Medical Policy

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Populations	Interventions	Comparators	Outcomes
Individuals: • With varicose veins/venous insufficiency and saphenous vein reflux	Interventions of interest are: • Endovenous thermal ablation (radiofrequency or laser)	Comparators of interest are: • Conservative therapy • Ligation and stripping	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Quality of life • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With varicose veins/venous insufficiency and saphenous vein reflux	Interventions of interest are: • Microfoam sclerotherapy	Comparators of interest are: • Conservative therapy • Ligation and stripping • Endovenous radiofrequency or laser ablation	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Quality of life • Treatment-related morbidity
Individuals: • With varicose veins/venous insufficiency and saphenous vein reflux	Interventions of interest are: • Mechanochemical ablation	Comparators of interest are: • Conservative therapy • Ligation and stripping • Endovenous radiofrequency or laser ablation • Microfoam sclerotherapy	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Quality of life • Treatment-related morbidity
Individuals: • With varicose veins/venous insufficiency and saphenous vein reflux	Interventions of interest are: • Cyanoacrylate adhesive	Comparators of interest are: • Conservative therapy • Ligation and stripping • Endovenous radiofrequency or laser ablation	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Quality of life • Treatment-related morbidity
Individuals: • With varicose veins/venous insufficiency and saphenous vein reflux	Interventions of interest are: • Cryoablation	Comparators of interest are: • Conservative therapy • Ligation and stripping • Endovenous radiofrequency or laser ablation	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Quality of life • Treatment-related morbidity
Individuals: • With varicose tributary veins	Interventions of interest are: • Ablation (stab avulsion, sclerotherapy, or phlebectomy) of tributary veins	Comparators of interest are: • Conservative therapy	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Quality of life • Treatment-related morbidity
Individuals: • With perforator vein reflux	Interventions of interest are: • Ablation (e.g., subfascial endoscopic perforator surgery) of perforator veins	Comparators of interest are: • Conservative therapy	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Quality of life • Treatment-related morbidity

DESCRIPTION

A variety of treatment modalities are available to treat varicose veins / venous insufficiency, including surgery, thermal ablation, and sclerotherapy, mechanochemical ablation (MOCA), cyanoacrylate adhesive (CAC), and cryotherapy. The application of each modality is influenced by the severity of the symptoms, type of vein, source of venous reflux, and the use of other (prior or concurrent) treatments.

Objective

The objective of this evidence review is to evaluate whether the use of ablative, chemical, and adhesive technologies to treat varicose veins/venous insufficiency arising from reflux in the saphenous, tributary, and perforator veins improves net health outcomes.

Background

Venous Reflux/Venous Insufficiency

The venous system of the lower extremities consists of the superficial veins (this includes the great and small saphenous and accessory, or duplicate, veins that travel in parallel with the great and small saphenous veins), the deep system (popliteal and femoral veins), and perforator veins that cross through the fascia and connect the deep and superficial systems. One-way valves are present within all veins to direct the return of blood up the lower limb. Because the venous pressure in the deep system is generally greater than that of the superficial system, valve incompetence at any level may lead to backflow (venous reflux) with pooling of blood in superficial veins. Varicose veins with visible varicosities may be the only sign of venous reflux, although itching, heaviness, tension, and pain may also occur. Chronic venous insufficiency secondary to venous reflux can lead to thrombophlebitis, leg ulcerations, and hemorrhage. The CEAP classification of venous disease considers the clinical, etiologic, anatomic, and pathologic characteristics of venous insufficiency, ranging from class 0 (no visible sign of disease) to class 6 (active ulceration).

Treatment of Saphenous Veins and Tributaries

Saphenous veins include the great and small saphenous and accessory saphenous veins that travel in parallel with the great or small saphenous veins. Tributaries are veins that empty into a larger vein. Treatment of venous reflux has traditionally included the following:

- Identification by preoperative Doppler ultrasonography of the valvular incompetence
- Control of the most proximal point of reflux, traditionally by suture ligation of the incompetent saphenofemoral or saphenopopliteal junction
- Removal of the superficial vein from circulation, e.g., by stripping of the great and/or small saphenous veins.
- Removal of varicose tributaries (at the time of the initial treatment or subsequently) by stab avulsion (phlebectomy) or injection sclerotherapy.

Minimally invasive alternatives to ligation and stripping have been investigated. They include forms of sclerotherapy, cyanocrylate adhesive, and thermal ablation using cryotherapy, high-frequency radio waves (200-300 kHz), or laser energy.

Thermal Ablation

Radiofrequency ablation is performed using a specially designed catheter inserted through a small incision in the distal medial thigh to within 1 to 2 cm of the saphenofemoral junction. The catheter is slowly withdrawn, closing the vein. Laser ablation is performed similarly; a laser fiber is introduced into the great saphenous vein under ultrasound guidance; the laser is activated and slowly removed, along the course of the saphenous vein. Cryoablation uses extreme cold. The objective of endovenous techniques is to injure the vessel, causing retraction and subsequent fibrotic occlusion of the vein. Technical developments since thermal ablation procedures were initially introduced include the use of perivenous tumescent anesthesia, which allows successful treatment of veins larger than 12 mm in diameter and helps to protect adjacent tissue from thermal damage during treatment of the small saphenous vein.

Sclerotherapy

The objective of sclerotherapy is to destroy the endothelium of the target vessel by injecting an irritant solution (either a detergent, osmotic solution, or chemical irritant), ultimately occluding the vessel. Treatment success depends on accurate injection of the vessel, an adequate injectate

volume and concentration of sclerosant, and compression. Historically, larger veins and very tortuous veins were not considered good candidates for sclerotherapy due to technical limitations. Technical improvements in sclerotherapy have included the routine use of Duplex ultrasound to target refluxing vessels, luminal compression of the vein with anesthetics, and a foam/sclerosant injectate in place of liquid sclerosant. Foam sclerosants are produced by forcibly mixing a gas (e.g., air or carbon dioxide) with a liquid sclerosant (e.g., polidocanol or sodium tetradecyl sulfate). Physician-compounded foam is produced at the time of treatment. A commercially available microfoam sclerosant with a proprietary gas mix is available that is proposed to provide smaller and more consistent bubble size than what is produced with physician-compounded sclerosant foam.

Endovenous Mechanochemical Ablation
Endovenous mechanochemical ablation uses both sclerotherapy and mechanical damage to the lumen. Following ultrasound imaging, a disposable catheter with a motor drive is inserted into the distal end of the target vein and advanced to the saphenofemoral junction. As the catheter is pulled back, a wire rotates at 3500 rpm within the lumen of the vein, abrading the lumen. At the same time, a liquid sclerosant (sodium tetradecyl sulfate) is infused near the rotating wire. It is proposed that mechanical ablation allows for better efficacy of the sclerosant, and results in less pain and risk of nerve injury without the need for the tumescent anesthesia used with endovenous thermal ablation techniques (radiofrequency ablation, endovenous laser ablation).

Cyanoacrylate Adhesive
A cyanoacrylate adhesive is a clear, free-flowing liquid that polymerizes in the vessel via an anionic mechanism (i.e., polymerizes into a solid material on contact with body fluids or tissue). The adhesive is gradually injected along the length of the vein in conjunction with ultrasound and manual compression. The acute coaptation halts blood flow through the vein until the implanted adhesive becomes fibrotically encapsulated and establishes chronic occlusion of the treated vein. Cyanoacrylate glue has been used as a surgical adhesive and sealant for a variety of indications, including gastrointestinal bleeding, embolization of brain arteriovenous malformations, and surgical incisions or other skin wounds.

Transilluminated Powered Phlebectomy
Transilluminated powered phlebectomy is an alternative to stab avulsion and hook phlebectomy. This procedure uses two instruments: an illuminator, which also provides irrigation, and a resector, which has an oscillating tip and suction pump. Following removal of the saphenous vein, the illuminator is introduced via a small incision in the skin and tumescence solution (anesthetic and epinephrine) is infiltrated along the course of varicosity. The resectoris then inserted under the skin from the opposite direction, and the oscillating tip is placed directly beneath the illuminated veins to fragment and loosen the veins from the supporting tissue. Irrigation from the illuminator is used to clear the vein fragments and blood through aspiration and additional drainage holes. The illuminator and resector tips may then be repositioned, thereby reducing the number of incisions needed when compared with stab avulsion or hook phlebectomy. It has been proposed that transilluminated powered phlebectomy might decrease surgical time, decrease complications such as bruising and lead to a faster recovery than established procedures.

REGULATORY STATUS
In 2015, the VenaSeal (TM) Closure System (Sapheon, part of Medtronic) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval (P140018) process for

the permanent closure of clinically significant venous reflux through endovascular embolization with coaptation. The VenaSeal Closure System seals the vein using a cyanoacrylate adhesive agent. FDA product code: PJQ.

In 2013, Varithena(R)(formerly Varisolve), a sclerosant microfoam made with a proprietary gas mix, was approved by the FDA under a new drug application (205-098) for the treatment of incompetent great saphenous veins, accessory saphenous veins, and visible varicosities of the great saphenous vein system above and below the knee.

The following devices were cleared for marketing by the FDA through the 501(k) process for endovenous treatment of superficial vein reflux:

In 1999, the VNUS Closure(R) System, a radiofrequency device, was cleared by the FDA through the 510(k) process for "endovascular coagulation of blood vessels in patients with superficial vein reflux." In 2005, the VNUS RFS(R) and RFS*Flex*(R) devices were cleared by the FDA for "use in vessel and tissue coagulation including treatment of incompetent (i.e., refluxing) perforator and tributary veins." In 2008, the modified VNUS ClosureFast(R) Intravascular Catheter was cleared by the FDA through the 510(k) process. FDA product code: GEI.

In 2002, the Diomed 810 nm surgical laser and EVLT(R) (endovenous laser therapy) procedure kit were cleared by the FDA through the 510(k) process ".....for use in the endovascular coagulation of the great saphenous vein of the thigh in patients with superficial vein reflux." FDA product code: GEX.

In 2005, a modified Erbe Erbokryo cryosurgical unit (Erbe USA) was approved by the FDA for marketing through the 510(k) process. A variety of clinical indications are listed, including cryostripping of varicose veins of the lower limbs. FDA product code: GEH.

In 2003, the Trivex system (InaVein), a device for transilluminated powered phlebectomy, was cleared by the FDA through the 510(k) process for "ambulatory phlebectomy procedures for the resection and ablation of varicose veins." FDA product code: DNQ.

In 2008, the ClariVein(R) Infusion Catheter (Merit Medical) was cleared by the FDA through the 510(k) process (K071468) for mechanochemical ablation. The FDA determined that this device was substantially equivalent to the Trellis Infusion System (K013635) and the Slip-Cath Infusion Catheter (K882796). The system includes an infusion catheter, motor drive, stopcock, and syringe, and is intended for the infusion of physician-specified agents in the peripheral vasculature. FDA product code: KRA

POLICY

I. SAPHENOUS VEINS - Great or Small Saphenous Veins

A. Treatment of the great or small saphenous veins by surgery (ligation and stripping) endovenous thermal ablation (radiofrequency or laser), or microfoam sclerotherapy may be considered **medically necessary** for symptomatic varicose veins / venous insufficiency when all the following criteria have been met:

1. There is demonstrated saphenous reflux and CEAP [Clinical, Etiology, Anatomy, Pathophysiology], class C2 or greater
   AND
2. There is documentation of 1 or more of the following indications:
   a. Ulceration secondary to venous stasis
      OR
   b. Recurrent superficial thrombophlebitis
      OR
   c. Hemorrhage or recurrent bleeding episodes from a ruptured superficial varicosity
      OR
   d. All of the following:
      1) Persistent pain, swelling, itching, burning, or other symptoms associated with saphenous reflux
         AND
      2) the symptoms significantly interfere with activities of daily living
         AND
      3) conservative management including compression therapy for at least 3 months has not improved the symptoms

B. Treatment of great or small saphenous veins by surgery, endovenous thermal ablation (radiofrequency or laser), or microfoam sclerotherapy that does not meet the criteria described above is considered **not medically necessary.**

C. Treatment of the great or small saphenous veins by cyanoacrylate adhesive is considered **not medically necessary** for symptomatic varicose veins / venous insufficiency (see Policy Guideline 1).

D. Treatment of varicose veins for cosmetic purposes is **not covered**.

II. ACCESSORY SAPHENOUS VEINS

A. Treatment of accessory saphenous veins by surgery (ligation and stripping), endovenous thermal ablation (radiofrequency or laser) or microfoam sclerotherapy may be considered **medically necessary** for symptomatic varicose veins / venous insufficiency when all the following criteria have been met:

1. One of the following:
   a. Incompetence of the accessory saphenous vein, when documentation of the anatomy supports the reflux is isolated
      OR
   b. The great or small saphenous veins had been previously eliminated (at least 3 months)

   AND
2. There is demonstrated accessory saphenous reflux
   AND
3. There is documentation of 1 or more of the following indications:
   a. Ulceration secondary to venous stasis
      OR
   b. Recurrent superficial thrombophlebitis
      OR
   c. Hemorrhage or recurrent bleeding episodes from a ruptured superficial varicosity
      OR
   d. All of the following:
      1) Persistent pain, swelling, itching, burning, or other symptoms associated with saphenous reflux
         AND
      2) the symptoms significantly interfere with activities of daily living
         AND
      3) conservative management including compression therapy for at least 3 months has not improved the symptoms

B. Treatment of accessory saphenous veins by surgery, endovenous thermal ablation (radiofrequency or laser), or microfoam sclerotherapy that do not meet the criteria described above is considered **not medically necessary**.

C. Treatment of accessory saphenous veins by cyanoacrylate adhesive is considered **not medically necessary** for symptomatic varicose veins / venous insufficiency (see Policy Guideline 1).

