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Interventions for great saphenous vein insufficiency: A systematic review and network meta-analysis

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Abstract

Background: Great saphenous vein insufficiency (GSVI) adversely affects the quality of life of affected individuals. Minimally invasive endo-venous ablation techniques have emerged as effective and safe treatments, despite the longstanding use of surgical interventions. We aim in our study to evaluate all the available interventions in the literature, either endo-venous or conventional approaches for the treatment of GSVI.

Methods: A thorough search was performed across four electronic databases to identify relevant studies. A frequentist network meta-analysis (NWM) was executed on the combined data to derive network estimates pertaining to the outcomes of concern. Risk ratios (RRs) were employed as the effect size metric for binary outcomes, while mean differences (MDs) were utilized for continuous outcomes, each reported with a 95% confidence interval. The qualitative review was conducted employing the Cochrane risk of bias assessment tool 1.

Results: Our NWM included 75 studies encompassing 12,196 patients. Regarding technical success rate within the first 5 years after treatment, Endo-venous Laser Ablation (EVLA) with High Ligation and Stripping (HL/S), EVLA alone, Cyanoacrylate Adhesive Injection, cryostripping, HL/S and Radiofrequency Ablation (RFA) were significantly better than Ultrasound-Guided Foam Sclerotherapy and F-care. Also, invagination stripping was inferior to all interventions. Conservative Hemodynamic Cure for Venous Insufficiency and Varicose Veins (CHIVA) demonstrated a significantly lower recurrence rate with a RR of 0.35 [0.15; 0.79] compared to RFA, but RFA was more effective in recurrence prevention than HL/S and Mechanochemical Ablation (MOCA), with a RR of 0.63 [0.41; 0.97] and 0.18 [0.03; 0.95], respectively. Endo-venous Steam Ablation (EVSA) emerged as the most effective in reducing post-intervention pain, showing a MD of −2.73 [−3.72; −1.74] compared to HL/S. In Aberdeen Varicose Vein Questionnaire outcome, our analysis favored MOCA over most studied interventions, with an MD of −6.88 [−12.43; −1.32] compared to HL/S. Safety outcomes did not significantly differ among interventions.

Conclusion: Our findings revealed significant variations in the technical success rates, recurrence rates, and post-intervention pain levels among different interventions. CHIVA exhibited enhanced performance in terms of lower recurrence rates, while EVSA emerged as a promising choice for mitigating post-intervention pain. Additionally, our analysis underscored the significance of patient-reported outcomes, with MOCA consistently yielding favorable results in terms of enhancing quality of life and expediting the return to regular activities.

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Keywords
Great saphenous vein insufficiency, great saphenous vein, network meta-analysis, endo-venous laser ablation, high ligation and stripping

Introduction

Among venous disorders, varicose veins are prevalent and commonly affect both the great saphenous vein (GSV) and the small saphenous vein. The severity of this condition can result in various symptoms, including pain, edema, pigmentation changes, itching, and ulceration.[1] A significant portion of the adult population, approximately half, experiences some form of venous issue, with lower-extremity varicose veins impacting around a quarter of individuals. Furthermore, more than a quarter of those with varicose veins exhibit truncal vein insufficiency in their legs.[2]

Great saphenous vein insufficiency (GSVI) adversely affects the quality of life of affected individuals. Minimally invasive endo-venous ablation techniques have emerged as effective and safe treatments despite the longstanding use of surgical interventions.[3] Treating symptomatic varicose veins has been proven to enhance quality of life.[4–6] A transformative shift from traditional open surgery to endo-venous ablation with catheter-based technologies, which can be performed in outpatient or office-based settings, has occurred.[7] The National Institute of Clinical Excellence and the American Venous Forum recommend endo-venous thermal ablations (ETAs), specifically radiofrequency ablation and endo-venous laser ablation, as the primary treatment for saphenous vein reflux.[8] ETAs exhibit advantages such as a short recovery period and cost-effectiveness compared to open surgery. Moreover, ETAs have reported occlusion rates exceeding 90% within up to 5 years of follow-up.[9–12]

Nevertheless, ETAs involve using thermal energy to denature the venous wall, which can lead to complications like pain, skin burns, skin pigmentation changes, nerve damage, and arteriovenous fistula formation.[13,14] Tumescent anesthesia is typically used to mitigate these complications but may increase procedural discomfort. Foam sclerotherapy is available as an alternative to ETAs; however, its long-term efficacy is inferior to other treatment modalities.[15]

To address the drawbacks associated with ETAs, nonthermal and nontumescent ablation techniques (NTNTs) have been developed. These NTNTs, including Mechanochemical ablation (MOCA) and cyanoacrylate adhesive injection (CAE), do not require the application of heat and, therefore, eliminate the need for tumescent anesthesia.[16,17] The National Institute of Clinical Excellence issued interventional procedure guidance for MOCA and CAE.[18,19]

Pain levels associated with NTNTs have been found to be comparable to or less than those of ETAs. NTNTs offer equivalent quality of life improvement, time to return to normal activities or work, and occlusion rates.[20–25] Consequently, NTNTs hold the potential to be considered a favorable alternative to ETAs in the treatment of varicose veins. In the most recent meta-analysis, seven interventions were compared for the treatment of GSVI. Still, they were limited by the small number of studies available for each intervention comparison and disparities in the definitions of outcomes as well as the time points reported.[26]

Furthermore, subsequent randomized controlled trials (RCTs) were conducted after this meta-analysis or were not included. So, as of the present moment, the available evidence remains inconclusive regarding the most effective treatment approach for GSVI. In our current network meta-analysis (NWM), our objective is to comprehensively evaluate all the available interventions (around 20 interventions) in the literature, including ETAs, NTNTs, as well as other conventional approaches, for the treatment of GSVI.

Methods

The study's design adhered to the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions and followed the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) extension for network meta-analysis.[27,28]

Literature search

We systematically queried multiple databases, including Web of Science, PubMed, Scopus, and Cochrane CENTRAL, covering the entire period from their inception until October 2023. To ensure thoroughness, we also retrieved and reviewed all references cited within the eligible articles and any previous meta-analyses pertaining to the same subject matter. The search strategy employed the following search terms: ("Saphenous veins" OR "saphenous vein" OR "saphenous incompetence" OR "saphenous varicose veins" OR "saphenous varicose vein" OR "varicose veins" OR "venous insufficiency" OR "saphenous vein insufficiency") AND (Ablation OR laser OR "cyanoacrylate glue" OR EVLT OR "Endo-venous Laser" OR "endo-venous radiofrequency" OR ligation OR stripping OR "endoluminal

therapies" OR sclerotherapy OR radiofrequency OR MOCA OR RFA OR cyanoacrylate).

