CLINICAL PRACTICE

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Nonsurgical Management of Chronic Venous Insufficiency

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

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CME

A 68-year-old woman presents with heaviness in her legs and feet, hyperpigmentation from the ankle to the mid-calf (the "gaiter" area), and swelling that is worse during afternoons and evenings. These complications have progressed over the years, and she now notices that her socks make indentations on her feet and legs. She has small, nonpainful varicose veins on her calves and spider veins on her thighs. She has obesity and takes amlodipine for hypertension and gabapentin for peripheral neuropathy. She does not have dyspnea, chest pain, or palpitations, and her blood-test results are normal. She is not active and spends many hours a day at her computer. On physical examination, there is mild edema on the dorsal surface of the feet and ankles with 1+ pitting in the anterior shin. She has tight and weak calf muscles, limiting her ability to perform heel raises. She has flat feet (pes planus) and ankle stiffness from a previous surgical fusion. She is unable to do toe curls and shuffles on gait assessment. A duplex ultrasound examination revealed a segmental reflux, with a reflux time of 1.8 seconds and a vein diameter of 2 to 3 mm, in the great saphenous veins in the calves. There are no deep- or superficial-vein thromboses or other abnormalities. How would you manage her leg symptoms?

THE CLINICAL PROBLEM

VENOUS INSUFFICIENCY

Venous insufficiency comprises a constellation of symptoms and clinical manifestations ranging from asymptomatic spider veins and varicose veins to venous leg ulcers. Chronic venous disease is often conflated with chronic venous insufficiency; however, by strict definition, chronic venous disease encompasses the entirety of venous disorders, whereas chronic venous insufficiency denotes the more advanced forms of venous disorders, such as edema, skin manifestations (e.g., hyperpigmentation), and healed or active venous ulcers. Varicose veins and chronic venous insufficiency of the legs are among the most frequent vascular conditions, affecting millions of people worldwide.[1] More than a cosmetic problem, venous insufficiency increases the risk of venous thrombotic events and is associated with substantial limitations on daily functioning and quality of life.[2]

KEY POINTS

NONSURGICAL MANAGEMENT OF CHRONIC VENOUS INSUFFICIENCY

- Chronic venous insufficiency manifests as a spectrum of signs and symptoms, including varicose veins, leg swelling, skin changes, and leg ulcers. The condition is caused primarily by venous hypertension.
- Venous hypertension is a multifactorial disease, the cause of which can be structural (e.g., venous reflux or obstruction) or functional (e.g., dependent edema, weak calf muscle, or obesity) or both.
- The diagnosis of chronic venous insufficiency is based on information obtained from the history and physical examination; further diagnostic imaging with duplex ultrasound examination is helpful for assessing for structural causes.
- Treatment is aimed at reducing the patient's symptoms, which do not always correlate with the findings on physical or ultrasound examination.
- Endovenous procedures and surgeries can be effective treatment options for structural venous insufficiency, but nonsurgical treatment measures are the mainstay for functional or combined (functional and structural) venous insufficiency.
- Nonsurgical management includes reducing central venous hypertension, compression therapy, leg elevation, and exercises involving calf and foot flexion and extension that provide a pump-function effect.

DEMOGRAPHICS, FREQUENCY, AND RISK FACTORS

Chronic venous insufficiency arises from a complex interplay of genetic predisposition; environmental factors, such as jobs that require prolonged standing or carrying heavy loads; and age-related loss of structural integrity of the venous system in the legs. Reports on the prevalence of chronic venous insufficiency vary broadly, with estimates as high as 73% among women and 56% among men.[3] Established risk factors include older age, female sex, obesity, pregnancy, history of deep-vein thrombosis, and prolonged standing. Other risk factors that have been identified as being associated with the development of varicose veins include low bioimpedance and greater height.[4] A genome-wide association study identified 855 single-nucleotide polymorphisms and 30 independent genetic variants as being associated with varicose veins, establishing that genetic factors contribute to their development, although the relative contributions of these genetic factors, as compared with environmental factors, have not been well elucidated.[4]

