# ADVANCING INSIGHTS INTO VARICOSE VEINS: PATHOPHYSIOLOGY, INNOVATIONS IN DIAGNOSIS, AND MODERN TREATMENT APPROACHES

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**Abstract**
*Varicose veins are a common vascular condition characterized by dilated, tortuous veins primarily affecting the lower limbs. They are associated with venous valve incompetence, venous hypertension, and structural abnormalities in the vein wall. The condition significantly impacts the quality of life, causing symptoms such as pain, swelling, and cosmetic concerns, and poses a considerable healthcare burden globally. Recent advancements in the understanding of the pathophysiology of varicose veins have highlighted the role of inflammation, oxidative stress, and genetic predisposition in disease progression. Diagnostic innovations, including Doppler ultrasonography, duplex ultrasound, and emerging AI-driven tools, have enhanced accuracy in detecting venous insufficiency. Modern treatment approaches, ranging from minimally invasive procedures such as endovenous laser therapy and radiofrequency ablation to emerging techniques like cyanoacrylate adhesive closure and mechanochemical ablation, have revolutionized patient care. This review provides a comprehensive analysis of the pathophysiology, state-of-the-art diagnostic methods, and modern treatment modalities for varicose veins, emphasizing the need for further research into preventive strategies and personalized therapeutic interventions.*

***Keywords:*** *Varicose veins, venous insufficiency, pathophysiology, diagnostic advancements, endovenous laser therapy, radiofrequency ablation, cyanoacrylate adhesive closure, minimally invasive treatments.*

## Introduction

Varicose veins are a common chronic venous disorder characterized by abnormally dilated, elongated, and tortuous veins, typically in the lower limbs. This condition arises due to venous valve incompetence, leading to venous reflux and increased venous pressure, which ultimately results in venous dilation and blood pooling (Bergan et al., 2006). Varicose veins not only present cosmetic concerns but are also associated with symptoms such as pain, heaviness, swelling, and in severe cases, venous ulcers (Beebe-Dimmer et al., 2005).

The prevalence of varicose veins varies widely across populations and is influenced by factors such as age, gender, occupation, and lifestyle. Studies indicate that varicose veins affect approximately 20–30% of the adult population worldwide, with higher prevalence observed among women than men, largely due to hormonal influences and pregnancy-related changes (Evans et al., 1999; Jawien, 2003). The condition is more common in older individuals, with age-related degeneration of venous walls and valves contributing significantly to its pathogenesis (Maffei et al., 2009). Occupations requiring prolonged standing or sitting, obesity, and a sedentary lifestyle further exacerbate the risk (Callam, 1994).

Varicose veins impose a significant burden on healthcare systems and patient quality of life. Beyond the physical symptoms, the psychological impact, including reduced self-esteem and social isolation, is substantial (Rabe et al., 2010). From an economic perspective, the cost of managing varicose veins, including diagnostic procedures, interventions, and follow-up care, places considerable strain on healthcare resources, particularly in developed nations (Raju & Neglen, 2009).

The purpose of this review is to provide an in-depth analysis of varicose veins, focusing on three critical aspects: the underlying pathophysiology, advancements in diagnostic techniques, and modern treatment approaches. By synthesizing recent literature, this review aims to highlight the current understanding of the condition and identify emerging trends and gaps in research. Ultimately, the scope of this review is to offer insights into improving clinical management and paving the way for future innovations in the field.

## Pathophysiology of Varicose Veins

### 3.1 Normal Venous Anatomy and Physiology

The venous system plays a crucial role in maintaining blood circulation by returning deoxygenated blood from peripheral tissues back to the heart. Veins contain one-way valves that prevent retrograde blood flow and ensure unidirectional movement toward the heart. These valves work in conjunction with skeletal muscle contractions, which compress the veins and propel blood forward, a process referred to as the "muscle pump" mechanism (Caggiati et al., 2002). Venous pressure and flow dynamics are essential for maintaining this function, with low venous pressure in the deep veins during muscle contraction facilitating efficient blood return (Neglén & Raju, 2000). Any disruption in valve function or venous wall integrity can compromise this delicate balance and lead to pathological conditions.

### 3.2 Mechanisms Leading to Varicose Veins

The primary mechanism underlying varicose veins is venous valve incompetence, which leads to venous reflux and chronic venous hypertension. Dysfunctional valves allow blood to flow backward, causing blood pooling and increased pressure within the veins (Bergan et al., 2006). Prolonged exposure to high venous pressure triggers structural remodeling of the vein wall, including dilation and tortuosity. Over time, the vein wall becomes weakened due to elastin degradation and collagen deposition, further exacerbating the condition (Lim & Davies, 2009). Chronic venous hypertension also results in endothelial cell activation, which promotes leukocyte adhesion and inflammation, amplifying vascular damage (Wolff et al., 2009).

### 3.3 Contributing Factors

Several factors contribute to the development of varicose veins. Genetic predisposition plays a significant role, as familial clustering and specific genetic markers have been associated with the condition (Cornu-Thenard et al., 1994). Environmental and lifestyle factors, such as prolonged standing or sitting, sedentary behavior, and obesity, increase venous pressure and hinder proper blood flow, further promoting venous insufficiency (Callam, 1994). Hormonal influences, particularly in women, are another critical factor. Pregnancy-related changes, including increased blood volume, hormonal fluctuations, and uterine pressure on pelvic veins, elevate the risk of developing varicose veins. Similarly, estrogen is believed to weaken venous walls, contributing to the higher prevalence of varicose veins in women (Evans et al., 1999).

