# Phlebolymphology

Vol 26 • No. 2 • 2019 • P45-80

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#### Aims and Scope

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

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

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

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

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

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Tel: +33 (1) 55 72 60 00

### Indexed in EMBASE, Index Copernicus, and Scopus.

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ISSN 1286-0107

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## Editorial

### Dear Readers,

In this new issue of Phlebolymphology, **René MILLERET** (France) presents the future perspectives concerning the treatment of varices by endovenous procedures focusing on the new gold-standard treatments in the years to come.

Sclerotherapy remains one of the most commonly used procedures for eliminating dilated intradermal and varicose veins. **Vadim BOGACHEV** (Russia) reports the beneficial results of using micronized purified flavonoid fraction for preventing adverse events after sclerotherapy of reticular veins and telangiectases in routine clinical practice settings.

**Fedor LURIE** (USA) provides an overview regarding the different pieces of the venous disease puzzle and discusses how to connect, recognize, and investigate in depth the relationships between the "acute" and "chronic" components of this condition.

*Marianne De MAESENEER* (Netherlands) highlights the key points that should be known by a phlebologist about anterior accessory saphenous veins.

Jean Luc GERARD (France) and Fedor LURIE (USA) use evidence to debate about whether or not to use compression therapy after sclerotherapy.

Enjoy reading this issue! Editorial Manager Dr H. Pelin Yaltirik

### Announcement from the editor in chief

### Dear Readers,

As the Editor in Chief of Phlebolymphology, I have the pleasure to inform you that you may now consult The Vein Glossary in Vein Academy portal (vein-academy.servier.com).

The Vein Glossary was edited several months ago by Servier. In its foreword, **Robert L. Kistner**, the father of deep venous reconstructive surgery for reflux, clearly highlighted the aim of glossary: to improve the communication in phlebology and venous surgery for physicians and researchers around the world.

To summarize, the glossary provides definitions for 910 terms used in phlebology, including anatomy, physiology, pathophysiology, pathology, clinical signs and symptoms and their treatment and indications. All term names defined have been translated into six languages: French, German, Italian, Portuguese, Russian, and Spanish. The Vein Glossary also contains 21 complementary figures and 6 references to the world consensus documents as supplements to the terms.

The Vein Glossary has been endorsed by several scientific societies, including the American Venous Forum, the Australia and New Zealand College of Phlebology, the European Venous Forum, the Indian Association of Phlebology, the International Union of Phlebology, and the Latin American Venous Forum

It was my privilege to serve as the main coordinator of The Vein Glossary with the help of **Bo Eklöf** (Sweden) and **Oscar Maleti** (Italy), 6 group leaders, and 20 participants.

Editor in chief Michel Perrin, MD Vascular Surgery



### What is the future of treatment of varices by endovenous procedures?

### Rene MILLERET MD, PhD

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### Keywords:

varicose vein; endovenous techniques; termal ablation.

Phlebolymphology. 2019;26(2):48-53 Copyright © LLS SAS. All rights reserved www.phlebolymphology.org

### Introduction

Endovenous techniques for varicose vein ablation were introduced clinically 20 years ago. They are now recommended as a first-choice option by the international guidelines.<sup>1,2</sup> While the technical evolution seems to have stabilized for thermal techniques, nonthermal techniques are the new trend. What will the new gold-standard treatment be in the years to come?

### Classification of endovenous ablation techniques

Garcia et al<sup>3</sup> proposed a classification based both on the mode of action (ie, physical or chemical) and on whether there is a necessity for adding tumescent anesthesia. Thus, we can define four types of ablation techniques: (i) thermal ablation with tumescence; (ii) thermal ablation without tumescence; (iii) chemical ablation with tumescence.

### Thermal ablation with tumescence

Thermal ablation techniques with tumescence use heat to ablate the endothelium and delaminate the collagen in the media, which causes some damage to the adventitial layer. Two techniques – radiofrequency ablation and laser ablation with radial fibers using a 1470-nm frequency – are used worldwide, with equivalent immediate- and mid-term results. A third technique is steam ablation, which was introduced more recently and has less clinical validation in studies. Tumescent anesthesia is technically the most demanding and time-consuming part of the surgery.

Each procedure has its drawbacks; for example, with all thermal techniques, burns are a risk because the veins are too close to the skin and need to be deepened by tumescence. In steam ablation, the catheter itself becomes hot and the entry point must be cooled during the procedure. These methods are better adapted to saphenous trunks, are more difficult to use in extra-saphenous varices (except steam, which can easily be used for cross-tortuosity and be applied to superficial varices). On the other hand, long-term studies, such as the 5-year randomized study by Lawaetz et al,<sup>4</sup> have proven the safety and efficacy of these methods.

While these techniques are more expensive for the hospital than stripping in terms of immediate costs, they are less expensive than are newer techniques. A recent study performed in Norway showed that steam ablation was the cheapest option.<sup>5</sup>

### Thermal ablation without tumescence

Thermal ablation techniques without tumescence can be performed using only local anesthesia at the entry point of the catheter because the procedure itself is not painful. Cryofibrosis, formally known as cryosclerosis, was proposed by Le Pivert and myself in 1981<sup>6</sup> at a time when the general anesthesia needed for a stripping procedure had a much higher rate of complications than today. We performed a high ligation of the saphenous trunk and its tributaries and then catheterized the vein downward using a cryoprobe with a 3-mm diameter. The tip of the probe was cooled down to -91°C using NO<sub>2</sub> gas. We only froze 1 cm of the vein every 3 to 5 cm, which was a mistake because we left segments of the endothelium that were not ablated. Thus, the mid-term results at 18 months showed a 25% to 30% rate of recurrence, which prompted many practitioners to stop using this method. It has been recently used again with improved results. We have performed a feasibility study using a freezing catheter, without high ligation, and the preliminary results were in line with those of tumescent heating techniques (Figure 1). The main advantage of cryofibrosis is the possibility of resterilizing the cryocatheter up to 50 times, which considerably lowers the cost of the procedure for the hospital.



Figure 1. A resterilizable cryoprobe (Erbe Medical).

Frullini and Fortuna<sup>8</sup> proposed another thermal nontumescent technique, a technique called laser-assisted foam sclerotherapy, which is not purely thermal because it involves heating the medial layer with a Holmium laser fiber, then injecting sclerosing foam into the venous trunk<sup>9</sup>; however, few studies have been published outside medical meetings. The cost is higher than using a 1470-nm radial fiber. A significant number of patients find the procedure painful, so it has not been widely used.

### Nonthermal ablation with tumescence

In these techniques, tumescence is not used to prevent pain or to protect adjacent nerves, but to compress the vein, thus reducing the lumen and decreasing the blood flow. Parsi initiated the use of a long catheter to deliver the foam.<sup>10</sup> We added external compression by using an Esmarch bandage in a technique called the alpha technique. The 1and 3-year follow-up results show that the technique was comparable to first-generation laser and radiofrequency devices.<sup>11</sup> This procedure makes sure the vein is empty of blood, thus avoiding the inactivation of the sclerosing agent with blood proteins described by Tessari et al.<sup>12</sup> To dispense with the Eshmarch bandage, Cavezzi et al added tumescent compression to the procedure and obtained good rates of medium-term obliteration.<sup>13</sup> These techniques are more efficient for small to medium diameter trunks (ie, up to 7 to 8 mm).

### Nonthermal nontumescent ablation

These are the most exciting techniques. Mechanochemical ablation is a combination of a mechanical effect to destroy the endothelium with a chemical action using either a liquid or a foam sclerosing agent. Two catheters are available - ClariVein<sup>®</sup> and Flebogrif<sup>®</sup>. The ClariVein<sup>®</sup> device<sup>14</sup> is a rotating tip catheter with a built-in battery and electric motor in the handle, and the liquid sclerosing agent is injected when the catheter is retracted. The medium-term followup studies comparing this method with radiofrequency ablation are available, showing that the occlusion rates are in the same bracket.<sup>15</sup> ClariVein® is a single-use device that is more expensive than thermal fibers, whereas the Flebogrif<sup>®16</sup> is a passive device where several spikes are expelled from the catheter to ablate the endothelium, while injecting a sclerosing foam. Full ablation of the endothelium is unlikely with this catheter. The long-term occlusion rates may be less favorable with these techniques than the rates achieved with thermal techniques - only time will tell!

Cyanoacrylate glue is the latest technique to be reimbursed in the US. The glue is applied drop by drop through a thin (4 F) catheter, while the vein is compressed with the ultrasound probe. No tumescence and no compression stockings are required. Mid-term results compared favorably with those of radiofrequency ablation in a recently published randomized study.<sup>17</sup> Some recurrent inflammatory reactions have been observed and, in rare cases, these reactions have led to redo surgery with surgical ablation of the treated vein. Several brands of glue are commercially available. The cost of the single-use kit is at least three times the cost of radiofrequency or laser catheters.

### What is next?

Endovenous techniques are ablative; they aim to close an incompetent venous segment in order to suppress the reflux, which is one etiology of venous hypertension. Thus, we will not expand on potential conservative techniques that may suppress the reflux by repairing the venous valves or replacing them with prosthetic valves. However, when technically feasible, it is logical to save the saphenous trunk. The CHIVA technique (Conservative Hemodynamic Correction of Venous Insufficiency) and the ASVAL concept (Ambulatory Selective Varicose vein Ablation under Local Anesthesia) are mainly used on early-stage varicose veins with saphenous trunk dilatations less than 7 to 8 mm.

### Are less invasive ablation methods around the corner?

The best candidates are transcutaneous ultrasound techniques. We have been working on such devices since 2005 using specific high-intensity focused ultrasound (HIFU) probes. HIFU probes are already being used clinically for cancer removal, glaucoma treatment, and other applications. Two different approaches – thermal transcutaneous ablation and transcutaneous cavitation – have been tested on animals and/or humans. Thermal transcutaneous ablation was developed from research performed by the Inserm unit - the Thau lab in Lyon starting in 200518; this technique was licensed to the French company Theraclion®. The Echopulse® device is a robotized instrument. The treatment is planned on an ultrasound image of the vein to be treated, which must be compressed by the probe. A segment of the volume of a grain of rice is heated to 85°C in 20 seconds. The process is repeated until all of the predefined target has been heated.<sup>2,3</sup> The probe incorporates a skin cooling system, but tumescent anesthesia is still necessary in the majority of patients. Obermayer<sup>19</sup> reported the first clinical results of this system and confirmed its safety and short-term efficiency for closing short segments, such as perforators and recurrences. With the existing device, it is not possible to ablate a saphenous trunk over its entire length, as it would take a very long time and the patient must stay motionless. Future improvements will open more possibilities.