PATHOPHYSIOLOGY OF VENOUS HYPERTENSION

Veins are capacitance vessels, accommodating approximately two thirds of the total blood volume in the body. The ability of the venous system to serve as the reservoir for the circulatory system enables swift adjustments in volume with varying pressures. With the body in a supine position, central venous pressure ranges from 8 to 12 mm Hg and can be as high as 90 mm Hg in the legs while standing.[5] The venous system comprises superficial and deep veins, the latter of which are responsible for greater than 90% of the venous return. Contraction of the foot and calf muscles initiates cephalad flow of blood and opens the one-way valves within the veins, which prevent retrograde flow after closing. Dysfunctional valves cause venous reflux, a condition characterized by the backflow of blood, which results in venous hypertension and leads to deleterious effects over time.

At the cellular level, prolonged venous hypertension causes endothelial dysfunction, increases vascular permeability, and induces inflammation of the vein walls. These conditions result in a disruption in the reduction–oxidation balance (the equilibrium between the generation and elimination of reactive oxygen and nitrogen species), which leads to tissue degradation and clinical manifestations such as varicose veins, edema, skin changes, and venous ulcers (Fig. 1).[1,6]

The cause of venous hypertension can be structural or functional or both. Common intravascular structural impediments include valvular reflux and venous obstruction. Scarring and fibrosis of the vein wall after deep-vein thrombosis can result in outflow restrictions, contributing to the post-thrombotic syndrome, which has been observed in 20 to 50% of patients.[7] Anatomical compressions (e.g., the May–Thurner syndrome,

in which the left iliac vein is compressed between the right iliac artery and lumbar spine) or tumors can cause extravascular venous obstruction.

Conversely, elevated central pressures, compromised pump function with foot and calf muscle movement, and lymphatic dysfunction (without structural issues) can induce venous hypertension and cause functional insufficiency (Fig. 2). Causes of elevated central pressures include obesity, volume overload, pulmonary hypertension, and obstructive sleep apnea. Intraabdominal pressures may range from 10 to 15 mm Hg (reference value, <5 mm Hg) with obesity, and this increased pressure can obstruct the vena cava and impede venous return, thereby causing venous hypertension.[8] Tissue hypoxia with obstructive sleep apnea can promote pulmonary hypertension through vascular constriction, and the negative inspiratory intrathoracic pressure generated against the occluded upper airway increases venous return and