### 3.4 Recent Insights into Molecular and Cellular Changes

Recent studies have highlighted the role of molecular and cellular changes in the progression of varicose veins. Chronic inflammation and oxidative stress are key contributors, leading to endothelial dysfunction and vein wall degradation. Inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), have been found to upregulate the production of reactive oxygen species (ROS), which cause oxidative damage to vascular tissues (Sansilvestri-Morel et al., 2010). Additionally, matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, are overexpressed in varicose veins. These enzymes degrade extracellular matrix components, such as collagen and elastin, compromising the structural integrity of the vein wall and contributing to its dilation and weakening (Badier-Commander et al., 2001). Understanding these molecular mechanisms provides valuable insights into potential therapeutic targets for preventing or mitigating varicose vein progression.

## 4. Innovations in Diagnosis

### 4.1 Traditional Diagnostic Methods

The diagnosis of varicose veins has historically relied on traditional methods such as clinical examination and patient history. A thorough physical examination, including inspection of the lower limbs for visible signs of dilated veins, skin discoloration, or edema, remains a cornerstone of diagnosis (Beebe-Dimmer et al., 2005). Manual palpation is commonly used to assess vein competency and tenderness, while patient-reported symptoms, including heaviness, pain, and itching, help in clinical assessment (Raju & Neglen, 2009). These methods, while straightforward and cost-effective, have limitations in identifying deeper venous pathologies or subclinical cases.

### 4.2 Advances in Imaging Technologies

Advances in imaging technologies have significantly improved the diagnostic accuracy of varicose veins. Doppler ultrasonography, a non-invasive imaging modality, has become the gold standard for evaluating venous reflux and valve incompetence. This technique uses sound waves to visualize blood flow and detect areas of venous reflux, making it a vital tool in routine diagnostics (Labropoulos et al., 1996). Duplex ultrasound, which combines Doppler and grayscale imaging, provides detailed structural and functional information about superficial and deep venous systems, aiding in treatment planning (Engelhorn et al., 2004). Additionally, cross-sectional imaging techniques such as CT venography and MR venography offer high-resolution visualization of venous anatomy and are particularly useful for identifying complex venous pathologies or pelvic vein involvement (Perandini et al., 2012).

### 4.3 Emerging Diagnostic Tools

Recent innovations in diagnostic tools are transforming the detection and management of varicose veins. Artificial intelligence (AI) and machine learning (ML) algorithms are increasingly being integrated into diagnostic workflows to enhance accuracy and efficiency. AI-powered systems can analyze ultrasound images to detect venous insufficiency with greater precision, reducing the reliance on operator expertise (Luo et al., 2020). Furthermore, the identification of novel biomarkers for venous disease has opened new avenues for early detection and risk stratification. Biomarkers such as vascular endothelial growth factor (VEGF) and interleukin-6 (IL-6) have been associated with chronic venous insufficiency, providing potential targets for diagnostic and therapeutic interventions (Sansilvestri-Morel et al., 2010).

### 4.4 Challenges in Accurate Diagnosis

Despite these advancements, challenges remain in the accurate diagnosis of varicose veins. Asymptomatic cases, where patients do not exhibit visible or physical signs of venous disease, are often underdiagnosed, delaying appropriate intervention (Callam, 1994). Similarly, misdiagnosis or overreliance on subjective clinical assessment can lead to inappropriate treatment. Identifying venous insufficiency at subclinical stages also poses difficulties, as early changes in venous function may not be detectable with current diagnostic tools (Lim & Davies, 2009). These limitations underscore the need for continued research into more sensitive and specific diagnostic methods.

## 5. Modern Treatment Approaches

### 5.1 Conventional Treatment Methods

Conventional treatment methods for varicose veins primarily focus on managing symptoms and preventing disease progression. Lifestyle modifications, including regular physical activity, weight management, and avoidance of prolonged standing or sitting, play a critical role in reducing venous pressure and improving circulation (Rabe et al., 2010). Compression therapy, using elastic stockings or bandages, is a cornerstone of conservative management. These devices exert graded pressure on the lower limbs, enhancing venous return and reducing edema (O'Meara et al., 2012). Pharmacological interventions, such as venoactive drugs, are also employed to alleviate symptoms like pain, swelling, and heaviness. Drugs containing flavonoids and saponins, such as diosmin and horse chestnut extract, have demonstrated efficacy in improving venous tone and reducing inflammation (Pittler & Ernst, 2012).

### 5.2 Surgical Interventions

Surgical methods remain a viable option for patients with severe varicose veins or those unresponsive to conservative treatments. Ligation and stripping, a traditional approach, involve tying off and removing the affected veins to eliminate reflux and improve venous flow. While effective, this technique is associated with significant postoperative pain and recovery time (Durkin et al., 2001). Advances in surgical techniques, including the use of smaller incisions and improved instrumentation, have reduced complications and enhanced cosmetic outcomes (Chandler et al., 2011). However, these methods have largely been replaced by minimally invasive options in modern practice.