Transcutaneous cavitation devices are being developed by the same Inserm research unit and the Veinsound<sup>®</sup> team. Cavitation is a nonthermal biological effect of an ultrasound. Pulses of HIFU cause rapid changes in tissue pressure, which, in liquid blood, generates microbubbles. These cavitation bubbles oscillate and exert shear stress on the surrounding tissue, ie, venous endothelium, and expand rapidly then collapse. Before collapsing, the cavitation bubbles reflect the ultrasound waves, generating more bubbles in a "cavitation cloud." The energy released ablates the endothelium and damages the media, with a sclerotherapy-like effect being achieved.<sup>4,5</sup> The treatment is

### Before thermal treatment



### After thermal treatment



Figure 2. Thermal ultrasound of a sheep saphenous vein before and after ultrasound heating (Veinsound®).

performed under ultrasound imaging, as it is faster than using thermal ultrasound and painless; tumescence is not necessary.

The full length of the saphenous trunks can be treated, as well as superficial varices because there is a lower risk of skin damage. This technique has been tested on sheep (*Figures 2-4*) and clinical studies are expected to begin before 2020.



Figure 3. Histologic aspect before and after heating (Veinsound®).

#### Before cavitation treatment



### After cavitation treatment



Figure 4. Cavitation in a saphenous vein of a sheep (Veinsound®).

### Discussion

How will we choose a technique in the near future? Ultrasound techniques are noninvasive (cavitation, thermal ablation without tumescence) or minimally invasive (thermal ablation with tumescence). Thus, an operating theater or dedicated room is no longer necessary, neither is a specialized nurse to help the surgeon. Therefore, health care providers can achieve significant savings.

The economic models for the new techniques are different due to the cost of the equipment. Theraclion® rents out the Echoplulse® HIFU device and the hospital pays a user fee for each treatment performed, covering the rental cost and the single-use accessories (cooling system). This amount should be close to or higher than the cost of a sterile cyanoacrylate glue kit. The Veinsound® cavitation machine is bought by the health care provider, at the price of a high-end echography device. The cost of single-use items is the same as a radial laser fiber kit. Thus, if the hospital performs a high number of treatments, cavitation will lead to more savings compared with endovenous techniques. However, it can be expected that a large number of patients with varicose veins will be treated in-office, leading to a fundamental shift in the medical practice whereby the angiologist will offer a full expertise, from diagnosis to treatment. The time scale of such changes can be fixed around 8 to 10 years.

Ultrasound techniques are at the early stage of clinical application, so randomized comparative studies against endovenous techniques will not be available before 3 to 5 years. In countries where it is possible, reimbursement by state or private insurances will not be considered



Figure 5. Ultrasound probe for transcutaneous treatment.

before mid- to long-term randomized controlled trials are performed, showing noninferiority against the current goldstandard treatment, which is segmental radiofrequency.

Public and private hospitals do not have the same incentives to turn to new techniques. In the state-owned hospitals, more than 80% of patients are still treated with ligation and stripping because surgeons are only allowed this treatment modality for financial reasons. In less developed countries, foam is the treatment of choice. Neither thermal endovenous methods nor the new nontumescent catheters can be competitive on a cost-of-device basis; they will be progressively replaced by transcutaneous methods. Cryofibrosis, using a reusable probe, would be the only option, as it is a less expensive endovenous method and can easily be performed under purely local anesthesia and in a day-surgery organization. In private clinics, who mainly perform laser and radiofrequency ablation, these methods will continue to be the main option until ultrasound techniques are proven to have long-term efficacy in randomized studies. Enrollment in these studies will be difficult because most patients will favor the less aggressive option. Steam and laser-assisted foam sclerotherapy are not widely used, as the companies that introduced these interesting methods are not big enough to finance the studies that would be necessary to convince vascular surgeons and health care providers. This situation

may change if they are acquired by larger companies, but it may be too late, as less invasive techniques will come to the market.

Nevertheless, steam ablation will remain a technique of choice in some clinical situations, such as popliteal perforators, where its ability to treat cross-tortuosities is a definite advantage.<sup>20</sup> Mechanochemical ablation and glue catheters will remain more expensive for the patient, as they will have to pay for the consumables. The US is a specific case, as glue is now coded and reimbursed by some providers. It may still be used in this country, except if too many explantations must be performed in the years to come. The learning curve is another factor that may help or hinder the adoption of a new technology. Ultrasound therapy is easy to use for specialists who routinely perform echography examinations. Radiologists could then play a significant part and add this treatment modality to their practice.

### Conclusion

Endovenous techniques for vein ablation have been used clinically for more than 10 years before becoming the first-choice option to be advocated by the international guidelines. New transcutaneous ultrasound methods will replace them in an unstoppable quest for less aggressive treatments. However, it will take the same amount of time, as it is reasonable to ask for a 5-year follow-up to estimate their real potential.



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### Benefits of MPFF in combination with sclerotherapy

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### Abstract

This article presents the results of using micronized purified flavonoid fraction for preventing adverse events after sclerotherapy of reticular veins and telangiectases. Based on experimental and clinical studies, the author concludes that administration of micronized purified flavonoid fraction in a daily dose of 1000 mg for the period of the sclerosing treatment significantly reduces the severity of local vein-specific inflammation and the rates of associated typical adverse events after sclerotherapy.

### Introduction

Sclerotherapy, despite its long history, remains one of the most commonly used procedures for eliminating dilated intradermal and varicose veins. Such a great popularity of sclerotherapy is explained by high rates of complaints related to the dilated reticular veins and telangiectases on the one hand and the relative simplicity of this procedure and optimal price-quality ratio on the other hand.<sup>1-2</sup>

### Mechanism of sclerotherapy

In sclerotherapy, agents with different modes of action (detergents, hyperosmotic, and corrosive agents) are used for the destruction, in one way or another, of the endothelium and creating conditions for the fast parietal thrombosis resulting in ablation and fibrosis of the target vein. In particular, a chain of sequential events taking place during sclerotherapy of a vein of any caliber includes chemical injury or burn to the endothelium, exposure of the collagen-rich basement membrane, thrombus formation, obliteration followed by fibrosis or recanalization of the target vein (*Figure 1*). Moreover, these processes occur regardless of the type of sclerosing agent, route of its administration, presence or absence of compression of the target vein, and other factors.

Obviously, the endothelial lesion caused by a sclerosing agent, with the formation and evolution of a thrombus, is accompanied by an inflammatory reaction, the severity of which is determined by a number of factors. The most important of them are caliber, location and length of the target vein, type of sclerosing agent

### Keywords:

ecchymosis; hyperpigmentation; matting; micronized purified flavonoid fraction; phlebitis; sclerotherapy

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Figure 1. Mechanism of sclerotherapy.

and its aggregate form (liquid or microfoam), and the presence and level of compression.

### Adverse events after sclerotherapy

Sclerotherapy demonstrates high efficacy in eliminating reticular veins and telangiectases. However, fast and reliable ablation of target veins is accompanied by various adverse reactions, the most frequent of which are ecchymosis, hyperpigmentation, and neovascularization (matting), with the total incidence of 10% to 30% or more.<sup>3</sup> The cause of the development of ecchymosis is a mechanical and chemical lesion to the vessel wall in combination with the anticoagulant effect of sclerosing detergent solutions.

Routine prevention of ecchymosis includes the use of thin needles, slow injection of the sclerosing agent, which prevents hydraulic rupture of the target vein, and immediate external compression. In addition to these measures, the precooling of the sclerosing agent and syringe, as well as the use of external cooling of the sclerotherapy area using a thermal gel or a jet of cold air from special generators also prevents the formation of ecchymosis. To speed up the resorption of ecchymosis, various local treatments based on heparin and venoactive drugs are commonly used.

Hyperpigmentation is caused by penetration of hemoglobin into paravasal tissues, where it is converted into the dark pigment hemosiderin, which gives the skin a brown or reddish brown color of varying intensity. With the natural desquamation of the epithelium, hyperpigmentation gradually disappears; however, this process can last for several months to a year or more. It is obvious that hyperpigmentation after sclerotherapy, performed according to cosmetic indications, significantly reduces the patient's quality of life, and sometimes the newly acquired cosmetic defect exceeds the problems associated with dilated veins. General recommendations for the prevention of hyperpigmentation include careful performance of sclerotherapy, use of adequate concentrations of the sclerosing agent, prolonged compression, and timely removal of coagula. For the treatment of persistent hyperpigmentation, various methods of medical and laser peeling or masking cosmetics are used.

Neovasculogenesis with the formation of small red intracutaneous vessels (matting) in the sclerotherapy area is associated with the development of local hypoxia, leading to the activation of vascular endothelial growth factor (VEGF) and other vasoactive substances. For the prevention of matting, it is proposed to use low concentrations of detergents or hyperosmotic sclerosing agents. Usually, matting disappears spontaneously within a few months after sclerotherapy. In case of persistent matting, repeated sclerotherapy or percutaneous laser coagulation is used.

Hyperpigmentation and matting are often preceded by phlebitis of a sclerosed vein. Treatment of hyperpigmentation and matting can be time consuming and require significant additional costs, which is why the search for new methods of preventing adverse events after sclerotherapy is highly relevant.

### The role of MPFF in the prevention of adverse events after sclerotherapy

A number of experimental and clinical studies has shown that micronized purified flavonoid fraction (MPFF) has a pluripotent mode of action, the main components of which are an increase in tolerance of the venous wall to mechanical damage, suppression of vein-specific inflammation with a reduction in leukocyte activity and a proinflammatory endothelium phenotype. These features make it possible to actively use MPFF to reduce the incidence of adverse reactions during stripping of varicose veins. Earlier studies have shown that administration of MPFF in the perioperative period significantly reduces the severity of pain, intensity, and duration of ecchymosis, and it prevents posttraumatic edema.

