MANAGEMENT OF CHRONIC VENOUS DISORDERS OF THE LOWER LIMBS

GUIDELINES ACCORDING TO SCIENTIFIC EVIDENCE

PART II (CHAPTERS 9-18)

(For Part I please see International Angiology 2018;37:181-232)

Document developed under the auspices of
The European Venous Forum
The International Union of Angiology
The Cardiovascular Disease Educational and Research Trust (UK)
Union Internationale de Phlébologie

EDIZIONI MINERVA MEDICA
TORINO 2020

DISCLAIMER

Due to the evolving field of medicine, new research may, in due course, modify the recommendations presented in this document. At the time of publication, every attempt has been made to ensure that the information provided is up to date and accurate. It is the responsibility of the treating physician to determine the best treatment for the patient. The authors, committee members, editors, and publishers cannot be held responsible for any legal issues that may arise from the citation of this statement.

RULES OF EVIDENCE

Management of patients with chronic venous disorders has been traditionally undertaken subjectively among physicians, often resulting in less than optimal strategies. In this document, a systematic approach has been developed with recommendations based upon cumulative evidence from the literature.

Levels of evidence range from Level A to Level C and strength of recommendation is either 1 or 2.[1, 2]

Level A evidence derives from two or more scientifically sound randomized controlled trials (RCT) or systematic reviews and meta-analyses in which the results are clear-cut and are directly applicable to the target population. Level A evidence implies that further research is very unlikely to change our confidence in the estimate of effect.

Level B evidence is provided by one well conducted RCT or more than one RCT with less consistent results, limited power or other methodological problems, which are directly applicable to the target population as well as by RCT extrapolated to the target population from a different group of patients. Level B evidence implies that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Level C evidence results from poorly designed trials, observational studies or from small case series. Level C evidence implies that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

A strong recommendation (1) is made if benefits do, or do not, outweigh risks. A weak recommendation is made (2) if the benefits and risks are closely balanced or if there is uncertainty about the magnitude of the benefits and risks.

GLOSSARY

AVVSS: Aberdeen Varicose Vein Severity Score
bFGF: Fibroblast growth factor
CEN: *Comité Européen de Normalisation*
CVDs: Chronic venous disorders
CVD: Chronic venous disease
CVI: Chronic venous insufficiency
DVT: Deep vein thrombosis
EGF: Endothelial growth factor
EMMPRIN: Extracellular inducer of MMP
EVLA: Endovenous laser ablation
GSV: Great saphenous vein
ICAM-1: Intercellular adhesion molecule-1
IL-1: Interleukin-1
IPC: Intermittent pneumatic compression
IPVs: Incompetent perforating veins
IVUS: Intravascular ultrasound
LDS: Lipodermatosclerosis
MPFF: Micronized purified flavonoid fraction
MMPs: Matrix metalloproteinases
MT1-MMP: Membrane type 1 MMP
MT2-MMP: Membrane type 2 MMP
PDGFR-α: Platelet derived growth factor receptor alpha
PDGFR-β: Platelet derived growth factor receptor beta
PE: Pulmonary embolism
PG: Prostaglandins
PGE1: Prostaglandin E1
PGE2: Prostaglandin E2
Proximal DVT: DVT in popliteal or more proximal veins
QOL: Quality of life
PTS: Post-thrombotic syndrome
RF: Radio-frequency
SEPS: Subfacial endoscopic perforator ligation surgery
SFJ: Saphenofemoral junction
SMC: Smooth muscle cells
SPJ: Saphenopopliteal junction
SSV: Small saphenous vein
$tcPO_2$: Transcutaneous PO_2
TGF-β1: Tumor growth factor- β1
TIMPs: Tissue inhibitors of metalloproteinases
uPA: Urokinase plasminogen activator
VADs: Venoactive drugs
VCSS: Venous clinical severity score
VEGF: Vascular endothelial growth factor
VTE: Venous thromboembolism
VVs: Varicose veins

ACKNOWLEDGEMENTS

The faculty that was responsible for the 2014 version of the Guidelines was: N. Baekgaard (Denmark), G. Bates (UK), H. Bjarnason (USA), A. Bradbury (UK), R. Broholm (Denmark), M. Cairols (Spain), A. Comerota (USA), M. De Maeseneer (Belgium/Netherlands), B. Eklof (Sweden), T. Gasparis (USA), N. Georgiou (Cyprus), G. Geroulakos (UK), A. Giannoukas (Greece), A. Jawien (Poland), S. Kakkos (Greece), E. Kalodiki (UK), T. Kölbel (Germany), N. Labropoulos (USA), L. Nonn (Denmark), M. Lugli (Italy), O. Maleti (Italy), D. Milic (Serbia), G. Mosti (Italy), K. Myers (Australia), P. Neglen (Cyprus), O. Nelzen (Sweden), S. Pappas (Cyprus), H. Partsch (Austria), M. Perrin (France), A.A. Ramelet (Switzerland), Z. Rybak (Poland), E. Shaydakov (Russia), C. Wittens (Netherlands).

References

1. Guyatt GH, Cook DJ, Sackett DL, Eckman M, Pauker S. Grades of recommendation for antithrombotic agents. Chest 1998;114(Suppl):441S–4S.

2. Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, Phillips B, *et al.* Grading strength of recommendations and quality of evidence in clinical guidelines: report from an american college of chest physicians task force. Chest 2006;129:174–81.

CHAPTER 9

Treatment of superficial and perforating vein incompetence

A. Treatment of superficial incompetence

Introduction

For the last 100 years, open surgery (OS) has been the most recommended and used procedure for treating varicose veins (VVs). During the past 30 years, the development of minimally invasive correction of primary superficial venous reflux in patients with chronic venous disease (CVD) of the lower limbs by endovenous techniques[1] has provided a patient-friendly means to treat this disorder as an office-based procedure with ablation of the saphenous veins and varicosities including radiofrequency ablation (RFA), endovenous laser ablation (EVLA), ultrasound guided foam sclerotherapy (UGFS), steam, cyanoacrylate glue and mechachemical ablation. In addition, surgery preserving the great saphenous vein was developed in parallel including the "Cure Hemodynamique de l'Insuffisance Veineuse en Ambulatoire" (CHIVA)[2] and "Ablation Selective des Varices sous Anesthésie Locale" (ASVAL) techniques.[3]

Surgery

Modern open surgery can be performed under local anesthesia, as an outpatient procedure, based on preoperative assessment and mapping using duplex ultrasound. If there is a benefit of performing surgery under tumescent anaesthesia has not yet been studied. The traditional flush ligation of the saphenofemoral junction (SFJ) is completed by invagination stripping of the proximal (down to the knee level) saphenous vein. Stripping can be also done by using a cryo-probe. Treatment of the incompetent small saphenous vein (SSV) usually involves ligation of the saphenopopliteal junction (SPJ) and proximal excision by invagination. Stripping of the distal SSV or the GSV below the knee may reduce VV recurrence but is associated with increased risk of sural or saphenous nerve injury, respectively.[4, 5] The necessity of flush ligation has been called into question[6, 7] but recent long-term recurrence data seem not to agree. Remaining non-truncal varicosities can be either excised by phlebectomy or managed by sclerotherapy in the same session or later. There is general agreement for recommending elastic compression stockings up to one week after operation.[8-11]

Complications of surgery

Early complications of surgery include discomfort (common), bruising (common), bleeding (rare), lymphatic vessel complications (rare), femoral vein injury (very rare), wound infections (2-6%), and injury of the saphenous or sural nerve (rare). Deep vein thrombosis (DVT) and pulmonary embolism (PE) rates, symptomatic or asymptomatic, following open surgery vary from 0.4% to 5.3% and from 0% to 0.5%, respectively. Late complications include permanent neuropraxia (≤5%) and recurrence which increases with duration follow-up (20-50%).

Radiofrequency ablation (RFA)

Ablation of the treated vein is achieved by heat delivered into the vein through the percutaneously placed radiofrequency catheter. The heat causes a direct thermal injury to the vein wall, resulting in destruction of the endothelium, collagen denaturation of the media, and finally thrombotic and fibrotic occlusion of the vein. The RFA is performed under local-tumescent anesthesia with ultrasound-guided percutaneous catheter placement as an outpatient procedure.

The first-generation device was a bipolar electrode that looked like a flower, located at the tip of the endovenous

catheter (ClosurePlus) that was heated to 85 °C and slowly withdrawn. The current ClosureFast RF catheter, introduced in 2007, is user-friendly and treatment is performed in a shorter time compared to ClosurePlus. A temperature of 120 °C is generated and the entire pullback time is 3-4 minutes.

Another RFA system of bipolar RF-induced closure, Celon RFITT, is available (Olympus Medical Systems). This system generates heat at 60-85 °C and operates with a continuous pullback speed of 1 cm/s.

Endovenous laser ablation (EVLA)

Similar to RFA, the heat generated by laser causes a direct thermal injury to the vein wall. However, EVLA provides direct heat injury to the blood also. Blood coagulates at 70 to 80 °C, steam bubbles form at 100 °C and carbonization of the coagulum is observed at 200 to 300 °C.

Currently available laser fibers include hemoglobin-specific laser wave lengths (810, 940, and 980 nm) and water-specific laser wavelengths (1319, 1320, and 1470 nm). Even longer wavelengths have been tested. Initially, the fibers were bare-tipped, but the new radial or jacket-tipped fibers have now become the standard. Laser devices are made by several different manufacturers. Like RFA, EVLA is also performed under local-tumescent anesthesia with ultrasound-guided percutaneous catheter placement as an outpatient procedure.

The techniques for EVLA and RFA are similar and preferably involve use of a micro-access kit with placement of a 4-Fr or 5-Fr micro sheath which is exchanged for a 6Fr for EVL (5 Fr for slim fibres) and 7 Fr for closure Fast RF. Then the laser fiber can be introduced with the tip positioned at 2 cm distal to the SFJ or SPJ. With the new radial emitting fibers, the tip can be placed closer to the SFJ (0.5 cm). The laser fiber is activated and withdrawn at a rate of 1 to 2 mm/s for the first 10 cm and 2 to 3 mm/s for the remaining vein length. Energy settings of 70 to 80 J/cm are recommended. The post-ablation procedures are similar to RFA.

Complications of thermal ablation

Reviews analyzing RCTs involving RFA (N.=317 patients), EVLA (N.=1057 patients) and OS (N.=975 patients) provided a list of short-term complications. There was a significantly higher rate of wound infection for OS (2.3%; 95% CI, 1.3-3.1%) vs. EVLA (0.5%; 95% CI, 0.3-1.3%; P=0.006), but not between OS and RFA (1.5%; 95% CI, 0.4-3.0%; P=0.094). The incidence of paresthesiae was significantly lower with EVLA (3.8%; 95% CI, 2.4-4.5%) compared with RFA (5.2%; 95% CI, 3.1-7.9%; P<0.001) and OS (7.4%; 95% CI, 5.3-8.3%; P<0.001). The incidence of thrombophlebitis was significantly lower for OS (3.0%; 95% CI, 2.9-4.0%) compared with RFA (5.5%; 95% CI, 3.0-7.8%; P=0.003) and EVLA (5.6%; 95% CI, 4.2-7.0%; P=0.003). There was no difference in the rate of thermal skin burns between RFA and EVLA.[12-14]

Steam ablation

Steam is the latest of the thermal endovenous techniques to enter clinical use. It was introduced in 2006 by R. Milleret as a less expensive alternative to laser and radio frequency.[15] The principle is to inject inside the vein pulses of water vapor at 120 °C, each pulse delivering 60 Joules of energy into the lumen. Steam is injected under pressure: the first pulse dislodges the blood and the next ones heats the vein wall. A 5Fr stainless steel catheter is used, which it is flexible enough to navigate through tortuosities without using a guide wire. Two lateral holes close to the tip eject the steam, avoiding the risk of heating-up the deep veins when the catheter is used close to the SFJ. A comparative animal study by Thomis *et al.*[16] showed that immediate shrinking was more pronounced with steam than with both Closure Fast ®RF and 1470 nm TULIP® fiber laser catheters. Perivenous damage occurred less often, although the number of cases was not sufficient to obtain statistical significance.

A pilot study by van den Bos *et al.*[17] showed full obliteration in 11 out of 19 veins treated at 6 months with partial reopening in the other cases, but the energy delivered was too low, 1 pulse/cm instead of 2 to 4 advised by the promoters of the technique. One-year results showed non-inferiority compared with EVLA.[18]

In a series of 75 patients the complications included a thrombus protrusion into the femoral vein, one ecchymosis at the entry site in one case and moderate pain for 8 days in 6 patients.[15]

Sclerotherapy

Injection of a sclerosing agent into the vein to achieve endoluminal fibrosis and obstruction of the vein has been used for almost a century. Although liquid sclerotherapy has been used primarily for obliteration of spider veins or telangiectasiae, interest in the use of sclerotherapy greatly increased when Cabrera *et al.*[19] reported in 1995 and 2000 that foam prepared by mixing gas with the detergent polidocanol was effective for obstruction of larger veins. Ultrasound-guided foam sclerotherapy (USGFS) has rapidly spread for treatment of primary and recurrent varicose

veins, including the GSV and SSV, perforating veins and venous malformations.

The mechanisms of action of sclerosing solutions include the destruction of venous endothelial cells, exposure of subendothelial collagen fibers, and ultimately, the formation of fibrotic obstruction. Delivery of the solution as a foam prolongs the time of contact and amplifies the effect of the chemical. In Europe approved agents for sclerotherapy include sodium tetradecyl sulphate (STS), polidocanol, sodium morrhuate, and glycerine. Hypertonic saline has also been used for many years.

Sodium tetradecyl sulphate 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 in higher concentration, extravasation may result in tissue necrosis. Hyperpigmentation, matting, and allergic reactions have been described. Foaming of this agent is easy.

Polidocanol is another detergent, which is safe and painless when injected, with a low risk of tissue necrosis when used in low concentration. It may cause hyperpigmentation but has a very low rate of allergic or anaphylactic reactions.

Sodium morrhuate is a detergent that is used less frequently because of the relatively higher incidence of skin necrosis observed with extravasation and because of the higher risk of anaphylactic reactions.

Glycerine is a corrosive agent that destroys the cell surface proteins by affecting chemical bonds. Chromated glycerine is used most frequently as a solution of glycerine, sterile water, and benzyl alcohol. Chromated glycerine is safe and rarely leads to tissue necrosis, hyperpigmentation, or allergy. It is suitable for treatment of small veins or telangiectasiae.

Hypertonic saline 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 is performed using small tuberculin syringes and a 30- or 32-gauge needle. Treatment is usually started with larger varicose veins and ends with reticular veins and telangiectasiae. The proximal part of the limb is treated first followed by the distal part. Use of loupes for magnification and transillumination helps intraluminal injection and avoids extravasation of the drug. Severe pain during injection may signal extravasation, and further injection should be avoided. Despite poor evidence, the patient is often instructed to wear high compression class (30-40 mm Hg) graduated compression stockings for 1-3 days after treatment for telangiectasiae and reticular veins and at least 1 week after treatment for varicose veins and perforating veins.

USGFS of the saphenous vein is the least invasive of the endovenous ablation techniques. The European guidelines for sclerotherapy in chronic venous disorders in 2014[20] reported that foam was an effective, safe and minimally invasive endovenous treatment for varicose veins with a low rate of complications. The most popular technique currently in use was developed by Tessari using a three-way stopcock connected with two syringes. Experts recommend a ratio of one-part solution of STS or polidocanol to four or five parts of 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 less than 100 μm. The veins are cannulated in supine patients and some experts suggest that the limb should be elevated 30 degrees to inject the foam. Ultrasonography is used to monitor the movement of foam in the veins. The great or small saphenous vein is injected first, followed by varicose veins and perforating veins if indicated. A maximum of 10 mL of foam is injected during one session. Some experts recommend to complete the procedure by placing a short stretch bandage or a 30 to 40 mm Hg graduated compression stocking on the limb. Most experts recommend compression for 1 to 2 weeks. Complications of USGFS are usually classified into two categories (a) severe complications: anaphylaxis (extremely rare), large tissue necrosis (extremely rare), stroke and transient ischemic attack (extremely rare), distal DVT (very rare), PE (extremely rare), motor nerve injury (extremely rare) and (b) benign complications: 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), embolia cutis medicamentosa (very rare).[20]

Cyanoacrylate glue ablation

A new non-thermal technique using a formulation of cyanoacrylate (CA) adhesive delivered intravenously, has been developed to improve some of the limitations with RF, EVL and sclerotherapy ablation. Upon intravascular injection, CA rapidly solidifies *via* a polymerization reaction and results in an inflammatory reaction of the vein wall. In an experimental model a granulomatous foreign body reaction was observed in the venous lumen. At 60

days fibroblasts were seen invading the contents of the vein lumen and 100% occlusion was observed. The primary potential advantage with this new technique is that it does not require tumescent anesthesia, and the patients do not need postoperative compression stockings.

The disposable Sapheon Closure System (SCS) includes 4 mL of Sapheon Cyanoacrylate Adhesive (SCA) and a Sapheon Delivery System (SDS). The SDS consists of a 7-Fr introducer sheath/dilator, a 5-Fr delivery catheter, a 3-mL syringe, and a dispenser gun. The 5-Fr delivery catheter has a hydrophobic design to help prevent CA adhesion to the vein wall and a novel configuration with air-filled microchannels to enhance sonographic visibility. The dispenser gun will deliver either 0.08 or 0.16 mL of SCA with each trigger pull. The venous system is mapped under ultrasound guidance and the GSV is accessed percutaneously with a micropuncture introducer kit followed by insertion of a 0.035" J guide wire. Using ultrasound control the 7-Fr introducer sheath/dilator is advanced to the SFJ and positioned 1.5-2 cm caudal to the SFJ. After extracting the SCA with a 3-mL syringe, the latter is attached to the delivery catheter. The catheter is primed with the dispenser gun to fill all but the final 3 cm of catheter tubing; this step ensures that the catheter tip is empty upon venous insertion to prevent premature contact of SCA with blood. The primed delivery catheter is inserted into the introducer sheath and secured with spin-lock mechanism. The 5 cm of the catheter tip is exposed distal to the tip of the sheath and positioned 4 cm from the SFJ. The technique basically consists of segmental pullback and compression of the vein after glue injection via the catheter. Prior to delivery of the SCA, the ultrasound transducer is positioned transversely just cephalad to the catheter tip near the SFJ. Once positioned, pressure is applied on the transducer to compress the vein leading to vein wall coaptation 4 cm caudal to the SFJ. Using continuous compression, 2 injections of 0.08 mL of SCA are delivered into the vein by depressing and holding the dispenser gun trigger. The entire delivery system is immediately retracted by 3 cm, and the vein walls are coapted using compression over the treatment segment for three minutes. The next segment is then treated by repositioning the ultrasound transducer just cephalad to the catheter tip, compression applied, and another 0.08 mL is delivered with one trigger depression, followed by 3 cm catheter pullback and compression of the treated vein for 30 seconds. This injection/retraction process is repeated until the entire length of the target segment is treated. After venous closure is confirmed by ultrasound, the catheter is removed, and compression applied to catheter entry site until hemostasis is achieved. A single band-aid is applied; compression stockings are not required. The patient is discharged and instructed to resume normal activities but avoid strenuous exercise.[21]

The effectiveness of venous ablation using cyanoacrylate has been extensively reviewed in several clinical trials. Currently there are three RCTs regarding glue comparing with RF and/or EVLA.[22-24]

In the VeClose trial, in which 222 patients were randomly allocated to either cyanoacrylate glue ablation or radiofrequency ablation, the anatomical results were proven to be non-inferior to the RFA group, with 97% success rate reported for both groups at 1 year follow-up.[25] Three year results are now available.[22] These results were supported by several other clinical trials, with similar one-year patency rates, such as the eSCOPE study (93%).[26] Nonetheless, in two recent publications, reported success rates at 1-year follow-up were lower (76%). In these studies, a correlation between anatomical failure and larger diameter veins was found, suggesting the need for proper patient selection.[27, 28]

Regarding the application of cyanoacrylate glue in the treatment of non-GSV trunks, not much evidence is available. The only known prospective trial conducted in this setting was the WAVES trial, which studied not only venous ablation of the great saphenous vein (N.=48), but also small saphenous (N.=8) and accessory saphenous veins (N.=14).[29] This study reported a 100% success rate for venous occlusion of all territories, although these results are limited by the short follow-up period considered, which was only one month.[29] Cyanoacrylate is absolutely contra-indicated in patients with history of hypersensitivity to this drug, as well as previous acute venous thromboembolism or sepsis. Since this is an endovenous treatment, vessel tortuosity can be considered a relative contra-indication, as it can prevent proper proximal placement of the catheter. Vessel diameter, although not representing an actual contra-indication, should be taken into consideration, since only veins not exceeding 12 mm in diameter were included in the majority of safety and efficacy studies.[30]

Regarding procedure complications, post-procedural phlebitis reaction is the most commonly reported, affecting up to 4-20% of the patients.[26, 28, 31] Deep venous thrombosis and pulmonary embolism are, in theory, possible complications, although there are no reports of these events in current literature. Infections at the puncture site are possible, but rare.[30]

Rarely, patients may show allergic reactions to the injected glue and ulcerated granuloma formation has recently been reported.[32, 33]

Mechanochemical ablation (MOCA)

A mechanochemical device (ClariVein) was developed to minimize the negative aspects of both endothermal ablation and USGFS for treatment of saphenous incompetence, while incorporating the benefits of each. 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. The mechanochemical method achieves venous occlusion utilizing a wire rotating within the lumen of the vein at 3500 rpm which injures the intima to allow for better efficacy of the sclerosant. A liquid sclerosant (sodium tetradecyl sulphate) 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. It is connected to an interface cartridge unit for connection to the 9 V DC battery 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 plus the catheter sheath are inserted into the vein percutaneously with the patient in reversed Trendelenburg position. The catheter sheath is retracted to expose the wire tip, which is positioned 2 cm from the SFJ. The patient is then placed into the supine position for the remainder of the procedure. The catheter motor is turned on and, with the wire rotating and the sclerosant being infused, the catheter is pulled down the vein at a rate of approximately 1-2 mm/s. After removal of the catheter, occlusion of the GSV and patency of the common femoral vein is checked by duplex ultrasound. Compression is applied for 2 weeks without restriction of patient activity. The most frequently reported complications in the MOCA studies were induration (12-18%), thrombophlebitis (2-13%) and ecchymosis (8-10%). Less frequently reported were deep venous thrombosis (0-1%) and hyperpigmentation (5%). No other major complications have been reported using MOCA in the treatment of saphenous vein incompetence.[34-39]

Two RCTs have been performed with contradicting results regarding periprocedual pain scores where one study showed less pain compared with RF and the other showed no difference against RF and EVLA.[40, 41] After one year the occlusion rate was significantly higher after endothermal treatments.[41]

Surgery with preservation of the saphenous trunk

CHIVA

The CHIVA technique is a conservative approach to redistribute the reflux from superficial to deep system through strategically selected ligation sites on the GSV or tributaries in order to avoid ablation of the GSV as a possible future vascular graft.[2] CHIVA is a complex approach demanding careful mapping and understanding of the anatomy and function of the superficial system by well trained and experienced physicians.[42]

ASVAL

Stab phlebectomy of all varicose tributaries can lead to an improvement or abolition of the saphenous vein reflux. Most patients operated upon with this method had less advanced stage of varicose veins. The ASVAL method is a procedure based on the ascending or multifocal approach of the CVD allowing a reduction or suppression of the saphenous reflux by removing the tributaries, whereas the CHIVA is based on the descending theory. The goal of ASVAL is to remove the distal venous reservoir by phlebectomy of incompetent tributaries and preserve the GSV.[3]

Pelvic and ovarian vein embolization

When VVs are fed by incompetent pelvic and ovarian veins, embolization of the refluxing veins by coils and sclerosing agent is a minimally invasive method. Nevertheless when reflux is related to iliac vein compression, iliac stenting is also a useful technique.

Outcome after intervention

RFA versus *open surgery*

There are 7 RCTs in 9 articles comparing RFA with OS and almost all of them conclude that after radiofrequency ablation there was less postoperative pain, faster recovery and earlier return to work and normal activities, as well as higher patient satisfaction.[43-51] The longest follow-up was 3 years and there was no difference in terms of clinical result between OS and RFA. It must be noted that in all series the bipolar catheter (Closure Plus) was used. We now know that the new ClosureFast® catheter has demonstrated better results in published observations.[52] It should however be pointed out that modern less invasive open surgery under local or anesthesia in the office setting is showing similar good outcomes.

EVLA versus *open surgery*

15 RCTs (22 publications) compared EVLA with OS and all used bare tipped fibers.[53-74]

Quality of safety and early efficacy was high with no significant difference between the groups. After two years no significant difference was found in clinical or duplex scanning recurrence, clinical severity or QoL.

The results from several studies described above are maintained in a five-year follow-up.[66, 67, 71, 72, 74] No RCT has been reported with the new radial or jacket-tipped laser fibers compared to open surgery.

EVLA variations

Six RCTs compared modifications of EVLA with OS.[75-80] High ligation in association with EVLA did not modify the 2-year outcome. EVLA that included the below knee GSV needed less complementary sclerotherapy and was not associated with saphenous nerve injury. A 1470 nm radial fiber was superior to a 980 nm bare-tip fiber in terms of pain, ecchymosis and induration in the immediate postoperative course.[76] In another study, a 1500 nm bare-tip fiber had a better immediate postoperative course, with reduced induration around the treated vein and use of analgesics, and better quality of life compared with the 980 nm bare-tip fiber.[75] At 6 months the occlusion rate was similar in both groups. In a study on the 1470 bare tip fiber there was no difference in occlusion rate between warm or cold tumescence anesthesia.[81]The cold tumescence group had pain reduction with a reduced need for analgesics. A comparison between the bare tip and the tulip tip (1470 nm laser) concluded that the latter had less postoperative pain and better QoL scores.[77] Compression for one week (compared with 2 days) provided less postoperative pain.[80]

RFA versus *EVLA*

Seven RCTs (8 publications) compared RFA with EVLA.[81-88]

There was less bruising and less pain with ClosureFast. Subsequently, new laser fibers were developed e.g. radial or jacket-tip fibers. Kabnick has reported on a pilot study comparing RFA (ClosureFast in 50 patients) versus EVLA (980 nm jacket-tipped fiber in 35 patients).[89] At 72 hours there was 100% closure in both groups. At one-week pain and bruising scores were identical in the two groups. His results suggested that jacket-tipped laser fibers generated a uniform thermal reaction similar to ClosureFast. His conclusion was that the most current RFA and jacket-tip laser methods and devices are similar regarding efficacy and short-term complications. With procedure time and tumescent anesthesia also equivalent, these procedures present no genuinely significant difference to patients.

An updated meta-analysis with 12 studies including 1577 patients concluded that EVLA and RFA seem to have the same efficacy and safety.[90]

RFA versus *electrocoagulation*

RFA was compared to electrocoagulation (EC) in a RCT involving 85 limbs. The main postoperative complication was paresthesia; however, there was no statistical significance between the groups (P=0.320) regarding its presence. Time to return to routine activities was lower in the EC group than in the RFA group (P=0.026). There was no difference between the groups at the 3-month (P=0.157) and 6-month (P=0.157) follow-up in occlusion of the GSV and improvement of the quality of life score (P=0.786 and P=0.401, respectively). The authors concluded that EC was an effective method for ablation of the GSV, with venous occlusion rate, occurrence of complications, and effect on quality of life similar to those with RFA.[91]

EVLA versus *cryostripping*

Disselhoff and his team presented the results of 2 RCTs in three publications comparing high ligation and cryostripping versus EVLA.[92-94] Cryostripping was significantly faster while EVLA was associated with significantly less postoperative pain and quicker return to normal activities. However, there was no significant difference in terms of recurrence, quality of life, or cost.

Foam sclerotherapy vs. *open surgery*

9 RCTs (9 publications) compared foam sclerotherapy with surgery.[95-101]The outcome up to 12 months follow-up did not give any conclusive results. Geroulakos' group reported their 5-year follow-up and concluded that the treatment was equally effective in both groups as demonstrated by improvements in venous clinical severity score (VCSS), venous segmental disease score (VSDS), and the physical component of the SF-36 score.[98] Aberdeen varicose vein questionaire (AVVQ) score was better in the surgical group. A recent published RCT with an 8-year follow-up concluded that OS had a technically better outcome in terms of recurrence of GSV and SFJ reflux than USGFS in the long term and significant clinical progression of venous disease measured by VCSS in both groups, but less after surgery.[102] GSV high ligation and UGFS in one session was compared with GSV high ligation and stripping combined with multistab avulsion in a recent RCT involving 177 patients with primary GSV reflux (C4-C6).[103] At the end of 12 months, the cumulative reflux recurrence rate was 13.8% in the UGFS group and 13.5% in the control

group (P=0.955). In the UGFS and control group, minor complications (27.7% *vs*. 21.6%, P=0.406) and major complications (3.1% *vs*. 2.7%, P=0.895) were not significantly different. The patient satisfaction rate reached 92.3% in the UGFS group and 89.2% in the control group 12 months after operation (P=0.270). The authors concluded that the outcomes indicated that UGFS combined with GSV high ligation was safe and effective for severe lower extremity varicosis.

Foam sclerotherapy versus *EVLA*

Again in RCTs from Geroulakos' group the effectiveness and costs were compared between USGFS and EVLA.[104-106] There were no differences in occlusion rate, AVVQ, VCSS or venous filling index (VFI) between the two procedures, but USGFS outperformed EVLA in cost, treatment duration, pain, analgesia requirements and recovery.

OS vs. *thermal* vs. *foam sclerotherapy*

In one RCT, which compared OS with thermal and chemical ablation, outcome was assessed at 1 and 3 years.[66, 107] Results after 1 year showed that all treatments were effective with a higher technical failure rate after foam sclerotherapy; RFA and foam sclerotherapy were associated with a faster recovery, less postoperative pain and superior QoL scores compared with EVLA and surgery. At three years the results were similar with less occlusion rate and higher re-operation rates after foam sclerotherapy. However, according to ardent supporters of foam the short catheter used as well as the injection site were not the ideal techniques for USGFS. There was no difference in clinical recurrence rate and all groups improved in VCSS, AVVSS and QoL. At 5 years most recanalizations of the GSV occurred after USGFS and no difference in the technical efficacy was found between the other modalities.[108]

Two recently published RCT evaluated the long-term results of surgery, EVLA and USGFS in the treatment of GSV reflux. The main outcome measure was the occlusion rate of the GSV 5 years after intervention and USGFS showed significantly inferior occlusion rates.[109, 110]

A recently published meta-analysis included 9 RCTS in which 1352 legs were followed for longer than 5 years. Included studies compared OS to EVLA, RFA and USGF. Although pooled risk ratios for long-term recurrences (1.35) and re-interventions (1.45) favored OS, the available sample size was too small to reach statistical significance (95% CI 0.76-2.37, and 0.8-2.51). However, the GSV recanalization rate was statistically significant in favor of OS (pooled RR=2.28, 95% CI 1.2-4.3), and neovascularization rate significantly favored endovascular treatment (pooled RR=0.24, 95% CI 0.07-0.82).[111]

Another systematic review and meta-analysis of RCTs that was focused on the causes of recurrences has reached similar conclusions. It showed no difference in recurrence rates between OS and endovenous ablations, but different pattern of causes of REVAS. Neovascularization was more prevalent after OS, and recanalization was more frequent after endovenous ablations. Both treatment options resulted on average in 22% of recurrences, of which 60% required re-interventions.[112]

A different meta-analysis was recently published and included 3 RCTs and 10 follow-up studies of RCTs with follow-up >5 years. Thermal ablation and OS showed higher success rates than USGFS after GSV treatment. Recurrent reflux rates at the SFJ were significantly lower in OS than USGFS and thermal ablation. VCSS scores were similar between thermal ablation and OS.[113]

The latest Cochrane analysis to compare the effectiveness of EVLA, RFA and USGFS *versus* OS in the treatment of SSV identified only 3 RCTs, all of which compared EVLA with OS; one also compared USGFS with OS and there were no trials comparing RFA with OS. The authors concluded that the quality of the evidence is low and further RCTs for all comparisons are required with longer follow-up.[114]

OS versus *microwave ablation*

One single center RCT has reported the results of OS compared with microwave ablation plus high ligation of the GSV with a 2-year follow-up.[115] The recurrence rate was 14.3% in the microwave ablation and 28.2% on the OS group and there was no difference in the AVVQ and VCSS between the two groups. However, skin burns 10.2% were related to subcutaneous tributaries treated by microwave.

MOCA versus *thermal ablation*

One RCT has reported the results of MOCA (Clarivein) compared with thermal ablation (EVLA or RFA) with a 1-year follow-up. The GSV occlusion rate was significantly higher after EVLA and RFA than after MOCA. Quality of life was similar between interventions.[41]

A different multi-center RCT comparing RFA vs MOCA in 170 patients concluded that both techniques had similar short-term technical, quality of life and safety outcomes.[40] At 6 months patients in the MOCA group experienced significantly less maximum pain during the procedure by Visual Analogue Scale (MOCA median 15 mm (interquartile

range 7-36 mm) *versus* RFA 34 mm (interquartile range 16-53 mm), P=0.003) and number scale (MOCA median 3 (interquartile range 1-5) *versus* RFA 4 mm (interquartile range 3-6.5), P=0.002). Occlusion rates, clinical severity scores, disease specific and generic quality of life scores were similar between groups at one and six months. The authors concluded that pain secondary to truncal ablation is less painful with MOCA than RFA with similar short-term technical, quality of life and safety outcomes.

The most recently publiched RCT compared MOCA with EVLA and RF showing a significantly higher occlusion rate at one year for the thermal techniques.[41]

Glue vs. *EVLA* vs. *RFA*

A recently published RCT has reported the results of Glue (N-Butyl Cyanoacrylate) compared with EVLA and RFA with a 2-year follow-up. No differences were observed in occlusion rates between the three modalities.[24] Most studies have compared glue with EVLA giving similar outcomes at one year.[23, 25, 116-118]

Another RCT evaluated the 36-month efficacy and safety of cyanoacrylate closure for the treatment of GSV in comparison with RFA. The closure rate and improvement in quality of life outcomes were similar between the two treatment groups.[22]

Glue versus *EVLA*

Cyanoacrylate glue was compared with EVLA in a RCT involving 400 patients. There were 208 procedures in cyanoacrylate ablation group and 204 in EVLA group. Operative time was 13±3.4 minutes in the CAA and 31.7±8.8 minutes in the EVLA (P<0.001). All procedures in both groups were successful, and the target vein segments were fully occluded at the end of the procedure. Periprocedural pain was less in the CAA (P<0.001). Induration, ecchymosis, and paresthesia rates were significantly higher after EVLA (P<0.001). The mean length of follow-up was 14 months (range 10-16). The 3, 6 and 12 months closure rates were 97.4%, 95.6%, and 94.1% for EVLA and 98.6%, 97.1% and 96.6% for glue respectively. In both groups, the VCSS and Chronic Venous Insufficiency Quality of Life Questionnaire declined significantly with no difference between groups. The authors concluded that management of incompetent great saphenous veins both endovenous cyanoacrylate ablation and laser ablation result in high occlusion rates. Endovenous cyanoacrylate ablation technique is fast and simple with low periprocedural pain that does not require tumescent anesthesia and compression stockings.[23]

OS *versus* conservative treatment

A RCT compared conservative treatment limited to life style advice *versus* OS in C_{2s} patients.[119, 120] After 2-year follow-up OS was credited with cosmetic and QoL improvement, and symptomatic relief. However, the benefit was modest for relatively little national health service cost.

OS *versus* CHIVA

Two RCTs have compared OS with CHIVA.[121, 122] The Carandina RCT[121] was limited to shunt I+II varicose veins according to the CHIVA nomenclature, while the article by Parés *et al.*[122] encompasses all kinds of primary varicose veins. Nevertheless, this large, well-documented randomized, open-label, controlled, single-center study raises some questions. First, more than 90% of patients presented uncomplicated varicose veins (C_2). Second, one outcome assessment is not considered in this article, *i.e.* patient evaluation. This point is particularly important given that one of patients' main complaints after CHIVA is a persistent cosmetic problem.

OS *versus* cryostripping

Though cryostripping is not at present frequently used, two randomized controlled trials have compared it with OS.[123, 124] There was no difference between postoperative pain or clinical results. However, postoperative hematoma was less frequent with cryostripping.

OS *vs.* high ligation + phlebectomies

Campanello *et al.* in Sweden in 1996 presented a randomized clinical trial on preservation of the GSV after high ligation, phlebectomies and perforating vein ligation. Later an English team repeated the same RCT with a longer follow-up. In both studies there was no difference in the rate of recurrence in the two groups.[125-127] However, high ligation plus tributary phlebectomies with perforating veins ligation is not used today. The explanation lies probably in both the more precise information provided by duplex ultrasound investigation of the saphenofemoral junction (SFJ) and the outcome after endovenous ablation. Duplex ultrasound has shown that reflux at the SFJ is absent in many patients presenting with VVs and that the terminal valve is competent in about 50% of cases in the presence of GSV reflux. When thermal or chemical ablation is used, the termination of the SFJ remains open and this does not seem to negatively influence the results. Furthermore, high ligation tends to enhance recurrence related to neovascularization. Many variations of OS related to technique or anesthesia have been described.[128-132]

Long-term results of RCT

At least 11 RCTs have reported long term results, most often five-year outcomes. Interestingly they generally show more groin recurrence following thermal treatments and foam than after OS.[113, 133, 134]

Most likely the cause of this is the frequently used safety margin of around 2 cm to the SFJ. The groin recurrence following the endovenous techniques were caused by SFJ incompetence and very often combined with anterior accessory saphenous vein incompetence or GSV recanalization. Neovascularisation was mostly seen after OS but not as frequent as groin recurrence among endovenously treated patients. Clearly it is necessary to reassess the need for a safety margin following thermal treatments. Radial emitting fibers can be placed closer to the SFJ according to company representatives, but this has not yet been verified in any scientific study. Clearly the risk of EHIT is a major concern. Regarding the subjective outcome variable clinical recurrence, no clear differences were detected, and symptomatic recurrence was not assessed in any study.

Indications for operative treatment

Indications for operative treatment rely both on the clinical status of the patient and information provided by ultrasound investigation.

There is no indication for surgery in patients with C_0 and C_1 CVD. In patients with superficial reflux causing C_2 to C_6 CVD operative treatment should be considered particularly in C_3-C_6 class. The choice of procedure depends on many factors which include personal mastery of a technique, cover/reimbursement by the health services/health insurance which varies from country to country and the patient's own choice, influenced by possible postoperative problems, recovery time and time off work, the procedure type that allows easiest control of recurrences and information from friends, literature or the internet.

Presence of varices after interventional treatment (PREVAIT) represents a particular situation in terms of indications. There is general agreement that USGFS is the first line treatment in almost all cases except in patients presenting with lower limb VVs fed by reflux from pelvic veins. The European guidelines for sclerotherapy give a Grade 1B to this procedure.[20] However, this recommendation is based on case series.[135, 136]

Strength of recommendation and grades of evidence

Considering the recurrence rates which are similar (20% at 5 years) and other relatively small advantages and disadvantages of the methods as presented above the following recommendations have been given:

- open surgery: 2A;
- modern open surgery: 1A;
- thermal ablation with laser or RFA: 1A;
- USGFS: 1A;
- steam (awaiting long-term results): 1B;
- CA (glue) (awaiting long-term results): 1B;
- MOCA (awaiting long-term results): 1B;
- cryostripping: 1B.