D. Treatment of varicose veins for cosmetic purposes is **not covered**.

III. SYMPTOMATIC VARICOSE TRIBUTARIES

A. When physical findings support medical necessity; the following treatments are considered **medically necessary** as a component of the treatment of symptomatic varicose tributaries (none of these techniques has been shown to be superior to another):
   1. Stab avulsion
   2. Hook phlebectomy
   3. Sclerotherapy
   4. Transilluminated powered phlebectomy

B The sole treatment of varicose vein tributaries in the presence of saphenofemoral or saphenopopliteal reflux is considered **not medically necessary**.

C. Treatment of tributary veins less than 3 mm is considered **cosmetic and not covered.**

IV. PERFORATOR VEINS

A. Surgical ligation (including subfascial endoscopic perforator surgery) or endovenous thermal ablation (radiofrequency or laser) of incompetent perforator veins may be considered **medically necessary** as a treatment of leg ulcers associated with chronic venous insufficiency when all the following conditions have been met:
   1. There is demonstrated perforator reflux
      AND
   2. The superficial saphenous veins (great, small, or accessory saphenous and symptomatic varicose tributaries) have been previously eliminated
      AND
   3. Ulcers have not resolved following combined superficial vein treatment and compression therapy for at least 3 months
      AND
   4. The venous insufficiency is not secondary to deep venous thromboembolism

B. Treatment of incompetent perforator veins without refractory stasis ulceration is considered **not medically necessary** as discussed in reference 5:
   1. "Patients with isolated reflux in perforator veins…are generally asymptomatic; reflux at multiple valve sites is required for symptom expression."
   2. "Reflux in perforator veins that are smaller than 4mm in diameter is not considered to be clinically significant.
   3. "In complex venous disease, comprehensive correction is neither feasible nor necessary; partial correction of multifocal disease often relieves symptoms."
   4. "The role of interruption of the perforator vein is controversial because of doubts about the pathologic significance of reflux involving this vein and because its specific efficacy is uncertain."
   5. "The role of perforator vein ablation awaits results, of properly conducted randomized controlled trials."
   6. Perforator reflux often resolves following saphenous ablation.

C. Ligation or ablation of incompetent perforator veins performed concurrently with superficial venous surgery is **not medically necessary**.

V. Telangiectasia

Treatment of telangiectasia such as spider veins, angiomata, and hemangiomata is considered **cosmetic and not covered**.

VI. Other Veins

A. Techniques for conditions not specifically listed above are **experimental / investigational** including, but not limited to:
   1. Sclerotherapy techniques, other than microfoam sclerotherapy, of great, small, or accessory saphenous veins
   2. Sclerotherapy of perforator veins
   3. Sclerotherapy of isolated tributary veins without prior or concurrent treatment of saphenous veins
   4. Stab avulsion, hook phlebectomy, or transilluminated powered phlebectomy of perforator, great or small saphenous, or accessory saphenous veins.
   5. Endovenous radiofrequency or laser ablation of tributary veins
   6. Mechanochemical ablation of any vein
   7. Endovenous cryoablation of any vein

Policy Guidelines

1. For a service to be considered medically necessary, it should not be more costly than an alternative service or supply or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results for the illness, injury, or disease.

2. The standard classification of venous disease is the CEAP (Clinical, Etiologic, Anatomic, Pathophysiologic) classification system. Table PG1 provides is the Clinical portion of the CEAP.

Table PG1. Clinical Portion of the CEAP Classification System

Class	Definition
C_0	No visible or palpable signs of venous disease
C_1	Telangiectasies or reticular veins
C_2	Varicose veins
C_{2r}	Recurrent varicose veins
C_3	Edema
C_4	Changes in skin and subcutaneous tissue secondary to CVD
C_{4a}	Pigmentation and eczema
C_{4b}	Lipodermatosclerosis or atrophie blanche
C_{4C}	Corona phlebectatica
C_5	Healed
C_6	Active venous ulcer
C_{6r}	Recurrent active venous ulcer
S	Symptomatic
A	Asymptomatic

Adapted from: https://www.jvsvenous.org/article/S2213-333X(20)30063-9/pdf
CVD, Chronic venous disease. Each clinical class subcharacterized by a subscript indicating the presence (symptomatic, s) or absence (asymptomatic, a) of symptoms attributable to venous disease.
CEAP: Clinical, Etiologic, Anatomic, Pathophysiologic classification system.

3. A clear and complete description of the physical exam of the lower extremities that documents the medical necessity of treatment for venous insufficiency for medical, not cosmetic purposes, is required. Physical findings that support medically significant venous hypertension must be clearly documented. Treatment of varicose veins for cosmetic purposes is **not covered**. Photographs may be requested.

4. Up to 20 injections in each leg may be treated in any one session and up to 3 sclerotherapy sessions for each leg may be considered medically necessary if selection criteria are met.

5. Following successful ablation of the greater saphenous vein, tributary veins can become more prominent, but usually improve over time; therefore, delaying treatment of these smaller veins will minimize the number of veins that need treatment.

6. Patients with combined deep and superficial venous insufficiency are often not good candidates for ablation therapy. Varicose vein recurrence and ulcer recurrence rates following intervention are much higher. However, deep vein insufficiency is not a contraindication to superficial vein treatment.

7. It should be noted that the bulk of the literature discussing the role of ultrasound guidance refers to sclerotherapy of the saphenous vein, as opposed to the varicose tributaries. When ultrasound guidance is used to guide sclerotherapy of the varicose tributaries, it would be considered either not medically necessary or incidental to the injection procedure.

Claims Submission Instructions

1. CPT code 36470 should be used when only one vein is injected on a given date of service.
2. CPT code 36471 should be used when more than one vein in the same leg is injected on a given date of service.
3. If both legs are injected, right and left modifier should be used on claims with the codes to indicate which leg is being treated. The following coding conventions should be used:
   - One vein on the left; two veins on the right: 36470 LT and 36471 RT. Injections for each leg should be reported on a separate line.
   - One vein on each leg: Use 36470 RT and 36470 LT.
   - Two veins on the right; three on the left: 36471
   - RT and 36471 LT.
   - In each case, the correct quantity to bill is one unit per code.
4. For less than 10 phlebectomies, CPT code 37799 should be used, modifier 22 added and box 19 of the claim form populated with "phlebectomies less than 10".

Reimbursement

1. The use of the following ultrasound guidance procedures (76937, 76942, 76998, 76999, 93965, 93970, 93971, S2202) during varicose vein surgery is considered content of service.
2. CPT codes 93965, 93970 or 93971 Doppler ultrasound should not be billed for intraoperative procedures. If these codes are billed separately as the initial diagnostic tool for mapping, the claim will be allowed if medically necessary. Any additional scans over the initial mapping may be reviewed for medical necessity.
3. Selective catheter placement is content of service of a covered procedure.
4. Reimbursement for sclerotherapy will be limited to 3 sessions.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through April 6, 2021.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

TREATMENT OF SAPHENOUS VEINS

Clinical Context and Therapy Purpose

Treatment of venous reflux/venous insufficiency seeks to reduce abnormal pressure transmission from the deep to the superficial veins. Conservative medical treatment consists of elevation of the extremities, graded compression, and wound care when indicated. Conventional surgical treatment consists of identifying and correcting the site of reflux by ligation of the incompetent junction followed by stripping of the vein to redirect venous flow through veins with intact valves. While most venous reflux is secondary to incompetent valves at the saphenofemoral or saphenopopliteal junctions, reflux may also occur at incompetent valves in the perforator veins or the deep venous system. The competence of any single valve is not static and may be pressure-dependent. For example, accessory saphenous veins may have independent saphenofemoral or saphenopopliteal junctions that become incompetent when the great or small saphenous veins are eliminated, and blood flow is diverted through the accessory veins.

The following section addresses the efficacy of the conventional treatments, specifically on the appropriate length of a trial of compression therapy and evaluation of recurrence rates for surgical treatment (i.e., ligation and stripping) compared with compression therapy.

Compression Therapy
A Cochrane review by O'Meara et al (2009) evaluated compression for venous leg ulcers included 39 RCTs with 47 different comparisons.[1,] This review was updated in 2012 and included 48 RCTs with 59 different comparisons.[2,] Most RCTs were small. Measures of healing were the time to complete healing, the proportion of ulcers healed within the trial period (typically 12 weeks), the change in ulcer size, and the rate of change in ulcer size. Evidence from 8 trials indicated that venous ulcers healed more rapidly with compression than without. Findings suggested that multicomponent systems (bandages or stockings) were more effective than single-component compression. Also, multicomponent systems containing an elastic bandage appeared more effective than those composed mainly of inelastic constituents. Although these meta-analyses did not include time to healing, studies included in the review reported the mean time to ulcer healing was approximately 2 months, while the median time to healing in other reports was 3 to 5 months.

A Cochrane review by Shingler et al (2011) assessed compression stockings as initial treatment for varicose veins in patients without venous ulceration.[3,] Selected were 7 studies involving 356 participants with varicose veins without healed or active venous ulceration (CEAP [Clinical, Etiology, Anatomy, Pathophysiology] class C2-C4). Six studies compared different types or pressures of stockings. Subjectively, participants' symptoms improved, but results were not compared with a control arm. Due primarily to inadequate reporting, the methodologic quality of the selected trials was unclear. Meta-analyses were not performed due to inadequate reporting and suspected heterogeneity. Reviewers concluded that there was insufficient high-quality evidence to determine whether compression stockings were effective as the sole and initial treatment of varicose veins in patients without venous ulceration, or whether any type of stocking was superior to another type.

Ligation and Stripping
Systematic literature reviews have indicated a similar healing rate of venous ulcers with superficial vein surgery and conservative compression treatments but a reduction in ulcer recurrence rate with surgery.[4,5,] In general, recurrence rates after ligation and stripping are estimated at 20% in short-term follow-up. Jones et al (1996) reported on the results of a trial that randomized 100 patients with varicose veins to ligation alone or ligation plus stripping.[6,] At 1 year, reflux was detected in 9% of patients, rising to 26% at 2 years. Rutgers and Kitslaar (1994) reported on the results of a trial that randomized 181 limbs to ligation and stripping or to ligation plus sclerotherapy.[7,] At 2 years, Doppler ultrasound demonstrated reflux in approximately 10% of patients after ligation and stripping, increasing to 15% at 3 years.

Alternatives to Ligation and Stripping
The purpose of endovenous thermal ablation (radiofrequency or laser), microfoam sclerotherapy, mechanochemical ablation (MOCA), cyanoacrylate adhesive (CAC), or cryoablation in patients who have varicose veins/venous insufficiency and saphenous vein reflux is to provide a treatment option that is an alternative to or an improvement on existing treatments.

The question addressed in this evidence review is: Do these alternative treatments improve the net health outcome in individuals who have varicose veins/venous insufficiency and saphenous vein reflux?

The following PICO was used to select literature to inform this review.

Patients
The relevant populations of interest are those who have varicose veins/venous insufficiency and saphenous vein reflux.

Interventions
The therapies being considered are endovenous thermal ablation (radiofrequency or laser), microfoam sclerotherapy, mechanochemical ablation, cyanoacrylate adhesive, or cryoablation.

Comparators
Established treatments for varicose veins/venous insufficiency and saphenofemoral junction reflux are conservative therapy with compression bandages and ligation and stripping, with which the endovenous thermal procedures are compared. The less invasive endovenous thermal ablation (radiofrequency or laser) have become the standard treatments by which the newer treatments are compared. Endovenous thermal ablation techniques require tumescent anesthesia, which involves multiple injections along the vein and is associated with moderate pain. Compression stockings and avoidance of strenuous activities are recommended. Procedures that have more recently been developed (MOCA, CAC, and cryotherapy) do not require tumescent anesthesia are now compared with the thermal ablation procedures.

Outcomes
Outcomes of interest for venous interventions include healing and recurrence, recanalization of the vein, and neovascularization. Recanalization is the restoration of the lumen of a vein after it has been occluded; this occurs more frequently following treatment with endovenous techniques. Neovascularization is the proliferation of new blood vessels in tissue and occurs more frequently following vein stripping. Direct comparisons of the durability of endovenous and surgical procedures are complicated by these mechanisms of recurrence. Relevant safety outcomes include the incidence of paresthesia, thermal skin injury, thrombus formation, thrombophlebitis, wound infection, and transient neurologic effects.

Specific measures may include the visual analog score (VAS) for pain, the Venous Clinical Severity Score (VCSS), and the Aberdeen Varicose Veins Questionnaire (AVVQ). AVVQ scores range from 0 to 100 (worst possible quality of life). Follow-up at 1 and 2 years from RCTs is of interest to monitor treatment success (vein occlusion and recanalization), with follow-up to 5 years to assess durability of the treatment.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

TREATMENT OF SAPHENOUS VEINS: ENDOVENOUS THERMAL ABLATION (LASER OR RADIOFREQUENCY)

Systematic Reviews

A Cochrane review by Nesbitt et al (2014) compared endovenous ablation (radiofrequency and laser) with foam sclerotherapy or ligation and stripping for saphenous vein varices.[8,] Included in the review were 13 randomized studies (N=3081 patients). The overall quality of the evidence was moderate. There was no significant difference between sclerotherapy and surgery in the rate of recurrence, as rated by clinicians (odds ratio [OR], 1.74; p=.06) or for symptomatic recurrence (OR=1.28). For endovenous laser ablation vs surgery, there were no significant differences between the treatment groups for clinician-reported or symptomatic recurrence, or for recanalization. Neovascularization and technical failure were reduced in the laser group (OR=0.05, p<.001; OR=0.29, p<.001, respectively). For endovenous radiofrequency ablation (RFA) versus surgery, there were no significant differences between groups in clinician-reported recurrence, recanalization, neovascularization, or technical failure. Reviewers concluded that sclerotherapy, endovenous laser ablation, and RFA are at least as effective as surgery in the treatment of great saphenous varicose veins.

