Phlebolymphology

ISSN 1286-0107

Vol 23 • No. 1 • 2016 • P1-56 No. 88

Phlebolymphology

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Aims and Scope

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

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

Phlebolymphology is scientifically supported by a prestigious editorial board.

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

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

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Indexed in EMBASE, Index Copernicus, and Scopus.

ISSN 1286-0107

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Editorial

Lourdes REINA GUTTIEREZ

Dear Readers,

In this new issue, ***Michel Perrin*** *presents the first of two chapters on the updates in operative treatments for primary superficial vein incompetence. In this chapter, the various procedures for varicose vein ablation (endovenous thermal ablation, surgery, chemical ablation, mechanochemical ablation) and their possible complications are described. Endovenous treatment provides an office-based procedure that improves both the postoperative course and convalescence duration.*

For prevention of the postthrombotic syndrome, catheter-directed thrombolysis can be used in acute iliofemoral venous thrombosis with promising long-term results. According to the review by ***Niels Baekgaard*** *and* ***Rikke Broholm****, stenting of all residual obstructive lesions is mandatory. However, these results come from many single-center studies and a few randomized controlled trials. To shorten the treatment duration, the addition of mechanical devices to catheter-directed thrombolysis is currently under investigation.*

Luigi Pascarella *reviews the new pharmacological targets in chronic venous disease and explains the strong link between venous hypertension, valve failure, and venous inflammation. Currently, Daflon is the only drug with evidence for protection against venous inflammation–related damage. The effects of Daflon on microvalves are still unknown, but clearly, this deserves further investigation.*

In 2013, social alarm broke out in Europe after some studies reported a significantly increased risk of venous thromboembolism with the use of oral hormonal contraceptives combining estrogen and a third- or fourth-generation progestin. ***Christian Jamin*** *reviews the results of the earlier studies that have been called into question due to methodological limitations. The article summarizes the recommendations from the official agencies (ie, WHO, FDA, EMA) that reviewed the recent epidemiological studies. They concluded that, although there may be differences in the risk of venous thromboembolism between products with different progestins, the absolute risk is very small and the benefit-risk ratio of all combined contraceptives is positive.*

Marian Simka *reviews the controversy surrounding the association of so-called venous symptoms with chronic venous disease and summarizes the research related to this problem in an attempt to explain conflicting results and interpretations of the studies.*

For the first time, ***Dmitry Lishov*** *and colleagues present the results of the Russian VEIN Act Program, a multicenter, prospective, observational survey designed to assess compliance with nonsurgical treatment for chronic venous disorders. The VEIN Act Program reflects the profile of chronic venous disorders among Russian patients consulting phlebologists and their behavior toward nonoperative treatments.*

Enjoy reading this issue!
Lourdes Reina

An update on operative treatments of primary superficial vein incompetence: part I.

This is the first of two chapters that will comprise the "Update on operative treatments of primary superficial vein incompetence." These two chapters will be published consecutively.

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Abstract

For more than a century, open surgery and liquid sclerotherapy were the only options used for operatively treating primary varices. In the last 20 years, management of primary varices has dramatically changed due to ultrasound investigations and innovative techniques. Development of endovenous treatments, including thermal ablation and/or chemical ablation, has provided a patient-friendly option for an office-based procedure, improving both the postoperative course and convalescence duration. This article will be published in two parts. The first part will describe all the procedures used for treating varices and their possible complications. The second part, which will be published in a later issue, will analyze the outcomes of all procedures for short-, mid-, and long-term follow-up.

Keywords:

ClariVein; cyanoacrylate glue ablation; endovenous laser ablation; radiofrequency ablation; steam ablation; surgery; ultrasound-guided foam sclerotherapy; varices; varicose veins

Preface

The term operative treatment has been intentionally chosen for this article instead of interventional treatment because interventional treatment means any kind of treatment that interferes with the natural history of the disease. For example, both compressive treatments and venoactive drugs modify the natural evolution of primary varicose veins.

Introduction

For a century, ancillary open surgery had the highest recommendation, and subsequently, was the most frequently used procedure for operatively treating varicose veins. In the past decade, the development of minimally invasive endovenous techniques for primary superficial venous reflux has provided a patient-friendly means of treating this disorder as an office-based procedure with ablation of the saphenous veins and tributary varicosities by using radiofrequency ablation, endovenous laser ablation, or sclerotherapy. Sclerotherapy regained favor for two reasons: (i) ultrasound investigation, which provided security for the procedure; and (ii) the use of foam, which enhances the efficacy of the sclerosing

Phlebolymphology. 2016;23(1):3-11

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agent. More recently, new procedures have been used, including steam ablation, ClariVein, laser-assisted foam sclerotherapy, and glue, and these procedures will be described in the present article.

Simultaneously, surgery, including the CHIVA procedure (cure hemodynamique de l'insuffisance veineuse en ambulatoire [conservative ambulatory hemodynamic management of varicose veins]),[1] and more recently, the ASVAL procedure (ablation selective des varices sous anesthésie locale [ambulatory selective vein ablation under local anesthesia]),[2] were developed to preserve the great saphenous vein.

Open surgery without conservation of saphenous trunks

Modern open surgery should be performed under local anesthesia and directed by preoperative ultrasound assessment and skin mapping. Treatment of the great saphenous vein involves flush ligation of the saphenofemoral junction, which is completed using saphenous invagination stripping. Stripping can also be done using a cryoprobe. Treatment of the incompetent small saphenous vein usually involves flush saphenopopliteal junction ligation and stripping by invagination. Nontruncal varicosities can be excised using stab avulsion–powered phlebectomy or they can be treated with sclerotherapy in the same session or later.

Stripping of both the great saphenous vein below the knee and the distal small saphenous vein may reduce varicose vein recurrence, but it is associated with an increased risk of nerve injury.[3] The usefulness of flush ligation was recently called into question after a randomized controlled trial.[4] In addition, there is a consensus for recommending elastic compression stockings for no more than 1 week after the operation.[5,6]

Complications of surgery

The early complications of surgery include discomfort (common), bruising (common), hematoma (rare), bleeding (very rare), lymphatic damage (rare), femoral vein or artery injury (extremely rare),[7] wound infections (2% to 6%), and injury of the saphenous or sural nerve (10%). Symptomatic and asymptomatic deep venous thrombosis and pulmonary embolism following open surgery vary from 0.4% to 5.3% and 0% to 0.5%, respectively.[8,9] The risk of complications, such as venous thromboembolisms, increase with redo surgery and surgery of the small saphenous vein.[8] Modern open surgery under local anesthesia has dramatically lowered the rate of thromboembolic complications. Late complications include permanent nerve damage (5%).[10]

Open surgery with preservation of the saphenous trunk

CHIVA

Due to the possible future use of the great saphenous vein as a vascular graft, it is necessary to preserve the vein.[1] The principle of the CHIVA technique consists of redistributing refluxes from the superficial to the deep system using staged ligations on the great saphenous vein or tributaries. CHIVA is a complex procedure that requires careful mapping and understanding of the anatomy and function of the superficial system by well-trained and experienced physicians who are aware of the shunt classifications.[11]

ASVAL

While CHIVA is based on a descending theory, the ASVAL method is based on an ascending or multifocal approach to the primary varicose veins. In order to improve or suppress the saphenous vein reflux, a stab phlebectomy of incompetent tributaries is performed to remove the distal venous reservoir. Compared with trunk varicose vein ablation, the major advantage of ASVAL is the preservation of the great saphenous vein. After the ASVAL procedure, most patients had less advanced stages of varicose veins.[2]

Endovenous ablation

Endovenous thermal ablation

The term "endovenous thermal ablation" includes radiofrequency ablation, endovenous laser ablation, endovenous steam ablation, and endovenous microwave ablation. In endovenous thermal ablation procedures, ablation of the treated vein is achieved using heat, which is delivered into the vein through a percutaneously placed catheter or probe. The heat causes a direct thermal injury to the vein wall, resulting in destruction of the endothelium, denaturation of collagen in the media, and subsequently, thrombotic and fibrotic occlusion of the vein. Endovenous thermal ablation is performed under local tumescent anesthesia (except for endovenous microwave ablation) to provide anesthesia; protect the perivenous tissue from the heat created by the catheter, probe, or wire when activated; and spasm the vein to obtain the best contact with the heating device. In addition, all endovenous thermal ablation procedures are performed using ultrasound guidance and conducted as an outpatient-based procedure.

For the great saphenous vein, echo-guided vascular access occurs just below the knee (except for endovenous microwave ablation); therefore, heating is done from the groin (2 cm below the saphenofemoral junction) down to the distal part of the vein, usually just below or above the knee. For the small saphenous vein, echo-guided access occurs at the lower one-third of the lower leg, and heating is done from the popliteal fossa (2 cm below the saphenopopliteal junction) down to just above (8 to 10 cm) the tibial malleolus.

Radiofrequency ablation

Introduced in 2007, the current ClosureFAST radiofrequency catheter (VNUS Medical Technologies/Covidien) *(Figures 1 and 2)* is easy to use. The entire pullback time takes 3 to 4 minutes, generating heat around 120°C. Celon RFITT, another radiofrequency ablation system for bipolar radiofrequency-induced closure, is now available (Olympus Medical Systems). This system generates heat at 60 to 85°C and operates with a continuous pullback speed of 1 to 1.4 cm/second.

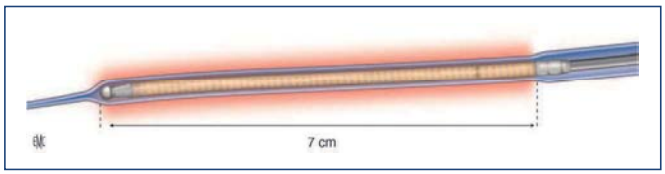


Figure 1. ClosureFAST catheter.*

The first 7 cm (left) of the coated heating element and the thermocouple (right).

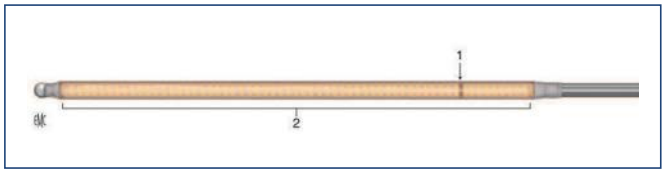


Figure 2. ClosureFAST heater and thermocouple catheter.*

The thermocouple (1) is mounted distally to the heating element (2).

** From Perrin M. Traitement chirurgical endovasculaire des varices des membres inférieurs. Techniques et résultats, EMC (Elsevier Masson SAS, Paris. All rights reserved), Techniques-chirurgicales-chirurgie vasculaire, 43-161-C, 2007.*

Endovenous laser ablation

Fiber lasers can provide either low wavelength beams (810, 940, and 980 nm) or high wavelength beams (1319, 1320, 1470, and 1500 nm). Theoretically, light of lower wavelengths is less specifically absorbed by the chromophores (hemoglobin, water, proteins) compared with the light of higher wavelength lasers.[12] Previously, the fibers were bare tipped, but the new radial fibers are more effective and include the Radial fiber R (Biolitec) *(Figure 3)*, Never-Touch R (Angiodynamics), and Tulip fiber R (Tobric). A continuous withdrawal technique is the current rule and it is recommended to deliver 50 to 70 J/cm of energy.

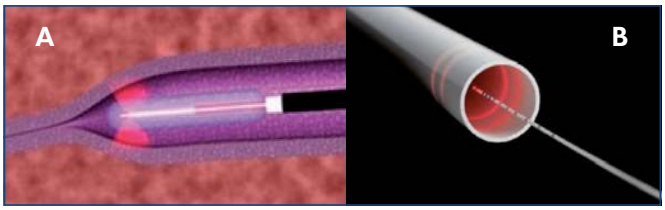


Figure 3. Fiber with radial emission.

Fiber with single radial emission (Panel A) and double radial emission (Panel B).

Radiofrequency ablation vs endovenous laser ablation

Endovenous laser ablation and radiofrequency ablation are similar techniques that treat similar patient profiles. After percutaneous access, the radiofrequency ablation catheter or laser fiber is pushed proximally until the tip is positioned 2 cm from the saphenofemoral junction or saphenopopliteal junction *(Figure 4)*. After tumescent anesthesia, the vein is ablated in a retrograde fashion. The postablation procedures are similar for both techniques.

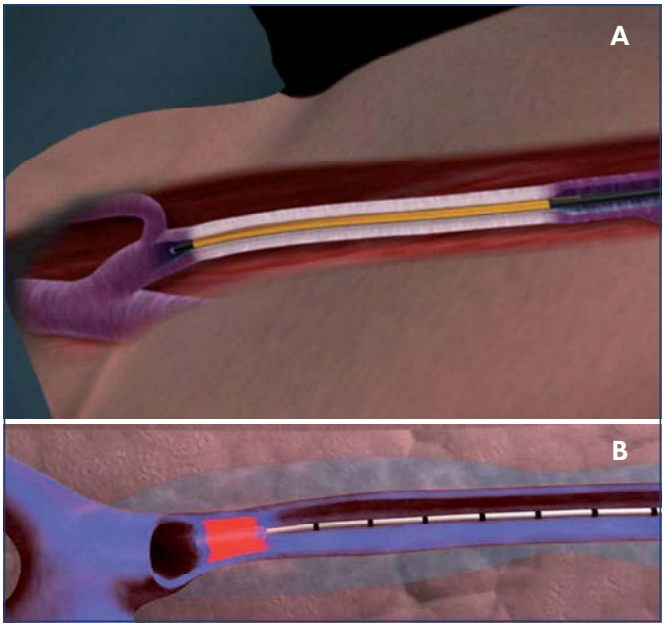


Figure 4. Positioning of the ClosureFAST catheter (A) and the laser fiber (B).

Panel A. The ClosureFAST catheter is positioned 2 cm below the saphenofemoral junction at the beginning of the procedure before generator activation. Panel B. The laser fiber catheter is positioned 2 cm below the saphenofemoral junction at the beginning of the procedure before activation. The veins are colored blue.

Endovenous steam ablation

In 2006, Milleret et al introduced steam as a cheaper alternative to laser and radiofrequency ablation. The principle consists of injecting pulses of water vapor at 120°C in the vein to be ablated, with each pulse delivering 60 J of energy into the lumen. Steam is injected under pressure, whereby the first pulse dislodges the blood and the subsequent ones heat the vein wall. A 5F gauge stainless steel catheter is used because it is flexible enough to navigate through the tortuosity without using a guide wire. Two lateral holes close to the tip eject the steam, avoiding the risk of heating deep veins when heating the junctions.

A comparative animal study by Thomis et al compared steam with either ClosureFAST radiofrequency or a 1470 nm TULIP fiber laser. The three methods generated comparable results regarding scores for low perivenous tissue destruction and high vein wall destruction.[13]

In a pilot study by van den Bos et al, 11 out of the 19 veins treated were completely obliterated at 6 months, with a partial reopening in the other veins. However, the energy delivered was too low, 1 pulse/cm instead of the 2 to 4 pulses/cm that is advised by the manufacturers of the technique.[14] In a series of 75 patients, the complications included a thrombus protrusion in the femoral vein, an ecchymosis at the entry site in 1 patient, and moderate pain lasting 8 days in 6 patients.[15] Subsequently, a randomized controlled trial was designed and it is still ongoing.

Endovenous microwave ablation

After ligation of the saphenofemoral junction, the microwave treating wire is inserted into the great saphenous vein until the medial aspect of the ankle and is guided by the illuminated tip of the wire. The treating wire is withdrawn from distal to proximal at 2 to 4 mm/s, delivering 80 J/cm of energy. In 16.4% of patients, the treating wire could not be passed to the ankle; therefore, it was inserted in the great saphenous vein at a puncture in the ankle and the vein ablation was conducted from groin to ankle. In the same session, all superficial varicose veins and perforators are ablated using short-wire power (10 to 15 W) under ultrasound guidance.[16]

Complications of endovenous thermal ablation

In a review analyzing randomized controlled trials conducted on radiofrequency ablation (317 patients), endovenous laser ablation (1057 patients), and open surgery (975 patients), the short-term complications included venous thromboembolism, wound infection, and paresthesia. There was a significantly higher rate of wound infection for open surgery (2.3%; 95% CI, 1.3%-3.1%) vs endovenous laser ablation (0.5%; 95% CI, 0.3%-1.3%; *P*=0.006), but not between open surgery and radiofrequency ablation (1.5%; 95% CI, 0.4%-3.0%; *P*=0.094). The paresthesia rate was significantly lower with endovenous laser ablation (3.8%; 95% CI, 2.4%-4.5%) compared with radiofrequency ablation (5.2%; 95% CI, 3.1%-7.9%; *P*<0.001) and open surgery (7.4%; 95% CI, 5.3%-8.3%; *P*<0.001). The rate of thrombophlebitis was significantly lower for open surgery (3.0%; 95% CI, 2.9%-4.0%) compared with both radiofrequency ablation (5.5%; 95% CI, 3.0%-7.8%; *P*=0.003) and endovenous laser ablation (5.6%; 95% CI, 4.2%-7.0%; *P*=0.003). Thermal skin burns occurred with equal frequency between radiofrequency ablation and endovenous laser ablation.[17]

A review of radiofrequency ablation complications has been reported and this method has been compared with those of other operative procedures. Early complications include pain, phlebitis (7% to 9.6%), arteriovenous fistula (0.15%), endovenous heat-induced thrombosis (EHIT), deep vein thrombosis (<0.01%), lidocaine toxicity, wound problems (6% to 8%), and skin burns (0.5%). Late complications are mostly transient and may include skin pigmentation (6% to 19%) and nerve damage (4% to 20%).[18] Complications from endovenous laser ablation have also been compiled and include phlebitis (1.87%), skin burns (0.46%), nerve injury (3.08%), arteriovenous fistula (0.15%), endovenous heat-induced thrombosis, and deep venous thrombosis (0.27%).[19]

Only one multicenter trial has reported the outcomes of endovenous steam ablation (n=117). Postprocedural pain was lower in endovenous steam ablation compared with endovenous laser ablation. Other outcomes included thrombophlebitis (9.2%), nerve injury (0.9%), and hyperpigmentation (4.6%), but no deep vein thrombosis or skin burns were identified.[20] Complications after endovenous microwave ablation have been reported in a single-center study, where endovenous microwave ablation was responsible for skin burns related to ablation of subcutaneous tributaries (10.2%).[16]

Chemical ablation

Sclerotherapy

Sclerotherapy refers to the introduction of a foreign substance into the lumen of a venous vessel to damage the

venous wall and occlude the vessel. Liquid sclerotherapy has been used primarily for obliteration of spider veins. However, interest in using sclerotherapy for telangiectasia and varicose veins significantly increased in 1995 when Cabrera et al reported that foam, prepared by mixing gas with the detergent polidocanol, was effective for obstruction of larger veins.[21] The use of ultrasound-guided foam sclerotherapy has rapidly spread for the treatment of primary and recurrent varicose veins, including the great saphenous vein, small saphenous vein, saphenous tributaries, and perforating veins.

Sclerosing agents

The mechanism of action for sclerosing agents includes destruction of venous endothelial cells, exposure of subendothelial collagen fibers, and ultimately, the formation of a fibrotic obstruction. Delivery of the solution as a foam prolongs the contact time and amplifies the effect of the chemical substance. For producing endothelial injury, sclerosing solutions can be classified into three categories: detergent, osmotic, or chemical irritant.

In Europe, approved agents for sclerotherapy include sodium tetradecyl sulfate, polidocanol, morrhuate sodium, hypertonic saline, and glycerin.

- Sodium tetradecyl sulfate is a detergent that destroys the endothelium by denaturation of the cell surface proteins. The solution is safe and painless when injected. When the solution is injected at higher concentrations, extravasation may result in tissue necrosis. Hyperpigmentation, matting, and allergic reactions have been described, but rarely occurred. Generating foam with a sodium tetradecyl sulfate agent is easy.

- Polidocanol is another detergent that is safe and painless when injected and has a low risk of tissue necrosis when used at low concentrations. It may cause hyperpigmentation, but has a very low rate of allergic or anaphylactic reactions. There is a consensus that polidocanol has fewer overall complications compared with sodium tetradecyl sulfate.

- Sodium morrhuate is a detergent that is used less frequently due to a relatively higher incidence of skin necrosis observed with extravasation and a higher risk of anaphylactic reactions within a few minutes after injection.

- Glycerin is a chemical irritant that destroys the cell surface proteins by affecting chemical bonds. Chromated glycerin is frequently used as a solution of glycerin, sterile water, and benzyl alcohol. Chromated glycerin is safe and rarely leads to tissue necrosis, hyperpigmentation, or allergies, but frequently there is local pain at the injection site. This treatment is particularly suitable for treating small veins or telangiectasia.

- Hypertonic saline, an osmotic agent, is a weak sclerosing agent that causes dehydration of endothelial cells through osmosis, which leads to endothelial cell death. Burning pain is frequent during injection. Extravasation may cause skin ulcers and tissue necrosis.

Liquid sclerotherapy

Liquid sclerotherapy is currently used for treating reticular veins and telangiectasia.

Foam sclerotherapy

Due to the enhanced sclerosing properties of foam, ultrasound-guided foam sclerotherapy has been shown to be more effective than liquid sclerotherapy, Tessari et al used a three-way stopcock connected to two syringes to produce foam and they developed the most popular technique used today.[22] Other techniques for producing foam involve a two-way female-to-female connector.

