prox1, Vegfr3, and integrin- $\alpha$ 9).<sup>4</sup> Ephrin-B2 and integrin- $\alpha$ 9 signaling is also necessary for the maintenance of VVs.<sup>4</sup> Finally, Bazigou and colleagues also found that, at the molecular level, the endothelial cells of VVs closely resemble lymphatic endothelium, which suggests that terminally differentiated endothelial cells exhibit plasticity in their ability to take on a different phenotypic identity.<sup>5</sup> Finally, Mellor and colleagues demonstrated the possible role of FoxC2, NFATc1, and VEGFR3 mutations in determining the presence of abnormalities in valve function in great saphenous vein specimens from patients with Milroy’s disease.<sup>6,7</sup>

VVs only develop after the onset of “a certain pressure gradient along the vein,” as correctly stated in 1926 by Jäger.<sup>8</sup> In fact, according to Kampmeier and Birch, the earliest valves of the lower extremity appear “only after the heart begins to beat and the primordial muscles begin to move.” In the lower limbs, VVs appear at approximately 3 to 4 months in the deep veins of the femoral trigone and popliteal fossa and in the upper end of the great saphenous vein.<sup>3</sup>

Then, VVs increase in number in all areas during prenatal life. Differences in the distribution and characteristics of VVs in different areas of the human body start immediately after birth. In 1981, Maros pointed out that “certain findings suggest a reorganization after birth of the venous valves which are frequently met in fetus (sic). The close relation between hemodynamic mechanisms and the blood guiding structures may explain the changes (disappearance or persistence) of venous valves in some areas after birth.”<sup>9</sup>

### Age-related changes in venous valve morphology

Age-related morphological changes in VV leaflets were comprehensively described by Saphir and Lev in the femoral vein:<sup>10</sup> “Starting after the age of 30, the loose areolar collagen stroma of the cusp is gradually replaced by thick and fibrous tissue. After 40, an increase in elastic tissue starts at the base of the cusp, to gradually spar the free margin. In the parietal portion of the leaflet accumulation of dense-collagenous fibers. In the luminal, deposition of collagen between endothelium and elastic membrane.”

Similar changes demonstrating leaflet thickening were described in the great saphenous<sup>11</sup> and renal<sup>12</sup> veins. Both

histology<sup>11,12</sup> and duplex ultrasonography<sup>13</sup> confirmed these results. Van Langevelde et al demonstrated the presence of thicker valves in older humans: the mean leaflet thickness was 0.35 mm (range, 0.25 to 0.44 mm) in individuals aged between 20 and 30 years and 0.59 mm (range, 0.30 to 1.21 mm) in individuals aged between 71 and 80 years.<sup>13</sup> The increase in valve thickness per year (linear regression coefficient) was 0.004 mm (95% confidence interval, 0 to 0.009). Van Langevelde et al noted that valve function was not directly associated with age but that valve thickness was inversely associated with valve function and that there was a correlation between the age-related increase in valve thickness and the age gradient seen in the incidence of venous thrombosis.<sup>13</sup> Interestingly, Chopard and colleagues noted that while the renal vein wall undergoes atrophic changes with increasing age, the corresponding valves show a gradual thickening as a result of an increased number of collagen fiber bundles.<sup>12</sup> In conclusion, age-related changes in VVs may be attributed to muscular contractions and the physiologic hemodynamic stress related to the standing position rather than significant reflux due to VV dysfunction.

Other authors have postulated that the age-related increase in VV thickness results in a progressive decline in valve function, as demonstrated by the parallel decrease in calf muscle pump efficiency.<sup>14</sup> These age-related morphologic changes in VVs may also partly explain why aging is such an important risk factor for venous thrombosis.<sup>15</sup>

These data agree with findings from Marinov, who established that in parallel with aging the number of fully developed valves is reduced while that of “partial” valves is increased, with the process being most pronounced during the period from 25 years to 60 years. In subjects older than 60 years, the number of partial valves represents between 1/5 and 1/10 of the total number of VVs.<sup>16</sup>

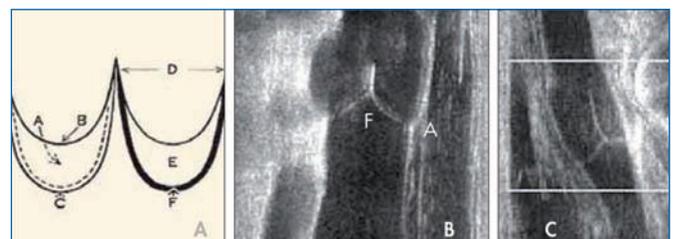
These findings seem to confirm the theory proposed by Bardeleben in 1880<sup>17</sup> of a systematic and physiologic reduction in the number of VVs in the fetal period and extend it to the whole duration of life. Powell and Lynn also proposed a lifelong progressive reduction in the number of VVs and attributed it to involutive noninflammatory phenomena.<sup>18</sup> This is in contrast with the findings of Leu et al,<sup>19</sup> who confirmed in 1979 what Klotz had demonstrated in 1887, ie, that the number

of VVs does not decrease with age, but that it is the number of incompetent VVs that increases.<sup>20</sup> This was also strengthened by Gottlob and May’s observation that VVs cannot disappear but pathological processes may cause them to become incompetent.<sup>21</sup> This can be due to the well-known effects of massive thrombosis, but also to subclinical localized thrombosis of the valvular sinus as described by Sevitt in 1974,<sup>22</sup> dilation of the valvular anlage (like in varicose veins), and to other ill-defined regressive phenomena.

In any case, these regressive phenomena are subject to regional differences. According to Gottlob and May, “Venous systems, in which unidirectional flow conditions are prevalent, tend to lose their ‘superfluous’ valves more readily, whereas systems, in which heavier strain is exerted on the valves due to hydrostatic stress or reversed flow, preserve their valves throughout life.”<sup>21</sup>

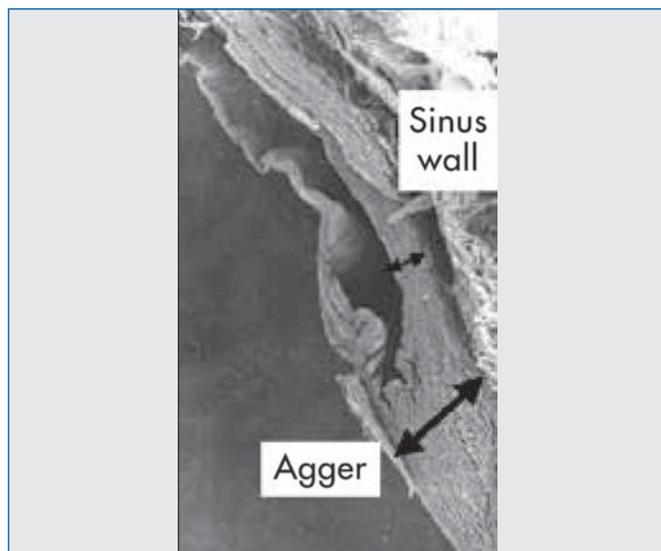
### 3. ANATOMY AND TERMINOLOGY OF THE VENOUS VALVES

According to Saphir and Lev, the cusps of the VVs consist of thin collagen half-moon-shaped folds covered by endothelium, which spring from the wall of the vein very close to each other.<sup>10</sup> Their free margins diverge to become attached again at the opposite section of the vein wall. The space between the attachment of the free margins of the cusps is called the *commissure* (Figure 3). The commissure itself is slightly raised because of a thickening of the vein wall in that area. The cusps are thicker at their bases, where they join the wall of the vein. This thickened attachment of the cusp framework was called “*agger*” by Franklin,<sup>23</sup> and “*limbus*” or “*tuberculum*” by others. It is shaped like a double horseshoe with the convex sides arranged distally, and contains smooth muscle cells. The continuations of the free border of the cusp where it meets the vein wall



**Figure 3.** The nomenclature of the venous valves (Panels A and B) showing the sinus (A), free (B) and attached (C) borders. D indicates the cornua, E indicates the valve cusps, and F indicates the agger. Panel C shows that the length of the cusps is about twice the diameter of the vessel.

are named “*cornua*.” The valvular sinus (or pocket) is the space between the cusps and venous wall, which is particularly thin at that level (Figure 4).



**Figure 4.** Scanning electron micrograph demonstrating the difference in wall thickness between the agger and the sinus.

The length of the cusps varies greatly compared with the caliber of the veins. Franklin<sup>8</sup> suggested, as a general rule, that the vertical length of the cusps is about twice the diameter of the vessel (Figures 3 and 4).

The cusps can be designated by two faces: *luminalis*, the part of the cusp close to the lumen of the vein and facing the circulating blood stream, and *parietalis*, the part of the cusp facing the vein wall of the sinus.

The luminalis is lined by one layer of endothelial cells, which are elongated along the major axis of the vessel. Beneath this layer of endothelial cells is a small amount of connective tissue that is especially noticeable in childhood. Immediately beneath it, there are moderately thick and slightly wavy elastic lamellae, the continuation of the internal elastic lamina. The parietalis is lined by a layer of endothelial cells elongated transversely. The remainder of the parietalis consists of loose connective tissue. At the base of the cusp, the parietalis contains scattered smooth muscle cells extended from the longitudinal muscular bundles of the vein intima. The luminalis and the parietalis join or fuse at the distal end of the cusp, which is thinner than the rest of the cusp. Elastic and connective fibers are thinner there, too. No blood vessels are found within the cusps.

Using scanning electron microscopy of mouse and human VVs, Bazigou<sup>4</sup> recently demonstrated morphological differences between the endothelial cells in different parts of the vessel: the cells located upstream of the valve are elongated and aligned in the direction of flow, whereas the cells on the leaflet and downstream of the valve have a rounded morphology, as previously described in venules<sup>5</sup> and lymphatic valves. Such differences likely arise from differential exposure to fluid shear stress, which suggests that flow patterns are involved in modulating endothelial cell phenotypes within the valve.

A recent study showed that the valvular sinus endothelium plays an important role in maintaining a thromboresistant state. This is achieved by upregulation of anticoagulant proteins such as the endothelial protein C receptor (EPCR) and thrombomodulin in the valvular sinus endothelium as opposed to the vein luminal endothelium.<sup>24</sup> Von Willebrand factor, a procoagulant protein, is downregulated in the valvular sinus. It may well be that interindividual or age-related differences in the thromboresistance profile of the valvular sinus endothelium can modulate thrombosis risk.<sup>24</sup>

The vein wall is thicker at the base of the valve cusps, due to an increase in smooth muscle cells of the media (Figure 4). Part of these cells run circumferentially in bundles, and some run longitudinally and seem to split off from the inner portion of the media to extend into the cusp for a variable extension. Above the agger, the muscular tissue of the vein wall decreases.

Elastic fibers from the internal elastic lamina of the vein extend along the cusp close to the basement membrane of the endothelium. In addition, elastic bundles reinforce the base of the cusps.

Due to its thickness and muscular content, the valvular agger is credited with preventing venous dilation, as first stated in 1603 by Hieronymus Fabricius ab Aquapendente: “*quoque venarum distensionem fuisse ostiola a Summo Opifice fabrefacta.*” (The Supreme Artificer made valves to prevent venous distension.)

Moreover, the tissue organization of the valve sites suggests that the action of valves is not merely that of passive flaps, but that they can also actively regulate the flow, especially in conditions of low velocity. According to Fegan<sup>25</sup> “*Contraction of the circular bundles at the base of*

*the cusps reduces the diameter of the vein. Contraction of the longitudinal muscular fibers of the cusps reduces their length and increases their thickness. In addition, the cusps are drawn down towards their roots, and away from each other, but the sphincteric action of the circular bundles compensates for this. The upper free parts of the cusps press against the vein wall at the lateral attachments of the valve, and thus, with the intimal cushions, help to seal this potential leaks...*"

### 3. DISTRIBUTION OF VENOUS VALVES IN THE LOWER LIMBS

Kampmeier and Birch correctly stated that, as a general rule, "Valves are present in those vessels which are subject to pressure from without and in those in the immediate sphere of muscular performance, such as in the veins of the extremities and stomach."<sup>3</sup>

Many studies have dealt with the number and location of VVs in the inferior vena cava region.<sup>26-29</sup> Data provided by different authors regarding the distribution of valves in the veins of the lower limbs are summarized in the following paragraphs.