A Cochrane review by Paravastu et al (2016) compared endovenous laser ablation or RFA with surgical repair for small saphenous veins with reflux at the saphenopopliteal junction.[9,] Three RCTs identified compared endovenous laser ablation with surgery. There was moderate-quality evidence that recanalization or persistence of reflux at 6 weeks occurred less frequently after endovenous laser ablation than after surgery (OR=0.07; 95% [CI], 0.02 to 0.22), and low-quality evidence that recurrence of reflux was lower after endovenous laser ablation at 1 year (OR=0.24; 95% CI, 0.07 to 0.77).

Randomized Controlled Trials

The largest RCT was reported by Brittenden et al (2014) and compared foam sclerotherapy, endovenous laser ablation, and surgical treatment in 798 patients.[10,] The trial was funded by the U.K.'s National Institute for Health Research. Veins greater than 15 mm in diameter were excluded from the trial. At the 6-week follow-up visit, patients assigned to treatment with foam or laser had the option of treatment with foam for any residual varicosities; this optional treatment was performed in 38% of patients in the foam group and 31% of patients in the endovenous laser ablation group. Disease-specific quality of life was similar for the laser and surgery groups. The frequency of procedural complications was similar for the foam sclerotherapy (6%) and surgery (7%) groups but was lower for the laser group (1%).

The 2012 Comparable effectiveness of endovenous laser ablation and high ligation with stripping of the great saphenous vein (RELACS) study randomized 400 patients to endovenous laser ablation performed by a surgeon at 1 site or to ligation and stripping performed by a different surgeon at a second location.[11,] At 2-year follow-up, there were no significant differences between groups for clinically recurrent varicose veins, medical condition measured on the Homburg Varicose Vein Severity Score, or disease-related quality of life. Saphenofemoral reflux

was detected by ultrasonography more frequently after endovenous laser treatment (17.8% vs 1.3%). The follow-up rate at 5 years was 81%.[12,] Same-site recurrences were more frequent in the endovenous laser ablation group (18% with endovenous laser ablation vs 5% with surgery, p=.002), but different-site recurrences were more frequent in the surgically treated group (50% with surgery vs 31% with endovenous laser ablation, p=.002). Overall, there was no significant difference in recurrence rates between groups. There were also no significant differences between groups in disease severity or quality of life at five years.

Christenson et al (2010) compared endovenous laser ablation with ligation and stripping in 200 limbs (100 in each group).[13,] At 1-year follow-up, 98% of the limbs were reported to be free of symptoms. At 2-year follow-up, the endovenous laser ablation group had 2 veins completely reopened and 5 partially reopened, which was significantly greater than in the ligation and stripping group. In the 2013 Comparative Study of the Treatment of Insufficient Greater Saphenous Vein: Surgery vs Ultrasound Guided Sclerotherapy With Foam and Endovenous Laser Therapy (MAGNA) trial, 223 consecutive patients (240 legs) with great saphenous vein reflux were randomized to endovenous laser ablation, ligation and stripping, or foam sclerotherapy.[14,] At 1-year follow-up, the anatomic success rates were similar for endovenous laser ablation (88.5%) and stripping (88.2%), which were both superior to foam sclerotherapy (72.2%). Ten percent of the stripping group showed neovascularization. At five years, health-related quality of life and CEAP classification improved in all groups with no significant differences among them.[15,] Grade I neovascularization was higher in the conventional surgery group (27% vs 3%, p<.001), while grade II neovascularization did not differ significantly between surgical (17%) and endovenous laser ablation (13%) groups.

Wallace et al (2018) published the 5-year outcomes of an RCT consisting of endovenous laser ablation compared with conventional surgery for great saphenous varicose veins comparing surgery and endovenous laser ablation (EVLA) as treatments for symptomatic great saphenous varicose veins.[16,] Data from 218 patients were available at 5-year follow-up. The clinical recurrence rate was 34.4% for the surgery group and 20.9% for EVLA (p=.010). Patients-quality of life, assessed using EuroQol Five Dimensions (EQ-5D) and AVVQ, was significantly improved from baseline for both surgery (EQ-5D: 0.859 to 1.0, p=.002; AVVQ: 13.69 to 4.59, p<.001) and EVLA (EQ-5D: 0.808 to 1.0, p=.002; AVVQ: 12.73 to 3.35, p<.001). Technical success assessed by duplex ultrasound examination was 85.4% for surgery and 93.2% for EVLA (p=.074).

The primary limitation of all of the studies was the lack of blinding.

Table 1. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Brittenden (2014)[10,]	UK	11	2008-2012	Individuals with primary varicose veins	Foam sclero-therapy (n=286) or EVLA (n=210)	Surgical treatment (n=289)

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
Rass (2012);[11,] RELACS	US	2	2004-2007	Individuals with GSV insufficiency	EVLA (n=185)	Surgical treatment (n=161)
Wallace (2018)[16,]	UK	1	2004-2009 [1]	Individuals with GSV insufficiency	EVLA (n=108)	Surgical treatment (n=110)

RCT: randomized controlled trial; GSV: great saphenous vein; EVLA: endovenous laser ablation.
[1] Date of original intervention study

Table 2. Summary of Key RCT Results

Study	AVVQ Score at Baseline;6 Months	Frequency of Procedural Complications	Rate of Same-Site Recurrence	Clinically Recurrent Varicose Veins	AVVQ Score at Baseline;5 years
Brittenden (2014)[10,]					
Foam	17.69.9; 9.17.9	6%			
Laser	17.89.1; 7.98.4	1%			
Surgery	18.29.1; 7.87.5	7%			
P-value		<.001			
Rass (2012)[11,] RELACS					
Laser			18%	16.2%	
Surgery			5%	23.1%	
P-value			.002	.15	
Wallace (2018)[16,]					
Laser				20.9%	13.69; 4.59
Surgery				34.3%	12.73; 3.35
P-value				.010	<.001

AVVQ: Aberdeen Varicose Veins Questionnaire; RCT: randomized controlled trial; RELACS: A prospective, Randomised, two-centre study to evaluate surgical treatments of great saphenous vein insufficiency: Endovenous LAser treatment versus Crossectomy and Stripping.

The literature on the isolated treatment of the anterior accessory saphenous vein is limited. In a study by Theivacumar et al (2009), outcomes from a cohort of 33 patients who underwent endovenous laser ablation of the anterior accessory saphenous vein were compared with 33 matched controls undergoing endovenous laser ablation of the great saphenous vein.[17,] For 21 (64%) of the patients in the accessory saphenous vein group, there had been no previous treatment of the great saphenous vein. At 12-month follow-up, there was no evidence of reflux in these patients, and the treated accessory saphenous vein was not visible with ultrasound. AVVQ scores had improved in both groups, with no significant difference between them. Patient satisfaction scores were also similar.

Subsection Summary: Endovenous Thermal Ablation (Laser or Radiofrequency)
There are multiple large RCTs and systematic reviews of RCTs assessing endovenous ablation using radiofrequency or laser energy of the saphenous veins. Comparison with ligation and stripping at 2- to 5-year follow-up has indicated similar recurrence rates for the different treatments. Evidence has suggested that ligation and stripping may lead to neovascularization, while thermal ablation may lead to recanalization, resulting in similar outcomes for endovenous thermal ablation and surgery. Laser ablation and RFA have similar success rates.

TREATMENT OF SAPHENOUS VEINS: SCLEROTHERAPY

Physician-Compounded Sclerotherapy

Hamann et al (2017) conducted a meta-analysis of RCTs reporting 5-year follow-up.[18,] The meta-analysis (3 RCTs, 10 follow-up studies) included 611 legs treated with endovenous laser ablation, 549 treated with high ligation and stripping, 121 with sclerotherapy, and 114 with high ligation and endovenous laser ablation. Ultrasound-guided sclerotherapy had significantly worse outcomes than the other 3 treatments, with anatomic success rates of 34% for sclerotherapy compared with 83% to 88% for the other 3 treatments ($p<.001$).

In the 2013 MAGNA trial (previously described), 223 consecutive patients (240 legs) with great saphenous vein reflux were randomized to endovenous laser ablation, ligation and stripping, or physician-compounded foam sclerotherapy (1 mL aethoxysclerol 3%: 3 cc air).[14,] At 1-year follow-up, the anatomic success rate of foam sclerotherapy (72.2%) was inferior to both endovenous laser ablation (88.5%) and stripping (88.2%). Twenty-one patients in the sclerotherapy group had partial occlusion with reflux, though the clinical complaint was completely relieved. At 5-year follow-up, obliteration or absence of the great saphenous vein was observed in only 23% of patients treated with sclerotherapy compared with 85% of patients who underwent conventional surgery and 77% of patients who underwent endovenous laser ablation.[15,] Thirty-two percent of legs treated initially with sclerotherapy required one or more reinterventions during follow-up compared with 10% in the conventional surgery and endovenous laser ablation groups. However, clinically relevant grade II neovascularization was higher in the conventional surgery (17%) and endovenous laser ablation (13%) groups than in the sclerotherapy group (4%). EQ-5D scores improved equally in all groups.

Vahaaho et al (2018) published a study looking at the 5-year follow-up of patients with symptomatic great saphenous vein (GSV) insufficiency.[19,] Between 2008 and 2010, 166 individuals were randomized to receive open surgery, EVLA, or ultrasound-guided foam sclerotherapy. The GSV occlusion rate was 96% (95% CI: 91-100%) for open surgery, 89% (95% CI: 82-98%) for EVLA, and 51% (95% CI: 38-64%) for ultrasound-guided foam sclerotherapy ($p<.001$). For patients with no additional treatment during follow-up, occlusion rates for open surgery, EVLA, and ultrasound-guided foam sclerotherapy were 96%, 89%, and 41%, respectively. The study was limited by the lack of blinding and by non-standardized foam application.

A noninferiority trial by Shadid et al (2012) compared foam sclerotherapy with ligation and stripping in 430 patients.[20,]The analysis was per protocol. Forty (17%) patients had repeat sclerotherapy. At 2 years, the probability of clinical recurrence was similar in both groups (11.3% sclerotherapy vs 9.0% ligation and stripping), although reflux was significantly more frequent in the sclerotherapy group (35% vs 21%). Thrombophlebitis occurred in 7.4% of patients after sclerotherapy. Two serious adverse events in the sclerotherapy group (deep venous thrombosis,

pulmonary emboli) occurred within 1 week of treatment. Lam et al (2018) reported 8-year follow-up with 53% of the patients in the original trial.[21,] All measures of treatment success (e.g., symptomatic GSV reflux, saphenofemoral junction failure, and recurrent reflux in the GSV) were lower in the physician-compounded sclerotherapy group compared to the ligation and stripping group.

Microfoam Sclerotherapy

In 2013, polidocanol microfoam (Varithena) was approved under a new drug application for the treatment of varicose veins. Efficacy data derived from 2 randomized, blinded, multicenter studies.[22,] One compared polidocanol at 0.5%, 1.0%, and 2.0% with endovenous placebo or a subtherapeutic dose of polidocanol foam. The primary endpoint was an improvement in symptoms at week 8, as measured by the Varicose Vein Symptoms Questionnaire. The improvement in symptoms was greater in the pooled polidocanol treatment group ($p<.001$) and in each of the individual dose-concentration groups compared with vehicle alone. Secondary and tertiary endpoints (appearance, duplex ultrasound response, quality of life) were also significantly better for the polidocanol groups compared with controls. This second study, VANISH-2, was published by Todd et al (2014).[23,] At the 8-week assessment, there was elimination of reflux and/or occlusion of the previously incompetent vein in 85.6% of the combined 0.5% and 1.0% groups, 59.6% of patients in the 0.125% group, and 1.8% of the placebo group. Analysis of data from both studies showed a dose-response from 0.5% to 2.0% for improvement in appearance and from 0.5% to 1.0% for Duplex responders. The polidocanol 1.0% dose was selected for the U.S. Food and Drug Administration (FDA) approval. Safety analysis found deep vein thrombosis detected by ultrasound in 2.8% of polidocanol-treated patients, with 1% of patients having proximal symptomatic thrombi; these patients were treated with anticoagulants. There was no sign of an increase in neurologic adverse events, and there were no adverse cardiac or cardiopulmonary effects following treatment with polidocanol injectable foam. Rates of occlusion with Varithena are similar to those reported for endovenous laser ablation or stripping. A randomized trial comparing endovenous laser ablation and stripping with this new preparation of foam sclerotherapy is needed to evaluate its comparative effectiveness. Evaluation out to 5 years is continuing.

Vasquez et al (2017) reported on a double-blinded RCT that evaluated the addition of polidocanol microfoam to endovenous thermal ablation.[24,] A total of 117 patients who were candidates for both endovenous thermal ablation and treatment of visible varicosities received endovenous thermal ablation plus placebo (n=38) or polidocanol 0.5% (n=39) or 1% (n=40). At 8-week follow-up, physician-blinded vein appearance was significantly better with the combined polidocanol groups ($p=.001$), but the improvement in patient ratings was not statistically significant. At 6-month follow-up, the percentages of patients who achieved a clinically meaningful change were significantly higher in both physician (70.9% vs 42.1%, $p=.001$) and patient (67% vs 50%, $p=.034$) ratings. The proportion of patients who received additional treatment for residual varicosities between week 8 and month 6 was modestly reduced (13.9% for the polidocanol vs 23.7% for placebo, $p=.037$).

Deak (2018) reported a retrospective review of 250 patients with symptomatic chronic venous insufficiency who were treated with polidocanol microfoam in a community practice.[25,] Patients who had tortuous veins that were not accessible with a catheter or who had a history of a previous vein ablation procedure with scarring in the lumen were selected for treatment with the microfoam scleroscent. It was reported that some patients required additional treatments

between 5 days and 2 years for the vein to close, but the publication did not report how many additional treatments were given. After all the treatments were completed, 94.4% of patients showed elimination of venous valvular reflux and symptom improvement in this chart review. In addition to the lack of information on the number of treatments given, the time of patient follow-up was variable (from 1 month to 2 years), precluding any conclusions regarding the durability of the treatment.