The effects of adjuvant therapy with MPFF during sclerotherapy have been evaluated in several studies. In an experimental study, 22 rabbits were allocated into two groups of 11 animals (or 22 ears) each. The study group received MPFF at a dose of 300 mg/kg/day (2 mL/kg

of body weight of the working solution) starting 7 days before the procedure. The control group received a similar volume of 10% lactose as a placebo. After preliminary local application of anesthesia with 5% prilocaine, 5% ethanolamine oleate was injected into the dorsal vein of the rabbit ear. The diameters of venules and arterioles, functional capillary density, microvascular permeability, as well as severity of rolling and leukocyte adhesion to the endothelium were evaluated at 24 hours and 8 days after sclerotherapy.<sup>4</sup>

The increase in diameter of venules and arterioles was found to be significantly lower in the MPFF group compared with the control group. The decrease in the number of functional capillaries occurred in both groups, but was greater in the control group. During the first 2 and 24 hours, the abnormal microvascular permeability was significantly lower in the study group. However, 8 hours after the injection of the sclerosing agent, there were no significant differences in the microvascular permeability between the study and control groups. The leukocyte-endothelial reaction at 2 hours after sclerotherapy in the study group was significantly less prominent. After 24 hours, it was impossible to assess the severity of rolling and leukocyte adhesion in the control group due to severe edema. After 8 days, the number of rolling and adherent leukocytes in the study and control groups was comparable. The photography of the rabbit ears performed on day 14 showed an occlusion and partial disappearance of the dorsal vein in the MPFF group and a persistent paravasal inflammatory process in the control group.

In a clinical study, 60 female patients with reticular veins and telangiectases (CEAP clinical class C<sub>1</sub>) located on the lateral side of the thighs were divided into 2 groups of 30 people each. In the main group, MPFF at a daily dose of 1000 mg was prescribed 2 weeks before the scheduled sclerotherapy and continued for 2 months after the procedure. Prior to the injection of sclerosing agent into the target intracutaneous vessels, blood was taken with a vacutainer from the "central" vein for measuring the levels of high-sensitivity C-reactive protein (hsCRP), histamine, interleukin 1 (IL-1), tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), and VEGF. To monitor the systemic inflammatory response, blood from a forearm vein was taken in 15 patients of the control group.<sup>5</sup> Sclerotherapy was performed using the standard method and with the same sclerosing agent (0.2% Fibrovein or 0.5% aethoxysklerol). The repeated blood sampling from the "central" vein was carried out at day 10 and followed by sclerotherapy of this vein using the agent in a higher concentration.

In blood samples obtained from the "central" vein of the target vascular cluster before microsclerotherapy, there were no statistically significant differences between the main and control groups in the basal levels of inflammatory and endothelial dysfunction markers. In the blood samples obtained from the "central" vein on day 10 postsclerotherapy, a statistically significant increase in the levels of key markers of endothelial damage was recorded. At the same time, in blood samples obtained from a forearm vein, the levels of proinflammatory cytokines before and after sclerotherapy were not different. Therefore, standard doses of low-concentration sclerosing agents caused only a local proinflammatory response, and the markers of this response deserve special discussion.

hsCRP stimulates a number of proinflammatory cytokines, such as IL-1, TNF- $\alpha$ , and especially interleukin 6 (IL-6). CRP is involved in the activation of complement (a group of proteins that are part of the immune system), monocytes and stimulation of the expression of the adhesion molecules ICAM-1, VCAM-1, and E-selectin on the surface of the endothelium. According to recent studies, persistent inflammation in the vein wall leads to the development of varicose fibrosis. The normal CRP value is 1.0 mg/L. In our study, with similar baseline levels in the main and control groups, a significant local increase in CRP was observed on day 10 postsclerotherapy, which was greater in the control group ( $6.0\pm0.9$  mg/L vs  $8.3\pm1.0$  mg/L). The differences are significant with a *P* value <0.001 (*Figure 2*).



Figure 2. High-sensitivity C-reactive protein (hsCRP) levels.



Figure 3. Histamine levels.



Figure 4. Interleukin 1 (IL-1) levels.



Figure 5. Tumor necrosis factor  $\alpha$  levels.

Another proinflammatory agent produced due to the endothelial-leukocyte interaction is histamine. Histamine causes a variety of systemic and local reactions. In relation to sclerotherapy, a local increase in histamine levels leads to an increase in the permeability of the vascular wall and the development of edema. On day 10 postsclerotherapy, a significant (P<0.001) increase in local histamine levels was observed in the main and control groups compared with the baseline values ( $87.0\pm9.8 \ \mu g/L \ vs \ 156.9\pm33.9 \ \mu g/L$ ). At the same time, with comparable baseline values of histamine, in patients in the main group, the histamine level was almost 2 times lower in comparison with the control group (*Figure 3*).

MPFF provided a reduction in the level of IL-1. IL-1 is one of the important factors for the activation of leukocytes and macrophages, as well as the stimulation of the development of venous thrombosis and thrombophlebitis. In this study, the IL-1 levels significantly increased in the main and control groups, reaching  $5.9\pm0.4$  pg/mL and  $7.6\pm0.6$  pg/mL, respectively (*Figure 4*). Meanwhile, in the main group, the IL-1 level was significantly lower than in the control group (*P*<0.0003). Inhibition of the expression of certain interleukins is a feature of MPFF that has been shown in vitro and in animal experiments.

TNF- $\alpha$  is produced by activated macrophages and largely duplicates the actions of IL-1. In particular, TNF- $\alpha$  activates leukocytes, dramatically increasing the formation of hydrogen peroxide and other free radicals by macrophages and neutrophils. High levels of TNF- $\alpha$ have been associated with adverse effects of sclerotherapy, such as phlebitis, thrombophlebitis, and skin necrosis. After sclerotherapy, an increase in TNF- $\alpha$  levels was reported in both the main and control groups (5.9±0.9 pg/mL vs 7.5±0.4 pg/mL). However, compared with the control group with a significant increase in TNF- $\alpha$  level versus baseline (P<0.001), no significant differences versus both baseline and induced levels were observed in the main group (P=0.49) (*Figure 5*).

Various impairments in neovasculogenesis have been associated with an increase in the VEGF levels. In the early stage after sclerotherapy, an increased expression of VEGF stimulates the occurrence of matting, while, in the late stage, it, presumably, causes the recurrence of telangiectases. An increase in VEGF levels in response to sclerotherapy was reported in both the main and control groups (to  $252.3\pm26.0$  pg/mL and  $325.1\pm47.7$  pg/mL, respectively). At the same time, in contrast to the control group, the increase in VEGF level in the main group was not significant (*P*=0.5) (*Figure 6*).



Figure 6. Vascular endothelial growth factor levels.

The assessment of MPFF efficacy was carried out based on the rates of adverse events (*Table I*). There where significantly less ecchymoses, phlebitis, hyperpigmentation and neoangiogenesis in patients treated with MPFF when compared with the control group.

The rationale for the MPFF use in routine clinical practice was demonstrated in the observational program Vein Act Pro-C1, with participation of 70 doctors from various regions of the Russian Federation who included 1150 patients (79 men and 1071 women) with chronic venous disease of CEAP class C<sub>1s</sub> who were undergoing sclerotherapy.<sup>6</sup> In a proportion of patients, the doctors prescribed MPFF at a daily dose of 1000 mg at their own discretion. The patients started to take MPFF 2 weeks before the scheduled sclerotherapy and continued it for the next 6 weeks after the procedure. The primary efficacy end point for the MPFF treatment was the rate of adverse reactions in patients in the study and control groups at 4 weeks after the completion of sclerotherapy (*Table II*). There was significantly less pigmentation in patients treated with MPFF at 60 days when compared with the control group.

### Discussion

The main mechanism of sclerotherapy, regardless of the type of sclerosing drug, is the irreversible lesion of the endothelium of the target vein. At the same time, an acute local vein-specific inflammatory reaction develops, which is accompanied by the synthesis of various proinflammatory cytokines and leukocyte activation. It is obvious that the cause of adverse events after sclerotherapy is extravasation of inflammation with damage to the paravasal tissues.

Based on the presented experimental and clinical data, the beneficial effects of MPFF during sclerotherapy may include prolongation of the noradrenergic activity of

Adverse events	MPFF (n=30)		Control (n=30)		P value
Auverse evenis	Day 30	Day 90	Day 30	Day 90	
Ecchymoses	19/63.3%*	0	30/100%*	0	0.004
Phlebits	3/10%*	0	6/20%*	0	0.003
Hyperpigmentation	5/16.7%*	3/10%*	11/36.7%*	8/26.7%*	0.003
Neoangiogenesis	1/3.3%*	2/6.7%*	8/26.7%*	10/33.3%*	0.002

Table I. Rates of adverse events occurred in patients treated and not treated with MPFF during the sclerotherapy.

Adverse event	Patients treated with MPFF for 60 days (n=905)		Patients not treated with MPFF (n=245)		P value
	Abs No.	%	Abs No.	%	
Phlebitis	68	7.51	22	8.98	0.449
Pigmentation	307	33.92	101	41.22	0.034*
Neoangiogenesis	40	4.42	16	6.53	0.173
Necrosis	6	0.66	0	0.00	0.201

Table II. Comparative evaluation of adverse reactions for phlebosclerosing treatment with or without MPFF.

smooth muscle fibers, preventing dilatation and hydraulic rupture of the target vein, which increases the efficacy of the sclerosing agent and reduces the likelihood of leukocyte and erythrocyte extravasation. MPFF reduces the severity of rolling and leukocyte adhesion, which prevents the occlusion of microvasculature vessels and reduces local hypoxia. Due to the nonspecific antihistamine activity of MPFF, vascular wall permeability decreases, preventing local edema and extravasation of erythrocytes, along with the development of ecchymosis and hyperpigmentation.

MPFF is able to maintain the functional capillary density, the reduction of which is accompanied by a violation of soft tissue metabolism and increased inflammation with possible skin necrosis. MPFF reduces the synthesis of VEGF and provides better oxygenation of the interstitium around the sclerosed vein, which prevents the development of matting. Suppression of VEGF and TNF- $\alpha$  synthesis in patients receiving MPFF can prevent the recurrence of reticular veins and telangiectases in the future.

Analysis of the clinical outcomes of using MPFF during sclerotherapy on reticular veins and telangiectases has shown a reduction in the rates of most typical adverse effects, such as ecchymosis, matting, phlebitis, and hyperpigmentation. At the same time, both of these clinical studies have reported a significant decrease in the rate of hyperpigmentation after sclerotherapy. As for the discrepancy in the significant reduction in the rate of other adverse events noted in the above-mentioned clinical studies, this fact can be explained by a greater heterogeneity of the clinical observational study Vein Act Pro-C1. At the same time, a clear trend toward a reduction in the rate of all adverse events after sclerotherapy, noted in the Vein Act Pro-C1 study, suggests the efficacy of MPFF in sclerotherapy of the dilated reticular veins and telangiectases.