Eligibility criteria

In accordance with our systematic review methodology, two independent reviewers conducted a rigorous screening of the retrieved references, adhering to the specified eligibility criteria. The inclusion criteria for randomized clinical trials (RCTs) in our systematic review were as follows: 1) RCTs involving patients with great saphenous vein insufficiency (GSVI); 2) Studies compared between two or more of the following interventions: CAA, CAC, CAE, CHIVA, Cryostripping, EVLA, EVLS, EVSA, F-care, Flebogrif Ablation, Foam Sclerotherapy, HL/S, MOCA, Invagination Stripping, Ultrasound-Guided Foam Sclerotherapy (UGFS), RFA, and Polidocanol FS 4) Studies assessing any of the following outcomes: recurrence rate, success rates, pain, quality of life, and adverse events categorized as major event including deep venous thrombosis (DVT), venous thromboembolism, and pulmonary embolism, and minor events including bruising, hematoma, paresthesia, phlebitis, pigmentation, and wound infection. Studies that did not meet these criteria were excluded from consideration. Exclusion criteria were: 1) Animal studies, 2) Studies not written in English, 3) Studies available solely in abstract form, and 4) Unpublished study data.

Data extraction

For the data extraction process, we employed a standardized data extraction form to collect information regarding study characteristics and outcome data from each included study. The extracted data encompassed the following aspects: study design, site, compared arms, number of participants in each arm, age, gender distribution, clinical CEAP classification, pain score, duration of follow-up, inclusion criteria for each study, and conclusion.

Risk of bias assessment

The quality of the included trials was assessed using the Cochrane risk of Bias Assessment Tool 1 (ROB1) for interventional studies.[29] This tool comprises the following parameters: selection, performance, detection, attrition, reporting, and other possible sources of bias. The authors' judgment was categorized as "high", "low", and "unclear" risk of bias. Discrepancies were resolved through discussion or by a third assessor.

Data analysis

We performed a frequentist network meta-analysis (NWM) of the data to obtain network estimates for the outcomes of interest. Whenever available, outcomes were assessed at two different time points: some less and more than 5 years, and others with less and more than 3 months. We used risk ratios (RR)s as the effect size for dichotomous outcomes and mean differences (MD)s for continuous outcomes with a 95% confidence interval (CI). A significance level of $p < 0.05$ was adopted as the threshold for statistical significance. We also assessed the statistical heterogeneity among the studies utilizing the I^2 statistic and the chi-squared test. A p-value less than 0.1 was interpreted as indicative of heterogeneity, while an I^2 value equal to or exceeding 50% suggested a substantial degree of high heterogeneity. All statistical analyses were done using R software (version R 4.3.1) with netmeta statistical package.[30]

Results

Literature search results

Our search strategy across four distinct databases yielded a total of 15,642 studies. Subsequently, after eliminating duplicate entries, 10,480 studies remained eligible for initial screening. A meticulous evaluation of titles and abstracts led to identifying 227 articles deemed suitable for comprehensive full-text scrutiny. Within this selection, 152 articles were excluded based on predefined criteria, ultimately resulting in the inclusion of 75 articles aligning with our established criteria for our systematic review and NWM.[4,10,22,25,26,31–100] A visual representation of the study selection process is illustrated in the PRISMA flow diagram in Figure 1.

Included studies characteristics

In our NWM, we included 75 studies encompassing 12,196 patients from 17 different countries that discuss different interventions used for GSVI (Figure 2).[4,10,22,25,26,31–100] The most used interventions in these studies were: EVLA (3448 patients), HL/S (3063 patients), RFA (2406 patients), and UGFS (1036 patients) (Figure 3). Primary endpoints for most studies were approximate: success rate (33 studies), recurrence rate (24 studies), and pain score or assessment (19 studies). Baseline characteristics and summary of our included studies are comprehensively discussed in Supplemental Table 1.

Risk of bias evaluation

In the ROB1 tool, most of our included studies have a high risk of bias in blinding either the patient or the outcome assessment. Most studies have a low risk of bias in randomization and reporting domains. Figure 4 shows the summary of the risk of bias according to the ROB 1 tool.