Subsection Summary: Sclerotherapy

For physician-compounded sclerotherapy, there is high variability in success rates of the procedure and some reports of serious adverse events. Results of a noninferiority trial of physician-compounded sclerotherapy indicated that once occluded, recurrence rates at 2 years are similar to those of ligation and stripping. By comparison, rates of occlusion with the FDA-approved microfoam sclerotherapy (polidocanol 1%) are similar to those reported for endovenous laser ablation or stripping.

TREATMENT OF SAPHENOUS VEINS: MECHANOCHEMICAL ABLATION

Randomized Trials

Four RCTS with over 100 patients each (range, 132 to 213) have been identified that compared MOCA to thermal ablation. Study characteristics and study results are presented in Tables 3 and 4. Study limitations are described in Tables 5 and 6.

Two publications (Bootun et al [2016], Lane et al [2017]) reported on early results from an RCT of 170 patients that compared ClariVein with RFA.[26,27,] Maximum visual analog scale pain scores (out of 100) during the procedure were significantly lower in the MOCA group (median, 15 mm) than in the RFA group (median, 34 mm; p=.003). Average visual analog scale pain scores during the procedure were also modestly lower in the MOCA group (median, 10 mm) than in the RFA group (median, 19.5 mm; p=.003). Occlusion rates, clinical severity scores, disease-specific quality of life, and generic quality of life scores were similar between groups at 1 and 6 months. Limitations of this study are described in Tables 5 and 6. Only 71% of patients were available for follow-up at 6 months, limiting the evaluation of closure rates at this time point (see Table 6).

Vahaaho et al (2019) reported an RCT that compared MOCA with endovenous thermal ablation (EVLA or RFA).[19,] Liquid sclerosant at a concentration of 1.5% was used. Out of 132 patients enrolled, 7 patients were later excluded and 117 (88.6%) attended the 1-year follow-up evaluation. Occlusion of the great saphenous vein was observed in 45 of 55 (82%) of the MOCA group compared to 100% of the EVLA and RFA groups (p=.002). Another randomized trial (Lam et al [2016]) reported interim results of a dose-finding study, finding greater closure with use of polidocanol 2% or 3% (liquid) than with polidocanol 1%.[28,] Therefore, it is uncertain whether the concentration of sclerosant in the study by Vahaaho et al (2019) was optimal (see Table 5).

Three percent policocanol was tested in the Mechanochemical endovenous Ablation to RADiOfrequeNcy Ablation (MARADONA) non-inferiority trial reported by Holewijn et al (2019).[29,] Although the study was powered for 400 participants, only 213 patients were randomized before reimbursement for the procedure was suspended. Pain scores in the 14 days after the procedure were slightly lower, but hyperpigmentation was higher. Anatomic failures were significantly greater in the MOCA group at 1 year and approached significance at 2-years; with the note that the study was underpowered for anatomic failures because of the early

stoppage of the study. At 1 and 2-years, clinical and quality of life outcomes were similar in the 2 groups.

A fourth RCT reported by Mohamed et al (2020) is the ongoing Randomized Clinical Trial Comparing Endovenous Laser Ablation and Mechanochemical Ablation (ClariVein) in the Management of Superficial Venous Insufficiency (LAMA).[30,] Patients (n=150) were randomized to MOCA with 1.5% sodium tetradecyl sulfate or to EVLA. Anatomic success (occlusion) rates were lower in the MOCA group 77% compared to the EVLA group (91%) with no significant difference between the 2 treatments in intraprocedural pain scores. In contrast to the difference in anatomical occlusion rates, clinical severity and quality of life scores were not significantly different between the groups at 1 year follow-up. Follow-up is continuing to evaluate durability of the treatments.

Table 3. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Booton et al (2016),[26,] Lane et al (2017)[27,]				170 patients with varicose veins	MOCA	RFA
Vahaaho et al (2019) [19,]				132 patients with varicose veins	MOCA with 1.5% polidocanol	Thermal ablation (EVLA or RFA)
Holewijn et al (2019)[29,] (MARADONA)	E.U.	4	2012-2015	213 patients with GSV incompetence and CEAP C2 - C5	MOCA wit 2 mL of 3% polidocanol for the first 10 to 15 cm and 1.5% polidocanol for the remainder	RFA
Mohamed et al (2020)[30,] (LAMA)	U.K.	1	2015-2018	150 patients with symptomatic superficial venous incompetence CEAP grades 2 to 6	MOCA (n=75) with 1.5% sodium tetradecyl sulfate	EVLA (n=75)

CEAP: clinical etiologic anatomic pathological; EVLA: endovenous laser ablation; GSV: Great saphenous vein; LAMA: A Randomised Clinical Trial Comparing Endovenous Laser Ablation and Mechanochemical Ablation (ClariVein) in the Management of Superficial Venous Insufficiency;
MOCA: mechanochemical ablation; RCT: randomized controlled trial; RFA: radiofrequency ablation.

Table 4. Summary of Key RCT Results

Study	Pain	Post-procedure Occlusion Rate	Occlusion Rate at Follow-up	Clinical Severity	Clinical Severity at Follow-up		Quality of Life
Booton (2016),[26] Lane (2017)[27]	During Procedure -VAS		6 mo occlusion rates				
N			71%		71%		
MOCA	10 mm						
RFA	19.5 mm						
p-value	.003	NS	NS	NS	NS		NS
Vahaaho (2019)[19]			1 yr		1 yr		
N			117 (88.6%)		117 (88.6%)		
MOCA			45 of 55 (82%)				
EVLA or RFA			100%				
p-Value			.002				
Holewijn et al (2019)[29] (MARADONA)	For 14 days after the procedure median (range)	30 day failure rate	1 yr recanalization rate	2 yr recanalization rate	1 yr VCSS	2 yr VCSS	AVVQ improved
N			153 (72%)	157 (73%)	153 (72%)	157 (73%)	
MOCA	0.2 (0.0-0.8)	5 (4.9%)	15 (16.5%)	21 (20%)	1.8	1.0	88%
RFA	0.5 (0.2-1.3)	1 (1%)	5 (5.8%)	12 (11.7%)	1.7	1.0	89%
p-Value	.01	.10	.025	.066	.695	.882	.90
Mohamed et al (2020)[30] (LAMA)	Median (IQR)		Occlusion at 1 yr		VCSS		AVVQ Median (IQR)
N			138 (92%)				
MOCA	15 (9-29)		53/69 (77%)				2.0 (0.0–5.3)

Study	Pain	Post-procedure Occlusion Rate	Occlusion Rate at Follow-up	Clinical Severity	Clinical Severity at Follow-up		Quality of Life
EVLA	22 (9–44)		63/69 (91%)				2.0 (0.0–4.8)
p-Value	.21		.020		NS		NS

AVVQ: Aberdeen varicose vein questionnaire; EVLA: endovenous laser ablation; IQR: intraquartile range; LAMA: A Randomised Clinical Trial Comparing Endovenous Laser Ablation and Mechanochemical Ablation (ClariVein) in the Management of Superficial Venous Insufficiency
MARADONA: Mechanochemical endovenous Ablation to RADiOfrequeNcy Ablation; MOCA: mechanochemical ablation; NS: not significant; RCT: randomized controlled trial; RFA: radiofrequency ablation; VAS: visual analog scale.; VCSS: venous clinical severity score

Table 5. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Bootun et al (2016);[26,] Lane et al (2017)[27,]				1.Primary outcome was pain during the procedure	1. Outcomes only out to 6 mo, which is insufficient to assess durability
Vahaaho et al (2019)[19,]	4. Strict inclusion criteria that may not be representative of intended use.	3. The concentration of sclerosant (1.5% polidocanol) may not have been optimal.			1. Outcomes only out to 1 yr, which is insufficient to assess durability
Holewijn et al (2019)[29,] (MARADONA)	4. Patients with bilateral reflux were excluded due to dosing limits of polidocanol				
Mohamed et al (2020)[30,] (LAMA)					1. Outcomes out to 1 yr, follow-up is continuing

LAMA: A Randomised Clinical Trial Comparing Endovenous Laser Ablation and Mechanochemical Ablation (ClariVein) in the Management of Superficial Venous Insufficiency; MARADONA: Mechanochemical endovenous Ablation to RADiOfrequeNcy Ablation
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b]Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 6. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Bootun et al (2016);[26,] Lane et al (2017)[27,]		1. Patients not blinded to treatment (assessors of duplex ultrasound were blinded)		1. There was high loss to follow-up (76% follow-up at 1 mo and 71% follow-up at 6 mo)		
Vahaaho et al (2019)[19,]		1, 2, 3. Patients, surgeons, and assessors were not blinded to treatment				
Holewijn et al (2019)[29,] (MARADONA)		1, 2, 3. Patients, surgeons, and assessors were not blinded			3. Underpowered for anatomic success due to early termination	4. Results of non-inferiority analysis were not reported

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
		to treatment			of recruitment	
Mohamed et al (2020) [30,] (LAMA)		1, 2, 3. Patients, surgeons, and assessors were not blinded to treatment				2. 14 day pain scores were not analyzed by repeated measures ANOVA

ANOVA: analysis of variance; LAMA: A Randomised Clinical Trial Comparing Endovenous Laser Ablation and Mechanochemical Ablation (ClariVein) in the Management of Superficial Venous Insufficiency; MARADONA: Mechanochemical endovenous Ablation to RADiOfrequeNcy Ablation

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

[b]Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

[d]Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

[f] Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. s and/or p values not reported; 4.Comparative treatment effects not calculated.

Prospective Cohort Studies

A prospective cohort study that had 5 year follow-up was reported by Thierens et al (2019).[31,] Study inclusion criteria are described in Table 7. Anatomic and clinical follow-ups were performed at 4 weeks, 6 months, and 1, 3, and 5 years after the procedure (Table 8). With slightly less than half of the participants remaining in the study through 5 years, 79% had freedom from anatomic failure and clinical measures had worsened. Nearly 15% of the recanalizations occurred in the first year, which the authors considered to be due to technical issues when the procedure was initially introduced. For example, there has been an increase in the concentration of sclerosant over time. It should be noted, however, that the more recent MARADONA trial from the same group of investigators using 3% polidocanol (described above) also saw a rate of recanalization of 16.5% in the first year and 20% in the second year.[29,] Without a control condition, it cannot be determined whether the loss of clinical improvement in this cohort study is due to recanalization or the usual progression of venous disease over time.

Table 7. Summary of Prospective Cohort Study Characteristics

Study	Country	Participants	Treatment Delivery	Follow-Up
Thierens et al, (2019)[31,]	Netherlands	C2 to C5 varicose veins, GSV diameter of 3 to 12 mm and primary GSV insufficiency determined by duplex ultrasound examination	MOCA with 2% polidocanol as sclerosant	5 yr

GSV: Great saphenous vein; MOCA: mechanochemical ablation

Table 8. Summary of Prospective Cohort Study Results

Outcome Measure	Baseline	1 yr	3 yr	5 yr
Thierens et al, (2019)[31,]	n=94	90	71	58
Freedom from anatomic failure (SE)		85.6% (0.033)	80.1% (0.039)	78.7% (0.041)
AVVQ score	8.9	2.3	5.6	6.3
VCSS score	4.0	1.0	1.0	2.0
Clinical improvement		80%	74%	65%

AVVQ: Aberdeen varicose vein questionnaire; MOCA: mechanochemical ablation; VCSS: venous clinical severity score; SE: standard error

Subsection Summary: Mechanochemical Ablation

MOCA is a combination of liquid sclerotherapy and mechanical abrasion of the lumen. The evidence on MOCA includes 4 RCTs that compared MOCA to thermal ablation with 6 months to 2 year results, a prospective cohort with follow-up out to 5 years, and retrospective case series. Results to date have been mixed regarding a reduction in intraprocedural pain, which is a proposed benefit of MOCA compared to thermal ablation procedures. Occlusion rates at 6 months to 2 years in the RCTs indicate lower anatomic success rates compared to thermal ablation, but a difference in clinical outcomes at these early time points has not been observed. Experience with other endoluminal ablation procedures suggests that lower anatomic success in the short term is associated with recanalization and clinical recurrence between 2 to 5 years. The possibility of later clinical recurrence is supported by a prospective cohort study with 5-year follow-up following treatment with MOCA. However, there have been improvements in technique since the cohort study was begun, and clinical progression is frequently observed with venous disease. Because of these limitations of the single arm studies, longer follow-up in the more recently conducted RCTs is needed to establish the efficacy and durability of this procedure compared with the criterion standard of thermal ablation.

Treatment of Saphenous Veins: Cyanoacrylate Adhesive

The VenaSeal pivotal study (VeClose), a multicenter noninferiority trial with 222 patients, compared VenaSeal with RFA for the treatment of venous reflux.[32,33,] The pivotal registration study for the VeClose study and follow-up through 36 months have been published. These reports are summarized in Tables 9 and 10. The primary endpoint (the proportion of patients with complete closure of the target GSV at 3 months measured by ultrasound) was noninferior to RFA, with a 99% closure rate for VenaSeal compared with 96% for RFA. The secondary endpoint (intraoperative pain) was similar for both groups (2.2 on a 10-point scale for VenaSeal vs 2.4 for RFA, p=.11). Ecchymosis at day 3 was significantly lower in the cyanoacrylate group; 67.6% of patients treated with cyanoacrylate had no ecchymosis compared with 48.2% of patients following RFA (p<.01). Scores on the AVVQ and Venous Clinical Severity Score improved to a similar extent in both groups. The mean time to return to work in a prospective cohort of 50 patients reported by Gibson and Ferris (2017) was 0.2 days.[34,]

For the CAC and RFA groups, the complete occlusion rates were 97.2% and 97.0%. Freedom from recanalization was also similar between the 2 groups (p=.08).[35,] Twenty-four month results were reported by Gibson et al (2018), which included 171 patients (87 from CAC and 84 from RFA).[36,] Thirty-six month results were reported by Morrison et al (2019), with follow-up on 146 (66%) patients (72 from CAC and 74 from RFA).[37,] Loss to follow-up was similar in the two groups. The complete closure rates for CAC and RFA were 94.4% and 91.9% (p=.005 for non-inferiority), respectively. Recanalization-free survival through 36 months was not statistically different for the 2 groups. No significant device- or procedure-related adverse events were reported for either group.