### Conclusion

Due to the complex and unique mode of action, MPFF is able to reduce the severity of vein-specific inflammation associated with the effects of sclerosing agents and prevent extravasation of the agent. This effect of MPFF provides a reduction in the rate of typical adverse events, such as the formation of ecchymosis, hyperpigmentation, and matting, with no negative influence on the time and quality of ablation of the target vein. Thus, the appointment of an intraoperative positioning system during sclerotherapy of reticular veins and telangiectases can be recommended for routine clinical practice. Therefore, the MPFF could have a role in preventing adverse events after sclerotherapy in routine clinical practice settings.



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### The venous puzzle: from hemodynamics to chronic disease to DVT

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### Keywords:

acute; chronic; chronic venous disease; deep vein thrombosis

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### Abstract

The majority of acquired venous disorders are usually classified into two main categories – acute and chronic. Deep vein thrombosis (DVT) exemplifies an acute disease, while morphological and functional abnormalities of the venous system of long duration defines the chronic venous disease (CVD). These definitions, however, resulted from a simplified view on the underlying pathology of these two conditions. Current evidence suggests that the majority of venous thromboses occur in patients already affected by chronic venous disease (CVD). Primary CVD starts early in life, predisposing patients to an acute DVT. At least half of DVTs are subclinical, but they significantly increase the risk of recurrence. Therefore, when a symptomatic DVT occurs, it is more likely to be a stage of chronic venous disease, then an independent event. It is not dissimilar to the relationships between atherosclerosis and acute cardiovascular events, such a stroke or myocardial infarction. The value of recognizing the underlying common pathology of these acute events is in enabling primary and secondary prevention.

### Introduction

The majority of acquired venous disorders are usually classified into two main categories – acute and chronic. At first glance, defining these conditions is a simple task. Deep vein thrombosis (DVT), defined as a "formation of thrombi in deep veins...,"<sup>1</sup> exemplifies an acute disease. The definition of chronic venous disease (CVD) is "morphological and functional abnormalities of the venous system of long duration."<sup>2</sup> However, a closer look at these definitions reveals that they are not as simple as suggested. For example, it can take a long time for a thrombus to lyse, making the term "acute" imprecise. When the thrombus organizes and transforms into fibrotic tissue, it is no longer appropriate to call it "thrombosis." At the same time, it may not yet meet the "long duration" criterion of the CVD definition. What is the appropriate category for the condition where the thrombus is rapidly and completely lysed, but damages venous valves and causes vein wall remodeling? These patients can remain asymptomatic for many years or become severely symptomatic within a few months. Does venous disease really need to be "of long duration" to become "chronic"?

What seems to be simply a terminology issue has farreaching implications. Imprecision in the definitions used in clinical trials leads to inappropriate assignment of patients to the treatment group and erroneous interpretations of the outcomes. Results of observational studies become questionable because misclassification bias within the studies is difficult to assess. Moreover, animal models developed for studying pathological mechanisms of venous disease may lack key relevant features of the disease process. Furthermore, patient management varies significantly depending on the practitioner's judgment of acuteness or chronicity of the venous condition.

Consensus-based definitions are helpful for current practice and for systematic collection of analyzable data. However, such definitions are frequently based on clinical and phenotypical features of the disease, not on the underlying pathological processes. As our understanding of the disease mechanisms changes, so do consensusbased terms. The history of medicine demonstrates many examples of decades- and centuries-long transitions from one set of terminology to another. The field of oncology perhaps best illustrates how an increasing knowledge of cellular and molecular mechanisms of neoplasms results in pathology-based terms to replace the prior clinical terms.

For more than a century, medical students have learned about pathological processes involved in the evolution of a venous thrombus. Unless embolized or lysed, the thrombus undergoes an organization and in a few weeks is replaced by connective tissue. Yet graduates use the terms "chronic thrombosis" and describe the 2-month old process noted in the previous sentence as "thrombus."

The challenges in connecting the pathological process with clinical manifestations are many. Rethrombosis is one of them. The clinical differentiation between the deterioration of postthrombotic disease and acutely developed rethrombosis is difficult and in many cases impossible. Clinical severity and the timing of clinical manifestations of postthrombotic disease vary from one patient to another, sometimes without an apparent difference in the underlying pathology. Even what appears to be the first episode of acute venous thrombosis in a patient may in fact be a recurrent event, since an estimated 50% of all DVTs are clinically silent.

The last statement deserves some discussion. It migrates within the literature without clear origin or solid confirmation. Despite this, clinical observations consistently support, if

not the 50% assertion, the high prevalence of identifiable postthrombotic changes in veins in asymptomatic individuals with no signs of venous disease and no history of DVT.<sup>3</sup> It is also a consistent observation that the majority of patients who are accidentally diagnosed with DVT by routine duplex ultrasound surveillance have no symptoms or signs of venous disease.<sup>4,5</sup> The annual incidence of acute symptomatic DVT in the United States is estimated to be about 6 in 10 000,<sup>6</sup> suggesting that between 100 000 and 200 000 people develop subclinical DVT every year. The more accurate estimate of the DVT incidence in the United States, however, is in the range of 200 000 to 400 000 people per year. In addition, after the first episode of DVT, 7% to 10% of patients develop recurrent thrombosis.<sup>7,8</sup> Although the incidence of postthrombotic changes in the veins after acute DVT is unknown, the fact that 40% to 50% of patients with iliofemoral DVT have identifiable postthrombotic changes in their veins after thrombolysis<sup>9,10</sup> suggests that it is substantial. Combining the high incidence of asymptomatic DVT and DVT recurrences with the significant frequency of postthrombotic vein changes in these patients (which also significantly increases the risk of recurrent thrombosis<sup>11</sup>) indicate that many patients who appear to have their first DVT episode have in fact a recurrent event and preexisting subclinical postthrombotic disease. Based on these numbers, at least one-third of all first-time DVT patients have preexisting postthrombotic vein changes. Using the clinical, etiological, anatomical, and pathophysiological (CEAP) classification,<sup>12</sup> such patients should be classified as having secondary CVD (E\_), even if they have no signs or symptoms ( $C_{0'}$  E,  $A_{d'}$  P). The importance of such a classification is the recognition of an existing pathology. Patients with asymptomatic secondary CVD may remain subclinical for a very long time, but they should not be considered free from venous disease or having a best treatment outcome, especially when enrolled in clinical trials.

Our understanding of the relationship between primary CVD and acute venous thrombosis has also been changing during the last decades. Acute superficial vein thrombosis most frequently occurs in the limbs with varicose veins.<sup>13</sup> The common explanation that blood flow disturbances in varicose veins cause the thrombosis neither explains the propagation of the thrombus to and within the saphenous vein nor the cases of thrombosed saphenous veins with no varicose vein involvement. Recent studies demonstrated that endothelium in the area of the valves in superficial veins has unique biological properties protective against thrombosis.<sup>14</sup> Due to the vascular remodeling in primary

CVD, these areas are affected, increasing the risk of thrombosis.<sup>15,16</sup> Varicose veins, a known risk factor for DVT<sup>17</sup> are just one of the many manifestations of primary CVD. Pathological studies suggest that primary CVD is a systemic disorder that affects not only superficial veins, but also deep veins and other tissues. Similar pathological changes are present in the wall of varicose veins, in other veins, and even in the skin of distant areas of the body.<sup>18,19</sup> Similar to superficial veins, the endothelium of normal deep vein valves has antithrombotic and anti-inflammatory properties.<sup>20</sup> Primary CVD alters these properties, and, when combined with venous reflux, leads to activation of prothrombotic and inflammatory pathways.<sup>19</sup> Perhaps it should not be surprising that the presence of venous reflux, even without varicose veins, increases the risk of DVT 5-fold.<sup>21</sup> Such a strong association suggests that a substantial proportion of patients with DVT have preexisting primary CVD. As in the case of postthrombotic disease, patients with primary CVD may or may not have symptoms and/or clinical signs. Using the CEAP classification, their clinical class can range from  $C_0$  to  $C_{6'}$  etiology  $E_{n'}$  anatomical component  $A_{5'}$   $A_{d'}$  or A<sub>sd</sub>, and pathophysiology P.

Since the time of Trendelenburg and Brodie, studies of primary CVD were predominantly focused on its hemodynamic component. The impact of the failure of venous valves to secure unidirectional flow on venous pressure and blood flow parameters were extensively investigated in basic and clinical research. Accumulated knowledge allowed recent studies to elucidate the biological effects of abnormal venous flow.<sup>22</sup> It became clear that normal venous valves create complex hemodynamic phenomena. In vitro and animal models predicted the existence of an isolated stable vortex in the valve pockets of a normal valve, which become hypoxic when the flow lost normal phasicity.<sup>23,24</sup> Direct observations confirmed this prediction as well as the active role of the valves in creating and maintaining phasic flow cycle.<sup>25,26</sup> These findings substantiate a base for the "valve cusp hypoxia" hypothesis, stating that either hypoxia or reperfusion injury after a prolonged period of hypoxia in the valve pocket plays the key role in the initiation of venous thrombosis.<sup>16,27</sup> Abnormal venous valves not only cause venous reflux, but also disrupt the pattern of forward flow.<sup>28,29</sup> Computational models based on duplex ultrasound data predicted thrombogenic patterns of blood flow passing the diseased valve, which corresponded to the distribution of platelets in the venous thrombi obtained from autopsy.<sup>30</sup> These findings, along with the valve cusp hypoxia hypothesis, explain earlier observations of the sites where venous thrombi originate.<sup>31</sup> Interestingly, proposed mechanisms of thrombus initiation do not require mechanical damage of the endothelium and exposure of collagen. All mentioned mechanisms-dysfunctional valves, venous reflux, abnormal flow through the valves, prolonged periods of nonphasic flow, and endothelial dysfunction-are features of primary CVD. Therefore, current basic science evidence not only support biological plausibility of the association between primary CVD and acute DVT, but also suggests that these relationships may be causal.

It is unlikely that primary CVD somehow protects patients with DVT from developing secondary (postthrombotic) CVD; therefore, its prevalence in patients with secondary CVD should be the same or higher than in patients with first-time DVT. Clinical trials and observational studies of postthrombotic syndrome support this statement. An analysis of a large registry of patients with a first episode of DVT showed that close to half of the patients who develop postthrombotic syndrome at 6 months had preexisting symptomatic CVD.<sup>32</sup> Of course, the proportion of patients with asymptomatic CVD remains unknown. Unlike secondary CVD that is defined by underlying pathology, the current diagnosis of postthrombotic syndrome is based on a severity score, most frequently using the Villalta scale. Using this score, postthrombotic syndrome has become popular in observational studies because it does not require any objective tests, decreasing cost and simplifying research logistics. However, if signs and symptoms do not reach a certain severity level, a patient is considered "healthy" even if they have occluded iliac veins or a refluxing femoropopliteal venous segment. Thus, the Villalta scale has an exceptionally large misclassification bias,<sup>33</sup> making it difficult to differentiate between patients who have true secondary CVD from those whose signs and symptoms after DVT are caused by preexisting primary CVD.