Experts recommend a ratio of 1 part sodium tetradecyl sulfate or polidocanol to 4 or 5 parts air. Mixing the drug with air using the two syringes and pushing the mixture from one syringe into the other 20 times results in an approximate bubble size of <100 μm. Coleridge Smith advises puncturing the veins in supine patients and then elevating the limb 30 degrees to inject the foam.[23] Ultrasonography is used to monitor the movement of foam in the veins. The saphenous vein is injected first, followed by varicose and perforating veins, if indicated. A maximum of 10 mL of foam is injected during one session. The procedure is completed by placing a short-stretch bandage or a 30 to 40 mm Hg graduated compression stocking on the limb. Most experts recommend 1 to 2 weeks of compression.

Severe complications of ultrasound-guided foam sclerotherapy comprise anaphylaxis (extremely rare), large tissue necrosis (extremely rare), stroke and transient ischemic attack (extremely rare), distal deep venous thrombosis (very rare), pulmonary embolism (extremely rare), and

motor nerve injury (extremely rare). Benign complications are visual disturbances (uncommon), headaches and migraines (uncommon), sensory nerve injury (rare), chest tightness (very rare), dry cough (very rare), superficial thrombophlebitis (unclear), skin reaction (very rare), matting (common), residual pigmentation (common), minimal skin necrosis (very rare), and embolia cutis medicamentosa (very rare).

The complications are listed in the European guidelines for sclerotherapy in chronic venous disorders, along with recommendations to avoid and manage these complications. Ultrasound-guided foam sclerotherapy of the saphenous vein is the least invasive of the endovenous ablation techniques. In 2008, the European Consensus Meeting on Foam Sclerotherapy reported that foam was an effective, safe, and minimally invasive endovenous treatment for varicose veins with a low rate of complications.[24] The most complete book on sclerotherapy was written by a team of editors in 2007.[25]

Cyanoacrylate glue ablation

A new nonablative procedure that intravenously delivers a cyanoacrylate adhesive mixture has been developed to improve some of the limitations of radiofrequency ablation, endovenous laser ablation, and sclerotherapy ablation. Upon intravascular injection, the cyanoacrylate adhesive rapidly solidifies via a polymerization reaction and results in an inflammatory reaction in the vein wall.

The disposable Sapheon Closure System includes 4 mL of Sapheon Cyanoacrylate Adhesive and a Sapheon delivery system *(Figure 5)*. The Sapheon delivery system consists of a 7F-introducer sheath/dilator, a 5F-delivery catheter, a 3 mL syringe, and a dispenser gun. The hydrophobic 5F-delivery catheter has a novel configuration with air-filled microchannels to enhance sonographic visibility. The dispenser gun will deliver 0.08 to 0.16 mL of Sapheon Cyanoacrylate Adhesive with each trigger pull. Access to the great saphenous vein is achieved by applying the Seldinger technique, which uses a standard micropuncture kit under ultrasound localization. The Sapheon introducer sheath and dilator is advanced to the saphenofemoral junction over a 0.035 J guide wire.[26] The cyanoacrylate adhesive is extracted from its glass vial and loaded into a syringe, which is then attached to the 5F delivery catheter. The combined syringe and catheter are connected to a dispenser gun. The catheter is then primed by advancing the glue with the dispenser gun to within 3 cm of the catheter tip. To prevent thrombus extension through the saphenofemoral junction, the hydrophobic delivery catheter is placed approximately 5 cm below the saphenofemoral junction. The saphenofemoral junction is manually compressed with the ultrasound transducer and the proprietary adhesive is delivered using the Sapheon delivery system using two injections at 1 cm intervals. Compression of the saphenofemoral junction and the delivery site is maintained for 3 minutes. The adhesive is delivered at 3 cm intervals through the remainder of the target vein using 30 seconds of compression for each subsequent delivery of adhesive *(Figure 6)*. The last injection site is 2 to 4 cm from the entrance site to prevent the glue from migrating outside the vein. After venous closure is confirmed by ultrasound imaging, the catheter is removed and compression is applied to the catheter entry site until hemostasis is achieved. A single adhesive bandage is applied; neither compression stockings nor compression bandages are used. This protocol has been described in details in two articles.[26,27] Postoperative complications were minimal.

Almeida et al reported a series of 38 patients treated for great saphenous vein incompetence. Postoperative side effects included a thread-like thrombus or glue extension

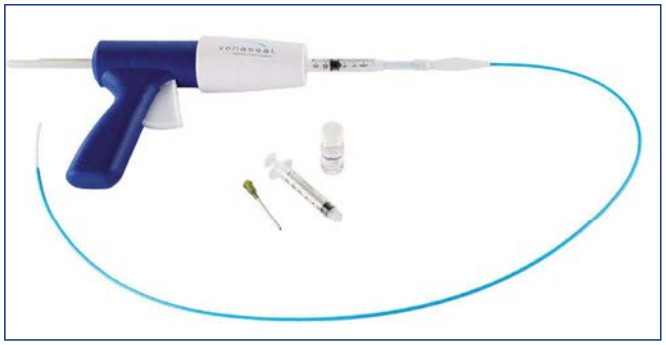


Figure 5. Sapheon kit that includes the Sapheon delivery system and the Sapheon cyanoacrylate adhesive flask.

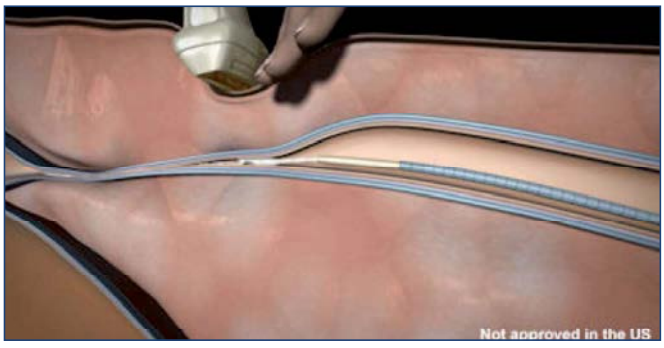


Figure 6. Compression of the treated vein using an ultrasound transducer above the catheter and injected glue.

across the saphenofemoral junction (21.1%), which resolved at 3 months, transient thrombophlebitis (16%), and hyperpigmentation (2.4%).[28] In another series including 43 great saphenous veins and 22 small saphenous veins, thrombophlebitis of the great saphenous vein occurred 4 times.[26] The primary potential advantage with this new technique is that it does not require tumescent anesthesia and patients do not need postoperative compression stockings.

Mechanochemical ablation

Recently, a new hybrid mechanochemical device (ClariVein) has been developed. Mechanochemical endovenous ablation (MOCA) achieves venous occlusion by utilizing a wire within the lumen of the vein that rotates at 3500 rpm, which abrades the intima and causes venospasms, thereby increasing the efficacy of the sclerosant *(Figures 7 and 8)*. A liquid sclerosant (sodium tetradecyl sulfate or polidocanol) is concomitantly infused through an opening close to the distal end of the catheter near the rotating wire. These two modalities–mechanical and chemical–achieve venous occlusion results equal to endothermal methods. The system includes an infusion catheter, motor drive, stopcock, and syringe. The dispersion wire extends through the catheter lumen and it is connected to an interface cartridge unit for connection to the 9V DC battery of the motorized handle unit on the proximal end, which controls wire rotation. The handle unit also provides a grip and syringe holder to facilitate physician-controlled infusion. The wire and the catheter sheath are inserted percutaneously into the vein under site anesthesia while the patient is in a reversed Trendelenburg position. The catheter sheath is retracted to expose the wire tip, which is positioned 2 cm from the saphenofemoral junction. The patient is then rotated into a flat position for the remainder of the procedure. The catheter motor is turned on and the catheter is pulled down the vein at a rate of approximately 1 to 2 mm/second, while the wire rotates and the sclerosing agent is infused. After removal of the catheter, occlusion of the great saphenous vein and patency of the common femoral vein is checked by duplex ultrasound.

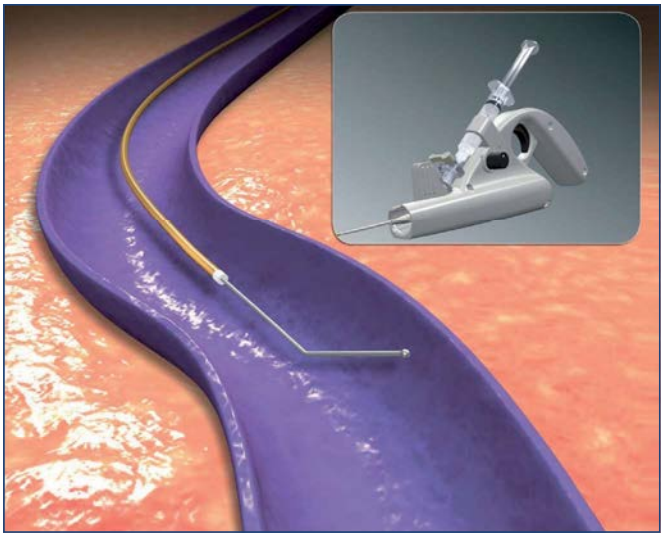


Figure 7. The vein lumen was catheterized using the ClariVein rotating wire.

Figure 8. The ClariVein rotating wire abrades the vein wall, while the sclerosing agent is infused through the catheter opening.

The advantages of this hybrid system are claimed to be standard percutaneous access, endovenous treatment, local anesthesia only (without the need for tumescent anesthesia), and short procedure time. Since the system does not use thermal energy, the potential for nerve damage is minimized. Compression is applied for 2 weeks without restricting the patient's activity.[29]

In a small series of 25 patients presenting with great saphenous vein incompetence, minor postoperative complications were identified, including localized ecchymosis at the puncture site in 9 patients and transient thrombophlebitis of distal tributaries in 4 patients.[30] In a series of 50 patients presenting with small saphenous vein incompetence, minor postoperative complications were identified, including localized ecchymosis induration around the puncture site (12%) and transient thrombophlebitis of the treated vein (14%).[31]

Pelvic and ovarian vein embolization

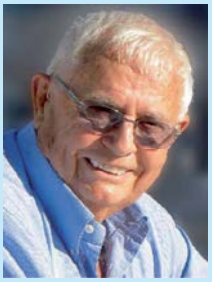
When varicose veins are fed by incompetent pelvic and ovarian veins through the pelvic floor, which may or may not be related to left renal or iliac vein compression,

embolization of the refluxive veins by coils and sclerosing agents is a minimally invasive method. Nevertheless, when reflux is related to iliac vein compression iliac stenting, another noninvasive technique, is the first-line treatment.[32,33]

Conclusions

Currently, there are a number of surgical options for treating varicose veins, but there is no definitive system for identifying which people will benefit the most from interventional treatment and no established framework for the diagnosis and management of varicose veins. Conversely, perioperative investigations are well stated and described. In a review of the randomized controlled trials on the treatment of varicose veins, the authors concluded that there are many treatment options available for the ablation of varicose veins, not solely thermal ablation.[34,35]

Part II of the present article will describe the outcomes of the various procedures for varicose vein ablation, the guidelines that have been recently established, and the tentative recommendations for the use of endovenous techniques.



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The history of catheter-directed thrombolysis of deep venous thrombosis

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Keywords:

catheter-directed thrombolysis; iliofemoral deep venous thrombosis; pharmacomechanical thrombolysis

Phlebolymphology. 2016;23(1):12-19

www.phlebolymphology.org

Abstract

Catheter-directed thrombolysis (CDT) is a relatively new treatment modality that actively removes a venous thrombosis. CDT has been chiefly practiced for acute iliofemoral deep venous thrombosis because this vein segment has a poor rate of spontaneous recanalization compared with more distal vein segments. This can be explained by the frequent occurrence of the May-Thurner syndrome (also known as Cockett's syndrome or iliac vein compression syndrome), which was described more than 50 years ago. CDT works with different guide-wires, catheters, and delivery systems to allow a stenting procedure for any residual iliac obstruction that remains after thrombolysis. CDT is a simple technique that, with the right inclusion and exclusion criteria, can obtain results superior to conventional treatment with anticoagulation and compression stockings and reduces the development of postthrombotic syndrome. These results are based on many single-center studies and a few randomized controlled trials. CDT has been modified over the years with a combination of mechanical devices to shorten the treatment time from days to hours. The main purpose of this review is to describe the development of the basic method of CDT and provide general considerations for completing this intrathrombus-removal strategy.

Introduction

Thrombolysis, as a method for removing deep venous thrombosis (DVT), has been used for many years; first it was systemically used, even in the trials against anticoagulation.[1,2] Thrombolysis had serious side effects and resulted in inadequate restoration of the iliac lumen; however, it was better than anticoagulation. Without a doubt, the next step was to administer thrombolysis into the thrombus area (ie, regional thrombolysis) by injecting the solution into the pedal vein; however, no further benefit was observed.[3] After these attempts, with suboptimal results, it was logical to deliver the lytic fluid directly into the thrombus itself. Catheter-directed thrombolysis was defined and described for the first time by Okrent et al in a case story from 1991,[4] and seems to be an extremely logical strategy for intrathrombus removal. CDT requires guide wires, catheters, delivery systems, and stenting procedures to treat uncovered persistent obstructive iliac lesions.

Stenting is the most conspicuous advantage in working with the wire-systems. Many studies have addressed CDT in the "pure form," and later, in combination with techniques using mechanical devices and aspiration to speed up the treatment time. This paper will address many aspects of basic CDT and highlight the most important results with recommendations based on the existing literature. The article will follow the terms, which are recommended as reporting standards.[5]

Why use catheter-directed thrombolysis?

The rationale for CDT is the lack of sufficient recanalization after DVT, which leads to obstruction, as either occlusion or stenosis, and is sometimes found in combination with valve incompetence. The femoral vein segments are able to recanalize in 80% of cases after 3 months, but the iliofemoral outflow tract will, especially on the left side, only recanalize in 20% to 25% of cases.[6] The consequences are pathophysiological changes that include ambulatory venous hypertension and postthrombotic syndrome, where the later occurs more frequently after iliofemoral DVT and accounts for almost 50% of cases.[6,7] According to the definition, the iliofemoral segment includes the common femoral vein, external iliac vein, and common iliac vein.[5] Obstruction of these vein segments will negatively influence the outflow. Fortunately, iliofemoral DVT is only a minor part of the total DVT population, but is observed in one-quarter to one-third of the patients.[8] CDT may overcome the problem of DVT, which seriously affects health and quality of life.[9]

Which patients can be considered for catheter-directed thrombolysis?

Only a small set of patients with iliofemoral DVT can be considered for CDT. Patients excluded from CDT due to a higher risk of bleeding include patients with severe hypertension, hepatic insufficiency, renal insufficiency, bleeding disorders, previous cerebral hemorrhage, surgery within the last 7 to 10 days, pregnancy, delivery within the last 7 days, and an international normalized ratio (INR) >2.[5,10] The most debated criterion is whether CDT is suitable for patients with DVT and cancer. Most studies have excluded patients with active cancer due to a risk of bleeding and rethombosis, but have accepted patients that have been cured of cancer or have been cancer free for at least 1 to 2 years. Another questionable issue is the duration of symptoms. Based on a few animal experiments and duplex findings, it seems that thrombus material may probably irreversibly damage the vein wall after 2 weeks, leading to chronic changes.[11] Several international guidelines highlight that the maximum efficacy for CDT occurs within the time limit of 2 weeks.[12,13]

What are the pharmacological principles involved in catheter-directed thrombolysis?

The direct pathway to degrade the fibrin component of a thrombus occurs via proteolytic cleavage of plasminogen to plasmin. An increase in D-dimer, a fibrin degradation product, signals that fibrin has been degraded. Several plasminogen activators are known, including streptokinase, urokinase, and recombinant human tissue-type plasminogen activator (rt-PA). Previously, streptokinase was systemically administered, but it was abandoned due to massive allergic reactions and side effects. Urokinase is still used, but rt-PA is the most utilized fibrinolytic drug with the shortest half-life (≈5 minutes) *(Figure 1)*. The clearance of rt-PA is more than 90% effective in the first pass via the liver. In 2004, a study compared rt-PA (0.5 mg/hour) with urokinase (120 000 U/hour) in CDT and no differences were observed concerning infusion time, success rate, and complication rate, but rt-PA was less expensive.[14]

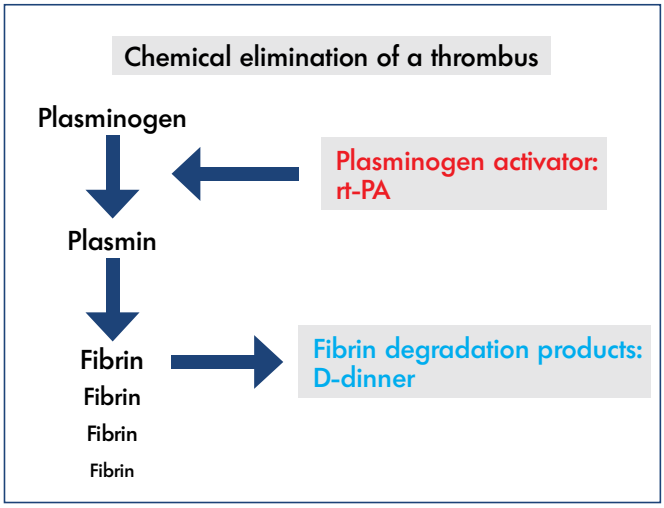


Figure 1. Degradation of the fibrin component of a thrombus to eliminate the thrombus.

May-Thurner Syndrome

Understanding the May-Thurner syndrome (also known as Cockett's syndrome or iliac vein compression syndrome) is necessary before describing CDT. In 1957, May and

Thurner (both from Austria) published the results of a large-scale study that described how the right common iliac artery compresses the left common iliac vein against the fifth lumbar vertebra.[15] They investigated cadavers and embryos and the findings were analyzed 10 years later by Cockett et al related to a possible explanation for DVT.[16] In later studies, iliac compression was diagnosed using computed tomographic venography, and 66% of "normal" subjects had a >25% reduction in the vein lumen and this was more predominant in females.[17] Often the iliac vein is widened and flattened with translucency to be seen on an image *(Figure 2 and 3)*. Patients with left-sided iliofemoral DVT revealed compression in 74% of cases compared with only 28% in a control group (P=0.05),[18] and one-half to two-thirds of these patients had perivenous fibrosis, causing webs and spurs inside the thrombus lumen due to repetitive mechanical compression and arterial pulsations.[19]

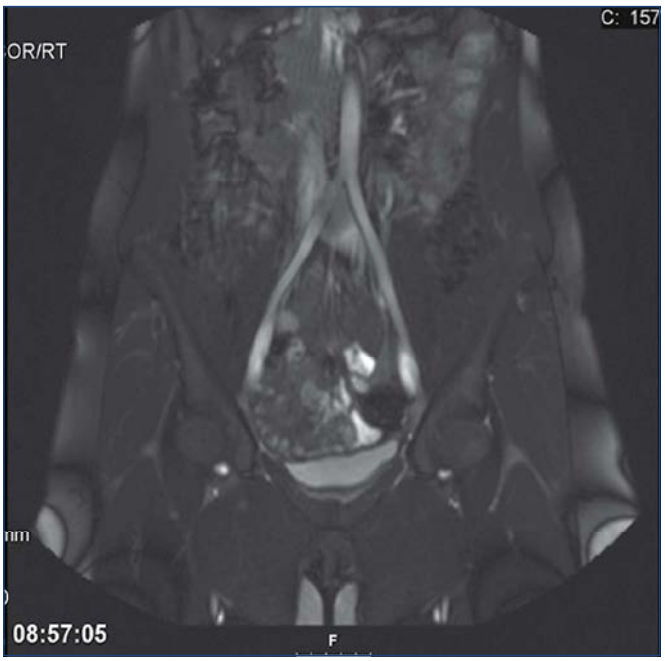


Figure 2. May-Thurner syndrome.

Illustration of the translucency and widened left common iliac vein due to the compression from the right common iliac artery using magnetic resonance venography.

From reference 25: Bækgaard et al. Phlebology. 2014;29(suppl 1):118-118. © 2014, SAGE Publications.

In addition, compression can sometimes occur along the entire length of the iliac vein, both the left and right side. Collateral veins can be seen depending on the grade of obstruction. It is believed that the DVT process originates in the diseased iliac vein and propagates in a descending direction, resulting in a fully occluded vein segment. In the initial DVT process, no collateral veins are seen. During thrombolysis, the previously created and now thrombosed collaterals can be cleared and a preexisting obstruction is then documented.

