OTHER PAIN (A. KAYE AND N. VADIVELU, SECTION EDITORS)

Current Therapeutic Interventions in Lower Extremity Venous Insufficiency: a Comprehensive Review

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Abstract

Purpose of Review Chronic venous disease (CVD), although affecting up to 40% of the US population, is often underdiagnosed by healthcare professionals due to an incomplete understanding of the presenting symptoms. CVD is a common cause of lower extremity pain and discomfort, including aching, cramping, tingling, burning, swelling, heaviness, restlessness, and fatigue, and may lead to significant morbidity if left untreated. The negative impact of CVD on quality of life is well established and the optimization of management strategies is an important area of evolving research.
Recent Findings Management of CVD has rapidly evolved over the last two decades with the development of minimally invasive endovenous ablative techniques, now the mainstay of treatment. We discuss the data supporting various methods of CVD treatment with an emphasis on the impact on patient comfort and quality of life.
Summary Both radiofrequency ablation (RFA) and endovenous laser therapy (EVLA) are excellent options for treatment of lower extremity venous disease, but RFA is associated with less post-procedure discomfort. Ultrasound-guided foam therapy is best reserved for the adjuvant setting or for patients ineligible for RFA or EVLA.

Keywords Chronic venous disease · Ablation · Radiofrequency · Laser · Treatment · Varicose vein

Introduction

Lower extremity chronic venous disease (CVD) is a common and under-recognized cause of lower extremity pain and discomfort. Venous disease develops when peripheral blood return is impaired and venous pressure is increased due to several factors including muscular pump dysfunction and valvular incompetence. Valvular incompetence, primarily at the junction of the great saphenous vein with the common femoral vein (saphenofemoral junction or

SFJ) and the small saphenous vein at the level of the popliteal vein (sapheno-popliteal junction or SPJ) leads to position-dependent retrograde blood flow, causing venous hypertension. The consequences of venous hypertension range from the development of varicose veins (as well as reticular veins and telangiectasias) and edema to skin changes and frank ulceration. CVD is formally described according to the CEAP (clinical, etiologic, anatomic, pathophysiologic) classification (Table 1) [1]. The degree of clinically appreciable disease ranges from normal-appearing legs (C0) to severe venous stasis with ulceration (C6), with or without symptoms (S or A). C4-C6 disease is referred to as chronic venous insufficiency (CVI), with the essential condition being ambulatory venous hypertension, and there is evidence that if left untreated, up to half of even mild clinical disease will progress to this stage [2]. Functional disease, defined as documented reflux (typically retrograde blood flow of > 500 ms duration) on ultrasonography, may be present at the SFJ, SPJ, or both and concurrent reflux in the deep venous system may be present as well in a minority of patients [1].

Multiple large-scale cross-sectional studies have demonstrated that CVD is the most common vascular disorder, with

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Table 1 Chronic venous disease is formally described according to the CEAP (clinical, etiologic, anatomic, pathophysiologic) classification. CEAP clinical score and corresponding description

CEAP clinical score		Description
C0		No visible or palpable varicose veins
C1		Telangiectasia (thread veins/spider veins/broken veins)
C2	C2A	Varicose veins without any symptoms (asymptomatic)
	C2S	Varicose veins with symptoms
C3		Swollen ankle (edema) due to varicose veins or hidden varicose veins (venous reflux)
C4		Skin damage due to varicose veins or hidden varicose veins (venous reflux)
C5		Healed venous leg ulcer
C6		Venous leg ulcer

at least 15% of men and 25% of women suffering from functional disease [3–5]. Typical symptoms of venous disease include aching, cramping, fatigue, heaviness, restlessness, and swelling. Symptoms are due to a number of causes, including inflammation and pressure on adjacent nerves by dilated veins, and often worsen with prolonged standing and warm weather. Symptoms have a cumulative profound effect on patient mobility and quality of life. The most common tool used to assess symptom burden is the venous clinical severity score (VCSS), a ten-item clinician-administered evaluation, with each item assigned a value 1–3, for a total score of up to 30 [6]. The correlation between symptom burden and degree of clinical venous disease has been well established, with all typical symptoms reported more frequently with increasing clinical disease category [3]. A recent multivariate analysis of a large cross-sectional study accounted for confounding factors such as age, obesity, and gender and found that the presence of even C2 disease significantly increases reported leg symptoms (OR 1.5 CI 1.04–2.1). For more significant clinical disease C4 or greater, a strong association with symptom burden is noted, OR of 4.0 (CI 1.1–8.1) [7••].