#### Abdominopelvic cavity

The inferior vena cava is without VVs. Sporadic monocuspid valves were exceptionally reported.<sup>23</sup> Occasionally, one sporadic and mostly incomplete valve, similar to a spur, is reported in the common iliac vein of 1% to 7% of human limbs.<sup>30,31</sup> One VV is in the external iliac vein of about one-fourth of white subjects. In 1882, Friederich noted that one VV is in about 35% of external iliac veins, "...but often mainly decadent."<sup>32</sup> Le Page et al<sup>33</sup> reported one well-developed VV located within 2 cm distal to the entrance of the internal iliac vein in 26% of legs and that the external iliac vein has almost three times as many valves as the left (39.6% vs 14.6%). According to Kampmeier and Birch,<sup>3</sup> the internal iliac vein is avalvular, whereas its main tributaries (gluteal, sacral, and obturator) are valvular. By contrast, more recently, La Page et al stated that in 7.6% of individuals a well-developed ostial valve is present and that parietal valves are found in only 2.2%.<sup>33</sup> Finally, its tributaries are valvular in only 10% of cases.

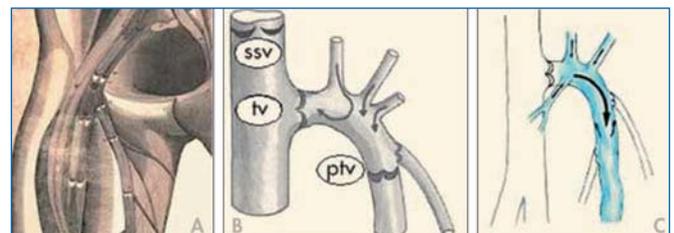
#### Deep veins of the lower limbs

The common femoral vein shows one VV above the saphenofemoral junction (SFJ), known as the "suprasaphenic valve".<sup>34</sup> It is present in about 70% of limbs<sup>35</sup> and protects the saphenous axis against increases

in intra-abdominal venous pressure.<sup>34</sup> According to Basmajan, two VVs are located in the same tract in about 5% of normal limbs.<sup>26</sup> The femoral vein shows about 3 valves. The more constant valve (found in about 90%-100% of cases, according to Banjo<sup>31</sup>), is located just below the conjunction of the deep femoral vein.<sup>36</sup> No data are available with regard to the lateral and medial circumflex veins. The deep femoral vein and the deep femoral perforators are valvular.<sup>21</sup> The popliteal veins display between 1 and 3 VVs. Finally, the deep veins of the leg are richly valvular. According to Gottlob and May, 8 to 19 VVs are located in each of the posterior tibial veins, and 8 to 11 VVs are found in both the anterior tibial and peroneal veins.<sup>21</sup>

#### Superficial veins

Cotton calculated that  $7.2 \pm 2.3$  valves are located along the entire length of the great saphenous vein (GSV).<sup>37</sup> According to Raivio, between 1 and 7 valves are located along the thigh portion of the GSV (mean value: 3.5), 2 to 6 are located at the leg (mean value: 4), and, finally, 1 to 4 are located along the marginal veins of the foot.<sup>38</sup> The valves of the SFJ are of particular clinical relevance. In 1603, Fabricius stated that the terminal portion of the GSV has a "bicuspid valve at the orifice, then at two fingers' distance a further another set of twin-valves" (Figure 5). The first is the well-known terminal valve situated at the termination of the GSV to prevent reflux from the femoral vein. The more distal one is the preterminal valve (PTV), which lies just below the openings of the SFJ tributaries. The PTV prevents venous reflux from the SFJ tributaries into the GSV trunk, while the terminal valve is closed. Incompetence of the PTV is the reason for reflux in the GSV in cases in which the terminal valve is still competent.<sup>34</sup>



**Figure 5.** Scanning electron microscopy demonstrating the difference in wall thickness between the agger and the sinus.

The terminal valve is present in 98% to 99% of normal legs, whereas the PTV is found in only about 70% to 85%. Finally, in about 2% of limbs, no valves are present in the last portion of the GSV.<sup>39</sup>

According to Raivio, the average number of VVs along the small saphenous vein (SSV) is 8.2.<sup>38</sup> The terminal valve is found in about 95% of legs with a saphenopopliteal junction, while the PTV is found in only 64%.<sup>40</sup> No data are available on the presence of VVs along the thigh extension of the SSV, which shows, in normal conditions, an antegrade flow directed toward the GSV or toward tributaries of the internal iliac veins (inferior gluteal or ischiatic veins).

**Saphenous accessories and other superficial veins**

Fabricius affirmed that smaller superficial veins (saphenous tributaries, communicating veins, reticular veins) are avalvular. On the contrary, Bouchet<sup>41</sup> affirmed

that they are valvular at their end, along their course, and at the point of entry of a smaller vein. Duplex ultrasonography easily demonstrates the terminal location of valves in saphenous tributaries (Figures 6-7). Finally, avalvular superficial veins connect the main valvular superficial veins (oscillating veins).<sup>42</sup>

**Perforating veins**

It is well known that perforating veins are furnished with valves. The number of VVs in perforating valves ranges between 1 and 5 (mean, 2). In 1978, Pirner affirmed that *“all valves were found in the subfascial part of the perforating veins.”*<sup>43</sup> In the same year, Van Limborgh and Hage noted that *“the number of valves in the epifascial part of the perforators was significantly less in those (perforating) veins which frequently become incompetent.”*<sup>44</sup> However, Raivio reported that only 75% of the perforating veins are valvular.<sup>38</sup>

Avalvular perforating veins are mainly located in the foot, hand, and forearm. However, avalvular perforating veins are reported elsewhere in the human body and work like oscillating veins connecting deep and superficial regions.<sup>45,46</sup> This was confirmed by duplex ultrasonography investigations, which demonstrated bidirectional flow in the perforating veins of persons without any sign of venous disease.<sup>47-49</sup>

**Number of venous valves and varicose disease**

While valvular agenesis is a known, but rare, cause of venous insufficiency, the relationship between the number of valves and varicose disease has been poorly investigated. Sales and colleagues demonstrated that the mean number of valves in varicose saphenous veins differed from that of nonvaricose ones ( $2.3 \pm 0.83$  vs  $4.8 \pm 2.01$ , respectively).<sup>50</sup> Banjo comparatively evaluated the presence of VVs in whites and Africans and demonstrated that the number of valves is higher in the latter.<sup>31</sup> This may account for the high prevalence (10%-18%) of varicose veins in whites and the low prevalence (1%-2%) of the condition in Africans.

**5. VALVES IN MICROVEINS**

Anatomists, physiologists, and clinicians still consider the venous bed to be “valveless” from the venular level up to 2-mm veins. On the contrary, microscopic venous valves (MVs) have been described in the microvascular bed (postcapillary venules and venular efferents of arteriovenous anastomoses), in collecting

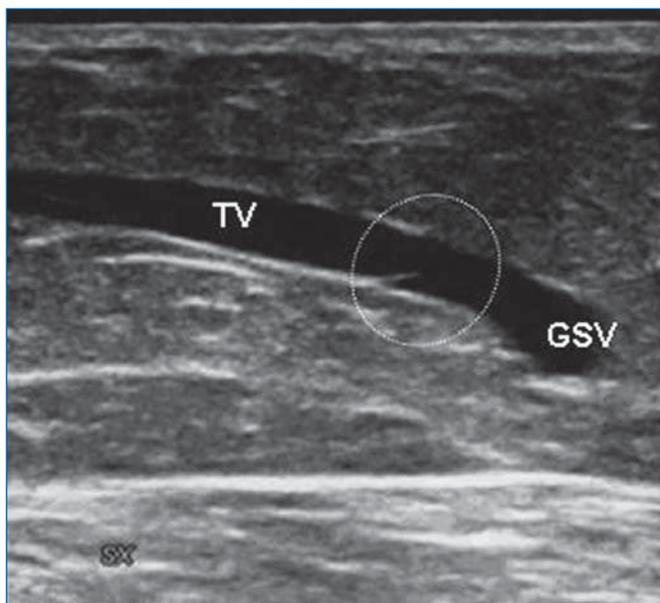


Figure 6. A valve located at the end of a tributary of the great saphenous vein. GSV, great saphenous vein; TV, terminal valve.

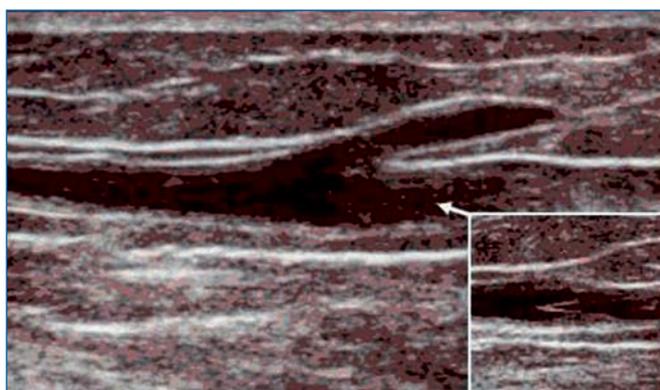


Figure 7. A valve located in the saphenous trunk just below the opening of the tributary veins.

venules and in small-caliber veins (with diameters up to 800-1000  $\mu\text{M}$ ).<sup>51</sup>

MVV's have been found in the subcutaneous layer and in muscles of various areas of the human body (Table I). Generally, MVV's are described as bicuspid. MVV's are arranged in series along a vein or are situated at the merging point of two veins. The valves always point in the direction of the larger vessel as in collecting veins. Two layers of endothelial cells surround a core of basement membrane material in which bundles of collagen fibrils are embedded.

Popoff, 1934	Digital skin
Pirro, 1950	Calf muscles
Miani and Ruberti, 1958	Skin of the sole of the foot
Braverman et al., 1983	Abdominal wall
Curri et al., 1987	Vastus lateralis, gastrocnemius
Caggiati et al., 1987	Vastus lateralis
Miyake et al., 1996	Human maxillofacial
Aharinejad et al., 1997	Exocrine pancreas
Aharinejad et al., 1997	Human dorsal thoracic fascia
Aharinejad et al., 1998	Skin of the scapular area
Aharinejad et al., 2001	Skin of the lower limbs
Shangkuan et al., 2001	Tongue
Phillips et al., 2004	Skin of the lower limbs

**Table I.** Presence of microscopic venous valves (MVV's) in tissues and organs.

MVV's are identical in structure, location, and orientation to the VV's of the leg macroscopic veins. This has led to the hypothesis that their role is to resist blood reflux in small-sized veins and collecting venules, and to prevent reflux from postcapillary venules to the capillary bed and arteriovenous anastomoses.<sup>48</sup> This hypothesis is corroborated by two pieces of evidence: (i) the absence of MVV's in regions with a favorable venous return. (ii) the abundance of MVV's in regions subject to gravitational backflow and where blood flow is irregular or altered by muscular contraction, as with VV's. The absence of MVV's, as well their incompetence, could explain clinical syndromes characterized by signs and symptoms of chronic venous insufficiency in limbs with competent VV's in large veins.<sup>52</sup>

A recent investigation by Vincent et al has greatly contributed to the knowledge of the anatomy, function, and pathophysiology of microvenous valves in the skin of the lower leg.<sup>52</sup> Vincent and colleagues compared findings obtained by scanning electron microscopy of retrograde corrosion casts in legs without detectable venous disease with those of limbs with venous disease, including venous ulcers.