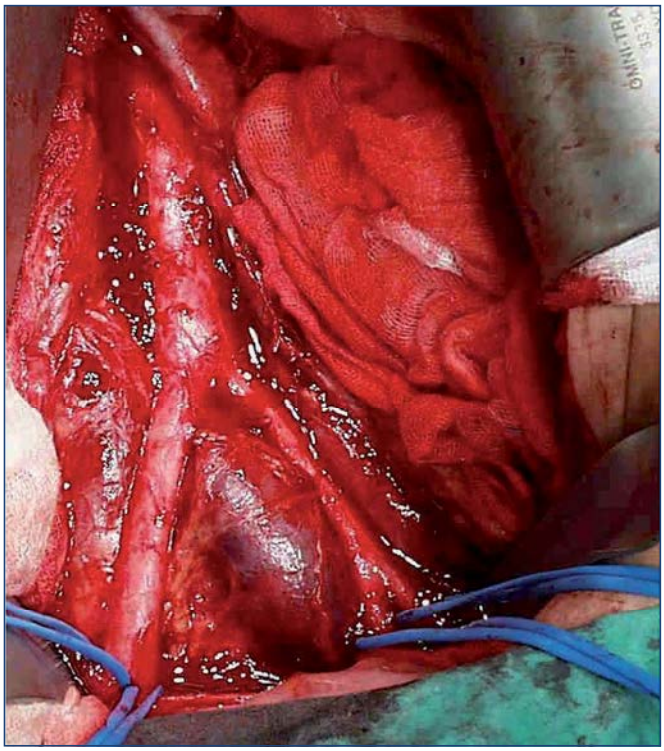


Figure 3. Iliac vein compression seen from the outside.

From reference 25: Bækgaard et al. Phlebology. 2014;29(suppl 1):118-118. © 2014, SAGE Publications.

Technique of catheter-directed thrombolysis

After diagnosing DVT using duplex ultrasonography, computed tomographic venography, or magnetic resonance venography, an access for puncture has to be chosen. An open popliteal vein is the most commonly used access site, and the puncture is performed using a micropuncture technique in the prone position under local anesthesia and with ultrasound guidance. The distal posterior tibial vein at the ankle can be used in the event of crural involvement as well. A publication has used the popliteal access, even with a concomitant thrombosis in this vein or more distally, and the follow-up revealed a patent popliteal vein in 90% of cases after 8 months.[20] Different lengths of sheaths could be inserted at this point. A hydrophilic guide-wire is manipulated through the thrombus and can sometimes be used with a looping technique, especially in the area of the occlusive lesion at the iliac level. During the procedure, fluoroscopy and repeated venograms in several planes are necessary to secure the right intraluminal placement with

a final destination in the inferior vena cava or at least in a thrombus-free vein segment. Different guide wires, with a higher or lower stiffness, can be used and is user dependent. In special cases, it is possible to use a contralateral femoral and jugular access. A daily venogram control is necessary to monitor the treatment and to reposition the thrombolysis catheter, if necessary.

Thrombolytic composition and thrombolysis procedure

For thrombolysis, five components are important and include: (i) thrombolytic drug choice; (ii) heparin; (iii) volume of the infusion; (iv) type of infusion; and (v) intermittent pneumatic compression. The thrombolytic drug with the highest recommendation is rt-PA due to its short half-life (≈5 minutes), which is essential when bleeding occurs. The short half-life means that when the infusion is stopped, further influence of the drug is neutralized immediately. With reference to arterial thrombolysis, an older recommendation suggests using 1 to 2 mg rt-PA per hour daily.[21] In Copenhagen, 1.2 mg rt-PA per hour is used without an upper total limit.[10] The large-scale ATTRACT trial (Acute venous Thrombosis: Thrombus Removal with Adjunctive Catheter-directed Thrombolysis) set the maximal dose at 35 mg.[22]

The infusion acts optimally in combination with heparin as either unfractionated heparin or low-molecular-weight heparin to keep the lysed vein segments open. The dose of unfractionated heparin was adjusted to keep the activated partial thromboplastin time (aPTT) between 50 and 60 seconds, and upwards of 90 seconds.[10,23] A weight-adjusted dose of low-molecular-weight heparin is given according to general recommendations. A continuous drip-infusion can be used[23]; however, the pulse-spray technique using a multiple side-hole catheter with tip occlusion seems to be more efficient, suggesting that there is a mechanical effect on the thrombus.[10] The total amount of infusion liquid can be up to 3 L per day.[10] Use of intermittent pneumatic compression on the legs is recommended based on a Japanese randomized controlled trial,[24] as it was shown to facilitate inflow, probably by increasing endogenous fibrinolytic activity.

Stenting

Unlike arteries, veins react differently to stenting, as veins tolerate extensive dilations without rupturing, and despite extrinsic compression, the affected vein wall retains some elasticity. Therefore, any uncovered obstructive lesions after thrombolysis in the iliac vein segment must be dilated and stented with self-expandable stents. Balloon angioplasty alone is insufficient due to relapse or recoiling of the vein

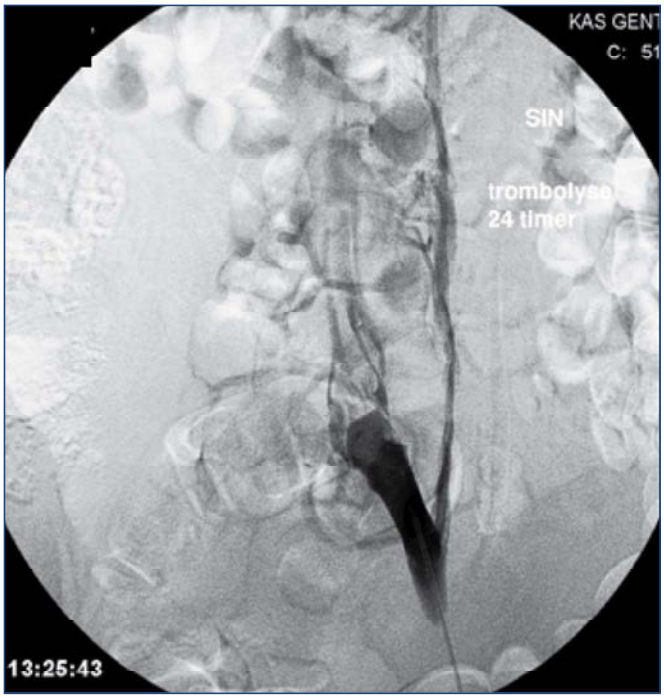


Figure 4. Persistent obstruction after CDT.

All thrombus material has been removed, but the obstruction has to be stented.

Abbreviations: CDT, catheter-directed thrombolysis

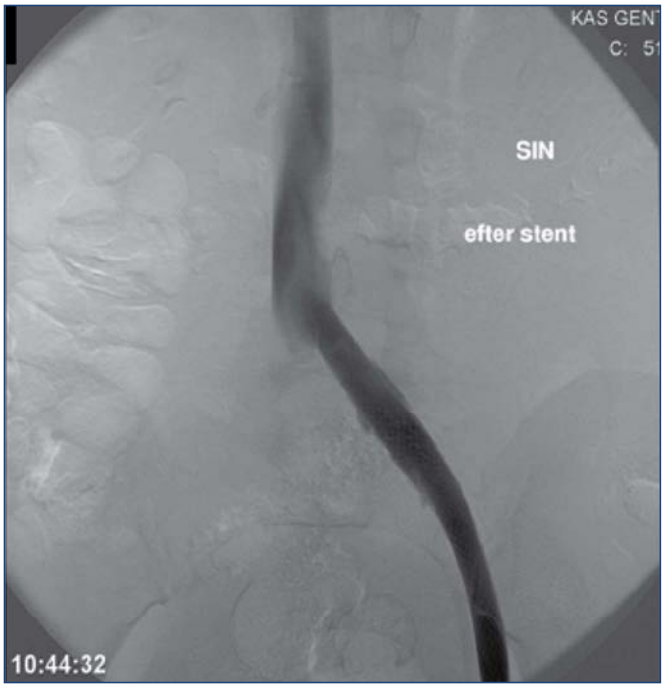


Figure 5. A successfully placed stent.

wall, but pre- and postdilatation is necessary in combination with stenting. Kissing stents are not necessary in the iliac confluence unless both veins are affected. Success criteria after CDT and stent insertion include an unobstructed vein with spontaneous flow (rapid clearance of contrast medium) and disappearance of collateral veins *(Figures 4 and 5)*.[25]

The most commonly used stent has been the Wallstent (Boston Scientific, Inc), which was originally constructed for the arterial system. The stent is characterized by pronounced radial force, but without sufficient flexible properties after insertion. One disadvantage of the Wallstent is shortening during placement due to its braided construction. This stent is the only stent made of stainless steel, as other stents are made of nitinol with a closed-cell design developed for sufficient attachment to the vein wall.[25] New stent designs with an open-cell structure have emerged, demonstrating more flexibility, while maintaining a high radial force suitable for the curved iliac vein, especially on the left side. Several designs are currently being tested. The rate of stenting varies. CDT with a treatment duration of a couple of days has been associated with a stenting rate of 50% to 60%, but much lower rates have been reported.[23,26]

Intravascular ultrasound

Intravascular ultrasound has not found its place in CDT compared with its recommended use in chronic venous disease. A possible explanation may be due to the remaining obstructive changes in the iliac vein segment that often have a shorter extension in patients with iliofemoral DVT. Therefore, it may be easier to visualize the length of the diseased vein segment using multiplane venograms. Only one publication has used intravascular ultrasound to identify residual thrombus, resulting in continued CDT.[27] Another paper had previously shown that residual thrombus is associated with an increased risk of postthrombotic syndrome.[28]

Inferior vena cava filter

The use of an inferior vena cava filter (Günther Temporary Vena Cava Filter, Cook Medical) during CDT has been described mostly for cases where a floating thrombus was identified in the inferior vena cava.[23,26] The value of protecting against pulmonary emboli has often been questioned, as insertion and withdrawal of the filter can be accompanied by additional difficulties and problems. If inserted, the filter must be removed immediately after the CDT procedure. A forgotten filter itself can cause an occluding thrombosis in the inferior vena cava, and a few groups have successfully stented such occlusions.[29] Due to these concerns, prophylactic inferior vena cava filter placement is not routinely performed.[5]

Complications

Very few fatal episodes have been published.[30] The most frequent complication is either major or minor bleeding. Minor bleeding can be managed with simple compression at the puncture site, sheath upsizing, or dose alteration.[5] Major bleeding is defined as intracranial bleeding or bleeding severe enough to result in death, surgery, cessation of therapy, or blood transfusion. The frequency of minor bleeding episodes seldom exceeds 10% to 20%, whereas the frequency of major bleeding episodes varies in the literature, but normally does not surpass more than a few percent.[31] During CDT, transient hematuria is frequent and pulmonary emboli are rare.[26]

Biochemical monitoring

Due to fibrinolysis, D-dimer will increase during CDT. A significant increase in D-dimer indicates a new and large thrombus, whereas a minor increase may indicate an older thrombus. During our experiences in Copenhagen, we measured the levels of D-dimer daily during treatment, and successful treatment was defined as a continuous decline in D-dimer levels. In patients with a restored lumen on a venogram, but whose levels of D-dimer were still elevated, we continued the lytic infusion for another 6 hours, which successfully eliminated the thrombus. We have not published separate data on this strategy, but it has been incorporated in the results.[26] However, there is a new publication presenting results on this specific monitoring tool. D-dimer above 18.4 µg/mL at the 12 hours had a high predictive rate of more than 50 % lysis at the end of CDT in 24 patients.[32]

A marked decrease in fibrinogen and hemoglobin may indicate a risk of bleeding or actual bleeding and requires a careful physical examination. The greatest risk of bleeding occurs during the final stage of CDT when the lumen is restored to an almost normal state, with more run-off from the infusion.

Posttreatment and follow-up

It is recommended to use compression stockings (up to 2 years) and anticoagulation therapy (6 to 12 months) after

CDT without any evidence of recurrence. In some studies, patients with severe thrombophilia, which is observed five times more frequently in patients with thrombi, are kept on life-long anticoagulation therapy. To monitor these patients properly, a close follow-up is necessary to identify patients who need a reintervention and to determine patency, valve function, the clinical, etiological, anatomical, and physiological (CEAP) score, and signs of postthrombotic syndrome. An assessment of the patient's health-related quality of life is recommended.[10,23]

Results and discussion

The first review on CDT was published in 1998 after collecting 15 studies with 263 patients with iliofemoral DVT.[33] Many valuable conclusions were drawn from this review. Short-term success varied from 68% to 100%, even without knowing the exact meaning of success. Patients with clots older than 4 weeks had inferior results compared with patients with younger clots. Blood transfusion was only required in 5% of patients. Inferior vena cava filters were used in 49 patients, of which 31 were retrievable filters. Only a minority of patients were stented, 1 patient died, and only 2 patients had a nonfatal pulmonary embolism.

Until now, the largest study conducted was a multicenter venous registry from the US in 1999.[30] A total of 221 patients with iliofemoral DVT were treated. Urokinase was used as the lytic agent, duration of symptoms before treatment was accepted for up to 3 weeks, and almost one-third had a previous DVT. Stenting was done when needed and accounted for one-third of patients. The mortality rate was <1%. The most important result from this study was that iliac patency was significantly superior 1 year after stenting compared with the group of patients without stenting (74% vs 53%, *P*=0.001), meaning that stenting positively influenced the outcome after CDT. Another lesson learned was the disappointing results after stenting of the femoral vein, which has been abandoned ever since.

Only two randomized controlled trials have been published. One included only a small number of patients, and the results showed an advantage of CDT vs anticoagulation.[34] To date, the second trial from Oslo–the CaVenT study (Catheter-directed Venous thrombolysis in acute iliofemoral vein Thrombosis)–is the most comprehensive randomized controlled trial on CDT. A total of 90 patients were randomized to CDT and 99 patients to anticoagulation.[35] The occurrence of postthrombotic syndrome was significantly lower in the CDT group compared with the anticoagulation group (*P*=0.047), but quality of life was equal in both groups after 2 years. The results were less favorable than expected. Several factors might explain these results: (i) only half of the included patients had iliac involvement; (ii) symptom duration before treatment was tolerated up to 3 weeks; (iii) the iliac stenting rate was only 17%; and (iv) balloon angioplasty was performed in some cases. This study demonstrated the importance of using strict inclusion criteria, especially the involvement of the pelvic vein segment, which will benefit from CDT, including a sufficient rate of stenting without balloon expansion alone.[36]

In 2010, we reported on 103 lower extremities, which were diagnosed for the first time with iliofemoral DVT and were treated using a pulse-spray infusion technique with 1.2 mg rt-PA per hour, 120 mL infusion volume per hour, and intermittent pneumatic compression during treatment.[26] More than 50% of the patients had stenting mostly on the left side (84%). The treatment time was 2.5 days on average. Kaplan-Meier analysis showed that 82% had competent veins (patent veins in the entire treated segment, including normal valve function) at 6 years with a median follow-up of 52 months. A total of 16% of the patients had postthrombotic syndrome (half of which were mild) after a median follow-up of 71 months.[9] The technique has also been successfully used for patients with inferior vena cava atresia and DVT in the pelvic area.[37]

Residual thrombus material after CDT is a predictor of an increased rate of postthrombotic syndrome, as was shown in a single-center study.[28] This observation was highlighted in the CaVenT study. Both reflux and lack of patency at 6 months were independent predictors for development of postthrombotic syndrome after 24 months.[38] The authors of this study are in support of the "open vein hypothesis," which states that effective removal of an acute venous thrombus will reduce the risk of postthrombotic syndrome. Another issue is the fact that the Villalta score, a global score system for determining the severity of postthrombotic syndrome, may overestimate symptoms from the superficial system and underestimate symptoms, such as venous claudication, caused by pelvic venous obstruction. Furthermore, quality of life score systems cannot sufficiently identify or estimate outcomes.

A meta-analysis on four studies (some of which have been mentioned above) from 2012 concluded that there is a significant increase in patency (risk ratio, 0.38; 95% CI,

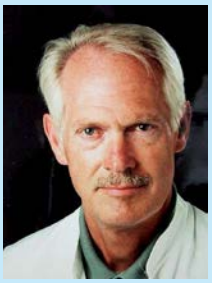
0.18-0.37) after CDT combined with stenting.[39] It strengthens the necessity for reporting on the restoration and function of the venous anatomy after CDT.

Catheter-directed thrombolysis combined with other treatment modalities

A criticism against CDT has been the length of treatment time, which is mostly because patients in many countries had to be placed in the intensive care unit with a considerable increase in cost. In Copenhagen, patients are treated in the ordinary ward with dedicated nurses.[26] One reason for adding "mechanical" devices to CDT is the desire for a more rapid treatment in general. Two very different methods are available–suction and ultrasound enhanced CDT. The suction method uses the Venturi effect to create a backward jet stream, but it can also be performed with a simple syringe technique. The other method has the purpose to create permeability of the thrombus.[40-42] In addition to the shorter treatment time, a positive consequence is that a lower amount of lytic infusion is required; therefore, reducing the risk for bleeding, which is essential for many patients, eg, cancer patients. However, it seems that the rate of stenting is higher using shorter treatment times, which must be addressed in the future. Newly designed stents demand great durability, in patency and physical properties, concerning possible kinking, migration, and fracture.

Conclusion

CDT is a very simple technique. The optimal patients to treat are those with acute iliofemoral DVT. Optimal treatment involves using rt-PA combined with heparin in a high-volume infusion per hour and intermittent pneumatic compression. Biochemical control and daily multiplane venograms, with stenting of all residual obstructive lesions, even minor lesions, is mandatory. Intravascular ultrasound may also be considered. The results are promising, even in the long term. Some mechanical devices can be added to CDT to shorten the treatment time, and these devices are currently being validated in ongoing trials.[22,43]



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Daflon and the protection of venous valves

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Keywords:

chronic venous disorders, inflammation, MPFF, venous valve

Abstract

Increased venous pressure underlies all the clinical manifestations of chronic venous disorders. Venous hypertension is the result of incompetent venous valves in the superficial veins for most patients. A strong link between venous hypertension, valve failure and venous inflammation has been evoked through pharmacological studies and confirmed in a variety of animal models. A cascade of inflammatory reactions results in adverse changes in the venous valve and venous wall that eventually produce venous hypertension. Symptoms, telangiectasias, varicose veins, and eventually venous leg ulcers appear to be a consequence of the changes induced by venous hypertension. Treatment to inhibit inflammation and hamper venous hypertension may offer the greatest opportunity to prevent progression of the disease and related complications. Inflammation-dependent valve failure is considered as a target for drugs. Daflon, a venoactive drug containing purified micronized diosmin, hesperidin, linarin, isorhoifolin, and diosmetin at optimized doses, is the only drug with evidence on the preservation of valve structures in animal models and on the suppression of commissural transitory reflux that occurs in symptomatic patients after prolonged standing. Daflon also has been shown to protect the microcirculation in animal models. This is translated into clinical benefits, such as edema reduction, hematoma resorption after surgery, acceleration of ulcer healing, and amelioration of lymphatic drainage. The role of Daflon in the attenuation of the various elements of venous inflammation is now better known and would deserve a deeper exploration in the future.

Introduction

Venous valves were first described by Dutch physician Jacques Dubois, but their true function was later discovered by William Harvey.[1]

Most veins of the superficial and deep system in the lower extremities are equipped with a series of one-way bicuspid valves that open to allow blood to flow toward the heart and close to prevent reverse blood flow toward the feet. Particularly in the erect position, the venous valves are essential in assuring that

Phlebolymphology. 2016;23(1):20-30

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blood flows in the correct direction, traveling against gravity and other pressures.[2] Venous pathology develops when venous pressure increases and blood return is impaired by incompetent valves in the axial deep or superficial veins, perforator veins, or venous tributaries for most patients. Chronic venous disorders may also result from venous obstruction or a combination of both valve incompetence and obstruction. These mechanisms serve to produce global or regional venous hypertension, particularly with standing or walking.[3] The subsequent macrocirculatory hemodynamic disturbances contribute to the large variety of clinical presentations seen in chronic venous disorders. Prolonged periods of venous hypertension in the legs, in turn, alter the microcirculation, resulting in dermal changes with hyperpigmentation, lipodermatosclerosis, and eventual ulceration.

The presentation of chronic venous disorders includes symptoms and signs. A recent large-scale epidemiological study has shown that the most commonly expressed chronic venous disorders–related symptoms include (in order of frequency): heaviness; leg pain; swelling sensation; nighttime cramps; sensation of "pins and needles" in the legs; and sensation of burning and itching.[4] Signs of chronic venous disorders are described in the Clinical, Etiological, Anatomical, Pathophysiological (CEAP) classification and comprise telangiectasia, varicose veins, edema, skin changes, and healed or active venous leg ulcers.[5]

A strong link is evoked between venous hypertension and valve failure

In most cases, venous hypertension is caused by reflux through incompetent venous valves *(Figure 1)*.[3,6]

Examination of surgical specimens removed from limbs with chronic venous insufficiency, and more recently, the direct observation offered by angioscopy, has revealed lesions involving the venous wall, valvular annulus, and valve cusps.[7,8] Failure of the valve and the valvular annulus is responsible for progression of the disease via maintenance and further increases in venous hypertension.