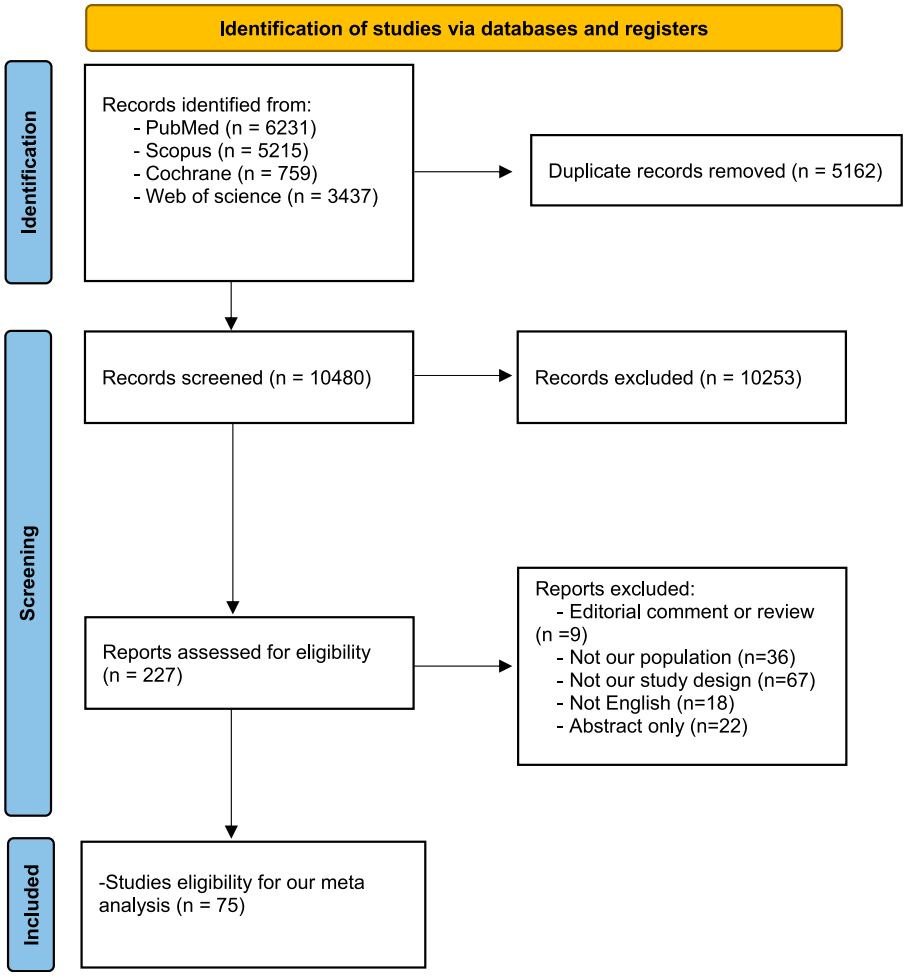

Figure 1. PRISMA flow chart.

Outcomes

Technical success rate. Regarding the technical success rate at or less than 5 years follow-up period, all the available interventions had significantly better success rates compared to invagination stripping as the following (arranged by p-score): EVLA and HL/S (31.20 [4.51; 215.81]), EVLA (29.63 [4.30; 204.36]), CAE (29.78 [4.31; 205.62]), cryostripping (29.61 [4.28; 204.94]), HL/S (29.06 [4.22; 200.36]), RFA (28.71 [4.16; 197.99]), UGFS and HL/S (28.01 [4.02; 195.05]), MOCA (28.11 [4.07; 194.17]), EVSA (26.52 [3.83; 183.71]), UGFS (25.68 [3.72; 177.05]), F-care (22.73 [3.26; 158.65]). Also, EVLA and HL/S, EVLA, CAE, cryostripping, HL/S and RFA were significantly better than UGFS and F-care. Furthermore, NWM of technical success rate for more than a 5-year follow-up period showed that EVLA with HL/S, EVLA alone, and HL/S alone were significantly superior to UGFS; 2.65 [1.04; 6.79], 2.61 [1.18; 5.74], 2.04 [1.06; 3.95], respectively. The pooled studies at both time points were heterogeneous with Chi^2 -p > 0.10. Figures 5 and 6, respectively.

Recurrence rate. During the 5-year period from interventions, CHIVA had a significantly lower recurrence rate compared to RFA, UGFS, EVLA, HL/S, cryostripping, and MOCA with RRs and 95% CI as follows: 0.35 [0.15; 0.79], 0.33 [0.10; 1.10], 0.24 [0.09; 0.63], 0.23 [0.10; 0.56], 0.22 [0.09; 0.51], 0.12 [0.02; 0.61], and 0.06 [0.01; 0.39], respectively. Also, RFA was significantly better in the recurrence rate than HL/S and MOCA 0.63 [0.41; 0.97] and 0.18 [0.03; 0.95], respectively. Additionally, NWM of recurrence rate for more than a 5-year period showed no significant differences between the studies' interventions. RR for EVLA compared to HL/S was 0.98 [0.65; 1.48]. The pooled studies at both time points were heterogeneous with Chi^2 -$p > 0.10$ (Figures 7 and 8) respectively.

Pain scores assessed post-interventions. In our NWM, EVSA was significantly superior to other interventions used to GSVI in decreasing pain post-intervention assessed by VAS, namely, CAE, MOCA, RFA, UGSF, F-care, EVLA,

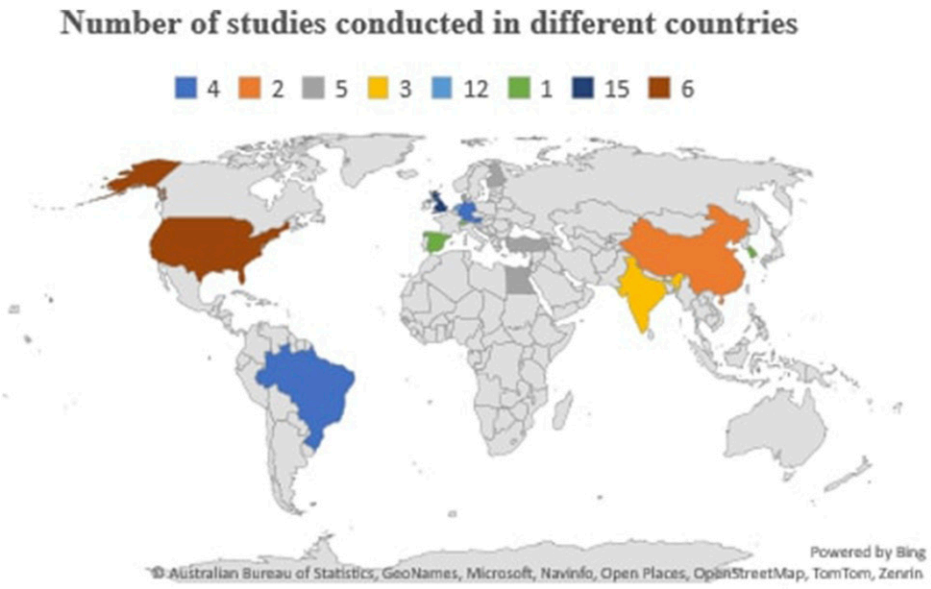

Figure 2. Map graph for studies included in our review across countries.

