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Comprehensive Review

Chronic Venous Disease of the Lower Extremities: A State-of-the Art Review

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ABSTRACT

Chronic venous disease is a common disease, the prevalence of which increases with age, and can cause debilitating symptoms that adversely affect the quality of life. The risk factors include family history, female sex, obesity, pregnancy, parity, and history of deep vein thrombosis. Moreover, it is associated with venous obstruction, reflux, or both, which, in turn, leads to ambulatory venous hypertension. Chronic venous disease is the leading cause of leg ulcers, which place a significant cost burden on the health care system. Compression therapy remains the cornerstone of treatment, particularly for more advanced disease. Superficial saphenous vein reflux can be associated with significant symptoms. Catheter techniques, both thermal and nonthermal, have demonstrated efficacy and safety in successful closure and symptom improvement. Deep vein obstruction can be broadly divided into thrombotic and nonthrombotic and can lead to symptomatic chronic venous disease. Recanalization using balloons and stents has been increasingly used and studied in such patients. It is critical to develop training opportunities and guidelines to improve evidence-based and appropriate care for cardiologists treating chronic venous disease.

Introduction

Lower-extremity venous disease is more prevalent than peripheral arterial disease[1] and can be associated with progressive leg discomfort, heaviness, edema, discoloration, and ulceration.[2-6] Its prevalence increases with age and can impose a significant burden on patients' quality of life.[7,8] In the United States (US), >25 million adults have chronic venous insufficiency (CVI).[8]

Studies on the prevalence of varicose veins have reported values as high as 57% in men and 73% in women.[8,9] In addition to age, the risk factors for chronic venous disease include positive family history, female sex, obesity, pregnancy and parity, history of deep vein thrombosis (DVT), and prolonged standing.[10-12] More severe manifestations of the disease, such as edema and ulcers, are more common in patients aged >65 years.[3]

The prevalence of venous leg ulcers can be as high as 2% of the population.[13,14] Venous insufficiency and varicose veins are widespread worldwide and are common in Western countries.[8,12,15] A US analysis of >20,000 individuals suggested that compared with Caucasians, African Americans present with more advanced venous disease and at a younger age.[16]

Chronic venous disease is the leading cause of leg ulcers.[17] Individuals with CVI and skin changes appear to be at a greater risk of developing venous ulceration.[18] Venous ulcers can frequently secrete exudate, be painful and malodorous, and take months to heal.[8,19,20] They are typically found in the gaiter zone of the legs (particularly at the medial and lateral aspects of malleoli and pretibial regions). They are associated with depression and poor quality of life.[21]

An analysis of the United Kingdom National Health Service data between 2007 and 2017 put the cost of care of patients with venous leg ulcers at >£2 billion per annum, with home nurse visits being a major driver of the cost.[22] In the US, an estimated 2.2% of Medicare beneficiaries have venous leg ulcers, with an annual payer burden of $14.9 billion.[23]

Over the past decade, there has been a dramatic rise in the number of endovascular venous procedures performed, with cardiology being one of the leading specialties providing care.[24]

Pathophysiology

From the mechanical standpoint, chronic venous disease can be associated with venous obstruction, reflux, or both, which is thought to

Abbreviations: CAC, cyanoacrylate adhesive closure; CEAP, clinical, etiology, anatomy, pathology; CVI, chronic venous insufficiency; DVT, deep vein thrombosis; EHIT, endothermal heat-induced thrombosis; EVLA, endovenous laser ablation; GSV, great saphenous vein; MTS, May-Thurner syndrome; SSV, small saphenous vein; VCSS, Venous Clinical Severity Score.

Keywords: chronic venous disease; chronic venous insufficiency; May-Thurner syndrome; postthrombotic syndrome; saphenous vein ablation; varicose veins.

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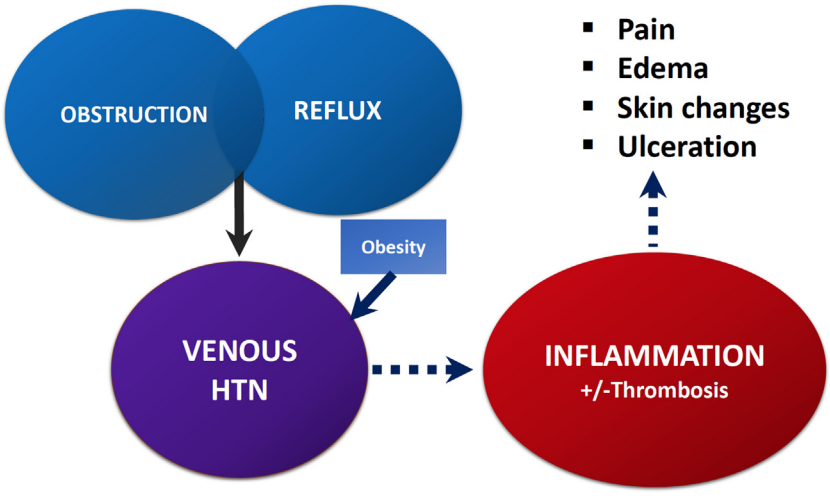

Central Illustration.
Schematic representation of the pathophysiology of chronic venous disease. HTN, hypertension.

result in ambulatory venous hypertension (Central Illustration).[25] This, in turn, can lead to inflammation.[26,27] Veins possess thinner media than arteries, are more distensible, and have unidirectional valves to assist with antegrade flow. The calf muscles (particularly, the soleus muscle) can act as pumps to assist in venous return.[28,29] Elevated venous pressures can lead to remodeling of the venous walls, leading to development of enlarged and tortuous veins (Figure 1).[30] Animal studies have demonstrated that venous hypertension is associated with valve remodeling and leukocyte infiltration.[31-33] Ambulatory venous hypertension is associated with greater damage and ulceration of leg skin.[34,35]

A human study in which venous congestion was induced led to greater expression of endothelin-1, a mediator of inflammation.[36] Alterations in the levels of matrix metalloproteinase may play a role in venous structure and function[37]; furthermore, in patients with lipodermatosclerosis, there is overexpression of matrix metalloproteinase[38] and venous ulcers, with poor healing.[39] There is greater dermal expression of mononuclear cells in patients with CVI,[40] and mast cell activation may be the etiology of pruritus, which is experienced by many patients.[41]