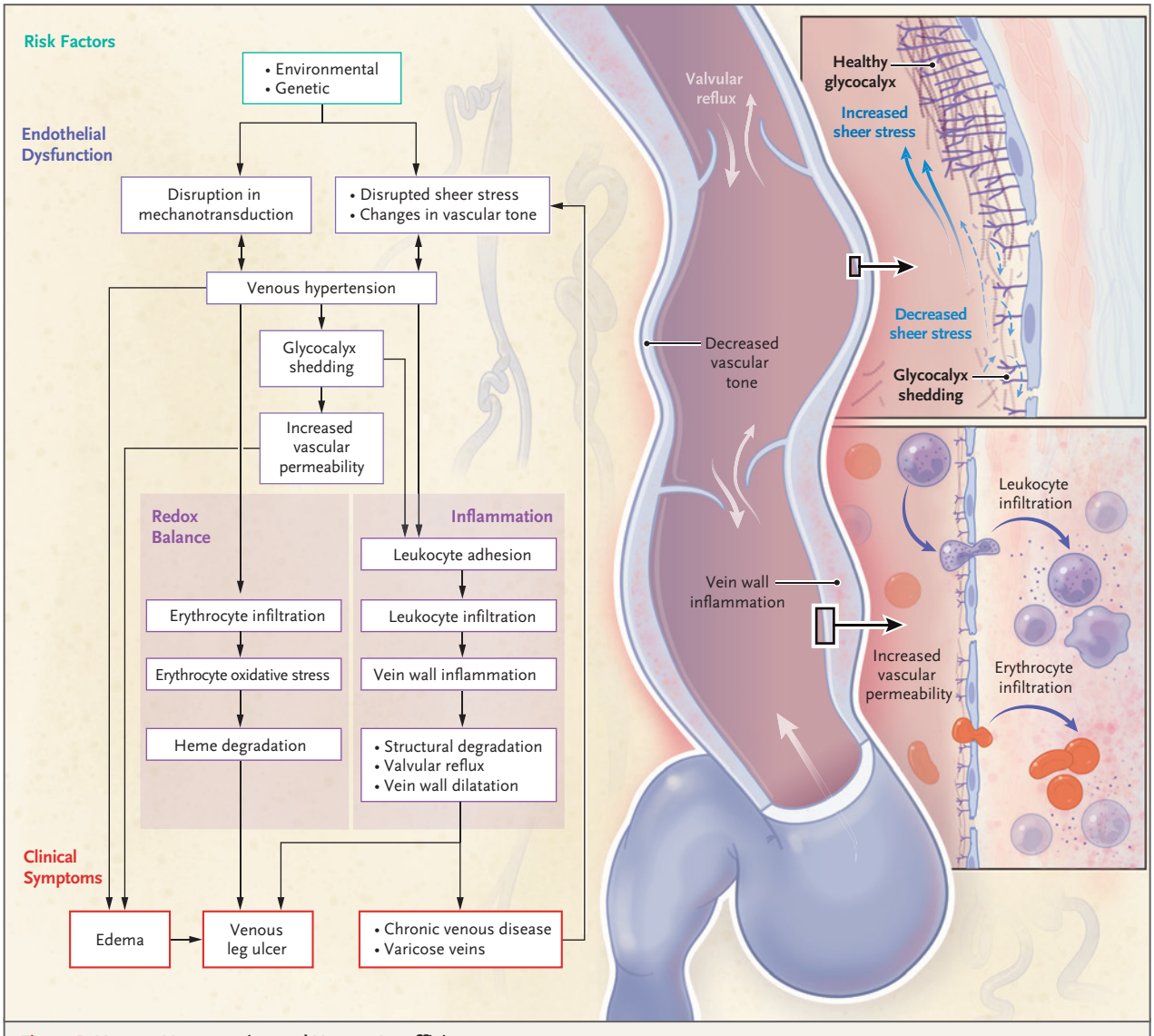
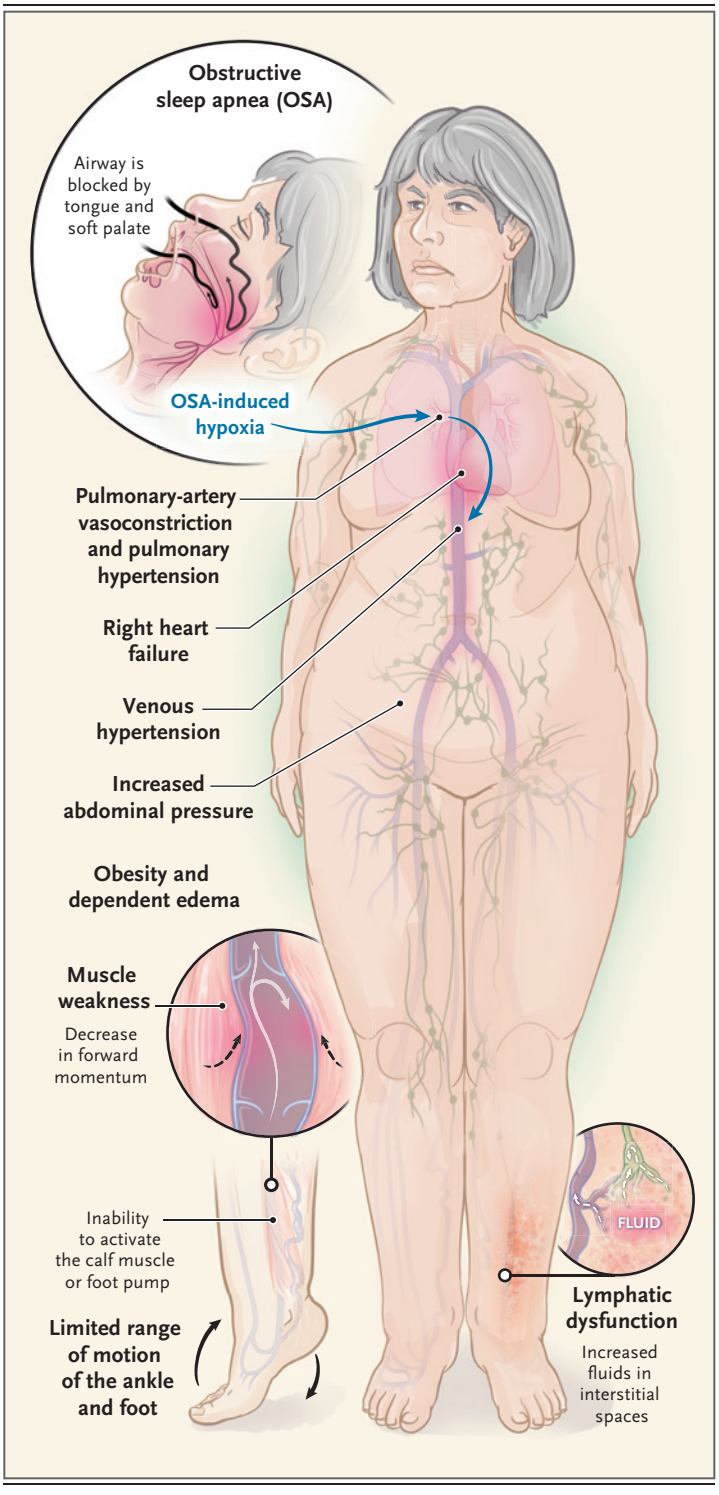