VariClose CAC was compared with RFA and EVLA by Eroglu and Yasim (2018) in an RCT with 525 patients (Table 9).[38,] Periprocedural outcomes showed a shorter intervention time, less pain, and shorter return to work with CAC compared to endovenous thermal ablation (see Table 10). There was no significant difference in occlusion rates between the three treatments at 6, 12, and 24 month follow-up.

Table 9. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions[2]	
					Active	Comparator
FDA SSED (2015);[32,] Morrison et al (2015, 2017, 2019);[33,39,37,] Gibson et al (2018);[34,][VeClose trial]	US	10	2013-2014	Age ≥21 and ≤ 70 years with symptomatic[1] GSV reflux and CEAP C2- C4b GSV diameter while standing of 3-12 mm	108 VenaSeal CAC	114 RFA
Eroglu and Yasim (2018)[38,]	Asia	1	NR	525 patients ≥ 18 years with incompetence of the GSV (>5.5 mm in diameter) or SSV (>4 mm in	175 VariClose CAC	125 RFA and 125 EVLA

Study; Trial	Countries	Sites	Dates	Participants	Interventions[2]	
				diameter) and reflux >0.5 sec.		

CAC: cyanoacrylate ; CEAP: Clinical Etiology Anatomy Pathophysiology; EVLA: endovenous laser ablation; FDA: Food and Drug Administration; GSV: great saphenous vein; NR: not reported; RCT: randomized controlled trial; RFA: radiofrequency ablation; SSV: small saphenous vein; SSED; Summary of Safety and Effectiveness Data;
[1] One or more of the following symptoms related to the target vein: aching, throbbing, heaviness, fatigue, pruritus, night cramps, restlessness, generalized pain or discomfort, swelling.
[2] Protocol mandated use of compression stockings for 7 days post-procedure

Table 10. Periprocedural Outcomes

Eroglu and Yasim (2018)[38,]	**Duration of Procedure min (SD)**	**Average Periprocedural Pain[1]**	**2 or More Analgesics Used Daily n (%)**	**1 Day to Return to Work n (%)**	**2 Days to Return to Work n (%)**	**3 or More Days to Return to Work n (%)**
N	503	503	456	456	456	456
VariClose	15.3 (2.6)	1 (mild)	105 (62.5)	161 (95.8)	7 (4.2)	0 (0)
RFA	27.3 (7.7)	2 (moderate)	98 (65.8)	75 (50.3)	53 (35.6)	21 (14.1)
EVLA	35.0 (5.2)	2 (moderate)	105 (75.5)	105 (75.5)	24 (17.3)	10 (7.2)
p-Value	<.001		.1472	<.0012		

[1]Scale of 1 to 4; [2]overall p-Value
EVLA: endovenous laser ablation; RFA: radiofrequency ablation.

Table 11. Summary of Key RCT Results

Study	**Vein Closure[1] n (%)**	**Vein Closure 12 months n (%)**	**Vein Closure 24 months n (%)**	**Vein Closure 36 months n (%) or VCSS**	**Device Related Event n (%)**
FDA SSED (2015);[32,] Morrison et al (2015, 2017, 2019);[33,39,37,]Gibson et al (2018);[34,][VeClose trial]	**3 months**				
N	222	189	171	146	222
VenaSeal	107 (99.1%)[2]	92 (96.7%)	82/86 (95.3%)	68/72 (94.4%)	31 (27%)
RFA	109 (95.6%)[2]	91 (96.8%)	79/84 (94.0%)	68/74 (91.9%)	7 (6%)
Eroglu and Yasim (2018)[38,]	**6 months**			**VCSS at 24 months**	
N		503	456	456	
VariClose	98.1%	94.1%	95.1%	2.7	

Study	Vein Closure[1] n (%)	Vein Closure 12 months n (%)	Vein Closure 24 months n (%)	Vein Closure 36 months n (%) or VCSS	Device Related Event n (%)
RFA	94.7%	92.5%	94.2%	3.7	
EVLA	92.6%	90.9%	91.5%	3.5	
p-Value	NS	NS	NS	<.001	

EVLA: endovenous laser ablation; FDA: Food and Drug Administration; NS: not significant; RCT: randomized controlled trial; RFA: radiofrequency ablation; SSED: Summary of Safety and Effectiveness Data; VCSS: venous clinical severity score.
[1]Complete closure defined as Doppler ultrasound showing vein closure along entire treated vein segment with no discrete segments of patency exceeding 5 cm. Central laboratory confirmation.
[2] Used prespecified data imputation method (Last Observation Carried Forward)

Notable limitations of the studies are shown in Tables 12 and 13. The primary limitation of the pivotal study of VenaSeal is the loss to follow-up at 2 and 3 years, although loss to follow-up was similar in the 2 groups. The study by Eroglu and Yasim (2018) had unequal loss to follow-up after patients were informed of the treatment allocation. Different expectations in the CAC group compared to the control groups may have influenced subjective outcomes. In addition, VariClose is not currently approved for marketing in the U.S.; both CAC products use N-butyl cyanoacrylate.

Table 12. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Morrison (2015), [33,]Morrison (2017),[39,]Gibson (2018)[36,]Morrison (2019)[37,] [VeClose trial]					1.Follow-up scheduled to continue to 60 months
Eroglu and Yasim (2018)[38,]		2. This specific cyanoacrylate product is not currently available in the US			

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3.Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 13. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[d]	Data Completeness[e]	Power[d]	Statistical[f]
Morrison (2015), [33,]Morrison (2017),[39,] Gibson (2018)[36,]Morrison (2019)[37,] [VeClose trial]		1, 2, 3. The outcome was assessed by the treating physician and patients were not blinded		1. >20% loss to follow-up		3.variable reporting of CI and p values
Eroglu and Yasim (2018)[38,]		1, 2, 3. Patients were notified of the group assignment a day before the procedure		6. Not intent-to-treat analysis and unequal loss to follow-up. 21 patients did not receive the allocated intervention, 19 of whom were in the control groups		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3.Evidence of selective publication.
[d]Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. s and/or p values not reported; 4.Comparative treatment effects not calculated.

Eroglu et al (2017) reported closure rates of 94.1% at 30 months in a prospective cohort of 159 patients.[40,] Thirty-three-month follow-up was reported by Zierau (2015) for 467 (58.7%) of 795 veins treated at 1 institution in Germany.[41,] An inflammatory reddening of the skin was observed at 1 week posttreatment in 11.7% of cases. No permanent skin responses were observed. Of the 467 veins reexamined, the sealing rate was 97.7%. This series had a high loss to follow-up.

Section Summary: Cyanoacrylate Adhesive
Evidence assessing CAC for the treatment of varicose veins and venous insufficiency includes a multicenter noninferiority trial with follow-up through 36 months, an RCT with follow-up through 24 months, and a prospective cohort with 30 month follow-up. The short-term efficacy of VenaSeal CAC has been shown to be noninferior to RFA at up to 36-month follow-up. At 24 and 36 months the study had greater than 20% loss to follow-up, but loss to follow-up was similar in the 2 groups at the long-term follow-up and is not expected to influence the comparative results. A second RCT (n=525) with the same active CAC ingredient (N-butyl cyanoacrylate) that is currently available outside of the U.S. found no significant differences in vein closure between

CAC and thermal ablation controls at 24-month follow-up. The CAC procedure and return to work were shorter and pain scores were lower compared to thermal ablation; the subjective pain scores may have been influenced by differing expectations in this study. A prospective cohort reported high closure rates at 30 months. Overall, results indicate that outcomes from CAC are at least as good as thermal ablation techniques, the current standard of care.

Treatment of Saphenous Veins: Cryoablation

Klem et al (2009) reported on a randomized trial that found endovenous cryoablation (n=249) to be inferior to conventional stripping (n=245) for treating patients with symptomatic varicose veins.[35,] Forty-four percent of patients had residual GSV remaining with cryoablation while 15% had residual vein remaining with conventional stripping. AVVQ scores also showed better results for conventional stripping (score, 11.7) than cryoablation (score, 8.0). There were no differences between groups in 36-Item Short-Form Health Survey summary scores or neural damage (12% in both groups).

Disselhoff et al (2008, 2011) reported on 2- and 5-year outcomes from a randomized trial that compared cryoablation with endovenous laser ablation.[42,43,] Included were 120 patients with symptomatic uncomplicated varicose veins (CEAP class C2) with saphenofemoral incompetence and GSV reflux. At 10 days after treatment, endovenous laser ablation provided better results than cryoablation with respect to pain scores over the first 10 days (2.9 vs 4.4), resumption of normal activity (75% vs 45%), and induration (15% vs 52%), all respectively. At 2-year follow-up, freedom from recurrent incompetence was observed in 77% of patients after endovenous laser ablation and in 66% of patients after cryoablation (p=*NS*). At 5 years, 36.7% of patients were lost to follow-up; freedom from incompetence and neovascularization were found in 62% of patients treated with endovenous laser ablation and in 51% of patients treated with cryoablation (p=*NS*). Neovascularization was more common after cryoablation, but incompetent tributaries were more common after endovenous laser ablation. There were no significant differences between groups in the Venous Clinical Severity Score or AVVQ scores at either the two or five-month follow-ups for endovenous laser ablation.

Subsection Summary: Cryoablation

Two RCTs have suggested that cryotherapy is ineffective for treating varicose veins compared with available alternatives.

TRIBUTARY VARICOSITIES

Clinical Context and Therapy Purpose

The purpose of ablation (stab avulsion, sclerotherapy, or phlebectomy) of tributary veins in patients who have varicose tributary veins is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of ablation (stab avulsion, sclerotherapy, or phlebectomy) of tributary veins improve the net health outcome in individuals who have varicose tributary veins?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who have varicose tributary veins.

Interventions
The therapy being considered is ablation (stab avulsion, sclerotherapy, or phlebectomy) of tributary veins.

Transilluminated powered phlebectomy (TIPP) is an alternative to stab avulsion and hook phlebectomy. This procedure uses 2 instruments: an illuminator, which also provides irrigation, and a resector, which has an oscillating tip and suction pump. Following removal of the saphenous vein, the illuminator is introduced via a small incision in the skin and tumescence solution (anesthetic and epinephrine) is infiltrated along the course of varicosity. The resectoris then inserted under the skin from the opposite direction, and the oscillating tip is placed directly beneath the illuminated veins to fragment and loosen the veins from the supporting tissue. Irrigation from the illuminator is used to clear the vein fragments and blood through aspiration and additional drainage holes. The illuminator and resector tips may then be repositioned, thereby reducing the number of incisions needed when compared with stab avulsion or hook phlebectomy. It has been proposed that TIPP might decrease surgical time, decrease complications such as bruising and lead to a faster recovery than established procedures.

Comparators
The following therapy is currently being used to treat varicose tributary veins: conservative therapy.

Outcomes
The general outcomes of interest are reductions in symptoms and morbid events, change in disease status, and improvements in quality of life. Follow-up at 6- and 12-months is of interest for ablation (stab avulsion, sclerotherapy, or phlebectomy) of tributary veins to monitor relevant outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Sclerotherapy and Phlebectomy
Early studies established ligation and stripping as the criterion standard for treating saphenofemoral incompetence based on improved long-term recurrence rates, with sclerotherapy used primarily as an adjunct to treat varicose tributaries. A Cochrane review by Tisi et al (2006), based primarily on RCTs from the 1980s, concluded that: "The evidence supports the current place of sclerotherapy in modern clinical practice, which is usually limited to treatment of recurrent varicose veins following surgery and thread veins."[44,]Sclerotherapy and phlebectomy are considered appropriate in the absence of reflux of the saphenous system (e.g., post- or adjunctive treatment to other procedures such as surgery).[45,] El-Sheikha et al (2014) reported on

a small randomized trial of concomitant or sequential (if needed) phlebectomy following endovenous laser ablation for varicose veins.[46,]Quality of life and clinical severity scores were similar between the groups by 1 year, with 16 (67%) of 24 patients in the sequential phlebectomy group receiving a secondary intervention.

The bulk of the literature discussing the role of ultrasound guidance refers to sclerotherapy of the saphenous vein, as opposed to the varicose tributaries. For example, Yamaki et al (2012) reported on a prospective RCT that compared visual foam sclerotherapy plus ultrasound-guided foam sclerotherapy of the GSV with visual foam sclerotherapy for varicose tributary veins.[47,] Fifty-one limbs in 48 patients were treated with ultrasound-guided foam sclerotherapy plus visual foam sclerotherapy of the varicose tributaries, and 52 limbs in 49 patients were treated with foam sclerotherapy alone. At 6-month follow-up, complete occlusion was found in 23 (45.1%) limbs treated with ultrasound plus visually guided foam sclerotherapy and in 22 (42.3%) limbs treated with visual sclerotherapy alone. Reflux was absent in 30 (58.8%) limbs treated with ultrasound plus visual guidance and in 37 (71.2%) treated with visual guidance alone (p=*NS*). The authors noted that, for the treatment of tributary veins in clinical practice, most patients receive a direct injection of foam without ultrasound guidance.