The levels of type III collagen, elastin, and laminin, important for elasticity, are decreased in varicose veins.[42-44] Vascular smooth muscles can lose their contractility.[45,46] Saphenous veins in humans with venous insufficiency and varicose veins showed less contractile responses to norepinephrine and angiotensin II.[47]

Increased endothelial permeability leads to extravasation of red blood cells, which then break down in the interstitium into ferric iron and hemoglobin, potentially leading to hemosiderin deposition, inflammation, and hyperpigmentation.[48,49]

The levels of inflammatory markers, such as C-reactive protein, interleukin 6, and d-dimer, are increased in blood collected from varicose veins.[50,51] Blood collected directly from limbs of patients with venous insufficiency has a lower white cell count than control blood samples, lending credence to the likelihood of white blood cell trapping.[52] Additionally, there is increased expression of the adaptor protein insulin receptor substrate-4 in the varicose veins of individuals with chronic venous disease[53]; however, its precise physiologic role is unclear.

There are data to support the importance of adequate venous return for cardiac functioning. For example, as far back as 1970, it was known that ligation of the inferior vena cava could lead to exertional dyspnea.[54] These patients could not adequately augment their cardiac index with exercise. It may be plausible that impaired venous return, such as that due to obstruction, can lead to exercise intolerance.[55] A single-center retrospective analysis of 85 patients with varicose vein disease who had undergone echocardiography suggested that they had lower tricuspid and mitral inflow velocities in early diastole but higher late diastolic velocities.[56] A prospective study (n = 129) reported similar findings, particularly with patients with more advanced venous disease.[57] This might suggest an increased compensatory atrial ejection fraction in patients with venous insufficiency. However, there were many confounders in this study, and it is unclear how well the characteristics of the control group were otherwise matched.

Utilizing the German Gutenberg Health Study database of >12,000 participants from a large single-center cohort, multivariate regression models showed that more advanced classes of venous insufficiency were associated with a higher 10-year risk of incident cardiovascular disease. More advanced classes of venous insufficiency were also associated with a greater risk of all-cause mortality.[58] The reason for this is unclear but may represent shared risk factors. Furthermore, the Framingham Heart Study noted an association between varicose veins and future atherosclerotic disease.[1] A statistically significant risk of coronary artery disease was noted in women with varicose veins. However, women with varicose veins had higher blood pressures and were more obese and sedentary.

Classification and symptom scores

The clinical, etiology, anatomy, pathology classification of the description of venous disease was developed in 1993, and the most recent revision was published in 2020.[59] The C (clinical) class, ranging from 1 to 6, is often utilized alone to describe the severity of the disease (Table 1). For example, corona phlebectatica, found in the ankle region (Figure 2), and hyperpigmentation (Figure 3) are included in the C4 class, which denotes advanced disease. Ulceration (C6 disease) is the most advanced class (Figure 4).

The E (etiology) class can be designated as primary, secondary, congenital, or as no cause identified. The A (anatomy) class refers to the site of pathology: deep, superficial, or perforator veins. The P (pathology) class includes reflux, obstruction, both, or none.

The Venous Clinical Severity Score (VCSS) is a validated symptom score[60] to measure the severity of venous disease and response to treatment.[61,62] It has been utilized in numerous venous intervention trials. In a prospective evaluation of patients with varicose veins, VCSS was strongly correlated with 2 other scores, the Aberdeen Varicose Vein

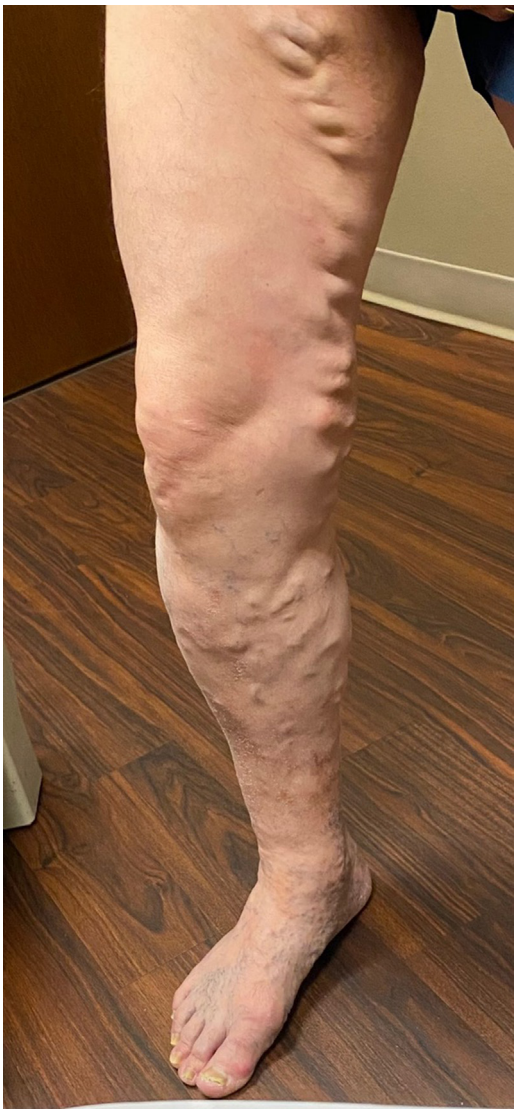

Figure 1.
Varicose veins in the anteromedial aspect of the thigh and calf extending into the ankle and foot.

Questionnaire and the Chronic Venous Insufficiency quality-of-life Questionnaire scores ($r = 0.7$, $P < .0001$).[63] A number of other venous quality-of-life or symptom severity scores, including Euro-QoL-5D[64] and VEINES-QoL, have been utilized.[65] The VVSym Q (HASTI) score incorporates 5 symptoms (heavy, aching, swelling, throbbing, and itching legs), with 5 possible responses ranging from all of the time (1) to none of the time (5). Therefore, higher scores indicate milder disease. Moreover, the score is correlated well with VEINES-QoL.[66]

The Villalta score has been most frequently used, to date, for diagnosing postthrombotic syndrome (PTS) and quantifying its severity.[67-69] It incorporates 5 patient-reported symptoms and 6 physician-reported findings into a single value (5-9, mild; 10-14, moderate; ≥15 or presence of venous ulcer, severe).