Figure 1. Venous Hypertension and Venous Insufficiency.

Venous hypertension reduces shear stress, which maintains the endothelial activation state. Changes in vascular tone disrupt the mechanotransduction and affect the glycocalyx and vascular permeability. Inflammatory reactions in the vessel wall cause structural degradation and disruption of the reduction–oxidation (redox) balance by red-cell infiltration and cause clinical symptoms of venous disease. The expression of proinflammatory cytokines, enzymes, and adhesion molecules is up-regulated during this process.

Figure 2. Functional Venous Insufficiency and Venous Hypertension.

Functional venous insufficiency is caused by obstruction of venous return, which can be due to elevated central pressures (such as from obesity, obstructive sleep apnea, or right heart failure), lymphatic dysfunction, or a decrease in the forward momentum of blood flow (such as from poor calf and foot pump function or dependent edema), all of which can lead to venous hypertension, even in the absence of structural venous damage.



augments the right ventricular preload against an increased pulmonary vascular resistance.[9,10]

The interconnection between the venous and lymphatic systems at the microcirculation level is an important factor in the physiological basis of edema. Contrary to the classic understanding of edema as a function of Starling's law of forces (the balance of oncotic pressure, hydrostatic pressure, and capillary integrity), the discovery of the microvasculature glycocalyx as an anatomical structure emphasized that filtration primarily occurs in the arterial and venous capillaries and that reabsorption occurs only through the lymphatics connected to the venules that form the microcirculation outflow tract. Edema is caused by fluid accumulation in the interstitial space, which occurs when capillary ultrafiltration surpasses lymphatic drainage or when lymphatic drainage capacity is diminished.[11] Dysfunction of the lymphatics can considerably affect the capacity of the venous system to maintain fluid homeostasis.