A small proportion of patients may present with tributary varicosities in the absence of saphenous reflux. For example, as reported by Michaels et al (2006), of 1009 patients recruited for an RCT, 64 patients had minor varicose veins without reflux, 34 of whom agreed to be randomized to sclerotherapy or conservative treatment.[48,] At baseline, 92% had symptoms of heaviness, 69% had cosmetic concerns, 53% reported itching, and 30% reported relief of symptoms using compression hosiery. At 1-year follow-up, there was an improvement in clinicians-assessment of the anatomic extent of varicose veins, with 85% of patients in the sclerotherapy group showing improvement compared with 29% of patients in the conservative therapy group. Symptoms of aching were milder or eliminated in 69% of the sclerotherapy group and 28% of the group treated with conservative therapy.

Transilluminated Powered Phlebectomy

A meta-analysis by Luebke and Brunkwall (2008) included 5 studies that compared TIPP with conventional surgery.[49,] Results showed a significant advantage of TIPP over the conventional treatment for the number of incisions, mean cosmetic score, and duration of the procedure. However, TIPP also increased the incidence of hematoma and resulted in worse mean pain scores. Included in the meta-analysis was an RCT by Chetter et al (2006) that compared TIPP (n=29) with a multiple stab incision procedure (n=33).[50,] A single surgeon performed all but 2 of the procedures, and there was no difference in operating time. Patients treated with TIPP had an average of 5 incisions, compared with 20 for the multiple stab procedure. However, the blinded evaluation revealed that bruising or discoloration was higher for the TIPP group at 1 and 6 weeks postsurgery. At 6 weeks after surgery, patients in the TIPP group showed no reductions in pain (-2 points on the Burford Pain Scale), while patients in the multiple stab incision group had a significant reduction in pain scores compared with presurgical baseline (-20 points). Six weeks postsurgery, quality of life measures had improved in the multiple stab incision group but not in the TIPP group. Thus, although TIPP required fewer surgical incisions, in this single-center study, it was associated with longer recovery due to more extensive bruising, prolonged pain, and reduced early postoperative quality of life.

Section Summary: Tributary Varicosities
The evidence on the use of stab avulsion, sclerotherapy, and phlebectomy includes RCTs and systematic reviews of RCTs. The literature has indicated that sclerotherapy is effective for the treatment of tributary veins following occlusion of the saphenofemoral or saphenopopliteal junction and saphenous veins. No studies have been identified comparing RFA or laser ablation of tributary veins with standard procedures (microphlebectomy and/or sclerotherapy). TIPP is effective at removing varicosities; outcomes are comparable with available alternatives such as stab avulsion and hook phlebectomy. However, there is limited evidence that TIPP is associated with more pain, bruising, discoloration, and a longer recovery, and the current literature does not show an advantage of TIPP over conventional treatment.

PERFORATOR REFLUX

Clinical Context and Therapy Purpose
Perforator veins cross through the fascia and connect the deep and superficial venous systems. Incompetent perforating veins were originally treated with an open surgical procedure, called the Linton procedure, which involved a long medial calf incision to expose all posterior, medial, and paramedial perforators. While this procedure was associated with healing of ulcers, it was largely abandoned due to a high incidence of wound complications. The Linton procedure was subsequently modified by using a series of perpendicular skin flaps instead of a longitudinal skin flap to provide access to incompetent perforator veins in the lower part of the leg. The modified Linton procedure may occasionally be used to close incompetent perforator veins that cannot be reached by less invasive procedures.

The question addressed in this evidence review is: Does the use of ablation of perforator veins reduce venous insufficiency in individuals who have perforator vein reflux?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals who have perforator vein reflux.

Interventions
The therapy being considered is ablation with subfascial endoscopic perforator surgery (SEPS) of perforator veins. SEPS is a less invasive surgical procedure for the treatment of incompetent perforators and has been reported since the mid-1980s. Guided by Duplex ultrasound scanning, small incisions are made in the skin, and the perforating veins are clipped or divided by endoscopic scissors. The surgery can be performed as an outpatient procedure. Endovenous ablation of incompetent perforator veins with sclerotherapy, radiofrequency, and laser ablation has also been reported.

Comparators
The following is currently being used to treat perforator vein reflux: conservative therapy or treatment of saphenous veins alone.

Outcomes
The general outcomes of interest are reductions in symptoms and morbid events, change in disease status, and improvements in quality of life. These may be assessed by VAS, AVVQ, and VCSS, along with ulcer healing and recurrence.

Follow-up at 2 years is of interest for ablation (e.g., SEPS) of perforator veins to monitor relevant outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
A systematic literature review by O'Donnell (2008) indicated there was a lack of evidence on the role of incompetent perforator vein surgery performed in conjunction with superficial saphenous vein surgery.[5,] These conclusions were based on 4 RCTs published since 2000 that compared superficial vein surgery with conservative therapy for advanced chronic venous insufficiency (CEAP classes C5-C6). The 4 trials included 2 level I (large subject population) and 2 level II (small subject population) studies. Two trials combined surgical treatment of the incompetent perforator veins with concurrent or prior treatment of the superficial saphenous veins; the other 2 treated the GSV alone. The 2 randomized studies (2004, 2007) in which the GSV alone was treated (including the ESCHAR trial) showed a significant reduction in ulcer recurrence compared with conservative therapy.[51,52,]

Treatment of the GSV alone has been reported to improve perforator function. For example, Blomgren et al (2005) showed that reversal of perforator vein incompetence (28 [41%] of 68 previously incompetent perforators) was more common than new perforator vein incompetence (41 [22%] of 183 previously competent perforators) following superficial vein surgery.[53,] O'Donnell (2008) discussed additional (lower quality) evidence to suggest deep venous valvular involvement rather than incompetent perforators in venous insufficiency. [5,] Thus, although incompetence of perforator veins is frequently cited as an important etiologic factor in the pathogenesis of venous ulcer, current evidence does not support the routine ligation or ablation of perforator veins.

Lawrence et al (2020) reported a multicenter retrospective review of 832 consecutive patients who met criteria and were treated for venous leg ulcers in the U.S.[54,] Of the 832 patients, 187 were managed with compression alone (75% ulcer healing) and 528 received superficial vein treatment after failure of a mean of 23 months of compression. Of the 528, 344 also underwent ablation of an average of 1.8 perforator veins. Techniques included radiofrequency, laser, and sclerotherapy. The ulcer healing rate was 17% higher in patients treated for perforator reflux (68%) in comparison with superficial vein treatment alone (51%; hazard ratio 1.619; 95% CI 1.271 to 2.063), even though the ulcers were larger at baseline. Perforator vein treatment did not affect recurrence rates in ulcers that had healed. Larger ulcers were associated with reflux in more than 1 level, and deep vein stenting was performed in 95 patients, some in combination with superficial vein treatment and some in combination with both superficial and perforator vein treatment. The ulcer healing rate in patients who underwent all 3 procedures was 87% at 36 months with an ulcer recurrence of 26% at 24 months.

Subfascial Endoscopic Perforator Surgery

A Cochrane review by Lin et al (2019) evaluated the efficacy of SEPS for the treatment of venous ulcers.[55,] They identified 4 RCTs, 2 compared SEPS plus compression with compression alone (n=208), one compared SEPS with the Linton procedure (n=39), and one compared SEPS plus saphenous vein surgery with saphenous vein surgery alone (n=75). Results are shown in Table 14. The authors concluded that:

- Compared with compression alone, there was low certainty evidence that SEPS may increase the rate of ulcer healing compared to compression alone, but it was uncertain whether SEPS reduced the rate of ulcer recurrence.
- Compared with the Linton procedure, it was uncertain whether there was a difference in ulcer healing, and very uncertain whether there was a difference in ulcer recurrence. Based on very low certainty evidence, the Linton procedure was possibly associated more adverse events.
- Compared to saphenous vein surgery alone, it was uncertain whether there was a difference in ulcer healing or the risk of ulcer recurrence. It was uncertain whether SEPS led to an increase in adverse events (very low certainty due to imprecision and risk of reporting bias)

Table 14. Meta-analysis Results

Comparator	Ulcer Healing	Ulcer Recurrence	Adverse Events
Compression alone N	196	208	
Risk ratio (95% CI)	1.17 (1.03 to 1.33)	0.85 (0.26 to 2.76)	
Linton Procedure N	39	39	39
Risk ratio (95% CI)	0.95 (0.83 to 1.09)	0.47 (0.10 to 2.30)	0.04 (0.00 to 0.60)
Saphenous Vein Surgery	22	75	75
Risk ratio (95% CI)	0.96 (0.64 to 1.43)	1.03 (0.15 to 6.91)	2.05 (0.86 to 4.90)

CI: ; NNT: number needed to treat.

[1] If the M-A includes a quantitative synthesis then include numbers analyzed, measures of effect (absolute or relative) with CI and measure of heterogeneity. If the M-A includes only a qualitative synthesis then include the ranges of N and effects.

In a meta-analysis of subfascial endoscopic perforator surgery for chronic venous insufficiency, Luebke and Brunkwall (2009) concluded that "its use should not be employed routinely and could only be justified in patients with persistent ulceration thought to be of venous origin, and in whom any superficial reflux has already been ablated and postthrombotic changes excluded."[56,] Reviewers also stated that the "introduction of less invasive techniques for perforator vein ablation, such as ultrasound-guided sclerotherapy or radiofrequency ablation, may diminish the role of subfascial endoscopic perforator surgery in the future."

Section Summary: Perforator Reflux

The literature has shown that the routine ligation and ablation of incompetent perforator veins is not necessary for treating varicose veins and venous insufficiency concurrent with superficial vein procedures. However, when combined superficial vein procedures and compression therapy have failed to improve symptoms (i.e., ulcers), treatment of perforator vein reflux may be as beneficial as any alternative (e.g., deep vein valve replacement). Comparative studies are needed to

determine the most effective method of ligating and ablating incompetent perforator veins. There is some low quality evidence that SEPS is as effective as the Linton procedure with a reduction in adverse events. Endovenous ablation with specialized laser or RFA probes has been shown to effectively ablate incompetent perforator veins with a potential decrease in morbidity compared with surgical interventions.

SUMMARY OF EVIDENCE

Saphenous Veins

For individuals who have varicose veins/venous insufficiency and saphenous vein reflux who receive endovenous thermal ablation (radiofrequency or laser), the evidence includes RCTs and systematic reviews of controlled trials. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life, and treatment-related morbidity. There are a number of large RCTs and systematic reviews of RCTs assessing endovenous thermal ablation of the saphenous veins. Comparison with the standard of ligation and stripping at 2- to 5-year follow-up has supported the use of both endovenous laser ablation and RFA. Evidence has suggested that ligation and stripping lead to more neovascularization, while thermal ablation leads to more recanalization, resulting in similar clinical outcomes for endovenous thermal ablation and surgery. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have varicose veins/venous insufficiency and saphenous vein reflux who receive microfoam sclerotherapy, the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life, and treatment-related morbidity. For physician-compounded sclerotherapy, there is high variability in success rates and some reports of serious adverse events. By comparison, rates of occlusion with the microfoam sclerotherapy (polidocanol 1%) approved by the FDA are similar to those reported for endovenous laser ablation or stripping. Results of a noninferiority trial of physician-compounded sclerotherapy have indicated that once occluded, recurrence rates at 2 years are similar to those of ligation and stripping. Together, this evidence indicates that the more consistent occlusion with the microfoam sclerotherapy preparation will lead to recurrence rates similar to ligation and stripping in the longer term. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have varicose veins/venous insufficiency and saphenous vein reflux who receive MOCA, the evidence includes 4 RCTs with 6 month to 2 year results that compared MOCA to thermal ablation, a prospective cohort with follow-up out to 5 years, and retrospective case series. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life, and treatment-related morbidity. MOCA is a combination of liquid sclerotherapy with mechanical abrasion. A potential advantage of this procedure compared with thermal ablation is that MOCA does not require tumescent anesthesia and may result in less pain during the procedure. Results to date have been mixed regarding a reduction in intraprocedural pain compared to thermal ablation procedures. Occlusion rates at 6 months to 2 years from RCTs indicate lower anatomic success rates compared to thermal ablation, but a difference in clinical outcomes at these early time points has not been observed. Experience with other endoluminal ablation procedures suggests that lower anatomic success in the short term is associated with recanalization and clinical recurrence between 2 to 5 years. The possibility of later clinical recurrence is supported by a prospective cohort study with 5-year follow-up following treatment with MOCA. However, there have been improvements in technique since the cohort study was begun, and clinical

progression is frequently observed with venous disease. Because of these limitations of the single arm studies, longer follow-up in the more recently conducted RCTs is needed to establish the efficacy and durability of this procedure compared with the criterion standard of thermal ablation. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have varicose veins/venous insufficiency and saphenous vein reflux who receive CAC, the evidence includes 2 RCTs and a prospective cohort. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life, and treatment-related morbidity. Evidence includes a multicenter noninferiority trial with follow-up through 36 months, an RCT with follow-up through 24 months, and a prospective cohort with 30-month follow-up. The short-term efficacy of VenaSeal CAC has been shown to be noninferior to RFA at up to 36 months. At 24 and 36 months the study had greater than 20% loss to follow-up, but loss to follow-up was similar in the 2 groups at the long-term follow-up and is not expected to influence the comparative results. A second RCT (n=525) with the same active CAC ingredient (N-butyl cyanoacrylate) that is currently available outside of the U.S. found no significant differences in vein closure between CAC and thermal ablation controls at 24-month follow-up. The CAC procedure and return to work were shorter and pain scores were lower compared to thermal ablation, although the subjective pain scores may have been influenced by differing expectations in this study. A prospective cohort reported high closure rates at 30 months. Overall, results indicate that outcomes from CAC are at least as good as thermal ablation techniques, the current standard of care. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have varicose veins/venous insufficiency and saphenous vein reflux who receive cryoablation, the evidence includes RCTs and multicenter series. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life, and treatment-related morbidity. Results from a recent RCT of cryoablation have indicated that this therapy is inferior to conventional stripping. Studies showing a benefit on health outcomes are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Varicose Tributary Veins

For individuals who have varicose tributary veins who receive ablation (stab avulsion, sclerotherapy, or phlebectomy) of tributary veins, the evidence includes RCTs and systematic reviews of RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life, and treatment-related morbidity. The literature has shown that sclerotherapy is effective for treating tributary veins following occlusion of the saphenofemoral or saphenopopliteal junction and saphenous veins. No studies have been identified comparing RFA or laser ablation of tributary veins with standard procedures (microphlebectomy and/or sclerotherapy). TIPP is effective at removing varicosities; outcomes are comparable to available alternatives such as stab avulsion and hook phlebectomy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Perforator Veins

For individuals who have perforator vein reflux who receive ablation (e.g., subfascial endoscopic perforator surgery) of perforator veins, the evidence includes RCTs and systematic reviews of RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life,

and treatment-related morbidity. The literature has indicated that the routine ligation or ablation of incompetent perforator veins is not necessary for the treatment of varicose veins/venous insufficiency at the time of superficial vein procedures. However, when combined superficial vein procedures and compression therapy have failed to improve symptoms (i.e., ulcers), treatment of perforator vein reflux may be as beneficial as an alternative (e.g., deep vein valve replacement). Comparative studies are needed to determine the most effective method of ligating or ablating incompetent perforator veins. Subfascial endoscopic perforator surgery is possibly as effective as the Linton procedure with a reduction in adverse events. Endovenous ablation with specialized laser or radiofrequency probes has been shown to effectively ablate incompetent perforator veins with a potential decrease in morbidity compared with surgical interventions. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 4 physician specialty societies while this policy was under review in 2015. There was no agreement on the need to treat varicose tributaries to improve functional outcomes in the absence of saphenous vein disease. Input was also mixed on the use of mechanochemical ablation and cyanoacrylate adhesive.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Venous Forum et al

In 2020, in response to published reports of potentially inappropriate application of venous procedures, the American Venous Forum, Society for Vascular Surgery, American Vein and Lymphatic Society, and the Society of Interventional Radiology published appropriate use criteria for the treatment of chronic lower extremity venous disease.[57,] Appropriate use criteria were developed using the RAND/UCLA method incorporating best available evidence and expert opinion.