Their study confirmed the existence of valves in microveins of the skin and demonstrated their strategic location along the microvascular tree. Moreover, Vincent and colleagues demonstrated that valvular incompetence at this level can exist independently of valvular competence in the GSV and its accessory tributaries and that tortuosity and distension of varicosities can be found with a normally functioning GSV. They also demonstrated that in the presence of GSV reflux, the competence of valves along the microveins may play a critical role in preventing the progression of the skin changes of venous insufficiency. Finally, they introduced the concept of "boundary valves," designating those valves located in the more distal veins that appear to prevent reflux in the skin.

These original data strongly support the hypothesis that valve incompetence in both the larger vessel network and the microvenous networks are necessary for skin changes to occur. The authors concluded that the presence/absence and competence/incompetence of valves in the microveins may shed light on several debated clinical questions such as why some patients with very large varicose veins do not experience skin changes.



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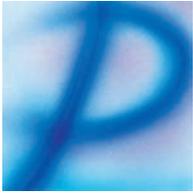
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# Thrombosis and pulmonary embolism risk in patients undergoing varicose vein surgery

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## ABSTRACT

Varicose veins are not by themselves dangerous. Nevertheless, when treating them, it is important to prevent the occurrence of complications with potentially serious consequences such as deep vein thrombosis or pulmonary embolism. Vein operations are among the procedures carrying the lowest risk of all surgical interventions. Publications on thromboembolism after vein surgery show a striking discrepancy in the number of reported cases of thromboembolism, which is partially due to the different methods used to record them.

Most thromboses are localized in the calf and their damage potential is limited, which has made some authors question the need for antithrombotic prophylaxis. Moreover, it is still unclear what the appropriate duration for this prophylaxis should be. Vein surgery may induce superficial phlebitis, which is known to flare up after several weeks.

This article describes our continuously recorded data on the occurrence of clinical thromboembolic events in 8639 operations on 12724 legs. The conclusion is that an atraumatic operation, extensive mobilization, and appropriate antithrombotic prophylaxis are useful tools to reduce the risk of complications to well below 0.4%.

## REPORTED DATA ON THE INCIDENCE OF THROMBOEMBOLISM AFTER VARICOSE VEIN SURGERY

The comparison of published data on thrombosis and pulmonary embolism following varicose vein surgery reveals an astonishing discrepancy of 1:350, ranging from 0.015%<sup>1</sup> to 5.3%.<sup>2</sup> There are even some reports (not discussed here!) boasting a rate of 0%! The reluctance of some surgeons to acknowledge—or even report—the occurrence of complications may play an important role here.

Nevertheless, even creditable reports suffer from a considerable observer bias, which is the consequence of the accuracy of investigation. After vein surgery, many patients show some minor local symptoms that can reveal a

### Keywords:

risk factors, surgery, thromboembolism, varicose veins

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*Phlebology*. 2013;20(2):96-100.



**Figure 1.** Patient 24 hours after state-of-the-art surgery with pin-stripping of the great saphenous vein and hook phlebectomy. Temporary bruising may appear later in the distal thigh.



**Figure 2.** One day after surgery for varicose veins. The leg will be bandaged for 4 days (day and night) after surgery. The bandages will be replaced by elastics stockings for another 3 to 4 weeks.

(probably inconsequential) small thrombosis (*Figure 1*). Technical and financial constraints make it impossible to apply all the available diagnostic methods in each and every case, unless a scientific investigation is being carried out to determine the exact number of events. Due to feasibility requirements, many studies on thromboembolism therefore only enroll patients with clinical symptoms and the figures obtained in those studies will thus be far below the figures that would be obtained by the systematic examination of all patients. (*Figure 2*)

Endovenous treatments require consecutive serial ultrasound checks to assess the result; in contrast to

surgery, where these checks are not necessary and where smaller thromboses may remain unnoticed. This difference should be taken into account when comparing the two modalities for the development of thromboembolism.

The third point to consider is the steadily increasing sensitivity of the methods used to detect both thrombosis and pulmonary embolism. The blurred pictures of pulmonary scintigraphy—the only method to investigate embolism in former times—gave too much leeway for interpretation, much in contrast to the current state-of-the-art technique of helical computer tomography. The same is true for the detection of thromboses. Phlebography is an unpleasant invasive examination that doctors used to be reluctant to prescribe for minor problems. Moreover, it could not identify thromboses of the calf veins, which have actually been found, with the wide application of color duplex imaging, to account for a substantial proportion of all recorded thromboses.

### HOW IMPORTANT ARE SMALL VEIN THROMBOSES?

The highest incidence of thrombosis, a staggering 5.3%, was given in the publication of Van Rij et al.<sup>2</sup> The aim of this well-documented study was to determine the absolute number of vein thromboses occurring after stripping of the long saphenous vein. All patients were examined by color ultrasound preoperatively and again postoperatively after 2 weeks, 6 months, and 12 months. Ninety percent (90%) of the thromboses were found in the calf veins; 60% were asymptomatic. There was no pulmonary embolism in this series of 20 patients and, after 12 months, valvular dysfunction had been restored in 50% of them.

All in all this study shows that meticulous serial examination reveals an unexpected high rate of small vein thromboses, but at the same time it shows that—fortunately—most of them have little or no clinical impact. The question therefore arises of whether it is worthwhile detecting subclinical thromboses.

### IS ANTITHROMBOTIC PROPHYLAXIS NECESSARY AFTER VEIN SURGERY?

If there were only small thromboses, we also could omit antithrombotic prophylaxis after vein surgery. An interesting contribution to this topic is a French

prospective study published in 2004,<sup>3</sup> in which only 3.7% of the patients received prophylaxis. In this survey of 4206 operations, 17 thromboses were registered, which corresponds to a 0.40% rate. These results were assessed by clinical examination on day 1, day 8, and day 30 after surgery; ultrasound examination was carried out in the case of symptoms suggestive of deep vein thrombosis. Pulmonary embolism was observed in 1 patient (0.02%). The authors found an increased risk for thromboembolism after surgery of the short saphenous vein (3 times greater than for long saphenous vein interventions) and in repeat surgery (3 times greater than for primary interventions). Seventy-one percent (71%) of the thromboses were confined to the calf veins, and 4 of them occurred in the group of 155 patients receiving antithrombotic prophylaxis.

The authors concluded that prophylaxis can be restricted to high-risk patients, which would save 44 euros per patient.

### OUR RESULTS FROM 1985 TO 2010

Following the launch of my practice in 1985, I started prospectively and systematically to record all complications. The idea was to develop an internal quality control system to avoid the occurrence of similar complications in the future. It goes without saying that great importance was given to the recording of all symptomatic deep vein thromboses and pulmonary embolisms. Symptoms suggestive of thromboembolism were further investigated until a clear diagnosis could be made. The results were regularly updated for numerous oral presentations and occasionally published.<sup>4,5</sup> The last update—covering 25 years of practice—was made in 2011 and included 8639 vein operations on 12 724 legs. With the exception of low-risk ambulatory phlebectomies, antithrombotic prophylaxis was administered to all patients for 1 to 10 days; this is much in contrast to the 3.7% in the above-mentioned French study. It is clear that in those 25 years, the antithrombotic agents as well as the diagnostic methods used to detect thromboembolism improved steadily.

Our results: 1985 – 2010

- Prospective recording of clinical DVT and PE within 2 months
- 8639 operations on 12 724 legs
- Prophylaxis 1 to 10 days, except for phlebectomies

All patients underwent clinical examination 2 months after surgery. At the end of these 2 months, 33 events were recorded (22 thromboses and 14 pulmonary embolisms), corresponding to an overall incidence of 0.38% per patient, or 0.26% per operated leg. The 22 thromboses were localized as follows:

Our results: 1985 – 2010

- 33 events recorded: 22 DVTs and 14 PEs
- Overall incidence after 2 months: 0.38%/patient; 0.26%/leg

Localization of 22 DVTs

- Pelvis and proximal thigh: None
- Popliteal vein: 7
- Lower leg: 15
- 2 Patients with persistent damage (0.02%)

Compared with the French study mentioned above, the rates of bilateral operations as well as those of pulmonary embolisms are substantially higher, presumably an effect of different national insurance systems and of the availability of institutions specialized in the detection of emboli.

It is reassuring to see that there was not a single DVT in the groin. The proportion of calf vein thromboses has steadily increased. The 2 patients with persistent damage (one thrombosis of the popliteal vein resulting in a slightly swollen leg, one homonymous hemianopsia, possibly due to crossed embolism) were operated in the late 1980s.

Another interesting finding that resulted from the 2-month observation period was that 24 of the 33 events occurred in the first 4 weeks following the procedure and that another 9 PEs (27%) were recorded in the second month, raising the question of how long prophylaxis should be administered for.

### HOW LONG ARE PATIENTS AT RISK FOR THROMBOEMBOLISM AFTER SURGERY?

Every treatment on the superficial veins induces a limited superficial phlebitis at its borders, which may propagate into the deep venous system. This localized effect is demonstrated with statistical significance by

the fact that all 22 thromboses were localized in the operated legs.

The progression of superficial phlebitis was investigated in 2003 in the Stenox study,<sup>6</sup> which showed that this process persists for at least 3 months with a rebound effect after withdrawal of low-molecular-weight heparin after 10 days—in fact, patients treated with a much cheaper oral nonsteroidal anti-inflammatory agent eventually showed identical results. In the 2010 Calisto Study, the antithrombotic prophylaxis was extended to 45 days and a clear advantage was demonstrated.<sup>7</sup>

But can our health care systems afford such a high-priced approach considering the relatively few complications of this type of surgery?

#### Type of Surgery

- Small saphenous vein: 1.0%; great saphenous vein: 0.46%
- Ambulatory phlebectomy: 0.07%
- No DVT in nonoperated legs!

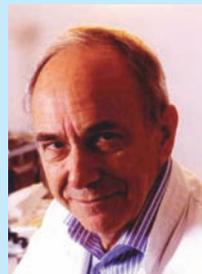
## PERSONAL INTERPRETATION AND CONCLUSIONS

The risk of thromboembolism depends on various factors: coagulation disorders—which often go unnoticed until the first event occurs—age and the presence of concomitant diseases, and finally the extent and duration of the surgical intervention. It is generally accepted that small saphenous vein (SSV) surgery carries a greater thrombotic risk than GSV surgery; in our survey, this ratio was 2:1 (1% for SSV operations, 0.46% for GSV operations); at the opposite end of the spectrum, the risk after ambulatory phlebectomy is only 0.07%.

The topic of postoperative thromboembolism (and other possible complications) should be discussed well in advance with every patient, in particular to protect the surgeon against litigation. It is my impression that anxious patients who worry about pulmonary embolism seem to attract this complication. The worst thing to do would be to omit prophylaxis in this group of patients.

Prophylaxis is not restricted to the use of pharmacological agents, it also includes early and extensive mobilization, which requires careful attention from the surgeon in order to minimize postoperative pain and immobility.

Hook phlebectomy and pin-stripping have substantially diminished postoperative bruising and pain (*Figures 1 and 2*). Today, only 1 out of 4 patients needs painkillers after being discharged from hospital, which allows for a painless and extensive mobilization. I used to tell my patients to walk two or three times a day; now I encourage them to walk as much as possible, which seems to be beneficial in lowering the thrombotic risk and also shortens the period of disability, which actually amounts to just 7 days for bilateral stripping.<sup>8</sup>



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# Conservative treatment of chronic venous disease: the Italian experience

(This article is adapted from a publication in *Minerva Cardioangiol* 2011;59:285-298.)