Immunohistochemical studies using a monoclonal antibody specific for monocytes and macrophages have demonstrated a monocyte/macrophage infiltration into the valve leaflets and venous wall of C_2 patients with varicose

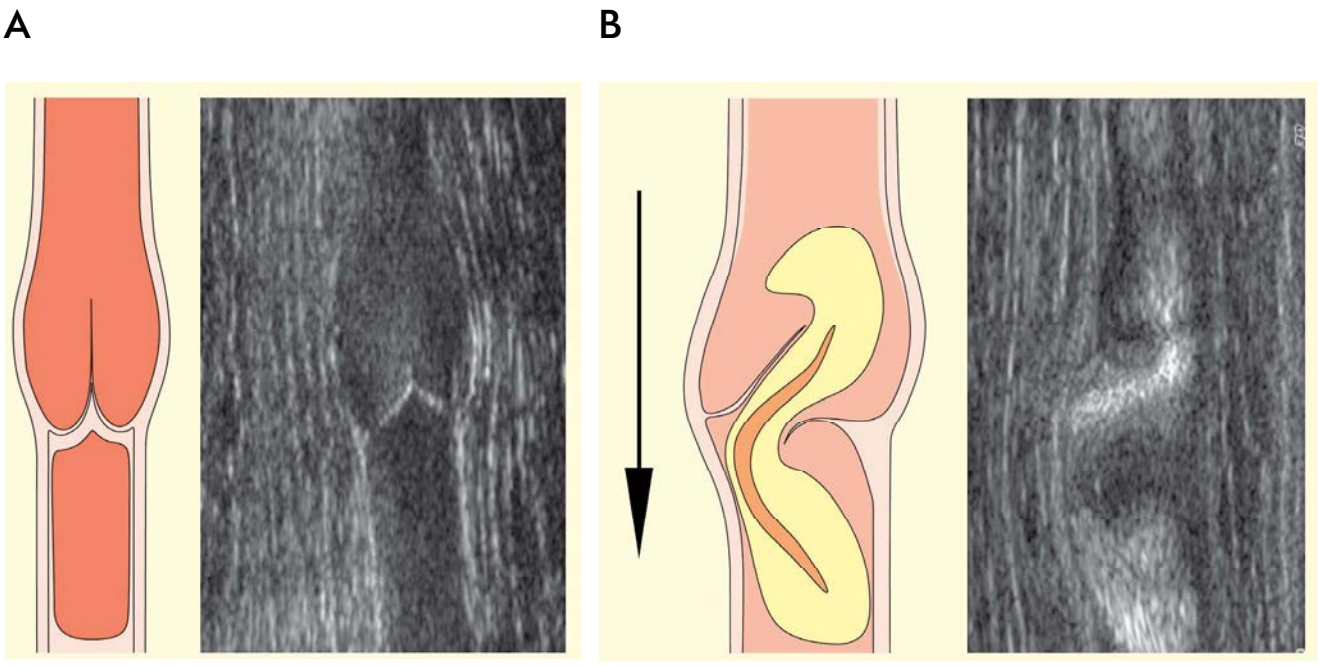

Figure 1. Visualization of competent and incompetent venous valves.

Competent (Panel A) and incompetent (Panel B) venous valves showing schematic and B-flow ultrasound images. In Panel B, the valve sinus is distorted. The cusp above the dilatation is frozen and the adjacent cusp is prolapsed. The high-velocity retrograde streaming deviates laterally above a prolapsing cusp.

From reference 6: Lane et al. Phlebolymphology. 2007;14:105-115. Image courtesy of the author.

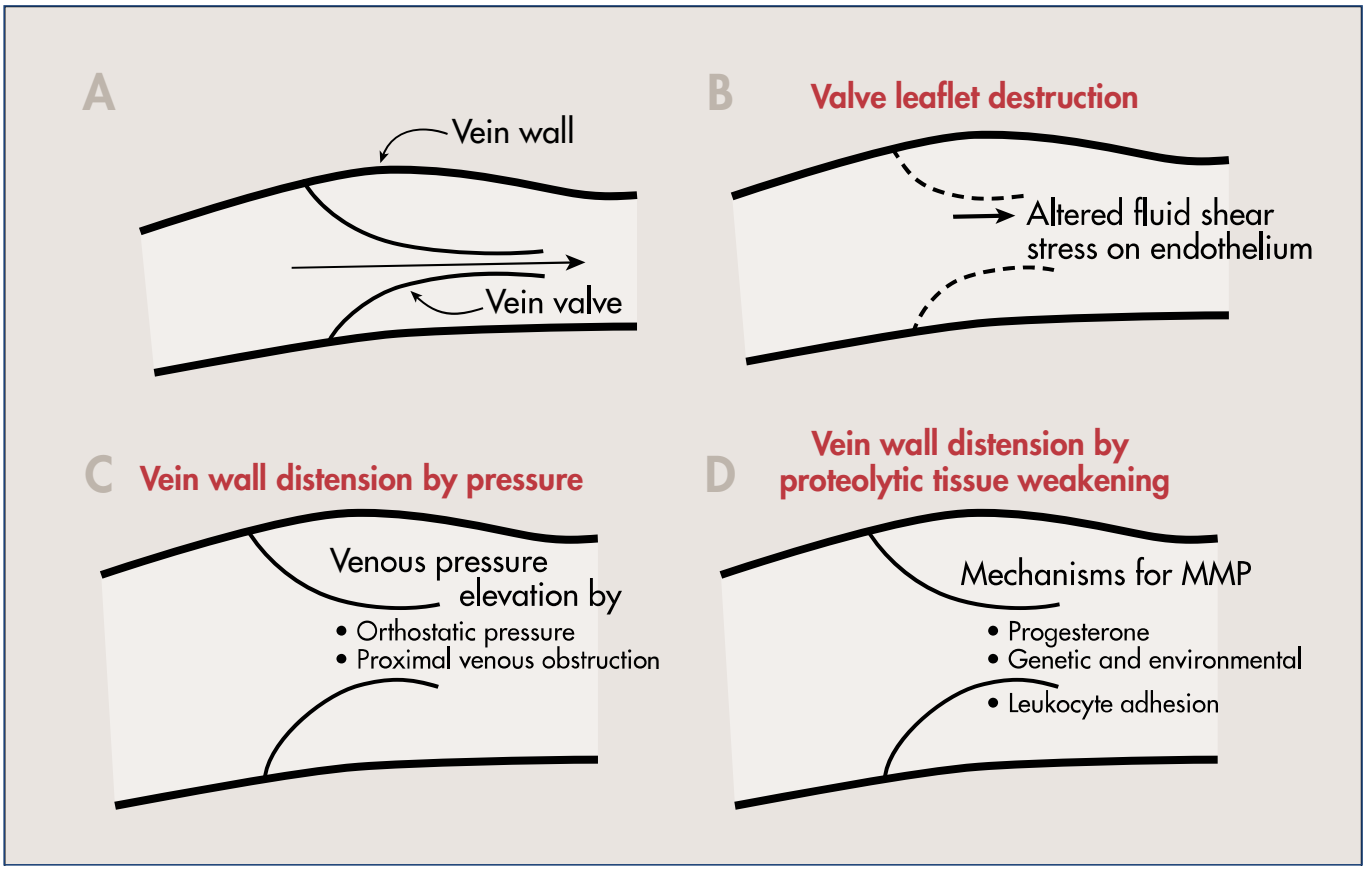

Figure 2. A schematic diagram illustrating selected mechanisms that may control inflammation of the vein wall and valve leaflet.

A normal vein valve and wall is shown in Panel A. Valve leaflets may be subject to inflammatory damage by alteration in magnitude and direction of fluid shear stress on the endothelium (Panal B). Venous valves may become unable to close their leaflets due to vein wall distension by elevated venous pressure (Panel C), or by weakening of the vein wall due to proteolytic degradation of its extracellular matrix (Panel D).

Abbreviation: MMP, matrix metalloproteinases

From reference 11: Schmid-Schönbein. Medicographia. 2008;30:121-126. Image courtesy of the author.

veins.[9] Monoclonal antibody studies have found leukocyte infiltration to be greater at both the base of the valve leaflets and in the proximal venous wall.

Venous valves have been found to be prominent in regions of low shear stress with venous eddies and recirculation *(Figure 2)*.[10,11] It may be that these phenomenon explain how the leukocytes are preferentially deposited in these regions. Ultimately, macrophages become the instrument of tissue damage that softens the venous wall and favors valve destruction.[12] Venous valve failure, and the subsequent reflux that results in distal venous hypertension, may contribute to the sustained and chronic hypertension that is responsible for leukocyte activation at the endothelium and leukocyte destruction of skin and subcutaneous tissues at the ankle. In addition to leukocyte activation, increased mast cell infiltration into the venous wall may have a role in the development of varicose veins. Increased expression of intercellular adhesion molecule 1 (ICAM-1) and CD68 on the endothelial surface of venous walls in patients with venous insufficiency has been demonstrated and this increased expression may be related to the development of varicose veins.[12] This finding suggests a continuing inflammatory reaction that is related to venous wall remodeling.[13,14] Additionally, endothelial cells must be activated to allow leukocytes to migrate through the endothelial cell layer into the tissue.[12] It is believed that endothelial stretching of the vein due to changes in blood flow and fluid shear stress may induce activation of the endothelium. Fluid shear stress is a key regulatory component of endothelial cells and a reduction in the rate of shear stress leads to enhanced adhesion of leukocytes to the endothelium.[9]

Clinical observations are confirmed in animal models

Since the mechanisms responsible for venous valve failure in primary chronic venous disorders cannot be evidenced in vivo in human beings, animal models were set up for the experimental research. Lalka et al described a simple, reproducible model of hind-limb valve disruption in the greyhound.[15] After this acute valve degeneration, animals developed an immediate increase in poststimulation segmental venous pressure that persisted for as long as 14 weeks. Despite demonstrating reflux in the segments with the disrupted valves, there was no extension into the tributaries and no evidence of varicose vein development. It was hypothesized that this was due to the relatively short hydrostatic column present in the quadruped hind limb.[16]

To elucidate the possible mechanisms for the valve remodeling in chronic venous disorders, another model involved developing an arteriovenous fistulae (AVF). Unfortunately, an arterialized pressure profile occurred in the distal veins, making this model unsuitable for studying this chronic disease. The combination of outflow obstruction and AVF to produce a model of sustained venous hypertension was developed by van Bemmelen[17] and applied to the study of reflux development by Bergan's team.[18] In a series by Takase et al, rat saphenous vein valves were examined, in which femoral venous hypertension was elevated for a period of 3 weeks using the van Bemmelen model. In this model, venous reflux developed in response to venous hypertension around 100 mm Hg.

Examination of vein morphology revealed that valve failure occurred as a result of venous wall dilation and valve leaflet shortening to the point of incomplete valve closure and subsequent reflux. Assessment of the valves for molecular inflammatory markers revealed an enhanced leukocyte infiltration with granulocytes, monocytes, and T lymphocytes. In addition, the expression of P-selectin and ICAM-1, two endothelial cell membrane adhesion molecules, on the endothelial cells of the saphenous vein wall was increased.[18] In this study, the leaflets were still able to close properly in the early stages after placement of the arteriovenous fistula, suggesting that pressure per se may not necessarily be the variable responsible for compromising the leaflets. However, at the time that the leaflets fail and reflux occurs, there was an observed reduction in the leaflet dimensions. A possible explanation of the sequence of events leading to morphological abnormalities in venous valves is that as the venous wall dilates, there may be a point reached when reflux develops across the leaflets. An abnormal fluid shear stress produced at the surface of the leaflets during venous reflux would be highly inflammatory for the endothelial cells on the valve leaflets and may trigger destruction of the leaflets, increasing venous hypertension and promoting a vicious circle of venous hypertension/venous inflammation.

A new animal model of low flow and high pressure in veins to avoid the pitfalls of previous models is being developed by Bouskela's team. The objectives of such a model are to achieve long periods of observation, study alterations in venous pressure over time, assess changes in microcirculatory parameters, and determine the inflammatory profile of the model. It will allow for an assessment of venous pressure and its evolution with time, and an exploration of the microcirculatory parameters with a Cytoscan® device and intravital microscopy.

Inflammation-dependent valve failure as a new drug target: the example of Daflon

Intervention in the inflammatory reaction that occurs as part of the progress of chronic venous disorders may be a new pharmacological target. For this reason, the models by Bergan and Bouskela have been used to assess the effect of Daflon*, a venoactive drug (VAD).

Chemical family of Daflon

Daflon is produced from a plant extract from the epicarp of *Citrus aurantium* var *amara*. It belongs to the chemical family of flavonoids that are included in the six main categories of venoactive drugs *(Table I)*. Daflon contains purified micronized diosmin, hesperidin, linarin, isorhoifolin, and diosmetin at optimized doses.[19] Each of the active ingredients in Daflon contribute to its action and explains its superior beneficial effect over other VADs on the reduction in capillary permeability.[19]

Daflon's mode of action

The pharmacodynamic effects of Daflon and their clinical consequences are summarized in Table II.[20-23]

Preservation of venous valve structures

Daflon is the only VAD with evidence on the preservation of valve structures in animal models and on the suppression of commissural transitory reflux that occurs in symptomatic patients after prolonged standing.[24] In two trials of pharmacological postoperative recovery for patients with

Chemical group	Plant of extraction *Latin name* (common name)	Major active ingredient (part of plant)	Drug tradename
Flavonoids (flavons and flavonols)	Citrus species *Citrus aurantium* L. ssp *amara* (bitter orange)	Diosmin, (pericarp)	Daflon*
	Ginkgo biloba L. (ginkgo)	Quercetol, rutoside (leaf)	Ginkor Fort
	Vitis vinifera L. (common grape vine)	Quercetol, isoquercetol (leaf)	
	Sophora japonica L. (Japanese pagoda tree)	Rutoside, troxerutin (bud)	Ginkor Fort Venoruton
	Viburnum prunifolium L. (blackhaw)	Amentoflavon (stem bark)	Jouvence
Flavonoids (flavanons)		Hesperidin Methylchalcon	Daflon* Cyclo-3; Bi-Cirkan
Anthocyanins	*Vaccinium myrtillus* L. (blueberry)	Anthocyans (leaf, fruit)	Pycnogenol
	Ribes nigrum L. (blackcurrent tree)	Anthocyans (leaf, fruit)	
Tannins	*Hamamelis virginiana* L. (American witch-hazel)	Gallic acid, ellagique (stem bark, leaf)	Jouvence Hamamelis Boiron
Procyanidolic oligomers (PCO), precursors of tannins	*Pinus maritimus* (maritime pine)	PCO (branch)	
	Vitis vinifera L. (common grape vine)	PCO (grape seed)	Endotelon
Saponosides	*Aesculus hippocastanum* L. (horse chestnut)	Escin (stem bark, seed)	
	Centella asiatica L. (hydrocotyle)	Asiaticoside, centelloside, madecassoside (bud)	Madecassol
	Ruscus aculeatus L. (holly)	Ruscin (roots)	Cyclo-3
Coumarins	*Melilotus officinalis* L. (yellow sweet clover)	Melilotoside (bud)	SB-Lot

Table I. Main categories of venoactive drugs.

varicose veins who underwent phlebectomy, Daflon helped attenuate postoperative pain and improve the quality of life.[25-28]

Protection of the microcirculation

Experimental in vivo models have been used to study the effect of drugs on the microcirculation. Microcirculatory preparations include hamster cheek pouch, hamster or mouse skinfold, rat or hamster mesentery, rat, hamster or mouse cremaster, etc.[29] Numerous pharmacological trials have shown that VADs increase capillary resistance and reduce capillary filtration, resulting in the prevention of capillary leakage. Daflon has shown evidence for improved microvascular reactivity and functional capillary density (number of capillaries with flowing red blood cells per unit of tissue) after ischemia-reperfusion injury,[30] and Daflon also induced a significant dose-related reduction in the increased permeability.[31] Such protective microcirculatory properties of Daflon result in clinical benefits. In a recent meta-analysis, ten publications dated between 1975 and

Pharmacodynamic effects (Adapted from references 20-23)	Clinical consequences
MPFF suppresses damage to valves and preserves their structure	
• Reduces the number of activated leukocytes in venous valves in an arteriovenous fistula (AVF) animal model • Maintains the valve diameter in an AVF model • Reduces reflux rate in a AVF model • Prolongs the vasoconstrictor effect of noradrenaline (norepinephrine) on the vessel wall, reduces the gap between valve leaflets, and reduces blood venous stasis in vitro • Increases mechanical tension on bovine metacarpal vein rings in vitro	• Eliminates the evening commissural reflux in C_{0s} patients, decreases the vein diameter, which results in beneficial effects on symptom relief and quality of life improvement[24] • Compared with controls, improves postoperative pain and quality of life of C_2 patients having undergone stripping surgery[25-28]
MPFF protects the microcirculation	
• Reduces diameter of capillary bulk (DCB) and diameter of dermal papilla (DDP) in premenopausal women compared with placebo, indicating a protective effect of MPFF against the morphological changes that occur in the capillaries and an ability of MPFF to prevent capillary leaks and edema • Maintains the number of functional capillaries (FCD) in premenopausal women • Improves microvascular reactivity and functional capillary density after ischemia-reperfusion injury in the hamster cheek pouch • Prevents capillary leakage in a significantly higher proportion of capillaries than a single diosmin (in the hamster cheek pouch) • Decreases permeability more than any of its single constituents, showing that the flavonoids present in its formulation have a synergistic action in the hamster cheek pouch • Inhibits the increase in microvascular permeability that is induced by bradykinin or ischemia in rat cremaster muscle, and induced by histamine, bradykinin, leukotriene B4, ischemia-reperfusion injury, or oxidant challenge in the hamster cheek pouch	• Shows a decrease in ankle edema that is at least 25% more than ruscus extract, diosmin, or hydroxyethylrutoside in C_3 patients[32] • Reduces hematomas by 30% compared with controls in C_2 patients after stripping[25-28] • As adjunctive treatment to compression therapy, accelerates ulcer healing by 32% and shortens time to healing by 5 weeks in C_6 patients[33]
MPFF increases lymphatic drainage	
• Increases contractility of sheep mesenteric lymphatic collecting ducts in vitro • Increases the frequency of spontaneous contractions in bovine mesenteric lymphatics in vitro • Improves lymphatic drainage in sheep and dogs • Decreases thigh weight, protein concentration in tissue, and fibroblast number in rats with acute leg lymphostasis	• Significantly ameliorates skin hardness and heaviness of upper limbs with a 6-month treatment in patients with lymphedema[40] • Significantly decreases upper limb circumference with a 6-month treatment in patients with lymphedema[40] • Improves symptoms in patients with filariasis[41]
MPFF has potent venous anti-inflammatory effects	
• Decreases expression of CD11B, a neutrophil receptor, and CD62L, a monocyte and neutrophil ligand, in C_2 to C_6 patients • Inhibits intercellular adhesion molecule 1 (ICAM-1) expression in skeletal muscle ischemia-reperfusion injury in rats • Inhibits leukocyte adhesion and/or migration after ischemia-reperfusion injury in hamster skin fold or rat skeletal muscle, oxidant challenge in hamster cheek pouch, and venular mesenteric occlusion and reperfusion in rats • Inhibits oxygenated free radical production in zymosan-stimulated human neutrophils or mouse macrophages in vitro • Inhibits synthesis of prostaglandin E_2 or $F_{2\alpha}$ and thromboxane B_2 in inflammatory granulomas in rats	• Reduces VAS scores of pain, heaviness, sensation of swelling, cramps, paresthesia in C_2 to C_6 patients[44] • Halves postoperative pain and significantly reduces analgesic consumption in C_2 patients[25] • As adjunctive treatment to compression therapy, a 30% reduction in the pain is associated with venous ulcers[23]

Table II. Overview of the pharmacodynamics and clinical properties of Daflon.

2009 analyzed 1010 patients for the benefits of Daflon, hydroxyethylrutoside, ruscus extracts, and diosmin on edema reduction. Mean reduction in ankle circumference was -0.80±0.53 cm with Daflon, -0.58±0.47 cm with Ruscus extract, -0.58±0.31 cm with hydroxyethylrutoside, -0.20±0.5 cm with single diosmin, and -0.11±0.42 cm with placebo. The comparison between Daflon and other VADs on ankle reduction in edema was in favor of Daflon (P<0.0001).[32]

Daflon, used postsurgery after varicose vein stripping, helped decrease postoperative hematomas and helped accelerate their resorption.[25-28]

The complications of chronic venous disorders are related to chronic venous hypertension and are visualized in the skin, which is the final target of chronic venous hypertension. The hypertension is a cause of chronic inflammation manifested by persistent and sustained injury. Ultimately, the dermal capillary circulation is the most severely impaired in limbs with chronic venous insufficiency.