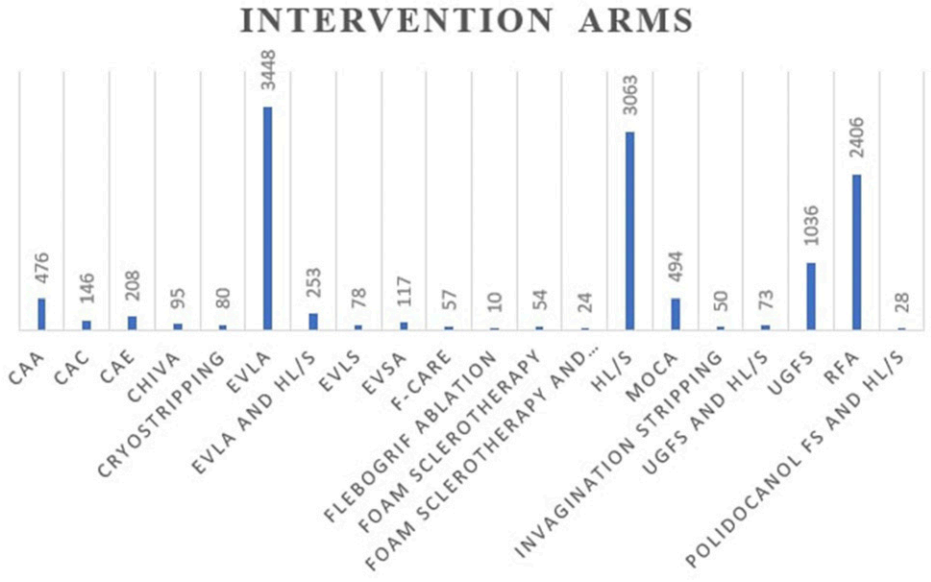

Figure 3. Different arms analyzed in our study with patients encompassed in each arm.

Flebogrif Ablation, HL/S, and cryostripping with the following MDs −1.74 [−2.81; −0.67], −1.75 [−2.79; −0.70], −1.78 [−2.77; −0.78], −1.95 [−3.14; −0.75], −2.36 [−3.67; −1.05], −2.50 [−3.46; −1.54], −2.78 [−4.76; −0.81], −2.73 [−3.72; −1.74], and −4.00 [−5.31; −2.69], respectively. Additionally, CAE showed a significant decrease in MD of patients' VAS compared to EVLA, Flebogrif Ablation, HL/S, and cryostripping: MDs = −0.76 [−1.25; −0.28], −1.04 [−2.82; 0.73], −0.99 [−1.47; −0.51], and −2.26 [−3.28; −1.24], respectively. MOCA was also substantially superior to EVLA and cryostripping −0.75 [−1.16; −0.34] and −2.25 [−3.24; −1.27], respectively. The pooled studies for VAS scores were heterogeneous with Chi^2 -$p > 0.10$ (Figure 9). Comparison regarding post-operative pain score did not significantly prioritize any of the following interventions over each other: MOCA, RFA, CAE, EVLA, UGFS, and HL/S. The net league

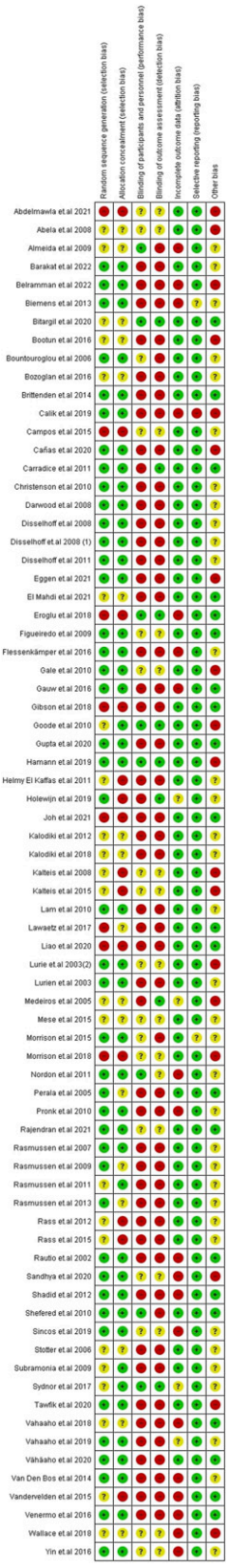

Figure 4. Risk of bias summary of our included RCTs.

table for post-operative pain score outcome is provided in Supplemental Figure 1.

VCSS. The combination of UGFS and HL/S was substantially superior to other comparable interventions in decreasing VCSS. Namely, this combination showed lower MD than MOCA, F-care, RFA, CHIVA, CAE, EVLA and HL/S combined, HL/S alone, EVLA, cryostripping, and UGFS alone: −1.55 [−2.30; −0.79], −1.70 [−2.65; −0.76], −1.91 [−2.61; −1.21], −1.91 [−2.90; −0.91], −1.97 [−2.70; −1.25], −2.00 [−3.02; −0.99], −2.00 [−2.67; −1.33], −2.00 [−2.71; −1.30], −2.20 [−3.04; −1.37], −2.87 [−4.47; −1.27], respectively. Additionally, MOCA showed better improvement in VCSS than most compared intervention: RFA, CAE, HL/S, EVLA, and cryostripping with pooled MD and 95% CI as follows in order: −0.36 [−0.69; −0.04], −0.42 [−0.77; −0.08], −0.45 [−0.80; −0.11], −0.46 [−0.76; −0.15], and −0.66 [−1.20; −0.11] (Supplemental Figure 2).

Quality of life outcomes. AVVQ outcome revealed that MOCA had significantly lower scores and better quality of life accordingly compared to HL/S, EVLA, UGFS, and cryostripping with MDs as follows: −6.88 [−12.43; −1.32], −7.31 [−12.51; −2.12], −8.19 [−14.25; −2.13], and −11.11 [−21.41; −0.82], respectively. Still, other interventions studied in the pooled analysis did not significantly differ. Furthermore, we assessed the change in quality of life by other tools apart from AVVQ, such as CVIQQ, ED-5D, SF-MCS, SF-PCS. However, there were no significant differences in the pairwise comparison between any interventions for GSVI (Supplemental Figures 3–7) respectively.

Safety outcomes. Total adverse events analyzed in our NWM did not reveal any significant differences between these interventions: MOCA, RFA, UGFS, CHIVA, CAE, EVLA, and HL/S. The pooled RRs between MOCA and the following: RFA, CHIVA, EVLA were: 0.97 [0.78; 1.22], 0.54 [0.20; 1.43], and 0.38 [0.11; 1.28], respectively (Supplemental Figure 8).