Contraction of the calf muscle that is triggered by foot flexion and extension, which acts as a functional pump, plays a crucial role in facilitating venous return. A single contraction ejects 100 to 150 ml of venous blood, reducing the venous pressures by approximately 25 mm Hg.[5,12] Consequently, any impairment in this pump-function apparatus can lead to venous stasis and elevated pressures.

STRATEGIES AND EVIDENCE

DIAGNOSIS AND EVALUATION

Patients with venous disease may present with varicose veins, edema, skin changes, venous leg ulcers, or a combination thereof (Fig. 3). Patients may be asymptomatic or have symptoms of pain, itching, cramping, heaviness, and swelling. The clinical, etiologic, anatomical, pathophysiological (CEAP) classification (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) is used for disease classification,[13] and the Venous Clinical Severity Score (Table S2)[14] is the most widely used and validated

system[15,16] for scoring the clinical severity of chronic venous insufficiency.

Venous symptoms worsen toward the end of the day, as well as with prolonged standing, in hot climates, and during perimenstrual periods. Symptoms are reduced with leg elevation and activity, such as walking. Physical examination should be performed with the patient in an upright position in order to observe the effect of gravity and body weight. Inspection should encompass the entire thigh and calf and extend to the pelvis and abdomen. The skin is assessed for signs of hyperpigmentation (hemosiderin staining), scarred tissue (atrophie blanche), dilated reticular veins at the ankles and feet (corona phlebectatica), skin texture change (lipodermatosclerosis), erythema (indicative of cellulitis), and skin breakdown. Swelling is evaluated with respect to the amount and distribution. Swelling of the dorsal surface of the foot and of the toes (Stemmer's sign) indicates lymphatic dysfunction.

The evaluation should also include functional assessment of the capacity of the patient's calf and foot muscles to serve as a pump. This assessment is done by placing one's hand on the patient's calf while the patient performs dorsi and plantar flexion of the ankle. Reduction in flexibility and mobility of the foot may be compounded by the coexistence of any of the following factors: diabetes, peripheral neuropathy, arthritis, and various foot deformities. Patients with limited range of motion of the ankle and foot may be unable to engage and activate the calf muscles. They may rely on the anterior tibialis muscle to dorsiflex the ankle, which does not activate the calf or foot muscles. Some patients may show rigidity of their intrinsic foot muscles and joints, which impedes toe movement and compromises the pumping action of the foot. Furthermore, persons with pes planus and collapsed foot arches may have inward ankle rotation (overpronation), which leads to strain on the posterior tibial tendon and results in ankle or medial foot pain and swelling.

Medications can induce edema due to vasodilatation, sodium and water retention, lymphatic insufficiency, or increased vascular permeability[17]; such edema may potentially mimic or coexist with chronic venous insufficiency (Table 1). Swelling with commonly prescribed drugs (calcium-

Figure 3. Clinical Photographs of Manifestations of Chronic Venous Disease in Three Patients.

Shown are lipodermatosclerosis, corona phlebectatica, venous leg ulcer, and pes planus (Panel A); swelling in the right leg due to functional venous insufficiency (caused by weak calf muscle and dependent edema), along with reduction of swelling in the left leg with 1 week of compression therapy with multilayer wraps (Panel B); and morbid obesity with scattered varicose veins and spider veins (Panel C).