Table 1. The C classes of the clinical, etiology, anatomy, pathology classification system for chronic venous disease.

C class	Description
C_0	No visible or palpable signs of venous disease
C_1	Telangiectasias or reticular veins
C_2	Varicose veins
C_{2r}	Recurrent varicose veins
C_3	Edema
C_4	Changes in skin or subcutaneous tissue secondary to chronic venous disease
C_{4a}	Pigmentation or eczema
C_{4b}	Lipodermatosclerosis or atrophie blanche
C_{4c}	Corona phlebectatica
C_5	Healed
C_6	Active venous ulcer
C_{6r}	Recurrent active venous ulcer

Higher scores denote more severe forms of disease.
r, recurrent.

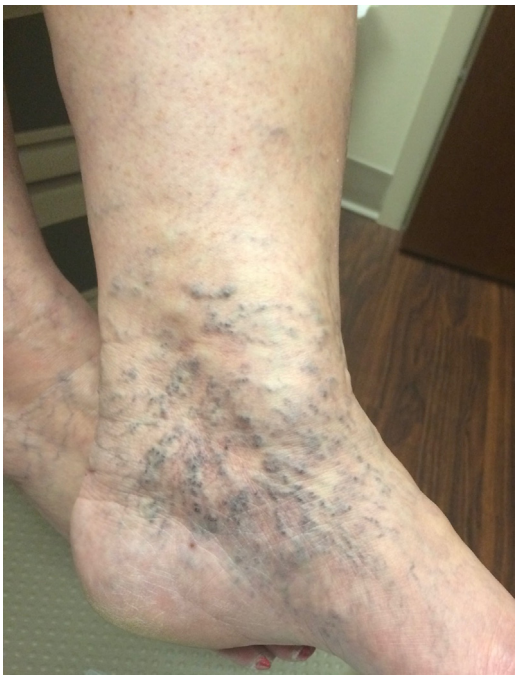

Figure 2.
Corona phlebectatica.

Compression therapy

Compression therapy is the cornerstone of the treatment of chronic venous disease,[70,71] particularly in its more advanced states.[72] Conrad Jobst's observation that hydrostatic pressures in a pool (which increase with depth) relieved the symptoms of venous insufficiency led to him developing compression stockings to emulate the same effect.[73] Fundamentally, compression should be graduated, applying higher pressures at the ankle level than more cephalad. The increased lower-limb venous pressure in patients with CVI that accompanies standing can drive fluid into interstitial spaces.[74,75] Although compression does not necessarily lower vein pressure, it can reduce interstitial pooling and, in turn, decrease inflammation.[76] The levels of inflammatory cytokines within venous ulcers decrease with compression therapy.[77]

Compression garments for the legs can take the form of stockings, bandages, Velcro wrap devices, pumps, or a combination.[78-80] Compression stockings can assist in improving venous return and reduce edema.[81] Compression for lower severity of venous disease (C2-C3) can decrease discomfort and edema, even as stand-alone therapy.[82] Compression, particularly at higher pressures (30-40 mm Hg), has been shown to improve venous ulcer healing and decrease recurrence.[79,80] There is no strong evidence that compression therapy improves procedural success after vein ablation; however, it may lower postprocedural edema and discomfort.[83]

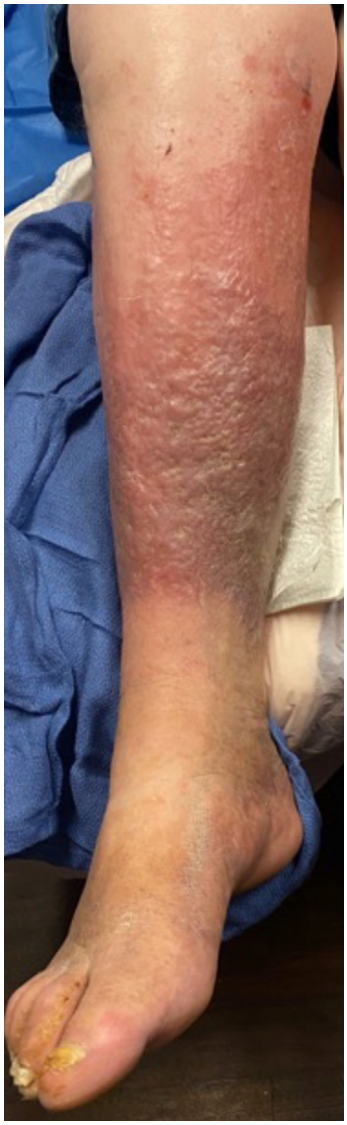

Figure 3.
Pigmentation, inflammation, and edema (lipodermatosclerosis).

The grades of compression measured at the ankle can be divided into light (<20 mm Hg), class I (21-30 mm Hg), class II (31-40 mm Hg), and class III (>40 mm Hg), although other classification systems exist.[80] Trials of varying quality have been performed to evaluate the potential role of compression therapy following saphenous vein thermal ablation and sclerotherapy. The main benefit appears to be to lessen post-procedural discomfort.[83,84]

Compression therapy improves venous ulcer healing and lowers recurrence.[72] Stronger compression pressures appear to be more effective.[85]

There are conflicting data on the efficacy of compression therapy in the prevention of PTS after acute lower-limb DVT. Compression therapy has been utilized after DVT; however, there have been mixed findings on its efficacy in lowering the rates of PTS. A prospective control study conducted in China did demonstrate lower rates of PTS at 24 months with knee-high compression stockings with a pressure of 30 to 40 mm Hg.[86] This is in contrast to the SOX trial, in which no benefit was observed. As a differentiator among studies, in the SOX trial, participants were mailed stockings 2 weeks following DVT and appeared to have lower compliance with compression.[87]

