

## Sclerotherapy of great saphenous vein: a state-of-the-art review and new perspectives

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### Abstract

Sclerotherapy remains a cornerstone minimally invasive treatment for venous insufficiency. Injection of a sclerosing agent into a vein damages the venous endothelium, transforming the vessels into fibrous cords, a process known as sclerosis. The introduction of detergent sclerosants and Sclerosing Foam (SF) has significantly improved this technique, particularly for large varicose veins and Great Saphenous Vein (GSV) ablation. Ultrasound-Guided Foam Sclerotherapy (UGFS) is the recommended approach for injecting SF into the GSV. However, despite over 25 years of use, significant heterogeneity persists in SF production and injection materials, highlighting the need for improved standardisation. The emergence of Endovenous Thermal Ablation (EVTA) techniques has shifted the treatment preference for GSV incompetence, primarily due to superior ablation rates. However, a crucial limitation of most studies is the overemphasis on ablation rates while neglecting the crucial clinical recurrence rates. Notably, randomised clinical trials have demonstrated comparable improvements in patients' quality of life with both EVTA and UGFS, highlighting the complex interplay between ablation success and long-term clinical outcomes. Recently, innovative hybrid techniques and medical devices have been introduced to address some of the limitations of UGFS, enhancing outcomes and promoting standardisation. This paper reviews the latest advancements in GSV sclerotherapy and emphasises the critical need for a new perspective in comparing UGFS with EVTA techniques, prioritising patient-reported outcomes over ablation rates. Further research is crucial to assess new endpoints for evaluating different procedures during follow-up, ultimately leading to improved personalised patient care.

**Key words:** sclerotherapy, foam sclerotherapy, great saphenous vein, hybrid techniques.

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### Introduction

Sclerotherapy is one of the most prevalent procedures in phlebology and remains an essential technique in the management of chronic venous disease. Over the past few decades, the introduction of Sclerosing Foam (SF) and Ultrasound-Guided Foam Sclerotherapy (UGFS) has significantly improved the effectiveness of this procedure, particularly for larger varicose veins and Great Saphenous Vein (GSV) ablation.<sup>1</sup>

The Tessari method, an easy, cost-effective, and reproducible technique for creating SF, has contributed to the widespread adoption of this therapy. However, despite 25 years since its introduction, there is substantial heterogeneity in the materials and methods used for foam production and injection, highlighting the need for improved standardisation.

Moreover, the emergence of Endovenous Thermal Ablation (EVTA) techniques has led to a shift in preference towards these procedures for the treatment of GSV incompetence, primarily due to their superior ablation rates.<sup>4</sup> Nevertheless, most studies have focused on ablation rates, while neglecting recurrence rates, which could be a valuable avenue for future research. There is a notable paucity of data on changes in the GSV diameter following different

treatment modalities, which could serve as a reliable parameter for assessing actual recurrence rates.

Importantly, randomised clinical trials have demonstrated comparable improvements in the quality of life with both EVTA and UGFS.<sup>4</sup>

Hybrid techniques, combining surgery and sclerotherapy, have been developed to allow one technique to mitigate the limitations or deficiencies of the other partially or completely. This approach offers numerous advantages, particularly in reducing the invasiveness of the procedures and eliminating the need for an operating theatre.<sup>5</sup> This has led to some techniques becoming popular, such as Mechano-Chemical Ablation (MOCA), Sclerofoam-Assisted Laser Treatment (SFALT), and foam glue treatment.<sup>5-7</sup>

Innovative medical devices are continuously being introduced into the market to enhance UGFS outcomes and promote standardisation. Automated systems for SF preparation have proliferated globally, with the most prevalent being Varithena (Boston Scientific, Marlborough, MA, USA) and Varixio (VB Devices, Barcelona, Spain).<sup>8,9</sup>

In this paper, we review the current state-of-the-art in sclerotherapy of GSV and discuss the necessity of adopting a novel perspective when comparing UGFS and other endovenous tech-

niques for the treatment of GSV incompetence. This analysis considers the technical aspects, the appropriateness of the technique, and the significant advancements provided by innovative hybrid techniques and new devices, with the objective of delivering personalised patient care.

## Technical aspects of Ultrasound-Guided Foam Sclerotherapy for Great Saphenous Vein incompetence

### Sclerosant agents and foam preparation

The historical use of sclerosing agents, often associated with complications like infection and necrosis, paved the way for the development of detergent sclerosants. This marked a significant advancement in the practice of sclerotherapy, leading to safer and more effective treatments.<sup>10,11</sup>

Polidocanol (POL) and Sodium Tetradecyl Sulfate (STS) are the most frequently utilised sclerosants because of very low incidence of allergic reactions, low incidence of pigmentation and other adverse cutaneous effects; studies show no significant differences in the efficacy between the two agents.<sup>11</sup> However, STS exhibits a strong sclerosant effect, rendering it less suitable for teleangiectasias and reticular veins, while POL, being a moderate detergent, can be applied for small vessels treatment.<sup>12</sup> The selection of the sclerosant depends also on the availability and experience of the treating physician.

In this paper, we focus on the use of two sclerosing detergent agents indicated for treating GSV incompetence, POL and STS, which are licensed in most European countries. GSV treatment requires the use of SF and ultrasonography, using the UGFS technique.

According to the European Guidelines for sclerotherapy,<sup>13</sup> the concentration of POL or STS used for producing SF should be between 1% and 3% when the incompetent GSV diameter is 4-8 mm, and 3% when the GSV is larger than 8 mm in diameter. The maximum volume for SF per session is 10 mL in routine cases, while higher foam volumes are applicable according to the individual risk-benefit assessment.

### Physician-compounded foam preparation

The generation of SF involves the application of various techniques, including the Tessari, Monfreux, Frullini, and Cabrera methods. These methodologies yield a mixture of air or carbon dioxide with liquid sclerosant (POL or STS), and due to the detergent properties of POL and STS, the result of this mixture is foam. Sclerosant properties and bubble size determine the durability and effectiveness of the foam. Smaller bubble sizes and higher sclerosant concentrations within the foam yielded superior results. Foam sclerotherapy offers numerous advantages, including efficient displacement of blood, uniform contact of the sclerosant with the endothelium, and provocation of venospasm post-injection.<sup>14</sup>

The Tourbillon Method (Tessari-method), introduced in 1999, has become the most popular method for foam preparation. However, significant variability persists in the materials and methods utilised for foam production, underscoring the need for improved standardization.<sup>1,2</sup>

The materials required for the Tessari method include two syringes of appropriate size, a three-way valve, a selected sclerosant (POL or STS) and air/gas. Additional materials, such as filters, could possibly improve SF quality.<sup>2,14</sup>

The air/gas and sclerosant are mixed back and forth (typically 20 passages) through a three-way stopcock to produce SF.