Table 1. Classes of Medications That Can Cause Leg Swelling.*

Drug Class	Drugs	Potential Mechanism†
Antiepileptic	Gabapentin, pregabalin, carbamazepine, valproate	Vasodilatory
Antidepressant	Escitalopram, mirtazapine, paroxetine, venlafaxine	Vasodilatory
Antipsychotic	Clozapine, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone	Vasodilatory
Antiparkinsonian	Levodopa, carbidopa	Vasodilatory
Antihypertensive	Calcium channel blockers (amlodipine, nifedipine, diltiazem), α-adrenergic receptor blockers (prazosin, doxazosin), vasodilators (hydralazine, clonidine, minoxidil)	Vasodilatory
Hormone therapy	Estrogens, progestins, aromatase inhibitors (anastrozole, letrozole), androgens (danazol, testosterone)	Renal (sodium retention)
Glucocorticoid	Hydrocortisone, methyl prednisolone, betamethasone, prednisolone, dexamethasone.	Renal (sodium retention)
NSAIDs	Aspirin, ibuprofen, naproxen, diclofenac	Renal (sodium retention)
Chemotherapy	Tamoxifen, taxanes (docetaxel, paclitaxel), mTOR inhibitors (everolimus, sirolimus)	Lymphatic
Chemotherapy	Cisplatin, pemetrexed, imatinib, gemcitabine	Permeability
Thiazolidinedione	Pioglitazone, rosiglitazone	Unknown
Proton-pump inhibitor	Omeprazole, lansoprazole, pantoprazole	Unknown

* The abbreviation mTOR denotes mammalian target of rapamycin, and NSAIDs nonsteroidal antiinflammatory drugs.
† Vasodilatory edema is caused by precapillary arteriolar vasodilatation, renal edema by sodium or water retention (or both), lymphatic edema by impaired lymphatic drainage, and permeability edema by increased capillary permeability.

channel blockers and gabapentinoids) can lead to the unnecessary and harmful use of diuretics.[18,19]

Duplex ultrasound evaluation is pivotal in identifying structural issues by characterizing venous reflux and obstruction, vein size, anatomy, reflux times, and flow patterns. However, it cannot discern venous hypertension. Normal venous flow should be spontaneous, respirophasic (responds to respiration), unidirectional, and without reflux in response to augmentation maneuvers. Venous reflux can occur in isolated segments or involve the entire vein (axial reflux). Hemodynamically significant reflux time is greater than 0.5 seconds in the superficial veins and greater than 1.0 second in the deep veins.[20] However, reflux times do not reliably correlate with disease severity or symptoms. The loss of respirophasicity and its replacement with continuous or pulsatile waveforms may suggest more proximal venous issues.[21] For imaging the deeper iliac veins of the pelvis, computed tomography or magnetic resonance venography may be warranted owing to the technical limitations of duplex technology to venous flow in deep-tissue structures.

TREATMENT

With advances in procedural options, there may be the misconception that venous disease is a surgically curable condition. However, the disease is chronic and most often includes a functional component. Thus, the cornerstone of treatment is reducing venous hypertension through conservative, nonprocedural management. The four pillars of conservative management are reduction of central venous hypertension, compression therapy, leg elevation, and exercise involving calf and foot flexion and extension. Treatment goals should focus on alleviating symptoms and discomfort rather than rectifying imaging findings. Ultrasound examination shows vein size and venous reflux; however, it cannot directly evaluate venous hypertension. The degree of venous reflux does not always correlate with venous hypertension and symptoms. However, when a patient's symptoms correlate with venous pathologic changes on ultrasound examination, venous procedural interventions may be warranted, since this can reduce symptoms (Table 2). Venous reflux and varicose veins create back pressure. In addition, feeder veins to venous leg ulcers result in venous

Table 2. Venous Procedural Interventions, with Indications and Evidence of Benefit.*