The impact of symptoms on quality of life has been studied extensively, with most major trials of CVD treatment evaluating patient-reported overall and disease-specific quality of life in addition to clinician assessment of symptom burden. The two most common validated tools assessing disease-specific QOL are the Aberdeen Varicose Vein Questionnaire Score (AVVQ) [8] and the Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ) [9]. Both of these show a strong association with general QOL scores used by the broader medical community such as the EQ-5D [10].

Treatment of symptomatic CVD can be conservative or definitive. Conservative treatment consists mainly of medical-grade compression stockings, exercise, and weight loss. Definitive therapy includes elimination of the culprit vein (great saphenous, small saphenous or both) with adjunct treatment of perforating veins and symptomatic varicosities. Due to the relatively low efficacy of conservative therapy, immediate definitive therapy is recommended for patients with symptomatic disease and documented reflux under current guidelines in the USA [11, 12••].

Historically, treatment of CVD was primarily surgical, typically ligation and stripping of the GSV and SSV at the SFJ and SPJ respectively, with concurrent distal phlebectomy of bulging symptomatic varicosities. Multiple studies demonstrated improvement in symptom burden (VCSS) after surgery [13, 14]. Direct evidence of a quality of life benefit is available as well; an RCT comparing surgery to conservative therapy showed a profound QOL impact and demonstrated cost-efficacy [15]. However, in addition to incurring patient anxiety, these procedures required a relatively prolonged recovery period of up to 2 weeks and were associated with typical surgical complications including hematoma, cellulitis, and abscess formation in up to 3% of patients [16]. Recurrence rates were often high as well, with up to 30% of patients requiring additional procedures with extended follow up [17].

Over the past two decades, three minimally invasive techniques of vein ablation have largely supplanted surgery. The first to emerge, sclerotherapy, relies on injection of a chemical agent into the vein causing endothelial damage, adhesion, and fibrosis. Subsequently, systems delivering thermal energy to the vein endothelium either via radiofrequency or laser light energy were developed. Application of thermal energy results in a similar process of damage, adhesion, and fibrosis of residual venous tissue. More recently, catheter-based delivery of an adhesive agent has emerged as a novel technique to consider alongside sclerotherapy and endoluminal thermal ablation. As each method came into practice, trials were conducted comparing it to surgery. Several trials have examined different methods of endoluminal ablation in comparison to one another, even as the technology continues to be rapidly refined and improved. Endpoints vary among trials but include clinical success, defined by persistent GSV closure, by the absence of recurrent varicose veins and an improvement in CEAP category. Arguably more important endpoints include reduction in clinician-assessed symptom burden (VCSS) and health-related and disease-specific quality of life (generally assessed using the tools described above). We review the different endoluminal ablation methods in subsequent sections then conclude by discussing the latest evidence and future directions in the field.