B. Treatment of incompetent prforating veins

Introduction

The hemodynamic and clinical significance of incompetent perforating veins (IPs) when combined with primary superficial incompetence remains debated.

Operative treatment procedures

It is widely accepted that a minimally invasive approach is preferred to reduce morbidity and particularly to avoid delayed wound healing and infection, but there is no consensus as to the best technique.[137-160]

Outcome after operative treatment

Numerous case-series with no control groups have suggested that subfacial endoscopic surgery (SEPS) might have a beneficial effect upon the natural history of CVD and in particular chronic venous ulceration.[161-170] However, it is not clear as to whether benefits observed are due to the SEPS procedure or to concomitant saphenous surgery undertaken in most patients.[171-174] In addition, it has been suggested by data from retrospective case-series that deep venous reflux (especially in post-thrombotic patients) may diminish the benefits of SEPS[171, 173-175] although this has not been a universal finding.

It has never been shown that interrupting perforating veins in addition to standard saphenous surgery confers additional benefit in patients with CEAP C_2 disease in terms of symptom relief, hemodynamic improvement and QoL or recurrence. This may be because in the absence of deep venous reflux, complete eradication of superficial venous reflux will result in some incompetent perforating veins regaining competence.[176, 177] Three RCTs have, however, shown that perforating veins regain competence in more than one third of legs from GSV treatment alone.[129, 178, 179]

Furthermore, there is no level A evidence that the addition of perforating veins surgery to standard saphenous surgery confers additional benefit in patients with

CEAP C_{4-6} disease in terms of symptom relief, hemodynamic improvement,[180, 181] QoL, ulcer healing or recurrence.[158, 182-186] even in the presence of deep venous reflux[182, 183, 187] This may be because appropriate subgroups that might benefit have not yet been identified. Two long-term prospective cohort studies showed however, very low rates of recurrent venous ulceration following superficial venous surgery and SEPS.[188, 189]

The role of perforating veins has been assessed in the short term by one Swedish RCT, where patients with venous ulcers and incompetent GSV and perforating veins incompetence were randomized into GSV high ligation alone or combined with a SEPS procedure. At one year there were no significant differences between the groups regarding healing or recurrence.[179] A prospective, randomized multicenter trial was conducted to study if ambulatory compression therapy with venous surgery including SEPS and superficial vein ligation (97 patients) was a better treatment than compression therapy alone (103 patients) for patients with venous leg ulcers. There was no significant difference in healing rates between the two groups and recurrence rates were the same. However, patients with recurrent ulcers or medially located ulcers in the surgical group had a longer ulcer-free period than those treated conservatively.[190]

Cohort studies on hard to heal venous ulcers have shown a benefit from perforator ablation in order to achieve final ulcer healing.[191, 192]

Indications for treating incompetent perforating veins

There is no consensus on this point, but in $C_{2,3,4a}$ patients most phlebologists agree to treat only superficial incompetence. In $C_{4b,5,6}$ the majority will treat only VVs and reserve perforating veins ablation to patients whose clinical status is worsening or in case of ulcer recurrence, while others will combine superficial and perforating veins operative treatment. Guidelines regarding venous ulcer management generally recommend treatment of incompetent perforating veins to improve healing and prevent recurrence.[193-195]

C. Gastrocnemius vein reflux

Duplex scanning is mandatory before surgery for superficial vein reflux arising in the popliteal fossa. It determines the anatomy of termination of the SSV and gastrocnemial veins.[196, 197] Their termination can be separate, or they can share a common ostium or terminal trunk. Persistence of an incompetent gastrocnemius vein missed at operation is a common cause of recurrence so that adequate ligation has been considered essential in cases of SSV surgery. In one study, it was associated with 42% of SSV recurrence[198] and with 34% in another.[199]

At present, most SSV are treated endovenously or with foam. Unfortunately, there is no data on the fate of the gastrocnemial vein and the effect on potential recurrence in case of persisting reflux of the latter.

D. Final remarks

The evolution of materials and devices for the treatment of CVD is rapid, and when long- or medium-term outcomes comparing new treatment techniques become available, the material or device employed in the RCT is no longer used.

Most new procedures are operator-dependent and when two or more are tested in a RCTs it is important that the investigators are well trained in all of them.

A brief description of a procedure does not indicate precisely how it was performed, *e.g.* the high ligation and stripping technique has evolved and is now less aggressive and invasive than it was in the past. Unfortunately, it is ignored by many surgeons.

RCTs are important in the evaluation of new procedures. Skepticism about conventional RCTs in non-pharmacological interventions such as surgery remains and so-called expertise based RCTs are suggested as an alternative where participants are randomized to clinicians with expertise in intervention A or clinicians with expertise in intervention B, and the clinicians perform only the procedure they are experts in.

Accurate analysis of RCTs is difficult as hidden bias can be hard to identify. For illustrating this point in some RCTs, operative procedures for VVs were performed either under local tumescent anesthesia or general anesthesia that should influence short term evaluation.

References

1. Vuylsteke ME, Klitfod L, Mansilha A. Endovenous ablation. Int Angiol 2019;38:22–38.

2. Franceschi C. Théorie et Pratique de la Cure Conservatrice et Hémodynamique de l'Insuffisance Veineuse en Ambulatoire. Precy-sous-Thil: Editions de l'Armancon; 1988.

3. Pittaluga P, Chastanet S, Rea B, Barbe R. Midterm results of the surgical treatment of varices by phlebectomy with conservation of a refluxing saphenous vein. J Vasc Surg 2009;50:107–18.

4. Morrison C, Dalsing MC. Signs and symptoms of saphenous nerve injury after greater saphenous vein stripping: prevalence, severity, and relevance for modern practice. J Vasc Surg 2003;38:886–90.

5. Sam RC, MacKenzie RK, Paisley AM, Ruckley CV, Bradbury AW. The effect of superficial venous surgery on generic health-related quality of life. Eur J Vasc Endovasc Surg 2004;28:253–6.

6. Pittaluga P, Chastanet S, Guex JJ. Great saphenous vein stripping with preservation of sapheno-femoral confluence: hemodynamic and clinical results. J Vasc Surg 2008;47:1300–4, discussion 1304–5.

7. Pittaluga P, Chastanet S, Locret T, Rousset O. Retrospective evaluation of the need of a redo surgery at the groin for the surgical treatment of varicose vein. J Vasc Surg 2010;51:1442–50.

8. Huang TW, Chen SL, Bai CH, Wu CH, Tam KW. The optimal duration of compression therapy following varicose vein surgery: a meta-analysis of randomized controlled trials. Eur J Vasc Endovasc Surg 2013;45:397–402.

9. Mariani F, Marone EM, Gasbarro V, Bucalossi M, Spelta S, Amsler F, *et al.* Multicenter randomized trial comparing compression with elastic stocking versus bandage after surgery for varicose veins. J Vasc Surg 2011;53:115–22.

10. Lurie F, Lal BK, Antignani PL, Blebea J, Bush R, Caprini J, *et al.* Compression therapy after invasive treatment of superficial veins of the lower extremities: Clinical practice guidelines of the American Venous Forum, Society for Vascular Surgery, American College of Phlebology, Society for Vascular Medicine, and International Union of Phlebology. J Vasc Surg Venous Lymphat Disord 2019;7:17–28.

11. Nicolaides A, Kakkos S, Baekgaard N, Comerota A, de Maeseneer M, Eklof B, *et al.* Management of chronic venous disorders of the lower limbs. Guidelines According to Scientific Evidence. Part I. Int Angiol 2018;37:181–254.

12. Dermody M, O'Donnell TF, Balk EM. Complications of endovenous ablation in randomized controlled trials. J Vasc Surg Venous Lymphat Disord 2013;1:427–436.e1.

13. Anwar MA, Lane TR, Davies AH, Franklin IJ. Complications of radiofrequency ablation of varicose veins. Phlebology 2012;27(Suppl 1):34–9.

14. Dexter D, Kabnick L, Berland T, Jacobowitz G, Lamparello P, Maldonado T, *et al.* Complications of endovenous lasers. Phlebology 2012;27(Suppl 1):40–5.

15. Milleret R, Huot L, Nicolini P, Creton D, Roux AS, Decullier E, *et al.* Great saphenous vein ablation with steam injection: results of a multicentre study. Eur J Vasc Endovasc Surg 2013;45:391–6.

16. Thomis S, Verbrugghe P, Milleret R, Verbeken E, Fourneau I, Herijgers P. Steam ablation versus radiofrequency and laser ablation: an in vivo histological comparative trial. Eur J Vasc Endovasc Surg 2013;46:378–82.

17. van den Bos RR, Milleret R, Neumann M, Nijsten T. Proof-of-principle study of steam ablation as novel thermal therapy for saphenous varicose veins. J Vasc Surg 2011;53:181–6.

18. van den Bos RR, Malskat WS, De Maeseneer MG, de Roos KP, Groeneweg DA, Kockaert MA, *et al.* Randomized clinical trial of endovenous laser ablation versus steam ablation (LAST trial) for great saphenous varicose veins. Br J Surg 2014;101:1077–83.

19. Cabrera J, Cabrera J Jr, Garcia-Olmedo MA. Sclerosants in microfoam. A new approach in angiology. Int Angiol 2001;20:322–9.

20. Rabe E, Breu FX, Cavezzi A, Coleridge Smith P, Frullini A, Gillet JL, *et al.*; Guideline Group. European guidelines for sclerotherapy in chronic venous disorders. Phlebology 2014;29:338–54.

21. Lawson J, Gauw S, van Vlijmen C, Pronk P, Gaastra M, Mooij M, *et al.* Sapheon: the solution? Phlebology 2013;28(Suppl 1):2–9.

22. Morrison N, Kolluri R, Vasquez M, Madsen M, Jones A, Gibson K. Comparison of cyanoacrylate closure and radiofrequency ablation for the treatment of incompetent great saphenous veins: 36-Month outcomes of the VeClose randomized controlled trial. Phlebology 2019;34:380–90.

23. Çalık ES, Arslan Ü, Erkut B. Ablation therapy with cyanoacrylate glue and laser for refluxing great saphenous veins - a prospective randomised study. Vasa 2019;48:405–12.

24. Eroglu E, Yasim A. A Randomised Clinical Trial Comparing N-Butyl Cyanoacrylate, Radiofrequency Ablation and Endovenous Laser Ablation for the Treatment of Superficial Venous Incompetence: Two Year Follow up Results. Eur J Vasc Endovasc Surg 2018;56:553–60.

25. Morrison N, Gibson K, McEnroe S, Goldman M, King T, Weiss R, *et al.* Randomized trial comparing cyanoacrylate embolization and radiofrequency ablation for incompetent great saphenous veins (VeClose). J Vasc Surg 2015;61:985–94.

26. Proebstle TM, Alm J, Dimitri S, Rasmussen L, Whiteley M, Lawson J, *et al.* Twelve-Month Follow-up of the European Multicenter Study on Cyanoacrylate Embolization of Incompetent Great Saphenous Veins. J Vasc Surg Venous Lymphat Disord 2014;2:105–6.

27. Chan YC, Law Y, Cheung GC, Cheng SW. Predictors of Recanalization for Incompetent Great Saphenous Veins Treated with Cyanoacrylate Glue. J Vasc Interv Radiol 2017;28:665–71.

28. Chan YC, Law Y, Cheung GC, Ting AC, Cheng SW. Cyanoacrylate glue used to treat great saphenous reflux: measures of outcome. Phlebology 2017;32:99–106.

29. Gibson K, Ferris B. Cyanoacrylate closure of incompetent great, small and accessory saphenous veins without the use of post-procedure compression: initial outcomes of a post-market evaluation of the VenaSeal System (the WAVES Study). Vascular 2017;25:149–56.

30. Lam YL, De Maeseneer M, Lawson J, De Borst GJ, Boersma D. Expert review on the VenaSeal® system for endovenous cyano-acrylate adhesive ablation of incompetent saphenous trunks in patients with varicose veins. Expert Rev Med Devices 2017;14:755–62.

31. Almeida JI, Javier JJ, Mackay E, Bautista C, Proebstle TM. First human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. J Vasc Surg Venous Lymphat Disord 2013;1:174–80.

32. Parsi K, Kang M, Yang A, Kossard S. Granuloma formation following cyanoacrylate glue injection in peripheral veins and arteriovenous malformation. Phlebology 2020;35:115–23.

33. Lew PS, Chong TT, Tang TY. Venaseal™cyanoacrylate glue rejection following endovenous ablation – another new complication. Biomed J Sci Tech Res 2019;17:12993–4.

34. Elias S, Lam YL, Wittens CH. Mechanochemical ablation: status and results. Phlebology 2013;28(Suppl 1):10–4.

35. van Eekeren RR, Boersma D, Elias S, Holewijn S, Werson DA, de Vries JP, *et al.* Endovenous mechanochemical ablation of great saphenous vein incompetence using the ClariVein device: a safety study. J Endovasc Ther 2011;18:328–34.

36. Boersma D, van Eekeren RR, Werson DA, van der Waal RI, Reijnen MM, de Vries JP. Mechanochemical endovenous ablation of small saphenous vein insufficiency using the ClariVein(®) device: one-year results of a prospective series. Eur J Vasc Endovasc Surg 2013;45:299–303.

37. Vos CG, Ünlü Ç, Bosma J, van Vlijmen CJ, de Nie AJ, Schreve MA. A systematic review and meta-analysis of two novel techniques of nonthermal endovenous ablation of the great saphenous vein. J Vasc Surg Venous Lymphat Disord 2017;5:880–96.

38. van Eekeren RR, Boersma D, Konijn V, de Vries JP, Reijnen MM. Postoperative pain and early quality of life after radiofrequency ablation and mechanochemical endovenous ablation of incompetent great saphenous veins. J Vasc Surg 2013;57:445–50.

39. Elias S, Raines JK. Mechanochemical tumescentless endovenous ablation: final results of the initial clinical trial. Phlebology 2012;27:67–72.

40. Lane T, Bootun R, Dharmarajah B, Lim CS, Najem M, Renton S, *et al.* A multi-centre randomised controlled trial comparing radiofrequency and mechanical occlusion chemically assisted ablation of varicose veins - Final results of the Venefit versus Clarivein for varicose veins trial. Phlebology 2017;32:89–98.

41. Vähäaho S, Mahmoud O, Halmesmäki K, Albäck A, Noronen K, Vikatmaa P, *et al.* Randomized clinical trial of mechanochemical and endovenous thermal ablation of great saphenous varicose veins. Br J Surg 2019;106:548–54.

42. Lee BB, Nicolaides AN, Myers K, Meissner M, Kalodiki E, Allegra C, *et al.* Venous hemodynamic changes in lower limb venous disease: the UIP consensus according to scientific evidence. Int Angiol 2016;35:236–352.

43. Perälä J, Rautio T, Biancari F, Ohtonen P, Wiik H, Heikkinen T, *et al.* Radiofrequency endovenous obliteration versus stripping of the long saphenous vein in the management of primary varicose veins: 3-year outcome of a randomized study. Ann Vasc Surg 2005;19:669–72.

44. Hinchliffe RJ, Ubhi J, Beech A, Ellison J, Braithwaite BD. A prospective randomised controlled trial of VNUS closure versus surgery for the treatment of recurrent long saphenous varicose veins. Eur J Vasc Endovasc Surg 2006;31:212–8.

45. Sincos IR, Baptista AP, Coelho Neto F, Labropoulos N, Alledi LB, Marins EM, *et al.* Prospective randomized trial comparing radiofrequency ablation and complete saphenous vein stripping in patients with mild to moderate chronic venous disease with a 3-year follow-up. Einstein (Sao Paulo) 2019;17:eAO4526.

46. Lurie F, Creton D, Eklof B, Kabnick LS, Kistner RL, Pichot O, *et al.* Prospective randomized study of endovenous radiofrequency obliteration (closure procedure) versus ligation and stripping in a selected patient population (EVOLVeS Study). J Vasc Surg 2003;38:207–14.

47. Lurie F, Creton D, Eklof B, Kabnick LS, Kistner RL, Pichot O, *et al.* Prospective randomised study of endovenous radiofrequency obliteration (closure) versus ligation and vein stripping (EVOLVeS): two-year follow-up. Eur J Vasc Endovasc Surg 2005;29:67–73.

48. Rautio T, Ohinmaa A, Perälä J, Ohtonen P, Heikkinen T, Wiik H, *et al.* Endovenous obliteration versus conventional stripping operation in the treatment of primary varicose veins: a randomized controlled trial with comparison of the costs. J Vasc Surg 2002;35:958–65.

49. Stötter L, Schaaf I, Bockelbrink A. Comparative outcomes of radiofrequency endoluminal ablation, invagination stripping, and cryostripping in the treatment of great saphenous vein insufficiency. Phlebology 2006;21:60–4.

50. Subramonia S, Lees T. Radiofrequency ablation vs conventional surgery for varicose veins - a comparison of treatment costs in a randomised trial. Eur J Vasc Endovasc Surg 2010;39:104–11.

51. Helmy ElKaffas K, ElKashef O, ElBaz W. Great saphenous vein radiofrequency ablation versus standard stripping in the management of primary varicose veins-a randomized clinical trial. Angiology 2011;62:49–54.

52. Proebstle TM, Alm J, Göckeritz O, Wenzel C, Noppeney T, Lebard C, *et al.*; European Closure Fast Clinical Study Group. Three-year European follow-up of endovenous radiofrequency-powered segmental thermal ablation of the great saphenous vein with or without treatment of calf varicosities. J Vasc Surg 2011;54:146–52.

53. Samuel N, Carradice D, Wallace T, Mekako A, Hatfield J, Chetter I. Randomized clinical trial of endovenous laser ablation versus conventional surgery for small saphenous varicose veins. Ann Surg 2013;257:419–26.

54. Carradice D, Mekako AI, Mazari FA, Samuel N, Hatfield J, Chetter IC. Clinical and technical outcomes from a randomized clinical trial of endovenous laser ablation compared with conventional surgery for great saphenous varicose veins. Br J Surg 2011;98:1117–23.

55. Darwood RJ, Theivacumar N, Dellagrammaticas D, Mavor AI, Gough MJ. Randomized clinical trial comparing endovenous laser ablation with surgery for the treatment of primary great saphenous varicose veins. Br J Surg 2008;95:294–301.

56. de Medeiros CA, Luccas GC. Comparison of endovenous treatment with an 810 nm laser versus conventional stripping of the great saphenous vein in patients with primary varicose veins. Dermatol Surg 2005;31:1685–94, discussion 1694.

57. Vuylsteke M, Van den Bussche D, Audenaert EA, Lissens P. Endovenous laser obliteration for the treatment of primary varicose veins. Phlebology 2006;21:80–7.

58. Rasmussen LH, Lawaetz M, *et al.* Randomized trial comparing endovenous laser ablation of the GSV with high ligation and stripping in patients with varicose veins. Short term results. American Venous Forum. Rancho Bernardo, USA, 2007.

59. Kalteis M, Berger I, Messie-Werndl S, Pistrich R, Schimetta W, Pölz W, *et al.* High ligation combined with stripping and endovenous laser ablation of the great saphenous vein: early results of a randomized controlled study. J Vasc Surg 2008;47:822–9, discussion 829.

60. Theivacumar NS, Darwood R, Gough MJ. Neovascularisation and recurrence 2 years after varicose vein treatment for sapheno-femoral and great saphenous vein reflux: a comparison of surgery and endovenous laser ablation. Eur J Vasc Endovasc Surg 2009;38:203–7.

61. Christenson JT, Gueddi S, Gemayel G, Bounameaux H. Prospective randomized trial comparing endovenous laser ablation and surgery for treatment of primary great saphenous varicose veins with a 2-year follow-up. J Vasc Surg 2010;52:1234–41.

62. Pronk P, Gauw SA, Mooij MC, Gaastra MT, Lawson JA, van Goethem AR, *et al.* Randomised controlled trial comparing sapheno-femoral ligation and stripping of the great saphenous vein with endovenous laser ablation (980 nm) using local tumescent anaesthesia: one year results. Eur J Vasc Endovasc Surg 2010;40:649–56.

63. Rasmussen LH, Bjoern L, Lawaetz M, Lawaetz B, Blemings A, Eklöf B. Randomised clinical trial comparing endovenous laser ablation with stripping of the great saphenous vein: clinical outcome and recurrence after 2 years. Eur J Vasc Endovasc Surg 2010;39:630–5.

64. Carradice D, Mekako AI, Mazari FA, Samuel N, Hatfield J, Chetter IC. Randomized clinical trial of endovenous laser ablation compared with conventional surgery for great saphenous varicose veins. Br J Surg 2011;98:501–10.

65. Rass K, Frings N, Glowacki P, Hamsch C, Gräber S, Vogt T, *et al.* Comparable effectiveness of endovenous laser ablation and high ligation with stripping of the great saphenous vein: two-year results of a randomized clinical trial (RELACS study). Arch Dermatol 2012;148:49–58.

66. Rasmussen L, Lawaetz M, Bjoern L, Blemings A, Eklof B. Randomized clinical trial comparing endovenous laser ablation and stripping of the great saphenous vein with clinical and duplex outcome after 5 years. J Vasc Surg 2013;58:421–6.

67. Flessenkämper I, Hartmann M, Stenger D, Roll S. Endovenous laser ablation with and without high ligation compared with high ligation and stripping in the treatment of great saphenous varicose veins: initial results of a multicentre randomized controlled trial. Phlebology 2013;28:16–23.

68. Roopram AD, Lind MY, Van Brussel JP, Terlouw-Punt LC, Birnie E, De Smet AA, *et al.* Endovenous laser ablation versus conventional surgery in the treatment of small saphenous vein incompetence. J Vasc Surg Venous Lymphat Disord 2013;1:357–63.

69. Lin Y, Ye CS, Huang XL, Ye JL, Yin HH, Wang SM. [A random, comparative study on endovenous laser therapy and saphenous veins stripping for the treatment of great saphenous vein incompetence]. Zhonghua Yi Xue Za Zhi 2007;87:3043–6. Chinese.

70. Kalteis M, Adelsgruber P, Messie-Werndl S, Gangl O, Berger I. Five-year results of a randomized controlled trial comparing high ligation combined with endovenous laser ablation and stripping of the great saphenous vein. Dermatol Surg 2015;41:579–86.

71. Nandhra S, El-sheikha J, Carradice D, Wallace T, Souroullas P, Samuel N, *et al.* A randomized clinical trial of endovenous laser ablation versus conventional surgery for small saphenous varicose veins. J Vasc Surg 2015;61:741–6.

72. Rass K, Frings N, Glowacki P, Gräber S, Tilgen W, Vogt T. Same Site Recurrence is More Frequent After Endovenous Laser Ablation Compared with High Ligation and Stripping of the Great Saphenous Vein: 5 year Results of a Randomized Clinical Trial (RELACS Study). Eur J Vasc Endovasc Surg 2015;50:648–56.

73. Flessenkämper I, Hartmann M, Hartmann K, Stenger D, Roll S. Endovenous laser ablation with and without high ligation compared to high ligation and stripping for treatment of great saphenous varicose veins: results of a multicentre randomised controlled trial with up to 6 years follow-up. Phlebology 2016;31:23–33.

74. Gauw SA, Lawson JA, van Vlijmen-van Keulen CJ, Pronk P, Gaastra MT, Mooij MC. Five-year follow-up of a randomized, controlled trial comparing saphenofemoral ligation and stripping of the great saphenous

vein with endovenous laser ablation (980 nm) using local tumescent anesthesia. J Vasc Surg 2016;63:420–8.

75. Vuylsteke M, De Bo TH, Dompe G, Di Crisci D, Abbad C, Mordon S. Endovenous laser treatment: is there a clinical difference between using a 1500 nm and a 980 nm diode laser? A multicenter randomised clinical trial. Int Angiol 2011;30:327–34.

76. Doganci S, Demirkilic U. Comparison of 980 nm laser and bare-tip fibre with 1470 nm laser and radial fibre in the treatment of great saphenous vein varicosities: a prospective randomised clinical trial. Eur J Vasc Endovasc Surg 2010;40:254–9.

77. Disselhoff BC, der Kinderen DJ, Kelder JC, Moll FL. Randomized clinical trial comparing endovenous laser ablation of the great Saphenous vein with and without ligation of the sapheno-femoral junction: 2-year results. Eur J Vasc Endovasc Surg 2008;36:713–8.

78. Theivacumar NS, Dellagrammaticas D, Mavor AI, Gough MJ. Endovenous laser ablation: does standard above-knee great saphenous vein ablation provide optimum results in patients with both above- and below-knee reflux? A randomized controlled trial. J Vasc Surg 2008;48:173–8.

79. Pannier F, Rabe E, Maurins U. 1470 nm diode laser for endovenous ablation (EVLA) of incompetent saphenous veins - a prospective randomized pilot study comparing warm and cold tumescence anaesthesia. Vasa 2010;39:249–55.

80. Bakker NA, Schieven LW, Bruins RM, van den Berg M, Hissink RJ. Compression stockings after endovenous laser ablation of the great saphenous vein: a prospective randomized controlled trial. Eur J Vasc Endovasc Surg 2013;46:588–92.

81. Gale SS, Lee JN, Walsh ME, Wojnarowski DL, Comerota AJ. A randomized, controlled trial of endovenous thermal ablation using the 810-nm wavelength laser and the ClosurePLUS radiofrequency ablation methods for superficial venous insufficiency of the great saphenous vein. J Vasc Surg 2010;52:645–50.

82. Almeida JI, Kaufman J, Göckeritz O, Chopra P, Evans MT, Hoheim DF, *et al.* Radiofrequency endovenous ClosureFAST versus laser ablation for the treatment of great saphenous reflux: a multicenter, single-blinded, randomized study (RECOVERY study). J Vasc Interv Radiol 2009;20:752–9.

83. Shepherd AC, Gohel MS, Brown LC, Metcalfe MJ, Hamish M, Davies AH. Randomized clinical trial of VNUS ClosureFAST radiofrequency ablation versus laser for varicose veins. Br J Surg 2010;97:810–8.

84. Nordon IM. EVVERT comparing laser and radiofrequency: An update on endovenous treatment options. BIBA Publishing; 2011. p. 381–8.

85. Goode SD, Chowdhury A, Crockett M, Beech A, Simpson R, Richards T, *et al.* Laser and radiofrequency ablation study (LARA study): a randomised study comparing radiofrequency ablation and endovenous laser ablation (810 nm). Eur J Vasc Endovasc Surg 2010;40:246–53.

86. Shepherd AC, Ortega-Ortega M, Gohel MS, Epstein D, Brown LC, Davies AH. Cost-Effectiveness of Radiofrequency Ablation Versus Laser for Varicose Veins. Int J Technol Assess Health Care 2015;31:289–96.

87. Bozoglan O, Mese B, Eroglu E, Erdogan MB, Erdem K, Ekerbicer HC, *et al.* Comparison of Endovenous Laser and Radiofrequency Ablation in Treating Varicose Veins in the Same Patient. Vasc Endovascular Surg 2016;50:47–51.

88. Sydnor M, Mavropoulos J, Slobodnik N, Wolfe L, Strife B, Komorowski D. A randomized prospective long-term (>1 year) clinical trial comparing the efficacy and safety of radiofrequency ablation to 980 nm laser ablation of the great saphenous vein. Phlebology 2017;32:415–24.

89. Kabnick LS. Commentary on "Radiofrequency ablation of the great saphenous vein performed in the office: tips for better patient convenience and comfort and how to perform it in less than an hour". Perspect Vasc Surg Endovasc Ther 2007;19:315–6.

90. He G, Zheng C, Yu MA, Zhang H. Comparison of ultrasound-guided endovenous laser ablation and radiofrequency for the varicose veins treatment: an updated meta-analysis. Int J Surg 2017;39:267–75.

91. Beteli CB, Rossi FH, de Almeida BL, Izukawa NM, Onofre Rossi CB, Gabriel SA, *et al.* Prospective, double-blind, randomized controlled trial comparing electrocoagulation and radiofrequency in the treatment of patients with great saphenous vein insufficiency and lower limb varicose veins. J Vasc Surg Venous Lymphat Disord 2018;6:212–9.

92. Disselhoff BC, der Kinderen DJ, Moll FL. Is there a risk for lymphatic complications after endovenous laser treatment versus cryostripping of the great saphenous vein? A prospective study. Phlebology 2008;23:10–4.

93. Disselhoff BC, der Kinderen DJ, Kelder JC, Moll FL. Randomized clinical trial comparing endovenous laser with cryostripping for great saphenous varicose veins. Br J Surg 2008;95:1232–8.

94. Disselhoff BC, Buskens E, Kelder JC, der Kinderen DJ, Moll FL. Randomised comparison of costs and cost-effectiveness of cryostripping and endovenous laser ablation for varicose veins: 2-year results. Eur J Vasc Endovasc Surg 2009;37:357–63.

95. Bountouroglou DG, Azzam M, Kakkos SK, Pathmarajah M, Young P, Geroulakos G. Ultrasound-guided foam sclerotherapy combined with sapheno-femoral ligation compared to surgical treatment of varicose veins: early results of a randomised controlled trial. Eur J Vasc Endovasc Surg 2006;31:93–100.

96. Abela R, Liamis A, Prionidis I, Mathai J, Gorton L, Browne T, *et al.* Reverse foam sclerotherapy of the great saphenous vein with saphenofemoral ligation compared to standard and invagination stripping: a prospective clinical series. Eur J Vasc Endovasc Surg 2008;36:485–90.

97. Liu X, Jia X, Guo W, Xiong J, Zhang H, Liu M, *et al.* Ultrasound-guided foam sclerotherapy of the great saphenous vein with sapheno-femoral ligation compared to standard stripping: a prospective clinical study. Int Angiol 2011;30:321–6.

98. Kalodiki E, Lattimer CR, Azzam M, Shawish E, Bountouroglou D, Geroulakos G. Long-term results of a randomized controlled trial on ultrasound-guided foam sclerotherapy combined with saphenofemoral ligation vs standard surgery for varicose veins. J Vasc Surg 2012;55:451–7.

99. Figueiredo M, Araújo S, Barros N Jr, Miranda F Jr. Results of surgical treatment compared with ultrasound-guided foam sclerotherapy in patients with varicose veins: a prospective randomised study. Eur J Vasc Endovasc Surg 2009;38:758–63.

100. Shadid N, Ceulen R, Nelemans P, Dirksen C, Veraart J, Schurink GW, *et al.* Randomized clinical trial of ultrasound-guided foam sclerotherapy versus surgery for the incompetent great saphenous vein. Br J Surg 2012;99:1062–70.

101. Wright D, Gobin JP, Bradbury AW. Varisolve ® polidocanol microfoam compared with surgery or sclerotherapy in the management of varicose veins in the presence of trunk vein incompetence: european randomized controlled trial. Phlebology 2006;21:180–90.

102. Lam YL, Lawson JA, Toonder IM, Shadid NH, Sommer A, Veenstra M, *et al.* Eight-year follow-up of a randomized clinical trial comparing ultrasound-guided foam sclerotherapy with surgical stripping of the great saphenous vein. Br J Surg 2018;105:692–8.

103. Yin H, He H, Wang M, Li Z, Hu Z, Yao C, *et al.* Prospective Randomized Study of Ultrasound-Guided Foam Sclerotherapy Combined with Great Saphenous Vein High Ligation in the Treatment of Severe Lower Extremity Varicosis. Ann Vasc Surg 2017;39:256–63.

104. Lattimer CR, Azzam M, Kalodiki E, Shawish E, Trueman P, Geroulakos G. Cost and effectiveness of laser with phlebectomies compared with foam sclerotherapy in superficial venous insufficiency. Early results of a randomised controlled trial. Eur J Vasc Endovasc Surg 2012;43:594–600.

105. Lattimer CR, Kalodiki E, Azzam M, Geroulakos G. Validation of a new duplex derived haemodynamic effectiveness score, the saphenous treatment score, in quantifying varicose vein treatments. Eur J Vasc Endovasc Surg 2012;43:348–54.

106. Lattimer CR, Kalodiki E, Azzam M, Makris GC, Somiayajulu S, Geroulakos G. Interim results on abolishing reflux alongside a randomized clinical trial on laser ablation with phlebectomies versus foam sclerotherapy. Int Angiol 2013;32:394–403.

107. Rasmussen LH, Lawaetz M, Bjoern L, Vennits B, Blemings A, Eklof B. Randomized clinical trial comparing endovenous laser ablation, radio-

frequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins. Br J Surg 2011;98:1079–87.

108. Lawaetz M, Serup J, Lawaetz B, Bjoern L, Blemings A, Eklof B, *et al.* Comparison of Endovenous Radiofrequency Ablation, Laser Ablation, Foam Sclerotherapy and Surgical Stripping for Great Saphenous Varicose Veins. Extended 5-Year Follow-up of a RCT. Eur J Vasc Endovasc Surg 2017;53:e14.

109. van der Velden SK, Biemans AA, De Maeseneer MG, Kockaert MA, Cuypers PW, Hollestein LM, *et al.* Five-year results of a randomized clinical trial of conventional surgery, endovenous laser ablation and ultrasound-guided foam sclerotherapy in patients with great saphenous varicose veins. Br J Surg 2015;102:1184–94.

110. Vähäaho S, Halmesmäki K, Albäck A, Saarinen E, Venermo M. Five-year follow-up of a randomized clinical trial comparing open surgery, foam sclerotherapy and endovenous laser ablation for great saphenous varicose veins. Br J Surg 2018;105:686–91.

111. Kheirelseid EA, Crowe G, Sehgal R, Liakopoulos D, Bela H, Mulkern E, *et al.* Systematic review and meta-analysis of randomized controlled trials evaluating long-term outcomes of endovenous management of lower extremity varicose veins. J Vasc Surg Venous Lymphat Disord 2018;6:256–70.

112. O'Donnell TF, Balk EM, Dermody M, Tangney E, Iafrati MD. Recurrence of varicose veins after endovenous ablation of the great saphenous vein in randomized trials. J Vasc Surg Venous Lymphat Disord 2016;4:97–105.

113. Hamann SA, Giang J, De Maeseneer MG, Nijsten TE, van den Bos RR. Editor's Choice - Five Year Results of Great Saphenous Vein Treatment: A Meta-analysis. Eur J Vasc Endovasc Surg 2017;54:760–70.

114. Paravastu SC, Horne M, Dodd PD. Endovenous ablation therapy (laser or radiofrequency) or foam sclerotherapy versus conventional surgical repair for short saphenous varicose veins. Cochrane Database Syst Rev 2016;11:CD010878.

115. Yang L, Wang XP, Su WJ, Zhang Y, Wang Y. Randomized clinical trial of endovenous microwave ablation combined with high ligation versus conventional surgery for varicose veins. Eur J Vasc Endovasc Surg 2013;46:473–9.

116. Bozkurt AK, Yılmaz MF. A prospective comparison of a new cyanoacrylate glue and laser ablation for the treatment of venous insufficiency. Phlebology 2016;31(Suppl):106–13.

117. Kolluri R, Gibson K, Cher D, Madsen M, Weiss R, Morrison N. Roll-in phase analysis of clinical study of cyanoacrylate closure for incompetent great saphenous veins. J Vasc Surg Venous Lymphat Disord 2016;4:407–15.

118. Morrison N, Gibson K, Vasquez M, Weiss R, Cher D, Madsen M, *et al.* VeClose trial 12-month outcomes of cyanoacrylate closure versus radiofrequency ablation for incompetent great saphenous veins. J Vasc Surg Venous Lymphat Disord 2017;5:321–30.

119. Michaels JA, Brazier JE, Campbell WB, MacIntyre JB, Palfreyman SJ, Ratcliffe J. Randomized clinical trial comparing surgery with conservative treatment for uncomplicated varicose veins. Br J Surg 2006;93:175–81.

120. Ratcliffe J, Brazier JE, Campbell WB, Palfreyman S, MacIntyre JB, Michaels JA. Cost-effectiveness analysis of surgery versus conservative treatment for uncomplicated varicose veins in a randomized clinical trial. Br J Surg 2006;93:182–6.

121. Carandina S, Mari C, De Palma M, Marcellino MG, Cisno C, Legnaro A, *et al.* Varicose vein stripping vs haemodynamic correction (CHIVA): a long term randomised trial. Eur J Vasc Endovasc Surg 2008;35:230–7.

122. Parés JO, Juan J, Tellez R, Mata A, Moreno C, Quer FX, *et al.* Varicose vein surgery: stripping versus the CHIVA method: a randomized controlled trial. Ann Surg 2010;251:624–31.

123. Menyhei G, Gyevnár Z, Arató E, Kelemen O, Kollár L. Conventional stripping versus cryostripping: a prospective randomised trial to compare improvement in quality of life and complications. Eur J Vasc Endovasc Surg 2008;35:218–23.

124. Klem TM, Schnater JM, Schütte PR, Hop W, van der Ham AC, Wittens CH. A randomized trial of cryo stripping versus conventional stripping of the great saphenous vein. J Vasc Surg 2009;49:403–9.

125. Campanello M, Hammarsten J, Forsberg C, Bernland P, Henrikson O, Jensen J. Standard Stripping versus Long Saphenous Vein-Saving Surgery for Primary Varicose Veins: A Prospective, Randomized Study with the Patients as Their Own Controls. Phlebology 1996;11:45–9.

126. Dwerryhouse S, Davies B, Harradine K, Earnshaw JJ. Stripping the long saphenous vein reduces the rate of reoperation for recurrent varicose veins: five-year results of a randomized trial. J Vasc Surg 1999;29:589–92.

127. Winterborn RJ, Foy C, Earnshaw JJ. Causes of varicose vein recurrence: late results of a randomized controlled trial of stripping the long saphenous vein. J Vasc Surg 2004;40:634–9.

128. Corder AP, Schache DJ, Farquharson SM, Tristram S. Wound infection following high saphenous ligation. A trial comparing two skin closure techniques: subcuticular polyglycolic acid and interrupted monofilament nylon mattress sutures. J R Coll Surg Edinb 1991;36:100–2.

129. Kianifard B, Holdstock J, Allen C, Smith C, Price B, Whiteley MS. Randomized clinical trial of the effect of adding subfascial endoscopic perforator surgery to standard great saphenous vein stripping. Br J Surg 2007;94:1075–80.

130. Nisar A, Shabbir J, Tubassam MA, Shah AR, Khawaja N, Kavanagh EG, *et al.* Local anaesthetic flush reduces postoperative pain and haematoma formation after great saphenous vein stripping—a randomised controlled trial. Eur J Vasc Endovasc Surg 2006;31:325–31.

131. Scheltinga MR, Wijburg ER, Keulers BJ, de Kroon KE. Conventional versus invaginated stripping of the great saphenous vein: a randomized, double-blind, controlled clinical trial. World J Surg 2007;31:2236–42.

132. Butler CM, Scurr JH, Coleridge Smith PD. Prospective randomised trial comparing conventional (babcock) stripping with inverting (pin) stripping of the long saphenous vein. Phlebology 2002;17:59–63.

133. Nelzén O. Reconsidering the endovenous revolution. Br J Surg 2016;103:939–40.

134. Wallace T, El-Sheikha J, Nandhra S, Leung C, Mohamed A, Harwood A, *et al.* Long-term outcomes of endovenous laser ablation and conventional surgery for great saphenous varicose veins. Br J Surg 2018;105:1759–67.