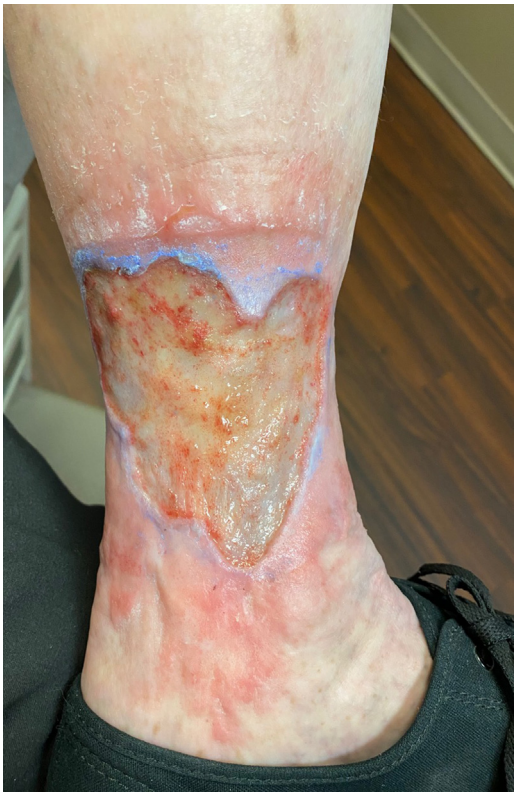

Figure 4.
Venous ulcer, with periulcer inflammation.

Chronic edema of the leg can be due to a number of causes, including lymphedema, venous obstruction or valvular reflux, congestive heart failure, or obesity. It is a known risk factor for recurrent cellulitis, and compression therapy was shown to significantly reduce recurrent cellulitis in a prospective randomized controlled trial (RCT).[88]

A proportion of patients with venous leg ulcers have concurrent peripheral arterial disease. There has been reluctance among some clinicians to recommend compression garments for so-called mixed arteriovenous ulcers. In a review of 10 studies of mixed ulcers, compression with stockings with a pressure of 20- to 30 mm Hg appeared to be both safe and beneficial for ulcer healing, with an ankle brachial pressure index (ABI) of $\geq$0.5.[89] Patients with lower ABIs may be considered for arterial revascularization prior to initiation of compression. In a small retrospective study (n = 20), patients with venous ulcers and ABI between 0.5 and 0.75 who underwent arterial revascularization first healed (on an average of 8 weeks) faster.[90] Similarly, a single-arm study suggested faster ulcer healing when arterial revascularization was performed, with 75% of ulcers healing by 10 weeks.[91]

A common challenge with compression therapy is noncompliance because of discomfort and inability to apply (don) and remove (doff).[92,93] At least 15% of the elderly cannot apply compression wear at all.[94] The presence of joint arthritis, frailty, and lack of flexibility may all contribute. In an analysis of 58 clinical studies, good compliance, defined as wearing compression >50% of the time, was reported in only two-thirds of patients (at a median of 12 months of follow-up).[95] The

Table 2. Venous ablation modalities.

Thermal	Nonthermal
Radiofrequency[99]	Adhesive[100]
Laser[101]	Mechanochemical[102]
	Chemical[103,104]

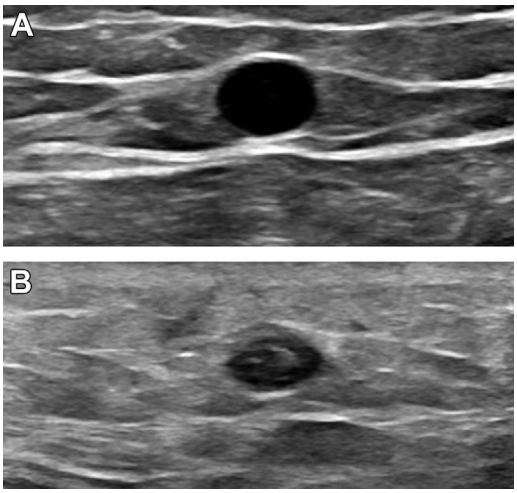

Figure 5.
(**A**) A transverse view of the great saphenous vein observed using duplex ultrasound. (**B**) The great saphenous vein 2 weeks after ablation, which was noncompressible and with hyperechoic content.

compliance was lower with higher-pressure (>25 mm Hg) stockings. In addition, in the US, compression hosiery is typically not reimbursed by health insurance.

Superficial venous reflux

Varicose veins are more common in women than in men.[1] Superficial valvular incompetence has been frequently found in individuals with CVI and venous ulcers.[96]

Various surgical techniques for the treatment of varicose veins have been used in the past century. A common approach has been flush ligation of the saphenofemoral junction, accompanied by stripping of the great saphenous vein (GSV) down to the knee level.[97,98] Additionally, stab phlebectomy can be performed concurrently or subsequently. In addition, the small saphenous vein (SSV) can be stripped in a similar manner. The complications of surgery include infection (<6%), DVT (<5%), and, rarely, saphenous or sural nerve injury.

Surgical stripping of the saphenous veins has largely been replaced, particularly in Western countries, by ablation (Table 2).[99-104] Thermal ablation is a percutaneous ultrasound-guided technique. The GSV is easily identifiable using duplex ultrasound (Figure 5) and can be interrogated, with the patient preferably in the standing position, to look for reflux (Figure 6). Endovenous laser ablation (EVLA) and radiofrequency ablation (RFA) are percutaneous modes of thermal ablation. Intravenously, both devices employ a low-profile fiber, directly delivering heat energy to the venous endothelium, leading to injury, thrombosis, and eventual fibrosis and occlusion of the vein. Using ultrasound guidance, a sheath is inserted into the target vein, through which the ablation fiber or catheter is advanced, ensuring that its tip is at least 2 cm distal to the deep venous system. Tumescent anesthesia is percutaneously injected around the target vein under ultrasound guidance, before application of thermal ablation. Tumescent preparations typically contain lidocaine, epinephrine, bicarbonate, and saline. They act as anesthetics and heat sinks for thermal ablation and protect surrounding structures from thermal injury. Epinephrine can constrict the vein, allowing for better contact with the ablation device.