Sclerotherapy

Sclerotherapy was initially used as an adjunct to surgery, with the injection of a liquid sclerosant into residual reticular or varicose veins after surgery was performed to address the GSV or SSV. Dose limitations for systemic delivery precluded the use of liquid sclerosants in larger veins. However, mixing liquid sclerosant with gas to create a foam which could be injected into the vein under ultrasound guidance allowed for more controlled delivery as well as coverage of a much greater surface area using a smaller volume of sclerosant [18]. The efficacy of ultrasound-guided foam sclerotherapy (UGFS) was explored further in several trials. A large series ($n = 500$) demonstrated obliteration of the GSV in 81% of patients with UGFS, and larger veins were associated with a higher rate of failure [19]. A subsequent three-arm RCT compared foam to liquid sclerotherapy and surgery. A trend towards higher efficacy was noted in the surgery group at 1 year, with 86% persistent occlusion compared to 79% treated with UGFS, but this difference did not achieve statistical significance. These investigators did not assess quality of life but did note that patients treated with UGFS were able to return to work after only 2 days, compared to 13 day for surgery [20]. In another RCT ($N = 530$) comparing surgery to UGFS, treatment failure with GSV reflux on ultrasound was more frequent in the UGFS group compared to surgery at 2 years (35 vs 21%, $p = 0.003$) but there was no statistically significant difference in symptom burden (VCSS) which was significantly improved in both groups. In addition, health-related quality of life (EQ-5D) was significantly improved for all patients [21]. More recent studies that include several different modalities of endoluminal ablation confirm improvements in QOL using disease-specific quality of life tools when UGFS is employed [22••, 23, 24••].

Radiofrequency Ablation

Endothelial damage caused by thermal energy is an effective tool for closure of vessels, and applying this technology to the treatment of CVD was a natural evolution. In radiofrequency ablation (RFA), thermal energy is generated via a rapidly alternating current transmitted through an electrode and applied to the venous endothelium. RFA devices are introduced under ultrasound guidance and placed just distal to the superficial venous junction. First-generation devices relied on continuous gradual withdrawal of the probe; more recently, fixed cycles of energy delivery with staged withdrawal have been employed. To provide anesthesia as well as to spare surrounding structures from thermal damage, a tumescent solution of lidocaine and saline is administered into the tissue surrounding the vein. Initial trials comparing RFA to surgery showed that it was clinically effective with durable GSV closure of 82–95% at least 2 years of follow up [24••, 25, 26]. Two studies specifically evaluated patient pain in the first week following the procedure and found a statistically significant difference favoring RFA. Median time to resumption of normal activity was evaluated in two studies and found to be significantly better for RFA (1–3 days) compared to surgery (4–12.5 days) [25, 27] with an analogous benefit of shorter post-procedural hospital stay noted in a third study [26]. The impact on patient quality of life has been evaluated extensively as well, with a demonstrable benefit in all studies [25–27]. In two of the studies [25, 27], the disease-specific quality of life benefit achieved with RFA was significantly more substantial than with surgery.

Endovenous Laser Ablation

Endovenous laser ablation (EVLA) is performed in a manner similar to RFA. A catheter is placed under ultrasound guidance and thermal energy is delivered to the vein endothelium. Tumescent anesthesia is delivered under ultrasound guidance to spare surrounding structures and several iterations of devices (using different laser wavelengths) have been studied at this time. A large-scale cohort study demonstrated durable efficacy and tolerability, with 93% vein closure rates at 2 year follow up [28]. Subsequent randomized controlled trials comparing EVLA to surgery showed similar clinical efficacy that did not differ between groups [29, 30]. Both of these trials showed significant improvement in disease-specific quality of life with a trend towards EVLA over surgery that did not reach statistical significance. A similar positive impact on overall QOL was seen with both surgery and EVLA. A more recent study comparing EVLA to surgery reported a significantly decreased rate of recurrent reflux (clinically or ultrasonographically) with EVLA relative to surgery and an improvement in disease-specific quality of life when compared to surgery.