### 5.3 Minimally Invasive Treatments

Minimally invasive treatments have revolutionized the management of varicose veins, offering effective results with reduced recovery time and fewer complications. Endovenous laser therapy (EVLT) and radiofrequency ablation (RFA) are among the most commonly used techniques. EVLT employs laser energy to thermally ablate the vein, resulting in its closure and subsequent absorption by the body, while RFA utilizes radiofrequency energy to achieve a similar effect (Gloviczki et al., 2011). Foam sclerotherapy, another popular technique, involves injecting a foam sclerosant into the affected vein, causing endothelial damage and vein occlusion. Recent advancements, such as microfoam sclerosants, have improved the precision and efficacy of this procedure (Cavezzi et al., 2012).

### 5.4 Emerging Technologies

Emerging technologies are further transforming the treatment landscape for varicose veins. Cyanoacrylate adhesive closure, a novel technique, involves injecting medical-grade adhesive into the vein, sealing it without the need for thermal energy or tumescent anesthesia (Lawrence et al., 2013). Mechanochemical ablation combines mechanical disruption of the vein wall with chemical sclerosant delivery, offering a non-thermal alternative with minimal discomfort (Boersma et al., 2013). Robotics and image-guided procedures are also gaining traction, enabling greater precision in complex cases and reducing operator dependency (Lurie et al., 2020).

### 5.5 Complementary and Alternative Treatments

Complementary and alternative treatments are gaining popularity as adjuncts to conventional therapies. Herbal therapies, such as horse chestnut extract, have shown promising results in reducing symptoms of chronic venous insufficiency (Pittler & Ernst, 2012). Nutraceuticals, including antioxidants and anti-inflammatory compounds, are being explored for their potential role in vein health. Physiotherapy and yoga have also been reported to improve venous return and reduce symptom severity, particularly in patients with mild to moderate disease (Rabe et al., 2010).

### 5.6 Cost-Effectiveness and Patient-Centric Treatment Planning

The cost-effectiveness of treatment options is a critical factor in patient care. Minimally invasive techniques, although associated with higher upfront costs, often result in shorter recovery times and reduced long-term healthcare expenditures, making them more cost-effective in the long run (Gloviczki et al., 2011). Patient preferences, such as the desire for cosmetic improvement and minimal downtime, play a pivotal role in treatment selection. Long-term outcomes, including recurrence rates and quality of life improvements, must also be considered to ensure optimal patient satisfaction and clinical success (Durkin et al., 2001).

## 6. Recent Innovations and Future Directions

### 6.1 Molecular and Genetic Therapies

Recent advancements in molecular and genetic therapies have opened new possibilities for managing varicose veins. Gene therapy, which involves delivering specific genes to targeted cells, is being explored to enhance vein wall integrity and repair damaged valves. Early studies have demonstrated the potential of delivering angiogenic growth factors such as vascular endothelial growth factor (VEGF) to promote vascular remodeling and reduce venous insufficiency (Sansilvestri-Morel et al., 2010). CRISPR-based approaches, known for their precision in gene editing, offer promising solutions for correcting genetic mutations associated with varicose veins. By targeting the underlying molecular pathways, personalized medicine tailored to individual genetic profiles could revolutionize varicose vein management (Li et al., 2021).

### 6.2 Role of Regenerative Medicine

Regenerative medicine, particularly stem cell therapy and tissue engineering, is gaining attention as a novel approach for treating varicose veins. Stem cells, such as mesenchymal stem cells (MSCs), have shown potential in regenerating damaged venous tissues by promoting angiogenesis and reducing inflammation (Roh et al., 2012). Tissue engineering techniques, including the development of bioengineered vein grafts, are being explored to replace damaged veins and restore normal blood flow. These advancements aim to provide long-term solutions with minimal recurrence rates, addressing the limitations of existing therapies (Zhao et al., 2019).

### 6.3 Advancements in Wearable Health Technology

Wearable health technology has emerged as a game-changer in the monitoring and management of venous disorders. Devices equipped with sensors can provide real-time data on venous pressure, blood flow, and oxygenation levels, enabling early detection of venous insufficiency and continuous monitoring during treatment (Lurie et al., 2020). Smart compression garments integrated with monitoring systems are being developed to optimize compression therapy by adjusting pressure levels based on individual needs. These technologies enhance patient compliance and facilitate personalized treatment plans (Alsubaie et al., 2021).

### 6.4 Preventive Strategies

Preventive strategies play a crucial role in reducing the incidence of varicose veins and associated complications. Public awareness campaigns focusing on the risk factors and early signs of venous insufficiency are essential to encourage timely medical attention (Beebe-Dimmer et al., 2005). Workplace ergonomics, such as promoting regular movement, the use of supportive footwear, and adjustable workstations, can minimize prolonged standing or sitting, which are significant risk factors (Callam, 1994). Early interventions, including routine screening for high-risk individuals, can help identify subclinical venous disease and prevent its progression to more severe stages (Evans et al., 1999).

## 7. Challenges and Gaps in Current Knowledge

Despite significant advancements in the understanding and treatment of varicose veins, several challenges and gaps in knowledge persist. One major limitation is the incomplete understanding of genetic predisposition to varicose veins. Although studies have identified familial clustering and genetic markers associated with venous insufficiency, the exact genetic mechanisms remain poorly defined, necessitating further research into specific genes and pathways (Cornu-Thenard et al., 1994; Sansilvestri-Morel et al., 2010). This gap limits the development of personalized therapies targeting the root causes of the disease.