Endovenous laser ablation was approved in the US in 2001. The EVLA devices currently available in the US market include VenaCure (AngioDynamics) and Vari-Lase (Teleflex). The laser wavelength can target water or hemoglobin.[105] The 1-year vein occlusion rates can surpass 90% with EVLA.[101]

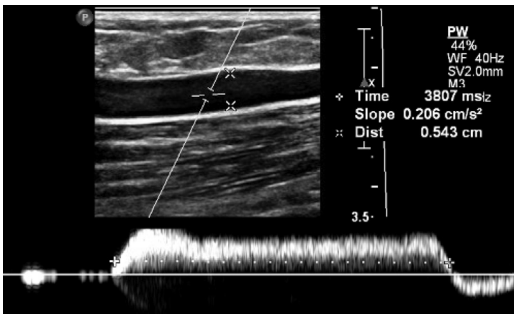

Figure 6.
Great saphenous vein reflux demonstrated using pulsed-wave Doppler. The reflux time in this case was 3807 milliseconds (>500 milliseconds is considered abnormal).

Radiofrequency ablation was approved for vein ablations in 1999. The RFA devices currently available in the US are ClosureFast (Medtronic) and Venclose (Becton Dickinson). Five-year follow-up after RFA in patients with venous insufficiency revealed an occlusion rate of 92% and sustained symptom improvement.[99] A 2016 meta-analysis revealed technical success rates of 89% for RFA and 85% for EVLA for the treatment of GSV incompetence.[106] Compared with RFA, there is probably greater postprocedural pain and bruising after EVLA.[107]

Both EVLA and RFA procedures may be complicated by endothermal heat-induced thrombosis in <1% cases, wherein a thrombus may propagate into the deep system.[108] However, the risk of pulmonary embolism as a result of endothermal heat-induced thrombosis is very low.[109]

A number of nonthermal ultrasound-guided methods have also been adopted to close the saphenous veins, including cyanoacrylate adhesive closure (CAC), mechanochemical ablation (MOCA), and foam sclerotherapy. These so-called nontumescent, nonthermal techniques have several advantages. They do not cause thermal injury such as burns or nerve damage. Without the need for tumescent application, they are typically less painful. The cyanoacrylate adhesive is delivered to the target vein percutaneously, where it rapidly polymerizes, leading to immediate closure and gradual fibrosis.

Sclerotherapy utilizes agents that once injected into a target vein, cause denaturation of surface proteins, luminal fibrosis, and obstruction.[110] Sclerosants have been used for telangiectasis as well as reticular and varicose veins.[111] Sclerotherapy improves the cosmetic appearance of varicose veins and, possibly, quality of life.[112] In larger veins (eg, 3 mm), the sclerosing agent can be injected as a foam to displace more blood and enhance contact between the sclerosant and venous wall.[113-115] Both air and CO_2 have been utilized for foam formation. Both sodium tetradecyl sulfate and polidocanol have been approved for use as sclerotherapy agents in the US. Both are detergents. The potential complications with their use include hyperpigmentation and telangiectatic matting. There is little evidence to suggest clinically significant right-to-left shunting of sclerosants.[116] There are reports of transient visual disturbance after sclerotherapy, although it is rare.[117] DVT or ulceration is also rare. Intra-arterial injection can lead to tissue necrosis.[118]

There are few robust RCTs on the relative efficacy of the types of sclerosants or formulations.[112,119] A proprietary formulation of 1% polidocanol named Varithena (Boston Scientific)[103] was approved by the Food and Drug Administration (FDA) in 2013. The efficacy of Varithena in reducing the symptoms of venous reflux was demonstrated in VANISH-2.[104] Proximal DVT occurred in 2.6% of patients.[120] A small multicenter, prospective RCT (n = 77) reported extension of Varithena into the common femoral vein in 5.1%, tibial or peroneal vein DVT in 2.6%, isolated gastrocnemius or soleus vein DVT in 7.7% of the patients, with no pulmonary emboli.[66]

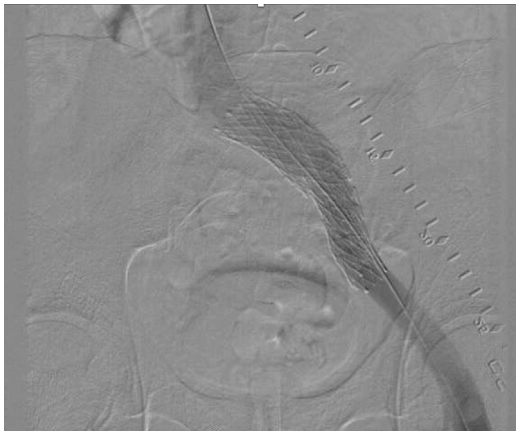

Figure 7.
Digital subtraction venogram of a left iliac vein stent after deployment. A radiopaque ruler (in conjunction with intravenous ultrasound) can be used to identify the optimal stent landing zone.

In MOCA (ClariVein; Merit Medical), a rotating metallic tip is used to scrape the venous endothelium at 3500 rpm while the operator simultaneously injects a sclerosant and slowly withdraws the rotating tip, leading to eventual endothelial fibrosis and vein occlusion.[102] The device is advanced through a small sheath under ultrasound guidance. At 1 year of follow-up, MOCA demonstrated an 88% GSV occlusion and significant improvement of venous symptoms.[102] However, MOCA can be complicated by hematoma, phlebitis and, rarely, DVT.[121] An RCT comparing MOCA with thermal ablation found lower GSV saphenous occlusion rates with MOCA but equivalent symptom score improvements at 1 year.[122]

VenaSeal CAC (Medtronic) was FDA approved in 2015. Similar to other ablation techniques, using ultrasound, a sheath is advanced into the saphenous vein, through which cyanoacrylate is delivered and manual compression applied. In a head-to-head RCT, at 5 years, CAC demonstrated equivalent GSV occlusion rates and relief of symptoms compared with RFA.[100] In both the arms of the study, ~64% of participants received adjunctive sclerotherapy at 6 months ($P = .77$).[123] A hypersensitivity (phlebitis-like) reaction was observed in up to 23% of CAC cases after the procedure.[124,125]