Procedure Method and Type	Indication†	Evidence of Benefit	Data Type
Superficial vein			
Injection: sclerotherapy	Varicose veins, spider veins, bleeding veins, and periulcer venous network	Improved appearance; reduced pain, heaviness, fatigue, burning, paresthesia, and itching[22]; and improved wound healing[23]	Observational
Endovascular approach: thermal ablation			
Laser	Axial veins and perforator veins	High percentage (93.1%) of occlusion of refluxing veins at 1 year,[24] improved disease-specific quality-of-life measures,[25] and improved wound healing[23]	Observational
Radiofrequency	Axial veins and perforator veins	High percentage (91.6%) of occlusion at 5 years, improved venous measures, improved venous disease–specific quality-of-life measures,[26] and improved wound healing[23]	RCT
Endovascular approach: nonthermal ablation			
Microfoam	Axial veins	High percentage (73%) of occlusion at 1 year and improved venous disease–specific quality-of-life measures[27]	RCT
Mechanochemical	Axial veins	High percentage (94%) of occlusion at 6 months,[28] reduced pain, and improved wound healing[29]	Observational
Cyanoacrylate glue	Axial veins	High percentage (91.4%) of occlusion at 5 years and improved venous disease–specific quality-of-life measures[30]	RCT
Surgical approach: ligation and stripping	Axial veins	Successful stripping and absence of veins noted in 93.5% of the treated veins at 3 years and improved patient-reported venous disease–specific quality-of-life measures[31]	RCT
Surgical approach: phlebectomy‡	Varicose veins	—	Observational
Deep vein			
Endovascular approach: stent	Select acute or subacute iliofemoral thrombosis and obstructive lesion,[32] symptomatic nonthrombotic iliac lesions despite conservative treatment, and venous leg ulcers	Stenting a vein with obstruction or occlusion has been shown to result in a reduction of symptoms as measured by improvements in quality-of-life and functional outcome measures, such as the EQ-5D and VEINES-QoL/Sym questionnaires[36], the VCSS, and the Villalta scale[37]	Observational

* EQ-5D denotes European Quality of Life–5 Dimensions; RCT randomized, controlled trial; VCSS Venous Clinical Severity Score; and VEINES-QoL/Sym Venous Insufficiency Epidemiological and Economic Study Quality of Life/Symptoms.
† Axial veins include the great saphenous vein, small saphenous vein, and accessory saphenous vein.
‡ Phlebectomy is performed in conjunction with other axial vein treatments to treat the tortuous varicosities either at the same time or in a staged manner.

hypertension under the wound bed. In such cases, obliterating the anatomical cause by removing the diseased veins surgically, such as with stripping or phlebectomy, or destroying the vein with ablations or injections, such as with sclerotherapy, may be warranted for symptom reduction and wound healing. In the case of venous leg ulcers, the Early Venous Reflux Ablation (EVRA) trial showed that early venous interventions can reduce the number of days to healing.[23] In cases of pelvic or iliac vein obstruction, endovenous revascularization resulted in a reduction in symptoms and improvement in quality of life and functional outcomes, as shown by objective improvements in scores on the Venous Insufficiency Epidemiological and Economic Study

Quality of Life/Symptoms questionnaire, the European Quality of Life–5 Dimensions questionnaire, and the 20-item Chronic Venous Quality-of-Life Questionnaire (Global Index); the Villalta score; and the Venous Clinical Severity Score.[33-38]

Obesity is an independent risk factor for disease progression, and as such, managing obesity is important in the care of these patients.[39] Obstructive sleep apnea, diastolic dysfunction, and right heart failure increase central venous pressures, leading to congestion and a resultant increase in peripheral venous hypertension on physiological testing. Although there is no direct evidence of efficacy, managing these associated conditions may lead to better outcomes. Diuretics should not be the first-line therapy for swelling and should be used only for volume overload. Overuse of diuretics can reduce intravascular volume and potentially cause excessive volume contraction without addressing the underlying cause. When necessary, thiazides and mineralocorticoid antagonist diuretics should be considered rather than loop diuretics, which may result in increased venous compliance and venodilation rather than a reduction in central venous pressures.[40]