Adhesive Therapy

The newest endoluminal treatment option to emerge is catheter-based injection of an adhesive agent, cyanoacrylate (CAE). Unlike EVLA and RFA, this procedure does not require tumescent anesthesia, potentially shortening procedure times and leading to less significant ecchymosis and swelling in the treated limb. A pilot study demonstrated efficacy and tolerability with a 92% closure rate at 2 years of follow up, comparable to other therapies using current technology. A significant and substantial decrease in symptom burden (VCSS) from baseline was detected as well ($p < 0.001$) [31]. A subsequent prospective trial evaluated perioperative functional status and disease-specific quality of life. The median time to resumption of normal activities was 2 days,

comparable or superior to other endovenous therapies. At 3 months of follow up, the investigators reported 100% persistent vein closure and significant improvements in both physician-assessed symptom burden (VCSS) and patient-documented disease-specific QOL (AVVQ) [32••]. A single RCT (N = 222) comparing cyanoacrylate to RFA reported initial results of comparable efficacy at 3-month follow up with 99% closure rate for CAE and 96% for RFA. Patient-reported pain scores were low and similar for both groups with a small but statistically significant decrease in bruising noted after CAE at 3 days post-intervention [33].

Discussion

Each of the minimally invasive endoluminal ablation therapies have proven clinical efficacy and quality-of-life benefits comparable (or superior) to surgery. The focus of research at this time has shifted to monitoring long-term (> 5 years) durability of therapy and comparing different treatment modalities within the same trial.

A Scandinavian RCT enrolled 214 patients with symptomatic C2-C4 disease and GSV reflux and randomized them to surgery, EVLA or UGFS, with primary endpoints of disease-specific quality of life and successful GSV closure [34]. At 1 year, they found that surgery and EVLA were equally effective, with a 97% closure rate in both groups. UGFS was inferior to both of the other treatments, with a closure rate of only 51% at 1 year ($p < 0.001$). However, all three groups experienced a disease-specific quality-of-life benefit (AVVQ) with no difference in benefit between the groups. Time to return to work was also measured and was significantly better for the UGFS group (1 day) than for EVLA (8 days) and surgery (12 days) ($P < 0.001$). Of note, six patients randomized to EVLA were treated with surgery due to the preference of the operating surgeon but analyzed with intention-to-treat in the EVLA category. Concurrent phlebectomies of residual varicose veins were performed on patients receiving EVLA, perhaps accounting for the delayed return to work relative to UGFS [34]. At 5 years of follow up, the investigators reported a 96% closure rate (CI 91–100) for surgery, 89% (CI 82–98) for EVLA, and 51% (CI 38–64) after UGFS ($p < 0.001$). Of note, a significant number of patients in the UGFS group had received additional therapy, and the primary treatment was only successful in 21% of patients. A minority (< 10%) of patients in the EVLA and surgery groups required additional treatments for recanalization of the vein or the development of new varicosities. There was a trend towards a lower chance of requiring a repeat procedure favoring EVLA compared to surgery, but it did not approach statistical significance. The impact on disease-specific quality of life is not discussed in detail in this publication, but it indicates that it remained improved in all three groups without a statistically significant difference [23].

A second study (MAGNA trial) of comparable size (N = 224) also randomized symptomatic patients to EVLA, UGFS, or surgery for treatment of the GSV with 5 year follow up available. The primary endpoint was clinical success, defined by obliteration or absence of the GSV. Secondary endpoints included disease-specific quality of life and overall quality of life. They noted similar but slightly lower rates of GSV closure of 85% (CI 75–92) for surgery, 77% (CI 66–86) for EVLA, and 25% (CI 14–33) for UGFS. Although disease-specific quality of life improved significantly in all groups from baseline, it reached a plateau and then deteriorated slightly in the UGFS group. Unlike in the previous study, this trend was statistically significant, with a stronger benefit to EVLA and surgery compared to UGFS. Overall health-related quality of life improved in all three groups from baseline [35••].

A third, larger (N = 798) study from the UK (CLASS trial) randomized patients to EVLA, UGFS, or surgery for treatment of the GSV, SSV, or both. In this trial, concurrent surgery with phlebectomies was not performed on the EVLA patients; instead, they received foam to residual varices after a delay. The primary outcome analyzed was disease-specific quality of life using the AVVQ as well as generic QOL scoring using the EQ-5D. Secondary outcomes included clinical efficacy via VCSS and duplex scanning, cost-efficacy, and resumption of normal activities. Six-month data is currently available and revealed anatomic failure rates of 5.8%, 10.2%, and 26.9% for EVLA, surgery, and GFS, respectively ($p < 0.001$ for foam vs. surgery and foam vs. EVLA, no difference between EVLA and surgery). For the primary outcome of disease-specific quality of life, there was a statistically significant improvement in the AVVQ in all three treatment groups, without a statistically significant difference between the three at both 6 weeks and 6 months. Overall quality of life scores improved as well, with a greater improvement noted in the EVLA group at 6 weeks ($p = 0.004$) that was no longer apparent relative to the other two treatments at 6 months [35••].