In a prospective, randomized, multicenter study of 798 patients treated for symptomatic varicose veins, the outcomes of EVLA, foam sclerotherapy, and surgery (high ligation and stripping) were compared.[126] GSV or SSV reflux was required for inclusion. Compared with the scores at baseline, all the groups demonstrated improvement of the Aberdeen Varicose Vein Questionnaire quality-of-life score at 5 years. The EVLA and surgery groups experienced greater improvement than the sclerotherapy group. However, it must be noted that in 31% of patients in the EVLA group, sclerotherapy was also utilized at least once. EVLA was the most cost effective. Another prospective, randomized trial compared EVLA, RFA, sclerotherapy, and surgical stripping for symptomatic GSV reflux. There was greater postprocedural pain in the surgery and EVLA groups. At 1 year, in the sclerotherapy group, GSVs remained patent in 16.3% of patients, significantly higher than that for the other modalities.[127] A 2021 Cochrane review of interventions for GSV reflux found equivalent technical success (GSV closure) up to 5 years and probably similar recurrence rates between RFA and EVLA.[128] EVLA and high ligation with stripping were probably superior to (ultrasound-guided) foam sclerotherapy in terms of technical success.

The Early Venous Reflux Ablation (EVRA) trial compared compression therapy alone with compression therapy plus early endovenous ablation in patients with venous ulcers and superficial reflux. It demonstrated faster ulcer healing and lower ulcer recurrence rates in the compression plus early ablation group.[129,130]

Varicose veins can recur in ~22% of cases after endovenous ablation (at 2 years of follow-up), with the most common underlying causes being recanalization of the GSV, followed by development of incompetence in the anterior accessory GSV.[131] Additional factors can be SSV and perforator reflux.[132] The potential contribution of pelvic vein disease has not been well studied.

There are limited quality data on the role of perforator ablation. Ablation of incompetent perforator veins may be considered in the setting of venous ulcer disease.[133] It is typically reserved for cases in which wound care, compression, and ablation of the saphenous veins have already been attempted, without improvement, and the perforator(s) of interest are directed toward the affected area. RFA, EVLT, and sclerotherapy have demonstrated efficacy.[134,135] Ultrasound-guided foam sclerotherapy appears to result in lower perforator closure rates than thermal ablation.[135] The nerve injury rates and DVT rates are <1% with thermal perforator ablation.[136] One study of ultrasound-guided perforator vein foam sclerotherapy reported calf DVT in 3% of patients.[137] Moreover, great care must be taken to avoid intra-arterial foam injection, which can result in skin necrosis.

Deep venous reflux

Deep vein reflux can coexist with superficial reflux and appears to contribute to the severity of the symptoms of venous disease, including

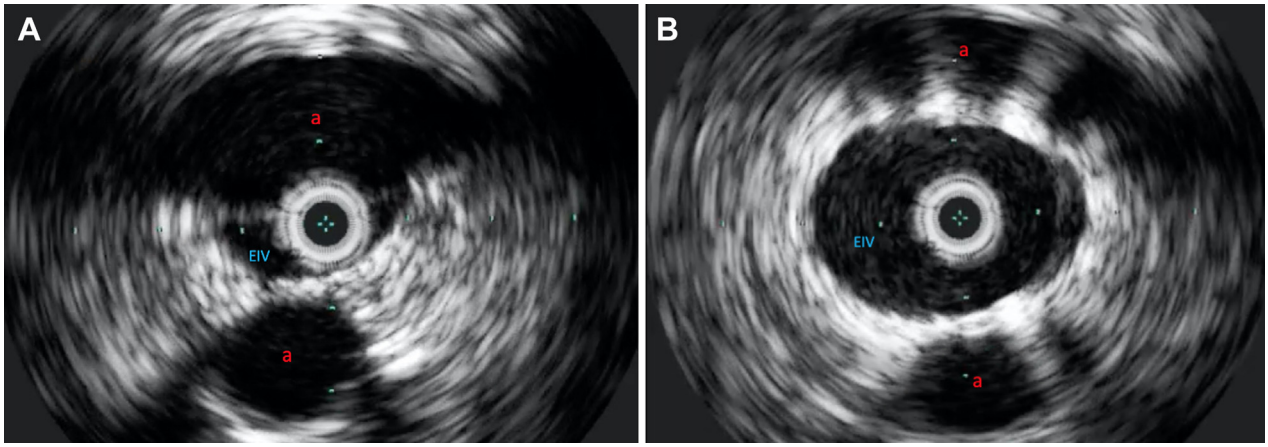

Figure 8.
(**A**) An intravenous ultrasound image of the right external iliac vein compressed between the right internal and external iliac arteries. (**B**) Intravenous ultrasound after stent deployment within the right external iliac vein showed a markedly improved lumen area. a, artery.

skin changes.[138] One estimate placed the prevalence of deep vein reflux in patients with C4-6 disease at 10%; however, it may be higher.[139,140] Deep vein reflux can also occur after DVT, which can contribute to PTS.[141] Furthermore, thrombotic and nonthrombotic iliac vein obstructions may be associated with deep venous reflux.[142,143]

A number of surgical techniques have been attempted to restore deep valvular function, including transposition, transplantation, valvuloplasty, and neovalve formation, but are technically challenging, invasive, and rarely utilized.[144-148] Early trials of BlueLeaf (InterVene), a catheter-based device to fashion venous valves from the vein wall, did not demonstrate efficacy in reducing deep vein reflux.[149]

There are some data to suggest that deep vein reflux improves in a subset of patients after their refluxing great saphenous veins undergo stripping or ablation.[140,150] The improvement has been hypothesized to be related to the correction of "overflow" into the deep system using perforators.[151,152]

Nonthrombotic deep vein obstruction

In the classic form of May-Thurner syndrome, the left common iliac vein is compressed by the adjacent right common iliac artery against the lumbar vertebrae, although multiple other areas of potential compression can exist.[153,154] Additional mechanisms of compression have been reported, such as secondary to iliac artery stents,[155] tumors,[156,157] and anterior lumbar disc migration,[158] to name a few.