135. Darvall KA, Bate GR, Adam DJ, Silverman SH, Bradbury AW. Duplex ultrasound outcomes following ultrasound-guided foam sclerotherapy of symptomatic recurrent great saphenous varicose veins. Eur J Vasc Endovasc Surg 2011;42:107–14.

136. Kakkos SK, Bountouroglou DG, Azzam M, Kalodiki E, Daskalopoulos M, Geroulakos G. Effectiveness and safety of ultrasound-guided foam sclerotherapy for recurrent varicose veins: immediate results. J Endovasc Ther 2006;13:357–64.

137. Hauer G, Bergan JJ, Werner A, Mitterhusen M, Nasralla F. Development of endoscopic dissection of perforating veins and fasciotomy for treatment of chronic venous insufficiency. Ann Vasc Surg 1999;13:357–64.

138. Jugenheimer M, Junginger T. Endoscopic subfascial sectioning of incompetent perforating veins in treatment of primary varicosis. World J Surg 1992;16:971–5.

139. Bergan JJ. Advances in venous surgery: SEPS and phlebectomy for chronic venous insufficiency. Dermatol Surg 2002;28:26–8.

140. Jugenheimer M, Mayer W, Uckele M. Endoscopic subfascial dissection of the perforating veins: treatment results. Surg Technol Int 2003;11:202–5.

141. Proebstle TM, Bethge S, Barnstedt S, Kargl A, Knop J, Sattler G. Subfascial endoscopic perforator surgery with tumescent local anesthesia. Dermatol Surg 2002;28:689–93.

142. Lacroix H, Smeets A, Nevelsteen A, Suy R. Classic versus endoscopic perforating vein surgery: a retrospective study. Acta Chir Belg 1998;98:71–5.

143. Sato DT, Goff CD, Gregory RT, Walter BF, Gayle RG, Parent FN

3rd, *et al.* Subfascial perforator vein ablation: comparison of open versus endoscopic techniques. J Endovasc Surg 1999;6:147–54.

144. Lee DW, Chan AC, Lam YH, Wong SK, Ng EK, Law BK, *et al.* Subfascial endoscopic perforator vein surgery (SEPS) using the ultrasonic scalpel. Surg Endosc 2001;15:1491–3.

145. Stuart WP, Adam DJ, Bradbury AW, Ruckley CV. Subfascial endoscopic perforator surgery is associated with significantly less morbidity and shorter hospital stay than open operation (Linton's procedure). Br J Surg 1997;84:1364–5.

146. Pierik EG, van Urk H, Hop WC, Wittens CH. Endoscopic versus open subfascial division of incompetent perforating veins in the treatment of venous leg ulceration: a randomized trial. J Vasc Surg 1997;26:1049–54.

147. Sybrandy JE, van Gent WB, Pierik EG, Wittens CH. Endoscopic versus open subfascial division of incompetent perforating veins in the treatment of venous leg ulceration: long-term follow-up. J Vasc Surg 2001;33:1028–32.

148. Nelzén O. Prospective study of safety, patient satisfaction and leg ulcer healing following saphenous and subfascial endoscopic perforator surgery. Br J Surg 2000;87:86–91.

149. Geselschap JH, van Gent WB, Wittens CH. Complications in subfascial endoscopic perforating vein surgery: a report of two cases. J Vasc Surg 2001;33:1108–10.

150. Queral LA, Criado FJ. Miniincisional ligation of incompetent perforating veins of the legs. J Vasc Surg 1997;25:437–41.

151. Whiteley MS, Smith JJ, Galland RB. Subfascial endoscopic perforator vein surgery (SEPS): current practice among British surgeons. Ann R Coll Surg Engl 1998;80:104–7.

152. Mozes G, Gloviczki P, Menawat SS, Fisher DR, Carmichael SW, Kadar A. Surgical anatomy for endoscopic subfascial division of perforating veins. J Vasc Surg 1996;24:800–8.

153. Bengisun U, Tagil SM, Elhan A. Accessibility of calf perforating veins from the superficial posterior compartment: an anatomic dissection study. Eur J Vasc Endovasc Surg 2003;25:552–5.

154. Thomson H. The surgical anatomy of the superficial and perforating veins of the lower limb. Ann R Coll Surg Engl 1979;61:198–205.

155. Staubesand J, Hackländer A. Topography of the perforating veins on the medial side of the leg (Cockett's veins). Clin Anat 1995;8:399–402.

156. Corbett CR, McIrvine AJ, Aston NO, Jamieson CW, Thomas ML. The use of varicography to identify the sources of incompetence in recurrent varicose veins. Ann R Coll Surg Engl 1984;66:412–5.

157. Thomas ML, Bowles JN. Incompetent perforating veins: comparison of varicography and ascending phlebography. Radiology 1985;154:619–23.

158. Darke SG, Penfold C. Venous ulceration and saphenous ligation. Eur J Vasc Surg 1992;6:4–9.

159. Hanrahan LM, Araki CT, Fisher JB, Rodriguez AA, Walker TG, Woodson J, *et al.* Evaluation of the perforating veins of the lower extremity using high resolution duplex imaging. J Cardiovasc Surg (Torino) 1991;32:87–97.

160. Dillavou ED, Harlander-Locke M, Labropoulos N, Elias S, Ozsvath KJ. Current state of the treatment of perforating veins. J Vasc Surg Venous Lymphat Disord 2016;4:131–5.

161. Tawes RL, Barron ML, Coello AA, Joyce DH, Kolvenbach R. Optimal therapy for advanced chronic venous insufficiency. J Vasc Surg 2003;37:545–51.

162. Hauer G, Barkun J, Wisser I, Deiler S. Endoscopic subfascial discission of perforating veins. Surg Endosc 1988;2:5–12.

163. Bergan JJ, Murray J, Greason K. Subfascial endoscopic perforator vein surgery: a preliminary report. Ann Vasc Surg 1996;10:211–9.

164. Gloviczki P, Cambria RA, Rhee RY, Canton LG, McKusick MA. Surgical technique and preliminary results of endoscopic subfascial division of perforating veins. J Vasc Surg 1996;23:517–23.

165. Iafrati MD, Welch HJ, O'Donnell TF Jr. Subfascial endoscopic perforator ligation: an analysis of early clinical outcomes and cost. J Vasc Surg 1997;25:995–1000, discussion 1000–1.

166. Sparks SR, Ballard JL, Bergan JJ, Killeen JD. Early benefits of subfascial endoscopic perforator surgery (SEPS) in healing venous ulcers. Ann Vasc Surg 1997;11:367–73.

167. Olivencia JA. Subfascial endoscopic ligation of perforator veins (SEPS) in the treatment of venous ulcers. Int Surg 2000;85:266–9.

168. Ciostek P, Myrcha P, Noszczyk W. Ten years experience with subfascial endoscopic perforator vein surgery. Ann Vasc Surg 2002;16:480–7.

169. Lee DW, Lam YH, Chan AC, Chung SC. Subfascial endoscopic perforator surgery for venous ulcers. Hong Kong Med J 2003;9:279–82.

170. Ting AC, Cheng SW, Ho P, Wu LL, Cheung GC. Clinical outcomes and changes in venous hemodynamics after subfascial endoscopic perforating vein surgery. Surg Endosc 2003;17:1314–8.

171. Bianchi C, Ballard JL, Abou-Zamzam AM, Teruya TH. Subfascial endoscopic perforator vein surgery combined with saphenous vein ablation: results and critical analysis. J Vasc Surg 2003;38:67–71.

172. Iafrati MD, Pare GJ, O'Donnell TF, Estes J. Is the nihilistic approach to surgical reduction of superficial and perforator vein incompetence for venous ulcer justified? J Vasc Surg 2002;36:1167–74.

173. Jeanneret C, Fischer R, Chandler JG, Galeazzi RL, Jäger KA. Great saphenous vein stripping with liberal use of subfascial endoscopic perforator vein surgery (SEPS). Ann Vasc Surg 2003;17:539–49.

174. Proebstle TM, Weisel G, Paepcke U, Gass S, Weber L. Light reflection rheography and clinical course of patients with advanced venous disease before and after endoscopic subfascial division of perforating veins. Dermatol Surg 1998;24:771–6.

175. Padberg FT Jr. Endoscopic subfascial perforating vein ligation: its complementary role in the surgical management of chronic venous insufficiency. Ann Vasc Surg 1999;13:343–54.

176. Al-Mulhim AS, El-Hoseiny H, Al-Mulhim FM, Bayameen O, Sami MM, Abdulaziz K, *et al.* Surgical correction of main stem reflux in the superficial venous system: does it improve the blood flow of incompetent perforating veins? World J Surg 2003;27:793–6.

177. Stuart WP, Adam DJ, Allan PL, Ruckley CV, Bradbury AW. Saphenous surgery does not correct perforator incompetence in the presence of deep venous reflux. J Vasc Surg 1998;28:834–8.

178. Gohel MS, Barwell JR, Wakely C, Minor J, Harvey K, Earnshaw JJ, *et al.* The influence of superficial venous surgery and compression on incompetent calf perforators in chronic venous leg ulceration. Eur J Vasc Endovasc Surg 2005;29:78–82.

179. Nelzén O, Fransson I; Swedish SEPS Study Group. Early results from a randomized trial of saphenous surgery with or without subfascial endoscopic perforator surgery in patients with a venous ulcer. Br J Surg 2011;98:495–500.

180. Stacey MC, Burnand KG, Layer GT, Pattison M. Calf pump function in patients with healed venous ulcers is not improved by surgery to the communicating veins or by elastic stockings. Br J Surg 1988;75:436–9.

181. Bradbury AW, Ruckley CV. Foot volumetry can predict recurrent ulceration after subfascial ligation of perforators and saphenous ligation. J Vasc Surg 1993;18:789–95.

182. Puggioni A, Lurie F, Kistner RL, Eklof B. How often is deep venous reflux eliminated after saphenous vein ablation? J Vasc Surg 2003;38:517–21.

183. Adam DJ, Bello M, Hartshorne T, London NJ. Role of superficial venous surgery in patients with combined superficial and segmental deep venous reflux. Eur J Vasc Endovasc Surg 2003;25:469–72.

184. Ioannou CV, Giannoukas AD, Kostas T, Kafetzakis A, Liamis A, Touloupakis E, *et al.* Patterns of venous reflux in limbs with venous ulcers. Implications for treatment. Int Angiol 2003;22:182–7.

185. Mendes RR, Marston WA, Farber MA, Keagy BA. Treatment of superficial and perforator venous incompetence without deep venous insufficiency: is routine perforator ligation necessary? J Vasc Surg 2003;38:891–5.

186. Danielsson G, Jungbeck C, Peterson K, Norgren L. Venous function after restoring valve competence of the great saphenous vein. J Endovasc Ther 2003;10:350–5.

187. Maleti O, Lugli M, Perrin M. After Superficial Ablation for Superficial Reflux Associated with Primary Deep Axial Reflux, Can Variable Outcomes be Caused by Deep Venous Valve Anomalies? Eur J Vasc Endovasc Surg 2017;53:229–36.

188. Nelzén O, Fransson I. True long-term healing and recurrence of venous leg ulcers following SEPS combined with superficial venous surgery: a prospective study. Eur J Vasc Endovasc Surg 2007;34:605–12.

189. Obermayer A, Göstl K, Walli G, Benesch T. Chronic venous leg ulcers benefit from surgery: long-term results from 173 legs. J Vasc Surg 2006;44:572–9.

190. van Gent WB, Hop WC, van Praag MC, Mackaay AJ, de Boer EM, Wittens CH. Conservative versus surgical treatment of venous leg ulcers: a prospective, randomized, multicenter trial. J Vasc Surg 2006;44:563–71.

191. Lawrence PF, Alktaifi A, Rigberg D, DeRubertis B, Gelabert H, Jimenez JC. Endovenous ablation of incompetent perforating veins is effective treatment for recalcitrant venous ulcers. J Vasc Surg 2011;54:737–42.

192. Seren M, Dumantepe M, Fazliogullari O, Kucukaksu S. Combined treatment with endovenous laser ablation and compression therapy of incompetent perforating veins for treatment of recalcitrant venous ulcers. Phlebology 2017;32:307–15.

193. O'Donnell TF Jr, Passman MA, Marston WA, Ennis WJ, Dalsing M, Kistner RL, *et al.*; Society for Vascular Surgery; American Venous Forum. Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery ® and the American Venous Forum. J Vasc Surg 2014;60(Suppl):3S–59S.

194. Mosti G, De Maeseneer M, Cavezzi A, Parsi K, Morrison N, Nelzen O, *et al.* Society for Vascular Surgery and American Venous Forum Guidelines on the management of venous leg ulcers: the point of view of the International Union of Phlebology. Int Angiol 2015;34:202–18.

195. Franks PJ, Barker J, Collier M, Gethin G, Haesler E, Jawien A, *et al.* Management of Patients With Venous Leg Ulcers: Challenges and Current Best Practice. J Wound Care 2016;25(Suppl 6):S1–67.

196. Vasdekis SN, Clarke GH, Hobbs JT, Nicolaides AN. Evaluation of non-invasive and invasive methods in the assessment of short saphenous vein termination. Br J Surg 1989;76:929–32.

197. Gillet JL, Perrin M, Hiltbrand B, Bayon JM, Gobin JP, Calvignac JL, *et al.* [Pre- and postoperative contribution of Doppler ultrasonography in superficial venous surgery of the popliteal fossa]. J Mal Vasc 1997;22:330–5. French.

198. Juhan C, Barthélémy P, Alimi Y, Di Mauro P. [Recurrence following surgery of the gastrocnemius veins]. J Mal Vasc 1997;22:326–9. French.

199. Tong Y, Royle J. Recurrent varicose veins after short saphenous vein surgery: a duplex ultrasound study. Cardiovasc Surg 1996;4:364–7.

CHAPTER 10

Treatment of deep venous reflux

The significance and frequency of deep venous reflux in CVD has only been fully realized in the last 30 years owing to the use of duplex ultrasound scanning.[1, 2] Venous reflux involving deep veins is found in less than 10% of patients with skin changes and ulceration (C_4-C_6)[3] and is associated with superficial reflux and/or perforating veins incompetence in most patients. The most common cause of deep venous reflux is post-thrombotic changes accounting for an estimated 60-85% of patients. Primary reflux is less common and is the result of structural abnormalities in the vein wall and the valves.[3] A very rare cause of reflux is congenital absence of valves. Reflux may be associated with iliac obstruction in both post-thrombotic and non-thrombotic disease.[4]

Surgical techniques for treating deep venous reflux can be classified into two groups.[5] The first group requires phlebotomy and includes internal valvuloplasty,[6-9] transposition[10] and transplantation,[1, 11, 12] neovalve creation,[13, 14] and implantation of cryopreserved valves.[15, 16] The second group does not require phlebotomy and includes wrapping,[17, 18] external valvuloplasty (transmural[19] or transcommissural)[20] with or without angioscopy assistance.[21-23]

Patients who are considered for deep reflux repair should have advanced symptoms of pain, swelling, skin changes, and/or ulcer (C_{4-6}) affecting quality of life despite adequate conservative treatment. Deep valve reconstruction should follow correction of iliac venous outflow obstruction. In cases of combined superficial and deep venous reflux, it has been recommended to treat first superficial reflux, but there was no consensus on this issue. Recently an answer to this problem has been suggested. When incompetent valves are asymmetrical correction of superficial reflux does not improve the deep reflux.[24] Surgical correction of deep reflux requires detailed mapping of obstruction and reflux and is only indicated in the presence of extensive deep axial reflux (from groin into calf veins).[5, 25]

Investigations

Patients considered for deep valve repair in addition to duplex scanning require preoperative phlebographic evaluation to assess operability (ascending, transfemoral and/or brachial phlebography). Pre-operative air-plethysmography and ambulatory venous pressure (AVP) measurements provide baseline quantitative information that may be useful for follow-up. The choice of investigation is determined by the clinical context and whether or not there are contraindications for surgical intervention.

Valve repair in primary deep vein incompetence

The goal of surgery for deep venous reflux is to correct the reflux at a sub-inguinal level. The most frequent procedure performed for primary deep venous reflux is internal valvuloplasty. This is credited with achieving a good result in 70% of cases (Table I).[2, 20, 26-33] in terms of clinical outcome defined as freedom of ulcer recurrence and reduction of pain, valve competence, and hemodynamic improvement over a follow-up period of more than 5 years. In all series, a good correlation has been observed between these three criteria. External transmural valvuloplasty does not seem to be as reliable as internal valvuloplasty in providing long-term valve competence or ulcer free survival.[5, 34, 35] Wrapping has been used both in primary venous reflux and the post-thrombotic syndrome (PTS) providing variable results. A large retrospective series reported by Chinese authors reported a long-term ulcer recurrence of 3.63% in a group of patients where 89.78% had deep vein reflux of primary etiology (Table II).[17, 27, 35-38]

TABLE I.—*Results of valvuloplasty for deep venous reflux.*[2, 20, 26-33]

Study	Surgical technique	N. of limbs (N. of valves repaired)	Etiology: PVI/total	Follow-up, months (mean)	Ulcer recurrence or unhealed ulcers	Hemodynamic results	
						Competent valve	AVP □ VRT ■
Masuda 1994[29]	I	32	27/32	48-252 (127)	28%	24/31 (77%)*	□ ↑ 81% (av) ■ ↑ 50% (av)
Raju 1985[31]	I	68 (71)	–	12-144	16/68 (26%)	30/71 (42%)	
Raju 1996[27]	TMEV	47 (111)	–	12-70	14/47 (30%)	72/111	
Sottiurai 1996[26]	I	118	–	8-146 (71)	9/42 (21%)	89/118 (75%)	
Perrin 2000[2]	I	85 (94)	65/85	12-96 (58)	10/35 (29%)	72/94 (77%)	■ Normalized 63% (av)
Raju 2000[20]	TCEV	141 (179)	98/141	1-42	37%	59%	□ ↑ 15% (av) ■ Normalized 100%
Tripathi 2004[28]	I	90 (144)	118	(24)	32%	79.8%	
	TMEV	12 (19)			50%	31.5%	
Rosales 2006[33]	TMEV	17 (40)	17/17	3-122 (60)	3/7 (43%)	52%	□ ↑ 50% (av)
Wang 2006[30]	TMEV	(40)	40/40	(36)	–	91%	■ ↑ 50% (av)
Lehtola 2008[32]	I	12	5/12	24-78 (54)	–	55%	–
	TMEV	7	3/7				
	I+TMEV	1	0/1				

I: internal valvuloplasty; PVI: primary venous insufficiency; TMEV: transmural external valvuloplasty; TCEV: transcommissural external valvuloplasty; AVP: ambulatory venous pressure; VRT: venous refill time; av: average; ↑: improved.
*No reflux or less than 1 s.

TABLE II.—*Results of banding, cuffing, external stenting and wrapping for deep venous reflux.*[17, 27, 35-38]

Study	N. of extremities treated (N. of valves repaired)	Site	Etiology: PVI/total	Follow-up, months (average)	Ulcer recurrence or unhealed ulcer (%)	Hemodynamic results	
						Competent valve/vein	AVP □ VRT ■
Camilli 1994[36] (Dacron)	54	F	54/54	4-63	–	41/54 (76%)	–
Raju 1996[27] (Dacron)	96	F, P, T	–	12-134	6/22 (27%)	60/72 (83%)	–
Akesson 1999[35] (Venocuff I)	20 (27)	F, P	7/20	5-32 (19)	2/10 (20%) both PTS	PVI 7/7(100%)	PVI: □ ↑ 10% (av) ■ ↑ 10% (av) PTS: □ ↑ 10% (av) ■ ↑ 100% (av)
Lane 2003[17] (Venocuff II)	42 (125)	F, P	36/42	64-141 (93)	20%	90%	□ ↑ ? ■ ↑ 100% (av)
Makhatilov 2009[37] (Vedensky Spiral)	24 (54)	F	28/28	12-60 (29)	No C_6	–	–
Ma 2016[38] (polyester urethane)	1252	P	1124/1252	9-183 (55.12)	7/193	Duration of reflux, reflux volume P>0.001 between preop and postop measurements	P>0.001 between preop and postop measurements

PVI: primary venous insufficiency; AVP: ambulatory venous pressure; VRT: venous refill time; av: average; ↑: improved; F: femoral vein; P: popliteal vein; T: tibial (posterior) vein; PTS: post-thrombotic syndrome.

Valve repair in post-thrombotic disease

Long -term results after surgery for PTS are also available for transposition (Table III).[2, 26, 29, 32, 39, 40] and transplantation (Table IV).[2, 11, 26-28, 32, 41-47] In terms of clinical results and valve competence, a meta-analysis demonstrated that a good result was achieved in 60% and 40% in transposition and transplantation, respectively, over a follow-up period of more than 5 years (with a poor correlation between clinical and hemodynamic outcome). Other techniques

TABLE III.—*Results of transposition for deep venous reflux.*[2, 26, 29, 32, 39, 40]

Study	N. of extremities treated	Etiology: PTS/total	Follow-up, month	Ulcer recurrence or unhealed ulcer (%)	Hemodynamic results	
					Competent valve	AVP □ VRT ■
Johnson 1981[40]	12	12/12	12	4/12 (33%)	–	□ Unchanged ■ Unchanged
Masuda 1994[29]	14	–	48-252	7/14 (50%)	10/13 (77%)	□ ↑ 70% (av) ■ ↑ 70% (av)
Sottiurai 1996[26]	20	20/20	9-149	9/16 (56%)	8/20 (40%)	–
Cardon 1999[39]	16	16/16	24-120	4/9 (44%)	12/16 (75%)	–
Perrin 2000[2]	17	16/17	12-168	2/8 (25%)	9/17 (53%)	–
Lehtola 2008[32]	14	12/14	24-78	–	43%	–

AVP: ambulatory venous pressure; VRT: venous refill time; av: average; ↑: improved; PTS: post-thrombotic syndrome.

TABLE IV.—*Results of transplantation for deep venous reflux.*[2, 11, 26-28, 32, 41-47]

Study	N. of extremities treated	Site	Etiology: PTS/total	Follow-up, month (average)	Ulcer recurrence or unhealed ulcer	Hemodynamic results	
						Competent valve	AVP □ VRT ■
Taheri 1982[11]	71	F, P	–	–	1/18 (6%)	28/31 (90%)	□ ↑ 15% (av)
Bry 1995[44]	15	P	–	15/132	3/14 (21%)	7/8 (87%)	□ Unchanged ■ Unchanged
Eriksson 1988[41]	35	F, P	35/35	6-60	–	11/35 (31%)	■ Unchanged
Kabbani 2011[45]	19	FC, P, GSV	12/18	(37)	6/8 (80%)	8/19 (42%)	
Lehtola 2008[32]	29	F, P	25/29	24-78 (54)	–	16%	–
Mackiewicz 1995[46]	18	F	–	43/69	5/14 (36%)	–	■ ↑
Nash 1988[42]	25	P	25/25	–	3/17 (18%)	18/23 (77%)	□ ↑ 18% (av)
Perrin 2000[2]	32	F	31/32	12-124 (66)	9/22 (41%)	8/32 (25%)	■ ↑ 19% (av)
Raju 1999[43]	83 §	F, P, T	83/83	12-180	40% 6 years	38% 4 years	□ Unchanged
Raju 1996[27]	54	F	–	12-180	–	16/44 (36%)	–
Rosales 2008[47]	22 including 2 double Tr. Tr. + other procedure	F, P	22/22	6-108	–	GSV Tr. 14/26 AV Tr. 3/6	–
Sottiurai 1996[26]	18	F, P	–	7-144	6/9 (67%)	6/18 (33%)	–
Tripathi 2004[28]	35	F, P	35/35	(24)	45%	41%	–

Tr.: transposition; GSV: great saphenous vein; AVP: ambulatory venous pressure; VRT: venous refill time; av: average; ↑: improved; F: femoral vein; FC: common femoral vein; P: popliteal vein; T: tibial (posterior) vein; PTS: post-thrombotic syndrome.
§ Axillary vein transfer in trabeculated (poorly recanalized) vein.

TABLE V.—*Results of neo-valve construction for deep venous reflux.*[14, 48-50]

Study	Technique	N. of extremities	Etiology: PTS/total (extremity)	Follow-up, month (mean)	Unhealed ulcer or ulcer recurrence	Hemodynamics results	
						Competent valve	AVP □ VRT ■
Plagnol 1999[14]	Bicuspid neo valve constructed with superficial vein	44	44/44	6-47 (18)	3/32 (17%)	38/44 (86%)	
Opie 2008[49]	Monocuspid neo valve constructed with deep vein wall + PTFE patch	14	KN	(48)	0/6	13/14 (92%)	
Labas 2009[50]	Wilson technique on transplanted axillar vein ± FV valvuloplasty + sclerotherapy	56	KN	4-21 (10.7)	18%	51/56	
Lugli 2009[48]	Monocuspid or bicuspid neo valve constructed with deep vein wall	19+21 = 40 2 different techniques	40/40	2-78 (28.5)	7/40 (17%)	13/19 (68%) 21/21 (100%)	■ ↑ in 75%

AVP: ambulatory venous pressure; PTS: post-thrombotic syndrome.

include neovalve construction (Table V).[14, 48-50] Nevertheless, Lugli *et al*. reported excellent clinical results and neovalve competence in 34/40 cases after mean follow-up of 28.5 months.[48]

Large randomized controlled trials comparing conservative treatment and surgery for deep venous reflux would be difficult to conduct so that it is necessary to rely on the outcome of available series of deep venous reconstructive surgery. Their analysis provides a grade 1C recommendation in primary etiology and 2C in secondary.

References

1. O'Donnell TF Jr, Mackey WC, Shepard AD, Callow AD. Clinical, hemodynamic, and anatomic follow-up of direct venous reconstruction. Arch Surg 1987;122:474–82.

2. Perrin M. Reconstructive surgery for deep venous reflux: a report on 144 cases. Cardiovasc Surg 2000;8:246–55.

3. Kistner RL, Ferris EB, Randhawa G, Kamida C. A method of performing descending venography. J Vasc Surg 1986;4:464–8.

4. Raju S, Neglen P. High prevalence of nonthrombotic iliac vein lesions in chronic venous disease: a permissive role in pathogenicity. J Vasc Surg 2006;44:136–43, discussion 144.

5. Maleti O, Perrin M. Reconstructive surgery for deep vein reflux in the lower limbs: techniques, results and indications. Eur J Vasc Endovasc Surg 2011;41:837–48.

6. Sottiurai VS. Technique in direct venous valvuloplasty. J Vasc Surg 1988;8:646–8.

7. Kistner RL. Surgical repair of the incompetent femoral vein valve. Arch Surg 1975;110:1336–42.

8. Raju S. Venous insufficiency of the lower limb and stasis ulceration. Changing concepts and management. Ann Surg 1983;197:688–97.

9. Tripathi R, Ktenidis KD. Trapdoor internal valvuloplasty—a new technique for primary deep vein valvular incompetence. Eur J Vasc Endovasc Surg 2001;22:86–9.

10. Kistner RL, Sparkuhl MD. Surgery in acute and chronic venous disease. Surgery 1979;85:31–43.

11. Taheri SA, Lazar L, Elias S. Status of vein valve transplant after 12 months. Arch Surg 1982;117:1313–7.

12. Raju S. A pressure-based technique for the detection of acute and chronic venous obstruction. Phlebology 1988;3:207–16.

13. Maleti O. Venous valvular reconstruction in post-thrombotic syndrome. A new technique. J Mal Vasc 2002;27:218–21.

14. Plagnol P, Ciostek P, Grimaud JP, Prokopowicz SC. Autogenous valve reconstruction technique for post-thrombotic reflux. Ann Vasc Surg 1999;13:339–42.

15. Dalsing MC, Raju S, Wakefield TW, Taheri S. A multicenter, phase I evaluation of cryopreserved venous valve allografts for the treatment of chronic deep venous insufficiency. J Vasc Surg 1999;30:854–64.

16. Neglén P, Raju S. Venous reflux repair with cryopreserved vein valves. J Vasc Surg 2003;37:552–7.

17. Lane RJ, Cuzzilla ML, McMahon CG. Intermediate to long-term results of repairing incompetent multiple deep venous valves using external valvular stenting. ANZ J Surg 2003;73:267–74.

18. Hallberg D. A method for repairing incompetent valves in deep veins. Acta Chir Scand 1972;138:143–5.

19. Kistner RL. Surgical technique of external venous valve repair. Straub Found Proc 1990;55:15–6.

20. Raju S, Berry MA, Neglén P. Transcommissural valvuloplasty: technique and results. J Vasc Surg 2000;32:969–76.

21. Nishibe T, Kudo F, Flores J, Miyazaki K, Yasuda K. Femoral vein valve repair with angioscopy-assisted anterior valve sinus plication. Early results. J Cardiovasc Surg (Torino) 2001;42:529–35.

22. Gloviczki P, Merrell SW, Bower TC. Femoral vein valve repair under direct vision without venotomy: a modified technique with use of angioscopy. J Vasc Surg 1991;14:645–8.

23. Pavcnik D, Uchida BT, Timmermans HA, Corless CL, O'Hara M, Toyota N, *et al.* Percutaneous bioprosthetic venous valve: a long-term study in sheep. J Vasc Surg 2002;35:598–602.

24. Maleti O, Lugli M, Perrin M. After Superficial Ablation for Superficial Reflux Associated with Primary Deep Axial Reflux, Can Variable Outcomes be Caused by Deep Venous Valve Anomalies? Eur J Vasc Endovasc Surg 2017;53:229–36.

25. Danielsson G, Arfvidsson B, Eklof B, Kistner RL, Masuda EM, Satoc DT. Reflux from thigh to calf, the major pathology in chronic venous ulcer disease: surgery indicated in the majority of patients. Vasc Endovascular Surg 2004;38:209–19.

26. Sottiurai VS. Current surgical approaches to venous hypertension and valvular reflux. Int J Angiol 1996;5:49–54.

27. Raju S, Fredericks RK, Neglèn PN, Bass JD. Durability of venous valve reconstruction techniques for "primary" and postthrombotic reflux. J Vasc Surg 1996;23:357–66, discussion 366–7.

28. Tripathi R, Sieunarine K, Abbas M, Durrani N. Deep venous valve reconstruction for non-healing leg ulcers: techniques and results. ANZ J Surg 2004;74:34–9.

29. Masuda EM, Kistner RL. Long-term results of venous valve reconstruction: a four- to twenty-one-year follow-up. J Vasc Surg 1994;19:391–403.

30. Wang SM, Hu ZJ, Li SQ, Huang XL, Ye CS. Effect of external valvuloplasty of the deep vein in the treatment of chronic venous insufficiency of the lower extremity. J Vasc Surg 2006;44:1296–300.

31. Raju S. Valvuloplasty and valve transfer. Int Angiol 1985;4:419–24.

32. Lehtola A, Oinonen A, Sugano N, Albäck A, Lepäntalo M. Deep venous reconstructions: long-term outcome in patients with primary or post-thrombotic deep venous incompetence. Eur J Vasc Endovasc Surg 2008;35:487–93.

33. Rosales A, Slagsvold CE, Kroese AJ, Stranden E, Risum Ø, Jørgensen JJ. External venous valve plasty (EVVP) in patients with primary chronic venous insufficiency (PCVI). Eur J Vasc Endovasc Surg 2006;32:570–6.

34. Perrin M. [Surgery for deep venous reflux in the lower limb]. J Mal Vasc 2004;29:73–87. French.

35. Akesson H, Risberg B, Björgell O. External support valvuloplasty in the treatment of chronic deep vein incompetence of the legs. Int Angiol 1999;18:233–8.

36. Camilli S, Guarnera G. External banding valvuloplasty of the superficial femoral vein in the treatment of primary deep valvular incompetence. Int Angiol 1994;13:218–22.

37. Makhatilov G, Askerkhanov G, Kazakmurzaev MA, Ismailov I. Endoscopically directed external support of femoral vein valves. J Vasc Surg 2009;49:676–80, discussion 680.

38. Ma T, Fu W, Ma J. Popliteal vein external banding at the valve-free segment to treat severe chronic venous insufficiency. J Vasc Surg 2016;64:438–445.e1.

39. Cardon JM, Cardon A, Joyeux A, Mangialardi N, Noblet D, Nguyen T, *et al.* Use of ipsilateral greater saphenous vein as a valved transplant in management of post-thrombotic deep venous insufficiency: long-term results. Ann Vasc Surg 1999;13:284–9.

40. Johnson ND, Queral LA, Flinn WR, Yao JS, Bergan JJ. Late objective assessment of venous value surgery. Arch Surg 1981;116:1461–6.

41. Eriksson I, Almgren B. Surgical reconstruction of incompetent deep vein valves. Ups J Med Sci 1988;93:139–43.

42. Nash T. Long term results of vein valve transplants placed in the pop-

liteal vein for intractable post-phlebitic venous ulcers and pre-ulcer skin changes. J Cardiovasc Surg (Torino) 1988;29:712–6.

43. Raju S, Neglén P, Doolittle J, Meydrech EF. Axillary vein transfer in trabeculated postthrombotic veins. J Vasc Surg 1999;29:1050–62, discussion 1062–4.

44. Bry JD, Muto PA, O'Donnell TF, Isaacson LA. The clinical and hemodynamic results after axillary-to-popliteal vein valve transplantation. J Vasc Surg 1995;21:110–9.

45. Kabbani L, Escobar GA, Mansour F, Wakefield TW, Henke PK. Longevity and outcomes of axillary valve transplantation for severe lower extremity chronic venous insufficiency. Ann Vasc Surg 2011;25:496–501.

46. Mackiewicz Z, Molski S, Jundzill W, Stankiewicz W. Treatment of postphlebitic syndrom with valve transplantation: five year experience. In Bergan JJ, Shortell CK, editors. Eurosurgery. Bologna: Monduzzi, 1995. p. 305–10.

47. Rosales A, Jørgensen JJ, Slagsvold CE, Stranden E, Risum Ø, Kroese AJ. Venous valve reconstruction in patients with secondary chronic venous insufficiency. Eur J Vasc Endovasc Surg 2008;36:466–72.

48. Lugli M, Guerzoni S, Garofalo M, Smedile G, Maleti O. Neovalve construction in deep venous incompetence. J Vasc Surg 2009;49:156–62, 162.e1–2, discussion 162.

49. Opie JC, Izdebski T, Payne DN, Opie SR. Monocusp - novel common femoral vein monocusp surgery uncorrectable chronic venous insufficiency with aplastic/dysplastic valves. Phlebology 2008;23:158–71.

50. Labas P, Cambal M. Autogenous venous valve construction. Int Angiol 2009;28:147–50.

CHAPTER 11

Treatment of venous outflow obstruction

The pathophysiology of chronic venous insufficiency (CVI) has for decades been focused on deep and superficial reflux. With the development of percutaneous technology to treat obstruction invasively, the important contribution of obstruction was realized. The main emphasis on interventions is to relieve chronic non-thrombotic and post-thrombotic ilio-femoral venous outflow obstructions (obliteration of the common femoral and ilio-caval veins).

Obstruction is the principal cause of symptoms in approximately one third of post-thrombotic limbs and combined with reflux in 55% of symptomatic patients with CVI.[1, 2] It leads to the highest levels of venous hypertension and the most severe symptoms as compared to either alone.[3, 4] Following iliofemoral DVT, only 20-30% of iliac veins completely recanalize spontaneously, while the remaining veins have residual obstruction and varying degrees of collaterals.[5, 6] Symptoms such as venous claudication, pain, swelling and ulcer are more frequent and severe and the quality of life worse with ilio-femoral venous obstruction than when the obstruction is limited to the femoro-popliteal segment.[7-10] In addition, the risk of having recurrent DVT and to develop severe post-thrombotic syndrome (PTS) is 3.4 times and 2.4 times more likely, respectively.[11, 12] Correction of obliteration by venoplasty and stent placement alone has been shown to be a sufficient therapy in most patients even in the presence of reflux.[13]

The impact of non-thrombotic iliac vein lesions (NIVL) (such as May-Thurner Syndrome or Cockett's Iliac Compression Syndrome) is less evident. NIVLs of various degrees are frequently seen in the asymptomatic population. The frequency of >50% stenosis in this population may be up to 24%.[14] Although this frequency is likely to be higher in the patients with symptomatic non-thrombotic chronic venous disease,[15] there is an inherit risk to overtreat non-thrombotic iliac vein obstructions.

Diagnosis and selection of patients

It is important for the physician to be aware that there may be ilio-femoral venous outflow obstruction. Patients presenting with C-classes 3-6, particularly those with venous claudication on challenged exercise,[10] those with pain out of proportion to detected lesion and those with PTS. It is unknown at what degree a chronic ilio-femoral obstruction becomes hemodynamically significant; consequently, no adequate test exists. This lack of "gold standard" is the major obstacle for selecting limbs for treatment and evaluating outcome. Although a positive available non-invasive or invasive test may support to proceed with further investigation, a negative test should not exclude it. The diagnosis of outflow obstruction must rely on morphological investigations. Presently the reduction of the lumen area or diameter >50% is considered an indication for treatment.