Appropriate use criteria were determined for various scenarios (e.g., symptomatic, asymptomatic, CEAP [Clinical, Etiology, Anatomy and Pathophysiology] class, axial reflux, saphenofemoral junction reflux) for the following:

- Saphenous vein ablation
    - Great saphenous vein
    - Small saphenous vein

    - Accessory great saphenous vein
- Nontruncal varicose veins
- Diseased tributaries associated with saphenous ablation
- Perforator Veins
- Iliac Vein or inferior vena cava stenting as a first line treatment
- Duplex ultrasound
- Timing and Reimbursement.

Treatment of saphenous veins for asymptomatic CEAP class 1 and 2, or symptomatic class 1, was considered to be rarely appropriate or never appropriate, and treatment of symptomatic CEAP class 2, 3, and 4-6 without reflux was rated as never appropriate. Based on the 2011 Guidelines from the Society for Vascular Surgery and American Venous Forum (see below), treatment of perforator veins for asymptomatic or symptomatic CEAP class 1 and 2 was considered to be rarely appropriate or never appropriate. Perforator vein treatment was rated as appropriate for CEAP classes 4-6, and may be appropriate for CEAP class 3. Except for a recommendation to use endovenous procedures for perforator vein ablation, techniques used to treat veins in these scenarios were not evaluated.

Society for Vascular Surgery and American Venous Forum
The Society for Vascular Surgery and the American Venous Forum (2011) published joint clinical practice guidelines. Table 15 provides the recommendations.

Table 15. Guidelines on Management of Varicose Veins and Associated Chronic Venous Diseases

Recommendation	Grade[a]	SOR	QOE
Compression therapy for venous ulcerations and varicose veins			
Compression therapy is recommended as the primary treatment to aid healing of venous ulceration	1B	Strong	Moderate
To decrease the recurrence of venous ulcers, ablation of the incompetent superficial veins in addition to compression therapy is recommended	1A	Strong	High
Use of compression therapy for patients with symptomatic varicose veins is recommended	2C	Weak	Low
Compression therapy as the primary treatment if the patient is a candidate for saphenous vein ablation is not recommended	1B	Strong	Moderate
Treatment of the incompetent great saphenous vein			
Endovenous thermal ablation (radiofrequency or laser) is recommended over chemical ablation with foam or high ligation and stripping due to reduced convalescence and less pain and morbidity. Cryostripping is a technique that is new in the United States, and it has not been fully evaluated.	1B	Strong	Moderate
Varicose tributaries			
Phlebectomy or sclerotherapy are recommended to treat varicose tributaries	1B	Strong	Moderate
Transilluminated powered phlebectomy using lower oscillation speeds and extended tumescence is an alternative to traditional phlebectomy	2C	Weak	Low

Recommendation	Grade[a]	SOR	QOE
Perforating vein incompetence			
Selective treatment of perforating vein incompetence in patients with simple varicose veins is not recommended	1B	Strong	Moderate
Treatment of pathologic perforating veins (outward flow of ≥500 ms duration, with a diameter of ≥3.5 mm) located underneath healed or active ulcers (CEAP class C5-C6) is recommended	2B	Weak	Moderate

QOE: quality of evidence; SOR: strength of recommendation.
[a] Grading: strong = 1 or weak = 2, based on a level of evidence that is either high quality = A, moderate quality = B, or low quality = C.

American Vein and Lymphatic Society
In 2015, the American Vein and Lymphatic Society (AVL, previously named the American College of Phlebology) published guidelines on the treatment of superficial vein disease.[58,]

AVL gave a Grade 1 recommendation based on high quality evidence that compression is an effective method for the management of symptoms, but when patients have a correctable source of reflux definitive treatment should be offered unless contraindicated. AVL recommends against a requirement for compression therapy when a definitive treatment is available. AVL gave a strong recommendation based on moderate quality evidence that endovenous thermal ablation is the preferred treatment for saphenous and accessory saphenous vein incompetence, and gave a weak recommendation based on moderate quality evidence that mechanochemical ablation may also be used to treat venous reflux.

In 2017, AVL published guidelines on the treatment of refluxing accessory saphenous veins.[36,] The College gave a Grade 1 recommendation based on level C evidence that patients with symptomatic incompetence of the accessory saphenous veins be treated with endovenous thermal ablation or sclerotherapy to reduce symptomatology. The guidelines noted that although accessory saphenous veins may drain into the great saphenous vein before it drains into the common femoral vein, they can also empty directly into the common femoral vein.

National Institute for Health and Care Excellence
In 2013, the U.K.s National Institute for Health and Care Excellence (NICE) updated its guidance on ultrasound-guided foam sclerotherapy for varicose veins.[59,] NICE stated that:
"1.1 Current evidence on the efficacy of ultrasound-guided foam sclerotherapy for varicose veins is adequate. The evidence on safety is adequate, and provided that patients are warned of the small but significant risks of foam embolization (see section 1.2), this procedure may be used with normal arrangements for clinical governance, consent and audit.

1.2 During the consent process, clinicians should inform patients that there are reports of temporary chest tightness, dry cough, headaches and visual disturbance, and rare but significant complications including myocardial infarction, seizures, transient ischemic attacks and stroke."

In 2015, NICE published a technology assessment on the clinical effectiveness and cost-effectiveness of foam sclerotherapy, endovenous laser ablation, and surgery for varicose veins.[60,]

In 2016, NICE revised its guidance on endovenous mechanochemical ablation, concluding that "Current evidence on the safety and efficacy of endovenous mechanochemical ablation for varicose veins appears adequate to support the use of this procedure...."[61,]

U.S. Preventive Services Task Force Recommendations
Not applicable.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 16.

Table 16. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03392753	Randomised Controlled Trial of Mechanochemical Ablation Versus Cyanoacrylate Adhesive for the Treatment of Varicose Veins	180	Dec 2021
NCT02627846	A Randomised Clinical Trial Comparing Endovenous Laser Ablation and Mechanochemical Ablation (ClariVein) in the Management of Superficial Venous Insufficiency (LAMA)	150	Aug 2025
NCT04737941	Finnish Venous Ulcer Study	248	Mar 2026
NCT03820947[a]	Global, Post-Market, Prospective, Multi-Center, Randomized Controlled Trial of the VenaSeal™ Closure System vs. Surgical Stripping or Endothermal Ablation (ETA) for the Treatment of Early & Advanced Stage Superficial Venous Disease	806	Oct 2027
Unpublished			
NTR4613[a]	Mechanochemical endovenous ablation versus radiofrequency ablation in the treatment of primary small saphenous vein insufficiency (MESSI trial)	160	Apr 2020
NCT03722134	Mechanochemical Ablation vs Thermal Ablation in Patients With Great Saphenous Vein Insufficiency	132	Dec 2020
NCT03835559	Randomized Controlled Trial Comparing the Clinical Outcomes After Cyanoacrylate Closure and Surgical Stripping for Incompetent Saphenous Veins	146	Feb 2021

NCT: national clinical trial. NTR: Netherlands Trial Registry.
[a] Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS

36465	Injection of non-compounded foam sclerosant with ultrasound compression maneuvers to guide dispersion of the injectate, inclusive of all imaging guidance and monitoring; single incompetent extremity truncal vein (e.g., great saphenous vein, accessory saphenous vein)
36466	Injection of non-compounded foam sclerosant with ultrasound compression maneuvers to guide dispersion of the injectate, inclusive of all imaging guidance and monitoring; multiple incompetent truncal veins (e.g., great saphenous vein, accessory saphenous vein), same leg
36468	Single or multiple injections of sclerosing solutions, spider veins (telangiectasia); limb or trunk
36470	Injection of sclerosing solution: single vein
36471	Injection of sclerosing solution; multiple veins, same leg
36473	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, mechanochemical; first vein treated
36474	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, mechanochemical; subsequent vein(s) treated in a single extremity, each through separate access sites (List separately in addition to code for primary procedure)
36475	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, radiofrequency; first vein treated
36476	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, radiofrequency; second and subsequent veins treated in a single extremity, each through separate access sites (list separately in addition to code for primary procedure)
36478	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, laser; first vein treated
36479	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, laser; second and subsequent veins treated in a single extremity, each through separate access sites (list separately in addition to code for primary procedure)
36482	Endovenous ablation therapy of incompetent vein, extremity, by transcatheter delivery of a chemical adhesive (e.g., cyanoacrylate) remote from the access site, inclusive of all imaging guidance and monitoring, percutaneous; first vein treated

36483 Endovenous ablation therapy of incompetent vein, extremity, by transcatheter delivery of a chemical adhesive (e.g., cyanoacrylate) remote from the access site, inclusive of all imaging guidance and monitoring, percutaneous; subsequent vein(s) treated in a single extremity, each through separate access sites (List separately in addition to code for primary procedure)
37500 Vascular endoscopy, surgical, with ligation of perforator veins, subfascial (SEPS)
37700 Ligation and division of long saphenous vein at saphenofemoral junction, or distal interruptions
37718 Ligation, division, and stripping, short saphenous vein
37722 Ligation, division, and stripping, long (greater) saphenous veins from saphenofemoral junction to knee or below
37735 Ligation and division and complete stripping of long or short saphenous veins with radical excision of ulcer and skin graft and/or interruption of communicating veins of lower leg, with excision of deep fascia
37760 Ligation of perforator veins, subfascial, radical (Linton type), including skin graft, when performed, open, 1 leg
37761 Ligation of perforator vein(s), subfascial, open, including ultrasound guidance, when performed, 1 leg
37765 Stab phlebectomy of varicose veins, 1 extremity; 10-20 stab incisions
37766 Stab phlebectomy of varicose veins, 1 extremity; more than 20 incisions
37780 Ligation and division of short saphenous vein at saphenopopliteal junction (separate procedure)
37785 Ligation, division, and/or excision of varicose vein cluster(s), 1 leg
37799 Unlisted procedure, vascular surgery
76937 Ultrasound guidance for vascular access requiring ultrasound evaluation of potential access sites, documentation of selected vessel patency, concurrent real time ultrasound visualization of vascular needle entry, with permanent recording and reporting (List separately in addition to code for primary procedure)
76942 Ultrasonic guidance for needle placement (e.g., biopsy, aspiration, injection, localization device), imaging supervision and interpretation
76998 Ultrasonic guidance, intraoperative
76999 Unlisted ultrasound procedure (e.g. diagnostic, interventional)
93970 Duplex scan of extremity veins including responses to compression and other maneuvers; complete bilateral study
93971 Duplex scan of extremity veins including responses to compression and other maneuvers; unilateral or limited study
0524T Endovenous catheter directed chemical ablation with balloon isolation of incompetent extremity vein, open or percutaneous, including all vascular access, catheter manipulation, diagnostic imaging, imaging guidance and monitoring (Effective 01-01-2019)
S2202 Echosclerotherapy

- Note: The bulk of the literature discussing the role of ultrasound guidance refers to sclerotherapy of the saphenous vein, as opposed to the varicose tributaries. If ultrasound guidance (CPT code 76942) is used to guide sclerotherapy of the varicose tributaries, it would be considered content of service to the injection procedure.