The prevalence of May-Thurner syndrome in the general population is variable, with rates of up to ~25%[159] and even higher among symptomatic patients.[142,159] Although often clinically silent, it can lead to unilateral edema and even thrombosis of the lower limbs.[160] Its diagnosis can be made using magnetic resonance, computed tomography venography, or invasive venography with intravascular ultrasound (IVUS). There are many areas that require further study, including the degree of stenosis that may be clinically significant. Values around the range of 50% to 60% have been proposed.[161-163]

Endovenous stenting of compressed or stenotic segments has become the invasive treatment of choice for symptomatic patients (Figures 7 and 8).[164-166] A 2015 systematic review reported iliofemoral stent primary and secondary patency rates of 96% and 99%, respectively, at 1 year.[167] Published reports of endovenous (caval) stenting began appearing in the 1980s and 1990s with the Gianturco stent.[168-170] Unlike peripheral arterial stenoses, for which balloon interventions can suffice, iliocaval obstructions are best stented to overcome extrinsic compression or recoil and reobstruction.[171] Venous stents must be flexible, possess radial strength, accommodate the relatively larger diameter of veins, and conform to the vessel's curvature. The venous circulation is a low-pressure, slow-flow system. Undersizing of stent diameter can impede venous flow, may lower patency rates,[172] and can even result in stent migration.[173]

With hip flexion, both the common femoral vein and iliac confluence become angulated.[174] A study using computed tomography suggested that the common femoral vein can be compressed during hip flexion by the superior pubic ramus.[175]

A number of "dedicated" self-expanding venous stents have been approved by the FDA, including Venovo[176] (Bard), Zilver Vena (Cook Medical), Abre[177] (Medtronic), and Veniti Vici[178] (Boston Scientific). All, except Vici, have an open cell design. None has demonstrated the significant foreshortening during deployment that characterizes Wallstents (Boston Scientific).

A number of techniques have been adopted for iliocaval bifurcation stenting, such as a double-barrel, fenestrated (similar to the coronary T-stent technique), or Z-stent.[179] However, there are limited quality comparison data on their relative efficacy. The Gianturco Z-stent (Cook Medical) is rigid, with wide gaps between struts,[180,181] allowing for deployment within the iliac confluence in conjunction with overlapping iliac stents.

There is lack of clarity on which patient subsets may benefit from venous stenting. The Venogram versus Intravascular ultrasound for Diagnosing and treating Iliofemoral Vein Obstruction (VIDIO) trial prospectively enrolled 100 patients with C4-C6 venous disease, of whom 68 underwent stenting based on imaging findings. The study demonstrated increased sensitivity of IVUS compared with that of venography for the detection of venous stenosis and >54% to be the optimal lumen area stenosis threshold using IVUS to intervene.[182] However, the clinical outcomes of stenting were disappointing. At 6 months, only 41% of the patients had VCSS improvements of >4 points. In fact, 7.3% of the patients showed no change, and 13.2% showed worsening of VCSS.[182]

More recently, Jayaraj et al[183] published a retrospective study on iliofemoral stenting. Their findings suggested that after stenting, patients with apparently less severe (<50% area) stenosis appear to improve just as much as those with >50% area stenosis. Moreover, when present, the ulcer healing rates were not significantly different between the groups. There clearly remains more to be learnt about identifying who needs and will benefit from iliac stents.

During knee extension, in ~25% of individuals, the popliteal vein can become compressed by the gastrocnemius muscles.[184] Although normally asymptomatic, occasionally, this can lead to symptoms and is referred to as popliteal vein entrapment syndrome.[185,186] Patients with this syndrome can present with edema[187] and, sometimes, DVT[188] on the affected side. Its treatment includes compression stockings, with surgical decompression reserved for more severe cases.[189]

Thrombotic deep vein obstruction and PTS

Acute DVT of the lower extremities can lead to PTS, a chronic and, sometimes, debilitating condition, with limb venous hypertension and inflammation associated with chronic obstruction with or without reflux.[143,190] Following DVT, the affected vein can be left with permanent luminal scarring and stenosis associated with synechiae. PTS is typically diagnosed 3 months after the original insult. The frequency of PTS (depending on the diagnostic methodology) has been estimated to range from 20% to >40%.[191-193] It can lead to long-term pain, edema, discoloration, weeping, and ulceration, with diminished quality of life.[194,195] The risk factors for PTS include more proximal location of DVT (the iliocaval or common femoral vein) and recurrent DVT.[196,197] A number of symptom scales have been proposed, with the Villalta score being the most widely used.[69]

In 1960, Palma[198] described a surgical technique to relieve postthrombotic unilateral obstruction by grafting the GSV between the 2 common femoral veins, allowing for diversion of venous outflow. Since then, a number of endovascular recanalization techniques have been described to relieve venous outflow obstruction.[166] Recanalization can be combined with thrombolytic devices.[199]

Postthrombotic chronic total occlusions can be very challenging to cross because of the hard texture of the occluded lumen, ambiguous visualization of the true lumen, and large collaterals that are often formed. Supportive catheters and even sharp recanalization techniques have been used.[200-202] The primary and secondary patency rates for postthrombotic iliac vein stents at 1 year have been shown to be ~79% and 94%, respectively.[167]

At the time of writing of this article, there were no published RCTs to demonstrate the efficacy of deep vein interventions in relieving the symptoms of PTS, although there were predominantly retrospective data.[166,203-205] Most of the published literature is on Wallstents. A 2020 systematic review of iliocaval stenting studies found no reports of periprocedural mortality or pulmonary embolism.[204] The mean complication rate was 3%, and the complications included access-site hematoma, stent thrombosis, and bleeding. The primary and secondary patency rates (after a median of 33 months) were 64% and 85%, respectively. The ongoing National Institutes of Health-funded

C-TRACT (Chronic venous Thrombosis: Relief with Adjunctive Catheter-Directed Therapy) trial (NCT03250247) seeks to evaluate the effect of iliac vein stenting, with or without superficial vein ablation, on the severity of PTS.