Fewer trials comparing RFA to EVLA or UGFS have been conducted, perhaps due to the rapid progression of radiofrequency technology. One trial (CLOSURE trial) enrolled 118 patients and randomized them to EVLA or RFA. Twenty-four of the patients had bilateral disease and were treated on one leg with RFA and one leg with EVLA. Primary endpoints included closure on duplex ultrasound, CEAP class, and VCSS. Patient pain scores were evaluated in the peri-procedural period. Disease-specific quality of life was assessed (CIVIQ) for the patients with unilateral disease. At 1 week follow up, there was a slightly higher rate of bruising associated with EVL compared to RFA ($p = 0.01$). At 1 year, there was a slightly higher rate of anatomic failure in the RFA group, but disease-specific quality of life was significantly improved

in both groups, with no difference between the two [36••]. A second RCT (RECOVERY study) of 69 patients using the same two devices re-demonstrated the advantage of RFA in the peri-procedural period, with a significant difference in pain scores favoring RFA that persisted up to 2 weeks post-procedure and a difference in ecchymoses (again favoring RFA) that persisted through the entire 1-month follow-up period. In addition, investigators noted a significant difference in VCSS favoring RFA, although this is likely attributable to decreased post-procedural pain. Finally, both disease-specific and global QOL scores favored RFA in the first month of follow up, after which time they were improved for all patients and not statistically different between the groups [37]. One small cohort study (LARA study) of 17 patients with bilateral GSV disease treated one leg with EVLA and one leg with RFA. The patients reported increased pain and bruising in the EVLA-treated leg relative to the RFA leg on postoperative days 2–11, with no difference in GSV occlusion rates (95% for both groups) [38].

Only one trial is available comparing all three minimally invasive modalities. Five hundred patients were randomized to surgery, EVLA, RFA, or UGFS. For all groups, mini-phlebectomies of varicose veins were performed concurrently. Clinical success with GSV closure on ultrasound was the primary outcome. Post-operative pain, VCSS, disease-specific quality of life, and resumption of normal activity were secondary outcomes. In an initial publication, failure rates at 1 year were 4%, 6%, 7%, and 20% for surgery, RFA, EVLA, and UGFS, respectively ($p < 0.001$). Patients treated with RFA and UGFS reported lower post-operative pain than those treated with surgery or EVLA ($p < 0.001$). The time to resumption of normal activities was 1 day for RFA and UGFS compared to 2 days for EVLA and 4 days for surgery; again, this difference was statistically significant for RFA and UGFS compared to surgery and EVLA ($p < 0.01$). Disease-specific QOL, however, improved significantly in all four groups at 1 year [22••]. At 3 years, disease-specific QOL and VCSS were persistently improved from baseline without a difference between all groups but a significant minority of patients in all four groups required retreatment—15.5%, 11%, 12.5%, and 31.6% for surgery, RFA, EVLA, and UGFS respectively ($p < 0.01$ for UGFS vs. all other modalities) [39•]. More recent data from this trial describe a 5-year failure rate of 6.3% for surgery, 5.8% for RFA, 6.8% for EVLA, and 31.5% for 377 UGFS ($p < 0.001$). Rates of clinical recurrence determined by recurrent varices were higher, with a 34% recurrence rate for surgery, 18.7% recurrence rate for RFA, and 38.6% for UGFS. Quality of life was not assessed in this publication. In this regard, in a recent study involving 224 patients, EVLA and conventional surgery were more effective than UGFS in obliterating the GSV 5 years after intervention [40•].