Data from recent randomized trials provide some insight into the true prevalence of preexisting primary CVD in patients with postthrombotic syndrome. The Sox trial (compression StOckings to prevent the post-thrombotic syndrome after symptomatic proXimal deep venous thrombosis) reported 33 patients who developed venous ulcers during the 2-year follow up.<sup>34</sup> The ATTRACT trial (Acute venous Thrombosis: Thrombus Removal with Adjunctive Catheterdirected Thrombolysis) reported 29 patients with venous ulcers.<sup>35</sup> In both of these trials, the proportion of patients who developed venous ulcers was exactly the same 4%. This is similar to the 3% prevalence of venous ulcers among patients with primary CVD,<sup>36</sup> but the timing is very different from studies on the natural history of CVD.<sup>37,38</sup> primary CVD starts at a very early age<sup>39</sup> and progresses slowly. It takes more than a decade for patients to progress from class  $C_2$ to  $C_4$  and even longer to develop an ulcer.<sup>40</sup> Secondary CVD progresses faster, but still requires more than 5 years to develop venous ulcers.<sup>37</sup> In order to observe a 4% ulceration rate in just 2 years, the study patient population has to have an absolute majority of patients with preexisting primary CVD.

It would appear that two pieces of the puzzle are connected. Patients with primary CVD have an increased risk of venous thrombosis. Of those who developed DVT, about half remain subclinical, with a very high risk of symptomatic recurrence. Patients with recurrent DVT are more likely to develop symptomatic secondary CVD. In summary, a large proportion of patients with secondary CVD disease must have preexisting primary CVD, and the natural history of venous disease is full of transitions from chronic conditions to acute events (*Figure 1*). The CVD itself may be just one disease with two different entry points. It starts in the majority of patients as primary CVD and slowly progresses to different clinical states. Some of these patients undergo one or more episodes of acute thrombosis. In some patients, these episodes significantly increase CVD severity and speed its progression. How frequently and in which patients the DVT episode does not change the CVD dynamics or may even decrease CVD severity remains an open question. Another entry point is acute DVT in patients who do not have preexisting primary CVD. Some of them develop CVD as a sequelae of DVT. Apparently, this happens infrequently. Only 30% of DVT patients develop postthrombotic syndrome,<sup>41</sup> and the majority have preexisting primary CVD. The incidence of secondary CVD in patients without primary CVD should not exceed 10%. Future studies will show if this number is even lower.

The "semantic" question of what is acute and what is chronic disease turns out to be a quite complicated subject. Current evidence suggests that the majority of venous thromboses are a stage of chronic venous disease. It is not dissimilar to the relationships between atherosclerosis and acute cardiovascular events, such as stroke or myocardial infarction. The value of recognizing the underlying common pathology of these acute events is in enabling primary and secondary prevention. Separating acute and chronic venous disease creates a barrier for investigating their connection.



Figure 1. The natural history of chronic venous disease.

Abbreviations: CVD, chronic venous disease; PCVD, primary chronic venous disease; CVI, chronic venous insufficiency; DVT, deep vein thrombosis.

Almost all studies of mechanisms of venous thrombosis ignore the existence of CVD. Limiting the role of the venous wall and venous valves in the initiation of thrombosis to "endothelial dysfunction" is an inaccurate simplification. Clinical trials routinely ignore the role preexisting CVD plays in the natural history and severity of clinical manifestations. How much of an observed difference in the treatment outcomes of acute DVT should be attributed to the underling CVD remains unknown, making validity of the trials highly debatable. It is time to connect the pieces of the venous disease puzzle, to recognize and investigate in depth the relationships between the "acute" and "chronic" components of this condition.



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### What a phlebologist should know about the anterior accessory saphenous vein?

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### Keywords:

anterior accessory saphenous vein; chronic venous disease; endovenous thermal ablation; phlebectomy; recurrent varicose veins; ultrasound-guided foam sclerotherapy

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### Abstract

The anterior accessory saphenous vein (AASV) is not only a tributary of the saphenofemoral junction, but it is one of the saphenous trunks, situated in its own saphenous compartment in the thigh, lateral to the great saphenous vein (GSV). Incompetence of the AASV, often without GSV incompetence, is found in about 10% of limbs with varicose veins. As to the clinical appearance of isolated AASV incompetence, this typically presents as varicose veins, coursing from the anterior thigh to the lateral knee and calf. The vast majority of these limbs can be classified as C2 according to the clinical, etiological, anatomical, and pathophysiological (CEAP) classification. Duplex ultrasound of patients with varicose veins should always include investigation of the AASV, before planning any treatment. Treatment of AASV incompetence used to be a classic high ligation procedure with ligation of the GSV and stripping of the AASV, in combination with phlebectomies. Nowadays, this has been replaced by endovenous thermal ablation with subsequent ultrasound-guided foam sclerotherapy (UGFS) or in combination with phlebectomies. A useful alternative is to perform UGFS of the AASV and its varicose tributaries. Both strategies received a recommendation arade I C in recent guidelines for AASV treatment. Another possibility is to perform only phlebectomies of the visible varicose veins. In patients with recurrent varicose veins both after surgery and endovenous ablation of the GSV, the AASV is often involved. The optimal strategy for prevention of such AASV recurrence is still a matter of debate.

### Anatomy and duplex anatomy of the AASV

While the anatomy of the saphenofemoral junction (SFJ) and the great saphenous vein (GSV) in the thigh has been extensively described based on anatomical dissections, surgical findings, and duplex ultrasound (DUS) findings, and hence is obvious to all practitioners, there is a lot of persisting confusion about the anterior accessory saphenous vein (AASV). The reason for this confusion is mainly because Caggiati et al<sup>1</sup>, in a consensus document, used cadaver dissection-based anatomical definitions to define accessory veins as "venous segments that ascend parallel to the saphenous veins, either anterior, posterior, or more superficial to

the main trunk." According to this rather vague definition, it was not clear whether accessory saphenous veins were running inside or outside of the saphenous compartment. Subsequently, along with increasing understanding of the so-called "duplex anatomy," a refinement of the anatomical nomenclature was developed and published again in the Journal of Vascular Surgery in 2005.<sup>2</sup> It stated that the AASV "at the upper thigh courses deeply (superficial to the muscular fascia, like the GSV) to a hyperechoic fascia that resembles the GSV covering. However the AASV can be easily identified, because it courses more anteriorly with respect to the GSV, with a path corresponding to that of the underlying femoral artery and veins."<sup>2</sup> This means that, on DUS, the AASV can easily be recognized in its own saphenous compartment or "saphenous eye," which can be clearly distinguished from the saphenous compartment of the GSV.<sup>3</sup> In the upper third of the thigh, two saphenous eyes can often be distinguished, one of the GSV and the other one of the AASV, the latter being recognizable by the alignment sign (Figure 1).<sup>3</sup> Duplex ultrasound investigation made it clear that the AASV is a real truncal saphenous vein, different from the GSV. Therefore, the often erroneously used name "anterior accessory great saphenous vein" and its abbreviation ("AAGSV") should be completely abandoned. Nowadays, investigation of the AASV has become an intrinsic part of the routine DUS of patients with chronic venous disease before treatment.<sup>4</sup>

In very exceptional cases (less than 1% of GSVs), there is a duplication of the GSV itself, with two parallel veins running



Figure 1. Duplex ultrasound of the left thigh (transverse view), about 5 cm under the groin.

The GSV has a smaller caliber than the AASV. The AASV is situated in front of the SFA and femoral vein ("alignment sign"). Abbreviations: AASV, anterior accessory saphenous vein; GSV, great saphenous vein; SFA, superficial femoral artery. in a unique saphenous compartment. In such rare cases, the more anteriorly situated vein of the two is not called the AASV, but is one of the two GSVs of a duplicated GSV.

One of the typical characteristics of the AASV is that it has a relatively short course (5 to 20 cm from the SFJ) and it never reaches below the knee. If the AASV is incompetent, it typically results in visible varicose veins that are often coursing obliquely on the anterior side of the thigh to the lateral side of the knee and lower leg (*Figure 2*). These varicosities should not be called extrafascial AASV, but rather anterolateral tributaries of the AASV. Previously, these tortuous tributaries of the AASV were also described as the "vena circumflexa femoris anterior" or "varix semicircularis anterior," and French phlebologists used to call it "*la cravate antérieure*," all outdated terminology from the era before DUS investigation was introduced.



Figure 2. Typical clinical appearance of isolated incompetence of the right anterior accessory saphenous vein. Image courtesy of Dr. Claudine Hamel-Desnos

The AASV usually joins the GSV between 0.5 and 2 cm from the SFJ. On DUS, the "Mickey Mouse" image may be seen with a "double ear" at one side if the junction between the AASV and the GSV is very close to the SFJ (*Figure 3*). In some rare cases, the AASV even has a separate junction with the common femoral vein, which results in a "double" SFJ. It is important to mention that veins from the lymph nodes in the groin are not only draining into the GSV, but also into the AASV.<sup>5</sup> Near the SFJ, lymph nodes can be typically seen on ultrasound, surrounding the AASV.



Figure 3. Duplex ultrasound of the left saphenofemoral junction (transverse view) illustrating the junction of the GSV and the AASV, the latter showing reflux at Valsalva maneuver.

Abbreviations: AASV, anterior accessory saphenous vein; CFA, common femoral artery; CFV, common femoral vein; GSV, great saphenous vein; SFJ, saphenofemoral junction.



Figure 4. Diagram of the right incompetent saphenofemoral junction with isolated incompetence of the AASV. The red arrow indicates the course of reflux.

Abbreviations: AASV, anterior accessory saphenous vein; CFV, common femoral vein; GSV, great saphenous vein.