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## ABSTRACT

Chronic venous disease (CVD) is a highly prevalent clinical condition with substantial epidemiological implications and socioeconomic repercussions. CVD is a worldwide problem and does not only affect patients in Western countries. The consequences of its high prevalence, diagnosis and therapy costs, significant worker absenteeism, and its impact on patients' quality of life are well known. Pharmacotherapy for CVD, solely represented by venoactive drugs, has seen great developments over the last 40 years. Venoactive drugs are widely used in the symptomatic treatment of CVD together with compression therapy in order to relieve patient suffering. The clinical efficacy of venoactive drugs on symptoms (sensations of heaviness, leg pain, paresthesia, sensations of warmth and burning, swelling, night cramps, etc) has long been confirmed by both open and end-controlled studies. We carried out a joint analysis of the management and costs of CVD in Italy and found that pharmacotherapy is very useful in both. Double-blind randomized trials have used micronized purified flavonoid fraction, rutosides, escin, anthocyanosides, and synthetic calcium dobesilate in the treatment of CVD. In the following state-of-the-art review article, we have used evidence-based medicine methods to review publications found in the medical literature. Particular consideration was given to the evidence obtained in meta-analyses, guidelines, and consensus statements. Currently, the evidence for pharmacological agents such as venoactive drugs in the treatment of CVD suggests their wide use for the resorption of venous edema and the relief of venous symptoms associated with all classes of the CEAP classification.

## Introduction

Chronic venous disease (CVD), defined as morphological and functional abnormalities of the venous system of long duration, manifested by symptoms or signs or both indicating the need for investigation and/or care,<sup>1</sup> has a documented socioeconomic impact, affecting 50% to 85% of Western populations, and consuming 2% to 3% or more of community health care budgets.<sup>1</sup>

For a long time and until the early 1990s, the definition of CVD had been limited solely to the presence of varicose veins and/or ulcers, managed with

## Keywords:

chronic venous disease; compression therapy; randomized controlled trial; vein; venoactive drug

a single treatment, ie, surgical crossectomy/stripping of the diseased vein, and the management of venous ulcers. This is reflected in the epidemiological studies published at the time, which focused on these two conditions.<sup>2</sup> However, not all specialists were in favor of systematic resection of the diseased veins in patients with varicose veins, and some renowned specialists such as Felix Jaeger and Edmondo Malan recommended varicose vein ablation only after careful examination and investigation. Venous pain and symptoms usually associated with varicose veins and ulcers were not taken into account.

It was only in February 1994, at the Sixth Annual Meeting of the American Venous Forum (AVF), that an international ad-hoc committee with representatives from Australia, Europe, and the USA, proposed a more comprehensive view of phlebology and its associated conditions. This commission produced a consensus statement for the classification of all stages of CVD referred to by the acronym “CEAP” and based on the clinical manifestations (C), etiological factors (E), anatomical distribution (A), and pathophysiological findings (P) of venous disease. The goal was to provide an objective, comprehensive classification that could be used worldwide, first in scientific research, then in specialist clinical practice, and lastly in general medical practice.<sup>3</sup> According to the CEAP classification, the clinical signs in the affected legs are categorized into seven classes designated C0 to C6. Leg symptoms associated with CVD include tingling, aching, burning, pain, muscle cramps, sensation of swelling, sensations of throbbing or heaviness, itching skin, restless legs, leg tiredness and/or fatigue.<sup>1</sup> Although not pathognomonic, these signs and symptoms may be suggestive of CVD, particularly if they are exacerbated by heat or dependency during the course of the day and relieved with leg rest and/or elevation.<sup>1</sup> Limbs categorized in any clinical class may be symptomatic (S) or asymptomatic (A). The latest revision of the CEAP classification in 2004 included a new descriptor for the E, A, and P sections of the CEAP classification, when no anomaly is found in the etiology, anatomy, or pathophysiology of the disease.<sup>4</sup> This new descriptor introduced new categories such as C0s (“symptoms only”), En, An, Pn (“no etiology, no location, no pathophysiology identified”), reflecting those subjects complaining of leg symptoms before the occurrence of any sign, reflux, or even obstruction. The latter is usually difficult to identify. C0s patients are frequently encountered in primary care practice.

In the CEAP classification, the old term “varicose” has now been replaced by more complex definitions whereby “chronic venous disorders” is the term used for the description of the full spectrum of signs and symptoms associated with classes C0s to C6, the term “chronic venous disease” encompasses the CEAP clinical classes C1 to C6, and the term “chronic venous insufficiency” (CVI) is generally restricted to disease of greater severity (ie, classes C3 to C6).<sup>1</sup>

All stages of the disease require medical attention, generally from the end of the first stages, when symptoms and signs are apparent, but also right from the onset of the disease when patients present with simple cosmetic imperfections, before any possible serious and disabling adverse effects such as ulceration, or potentially lethal events such as episodes of venous thromboembolism occur.

Given the broad spectrum of conditions that CVD encompasses and the high incidence of the first stages of the disease (before the occurrence of varicose veins), it is clear that CVD is of primary interest for conservative management—as evidenced by recent guidelines (Figure 1).<sup>5-7</sup> Despite this, the use of conservative treatment will likely regress, since, for the sake of necessary savings, health care policies have contributed to shift the treatment of CVD from the expertise of venous specialists to generic and cosmetic approaches, the so-called “alternative therapies.”

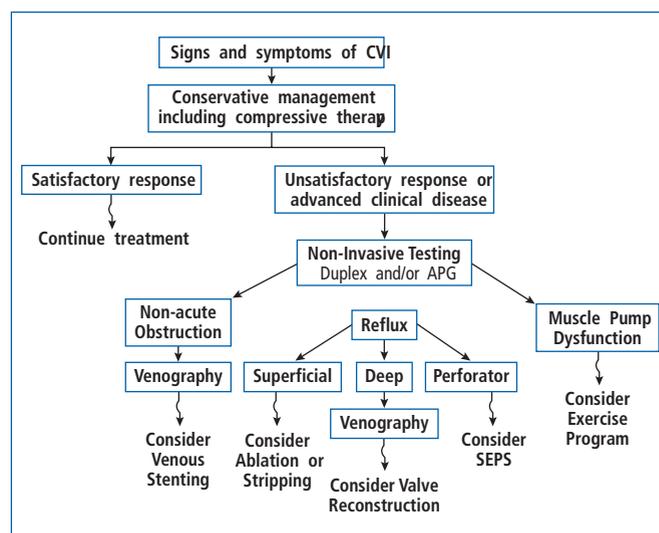


Figure 1. Management of chronic venous disease: clinical algorithm (adapted from reference 7: Eberhardt RT, et al).

**Epidemiology**

Since 2000, most epidemiological studies on CVD have used the CEAP classification. Among them, the recent international epidemiological program named “Vein Consult Program” (VCP) initiated by the *Union Internationale de Phlébologie* has provided reliable results on the global epidemiology of CVD in 20 countries and 5 continents and shows that CVD affects a significant part of the world’s population. The prevalence of CVD was found to be 64%, when considering patients classified between the C1 and the C6 class.<sup>8</sup> This prevalence, which may seem high, is in fact comparable to and even lower than the corresponding figures from other studies carried out with the use of the CEAP: 90% in the Bonn Vein Study (Germany),<sup>9</sup> 49% in Poland,<sup>10</sup> 77% in the Italian study by Chiesa et al<sup>11</sup> that included 24 Italian towns, 83% in Bulgaria,<sup>12</sup> and 71% in the USA.<sup>13</sup> The prevalence of CVD in the VCP even rose to 84% when C0s subjects were included, with 20% of subjects being in the C0s class, 22% in the C1 class (telangiectasias), 18% in the C2 class (varicose veins), 15% in the C3 class (edema), and 9% in the C4 to C6 classes (complications of CVD).<sup>8</sup> Healed and active ulcers were equally present in men and women in the VCP population. This is in line with the results of the Bonn Vein Study.<sup>9</sup> In most epidemiological studies, active ulceration in the lower limbs (C6) has been reported in about 0.3% of the adult population of Western countries. However, the number of these ulcers, including those that had healed (class C5: with signs of ulceration of the skin), amounts to at least 1% of the population. The findings of the VCP were close to these figures: 1.4% of subjects were in

C5 and 0.7% in C6. These findings suggest a worldwide progression of CVD, which affects not only Western countries, as is too often believed, but all continents.

Globally, the quality of life was worse in all subjects diagnosed as CVD patients in the VCP study, and not only for those with advanced stages of the disease. This is in line with a number of previous studies.<sup>14,15</sup> Despite this, it is noteworthy that the diagnosis of CVD is usually underestimated, especially in the early stages and, consequently, conservative treatment—venoactive drugs and compression therapy—is underprescribed. An Italian study assessing the self-management of CVD in a selected Italian population and the pattern of prescription by selected Italian phlebologists revealed that physicians tended to suggest a treatment to more people than those already under treatment, and they also tended to recommend the same therapy as the one already used by their patients (*Figure 2*).<sup>14</sup> The patients preferred conservative treatment—mainly drug therapy—over surgery or sclerotherapy. As a result, the recommendation to use compression stockings, believed to be the treatment of choice in CVD, was progressively replaced by the recommendation to use venoactive drugs (*Figure 2*).

**Management of chronic venous disease: the example of recent health policy decisions in Italy**

Over the last 15 years, various health policy instruments have influenced the comparison of the scientific and economic aspects of CVD. In Italy, we have produced the first evidence-based guidelines in the management

Therapy carried out		Therapy prescribed			
		Compression stockings	Sclerotherapy	Surgery	
Drug therapy	Yes	86.8%	68.5%	24.6%	25.3%
	No	66.8%	52.3%	17.9%	16.0%
Compression stockings	Yes	85.9%	54.2%	23.8%	32.1%
	No	70.3%	88.1%	15.1%	13.9%
Sclerotherapy	Yes	82.2%	78.2%	45.2%	29.2%
	No	69.9%	54.2%	17.5%	17.0%
Surgery	Yes	77.8%	78.9%	21.7%	49.0%
	No	70.2%	54.0%	19.0%	15.4%

*Figure 2. Correlation between recommendation by the phlebologist of a therapy and reports of this therapy having been carried out by the respondents (from reference 14: Marone EM, et al.).*

of chronic venous disorders in order to implement a correct approach to the diagnostic and therapeutic management of CVD.<sup>16</sup> The Italian guidelines state that, in a patient with varicose vein disease, *“the indication for surgery should be thoroughly discussed, independently of the surgical option chosen. The aim of surgery is total removal of all varicose veins, and this itself must be viewed in the context of the underlying pathology—CVD—and the troublesome problem of varicose veins recurring and new ones appearing after surgery. The main aim of treating patients with CVD is to cure or relieve the symptoms and to prevent or treat complications.”* Regarding the use of drug therapy, the Italian guidelines state that *“there is ample evidence in favor of a therapeutic strategy including venoactive drugs when surgery is not indicated or not feasible. Venoactive drugs are indicated for subjective symptoms related to CVD, whatever the stage of the disease (fatigue, nighttime cramps, restless legs, heaviness, tension), to reduce edema and according to a meta-analysis, as adjunctive treatment in the healing of venous leg ulcers (only adjunctive micronized purified flavonoid fraction [MPFF]\* was shown to be effective in leg ulcer healing).”<sup>16</sup>*

\*MPFF is registered as: Alvenor®, Ardium®, Arvenum® 500, Capiven®, Daflon 500 mg®, Detralex®, Elatec®, Flebotropin®, Variton®, Venitol®

However, the problem of rising health care costs has prompted a reform in Italy, which resulted in counterproductive measures. The dereimbursement of venoactive drugs in 1994, combined with the ongoing nonreimbursement of elastic stockings (despite the fact that stockings are reimbursed in all other European countries), caused a significant fall in the number of visits to family doctors and in the number of prescriptions, including those for venoactive drugs. This left the burden on patients with CVD and has had a definite negative impact on their health (Figure 3).<sup>17</sup>

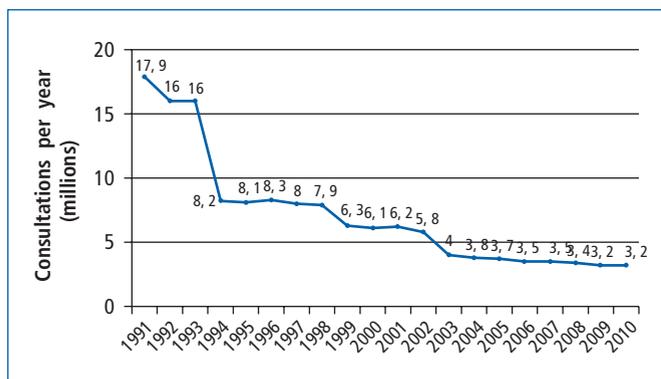


Figure 3. Number of chronic venous disease-related general practitioner office visits/year (1991 to 2010) (from reference 17: Allegra C.).