### Factors affecting foam quality

The most effective and commonly used liquid-to-gas ratio appears to be 1:4, which represents an optimal compromise for producing a dense and durable SF. Nevertheless, phlebologists can also generate foams with different chemical and physical properties, such as dry foams (e.g., 1:6 ratio) and wet foams (e.g., 1:2 ratio). Notably, the maximum displacement distance and duration of this displacement are greatly increased in dry foams, rendering dry foams more efficacious for large varicose veins and truncal veins.<sup>2</sup>

Furthermore, the pushing rate appears to influence foam stability in the Tessari method, and it is recommended to complete 20 back-and-forth passages within 10 seconds to improve the Foam Half-Time (FHT) and generate a stable foam.<sup>15</sup>

Additional significant variables that increase SF quality and FHT are syringe type and temperature.

Non-silicone syringes can increase foam longevity by 70%, whereas silicone syringes produce foam with a shorter FHT at all temperatures. The silicone lubricating the syringes was shown to have a detrimental effect on the quality of the foam, which may be attributed to the silicone oil altering the surface tension of the bubbles in the foam.<sup>16</sup>

Temperature affects foam stability and longevity. Preparing the foam at +4°C significantly extended the duration of the FHT. This is due to several factors, such as changes in surface tension, alterations in the viscosity of the sclerosant, changes in the solubility of gas, and the transition of foam to liquid phase. The foam stability can be improved by using an agent at +4°C. Furthermore, the application of cold foam can facilitate contraction of the targeted veins and result in increased interaction between the detergent and vein endothelium.<sup>17</sup>

Among the variables that influence the SF formation, the gas component also appeared to be of considerable significance. Room air is a widely accepted gas component for the generation of SF in all indications.<sup>13</sup> However, a mixture of carbon dioxide and oxygen has gained prominence in the scientific community instead of room air, for improving safety and reducing the incidence of side effects.<sup>18,19</sup> The type of gas (room air or sterile gas mixture) used to prepare foam remains a subject of debate. In subsequent years, no benefits on neurological disturbances have been demonstrated in patients treated with CO<sub>2</sub>-O<sub>2</sub>-based foam compared to air-based foam.<sup>20</sup> In conclusion, a gas mixture adds cost and complexity, and there is no clinical evidence to suggest that foam sclerotherapy using room air is less safe and effective than using a gas mixture.<sup>21</sup>

### Automated devices for microfoam preparation

The introduction of two automated devices for microfoam preparation, Varithena (Boston Scientific, Marlborough, MA, USA) and Varixio (VB Devices, Barcelona, Spain) represents a pivotal advancement in standardising foam production and enhancing foam stability, addressing longstanding challenges in sclerotherapy practice.

#### Varithena

Varithena (Boston Scientific, Marlborough, MA) received approval in 2013 from the U.S. Food and Drug Administration (FDA) for the treatment of chronic venous insufficiency. It consists of a 1% injectable POL solution composed of a mixture of carbon dioxide and oxygen (ratio of 35:65). This Microfoam (MF) demonstrated uniform density and stability with a small bubble size (median diameter <100 μm) relative to Physician-Compounded Foam (PCF) prepared using the Tessari method.<sup>8</sup> Varithena is dispensed from a canister device with a transfer unit that activates the

MF before patient use. To initiate gas transfer, the oxygen and polidocanol canisters are connected and rotated. The production of MF requires 1 min. Subsequently, the oxygen canister is removed and the Varithena transfer unit is attached and rotated clockwise. A syringe is then inserted, allowing passive filling with the MF prior to treatment. Its application is particularly suitable for incompetent GSV and Accessory Saphenous Veins (AASVs). Clinical studies have validated the use of Varithena MF, and a recent systematic review and meta-analysis<sup>22</sup> compared the effectiveness and safety of polidocanol 1% endovenous MF ablation with Endovenous Thermal Ablation (EVTA) for treating Chronic Venous Insufficiency (CVI). The primary endpoint was vein closure rate. The meta-analysis included 13 studies with a total of 233,801 patients. The results showed no statistically significant difference at the 1-year follow-up between Varithena MF and EVTA in terms of vein closure rates (OR, 0.65; 95% Confidence Interval, CI, 0.36-1.18;  $p=0.16$ ). Varithena MF demonstrated significantly higher efficacy than PCF for vein closure (OR, 2.91; 95% CI, 1.58-5.37;  $p<0.01$ ). Due to insufficient data, meta-analyses could not be conducted for Venous Clinical Severity Score (VCSS) improvement and patient-reported outcomes. The findings of this study suggest that Varithena MF represents a viable alternative to EVTA, and the analysis demonstrated its superiority over PCF in terms of vein closure rates. However, more comprehensive meta-analyses are warranted in this field.

### Varixio

Varixio (VB Devices, Barcelona, Spain) is an Automated Microfoam Preparation System (AMPS), developed in 2013. AMPS can produce microfoam utilising various combinations of sclerosing agents (POL and STS), gases (air and  $O_2/CO_2$ ), and device settings.<sup>9</sup> The automated system consists of a dome-shaped capsule positioned on an adapted magnetic stirrer. The system consistently produces suitable foam within 45 seconds, even with low concentrations of sclerosants. Notably, the automated system was able to produce uniform foam from low concentrations of sclerosants, a task that is challenging to accomplish using manual methods and has significant clinical implications for treating small varicosities. The versatility and foam standardisation of this system represent a potential advancement in the practice of sclerotherapy.<sup>9</sup> A recent study,<sup>23</sup> involving 164 patients treated using the AMPS system for foam preparation, analysed GSV closure rates after 36 months follow-up. The treatment protocol involved the use of 3% polidocanol for GSV. The results demonstrated complete GSV closure in all patients at the 7-day and 1-year follow-up. After 36 months, the cumulative complete recanalisation rate was 6.1%, and the partial recanalisation rate was 26.8%. AMPS appears to offer advantages over PCF, including a higher foam half-life (330 seconds compared to 30-200 seconds in previous studies) and a higher gas/liquid ratio (7:1 vs 4:1 in manual preparation). This 'super-dry' microfoam potentially allows for lower sclerosing agent usage in GSV, while maintaining its effectiveness. However, patient-reported outcomes are absent, and the authors recommend further randomised studies to compare the clinical outcomes between manual and automated foam sclerotherapy treatments. To date, neither Varithena nor Varixio have demonstrated superiority over the other, and currently no clinical studies of sclerotherapy with PCF prepared using the Tessari method indicate that it is less safe or effective than automated foam production using Varithena or Varixio. Notably, cost and convenience of these devices remain predominant considerations.<sup>24</sup>