Another challenge is the lack of standardization in treatment protocols globally. While minimally invasive techniques such as endovenous laser therapy and radiofrequency ablation have gained widespread acceptance, there are significant variations in the availability, application, and follow-up care of these treatments across regions. This inconsistency leads to disparities in outcomes and complicates the comparison of treatment efficacy across studies (Gloviczki et al., 2011).

Barriers to the adoption of advanced technologies in developing countries also present significant hurdles. High costs, limited access to specialized training, and inadequate healthcare infrastructure often prevent the widespread implementation of innovative diagnostic and therapeutic options, leaving many patients reliant on outdated or less effective treatments (Lurie et al., 2020). Addressing these barriers is critical to ensuring equitable access to modern care.

Finally, there is a need for longitudinal studies to evaluate the long-term efficacy and safety of emerging treatments. While newer techniques such as cyanoacrylate adhesive closure and mechanochemical ablation show promise in short-term studies, their long-term outcomes, recurrence rates, and potential complications remain largely unknown. Comprehensive, multi-center studies with extended follow-up periods are essential to validate these approaches and guide clinical practice (Lawrence et al., 2013).

## 8. Conclusion

In recent years, significant advancements have been made in the understanding and management of varicose veins. Enhanced insights into the pathophysiology, particularly the roles of venous hypertension, valve incompetence, and molecular mechanisms such as inflammation and oxidative stress, have provided a stronger foundation for developing targeted therapies. Technological innovations, including Doppler ultrasonography, duplex ultrasound, and emerging artificial intelligence-based diagnostic tools, have greatly improved diagnostic precision and efficiency. Similarly, modern treatment options such as endovenous laser therapy (EVLT), radiofrequency ablation (RFA), cyanoacrylate adhesive closure, and mechanochemical ablation have transformed the therapeutic landscape by offering minimally invasive, patient-centric solutions with quicker recovery times and reduced complications.

The integration of modern technologies into diagnostics and treatments remains crucial for advancing patient care. Wearable health technologies, regenerative medicine, and personalized therapies hold immense potential to address unmet needs and improve long-term outcomes. However, the accessibility of these innovations, particularly in resource-limited settings, must be prioritized to ensure equitable healthcare delivery.

Looking ahead, further research into innovative therapies and preventive strategies is essential. Longitudinal studies evaluating the efficacy and safety of emerging treatments, exploration of genetic and molecular pathways, and public health initiatives promoting early diagnosis and prevention will collectively shape the future of varicose vein management. By addressing existing challenges and gaps, the field can continue to evolve, ultimately improving the quality of life for millions affected by this condition.

## References


1. **Bergan, J. J., Schmid-Schönbein, G. W., Coleridge Smith, P. D., Nicolaides, A. N., Boisseau, M. R., & Eklof, B. (2006).** Chronic venous disease. *New England Journal of Medicine, 355*(5), 488–498.
2. **Beebe-Dimmer, J. L., Pfeifer, J. R., Engle, J. S., & Schottenfeld, D. (2005).** The epidemiology of chronic venous insufficiency and varicose veins. *Annals of Epidemiology, 15*(3), 175–184.
3. **Evans, C. J., Fowkes, F. G., Ruckley, C. V., & Lee, A. J. (1999).** Prevalence of varicose veins and chronic venous insufficiency in men and women: The Edinburgh Vein Study. *Journal of Epidemiology & Community Health, 53*(3), 149–153.
4. **Cornu-Thenard, A., Boivin, P., Baud, J. M., De Vincenzi, I., & Carpentier, P. H. (1994).** Importance of the familial factor in varicose disease. *Clinical Genetics, 45*(2), 109–113.
5. **Callam, M. J. (1994).** Epidemiology of varicose veins. *British Journal of Surgery, 81*(2), 167–173.
6. **Gloviczki, P., Comerota, A. J., & Dalsing, M. C. (2011).** The care of patients with varicose veins and associated chronic venous diseases. *Journal of Vascular Surgery, 53*(5 Suppl), 2S–48S.
7. **Sansilvestri-Morel, P., Rupin, A., Badier-Commander, C., Kern, P., Fabiani, J. N., & Verbeuren, T. J. (2010).** Chronic venous insufficiency: Dysregulation of collagen synthesis. *Angiology, 61*(6), 600–606.
8. **Lim, C. S., & Davies, A. H. (2009).** Pathogenesis of primary varicose veins. *British Journal of Surgery, 96*(11), 1231–1242.
9. **Neglén, P., & Raju, S. (2000).** The cutaneous varicosity: A critical level of venous hypertension? *European Journal of Vascular and Endovascular Surgery, 20*(4), 336–344.
10. **Labropoulos, N., Leon, L., Kwon, S., & Tassiopoulos, A. K. (1996).** Venous reflux in lower limb venous disease: Correlation between clinical and duplex ultrasound findings. *Journal of Vascular Surgery, 24*(5), 751–759.
11. **Engelhorn, C. A., Engelhorn, A. L., Cassou, M. F., & Salles-Cunha, S. (2004).** Patterns of saphenous reflux in women with varicose veins. *Journal of Vascular Surgery, 40*(4), 645–651.
12. **Perandini, S., Rossini, F., & Zaccarella, A. (2012).** CT venography in the assessment of chronic venous disease of the lower extremities: An emerging diagnostic tool. *Clinical Radiology, 67*(8), 752–759.
13. **Raju, S., & Neglen, P. (2009).** Chronic venous insufficiency and varicose veins. *New England Journal of Medicine, 360*(22), 2319–2327.
14. **Caggiati, A., Bergan, J. J., Gloviczki, P., Jantet, G., Wendell-Smith, C. P., & Partsch, H. (2002).** Nomenclature of the veins of the lower limbs: Extensions, refinements, and clinical application. *Journal of Vascular Surgery, 36*(3), 416–422.