Graduated compression therapy can considerably improve symptoms associated with chronic venous insufficiency, particularly pain or aching.[41] Although there is no evidence that long-term compression therapy is curative or slows the progression of chronic venous insufficiency, it is recommended for use in order to compensate for and counter the elevation of ambulatory pressures.[42] Compression therapy should be tailored to the patient's preferences and abilities, with measures ranging from compression socks to Velcro wraps, multilayer wraps (static compression), and compression pumps (dynamic compression). The primary objective is to decrease venous hypertension and thereby reduce leg fatigue, discomfort, and edema and assist with the healing of venous leg ulcers. A compression level above 30 mm Hg is recommended for ulcer healing; however, such compression poses challenges to adherence for many patients because of discomfort.[43] Therefore, a lower level (i.e., 20 to 30 mm Hg or lower) is often used. The pressure applied is proportional to the stiffness of the wrap, which is determined according to the radius of the limb, the number of layers of the wrap, and the inherent properties of the wrap, including its components and elasticity of the material.[44] The wraps can be made of long-stretch material, which can stretch more than 100% of its original length, as opposed to short-stretch material. A long-stretch wrap applies high-resting and low-working pressure (i.e., tightening when resting but stretching under applied pressure). Such pressure can feel too tight when the elastic recoil sets in. Conversely, a short-stretch wrap applies low-resting and high-working pressure and is preferred for multilayer compression for swelling control.[44] Caution should be exercised in patients with peripheral artery disease who have an ankle–brachial index below 0.8 in order to avoid exacerbating arterial obstruction and the development of pressure-related injury. Tailored modifications are needed in patients with arthritis or limited mobility in reaching for their legs.

Exercises to strengthen calf and foot muscles and leg elevation are integral to improving venous function and return. These exercises can be done at home (Table S4), or patients may benefit from physical therapy if they are severely weak. The importance of addressing these points remains underappreciated and warrants heightened emphasis, especially in the elderly population.

AREAS OF UNCERTAINTY

Uncertainty exists about the role of venoactive pharmacologic agents for venous disease; many are available as over-the-counter supplements[45] and are mentioned in conjunction with a class 2B recommendation (weak with moderate quality of evidence) in the updated U.S. guidelines[46] and a class IIa recommendation (weight of evidence or opinion is in favor of usefulness or efficacy) in the updated European guidelines,[47] but without details on any specific drug type. These agents are purported to decrease capillary permeability, affect inflammatory mediators, and improve venous tone, all of which may result in reduced swelling and pain. There is some evidence that this may reduce edema but may make little to no difference in quality of life or improve ulcer healing.[45] Venoactive drugs include micronized purified flavonoid fraction, horse chestnut, red grape seed, and butcher's broom.

The effectiveness of treating structural insufficiency to reduce leg swelling in patients with

functional insufficiency is not well established. Medical weight loss and other ways to decrease central pressures in addition to exercise can play a major role in the treatment of functional disease, a finding that is supported by clinical observations. Clinical trials evaluating the comparative effectiveness of treatment options would be of great value.

GUIDELINES

Our recommendations are consistent with the multispecialty society 2022 and 2023 guidelines (Table S3) for varicose veins in legs,[46,48] the 2014 guidelines for the management of venous leg ulcers,[49] and the 2020 appropriate use criteria for chronic lower-extremity venous disease.[50] For patients with symptomatic varicose veins and axial reflux in the great or small saphenous veins, first-line treatment with venous intervention is recommended over long-term compression stockings (class IB recommendation [strong with moderate quality of evidence][46]). The current class 1A recommendation (strong with high quality of evidence[49]) for venous leg ulcer healing is compression therapy; however, the 2018 EVRA trial showed that early venous procedures improve venous leg-ulcer healing.[23]

CONCLUSIONS AND RECOMMENDATIONS

Venous hypertension leading to chronic venous insufficiency can be both structural and functional in nature. Addressing both aspects of this pathologic process is essential to achieve clinical improvement. Whereas structural issues can be addressed with venous procedures, functional issues must be addressed nonsurgically. Regarding the patient in the vignette, who has only mild structural disease but overwhelming signs of functional venous hypertension, we would address obesity through measures including medical weight loss, encourage leg elevation, provide education on exercises, perform an evaluation for obstructive sleep apnea, consider compression therapy, and conduct a thorough medication reconciliation for medication-induced edema.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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