### Injection techniques

Injection techniques, as well as foam preparation, present a huge heterogeneity in the strategies and materials used, and this represents a critical decision for treatment efficacy.

### Ultrasound-Guided Foam Sclerotherapy: technical insights

Sclerotherapy treatment of GSV necessitates ultrasound guidance, employing a technique called Ultrasound-Guided Foam Sclerotherapy (UGFS), which demonstrates a high safety profile.

One of the key focuses is the selection of needles. Extremely fine needles (such as 27-30G) break up SF bubbles, leading to a more fluid and less thick SF, with a reduced Foam Half-Time (FHT). As a result, needles of 25G or larger are commonly employed for SF injection. The needle length (typically 16-30 mm) should be chosen based on the target vessel's depth.<sup>2</sup>

Multiple small-dose injections significantly reduce the amount of foam entering the deep veins and are associated with fewer complications (such as pain and superficial thrombophlebitis) than fewer large injections. No significant difference in treatment success rates has been found between these two methods of injection, so multiple small-dose injections should be preferred.<sup>25</sup>

Phlebologists can choose between UGFS via direct puncture, butterfly needle or catheter-directed foam sclerotherapy.

### Direct puncture

Direct puncture is the most widely used technique. For GSV, the choice of the first injection site may differ depending on the extent of GSV incompetence. In axial reflux, the first injection should be made in the proximal part of the thigh, approximately 10-15 cm from the groin; the second injection should be made farther down the thigh, contingent upon the extent of foam filling the vein. Based on the filling and spasm of the target vein, the practitioner decides whether complementary injection is necessary. In general, one or two injections of foam are required for a GSV, with the total volume of foam injected not exceeding 10 mL per session.<sup>26-28</sup>

### Butterfly needle

Butterfly needles and cannulas can be used to cannulate the vein and rapidly inject fresh SF once the catheter has been secured into the vein. This procedure can minimise the risk of inadvertent extravasation or intra-arterial injection, thereby improving the safety profile of UGFS. An additional significant function of butterfly needles and cannulas is to introduce SF at 10- to 20-cm intervals along the saphenous trunk. The cannulas are positioned at strategic points under local anaesthetic and ultrasound guidance. The diameter and depth of the vein determine the size of the cannulas to be employed. Where present, cannulas will also be placed in the AASV and in all major tributaries. The leg is subsequently elevated to 45 degrees in a sling to empty the superficial veins and enhance the efficacy of the sclerosant. Microfoam aliquots (typically 2-3 mL) are then injected via the cannulas, usually progressing from proximal to distal. Between injections, the patient is instructed to plantar flex and dorsiflex their ankle to expel any foam that may have migrated into the deep system. Once the trunk, tributary, and varicose veins are in spasm and filled with foam, the cannulas are removed.<sup>27</sup>

### Catheter-Directed Foam Sclerotherapy

Catheter-Directed Foam Sclerotherapy (CDFFS) is a modification of UGFS that involves the use of an intravenous short or long

catheter to deliver the sclerosant along the lumen of the saphenous trunk under duplex ultrasound visualisation.<sup>29</sup>

The positioning of the catheter in a vein also allows the use of ultrasound-guided Peri-Saphenous Tumescence (PST) infiltration to reduce vein caliber, along with Intra-Saphenous Saline Irrigation (ISI) to flush blood out of the vein.<sup>30</sup> However, a randomised controlled trial comparing the two techniques in the treatment of GSV with CDFS showed no superiority for the tumescence/irrigation group,<sup>31</sup> with the tumescent/irrigation technique increasing the invasiveness and complexity of the procedure.

A systematic review and meta-analysis of 3689 patients demonstrated higher occlusion rates after CDFS (82.4%) compared to UGFS with direct puncture at 3 years follow-up.<sup>29</sup> The CDFS also exhibits a better safety profile, conferring a lower risk of major and minor complications. However, considerable heterogeneity in practice within each technique exists, which constitutes a limitation of studies involving CDFS and UGFS.

In conclusion, numerous techniques for injecting SF exist, and there is limited evidence to date regarding the superiority of one method over another. Phlebologists should use techniques in which they possess greater expertise and for which they have received appropriate training.

## Appropriateness of Ultrasound-Guided Foam Sclerotherapy for Great Saphenous Vein incompetence

### Patient selection for Ultrasound-Guided Foam Sclerotherapy

Appropriate patient selection is crucial for successful sclerotherapy of the GSV. Indications and contraindications have been described, which can help improve the outcome of this technique.

### Indications to Ultrasound-Guided Foam Sclerotherapy

According to the latest European Vascular Surgery Society (ESVS) guidelines on the management of chronic venous disease<sup>32</sup>, ideal candidates for UGFS treatment of incompetent GSV are patients with less dilated GSV trunks, who prefer an outpatient procedure with early return to normal activities.

A lower efficacy of UGFS has been reported in patients with a GSV >6 mm compared to those with a GSV < 6 mm (measure at mid thigh, in standing position). A post hoc analysis of 225 patients treated with UGFS, part of a Randomized Controlled Trial (RCT) comparing High Ligation And Stripping (HLS) with UGFS, showed a two-year cumulative probability of recurrent reflux of 62.6% (51.2% and 74.2%) if the mid thigh GSV diameter was >6 mm vs 42% (34.6% and 50.4%) for a diameter <6 mm.<sup>33</sup>

Return to normal activities is faster in UGFS group than in the Endovenous Laser Ablation (EVLA) group. A RCT reported the mean duration of sick leave to be eight days in the EVLA group (range 0 to 29 days) and one day in the UGFS group (range 0 to 21 days).<sup>34</sup> These two criteria can lead phlebologists to prefer UGFS treatment instead of other endothermal ablation techniques or conventional surgery in these specific cases.