Investigations should provide full assessment of lower limb veins including the ilio-caval outflow. Initial duplex ultrasound scanning (DUS) of the entire lower limb including the pelvis to determine the extent of obliteration must be performed. Visualization of the supra inguinal and abdominal vessels often need the use of computed tomography venography (CT-V) or magnetic resonance imaging venography (MR-V).[16, 17] Patients identified with disease in the CFV or potentially poor inflow from the deep veins in the thigh may require an ascending venogram to delineate the anatomy clearly. If there is doubt regarding the presence or absence of outflow obstruction, the workup should include diagnostic intravascular ultrasound (IVUS), as there are no data on sensitivity or speci-

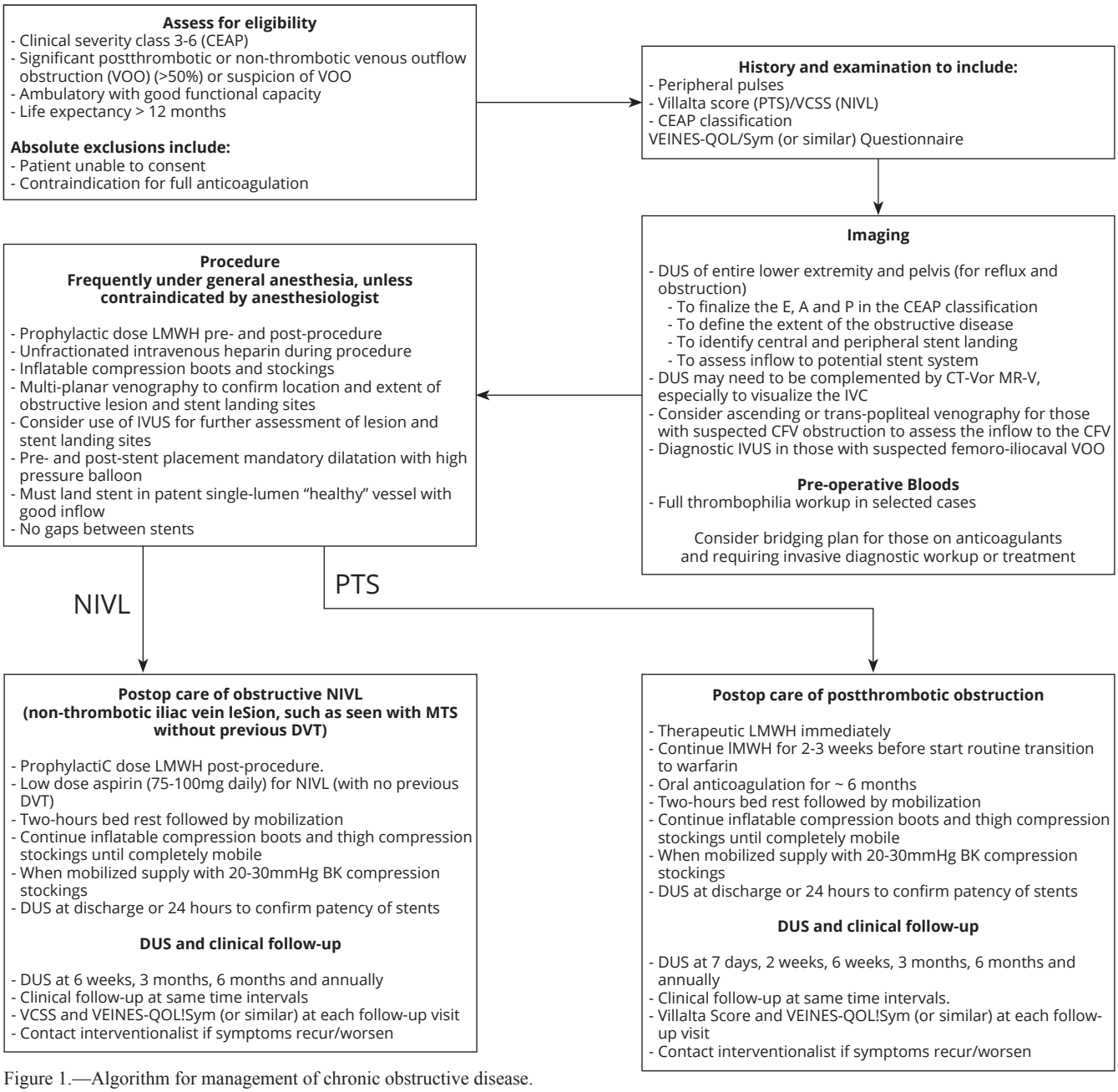

Figure 1.—Algorithm for management of chronic obstructive disease.

ficity of either CT-V or MR-V to identify an outflow obstruction. IVUS is considered the "gold standard" investigation to estimate the morphological degree and extent of iliac vein obliteration and being able visualize details of intraluminal and external compressive lesions.[18-20] An algorithm for management of chronic obstructive venous disease is given in Figure 1.

Femoro-ilio-caval stenting

The introduction of percutaneous iliac venous balloon dilation and stenting has dramatically expanded the scope of treatment. This is now considered the "method-of- choice" to treat ilio-femoral venous obstruction. Formative contributions by Neglen and Raju reported excellent long-term

results for both post-thrombotic and non-thrombotic obstructions of the femoro-ilio-caval venous outflow, with low morbidity, no mortality and excellent clinical success.[15, 21-23] The complication rate was minimal and the mortality was nil. In a study that included 982 patients treated with stent placement, Neglen *et al.* observed primary, primary-assisted and secondary cumulative patency rates at 6 years of 79%, 100% and 100% and 57%, 80% and 86% in patients with NIVL and PTS, respectively.[22]

Severe in-stent stenosis defined as greater than 50% diameter decrease on single plane anterior-posterior venogram or duplex ultrasound scanning (DUS), is infrequent occurring in only 5% at 6 years in one study.[22] The cumulative rate was higher in thrombotic limbs at 10% compared with 1% in NIVL limbs. Factors associated with in-stent stenosis are like those associated with stent occlusion, namely post-thrombotic obstruction, extent of obstruction and degree of stenosis, but not age. Of interest was that thrombophilia was more frequent in PTS limbs, but there was no statistically association with stent occlusion or in-stent stenosis.[22] At 5 years, cumulative rates of complete relief of pain and swelling were 62% and 32%, respectively, and ulcer healing was 58%. The mean CIVIQ scores of QOL improved significantly in all categories.[22]

Recently three meta-analysis of femoro-ilio-caval stent placement have been published.[24-26] The most comprehensive by Razavi *et al.* includes 37 studies analyzing 34 treatment effects in 2869 unique patients.[24] The technical success rate ranged from 94 to 96%. Cumulative primary and secondary patency rates at one year in patients stented for NIVL, post-thrombotic obstruction and following early clot removal of acute DVT were 96% and 99%, 79% and 94%, and 87%% and 89%, respectively. Primary and secondary patency remained higher in non-thrombotic patients *versus* those with acute DVT or post-thrombotic obstruction through 5 years. This study confirmed that iliac stenting has low and acceptable rate of complication and that clinical outcome was favorable (Table I).[24] Most impressive is the observed sustained high ulcer healing rate, frequently after failed aggressive non-invasive treatment. The results were similar in the other two meta-analysis studies.

While the clinical outcome is quite impressive, they are still based on single-center cohort studies.[22, 27, 28] Symptomatic improvement with patient reported outcomes and quality of life assessments are inconsistently reported. The evidence to support venous stenting is still considered weak to moderate, the main flaw being the lack of control groups. Although unlikely, the clinical improvement could be part of the natural progression of the disease or, perhaps, an improved conservative treatment after compared with before intervention. A well-controlled multicenter prospective randomized study comparing best medical treatment with stent placement is desirable. The design of such a study has challenges to overcome, not the least to ensure that the best medical treatment is sufficiently standardized with good patient compliance in all centers and that the venous pathology is at least similar in both groups (including the presence and degree of deep and superficial reflux; degree, extent and etiology of the obstruction). An alternative would be to perform well-controlled multicenter non-randomized cohort studies with core lab evaluation and neutral assessment of the clinical outcome after a period of best medical treatment.

TABLE I.—*Complications rates and clinical result after stenting in patients for non-thrombotic iliac vein lesion (NIVL), for postthrombotic obstruction (PTS) and following early clot removal of acute ilio-femoral DVT (Acute DVT).*[24]

	NIVL (N.=1122) (%)	PTS (N.=1118) (%)	Acute DVT (N.=629) (%)
Complications			
Major bleeding	0.3	0.9	1.1
Pulmonary embolism	0.2	0.6	0.9
Peri-procedural mortality	0.1	0.3	0.7
Early thrombosis	1.0	6.8	6.5
Symptoms			
Complete pain relief†	81.5	69.3	100*
Complete edema relief†	68.0	63.6	100*
Complete ulcer healing†	81.1	70.8	NA

*Meta analysis not conducted because of single study contributing data.
†At the final follow-up visit.

Hybrid intervention and endophlebectomy

In patients with poor inflow and where percutaneous stenting to the peripheral CFV or proximal profunda vein would result in poor patency, consideration can be given to perform endophlebectomy, patch and temporary arteriovenous fistula. The intention is to create a peripheral stent landing site and to increase inflow to the stent system. However, endophlebectomy and fistula is technically demanding and is associated with significant morbidity. Patients should be counseled prior to the procedure with respect to the increased risks and decreased patency related to this procedure. Endophlebectomy alone may be performed in selected patients with segmental femoral obstruction to improve venous outflow of the lower limb or to create a single lumen at the receiving site of an axillary transplantation.[29-31]

Open surgical reconstruction

Indications for surgical reconstruction has changed and should only be considered in patients fit to have surgery, after unsuccessful attempt of stent placement or with occluded stent system. Most of these patients have advanced CVI including ulcer due to extensive postthrombotic disease. The exception is when the occlusive disease is limited to the CFV alone, when primary surgical reconstruction (endophlebectomy or interposition graft) appears to be superior.

There is little evidence for surgical reconstruction.[32] The results following open reconstructions are usually presented in series with small numbers of treated limbs, short observations times and usually poor reporting standards and rarely presenting cumulative patency and success rates. Bypass grafting appears to have relatively poor long-term patency, perhaps for several reasons such as low velocity flow, external compression of low pressure bypass, inherent thrombogenicity of non-saphenous graft material, frequent presence of thrombophilia such as antiphospholipid antigen or antithrombin III deficiency, and the poor distal inflow due to extensive distal obstructive disease.[33, 34] The Mayo clinic has reported one of the largest experiences of various surgical venous procedures, which are reasonably well followed. The cumulative patency of 64 various venous reconstructions performed from 1985 to 2009 had a cumulative primary patency of 54%, 42% and 33%, a primary assisted patency of 62%, 47%, and 41% and a secondary patency of 73%, 59%, and 53% at one, five and ten years respectively.[32] Thus, the patency rates are lower than those achieved by percutaneous stent placement.

The cross-over bypass

The autogenous femoro-femoral venous bypass[35] needs a contralateral great saphenous vein of good quality with at least a 5 mm diameter. This graft appears to be less thrombogenic with better patency than prosthetic grafts.[36] Outcomes are especially good in patients with minimal infra-inguinal disease. Halliday *et al.* performed a cumulative analysis of 47 limbs showing a 75% cumulative venographic patency rate at 5 years.[37]

The in-line bypass

Anatomic in-line bypass reconstruction can be used in the femoro-ilio-caval axial outflow axis with segmental obstruction in the presence of a sufficient venous in- and outflow of the graft. Most commonly ePTFE grafts are used and the bypass is always supported by a femoral arteriovenous fistula. It appears that shorter in-line bypasses fair better than longer.[32] Cumulative patency of the 3 most common bypass procedures, the Mayo Clinic experience is as follows.[32] For femoro-iliac/ilio-caval bypass at one and ten years was 86% and 86% respectively; for Palma vein bypass it was 78% and 65% respectively; for femoro-caval, it was 76% and 57% respectively.

Sapheno-popliteal bypass

Sapheno-popliteal vein bypass is a rarely performed surgery for outflow obstruction because of stringent selection criteria. The few reported series of patients,[38-42] show a clinical success and patency rates of 31-83% and 56-100%, respectively, at follow-up of 1-5 years.

References

1. Johnson BF, Manzo RA, Bergelin RO, Strandness DE Jr. The site of residual abnormalities in the leg veins in long-term follow-up after deep vein thrombosis and their relationship to the development of the postthrombotic syndrome. Int Angiol 1996;15:14–9.

2. Johnson BF, Manzo RA, Bergelin RO, Strandness DE Jr. Relationship between changes in the deep venous system and the development of the postthrombotic syndrome after an acute episode of lower limb deep vein thrombosis: a one- to six-year follow-up. J Vasc Surg 1995;21:307–12, discussion 313.

3. Nicolaides AN, Hussein MK, Szendro G, Christopoulos D, Vasdekis S, Clarke H. The relation of venous ulceration with ambulatory venous pressure measurements. J Vasc Surg 1993;17:414–9.

4. Nicolaides AN, Sumner DS. Investigations of patients with deep vein thrombosis and chronic venous insufficiency. Los Angeles, CA: Med-Orion Publishing Co; 1991.

5. Plate G, Akesson H, Einarsson E, Ohlin P, Eklöf B. Long-term results of venous thrombectomy combined with a temporary arterio-venous fistula. Eur J Vasc Surg 1990;4:483–9.

6. Mavor GE, Galloway JM. Iliofemoral venous thrombosis. Pathological considerations and surgical management. Br J Surg 1969;56:45–59.

7. Akesson H, Brudin L, Dahlström JA, Eklöf B, Ohlin P, Plate G. Venous function assessed during a 5 year period after acute ilio-femoral venous thrombosis treated with anticoagulation. Eur J Vasc Surg 1990;4:43–8.

8. Kahn SR, Hirsch A, Shrier I. Effect of postthrombotic syndrome on health-related quality of life after deep venous thrombosis. Arch Intern Med 2002;162:1144–8.

9. Kahn SR, M'Lan CE, Lamping DL, Kurz X, Bérard A, Abenhaim L; Veines Study Group. The influence of venous thromboembolism on quality of life and severity of chronic venous disease. J Thromb Haemost 2004;2:2146–51.

10. Delis KT, Bountouroglou D, Mansfield AO. Venous claudication in iliofemoral thrombosis: long-term effects on venous hemodynamics, clinical status, and quality of life. Ann Surg 2004;239:118–26.

11. Douketis JD, Crowther MA, Foster GA, Ginsberg JS. Does the location of thrombosis determine the risk of disease recurrence in patients with proximal deep vein thrombosis? Am J Med 2001;110:515–9.

12. Yamaki T, Hamahata A, Soejima K, Kono T, Nozaki M, Sakurai H. Factors predicting development of post-thrombotic syndrome in patients with a first episode of deep vein thrombosis: preliminary report. Eur J Vasc Endovasc Surg 2011;41:126–33.

13. Raju S, Darcey R, Neglén P. Unexpected major role for venous stenting in deep reflux disease. J Vasc Surg 2010;51:401–8, discussion 408.

14. Kibbe MR, Ujiki M, Goodwin AL, Eskandari M, Yao J, Matsumura J. Iliac vein compression in an asymptomatic patient population. J Vasc Surg 2004;39:937–43.

15. Raju S, Neglén P. High prevalence of nonthrombotic iliac vein lesions in chronic venous disease: a permissive role in pathogenicity. J Vasc Surg 2006;44:136–43, discussion 144.

16. Chung JW, Yoon CJ, Jung SI, Kim HC, Lee W, Kim YI, *et al*. Acute iliofemoral deep vein thrombosis: evaluation of underlying anatomic abnormalities by spiral CT venography. J Vasc Interv Radiol 2004;15:249–56.

17. Fraser DG, Moody AR, Morgan PS, Martel A. Iliac compression syndrome and recanalization of femoropopliteal and iliac venous thrombosis: a prospective study with magnetic resonance venography. J Vasc Surg 2004;40:612–9.

18. Neglén P, Raju S. Intravascular ultrasound scan evaluation of the obstructed vein. J Vasc Surg 2002;35:694–700.

19. Forauer AR, Gemmete JJ, Dasika NL, Cho KJ, Williams DM. Intravascular ultrasound in the diagnosis and treatment of iliac vein compression (May-Thurner) syndrome. J Vasc Interv Radiol 2002;13:523–7.

20. Satokawa H, Hoshino S, Iwaya F, Igari T, Midorikawa H, Ogawa T. Intravascular Imaging Methods for Venous Disorders. Int J Angiol 2000;9:117–21.

21. Neglén P, Raju S. Balloon dilation and stenting of chronic iliac vein obstruction: technical aspects and early clinical outcome. J Endovasc Ther 2000;7:79–91.

22. Neglén P, Hollis KC, Olivier J, Raju S. Stenting of the venous outflow in chronic venous disease: long-term stent-related outcome, clinical, and hemodynamic result. J Vasc Surg 2007;46:979–90.

23. Raju S, Neglén P. Percutaneous recanalization of total occlusions of the iliac vein. J Vasc Surg 2009;50:360–8.

24. Razavi MK, Jaff MR, Miller LE. Safety and effectiveness of stent placement for iliofemoral venous outflow obstruction: systematic review and meta-analysis. Circ Cardiovasc Interv 2015;8:e002772.

25. Seager MJ, Busuttil A, Dharmarajah B, Davies AH. Editor's Choice— A Systematic Review of Endovenous Stenting in Chronic Venous Disease Secondary to Iliac Vein Obstruction. Eur J Vasc Endovasc Surg 2016;51:100–20.

26. Wen-da W, Yu Z, Yue-Xin C. Stenting for chronic obstructive venous disease: A current comprehensive meta-analysis and systematic review. Phlebology 2016;31:376–89.

27. Hartung O, Barthelemy P, Arnoux D, Boufi M, Alimi YS. Management of pregnancy in women with previous left ilio-caval stenting. J Vasc Surg 2009;50:355–9.

28. Ye K, Lu X, Li W, Huang Y, Huang X, Lu M, *et al.* Long-term outcomes of stent placement for symptomatic nonthrombotic iliac vein compression lesions in chronic venous disease. J Vasc Interv Radiol 2012;23:497–502.

29. Puggioni A, Kistner RL, Eklof B, Lurie F. Surgical disobliteration of postthrombotic deep veins—endophlebectomy—is feasible. J Vasc Surg 2004;39:1048–52, discussion 52.

30. Vogel D, Comerota AJ, Al-Jabouri M, Assi ZI. Common femoral endovenectomy with iliocaval endoluminal recanalization improves symptoms and quality of life in patients with postthrombotic iliofemoral obstruction. J Vasc Surg 2012;55:129–35.

31. Verma V, Tripathi RK. Common femoral endovenectomy in conjunction with iliac vein stenting to improve venous inflow in severe postthrombotic obstruction. Vasc Surg: Venous and Lym Dis 2017;5:138-42.

32. Garg N, Gloviczki P, Karimi KM, Duncan AA, Bjarnason H, Kalra M, *et al.* Factors affecting outcome of open and hybrid reconstructions for nonmalignant obstruction of iliofemoral veins and inferior vena cava. J Vasc Surg 2011;53:383–93.

33. Lalka SG, Lash JM, Unthank JL, Lalka VK, Cikrit DF, Sawchuk AP, *et al.* Inadequacy of saphenous vein grafts for cross-femoral venous bypass. J Vasc Surg 1991;13:622–30.

34. Eklof B, Albrechtson U, Einarsson E, Plate G. The temporary arteriovenous fistula in venous reconstructive surgery. Int Angiol 1985;4:455–62.

35. Palma EC, Esperon R. Vein transplants and grafts in the surgical treatment of the postphlebitic syndrome. J Cardiovasc Surg (Torino) 1960;1:94–107.

36. Jost CJ, Gloviczki P, Cherry KJ Jr, McKusick MA, Harmsen WS, Jenkins GD, *et al.* Surgical reconstruction of iliofemoral veins and the inferior vena cava for nonmalignant occlusive disease. J Vasc Surg 2001;33:320–7, discussion 327–8.

37. Halliday P, Harris J, May J. Femoro-femoral crossover grafts (Palma operation): A long-term follow-up study. Surgery of the veins. Orlando, FL: Grune & Stratton, 1985: 241-54.

38. Husni EA. In situ saphenopopliteal bypass graft for incompetence of the femoral and popliteal veins. Surg Gynecol Obstet 1970;130:279–84.

39. Frileux C, Pillot-Bienayme P, Gillot C. Bypass of segmental obliterations of ilio-femoral venous axis by transposition of saphenous vein. J Cardiovasc Surg (Torino) 1972;13:409–14.

40. AbuRahma AF, Robinson PA, Boland JP. Clinical, hemodynamic, and anatomic predictors of long-term outcome of lower extremity venovenous bypasses. J Vasc Surg 1991;14:635–44.

41. Shaydakov E, Porembskaya O, Geroulakos G. The May-Husni Procedure: A Reappraisal. Eur J Vasc Endovasc Surg 2015;50:513–7.

42. Coleman DM, Rectenwald JE, Vandy FC, Wakefield TW. Contemporary results after sapheno-popliteal bypass for chronic femoral vein occlusion. J Vasc Surg Venous Lymphat Disord 2013;1:45–51.

CHAPTER 12

Assessment of efficacy of therapies

Introduction

To validate therapeutic efficacy, it is necessary to evaluate individual signs, symptoms and quality of life as well as morphological and functional venous parameters in properly powered studies. These clinical outcome parameters should have been previously validated.

The method of choice to assess clinical outcome after treatment for chronic venous disease (CVD) depends to a great extent on the clinical presentation. It is difficult to evaluate improvement in cosmetic appearance or subjective symptoms such as cramps, itching, pain or fatigue. Also, the patient's preference and acceptance of different treatments must be considered. It is much easier to accurately measure improvement of clinical signs such as diminishing size, healing or recurrence of an ulcer or change in the circumference or volume of the extremity than to evaluate symptoms.

The efficacy of treatment is best established by documenting improved signs and symptoms supported if possible by laboratory tests, recording all adverse effects of treatment, and with a long-term follow-up especially when prevention of progression is targeted.[1]

Adverse effects from treatment must be recorded. Complications from surgery, endovenous ablation or sclerotherapy such as mortality, wound infection, superficial vein thrombosis, cellulitis and saphenous nerve injury should be reported.

Available methods for measurement are summarized below.

Evaluation of signs

Telangiectasiae and reticular veins

Telangiectasiae and reticular veins can be assessed visually with photographs and diagrams.

Varicose veins

Varicose veins can be assessed visually with photographs and diagrams and by venous diameter and area assessments.

Edema and leg volume

An international consensus meeting considered that water displacement volumetry is the gold standard to prove and compare the efficacy of any treatment to reduce edema in CVD.[2] This is an old,[3, 4] but recently updated noninvasive technique. Volumetry does not quantify edema, but measures short-term variations which reflect changes in edema.[5-7] It is reproducible provided measurement conditions are carefully standardized. Volumetry allows accurate comparison of changes in the same leg over time or with changing conditions as displayed by different amounts of edema, *e.g.* morning versus evening (vesperal) edema, supine or standing, resting or after exercise, before and after the application of a venous tourniquet, before and after treatment and at the beginning compared with the end of the follow-up period. The repeatability for the method is 0.7% for two consecutive measurements in the same leg by two different observers, and its intra-individual variability is 1.3% under the same conditions.[6]

Volumetry has already demonstrated that legs that ache are those that swell the most,[8] that leg volume increases during daily activity and that this increase correlates with the severity of CVD;[6] that leg volume may increase during long distance flights and that it diminishes after venous surgery,[9] and after different drug treatments for venous or lymphatic insufficiency.[10-12]

Other methods to assess edema include leg circumference measurements using a tape measure,[13-15] and optoelectronic volumetry.[16-18]

Skin changes and lipodermatosclerosis

The degree of induration caused by lipodermatosclerosis can be measured by different techniques including high resolution ultrasound B-scan,[19] and a "durometer."[20, 21] Ankle joint movements can be quantified by goniometry.[22, 23] However, none of these techniques have been validated so far as tools for comparing therapeutic methods in CVD.

Ulcer healing

Complete healing of an ulcer is the most clinically significant outcome measurement for patients with C6 disease,[1] and can be assessed with life table analysis.[24]

Surface area reduction is the surrogate criterion that is used most often. The area of the ulcer can be measured by planimetry using its outline drawn on a transparent sheet, by scaled photography or by direct ultrasonic digitized measurements using a light pen.[25] Alternatively, it can be approximated by multiplying the two maximal perpendicular diameters to obtain an area in cm^2; if this is then multiplied by $\pi/4$ the calculated rectangular area is transformed to an elliptic one. Gillman has published a method for calculating wound healing rates that corrects for differing sizes and shapes by dividing the ulcer area by its perimeter.[26]

The above changes in geometrical measurements per unit time are often used in clinical trials.[27, 28] However, complete healing and the initial healing rate are the most common endpoints used.[29, 30] The initial healing rate is defined as the rate of healing over the course of a first time period.

Percentage of area decrease per unit time is not a valid endpoint, since this depends on the initial size of the ulcer.[27] However, the Gillman equation corrects for different initial ulcer sizes so that it meets the needs of clinical studies for standardized and comparable measurements.[30-32]

Ulcer recurrence

Ulcer recurrence is the most important end-point in C5 patients and can be assessed in long-term follow-up studies using cumulative ulcer-free survival times,[33, 34] or a life-table analysis of proportion without recurrence over time.[24]

Evaluation of symptoms and quality of life

Symptoms

Symptoms can be evaluated by the clinician and/or by patient self-reporting. In the latter case, a questionnaire should be completed at leisure outside the doctor's office. This method is used most frequently for evaluation before, during and after treatment. Patients can be asked to give global ratings of improvement in symptoms or to use quantitative scales such as a Likert scale,[35] or a visual analog scale . Quantification of analgesic requirements can be useful as an additional assessment of pain.

Quality of life

Quality of life for patients with CVD has been assessed by generic and by disease-specific measures. The most frequently used generic measure is the Medical Outcome Study Short Form Health Survey (SF-36), a 36-item questionnaire that covers eight health dimensions including physical and social functioning, role limitations due to physical and emotional problems, mental health, vitality/energy, bodily pain and general health perceptions. The SF-36 has been used both in patients with varicose veins and with venous ulcers.[36, 37] In a study by Garratt *et al.*,[36] SF-36 satisfied strict psychometric criteria for validity and internal consistency and confirmed a significantly lower quality of life in patients with varicose veins compared to an age-adjusted sample from the normal population. EuroQol-5D (EQ-5D) is a shorter form of a generic QoL questionnaire including only five questions to be answered by patients. This form has been validated against SF-36.[38]

Because specific complaints from patients with CVD are not identified by currently used generic quality of life questionnaires, specific questionnaires have been developed to assess the functional and psychological effects of venous disease.[39, 40] The most recent of these is the Chronic Venous Insufficiency Questionnaire (CIVIQ) used by Launois *et al*.[40] This questionnaire has been validated and found to meet stringent psychometric criteria, including reliability, content, construct validity and responsiveness. In a randomized trial of 934 patients the CIVIQ showed that quality of life scores were significantly lower in patients with venous insufficiency than in controls without venous disease. The Aberdeen varicose vein questionnaire (AVVQ) has been frequently used in the UK.[41]

The VEnous INsufficiency Epidemiological and Economic Study on Quality of Life (VEINES-QoL) is a validated, patient-reported outcome score that evaluates quality of life and symptoms across a range of conditions (*e.g.* telangiectasias, varicose veins, edema, skin changes, leg ulcers) in chronic venous disorders of the leg.[42]

Health-related quality of life studies should be used in the future to assess overall outcome and justify treatment for CVD.[43, 44]

Venous Clinical Severity Score (VCSS)

VCSS[44] was designed to measure outcomes after surgical treatments and seems adequate for patients with advanced

TABLE I.—*Outcome parameters for therapeutic studies in patients with CVD.*

CEAP "C" Class	Clinical (*)	Morphology	Function
C1	Photographic analysis		
C2	Idem C1	Duplex, MRV, CTV: vein diameter and obstruction	Duplex: reflux and obstruction Plethysmography: pumping function and outflow resistance
C3	Idem C1 + Volume measurement	Idem C2	Idem C2 + Venous Pressure: venous pump impairment and obstruction
C4	Idem C3 + use of a chromameter, durometer and goniometer	Idem C2 + US: Skin thickness + Capillaroscopy: capillary density + Microlymphography	Idem C3 + $TcPO_2$ + laser Doppler fluxmetry
C5	Idem C4 + ulcer recurrence rate	Idem C4	Idem C4
C6	Idem C5 + ulcer healing rate	Idem C4	Idem C4

*The standardized evaluation tools for symptoms, quality of life and clinical severity scores can be used for symptomatic patients with C1 to C6.

CVD, but is less well adapted for patients with less severe venous disorders. It has been validated,[45] including its short-term repeatability.[46] The score has recently been revised,[47] and validated[48] (see Chapter 4).

Evaluation of morphological and functional venous parameters

Several morphological and functional parameters related to reflux and obstruction of the venous system can be measured by duplex ultrasound, MRV, CTV, plethysmographic techniques, pressure measurements and microvascular techniques. Their use depends on the C class and on the specific target of the treatment assessed (Table I).

References

1. Vanscheidt W, Heidrich H, Jünger M, Rabe E; Phlebology Study Group of the Austrian Society of Dermatology; German Society of Angiology; German Society of Phlebology; Swiss Society of Phlebology. Guidelines for testing drugs for chronic venous insufficiency. Vasa 2000;29:274–8.

2. Fowkes FG, Bosanquet N, Franks PJ, *et al.* Proposal of a consensus statement the role of oedema-protective agents in the treatment of chronic venous insufficiency. Phlebology 1996;11:39–40.

3. Keates JS, FitzGerald DE. Limb volume and blood flow changes during the menstrual cycle. I. Limb volume changes during the menstrual cycle. Angiology 1969;20:618–23.

4. Keates JS, FitzGerald DE. Limb volume and blood flow changes during the menstrual cycle. II. Changes in blood flow and venous distensibility during the menstrual cycle. Angiology 1969;20:624–7.

5. Barnes MD, Mani R, Barrett DF, White JE. How to measure changes in oedema in patients with chronic venous ulcers. Phlebology 1992;7:31–5.

6. Vayssairat M, Maurel A, Gouny P, Baudot N, Gaitz JP, Nussaume O. [Leg volumetry: a precise method for quantification in phlebology]. J Mal Vasc 1994;19:108–10. French.

7. Vayssairat M, Maurel A, Gouny P, Veraart JC, Neumann HA. Leg volume measurements. Phlebology 1995;10:173–4.

8. Hands L, Collin J. Legs that swell and ache: volume changes during the day in health young adults. Br Med J (Clin Res Ed) 1984;288:447–8.

9. Speakman MJ, Collin J. Are swelling and aching of the legs reduced by operation on varicose veins? Br Med J (Clin Res Ed) 1986;293:105–6.

10. Nocker W, Diebschlag W, Lehmacher W. [A 3-month, randomized double-blind dose-response study with 0-(beta-hydroxyethyl)-rutoside oral solutions]. Vasa 1989;18:235–8. German.

11. Rehn D, Hennings G, Nocker W, Diebschlag W. Time course of the anti-oedematous effect of O-(beta-hydroxyethyl)-rutosides in healthy volunteers. Eur J Clin Pharmacol 1991;40:625–7.

12. Casley-Smith JR, Morgan RG, Piller NB. Treatment of lymphedema of the arms and legs with 5,6-benzo-[alpha]-pyrone. N Engl J Med 1993;329:1158–63.

13. te Slaa A, Mulder P, Dolmans D, Castenmiller P, Ho G, van der Laan L. Reliability and reproducibility of a clinical application of a simple technique for repeated circumferential leg measurements. Phlebology 2011;26:14–9.

14. Bérard A, Kurz X, Zuccarelli F, Ducros JJ, Abenhaim L. Reliability study of the Leg-O-Meter, an improved tape measure device, in patients with chronic venous insufficiency of the leg. VEINES Group. (Venous Insufficiency Epidemiologic and Economic Study). Angiology 1998;49:169–73.

15. Brodovicz KG, McNaughton K, Uemura N, Meininger G, Girman CJ, Yale SH. Reliability and feasibility of methods to quantitatively assess peripheral edema. Clin Med Res 2009;7:21–31.

16. Blume J, Langenbahn H, Champvallins M. Quantification of oedema using the volometer technique: therapeutic application of Daflon 500 mg in chronic venous insufficiency. Phlebology 1992;2(suppl):37–40.

17. Schmidt C. [Opto-electronic volumetry: another method for quantification of edema]. J Mal Vasc 1994;19:326–7. French.

18. Veraart JC, Neumann HA. Leg volume measurements with a modified optoelectronic measurement system. Phlebology 1995;10:62–4.

19. Gniadecka M. Dermal oedema in lipodermatosclerosis: distribution, effects of posture and compressive theraphy evaluated by high-frequency ultrasonography. Acta Derm Venereol 1995;75:120–4.

20. Falanga V, Bucalo B. Use of a durometer to assess skin hardness. J Am Acad Dermatol 1993;29:47–51.

21. Romanelli M, Falanga V. Use of a durometer to measure the degree of skin induration in lipodermatosclerosis. J Am Acad Dermatol 1995;32:188–91.

22. Dix FP, Brooke R, McCollum CN. Venous disease is associated with an impaired range of ankle movement. Eur J Vasc Endovasc Surg 2003;25:556–61.

23. Back TL, Padberg FT Jr, Araki CT, Thompson PN, Hobson RW 2nd. Limited range of motion is a significant factor in venous ulceration. J Vasc Surg 1995;22:519–23.

24. Nelzén O, Fransson I. True long-term healing and recurrence of venous leg ulcers following SEPS combined with superficial venous surgery: a prospective study. Eur J Vasc Endovasc Surg 2007;34:605–12.

25. Solomon C, Munro AR, Van Rij AM, Christie R. The use of video image analysis for the measurement of venous ulcers. Br J Dermatol 1995;133:565–70.

26. Gillman TH. Parameter for measurement of wound closure. Wounds 1990;3:95–101.

27. Martin M. [Dynamic wound healing profile of venous ulcus cruris]. Vasa 1994;23:228–33. German.

28. Ibbotson SH, Layton AM, Davies JA, Goodfield MJ. The effect of aspirin on haemostatic activity in the treatment of chronic venous leg ulceration. Br J Dermatol 1995;132:422–6.

29. Skene AI, Smith JM, Doré CJ, Charlett A, Lewis JD. Venous leg ulcers: a prognostic index to predict time to healing. BMJ 1992;305:1119–21.

30. Gorin DR, Cordts PR, LaMorte WW, Manzoian JO. The influence of wound geometry on the measurement of wound healing rates in clinical trials. J Vasc Surg 1996;23:524–8.

31. Teepe RG, Roseeuw DI, Hermans J, Koebrugge EJ, Altena T, de Coninck A, *et al.* Randomized trial comparing cryopreserved cultured epidermal allografts with hydrocolloid dressings in healing chronic venous ulcers. J Am Acad Dermatol 1993;29:982–8.

32. Margolis DJ, Gross EA, Wood CR, Lazarus GS. Planimetric rate of healing in venous ulcers of the leg treated with pressure bandage and hydrocolloid dressing. J Am Acad Dermatol 1993;28:418–21.

33. Zamboni P, Cisno C, Marchetti F, Mazza P, Fogato L, Carandina S, *et al.* Minimally invasive surgical management of primary venous ulcers vs. compression treatment: a randomized clinical trial. Eur J Vasc Endovasc Surg 2003;25:313–8.

34. Barwell JR, Davies CE, Deacon J, Harvey K, Minor J, Sassano A, *et al.* Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. Lancet 2004;363:1854–9.

35. Laurent R, Gilly R, Frileux C. Clinical evaluation of a venotropic drug in man. Example of Daflon 500 mg. Int Angiol 1988;7(Suppl):39–43.

36. Garratt AM, Ruta DA, Abdalla MI, Buckingham JK, Russell IT. The SF36 health survey questionnaire: an outcome measure suitable for routine use within the NHS? BMJ 1993;306:1440–4.

37. Price P, Harding K. Quality of life. Lancet 1995;346:445.

38. Brazier J, Roberts J, Tsuchiya A, Busschbach J. A comparison of the EQ-5D and SF-6D across seven patient groups. Health Econ 2004;13:873–84.

39. Franks PJ, Wright DD, Fletcher AE, Moffatt CJ, Stirling J, Bulpitt CJ, *et al.* A questionnaire to assess risk factors, quality of life, and use of health resources in patients with venous disease. Eur J Surg 1992;158:149–55.

40. Launois R, Reboul-Marty J, Henry B. Construction and validation of a quality of life questionnaire in chronic lower limb venous insufficiency (CIVIQ). Qual Life Res 1996;5:539–54.

41. Nesbitt C, Wilson WR, Lees TA, Stansby G. Interpretation of patient-reported outcome measures for varicose vein surgery. Phlebology 2012;27:173–8.

42. Lamping DL, Schroter S, Kurz X, Kahn SR, Abenhaim L. Evaluation of outcomes in chronic venous disorders of the leg: development of a scientifically rigorous, patient-reported measure of symptoms and quality of life. J Vasc Surg 2003;37:410–9.

43. Mackenzie RK, Lee AJ, Paisley A, Burns P, Allan PL, Ruckley CV, *et al.* Patient, operative, and surgeon factors that influence the effect of superficial venous surgery on disease-specific quality of life. J Vasc Surg 2002;36:896–902.

44. Rutherford RB, Padberg FT Jr, Comerota AJ, Kistner RL, Meissner MH, Moneta GL. Venous severity scoring: an adjunct to venous outcome assessment. J Vasc Surg 2000;31:1307–12.

45. Kakkos SK, Rivera MA, Matsagas MI, Lazarides MK, Robless P, Belcaro G, *et al.* Validation of the new venous severity scoring system in varicose vein surgery. J Vasc Surg 2003;38:224–8.

46. Meissner MH, Natiello C, Nicholls SC. Performance characteristics of the venous clinical severity score. J Vasc Surg 2002;36:889–95.

47. Vasquez MA, Rabe E, McLafferty RB, Shortell CK, Marston WA, Gillespie D, *et al.*; American Venous Forum Ad Hoc Outcomes Working Group. Revision of the venous clinical severity score: venous outcomes consensus statement: special communication of the American Venous Forum Ad Hoc Outcomes Working Group. J Vasc Surg 2010;52:1387–96.

48. Passman MA, McLafferty RB, Lentz MF, Nagre SB, Iafrati MD, Bohannon WT, *et al.* Validation of Venous Clinical Severity Score (VCSS) with other venous severity assessment tools from the American Venous Forum, National Venous Screening Program. J Vasc Surg 2011;54(Suppl):2S–9S.

CHAPTER 13

Prevention of post-thrombotic syndrome

Introduction

Despite conventional anticoagulation therapy (LMWH for at least 5 days followed by warfarin) for deep venous thrombosis (DVT), 30-50% of all patients, depending on the anatomical level, will develop post-thrombotic syndrome (PTS).[1] One recent study has even shown PTS to be up to 70%.[2] The symptomatology of PTS includes limb swelling, pain, heaviness, pruritus (itching), venous claudication, skin changes and ulceration,[3] which is the single most predictive clinical finding. It may occur as early as 3 months.[4] Established PTS is a significant cause of chronic incapacity and inability to work with considerable consequences for both the patient and the society.[5-8]

The PTS is the result of venous hypertension produced by reflux (caused by remodelling of the venous wall and/or damaged valves) alone or combined with persisting outflow obstruction.[9] Venous hypertension is associated with chronic inflammation affecting not only the venous wall but also the microcirculation producing excessive capillary leakage and impairment of skin nutrition with skin changes and eventually skin ulceration.[10]

Factors that are associated with the development of the PTS include iliofemoral DVT[5, 6] especially if chronic iliofemoral vein obstruction persists,[11, 12] increased BMI, older age and female gender,[6, 12] recurrent DVT,[12] which often obstructs part of the collateral circulation and subtherapeutic anticoagulant therapy which allows DVT recurrence.[13] More recently, it has been demonstrated that elevated inflammatory biomarkers such as IL-6, ICAM-1 and CRP[14, 15] are also associated with increased rates of PTS following DVT.

In a multivariable analysis of 762 patients from the SOX Trial who had primary proximal DVT (popliteal vein and higher), presence of thrombus in the iliac vein, BMI $\geq$ 35 kg/m^2 and a Villalta score $\geq$ 4 at one month after the diagnosis of DVT were independent predictors of the development of PTS at 6 to18 months.[16] In this study PTS was defined according to the Ginsberg criteria of ipsilateral pain and swelling of at least one month's duration that were typical (worse at the end of the day or with prolonged sitting or standing and better in the morning or after leg elevation).

A recently published systematic review and meta-analysis included 12 prospective studies with 2684 patients with DVT, who had an ultrasonography (US) during follow-up assessing findings consistent with venous damage and a follow-up period of at least 6 months for assessment of PTS.[17] The majority of patients had proximal DVT (88%), and the duration of standard anticoagulation therapy varied between 3 and 18 months. Two US parameters measured at least 6 weeks after DVT proved to be predictive of PTS: residual thrombosis (OR 2,17; 95% CI, 1.70 to 2.63) and popliteal reflux (OR 1.34; 95% CI, 1.03 to 1.75).