Major adverse events. We assessed this outcome at two-time points: early assessment (less than 3 months) and late assessment (after 3 months). DVT and total adverse events were indifferent between any of the interventions in the pairwise analysis. For early assessment, the pooled RRs for total events in the case of MOCA versus RFA, CAE, and EVLA were 0.14 [0.01; 2.66], 0.07 [0.00; 2.94], and 0.04 [0.00; 3.16], respectively. For late assessment, the pooled RRs for total events in the case of RFA versus CAE, EVLA, HL/S, and UGFS were: 0.53 [0.11; 2.53],

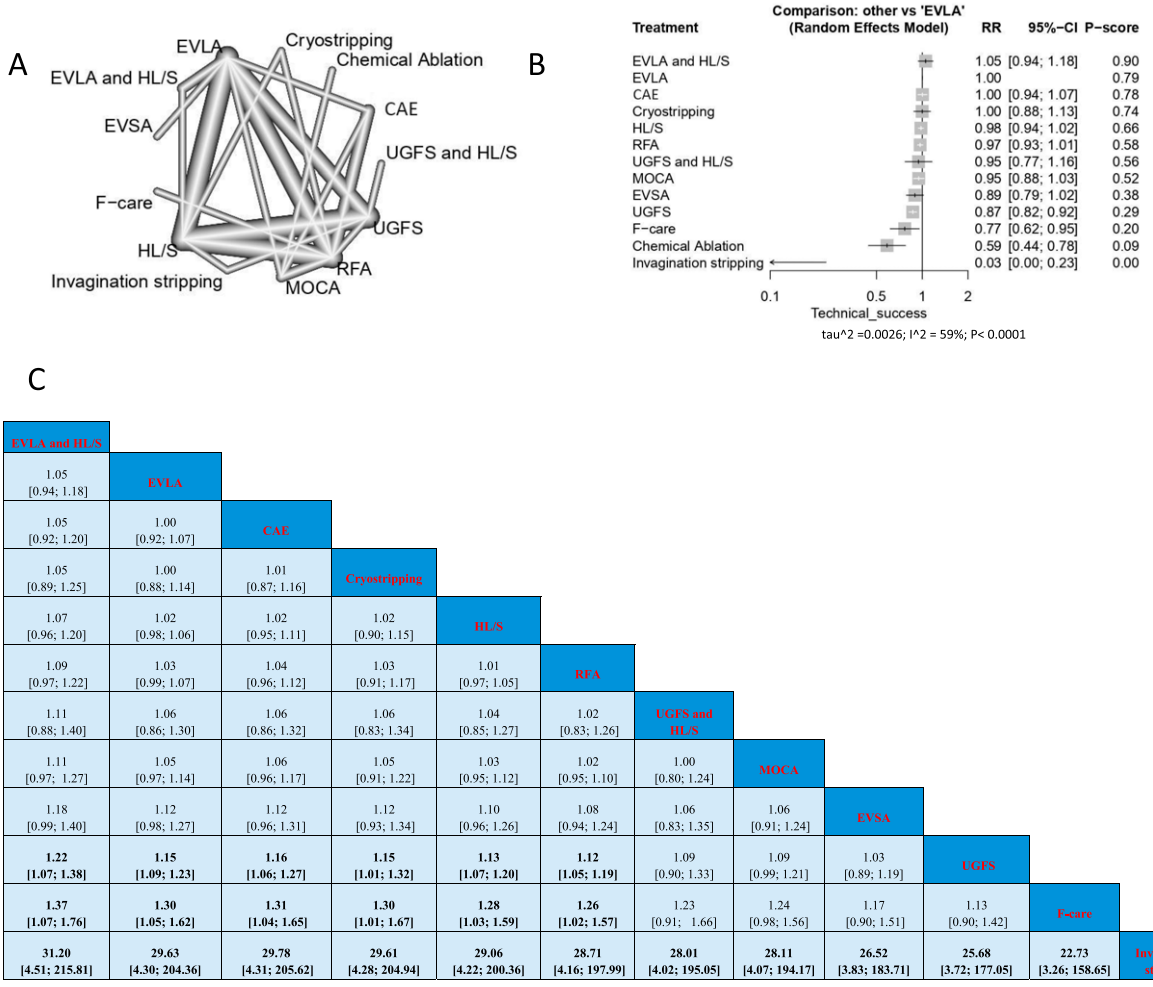

Figure 5. Technical success rate for less than a 5-year period; (A) Network graph showing direct evidence between the evaluated interventions. (B) A forest plot comparing all interventions. (C) The league table represents the network meta-analysis estimates for all interventions' comparisons.

0.25 [0.02; 3.25], 0.24 [0.02; 2.63], and 0.22 [0.02; 2.66], respectively (Supplemental Figures 9–12).

Minor adverse events. We also evaluated minor adverse events as the major ones at two points. However, unlike major events, the total events in this outcome differed significantly among studied interventions, either at early or late time points. Regarding early one, CAE, RFA, EVLA, UGFS and HL/S (combined), and HL/S had lower risk for total minor events compared to UGFS with RRs and 95% CI as follows: 0.13 [0.03; 0.63], 0.14 [0.03; 0.65], 0.65 [0.56; 0.75], 0.82 [0.33; 2.06], and 0.82 [0.74; 0.91], respectively. As to late events, RFA, CAE, and HL/S had lower RRs for total minor events compared to UGFS with RRs: 0.14 [0.02; 0.82],0.36 [0.18; 0.75], and 0.80 [0.68; 0.95], respectively. Regarding phlebitis, there were no significant differences among studied interventions except for HL/S versus UGFS in early and late time points and between HL/S versus RFA in late time points with RRs and 95% CI as follows: 0.20 [0.05; 0.88], 0.04 [0.00; 0.70], and 0.26 [0.09; 0.76], respectively (Supplemental Figures 13–27).

Discussion

The National Institute for Health and Care Excellence (NICE) guidelines advocate for a hierarchical treatment approach in the management of venous insufficiency.[101] Their recommended preference is for endothermal ablation. In cases where endothermal ablation is deemed unsuitable, ultrasound-guided foam sclerotherapy is the next recommended option. If ultrasound-guided foam sclerotherapy is also unsuitable, surgery is considered (NICE 2013a). These recommendations are based on a cost-effectiveness analysis.[101] In the realm of interventions for Great Saphenous Vein Insufficiency, the cost-effectiveness of invasive and non-invasive approaches is a critical consideration.