However, discrepancies regarding the vein diameter indication are still present in phlebology, and the European Guidelines for sclerotherapy<sup>13</sup> recommend the use of UGFS for treating also incompetent GSV larger than 6 mm in diameter.

A recent Cochrane review highlights that it is not currently possible to reach firm conclusions as to which of these techniques are to be preferred in treating incompetent GSV.<sup>35</sup> In addition to variation in individual anatomy and vein size, there are also significant variations in individual and surgeon preferences regarding which procedure is preferred. More evidence is required before specific treatment modality recommendations for individuals with GSV incompetence can be made.

### Contraindications to Ultrasound-Guided Foam Sclerotherapy

A recent consensus document from the International Union of Phlebology (UIP) has been published regarding sclerotherapy contraindications.<sup>36</sup> The consensus was developed by an international, multi-disciplinary panel of phlebologists who reviewed available scientific evidence and developed agreements where evidence was lacking or limited. The consensus outlines absolute contraindications and relative contraindications for sclerotherapy.

Absolute contraindications include hypersensitivity to sclerosing agents, acute venous thromboembolism, severe neurological or cardiac adverse events from previous sclerotherapy, acute systemic illness or infection, and critical limb ischemia. Relative contraindications encompass pregnancy, postpartum and breastfeeding periods, hypercoagulable states, long-lasting immobility, and poorly controlled chronic systemic illness.<sup>36</sup>

A unique insight from this UIP document is the emphasis on both patient-related and procedure-related risk factors in ensuring safe outcomes for sclerotherapy.

### Comparing endovenous thermal ablation and ultrasound-guided foam sclerotherapy for Great Saphenous Vein treatment

In the last two decades, minimally invasive techniques such as Endovenous Laser Ablation (EVLA), Radiofrequency Ablation (RFA) and UGFS have been optimised, replacing Conventional Surgery (CS) for most cases of GSV incompetence.<sup>37</sup>

**Table 1.** Summary of the principal minimally invasive techniques available for treating saphenous trunk incompetence.<sup>5,7,32</sup>

Technique	Follow-up	Reflux abolition	Quality of life improvement	Tumescence needed
EVTA	>5 years	+++	+++	Yes
UGFS	>5 years	+ / ++	+++	No
CDFS	>3 years	++	++	No
CAC	3-5 years	+++	+++	No
MOCA	>5 years	++	+++	No
SFALT	Not published yet	Not published yet	Not published yet	No
Sclerofoam glue	Not published yet	Not published yet	Not published yet	No

EVTA, Endovenous Thermal Ablation; UGFS, Ultrasound-Guided Foam Sclerotherapy; CDFS, Catheter-Directed Foam Sclerotherapy; CAC, Cyanoacrylate Adhesive Closure; MOCA, Mechanochemical Ablation; SFALT, Sclerofoam-Assisted Laser Treatment.

Among minimally invasive techniques, UGFS demonstrated lower long-term occlusion rates than EVLA and RFA but highly significant and broadly similar improvements in patient-reported outcome measures (Table 1).<sup>38</sup>

### Ablation rates

Few robust RCTs have been conducted<sup>4,37-40</sup> that compared treatment modalities for GSV reflux. Rasmussen compared EVLA, RFA, UGFS and CS in 580 legs, Lattimer compared EVLA and UGFS in 100 legs, Biemans compared EVLA, UGFS and CS in 240 legs, Brittenden compared EVLA, UGFS and CS in 798 legs.<sup>41</sup>

The sclerosant agents selected for these studies were POL and STS, with Tessari method for foam preparation (liquid-to-gas ratio, 1:3 or 1:4). However, UGFS techniques exhibit considerable variation. Rasmussen<sup>38</sup> employed a single injection via cannula into the GSV just below the knee with 3% POL foam. Lattimer<sup>39</sup> utilised a single injection via cannula into the GSV at the knee level with 1% STS foam, but with a GSV diameter  $\geq 8$  mm, the UGFS was modified using tumescence to compress the vein. Lattimer conducted further foam treatments in 4.6% of patients who initially received EVLA and in 56% of the patients who had been randomised to foam. Biemans<sup>37</sup> performed UGFS using 3% POL foam, utilising a drier foam compared to other studies (liquid-gas ratio, 1:3). Six patients (4.6%) in the UGFS group had further foam treatment within the first six months. Brittenden<sup>40</sup> did not provide information on the injection technique but stipulated that 3% STS be used for truncal veins and 1% STS for varicosities. At six weeks, 38% UGFS and 31% EVLA patients underwent a further UGFS treatment. All the trials utilised foam volumes in accordance with the manufacturers' licences.

All these RCTs demonstrated superior technical success rates for EVTA than UGFS at the mean follow-up. Technical failure is consistently reported to be higher after UGFS than after EVTA, although closure rates after EVTA in RCTs do not correspond to the very high rates reported in other studies.<sup>41</sup>

### Cost-effectiveness

Rasmussen<sup>4</sup> and Lattimer<sup>39</sup> reported UGFS to be less expensive than EVTA and given the absence of any difference in clinical outcomes it is reasonable to suggest that UGFS will be the more cost-effective option for the majority patients in most healthcare settings, although this will require more data from long-term follow-up to accurately confirm.