In a meta-analysis of 5 randomized controlled trials containing 723 C_6 patients, MPFF demonstrates efficacy in healing venous ulcers when used as an adjunct treatment to compression therapy and appropriate local therapy, particularly for large (>5 cm^2 in area) and/or persistent (>6-month duration) ulcers.[33]

Amelioration of lymphatic drainage

The draining function of lymphatic vessels is very important. Lymphatic vessels transport 4 L of efferent lymph into the bloodstream daily. The fluid turnover (including the volume of fluid reabsorbed in the lymph nodes) reaches up to two-thirds of the total volume of interstitial fluid every 24 hours.[34] The skin of the lower extremities contains a more dense and extensive network of lymphatic capillaries than the skin of the upper extremities.[35] Due to orthostatism, lower extremities have higher filtration pressure and fluid influx. It is thought that the capacity for lymph transport in the lower extremities is greater in order to compensate for the higher influx of interstitial fluid caused by the effects of orthostatism and gravity. Spontaneous contractility of lymphatic vessels is utilized in lymph transport. Regular contractions of lymph vessels, at a frequency of 2 to 4 per minute, were observed in vitro. Spontaneous contractions of prenodal lymphatic vessels have been observed in human legs and were shown to drive the lymph flow.[36] Internal extensions of lymphatic endothelial cells act as valves and guarantee a unidirectional lymph flow.[34] Lymphatic dysfunction and structural damages to the lymphatic network are associated with varicose veins, and the subsequent lymph stasis and reduced lymph transportation lead to inflammation.[37] This is associated with lipid accumulation in the media of the diseased veins, which may further damage adventitial lymphatic vessels.[37]

Pharmacological trials found that treatment with Daflon may help treat lymphedema by reducing protein and extracellular fluid accumulation,[38] stimulating lymph contractility and flow,[39] and reducing the excess protein in tissues with high protein edema. In a study investigating Daflon or placebo (n=48) over 6 months,[40] the treatment group experienced a 7% volume reduction, while the placebo group experienced a 10% volume increase. Both groups experienced significant reduction in reported discomfort, but the treatment group also had a significant reduction in heaviness. In addition, Daflon was found to be efficacious in reducing edema volume in bancroftian filarial lymphoedema.[41]

Potent anti-inflammatory effect

Disturbed venous flow patterns and chronic venous inflammation are two interlinked phenomena. It is thought that mediators resulting from disturbed blood flow, and subsequent inflammation, have an important role in the occurrence of venous pain. Locally released proinflammatory mediators, resulting from hemodynamic changes and hypoxia, can activate nociceptors located in close contact with the microcirculation including the venous wall, the space between endothelial and smooth muscle cells of the media,[42] and the perivenous space.

The primary activation site of venous and/or perivenous nociceptors may not happen in large venous vessels, which is suggested by the fact that pain is not closely correlated with objective parameters of varicose vein remodeling, incompetent venous valves, and inflammation. The efficacy of Daflon in the treatment of patients with symptoms of chronic venous disease has been widely evaluated in comparative and noncomparative clinical trials.[20,23] There is substantial evidence from meta-analyses[43] and the RELIEF study (Reflux assEssment and quaLity of lIfe improvEment with micronized Flavonoids), a large observational study,[44] that Daflon is efficacious in relieving venous symptoms and lower limb edema. In the latest recommendations for the management of active venous ulcers, Daflon was assigned a grade 1B for adjuvant therapy, keeping in mind that Daflon is also capable of reducing associated pain.[23]

Daflon's protective effect against inflammation-related valve damage in chronic venous disease

In pharmacological studies

The ability of Daflon to mitigate or block the effects of chronic inflammation in the micro- and macrocirculation has been demonstrated in animal models. In a model of venous occlusion and reperfusion, the subsequent elevation of venous blood pressure increased the inflammatory cascade and tissue injury.[45] In Daflon-treated animals, markers of inflammation were decreased in a dose-

dependent manner. Daflon also served to significantly reduce parenchymal cell death and leukocyte rolling, adhesion to postcapillary venules, and migration.[46] Important data supporting the protective effect of Daflon on the macrocirculation have been provided by Takase et al.[47] In animals treated with Daflon, there was a significant, dose-dependent reduction in the reflux rate (*Figure 3*). Daflon also reduced several indicators of the inflammatory reaction in a dose-dependent manner, including leukocyte infiltration, expression of P-selectin and ICAM-1, and the level of apoptosis. By delaying or blocking the inflammatory reaction, these data suggest that Daflon may delay the development of reflux and suppress damage to valve structures in the rat model of venous hypertension. These observations were recently confirmed in a new study using the same animal model. The administration of Daflon reduced edema and fistula blood flow produced by the acute AVF. Daflon also reduced granulocyte and macrophage infiltration into the valves, which is consistent with the previous study.[48]

In clinical trials

A 2-month treatment with Daflon at 1000 mg/day resulted in the elimination of transitory commissural reflux observed in patients presenting with subjective leg symptoms without visible signs of chronic venous disorders, the so-called C_{0s} patients *(Figure 4)*.[24] Transitory reflux elimination was paralleled with pain relief and quality of life amelioration. In this trial, consecutive C_{0s} patients were enrolled and assessed for the following: (i) symptom intensity using the visual analog scale (VAS); (ii) quality of life with the Chronic Venous Insufficiency quality of life Questionnaire (CIVIQ-20); and (iii) saphenous reflux duration and saphenous vein diameter by a Duplex scan examination performed twice a day (morning and evening). A total of 41 C_{0s} patients were enrolled in the study; and of these patients, 15 had no reflux in either the morning or evening and 26 had transitory evening reflux with 22 being commissural and 4 intervalvular. The saphenous vein diameter was greater in the subgroup of patients with transitory reflux

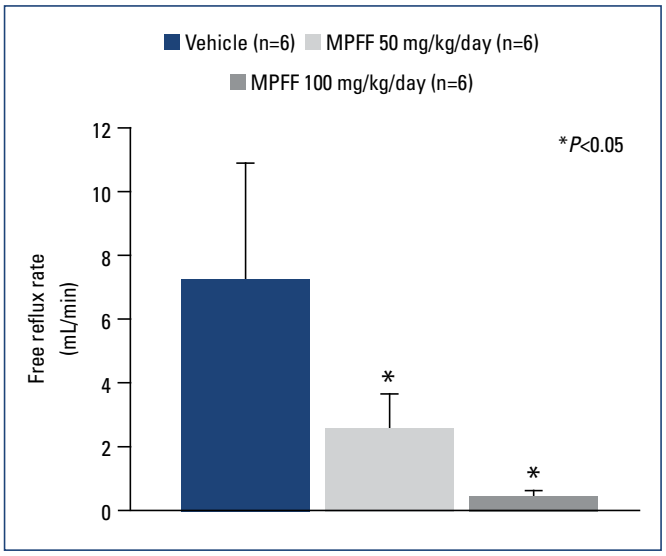

Figure 3. Reflux flow rates across the valve of the saphenous vein.

Reflux flow rates across the saphenous venous valve measured after 3 weeks of venous hypertension in control (vehicle)- and Daflon (MPFF)-treatment groups at a dose of 50 and 100 mg/kg/day. N is the number of rats in each treatment group. P<0.05 compared with control.

From reference 47: Takase et al. Eur J Vasc Endovasc Surg. 2004;28:484-493. © 2004, Elsevier Ltd.

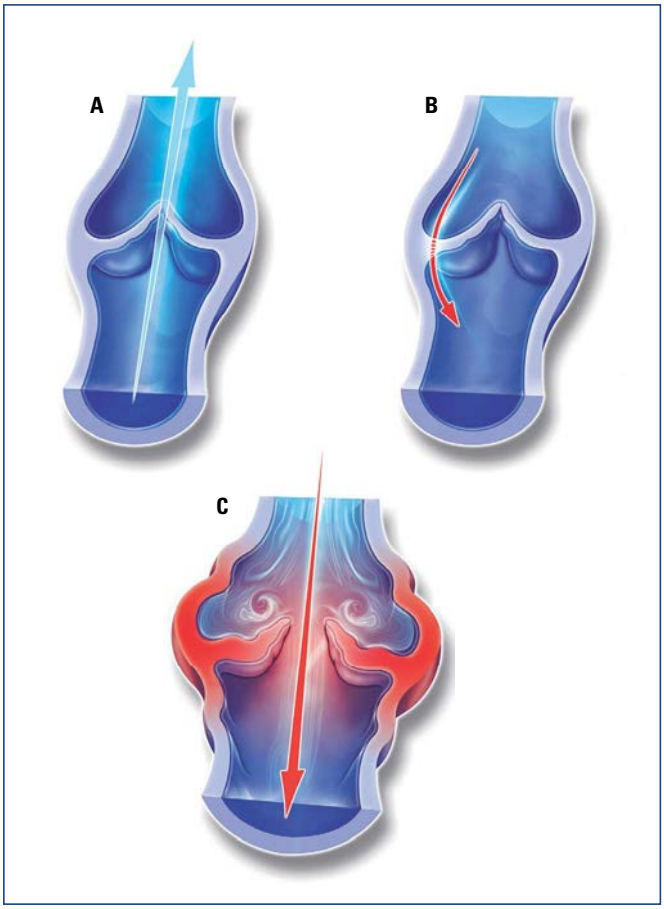

Figure 4. Illustrations of venous valves with and without reflux.

Illustrations of a normal venous valve without reflux (Panel A), a valve with a nonpathological commissural reflux usually seen in the evening after being in a prolonged upright position (Panel B), and a valve with a pathological intervalvular reflux (Panel C).

Modified from reference 24: Tsoukanov et al. Phlebolymphology. 2015;22:18-24. Image courtesy of the author.

compared with patients without reflux ($P<0.05$). After Daflon treatment, there was a trend toward a reduction in intervalvular reflux length (despite being nonsignificant), while transitory commissural refluxes (n=22) no longer appeared. Additionally, vein diameter returned to normal values. These results mirror the protective effect of Daflon on venous valve structures.

Venous valve protection opens perspectives for targeted pharmacological interventions

The practical purpose of elucidating the molecular steps involved in the development of valve lesions is to intervene with a targeted treatment. Studies have focused on available molecules known to modify the sequence of events involving leukocyte adhesion, endothelial interaction, activation, and migration, and the subsequent associated valvular damage in large veins, mainly the great saphenous vein. However, studies on the pathophysiology of chronic venous disorders have not yet acknowledged that this sequence of events is not limited to large veins including the saphenous veins, but extends down to venules, where valves and microvalves play important roles in venous hemodynamics. We know from recent findings that the majority of microvalves in lower limbs are present within channels less than 100 µm in luminal diameter.[49] The role that microvalves play is still unclear and their location and arrangement in normal lower limbs suggest that they prevent blood flow into the capillary bed *(Figure 5)*. This has been evidenced by Philips, who found no difference between lower limbs with venous ulcers and normal limbs with respect to the number and density of microvalves. However, microvalves in diseased limbs were stretched and incompetent, allowing retrograde flow from large veins into the dermal capillary bed.[49] Vincent and coworkers proposed two hypotheses: (i) degenerative changes in very small veins in leg skin may be related to the appearance of telangiectasias, reticular veins, and corona phlebectatica; and (ii) valve incompetence in both larger proximal vessels and small superficial veins, at the level of microvalves, would account for the appearance of severe skin changes in the event of venous insufficiency.[50]

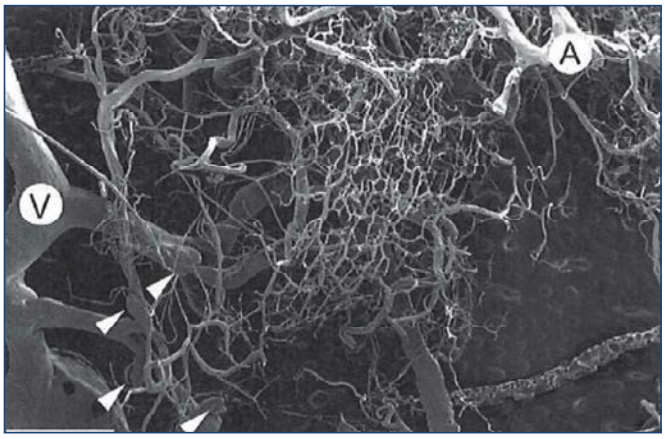

Figure 5. Arterial and venous capillary bed network.

Capillary bed network associated with an artery (A) and a vein (V). Four "microvalves" are visible (arrowheads). Scale bar=2 mm.

From reference 49: Phillips et al. Clin Anat. 2004;17:55-60. © 2003, Wiley-Liss, Inc.

Daflon currently possesses the most appropriate profile to protect venous valves and perhaps microvalves, even if its role remains to be more deeply explored in vivo.

**Also registered as Ardium®, Alvenor®, Arvenum® 500, Capiven®, Detralex®, Elatec®, Flebotropin®, Variton®, Venitol®*

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Combined hormonal contraceptives and the subsequent risk of a venous thromboembolism

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Keywords:

contraception; estrogen; guidelines; hormone; progestin; progestogen; pulmonary embolism; risk factor; thromboembolism

Phlebolymphology. 2016;23(1):31-36

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Abstract

Recent public alarm in European countries has renewed concerns about the safety of oral contraceptive pills (OCPs) after women sued manufacturers for potentially fatal venous thromboembolisms resulting from using OCPs (particularly those combining estrogen and the new generations of progestin). Earlier studies, reporting an increased risk of venous thromboembolisms, produced conflicting results and had methodological limitations, calling into question the validity of the findings and conclusions about the magnitude of the additional risk associated with using the new progestin-containing contraceptives. Finally, the World Health Organization, the United States Food and Drug Administration, and the European Medicines Agency reviewed the recent epidemiological studies and stated that these studies had not shown the magnitude of increased risk of venous thromboembolism events that have been reported in earlier studies as a result of using third- and fourth-generation combined oral contraceptives. However, since other factors, such as age and lifestyle factors, influence the risk of venous thromboembolism, health authorities advise health professionals to consider the possibility of the increased thromboembolic risk before prescribing OCPs.

Introduction

Oral contraceptive pills (OCPs) combining estrogen and a third- or fourth-generation progestin are commonly prescribed drugs for young women, with the greatest risk potentially being thromboembolisms. Data have been accumulating showing that some combined oral contraceptives containing new-generation and antiandrogenic progestogens have a higher risk of venous thromboembolism (VTE) than older drugs, such as levonorgestrel. This risk has been greatly overestimated in Europe and strongly discussed in the French media during the winter of 2013, which resulted in the removal of Diane®35, an oral contraceptive combining 35 µg of ethinyl estradiol (EE) and 2 mg of cyproterone acetate (CPA), a fourth-generation progestin, from the French market. For a time, this episode heaped opprobrium on all contraceptive pills containing third- and fourth-generation progestin.

The recent publication of three meta-analyses,[1-3] one Cochrane review,[4] and two original articles[5,6] renewed the concerns about the risk of VTE events among women using combined OCPs with different types of progestin. Results from these reviews were contradictory and the causal relationship was not clear. The latest editions from a variety of groups, including the World Health Organization (WHO), the United States Food and Drug Administration (FDA), and the European Medicines Agency (EMA), have commented on the factors to consider when choosing a particular contraceptive method. They have consistently concluded that, although there may be differences in the VTE risk between products with different progestins, the absolute risks are very small. The benefit-risk ratio of all combined contraceptives has been stated as positive.

Finally, the EMA asked the French Health Authorities to reintroduce Diane®35 on the market, meaning that the 2013 French controversy against contraceptive pills has been summarized as "*Much Ado About Nothing*" (William Shakespeare).

The aim of this review is to understand the possible biases in the studies on the relationship between VTE risk and OCPs, and help choose a contraceptive method according to the patient's personal history and characteristics.

Contraceptives and risk of thromboembolism: data from recent meta-analyses and prospective studies

A 2012 review[1] demonstrated a 6-fold higher risk of VTE events when using combined OCPs containing third- (desogestrel [DSG], gestodene [GSD]) and fourth- (drospirenone [DRSP], CPA]) generation progestin and when using the contraceptive vaginal ring compared with nonusers. The relative VTE risk between combined OCPs containing the new generations of progestin compared with OCPs containing levonorgestrel (LNG) was 1.5 to 2.8 in seven studies and 1.0 in two studies.[1] Based on this data, it was concluded that progestogen-only contraceptives did not confer an increased risk of VTE events. Nevertheless, most of the analyzed studies were rather old, which was the major critique of this review.[2]

Peragallo Urrutia et al compared the risk of VTE events in users vs nonusers of OCPs and confirmed that nonusers have a lower risk of developing venous thromboses *(Figure 1)*.[3] However, they did not report an increased risk of VTE events

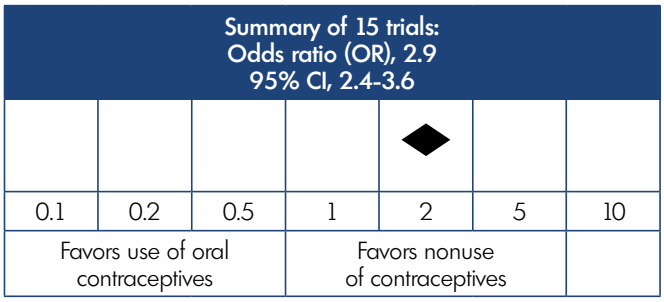

Figure 1. Risk of venous thromboembolism in users vs nonusers of oral contraceptives according to a meta-analysis of fifteen trials.

This figure is based on data from reference 3.

with third- and fourth-generation progestin vs second-generation progestin. First- (odds ratio [OR], 4.06; 95% CI, 2.66-6.19), second- (OR, 3.28; 95% CI, 2.49-4.31), third- (OR, 4.06; 95% CI, 3.09-5.32), and fourth- (OR, 5.36; 95% CI, 2.78-10.32) generation progestins were associated with an increased risk of VTE events in OCP users compared with nonusers as a reference group, with no difference according to the dose of EE and the type and generation of progestin *(Figure 2)*.[3]

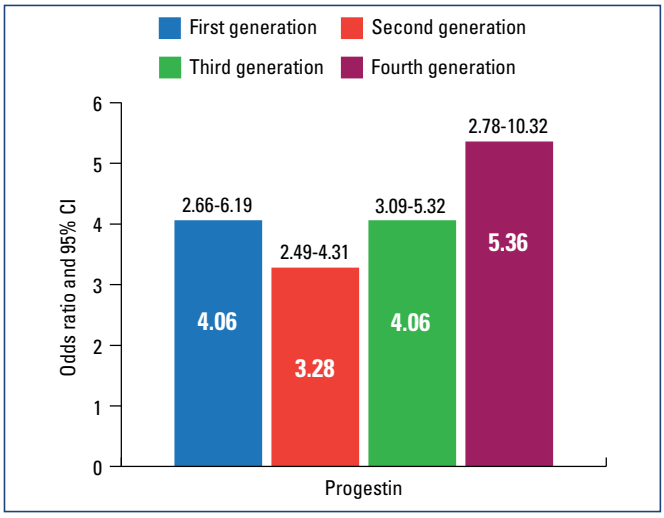

Figure 2. Risk of venous thromboembolism according to the generation of progestin.

This figure is based on data from reference 3.

A review by Stegeman et al also found an increased risk of VTE events with the use of combined OCPs compared with nonuse. The use of OCPs increased the risk of VTE events 4-fold compared with nonuse (relative risk [RR], 3.5; 95% CI, 2.9-4.3).[4] All generations of progestin were associated with an increased risk of VTE, and third-generation users (GSD, DSG) had a slightly higher risk compared with

second-generation users (LNG). However, the authors focused on the dose-related effect of EE–higher doses of EE were associated with a higher risk of thrombosis for all generations of progestin.

The same team published a Cochrane review discussing the respective role of progestin and EE in VTE events with the use of OCPs. The authors concluded that OCPs with the highest risk of VTE events associate LNG with a high EE dose, ie, 50 µg EE (50LNG). OCPs with an intermediate risk of a VTE event include the following: 30 µg EE+DRSP (30DRSP), 35 µg EE+CPA (35CPA), and 30 µg EE+DSG (30DSG). Finally, the OCPs 30LNG, 20LNG, and 20GSD have the lowest risk of VTE events.[5]

Dinger et al, in two prospective studies, compared the use of vaginal rings with OCPs[6] and the risks of short- and long-term use of an extended 24-day regimen of DRSP and EE (DRSP24d) with established combinations for the other OCPs.[7] The authors found that routinely using a vaginal ring, DRSP24d, and combined OCPs were associated with similar venous and arterial thromboembolic risks *(Table I)*.

		Incidence (events/10 000 woman-years)	
Clinical outcome	Subcohort	Point estimate	95% CI
VTE	Vaginal ring	8.3	5.0-12.9
	Combined OCPs	9.2	6.0-13.5
	Combined OCPs 2	8.9	5.5-13.6
	Combined OCPs 3	8.5	4.5-14.6
	Combined OCPs 4	7.8	1.6-22.7
ATE	Vaginal ring	2.2	0.7-5.1
	Combined OCPs	2.8	1.2-5.6
	Combined OCPs 2	2.5	0.9-5.5

Table I. Risk of venous and arterial thromboembolism in new users of vaginal rings vs other oral contraceptives.

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; OCPs, oral contraceptive pills; OCPs 2, oral contraceptive pills without desogestrel or gestodene; OCPs 3, oral contraceptive pills without desogestrel, gestodene, or drospirenone; OCPs 4, levonorgestrel-containing OCPs; VTE, venous thromboembolism.

This table is based on data from reference 7.

Methodological limitations and study bias

Methodological limitations have called into question the validity of recent and earlier findings and conclusions about the magnitude of the additional risk associated with using these products. Therefore, the following section will discuss the caveats of both study design and analysis.

Trial design

Randomized controlled trials

Due to the very-low baseline thrombosis rate in women (1 to 5 VTE events per year per 10 000 users), randomized controlled trials to compare VTE risks between the various existing OCPs are hardly feasible. Indeed, the sample size should be very large, with the enrollment of at least 500 000 women and a requirement of a 5- to 10-year follow-up. Therefore, only observational studies have been conducted, which are prospective for some and retrospective for others.