The question of the cost-effectiveness of venoactive drugs has been analyzed more frequently in other countries of the European Union.<sup>18</sup> The Italian study on the benefits of the reform, partly based on data collected in the Lombardy region,<sup>17</sup> has evidenced the impact produced by another measure of the reform of the social security system, and how it changed the direction of the treatment of CVD. Directive 119 of January 1st, 1995, by giving preference to surgical treatment over conservative therapy, has prompted an increase in the number of surgical procedures, which rose to 136 075 varicose vein ligations and stripping procedures in 2009 (according to official data). Actually, the post-reform cost redistribution from prescriptions and visits in favor of hospitalization—an aggressive form of treatment that is clearly inappropriate for certain indications—ended up increasing CVD management expenses. The World Health Organization (WHO) considers that preventing chronic diseases is a ‘vital investment’ and is deeply concerned by “the global neglect of chronic diseases.”<sup>19</sup> The post-reform results in Italy point to the need to consider “effective and feasible interventions that may halt and turn back the growing threats of chronic diseases with minimal spending” as reported by the WHO.<sup>19</sup>

The confusion created in recent years by the dissemination of dietary supplements allegedly considered as therapies and not as health adjuvants has also contributed to the reduction of venoactive drug use. The market for venoactive drugs seems to be increasingly driven by dietary supplements. The latter, which can be bought in “parapharmacies” [drug stores selling cosmetic products and dietary supplements], accounted for 20.4% of the total market share of venoactive agents in 2004, while they amounted to nearly 28% of the total market in 2010. Sales of dietary supplements are increasing at the expense of ethical venoactive drugs, which are dispensed in pharmacies.

The sales volume and indications for use of elastic stockings for CVD, including the purchase of at least two pairs per year, authorized by either the Social Security System or the private insurance system (depending on the countries considered), based on precise therapeutic indications,<sup>20</sup> are extremely difficult to determine. In the pharmaceutical industry in Europe (EUEOCOM), there are contrasting results. For example in France, with a population and number of patients affected by CVD similar to those in Italy, it is estimated that the

market amounts to 7 million pairs of stockings per year. In Germany, the number of pairs of stockings sold for curative purposes is 3.5 million per year. However, the criteria for prescription differ between the two countries. In Germany, stockings are prescribed free of charge with a request for a precise description of the disorder. On the contrary, in France, it is considered easier to obtain a prescription for stockings. But are these stockings actually worn by patients? In Italy there is a market for stockings prescribed for curative purposes and the available data show that about 500 000 to 600 000 pairs of stockings are sold per year. It is clear that some confusion still exists in the minds of many specialists about the use of stockings for curative and preventive purposes.

### Principles of conservative therapy

Conservative therapy of CVD is based on three cardinal tenets: i) lifestyle changes and correction of functional abnormalities with physical methods, ii) pharmacological therapy, and iii) compression therapy.

### Lifestyle changes

Changes in lifestyle are part of the 2010 directives of the Italian Ministry of Health, which in 2011 instituted the "National platform on diet, physical activity, and smoking," chaired by the Ministry of Health, and implemented a major program of prevention throughout the country entitled "Preserving your health: making healthy choices easier," which aimed at limiting the main risk factors for chronic venous disorders (as well as other disorders), ie, smoking, alcohol abuse, poor diet, and lack of physical activity. Such initiatives, considered innovative in Italy and relying on the responsibility of both patients and health care officials make medical advice a vital component in the early prevention of CVD.

There are different options for the correction of functional anomalies with physical methods and evidence of their efficacy has led to their widespread implementation being recommended. This is true for hydrotherapy, an ancient therapy, which from Kneipp's principles to modern spa therapy has now been confirmed by randomized studies as well as by phlebologists.<sup>16,21</sup> This is also true for venous-lymphatic massage therapy,<sup>22</sup> programs of tilt-table therapy, and physiotherapy for more advanced stages in the CEAP classification,<sup>16,23-25</sup> and correction of posture with plantar arch support.<sup>26,27</sup>

## Pharmacological therapy

### Potential therapeutic targets based on etiology

Modern pharmacological therapy of CVD should now specifically target the primary cause of the disease. Primary CVD is the result of increased and unabated venous hypertension caused mostly by reflux through incompetent venous valves, and sometimes by primary non-postthrombotic obstruction and reflux.<sup>28</sup> Venous hypertension is central to the alterations present in the superficial veins (less frequently in the deep veins), in capillaries, and eventually, skin changes.<sup>29</sup> Histological and ultrastructural studies of varicose veins have found alterations in the venous wall with hypertrophic segments alternating with hypotrophic segments. Hyperplasia of the intima, with increased collagen content and smooth muscle cell (SMC) disruption, is seen in hypertrophic areas, while atrophic areas show a lower number of SMCs and reduced extracellular matrix because of degradation of the matrix by proteolytic enzymes, including metalloproteinases (MMPs).<sup>29-31</sup> Remodeling of the venous wall probably arises from complex synergy between many factors, including alterations related to MMPs and tissue inhibitors of metalloproteinases (TIMPs), high levels of catechin and growth factors, which together promote extracellular matrix degradation.<sup>30,31</sup>

A growing body of evidence collected over the last few years shows that neutrophils, mast cells, and their interactions with the venous endothelium play an important role in initiating a specific inflammatory response leading to venous dysfunction.<sup>29</sup> The venous wall alterations resulting from inflammatory processes contribute to dilation of the veins of the lower limbs with loss of venous tone. The role of the microcirculation in this disease process should not be overlooked.

Leukocyte and endothelium interaction is the first phase of the inflammatory process causing the remodeling process of the venous wall and the venous valves. This process is characterized by the expression of the adhesion molecules VCAM-1 and ICAM-1 on the endothelial cells and by monocyte chemotaxis. The process of adhesion consists in the leukocytes rolling over the surface of the endothelial cells with intervention of the P- and E-selectins, VCAM-1, and ICAM-1. Then, a strong bond is established between the integrins, such as VLA-4 and CD11b/CD18, on the surface of the leukocytes and the

endothelial adhesion molecules, allowing entry of the leukocytes into the subendothelial layer.<sup>29</sup>

Migration of the leukocytes in the venous wall produces toxic metabolites and free radicals, which damage the venous valves and weakening the venous wall. Valvular incompetence of the superficial and perforating veins leads to increased pressure in the veins and venules in the cutaneous and subcutaneous tissue, leading to capillary damage, edema, skin changes (pigmentation), and lastly, venous ulceration.<sup>7,29</sup>

Lastly, the role of alterations in the glycoprotein providing the endothelial surface with an antiadhesive property is essential.<sup>32</sup> The lymphatic circulation is also involved in more advanced stages of the disease process.

**Potential targets of venoactive drugs**

The purpose of this article is not to express a new viewpoint on the etiopathogenic aspects of CVD. Dedicated state-of-the-art articles have already reviewed those events in depth.<sup>7,29</sup>

Basic research, however, may have a direct impact on the pharmacological treatment of CVD, which affects a large number of subjects as seen through epidemiological data and which should be resolutely applied before any surgical intervention. Actually, pharmacological therapy should not be reserved solely for those patients—particularly the elderly population—who are ineligible or unwilling to undergo venous surgery or endovenous treatment,<sup>33</sup> but should be considered from the earliest stages of the disease, right from the COs class. Venoactive drugs have been shown to have the following properties. They:

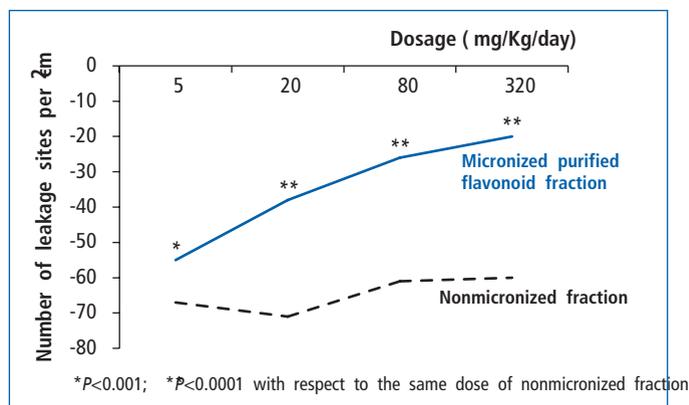
- increase venous tone;
- limit stasis in the microcirculation;
- improve lymphatic drainage;
- decrease capillary hyperpermeability;
- hamper inflammation in the vein wall, venous valves, and capillaries.

Therefore, by acting on the many targets responsible for the symptoms and signs of CVD, venoactive drugs have a beneficial effect on CVD and may prevent it from getting worse.

The effects of venoactive drugs on these physiological parameters, in particular, on venous tone, venous hemodynamics, capillary permeability, and lymphatic

drainage, can be evaluated experimentally or clinically, preferably with noninvasive methods.

Advanced technology processes, such as micronization, have improved the efficacy of some drugs. The most famous example is that of the micronized purified flavonoid fraction (MPFF) whose comprehensive mechanism of action can be attributed to its specific formulation, together with the micronization of its active ingredients. MPFF consists of 90% diosmin and 10% other flavonoids (hesperidin, diosmetin, linarin, and isorhoifolin). Each of the active ingredients acts synergistically with diosmin. In addition, the micronization process, which reduces active substance particles to a size of under 2 µm, increases the absorption and dose-dependent efficacy of MPFF compared with nonmicronized forms, for which an increase in dosage does not correspond to an increase in efficacy (Figure 4).<sup>34</sup>



**Figure 4.** Dose-dependent anti-edema efficacy of micronized purified flavonoid fraction compared with the nonmicronized form (from reference 34: Cyrino F, et al)

Most of the experimental and randomized controlled clinical trials that have been analyzed in reviews were carried out with MPFF,<sup>34-38</sup> rutosides,<sup>35,39-41</sup> escin, anthocyanosides, and synthetic calcium dobesilate.<sup>5,35</sup> Most venoactive drugs have been shown to increase venous tone by a mechanism related to the noradrenaline pathway. MPFF prolongs noradrenergic activity, thereby decreasing the metabolism of norepinephrine and prolonging its vasoconstrictor effects. Hydroxyethylrutosides act by blocking the inactivation of noradrenaline, and escin and ruscus extracts exert an agonist action on venous β1-adrenergic receptors.<sup>5,35</sup>

A number of pharmacological trials have shown that venoactive drugs increase capillary resistance and reduce capillary filtration, resulting in the prevention of

capillary leakage. This has been demonstrated for MPFF, rutosides, escin, ruscus extracts, proanthocyanidins, and calcium dobesilate.<sup>5</sup>

Pharmacological trials of oral pharmaceutical treatments including coumarin and its derivatives, hydroethylrutosides, calcium dobesilate, escin extracts, O-(beta-hydroxyethyl)-rutosides, and MPFF have found that such drugs may help in the treatment of lymphedema by reducing vascular permeability and protein and extracellular fluid accumulation, stimulating lymph contractility and flow, and reducing protein concentration and fibrotic induration in the tissues by stimulating proteolysis. In addition, microlymphography has shown that MPFF induces an increase in lymphatic function by improving lymph flow drainage and increasing the number of lymphatic vessels.<sup>5</sup>