Conclusion

Overall, the data suggest that both EVLA and RFA are well tolerated and effective treatment options for lower-extremity CVD leading to a significant decrease in symptom burden and an improvement in both disease-specific and overall quality of life. Both treatment options are associated with a decreased time to resumption of normal activities relative to surgery, usually 1–2 days. In several studies, the resumption of normal activities was longer, but these all describe performing concurrent phlebectomies.

In our practice, we favor RFA given the decreased post-procedural discomfort. In addition, we often chose to delay treatment of varicosities to minimize risk of deep venous thrombosis and because a substantial amount will improve or resolve following definitive treatment of superficial reflux. We also favor UGFS over stab phlebectomy for treatment of residual veins wherever clinically appropriate. UGFS, although associated with a low level of procedural discomfort and a rapid resumption of normal activities, is associated with a significantly higher failure rate relative to either other endoluminal therapy or to surgery. In our practice, we reserve UGFS for patients with small but very torturous veins, amenable to foam but precluding the safe utilization of a catheter.

In many studies, anatomic failure did not immediately lead to increased symptom burden and the disease-specific quality of life benefits of all endoluminal therapy tended to persist even in patients with recurrent reflux. It is possible that with longer follow up after treatment failure, symptom burden would increase and this benefit would no longer be apparent. The maturation of data from previous trials may shed light on this issue.

Finally, rapid evolution of technology in the field, with significant improvements in available EVLA and RFA devices, limits application of older data to our current practice and it is likely that efficacy with current models is higher than seen in the literature. Continued research efforts comparing current treatment options, including novel therapies such as adhesive implants, will help define the optimal treatment of symptomatic lower extremity venous disease.