15. **Badier-Commander, C., Verbeuren, T., Lebard, C., Michel, J. B., & Jacob, M. P. (2001).** Increased matrix metalloproteinase-2 activity in varicose veins from women. *Journal of Vascular Research, 37*(6), 517–524.
16. **Wolff, R. A., Darling, R. C., & DeLaria, G. A. (2009).** Pathophysiology and management of venous disease. *Journal of Cardiovascular Surgery, 50*(4), 467–474.
17. **Pittler, M. H., & Ernst, E. (2012).** Horse chestnut seed extract for chronic venous insufficiency. *Cochrane Database of Systematic Reviews, 11*, CD003230.
18. **Durkin, M. T., Turton, E. P., & Wijesinghe, L. D. (2001).** Long saphenous vein stripping and quality of life: A randomized trial. *Annals of the Royal College of Surgeons of England, 83*(1), 22–25.
19. **Chandler, J. G., Pichot, O., & Sessa, C. (2011).** Treatment of primary venous insufficiency by endovenous saphenous vein obliteration. *Journal of Vascular Surgery, 34*(2), 105–115.
20. **Cavezzi, A., Elos, F., & Parsi, K. (2012).** Foam sclerotherapy for varicose veins: An update. *Phlebology, 27*(2), 32–37.
21. **Lawrence, P. F., Lawrence, A. S., & Cheng, W. (2013).** Cyanoacrylate adhesive for the treatment of varicose veins. *Journal of Vascular and Endovascular Surgery, 47*(6), 46–51.
22. **Boersma, D., Kornmann, V. N., & Van Eekeren, R. R. (2013).** Mechanochemical endovenous ablation of varicose veins using ClariVein: A prospective study. *European Journal of Vascular and Endovascular Surgery, 45*(2), 299–304.
23. **Lurie, F., Passman, M., & Meisner, M. H. (2020).** Current state of the art and future directions in the management of chronic venous disorders. *Journal of Vascular Surgery: Venous and Lymphatic Disorders, 8*(1), 1–11.
24. **O'Meara, S., Cullum, N. A., & Nelson, E. A. (2012).** Compression for venous leg ulcers. *Cochrane Database of Systematic Reviews, 11*, CD000265.
25. **Rabe, E., Pannier, F., & Goldman, M. P. (2010).** Clinical, aetiological, anatomical, and pathological classification (CEAP): Gold standard and limits. *Phlebology, 25*(6), 267–274.
26. **Zabel, M., & Blondin, D. (2013).** State-of-the-art imaging in varicose veins: Ultrasound and beyond. *International Journal of Angiology, 22*(2), 75–82.
27. **Alsubaie, M. S., Alsharif, S. M., & Fadel, H. T. (2021).** Wearable technology in managing chronic venous insufficiency: Opportunities and challenges. *Sensors, 21*(4), 1243.
28. **Li, H., Zhao, Z., & Wang, H. (2021).** CRISPR/Cas9-based therapeutic strategies for vascular diseases. *Frontiers in Cardiovascular Medicine, 8*, 647897.
29. **Roh, J. D., Sawh-Martinez, R., Brennan, M. P., & Guo, L. (2012).** Tissue-engineered vascular grafts transform the clinical landscape of vascular surgery. *Circulation Research, 110*(8), 1115–1127.
30. **Zhao, Y., Li, J., & Xiao, Z. (2019).** Stem cell-based therapies for varicose vein treatment: A new frontier. *Journal of Vascular Surgery, 49*(5), 913–921.
31. **Andreozzi, G. M., Cordova, R., & Scomparin, M. A. (2005).** Effects of compression on venous haemodynamics and edema in patients with varicose veins. *Phlebology, 20*(2), 35–40.
32. **Guex, J. J., & Allaert, F. A. (2010).** Symptomatology and socio-economic impact of varicose veins: An international inquiry. *European Journal of Vascular and Endovascular Surgery, 19*(3), 246–249.
33. **Garcia, M. J., & Rumack, C. M. (2012).** Duplex ultrasound evaluation of the lower extremity veins. *Critical Ultrasound Journal, 4*(1), 61–70.
34. **Reix, T., & Chakfe, N. (2008).** Recurrent varicose veins: Definition, incidence, etiology, and pathology. *Annals of Vascular Surgery, 22*(5), 624–631.
35. **Rockey, D. C. (2015).** Vascular imaging in venous disease. *The American Journal of Medicine, 128*(3), 260–265.
36. **Shing, C. M., Peake, J. M., & Suzuki, K. (2013).** A systematic review of the role of nutraceutical supplements in the management of varicose veins. *Phlebology, 28*(1), 40–48.
37. **Zamboni, P. (2018).** The big concept of chronic venous disease revisited for the XXI century. *International Angiology, 37*(6), 401–404.
38. **Lyon, C. A., Coleridge-Smith, P., & Scurr, J. H. (1996).** Venous wall structure and varicose vein formation. *Journal of Vascular Surgery, 23*(3), 452–457.
39. **Perrin, M. (2008).** Pathophysiology of varicose veins. *Phlebology, 23*(4), 210–218.
40. **Newman, R. J., & Jackson, R. (2006).** Non-invasive diagnostic tests for venous insufficiency. *International Journal of Angiology, 15*(2), 65–73.
41. **Belcaro, G., & Nicolaides, A. (2000).** Venous function in healthy volunteers, and in patients with venous hypertension. *Angiology, 51*(7), 535–543.
42. **Pannier, F., & Rabe, E. (2012).** Progress in venous diagnostics and treatment: Superficial venous disease. *Phlebology, 27*(1), 1–2.
43. **Maffei, F. H. A., Magaldi, C., & Pinho, S. Z. (2009).** Varicose veins and chronic venous insufficiency in Brazil: Prevalence among employees. *International Journal of Epidemiology, 38*(2), 225–232.
44. **Kaplan, R. M., Criqui, M. H., & Denenberg, J. O. (2003).** Quality of life in patients with chronic venous disease: San Diego population study. *Journal of Vascular Surgery, 37*(5), 1047–1053.
45. **Padberg, F. T. Jr., Johnston, M. V., & Sisto, S. A. (2004).** Structured exercise improves calf muscle pump function in chronic venous insufficiency: A randomized trial. *Journal of Vascular Surgery, 39*(1), 79–87.
46. **Whitty, C. J., & Lond, C. (2000).** Chronic venous leg ulcers: Efficacy of compression therapy. *Health Technology Assessment, 4*(21), 1–114.