Prospective trials

Despite follow-up data from a very large sample of OCP users (>100 000), the number of VTE events remain limited at ≈50 to 60 events. Consequently, differences in the risk of VTE events between OCPs have never reached statistical significance. In addition, these trials are often supported by pharmaceutical companies commercializing OCPs, as suggested by some authors.[3]

Retrospective trials of the "health economic" type

A Danish study by Lidegaard et al analyzed the risk of VTE events in 3 million woman-years.[8] Unfortunately, this type of study usually contains a lot of bias, making interpretation of the results difficult.

Meta-analyses

Meta-analyses are not always the panacea because they are a review of studies that are often biased; making the subsequent meta-analyses also biased. However, preestablished criteria for retaining studies to be analyzed contribute to the selection of less biased trials and attenuate the flaws of each study taken separately. In addition to the selection criteria, the statistical evaluation of the studies homogeneity adds to the consistency of the results. For instance, in the 2013 review by Peragallo Urrutia et al, which analyzed carefully selected trials after application of rigorous criteria and the crossover of various confidence intervals, EE dose and the generation of progestin were found to have no influence on the risk of VTE events.[3]

Bias at inclusion

The following section identifies biases found in comparative studies.

Lack of randomization and missing patient characteristics at inclusion

Patient characteristics at inclusion must be homogeneous between comparison groups. In the 2009 version of the Danish study, patients' weight and family history of VTE were missing,[8] and yet, these two parameters have been shown to influence the risk of VTE events. A positive family history would be an independent risk factor for a VTE event that may reflect the presence of a hereditary thrombophilic disorder[9]; however, routine screening for such conditions is not justified.[10] On the other hand, overweight patients would have a higher risk of a VTE event.[11] Pomp et al reported a 24-fold higher thrombotic risk (OR, 23.78; 95% CI, 13.35-42.34) in women with a body mass index (BMI) ≥30 who used OCPs vs women with a normal BMI who did not use contraceptives *(Figure 3)*.[12]

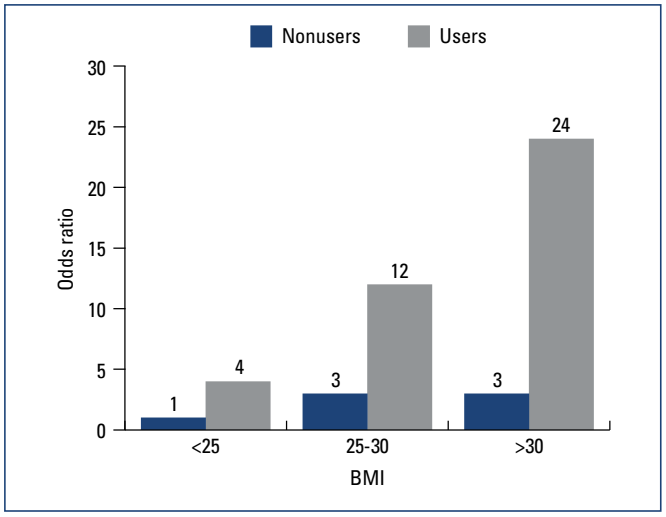

Figure 3. Risk of venous thromboembolism according to female BMI.

Abbreviations: BMI, body mass index; OCPs, oral contraceptive pills.

This figure is based on data from reference 12.

Lack of homogeneity between groups, together with the absence of randomization, may greatly bias the results. This was the case in the studies that put into question the safety of the third-generation progestins in combined OCPs (combined OCPs 3) compared with second-generation progestins (combined OCPs 2). After reanalysis of the results, we found that women assigned to the combined OCPs 2 group were at a higher risk of VTE events, even before they had taken their pills![13]

Number of new users in each group

During the first 6 months, new OCP users are at a 3- to 10-fold higher risk of VTE events.[4] Prospective studies by Dinger et al that homogenized the groups regarding weight at inclusion found no difference in VTE risk between new second-, third-, and fourth-generation progestin users.[6,7]

In a retrospective study by Sydney et al, DRSP was associated with a higher risk of venous and arterial thrombotic events in new users compared with low-dose estrogen OCPs.[14] However, weight and family history of VTEs were not considered in this last trial. Since pills containing DRSP have, for some time, been believed to prevent weight gain, overweight women might have been over represented in the DRSP group.

In August 2012, the FDA issued a safety communication stating that "drospirenone-containing birth control pills may be associated with a higher risk for blood clots than other progestin-containing pills," but emphasized that the available epidemiological studies showed conflicting results and other factors may have accounted for the differences.[15]

Number of women with acne

Women with acne are more likely to suffer from polycystic ovary syndrome (PCOS). Recently, Bird et al found a 2-fold and 1.5-fold higher risk of VTE events among women with PCOS who were taking combined OCPs and women with PCOS not taking OCPs, respectively.[16]

VTE diagnosis

A VTE diagnosis may occur after a clinical or biological examination, or it may be detected using imaging (Duplex scan [DS]). Over- or underestimation of VTEs will depend on the technique of investigation used. Hospitalized women with a presumption of a VTE event will often benefit from a DS investigation, while a VTE event in outpatient women will be clinically diagnosed. Lidegaard et al reported that among women who were diagnosed with a VTE at clinical examination, less than 50% had their VTE confirmed at DS investigation.[8] Changes in the results of coagulation tests as a result of using third- and fourth-generation combined OCPs have not been shown to be directly responsible for an increase in VTE events.

Choice of the evaluation criteria

The increased risk of VTE events should not be the only

evaluation criteria involved in the benefit-risk ratio of OCPs. Although the increased risk of VTE events seems ominous, it should be put in context of the very-low baseline thrombosis rate in young women (1 to 5/10 000). Most reviews estimate a number needed to harm of 300 for VTE events over 5 years of OCP use.

It is also important to remember that the contraceptive effect of OCPs is beneficial against adverse events associated with pregnancy. The FDA also underlined that "the risk of blood clots is higher when using any birth control pill than not using them, but still remains lower than the risk of developing blood clots during pregnancy and the postpartum period."[15] This is particularly true for "unwanted" pregnancies that are likely to be interrupted for which the risk of a VTE event is high.

Factors to consider when choosing a particular contraceptive method

As with all licensed medicines, combined OCPs are continuously monitored by the licensing authorities, who work to ensure that healthcare professionals and women have access to the best possible information on the risks and benefits of these medicines. In order to allow health professionals to make the best choice for contraception, factors to consider when choosing a particular contraceptive method include the characteristics of the potential user, the background risk of disease, safety and adverse effect profiles of the different products, cost, availability, and patient preferences.

In February 2013, the EMA started a new review of all available data on the risk of VTEs and arterial thromboembolisms with several combined hormonal contraceptives containing the following progestogens: chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, nomegestrol, norelgestromin, and norgestimate. An update from the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA on the use of these products was released in November 2013 and they concluded that the benefits of combined OCPs in preventing unwanted pregnancies continue to outweigh their risks, and that the well-known risk of VTE events with all OCPs is small.[17] Recommendations are summarized in *Table II*.

The risk of VTE events with combined OCPs differs among products depending on the type of progestogen they contain.

Having assessed the available data, the PRAC concluded that:

1. **The risk is lowest with the combined OCPs containing the progestogens levonorgestrel, norgestimate, and norethisterone: it is estimated that each year there will be between 5 and 7 VTE cases per 10 000 women who use these medicines.**
2. **The risk is estimated to be higher with the progestogens etonogestrel and norelgestromin, with between 6 and 12 cases per 10 000 women per year.**
3. **For combined OCPs containing chlormadinone, dienogest, and nomegestrol, the available data are insufficient to know the risk compared with the other combined OCPs, but further studies are ongoing or planned.**

Table II. Recommendations from the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency.

Abbreviations: OCPs, oral contraceptive pills; PRAC, Pharmacovigilance Risk Assessment Committee; VTE, venous thromboembolism.

This table is based on data from reference 17.

The EMA review reinforces:

> *"the importance of ensuring that clear and up-to-date information is provided to women who use contraceptives and to the healthcare professionals giving advice and clinical care.*
>
> *The product information of combined OCPs has been updated to help women make informed decisions about their choice of contraception together with their healthcare professional. It is important that women are made aware of the risk of VTE and its signs and symptoms, and that doctors take into consideration a woman's individual risk factors when prescribing a contraceptive. Doctors should also consider how the risk of VTE with a particular combined OCP compares with other OCPs.*
>
> *The review also looked at the risk of arterial thromboembolism (ATE, blood clots in arteries, which can potentially cause a stroke or heart attack). This risk is very low and there is no evidence for a difference in the level of risk between products depending on the type of progestogen."*[17]

Separately, the EMA conducted a review on the use of Diane®35 and its generics. The EMA reminded prescribers that these preparations should only be used for the

treatment of moderate to severe acne related to androgen sensitivity or hirsutism in women of reproductive age. Although the preparations also prevent conception, this is not their main purpose. It is essential that neither Diane®35 nor its generics be used with hormonal contraception.[18]

The WHO Medical Eligibility Criteria (2010) indicated that women with a history of deep venous thrombosis (DVT) or pulmonary embolism (PE), acute DVT/PE, DVT/PE and established on anticoagulant therapy, or women who have been through a major surgery with prolonged immobilization are not eligible to take combined OCPs.[19]

The WHO also convened a series of technical consultations between the 13th and 16th of May 2013 in order to plan the guideline updates by considering the evidence related to the risk of VTE events associated with oral contraceptive formulations with various progestogens. Once this process has been completed, the WHO will be in a position to provide global guidance on this issue.

However, at this time, there is no need to change existing practices, and the conclusions reached by medicine regulatory authorities can be used by health professionals and their clients when making informed choices between alternative contraceptive options.

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Controversies surrounding symptoms and signs of chronic venous disorders

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Keywords:

chronic venous disorders; quality of life; venous symptom

Abstract

Association of so-called venous symptoms (aching, itching, tingling, burning sensation, swelling, easily fatigued legs, leg heaviness, and leg restlessness) with chronic venous disease (CVD) still remains a controversial issue. Although these symptoms and a decreased quality of life are common in patients with venous incompetence, and are even more frequent in those with a history of venous thrombosis and/or recurrent and bilateral varicose veins, research has actually revealed that these complaints are poorly correlated with objective signs of venous insufficiency. A venous source for these complaints is obvious in patients with advanced CVD, but a substantial part of venous symptoms, especially in patients with telangiectasias and uncomplicated varicose veins, is actually not of venous origin. In addition, such symptoms can be reported by many patients presenting with nonvenous diseases, while uncomplicated varicose veins can cause few symptoms or be asymptomatic. In many venous patients, these symptoms are not permanent, but can only be seen at the end of the day. Therefore, it is important to consider and investigate an alternative cause of such "venous" complaints, especially because other pathologies can accompany CVD and produce similar symptoms. The most common pathologies that may be responsible and should be taken into account include spinal disc herniation, hip and knee arthrosis, peripheral arterial disease, joint and ligament overload due to obesity, peripheral neuropathy, and adverse drug reactions.

Introduction

There is a great deal of controversy surrounding the association of so-called venous symptoms with chronic venous disease (CVD). An uncertain association of the presence of uncomplicated varicosities with these symptoms has even lead some health care providers to restrict access to treatment for asymptomatic patients with varicose veins or those experiencing few symptoms.[1] Clinical symptoms that are thought to be caused by chronic venous insufficiency include aching leg pain, itching, tingling, burning sensation, swelling, easily fatigued legs, leg heaviness, and restlessness. These symptoms typically worsen as the day progresses.[2] The presence of such complaints usually correlates with a decreased quality of life (QOL). An association of these symptoms with CVD is not as obvious as is usually believed. While some researchers found significant correlations between venous symptoms and the signs of CVD

Phlebolymphology. 2016;23(1):37-43

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(venous reflux revealed by means of Doppler sonography, visible varicose veins, or skin changes typical for venous incompetence [hyperpigmentation, lipodermatosclerosis, and ulcers]), others argued that these symptoms poorly correlated with clinical signs of venous insufficiency. In this review, I will summarize the research related to this problem in an attempt to explain conflicting results and interpretations of the studies.

Correlating symptoms and signs

Severe chronic venous disease

The majority of patients with severe forms of CVD–those with leg edema (C_3 according to the clinical, etiological, anatomical, pathophysiological [CEAP] classification), skin changes (C_4), and venous ulcers (C_5 and C_6)–present with some of the above symptoms. The proportion of patients with venous symptoms significantly increases with the "C" class of the CEAP classification.[3] Usually, in patients with advanced CVD, an association of venous symptoms with venous incompetence is not questioned, even if other pathologies can accompany chronic venous insufficiency and may produce similar symptoms. Also, it has been demonstrated that these patients present with a decreased QOL, with progressive impairment in QOL from C_3 to C_5/C_6.[2,4,5]

Less severe chronic venous disease

Venous background of clinical symptoms in patients with less severe forms of CVD, C_1 and C_2, remains controversial. Many of these patients are asymptomatic despite the presence of an obvious venous pathology.[3,6-10] In many C_1/C_2 patients, these complaints may actually be rooted in another coexisting pathology, such as osteoarticular, neurological, or arterial pathology *(Figure 1)*. For example, in the VEINES study (VEnous INsufficiency Epidemiologic and economic Study; 1531 patients with CVD and 1313 controls were assessed), the authors did not find significant differences in venous symptoms between the controls and patients with varicose veins (C_2). Thus, the authors speculated that clinical symptoms in patients with varicose veins probably resulted from concomitant aspects of CVD and not from varicosities per se.[9]

Poor correlation between symptoms and signs

In the Edinburgh Vein Study, a cross-sectional population study that assessed 1566 individuals, the authors did not demonstrate an association between lower-limb symptoms (leg heaviness, aching, and itching) and the presence of visible varicose veins.[11] Nor did they reveal a significant correlation between venous reflux and lower-limb symptoms.[12] Consequently, they concluded that most of these symptoms probably had a nonvenous cause.[11]

A similar conclusion came from another study, where itching and burning sensations in the legs were not correlated with the severity of venous insufficiency.[13] Also, an observational study by Howlader et al that assessed 132 patients attending a vascular clinic, did not reveal an association between the severity of symptoms and anatomic distribution of venous reflux.[14]

Potential correlation between symptoms and signs

In the San Diego population study, a cross-sectional study that assessed 2209 individuals, the researchers revealed an association between clinical symptoms and the presence of venous disease. Leg edema was the most specific symptom related to venous incompetence. Other symptoms (eg, leg heaviness, aching, and itching), although more common in the patients with venous disease, were also found (5% to 15%) in individuals without CVD.[15]

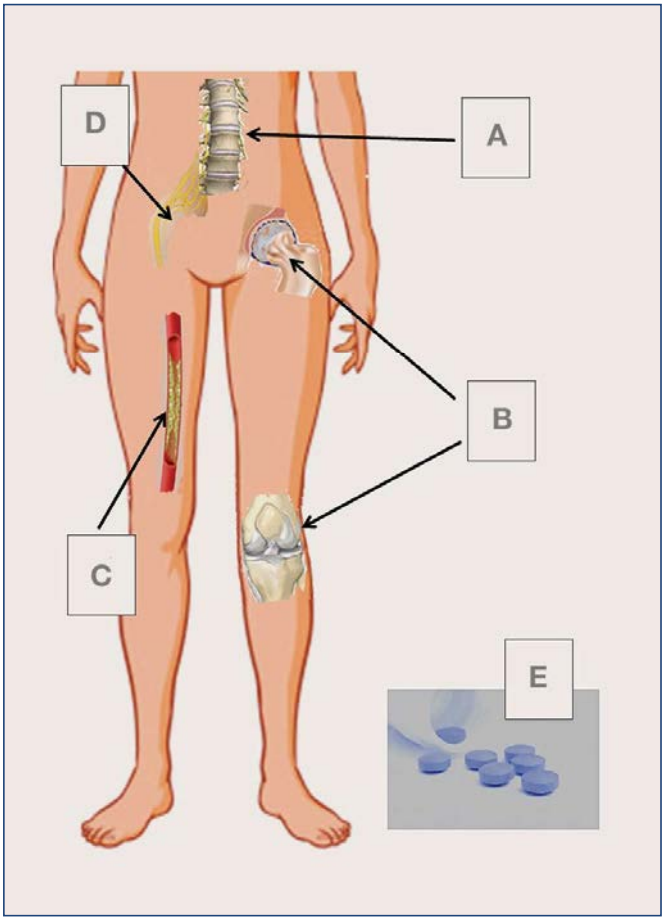

Figure 1. The most common nonvenous causes of the so-called "venous" symptoms.

A, Spinal disc herniation; B, hip and knee arthrosis; C, peripheral arterial disease; D, peripheral neuropathy; E, drug adverse reactions (calcium channel blocker or other medications).

Similar results were demonstrated in a recent Dutch study.[2] Except for swelling of the leg and itching, the authors revealed small and nonsignificant differences in the prevalence of venous symptoms between the patients with CVD and those suffering from other pathologies (eg, arthrosis, peripheral arterial disease, or spinal disc herniation). However, the patients with venous incompetence were more likely to experience symptoms at the end of the day, which was atypical in patients with other pathologies.[2]

In the recently published Bonn Vein Study 1, leg symptoms were more prevalent in subjects with varicose veins or chronic venous insufficiency, which was demonstrated using sonography. These symptoms were also more frequent in obese and underweight individuals. Some symptoms, ie, itching, leg heaviness, tightness, swelling, and pain after standing or sitting, were particularly associated with venous disease.[16]

In another study, the researchers found venous symptoms more frequently among patients with telangiectasias, and even more in patients with varicose veins. However, a substantial proportion of the individuals without venous disease also reported "venous" complaints (heaviness, swelling, aching, restless legs, cramps, itching, and tingling) and differences between the subjects with no visible venous pathology and those with either telangiectasias or varicose veins were modest.[17]

Similar conclusions also came from another survey. The authors of this cross-sectional study revealed venous symptoms in 60% of patients with varicose veins and demonstrated that this association was statistically significant. However, 33% of patients without varicose veins also suffered from venous symptoms. Risk factors that were significantly associated with these symptoms included prolonged sitting or standing and a history of thromboembolism. These symptoms were more common in older women and in tall (height >175 cm) and overweight (body mass index [BMI] >25 kg/m^2) men. Consequently, the authors concluded that varicose veins were not the only cause of venous symptoms. Other factors, primarily prolonged sitting and standing, could be a source of such symptoms, and improper clothes and shoes may also play a role. Of note, the researchers did not demonstrate a statistically significant correlation between these symptoms and a history of osteoarthritis. Still, venous symptoms were more common in such patients (20% vs 15% in patients with a negative history of osteoarthritis). Notably, in this study, the patients were not clinically examined to reveal an osteoarticular pathology.[8]

In another cross-sectional study on clinical features of CVD in 16 251 Italian patients, the researchers found a statistically significant positive correlation between the symptoms (eg, tired and heavy legs, leg pain, or leg edema) and severity of the venous disease (defined by the "C" grade of the CEAP classification). These venous symptoms were more prevalent in women and in patients with an increased BMI. However, almost all participants of this survey reported some complaints and only about 10% of the individuals surveyed were free of venous symptoms. An actual venous background of these complaints in the population studied remains questionable. Moreover, it was likely that relevant selection bias occurred in this study, since the individuals attending this survey were attracted by means of advertising in mass media. Therefore, the population was probably skewed toward people with some leg complaints that were not necessarily of a vascular origin.[10] To add to the confusion, in one study, patients with benign venous disease (C_2/C_3) reported more symptoms than those with complicated varicose veins (C_4/C_5).[14]

Venous background of leg symptoms in patients with telangiectasias and small epifascial veins (C_1) is even less certain. In a cross-sectional study that evaluated the clinical impact of small cutaneous veins, researchers found that venous symptoms, comprising leg edema, muscle cramps, and restless legs, were more common in patients with small varicosities in comparison with healthy controls (C_0), except for itching, which was less prevalent in individuals with dilated veins. However, when adjusted for age and sex, these differences—except for leg swelling—were no longer statistically significant. Thus, the authors concluded that although venous symptoms were quite common, even in C_1 patients, patients' age (older subjects) and sex (women) seemed to be a better explanation for these complaints than the presence of small cutaneous varicosities. Leg swelling can be related to dilated veins; however, their clinical relevance in the development of leg swelling seemed to be low (odds ratio, 1.3).[18]

Chronic venous disease and quality of life

Clinical stage

There are also conflicting results for studies on QOL in early stages of CVD. In the San Diego population study, the presence of venous disease, even of uncomplicated varicose veins, was associated with significant limitations on all functional scales (eg, physical functioning, role functioning, pain, and general health perception) of the Short Form 36 (SF-36) QOL questionnaire.[5] In another study, female sex was associated with a worse QOL in the patients referred to the varicose vein

clinic, but this effect was no longer observed when only C_2 patients were analyzed.[7] Similarly, the VEINES study did not reveal significant differences in QOL between C_2 patients and controls,[9] and there was no association between the "C" class and QOL impairment in a study assessing patients qualified for surgical treatment of varicose veins.[7] Also, an observational study on patients assessed in vascular laboratories did not demonstrate a decreased QOL in the C_1 and C_2 patients. Some QOL scores were even higher in varicose vein patients than in healthy people.[4,19] Likewise, in a study evaluating patients qualified for invasive varicose vein treatment, the authors found that an impaired QOL was independent of the clinical stage of venous disease.[20] However, a similar cross-sectional study (570 venous patients from Serbia) revealed a progressive worsening of QOL from C_1 to C_6. Even those patients presenting with C_1 and C_2 classes reported an impairment in QOL and did not consider their venous incompetence as a benign cosmetic problem, but rather as a real disease.[21] In another study, worsening QOL was also found in C_3 to C_6 patients as compared with the C_1 and C_2 patients.[22]