Compliance with Ethical Standards

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Eklof B, Rutherford RB, Bergan JJ, Carpentier PH, Gloviczki P, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg. 2004;40:1248–52.
2. Widmer LK, Mall TH, Martin H. Epidemiology and social medical importance of diseases of the veins. Munch Med Wochenschr. 1974;116:1421–6.
3. Langer RD, Ho E, Denenberg JO, Fronek A, Allison M, al e. Relationships between symptoms and venous disease. Arch Intern Med. 2005;165(12):1420–4.
4. Bradbury A, Evans C, Allan P, Lee A, Ruckley CV, et al. What are the symptoms of varicose veins? Edinborough Vein Study Cross Sectional Population Survey. BMJ. 1999;318:318–53.
5. Brand FN, Dannenberg AL, Abbott RD, Kannel WB. The epidemiology of varicose veins: the Framingham study. Am J Prev Med. 1998;4(2):96–101.
6. Vasquez MA, Rabe E, McLaffery RB, Shortell CK, al MWA e. Revision of the venous clinical severity score: venous outcomes consensus statement: special communication of the American venous forum ad hoc outcomes working group. J Vasc Surg. 2010;52(5):1387–96.
7.•• Wrona M, Jockel K-H, Pannier F, Hoffman B, Rabe E. Association of venous disorders with leg symptoms: results from the Bonn vein study. Eur J Endovasc Surg. 2015;50:360–7 **Large cross-sectional study establishing the association between symptoms of venous disease and CEAP stage**.
8. Garratt AM, MacDonald LM, Ruta DA, et al. Towards measures of outcome for patients with varicose veins. Qual Helath Care. 1993;2:5–10.
9. Launois R, Le Moine JG, Lozano FS. Construction and international validation of CIVIQ-14 (a short form of CIVIQ-20), a new questionnaire with a stable factorial structure. Qual Life Res. 2012;21:1051–8.
10. Kuet M, Lane T, Anwar MA, Davies A. Comparison of disease-specific quality of life tools in patients with chronic venous disease. Phlebology. 2014;29(10):648–53.
11. Gloviczki P, Comerota AJ, Dalsing MC, Eklof BG, Gillespie DL, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg. 2011;53:2S.
12.•• O'Flynn N, Vaughan M, Kelley K. Diagnosis and management of varicose veins in the legs: NICE guideline. Br J Gen Pract. 2014;64(623):314–5 **Current Practice Guidelines for diagnosis and management of varicose veins**.
13. MacKenzie RK, Paisley A, Allan PL, Lee AJ, Ruckley CV, Bradbury AW. The effect of long saphenous vein stripping on quality of life. J Vasc Surg. 2002;35(6):1197–203.
14. Baker DM, Turnbull NB, Pearson JC, Makin GS. How successful is varicose vein surgery? A patient outcome study following varicose vein surgery using the SF-36 health assessment questionnaire. Eur J Vasc Endovasc Surg. 1995;9(3):299–304.
15. Ratcliffe J, Brazier JE, Campbell WB, Palfreyman S, MacIntyre JB, Michaels JA. Cost-effectiveness analysis of surgery versus conservative treatment for uncomplicated varicose veins in a randomized clinical trial. Br J Surg. 2006;93(2):182–6.
16. Critchley G, Handa A, Maw A, Harvey MR, Corbett CR. Complications of varicose vein surgery. Ann R Coll Engl. 1997;79(2):105–10.
17. Fischer R, Chandler JG, De Maeseneer MG, Frings N, Lefebvre-Vilarbedo, et al. The unresolved problem of recurrent Saphenofemoral reflux. J Am Coll Surg. 2002;195(1):80–94.
18. Tessari L, Cavezzi A, Frullini A. Preliminary experience with a new sclerosing foam in the treatment of varicose veins. Dermatol Surg. 2001;27(1):58–60.
19. Cabrera J, Cabrera JJ, Garcia-Olmedo MA. Treatment of varicose long saphenous veins with sclerosant in microfoam form: long-term outcomes. Phlebology. 2000;15:19–23.
20. Wright D, Gobin JP, Bradbury A, Coleridge-Smith P, Spoelstra H, Berridge D, et al. Varisolve polidocanol microfoam compared with surgery or sclerotherapy in the management of varicose veins in the presence of trunk vein incompetence: European randomised controlled trial. Phlebology. 2006;21:180–90.
21. Shadid N, Ceulen R, Nelemans P, Dirksen C, Veraart J, Schurink GW, et al. Randomized clinical trial of ultrasound-guided foam sclerotherapy versus surgery for the incompetent great saphenous vein. Br J Surg. 2012;99:1062–70.
22.•• Rasmussen LH, Lawaetz M, Bjoern L, Vennits B, Blemings A, Eklof B. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins. Br J Surg. 2011;98(8):1079–87 **Trial comparing all the modalities of varicose vein treatment**.
23. Vähäaho S, Halmesmäki K, Albäck A, Saarinen E, Venermo M. Five-year follow-up of a randomized clinical trial comparing open surgery, foam sclerotherapy and endovenous laser ablation for great saphenous varicose veins. BJS. 2018;105:686–91.
24.•• Lawaetz M, Serup J, Lawaetz B, Bjoern L, Blemings A, Ecklof E, et al. Comparison of endovenous ablation techniques, foam sclerotherapy and surgical stripping for great saphenous varicose veins. Extended 5-year follow-up of a RCT. Int Angiol. 2017;36(3):281–8 **5-Year Follow Up of RCT Comparing EndoVenous Ablation vs. Surgery vs. Foam and Demonstrating a Quality of life Benefit with Endovenous Ablation Relative to Surgery**.
25. Lurie F, Creton D, Eklof B, Kabnick LS, Kistner RL, Pichot O, et al. Prospective randomised study of endovenous radiofrequency obliteration (closure) versus ligation and vein stripping (EVOLVeS): two-year follow-up. Eur J Vasc Endovasc Surg. 2005;29(1):67–73.
26. Helmy ElKaffas K, ElKashef O, ElBaz W. Great saphenous vein radiofrequency ablation versus standard stripping in the management of primary varicose veins-a randomized clinical trial. Angiology. 2011;62(1):49–54.
27. Subramonia S, Lees T. Randomized clinical trial of radiofrequency ablation or conventional high ligation and stripping for great saphenous varicose veins. Br J Surg. 2010;7(3):328–36.
28. Min RJ, Khilnani N, Zimmet S. Endovenous laser treatment of saphenous vein reflux: long-term results. J Vasc Interv Radiol. 2003;14:991–6.
29. Rass K, Frings N, Glowacki P, Hamsch C, Graber S, Vogt T, et al. Comparable effectiveness of endovenous laser ablation and high ligation with stripping of the great saphenous vein: two-year results of a randomized clinical trial (RELACS study). Arch Dermatol. 2012;148:49–58.
30. Darwood RJ, Theivacumar N, Dellagrammaticas D, Mavor AI, Gough MJ. Randomized clinical trial comparing endovenous laser ablation with surgery for the treatment of primary great saphenous varicose veins. Br J Surg. 2008;95(3):294–301. https://doi.org/10.1002/bjs.6101.