Prevention of primary DVT

Prevention of DVT should reduce the prevalence of PTS. There is an association between PTS and recurrent DVT and patients with recurrent DVT have a high incidence of PTS.[18] Recurrent DVT in the same leg results not only in a higher frequency but also in increased severity of the PTS. Until recently PTS was viewed as a late complication. However, recent data show that PTS occurs early and that review of signs and symptoms at one month after the onset of DVT is highly predictive of the subsequent development of PTS.[7] Prevention of recurrence in patients with DVT should lessen the severity and frequency of PTS. The evidence and guidelines for primary prevention has been summarized in the international consensus document on

the prevention and management of venous thromboembolism in sections 3-12 and for secondary prevention in sections 14,15,17 and 18. Guidelines aiming to reduce the PTS and leg ulcers by 50% in the next ten years have been published.[19, 20]

Prevention of recurrent DVT

Recurrence of deep vein thrombosis (DVT) after completion of conventional oral anticoagulation therapy is high. For patients with unprovoked DVT the incidence of recurrence is 11% at one year, 30% at 5 years and 40% at 10 years. For patients with provoked DVT the recurrence rate is approximately half the above values.[21] As indicated above, recurrence of DVT may result in severe post-thrombotic syndrome and reduced quality of life.[6] Recent randomised controlled trials with new anticoagulant and antithrombotic medications, which have resulted in a number of strategies that can reduce the incidence of DVT recurrence are presented below.

Aspirin trials

Two RCTs (WARFASA and ASPIRE) involving a total of 1284 patients who had completed 6 to 18 months of oral anticoagulant treatment for a first unprovoked DVT have tested the efficacy of aspirin 100 mg daily in preventing DVT recurrence. In a pooled analysis of both studies the DVT recurrence rate was 13.8% in the aspirin groups and 19.1% in the placebo groups (Hazard ratio, 0.68; 95% CI 0.51 to 0.90) (P=0.007).[22, 23] Adverse events were similar in the 2 groups.

Dabigatran

Dabigatran was compared to warfarin in one study and to placebo in a second study of patients who had completed treatment for unprovoked DVT (RE-SONATE study).[24]

In the active-control study which involved 2,856 patients, recurrent venous thromboembolism occurred in 1.8% patients in the dabigatran group and 1.3% patients in the warfarin group (hazard ratio with dabigatran, 1.44; 95% confidence interval [CI], 0.78 to 2.64; P=0.01 for noninferiority). Major bleeding occurred in 0.9% patients in the dabigatran group and 1.8% patients in the warfarin group (hazard ratio, 0.52; 95% CI, 0.27 to 1.02). Major or clinically relevant bleeding was less frequent with dabigatran (hazard ratio, 0.54; 95% CI, 0.41 to 0.71).

In the placebo-control study which involved 1,343 patients, recurrent venous thromboembolism occurred in 0.4% patients in the dabigatran group and 5.6% patients in the placebo group (hazard ratio, 0.08; 95% CI, 0.02 to 0.25; P<0.001). Major bleeding occurred in 2 patients in the dabigatran group (0.3%) and 0 patients in the placebo group. Major or clinically relevant bleeding occurred in 5.3% patients in the dabigatran group and 1.8% patients in the placebo group (hazard ratio, 2.92; 95% CI, 1.52 to 5.60).

It was concluded that dabigatran was effective in the extended treatment of venous thromboembolism and carried a lower risk of major or clinically relevant bleeding than warfarin but a higher risk than placebo.

Rivaroxaban

An open-label, randomized, event-driven, noninferiority study was performed that compared oral rivaroxaban alone (15 mg twice daily for 3 weeks, followed by 20 mg once daily) with subcutaneous enoxaparin initially, followed by a vitamin K antagonist (either warfarin or acenocoumarol) for 3, 6, or 12 months in patients with acute, symptomatic DVT (EINSTEIN Investigators 2010).[25]

In parallel, a double-blind, randomized, event-driven superiority study was performed. This study, compared rivaroxaban alone (20 mg once daily) with placebo for an additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for venous thromboembolism.[25]

The study of rivaroxaban for acute DVT included 3449 patients: 1731 given rivaroxaban and 1718 given enoxaparin plus a vitamin K antagonist. Rivaroxaban had noninferior efficacy with respect to the primary outcome (36 events [2.1%], *vs.* 51 events with enoxaparin-vitamin K antagonist [3.0%]; hazard ratio, 0.68; 95% confidence interval [CI], 0.44 to 1.04; P<0.001). The principal safety outcome occurred in 8.1% of the patients in each group.

In the continued-treatment study, which included 602 patients in the rivaroxaban group and 594 in the placebo group, rivaroxaban had superior efficacy (8 events [1.3%], *vs.* 42 with placebo [7.1%]; hazard ratio, 0.18; 95% CI, 0.09 to 0.39; P<0.001). Four patients in the rivaroxaban group had nonfatal major bleeding (0.7%), *versus* none in the placebo group (P=0.11). Major or clinically relevant bleeding occurred in 6.0% patients in the rivaroxaban group and 1.2% patients in the placebo group (hazard ratio, 5.19; 95% CI, 2.3 to 11.7). It was concluded that rivaroxaban offered a simple, single-drug approach to the short-term and continued treatment of venous thrombosis that may improve the benefit-to-risk profile of anticoagulation.

Apixaban

A double-blind study involving 2,486 patients compared two doses of apixaban (2.5 mg and 5 mg, twice daily) with placebo in patients with venous thromboembolism who

had completed 6 to 12 months of anticoagulation therapy and for whom there was clinical equipoise regarding the continuation or cessation of anticoagulation therapy.[26] The study drugs were administered for 12 months.

Symptomatic recurrent venous thromboembolism or death from venous thromboembolism occurred in 8.8% patients in the placebo group, compared with 1.7% patients in the 2.5 mg of apixaban group (a difference of 7.2 percentage points; 95% CI, 5.0 to 9.3) and 1.7% patients in the 5 mg of apixaban group (a difference of 7.0 percentage points; 95% CI, 4.9 to 9.1) (P<0.001 for both comparisons). The rates of major bleeding were 0.5% in the placebo group, 0.2% in the 2.5-mg apixaban group, and 0.1% in the 5-mg apixaban group. The rates of clinically relevant non-major bleeding were 2.3% in the placebo group, 3.0% in the 2.5-mg apixaban group (HR 1.20, 95% CI 0.69 to 2.10; P= NS), and 4.2% in the 5-mg apixaban group (HR 1.62, 95% CI 0.96 to 2.73; P=NS). The rate of death from any cause was 1.7% in the placebo group, compared with 0.8% in the 2.5-mg apixaban group and 0.5% in the 5-mg apixaban group.

It was concluded that extended anticoagulation with apixaban at either a treatment dose (5 mg) or a thromboprophylactic dose (2.5 mg) reduced the risk of recurrent venous thromboembolism without increasing the rate of major bleeding.

Sulodexide

In a multicenter, double-blind study, 615 patients with first-ever unprovoked venous thromboembolism who had completed 3 to 12 months of oral anticoagulant treatment were randomly assigned to sulodexide 500 lipasemic units twice daily or placebo for 2 years, in addition to elastic stockings.[27]

Venous thromboembolism recurred in 15 of the 307 patients who received sulodexide and in 30 of the 308 patients who received placebo (hazard ratio, 0.49; 95% CI 0.27-0.92; P=0.02). The analysis in which patients lost to follow-up were assigned to failure yielded a risk ratio among treated *versus* control subjects of 0.54 (95% confidence interval, 0.35-0.85; P=0.009). No major bleeding episodes occurred; 2 patients in each treatment group had clinically relevant bleeding episodes. Adverse events were similar in the 2 groups.

It was concluded that sulodexide given after discontinuation of anticoagulant treatment reduced the risk of recurrence in patients with unprovoked venous thromboembolism, with no apparent increase of bleeding risk.

A 5-year follow-up for development of PTS was performed in a registry of patients with DVT.[28] Patients were admitted to the registry after completion of anticoagulation period. A group of 167 patients received "standard therapy" of elastic compression, a second group of 124 patients received sulodexide and a third group of 48 received aspirin. The incidence of PTS was 14.9% at one year and 19.5% at 5 years in the "standard therapy" group. It was 8.8% at one year and 12.2% at 5 years in the sulodexide group. It was 23.5% at 54 months in the aspirin group compared with 12.2% in the sulodexide and 18.2% in the "Standard therapy" groups. RCT are needed to validate these results.

Strategies to identify patients at increased risk of recurrence

(a) Residual thrombus and recurrence of DVT

In the DACUS study ultrasound was used to determine the presence of residual thrombus. Residual venous thrombus was considered present (RVT+) if on compression organized thrombus occupied more than 40% of the vein diameter. It was considered absent (RVT-) if thrombus occupied less than 40% of the vein diameter.[29]

Patients with a first episode of DVT, treated with oral anticoagulant therapy for 3 months, were managed according to residual thrombus findings. Those who were RVT+ were randomized to either stop or continue anticoagulants for 9 additional months, whereas in those who were RVT-, anticoagulant therapy was stopped. Outcomes were recurrent venous thromboembolism and/or major bleeding. Residual thrombosis was detected in 180 (69.8%) of 258 patients; recurrent events occurred in 27.2% of those who discontinued (25/92; 15.2% person-years) and 19.3% of those who continued with anticoagulant therapy (17/88; 10.1% person-years). The relative adjusted hazard ratio (HR) was 1.58 (95% CI, 0.85-2.93; P=.145). Of the 78 (30.2%) patients with RVT-, only 1 (1.3%; 0.63% person-years) had a recurrence. The adjusted HR of patients with RVT+ *versus* those with RVT- was 24.9 (95% CI, 3.4-183.6; P=.002). One major bleeding event (1.1%; 0.53% person-years) occurred in patients who stopped and 2 occurred (2.3%; 1.1% person-years) in those who continued anticoagulant therapy. It was concluded that absence of residual venous thrombus (RVT-) identified a group of patients at very low risk for recurrent thrombosis who could safely stop anticoagulant therapy.

The extended DACUS study was a prospective study to assess the optimal duration of vitamin K antagonist (VKA) therapy considering the risk of recurrence of thrombosis according to residual vein thrombosis.[30] Patients with a

first unprovoked DVT were evaluated for the presence of residual vein thrombosis after 3 months of VKA administration; those who were RVT- suspended VKA, while those who were RVT+ continued oral anticoagulation for up to 2 years. Recurrent thrombosis and/or bleeding events were recorded during treatment (RVT+ group) and 1 year after VKA withdrawal (both groups). Among 409 patients evaluated for unprovoked DVT, 33.2% (136 of 409 patients) were RVT- and VKA was stopped. The remaining 273 (66.8%) patients who were RVT+ received anticoagulants for an additional 21 months; during this period of treatment, recurrent venous thromboembolism and major bleeding occurred in 4.7% and 1.1% of patients, respectively. After VKA suspension, the rates of recurrent thrombotic events were 1.4% and 10.4% in the RVT- and RVT+ groups, respectively (relative risk = 7.4; 95% confidence interval = 4.9-9.9). These results indicate that in patients who are RVT-, a short period of treatment with a VKA is sufficient; in those who are RVT+, treatment extended to 2 years substantially reduces, but does not eliminate, the risk of recurrent thrombosis.

(b) D-dimer and recurrence of DVT

D-dimer testing 1 month after the discontinuation of anticoagulation in patients with a first unprovoked proximal deep-vein thrombosis or pulmonary embolism who had received a vitamin K antagonist for at least 3 months was performed in the study.[31] Patients with a normal D-dimer level did not resume anticoagulation, whereas those with an abnormal D-dimer level were randomly assigned either to resume or to discontinue treatment. The study outcome was the composite of recurrent venous thromboembolism and major bleeding during an average follow-up of 1.4 years.

The D-dimer assay was abnormal in 223 of 608 patients (36.7%). A total of 18 events occurred among the 120 patients who had elevated D-dimer and stopped anticoagulation (15.0%) compared with 3 events among the 103 patients who had elevated D-dimer and resumed anticoagulation (2.9%), for an adjusted hazard ratio of 4.26 (95% confidence interval [CI], 1.23 to 14.6; P=0.02). Thromboembolism recurred in 24 of 385 patients with a normal D-dimer level (6.2%). Among patients who stopped anticoagulation, the adjusted hazard ratio for recurrent thromboembolism among those with an abnormal D-dimer level, compared with those with a normal D-dimer level, was 2.27 (95% CI, 1.15 to 4.46; P=0.02).

It was concluded that patients with an abnormal D-dimer level 1 month after the discontinuation of anticoagulation have a significant incidence of recurrent venous thromboembolism, which is reduced by the resumption of anticoagulation.

(c) Strategy combining residual thrombus and D-dimer testing

In 620 consecutive outpatients with a first proximal DVT who had completed at least three months of anticoagulation (unprovoked in 483 and associated with minor risk factors in 137), the ultrasound presence of residual vein thrombosis (RVT+) was assessed and defined as an incompressibility of at least 4 mm.[32] In 517 patients who were RVT- and with negative D-dimer, anticoagulation was stopped and D-dimer was repeated after one and three months. Anticoagulation was resumed in 63 of the 72 patients in whom D-dimer reverted to positivity.

During a mean follow-up of three years, recurrent VTE developed in 40 (7.7%) of the 517 patients, leading to an annual rate of 3.6% (95% CI, 2.6 to 4.9): 4.1% (95% CI, 2.9 to 5.7) in individuals with unprovoked DVT, and 2.2% (95% CI, 1.1 to 4.5) in those with DVT associated with minor risk factors. Of the 233 patients with unprovoked DVT, 17 (7.3%) developed events in the first year of follow-up. Major bleeding complications occurred in 8 patients while on anticoagulation, leading to an annual rate of 1.2% (95% CI, 0.6 to 2.4).

It was concluded that discontinuing anticoagulation in patients with a first episode of proximal DVT based on the assessment of RVT and serial D-dimer led to an overall annual rate of recurrent VTE lower than 5.0%, which is the rate deemed as acceptable by the Subcommittee on Control of Anticoagulation of the International Society of Thrombosis and Haemostasis.

(d) Assessment of risk of recurrence vs. *risk of bleeding with adjustment of anticoagulation*

It is now established that the risk of recurrence of VTE and risk of bleeding are not the same in every patient. Methods that can assess these risks which have met with moderate success are now available.[33] In addition, as indicated in this review secondary effective prophylactic anticoagulation therapy is now available with very low risk of bleeding (Apixaban, Sulodexide). Thus, recommendations for secondary prophylaxis should be based on calculations for the risk of recurrence *versus* risk of bleeding with appropriate drug selection.

The risk of recurrence can be assessed empirically as High, Moderate or Low using established risk factors or calculated using the Vienna Nomogram[34, 35] or using the DASH score.[36] The Vienna nomogram is based on a prospective cohort study involving 929 patients and risk fac-

tors of: gender, type of VTE (PE, proximal DVT, distal DVT) and elevated D-dimer after stopping anticoagulants. It has been validated externally[37] in a separate cohort with an area under the curve (AUC) of 0.63. The DASH score is based on a patient-level meta-analysis involving 1,818 patients and the following risk factors: D-dimer after cessation of anticoagulation, age, gender and use of hormones at the onset of VTE.

The risk of bleeding can also be assessed empirically as High, Moderate or Low using a prediction model such as the RIETE score.[38] The latter has been derived from a large cohort of patients with VTE and is based on the following risk factors: age, recent bleeding, creatinine level, anaemia, malignancy, and symptomatic PE. It can identify patients at low, intermediate or high risk for major bleeding during the first 3 months of anticoagulation, but it has not yet been externally validated.

Based on the available medications and knowledge of risk of recurrence *vs.* risk of bleeding a health-care provider can make up a plan or algorithm for extended prophylaxis in patients with moderate or high risk of DVT. An example is given below.

Patients at high risk of recurrence

- (a) ***Low risk of bleeding:*** Any anticoagulant can be given (VKA, Rivaroxaban, Apixaban)
- (b) ***Intermediate risk of bleeding:*** Apixaban
- (c) ***High risk of bleeding:*** Low dose Apixaban, Sulodexide

Patients at intermediate risk of recurrence

- (d) ***Low risk of bleeding:*** Any anticoagulant can be given (VKA, Rivaroxaban, Apixaban)
- (e) ***Intermediate risk of bleeding:*** Apixaban
- (f) ***High risk of bleeding:*** Low dose Apixaban, Sulodexide, Aspirin

Patients at low risk of recurrence

Anticoagulants can be omitted, but if the patient prefers to continue with prophylaxis, then Aspirin or Sulodexide would be the author's choice.

The efficacy of such plans needs to be validated in prospective studies.

Treatment of DVT

Compression stockings

Effective compression stockings have been shown to reduce venous hypertension, edema and minimize the damage to the microcirculation.[39, 40] Four RCTs involving 745 patients have demonstrated that in patients with proximal (above-knee) DVT, knee length compression stockings used for 2 years reduce the incidence of PTS from 39% to 19% (RR 0.49; 95% CI 0.38 to 0.62).[41-44] One study has shown no difference between knee and thigh length compression stockings.[45] On the basis of the above it appeared that treatment with LMWH combined with early ambulation and elastic compression prevented further the development of PTS.[46, 47] However, in contradiction to previous publications, a large multicentre placebo-controlled RCT involving 794 patients with a first DVT has been recently published (SOX Trial) casting doubt on the effectiveness of compression in the prevention of PTS.[48] The interpretation of the results by the authors was "Elastic compression stockings (ECS) did not prevent PTS after proximal DVT, hence our findings do not support routine wearing of ECS after DVT. This study which contradicts previous publications has stimulated several groups to publish reviews and meta-analyses on this subject, all with the conclusion that further studies will be needed to achieve clear recommendations.

Early thrombus removal

Thrombectomy was popularized 30 years ago. Early surgical thrombectomy in a small RCT of patients with iliofemoral DVT was associated with increased iliac vein patency compared with standard anticoagulation therapy alone after 10-year follow-up (83% *vs.* 41%) and decreased incidence of PTS from 93% in the absence of thrombectomy to 58% when thrombectomy was performed (RR 0.63; 95% CI 0.44 to 0.90).[49, 50]

Another study showed that venous thrombectomy for iliofemoral DVT, even with crural involvement in 63% of cases, could achieve acceptable results regarding patency and occurrence of PTS at 5-year mean follow-up. This procedure was combined with peri-operative stenting of an underlying iliac obstruction and with an AV fistula.[51]

Recently, forty patients with iliofemoral DVT were treated with surgical thrombectomy and stenting for iliac obstruction but without AV fistula with achievement of 85% of the patients not having PTS after 2 years of follow-up.[52]

Catheter directed thrombolysis

Catheter directed thrombolysis (CDT) from observational cohort studies and comparative non-randomized studies appears to be associated with increased vein patency, valve preservation and a reduction in the incidence of PTS compared with conventional anticoagulation therapy.[53-55]

Two RCTs compared CDT with standard anticoagulation therapy involving a total of 138 patients with iliofemoral DVT.[56, 57] At six months, the patency rate was 70% in the catheter-directed thrombolysis group and 33% in the standard anticoagulation therapy group (RR 0.48; 95% CI 0.33 to 0.70). The second RCT continued recruitment to a total number of 209 patients and has recently reported on iliofemoral patency and PTS in 189 patients.[58] Iliofemoral patency at 6 months was 64% in the catheter-directed thrombolysis group and 47% in the conventional treatment group (RR for patency 1.42; 95% CI 1.09 to 1.85). At 24 months PTS was developed in 41% of patients in the catheter-directed thrombolysis group and 56% of patients in the standard anticoagulation therapy group (RR 0.74; 95% CI 0.55 to 1.00; P=0.047). Major bleeding events occurred in 2.9% of patients. The number needed to treat to prevent PTS in one patient (NNT) was 47. At 5 years the rates of PTS were 43% (95% CI 33-53) in the catheter-directed thrombolysis group and 71% (95% CI 61-79) (P<0.0001) in the control group. The NNT decreased to 4. No difference was found in QOL.

The ATTRACT trial which was published in 2017 involved 691 patients with iliofemoral (IF) or femoropopliteal (FP) DVT.[59] They were randomised to standard anticoagulant therapy alone (AT) or pharmacomechanical catheter-directed thrombolysis (PCDT+AT). The primary outcome was defined as Villalta score > 4 or development of venous ulcer or unplanned endovenous procedure to treat symptoms after 6 months from randomisation. Secondary endpoints were: leg pain (Likert scale of 7 points), calf circumference (CM) and health related QOL change from baseline to 24 months (SF36 and VEINES-QOL). At 24 months the primary outcome was 47% in the CDT+AT group and 48% in the AT group (P=0.56).

A subgroup analysis of the 311 patients with IF DVT in the ATTRACT study showed presence of PTS (Villalta scale > 4) in 49% in the CDT+AT group and 51% in the AT group (P=0.59). However, moderate and severe PTS (Villalta scale > 9) was present in 18% in the CDT+AT group and 28% in the AT group (P=0.021). Severe PTS (Villalta scale > 14) was present in 8.7% in the CDT+AT group and 15% in the AT group (P=0.048). In these subgroups the mean Villalta score was 3.82 in the CDT+AT group and 5.43 in the AT group (P<0.001). At 30 days after treatment the mean reduction of pain score from baseline was -2.36 in the CDT+AT group and -1.80 in the AT group (P=0.0082). Mean QOL score at 24 months was 21.5 in the CDT+AT group and 16.2 in the AT group (P=0.043).[60] Although the primary endpoint in the ATTRACT Trial was not reached, in patients with IF DVT CDT+AT resulted in reduction of PTS of any severity using VCSS, reduction of moderate/severe PTS using Villalta score, reduction of severe PTS using Villalta score, reduction of pain and swelling and improved disease specific QOL.

In the most recent publication, the CAVA study compared ultrasound-accelerated catheter-directed thrombolysis with standard therapy only for acute iliofemoral DVT.[61] This multicentre RCT resulted in 77 patients for intervention *versus* 75 patients with standard therapy for a median follow-up of 12 months. Major bleeding occurred in four (5%) patients in the intervention group. PTS occurred in 22 (29%) patients in the intervention group and 26 (35%) in the standard treatment alone (OR 0.75; 95% CI 0.38 to 1.50).

Relief of chronic iliofemoral obstruction

Prospective observational studies have indicated that percutaneous endovascular venoplasty and stenting to correct chronic venous obstruction may alleviate the symptoms of PTS (see Chapter 11 "Treatment of venous outflow obstruction").

In the largest published series on 982 lesions,[62] at 72 months, primary, assisted-primary, and secondary cumulative patency rates were 79%, 100%, and 100% in non-thrombotic disease and 57%, 80%, and 86% in post-thrombotic disease, respectively.[62] The frequency of severe leg pain (visual analogue scale >5) and leg swelling (grade 3) decreased from 54% and 44% before stent placement to 11% and 18% after stent placement, respectively. At 5 years, cumulative rates of complete relief of pain and swelling were 62% and 32%, respectively, and ulcer healing was 58%. The mean CIVIQ scores of QOL improved significantly in all categories.

Three meta-analyses have been published recently.[63-65] The largest[63] included 37 studies involving 2869 patients. Of these, 18 studies included 1118 chronic post-thrombotic patients reported separately. For the post-thrombotic group, at one year the primary patency was 79% (95% CI 76% to 83%) and secondary patency 94% (95% CI 90% to 96%). At 5 years primary patency was 62% and secondary patency 82%. Pain and edema relief reported in 7 studies occurred in 69% (95% CI 54% to 81%) and 64% (95% CI 45% to 79%) respectively (P<0.001). Ulcer healing reported in 11 studies occurred in 71% (95% CI 60% to 80%).

In the absence of RCT the quality of evidence to support the use of stenting in post-thrombotic venous obstruction is weak. However, stenting is safe and should be considered as a treatment option when the evidence is improved.

RCTs are needed to determine the efficacy of endovascular venoplasty and stenting in patients with chronic post-thrombotic iliofemoral obstruction.

Perhaps too much reliance has been placed on the severity of iliac stenosis as a criterion for stenting without measurement of the adequacy (or inadequacy) of collateral circulation or the severity of reflux in the deep veins that are so common and influence the development and severity of symptoms in patients with PTS. Global measurements of reflux in ml/sec and limb outflow resistance in mmHg/ml/min may eventually provide criteria for better selection of patients so that a higher rate of symptom relief may be obtained.[66, 67]

Long term anticoagulation with LMWH

Standard treatment of DVT (initial LMWH for at least 5 days followed by VKA) prevents thrombus extension and embolization but does not directly lyse the thrombus, which often results in partial recanalization. A number of studies have compared long-term treatment with LMWH *versus* standard therapy,[68-72] and demonstrated better recanalization in the long-term LMWH groups. A meta-analysis on 5 studies that reported on total recanalization demonstrated a risk ratio of 0.66 (95% CI 0.57 to 0.77; P<0.0001) in favor of long term LMWH.[73] In a large multicenter study involving 480 patients there was a reduction of the incidence of PTS with long-term LMWH compared with standard therapy (RR 0.77; P=0.001).[74] Pooled analysis of 2 studies reporting on the long-term development of leg ulcers as part of PTS,[74, 75] demonstrated an 87% risk reduction for venous ulcers when long-term LMWH was used instead of standard therapy (P=0.019).[74]

Rivaroxaban

Anecdotal reports of marked early vein recanalization in patients treated with rivaroxaban[76, 77] and a small study involving 102 patients with iliofemoral DVT[78] suggested that rivaroxaban was associated with rapid recanalization during the first 2 weeks of therapy. In this study, patients were subdivided into three groups. In group one 38 patients received standard therapy with low-molecular-weight heparin (enoxaprin) followed by warfarin combined with diosmin 600 mg once daily. In group two 33 patients received rivaroxaban at a dose of 15 mg twice daily for 3 weeks, followed by 20 mg once daily. In group three, 31 patients were also given rivaroxaban in the above-described standard regimen in combination with diosmin 600 mg once daily. The results indicated that rivaroxaban "from the first day of the disease made it possible to considerably improve and accelerate the processes of restoration of patency of deep veins of lower extremities as compared with the patients taking warfarin". In patients receiving rivaroxaban, there were no cases of residual thrombotic occlusions of the major veins, and recanalization in three fourths of patients was assessed as good and in the remaining third as moderate. In the warfarin group, occlusion in the iliac veins was noted to persist persisted in 13% of patients, with good recanalization observed only in half of the patients. In addition, a combination of diosmin with rivaroxaban was more efficient than a combination of diosmin with warfarin.

A post-hoc subgroup analysis of the EINSTEIN DVT trial was performed to assess the efficacy of rivaroxaban on the development of the PTS.[79] They included 336 patients of which 162 received rivaroxaban and 174 enoxaparin/VKA. At 5 years the hazard ratio of PTS development for rivaroxaban was 0.76 (95% CI 0.51 to 1.13). The authors concluded that rivaroxaban was associated with a numerically lower but statistically non-significant reduction in risk of PTS compared with enoxaparin/VKA treatment.

In a prospective study, 100 consecutive patients treated for DVT were included, of which 39 were treated with enoxaparin/warfarin and 61 with rivaroxaban.[80] The authors assessed symptoms and signs of PTS and calculated Villalta score at 23 months (median) after acute DVT diagnosis. Patients in the rivaroxaban group had a lower prevalence of PTS than those treated with warfarin (25% vs. 49%, P=0.013). Logistic regression showed an odds ratio of 2.9 (1.2-6.8, P=0.014) for PTS development in the warfarin group compared with rivaroxaban group. When adjusted for other variables, the odds ratio was 3.5 (1.1-11.0, P=0.035). The authors concluded that treatment of DVT with rivaroxaban might be associated with a lower risk for PTS development and that a larger randomized trial would be needed for stronger evidence.

In a subsequent study, 309 patients with an objectively confirmed DVT diagnosed between 2011 and 2014 and treated with either rivaroxaban (N.=161) or warfarin (N.=148) were assessed at 24±6 months after DVT diagnosis using the patient reported Villalta scale.[81] The incidence of PTS was 45% (95% CI 37% to 52%) in the rivaroxaban group and 59% (955 CI 51% to 66%) in the warfarin group. Absolute risk difference was 14% (95% CI 3% to 25% with odds ratio (OR) of 0.6 (P=0.01). The adjusted OR for development of PTS in those treated with rivaroxaban was 0.5 (95% CI 0.3 to 0.8; P=0.01). Health related quality of life was better in the rivaroxaban treated patients

as measured by WQ-VAS (P=0.002) and VEINES-QOL/Sym (P=0.005/P=0.003). The authors pointed out that these results should be interpreted with caution due to the limitation imposed by the study.

In the most recent publication, the relative hazard of PTS in patients with VTE treated with rivaroxaban or warfarin in routine US clinical practice was assessed using MarketScan claims data from January 2012 to June 2015.[82] Adults with a primary diagnosis code for VTE during a hospitalization/emergency department visit, ≥6 months of insurance coverage prior to the index event and newly started on rivaroxaban or warfarin within 30 days of the index VTE were identified. Differences in baseline characteristics between rivaroxaban and warfarin users were adjusted for using inverse probability of treatment weights based on propensity scores. In total, 10 463 rivaroxaban and 26 494 warfarin users were followed for a mean of 16±9 (range, 4-39) months. Duration of anticoagulation was similar between cohorts (median = 6 months). Rivaroxaban was associated with a 23% (95% CI: 16-30) reduced hazard of PTS *versus* warfarin. Rivaroxaban was associated with a significant risk reduction in symptoms of PTS compared with warfarin in patients with VTE treated in routine practice.

General conclusions

It appears that there are several modifiable risk factors that point to strategies that may reduce the risk of PTS.

Early and more extensive recanalization occurs when DVT is treated with anti Xa anticoagulants such as LMWH or rivaroxaban (Level of evidence B), which is associated with reduction in the incidence of PTS (Level of evidence B) compared with VKA anticoagulation.

Recurrence of DVT is reduced by extended therapy using rivaroxaban, apixaban and sulodexide (Level of evidence A). The evidence for reduction in the incidence of PTS using these methods is weaker (Level of evidence B) due to lack of large randomised controlled trials.

Strategies to determine the need and type of extended prophylaxis based on the balance of risk of DVT recurrence (residual thrombus on ultrasound and D-dimer blood levels or Vienna nomogram) and risk of bleeding are available (Level of evidence B).

Compression therapy using below knee elastic stockings for 2 years after DVT is associated with reduction of symptoms (level of evidence A) (see Part I, Chapter 7 Compression Therapy) and incidence of PTS (Level of evidence B).

Thrombectomy is also associated with reduction in the incidence of PTS (2 studies) (Level of evidence A).

In patients with iliofemoral DVT catheter directed thrombolysis is associated with reduction in the incidence of PTS (Level of evidence A) and improved QOL (Level of evidence B).

In the absence of RCT the quality of evidence to support the use of stenting in post-thrombotic venous obstruction is weak (Level of evidence C). However, stenting is safe and should be considered as a treatment option as the evidence for benefit becomes stronger and patient selection criteria are improved.

References

1. Prandoni P, Villalta S, Bagatella P, Rossi L, Marchiori A, Piccioli A, *et al.* The clinical course of deep-vein thrombosis. Prospective long-term follow-up of 528 symptomatic patients. Haematologica 1997;82:423–8.

2. Haig Y, Enden T, Grøtta O, Kløw NE, Slagsvold CE, Ghanima W, *et al.*; CaVenT Study Group. Post-thrombotic syndrome after catheter-directed thrombolysis for deep vein thrombosis (CaVenT): 5-year follow-up results of an open-label, randomised controlled trial. Lancet Haematol 2016;3:e64–71.

3. Kahn SR, Ginsberg JS. Relationship between deep venous thrombosis and the postthrombotic syndrome. Arch Intern Med 2004;164:17–26.

4. Rodger MA, Kahn SR, Le Gal G, Solymoss S, Chagnon I, Anderson DR, *et al.* Inter-observer reliability of measures to assess the post-thrombotic syndrome. Thromb Haemost 2008;100:164–6.

5. Delis KT, Bountouroglou D, Mansfield AO. Venous claudication in iliofemoral thrombosis: long-term effects on venous hemodynamics, clinical status, and quality of life. Ann Surg 2004;239:118–26.

6. Kahn SR, Shrier I, Julian JA, Ducruet T, Arsenault L, Miron MJ, *et al.* Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis. Ann Intern Med 2008;149:698–707.

7. O'Donnell TF Jr, Burnand KG, Clemenson G, Thomas ML, Browse NL. Doppler examination vs clinical and phlebographic detection of the location of incompetent perforating veins: a prospective study. Arch Surg 1977;112:31–5.

8. Monreal M, Martorell A, Callejas JM, Valls R, Llamazares JF, Lafoz E, *et al.* Venographic assessment of deep vein thrombosis and risk of developing post-thrombotic syndrome: a prospective study. J Intern Med 1993;233:233–8.

9. Shull KC, Nicolaides AN, Fernandes é Fernandes J, Miles C, Horner J, Needham T, *et al.* Significance of popliteal reflux in relation to ambulatory venous pressure and ulceration. Arch Surg 1979;114:1304–6.

10. Bergan JJ, Schmid-Schönbein GW, Smith PD, Nicolaides AN, Boisseau MR, Eklof B. Chronic venous disease. N Engl J Med 2006;355:488–98.

11. Meissner MH, Eklof B, Smith PC, Dalsing MC, DePalma RG, Gloviczki P, *et al.* Secondary chronic venous disorders. J Vasc Surg 2007;46(Suppl S):68S–83S.

12. Kahn SR, Partsch H, Vedantham S, Prandoni P, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of post-thrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardization. J Thromb Haemost 2009;7:879–83.

13. van Dongen CJ, Prandoni P, Frulla M, Marchiori A, Prins MH, Hutten BA. Relation between quality of anticoagulant treatment and the development of the postthrombotic syndrome. J Thromb Haemost 2005;3:939–42.

14. Shbaklo H, Holcroft CA, Kahn SR. Levels of inflammatory markers and the development of the post-thrombotic syndrome. Thromb Haemost 2009;101:505–12.

15. Roumen-Klappe EM, Janssen MC, Van Rossum J, Holewijn S, Van Bokhoven MM, Kaasjager K, *et al.* Inflammation in deep vein thrombosis and the development of post-thrombotic syndrome: a prospective study. J Thromb Haemost 2009;7:582–7.

16. Rabinovich A, Ducruet T, Kahn SR; SOX Trial investigators. Development of a clinical prediction model for the postthrombotic syndrome in a prospective cohort of patients with proximal deep vein thrombosis. J Thromb Haemost 2018;16:262–70.

17. Dronkers CE, Mol GC, Maraziti G, van de Ree MA, Huisman MV, Becattini C, *et al.* Predicting Post-thrombotic syndrome with ultrasonographic follow-up after deep vein thrombosis: A systematic review and meta-analysis. Thromb Haemost 2018;118:1428–38.

18. Kahn SR. The post-thrombotic syndrome. Hematology (Am Soc Hematol Educ Program) 2010;2010:216–20.

19. Nicolaides AN, Fareed J, Kakkar AK, Comerota AJ, Goldhaber SZ, Hull R, *et al.* Prevention and treatment of venous thromboembolism—International Consensus Statement. Int Angiol 2013;32:111–260.

20. Henke P, Kistner B, Wakefield TW, Eklof B, Lurie F. Reducing venous stasis ulcers by fifty percent in 10 years: the next steps. J Vasc Surg 2010;52(Suppl):37S–8S.

21. Prandoni P, Lensing AW, Prins MR. Long-term outcomes after deep venous thrombosis of the lower extremities. Vasc Med 1998;3:57–60.

22. Becattini C, Agnelli G, Schenone A, Eichinger S, Bucherini E, Silingardi M, *et al.*; WARFASA Investigators. Aspirin for preventing the recurrence of venous thromboembolism. N Engl J Med 2012;366:1959–67.

23. Brighton TA, Eikelboom JW, Mann K, Mister R, Gallus A, Ockelford P, *et al.*; ASPIRE Investigators. Low-dose aspirin for preventing recurrent venous thromboembolism. N Engl J Med 2012;367:1979–87.

24. Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, *et al.*; RE-MEDY Trial Investigators; RE-SONATE Trial Investigators. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med 2013;368:709–18.

25. Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, *et al.*; EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499–510.

26. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, *et al.*; AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013;368:699–708.

27. Andreozzi GM, Bignamini AA, Davì G, Palareti G, Matuška J, Holý M, *et al.*; SURVET Study Investigators. Sulodexide for the Prevention of Recurrent Venous Thromboembolism: The Sulodexide in Secondary Prevention of Recurrent Deep Vein Thrombosis (SURVET) Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. Circulation 2015;132:1891–7.

28. Luzzi R, Belcaro G, Dugall M, Hu S, Arpaia G, Ledda A, *et al.* The efficacy of sulodexide in the prevention of postthrombotic syndrome. Clin Appl Thromb Hemost 2014;20:594–9.

29. Siragusa S, Malato A, Anastasio R, Cigna V, Milio G, Amato C, *et al.* Residual vein thrombosis to establish duration of anticoagulation after a first episode of deep vein thrombosis: the Duration of Anticoagulation based on Compression UltraSonography (DACUS) study. Blood 2008;112:511–5.

30. Siragusa S, Malato A, Saccullo G, Iorio A, Di Ianni M, Caracciolo C, *et al.* Residual vein thrombosis for assessing duration of anticoagulation after unprovoked deep vein thrombosis of the lower limbs: the extended DACUS study. Am J Hematol 2011;86:914–7.

31. Palareti G, Cosmi B, Legnani C, Tosetto A, Brusi C, Iorio A, *et al.*; PROLONG Investigators. D-dimer testing to determine the duration of anticoagulation therapy. N Engl J Med 2006;355:1780–9.

32. Prandoni P, Vedovetto V, Ciammaichella M, Bucherini E, Corradini S, Enea I, *et al.*; Morgagni Investigators. Residual vein thrombosis and serial D-dimer for the long-term management of patients with deep venous thrombosis. Thromb Res 2017;154:35–41.

33. Fahrni J, Husmann M, Gretener SB, Keo HH. Assessing the risk of recurrent venous thromboembolism—a practical approach. Vasc Health Risk Manag 2015;11:451–9.

34. Eichinger S, Heinze G, Jandeck LM, Kyrle PA. Risk assessment of recurrence in patients with unprovoked deep vein thrombosis or pulmonary embolism: the Vienna prediction model. Circulation 2010;121:1630–6.

35. Eichinger S, Heinze G, Kyrle PA. D-dimer levels over time and the risk of recurrent venous thromboembolism: an update of the Vienna prediction model. J Am Heart Assoc 2014;3:e000467.

36. Tosetto A, Iorio A, Marcucci M, Baglin T, Cushman M, Eichinger S, *et al.* Predicting disease recurrence in patients with previous unprovoked venous thromboembolism: a proposed prediction score (DASH). J Thromb Haemost 2012;10:1019–25.

37. Marcucci M, Iorio A, Douketis JD, Eichinger S, Tosetto A, Baglin T, *et al.* Risk of recurrence after a first unprovoked venous thromboembolism: external validation of the Vienna Prediction Model with pooled individual patient data. J Thromb Haemost 2015;13:775–81.

38. Nieto JA, Solano R, Ruiz-Ribó MD, Ruiz-Gimenez N, Prandoni P, Kearon C, *et al.*; Riete Investigators. Fatal bleeding in patients receiving anticoagulant therapy for venous thromboembolism: findings from the RIETE registry. J Thromb Haemost 2010;8:1216–22.

39. Pierson S, Pierson D, Swallow R, Johnson G Jr. Efficacy of graded elastic compression in the lower leg. JAMA 1983;249:242–3.

40. Musani MH, Matta F, Yaekoub AY, Liang J, Hull RD, Stein PD. Venous compression for prevention of postthrombotic syndrome: a meta-analysis. Am J Med 2010;123:735–40.