Venous reflux and inflammatory markers

Similarly, a correlation between the degree of venous reflux and QOL reduction is uncertain. Although it is expected that profound venous reflux or an increased diameter of the incompetent saphenous trunk would be associated with more severe clinical symptoms and decreased QOL, research does not always confirm such a relationship. In one study, incompetence of the great or small saphenous veins had a greater impact on QOL than nonsaphenous varicosities.[7] Another study revealed either a weak correlation or no correlation between the diameter of the incompetent great saphenous vein and impaired QOL in patients with varicose veins.[23] Similarly, there was no association between venous symptoms and systemic inflammatory markers, such as the von Willebrand factor, intercellular adhesion molecule 1 [ICAM-1], vascular cell adhesion protein 1 [VCAM-1], E-selectin, P-selectin, L-selectin, vascular endothelial growth factor [VEGF], interleukin 1α (IL-1α), IL-1β, IL-6, and tumor necrosis factor α (TNF-α).[14]

Interventions

Some studies examined the impact of interventions aimed at reducing venous incompetence (compression therapy or ablation of varicose veins) on venous symptoms and QOL. It might be assumed that if the symptoms were produced by venous disease, then such treatments should result in fewer complaints and a better QOL. However, only some of the patients studied were free of symptoms after an otherwise successful treatment of their varicose veins.[24-26] On the other hand, a recurrence of venous incompetence was not always accompanied by a return of the symptoms.[27,28]

As expected, wearing compression stockings resulted in improved QOL, not only in advanced (C_3 to C_5) venous patients, but also in those with early (C_2) disease.[19] A similar improvement in QOL was demonstrated by another study in patients with incompetent great saphenous veins (clinically C_2 to C_4). The authors of this study revealed that improvement in QOL was mainly due to the relief of venous symptoms. In this study, an invasive treatment (radiofrequency ablation of the great saphenous vein together with phlebectomies of superficial varicosities) resulted in an even greater improvement in QOL. An important finding of this study was that relief of symptoms by compression therapy was a good predictor of successful surgical treatment. Patients who improved their symptoms with compression therapy were more likely to experience further clinical improvement after ablation of varicose veins. However, a substantial proportion of patients who did not improve their QOL after compression therapy benefited from surgical treatment of varicose veins. Thus, not all clinical symptoms of CVD could be relieved by compression alone.[29]

In an interventional study, QOL significantly improved (71% of the patients got better) after surgical excision of varicose veins. Patients with uncomplicated (C_2 to C_3) and complicated (C_4 to C_6) venous disease experienced a similar improvement in their QOL. In this study, the patients with a poorer QOL before surgery were more likely to benefit from the treatment.[30] Similarly, in an observational study on patients receiving ultrasound-guided foam sclerotherapy of symptomatic incompetent great or small saphenous veins (patients with asymptomatic varicosities were not included), there was a significant improvement in QOL after treatment. This improvement was seen in both C_2 to C_3 and C_4 to C_5 patients. Improvement in QOL was similar in patients with great and small saphenous vein varicosities. Also, considering the mental domains of the QOL questionnaire, there was no difference in terms of QOL according to whether uncomplicated (C_2 to C_3) or complicated (C_4 to C_5) varicose veins were treated. A similar improvement in QOL was observed in patients with symptomatic varicose veins in the great or small saphenous vein territories, who underwent ablation of incompetent veins, and were randomized for surgical stripping and phlebectomies, endovenous laser treatment, or foam sclerotherapy. This improvement in QOL was similar, irrespective of the method used to treat varicosities.[31] A comparable improvement in QOL was also seen in the studies that assessed patients with varicose veins after ultrasound-guided foam sclerotheraphy[32]

or endovenous laser ablation.[33] On the contrary, physical aspects of QOL were significantly worse in patients with C_4 to C_5 venous disease. Interestingly, regarding physical domains of QOL, the patients with uncomplicated varicosities benefited more from the treatment in comparison with those with complicated varicose veins.[6]

Other influencing factors

It seems that CVD is not a uniform clinical entity in terms of clinical symptoms and impaired QOL. Thrombotic events, bilateral varicosities, and recurrence of varicose veins significantly affect the natural history of the disease. In the VEINES study, a multivariable regression analysis revealed that a previous venous thromboembolism was a predictor of poorer QOL, independent of variables, such as age, sex, country of residence, education, BMI, duration of CVD, and the presence of comorbidities.[34] In this study, an analysis that adjusted for the CEAP clinical class, confirmed that a previous thromboembolism was an independent predictor of a decreased QOL.[34,35] Bilateral varicose veins were associated with worse QOL than unilateral venous incompetence,[7] while some studies showed that QOL was significantly reduced in patients with recurrent varicosities compared with patients with primary varicose veins.[6,36] In one study, QOL impairment was no worse in recurrent varicosities than primary varicosities.[7]

Conclusion

Considering the inconsistent results in the above-presented studies, a reasonable explanation of the enigma of venous symptoms is not easy to discern. Certainly, in many of these studies, a selection bias occurred, either skewing the cohorts studied toward the patients presenting with real symptomatic CVD (clinical symptoms actually caused by venous disease) or toward the patients suffering from alternative sources of complaints, primarily osteoarticular pathologies. The first scenario was more likely if the patients qualifying for surgical treatment of varicose veins were evaluated, since they were initially screened by an experienced clinician and those with nonvenous complaints were not very likely to enter such a study. The second scenario could occur in the surveys that used advertising in mass media to select participants, thus mostly attracting people with pain or other leg symptoms primarily associated with neurological and orthopedic problems, and not with venous incompetence. Some researchers speculated that differences between the studies in terms of association of venous symptoms with CVD could result from different expressions of such complaints in particular languages, making a comparison of the studies conducted in different countries difficult.[8]

Nonetheless, venous symptoms seem to be nonspecific for CVD and can be reported by patients presenting with other diseases. Many uncomplicated varicose veins can be asymptomatic or cause very few symptoms.[3,6-10] In some patients with varicose veins, the symptoms and impaired QOL may result from concomitant components of venous disease, such as inflammatory skin changes, and may not directly cause dilated veins. In many of these patients, clinical symptoms are not permanent, but can be seen at the end of the day (when clinical trials are not routinely performed) or only during hot periods of the year (again, not a typical season to perform studies). Moreover, the research is telling us that a large proportion of venous symptoms have their sources in coexisting nonvenous pathologies.[2,11,15] This is of particular importance in C_1 and C_2 patients, since those with more severe forms of venous incompetence usually experience symptoms caused by venous disease. The majority of symptoms in the patients with telangiectasias and uncomplicated varicose veins do not seem to be of venous origin. Rather, especially if such symptoms are severe, an alternative cause should be considered.[37]

Unfortunately, available QOL questionnaires do not include questions that facilitate recognition of the real cause of symptoms. In addition, a thorough medical history and clinical examination, together with a vascular sonographic assessment, were not used by most of the studies that evaluated an association of venous symptoms with the presence of venous disease. Instead, rather nonspecific QOL questionnaires and simple clinical tests were utilized.

Studies with better designs, such as the recent Dutch[2] or German[16] ones, may put an end to the controversy over this problem. For the time being, from a practical point of view, it is important to distinguish patients with actual symptomatic varicosities from those patients with other sources of pain and other "venous" complaints. If such patients are not properly diagnosed initially, it is inevitable that some of them will be dissatisfied by the treatment for varicose veins, since the real cause of their complaints (eg, hip arthrosis) will not be addressed by a vascular procedure. Currently, we lack solid information on the prevalence of the pathologies that cause such "venous" symptoms in the population of patients with CVD. Still, the most common pathologies that may be responsible and should be considered in clinical practice include spinal disc herniation, hip and knee arthrosis, peripheral arterial disease, joint and ligament overload due to obesity, and peripheral neuropathy. These nonvenous problems can be quite prevalent in patients with CVD, especially those presenting with severe disease. For example, in one study, researchers have found that the majority

of C_5 to C_6 patients presented with reduced ankle mobility and symptoms of peripheral neuropathy.[38] There are also many patients who suffer from leg pain and edema after the use of different medications, especially calcium channel blockers.[39] In the case of such adverse drug-related events occurring in patients with varicose veins, an invasive or pharmacological treatment for venous incompetence will not relieve symptoms. Instead, the medication should be discontinued. Similarly, in patients complaining of symptoms caused by osteoarticular, neurological, or arterial pathologies, the disease that is the source of the complaints should primarily be addressed.

This article is updated from the formerly published version in *Medicographia*. 2015;37:20-25.[40]

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Patients seeking treatment for chronic venous disorders: Russian results from the VEIN Act program

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Keywords:

chronic venous disorders; compliance, compression; drug; efficacy; lifestyle advice; satisfaction; stockings; venoactive drug.

Phlebolymphology. 2016;23(1):44-53

www.phlebolymphology.org

Abstract

Objective: The Russian VEIN Act program (chronic **VE**nous d**I**sorders ma**N**agement and Evalu**A**tion of **C**hronic venous disease treatment effec**T**iveness) was an observational, prospective survey, carried out under the auspices of the European Venous Forum that was designed to assess compliance with non-surgical treatments (lifestyle advice, venoactive drugs, and compression therapy) for chronic venous disorders (CVD) in the framework of ordinary specialized consultations.

Methods: Adult patients complaining of venous pain associated with signs of CVD underwent a leg examination. Following confirmation of a CVD diagnosis, a case report form was completed listing the patient's clinical presentation and history, reported symptoms, and prescribed nonsurgical treatments. Patients were advised to return for a follow-up visit at which compliance with prescribed treatments was assessed.

Results: A total of 1607 patients were enrolled by 82 phlebologists in Russia. The time gap between the first visit (V0) and the follow-up visit (V1) was 3 months. Patients were predominantly female (80%), aged 45.7±14 years, and with a mean body mass index (BMI) of 26.02±5.02 kg/m^2. A total of 92% patients reported that they had experienced venous symptoms over the last 4 weeks. More women than men complained of venous symptoms and the symptom prevalence increased with age in women (not in men), but sex did not influence the intensity of the symptoms. Symptom intensity increased with higher BMI and Clinical, Etiological, Anatomical, and Pathological (CEAP) class in both sexes.

Patients reported suffering the following CVD signs: telangiectases (65%), varicose veins (63%), edema (52%), skin changes (11%), and/or venous ulcers (2%). Edema was equally reported in men and women, but more women than men complained of telangiectases (72% vs 33%; P<0.0001); while more men than women presented with varicose veins (82% vs 57%; P<0.0001), skin changes

(13% vs 8%; *P*<0.0001), and venous ulcers (4% vs 1.5%; *P*<0.0001). All signs increased with age in either sex, except telangiectases, which was more often reported by younger women (*P*<0.0001).

Most patients (78%) were receiving a treatment combining lifestyle advice, venoactive drugs, and compression therapy. Only a few were receiving a single treatment (<3%). The type and combination of treatment did not vary according to patient profiles, except for CEAP.

At V1, patients who were prescribed a venoactive drug reported that they had correctly complied with the dosage in 98% of cases, but this dropped to 72% when the duration of treatment was longer than 9 weeks. Compliance with lifestyle advice was reported by 91% of patients. Only 75% of patients with a prescription for compression therapy attended the V1 appointment wearing the compression hosiery correctly, and 44% reported that they had worn the hosiery as prescribed. The majority did not follow the prescription and wore the hosiery either most days (30%), intermittently (19%), or not at all (6%). The reasons for not wearing the hosiery were: "too difficult to put on" in 47%; "not comfortable" in 32%; "too warm" in 22%; "itches" in 18%; and "not aesthetic" in 12%. Age group, sex, BMI, symptom intensity, and CEAP classification were variables that influenced compliance to treatment.

Of the 89 followed-up respondents who received micronized purified flavonoid fraction (MPFF) in isolation, symptom disappearance was seen in 5.3% of those with leg heaviness, 29.8% with pain, 32.5% with a feeling of swelling, and 20.6% with cramps. This was significant for pain (*P*=0.0017). The intensity of symptoms was significantly decreased on the VAS: (*P*<0.0001) -2.1±2.2 cm for leg heaviness, -2.6±2.2 cm for pain, -2.6±1.9 cm for a feeling of swelling, and -2.6±2.1 cm for cramps. The frequency and time (after prolonged standing or during the night) at which symptoms were felt were significantly reduced after MPFF treatment.

Conclusion: The VEIN Act Program reflects the profile of patients with CVD consulting phlebologists in Russia. CVD is a chronic and progressive disease and educational efforts are needed to raise awareness among Russian physicians, patients, and the scientific community about the necessity for earlier diagnosis, particularly in men, and for better treatment compliance.

Introduction

Chronic venous disorders (CVD) of the lower extremities are characterized by a wide range of symptoms and signs, resulting from abnormalities in the venous system.[1,2] All forms of CVD are related to venous hypertension, which is caused by reflux through faulty valves.[1,2] Cases of CVD can range from early to severe. Early symptoms include heavy legs, leg pain, a sensation of swelling, and pins and needles in the legs, and can progress to signs including varicose veins, edema and leg ulcers, the most chronic manifestation.

CVD is a common condition that has a significant impact on both the individuals affected and the health care system. It is estimated that 30% to 35% of the general population can be classed as C_0 and C_1 of the Clinical, Etiological, Anatomical, and Pathological (CEAP) classification system.[3,4] This includes the 20% of the adult population with venous symptoms, but no visible or palpable signs of venous disease (C_{0s}) and those with telangiectases or reticular veins (C_1).[5] In Europe, more severe stages of the disease, such as skin changes and active ulceration, may affect 5% to 15% of the population.[4,5] The quality of life (QOL) assessment is directly associated with the severity of venous disease.[6] Patients who have or have had venous ulcers report a QOL similar to patients suffering with congestive heart failure.[7] The initial management of CVD involves nonoperative measures to reduce symptoms and prevent development of secondary complications and progression of the disease. Nonoperative treatment includes lifestyle advice, pharmacological treatment using venoactive drugs (VADs), and compression stockings.[8] The specific treatment prescribed is based on the severity of disease with CEAP classes C_4 to C_6 and often requires invasive treatment. A referral to a vascular specialist should be made for patients with CEAP classes C_4 to C_6 (and probably also for CEAP class C_3 with extensive edema).[8] A healthy lifestyle, including maintaining an ideal body weight or weight reduction if overweight, may improve the manifestations of CVD as obesity is a well-established risk factor for its development.[9]

Some patients, however, will not comply with the prescribed treatment for various reasons. The problem of noncompliance is well known to venous specialists and how to improve it has been the subject of much debate.[10,11] Available data describing the extent of noncompliance in CVD have been limited to a series of patients with venous ulceration using compression therapy (CT).[12,13] The degree

of noncompliance to other noninvasive treatments and in other symptom subsets remains undefined.

Aims

The VEIN Act program (chronic **VE**nous d**I**sorders ma**N**agement and evalu**A**tion of **C**hronic venous disease treatment effec**T**iveness) was an international educational effort aimed at helping physicians, patients, and the scientific community assess compliance with nonsurgical treatments for CVD.

The program also aims to frame the profile of patients seeking medical care for CVD and assess the effects of nonsurgical treatments in patients with symptomatic CVD, in terms of symptom improvement, amelioration of daily activity, and patient satisfaction.

Materials and methods

Design

The VEIN Act program is a prospective, multicenter, observational survey carried out under the auspices of the European Venous Forum and supported by an unrestricted grant from the Servier Research Group. It was performed in the framework of ordinary consultations.

Patients

At first consultation (V0), patients complaining of pain in the lower limbs and consulting for any clinical presentation related to CVD were recruited. The suitability of the patients for involvement in the program was determined using the following criteria: male or female over 18 years old (not having ongoing treatment for CVD); informed of their involvement in the program, their right to refuse to participate fully or partly, and providing consent; not consulting for an emergency or for an acute episode of an ongoing event; and free of concomitant diseases that might interfere with venous treatment.

If these criteria were met, the patients were asked about venous signs and symptoms and then underwent a leg examination (if this was routine practice). If the patient presented with at least one venous symptom or venous sign or both, a case report form was completed with the following information: patient's clinical presentation and history, presence of CVD signs and/or symptoms, and the nonsurgical treatments prescribed, listing all treatment characteristics. Patients were advised to return for a routine follow-up visit (V1).

The V1 follow-up consultation was scheduled, if possible, at the end of the prescription duration. At this visit, compliance with and the effect of treatment were assessed, together with patient satisfaction. Reasons for noncompliance, if any, were also sought.

Characterization of chronic venous disorders symptoms and signs

Symptoms were confirmed as being related to CVD, if one of the four following symptoms was present (heavy legs, pain in the legs, a sensation of swelling, and cramps) and if there was an increase in severity in two of the following circumstances: "after prolonged standing," and/or "at the end of the day," and/or "during the night." CVD signs were described according to the Clinical, Etiological, Anatomical, Pathophysiological (CEAP) classification.[14]

Assessment of chronic venous disorder symptoms

The visual analog scale (VAS), which consists of a straight horizontal line 100 mm in length, is applicable to all patients regardless of language.[15] "No symptoms" was marked on the left side of the scale and "Unbearable symptoms" on the right side. Patients were requested to indicate the intensity of their symptoms by using the VAS and to circle on a 5-point verbal scale the daily frequency of the symptoms as: "throughout the day and night," "regularly," "occasionally," "rarely," or "never."

Description of chronic venous disorders signs

Patients were classified by physicians according to the clinical CEAP stage (the highest class was retained for the patient's classification) as follows: C_{0s}, no visible signs; C_1, telangiectases, reticular veins; C_2, varicose veins; C_3, edema; C_{4a}, skin changes with pigmentation or eczema; C_{4b}, skin changes with lipodermatosclerosis or atrophie blanche; C_5, healed ulcer; C_6, active ulcer.

Results

Enrollment in the survey

The Russian VEIN Act Program was performed between April 2013 and June 2014 by 82 venous specialists. A total of 1607 patients were enrolled at the first visit V0, and 1590 patients returned for a follow-up visit at V1. The mean time between visits V0 and V1 was 83 days, ie, around 3 months, and no statistical difference was observed between men and women regarding the time interval between visits (P=0.93).

Patients' profile at V0

Participants in the Russian VEIN Act Program were predominantly female (79.8%), had a mean age of 45.7±14 years, and a mean a body mass index (BMI) of 26.02±5.02 kg/m^2.

Symptoms and signs

Most patients reported that they had had symptoms over the last 4 weeks. The symptoms, in order of frequency, were: heaviness (91.8%); leg pain (70.2%); sensation of swelling (69.7%); and cramps (45.7%). Each patient complained of a mean of 2.8±1 symptoms with an intensity on the VAS ≥4 cm: heaviness (5.2±2 cm); leg pain (4.8±2.2 cm); sensation of swelling (4.9±2.3 cm); and cramps (4.0±2.5 cm). Symptom intensification occurred mostly at the end of the day for 89.1% of consulting patients and after prolonged standing for 59.5%.

On a daily basis, patients reported that their symptoms were present "regularly" and "throughout the day and night" in almost 60% of cases, and "occasionally," "rarely," or "never" in 40% of cases.

Women complained of their symptoms more often than men (91% vs 80%; *P*<0.0001), but symptom prevalence increased with age in men, but not in women. Symptom intensity increased with BMI and with increasing CEAP class in both sexes. The daily frequency of symptoms increased with age in both sexes.

Self-reported signs of CVD included: telangiectases (65%), and/or varicose veins (63%), edema (52%), skin changes (11%), venous ulcer (2%) (*Figure 1*). Swollen legs and edema were reported in an equal number of men and women (52%; *P*=NS). More women than men consulted with telangiectases (72% vs 33%; *P*<0.0001), while more men than women consulted with varicose veins (82% vs 57%; *P*<0.0001), skin changes (13% vs 8%; *P*<0.0001), and/or active or healed venous ulcers (4% vs 1.5%; *P*<0.0001). Younger women were more likely to consult for telangiectases than older women (64% of women ≤50 years vs 36% of women ≥51 years; *P*=0.0005), but this was not statistically significant in men. The presence of varicose veins caused younger men to consult more (56% of men ≤50 years vs 44% of men ≥51 years; *P*=0.0014), while this behavior was not related to age in women. The proportion of patients reporting clinical signs significantly increased with older age in both sexes (*P*<0.005).

In terms of CEAP classification, physicians found that 3.7% of patients presented with no signs, but only symptoms (C_{0s}) (*Figure 2*). Due to the fact that only the higher CEAP class was considered and that doctors could tick only one box (while patients could report several signs and tick several boxes), the prevalence of physician-reported clinical signs was lower than that of patient self-reported signs, as follows:

- 23% of the survey population consulting for leg problems was classified as C_1. Women consulted more often for telangiectases than men (5% of men and 28% of women; *P*<0.0001)
- 26% (35% of men and 24% of women; *P*<0.0001) were C_2
- 36% were C_3 with no difference between sexes (*P*=NS)
- 11.5% were C_4 to C_6 with a predominance of men over women (17.7% vs 9.8%; *P*<0.0001).