Regarding inflammation in the venous valves and wall, MPFF treatment significantly attenuated the reduction in valve height in pressurized veins, and the rate of retrograde blood flow at 3 weeks was markedly reduced with MPFF compared with control. MPFF showed a trend toward a reduction in granulocyte infiltration into the valves. When compared with the control, MPFF treatment inhibited the expression of the endothelial cell adhesion molecules P-selectin and ICAM-1, reduced leukocyte infiltration, and decreased the level of apoptosis in the valves in a dose-dependent manner. These data suggest that in the rat model of venous hypertension, MPFF attenuates the alterations in valve shape and lowers the subsequent hemodynamic disturbances. A concomitant decrease in leukocyte-mediated valve inflammation was observed. In a former study, MPFF was shown to decrease the expression of endothelial and leukocyte adhesion molecules (ICAM-1, VCAM, CD11b, CD62L). None of the other available drugs have been shown to attenuate leukocyte-endothelial interactions in vivo.<sup>5,29,42,43</sup>

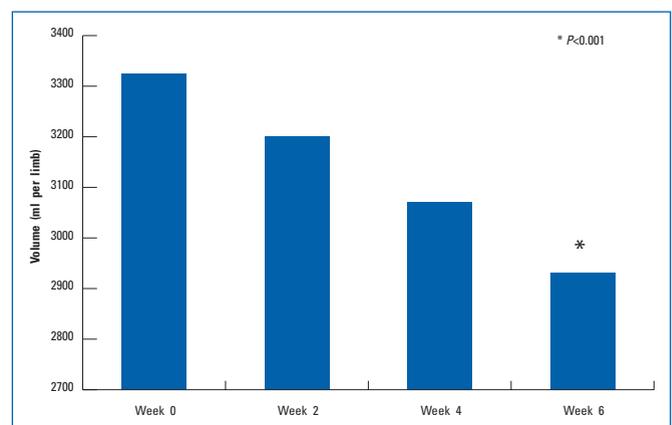
#### Indications for venoactive drugs

Well-conducted clinical trials with clear inclusion criteria and evaluable end points and compliance with ethical prerequisites constitute the best instrument to evaluate the clinical effects of venoactive drugs. Any clinical trial should be randomized, possibly double-blinded, with sufficient power to provide a response to a well-defined question. This is now simpler than in the past, with the introduction of the CEAP classification

providing a framework to improve patient description and report response to treatment.

From the standpoint of clinical research, let us keep in mind that venoactive drugs—products of natural, seminatural or synthetic origin—belong to the class of bioflavonoids in their vast majority. Some (such as MPFF) contain a combination of active substances for increased efficacy and perform better than others in improving clinical symptoms and signs.

Venoactive drugs can be administered at all stages of CVD to decrease symptoms (feeling of heaviness, pain, paresthesias, sensations of warmth and burning, nighttime cramps, pruritus), with various grades of evidence. MPFF has been shown to exert its action at all stages of CVD and has been found to be significantly more effective than nonmicronized diosmin in reducing the principal symptoms and signs of CVD. Also, clinical effectiveness on the principal target sign and symptom observed in CVD—edema—was evident with MPFF in a study conducted on patients with lower limb edema. In only 6 weeks, MPFF reduced the amount of fluid in the lower limbs by about one liter (*Figure 5*).<sup>44</sup>



**Figure 5.** Anti-edema efficacy over time of the active substances in the micronized purified flavonoid fraction (from reference 44: Blume et al.).

Lastly, in patients with venous ulceration, MPFF reduces the time to healing and increases the number of healed ulcerations. Furthermore, another series of studies points in this direction, with the use of sulodexide in the advanced stages of CVD, especially in postthrombotic syndrome. By demonstrating the utility of treatment in patients with venous ulceration, the latest North

American guidelines reported the effectiveness of MPFF and sulodexide and recommended their use.<sup>45</sup>

In addition to the clinical assessment of the beneficial effects of drugs, determination of patient quality of life (QOL) has been accorded increasing scientific attention in recent years, mainly because the question of the direct benefit of medical treatment for patients has been raised.

The use of the 20-item ChronIc Venous dIsease Questionnaire (CIVIQ-20) through the Reflux assEssment and quaLity of lIfe improvEment with micronized Flavonoids (RELIEF) study has confirmed that MPFF improves venous symptoms (pain, sensation of swelling, cramps), and reduces edema in the presence and/or absence of venous reflux.<sup>46</sup> The CIVIQ questionnaire has been used to assess the beneficial effect of various treatments.<sup>47</sup>

The paucity of “quality” studies on many venoactive drugs in the literature is evident in recent systematic revisions. A group of experts meeting at the 13th European Conference of the Society of Clinical Hemorrhology (Siena, 2005) identified only 83 studies that deserved further consideration.<sup>48</sup> Similar considerations emerged from the recent Cochrane reviews of horse chestnut seed extracts (HCSE),<sup>49</sup> and of venoactive drugs as a whole.<sup>50</sup> In the first review, only 17 of the 44 identified trials were analyzed, while in the second, 110 randomized trials were identified, but only 44 were retained.

Based on these reviews, significant and homogeneous results were found for most venoactive drugs on edema reduction, a decrease in restless legs, and improvement of trophic disorders.

Some venoactive drugs performed better than others in improving venous disorders. Considering the evidence, a higher grade recommendation (Grade A) for the treatment of symptoms and of edema was attributed only to MPFF and oxerutin,<sup>48</sup> while only MPFF and sulodexide were recommended in the treatment of patients with a venous ulceration.<sup>35</sup>

### Dietary supplements

Some mention should be made of the increased use of dietary supplements by patients with venous disease, already described above as a “commercial” phenomenon.

Most of these so-called ‘dietary supplements’ are medicinal products presented as having curative or preventive properties in humans or in animals, *herbal products* marketed as a food, dietary supplement, drug, or cosmetic,<sup>45</sup> or *dietary supplements*, defined as physiological and “noncurative” adjuvant products. Many doubts persist on the actual effectiveness of these treatments for which clinical evidence is scarce or anecdotal, in the absence of randomized clinical trials. With the exception of currently available drugs, no clinical evidence exists on the pharmacological efficacy against CVD of any other phytotherapy or herbal products on the market.

### Compression therapy

Compression therapy is considered to be a basic treatment for CVD of the lower limbs in different CEAP classes for its effects on venous hemodynamics, hydrostatic pressure in the large superficial and deep veins, the microcirculation, coagulation and fibrinolysis, and edema reduction.

Compression of venous vessels is obtained through the application of bands or of long bandages for medium-or short-term periods; elastic stockings of various shapes and sizes can be used in various cases depending on therapeutic requirements, with a certain preference for bandaging in treatment of acute cases, and stockings for chronic cases.

In the European Union, quantification of the levels of compression depends on national standards since a community-wide reference standard has not been adopted to date.

National and international guidelines are available on proper prescription and use of compression therapy.<sup>51-54</sup>

### Discussion

Due to the current prevalence and spread of CVD and its effect on quality of life,<sup>55</sup> some critical measures should be taken as the attention paid to CVD has decreased in recent years in Italy. In fact, a medico-scientific analysis of CVD should not disregard the economic, ethical, and intersocietal aspects as well as the overall impact of the disease.

From an economic standpoint, as discussed above, the dereimbursement of medicinal products for CVD and of elastic compression stockings, as well as the increase in taxation on these products, makes it more difficult

for family doctors and vascular specialists to prescribe conservative therapy for the prevention of this disease.

Meanwhile, little attention is being paid by national and regional health care authorities to the increasing use of inappropriate dietary supplements for this disorder. The economic disengagement of the government and the legal ramifications of prescribing noncurative substances remain largely ignored.

Also, insufficient attention is being paid to the current inappropriate emphasis on surgery, which is debatable in the current worsening economic situation. The increasing importance given to surgery is controlled by the irrational lowering of the fee schedules in diagnosis-related groups (DRGs) and the imposition of inappropriate surgical indications (from ordinary hospital admissions to daycare surgery, to ambulatory surgery for varicose veins).

In addition, surgery itself is now the source of a “decline” in the attention given to phlebology, because of the senseless dispute involving the use of different surgical techniques and strategies, such as stripping versus the CHIVA method (ambulatory and hemodynamic treatment of venous disease), stripping versus endovascular treatments, endovenous laser therapy versus foam sclerotherapy, etc. This dispute, sometimes extraneous to the discussion of scientific methodology (comparing results presented at congresses and in specialized scientific journals), is circulated in inappropriate places (newspapers, TV, internet) creating bewilderment and confusion in the same media and in governmental authorities, as well as confusion and anxiety for patients and family doctors.

Also, among the current criticisms, we should not overlook the underevaluation of CVD, and the current fragmentation created by too many scientific societies and active “groups” in the field of phlebology.

## CONCLUSIONS

Attention to the medical treatment of CVD should involve family doctors as well as vascular specialists and the other medical fields involved in CVD, in particular obstetrics-gynecology, orthopedics, etc. A commitment to lifestyle changes is required for the treatment of CVD, and this, for all the clinical classes of the CEAP classification.

Evidence-based medicine—randomized clinical trials, reviews, and meta-analyses—supports this attention, pointing to the efficacy of venoactive pharmacological therapy, together with more appropriate use of certified elastic stockings in the treatment of CVD.

Among medicinal products, MPFF is the only venoactive agent available in micronized form to have a well-known complete mechanism of action. This medicinal product and a few others have been shown to improve symptoms (such as pain) and signs (such as edema), which leads to a consistent improvement in quality of life.

The recommendations of national and international guidelines therefore suggest a wider treatment strategy for CVD along these lines.



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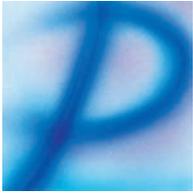
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# Venous endoscopy

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## ABSTRACT

Venous endoscopy, one of the latest technologies of invasive exploration of the veins, holds unexpected therapeutic potential. It allows the visualization of normal and pathological endovenous structures. While most pathological structural changes are usually acquired, some of them (intraluminal cords, strips) may be remnants of vein genesis. Normal valve dynamics vary with the pressure of the flow and so reflect functional and structural asymmetry, a fundamental characteristic of the living world. Information provided by venous endoscopy has allowed us to establish a rigorous classification of valvular lesions, but also to describe other types of endovenous lesions (endophlebitis, proliferative endophlebitis, intimal sliding, transvalvular thrombus, etc). Endoscopic and ultrasonographic study of reflux has helped clarify the pathogenesis of functional lesions of the cusps (commissural reflux slit, commissural reflux channel) and the consequences of eccentric-onset reflux (eccentric varicose dilation under the cusps). Venous hemodynamics is a field influenced by many traditional non-selective acquisitions and extrapolations of classical Newtonian fluid mechanics, far away from the reality of functional venous circulation, a living piping system in which flows a living anisotropic fluid.

The use of adapted and improved tools and video-endoscopic systems may allow endoscopic valvuloplasty and minimally invasive embolectomy avoiding valve damage, and help with stent placement etc, thereby resulting in better and faster recovery for patients with chronic venous disease.

## Introduction

Venous endoscopy is one of the most recent exploration technologies to have made possible the direct visualization of normal and pathological endovenous structures. The information acquired has shed some light on venous hemodynamics is a field influenced by many traditional non-selective acquisitions and extrapolations of classical Newtonian fluid mechanics, far away from the reality of functional venous circulation, a living piping system in which flows a living anisotropic fluid. The anisotropy of blood makes it impossible to use a laminar flow model, especially in the venous circulation, where deformation and changes in flow occur continuously. In addition, the presence of valves acting as true diaphragms and the frequent breaks in venous flow, even in physiological conditions, show the extraordinary

### Keywords:

endovenous lesions; venous endoscopy;  
venous hemodynamics, venous reflux

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*Phlebolympology*. 2013;20(2):112-118.

complexity and variability of venous hemodynamics. Venous modeling is related to the temporal perishability of living structures (in our case the valvular segments) and the hemodynamic variability of the veins is far more complex than that of the arteries. The direct visualization of normal valvular dynamics, transvalvular flow changes (phase transitions, turbulences, and vortices in the sinuses), and reflux has helped to improve and/or correct classical models. The identification of new types of endovenous injuries (commissural reflux slits, commissural reflux channels, cusp lesions, sliding of the endothelium, endophlebitis plaques, etc) and the understanding of their pathogenesis demonstrate the complexity of living systems. Their simplification and schematization are negative habits arising from a lack of information.