41. Prandoni P, Lensing AW, Prins MH, Frulla M, Marchiori A, Bernardi E, *et al.* Below-knee elastic compression stockings to prevent the postthrombotic syndrome: a randomized, controlled trial. Ann Intern Med 2004;141:249–56.

42. Ginsberg JS, Hirsh J, Julian J, Vander LaandeVries M, Magier D, MacKinnon B, *et al.* Prevention and treatment of postphlebitic syndrome: results of a 3-part study. Arch Intern Med 2001;161:2105–9.

43. Brandjes DP, Büller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, *et al.* Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet 1997;349:759–62.

44. Aschwanden M, Jeanneret C, Koller MT, Thalhammer C, Bucher HC, Jaeger KA. Effect of prolonged treatment with compression stockings to prevent post-thrombotic sequelae: a randomized controlled trial. J Vasc Surg 2008;47:1015–21.

45. Prandoni P, Noventa F, Quintavalla R, Bova C, Cosmi B, Siragusa S, *et al.*; Canano Investigators. Thigh-length versus below-knee compression elastic stockings for prevention of the postthrombotic syndrome in patients with proximal-venous thrombosis: a randomized trial. Blood 2012;119:1561–5.

46. Partsch H, Blättler W. Compression and walking versus bed rest in the treatment of proximal deep venous thrombosis with low molecular weight heparin. J Vasc Surg 2000;32:861–9.

47. Partsch H, Kaulich M, Mayer W. Immediate mobilisation in acute vein thrombosis reduces post-thrombotic syndrome. Int Angiol 2004;23:206–12.

48. Kahn SR, Shapiro S, Wells PS, Rodger MA, Kovacs MJ, Anderson DR, *et al.*; SOX trial investigators. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. Lancet 2014;383:880–8.

49. Plate G, Eklöf B, Norgren L, Ohlin P, Dahlström JA. Venous thrombectomy for iliofemoral vein thrombosis—10-year results of a prospective randomised study. Eur J Vasc Endovasc Surg 1997;14:367–74.

50. Comerota AJ, Gale SS. Technique of contemporary iliofemoral and infrainguinal venous thrombectomy. J Vasc Surg 2006;43:185–91.

51. Lindow C, Mumme A, Asciutto G, Strohmann B, Hummel T, Geier B. Long-term results after transfemoral venous thrombectomy for iliofemoral deep venous thrombosis. Eur J Vasc Endovasc Surg 2010;40:134–8.

52. Rodríguez LE, Aboukheir-Aboukheir A, Figueroa-Vicente R, Soler-Bernardini H, Bolanos-Avila G, Torruella-Bartolomei LJ, *et al.* Hybrid

operative thrombectomy is noninferior to percutaneous techniques for the treatment of acute iliofemoral deep venous thrombosis. J Vasc Surg Venous Lymphat Disord 2017;5:177–84.

53. Comerota AJ. Catheter-directed thrombolysis for the treatment of acute iliofemoral deep venous thrombosis. Phlebology 2001;15:149–55.

54. Markevicius N, Apanavicius G, Skerbinskas S. Comparison between long term results of catheter directed thrombolysis and anticoagulation in the treatment of acute iliofemoral deep vein thrombosis. Phlebology 2004;19:148–9.

55. Broholm R, Sillesen H, Damsgaard MT, Jørgensen M, Just S, Jensen LP, *et al.* Postthrombotic syndrome and quality of life in patients with iliofemoral venous thrombosis treated with catheter-directed thrombolysis. J Vasc Surg 2011;54(Suppl):18S–25S.

56. Elsharawy M, Elzayat E. Early results of thrombolysis vs anticoagulation in iliofemoral venous thrombosis. A randomised clinical trial. Eur J Vasc Endovasc Surg 2002;24:209–14.

57. Enden T, Kløw NE, Sandvik L, Slagsvold CE, Ghanima W, Hafsahl G, *et al.*; CaVenT study group. Catheter-directed thrombolysis vs. anticoagulant therapy alone in deep vein thrombosis: results of an open randomized, controlled trial reporting on short-term patency. J Thromb Haemost 2009;7:1268–75.

58. Enden T, Haig Y, Kløw NE, Slagsvold CE, Sandvik L, Ghanima W, *et al.*; CaVenT Study Group. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. Lancet 2012;379:31–8.

59. Vedantham S, Goldhaber SZ, Julian JA, Kahn SR, Jaff MR, Cohen DJ, *et al.*; ATTRACT Trial Investigators. Pharmacomechanical Catheter-Directed Thrombolysis for Deep-Vein Thrombosis. N Engl J Med 2017;377:2240–52.

60. Comerota AJ, Kearon C, Gu CS, Julian JA, Goldhaber SZ, Kahn SR, *et al.*; ATTRACT Trial Investigators. Endovascular Thrombus Removal for Acute Iliofemoral Deep Vein Thrombosis. Circulation 2019;139:1162–73.

61. Notten P, Ten Cate-Hoek AJ, Arnoldussen CW, Strijkers RH, de Smet AA, Tick LW, *et al.* Ultrasound-accelerated catheter-directed thrombolysis versus anticoagulation for the prevention of post-thrombotic syndrome (CAVA): a single-blind, multicentre, randomised trial. Lancet Haematol 2020;7:e40–9.

62. Neglén P, Hollis KC, Olivier J, Raju S. Stenting of the venous outflow in chronic venous disease: long-term stent-related outcome, clinical, and hemodynamic result. J Vasc Surg 2007;46:979–90.

63. Razavi MK, Jaff MR, Miller LE. Safety and Effectiveness of Stent Placement for Iliofemoral Venous Outflow Obstruction: Systematic Review and Meta-Analysis. Circ Cardiovasc Interv 2015;8:e002772.

64. Seager MJ, Busuttil A, Dharmarajah B, Davies AH. Editor's Choice— A Systematic Review of Endovenous Stenting in Chronic Venous Disease Secondary to Iliac Vein Obstruction. Eur J Vasc Endovasc Surg 2016;51:100–20.

65. Wen-da W, Yu Z, Yue-Xin C. Stenting for chronic obstructive venous disease: A current comprehensive meta-analysis and systematic review. Phlebology 2016;31:376–89.

66. Nicolaides A, Clark H, Labropoulos N, Geroulakos G, Lugli M, Maleti O. Quantitation of reflux and outflow obstruction in patients with CVD and correlation with clinical severity. Int Angiol 2014;33:275–81.

67. Nicolaides A, Maleti O, Lugli M, Guerzoni S. Non-invasive measurement of lower limb outflow resistance and implications for stenting. Vasc Investig Ther 2019;2:88–94.

68. Romera A, Cairols MA, Vila-Coll R, Martí X, Colomé E, Bonell A, *et al.* A randomised open-label trial comparing long-term sub-cutaneous low-molecular-weight heparin compared with oral-anticoagulant therapy in the treatment of deep venous thrombosis. Eur J Vasc Endovasc Surg 2009;37:349–56.

69. Daskalopoulos ME, Daskalopoulou SS, Liapis CD. Tinzaparin in long-term treatment of deep venous thrombosis. Eur J Vasc Endovasc Surg 2007;34:353–4.

70. Gonzalez-Fajardo JA, Arreba E, Castrodeza J, Perez JL, Fernandez L, Agundez I, *et al.* Venographic comparison of subcutaneous low-molecular weight heparin with oral anticoagulant therapy in the long-term treatment of deep venous thrombosis. J Vasc Surg 1999;30:283–92.

71. López-Beret P, Orgaz A, Fontcuberta J, Doblas M, Martinez A, Lozano G, *et al.* Low molecular weight heparin versus oral anticoagulants in the long-term treatment of deep venous thrombosis. J Vasc Surg 2001;33:77–90.

72. Kakkar VV, Gebska M, Kadziola Z, Saba N, Carrasco P; Bemiparin Investigators. Low-molecular-weight heparin in the acute and long-term treatment of deep vein thrombosis. Thromb Haemost 2003;89:674–80.

73. Hull RD, Liang J, Townshend G. Long-term low-molecular-weight heparin and the post-thrombotic syndrome: a systematic review. Am J Med 2011;124:756–65.

74. Hull RD, Pineo GF, Brant R, Liang J, Cook R, Solymoss S, *et al.*; LITE Trial Investigators. Home therapy of venous thrombosis with long-term LMWH versus usual care: patient satisfaction and post-thrombotic syndrome. Am J Med 2009;122:762–769.e3.

75. Daskalopoulos ME, Daskalopoulou SS, Tzortzis E, Sfiridis P, Nikolaou A, Dimitroulis D, *et al.* Long-term treatment of deep venous thrombosis with a low molecular weight heparin (tinzaparin): a prospective randomized trial. Eur J Vasc Endovasc Surg 2005;29:638–50.

76. Koitabashi N, Niwamae N, Taguchi T, Ohyama Y, Takama N, Kurabayashi M. Remarkable regression of massive deep vein thrombosis in response to intensive oral rivaroxaban treatment. Thromb J 2015;13:13.

77. Allegra C, Antignani PL. Does rivaroxaban have a fibrinolytic effect? Acta Phlebol 2015;16:107–9.

78. Kuznetsov MR, Sapelkin SV, Boldin BV, Leont'ev SG, Neskhodimov LA. [Recanalization of lower-limb deep veins as an index of efficacy of treatment for acute venous thrombosis]. Angiol Sosud Khir 2016;22:82–8. Russian.

79. Cheung YW, Middeldorp S, Prins MH, Pap AF, Lensing AW, Ten Cate-Hoek AJ, *et al.*; Einstein PTS Investigators Group. Post-thrombotic syndrome in patients treated with rivaroxaban or enoxaparin/vitamin K antagonists for acute deep-vein thrombosis. A post-hoc analysis. Thromb Haemost 2016;116:733–8.

80. Jeraj L, Jezovnik MK, Poredos P. Rivaroxaban versus warfarin in the prevention of post-thrombotic syndrome. Thromb Res 2017;157:46–8.

81. Utne KK, Dahm A, Wik HS, Jelsness-Jørgensen LP, Sandset PM, Ghanima W. Postthrombotic Syndrome in Patients Treated With Rivaroxaban or Warfarin for Venous Thromboembolism. Thromb Res 2018;163:6–11.

82. Coleman CI, Beyer-Westendorf J, Bunz TJ, Mahan CE, Spyropoulos AC. Postthrombotic syndrome in patients with rivaroxaban or warfarin for venous thromboembolism. Clin Appl Thromb Hemost 2018;24:575–82.

CHAPTER 14

Management of symptomatic individuals in the absence of clinical signs

Patients complaining of "venous" symptoms but who do not have any clinical signs, anatomic anomalies or physiological disorders that can be identified by the currently in use complementary investigations engaged in the CEAP classification are assigned to class $C_{0s,}$ $E_{n,}$ An, Pn.[1]

Such patients are not uncommon in practice. Recent epidemiological studies have demonstrated that patients with C_{0s} are common in the general population. C_{0s} prevalence was 13-23% in a Polish Study,[2] 15% in the San Diego Vein Study,[3] 19.7% in the worldwide Vein Consult Program[4] and 14% in the Belgium and Luxemburg subgroup of the Vein Consult Program.[5]

Pathophysiology of C_{0s}

The presence of CVD symptoms in the absence of any visible or palpable signs were described in the mid-1980's well before the development of the CEAP classification. Such patients were considered to have functional phlebopathy[6, 7] or more recently functional CVD.[8] They were studied in depth with photoplethysmography (PPG), strain gauge plethysmography (SGP) and laser Doppler as well as CW Doppler and Duplex scanning in the Acireale epidemiological study which involved 1031 subjects (age 30-59).[9] In this study, symptoms of CVD were present in 561 (54%). Of these, 325 (58%) *i.e.* 31% of the whole population studied did not have any visible or palpable varicose veins (C_{0s}). However, 163 (50%) of these had reflux in some veins (femoral, GSV above and below the knee, popliteal, SSV and tibial veins). The remaining 164 (15.9% of all the population) did not have any reflux on routine conventional duplex scanning. They were considered to have hypotonic phlebopathy (HP) on the basis of the findings summarized below.

In patients with HP the mean (±SD) PPG change in voltage from baseline (ΔR) after 10 plantar flexion movements was lower (200±15 V) compared with normal controls (275±40 V) ($P<0.005$) indicating reduced emptying of the venous reservoir. The mean refilling time was also lower (27±5 sec) compared with normal controls (35±10 sec) ($P<0.005$) indicating a relatively fuller reservoir or some reflux in small venules not examined by ultrasound. However, it was not as low as in patients with varicose veins (10±6 sec).

SGP demonstrated that the mean maximum incremental venous volume (MIVV) during venous occlusion was higher (4.5±0.4 mL%) in patients with HP than normal controls (2.9±0.3 mL%) ($P<0.005$) indicating increased venous compliance. The decrease in volume (ΔV) in the sitting position after 10 plantar flexion/dorsiflexion movements was 2.7±0.5 mL% compared with 1.5±0.4 mL% in the normal controls ($P<0.005$) confirming a larger volume in the calf reservoir.

In a subgroup of 20 patients with HP, duplex scanning demonstrated that the vein diameters of the popliteal, tibio-peroneal trunk and gastrocnemial veins were 2 to 3 times greater than in 10 normal controls.

In a subgroup of 10 patients with HP, laser Doppler showed an increase in standing and resting flux indicating increased cutaneous blood flow. In HP patients resting flux decreased from 10.4±1.9 in the supine position to 7.28±1.2 in the standing position (only 30% reduction) indicating impaired venoarteriolar reflex. In contrast, in 10 normal controls resting flux decreased from 8.0±0.9 in the supine position to 3.6±0.6 in the standing position indicating normal venoarteriolar reflex (>50% reduction) ($P<0.001$).

In another recent study, 16 C_{0a} normal asymptomatic individuals were compared with 16 patients with C_{0s}.[10] Routine duplex scanning in both groups excluded reflux in

superficial and deep main trunks. However, using a continuous wave flat probe on visually identified small venules on the lateral thigh and leg, medial leg and anterior tibial area it was possible to identify the presence of bidirectional flow in 54 sites in the C_{0s} group and only in 33 sites in the C_{0a} group (P=0.05) during exercise.

Using a different approach, Tsoukanov *et al.* investigated 41 C_{0s} women with duplex scanning in the morning (before 10 am) and in the afternoon (after 6 pm).[11] Fifteen of these patients did not have any reflux at any time. The remaining 26 patients had reflux in the GSV in the evening but not in the morning (situational reflux). Two patients had axial reflux and 24 segmental reflux. The evening diameter of the GSV was larger in those with reflux in the evening (P<0.05). The difference in the GSV between the evening and morning was also greater in the patients with evening reflux than those without any reflux. After 2 months of MPFF treatment, 22 patients no longer had reflux in the evening, the GSV diameter decreased and so did the difference in diameter between the morning and evening (P<0.0001). There was a parallel significant decrease in the intensity of symptoms as demonstrated by the VAS score and a significant improvement in QoL (P<0.001).

In a subsequent study by Tsukanov and Tsukanov[12] involving 294 patients, the prevalence of situational reflux in the GSV was investigated. It was detected in 21 (38.2%) of 55 patients classified as C_{0s}, 25 (49.0%) of 51 classified as C1s and in 32 (17.0%) of 188 classified as C_2. After treatment with MPFF 1000 mg for 90 days, in the 46 women with transient reflux in classes C_{0s} and C_{1s}, reflux disappeared in 76.1% and there was a significant decrease in the GSV diameters. The intensity of symptoms decreased from 5.2 to 1.7 (P<0.001) according to the 0-10 visual analog scale. The global index score (CIVIQ-20) decreased from 47.2±7.9 to 28.8±9.1 (P<0.001).

It appears from several studies summarized above that a significant number of patients in C_{0s} clinical class who do not have any reflux or obstruction on routine duplex examination are found to have abnormal venous function such as increased venous compliance and venous volume, reduced emptying of venous reservoir on calf muscle contraction, decreased VAR, evening venous reflux in the main venous trunks, reflux in small venules not normally examined by duplex and even anatomic changes in the skin dermal papillae. However, the number of patients in most studies is small and the findings need to be confirmed in larger studies.

Future studies should determine the prevalence of these functional abnormalities, their coexistence and which are the most predominant in patients with C_{0s}; also, the contribution of these abnormalities to individual symptoms, disease progression and response to venoactive drugs or compression. Knowledge of the above should help one provide a rational plan for investigation and management of C_{0s} patients.[13, 14]

Current management

After a thorough examination to exclude non-venous causes of symptoms, one should confirm the presence of varicose veins or other venous physiopathological anomalies using non-invasive techniques or even invasive investigations if necessary *e.g.* in the presence of severe symptoms (level III investigation),[1] several options are available although none are "evidence-based" except for veno-active drugs and compression.

Patient reassurance

This measure is self-evident and will help many patients, mostly those with a family history of varicose veins or leg ulcers who are anxious that they may also get venous problems. However, the value of reassuring patients has not been demonstrated and studies on quality of life (QoL) might improve our knowledge on this point.

Adaptation of lifestyle

In most phlebologists' experience, many symptoms will diminish if patients can adopt a better lifestyle including improved working conditions, performing tip-toes when obliged to stand-still, and developing recreational activities such as walking rather than driving, swimming or raising the legs during pauses or at night, and trying to lose weight when appropriate. However, the value of these measures has not been demonstrated.

Oral veno-active drugs

Their effect on symptoms in C_{0s} classification has been well demonstrated (see Chapter 8 in Part I).

Topical veno-active drugs and topical heparinoids

These drugs may relieve some complaints of heaviness or swelling. This may be due to the cooling effect of gels.

Compression therapy

Compression therapy, usually by wearing stockings, has been studied in class C_{0s}. In the San Diego Consensus conference, 3 trials have been considered to provide a Grade B recommendation.[15] In another study it was stated that

"*calf-length compression stockings with a pressure range between 11 and 21 mmHg were able to reduce or totally prevent evening edema and might therefore be recommended for people with a profession connected with long periods of sitting or standing*."[16, 17] It is then logical to prescribe light compression in C_{0s}, however, we need further trials to assess their effect.

References

1. Eklöf B, Rutherford RB, Bergan JJ, Carpentier PH, Gloviczki P, Kistner RL, *et al.*; American Venous Forum International Ad Hoc Committee for Revision of the CEAP Classification. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg 2004;40:1248–52.

2. Jawien A. The influence of environmental factors in chronic venous insufficiency. Angiology 2003;54(Suppl 1):S19–31.

3. Langer RD, Ho E, Denenberg JO, Fronek A, Allison M, Criqui MH. Relationships between symptoms and venous disease: the San Diego population study. Arch Intern Med 2005;165:1420–4.

4. Guex JJ, Rabe E, Escotto SI, Escudero JR, Scuderi A, Yuwono HS, *et al.* The "C0s" patient: worldwide results from the Vein Consult Program. Phlebolymphology 2012;19:182–92.

5. Vuylsteke ME, Colman R, Thomis S, Guillaume G, Degrande E, Staelens I. The influence of age and gender on venous symptomatology. An epidemiological survey in Belgium and Luxembourg. Phlebology 2016;31:325–33.

6. Bassi G. La patologia venosa funzionale. In Bassi G, editor. Compendio di terapia flebologica. Turin: Edizioni Minerva Medica; 1985.

7. Nicolaides A, Bouskela E. Pathophysiological mechanisms of chronic venous disease and their role in C0s clinical class. Vasc Invest Ther 2018;1:103–9.

8. Serra R, Andreucci M, De Caridi G, Massara M, Mastroroberto P, de Franciscis S. Functional chronic venous disease: A systematic review. Phlebology 2017;32:588–92.

9. Andreozzi GM, Signorelli S, Di Pino L, Garozzo S, Cacciaguerra G, Leone A, *et al.* Varicose symptoms without varicose veins: the hypotonic phlebopathy, epidemiology and pathophysiology. The Acireale project. Minerva Cardioangiol 2000;48:277–85.

10. Lugli M, Maleti O, Iabichella ML, Perrin M. Investigation of non-saphenous veins in C0S patients. Int Angiol 2018;37:169–75.

11. Tsoukanov YT, Tsoukanov AY, Nikolaychuk A. Great saphenous vein transitory reflux in patients with symptoms related to chronic venous disorders, but without visible sins (C0s), and its correction with MPFF treatment. Phlebolymphology 2015;22:18–24.

12. Tsoukanov YT, Tsukanov AY. Diagnosis and treatment of situational great saphenous vein reflux in daily medical practice. Phlebolymphology 2017;24:144–51.

13. Perrin M, Ramelet AA. Pharmacological treatment of primary chronic venous disease: rationale, results and unanswered questions. Eur J Vasc Endovasc Surg 2011;41:117–25.

14. Blazek C, Amsler F, Blaettler W, Keo HH, Baumgartner I, Willenberg T. Compression hosiery for occupational leg symptoms and leg volume: a randomized crossover trial in a cohort of hairdressers. Phlebology 2013;28:239–47.

15. Partsch H, Clark M, Bassez S, Benigni JP, Becker F, Blazek V, *et al.* Measurement of lower leg compression in vivo: recommendations for the performance of measurements of interface pressure and stiffness: consensus statement. Dermatol Surg 2006;32:224–32, discussion 233.

16. Partsch H, Winiger J, Lun B. Compression stockings reduce occupational leg swelling. Dermatol Surg 2004;30:737–43, discussion 743.

17. Raju S, Hollis K, Neglen P. Use of compression stockings in chronic venous disease: patient compliance and efficacy. Ann Vasc Surg 2007;21:790–5.

CHAPTER 15

Management of patients with varicose veins

Non-interventional therapy

There is evidence for the efficacy of veno-active drugs to relieve symptoms and improve venous edema in patients with varicose veins. Compression therapy may also be effective (see Chapters 7 and 8).

Non-interventional therapy is usually the main treatment modality during initial patient presentation until all work-up and interventional therapy is performed and for patients not willing to have interventional therapy. The latter group may include patients with transient symptoms, those with minimal symptoms not severe enough to make interventional therapy appealing and in cases of vague or atypical symptoms as a therapeutical trial, awaiting further investigation for other diseases that could explain them. Veno-active drugs are indicated in patients with the characteristics shown above, not able to tolerate compression including pruritic symptoms that worsen when compression is worn and residence in warm climates that prevents use of compression due to heat intolerance, especially during the warm seasons of the year.

Interventional Therapy

Intervention for varicose veins by means of surgery, endovenous techniques[1-4] and sclerotherapy[5] aim to eliminate reflux, normalize venous hemodynamics and remove visible varices in order to relieve symptoms and minimize the complications of CVD (see Chapter 9). In practice, this entails eliminating both axial reflux[6, 7] and varicose clusters. The former is accomplished by surgery, endovenous techniques or foam sclerotherapy and the latter by surgery or sclerotherapy.

Varicose veins are increasingly being treated by minimally invasive alternatives to surgery in the expectation that these methods will reduce morbidity, eliminate hospital stay and accelerate return to normal activity. There is also strong evidence that the new techniques will reduce recurrence caused by neovascularization,[8-13] but so far overall recurrence rates of varicose veins are similar in the available RCTs with 5 years follow-up (see Chapter 9). However, there is more neovascularization in the surgery groups and more SFJ and tributary recurrence in the laser groups. The important remaining question to be answered is whether these different manifestations of recurrence are equal regarding clinical severity.[14, 15] The hierarchy and relative indications of the above interventional treatment modalities are determined by the presence of saphenous vein reflux and/or varicose veins, availability of particular methods, local experience, and patient preference.

1. Elimination of saphenous reflux, when present, is clearly the initial step, preferably by endoluminal methods followed by phlebectomy, with the exception of recurrent varicose veins where sclerotherapy is considered an alternative to surgery because of the potentially hazardous redo nature of the latter.

2. Any co-existing varicose veins can be managed with phlebectomy, concurrently with saphenous surgery if this is performed or even at a second stage if endoluminal ablation is performed, as it is expected that these will become less prominent and bothersome. Some surgeons instead of varicose vein phlebectomy prefer sclerotherapy, which can be performed during operative or endoluminal management of the saphenous trunk, or at a later stage in the latter scenario. However, patients should be adequately informed that sclerotherapy is plagued by skin pigmentation, which also holds true for sclerotherapy of the main saphenous trunks.

3. In isolated varicose veins (*i.e.* saphenous vein incom-

petence does not exist, occurring often in primary varicose veins, recurrent varicose veins and no evidence of trunk incompetence at the time of patient presentation or in varicose veins of non-saphenous origin), phlebectomy or sclerotherapy are employed. Sclerotherapy is considered very often as the first choice in recurrent varicose vein. Additional parameters to be considered include potential contraindications of each method that should be discussed with the patient.

References

1. Merchant RF, DePalma RG, Kabnick LS. Endovascular obliteration of saphenous reflux: a multicenter study. J Vasc Surg 2002;35:1190–6.

2. Weiss RA, Weiss MA. Controlled radiofrequency endovenous occlusion using a unique radiofrequency catheter under duplex guidance to eliminate saphenous varicose vein reflux: a 2-year follow-up. Dermatol Surg 2002;28:38–42.

3. Min RJ, Khilnani N, Zimmet SE. Endovenous laser treatment of saphenous vein reflux: long-term results. J Vasc Interv Radiol 2003;14:991–6.

4. Goldman MP, Mauricio M, Rao J. Intravascular 1320-nm laser closure of the great saphenous vein: a 6- to 12-month follow-up study. Dermatol Surg 2004;30:1380–5.

5. Cabrera J, Cabrera JJ, Garcia-Olmedo MA. Sclerosants in microfoam. A new approach in Angiology. Phlebology 2000;15:19–23.

6. Dwerryhouse S, Davies B, Harradine K, Earnshaw JJ. Stripping the long saphenous vein reduces the rate of reoperation for recurrent varicose veins: five-year results of a randomized trial. J Vasc Surg 1999;29:589–92.

7. Winterborn RJ, Foy C, Earnshaw JJ. Causes of varicose vein recurrence: late results of a randomized controlled trial of stripping the long saphenous vein. J Vasc Surg 2004;40:634–9.

8. Lurie F, Creton D, Eklof B, Kabnick LS, Kistner RL, Pichot O, *et al.* Prospective randomised study of endovenous radiofrequency obliteration (closure) versus ligation and vein stripping (EVOLVeS): two-year follow-up. Eur J Vasc Endovasc Surg 2005;29:67–73.

9. Rautio TT, Perälä JM, Wiik HT, Juvonen TS, Haukipuro KA. Endovenous obliteration with radiofrequency-resistive heating for greater saphenous vein insufficiency: a feasibility study. J Vasc Interv Radiol 2002;13:569–75.

10. Pichot O, Kabnick LS, Creton D, Merchant RF, Schuller-Petroviae S, Chandler JG. Duplex ultrasound scan findings two years after great saphenous vein radiofrequency endovenous obliteration. J Vasc Surg 2004;39:189–95.

11. Stücker M, Netz K, Breuckmann F, Altmeyer P, Mumme A. Histomorphologic classification of recurrent saphenofemoral reflux. J Vasc Surg 2004;39:816–21, discussion 822.

12. van Rij AM, Jiang P, Solomon C, Christie RA, Hill GB. Recurrence after varicose vein surgery: a prospective long-term clinical study with duplex ultrasound scanning and air plethysmography. J Vasc Surg 2003;38:935–43.

13. Nyamekye I, Shephard NA, Davies B, Heather BP, Earnshaw JJ. Clinicopathological evidence that neovascularisation is a cause of recurrent varicose veins. Eur J Vasc Endovasc Surg 1998;15:412–5.

14. Disselhoff BC, der Kinderen DJ, Kelder JC, Moll FL. Five-year results of a randomized clinical trial comparing endovenous laser ablation with cryostripping for great saphenous varicose veins. Br J Surg 2011;98:1107–11.

15. Rass K, Frings N, Glowacki P, Hamsch C, Gräber S, Vogt T, *et al.* Comparable effectiveness of endovenous laser ablation and high ligation with stripping of the great saphenous vein: two-year results of a randomized clinical trial (RELACS study). Arch Dermatol 2012;148:49–58.

CHAPTER 16

Treatment of patients with post-thrombotic syndrome

There are no prospective randomized controlled studies comparing various treatment modalities in most of the CEAP clinical classes for patients with PTS so that a strong recommendation cannot be made.

Compression is the cornerstone for treating patients with PTS,[1] (see Chapter 7) but the optimal degree of compression is unknown. Below-knee compression is as effective as above-knee in most patients.[2] The grade of compression used is often tailored to the clinical class of CEAP and patient tolerance but not to the etiology, anatomic lesions or pathophysiological disorders due to lack of data. Anatomic lesions in severe PTS frequently combine deep, superficial and perforating vein reflux with obstruction in some[3] but we do not know precisely the value of compression for treating PTS in relation to these patterns. The same is true for adjuvant therapy with medications, physiotherapy or hydrotherapy.

Surgical or endovascular methods to relieve obstruction or reflux (see Chapters 10 and 11) are targeted to treat specific anatomic areas but various methods are frequently used in combination for superficial, perforating veins and deep reflux so that it remains difficult to identify which is most beneficial. Many patients with superficial venous incompetence also have deep vein reflux. There are studies which indicates that treating superficial vein reflux in patients with deep venous reflux in addition to the superficial reflux (and no deep obstruction), will often improve or correct the deep reflux.[4, 5]

Although drug treatment has been effective for reducing edema in short-term studies,[6-8] (see Chapter 8) compression remains the pivotal treatment in patients presenting $C_{3\text{-}6}$. In practice, compression is tailored according to its efficacy for controlling edema.

Intervention may be considered if severe symptomatic edema is not controlled by compression because of above inguinal ligament obstruction. Unfortunately, the hemodynamic severity is not easy to measure. According to Neglen and Raju[9] intravascular ultrasound (IVUS) is the most reliable investigation (Chapters 6 and 11). There is a large consensus for using balloon venoplasty and stenting rather than surgical bypass,[10, 11] for the relief of ilio-caval stenosis or occlusion. Raju and Neglen noted a high incidence of non-thrombotic iliac vein obstructions in patients with CVD and started treating patients with iliac vein obstruction and reflux with stents in the iliac vein. They found that placing iliac vein stents without treatment of the reflux was sufficient to reduce symptoms in the majority of patients having a combination of reflux and iliac vein obstruction.[12, 13]

Chronic obstructions of iliac veins and IVC are now commonly treated with recanalization and stent placement. Several reports have demonstrated high technical success with good clinical response and intermediate to long-term durability (see Chapter 11).[14]

In patients presenting with severe $C_{4\text{-}6}$ CVD, conservative treatment with compression and medications is a basic option. Surgery should only be considered after full investigation when skin or subcutaneous changes and symptoms do not improve. Superficial vein reflux should be dealt with as a first stage. If obstruction proximal to the inguinal ligament is identified, recanalization with angioplasty and stent placement should be considered. Endophlebectomy should be considered for treating obstruction above the inguinal ligament.[15] When deep venous reflux is combined with severe obstruction, the latter has to be managed as first step.

There is no consensus for the efficacy and the need for surgical treatment of incompetent perforating veins

TABLE I.—*Management of patients with chronic venous disease according to the CEAP classification.*

C Class	A: S, D P*	P: R, O, O+R	Calf Pump	Treatment
$C_{0\text{-}2\,S}$	S	R without O	Normal	Conservative treatment: Compression, Venoactive drugs Treatment of Superficial Reflux: Sclerotherapy Endovenous ablation Surgery
Mild $C_{3\,S}$ Severe $C_{3\,S}$	D Suprainguinal significant O	O	Normal	Conservative treatment: Compression, Venoactive drugs Failure of conservative Treatment: Angioplasty and stenting
$C_{4\text{-}6}$	D Suprainguinal significant O	O	Normal	Conservative treatment: Compression, Venoactive drugs Failure of conservative Treatment: Angioplasty and stenting
C_{6} Non healing ulcer Recurrent ulcer	D	R + O	Sometimes Normal	Conservative treatment: Compression, Venoactive drugs (see Chapter 18) Failure of conservative treatment: Treat obstruction first, and if needed do Valve transfer

A: anatomic; P: pathophysiologic; S: superficial; D: deep; P*: perforator; R: reflux; O: obstruction.

in PTS. In the absence of prospective randomized studies comparing perforating vein surgery with compression the pros and cons remain debatable. Nevertheless if surgery is to be performed there is a large agreement for using SEPS.[16] Ultrasound-guided foam sclerotherapy may also be used for treating incompetent lower leg perforating veins in PTS and has been demonstrated to be an effective treatment option.[17] Radiofrequency and specially laser mediated perforating vein ablation have become common practice and may replace other forms of perforating vein treatment where the technology is available even though the evidence may still be quite weak (see Chapter 19).[18]

Deep venous reconstructive surgery for treating reflux remains controversial (see Chapter 10). Among those that are in favour, there is a consensus for selecting only patients in whom conservative treatment has failed to heal the ulcer or patients with recurrent ulcers and other severe symptoms in the absence of contraindications (inefficient calf pump, severe and non-correctible coagulation disorder). As valvuloplasty is rarely feasible in PTS, transplantation of an axillary vein segment with valves or vein transposition are the recommended techniques to be used. Maleti et al have reported promising midterm results with the construction of a neo-valve in PTS.[19] Results provided by the different procedures are reported in the Chapters devoted to deep venous obstruction and reflux. However, surgery for deep venous reflux or obstruction has to be performed in specialized units with highly trained personnel.

Exercise training program for patients with acute DVT does not increase the risk of developing pulmonary emboli and does not negatively affect clinical outcome. There appears to be a trend towards improved outcome with prescribed exercise in one study.[20] Another exercise program appeared to improve ejection fraction and muscle strength but not valvular reflux, venous clinical severity scores or quality of life. Further studies are needed in order to clarify this issue (Table I).[21]

References

1. Partsch H. Compression therapy of the legs. A review. J Dermatol Surg Oncol 1991;17:799–805.

2. Partsch H, Winiger J, Lun B. Compression stockings reduce occupational leg swelling. Dermatol Surg 2004;30:737–43, discussion 743.

3. Magnusson MB, Nelzén O, Risberg B, Sivertsson R. A colour Doppler ultrasound study of venous reflux in patients with chronic leg ulcers. Eur J Vasc Endovasc Surg 2001;21:353–60.

4. Ting AC, Cheng SW, Ho P, Poon JT, Wu LL, Cheung GC. Reduction in deep vein reflux after concomitant subfascial endoscopic perforating vein surgery and superficial vein ablation in advanced primary chronic venous insufficiency. J Vasc Surg 2006;43:546–50.

5. Ciostek P, Michalak J, Noszczyk W. Improvement in deep vein haemodynamics following surgery for varicose veins. Eur J Vasc Endovasc Surg 2004;28:473–8.

6. Blume J, Langenbahn H, Champvallins M. Quantification of oedema using the volometer technique: therapeutic application of Daflon 500 mg in chronic venous insufficiency. Phlebology 1992;2(suppl):37–40.

7. de Jongste AB, Jonker JJ, Huisman MV, ten Cate JW, Azar AJ. A double blind three center clinical trial on the short-term efficacy of 0-(beta-hydroxyethyl)-rutosides in patients with post-thrombotic syndrome. Thromb Haemost 1989;62:826–9.

8. Menyhei G, Acsady G, Hetenyi A, Dubeaux D, Rado G. Chronobiology and clinical activity of Daflon 500 mg in chronic venous insufficiency. Phlebology 1994; Suppl 1:15–8.

9. Neglén P, Raju S. Intravascular ultrasound scan evaluation of the obstructed vein. J Vasc Surg 2002;35:694–700.

10. Raju S, Owen S Jr, Neglen P. The clinical impact of iliac venous stents in the management of chronic venous insufficiency. J Vasc Surg 2002;35:8–15.

11. Neglén P, Raju S. Balloon dilation and stenting of chronic iliac vein obstruction: technical aspects and early clinical outcome. J Endovasc Ther 2000;7:79–91.

12. Raju S, Neglen P. High prevalence of nonthrombotic iliac vein lesions in chronic venous disease: a permissive role in pathogenicity. J Vasc Surg 2006;44:136–43, discussion 144.

13. Raju S, Darcey R, Neglén P. Unexpected major role for venous stenting in deep reflux disease. J Vasc Surg 2010;51:401–8, discussion 408.

14. Kurklinsky AK, Bjarnason H, Friese JL, Wysokinski WE, McBane RD, Misselt A, *et al.* Outcomes of venoplasty with stent placement for chronic thrombosis of the iliac and femoral veins: single-center experience. J Vasc Interv Radiol 2012;23:1009–15.

15. Puggioni A, Kistner RL, Eklof B, Lurie F. Surgical disobliteration of postthrombotic deep veins—endophlebectomy—is feasible. J Vasc Surg 2004;39:1048–52, discussion 52.

16. Pierik EG, van Urk H, Hop WC, Wittens CH. Endoscopic versus open subfascial division of incompetent perforating veins in the treatment of venous leg ulceration: a randomized trial. J Vasc Surg 1997;26:1049–54.

17. Masuda EM, Kessler DM, Lurie F, Puggioni A, Kistner RL, Eklof B. The effect of ultrasound-guided sclerotherapy of incompetent perforator veins on venous clinical severity and disability scores. J Vasc Surg 2006;43:551–6, discussion 556–7.

18. O'Donnell TF. The role of perforators in chronic venous insufficiency. Phlebology 2010;25:3–10.

19. Maleti O, Lugli M. Neovalve construction in postthrombotic syndrome. J Vasc Surg 2006;43:794–9.

20. Kahn SR, Shrier I, Kearon C. Physical activity in patients with deep venous thrombosis: a systematic review. Thromb Res 2008;122:763–73.

21. Kahn SR, Shrier I, Shapiro S, Houweling AH, Hirsch AM, Reid RD, *et al.* Six-month exercise training program to treat post-thrombotic syndrome: a randomized controlled two-centre trial. CMAJ 2011;183:37–44.

CHAPTER 17

Management of leg ulcers

Compression Therapy

The management of venous hypertension and tissue edema with compression bandaging has been shown to encourage healing of venous leg ulcers. A Cochrane review concluded that compression increases ulcer-healing rate compared with no compression.[1] In addition, high grade compression is more effective than low grade compression.[1] A four-layer bandage system may produce a pressure of 42.5 mmHg at the ankle level that can be maintained for one week. After weekly bandaging with four-layer bandages, 110 of 148 legs with chronic venous ulcers healed within 12 weeks.[2] Four-layer bandaging is probably the most widely used method in the UK whereas short-stretch bandaging is the system of choice in most of continental Europe. Several randomized trials have been published that compare different bandaging systems. Some have shown a benefit for ulcer healing using 4 layer bandages *versus* short stretch bandages, while others have shown no difference.[3-5] A weakness of all available trials is that the exerted pressure at the ankle level was not measured.

Surgery for Superficial Veins

Superficial venous surgery without compression can heal venous ulcers.[6] A randomized controlled trial (ESCHAR) allocated patients with isolated superficial venous reflux and mixed superficial and deep venous reflux to either compression treatment with multilayer compression bandage (N.=258) *versus* a combination of compression treatment and superficial ablative surgery (N.=242).[7] Multilayer compression bandaging and surgery reduced the rate of recurrence at 12 months when compared with compression alone without affecting the healing rate.