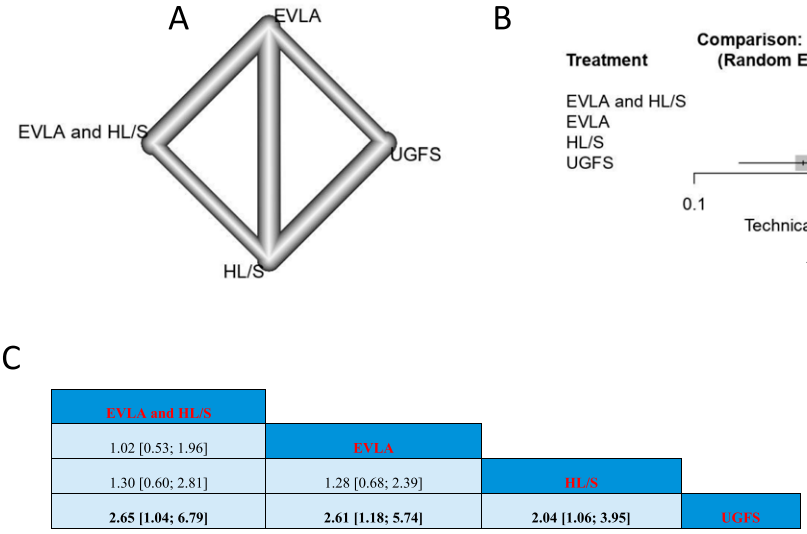

Figure 6. Technical success rate for more than a 5-year period; (A) Network graph showing direct evidence between the evaluated interventions. (B) A forest plot comparing all interventions. (C) The league table represents the network meta-analysis estimates for all interventions' comparisons.

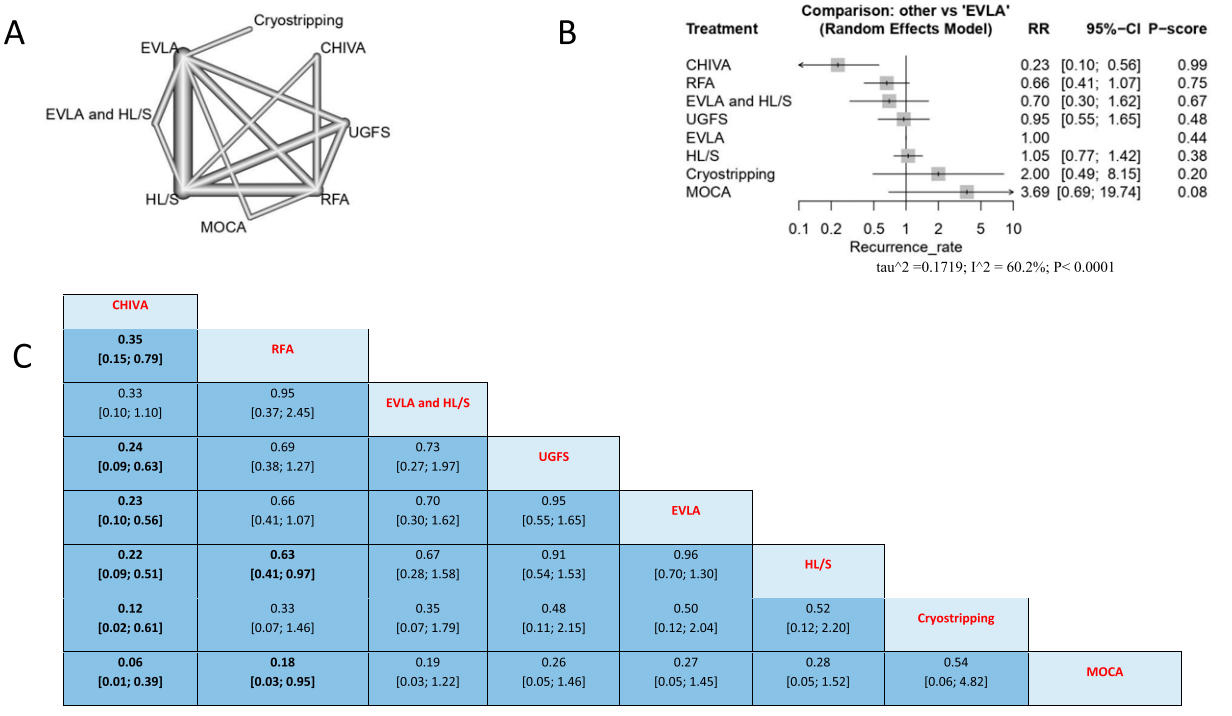

Figure 7. Recurrence rate for less than a 5-year period; (A) Network graph showing direct evidence between the evaluated interventions. (B) A forest plot comparing all interventions. (C) The league table represents the network meta-analysis estimates for all interventions' comparisons.

Minimally invasive techniques, such as EVLA and laser-sclerosing foam hybrid treatment, have emerged as viable options for managing this condition. These methods have shown promising results in terms of efficacy and patient outcomes. Studies have indicated that minimally invasive procedures like EVLA are effective and cost-effective compared to traditional surgical interventions.[4,46,101] The evidence suggests that minimally invasive interventions,

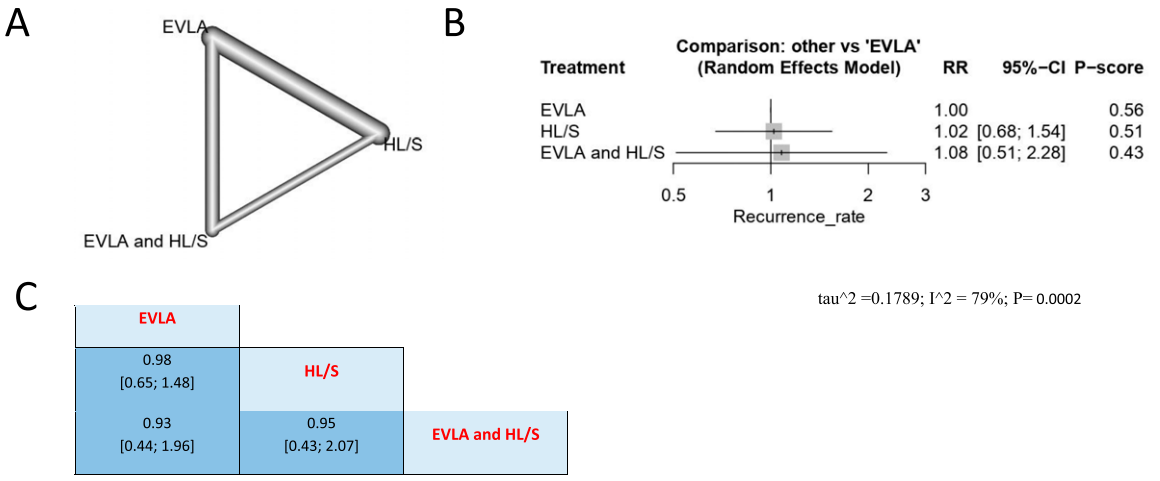

Figure 8. Recurrence rate for more than a 5-year period; (A) Network graph showing direct evidence between the evaluated interventions. (B) A forest plot comparing all interventions. (C) The league table represents the network meta-analysis estimates for all interventions' comparisons.