31. Almeida JI, Javier JJ, Mackay E, Proebstle TM. First human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. J Vasc Surg Venous Lymphat Disord. 2013;1(2):174–80.

32.•• Gibson K, Ferris B. Cyanoacrylate closure of incompetent great, small and accessory saphenous veins without the use of post-procedure compression: initial outcomes of a post-market evaluation of the VenaSeal System (the WAVES Study). Vascular. 2017;25(2):149–56 **Outcomes for the VenaSeal procedure; a newly FDA approved adhesive treatment for saphenous ablation**.

33. Morrison N, Gibson K, McEnroe S, Goldman M, King T, Weiss R, et al. Randomized trial comparing cryanoacrylate embolization and radiofrequency ablation for incompetent great saphenous veins (VeClose). J Vasc Surg. 2015;61(4):985–94.

34. Venermo M, Saarinen E, Eskelinen E, Vähäaho S. Saarinen et. al. randomized clinical trial comparing surgery, endovenous laser ablation and ultrasound-guided foam sclerotherapy for the treatment of great saphenous varicose veins. Br J Surg. 2016;103(11):1438–44.

35.•• Brittenden J, Cotton SC, Elders A, et al. A randomized trial comparing treatments for varicose veins. N Engl J Med. 2014;1218:371 **Large randomized control trial comparing various treatments for varicose veins**.

36.•• Gale SS, Lee JN, Walsh ME, et al. A randomized, controlled trial of endovenous thermal ablation using the 810-nm wavelength laser and the ClosurePLUS radiofrequency ablation methods for superficial venous insufficiency of the great saphenous vein. Vasc Surg. 2010;53(3):645–50 **Randomized control trial comparing RFA to Endovenous laser treatment and demonstrating comparable efficacy**.

37. Almeida JI, Kaufman J, Göckeritz O, Chopra P, Evans MT, et al. Radiofrequency endovenous ClosureFAST versus laser ablation for the treatment of great saphenous reflux: a multicenter, single-blinded, randomized study (RECOVERY study). J Vasc Interv Radiol. 2009;20(6):752–9.

38. Goode SD, Chowdhury A, Crockett M, Beech A, Simpson R, Richards T, et al. Laser and radiofrequency ablation study (LARA study): a randomized study comparing radiofrequency ablation and endovenous laser ablation (810nm). Eur J Endovasc Surg. 2010;40(2):246–53.

39.• Rasmussen L, Lawaetz M, Serup J, et al. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins and 3-year follow-up. J Vasc Surg Venous Lymphat Disord. 2013;1(4):349–56 **3-year results of the same trial demonstrating a significant QOL benefit**.

40. Van der Velden SK, Biemans AA, De Maeseneer MG, Kockaert MA, Cuypers PW, et al. A five-year results of a randomized clinical trial of conventional surgery, endovenous laser ablation and ultrasound-guided foam sclerotherapy in patients with great saphenous varicose veins. Br J Surg. 2015;102(10):1184–94.