When deep venous reflux is segmental and limited, and is associated with superficial venous reflux and leg ulcers, superficial venous surgery abolishes deep venous reflux in 50% of limbs and healing can be achieved at 12 months in 77% of leg ulcers.[8]

The fact that superficial vein surgery is of benefit in patients with segmental deep vein incompetence was also shown in the ESCHAR RCT, where there also seemed to be a trend favoring surgery in patients with axial reflux.[9] Low recurrence rate of ulcers in that group was also shown in a prospective series from Sweden where also perforators had been treated with SEPS in addition to superficial vein surgery.[10]

In the multicenter EVRA trial 450 patients with venous leg ulcers were assigned to receive compression therapy and undergo early (within 2 weeks) endovenous ablation of superficial venous reflux (early-intervention group) or to receive compression therapy alone, with consideration of endovenous ablation deferred until after the ulcer was healed or until 6 months after randomization if the ulcer was unhealed (deferred-intervention group).[11] The time to ulcer healing was shorter in the early-intervention group than in the deferred-intervention group; more patients had healed ulcers with early intervention (hazard ratio for ulcer healing, 1.38; 95% confidence interval [CI]: 1.13 to 1.68; P=0.001). The median time to ulcer healing was 56 days (95% CI: 49 to 66) in the early-intervention group and 82 days (95% CI: 69 to 92) in the deferred-intervention group. The authors concluded that early endovenous ablation of superficial venous reflux resulted in faster healing of venous leg ulcers and more time free from ulcers than deferred endovenous ablation. Subgroup analysis whether the results are applicable to patients with axial deep reflux is not available.

There is enough evidence today promoting early surgical intervention or endovenous ablation for superficial venous incompetence, in combination with effective compression therapy, in patients with venous ulcers, and there is no need to wait for the ulcer to heal. A cross-sectional study performed in Sweden has demonstrated that this approach makes a difference on a population basis, with the prevalence of venous ulcers being reduced by almost one half over a 14-year period.[12]

Surgery for Incompetent Perforating and Deep Veins

Ligation of perforating veins (SEPS), deep venous reconstruction and balloon dilatation with stenting has been discussed in Chapters 9, 10 and 11. It is reserved for patients whose ulcers do not respond to compression or compression combined with veno-active drugs.

Oral medications in combination with compression

Several studies have investigated the effect of oral medications when used as adjuvants to compression therapy.

A meta-analysis of 7 RCTs involving 659 patients demonstrated that at 8-24 weeks the healing rate increased from 40% in the compression group to 64% in the compression plus pentoxifylline group (RRR 33%; 95% CI:25% to 45%; P<0.001).[13]

A meta-analysis of 5 RCTs involving 616 patients demonstrated that at 6 months ulcers healed faster when the phlebotonic micronised purified flavonoid fraction was combined with a two-layer compression than compression alone. The RRR was reported as 32% (95% CI: 3% to 70%; P=0.03). This difference was present from the second month and was associated with a shorter time to healing (16 weeks *versus* 21 weeks; P=0.0034).[14]

Four RCTs involving 488 patients and a meta-analysis demonstrated an increased rate of healing at 2-3 months when sulodexide was combined with compression than compression alone. The overall healing rate increased from 32% in the compression group to 54% in the compression plus sulodexide group (RRR 41%; 95% CI: 27% to 52%; P<0.001).[15-19]

Intermittent pneumatic compression (IPC) (see also Chapter 7)

Four studies involving a total of 142 patients of which three were RCTs compared the effect of IPC on ulcer healing when used in conjunction with compression. Despite the small number of patients, considering all four studies IPC appeared to increase the incidence of ulcer healing from 35% to 71% (RR for healing 2.23; 95% CI: 1.50 to 3.33).[20-23]

A recent systematic review identified seven RCTs (including 367 patients in total).[24] However, only one trial was at low risk of bias having reported adequate randomization, allocation concealment and blinded outcome assessment. The authors concluded that IPC may increase healing compared with no compression, but it is not clear whether it increases healing when added to treatment with bandages, or if it can be used instead of compression bandages.

A RCT compared two different IPC regimens on ulcer healing.[25] 104 patients were randomized to rapid (3 cycles per minute) or slow (1 cycle per 3 minutes) compression IPC devices for one hour daily. Both devices applied the same pressure and no other compression treatment was applied during the study period. Complete healing occurred in 45 of the 52 patients treated with rapid IPC, and in 32 of the 52 patients treated with slow IPC. Life table analysis showed that the proportion of ulcers healed at six months was 86% in the group treated with the rapid IPC compared with 61% in the group treated with slow IPC (p=0.003, log-rank test). The mean rate of healing per day in the rapid IPC group was found to be faster compared to the slow IPC group (0.09 cm^2 *vs.* 0.04 cm^2, P=0.0002).

On the basis of the available evidence the current recommendation is that IPC can be used as alternative method when other methods have failed.[26] Further trials are required to determine the optimum type of IPC and optimum type of compression stockings it should be combined with.

Topical treatment

Regarding the topical preparations of antiseptics and other agents, there is some evidence to support the use of cadexomer iodine but there is no evidence to support the routine use of honey- or silver-based products. In respect to the effectiveness of povidone-iodine, peroxide-based preparations, ethacridine lactate, chloramphenicol, framycetin, mupirocin, ethacridine or chlorhexidine in healing venous leg ulceration further good quality research is needed to draw definite conclusions.[27] Because of the increasing problem of bacterial resistance to antibiotics it is recommended that antibacterial preparations to be used only when there is evidence of clinical infection and not for bacterial colonization. At present, no evidence is available to support the routine use of systemic antibiotics in promoting healing of venous leg ulcers.[27] Also, in a single study, the adjunctive use of propolis ointment was found to

increase the efficacy of the short stretch bandage compression stocking making this combination more effective than Unna's boot compression alone.[28]

While comparisons of different autolytic agents (hydrogel *versus* paraffin gauze; Dextranomer beads *versus* EUSOL and BWD *versus* non-adherent dressings) and Larvae *versus* hydrogel all showed statistically significant results for numbers of wounds debrided, the overall small number of participants, small number of studies and lack of meta-analysis precludes any strong conclusions of benefit.[29] Further trials including larger number of patients with follow up to healing are required.

The benefit from the therapeutic ultrasound (either high or low frequency) in the improvement of venous leg ulcers healing is uncertain as most of the existing evidence is not of good quality due to risk of bias and imprecision.[30]

The use of bilayer artificial skin in conjunction with compression bandaging increases the venous ulcer healing compared with a simple dressing plus compression. Nevertheless, further research is needed to assess whether other forms of skin grafts increase ulcer healing.[31]

The use of hyperbaric oxygen therapy for chronic venous leg ulcers may reduce the size of the wound.[32]

References

1. Cullum N, Nelson EA, Fletcher AW, Sheldon TA. Compression for venous leg ulcers. Cochrane Database Syst Rev 2001;(2):CD000265.

2. Blair SD, Wright DD, Backhouse CM, Riddle E, McCollum CN. Sustained compression and healing of chronic venous ulcers. BMJ 1988;297:1159–61.

3. Nelson EA, Iglesias CP, Cullum N, Torgerson DJ; VenUS I collaborators. Randomized clinical trial of four-layer and short-stretch compression bandages for venous leg ulcers (VenUS I). Br J Surg 2004;91:1292–9.

4. Partsch H, Damstra RJ, Tazelaar DJ, Schuller-Petrovic S, Velders AJ, de Rooij MJ, *et al.* Multicentre, randomised controlled trial of four-layer bandaging versus short-stretch bandaging in the treatment of venous leg ulcers. Vasa 2001;30:108–13.

5. Franks PJ, Moody M, Moffatt CJ, Martin R, Blewett R, Seymour E, *et al.*; Wound Healing Nursing Research Group. Randomized trial of cohesive short-stretch versus four-layer bandaging in the management of venous ulceration. Wound Repair Regen 2004;12:157–62.

6. Scriven JM, Hartshorne T, Thrush AJ, Bell PR, Naylor AR, London NJ. Role of saphenous vein surgery in the treatment of venous ulceration. Br J Surg 1998;85:781–4.

7. Barwell JR, Davies CE, Deacon J, Harvey K, Minor J, Sassano A, *et al.* Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. Lancet 2004;363:1854–9.

8. Adam DJ, Bello M, Hartshorne T, London NJ. Role of superficial venous surgery in patients with combined superficial and segmental deep venous reflux. Eur J Vasc Endovasc Surg 2003;25:469–72.

9. Gohel MS, Barwell JR, Taylor M, Chant T, Foy C, Earnshaw JJ, *et al.* Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomised controlled trial. BMJ 2007;335:83.

10. Nelzén O, Fransson I. True long-term healing and recurrence of venous leg ulcers following SEPS combined with superficial venous surgery: a prospective study. Eur J Vasc Endovasc Surg 2007;34:605–12.

11. Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, Cullum N, *et al.*; EVRA Trial Investigators. A Randomized Trial of Early Endovenous Ablation in Venous Ulceration. N Engl J Med 2018;378:2105–14.

12. Forssgren A, Nelzén O. Changes in the aetiological spectrum of leg ulcers after a broad-scale intervention in a defined geographical population in Sweden. Eur J Vasc Endovasc Surg 2012;44:498–503.

13. Jull A, Arroll B, Parag V, Waters J. Pentoxifylline for treating venous leg ulcers. Cochrane Database Syst Rev 2007;(3):CD001733.

14. Smith PC. Daflon 500 mg and venous leg ulcer: new results from a meta-analysis. Angiology 2005;56(Suppl 1):S33–9.

15. Coccheri S, Scondotto G, Agnelli G, Aloisi D, Palazzini E, Zamboni V; Venous arm of the SUAVIS (Sulodexide Arterial Venous Italian Study) Group. Randomised, double blind, multicentre, placebo controlled study of sulodexide in the treatment of venous leg ulcers. Thromb Haemost 2002;87:947–52.

16. Scondotto G, Aloisi D, Ferrari P, Martini L. Treatment of venous leg ulcers with sulodexide. Angiology 1999;50:883–9.

17. Kucharzewski M, Franek A, Koziolek H. Treatment of venous leg ulcers with sulodexide. Phlebologie 2003;32:115–20.

18. Zou YX, Feng X, Jing ZP. Efficacy and safety of sulodexide in the treatment of venous ulcers of leg. Pharm Care Res 2007;7:22–4. [Yaoxue Fuwu Yu Yanjiu]

19. Coccheri S, Bignamini AA. Pharmacological adjuncts for chronic venous ulcer healing. Phlebology 2016;31:366–7.

20. Pekanmäki K, Kolari PJ, Kiistala U. Intermittent pneumatic compression treatment for post-thrombotic leg ulcers. Clin Exp Dermatol 1987;12:350–3.

21. Hazarika EZ, Wright DE. Chronic leg ulcers. The effect of pneumatic intermittent compression. Practitioner 1981;225:189–92.

22. Dillon RS. Treatment of resistant venous stasis ulcers and dermatitis with the end-diastolic pneumatic compression boot. Angiology 1986;37:47–56.

23. Smith PC, Sarin S, Hasty J, Scurr JH. Sequential gradient pneumatic compression enhances venous ulcer healing: a randomized trial. Surgery 1990;108:871–5.

24. Nelson EA, Mani R, Thomas K, Vowden K. Intermittent pneumatic compression for treating venous leg ulcers. Cochrane Database Syst Rev 2011;(2):CD001899.

25. Nikolovska S, Arsovski A, Damevska K, Gocev G, Pavlova L. Evaluation of two different intermittent pneumatic compression cycle settings in the healing of venous ulcers: a randomized trial. Med Sci Monit 2005;11:CR337–43.

26. Kalodiki E. Use of intermittent pneumatic compression in the treatment of venous ulcers. Future Cardiol 2007;3:185–91.

27. O'Meara S, Al-Kurdi D, Ologun Y, Ovington LG, Martyn-St James M, Richardson R. Antibiotics and antiseptics for venous leg ulcers. Cochrane Database Syst Rev 2014;1:CD003557.

28. Kucharzewski M, Kózka M, Urbanek T. Topical treatment of non-healing venous leg ulcer with propolis ointment. Evid Based Complement Alternat Med 2013;2013:254017.

29. Gethin G, Cowman S, Kolbach DN. Debridement for venous leg ulcers. Cochrane Database Syst Rev 2015;9:CD008599.

30. Cullum N, Liu Z. Therapeutic ultrasound for venous leg ulcers. Cochrane Database Syst Rev 2017;5:CD001180.

31. Jones JE, Nelson EA, Al-Hity A. Skin grafting for venous leg ulcers. Cochrane Database Syst Rev 2013;1:CD001737.

32. Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE, Weibel S. Hyperbaric oxygen therapy for chronic wounds [Review]. Cochrane Database Syst Rev 2015;6:CD004123.

CHAPTER 18

Prevention of leg ulcer recurrence

Introduction

In western countries venous leg ulcers occur in approximately 0.3% of the adult population.[1-3] The combined prevalence of active and healed ulcers is around 1%.[4, 5] The vast majority of previously published studies are related to ulcer healing rate. Only a few studies relate to the problem of ulcer recurrence after healing and these are often not very robust. The incidence of recurrent ulceration after healing with conservative techniques varies in different studies from 24% to 69% at 12 months.[6-9] Various studies have reported ulcer recurrence rates of 28-57% at 2 years,[9, 10] 21-38% at 3 years[11, 12] and 48% at 5 years.[13]

Compression therapy

Compression therapy is believed to counteract the effects of venous hypertension and to control edema. There is fairly strong circumstantial evidence that not wearing compression stockings for various reasons is associated with ulcer recurrence.[10, 14-16]

A recent Cochrane review of compression to prevent ulcer recurrence,[17] identified four trials with 979 participants. One trial in patients with recently healed venous ulcers compared recurrence rates with and without compression and found that compression significantly reduced ulcer recurrence at six months.[18] Two trials compared high-grade compression hosiery with moderate-grade compression hosiery.[12, 19] The first study found no significant reduction in recurrence at five years with high-grade compression hosiery compared with moderate-grade compression,[19] while the second study assessed ulcer recurrence at three years and found that high-grade compression hosiery reduced recurrence compared with moderate-grade compression.[12] There was significantly higher compliance with moderate-grade compression than with high-grade compression hosiery in one and no significant difference in the second trial. A third trial found no statistically significant difference in recurrence rates between two types of compression hosiery with moderate-grade compression.[14] No trials of compression bandages for preventing ulcer recurrence were identified.

The recurrence rate was 2-20 times higher in noncompliant patients during an observation period of 1-156 months and the cumulative recurrence rate at 5 years was 29-31% and 83-100% in compliant and noncompliant "limbs," respectively.[15, 16, 20] McDaniel *et al.*[13] used univariate analysis of risk factors to show that poor compliance for use of stockings did not reach a significant level but tended to be associated with recurrence. Compliance for compression therapy has been included in the venous clinical severity score (VCSS).[21]

It is difficult to assess a patient's daily compliance. Lack of compliance can be due to several factors including lack of cosmetic appeal, discomfort, inability to put stockings on, allergy to material, lack of financial resources, and lack of patient understanding and education about their condition and these need to be addressed to improve compliance. Studies have shown great variations of compliance to stocking use ranging from 37-84%.[13, 15, 16, 22] Wearing compression hosiery was found to be positively associated with the participants' knowledge of the cause of their condition (P=0.002), higher self-efficacy scores (P=0.026) and lower depression scores (P=0.009).[23] In one study commonly cited factors, such as age, gender, difficulty in applying stockings and cosmetic appearance did not have any influence on stocking use.[24]

Compression is probably of value but the poor compli-

ance in many patients fails to allow satisfactory decrease of ulcer recurrence rates when analyzed by intention-to-treat in a population of ulcer patients.

Bed rest and leg elevation

Leg elevation and bed rest have been recommended to control edema, preferably with the leg elevated above the heart level. Having both full ankle movement and full mobility reduces the risk of recurrence.[25] Leg elevation, compression hosiery, high levels of self-efficacy and strong social support will help prevent recurrence.[26] However, there is no supportive evidence that either prevent ulcer recurrence.

Exercise and body weight

Morbid obesity is an increasing problem in the general population and has been linked to skin changes and ulcers of venous type with or without detection of CVD.[27-29] Greater body weight has been shown to be statistically associated with poor healing of venous ulcers,[30] and proportionally more patients with ulcer have been found to be obese compared with the general population in a study performed in Sweden.[31] Exercise and weight loss are often recommended to prevent or delay recurrence of venous ulcers but there is no conclusive evidence that they are effective.

Calf muscle pump failure

The function of the calf muscle pump is greatly influenced by the mobility of the ankle joint. It has been shown that ankle range of motion decreases with increasing severity of clinical symptoms of CVD, and is associated with poor calf pump function as measured by plethysmography.[22, 32] It would seem that improvement of the calf muscle pump by exercise would increase venous return and subsequently help the clinical situation. One study indicated that the amount of moderately strenuous activity in the study group was low compared with that of the general Dutch population; 35% of the patients did not have a 10-minute walk even once a week.[33]

Correction of underlying venous incompetence

Ulcer recurrence rates have been reported after correcting underlying venous pathology by superficial or deep venous interventions, but few appropriate prospective studies are available to indicate that correction of CVD results in a reduced incidence of ulcer recurrence.

Open surgery

The ESCHAR Study compared surgery and compression with compression alone in prevention of venous ulceration. This RCT concluded that overall 24-week healing rates were similar in the two groups, but the 12-month ulcer recurrence rate was significantly reduced in the group with compression and surgery compared with those with compression alone (12% and 28%, respectively).[34] Rates of ulcer recurrence at four years were 56% for the compression group and 31% for the compression plus surgery group ($P<0.01$).[35]

In a prospective, non-randomized study McDaniel *et al.*,[13] reported a significantly reduced cumulative recurrence rate at 48 months in limbs treated by a variety of operations compared with those treated without surgery (26% and 52%, respectively). The study found that patients who were not candidates or who elected to forego surgery had a 3.4 times higher rate of ulcer recurrence compared to surgical patients.

Subfascial endoscopic perforator surgery (SEPS)

Sundukov *et al.*[36] reported ulcer recurrence in 2 out of 68 patients treated with subfascial endoscopic perforator surgery (SEPS). From the level of evidence available by now it seems that SEPS, used as part of a treatment regimen for severe CVI, benefits most patients in the short term regarding ulcer healing and the prevention of ulcer recurrence.[37] It seems that SEPS combined with superficial venous surgery leads to healing with a low recurrence rate in patients with open and healed venous ulcers (8% and 18% at 3 and 5 years, respectively).[38] A prospective randomized trial performed by van Gent *et al.*[39] comparing the treatment of venous ulcers with SEPS and compression therapy *versus* compression therapy alone, revealed during follow-up of a mean of 29 months in the surgical group and 26 months in the conservative group, that in the surgical group, the ulcer-free rate was 72%, whereas in the conservative group this rate was 53% ($P=0.11$). Some studies are showing similar low recurrence rates for venous ulcers after SEPS procedure (2.4% after 1 year follow-up period).[40]

Thermal ablation of incompetent superficial and perforating veins

Recently published studies showed that combined treatment with compression therapy and thermal ablation of incompetent superficial and perforating veins significantly reduces ulcer recurrence compared to historical controls (4.8% and 67%, respectively).[41] Sufian *et al.* reported ulcer recurrence in one out of 18 patients with 25 venous ul-

cerations one year after superficial venous laser ablation.[42] Similar results were reported by Marroco *et al.*: 4.7% recurrence rate in patients with C5 disease and 20% cumulative non-healing and recurrence rate in patients with C6 disease.[43] Teo *et al.*[44] reported no recurrence at one year in 44 patients with non-healing venous ulcers treated with endovenous thermal ablation.

Ultrasound guided foam sclerotherapy (UGFS)

There is growing evidence that foam sclerotherapy could be beneficial to patients with venous ulcerations not just in terms of healing but in preventing venous ulcers also. One study showed that the 24-week healing rate was 71.1% whilst one- and four-year recurrence rates were 4.7% and 28.1%, respectively.[45] Pang et al reported a 4.9% Kaplan-Meier estimate of recurrence at 2 years after UGFS of superficial venous reflux,[46] and Darvall *et al.* reported a 7% recurrence rate in 27 patients with venous ulcers treated with UGFS and compression.[47]

Valve repair

Deep venous incompetence appears to be a major determinant for ulcer recurrence. The ulcer recurrence rate after superficial venous surgery or perforating veins ligation is markedly increased by associated deep venous disease. Cumulative recurrence rates at 4-5 years are reported to be 67-100% and 6-29% in limbs with and without deep venous involvement respectively.[13, 48, 49] Good results following superficial surgery with or without perforator interruption have been published, which makes surgery a treatment option to be considered also in the group of patients with combined superficial and deep vein incompetence.[35, 38]

It seems logical that deep valve repair should be beneficial, but the proof is circumstantial.[50] Prospective, randomized studies do not exist. Long-term follow up by Masuda and Kistner[51] after deep valve reconstruction reported a 40% ulcer recurrence over a long period but many had long ulcer-free periods for 5-10 years. Results after valve repair were superior for primary disease compared to PTS in some studies,[51, 52] but Raju *et al.*,[53] reported an approximately 40% 6-year cumulative ulcer recurrence rate after deep venous reconstruction, which was similar in primary and secondary disease.

In one study the ulcer recurrence rate, within the 5 year follow-up was 18% after autogenous venous valve reconstruction.[54] Lugli *et al.*[55] reported 3 ulcer recurrences in 37 patients who were treated by neovalve construction because of presence of venous ulcer and deep venous incompetence.

Venous stenting in deep reflux disease

Raju and Neglen[56] reported a freedom of ulcer recurrence in legs with healed ulcers (C5) to be 88% at 5 years follow up period after venous stenting in deep reflux disease.

Venous surgery produces beneficial results in prevention of venous ulcers not only in pure venous ulcerations, but also in patients with accompanying arterial disease (4% and 11%, respectively).[57] Treatment should intuitively change underlying pathophysiology to prevent recurrence. A decreased ulcer recurrence rate has been observed in limbs with less reflux as measured by Venous Filling Index (VFI) using air plethysmography where limbs with VFI of less than 4.0 mL/sec *versus* those with more than 4.0 mL/sec were associated with 28% and 53% recurrence, respectively.[13] Another study reported that the recurrence rate was only 14% if a venous filling time (VFT) more than 5 sec could be maintained compared with 45% when VFT was less than 5 sec.[58]

It is concluded that ulcer healing outcome data and physiological test results are circumstantial but they support surgery in patients who have recurrence during conservative treatment or in those who are unable to comply with conservative measures.

Prevention of recurrent DVT

Studies to evaluate whether prevention of recurrent DVT decreases the risk of ulcer recurrence have not been performed. Patients with chronic venous ulceration have a 41% prevalence of thrombophilia (2-30 times higher than the normal population), similar to that reported for patients with previous DVT.[59] In a series of patients who had a stent placed for venous obstruction, 51% of those with post-thrombotic occlusion had thrombophilia although thrombophilia was also found in 23% of patients considered to have primary disease.[60] It has been suggested that patients with venous ulceration may have subclinical thrombosis or undetected distal macro- and even microvascular disease due to thrombophilia. It is possible that long-term anticoagulation in selected patients may prevent recurrent thrombosis and decrease the risk of recurrent ulceration.

References

1. Brand FN, Dannenberg AL, Abbott RD, Kannel WB. The epidemiology of varicose veins: the Framingham Study. Am J Prev Med 1988;4:96–101.

2. Widmer LK. Peripheral venous disorders. Prevalence and socio-medical importance. Observations in 4529 apparently healthy persons. Basle III study. Bern, Switzerland: Hans Huber; 1978. p. 1-90.

3. Andersson E, Hansson C, Swanbeck G. Leg and foot ulcer prevalence and investigation of the peripheral arterial and venous circulation in a randomised elderly population. An epidemiological survey and clinical investigation. Acta Derm Venereol 1993;73:57–61.

4. Wille-Jørgensen P, Jørgensen T, Andersen M, Kirchhoff M. Postphlebitic syndrome and general surgery: an epidemiologic investigation. Angiology 1991;42:397–403.

5. Nelzén O, Bergqvist D, Lindhagen A. Leg ulcer etiology—a cross sectional population study. J Vasc Surg 1991;14:557–64.

6. Monk BE, Sarkany I. Outcome of treatment of venous stasis ulcers. Clin Exp Dermatol 1982;7:397–400.

7. Moffatt CJ, Dorman MC. Recurrence of leg ulcers within a community ulcer service. J Wound Care 1995;4:57–61.

8. Vowden KR, Barker A, Vowden P. Leg ulcer management in a nurse-led, hospital-based clinic. J Wound Care 1997;6:233–6.

9. Milic DJ, Zivic SS, Bogdanovic DC, Perisic ZD, Milosevic ZD, Jankovic RJ, *et al.* A randomized trial of the Tubulcus multilayer bandaging system in the treatment of extensive venous ulcers. J Vasc Surg 2007;46:750–5.

10. Erickson CA, Lanza DJ, Karp DL, Edwards JW, Seabrook GR, Cambria RA, *et al.* Healing of venous ulcers in an ambulatory care program: the roles of chronic venous insufficiency and patient compliance. J Vasc Surg 1995;22:629–36.

11. Marston WA, Carlin RE, Passman MA, Farber MA, Keagy BA. Healing rates and cost efficacy of outpatient compression treatment for leg ulcers associated with venous insufficiency. J Vasc Surg 1999;30:491–8.

12. Milic DJ, Zivic SS, Bogdanovic DC, Golubovic MD, Lazarevic MV, Lazarevic KK. A randomized trial of class 2 and class 3 elastic compression in the prevention of recurrence of venous ulceration. J Vasc Surg Venous Lymphat Disord 2018;6:717–23.

13. McDaniel HB, Marston WA, Farber MA, Mendes RR, Owens LV, Young ML, *et al.* Recurrence of chronic venous ulcers on the basis of clinical, etiologic, anatomic, and pathophysiologic criteria and air plethysmography. J Vasc Surg 2002;35:723–8.

14. Franks PJ, Oldroyd MI, Dickson D, Sharp EJ, Moffatt CJ. Risk factors for leg ulcer recurrence: a randomized trial of two types of compression stocking. Age Ageing 1995;24:490–4.

15. Mayberry JC, Moneta GL, Taylor LM Jr, Porter JM. Fifteen-year results of ambulatory compression therapy for chronic venous ulcers. Surgery 1991;109:575–81.

16. Dinn E, Henry M. Treatment of venous ulceration by injection sclerotherapy and compression hosiery: A 5-Year study. Phlebology 1992;7:23–6.

17. Nelson EA, Bell-Syer SE. Compression for preventing recurrence of venous ulcers. Cochrane Database Syst Rev 2012;8:CD002303.

18. Vandongen YK, Stacey MC. Graduated compression elastic stockings reduce lipodermatosclerosis and ulcer recurrence. Phlebology 2000;15:33–7.

19. Nelson EA, Harper DR, Prescott RJ, Gibson B, Brown D, Ruckley CV. Prevention of recurrence of venous ulceration: randomized controlled trial of class 2 and class 3 elastic compression. J Vasc Surg 2006;44:803–8.

20. Moffatt C, Kommala D, Dourdin N, Choe Y. Venous leg ulcers: patient concordance with compression therapy and its impact on healing and prevention of recurrence. Int Wound J 2009;6:386–93.

21. Rutherford RB, Padberg FT Jr, Comerota AJ, Kistner RL, Meissner MH, Moneta GL. Venous severity scoring: an adjunct to venous outcome assessment. J Vasc Surg 2000;31:1307–12.

22. Kiev J, Noyes LD, Rice JC, Kerstein MD. Patient compliance with fitted compression hosiery monitored by photoplethysmography. Arch Phys Med Rehabil 1990;71:376–9.

23. Finlayson K, Edwards H, Courtney M. The impact of psychosocial factors on adherence to compression therapy to prevent recurrence of venous leg ulcers. J Clin Nurs 2010;19:1289–97.

24. Jull AB, Mitchell N, Arroll J, Jones M, Waters J, Latta A, *et al.* Factors influencing concordance with compression stockings after venous leg ulcer healing. J Wound Care 2004;13:90–2.

25. Brooks J, Ersser SJ, Lloyd A, Ryan TJ. Nurse-led education sets out to improve patient concordance and prevent recurrence of leg ulcers. J Wound Care 2004;13:111–6.

26. Finlayson K, Edwards H, Courtney M. Relationships between preventive activities, psychosocial factors and recurrence of venous leg ulcers: a prospective study. J Adv Nurs 2011;67:2180–90.

27. Arfvidsson B, Eklof B, Balfour J. Iliofemoral venous pressure correlates with intraabdominal pressure in morbidly obese patients. Vasc Endovascular Surg 2005;39:505–9.

28. Padberg F Jr, Cerveira JJ, Lal BK, Pappas PJ, Varma S, Hobson RW 2nd. Does severe venous insufficiency have a different etiology in the morbidly obese? Is it venous? J Vasc Surg 2003;37:79–85.

29. Danielsson G, Eklof B, Grandinetti A, Kistner RL. The influence of obesity on chronic venous disease. Vasc Endovascular Surg 2002;36:271–6.

30. van Rijswijk L; Multi-Center Leg Ulcer Study Group. Full-thickness leg ulcers: patient demographics and predictors of healing. J Fam Pract 1993;36:625–32.

31. Nelzén O, Bergqvist D, Lindhagen A. Venous and non-venous leg ulcers: clinical history and appearance in a population study. Br J Surg 1994;81:182–7.

32. Back TL, Padberg FT Jr, Araki CT, Thompson PN, Hobson RW 2nd. Limited range of motion is a significant factor in venous ulceration. J Vasc Surg 1995;22:519–23.

33. Heinen MM, van der Vleuten C, de Rooij MJ, Uden CJ, Evers AW, van Achterberg T. Physical activity and adherence to compression therapy in patients with venous leg ulcers. Arch Dermatol 2007;143:1283–8.

34. Barwell JR, Davies CE, Deacon J, Harvey K, Minor J, Sassano A, *et al.* Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. Lancet 2004;363:1854–9.

35. Gohel MS, Barwell JR, Taylor M, Chant T, Foy C, Earnshaw JJ, *et al.* Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomised controlled trial. BMJ 2007;335:83.

36. Sundukov IV, Lipnitskiĭ EM, Alekberzade AV, Kapustniak DA, Lagunov MV, Krest'ianova IA. [Endoscopic subfascial dissection of perforating veins of lower legs in patients with venous ulcers]. Vestn Ross Akad Med Nauk 2009;(2):18–20.

37. Luebke T, Brunkwall J. Meta-analysis of subfascial endoscopic perforator vein surgery (SEPS) for chronic venous insufficiency. Phlebology 2009;24:8–16.

38. Nelzén O, Fransson I. True long-term healing and recurrence of venous leg ulcers following SEPS combined with superficial venous surgery: a prospective study. Eur J Vasc Endovasc Surg 2007;34:605–12.

39. van Gent WB, Hop WC, van Praag MC, Mackaay AJ, de Boer EM, Wittens CH. Conservative versus surgical treatment of venous leg ulcers: a prospective, randomized, multicenter trial. J Vasc Surg 2006;44:563–71.

40. Lin SD, Cheng KH, Lin TM, Chang KP, Lee SS, Sun IF, *et al.* Management of the primary varicose veins with venous ulceration with assistance of endoscopic surgery. Ann Plast Surg 2006;56:289–94.

41. Harlander-Locke M, Lawrence P, Jimenez JC, Rigberg D, DeRubertis B, Gelabert H. Combined treatment with compression therapy and ablation of incompetent superficial and perforating veins reduces ulcer recurrence in patients with CEAP 5 venous disease. J Vasc Surg 2012;55:446–50.

42. Sufian S, Lakhanpal S, Marquez J. Superficial vein ablation for the treatment of primary chronic venous ulcers. Phlebology 2011;26:301–6.

43. Marrocco CJ, Atkins MD, Bohannon WT, Warren TR, Buckley CJ, Bush RL. Endovenous ablation for the treatment of chronic venous insufficiency and venous ulcerations. World J Surg 2010;34:2299–304.

44. Teo TK, Tay KH, Lin SE, Tan SG, Lo RH, Taneja M, *et al.* Endove-

nous laser therapy in the treatment of lower-limb venous ulcers. J Vasc Interv Radiol 2010;21:657–62.

45. Kulkarni SR, Slim FJ, Emerson LG, Davies C, Bulbulia RA, Whyman MR, *et al*. Effect of foam sclerotherapy on healing and long-term recurrence in chronic venous leg ulcers. Phlebology 2013;28:140–6.

46. Pang KH, Bate GR, Darvall KA, Adam DJ, Bradbury AW. Healing and recurrence rates following ultrasound-guided foam sclerotherapy of superficial venous reflux in patients with chronic venous ulceration. Eur J Vasc Endovasc Surg 2010;40:790–5.

47. Darvall KA, Bate GR, Adam DJ, Silverman SH, Bradbury AW. Ultrasound-guided foam sclerotherapy for the treatment of chronic venous ulceration: a preliminary study. Eur J Vasc Endovasc Surg 2009;38:764–9.

48. Gloviczki P, Bergan JJ, Rhodes JM, Canton LG, Harmsen S, Ilstrup DM; The North American Study Group. Mid-term results of endoscopic perforator vein interruption for chronic venous insufficiency: lessons learned from the North American subfascial endoscopic perforator surgery registry. J Vasc Surg 1999;29:489–502.

49. Burnand K, Thomas ML, O'Donnell T, Browse NL. Relation between postphlebitic changes in the deep veins and results of surgical treatment of venous ulcers. Lancet 1976;1:936–8.

50. Rosales A, Jørgensen JJ, Slagsvold CE, Stranden E, Risum Ø, Kroese AJ. Venous valve reconstruction in patients with secondary chronic venous insufficiency. Eur J Vasc Endovasc Surg 2008;36:466–72.

51. Masuda EM, Kistner RL. Long-term results of venous valve reconstruction: a four- to twenty-one-year follow-up. J Vasc Surg 1994;19:391–403.

52. Perrin M. Reconstructive surgery for deep venous reflux: a report on 144 cases. Cardiovasc Surg 2000;8:246–55.

53. Raju S, Fredericks RK, Neglèn PN, Bass JD. Durability of venous valve reconstruction techniques for "primary" and postthrombotic reflux. J Vasc Surg 1996;23:357–66, discussion 366–7.

54. Labas P, Cambal M. Autogenous venous valve construction. Int Angiol 2009;28:147–50.

55. Lugli M, Guerzoni S, Garofalo M, Smedile G, Maleti O. Neovalve construction in deep venous incompetence. J Vasc Surg 2009;49:156–62, 162.e1–2, discussion 162.

56. Raju S, Darcey R, Neglén P. Unexpected major role for venous stenting in deep reflux disease. J Vasc Surg 2010;51:401–8, discussion 408.

57. Obermayer A, Göstl K, Partsch H, Benesch T. Venous reflux surgery promotes venous leg ulcer healing despite reduced ankle brachial pressure index. Int Angiol 2008;27:239–46.

58. Kalra M, Gloviczki P. Surgical treatment of venous ulcers: role of subfascial endoscopic perforator vein ligation. Surg Clin North Am 2003;83:671–705.

59. Mackenzie RK, Ludlam CA, Ruckley CV, Allan PL, Burns P, Bradbury AW. The prevalence of thrombophilia in patients with chronic venous leg ulceration. J Vasc Surg 2002;35:718–22.

60. Neglén P, Raju S. In-stent recurrent stenosis in stents placed in the lower extremity venous outflow tract. J Vasc Surg 2004;39:181–7.

PUBLISHED ERRATUM

Correction to:
CHAPTER 4
Classification, severity scoring systems and assessment for efficacy of therapies

In *Management of chronic venous disorders of the lower limbs - Part I*, Int Ang 2018 June;37(3):193-201, the correct version of Chapter 4 is:

A. CEAP Classification and definition of terms

Introduction

The **CEAP** (**C**linical, **E**tiological, **A**natomical, **P**athophysiological) classification of CVDs was created at the American Venous Forum (AVF) meeting in Maui in 1994 by an international consensus committee, was published in 26 journals and books in nine languages, and has been accepted world-wide (Table I). It was revised in 2004.[1] The aim of CEAP has been to facilitate meaningful communication and description for all forms of CVD.[1] It should be emphasized that CEAP refers to one limb, does not contain any descriptive information about symptoms, and provides only a snapshot for the stage of CVD. It is not constructed to serve as a severity scoring system or a continuous monitoring tool. CEAP is not a static classification, and the limb can be reclassified at any time so that the record should be followed by the date it was performed.

Basic and Advanced CEAP

Basic CEAP includes all four components shown in Table I. The highest descriptor is used for clinical class. However, the C-classification alone does not adequately describe CVD. Most patients have a duplex ultrasound scan that provides data for E, A and P.

Advanced CEAP is used for researchers and for reporting standards as it is a more detailed and precise classification where the extent of disease can be allocated to one or more of 18 named venous segments.

Example

A patient presents with painful swelling of the leg and varicose veins, lipodermatosclerosis and active ulceration. Duplex ultrasound scanning on August 14, 2012 showed axial reflux in the great saphenous vein above and below the knee, incompetent calf perforating veins, and axial reflux in the femoral and popliteal veins. There were no signs of post-thrombotic obstruction.

Classification according to basic CEAP: C6s, Ep, As,p,d, Pr (2012-08-14, LII).

Classification according to advanced CEAP: C2,3,4b,6s, Ep, As,p,d, Pr2,3,18,13,14 (2012-08-14, LII).

Need to Further Develop the CEAP Classification

Venous claudication is an important symptom in chronic deep venous insufficiency but is poorly defined. In the next revision of CEAP, we need to better classify the severity of venous claudication as well as other symptoms of venous disease, for example as absent (0), mild (1), moderate (2) or severe (3). A treadmill could be used to evaluate venous claudication.

The pathophysiologic classification (P) with Pr, Po, and Pro for different anatomic locations is satisfactory, but we need an addition for the severity and not just the presence of reflux and obstruction. The AVF has created a CEAP Task Force to plan a new revision of CEAP which should be finalized to be introduced at its annual meeting in February 2019.

Definition of Terms

During development of the CEAP classification, it was realized that some descriptive and anatomical terms that are frequently used needed more precise definition. The Arctic Fjords workshop on CVD that took place on board M/S Trollfjord.in October 2007 created an extended list of definitions with a more precise common scientific language for investigation and management of CVD. During this conference, an interdisciplinary faculty of experts under the auspices of the European Venous Forum, American Venous Forum, International Union of Phlebology, International Union of Angiology, American College of Phlebology, and the Society for Vascular Surgery met to provide recommendations for fundamental venous terminology. The group met again in February 2008 at the AVF meeting in Charleston, South Carolina, USA to finalize the document, which was endorsed by the organizations and eventually published as the VEIN-Term consensus document in the Journal of Vascular Surgery.[2] The definitions produced are summarized in the Appendix at the end of this chapter.

TABLE I.—*Revised CEAP.*[1]

Clinical Classification
C0: no visible or palpable signs of venous disease.
C1: telangiectasiae or reticular veins.
C2: varicose veins.
C3: edema.
C4a: pigmentation and/or eczema.
C4b: lipodermatosclerosis and/or atrophie blanche.
C5: healed venous ulcer.
C6: active venous ulcer
S: symptoms including ache, pain, tightness, skin irritation, heaviness, muscle cramps, as well as other complaints attributable to venous dysfunction.
A: asymptomatic.
Etiologic Classification
Ec: congenital.
Ep: primary.
Es: secondary (post-thrombotic).
En: no venous etiology identified.
Anatomic Classification
As: superficial veins.
Ap: perforating veins.
Ad: deep veins.
An: no venous location identified.
Pathophysiologic Classification
Basic CEAP:
Pr: reflux.
Po: obstruction.
Pr,o: reflux and obstruction.
Pn: no venous pathophysiology identifiable.
Advanced CEAP
Same as Basic CEAP with the addition that any of 18 named venous segments can be utilized as locators for venous pathology:
Superficial veins:
1. Telangiectasies/reticular veins.
2. Great saphenous vein (GSV) above knee.
3. GSV below knee.
4. Small saphenous vein.
5. Non-saphenous veins.