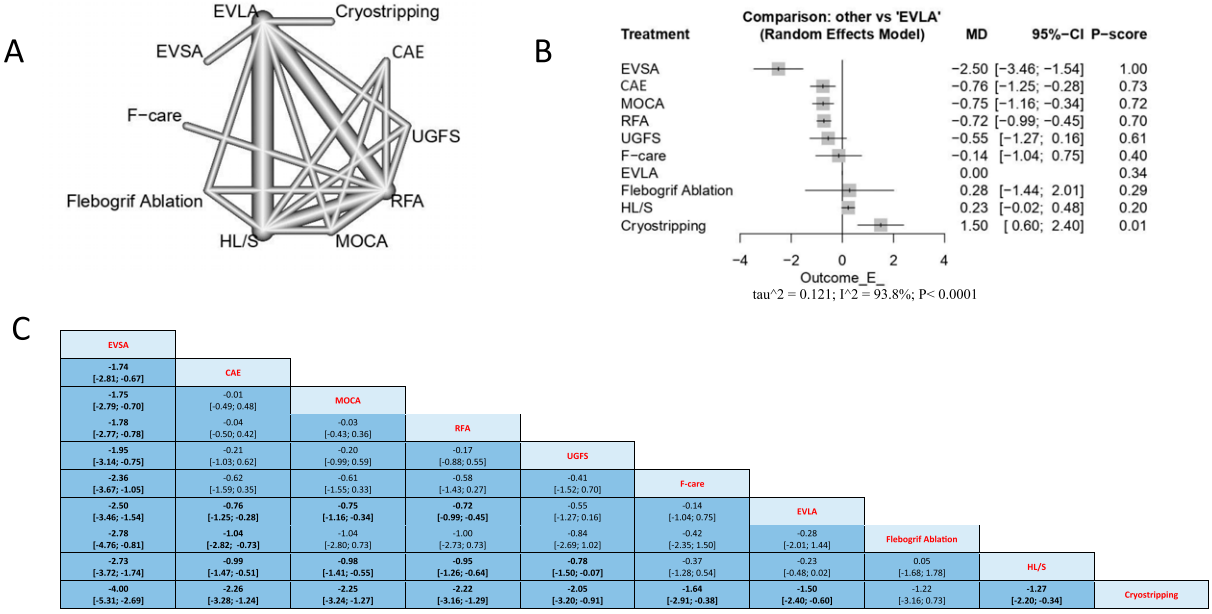

Figure 9. Post-operative pain visual analogue scale score; (A) Network graph showing direct evidence between the evaluated interventions. (B) A forest plot comparing all interventions. (C) The league table represents the network meta-analysis estimates for all interventions' comparisons.

such as EVLA and LSFHT, offer a cost-effective and efficient alternative to traditional surgical methods for managing Great Saphenous Vein Insufficiency.

In their meta-analysis, Whing et al. observed that technical success rates were generally similar across most treatment modalities. Specifically, they noted that EVLA may offer a potential advantage in terms of technical success compared to UGFS or HL/S. HL/S, in turn, might exhibit improved technical success compared to UGFS.[26] However, no significant evidence of a difference was identified in terms of recurrence rates, with the exception of a potential long-term benefit favoring RFA over EVLA or HL/S. Whing and colleagues emphasized the need for further studies that provide more comprehensive evidence regarding various treatment options. They also highlighted the importance of standardizing clinical terminology used to measure outcomes and the time points at which these measurements are taken in future trials.[26]

Table 1. Comparison for the most recent collective evidence for GSVI interventions.

Study	Key findings
Our NWM (75 studies)	Invagination stripping had lower technical success rates compared to alternatives. - Chemical Ablation had inferior technical success rates. - CHIVA had lower recurrence rates compared to several interventions. - RFA had lower recurrence rates than HL/S and MOCA. - EVSA was superior in post-intervention pain. - CAE showed significant pain reduction. - MOCA outperformed RFA, CAE, HL/S, EVLA, and cryostripping. - UGFS + HL/S had better VCSS. - MOCA, CAE, UGFS, RFA, and EVLA allowed quicker return to normal activities. - MOCA improved quality of life. - Safety outcomes had no significant differences except for phlebitis.
NICE Guidelines[101]	Preference for endothermal ablation was recommended. - Ultrasound-guided foam sclerotherapy is the next option. - Surgery considered if other options are unsuitable. - Recommendations based on cost-effectiveness analysis.
Whing et al. 2021- Meta-analysis[26]	Similar technical success rates across most treatments. - EVLA may have advantages in technical success over UGFS or HL/S. - HL/S may have improved technical success compared to UGFS. - No significant difference in recurrence rates except potential long-term benefit favoring RFA. - Need for standardized terminology and outcome measurement in future studies.
Gloviczki Review (SVS/AVF)[7]	Strong recommendation for endo-venous thermal ablation over SFJ (Saphenofemoral junction) ligation and stripping. - No preference between endothermal techniques. - UGFS was suggested as an alternative with weak recommendations based on low-quality evidence.
Kheirelseid 2018 Meta-analysis[90]	No significant difference in recurrence between EVLA and surgery. - UGFS had a higher recurrence rate than EVLA. - Surgery had lower recurrence compared to UGFS. - UGFS was less effective than RFA. - No analysis of QoL measures due to heterogeneity in reporting.
Hamann 2017 Meta-analysis[89]	UGFS was inferior to EVLA and HL/S in anatomical success at five years. - Elevated rates of recurrent reflux with UGFS. - VCSS scores comparable between EVLA and SFJ ligation and stripping.

GSVI: great saphenous vein insufficiency; NWM: network meta-analysis; SVS: vascular surgery; AVF: American venous forum; CHIVA: conservative hemodynamic cure for venous insufficiency and varicose veins; RFA: radiofrequency ablation; HL/S: high ligation and stripping; MOCA: mechanochemical ablation; EVSA: endo-venous steam ablation; CAE: cyanoacrylate adhesive injection; UGFS: ultrasound-guided foam sclerotherapy; EVLA: endo-venous laser ablation; VCSS: venous clinical severity score; QoL: quality of life.