Venous endoscopy may also hold unexpected therapeutic potential. Adapted instruments inserted through the endoscope working channel will allow endoscopic valvuloplasty, minimally invasive embolectomy avoiding valve damage, stent placement, etc, thereby promoting better and faster recovery for patients with chronic venous disease. Using the left subclavian vein path, we have reached the right atrium with an adapted endoscope (in collaboration with Constantin Bătăiosu MD, interventional cardiologist), making possible the correct positioning of pacemaker electrodes in the venous sinus. Interventional cardiology can be carried out using the new generation of faster video cameras, which will eliminate the distortions induced by cardiac motion.

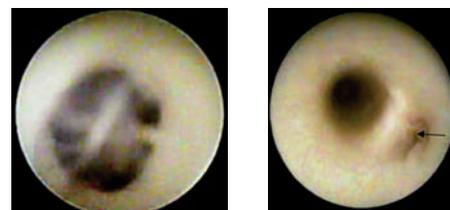
### Endoscopic anatomy

Venous endoscopy can identify normal endoluminal vein structures clearly. The venous valves are specific morphologic structures:

- Truncal valves are located on the deep venous trunks, saphenous trunks, or collateral veins. At the confluence of venous trunks (posterior tibial trunk and tibioperoneal trunk), the junction spur folds gradually creating a well-defined cusp, which, under increased pressure of the perfusion liquid, closes one or other tributary orifice randomly. Under gradually increasing liquid pressure, truncal valve dynamics are not symmetric in the sense that the cusps' opening process starts at one of the commissural corners, while the closing process is similar but in reverse. It is thus possible

to open the valve in order to explore the distal subvalvular segments by projecting an eccentric jet of fluid toward the commissure that opens initially. Instead, applying a high axial pressure makes the valve close tightly.

- Ostial valves are fibrous, strong, and usually bicuspid or—rarely—tricuspid and are located in the saphenous vein estuaries and at the junctions with perforating vein (*Figure 1*). We have sometimes observed an exuberant valve, with thick, translucent cusps situated at the ostium of the anterior accessory vein of the thigh, and found it very hard to open with a retrograde liquid jet.
- Ridge valves, which we consider to be specific to the deep veins, are located at the confluence of two veins converging to form a sinus. Ridge valves have ample S-shaped cusps, which inflect in opposite directions when the luminal pressure increases, with one half over one drainage orifice and the other half over the other orifice. When the ridge is the drainage spot of a third tributary, the valve consists of two large cusps with a terminal hem with the same S-shape, protecting the central orifice by apposition and the lateral ones by inflecting in opposite directions.<sup>1,2</sup> By agile and clever handling of the fluid jet, the cusps can be opened, revealing the ostium of the converging affluent (*Figure 2*).



**Figure 1.** Ostium valve of a great saphenous vein affluent. The blood is seen through the transparent cusps (A). A great saphenous vein affluent with a closed ostial valve (B).



**Figure 2.** Ridge valve through which a third affluent drains (A, B). S-shaped ridge valve (C).

- Occasionally the exploration can reveal other endoluminal structures, some of which may be congenital:
  - Endothelial cords traversing the lumen, attached to the two opposite walls
  - Inconstant endothelial strips, disposed as transversal bars parallel to the skin surface
  - Inconstant endothelial folds, which appear to be anchored to the venous wall especially in veins affected by endophlebitis in the past.

Our phleboendoscopic observations have revealed that the deep venous system (DVS) is more valvular than the superficial venous system (SVS) and has a higher number of tributaries. Hammersen’s research has proved that the free edge of the cusps, floating in the bloodstream, is like a curved fold presenting a full-length hem and an icicle-shaped extension (“Zapf”). In our observations, when the hem is obvious, the filamentary extensions are missing. The hem is much more constant than the extensions. Altered, shorter valves have more obvious borders. We believe that the icicle-shaped filamentary extension is also a secondary structure appearing following inflammation of the cusps.

The endothelium is smooth, supple, and of a whitish color. In the great saphenous vein (GSV), the venous wall is perforated by two types of orifices: some are tributaries of the collateral veins, characterized by well-defined valvular cusps, protecting the ostium (Figure 1); others are the emerging ostium of perforating veins where the valves are absent. The ostium has a circular shape, which sometimes looks like a funnel. In the case of reflux, the perforating vein must accept an extra volume of blood. The port of origin will become wider and deeper, with an oval shape caused by the dynamic blood vortex created at the entry of the perforating vein



**Figure 3.** Great saphenous vein with an insufficient truncal valve and reentry perforator vein with an oval ostium and reflux-modeled channel.

by the suction force (depression force) occurring in the DVS at the time of “muscle diastole” (reentry in the perforating vein). Often, a more obvious semicircular gutter appears at the orifice of the perforating vein (Figure 3).

The valves present under the level of the perforating vein ostium act like an antireflux dam, the reflux volume accepted by the perforating vein being higher. This protects the valve, relieving the increased pressure exerted on the cusps.

The major calf tributaries (anterior and posterior calf saphenous veins) are not always equipped with shedding ostial valves, which may explain their varicose transformation in the case of saphenous reflux.

Low-pressure compression maneuvers on the skin surface can help differentiate between superficial and deep walls and venous margins upon endoscopic examination. When compressing the calf or thigh, insufficient perforator veins can be identified by the appearance of a saphenous blood jet reflux (the blow-out phenomenon), which is pushed further distally by the perfusion liquid (Figure 4).



**Figure 4.** The blow-out phenomenon through an insufficient perforating vein of the calf.

Videoscopy alone cannot identify the venous tributaries. Venous affluents constantly drain the blood on the sides of the collectors. Van Cleef has identified affluents that open onto the collectors into venous sinuses.<sup>2,3</sup>

The venous tributaries are remarkably valvular. The origin of the popliteal vein often looks like “glove fingers” with a large sinus onto which multiple tributaries open, which confirms previous phlebographic observations.

There are always valves at the confluence of veins, with very well defined, strong cusps with a marginal hem.

**Endoscopic pathology**

Pathological processes, usually inflammatory, alter the valvular system but also the venous wall in its entirety. In certain circumstances, due to persistent hemodynamic disturbances, venous inflammation is prolonged, lasting up to a few years. An example of this is the postthrombotic syndrome, which in our opinion is progressive, with periods of attenuation interrupted by phases of acute venous lesions.

In such a context, the valves, the endothelium, and the whole wall present lesions of varying severity. Their topography is segmental, with maximum severity at the junctions, where the valves are inserted. These valves can remain present as heavily modified and completely nonfunctional artifacts.

Based on our endoscopic observations we have proposed a classification of venous valve lesions.<sup>2,4</sup>

**Classification of valvular lesions**

1. *Functional valve lesions (type I)* due to progressive and prolonged increases in venous pressure. Here we distinguish:

- Commissural reflux slit (type I) (Figure 5),
- Commissural reflux channel (type Ib) (Figure 6).

The difference between these two subtypes is morphological, and is obviously correlated with reflux



**Figure 5.** Racket-shaped type-Ia valvular lesion (commissural reflux slit)



**Figure 6.** Type-Ib Valvular lesion (commissural reflux channel). We can observe the threshold of the insertion ring.

volume. The eccentric character of these lesions is noteworthy.

2. *Traumatic organic valve lesions (type II)* - valvular ruptures:

- Commissural: clefts and tears (type IIa) (Figure 7),
- Cusp insertion lesions: linear perforations (type IIb) (Figure 8).



**Figure 7.** Type-IIa valvular lesions; the valvular rupture is at the commissure, which reflects the high-pressure stress exerted on this area of the cusp.



**Figure 8.** Type-IIb valvular lesions—linear perforations at points of cusp insertion. The transvalvular pressure loss through those perforations does not allow for an optimal distension of the lumen.

These lesion subtypes do not seem to be purely traumatic, with leukocytic infiltration of the cranial surface of the cusps<sup>2,5</sup> causing gaps in their structure as well as endothelial cell apoptosis. However, trauma is the most important factor explaining ruptures near the point of insertion of the cusps when the dynamic force of the reflux is very strong. In these cases, the direction of rupture is perpendicular to the direction of the reflux. We have frequently observed valvular tears located at the commissures of the cusps or more rarely at the base of the cusps, causing valvular insufficiency and reflux. The direction of the tear at the commissures is parallel to the axis of the venous segment (dynamic force in the direction of flow). The presence of tears at this level is a strong argument for the presence of a particular hemodynamic stress on the cusps. In keeping with other endoscopic observations, we did not find any

significant inflammatory changes on the valves, maybe due to poor blood supply.

3. *Inflammatory organic lesions (type III) (Figure 9).* Structural inflammatory rearrangement of the cusps was found only in the context of a broader involvement of the vein wall with altered parietal size, shape, elasticity, etc. Some authors believe that inflammatory valvular alterations are primary<sup>5</sup> and solitary, basing their argument on the significantly increased expression of adhesion molecules and the presence of monocytes in the endothelium of the cardiac surface of the cusps.



**Figure 9.** Type-III valvular lesions (chronic inflammatory alterations of the cusps). Parietal and valvular rearrangement – valvular vestiges, missing valvular sinus, thrombus situated under the cusps and adhering to the rigid wall, which has a narrowed, irregular lumen.

4. *Valvular vestiges (type IV) (Figure 10).* Here we include valvular debris left by an inflammatory process or iterative reflux trauma. This type of lesion is often and easily confused with endothelial folds or fringes. The venous sinus is absent and the vein is fully tubular.



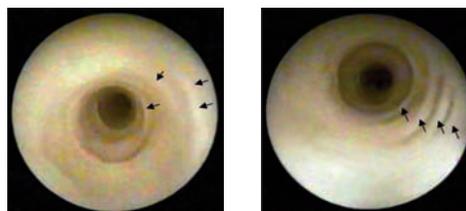
**Figure 10.** Type-IV valvular lesions (valvular vestiges)

In 1993, Hoshino classified the valvular lesions into three stages: stretched commissures, valve perforations, and valve splitting.<sup>6</sup> In 1997, based on endoscopic observations made in 1991, van Cleef proposed a 5-grade classification (from 0-normal valve to 4-severe lesions).<sup>2,3</sup>

In the absence of valves or valvular vestiges, endoscopy of the GSV cannot really assess the elasticity of the wall,

the perfusion liquid being easily drained into the DVS through the perforating veins. This difficulty may be substituted by compression on the venous path distal to the tip of the endoscope, so that we can achieve a strong enough pressure with the perfusion liquid in order to distend the venous wall and ensure good observation. In insufficient, tubular GSVs we have identified a “concentric beach gravel” appearance (Figure 11), which is evidence of the so-called process of “intimal sliding,” a phenomenon that can be anticipated by theoretical hemodynamic studies. Our histopathological observations found that the sliding phenomenon occurs in the internal elastic lamina and is accompanied by ruptures and the development of subintimal vacuoles (Figure 12).

The endothelium may present acute inflammatory lesions of endophlebitis with suggestive erysipelas-like polycyclic margins (Figure 13).



**Figure 11.** Intimal sliding secondary to the hemodynamic force of the reflux (“concentric beach gravel” appearance)

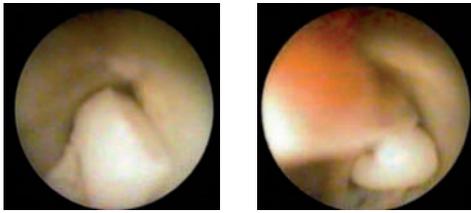


**Figure 12.** Internal elastic lamina tears with partial intimal disjunction and underlying vacuolar appearance visualized by immunohistochemistry.