Deep veins:
6. Inferior vena cava.
7. Common iliac vein.
8. Internal iliac vein.
9. External iliac vein.
10. Pelvic: gonadal, broad ligament veins, other.
11. Common femoral vein.
12. Deep femoral vein.
13. Femoral vein.
14. Popliteal vein.
15. Crural: anterior tibial, posterior tibial, peroneal veins (all paired).
16. Muscular: gastrocnemial, soleal veins, other.

Perforating veins:
17. Thigh.
18. Calf.

B. Disease Severity Scoring systems

The **V**enous **S**everity **S**coring (**VSS**) system has three components, Venous Disability Score (VDS), Venous Segmental Disease Score (VSDS) and Venous Clinical Severity Score (VCSS). It was developed in 2000 by an AVF ad hoc committee for venous outcomes assessment in order to supplement the CEAP classification by providing an instrument to assess a patient's condition during follow-up.[3] In contrast to CEAP, VSS includes symptoms as well as signs. It is an ideal tool to evaluate clinical outcome in randomized controlled trials, due to good intra- and inter-observer agreement and validation,[4, 5] applicability to all CEAP clinical classes, and ability to demonstrate subtle changes.[6]

The **Venous Disability Score (VDS)** has a maximum of 3, and is defined as: 0 = asymptomatic, 1 = symptomatic but able to carry out usual activities without compressive therapy, 2 = can carry out usual activities only with compression and/or limb elevation, 3 = unable to carry out usual activities even with compression and/or limb elevation. Usual activities are defined as the patient's activities *before* onset of disability from venous disease.

The **Venous Segmental Disease Score (VSDS)** combines the anatomic and pathophysiologic components of CEAP. VSDS is based on venous segmental involvement with major venous segments graded according to presence of reflux and/or obstruction. This scoring scheme is entirely based on venous imaging, primarily duplex ultrasound scanning but also venography, and weights 11 venous segments for their relative importance if involved with reflux and/or obstruction. There is one VSDS score for reflux (maximum score of 10) and another for obstruction (also a maximum score of 10).

The **Venous Clinical Severity Score (VCSS)** is based

on nine clinical characteristics (pain, varicose veins, venous edema, skin pigmentation, inflammation, induration, and number, duration and size of active ulcers), all graded from 0 to 3, with additional use of conservative therapy (compression and elevation) using the same points, to produce a 30 point-maximum flat scale.[2, 3]

Validation of the VSS scoring systems has been reported.[5, 7-9] It was shown that venous severity scores are significantly higher with advanced venous disease demonstrating correlation with anatomic extent. VCSS was equally sensitive and significantly better for measuring changes in response to superficial venous surgery than the CEAP clinical class, while VDS demonstrated comparable and even better performance.[5] It has been suggested that VCSS may have a more global application in determining the overall severity of venous disease.[9] A clear association has also been demonstrated between VCSS and duplex ultrasound findings, suggesting that it can be used as a screening tool.

VCSS was revised in 2010 to clarify its pain, inflammation and induration components.[10] For example, pain attribute was expanded to include other less severe symptoms and discomfort (aching, heaviness, fatigue, soreness, burning), presumed to be of venous origin. However, symptoms contribute only 3 points in the total score of 30 in the VCSS.

C. Scoring systems for assessing the post-thrombotic syndrome (PTS)

Three further scoring systems have been proposed that are specific to assess the PTS: **Brandjes**,[11] **Ginsberg**,[12] and **Villalta**.[13] All three use symptoms and signs, which are present or absent in the Brandjes system but graded in the other two. The Ginsberg system identifies the presence or absence of PTS without grading its severity. In contrast, the Villalta scale grades symptoms and signs and classifies patients into different PTS severity groups. A subcommittee on control of anticoagulation for the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis recommended that the Villalta scale should be used in clinical studies to diagnose and grade the severity of PTS because of its reliability, high correlation with relevant health outcomes, acceptability, responsiveness to changes in the severity of PTS, and successful use in clinical trials.[14, 15]

The Villalta Scale

This was first introduced in 1994 as a score for the PTS.[13] It scores both symptoms (cramps, pruritus, pain, heaviness, paresthesiae) and signs (pretibial edema, induration of the skin, hyperpigmentation, new venous ectasia, redness and pain during calf compression). It rates their severity from 0 (not present or minimal) to 3 (severe), for a maximum of 33 points, while the presence of a venous ulcer of the lower limb is also recorded. A total score of 15 or more on two consecutive visits or the presence of a venous ulcer indicates severe PTS. A total score of 5 to 14 on two consecutive visits indicates mild PTS. The higher score is used in patients with bilateral thrombosis. The Villalta Scale has been shown to be reproducible,[13] has good inter-observer reliability,[16] and is uniformly accepted to assess the PTS. A recent study compared the Villalta, Ginsberg, Brandjes, Widmer, CEAP and VCSS systems for interobserver reliability, association with ambulatory venous pressures, ability to assess severity of PTS, ability to assess change in condition over time, and association with patient-reported symptom severity.[17] Only the Villalta Score was able to fulfill all these criteria, findings that endorse its generalized use for PTS.

Using the Villalta scale is time-consuming as it requires both a clinician's and patient's assessment. This was compared with a visually-assisted form of Villalta Score in a series of 94 patients with DVT after a median follow-up of 3.5 years. The patients were provided with a comprehensive explanatory test in the local language (Norwegian) of all 11 elements of the Villalta Scale, showing their grading with an illustration for how to perform compression of the leg muscles. Agreement was very good (Kappa 0.82; 95% CI 0.71 to 0.94).[18]

D. REVAS Classification

Recurrent varicose veins are a common, complex and costly problem for both patients and physicians who treat venous diseases. It is frequently difficult to correctly classify the results of initial procedures performed by others and consequently to differentiate recurrent from residual varices. An international consensus meeting held in Paris in 1998 proposed definition, classification and management of **Re**current **Va**rices after **S**urgery (**REVAS**) to be used in combination with the CEAP classification. REVAS was evaluated for intra- and inter-observer reproducibility with a worldwide survey conducted in 2006.[19]

The **REVAS** classification considers six main items - sites, nature and sources of recurrence, magnitude of reflux and other possible contributory factors - shown in detail as follows:

T - Topographical sites of REVAS: g: groin, **t**: thigh, **p**: popliteal fossa, **l**: lower leg including ankle and foot, **o**: other).

S - Source of recurrence: 0: no source of reflux, **1**: pelvic/abdominal, **2**: sapheno-femoral junction, **3**: thigh perforating veins, **4**: **s**aphenopopliteal junction, **5**: popliteal fossa perforating veins, **6**: gastrocnemius veins, **7**: lower leg perforating veins.

R – Reflux: 1: clinical significance probable, **2**: clinical significance unlikely/uncertain. This estimate should be based on duplex ultrasound and venographic information, and evaluation as to how the degree of reflux relates to the overall clinical assessment.

N - Nature of sources

Ss - same site: **1**: technical failures, **2**: tactical failures, **3**: neovascularization, **4**: uncertain, **5**: mixed.

Ds - different (new) site **1**: persistent, known to have been present at the time of previous surgery, **2**: new, known to have been absent at the time of previous surgery, **3**: uncertain/not known, insufficient information at the time of previous surgery. This classifies the source as to whether or not it is the site of previous surgery and describes the cause and time-scale of recurrence.

C - Contribution from persistent incompetent saphenous trunks

AK: great saphenous (above knee), **BK**: great saphenous (below knee), **SSV**: small saphenous vein, **Ø**: neither/other.

Certain clinical data should be gathered and reported in the medical file:

F - Possible Contributory Factors; gF: General: Family history, obesity, pregnancy, hormones; **SF: Specific:** Primary deep venous incompetence, post-thrombotic syndrome, iliac vein compression, congenital (angiodysplasiae), lymphatic, calf pump dysfunction.

A reproducibility study of the eight items in REVAS found that intra-observer reproducibility was excellent for three items and good for five, and inter-observer reproducibility was good for six items and moderate for two.[19]

Classic surgery is no longer the most frequent operative procedure used for treating varicose veins in several countries. Chemical and thermal ablation on one hand and mini-invasive surgery including CHIVA and ASVAL on the other hand have greatly decreased the use of high ligation and stripping in most parts of the world. The previous acronym **REVAS** was only applicable to patients treated by surgery and not for these various new techniques. To deal with this change, recurrent and residual varices have been defined as shown in the terminology list below, and a new acronym **PREVAIT** (**PRE**sence of **V**arices (residual or recurrent) **A**fter **I**n**T**ervention) has been coined.

E. Assessment for efficacy of therapies

Benefit from treatment is best established by documenting improved signs and symptoms supported if possible by laboratory tests, recording all adverse effects of treatment, and with long-term follow-up, particularly if the target is to prevent progression.[20] To validate therapeutic efficacy requires properly powered studies to evaluate individual symptoms, signs and quality of life as well as morphological and functional venous parameters. The best method to assess clinical outcome after treatment for CVD depends to a great extent on the clinical presentation. It is difficult to evaluate improvement in cosmetic appearance or subjective symptoms such as cramps, itching, pain or fatigue. The patient's preference and acceptance of different treatments must be considered. It is much easier to accurately measure improvement of clinical signs as opposed to symptoms, such as diminishing size, healing or recurrence of an ulcer, or change in the circumference or volume of the extremity. Adverse effects from treatment must be recorded. Complications from surgery or sclerotherapy such as mortality, wound infection, superficial thrombophlebitis, cellulitis and nerve injury should be reported. Available methods to measure outcome are summarized below.

Evaluation of Signs

Telangiectases and reticular veins

Telangiectases and reticular veins can be assessed visually with photographs and diagrams.

Varicose veins

Varicose veins can be assessed visually with photographs and diagrams and by venous diameter and area assessments.

Edema and leg volume

An international consensus meeting considered that water displacement volumetry is the gold standard to prove and compare the efficacy of any treatment to reduce edema in CVD.[21] This is an old,[22, 23] but recently revisited noninvasive technique. It is reproducible provided measurement conditions are carefully standardized. Reproducibility was found to be 0.7% for two consecutive measurements by two different observers in the same leg, and its intra-individual variability was 1.3% under the same conditions.[24] Volumetry does not quantify edema but measures short-term variations which reflect changes in edema.[24-26] It allows accurate comparison of changes in the same leg over

time or with changing conditions as displayed by different amounts of edema: morning versus evening (vesperal) edema, supine or standing, resting or after exercise, before and after application of a venous tourniquet, before and after treatment, and at the beginning compared to the end of the follow-up period. Volumetry has demonstrated that legs that ache are those that swell the most,[27] that leg volume increases during daily activity and that this increase correlates with the severity of CVD;[24] that leg volume may increase during long distance flights, and that it diminishes after venous surgery[28] and after different drug treatments for venous or lymphatic insufficiency.[29-31] Other methods to assess edema include leg circumference measurements using a tape measure,[32-34] and opto-electronic volumetry.[35-37]

Skin changes and lipodermatosclerosis

The degree of induration caused by lipodermatosclerosis can be measured by different techniques including a high-resolution ultrasound B-scan[38] or a "durometer".[39, 40] Ankle joint movements can be quantified by goniometry.[41, 42] However, none of these techniques have been validated as yet for tools to compare therapeutic methods for CVD.

Ulcer healing

Complete healing of an ulcer is the most clinically significant outcome measurement for C6 patients,[20] and can be assessed with life-table analysis.[43] However, surface area reduction is a surrogate criterion that is used most often. The area of the ulcer can be measured by planimetry using its outline drawn on a transparent sheet, by scaled photography or by direct ultrasonic digitized measurements using a light pen.[44] Alternatively, it can be approximated by multiplying the two maximal perpendicular diameters to obtain an area in cm^2; and if this is then multiplied by $\pi/4$ then the calculated rectangular area is transformed to an ellipse. Gillman has published a method for calculating wound healing rates that corrects for differing sizes and shapes by dividing the ulcer area by its perimeter.[45] These changes in geometrical measurements per unit time are often used in clinical trials,[46, 47] although complete healing and the initial healing rate are the most common end-points used.[48, 49] The initial healing rate is defined as the rate of healing over the course of a first-time period. Percentage area decrease per unit time is not a valid end-point since this depends on the initial size of the ulcer.[46] However, the Gillman equation corrects for different initial ulcer sizes so that it meets the needs of clinical studies for standardized and comparable measurements.[49-51]

Ulcer recurrence

Ulcer recurrence is the most important end-point in C5 patients and can be assessed in long-term follow-up studies using cumulative ulcer-free survival times,[52, 53] or a life-table analysis of proportion without recurrence over time.[43]

Evaluation of Symptoms and Quality of Life

Symptoms

Symptoms can be evaluated by the clinician and/or self-reported by the patient. In the latter case, a questionnaire should be completed at leisure outside the doctor's office. This method is used most frequently for evaluation before, during and after treatment. Patients can be asked to give global ratings of improvement in symptoms or to use quantitative scales such as a Likert scale,[54] or a visual analog scale (VAS) (0-10 severity). Quantification of analgesic requirements can be useful as an additional assessment for pain.

Quality of life

Quality of life for patients with CVD has been assessed by generic and by disease-specific measures. The most frequently used generic measure is the Medical Outcome Study Short Form Health Survey (SF-36), a 36-item questionnaire that covers eight health dimensions including physical and social functioning, role limitations due to physical and emotional problems, mental health, vitality/energy, bodily pain and general health perceptions. The SF-36 has been used both in patients with varicose veins and with venous ulcers.[55, 56] Garratt *et al.*, used SF-36 to confirm a significantly lower quality of life in patients with varicose veins compared to an age-adjusted sample from the normal population,[55] and found that it satisfied strict psychometric criteria for validity and internal consistency. EuroQol-5D (EQ-5D) is a shorter form of a generic QoL questionnaire including only five questions to be answered by patients. This form has been validated against SF-36.[57]

Currently used generic quality of life questionnaires do not identify specific complaints from patients with CVD so that specific questionnaires have been developed to assess the functional and psychological effects of venous disease.[58, 59] The most recent of these is the Chronic Venous Insufficiency Questionnaire (CIVIQ) used by Launois *et al.*[59] This questionnaire has been validated in different languages and found to meet stringent psychometric criteria, including reliability, content, construct validity and responsiveness. CIVIQ has been used to show that quality of life scores were significantly lower in pa-

TABLE II.—*Outcome parameters for therapeutic studies in patients with CVD.*

CEAP "C" Class	Clinical (*)	Morphology	Function
C1	**Photographic analysis**		
C2	**idem C1**	**Duplex, MRV, CTV:** vein diameter and obstruction	**Duplex:** reflux and obstruction **Plethysmography:** Calf muscle pump function and outflow resistance
C3	**idem C1** **+ Volume measurement**	**idem C2**	**idem C2** **+ Venous Pressure:** venous pump impairment and obstruction
C4	**idem C3** **+ use of a** chromometer, durometer and goniometer	**idem C2** **+ US:** Skin thickness + **Capillaroscopy**: capillary density + **Microlymphography**	**idem C3** **+ $TcPO_2$** **+ laser Doppler fluxmetry**
C5	**idem C4** **+** ulcer recurrence rate	**idem C4**	**idem C4**
C6	**idem C5** + ulcer healing rate	**idem C4**	**idem C4**

*The standardized evaluation tools for symptoms, quality of life and clinical severity scores can be used for symptomatic patients with C1 to C6.

tients with CVD than in controls without venous disease in a randomized trial of 934 patients. Another specific questionnaire is the SQOR-V which provides fine clinical appraisal of all symptoms and consequences of CVD. Symptoms are graded 0-5. This is a proprietary VVSymQ instrument (simple software to ask patients about their symptoms at regular intervals). The correlation coefficient (r) of VVSymQ with VCSS was 0.33, with VEINES-QOL 0.72, and with duplex ultrasound findings 0.26.[60] The Aberdeen varicose vein questionnaire (AVVQ) has been frequently used in the UK.[61] Another specific questionnaire for varicose veins is the VVSymQ which is a patient reported outcome (PRO).[62] It is designed to evaluate symptom burden of varicose veins before and after treatment, and to assess the following symptoms: heaviness, aching, feeling of swelling, throbbing and itching. Health-related quality-of-life studies should be used in the future to assess overall outcome and justify treatment for CVD.[63, 64]

F. Morphological and functional measurements to assess disease severity

Several morphological and functional parameters related to reflux and obstruction of the venous system can be visualized and measured by duplex ultrasound, MRV, CTV, plethysmographic techniques, pressure measurements and microvascular techniques. Their use depends on the C class and on the specific target of the treatment assessed (Table II).

Methods to assess venous function listed in Table II have been extensively used in research but rarely in routine clinical practice for several reasons. First and foremost, they are unnecessary because clinical decisions can be made using morphological tests alone in most patients. Second, association between hemodynamic tests and CEAP class or VCSS is frequently moderate to poor. Third, functional tests are time-consuming and require specially trained personnel. However, there is increasing need in certain patients such as C4-6 classes and as recently shown in C0s, so that a comprehensive review of their application from the current literature is summarized in the next Chapter (Chapter 5), and appropriate recommendations are made in Chapter 6.

Appendix: defined terms

The term CVD includes all morphological and functional abnormalities of the venous system in the lower limbs. Some of these such as telangiectases are highly prevalent in the adult population, and in many cases the use of the term 'disease' is therefore inappropriate. The term chronic venous insufficiency (CVI) is entrenched in the literature and has been used to imply a functional abnormality (reflux, obstruction or a combination of both) of the venous system and it is usually reserved for patients with more advanced disease including those with edema (C3), skin changes (C4) or venous ulcers (C5/6). In the revised CEAP classification (1) the previous overall structure of CEAP has been maintained but more precise definitions have been added. The definitions used in the CEAP classification and the VEIN-Term consensus document are listed below in alphabetical order.

Atrophie blanche or white atrophy: Localized, often circular whitish and atrophic skin areas surrounded by dilated capillary spots and sometimes with hyperpigmentation. This is a sign of severe chronic venous disease. Scars of healed ulceration are excluded from this definition.

Axial reflux: uninterrupted retrograde venous flow from the groin to the calf.

Superficial: confined to the superficial venous system.
Deep: confined to the deep venous system.
Combined: involving any combination of the three venous systems (superficial, deep, perforating).
Chronic venous disease: morphological and functional abnormalities of the venous system of long duration manifested either by symptoms and/or signs indicating the need for investigation and/or care.
Chronic venous disorders: this term includes the full spectrum of morphological and functional abnormalities of the venous system.
Chronic venous insufficiency (C3-C6): a term reserved for advanced chronic venous disorders, which is applied to functional abnormalities of the venous system producing edema, skin changes or venous ulcers.
Corona phlebectatica: This term describes a fan-shaped pattern of numerous small intradermal veins on the medial or lateral aspects of the ankle and foot. This is commonly thought to be an early sign of advanced venous disease. Synonyms include malleolar flare and ankle flare.
Eczema: Erythematous dermatitis, which may progress to a blistering, weeping, or scaling eruption of the skin of the leg. It is often located near varicose veins but may be located anywhere in the leg. Eczema is usually caused by CVD or by sensitization to local therapy.
Edema: This is defined as a perceptible increase in volume of fluid in the skin and subcutaneous tissue characterized by indentation with pressure. Venous edema usually occurs in the ankle region, but it may extend to the leg and foot.
Endophlebectomy: removal of post-thrombotic residue from the venous lumen.
Lipodermatosclerosis (LDS): Localized chronic inflammation and fibrosis of the skin and subcutaneous tissues sometimes associated with scarring or contracture of the Achilles tendon. LDS is sometimes preceded by diffuse inflammatory edema of the skin which may be painful, and which is often referred to as hypodermitis. This condition needs to be distinguished from lymphangitis, erysipelas or cellulitis by their characteristic local signs and systemic features. LDS is a sign of severe chronic venous disease.
High ligation and division: ligation and division of the great saphenous vein (GSV) at its confluence with the common femoral vein, including interruption of all upper GSV tributaries.
Iliac vein obstruction syndrome: venous symptoms and signs caused by narrowing or occlusion of the common or external iliac vein.
May-Thurner syndrome: venous symptoms and signs caused by obstruction of the left common iliac vein due to external compression at its crossing posterior to the right common iliac artery.
Miniphlebectomy: removal of a vein segment through a small skin incision.
Neovascularization: presence of multiple new, small tortuous veins in anatomic proximity to a previous intervention.
Pelvic congestion syndrome: chronic symptoms, which may include pelvic pain, perineal heaviness, urgency of micturition, and postcoital pain, caused by ovarian and/or pelvic vein reflux and/or obstruction, and which may be associated with vulvar, perineal, and/or lower extremity varices.
Perforating vein ablation: disconnection or destruction of a perforating vein by mechanical, thermal or chemical means.
Perforating vein interruption: disconnection of a perforating vein by mechanical, thermal or chemical means.
Perforating vein ligation: interruption of a perforating vein by mechanical means.
Perforator incompetence: perforating veins with outward flow of abnormal duration.
Pigmentation: Brownish darkening of the skin initiated by extravasated blood, which usually occurs in the ankle region but may extend to the leg and foot.
Post-thrombotic syndrome: chronic venous symptoms and/or signs secondary to deep vein thrombosis.
PREVAIT: this acronym stands for **Pre**sence of **V**arices (residual or recurrent) **A**fter **I**n**T**ervention.
Recanalization: development of a new lumen in a previously obstructed vein.
Recurrent varicose veins: reappearance of varicose veins in an area previously treated successfully.
Residual varices: varicose veins remaining after treatment.
Reticular veins: Dilated bluish subdermal veins usually from 1 mm in diameter to less than 3 mm in diameter. They are usually tortuous. This excludes normal visible veins in people with transparent skin. Synonyms include blue veins, subdermal varices, and venulectasiae.
Sclerotherapy: obliteration of a vein by introduction of a chemical agent (liquid or foam).
Segmental reflux: localized retrograde flow in venous segments of any of the three venous systems (superficial, deep or perforating) in any combination in the thigh and/or the calf, BUT not in continuity from the groin to the calf.
Stripping: removal of a long venous segment, usually most of the GSV or the small saphenous vein by means of a device.
Telangiectasia: A confluence of dilated intradermal venules of less than 1 mm in caliber. Synonyms include spider veins, hyphen webs, and thread veins.
Varicocele: presence of scrotal varicose veins.
Varicose veins: Subcutaneous dilated veins equal to or more than 3 mm in diameter in the upright position. These may involve saphenous veins, saphenous tributaries, or non-saphenous veins. Varicose veins are usually tortuous, but refluxing tubular saphenous veins may be classified as varicose veins. Synonyms include varix, varices, and varicosities.
Venous ablation: removal or destruction of a vein by mechanical, thermal or chemical means.
Venous aneurysm: localized saccular or fusiform dilatation of a venous segment with a caliber at least 50% greater than the normal trunk.
Venous compression: narrowing or occlusion of the venous lumen as a result of extraluminal pressure.
Venous obstruction: partial or total blockage of venous flow.
Venous occlusion: total obliteration of the venous lumen.

Venous reflux: retrograde venous flow of abnormal duration in any venous segment:
Primary: caused by idiopathic venous valve dysfunction.
Secondary: caused by thrombosis, trauma, or mechanical, thermal, or chemical etiologies.
Congenital: caused by the absence or abnormal development of venous valves.
Venous signs: visible manifestations of venous disorders, which include dilated veins (telangiectasiae, reticular veins, varicose veins), leg edema, skin changes, and ulcers, as included in the CEAP classification.
Venous symptoms: complaints related to venous disease, which may include tingling, aching, burning, pain, muscle cramps, swelling, sensations of throbbing or heaviness, itching skin, restless legs, and leg tiredness and/or fatigue. Although not pathognomonic, these may be suggestive of chronic venous disease, particularly if they are exacerbated by heat or dependency in the day course, and relieved with leg rest and/or elevation.
Venous ulcer: Full thickness defect of the skin most frequently at the ankle that fails to heal spontaneously sustained by CVD.
Venous valvular incompetence: venous valve dysfunction resulting in retrograde venous flow of abnormal duration.

References

1. Eklöf B, Rutherford RB, Bergan JJ, Carpentier PH, Gloviczki P, Kistner RL, *et al.*; American Venous Forum International Ad Hoc Committee for Revision of the CEAP Classification. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg 2004;40:1248–52.

2. Eklof B, Perrin M, Delis KT, Rutherford RB, Gloviczki P; American Venous Forum; European Venous Forum; International Union of Phlebology; American College of Phlebology; International Union of Angiology. Updated terminology of chronic venous disorders: the VEIN-TERM transatlantic interdisciplinary consensus document. J Vasc Surg 2009;49:498–501.

3. Rutherford RB, Padberg FT Jr, Comerota AJ, Kistner RL, Meissner MH, Moneta GL. Venous severity scoring: an adjunct to venous outcome assessment. J Vasc Surg 2000;31:1307–12.

4. Vasquez MA, Wang J, Mahathanaruk M, Buczkowski G, Sprehe E, Dosluoglu HH. The utility of the Venous Clinical Severity Score in 682 limbs treated by radiofrequency saphenous vein ablation. J Vasc Surg 2007;45:1008–14, discussion 1015.

5. Kakkos SK, Rivera MA, Matsagas MI, Lazarides MK, Robless P, Belcaro G, *et al.* Validation of the new venous severity scoring system in varicose vein surgery. J Vasc Surg 2003;38:224–8.

6. Vasquez MA, Munschauer CE. Venous Clinical Severity Score and quality-of-life assessment tools: application to vein practice. Phlebology 2008;23:259–75.

7. Ricci MA, Emmerich J, Callas PW, Rosendaal FR, Stanley AC, Naud S, *et al.* Evaluating chronic venous disease with a new venous severity scoring system. J Vasc Surg 2003;38:909–15.

8. Meissner MH, Natiello C, Nicholls SC. Performance characteristics of the venous clinical severity score. J Vasc Surg 2002;36:889–95.

9. Passman MA, McLafferty RB, Lentz MF, Nagre SB, Iafrati MD, Bohannon WT, *et al.* Validation of Venous Clinical Severity Score (VCSS) with other venous severity assessment tools from the American Venous Forum, National Venous Screening Program. J Vasc Surg 2011;54(Suppl):2S–9S.

10. Vasquez MA, Rabe E, McLafferty RB, Shortell CK, Marston WA, Gillespie D, *et al.*; American Venous Forum Ad Hoc Outcomes Working Group. Revision of the venous clinical severity score: venous outcomes consensus statement: special communication of the American Venous Forum Ad Hoc Outcomes Working Group. J Vasc Surg 2010;52:1387–96.

11. Brandjes DP, Büller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, *et al.* Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet 1997;349:759–62.

12. Ginsberg JS, Hirsh J, Julian J, Vander LaandeVries M, Magier D, MacKinnon B, *et al.* Prevention and treatment of postphlebitic syndrome: results of a 3-part study. Arch Intern Med 2001;161:2105–9.

13. Villalta S, Bagatella P, Piccioli A, Lensing AW, Prins MH, Prandoni P. Assessment of validity and reproducibility of a clinical scale for the post-thrombotic syndrome. Haemostasis 1994;24(Suppl 1):158. [abstr]

14. Kahn SR. Measurement properties of the Villalta scale to define and classify the severity of the post-thrombotic syndrome. J Thromb Haemost 2009;7:884–8.

15. Kahn SR, Partsch H, Vedantham S, Prandoni P, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of post-thrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardization. J Thromb Haemost 2009;7:879–83.

16. Rodger MA, Kahn SR, Le Gal G, Solymoss S, Chagnon I, Anderson DR, *et al.* Inter-observer reliability of measures to assess the post-thrombotic syndrome. Thromb Haemost 2008;100:164–6.

17. Soosainathan A, Moore HM, Gohel MS, Davies AH. Scoring systems for the post-thrombotic syndrome. J Vasc Surg 2013;57:254–61.

18. Utne KK, Ghanima W, Foyn S, Kahn S, Sandset PM, Wik HS. Development and validation of a tool for patient reporting of symptoms and signs of the post-thrombotic syndrome. Thromb Haemost 2016;115:361–7.

19. Perrin M, Allaert FA. Intra- and inter-observer reproducibility of the Recurrent Varicose Veins after Surgery (REVAS) classification. Eur J Vasc Endovasc Surg 2006;32:326–32.

20. Vanscheidt W, Heidrich H, Jünger M, Rabe E; Phlebology Study Group of the Austrian Society of Dermatology; German Society of Angiology; German Society of Phlebology; Swiss Society of Phlebology. Guidelines for testing drugs for chronic venous insufficiency. Vasa 2000;29:274–8.

21. Fowkes FG, Bosanquet N, Franks PJ, *et al.* Proposal of a consensus statement the role of oedema-protective agents in the treatment of chronic venous insufficiency. Phlebology 1996;11:39–40.

22. Keates JS, FitzGerald DE. Limb volume and blood flow changes during the menstrual cycle. I. Limb volume changes during the menstrual cycle. Angiology 1969;20:618–23.

23. Keates JS, FitzGerald DE. Limb volume and blood flow changes during the menstrual cycle. II. Changes in blood flow and venous distensibility during the menstrual cycle. Angiology 1969;20:624–7.

24. Vayssairat M, Maurel A, Gouny P, Baudot N, Gaitz JP, Nussaume O. [Leg volumetry: a precise method for quantification in phlebology]. J Mal Vasc 1994;19:108–10. French.

25. Barnes MD, Mani R, Barrett DF, White JE. How to measure changes in oedema in patients with chronic venous ulcers. Phlebology 1992;7:31–5.

26. Vayssairat M, Maurel A, Gouny P, Veraart JC, Neumann HA. Leg volume measurements. Phlebology 1995;10:173–4.

27. Hands L, Collin J. Legs that swell and ache: volume changes during the day in health young adults. Br Med J (Clin Res Ed) 1984;288:447–8.

28. Speakman MJ, Collin J. Are swelling and aching of the legs reduced by operation on varicose veins? Br Med J (Clin Res Ed) 1986;293:105–6.

29. Nocker W, Diebschlag W, Lehmacher W. [A 3-month, randomized double-blind dose-response study with 0-(beta-hydroxyethyl)-rutoside oral solutions]. Vasa 1989;18:235–8. German.

30. Rehn D, Hennings G, Nocker W, Diebschlag W. Time course of the anti-oedematous effect of O-(beta-hydroxyethyl)-rutosides in healthy volunteers. Eur J Clin Pharmacol 1991;40:625–7.

31. Casley-Smith JR, Morgan RG, Piller NB. Treatment of lymphedema of the arms and legs with 5,6-benzo-[alpha]-pyrone. N Engl J Med 1993;329:1158–63.

32. te Slaa A, Mulder P, Dolmans D, Castenmiller P, Ho G, van der Laan L. Reliability and reproducibility of a clinical application of a simple technique for repeated circumferential leg measurements. Phlebology 2011;26:14–9.

33. Bérard A, Kurz X, Zuccarelli F, Ducros JJ, Abenhaim L. Reliability study of the Leg-O-Meter, an improved tape measure device, in patients with chronic venous insufficiency of the leg. VEINES Group. (Venous Insufficiency Epidemiologic and Economic Study). Angiology 1998;49:169–73.

34. Brodovicz KG, McNaughton K, Uemura N, Meininger G, Girman CJ, Yale SH. Reliability and feasibility of methods to quantitatively assess peripheral edema. Clin Med Res 2009;7:21–31.

35. Blume J, Langenbahn H, Champvallins M. Quantification of oedema using the volometer technique: therapeutic application of Daflon 500 mg in chronic venous insufficiency. Phlebology 1992;2(suppl):37–40.

36. Schmidt C. [Opto-electronic volumetry: another method for quantification of edema]. J Mal Vasc 1994;19:326–7. French.

37. Veraart JC, Neumann HA. Leg volume measurements with a modified optoelectronic measurement system. Phlebology 1995;10:62–4.

38. Gniadecka M. Dermal oedema in lipodermatosclerosis: distribution, effects of posture and compressive theraphy evaluated by high-frequency ultrasonography. Acta Derm Venereol 1995;75:120–4.

39. Falanga V, Bucalo B. Use of a durometer to assess skin hardness. J Am Acad Dermatol 1993;29:47–51.

40. Romanelli M, Falanga V. Use of a durometer to measure the degree of skin induration in lipodermatosclerosis. J Am Acad Dermatol 1995;32:188–91.

41. Dix FP, Brooke R, McCollum CN. Venous disease is associated with an impaired range of ankle movement. Eur J Vasc Endovasc Surg 2003;25:556–61.

42. Back TL, Padberg FT Jr, Araki CT, Thompson PN, Hobson RW 2nd. Limited range of motion is a significant factor in venous ulceration. J Vasc Surg 1995;22:519–23.

43. Nelzén O, Fransson I. True long-term healing and recurrence of venous leg ulcers following SEPS combined with superficial venous surgery: a prospective study. Eur J Vasc Endovasc Surg 2007;34:605–12.

44. Solomon C, Munro AR, Van Rij AM, Christie R. The use of video image analysis for the measurement of venous ulcers. Br J Dermatol 1995;133:565–70.

45. Gillman TH. Parameter for measurement of wound closure. Wounds 1990;3:95–101.

46. Martin M. [Dynamic wound healing profile of venous ulcus cruris]. Vasa 1994;23:228–33. German.

47. Ibbotson SH, Layton AM, Davies JA, Goodfield MJ. The effect of aspirin on haemostatic activity in the treatment of chronic venous leg ulceration. Br J Dermatol 1995;132:422–6.

48. Skene AI, Smith JM, Doré CJ, Charlett A, Lewis JD. Venous leg ulcers: a prognostic index to predict time to healing. BMJ 1992;305:1119–21.

49. Gorin DR, Cordts PR, LaMorte WW, Manzoian JO. The influence of wound geometry on the measurement of wound healing rates in clinical trials. J Vasc Surg 1996;23:524–8.

50. Teepe RG, Roseeuw DI, Hermans J, Koebrugge EJ, Altena T, de Coninck A, *et al.* Randomized trial comparing cryopreserved cultured epidermal allografts with hydrocolloid dressings in healing chronic venous ulcers. J Am Acad Dermatol 1993;29:982–8.

51. Margolis DJ, Gross EA, Wood CR, Lazarus GS. Planimetric rate of healing in venous ulcers of the leg treated with pressure bandage and hydrocolloid dressing. J Am Acad Dermatol 1993;28:418–21.

52. Zamboni P, Cisno C, Marchetti F, Mazza P, Fogato L, Carandina S, *et al.* Minimally invasive surgical management of primary venous ulcers vs. compression treatment: a randomized clinical trial. Eur J Vasc Endovasc Surg 2003;25:313–8.

53. Barwell JR, Davies CE, Deacon J, Harvey K, Minor J, Sassano A, *et al.* Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. Lancet 2004;363:1854–9.

54. Laurent R, Gilly R, Frileux C. Clinical evaluation of a venotropic drug in man. Example of Daflon 500 mg. Int Angiol 1988;7(Suppl):39–43.

55. Garratt AM, Ruta DA, Abdalla MI, Buckingham JK, Russell IT. The SF36 health survey questionnaire: an outcome measure suitable for routine use within the NHS? BMJ 1993;306:1440–4.

56. Price P, Harding K. Quality of life. Lancet 1995;346:445.

57. Brazier J, Roberts J, Tsuchiya A, Busschbach J. A comparison of the EQ-5D and SF-6D across seven patient groups. Health Econ 2004;13:873–84.

58. Franks PJ, Wright DD, Fletcher AE, Moffatt CJ, Stirling J, Bulpitt CJ, *et al.* A questionnaire to assess risk factors, quality of life, and use of health resources in patients with venous disease. Eur J Surg 1992;158:149–55.

59. Launois R, Reboul-Marty J, Henry B. Construction and validation of a quality of life questionnaire in chronic lower limb venous insufficiency (CIVIQ). Qual Life Res 1996;5:539–54.

60. Guex JJ, Zimmet SE, Boussetta S, Nguyen C, Taieb C. Construction and validation of a patient-reported outcome dedicated to chronic venous disorders: SQOR-V (specific quality of life and outcome response - venous). J Mal Vasc 2007;32:135–47.

61. Nesbitt C, Wilson WR, Lees TA, Stansby G. Interpretation of patient-reported outcome measures for varicose vein surgery. Phlebology 2012;27:173–8.

62. Paty J, Elash CA, Turner-Bowker DM. Content Validity for the VVSymQ® Instrument: A New Patient-Reported Outcome Measure for the Assessment of Varicose Veins Symptoms. Patient 2017;10:51–63.

63. Mackenzie RK, Lee AJ, Paisley A, Burns P, Allan PL, Ruckley CV, *et al.* Patient, operative, and surgeon factors that influence the effect of superficial venous surgery on disease-specific quality of life. J Vasc Surg 2002;36:896–902.

64. Lamping DL, Schroter S, Kurz X, Kahn SR, Abenhaim L. Evaluation of outcomes in chronic venous disorders of the leg: development of a scientifically rigorous, patient-reported measure of symptoms and quality of life. J Vasc Surg 2003;37:410–9.

Correction to:
CHAPTER 8
Venoactive drugs

In *Management of chronic venous disorders of the lower limbs - Part I*, Int Ang 2018 June;37(3):232-54, the correct version of Table VII in Chapter 8, p. 246, is:

TABLE VII.—*2018 update. Level of evidence that merits grade A or B for the effect of the main VADs on individual symptoms, signs and QoL with magnitude of effect: Number needed to treat (NNT) to benefit one patient or Standardized Mean Difference (SMD) are also shown. Only randomized placebo controlled trials and meta-analyses were considered.*

Symptom/sign	MPFF	Ruscus+ HMC+AA	Oxerutins	HCSE	Calcium dobesilate
Pain (NNT)	A (4.2)	A (5)	B	A (5.1)	B (1.4)
SMD	-0.25	-0.80	-1.07		
Heaviness (NNT)	A (2.9)	A (2.4)	B (17)		A (1)
SMD	-0.80	-1.23	-1.00		
Feeling of swelling (NNT)	A (3.1)	A (4)			
SMD	-0.99	-2.27			
Functional discomfort/ discomfort (NNT)	A (3.0)				B (4)
SMD	-0.87				
Leg fatigue (NNT)	NS	B			
SMD		-1.16			
Cramps (NNT)	B (4.8)	B/C	B		
SMD	-0.46		-1.7		
Paresthesiae (NNT)	B/C (3.5)	A (1.8)			B (2)
SMD	-0.11	-0.86			
Burning (NNT)	B/C	NS			
SMD	-0.46				
Pruritus/itching (NNT)		B/C		A (6.1)	
Tightness (NNT)	NS				
Restless legs (NNT)	NS				
Leg redness (NNT)	B (3.6)				
SMD	-0.32				
Skin changes (NNT)	A (1.6)				
Ankle circumference (NNT)	B	A	NS	A (4)	
SMD	-0.59	-0.74			
Foot or leg volume	NS	A	NS	A	A
SMD		-0.61		-0.34	-11.4
QoL	A				NS
SMD	-0.21				

NS: not significant.