According to the review conducted by Gloviczki in 2012, which the Society endorsed for Vascular Surgery (SVS) and the American Venous Forum (AVF) Venous Guideline Committee, endo-venous thermal ablation (such as EVLA or RFA) is strongly recommended over SFJ ligation and stripping for treating GSV incompetence (recommendation: GRADE 1 - strong, level of evidence: B - medium quality).[7] However, this review did not favor one endothermal technique over another. UGFS was suggested as an alternative for treating incompetent saphenous veins, but the recommendation for this approach was weak and based on low-to very-low-quality evidence.[7]

A meta-analysis conducted by Kheirelseid et al. compared the long-term recurrence rates after conventional surgery versus endo-venous treatments.[90] This analysis included nine randomized controlled trials (RCTs), with three trials excluded from the Cochrane Review due to not meeting inclusion criteria. In alignment with the Cochrane Review, Kheirelseid 2018 found no statistically significant difference between EVLA and surgery regarding recurrence.[90] UGFS exhibited a higher recurrence rate than EVLA. The recurrence rate was lower in surgery participants compared to those who underwent UGFS. UGFS was also found to be less effective than RFA. It's important to note that the review did not delve into QoL measures due to the heterogeneity in reporting this outcome.[90]

A meta-analysis by Hamann in 2017 assessed the 5-year efficacy of surgery, endo-venous laser therapy (EVLT, equivalent to EVLA), and UGFS.[89] The primary outcome was anatomical success, with secondary outcomes being recurrent reflux rate and changes in disease specific QoL using AVVQ and CIVIQ scales. The study included three RCTs and ten follow-ups of RCTs, seven of which were incorporated into this review.[89] In an effort to standardize the definitions of anatomical success and recurrent reflux across studies, Hamann et al. adjusted the definitions to enable data pooling, which could significantly influence the results. As reported in this review, UGFS was inferior to EVLA and HL/S regarding anatomical success at the 5-year mark.[89] Hamann et al. also noted elevated rates of recurrent reflux. VCSS scores were comparable between EVLA and SFJ ligation and stripping.[89] The key findings for our study and these studies are summarized in Table 1.

Still, we had many differences compared to the previous meta-analysis. First, our NWM discussed all available interventions for GSVI (around 20 interventions) with a very

large sample size of 12,196 patients, while the largest previous meta-analysis compared around seven interventions only with less than half the number of our patients. Second, we included all patients with GSVI from all different clinical classes according to CEAP classification. However, Whing et al.[26] excluded patients with healed ulcers (C5) or active ulcers (C6), and Kheirelseid et al. had only one study that included C6 patients.[90] So, their evidence was not well representative of this severe category. Third, Hamman et al. lack sufficient statistical power to adequately assess outcomes over a 5-year follow-up period.[89] Additionally, their aggregation of data pertaining to the QoL was not feasible, resulting in the presentation of purely descriptive findings. Furthermore, only a single study examined the long-term consequences of RFA, precluding its inclusion in their meta-analysis and preventing the formulation of robust conclusions from this specific technique's long-term effects.[89] The latter drawback was also the case in Whing et al..[26] Third, many studies have been conducted after the last meta-analysis, and others were not included in their comparison.[84–88,91,92,94–98,102,103]

However, our study was not free of limitations. First, all of our studies were unclear or even had a high risk of bias; some of them were supported by industry. Second, although we included a large number of patients, they needed more stratification, especially according to clinical status by CEAP or any other classifications. However, this was not feasible as the original data were not stratified concurrently. Third, although we included many comparison arms, many arms were less representative than others and had small sample sizes, which can limit the generalizability and statistical power of the findings. While our study provides valuable insights, it is essential to interpret the conclusions cautiously, considering the limitations posed by study sizes. Fourth, a significant level of heterogeneity was detected in many outcomes, which may be explained by the surgeons' different expertise and training. Fifth, the geographical scope of our review was confined to select regions around the globe, thereby potentially limiting the generalizability and applicability of the findings. Finally, due to the absence of stratification in studies that incorporated bilateral treatment of varicose veins, we encountered a challenge in excluding them from our review. This introduces a potential source of bias, as concurrent bilateral treatment of varicose veins can significantly influence various outcome measures, including quality of life scores, patients' satisfaction, and pain levels.

Conclusion

Our findings revealed significant variations in the technical success rates, recurrence rates, and post-intervention pain levels among different interventions. Interventions such as CHIVA demonstrated superior performance in terms of recurrence rates, while EVSA emerged as a promising option for minimizing post-intervention pain. Furthermore, our analysis highlighted the importance of patient-reported outcomes, with MOCA consistently delivering favorable results in terms of quality-of-life improvement and quicker return to normal activities. Despite these informative findings, the presence of unclear or high-risk bias in many of the included studies underscores the need for more rigorously designed investigations in this field. Stratification of patient data based on clinical status and bilateral treatment of varicose veins could enhance the accuracy of our conclusions but was hindered by data constraints. Future research endeavors should aim to address the limitations identified here, ensuring a more comprehensive understanding of these interventions and their impact on patients' well-being.

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Supplemental Material

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Abbreviations

CAA	conservative anterior access
CAC	cyanoacrylate closure
CAE	cyanoacrylate adhesive injection
CHIVA	conservative hemodynamic cure for venous insufficiency and varicose veins
EVLA	endo-venous laser ablation
EVLS	endo-venous laser sclerotherapy
EVSA	endo-venous steam ablation
F-care	foam sclerotherapy with compression
HL/S	high ligation and stripping
MOCA	mechanochemical ablation
UGFS	ultrasound-guided foam sclerotherapy
RFA	radiofrequency ablation
Polidocanol FS	polidocanol foam sclerotherapy
CEAP	clinical, etiological, anatomical and pathophysiological
VCSS	venous clinical severity score
QoL	quality of life
AVVQ	aberdeen varicose vein questionnaire
VAS	visual analogue scale
CIVIQ	chronic venous insufficiency quality of life questionnaire
EQ-5D	Euro quality of life-5D
SF–MCS	short form mental component score
SF-PCS	short form physical component score
NTNTs	nonthermal and nontumescent ablation techniques
ETA	endo-venous thermal ablations