While in the vast majority of cases the AASV diameter is smaller than the GSV diameter, it may be the other way round, mainly when the AASV is incompetent (*Figure 1*). According to thorough DUS studies in more than 2000 limbs of patients with varicose veins, in about 10% of cases, there was incompetence of an accessory saphenous vein, mostly the AASV, without involvement of the GSV.<sup>6</sup> In most such cases, the SFJ is incompetent and reflux is seen from the SFJ into the AASV during a Valsalva maneuver, while the preterminal valve of the GSV is competent and hence there is no reflux in the GSV (*Figure 4*).

### Symptoms and clinical presentation of AASV incompetence

Although the varices may be quite prominent, not all patients with AASV incompetence present with typical venous symptoms like heaviness, pain, nocturnal cramps, itching, and paresthesia. Many patients are mainly worried about the cosmetic aspect, complaining about their "ugly legs."

By far, the most typical presentation of AASV incompetence is varicose veins (C2, according to the clinical, etiological, anatomical, and pathophysiological [CEAP] classification<sup>7</sup>) that are visible on the anterior thigh, typically running obliquely to the lateral side of the knee and further down to the lateral calf (Figure 2), but other varices may also be seen (Figure 5, right leg). The most cranial varix indicates the connection with the AASV, which may be situated somewhere between the SFJ (or close to it) and the midthigh, as described above. In some cases, AASV tributaries connect with either the GSV (Figure 5, left leg) or the small saphenous vein (SSV), which may explain the presence of varicosities in the GSV or SSV territory as well. Development of edema (C3) or more advanced stages of chronic venous disease (C4-C6) are not very common in limbs with AASV incompetence. Unfortunately, detailed data, mentioning the CEAP classification in AASV incompetence in particular, have been rarely reported in the literature. In a study on 63 consecutive limbs in 62 patients (58 female, 5 male) with isolated AASV incompetence without GSV involvement, 57 limbs were classified as C2 (90%), 2 were classified as C3 (3%), 3 limbs as C4 (5%), and 1 with an ulcer (C6) in a morbidly obese patient (own series, unpublished data). In the majority of these cases, the venous clinical severity score ranged between 1 and 4. Theivacumar et al<sup>8</sup> published a small series of 33 patients with primary or recurrent varicose veins due to isolated AASV incompetence and they classified 28 patients as C2 (85%), 4 as C3 (12%),



Figure 5. Diagram of a patient with bilateral incompetence of the AASV with different patterns right/left of refluxing tributaries and course of reflux.

In the right leg, there are varicose veins both on the lateral and anterior side of the knee. In the left leg, there are varicose veins on the lateral side of the leg, but there is also a connection with the great saphenous vein, which becomes incompetent and gives rise to anterior varicose veins of the lower leg as well. Abbreviations: AASV, anterior accessory saphenous vein.

and 1 as C4 (3%). The Aberdeen Varicose Veins Symptoms Severity Score in this group was similar to an age- and sexmatched control group with GSV incompetence. Equally, a recent study did not find any difference in clinical severity between limbs with refluxing SFJ and AASV (n=23) vs limbs with refluxing SFJ and GSV (n=145); they found a higher percentage of C4-C6 (22%) limbs in the AASV group than in the two studies mentioned above.<sup>9</sup> In this study, the AASV group comprised significantly more females and the BMI was higher than in the GSV group.<sup>9</sup> The latter may also have influenced disease severity in the AASV group.

Finally, in some exceptional cases, patients with AASV incompetence may present with a bulging mass in the groin due to an aneurysm of the proximal AASV, which may even mimic an inguinal hernia and may be complicated by thrombosis of the aneurysm.<sup>10</sup>

### Diagnosis of AASV incompetence by duplex ultrasound

As for the diagnosis of all other patients with chronic venous disease (C2-C6), duplex ultrasound is mandatory, both for documenting the course of reflux and for planning an adequate treatment strategy. Duplex ultrasound investigation is performed with the patient standing. The AASV is identified as per the above-mentioned description. The diameter of the AASV can usually not be measured at mid-thigh, as is done for the GSV, but rather more cranially, preferably at about 5 cm from the SFJ and in a straight part of the vein (away from any focal dilatation or aneurysm). When there is a focal dilatation, exceeding 20 mm, this is defined as an AASV aneurysm, most frequently situated close to the SFJ.

### Advanced CEAP classification of limbs with AASV incompetence

At the time of publication of the revision of the CEAP classification,<sup>7</sup> the AASV was not really recognized yet as a separate saphenous trunk (see above). This causes a problem when trying to describe chronic venous disease properly in a limb presenting with symptomatic varicose veins due to isolated AASV incompetence, in particular to locate the reflux in the advanced CEAP classification. Some colleagues claimed C2S As Ep Pr5 was the correct way to describe this, whereas others were more in favor of mentioning it as C2S As Ep Pr2. The latter seemed more logical, as the AASV is a saphenous trunk above the knee, so the CEAP classification would be similar to the classification used for the GSV above the knee. The ongoing new revision of the CEAP classification will undoubtedly propose a solution to this problem.

### Treatment options for incompetence of the AASV and tributaries

Whereas the literature on the treatment of the GSV is quite extensive, not many studies have focused on the AASV; in addition, AASVs have probably been included as GSVs in clinical trials without distinction. On the other hand, in several recent randomized clinical trials, limbs with preoperative AASV incompetence have been excluded in order to study a homogeneous group of limbs with GSV incompetence and evaluate the postoperative fate of the AASV, in particular after thermal ablation of the GSV. In general, whenever AASV treatment is separately included in a series of GSV/AASV treatments, limbs with isolated AASV incompetence represent about 5% to 7% of all included limbs.  $^{11,12}$ 

Recently, the American College of Phlebology (present name: American Vein and Lymphatic Society [AVLS]) Guidelines Committee developed the guidelines for the "treatment of refluxing accessory veins," under the lead of Kathleen Gibson.<sup>13</sup> Recommendations were based on both a literature review and expert opinions to help physicians make evidence-based decisions (as much as possible) for the benefit of patients with chronic venous disease related to AASV incompetence (treatment of the posterior accessory saphenous vein was also included).

In practice, several treatment options are available and the choice of treatment in an individual patient will mainly depend on the patient's expectations, symptoms, clinical observations, and DUS findings.

### Historical classic high ligation and stripping of the AASV with phlebectomies

Before the introduction of endovenous ablation techniques, the treatment of choice for isolated AASV incompetence was high ligation at the SFJ, division and ligation of the GSV, and then stripping of the AASV (or just excision if it was very short, eg, only 5 cm). This treatment was combined with extensive phlebectomies of all tributaries; the intervention was usually performed under general anesthesia. Prinz et al<sup>14</sup> published a small retrospective study on a series of 30 patients treated with this technique. In two cases, the GSV thrombosed postoperatively and therefore it was decided to remove it. After a 3-year follow-up, the authors found reflux in the above-knee GSV at DUS in one-third of the limbs; however, the clinical results were not mentioned. In my own unpublished series mentioned above (62 patients, 63 limbs), the clinical results were excellent after a 1-year follow-up in all, but 1, patient. One patient developed neovascularization at the SFJ and symptomatic reflux in the GSV; she underwent additional stripping of the GSV. Duplex ultrasound after 1 year showed grade 2 neovascularization (more than 4 mm in diameter, with reflux) at the SFJ in 3 cases (5%), occlusion or absence of the proximal half of the GSV in 4 cases (6%), and asymptomatic reflux in the GSV from mid-thigh due to incompetence of a femoral vein perforator in another 4 cases (6%). Patient satisfaction was very high in this selected group of patients.

### Endovenous thermal ablation

According to the American College of Phlebology guidelines, endovenous laser ablation (EVLA) or radiofrequency ablation

(RFA) of the refluxing saphenous trunk is recommended for the treatment of symptomatic isolated AASV incompetence (recommendation grade I C).<sup>13</sup> This intervention is performed under local tumescent anesthesia and can be combined with either miniphlebectomies or ultrasound-guided foam sclerotherapy (UGFS) to treat the usually extensive varicose tributaries. In the previously mentioned prospective study by Theivacumar et al,<sup>8</sup> two similar groups of patients, having either GSV or AASV incompetence, were treated with EVLA of the refluxing saphenous trunk. Six weeks after EVLA of the AASV and GSV, additional UGFS was required in 61% and 42% of patients, respectively (nonsignificant difference). The same group also reported good results of EVLA and UGFS in recurrent varicose veins related to AASV incompetence after previous stripping of the GSV.<sup>15</sup> Other investigators reported excellent 1-year results of EVLA with concomitant UGFS in case of AASV incompetence (56 limbs).<sup>16</sup> The intervention was considered safe and the incidence of endovenous heat-induced thrombosis (EHIT) was not greater after EVLA or RFA of the AASV than of the GSV.17,18

### Ultrasound-guided foam sclerotherapy of the AASV and tributaries

In many patients with isolated AASV incompetence, UGFS may offer a simple and suitable solution, which can be performed in one (*Figure 6*) or more sessions and can easily be repeated. In the American College of Phlebology guidelines, it received a recommendation of grade I C, the same as endovenous thermal ablation.<sup>13</sup>

In a large retrospective study by Bradbury et al  $^{\rm 19}$  using foam sclerotherapy in more than 1200 limbs with varicose



Figure 6. Treatment of a refluxing anterior accessory saphenous vein and its tributaries by means of ultrasound-guided foam sclerotherapy in one session.

Panel A. Before treatment; Panel B. Immediately after foam injections. Panel C. Clinical appearance after 6 months. Image courtesy of Dr. Claudine Hamel-Desnos. veins, 139 limbs were treated for AASV incompetence (93 primary, 46 recurrent varicose veins). After a mean follow-up time of more than 2 years, recurrent reflux of the AASV was present in only 3.6% of cases.

### Other alternatives

An alternative strategy for patients with symptomatic AASV incompetence consists of performing single ambulatory phlebectomies under local tumescent anesthesia, without high ligation (contrary to the case with classic surgery - see above). This technique is known by the acronym ASVAL (Ambulatory Selective Varicose vein Ablation under Local anesthesia) and it has mainly been studied in the GSV, although the findings can easily be applied to the AASV.<sup>20,21</sup> Recently, a Spanish group reported results of what they described as a new strategy (modified CHIVA) for the refluxing AASV, consisting of single phlebectomies without high ligation, in the same way as the ASVAL technique prescribes.<sup>22</sup> They included 65 patients in a prospective study with a 1-year follow-up to analyze efficacy and safety. After 1 year, varicose veins recurred in only 8% of the patients. The mean diameter of the AASV was significantly reduced (from 6.4 to 3.4 mm) and the reflux was abolished in 82% of treated limbs.