ICD-10 Diagnoses

I83.011	Varicose veins of right lower extremity with ulcer of thigh
I83.012	Varicose veins of right lower extremity with ulcer of calf
I83.013	Varicose veins of right lower extremity with ulcer of ankle
I83.014	Varicose veins of right lower extremity with ulcer of heel and midfoot
I83.015	Varicose veins of right lower extremity with ulcer other part of foot
I83.018	Varicose veins of right lower extremity with ulcer other part of lower leg
I83.021	Varicose veins of left lower extremity with ulcer of thigh
I83.022	Varicose veins of left lower extremity with ulcer of calf
I83.023	Varicose veins of left lower extremity with ulcer of ankle
I83.024	Varicose veins of left lower extremity with ulcer of heel and midfoot
I83.025	Varicose veins of left lower extremity with ulcer other part of foot
I83.028	Varicose veins of left lower extremity with ulcer other part of lower leg
I83.11	Varicose veins of right lower extremity with inflammation
I83.12	Varicose veins of left lower extremity with inflammation
I83.211	Varicose veins of right lower extremity with both ulcer of thigh and inflammation
I83.212	Varicose veins of right lower extremity with both ulcer of calf and inflammation
I83.213	Varicose veins of right lower extremity with both ulcer of ankle and inflammation
I83.214	Varicose veins of right lower extremity with both ulcer of heel and midfoot and inflammation
I83.215	Varicose veins of right lower extremity with both ulcer other part of foot and inflammation
I83.218	Varicose veins of right lower extremity with both ulcer of other part of lower extremity and inflammation
I83.219	Varicose veins of right lower extremity with both ulcer of unspecified site and inflammation
I83.221	Varicose veins of left lower extremity with both ulcer of thigh and inflammation
I83.222	Varicose veins of left lower extremity with both ulcer of calf and inflammation
I83.223	Varicose veins of left lower extremity with both ulcer of ankle and inflammation
I83.224	Varicose veins of left lower extremity with both ulcer of heel and midfoot and inflammation
I83.225	Varicose veins of left lower extremity with both ulcer other part of foot and inflammation
I83.228	Varicose veins of left lower extremity with both ulcer of other part of lower extremity and inflammation
I83.811	Varicose veins of right lower extremities with pain
I83.812	Varicose veins of left lower extremities with pain
I83.813	Varicose veins of bilateral lower extremities with pain
I83.891	Varicose veins of right lower extremities with other complications
I83.892	Varicose veins of left lower extremities with other complications
I83.893	Varicose veins of bilateral lower extremities with other complications
I83.91	Asymptomatic varicose veins of right lower extremity
I83.92	Asymptomatic varicose veins of left lower extremity
I83.93	Asymptomatic varicose veins of bilateral lower extremities

REVISIONS	
05-04-2011	Description section updated
	In Policy section: ▪ Clarified policy by including within the Greater or Lesser Saphenous Veins, Accessory Saphenous Veins, and Symptomatic Varicose Tributaries sections of the policy the following: "B. Physical findings that support medically significant venous hypertension must be clearly documented." and "D. Treatment of varicose veins for cosmetic purposes is not covered." ▪ Clarified Policy Guidelines by: ▪ Adding to #1: "Physical findings that support medically significant venous hypertension must be clearly documented. Treatment of varicose veins for cosmetic

REVISIONS	
	purposes is not covered." to read "1. A clear and complete description of the physical exam of the lower extremities that documents the medical necessity of treatment for venous insufficiency for medical, not cosmetic purposes, is required. Physical findings that support medically significant venous hypertension must be clearly documented. Treatment of varicose veins for cosmetic purposes is not covered. Photographs may be requested." ▪ Revising #2: From "…up to 3 sclerotherapy sessions for both legs…" to "…up to 3 sclerotherapy sessions for each leg…" to read "Up to 20 injections in each leg may be treated in any one session and up to 3 sclerotherapy sessions for each leg may be considered medically necessary if selection criteria are met." ▪ Added to Policy Guidelines: "5. Patients with combined deep and superficial venous insufficiency are often not good candidates for ablation therapy. Varicose vein recurrence and ulcer recurrence rates following intervention are much higher." ▪ Removed from Policy Guidelines: "The severity of signs and symptoms of venous disease tends to correlate with the degree of reflux identified by duplex ultrasound." ▪ The intent of the policy language was not changed.
	Rationale section update
	Revision section: ▪ Removed revision details for 01-04-2008 and 07-18-2008
	References updated
09-06-2011	Description section updated.
	In Policy section: ▪ Within the subsection of Greater or Lesser Saphenous Veins moved the following wording as a stand alone Item B. to be included with the medically necessary criteria as item A. 3. to read, "Physical findings that support medically significant venous hypertension are clearly documented." This change was made to be clearer that in addition to meeting the medical necessity criteria, physical findings that support medically significant venous hypertension must be clearly documented. ▪ Within the subsection of Accessory Saphenous Veins moved the following wording as a stand alone Item B. to be included with the medically necessary criteria as item A. 4. to read, "Physical findings that support medically significant venous hypertension are clearly documented." This change was made to be clearer that in addition to meeting the medical necessity criteria, physical findings that support medically significant venous hypertension must be clearly documented. ▪ Within the subsection of Symptomatic Varicose Tributaries, Item A. was liberalized from, "The following treatments are considered medically necessary as a component of the treatment of symptomatic varicose tributaries when performed either at the same time or following prior treatment (surgical, radiofrequency or laser) of the saphenous veins…" to "The following treatments are considered medically necessary as a component of the treatment of symptomatic varicose tributaries.." ▪ Within the subsection of Symptomatic Varicose Tributaries, Item B. was revised from "Physical findings that support medically significant venous hypertension must be clearly documented." to "Physical findings must support medical necessity."
	Rationale section updated
	References updated
09-11-2012	Description section updated
	In Policy section: ▪ In I A 2 c and II A 3 c revised wording from "Recurrent hemorrhage or bleeding episodes…" to "Hemorrhage or recurrent bleeding episodes…" No policy intent change was made.

REVISIONS	
	▪ In I A 3 and II A 4 clarified the wording from "Physical findings…" to "Physical / visible findings…" ▪ Added to IV Perforator Veins "A. Surgical ligation (including subfascial endoscopic perforator surgery) or endovenous radiofrequency or laser ablation of incompetent perforator veins may be considered medically necessary as a treatment of leg ulcers associated with chronic venous insufficiency when the following conditions have been met: 1. There is demonstrated perforator reflux; AND 2. The superficial saphenous veins (greater, lesser, or accessory saphenous and symptomatic varicose tributaries) have been previously eliminated; AND 3. Ulcers have not resolved following combined superficial vein treatment and compression therapy for at least 3 months; AND 4. The venous insufficiency is not secondary to deep venous thromboembolism." ▪ Moved from Policy Guidelines to IV B the not medically necessary indication of: "6. Perforator reflux often resolves following saphenous ablation." ▪ Added the not medically necessary indication of IV C: " C. Ligation or ablation of incompetent perforator veins performed concurrently with superficial venous surgery is not medically necessary." ▪ In Policy Guidelines #4 added, "However, deep vein insufficiency is not a contraindication to superficial vein treatment." ▪ In Policy Guidelines Reimbursement sub-section item 1 revised, "…reimbursed at 25% of full." to read, "1. Endovenous ablation (36475, 36476, 36478 and 36479) other than the greater saphenous vein will be reimbursed at 50% of full."
	Rationale section updated
	In Revision section: ▪ Removed revision details for dates: 04-22-2009, 11-18-2009, 01-01-2010
	References updated
03-08-2013	In the Reimbursement section: ▪ Removed the reimbursement limitation stating, "Endovenous ablation (36475, 36476, 36478 and 36479) other than the greater saphenous vein will be reimbursed at 50% of full."
12-24-2014	Description section updated
	In Policy section: ▪ In Item I A and II A removed "Physical / visible findings that support medically significant venous hypertension are clearly documented." And added "…or microfoam sclerotherapy…" to read "…by surgery (ligation and stripping), endovenous radiofrequency or laser ablation, or microfoam sclerotherapy may be considered medically necessary for…" ▪ In Item I B added "…or microfoam sclerotherapy…" to read "…by surgery, endovenous radiofrequency or laser ablation, or microfoam sclerotherapy that do not meet the criteria described above is considered not medically necessary." ▪ In Item II A added "1. Incompetence of the accessory saphenous vein is isolated, OR" to read "Incompetence of the accessory saphenous vein is isolated, OR The greater or lesser saphenous veins had been previously eliminated (at least 3 months);" ▪ In Item III A added "When physical findings support medical necessity," (formerly standalone Item III B) to read, "When physical findings support medical necessity, the following treatments are considered medically necessary as a component of the treatment of symptomatic varicose tributaries (none of these techniques has been shown to be superior to another):" ▪ In new Item III B removed "Sclerotherapy as" to read, "The sole treatment of varicose vein tributaries…"

REVISIONS	
	▪ In Policy Guidelines added "5. It should be noted that the bulk of the literature discussing the role of ultrasound guidance refers to sclerotherapy of the saphenous vein, as opposed to the varicose tributaries." ▪ In Policy Guidelines removed "There is little evidence to support that ultrasound guidance makes a significant difference in outcomes from sclerotherapy when compared to non-ultrasound guided techniques."
	Rationale section updated
	In Coding section: ▪ Removed CPT Code: 36469 (Effective January 1, 2015) ▪ Coding comments updated ▪ ICD-10 Codes added
	In Revision section ▪ Removed Revision details for 10-11-2010.
	References updated
01-01-2016	In Coding section: ▪ Removed CPT codes: 37250, 37251
02-01-2019	Policy published 01-01-2019. Policy effective 02-01-2019.
	Description section updated
	In Policy section: ▪ Throughout the policy removed "lesser" and added "small" to read "great or small saphenous veins" ▪ In Item I revised to read "SAPHENOUS VEINS – Great or Small Saphenous Veins" ▪ In Item I A 1 added "and CEAP [Clinical, Etiology, Anatomy, Pathophysiology], class C2 or greater" to read "There is demonstrated saphenous reflux and CEAP [Clinical, Etiology, Anatomy, Pathophysiology], class C2 or greater" ▪ In Item I A 2a and II A 3a removed "that fails to respond to compressive therapy" to read "Ulceration secondary to venous stasis" ▪ In Item I A 2b and II A 3b removed "that fails to respond to compressive therapy" to read "Recurrent superficial thrombophlebitis" ▪ In Item I A 2d1) removed "or significant refractory edema or refractory stasis dermatitis when" to read "Persistent pain, swelling, itching, burning, or other symptoms associated with saphenous reflux" ▪ In Item II A 3d1) removed "or significant refractory edema or refractory stasis dermatitis when" and "accessory vein" to read "Persistent pain, swelling, itching, burning, or other symptoms associated with saphenous reflux" ▪ In Item II B added "veins by surgery, endovenous radiofrequency or laser ablation, or microfoam sclerotherapy" to read "Treatment of accessory saphenous veins by surgery, endovenous radiofrequency or laser ablation, or microfoam sclerotherapy, that do not meet the criteria described above is considered not medically necessary." ▪ In Item III A removed "When physical findings support medical necessity" and added "when performed either at the same time or following prior treatment (surgical, radiofrequency or laser) of the saphenous veins" to read "The following treatments are considered medically necessary as a component of the treatment of symptomatic varicose tributaries when performed either at the same time or following prior treatment (surgical, radiofrequency or laser) of the saphenous veins (none of these techniques has been shown to be superior to another):" ▪ In Item III B removed "The sole", "in the presence of saphenofemoral or saphenopopliteal reflux" and not medically necessary" and added "symptomatic", "when performed either at the same time or following prior treatment of saphenous veins using any other techniques than noted above" and "experimental / investigational" to read "Treatment of symptomatic varicose tributaries when performed either at the same time or

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	following prior treatment of saphenous veins using any other techniques than noted above reflux is considered experimental / investigational" ▪ In Item VI added "Veins" to read "Other Veins" ▪ In Item VI A revised "not medically necessary" to "experimental / investigational" to read "Techniques for conditions not specifically listed above are experimental / investigational, including, but not limited to:" ▪ In Item VI A added "techniques, other than microfoam sclerotherapy, of great, small, or accessory saphenous veins", "Sclerotherapy of perforator veins", "Mechanochemical ablation of any vein", "Cyanoacrylate adhesive of any vein" to read " 1. Sclerotherapy techniques, other than microfoam sclerotherapy, of great, small, or accessory saphenous veins 2. Sclerotherapy of perforator veins 3. Sclerotherapy of isolated tributary veins without prior or concurrent treatment of saphenous veins 4. Stab avulsion, hook phlebectomy, or transilluminated powered phlebectomy of perforator, great or small saphenous, or accessory saphenous veins. 5. Endovenous radiofrequency or laser ablation of tributary veins 6. Mechanochemical ablation of any vein 7. Cyanoacrylate adhesive of any vein 8. Endovenous cryoablation of any vein" ▪ Policy Guidelines updated
	Rationale section updated
	In Coding section: ▪ Added CPT Codes: 36465, 36466, 36473, 36474, 36482, 36483, 0524T ▪ Removed CPT Code: 93965
	References updated
09-13-2019	Policy published 08-14-2019. Policy effective 09-13-2019.
	Description section updated
	In Policy section: ▪ In Items I A, I B, II A, II B, IV A revised the phrase "endovenous radiofrequency or laser ablation" to read "endovenous thermal ablation (radiofrequency or laser)" Added Item I C "Treatment of the great or small saphenous veins by cyanoacrylate adhesive is considered not medically necessary for symptomatic varicose veins / venous insufficiency (see Policy Guideline 1)." ▪ In Item II A 1 a added "when documentation of the anatomy supports the reflux" to read "Incompetence of the accessory saphenous vein, when documentation of the anatomy supports the reflux is isolated" ▪ Added Item C "Treatment of accessory saphenous veins by cyanoacrylate adhesive is considered not medically necessary for symptomatic varicose veins / venous insufficiency (see Policy Guideline 1)." ▪ In Item VI A removed from the E/I statement "cyanoacrylate adhesive of any vein" ▪ In Policy Guidelines added: "1. For a service to be considered medically necessary, it should not be more costly than an alternative service or supply or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results for the illness, injury, or disease."
	Rationale section updated
	In Coding section: ▪ Updated coding notations.
	References updated
04-19-2021	Updated Description section
	In policy guideline 2

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	• Replaced the Table 1 Clinical Portion of the CEAP Classification System from 2004 with the current Clinical Portion of the CEAP Classification System Table
	Updated Rationale section
	Updated Reference section
07-02-2021	Updated Description section
	Updated Rationale section
	Updated Reference section

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