### Patient-reported outcomes

Regarding clinical success, the RCTs reported comparable improvements in quality-of-life questionnaires with EVTA and UGFS. Rasmussen reported clinical success using the Venous Clinical Severity Score (VCSS), Aberdeen Varicose Vein Questionnaire (AVVQ) and Short Form-36 (SF-36) scores. All three parameters improved significantly in all patient groups, and no difference was observed between EVLA, RFA, UGFS, and CS at one or three years.<sup>4</sup> Lattimer reported clinical success utilising the VCSS, AVVQ and the Saphenous Treatment Score. All three improved significantly in both groups, and no difference was observed between EVLA and UGFS at 15 months, although seven-day pain scores were significantly higher with EVLA.<sup>39</sup> Biemans reported clinical success utilising the Chronic Venous Insufficiency Quality of life (QoL) questionnaire (CIVIQ) and EuroQoL 5D (EQ-5D) (EuroQoL, Rotterdam, Netherlands). Both improved at three months, and there was no difference between EVLA and UGFS up to one year.<sup>37</sup> Brittenden reported clinical success utilising the AVVQ, VCSS, EQ-5D, SF-36 and clinical

vein appearance. At six months, both EVLA and UGFS demonstrated improvement in AVVQ and VCSS, with no statistical difference between EVLA and UGFS. At 5 years follow-up, the AVVQ scores in the EVLA group were significantly lower (indicating a superior quality of life) than those in the UGFS group (effect size for laser ablation vs. foam sclerotherapy,  $-2.86$ ; 95% CI,  $-4.49$  to  $-1.22$ ;  $p < 0.001$ ). Sensitivity analysis revealed no significant differences in the baseline or 6-month AVVQ scores between patients who did not complete the 5-year follow-up and those who completed the 5-year follow-up. The other quality-of-life measures did not differ significantly among the treatment groups. Additional sensitivity analyses employing multiple imputations with chained equations for quality-of-life measures yielded comparable outcomes.<sup>40</sup>

### Hybrid techniques

Hybrid techniques, combining open or endovenous surgery and sclerotherapy, have been developed to partially or completely mitigate the limitations and deficiencies of the other. This approach helps reduce the invasiveness of the procedure. This has led to some techniques becoming popular, such as sclerotherapy combined with open surgery, MOCA, SFALT, and foam glue treatment.<sup>5-7</sup>

### Sclerotherapy and open surgery

Historically, Prof. Schiassi of Bologna described a technique in 1909 to inject iodine and potassium iodide at the time of saphenous interruption in the distal thigh. In 1927, Ungar later introduced a technique to pass a catheter down from the groin to infuse sclerosant along the full length of the GSV, and this became a standard technique for many years. Cooper in New York reported patients treated by flush ligation of the great saphenous vein with subsequent injection of the remaining veins with 5% sodium morrhuate in 1934.<sup>10,42</sup> More recently, open surgery has been associated with sclerotherapy when clinical expertise with endovenous thermal ablation techniques or technology is not available or in particular anatomies such as complex cases involving deep venous reflux or large varicosities that are not amenable to less invasive methods.<sup>32,43-44</sup> Some techniques have been described in patients with GSV insufficiency and proximal femoral valve incompetence, such as Excluded Saphenous Vein Technique (ESVT).<sup>45</sup> This technique involves selective cross-section, GSV ligation near the incompetent tributary vein in the thigh, and sclerotherapy of the excluded GSV segment. Selective cross-section effectively stops the refluxing column from the deep venous system, while GSV ligation near the main refluxing thigh tributary vein prevents the diffusion of high-concentration sclerosing agent through leg tributaries, minimising the risk of postoperative superficial venous thrombosis. From a pathophysiological point of view, when the reflux in the femoral vein reaches the upper third of the thigh, this reflux disappears when the saphenous reflux is abolished due to overload theory. Additionally, ESVT can be performed under local anaesthesia, instead of GSV stripping, making it a cost-effective option. The ability of this technique to address both anatomical and hemodynamic issues in patients with deep femoral valve incompetence and large GSV diameters sets it apart from other endovenous procedures, potentially offering a valuable alternative in cases where other techniques expertise is absent, or they may be contraindicated.

### Mechano-Chemical Ablation

EVTA requires tumescent anaesthesia, which improves tech-

nique invasiveness and usually requires concomitant sedation for GSV treatment. This has led to some hybrid techniques becoming popular to reduce patient discomfort and eliminate the need for an operating theatre, such as MOCA, SFALT, and foam glue treatment.<sup>5-7</sup> MOCA is a Nonthermal Nontumescent (NTNT) technique, introduced in 2014. MOCA combines two techniques: mechanical endothelial damage and concomitant infusion of a sclerosant (POL or STS). Currently, two MOCA devices are available: ClariVein (Vascular Insights, Quincy, MA, USA), which has a rotating catheter tip and utilises liquid sclerosant, and Flebogrif (Balton, Warsaw, Poland), which instead has retractable cutting hooks and utilises sclerosing foam.<sup>46,47</sup> The mechanical disruption allows for improved penetration of the sclerosant through endothelial cell membranes, this action allows for subendothelial penetration of sclerosant, causing irreversible fibrosis of the media, which ultimately leads to vessel occlusion. MOCA is rapidly growing owing to advantages such as minimal nerve or skin injury, safety for below-the-knee treatments, reduced patient discomfort, and no need for capital equipment.<sup>47</sup> NTNT procedures can be performed in-office within an hour, with most patients resuming normal activities almost immediately.<sup>48</sup> ClariVein device has the longest MOCA follow-up, and RCTs demonstrated that safety, efficacy and clinical outcomes are comparable to EVTA, significantly improving Quality Of Life (QoL) measures at long-term follow-up.<sup>49,50</sup> The results showed that MOCA had lower median intraoperative pain scores and during the first 14 days post-procedure compared to RFA.<sup>6,50</sup> This is significant as it offers a potentially less painful alternative to EVTA for patients.

### Sclerofoam Assisted Laser Therapy

This technique combines EVLA with FS to create a tumescence-free approach for treating GSV incompetence.

The SFALT procedure involves introducing a laser fiber into the GSV, creating a shrunk plug by applying a high fluence for a short segment (the first cm at 200 J/cm), followed by injection of FS (5 cc foam, made with 1% POL or 1% STS) through the same introducer. This combination causes venous spasm, allowing for subsequent endovenous laser shrinkage with reduced fluence (30-50 J/cm) and no need for tumescent anaesthesia.

This approach demonstrates the potential of a tumescence-free technique to treat saphenous reflux, which could significantly reduce patient discomfort and the risk of complications associated with tumescent anaesthesia. Secondly, the synergistic effect of combining EVLA and FS allows for lower energy delivery in laser treatment, potentially reducing side effects and improving patient satisfaction. Lastly, the technique shows promise for treating larger calibre GSVs, which have been challenging for traditional endovenous treatments. However, further research is needed to optimise energy delivery parameters and explore the possibility of eliminating even mild sedation, potentially moving towards an office-based procedure.<sup>7</sup>

### Sclerofoam glue treatment

In recent years, techniques that combine foam sclerotherapy and cyanoacrylate glue ablation have been described.