In another small retrospective study, an interesting combination of techniques was reported. In 28 patients (29 legs) with isolated AASV incompetence and varicose tributaries, phlebectomies of all varicosities were performed under local tumescent anesthesia, which was followed by foam sclerotherapy of the refluxing AASV using polidocanol foam (1%, 2%, or 3%) that was injected 5 to 8 cm from the SFJ.<sup>23</sup> The authors mainly focused on the immediate follow-up, in view of potential thrombotic complications. At 1 week, DUS showed occlusion of the AASV and no deep vein thrombosis. In one case, there was a mild inflammatory reaction and, in another case, there was a more pronounced inflammatory reaction at the site of AASV treatment. Unfortunately, further follow-up was not well documented.

Finally, the nonthermal, nontumescent techniques (mechanochemical ablation, cyanoacrylate glue) have not yet been studied in isolated AASV incompetence, but the promising results of these techniques in GSV and SSV incompetence could probably also be achieved in isolated AASV incompetence.

### Role of the AASV in recurrent varicose veins after surgery and endovenous ablation: the eternal culprit?

After previous surgical or endovenous treatment of the GSV, recurrent varicose veins often originate from the groin, with recurrent or persisting reflux of the SFJ, new refluxing tributaries, and/or neovascularization.<sup>24</sup> One of the most "popular" pathways of recurrence, causing varicose veins at the thigh level, is an incompetence of the SFJ with reflux of the AASV.

Garner et al<sup>25</sup> evaluated a series of patients with recurrent varicose veins by means of DUS and found 141 groin recurrences, where a refluxing AASV was involved in 61 (43%) of these recurrences. They concluded that the AASV should be routinely looked at during preoperative DUS scanning and they advocated more thorough surgery at the SFJ, including dissecting/dividing the AASV beyond the side branches or stripping of the AASV, if identified during operation.

Nowadays, the situation is not that different after EVTA of the GSV. Several studies have reported new incompetence of the AASV to be responsible for recurrence of varicose veins in 8% to 35% of cases.<sup>26-28</sup> This is probably related to persisting incompetence of the SFJ after EVTA in certain cases, although the pathophysiology is not completely clear. Future studies will be needed, including prospective DUS follow-up, to unravel this issue further. Whether EVTA at the very SFJ (sometimes called laser or RFA crossectomy) or preventive ablation of a nonrefluxing AASV would reduce the number of recurrences from the groin and in particular involvement of the AASV in such recurrences remains unclear. Nevertheless, it can be concluded that the AASV remains an important culprit, so, *nihil novi sub sole* – nothing new under the sun.



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## DEBATE: Is compression after sclerotherapy mandatory?

### Compression after sclerotherapy is mandatory!

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### Keywords:

chronic venous disease; chronic venous insufficiency; compression schlerotherapy

Phlebolymphology. 2019;26(2):73-80 Copyright © LLS SAS. All rights reserved www.phlebolymphology.org The same terms frequently mean different things to different people and the term "evidence-based medicine" is no exception. It is alarming, though, when it is used to limit the clinical decision-making process to a narrow scope of specific evidence from clinical trials and systematic reviews. In fact, the clinical decision-making process has always been (and should be) based on the integration of all knowledge modalities, including knowledge of relevant basic science, awareness of the social and economic environment, and a clear understanding of patient preferences.<sup>12</sup>

A good example of how a narrow definition of evidence-based medicine can limit patient care is in the determination of whether to use compression following sclerotherapy. The argument against the use of compression is based solely on the lack of sufficient evidence from clinical research studies demonstrating benefit of compression after treating veins with sclerotherapy. However, the limitations and deficiencies of clinical studies related to compression therapy are well known. Nearly all of the studies were underpowered to answer the key question, so interpreting their inability to detect a difference in the outcomes as an evidence of equality is classic type 2 statistical error. The dose of compression and the time of application varied from study to study and frequently it was not specified or measured. Patients' compliance with compression was unknown and when estimated it was remarkably low. These and other deficiencies of published clinical studies often result in low or very low evidence levels for the use of compression in procedure-related outcomes; consequently, writing committees issue only weak practical recommendations.<sup>3</sup>

Using these recommendations as a guide, a practitioner may feel justified to withhold compression after sclerotherapy. However, this scenario represents a restrictive use of the concept of evidence-based medicine. Apart from the logical error that the absence of evidence is not evidence of absence, this position fails to recognize that the focus of clinical studies is on procedural outcomes, such as cosmesis and absence of side effects, which are relevant only to the treatment itself.<sup>3-5</sup> It also fails to integrate the knowledge from other disciplines that is relevant to the debated proposition.

Sclerotherapy is used to treat patients with a variety of forms and presentations of chronic venous disease (CVD). Patients with chronic venous insufficiency (CVI; classified as clinical classes  $C_3$ - $C_6$  of the clinical, etiological, anatomical, and pathophysiological [CEAP] classification<sup>4</sup>) have complex underlying pathology

that requires the use of multiple treatments, including, but not limited to, sclerotherapy. This is especially true for patients with secondary CVD and venous obstruction (E<sub>s</sub>, P<sub>o</sub> of the CEAP classification). CVD in general and CVI in particular have a progressive natural history. Currently existing interventional treatments for CVI patients are not curative, and, given sufficient time, recurrences are inevitable. Strong evidence exists that including compression therapy in the comprehensive treatment plan not only provides better clinical outcomes, but also delays CVI progression and prevents recurrences after interventions.<sup>5,6</sup> One can reasonably conclude that, in CVI patients, compression should be used after sclerotherapy for reasons not directly related to the procedural outcomes of this modality.

Patients with disease classified as  $C_1$ - $C_2$  may have pure cosmetic reasons for selecting sclerotherapy. However, epidemiological studies have demonstrated that the majority of these patients have some venous symptoms.<sup>7</sup> Since the cosmetic concern dominates prior to the treatment, patients may not clearly express symptom severity. Paradoxically, cosmetically successful treatment may turn patients' attention to their subjective feelings. Itching, focal aching, and other symptoms are frequently interpreted as side effects of sclerotherapy, while they could have existed before the treatment, at least in some patients. Multiple studies have consistently demonstrated that compression therapy is effective in treating venous symptoms and, for this reason, it should be considered in symptomatic  $C_1$ - $C_2$ patients.

The pathological basis of CVD is diverse and not always easily identifiable, especially in the early stages of the disease. Initial clinical manifestations may appear at a very young age as  $C_{1a}$ - $C_{2a'}$  but they ultimately progress to more advanced stages.<sup>8</sup> This clinical progression parallels deteriorating venous pathology.<sup>9</sup> Even at the first presentation, almost half of  $C_0$ - $C_1$  patients have venous reflux.<sup>10</sup> More than a quarter of these patients will progress to the  $C_2$  class and more than 10% to CVI.<sup>10</sup> Sclerotherapy of surface veins in these patients will not affect the disease progression and compression should be considered as a long-term option.

Long-term outcomes may not be the highest priority for patients with cosmetic concerns, but immediate cosmetic results always are a priority. Those results may not be ideal due to well-known side effects and complications of sclerotherapy, such as excessive thrombosis, phlebitis, matting, and pigmentation. The evidence from clinical studies regarding prevention of these conditions is even sparser than the evidence regarding compression, which is when a practitioner's basic science knowledge should be integrated in the clinical decision-making process. Two major pathological processes behind these complications are thrombosis and inflammation.<sup>11</sup> Individually or in combination, these two processes can cause extravasation of blood cells, hemosiderin deposits, and initiation of neovascularization. Keeping these processes under control should help minimize cosmetically unacceptable complications. Compression therapy acts upon exactly these two mechanisms. Its anti-inflammatory, antithrombotic, and thrombolytic effects have been demonstrated and used in a variety of clinical scenarios, from prevention and treatment of venous thrombosis and thrombophlebitis to cellulitis and muscle damage.<sup>12</sup> Using compression therapy after sclerotherapy can mitigate the damaging effects of excessive activation of thrombotic and inflammatory pathways. The magnitude of the effect of compression upon the incidence of sclerotherapy complications may not be as dramatic as in the case of edema, and large clinical trials are needed to confirm such influence. However, in the absence of such evidence, the data from basic science and the consistent finding of the benefits of compression in multiple small studies provide sufficient basis for considering compression for improving cosmetic outcomes after sclerotherapy.

In summary, considering the nature of the disease, its underlying pathology, and natural history, longitudinal compression therapy is a reasonable and recommended option for the management of patients with CVD. This modality should be viewed as a component of comprehensive management and it should not be discontinued after interventions, including sclerotherapy. In addition, it is likely to improve cosmetic outcomes of sclerotherapy of reticular veins and telangiectasias. For all of these reasons, compression therapy should be used in all patients after sclerotherapy.



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### Compression therapy after sclerotherapy is not mandatory

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Keywords:

compression compliance; compression therapy; edema; sclerotherapy

Phlebolymphology. 2019;26(2):76-80 Copyright © LLS SAS. All rights reserved www.phlebolymphology.org

### Introduction

It might be surprising to question the sacrosanct compression therapy. Compression therapy is widely accepted by the majority of physicians and the reasons for its usefulness seem obvious. However, have the right questions been asked? What is its effect on the veins, how long should it be worn, and with which therapeutic class? Finally, do the patients wear the compression garments correctly and with which observance? No study makes it possible to formally assert the effectiveness of compression and give indications on the most appropriate therapeutic class as well as when it should be worn. There is no consensus on the strength or duration of compression that should be applied following a particular treatment. These are the reasons for which the guidelines can only give us suggestions, sometimes with the lowest grade (2C) and never with a recommendation.<sup>1,2</sup>

### Compression therapy and evolution of varicose vein disease

even if these remarks are off-topic because it concerns the compression and not the compression after sclerotherapy it is interesting to note that, Palfreyman and Michaels<sup>3</sup> and, more recently, the most fervent defenders of compression,<sup>4</sup> cannot give any recommendations and conclude that insufficient data are available on the use of compression stockings for the prevention of chronic venous disease (CVD) progression. Neither compression stockings nor venoactive drugs can cure varicosities nor prevent the evolution of varicose veins and will just find their use in the presence of venous symptomatology.

### What is the role of compression after sclerotherapy?

Theoretically, the purpose of compression stockings is to narrow the vein diameter, thereby reducing postoperative pain, bruising, and the risk of deep vein thrombosis. In 2005, Partsch and Partsch<sup>5</sup> investigated the external pressure necessary to narrow and occlude leg veins in different body positions. In the sitting and standing positions, initial narrowing occurs with a pressure on the leg between 30 and 40 mm Hg. Complete occlusion of superficial and deep leg veins occurs with 20 to 25 mm Hg pressure in the supine position, between 50 and 60 mm Hg in the sitting position, and at about 70 mm Hg in the standing position.