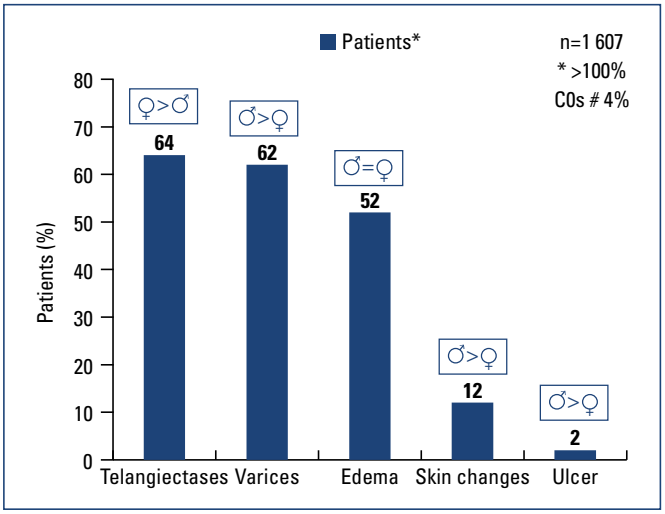

Figure 1. Self-reported signs by patients at V0.

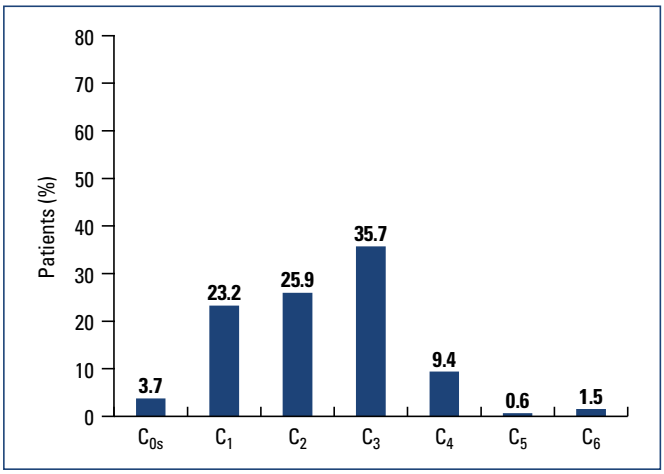

Figure 2. Physician-reported CEAP at V0.

Whatever the method used for reporting signs, the sex difference followed similar trends.

Treatment of chronic venous disorders

Almost 40% of patients had already consulted a doctor, and 31% had previously been treated for their leg problems. These figures significantly increased with older age, increasing BMI, symptom intensity, and CEAP class, whatever the patients' sex (P<0.0001). Nearly all patients (99.7%) who consulted for leg problems at V0 were prescribed a treatment, whichever CEAP clinical class they were assigned, including C_{0s} (P=NS). Nonsurgical treatment was prescribed in 66% of patients, and nonoperative plus sclerosing treatment was performed in 33.6% of patients. Only 0.4% underwent a single surgical procedure. Nonoperative treatment consisted of a combination of lifestyle advice, VADs and CT in 78% of cases, VADs plus CT in 10% of cases, and VADs + lifestyle advice in 5% of cases. A few patients received a single nonoperative treatment (<3%). The severity of disease according to the CEAP classification significantly influenced the type of prescribed treatment (P=0.0004), whereas sex, age, and BMI did not. While all C_{0s} patients received a nonoperative treatment alone, patients in other CEAP classes were often prescribed a dual nonoperative plus sclerosing treatment, and C_4 to C_6 patients could benefit from additional painkilling drugs.

At V0, the majority of patients (97%) were prescribed VADs in association with lifestyle advice and/or CT, or in isolation (2%). For 57% of patients, drugs were prescribed for more than 9 weeks, while the remaining 43% received a shorter treatment (≤8 weeks) at a dose of 2.0±0.2 tablets a day for any drug brand.

CT was prescribed to 92% of the survey population in association with other treatments. Stockings were preferred to bandages (98.5% vs 1.5%), at thigh level (84%) rather than below the knee (16%), and were prescribed for 8 weeks or less in 20% of patients and 9 weeks or more in most of patients (80%). It should be noted that for most patients, doctors prescribed CT for a longer duration than VADs. The majority of consulting patients received moderate strength CT (63%), 34% a light- or mild-strength CT, and 3% a high-strength CT. A single device was prescribed in 62% of patients, two devices in 36%, and more than two devices in 2%.

Assessment of compliance to treatments at V1

Lifestyle advice

Lifestyle advice was associated with either VADs, compression therapy, or both in 88% of consulting patients, and was rarely prescribed alone (1%). Among the patients who received lifestyle advice, 91% reported they had correctly followed the prescription, including choosing the right exercise (84%), aiding blood return by leg elevation (81%), moving legs in all circumstances (80%), wearing shoes with suitable heels (70%), avoiding warmth (59%), losing weight (52%), and massaging legs as often as possible (37%). Reasons for noncompliance were difficulty in adopting these measures daily (58%) and lack of time (38%).

Venoactive drugs

Among the patients who were prescribed VADs, 98% reported they had respected the dosage and 97% reported that they had purchased the prescribed drug brand name. The few who did not buy the prescribed brand stated that this was because the pharmacist had changed it for another brand (35%) or either the brand was not always available at the purchase point (16%). At V0, most patients were prescribed long-term treatment (≥9 weeks). At V1, 87% of the patients had complied with the prescription duration if it was ≤8 weeks and 72% if it was ≥9 weeks. The reasons for not respecting the treatment duration were described as: "forgot to take it" (27%), "took other pills" (14%), and "lack of efficacy" (13%). Younger patients (≤50 years) were more likely to forget to take their VAD, while older patients (>65 years) were more likely to complain about a lack of treatment efficacy.

Sex, BMI, CEAP class, and symptom intensity did not affect compliance with VADs or to lifestyle advice.

Compression therapy

Among the patients prescribed CT, only 75% attended the V1 appointment wearing the compression hosiery correctly. Almost half the patients (45%) reported using the stockings on a daily basis, 30% used them most days, and 19% used them less often. The remaining 6% did not use the stockings at all or abandoned them after a trial period.

The reasons for not wearing the compression hosiery included: "too difficult to put on" in 47% of patients; "not comfortable" in 32%; "too warm" in 22%; "itches" in 18%; "not aesthetic" in 12% and "ineffective" (2%). For the remainning 26%, no specific reason was given. Only

'too difficult to put on' and 'unattractive' were significantly dependent on CEAP class: patients in severe stages ($C_{5,6}$) more often felt that CT was 'too difficult to put on' (73% in $C_{5,6}$ *vs* 47% in all CT patients, *P*=0.0028), and those in C_1 found it particularly 'unattractive' (22% in C_1 vs 12% in all CT patients, *P*=0.023). A number of variables influenced the compliance to CT.

Women were more likely to find CT unattractive compared with men (14% vs 6%; *P*=0.04), while men were more likely to find the hosiery too warm (30% vs 20%; *P*=0.05). Age also had an impact on whether CT was worn: younger patients finding it unattractive (72% in patients ≤50 years vs 18% in those ≥51 years; *P*=0.008) or too warm (67% in patients ≤50 years *vs* 33% in those ≥51 years; *P*=0.02). Older patients were more likely to find CT too difficult to put on (53% in those ≥51 years vs 47% in those ≤50 years; *P*=0.0004). CEAP classification also influenced wearing of CT. Of the 1431 patients who responded to the question on compliance with CT, 636 (44%) reported they had worn the stockings "as prescribed": 17% in C_{0s}, 37% in C_1, 42% in C_2, 50% in C_3, 53% in C_4, and 38% in C_5-C_6 (sample size of C_{5-6} was small, only 6 patients). The higher the CEAP class (from C_{0s} to C_4), the better the compliance with the CT prescription. Only 5% had not worn stockings at all, mostly in the C_{0s} and C_{5-6} classes.

The strength of the purchased CT was described as "moderate" or "mild" in 95% of CT patients: 88% in C_{0s}, 96% in C_1, 98% in C_2, 96% in C_3, 83% in C_4, and 82% in C_{5-6} patients. Strong and very strong compression strengths were bought mainly by C_4 and C_{5-6} patients (16% in C_4 and 18% in C_{5-6} vs 3% in all CT patients, *P*<0.0001).

Assessment of treatment efficacy

Efficacy of combined treatment

A total of 1368 patients with combined treatment were followed-up at V1. Symptom disappearance was observed in 6.3% of patients with leg heaviness, 33.6% with pain, 28.8% with a feeling of swelling, and 43.8%

Presence of*:	N patients =89	Before MPFF treatment	After MPFF treatment	Improvement*** in symptom intensity	*P*-value
Heaviness		76 (85.4%)	74 (83.1%)	4 (5.3%)	NS
Leg pain		57 (64.0%)	43 (48.3%)	17 (29.8%)	0.0017
Sensation of swelling		40 (44.9%)	35 (39.3%)	13 (32.5%)	NS
Cramps		34 (38.2%)	32 (36.0%)	7 (20.6%)	NS
Quantification of the following symptoms (cm on visual analogue scale)*					
Heaviness	70	4.0±2.3	1.9±1.9	-2.1±2.2	<0.0001
Leg pain	38	4.3±2.3	1.7±1.6	-2.6±2.2	<0.0001
Sensation of swelling	26	4.5±2.4	1.8±1.9	-2.6±1.9	<0.0001
Cramps	26	4.0±2.5	1.3±1.4	-2.6±2.1	<0.0001
Time at which leg problems are most intense*:	87				
At the end of the day		80 (92.0%)	75 (86.2%)	7 (8.8%)	NS
After prolonged standing		35 (40.2%)	22 (25.3%)	17 (48.6%)	0.0046
During the night		18 (20.7%)	8 (9.2%)	11 (61.1%)	0.0039
Frequent symptoms**	95	84 (88.4%)	26 (27.4%)	58 (69.0%)	<0.0001

Table I. Symptom improvement after treatment with MPFF in terms of symptom disappearance and decreased symptom intensity and frequency.

* *Total of the items can exceed the total number of patients as patients can tick several boxes for this question*
** *Frequent = "Occasionally," "Regularly," and "Throughout the day and night" frequencies; Nonfrequent = "Never" and "Rarely" frequencies*
*** *Improvement is defined as a presence/frequency at V0 and an absence/no frequency at V1*

with cramps (*P*<0.0001). The intensity of symptoms on the VAS decreased by at least (-2.3±2.5 cm). The frequency at which symptoms were felt was significantly reduced from "Occasionally," "Regularly", and "Throughout the day and night" to "Never" and "Rarely" in 57% of patients; (*P*<0.0001). Among the patients who felt symptoms more intensively during the night, 75% no longer complained of symptom intensification at this time. In addition, 39% and 18% no longer complained of symptoms after prolonged standing, or at the end of day, respectively.

Efficacy of micronized purified flavonoid fraction on venous symptoms

A total of 89 respondents who received micronized purified flavonoid fraction (MPFF) treatment without any other combined treatment were followed-up at V1. Symptom disappearance was seen in 5.3% of those with leg heaviness, 29.8% with pain, 32.5% with a feeling of swelling, and 20.6% with cramps *(Table I)*. Due to the low sample size, this was significant for pain only (*P*=0.0017). The intensity of symptoms was significantly decreased on the VAS: -2.1±2.2 cm for leg heaviness, -2.6±2.2 cm for pain, -2.6±1.9 cm for a feeling of swelling, and -2.6±2.1 cm for cramps; *P*<0.0001 (*Figure 3*). The frequency at which symptoms were felt was significantly reduced from "Occasionally," "Regulary", and "Throughout the day and night" to a frequency of "Never" and "Rarely" in 69% of patients *P*<0.0001. Among the patients who felt symptoms more intensively during the night, 61% no longer complained of symptom intensification at this time, 48% no longer complained after prolonged standing, and 9% no longer complained of symptom intensification at the end of day *(Table I)*.

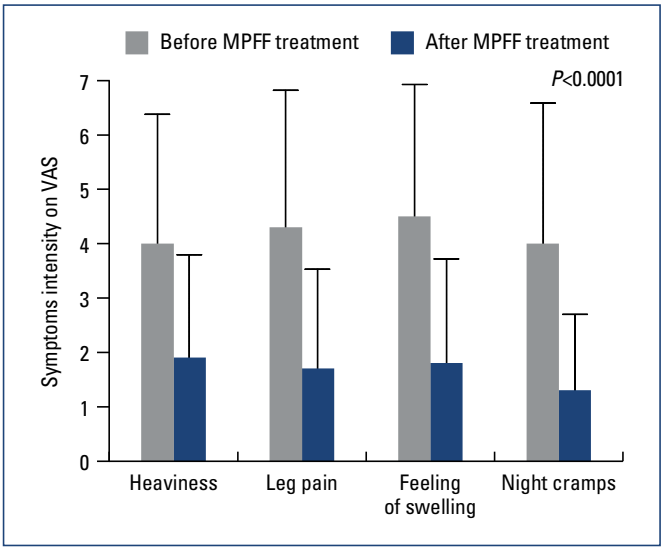

Figure 3. Improvement in venous symptoms with MPFF.

**Abbreviations: MPFF, micronized purified flavonoid fraction; VAS, 10 cm-visual analog scale.*

Patients' satisfaction with nonoperative treatment

Patients were rather, very, or extremely satisfied in 96% of cases with either combined nonoperative treatment or MPFF treatment alone *(Table II)*. The degree of patient satisfaction was not dependent on any variables (sex, age, BMI, CEAP class, or symptom intensity).

Level of satisfaction at V1	Nonoperative treatments (N=1607)	MPFF treatment (N=96)
Missing data	21	0
Not satisfied at all	5 (0.3%)	0 (0.0%)
Rather unsatisfied	60 (3.8%)	4 (4.2%)
Rather satisfied	598 (37.7%)	46 (47.9%)
Very satisfied	713 (45.0%)	28 (29.2%)
Extremely satisfied	210 (13.2%)	18 (18.8%)
Total	1586 (100.0%)	96 (100%)

Table II. Patient satisfaction with combined nonoperative treatment or MPFF alone.

Discussion

The VEIN Act Program provides a snapshot of individuals suffering from venous leg problems and seeking medical help in the framework of ordinary consultations in Russia. It revealed that women are more likely to consult for their leg problems than men. In addition, more women than men consulted with telangiectases, particularly at a younger age (≤50 years), whereas more men than women consulted with varicose veins, skin changes, and active or healed venous ulcers, suggesting that men are more hesitant to consult earlier in the disease process. Only 3% of consulting patients had symptoms without visible signs (C_{0s}), whatever their sex. In contrast, the Vein Consult Program revealed that almost 20% of the Russian adult population could be assigned to the C_{0s} class.[5] At this stage, patients are not aware that symptoms could hide an underlying venous disease.

Whatever the method used for reporting signs in consulting patients (patient self-reported signs or physician-reported CEAP), the trends were similar, particularly in terms of the

sex differences. However, the use of the simplified CEAP clinical classification for reporting signs does not entirely reflect reality and tends to underestimate the early signs of disease (eg, telangiectases, varices).

Almost all patients (99.7%) consulting phlebologists for their leg problems received nonoperative treatments, consisting of lifestyle advice, VADs, or CT (mostly in combination), or with sclerosing agents. Additional painkilling drugs were reserved for C_4 to C_6 patients.

Phlebologists tended to recommend advice that was easy to follow (leg elevation, leg movement, shoes with suitable heels), while weight loss and leg massages were less frequently proposed, providing a potential explanation for the high rate of compliance with lifestyle advice (91%) in this study. Patients prescribed VADs satisfactorily complied with the prescription duration if it was ≤8 weeks (87%), but less so if the treatment duration was ≥9 weeks (72%).

In the majority of patients prescribed CT (95%), the strength of compression purchased was "moderate" or "mild." Most patients were prescribed CT for a duration of ≥9 weeks, but less than half of the patients (44%) reported using the stockings as prescribed (ie, on a daily basis), 30% used them most days, and 19% used them intermittently. Noncompliance was due to physical reasons related to the stockings ("too difficult to put on," "uncomfortable," "too warm") in more than 22% of Russian patients. Another 26% of the patients in this series could not state a specific physical reason for noncompliance. As stated by Raju,[12,16] "*these patients are unwilling to tolerate the intangible sense of restriction imposed by daily stocking wear. There is probably considerable overlap between these two groups. In either case, the central factor behind noncompliance appears to be the pressure exerted by the compression stockings themselves–precisely the property that underpins efficacy in controlling symptoms, suggesting that many patients consider compression stockings a quality of life issue.*"

In the current study, nonoperative treatment, combined or in isolation (MPFF alone), proved efficient in terms of alleviating symptoms and reducing symptom intensity and daily frequency. Patients were relieved from heaviness, leg pain, feeling of swelling, and cramps. Relief from leg pain was significant with MPFF treatment (P=0.0017). There was a highly significant decrease in the intensity of all symptoms (at least 2 cm on the VAS) with combined nonoperative treatment or with MPFF alone (P<0.0001). The daily frequency at which symptoms were felt was also significantly reduced (P<0.0001) with combined nonoperative treatment or with MPFF alone.

Conclusion

The VEIN Act program reflects the profile of Russian patients with CVD consulting a phlebologist. It shows that educational efforts are needed to raise awareness among physicians, patients, and the scientific community about the necessity of earlier diagnosis, particularly among men. It also highlights the need for better treatment compliance, as CVD is a chronic and progressive disease. Nonoperative treatments, such as MPFF, proved easy for patients to comply with and efficient in terms of symptom relief and reduction in symptom intensity and daily frequency; thereby, improving patients' daily life.

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

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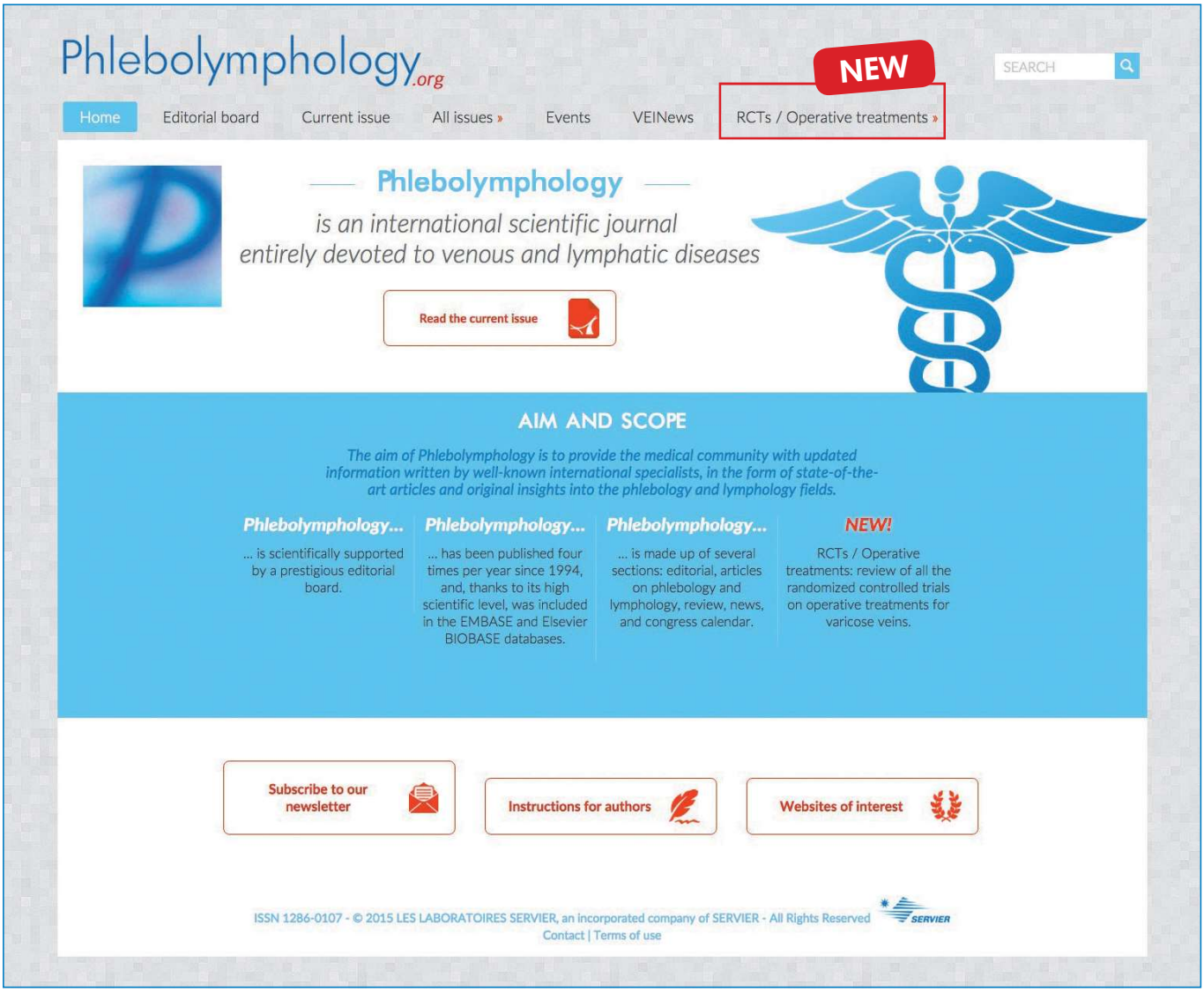

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