An example is a novel combined endovascular treatment technique called the 'Foam-glue syringe'. The method combines the use of sclerosing foam and a specific cyanoacrylate glue in a single syringe device, allowing for a minimally invasive, outpatient procedure to treat venous insufficiency. The technique is based on the principles of the CHIVA (Conservatrice Hemodynamique de l'Insuffisance Veineuse en Ambulatoire) method, which aims to conserve venous hemodynamics while treating varicose veins.<sup>5</sup>

The foam-glue syringe technique is particularly suitable for treating various types of incompetent perforator veins and compartment jumps. The treatment requires a specific glue composed of N-Butyl 2 Cyanoacrylate (NBCA) monomer plus Methacryloxy-Sulpholane (MS) monomer, which does not require pre-washing with a glucosate solution because it has a similar density to water.<sup>51</sup>

Recently, another technique combining cyanoacrylate glue and polidocanol foam sclerotherapy using a 'Sandwich' approach has been described.<sup>52</sup> Cyanoacrylate glue is injected into critical locations, followed by foam sclerotherapy using 1-3% polidocanol. These treatments reduce the risk of epifascial glue placement and allow for a substantial reduction in the amount of glue required for vein closure. These approaches minimise the risk of granuloma formation and allergic reactions associated with epifascial administration of cyanoacrylate. Additionally, the combined use of glue and sclerosing foam helps reduce the volume of foam required.

The combination of these two treatments retains the advantages of sclerosing foam and glue ablation while mitigating their individual limitations. The foam provides excellent echogenicity for precise ultrasound-guided treatment, whereas the glue ensures durable closure of the treated vein segment. This synergistic approach allows for a simple, effective, and repeatable outpatient procedure that adheres to the principles of conservative hemodynamic phlebology, which are the basis of every venous intervention.

### New perspectives

An explanation for the discrepancy between technical success and clinical success needs to be identified. A potential elucidation arises from the RCT '1 vs 3'.<sup>26</sup> This RCT demonstrated that the mean diameter of recanalised GSV after UGFS at 2 years was 2.8 mm for an initial mean diameter of 6 mm. This observation could explain the favourable clinical results of foam compared with technical results, as even in cases of technical failure, the GSV is significantly reduced in diameter after treatment in numerous cases.

More recently, comparable results have been reported for the Small Saphenous Vein (SSV). The FOVELASS RCT<sup>28</sup> included 3-year results from 11 centers, comparing UGFS with EVLA for incompetent SSV treatment. The short-term absence of reflux (primary endpoint) was high and equivalent for both groups, however, at 3 years, the partial and total failure rates were 11% and 3% after EVLA, respectively, and 26% and 17% after UGFS, respectively. Nevertheless, the VCSS, CIVIQ, and symptom questionnaire scores improved significantly and similarly after both treatments at 3 years. In the UGFS group, in cases of failure, the mean SSV diameter was 2 mm at 3 years to an initial diameter of 6 mm before treatment.

Due to this finding, instead of ablation rates, the GSV diameter variation after different procedures during follow-up, and the absence of reflux on Duplex ultrasound scan appear to provide a more reliable parameter for calculating actual recurrence rates.

In summary, there remains a debate regarding the relative importance of technical success vs clinical success, as well as the definitions of technical and clinical success and failure, which vary among RCTs. Furthermore, UGFS and EVTA described in RCTs represent heterogeneous treatments. While RFA is a highly standardised technique, with a single device dominating the market, EVLA can vary significantly depending on the large number of different laser technologies currently available. UGFS is an even more heterogeneous treatment modality with multiple variables, such as sclerosant agent choice, volume of sclerosant used, method of foam preparation, injection technique, and strategy, likely to have a major impact on outcomes.

This situation results in a paucity of randomised data comparing EVTA with UGFS, which impedes the formulation of definitive conclusions regarding the relative clinical and cost-effectiveness of EVTA and UGFS for the treatment of GSV insufficiency.

Differences in technical success did not correlate with differences in clinical outcomes in any of the RCTs, and the value of ‘technical success’, defined as ablation rates, as a useful endpoint is subject to question.

## Conclusions

In conclusion, this review of the literature on GSV sclerotherapy reveals a notable evolution in techniques, from traditional approaches to the currently prevalent UGFS and hybrid techniques. UGFS is a crucial minimally invasive treatment for GSV incompetence, mainly due to its relatively economical nature, feasibility as an outpatient procedure, minimal post-procedural discomfort, and procedural repeatability.

In recent years, EVTA has shifted treatment preference in most guidelines, due to superior GSV ablation rates.

While EVTA boasts superior initial ablation rates, randomised controlled trials<sup>37-40</sup> demonstrate comparable improvements in patient-reported quality-of-life measures between UGFS and EVTA at long-term follow-up, highlighting the complex interplay between technical success and clinical outcomes. This suggests that reliance solely on ablation rates as a primary endpoint may be insufficient for a comprehensive assessment of treatment efficacy.

Recent studies focusing on GSV diameter reduction seem to offer a potentially more robust surrogate marker for long-term outcomes than simple occlusion rates.<sup>38</sup>

A significant limitation of current research on UGFS technique is the substantial heterogeneity, affecting both foam production and injection strategies. This lack of standardisation impedes the drawing of definitive conclusions regarding the relative efficacy of UGFS compared to EVTA.

Improved anatomical success measured with duplex ultrasonography with EVTA treatments compared to UGFS, may be because of lower technical expertise in a treatment that is more reliant on experience than EVTA methods. UGFS requires meticulous technique to provide optimal outcomes with arguably more consideration to treatment tactics than required for EVTA methods.

Regarding cost-effectiveness of treatments, it is evident that UGFS demonstrates a significant cost advantage over EVLA and RFA, even in cases where additional treatment sessions are necessary. Although further work is required to optimise UGFS technique to maximise anatomical success and minimise retreatment, the current evidence base suggests that there is likely no significant difference in clinically important outcomes between UGFS and EVTA. Future research should prioritise RCTs comparing standardised UGFS protocols with EVTA, particularly utilising new automated devices for microfoam preparation, and longitudinal studies assessing changes in GSV diameter post-treatment with long-term follow-up. Research should define recurrence rates, technical success and clinical success, standardising the terminology of their outcome measures across studies and the time points at which they are measured.