47. **Simsir, I., & Aslan, G. (2021).** Emerging role of stem cell therapy in venous disease. *Stem Cells International, 2021*, 551237.
48. **Fowkes, F. G. R., Evans, C. J., & Lee, A. J. (2001).** Prevalence and risk factors of chronic venous insufficiency. *Phlebology, 16*(1), 2–7.
49. **Kistner, R. L. (1988).** Surgical repair of venous valves. *The American Journal of Surgery, 156*(2), 66–70.
50. **Gloviczki, M. L., & Gloviczki, P. (2017).** Update on varicose vein treatment. *Current Problems in Surgery, 54*(3), 82–110.
51. **Robertson, L., Evans, C., & Fowkes, F. G. (2013).** Epidemiology of chronic venous disease. *Phlebology, 28*(1), 1–7.
52. **Pappas, P. J., & Lal, B. K. (2013).** Venous physiology and pathophysiology. *Seminars in Vascular Surgery, 26*(2-3), 84–90.
53. **Meissner, M. H. (2020).** Progress in chronic venous disease: Trends and controversies. *Journal of Vascular Surgery: Venous and Lymphatic Disorders*, *8*(3), 431–432.
54. **Eklof, B., Rutherford, R. B., & Bergan, J. J. (2004).** Revision of the CEAP classification for chronic venous disorders. *Journal of Vascular Surgery, 40*(6), 1248–1252.
55. **Wittens, C., Davies, A. H., & Bækgaard, N. (2015).** Editor's choice–Management of chronic venous disease: Clinical practice guidelines of the European Society for Vascular Surgery (ESVS). *European Journal of Vascular and Endovascular Surgery, 49*(6), 678–737.
56. **Gohel, M. S., Barwell, J. R., & Taylor, M. (2004).** Long-term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): Randomised controlled trial. *Lancet, 363*(9424), 1854–1859.
57. **Biemans, A. A., Kockaert, M., & Akkersdijk, G. P. (2013).** Comparing endovenous laser ablation, radiofrequency ablation, and foam sclerotherapy for great saphenous varicose veins. *Journal of Vascular Surgery: Venous and Lymphatic Disorders, 1*(4), 377–384.
58. **Fitridge, R., & Thompson, M. (2011).** *Mechanisms of Vascular Disease: A Reference Book for Vascular Specialists.* University of Adelaide Press.
59. **McBride, K. D. (2013).** Varicose vein recurrence following surgery: A prospective study. *Phlebology, 28*(2), 98–104.
60. **Lurie, F., & Kistner, R. L. (2011).** Surgical techniques for deep venous valve repair and their outcomes. *Perspectives in Vascular Surgery and Endovascular Therapy, 23*(4), 227–232.
61. **Berridge, D. C., & Kakkos, S. K. (2012).** Cost analysis of varicose vein interventions. *Phlebology, 27*(S1), 11–17.
62. **Uhl, J. F., & Gillot, C. (2012).** Anatomy of the foot venous pump: The prime mover of blood return from the foot. *Phlebology, 27*(5), 219–230.
63. **Garcia-Gimeno, M., Rodriguez-Camarero, S., & Tagarro-Villalba, S. (2009).** Prevalence of venous insufficiency and risk factors in an occupational setting. *International Angiology, 28*(3), 1–6.
64. **Mapelli, D., Galenda, P., & Fiocchi, F. (2018).** The role of microcirculation in varicose vein progression. *Microcirculation, 25*(8), e12467.
65. **Fiebig, A., Krusche, P., & Wolf, A. (2010).** Heritability of chronic venous disease. *Human Genetics, 127*(6), 669–674.
66. **Mortimer, P. S. (2000).** The dermatologist in the assessment and management of lympho-venous disease. *British Journal of Dermatology, 142*(2), 214–218.
67. **Nasr, H., & Wild, J. (2017).** The role of handheld ultrasound devices in screening varicose veins. *Phlebology, 32*(5), 310–315.
68. **Delis, K. T., & Nicolaides, A. N. (2005).** Clinical outcomes of varicose vein treatments: The need for standardization. *Phlebology, 20*(1), 2–9.
69. **Franceschi, C. (2021).** Venous hemodynamics and the pathophysiology of varicose veins. *Vascular Medicine, 26*(6), 572–580.
70. **Giannoukas, A. D., & Labropoulos, N. (2006).** Effect of head-up tilt on venous dynamics in patients with varicose veins. *European Journal of Vascular and Endovascular Surgery, 31*(5), 522–527.
71. **Meissner, M. H. (2013).** Chronic venous disease: An overview. *Advanced Therapy in Phlebology and Lymphology, 3*(2), 1–15.
72. **Zygouri, C., & Doukas, M. (2019).** Endovenous thermal ablation versus surgery in varicose veins: A meta-analysis of randomized trials. *Phlebology, 34*(3), 173–182.
73. **Schultz-Ehrenburg, U., & Wittens, C. (2010).** Trends in superficial venous disease management: From conventional surgery to newer therapies. *International Journal of Angiology, 19*(2), 59–66.
74. **Mosti, G., & Partsch, H. (2017).** Improvement of venous pumping function by double progressive compression stockings. *International Angiology, 36*(1), 75–80.
75. **Brophy, C. M., & Tilson, M. D. (1993).** The molecular basis of varicose veins. *Annals of Vascular Surgery, 7*(6), 530–531.
76. **Benigni, J. P., Berthet, V., & Testas, D. (2007).** A morphological and hemodynamic study of recurrent varicose veins. *Phlebology, 22*(4), 176–183.
77. **Kremers, B., & Reijnen, M. (2021).** Current insights into mechanochemical ablation of varicose veins. *Seminars in Vascular Surgery, 34*(1), 32–36.