**Figure 13.** Posterior tibial vein under the confluence with the popliteal vein showing obvious erysipelas-like endothelitis

Endophlebitis usually appears in the proximity of older lesions. Endoscopy may reveal polyps of various sizes, which can develop either on large venous segments or at the confluence of the tributaries, with a “champagne cork” appearance and which are obviously obstructive and block the passage of the endoscope (*Figure 14*). It is possible that the starting point of this structure is the development of a thrombus in the ostial valve of the affluent. The discovery of these lesions is strictly related to the introduction of endoscopic examination, as they do not have any clinical symptoms at all.



**Figure 14.** Large endothelial polyps in the venous lumen

Endothelial strips, endothelial folds, and sometimes endothelial flaps can be seen in addition to polyps, all of them representing signs of endophlebitis, after restrictive or obstructive (thrombotic) phlebitic processes.

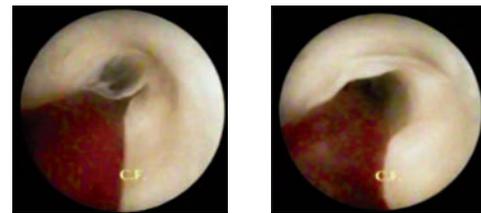
Sometimes, the venous wall is segmented, modified, rigid, and without flexibility and there are multiple polypoid lesions in the endothelium. In some cases, we found bulky sessile polyps obstructing the lumen.

The most frequent site of thrombosis is the DVS. After a recent thrombosis, the clot ascends several valvular floors, without adhering to the cusps, a minimal increase in the pressure of the perfusion liquid opening the valve so that the thrombus floats freely into the lumen. We often found that recent thrombi, which are rotten cherry-colored, highly elastic and with a diameter of 4 to 5 mm, end up in the lumen of the main sections of collateral affluents. I have personally never observed any recent thrombi originating in the valvular sinuses. However, the presence of a thrombus between the cusps of a valve acts as a wedge, blocking valve closure at successive levels, and opening up a long “path” for reflux. This explains the occurrence of edema and its rapid regression in the supine (reclining) position (*Figure 15*).

Old thrombi are pale, yellow, or white, sometimes threadlike, and adhere to the vestiges of the valves or

to areas of extreme rearrangement of the endothelium (*Figure 9*).

In postthrombotic syndrome the appearance of the lumen is completely altered, narrowed, almost laminated. We found recanalization always to be situated eccentrically near the wall. The intima is thickened and the endothelial surface is atrophic, irregular, and slightly rough. The lumen is often reduced to a semilunar slit crossed by multiple straps that anchor the thrombus surface to the wall. Sometimes, the venous endothelium is deeply modified, with damaged valves and a reduced and irregular lumen resembling proliferative endophlebitis (*Figures 9 and 16*).



**Figure 15.** Transvalvular thrombus. Increased perfusion liquid pressure opens up the valves, followed by multiple level reflux.



**Figure 16.** Proliferative endophlebitis. Complete rearrangement of the endothelium, which has a rough surface.

Lumen alterations are characterized by irregular contours, secondary to fibrous rearrangement and followed by wall hardening. In obstructive postthrombotic syndrome, the lumen is laminated and eccentric. The formation of new channels takes place most often marginally near the wall and, exceptionally, in the center of the thrombus. The trajectory of the new channels is sometimes a twisted path through endothelialized thrombus remains, the appearance of which is emphasized in color Doppler examination. In postthrombotic syndrome, the lesions are not stabilized. The potential for progression is high due to an increased risk of reigniting inflammatory lesions, pure phlebitis, and/or thrombosis. Alterations of the endothelium are the trigger. Sometimes, segmental inflammatory acute lesions can be found (areas of endophlebitis

with polycyclic slightly elevated margins resembling erysipelas) years after the initial thrombotic event.

Postthrombotic syndrome is by itself a permanent thrombophilia, so that any combination of other predisposing factors, insignificant under normal conditions, can trigger the recurrence of inflammatory phenomena, increase the extent of the lesions, and worsen hemodynamics. Thus, postthrombotic syndrome should be considered as a complex progressive damaging condition requiring lifelong treatment.

In the context of severe chronic ischemic syndromes we have observed extensive total destruction of the venous valves with the venous lumen subsequently becoming tubular and the venous sinuses being destroyed, so that the veins look like arteries.<sup>2,7</sup>

In conclusion, venous endoscopy is the examination that offers the richest information on the normal and pathological morphophysiology of the venous system of the lower limbs. In addition to its diagnostic value, the fundamental knowledge it has provided has proven useful in the surgical repair of insufficient valves. In the

future, early treatment of deep vein thrombosis will benefit from endoscopy performed with new adapted instruments.



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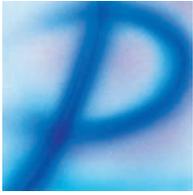
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# Instructions for authors

## AIM AND SCOPE

**Phlebology** 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.

## GENERAL INSTRUCTIONS

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.

**Submission:** Manuscripts may be submitted by e-mail<sup>1</sup>, double-spaced, 8 to 16 typed. All pages should be numbered. All corresponding authors should supply a portrait photograph for inclusion at the end of the article. This may be sent by e-mail, provided the resolution of the file is at least 300 dpi.

**Title page:** The title page should include a title, the full names of all the authors, the highest academic degrees of all authors (in country-of-origin language), affiliations (names of department[s] and institution[s] at the time the work was done), a short running title (no more than 50 letters and spaces), 5 to 10 keywords, the corresponding author's complete mailing address, telephone, fax, and e-mail, and acknowledgments.

**Abstract:** A 150-word abstract should be provided for all articles. The editorial department will edit abstracts that are too short or too long.

**Text:** Abbreviations should be used sparingly and expanded at first mention. The style of titles and subtitles should be consistent throughout the text. The editorial department reserves the right to add, modify, or delete headings if necessary. *Phlebology* uses SI units and generic names of drugs.

## REFERENCES

**Citation in text:** All references should be cited in the text and numbered consecutively using superscript Arabic numerals.

**Reference list:** Presentation of the references should be based on the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. *Ann Intern Med.* 1997;126:36-47 ("Vancouver style"). The author-date system of citation is not acceptable. "In press" references should be avoided. In the bibliography, titles of journals should be abbreviated according to *Index Medicus*. All authors should be listed for up to six authors; if there are more, only the first three should be listed, followed by "et al." Where necessary, references will be styled by the editorial department to *Phlebology* copyediting requirements. Authors bear total responsibility for the accuracy and completeness of all references and for correct text citation.

## 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.

**Web-based material:** Nicolaides AN. Investigation of chronic venous insufficiency: a consensus statement. American Heart Association, 2000. Available at: <http://www.circulationaha.org>. Accessed October 17, 2005.

**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.

## FIGURES AND TABLES

Figures should be of good quality or professionally prepared, with the proper orientation indicated when necessary (eg, "top" or "left"), and be identified by Arabic numerals, eg, *Figure 2*. Tables should be identified by roman numerals. Provide each table and figure on a separate sheet. Legends must be provided with all illustrations, including expansion of all abbreviations used (even if they are already defined in the text). All figures and tables should be numbered and cited in the text.

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# Congress and conference calendar

<b>DATES</b>	<b>CONGRESS</b>	<b>COUNTRY</b>	<b>CITY</b>
11-13 April 2013	62ND INTERNATIONAL CONGRESS OF THE ESCVS	Germany	Regensburg
18-19 April 2013	UKRAINIAN NATIONAL CONGRESS "ANGIOLOGY AND VASCULAR SURGERY"	Ukraine	KIEV
25-27 April 2013	CONGRESO DEL CAPÍTULO ESPAÑOL DE FLEBOLOGÍA	Spain	Málaga
25-27 April 2013	8TH INTERNATIONAL CONGRESS ON VASCULAR ACCESS	Czech Republic	Prague
May 2013	XX CONGRESO ARGENTINO E INTERNACIONAL DE FLEBOLOGÍA Y LINFOLOGÍA	Argentina	Buenos Aires
May 2013	NATIONAL ANNUAL CONGRESS OF GEORGIAN ASSISIATION OF ANGIOLOGISTS AND VASCULAR SURGEONS GAAVS	Georgia	Tbilisi
17-18 May 2013	6TH MEDIRERRANEAN MEETING OF VENOUS DISEASE	France	Nice
21-24 June 2013	XXVIII CONGRES DE LA SCV	France	Nice
31 May - 1 June 2013	ANNUAL MEETING OF THE BENELUX SOCIETY OF PHLEBOLOGY - 'A FOCUS ON ABDOMINO-PELVIC VEINS'	The Netherlands	Oisterwijk
31 May - 1 June 2013	RUSSIAN-UKRAINIAN VENOUS FORUM "FROM DNEIPER TO DON"	Russian Federation	Rostov-on-Don
31 May - 2 June 2013	CONGRÈS DE PRINTEMPS DE LA SOCIÉTÉ SUISSE DE PHLÉBOLOGIE	Suisse	Lucerne
June 2013	XIII ANNUAL CONGRESS OF THE PORTUGUESE SOCIETY OF ANGIOLOGY AND VASCULAR SURGERY	Portugal	-
9-11 June 2013	MEET2013 (MULTIDISCIPLINARY EUROPEAN ENDOVASCULAR THERAPY)	Italy	Rome

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## CONGRESS

<b>DATES</b>	<b>CONGRESS</b>	<b>COUNTRY</b>	<b>CITY</b>
Mid June 2013	XIII ANNUAL CONGRESS OF THE PORTUGUESE SOCIETY OF ANGIOLOGY AND VASCULAR SURGERY	Portugal	-
19-22 June 2013	XXI. SLOVAK ANGIOLOGY CONGRESS WITH INTERNATIONAL PARTICIPATION	Slovakia	Tatranska Lomnica
27-30 June 2013	14 <sup>TH</sup> ANNUAL MEETING OF THE EUROPEAN VENOUS FORUM	Serbia	Belgrade
28 - 30 June 2013	XXVIII INTERNATIONAL CONFERENCE NEW CONCEPTS AND APPROXIMATE RESULTS OF EXPOSED AND ENDOVASCULAR INTERVENTIONS IN VASCULAR TREATMENT	Russian Federation	Novosibirsk
September 2013	CHINA VASCULAR SURGERY 12 <sup>TH</sup>	China	TBD
12-14 September 2013	ASIAN CHAPTER INTERNATIONAL UNION OF ANGIOLOGY 6 <sup>TH</sup> NATIONAL SYMPOSIUM ON VASCULAR SURGERY	Indonesia	Jakarta
18-20 September 2013	THE EUROPEAN SOCIETY FOR VASCULAR SURGERY XXVII ANNUAL MEETING	Hungary	Budapest
18-21 September 2013	20 <sup>TH</sup> ANNUAL CONFERENCE OF VASCULAR SOCIETY OF INDIA	India	Kodaikanal
28 September-1 October 2013	21 <sup>ST</sup> EUROCHAP - EUROPEAN CONGRESS OF THE INTERNATIONAL UNION OF ANGIOLOGY	Italy	Rome
28 September-1 October 2013	NATIONAL CONGRESS OF ITALIAN SOCIETY FOR VASCULAR INVESTIGATION - SIDV	Italy	Rome
October 2013	XIV INTERNATIONAL SYMPOSIUM OF ANGIOLOGY AND VASCULAR SURGERY	Portugal	Oporto
2-5 October 2013	CONGRESS OF THE EUROPEAN FEDERATION OF INTERNAL MEDICINE (EFIM)	Czech Republic	Prague
3-5 October 2013	XXIII MLAVS 2013, MEDITERRANEAN CONGRESS OF ANGIOLOGY AND VASCULAR SURGERY, 4 <sup>TH</sup> EDUCATIONAL COURSE ON THROMBOSIS AND ANTITHROMBOTIC TREATMENT	Greece	Larissa
30 October - 1 November 2013	14 <sup>E</sup> CONGRÈS DE L'UNION DES SOCIÉTÉS SUISSES DES MALADIES VASCULAIRES	Suisse	Montreux

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