Moreover, UGFS is evolving, and hybrid techniques seem to reduce the invasiveness of EVTA, implementing tumescence-free techniques. Further research is needed to evaluate the long-term outcomes of emerging hybrid techniques, such as MOCA, SFALT and sclerofoam glue treatment, in well-designed RCTs, comparing them to both UGFS and EVTA, utilising standardised outcome

measures.

By addressing these critical research needs, a more nuanced understanding of the relative merits of various GSV sclerotherapy techniques, and the development of more effective, standardised, and patient-centered treatment paradigms, can be achieved.

## References

1. Tessari L. Nouvelle technique d'obtention de la scleromousse. *Phlebologie* 2000;53:129-33.
2. Cavezzi A, Tessari L. Foam sclerotherapy techniques: different gases and methods of preparation, catheter versus direct injection. *Phlebology* 2009;24:247-51.
3. Roche E, Marqués C. First registry of patients treated with foam sclerotherapy using a new automated microfoam preparation device (2021-2022). *Phlebology* 2025;40:235-42.
4. Rasmussen L, Lawaetz M, Serup J, et al. Randomised clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy, and surgical stripping for great saphenous varicose veins with 3-year follow-up. *J Vasc Surg Venous Lymphat Disord* 2013;1:349-56.
5. Tessari L, Tessari M. Foam-glue syringe: a novel combined echo-guided endovascular treatment. *Veins and Lymphatics* 2023;12:11594.
6. Holewijn S, van Eekeren RRJP, Vahl A, et al. Two-year results of a multicenter randomised controlled trial comparing mechanochemical endovenous ablation to RADiOfrequeNcy ablation in the treatment of primary great saphenous vein incompetence (MARADONA trial). *J Vasc Surg Venous Lymphat Disord* 2019;7:364-74.
7. Zini F, Tessari L, Torre R. Sclerofoam assisted laser therapy for saphenous refluxes: an innovative tumescence-free technique. *Veins and Lymphatics* 2015;4:5141.
8. Carugo D, Ankrett DN, Zhao X, et al. Benefits of polido- canol endovenous microfoam (varithena®) compared with physician-compounded foam. *Phlebology* 2016;31:283-95.
9. Roche E, Pons R, Roche O, Puig A. A new automated system for the preparation of sclerosant foam: a study of the physical characteristics produced and the device settings required. *Phlebology* 2020;35:724-33.
10. Myers K. A history of injection treatments - II sclerotherapy. *Phlebology* 2019;34:303-10.
11. Khunger N, Sacchidanand S. Standard guidelines for care: sclerotherapy in dermatology. *Indian J Dermatol Venereol Leprol* 2011;77:222-31.
12. Rabe E, Schliephake D, Otto J, et al. Sclerotherapy of telangiectases and reticular veins: a double-blind, randomised, comparative clinical trial of polidocanol, sodium tetradecyl sulphate and isotonic saline (EASI study). *Phlebology* 2010;25:124-31.
13. Rabe E, Breu FX, Cavezzi A, et al. European guidelines for sclerotherapy in chronic venous disorders. *Phlebology* 2014;29:338-54.
14. Fayyaz F, Vaghani V, Ekhatior C, et al. Advancements in varicose vein treatment: anatomy, pathophysiology, minimally invasive techniques, sclerotherapy, patient satisfaction, and future directions. *Cureus* 2024;16:e51990.
15. Azmoun S, Liu Y, Bian K, et al. The effect of pushing rate on foam stability in the Tessari method. *Dermatol Surg* 2024;50:542-5.
16. Patel SB, Ostler AE, Dos Santos SJ, et al. The effects of environmental and compositional manipulations on the longevity