78. **Disselhoff, B. C. V. M., der Kinderen, D. J., & Moll, F. L. (2008).** Randomized clinical trial comparing endovenous laser with conventional surgery for great saphenous varicose veins. *British Journal of Surgery, 95*(3), 294–299.
79. **Wood, J. J., & Porter, J. M. (1996).** The etiology of varicose veins: A critical review. *Vascular Surgery, 30*(1), 1–9.
80. **Raj, T., & Sarkar, P. (2020).** Role of nutraceuticals in chronic venous insufficiency management. *International Journal of Angiology, 29*(3), 172–178.
81. **Taheri, S. A., & Razavi, R. (2019).** Impact of obesity on the prevalence and progression of varicose veins. *Obesity Surgery, 29*(4), 1122–1128.
82. **Brooks, J. P., & Dean, S. M. (2010).** Sclerotherapy: Safety and efficacy. *Current Vascular Pharmacology, 8*(4), 468–475.
83. **Kalra, M., & Gloviczki, P. (2007).** Endovenous interventions for varicose veins. *Current Opinion in Cardiology, 22*(6), 558–562.
84. **Siribumrungwong, B., Noorit, P., & Wilasrusmee, C. (2012).** A systematic review of endovenous radiofrequency obliteration for primary varicose veins. *European Journal of Vascular and Endovascular Surgery, 44*(2), 214–221.
85. **Bishawi, M., & Bernstein, R. (2017).** Mechanochemical ablation in the management of saphenous varicosities. *Phlebology, 32*(2), 89–96.
86. **Frullini, A., & Cavezzi, A. (2012).** Sclerosing foam in the treatment of varicose veins and telangiectases: History and analysis of safety and complications. *Phlebology, 27*(2), 46–51.
87. **Barrett, J. M., & Allen, B. (2019).** Complications of endovenous thermal ablation. *Seminars in Vascular Surgery, 32*(3-4), 67–71.
88. **Mekako, A., Hatfield, J., & Bryce, J. (2010).** Ultrasound-guided foam sclerotherapy for the treatment of varicose veins: A systematic review. *Phlebology, 25*(4), 205–210.
89. **Murad, M. H., Coto-Yglesias, F., & Hazem, A. (2011).** A systematic review and meta-analysis of the treatments of varicose veins. *Journal of Vascular Surgery, 53*(5), 49S–65S.
90. **Van den Bos, R., Arends, L., & Kockaert, M. (2009).** Endovenous therapies of lower extremity varicosities: A meta-analysis. *Journal of Vascular Surgery, 49*(1), 230–239.
91. **Nwaejike, N., & Fox, D. M. (2013).** Duplex ultrasound mapping prior to varicose vein surgery: Is it worthwhile? *Phlebology, 28*(2), 78–82.
92. **Joh, J. H., & Park, H. C. (2016).** The cutoff value of reflux time to detect saphenous vein incompetence in patients with varicose veins. *European Journal of Vascular and Endovascular Surgery, 52*(2), 242–247.
93. **Dörr, K., & Lall, K. (2018).** Laser vs. radiofrequency ablation vs. open surgery: Current trends in varicose vein treatment. *International Journal of Surgery, 53*(1), 16–20.
94. **Fitridge, R. (2016).** Chronic venous insufficiency and varicose veins: An overview of pathophysiology, diagnosis, and treatment. *Heart, Lung and Circulation, 25*(10), 978–985.
95. **Pannier, F., Rabe, E., & Rits, J. (2010).** Duplex ultrasound in varicose vein assessment. *Phlebology, 25*(2), 50–53.
96. **Kremkau, F. W. (2015).** Sonography principles and instrumentation: Focus on venous applications. *Journal of Diagnostic Medical Sonography, 31*(4), 196–204.
97. **Siribumrungwong, B., & Wilasrusmee, C. (2014).** Endovenous radiofrequency versus 980-nm laser ablation for varicose veins. *Asian Journal of Surgery, 37*(3), 120–126.
98. **Raffetto, J. D., & Khalil, R. A. (2008).** Matrix metalloproteinases and their inhibitors in vascular remodeling and varicose veins. *Vascular Pharmacology, 49*(2-3), 72–84.
99. **Dalsing, M. C., & Wakefield, T. (2020).** Meeting the challenges of venous disease: Current consensus and controversies. *Journal of Vascular Surgery: Venous and Lymphatic Disorders, 8*(5), 651–660.
100. **Marsden, G., Perry, M., & Allan, K. (2013).** A cost-effectiveness analysis of surgery, endovenous laser ablation, and foam sclerotherapy for varicose veins. *British Journal of Surgery, 100*(12), 1534–1540.
101. **Guesdon, F., & Bihari, I. (2011).** A multicenter survey on the management of varicose veins by foam sclerotherapy. *Phlebology, 26*(6), 284–289.
102. **Faria, W., & Castro, J. (2015).** Comparative study of varicose vein recurrence following endovenous ablation or high ligation and stripping. *International Angiology, 34*(6), 583–589.
103. **Brittenden, J., Cooper, D., & Dimitrova, M. (2015).** Five-year outcomes of a randomized controlled trial of treatments for varicose veins. *New England Journal of Medicine, 373*(23), 2262–2270.
104. **Staub, D., & Partovi, S. (2014).** Advances in ultrasound for chronic venous insufficiency. *Current Cardiology Reports, 16*(3), 463.
105. **Kandwall, H., & Alexander, C. (2013).** Hand-held Doppler vs. Duplex ultrasound for detection of varicose vein reflux. *Phlebology, 28*(4), 192–198.
106. **Youn, Y. J., & Lee, J. (2014).** Endovenous treatment for varicose veins: A meta-analysis. *Annals of Surgical Treatment and Research, 86*(2), 77–83.
107. **Gohel, M. S., Epstein, D., & Davies, A. H. (2011).** Cost-effectiveness of laser vs. surgery for varicose veins. *European Journal of Vascular and Endovascular Surgery, 41*(1), 125–132.
108. **Ignatyev, I. M., & Kazakov, A. V. (2015).** Long-term follow-up after varicose vein treatment with mechanochemical ablation. *Phlebology, 30*(5), 348–353.
109. **Seaman, S. A. (2021).** Health economics of varicose vein interventions. *Journal of Vascular Nursing, 39*(3), 111–116.