In most studies, patients undergoing stenting for postthrombotic disease were placed on anticoagulation therapy.[204] There is currently a paucity of data on optimal anticoagulation or antiplatelet therapy after iliocaval stenting.[206]

Obesity and chronic venous disease

Obesity is a risk factor for chronic venous disease, and increased body mass index (BMI) appears to be correlated with the severity of its symptoms. Abdominal obesity may obstruct leg venous return and raise ambulatory venous pressures. In addition, high body mass is associated with poor ulcer healing.[207] The predisposition to recurrent cellulitis may lead to lymphatic damage and lymphedema, an additional cause of edema. Patients with obesity can have difficulty reaching their feet to apply compression hosiery. A retrospective study found a positive correlation between BMI and the severity of CVI symptoms, including ulceration. This correlation appeared to be exclusive of the severity of venous reflux.[208]

Obesity is associated with increased intra-abdominal pressure, which, in turn, is associated with increased deep (femoral) vein pressure.[209-211] Moreover, obesity is associated with lower venous wall shear stress,[212] which, in turn, can be proinflammatory.[213]

Among 20 patients (39 limbs) with a BMI of >40 kg/m^2 and clinical, etiology, anatomy, pathology class 4-6 venous disease, lower-extremity venous reflux was ruled out in 61% of the limbs using duplex ultrasound.[214] However, the subjects were not screened for venous outflow stenosis.

In a nonrandomized study, patients with CVI and a BMI of $\geq$35 kg/m^2 who were able to lose weight (with the mean BMI decreased from 50.1 to 32.9 kg/m^2) with bariatric surgery demonstrated improvement of venous symptom scores.[215]

Pharmacologic therapy for chronic venous disease

A number of pharmaceutical agents, including rutosides, diosmin, hesperidin, pine bark extract (pycnogenol), horse chestnut extract (escin), and micronized purified flavonoid fraction, have been evaluated for symptoms of chronic venous disease.[216,217] These agents, particularly micronized purified flavonoid fraction,[218] may reduce some symptoms, including edema and leg cramping. However, their mechanisms of action are not clear.[217,219] Rutosides may reduce capillary permeability.[220] Flavonoids may lower venous inflammation and enhance venous tone.[218] Pentoxifylline (400 mg 3 times daily) may have efficacy as an adjunct in venous ulcer therapy.[221,222] Pentoxifylline decreases blood viscosity and thrombus formation and inhibits tumor necrosis factor A.[223-225]

Education and guideline development

According to a survey, ~28% of venous procedures in the US are offered by medicine specialists, including the subspecialty of cardiology.[226] As a group, cardiologists are second only to vascular surgeons in the volume of endovenous ablations performed in the US.[227] The overall number of endovenous ablations performed have been rising.[227] However, there is variation in clinical practice[228] and, currently, lack of formal venous training in cardiovascular disease and interventional cardiology fellowships.

Although there has been a surge in published material on venous disease in both print and electronic media, its extent and scattered nature has made it more challenging for practitioners to consolidate and apply. A number of specialist societies, such as the American Venous Forum, Society for Vascular Surgery, American Vein and Lymphatic Society, Society of Interventional Radiology,[71] European Venous Forum,[229,230] Cardiovascular Interventional Radiological Society of Europe, and Canadian Interventional Radiology Association, have provided guidelines for the management of venous disease.[231] The Society for Cardiovascular Angiography & Interventions (SCAI), in conjunction with other societies, published the criteria for appropriate use of peripheral artery intervention[232] but not yet for venous disease at the time of writing of this article. However, efforts have begun to address this need.

There exist knowledge gaps and heterogeneity in the quality of venous studies published to date. High-quality data are scant compared with those on contemporary interventional cardiology. An SCAI guideline document will serve to assist cardiologists and interventional cardiologists who care for patients with venous disease to deliver safer, more efficacious, and evidence-based care.

Over the past 10 to 15 years, numerous medical specialties have entered the evaluation and management of CVI and, particularly, superficial venous disease. There have been no established standards for training, and because most procedures are performed in physicians' offices, there is a low bar for entry into the CVI space. There is a wide variety of training and exposure for patients with CVI for each specialty, and this creates potential for vast disparities in care. Many venous operators only offer a single modality of therapy, and referrals for adjunctive venous therapies are inconsistent and fractionated in many communities. Expanding the number of competent providers can help address unmet needs in most communities; however, this must be balanced with avoiding overutilization and substandard training.

The Venous and Lymphatic Medicine (VLM) Work Group was formed in 2021 as a collaborative effort to address these disparities. The VLM Work Group is a multisociety, multispecialty collaborative that intends to define the training and certification requirements of physicians treating the venous and lymphatic systems in the future. The group includes executive leadership from the American Vein and Lymphatic Society, American Venous Forum, Society of Vascular Surgery, Society of Interventional Radiology, Society of Vascular Medicine, American Association of Dermatology, and SCAI. It also includes representatives from the American Board of Surgery, American Board of Radiology, Accreditation Council for Graduate Medical Education, and American Board of Medical Specialties. The mission of this group is to define VLM as a distinct specialty and in a manner that would allow physicians from various specialties to receive proper and comprehensive Accreditation Council for Graduate Medical Education-accredited training on the entire scope of venous and lymphatic diseases rather than the 1 particular aspect that is most germane to their primary specialty. Moving forward, this group plans to map out the optimal way for specialty recognition and certification that is inclusive of those who have already demonstrated competence and experience in the field of venous diseases.

Conclusions

Chronic venous disease of the lower extremities is common and can be associated with debilitating symptoms that adversely affect the quality of life. It is associated with venous obstruction, reflux, or both and often leads to chronic inflammation. In addition to compressive and medical therapies, a number of minimally invasive techniques have shown promise for deep vein recanalization, the closure of incompetent superficial veins, and the elimination of varicose veins. More quality clinical trials and training in comprehensive care for patients with

venous diseases are critical to enhance patient care and advance the field.

Declaration of competing interest

Jeffrey G. Carr is a consultant for Becton Dickinson and on the advisory board for Medtronic. Robert R. Attaran reported no financial interests.

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Ethics statement

This work has adhered to relevant ethical guidelines.

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