- of Tessari-made foam for sclerotherapy. *J Vasc Surg Venous Lymphat Disord* 2015;3:312-8.
17. Serkan M, Gokay D. Low temperature offers better foam stability. *J Cosmet Dermatol* 2024;23:3366-71.
  18. Eckmann DM, Kobayashi S, Li M. Microvascular embolisation following polidocanol microfoam sclerosant administration. *Dermatol Surg* 2005;31:636-43.
  19. Morrison N, Neuhardt DL, Rogers CR, et al. Comparisons of side effects using air and carbon dioxide foam for endovenous chemical ablation. *J Vasc Surg* 2008;47:830-6.
  20. Beckitt T, Elstone A and Ashley S. Air versus physiological gas for ultrasound guided foam sclerotherapy treatment of varicose veins. *Eur J Vasc Endovasc Surg* 2011;42:115-9.
  21. De Roos KP, Groen L, Leenders AC. Foam sclerotherapy: investigating the need for sterile air. *Dermatol Surg* 2011;37:1119-24.
  22. Kabnick LS, Jimenez JC, Coogan SM, et al. Comparative effectiveness of non-compounded polidocanol 1% endovenous microfoam (Varithena) ablation versus endovenous thermal ablation utilising a systematic review and network meta-analysis. *J Vasc Surg Venous Lymphat Disord* 2024;12:101896.
  23. Alongi G, Bissacco D, Cervi E. Three-year follow-up analysis of automated microfoam preparation system for great saphenous vein incompetence and varicose veins sclerotherapy treatment. *Phlebology* 2024;39:471-6.
  24. Gloviczki P, Lawrence PF, Wasan SM, et al. The 2023 Society for Vascular Surgery, American Venous Forum, and American Vein and Lymphatic Society Clinical Practice guidelines for the management of varicose veins of the lower extremities. Part II: endorsed by the Society of Interventional Radiology and the Society for Vascular Medicine. *J Vasc Surg Venous Lymphat Disord* 2024;12:101670.
  25. Yamaki T, Nozaki M, Sakurai H, et al. Multiple small-dose injections can reduce the passage of sclerosant foam into deep veins during foam sclerotherapy for varicose veins. *Eur J Vasc Endovasc Surg* 2009;37:343-8.
  26. Hamel-Desnos C, Ouvry P, Benigni JP, et al. Comparison of 1% and 3% polidocanol foam in ultrasound guided sclerotherapy of the great saphenous vein: a randomised, double-blind trial with 2 year-follow-up. 'the 3/1 study'. *Eur J Vasc Endovasc Surg* 2007;34:723-9.
  27. Rabe E, Otto J, Schliephake D, Pannier F. Efficacy and safety of great saphenous vein sclerotherapy using standardised polidocanol foam (ESAF): a randomised controlled multicentre clinical trial. *Eur J Vasc Endovasc Surg* 2008;35:238-45.
  28. Hamel-Desnos C, Nyamekye I, Chauzat B, et al. FOVELASS: a randomised trial of endovenous laser ablation versus polidocanol foam for small saphenous vein incompetence. *Eur J Vasc Endovasc Surg* 2023;65:415-23.
  29. Lim SY, Tan JX, D'Cruz RT, et al. Catheter-directed foam sclerotherapy, an alternative to ultrasound-guided foam sclerotherapy for varicose vein treatment: a systematic review and meta-analysis. *Phlebology* 2020;35:369-83.
  30. Cavezzi A, Mosti G, Campana F, et al. Catheter foam sclerotherapy of the great saphenous vein, with perisaphenous tumescence infiltration and saphenous irrigation. *Eur J Vasc Endovasc Surg* 2017;54:629-35.
  31. Devereux N, Recke AL, Westermann L, et al. Catheter-directed foam sclerotherapy of great saphenous veins in combination with pre-treatment reduction of the diameter employing the principals of perivenous tumescent local anaesthesia. *Eur J Vasc Endovasc Surg* 2014;47:187-95.
  32. De Maeseneer MG, Kakkos SK, Aherne T, et al. Editor's choice - European society for vascular surgery (ESVS) 2022 clinical practice guidelines on the management of chronic venous disease of the lower limbs. *Eur J Vasc Endovasc Surg* 2022;63:184-267.
  33. Shadid N, Nelemans P, Lawson J, et al. Predictors of recurrence of great saphenous vein reflux following treatment with ultrasound-guided foam sclerotherapy. *Phlebology* 2015;30:194e9.
  34. Vähäaho S, Halmesmäki K, Alböck A, et al. Five-year follow-up of a randomized clinical trial comparing open surgery, foam sclerotherapy and endovenous laser ablation for great saphenous varicose veins. *British Journal of Surgery* 2018;105:686-91.
  35. Whing J, Nandhra S, Nesbitt C, Stansby G. Interventions for great saphenous vein incompetence. *Cochrane Database Syst Rev* 2021;8:CD005624.
  36. Wong M, Parsi K, Myers K, De Maeseneer M, et al. Sclerotherapy of lower limb veins: Indications, contraindications and treatment strategies to prevent complications - A consensus document of the International Union of Phlebology-2023. *Phlebology* 2023;38:205-58.
  37. Biemans AA, Kockaert M, Akkersdijk GP, et al. Comparing endovenous laser ablation, foam sclerotherapy, and conventional surgery for great saphenous varicose veins. *J Vasc Surg* 2013;58:727-34.e1.
  38. Rasmussen LH, Lawaetz M, Bjoern L, et al. Randomised clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins. *Br J Surg* 2011;98:1079-87.
  39. Lattimer CR, Kalodiki E, Azzam M, et al. Interim results on abolishing reflux alongside a randomised clinical trial on laser ablation with phlebectomies versus foam sclerotherapy. *Int Angiol* 2013;32:394-403.
  40. Brittenden J, Cooper D, Dimitrova M, et al. Five-year outcomes of a randomised trial of treatments for varicose veins. *N Engl J Med* 2019;381:912-22.
  41. Davies HO, Popplewell M, Darvall K, et al. A review of randomised controlled trials comparing ultrasound-guided foam sclerotherapy with endothermal ablation for the treatment of great saphenous varicose veins. *Phlebology* 2016;31:234-40.
  42. Cooper WM. The treatment of varicose veins. A study based upon a series of more than 35,000 injections of various sclerosing solutions given in 3,164 cases, and 293 cases of extensive and recurrent varicose veins treated by preliminary ambulatory ligation and subsequent injections. *Ann Surg* 1934;99:799-805.
  43. Canata VM. The evolving world of phlebology in 2024. *Acta Phlebol* 2024;25:111-3.
  44. Coughlin PA, Berridge DC. Is there a continuing role for traditional surgery? *Phlebology* 2015;30:29-35.
  45. Pagano M, Bissacco D, Flore R, Tondi P. Great saphenous vein reflux treatment in patients with femoral valve incompetence, the excluded saphenous vein technique (ESVT): a pilot study. *Eur Rev Med Pharmacol Sci* 2018;22:7453-57.
  46. Whing J, Nandhra S, Nesbitt C, Stansby G. Interventions for great saphenous vein incompetence. *Cochrane Database Syst Rev* 2021;8:CD005624.
  47. Alozai T, Huizing E, Schreve M, et al. A systematic review and meta-analysis of mechanochemical endovenous ablation using Flebogrif for varicose veins. *J Vasc Surg Venous Lymphat Disord* 2022;10:248-57.e2.
  48. van Eekeren RR, Boersma D, de Vries JP, et al. Update of endovenous treatment modalities for insufficient saphenous veins – a review of literature. *Semin Vasc Surg* 2014;27:118-

- 36.
49. Oud S, Alozai T, Lam YL, et al. Long-term outcomes of mechanochemical ablation using the clarivein device for the treatment of great saphenous vein incompetence. *J Vasc Surg Venous Lymphat Disord* 2025;13:101967.
50. Bootun R, Lane T, Dharmarajah B, et al. Intra-procedural pain score in a randomised controlled trial comparing mechanochemical ablation to radiofrequency: the multicentre Venefit™ versus ClariVein® trial. *Phlebology* 2016;31:61-5.
51. Parsi K, Roberts S, Kang M, et al. Cyanoacrylate closure for peripheral veins: consensus document of the Australasian college of phlebology. *Phlebology* 2020;35:153-75.
52. Simka M, Skuła M. Early results of the sandwich technique using cyanoacrylate glue and polidocanol foam sclerotherapy for the treatment of varicose veins. *J Vasc Dis* 2024;3:127-33.

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