Likewise another study,<sup>6</sup> using a CT scan with patients in the supine position, compared the great saphenous vein at the thigh wearing no compression or compression with different classes of stockings (II, III, or IV). Regardless of the level of compression, it was not enough to shrink the great saphenous vein on the thigh. This information can easily be checked using an echography on

patients in a standing position wearing compression or nothing. Measurements of the vein, even very superficial veins, are equivalent with elastic stockings (measurement through the stocking) or without (directly on the skin). Stockings at the thigh are useless because, regardless of the compression, there is no effect on the great saphenous vein on the thigh.<sup>7</sup>

More recently, using an MRI on patients in the standing position, Partsch et al<sup>8</sup> demonstrated that compression stockings with a pressure of 22 mm Hg were able to reduce the caliber of deep calf veins, but not of superficial varices, which were compressed only by using bandages exerting pressures between 51 and 83 mm Hg. Thus, surprisingly, we learned from this study that the deeper the vein, the more effective the compression. Therefore, this assumption of narrowing of superficial veins using compression stockings is very theoretical and not realistic. Consequently, for telangiectasias, the available compression stockings cannot be effective.

### Degree of graduated compression

Since at least 50 mm Hg is required to slightly compress superficial veins in a standing position, maximum compression stockings (class IV) must be provided. However, this is often not the case (in France, the maximum of stocking compression is 45 mm Hg) and there is no consensus on the subject. Consequently, to reinforce the pressure locally on certain veins, an eccentric compression device could be applied using cotton wool, cotton rolls, or rolled gauze compresses, which are affixed with tape strips or bandages. They take time to install, are painful, can irritate the skin, and may move, requiring reapplication of the materials, and can prevent regular personal hygiene. Special pads can be used, but again, these are painful and we have no idea for how long they should be worn. Althrough some studies have shown good results with these special pads<sup>9,10</sup> made of foam or silicone gel, they remain confidential, and not used regularly by the practitioners. In general, the highest level of compression that the patient can tolerate will probably be the most beneficial. Surprisingly, some studies have reported that low-compression stockings were as effective as highcompression stockings, but had a better compliance rate.

Furthermore, excessive compression can sometimes be potentially deleterious.<sup>7</sup> The common fibular nerve can

be palpated behind the head of the fibula and wraps around the neck of the fibula. Probably much more with bandages than with stockings, compression especially on the lateral aspect at the upper part of the leg, could damage the fibular nerve where it is very superficial.

### Duration of compression

Regularly, the optimal duration of compression has come into question. Should they be worn for 2 days, 1 to 4 weeks, or more? The UK recommendations (NICE)<sup>11</sup> suggest not offering compression bandaging or hosiery for more than 7 days after completion of interventional treatment of varicose veins. The American recommendations<sup>1</sup> are not very explicit and evade the question, leaving the practitioner to use his best clinical judgment to determine the duration of compression therapy after sclerotherapy.

### Compliance

Compliance rate with wearing elastic compression stockings is mediocre. Only 21% of patients<sup>12,13</sup> admit to using compression therapy as prescribed. Heat in hot countries<sup>14,15</sup> or during the hot season aggravates this poor compliance. Furthermore, over the long term, compliance gets worse. In addition, all of these compliance rates are only subjective, depending on the allegations of the patients. Very interesting, one study<sup>16</sup> was conducted that can give us the real compliance to compression therapy, which is objectively measured using a thermal probe inserted in the stocking that recorded the skin temperature every 20 minutes for 4 weeks. Therefore, compliance with wearing stockings was accurately recorded: the average daily wearing time was only 5.6 hours and the average number of days worn per week was only 3.4 days. When patients receive detailed recommendations, with an SMS message being sent once a week for four weeks, the average daily duration of wearing was increased to 8 hours and the average number of days worn per week was 4.8 days. Even with repeated and clear recommendations, compliance improved, but, on average, compression was not worn the entire day and not every day, which is the real objective. In order for patients to follow your recommendations, compression stockings must be carefully prescribed (neither too strong nor too light) and the benefits should be rigorously explained.

### Sclerotherapy and compression

In the literature, we found 7 randomized controlled trials of compression after sclerotherapy. In 1981, Raj<sup>17</sup> found no advantage of wearing compression bandages for 6 weeks compared with 8 hours. *Compression bandages* become loose with time in a walking patient, losing the benefit of the higher pressure exerted with bandages.

In 1985, Scurr<sup>18</sup> (261 patients) recommended compression stockings rather than high-compression bandages after sclerotherapy of varicose veins. Nowadays, there is a broad consensus to recommend, for active ulcers, compression bandages over stockings; however, for varicose veins, stockings are rather prescribed because they are easier to wear, esthetic, and more comfortable during the day.

In 2007, Kern<sup>19</sup> (96 patients) concluded that wearing compression stockings for 3 weeks improves the efficacy of sclerotherapy of leg telangiectasia at the thigh by improving the disappearance of clinical vessels in the photos according to independent experts, but patient satisfaction was similar in both groups. This is quite strange because, as we have seen previously, the compression of telangiectasia with stockings in the thigh is illusory and requiring patients to wear a compression stockings for 3 weeks is very restrictive for esthetic reasons.

In 2010, Hamel Desnos<sup>20</sup> (60 patients) found no difference in efficacy, adverse effects, satisfaction scores, symptoms, and quality of life between the two groups, with compression during 3 weeks or without after sclerotherapy. *This is the only study of the seven to give us the compliance rate and how to hope for better results with compression when you have the same efficacy without compression.* 

In 2010, O'Hare<sup>21</sup> (124 legs) concluded that after foam sclerotherapy, there was no advantage after foam sclerotherapy to compression bandaging (cotton wool to provide extrinsic compression plus 3 layers of bandage, which was covered with a thromboembolus deterrent stocking to hold it in place) for more than 24 hours (vs 5 days) and a thromboembolus deterrent stocking for a remainder of 14 days in both groups. Antiembolism stockings are designed for bedridden patients and do not meet the technical specifications for use by ambulatory patients. In 2011, Hamel Desnos<sup>22</sup> (40 patients) concluded that foam sclerotherapy has a minimal effect on some biological markers (inflammation and coagulation) and the occlusion rate of the veins was 100% with or without posttreatment compression. A moderate increase in D-dimers at day 1 to day 14 was observed in either the compression group or the no compression group.

More recently, in 2019, Cavezzi<sup>23</sup> (94 patients) concluded that compression for 24 hours per day for 7 days with 35 mm Hg versus 25 mm Hg medical compression stockings provided less adverse postoperative symptoms and better tissue healing.

The evidence for the benefit of compression stockings in these randomized controlled trials is equivocal; further studies are needed to be able to make evidence-based recommendations. The main problem of sclerotherapy is not whether or not to wear compression stockings after treatment, but sclerotherapy itself. The guidelines for sclerotherapy treatment exist and should be well known.<sup>2,24</sup>

Phlebology is a real culture in France; the French Society of Phlebology has existed since 1947. The treatment algorithm is now well established and must be followed according to strict rules to avoid under- or overdose reactions. According to the type of vein and its diameter, the results of sclerotherapy will depend on the concentration and the volume of the sclerosing agent injected. The benefits of using sclerotherapy in liquid or foam form, with or without ultrasound control, need to be understood. Minimal training is required. Compression stockings after poorly adapted sclerotherapy treatment will not change the results.

### Deep vein thrombosis and compression

Severe thromboembolic events (proximal DVT, pulmonary embolism) occur very rarely after sclerotherapy. The overall frequency of thromboembolic events is <1%. In 2007, Jia,<sup>25</sup> in a systematic review of foam sclerotherapy for varicose veins (69 studies), found that the median rates of pulmonary embolism and deep vein thrombosis was 0.6%, where most of the DVTs are distal. Most of the cases detected by DUS imaging during routine followup are asymptomatic.

Data on 1605 patients included in the French registry were reviewed with a maximum follow-up of 60 months,

covering 3357 patient-years.<sup>26</sup> Less than 1% of muscular vein thrombosis were observed in patients treated with liquid or foam sclerotherapy.

In Jia's meta-analysis, it is not clear whether or not patients wear their compression stockings, but in most countries they do. It can, therefore, be assumed that less than 1% corresponds to the rate of DVT with compression. In the French study by Guex,<sup>26</sup> they have the same rate, and, in France, most phlebologists do not usually prescribe compression treatment after sclerotherapy.

Thus, it can be hypothesized that the incidence of DVT is the same with or without compression after sclerotherapy. In contrast, the rate of DVT is more related to the use of larger volumes of sclerosant, especially in the form of foam and a maximum volume of 10 mL per session is recommended.<sup>2</sup>

### Edema

The absolute rule should be that, as soon as there is leg edema, even moderate edema, compression should be used. The key word should be edema: edema = compression. Thus, compression is mandatory in the cases of  $C_{3'}$   $C_{4'}$   $C_{5'}$  and  $C_6$  (active venous ulcer), and compression after sclerotherapy is not due to sclerotherapy, but to the disease. In the same way, the wearing of compression stockings in  $C_1$  and  $C_2$  patients with edema of the leg should be encouraged, but not because of sclerotherapy.

A systematic review of compression hosiery for uncomplicated varicose veins found that there is no evidence of an advantage of graduated compression stockings in uncomplicated varicose veins. The published literature was often contradictory and had methodological flaws.<sup>3</sup> For the patients with clinical class  $C_1$  or  $C_2$ , which occur most of the time without leg edema, compression could be prescribed in a reasonable way and never as an obligation that cannot be discussed. Thus, less than one-third of French vascular physicians regularly used elastic compression after sclerotherapy.<sup>27</sup> As there is no convincing evidence for using or not using compression therapy, you should let people feel free to assess whether they are benefiting from it or not. Compression must be a comfort and not a constraint.

### Conclusion

In view of the innocuous nature of elastic compression and its potentially beneficial effects, elastic compression stockings are routinely prescribed. However, a systematic prescription, just in case, is not reasonable. Regardless of the compression, the pressure is not enough to narrow superficial veins on the thigh. Thus, compression after sclerotherapy should not be mandatory, but should be recommended in symptomatic patients and strongly recommended to patients in case of edema. In summary, it is not compression due to sclerotherapy, but due to symptoms.



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