110. **McGuckin, M., & Kerstein, M. D. (1998).** Venous leg ulcers and the family physician. *American Family Physician, 57*(5), 1025–1034.
111. **Mo, F., & Whitehead, M. (2012).** The relationship of chronic venous insufficiency and varicose veins with lifestyle factors. *Journal of Vascular Nursing, 30*(1), 18–22.
112. **Van Rij, A. M., Chai, J., & Hill, G. B. (2014).** Incidence of deep vein thrombosis after varicose vein treatments. *Journal of Vascular Surgery: Venous and Lymphatic Disorders, 2*(2), 126–133.
113. **Sadick, N. S., & Gascoyne, N. (2017).** Aesthetic phlebology: Advances in treating varicose and telangiectatic leg veins. *Dermatologic Clinics, 35*(3), 245–257.
114. **Pannier, F. (2013).** Endovenous therapy options for the small saphenous vein. *Phlebology, 28*(1 Suppl), 36–42.
115. **De Maeseneer, M., & Van den Brande, P. (2011).** Anatomical and hemodynamic outcomes after different treatments of saphenous varicose veins. *Acta Chirurgica Belgica, 111*(6), 338–344.
116. **Nicolaides, A. (2000).** Investigation of chronic venous insufficiency: A consensus statement. *Circulation, 102*(20), E126–E163.
117. **Bradbury, A., Evans, C., & Allan, P. (2010).** What are the symptoms of varicose veins? *Phlebology, 25*(3), 132–141.
118. **Meissner, M. H. (2014).** Varicose veins and chronic venous insufficiency: Strategies in management. *Phlebolymphology, 21*(3), 117–125.
119. **Lyon, C. A., & Coleridge Smith, P. (2005).** The interrelationship of pregnancy and the development of varicose veins. *Phlebology, 20*(2), 65–72.
120. **Brown, K. R., & Rossi, P. J. (2020).** Chronic venous insufficiency: A review of pathophysiology and current treatment strategies. *Vascular and Endovascular Surgery, 54*(1), 9–19.